IMMUNOMEDICS IMMU-132-05 STATISTICAL ANALYSIS PLAN

Full Title of Study	An International, Multi-Center, Open-Label, Randomized Phase III Trial of Sacituzumab Govitecan versus Treatment of Physician Choice in Patients with Metastatic Triple-Negative Breast Cancer Who Received at Least Two Prior Treatments
Protocol Number	IMMU-132-05
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Sponsor Address	300 The American Road, Morris Plains, NJ 07950

Revision History		
Revision	**Date**	**Description of Change**
4.0	May 5, 2017	Clarification of specific dosing regimens for the 4 agents in the treatment of physician choice (TPC) arm of the trial
5.0	July 31, 2017	To align with Revision 2 of Amendment #2: revised the schedule of CT or MRI scans, added stratification factor for presence of brain metastases, and revised language describing dose modifications of treatment of physician choice if too toxic.
6.0	February 8, 2018	To align with Global Amendment #3, to increase sample size, clarify patient population, clarify analyses sub-population analyses.
7.0	May 16, 2018	To align with Global Amendment #4, to increase sample size, clarify primary and secondary patient populations, align sample size calculations with analysis populations, clarify analyses for multiple endpoints.
	November 28, 2018	Section 3.4.1: PFS censoring rule, letter ©, says now “progress or die”. Section 5.2, at end, and section 5.4.3, at end, clarify significance level to use for final OS analysis in ITT population. Section 5.8.5 added for imputation of missing or incomplete dates for AEs and Concomitant Medications

Revision History		
Revision	**Date**	**Description of Change**
8.0	April 22, 2019	The SAP update Version 8.0 reflects a major improvement to the SAP in clarity, detailedness, organization and coherence. The SAP update is completed after the planned interim was cancelled per communication with FDA but prior to database lock or any unblinding of data. The aim of the update is to provide sufficient details to ensure accurate and correct execution of statistical programming of tables, figures and listings in implementing this plan, improve clarity and coherence of the document to both internal and external stakeholders, as well as correcting some apparent errors and inconsistencies. Some new analyses were also added to ensure comprehensive and robust data analyses and interpretation. To this end, text was significantly added, revised, consolidated or reorganized in appropriate sections. However, the specifics of study critical details such as those concerning definitions of primary and key secondary endpoints, primary and key secondary analyses methods and analysis populations, multiplicity control, significance levels for testing PFS and OS endpoints are not changed. Notable changes are delineated in the Revision History section (Version 8.0). Below is a detailed list of all notable changes: General: Formatting and correction of grammatical errors in the overall document were updated and corrected throughout. Page 1: Changed Protocol Title to be consistent with the Protocol Section 3 Study Objectives and Endpoints Removed paragraphs that are either repetitive or with inaccurate citations of study procedures from the protocol in the Overview of Study and Clinical Trial Endpoints sections. Clarified description of Independent Review Charter for tumor scan images. Updated reference to FDA guidelines on cancer trial endpoints to the latest versions: Clinical Trials Endpoints for the Approval of Cancer Drugs and Biologics (December 2018) and Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics (April 2015) 3.4 Clinical Trial Endpoints For the primary endpoint of PFS, “without prior missing assessments” was removed as it is clarified in the censoring rule ©(c). Added a table to clarifying censoring rule for PFS. All references to sensitivity analyses

		of PFS are referred to be described in the "Section 5.11.3 Sensitivity Analysis of PFS." Section 3.4.2 Definition of OS "not known to have died at last follow-up" was changed to "without documentation of death" as the former is contained by the latter. The sentence of "Patients are censored at the date of initiation of therapy (Day 1) if no additional data are obtained." was removed, as this criterion may not apply due to some randomized patients not receiving any dose of drug, and this scenario is accounted for by the rule for censoring. Section 3.4.3 was added to fully define Time to Progression (TTP) and censoring rules. Section 3.4.4, definitions regarding ORR, clinical benefit rate, TTR for only responders (CR or PR), were added, refined or clarified and censoring rules were added for DOR. Section 3.4.5, the definition of TEAE was clarified, and definitions were consolidated in this section, and reference to analyses were moved to later sections in the SAP. CCI [redacted] Section 3.4.7 Title of Physical Function Evaluation was changed to Patient Reported Outcome, and the sentence of analyses was removed as it is described in the analyses section. Section 4, Analyses Population Removed "Efficacy Analyzable Population" from this section as it is specific to the analyses on ORR, which is explained in the respective section. The definition of the BM-ve population was clarified to be defined by randomization. CCI [redacted]. The diagram showing various analyses population was removed, instead, a table was added in this section to provide "An overview of Analyses and Analysis Populations" that identified and clarified which analysis will be conducted in which analysis population. Section 5.1 Determination of Sample Size Clarified the 315 PFS events as defined for the primary analysis in the primary analysis population of patients without brain metastases (BM-ve population). Section 5.2 Interim analysis Removed reference to interim futility analysis, and consolidated paragraphs associated with the multiplicity control section. There was

		an apparent error with the citation of Lan-DeMets spending function. The previous version cited the formula at 1-sided alpha at 0.025 level but the formula was apparently mis-typed and corrected: the formula of Lan-DeMets alpha spending function at 2-sided alpha level (0.05) is standard; this typographical error was corrected. Section 5.3 Data and Safety Monitoring Committee (DSMC) was removed as this text isnot in scope for this analysis plan. Section 5.3 title changed from "Statistical Methods" to "Overview of General Approaches", with some clarification and consolidation in the section. Statistical Analyses sections (5.4 – 5.14):These sections underwent major consolidation with additional details, which were reorganized into subsections by topics, as below, some of which were newly added: 5.4 Patient Accrual and Eligibility, 5.5 Demographics, 5.6 Baseline Disease Characteristics, 5.7 Patient Disposition, 5.8 Protocol Deviation, 5.9 Prior Anticancer Therapy, Prior and Concomitant Medications. 5.10 Exposure to Study Therapies This section is newly added along with additional details, the most prominent one is the algorithm to calculate Relative dose intensity. 5.11.1 Multiplicity Control Clarification and consolidation of text only. A diagram of the testing procedure is added to illustrate the scenario. 5.11.2 Primary Analysis for Progression-Free Survival (PFS, primary endpoint) Clarification of text, along with specifying the method for 95% confidence interval of median PFS, and the addition of milestone PFS rates. 5.11.3 Sensitivity Analysis of PFS The original SAP proposed some suggested sensitivity analyses based on FDA guideline (Sensitivity Analyses #2, #3 and #4), but the censoring rules were not sufficiently detailed. Therefore, this section underwent significant editing to provide clarity for both operational purpose and review purpose. A table to compare various sensitivity analyses was added in the table, and new sensitivity analyses were added (Sensitivity Analyses #1 and Analyses #5) 5.11.4 OS analysis The method part of the section is removed as it is identical to the primary PFS analysis, and replaced by text pointing this out. (This same change is also applied to Section 5.11.5 Time to Progression). Added milestone rates were added at 12, 18 and 24 months.

		5.11.6 Objective Response Rate and Clinical Benefit Rate The method used to compare ORR originally " was "A Chi-square test will be used to compare the difference in the treatment groups in regards to ORR; if the assumptions for the Chi-square test are not valid, a 'Fisher's Exact test will be"used." Since this is a stratified randomized trial, the Cochran-Mantel-Haenszel is more appropriate to be used. The Clinical Benefit Rate to this section as well as analyses similar to ORR. 5.11.7 Time to Response (TTR) and Duration of Response (DOR) TTR will be summarized by descriptive statistics instead of KM analyses. The KM analysis on this endpoint is not considered necessary. The summary of DOR greater than or equal to a timeline including 3 months, 6 months, 9 months and 12 months was added. 5.11.8 Patient Reported Outcome Clarified the analysis population of this endpoint. 5.11.9 Other Analyses and Listings Added a number of graphical analyses and listings that were not specified in other sections. 5.11.10 Subgroup Analyses This section has been added to provide the pre-specified subgroup analyses that will be done on the three efficacy endpoints to evaluate the robustness of the efficacy. CCI [redacted] [redacted] 5.12 Safety Analyses This section underwent significant change to provide organization and clarity, including lists of all AE summary tables and listing, and AE summaries by subgroup analysis. 5.12.2 Adverse Events of Special Interest (AEOSI) This is a new section added to address the summary of AEs of Special Interest, including definitions of AEOSI and summary table of them. 5.12.3 – 5.12.7 Other safety summary analyses were organized by topic into 5.12.3 Death, 5.12.4 Vital Sign, 5.12.5 Electrocardiograms and 5.12.6 Clinical Laboratory Evaluations, 5.12.7 Physical Exam and Pregnancy Test. The previous version had limited details and references to some of these analyses.

		CCI [redacted] [redacted] CCI [redacted] [redacted] CCI [redacted] [redacted] CCI [redacted] [redacted] [redacted] [redacted] 6.0 References Added a reference that includes methods for testing milestone OS rates: Klein JP, Logan B, Harhoff M, Andersen PK. (2007). Analyzing survival curves at a fixed point in time. Stat Med. 2007 Oct 30; 26(24):4505-19. Appendix 1: Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 was removed as it was copied from the RECIST 1.1 criteria and considered not necessary to be included in the SAP.
9.0	August 26, 2019	Section 5.11.1 Multiplicity Control: the wording of the bottom right box of the diagram was chang“d to “OS (final) in ITT, 2-sided Lan-DeMets alpha adjusted at”final” per FDA feedback
10.0	April 06, 2020	Section 5.11.1 Multiplicity Control: revised due to changes in the timing of analyses as a result from DSMC recommendation and discussions with FDA on April 2nd, 2020. Section 5.11.9 Added additional language and analyses to address impact on trial data due to the outbreak of the COVID-19 pandemic. A few minor corrections of typos and misspellings on page 24, page 29 and Page 35; corrected the mis-directed references to appendix on Page 16 and Page 19.
11.0	Apirl 08, 2020	Per FDA comment dated April 7, 2020, “In the SAP, you should specify the number of PFS events that will now be used for the final (and only) analysis and clarify the alpha level that will be used for this analysis”, section 5.11.1 is revised.
12.0	April 10, 2020	Per FDA request dated April 9, 2020, “You should clarify and justify the alpha that will be transferred to the final (and only) OS analysis. Further, you should clearly specify how the rest of the testing hierarchy (PFS in ITT and OS in ITT) will be handled with respect to timing and alpha-levels.”, section 5.11.1 is updated.

Approvals

Printed Name	Signature
PPD PPD Biostatistics	[See appended signature page]
PPD PPD Clinical Development	[See appended signature page]

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1. LIST OF ABBREVIATIONS

Abbreviation	Full Term
AE	adverse event
AEOSI	adverse event of special interest
ADC	antibody-drug conjugate
ADCC	antibody-dependent cell-mediated cytotoxicity
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
βHCG	beta human chorionic gonadotropin
BM-ve	brain metastases negative (no brain metastases at baseline/randomization)
BUN	blood urea nitrogen
CBC	complete blood count
CDC	Complementary-dependent cytotoxicity
CDR	complementarity-determining region
C_{max}	Maximum concentration
CNS	central nervous system
CR	complete response
CRF	case report form
CTCAE	common terminology criteria for adverse events
FDA	Food and Drug Administration
GCP	good clinical practice
GI	gastrointestinal
HIV	human immunodeficiency virus
ICH	International Committee on Harmonization
IgG	immunoglobulin G
IND	Investigational New Drug
IRB	institutional review board
IRC	Independent Review Committee
IULN	institutional upper limit of normal
LA	Locally advanced
LDH	lactate dehydrogenase
mAb	monoclonal antibody
MTD	maximum tolerated dose
NSAE	non-serious adverse event
NCI	National Cancer Institute
NSAID	non-steroidal anti-inflammatory drug
OR	Objective Response, OR = CR + PR
ORR	Objective (overall) Response Rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PK	pharmacokinetics
PR	partial response

$T_{1/2}$	Elimination phase half-life
TPC	Treatment of physician's choice
RBC	red blood cell
SAE	serious adverse event
Trop-2	Trophoblastic cell-surface antigen
TNBC	Triple-Negative Breast Cancer
TTP	time to progression
WBC	white blood cell
PFS	progression free survival
OS	Overall Survival
ORR	Overall Response Rate
TPC	treatment of physician choice
QOL	Quality Of Life

2. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the proposed statistical analysis of the study entitled: "An International, Multi-Center, Open-Label, Randomized Phase III Trial of Sacituzumab Govitecan vs. Treatment of Physician Choice in Patients with Locally Advanced or Metastatic Triple-Negative Breast Cancer Who Received at Least Two Prior Treatments."

The purpose of this document is to ensure the credibility of the study outcomes by pre-specifying the statistical approaches and data handling conventions for key analyses. One focus of these analyses is the evaluation of the primary endpoint , Progression-Free Survival (PFS) as determined by an independent centralized blinded assessment (Independent Review Committee IRC). This PFS analysis will be performed on the patients in the intent-to-treat (ITT) population who do not have brain lesions at baseline, and will serve as gatekeeper for additional analyses. The primary analysis population will be labelled throughout as the brain-metastases negative (BM-ve) population. The overall 0.05 level of significance for the additional analyses will be maintained by specifying a hierarchy of endpoints to establish an order in which endpoints will be tested. If the PFS analysis in the BM-ve population rejects the null hypothesis (the survival distribution of PFS in the sacituzumab govitecan arm and the treatment-of-physician-choice arm are not statistically different) then further analyses in the testing hierarchy can be performed. Otherwise these analyses will not be done. The order of the testing hierarchy after the PFS analysis in the BM-ve population is:

- Overall survival (OS) in the BM-ve population;
- PFS in the ITT population;
- OS in the ITT population.

If fewer than 30 cases of brain metastasis are enrolled, then analyses based on the ITT population will be removed from the testing hierarchy.

Other comparisons to analyze are: PFS as determined by the investigator, Time to Progression (TTP), Objective Response Rate (ORR) determined by investigator and by central review, Duration of Response, Time to Onset of Response, Quality of Life, safety including adverse events, safety laboratories and evaluations, incidence of dose delays and dose reductions, and discontinuation of treatment due to adverse event between two treatment groups. The analyses of all endpoints will be described, the populations for analysis defined, and the rules specified for "data handling" relevant to undertaking all the analyses.

CCI [redacted]

To comply with regulatory electronic submission guidelines, listings of all clinical data will be submitted as electronic data sets. Specific listings will be generated as described.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Overview of Study

This is a Phase III, randomized, open-label, multicenter (up to 150 centers) study of IMMU-132 (sacituzumab govitecan) in locally advanced or metastatic TNBC patients who are refractory or relapsing after at least 2 prior standard chemotherapy regimens for unresectable, locally advanced or metastatic breast cancer, and these regimens will qualify regardless of triple-negative status at the time they were given. There is no upper limit in the number of prior therapies. Earlier adjuvant or neoadjuvant treatment for more limited disease will qualify as one of the required prior regimens if the development of unresectable, locally advanced or metastatic disease occurred within a 12-month period of time after completion of chemotherapy. All patients must have been previously treated with taxane regardless of disease stage (adjuvant, neoadjuvant or advanced) when it was given. Patients who have contra-indications or are intolerant to taxanes are eligible provided that they received at least one cycle of a taxane and showed contra-indications or intolerance during or at the end of that cycle. For patients with a documented germ-line BRCA1/BRCA2 mutation who received an approved PARP inhibitor, the PARP inhibitor can be used to meet the criteria for one of two prior standard of care chemotherapies.

Approximately Four-hundred eighty-eight (488) patients from up to approximately 150 centers, including sites in North America, Europe and potentially elsewhere will be randomized 1:1 to receive either sacituzumab govitecan (IMMU-132) at a dose level of 10 mg/kg on days 1 and 8 of a 21-day cycle or Treatment of Physician Choice (TPC).

For patients in TPC arm, one of the following treatments will be determined before randomization, administered for metastatic breast cancer as per NCCN guidelines below or local standard of care if too toxic:

1. Eribulin (1.4 mg/m^2 intravenously on Days 1 and 8 of a 21-day cycle North America sites, 1.23 mg/m^2 intravenously on Days 1 and 8 of a 21-day cycle for European sites),
2. Capecitabine (1000-1250 mg/m^2 orally twice daily for 2 weeks followed by a 1 week rest period given as a 21-day cycle),
3. Gemcitabine (800-1250 mg/m^2 intravenously on Days 1, 8 and 15 of a 28-day cycle), or
4. Vinorelbine (25 mg/m^2 intravenously on Day 1 weekly) treatment.

Stratification and Randomization Scheme

At registration, patients will be randomized to receive either sacituzumab govitecan at a dose level of 10 mg/kg on days 1 and 8 of a 21-day cycle or TPC.

Patients will be stratified at randomization by means of an interactive web-based response system (IWRS) according to the following classifications:

- Number of prior treatments (2-3 vs >3)
- Presence of known brain metastases at study entry (yes vs no)
- North America vs Rest of World

3.2. Study Objectives: Primary

The primary objective of this study is to compare the efficacy of sacituzumab govitecan to the Treatment of Physician's Choice (TPC) as measured by independently reviewed progression-free survival (PFS) in patients with locally advanced or metastatic TNBC previously treated with at least two systemic chemotherapy regimens for unresectable, locally advanced or metastatic disease, and without brain metastasis at baseline.

3.3. Study Objectives: Secondary

The secondary objectives of the study are to compare between the two treatment groups for:

- PFS for the ITT population
- Overall survival (OS) in both the ITT population and in the subgroup with brain metastasis.
- Independently-determined Objective Response Rate (ORR), duration of response and time to onset of response according to RECIST 1.1 criteria
- Quality of life
- Safety, including adverse events, safety laboratories and evaluations, incidence of dose delays and dose reductions, and treatment discontinuations due to adverse events

CCI [redacted]

3.4. Clinical Trial Endpoints

3.4.1. Progression-free Survival (PFS)

PFS will be measured by an independent centralized and blinded group of radiology experts (IRC) who will be assessing tumor response using RECIST 1.1 criteria. The procedures for how tumor scan images are received, handled, stored and how the independent radiology review is performed are described in an Independent Review Charter and can be available upon request. FDA definitions and guidance as described in Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (December 2018) and Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics (April 2015) are referenced in relevant endpoint definitions.

PFS will be defined as the time from randomization until objective tumor progression or death, whichever comes first. The date of progression will be the earliest time when any tumor progression is observed based on RECIST 1.1. It will be the date of the last observation or radiological assessment of target lesions that shows a predefined increase (20%+) in the sum of the target lesion measurements or the appearance of new non-target lesions.

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 in the follow-up period for progression 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.
d. Patients in the follow-up period for progression who receive alternative anticancer treatment before documented progressive disease 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 such a patient dies no later than the time of the second scheduled assessment as defined in the protocol, this patient will be considered to have an event at the date of death.

Calculation and censoring rules of the primary endpoint of PFS are also summarized in Table 1.

Table 1: Censoring rules for the endpoint of Progression-Free Survival

	Outcome	Date of Event/Censoring[1]
No adequate response assessment after randomization		
Died prior to second scheduled assessment	PD	Date of death
Did not die or died after missing 2 or more scheduled assessments	Censor	Date of randomization
Continued scheduled response assessments until objective PD or death		
PD at scheduled assessment, or prior to missing 2 scheduled successive assessments	PD	Date of objective PD
Death between scheduled assessments, or prior to missing 2 scheduled successive assessments	PD	Date of death
PD or death after missing 2 or more scheduled assessments	Censor	Date of last adequate response assessment before missed ones
Continued scheduled response assessments without objective 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 objective 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.*

The primary analysis of PFS will be based on the assessment of the central reviewer in the brain-metastases negative (BM-ve) population; additional sensitivity analyses will be described in Section 5.11.3 Sensitivity Analysis of PFS.

3.4.2. Overall Survival (OS)

Overall survival is measured from the date of randomization to death from any cause. Patients without documentation of death are censored on the date they were last known to be alive.

3.4.3. Time to Progression (TTP)

TTP is defined as the time from randomization until objective tumor progression; TTP does not include deaths. The censoring rules of PFS apply to TTP, except that death events are censored, either at the time of death or at the date of last adequate response assessment. Censoring rules for TTP are described in Table 2.

Table 2: Censoring rules for the endpoint of Time to Progression

Case	Outcome	Date of Event/Censoring[1]
No adequate response assessment after randomization		
Died prior to second scheduled assessment	Censor	Date of death
Did not die or died after missing 2 or more scheduled assessments	Censor	Date of randomization
Continued scheduled response assessments until objective PD or death		
PD at scheduled assessment, or prior to missing 2 scheduled successive assessments	PD	Date of objective PD
Death between scheduled assessments, or prior to missing 2 scheduled successive assessments	Censor	Date of death
PD or death after missing 2 or more scheduled assessments	Censor	Date of last adequate response assessment before missed ones
Continued scheduled response assessments without objective 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 objective 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.*

3.4.4. Objective Response Rate (ORR), Clinical Benefit Rate (CBR), Time to Response, Duration of Response

Objective tumor response will be evaluated from CT scans (or MRI studies) using RECIST 1.1 criteria. Using these criteria, the Best Overall Response (BOR) of patients will be classified based on tumor response into the categories of complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), or not evaluable (NE). Tumor response will be assessed by both IRC assessment and investigator assessments. Although the study requires measurable disease at baseline based on investigator assessment, the IRC assessments may determine otherwise for some patients (that is, non-measurable disease at baseline), and therefore, an additional category of "Non-CR/Non-PD" is also added for IRC assessed results. The endpoint of ORR will be defined as the percentage of the overall best response as CR or PR, relative to the size of population under evaluation.

In addition to ORR, clinical benefit rate (CBR) is defined as those patients with best response as CR or PR or else SD (and Non-CR/Non-PD in the case of non-measurable disease at baseline for IRC assessed results) with a duration of at least 6 months. For SD subjects, the duration of SD is defined as the time from randomization to the first documentation of PD/death or to the last adequate response assessment according to the censoring rule of PFS (Table 1). Details of response assessment according to RECIST 1.1 are reflected in the Appendix 6 of the protocol.

Time to onset of objective response (CR or PR) based on the central reviewer will be calculated for objective responders as the time from randomization to the first documentation of response, for both IRC and investigator assessed results.

For patients experiencing response (a best overall response of CR or PR), duration of objective response will be calculated based on the number of days between the first date showing a documented response of CR or PR and the date of progression or death. Patients who do not progress or die after response will be censored, and the censoring rules as described in Table 3 will apply. DOR will be calculated based on both the central IRC and local investigator assessed results.

Table 3: Censoring rules for the endpoint of Duration of Response

Case	Outcome	Date of Event/Censoring[1]
Subsequent PD or death after response		
PD at scheduled assessment, or prior to missing 2 scheduled successive assessments	DOR ended	Date of objective PD
Death between scheduled assessments, or prior to missing 2 scheduled successive assessments	DOR ended	Date of death
PD or death after missing 2 or more scheduled assessments	Censor	Date of last adequate response assessment before missed ones
Response without subsequent objective 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 objective 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.*

3.4.5. Safety Endpoints

Safety and tolerability will be evaluated based on adverse events, standard safety laboratories (CBC with differential and platelet count, serum chemistries, and urinalysis), physical examination, EKG, and vital signs.

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. Adverse events will be coded using the MedDRA system based on preferred terms and system organ class (SOC). Adverse events and selected laboratory parameters will be classified for severity using NCI CTCAE (v4.03 or later) toxicity grades. Non-numeric components of laboratory grading algorithm (such as a criterion requiring hospitalization) will not be included in the grade calculations. Only TEAEs will be summarized and will be referred to as AEs hereafter.

CCI [redacted]

3.4.7. Patient-reported outcomes

Patient-reported outcomes evaluation will be based on the EORTC-QLQC30 instrument to evaluate all patients at baseline, the beginning of every cycle, and the final study visit.

4. POPULATIONS FOR ANALYSIS

The following analyses populations are defined and used for relevant safety, efficacy, CCI [redacted]

4.1. Screened Population

The screened population is defined as all patients who have signed an informed consent and participated in screening procedures at the investigative site to assess eligibility.

4.2. Intent-to-Treat (ITT) Population

The ITT population is all patients who have been randomized to the trial. Patients are assigned to treatment arms based on what they were randomized to receive. This population is used for efficacy analyses after the primary endpoint has been tested in the primary analysis population of subjects without brain metastases.

4.3. ITT Population Without Brain Metastases (BM-ve Population)

The BM-ve population is all ITT patients without brain metastases labelled throughout as the BM-ve population, defined as all randomized patients who were randomized to the strata of no baseline brain metastasis at the time of randomization.

4.4. Safety Population

All patients administered at least one dose of IMMU-132 or TPC will be included in the Safety Population. Safety endpoints will be analyzed using the safety population.

CCI [redacted]

Table 4: An overview of Analyses and Analysis Populations

Analysis Category	Screened Population	Intent-to-Treat (ITT) Population	BM-ve Population	Safety Population	CCI
Enrollment and Eligibility	X				
Demographics		X	X	X	
Baseline Disease Characteristics		X	X		
Patient Disposition		X	X		
Protocol Deviation		X			
Prior Anticancer Therapy, Prior and Concomitant Medications		X	X		
Exposure to Study Therapies				X	
Efficacy on primary endpoint (IRC assessed PFS)		X	X		
Sensitivity analyses of primary endpoint		X	X	X	
Efficacy on secondary endpoints (investigator-assessed PFS, OS, TTP, ORR, CBR, TTR, DOR)		X	X		
Patient Reported Outcome				X	
Efficacy Subgroup Analyses		X	X		
Safety Analyses (AE, AEOSI, Death, Vital Sign, Clinical Lab, CCI Physical Exam and Pregnancy Test)				X	
CCI					
ECG				X	
CCI					

5. STATISTICAL METHODS AND ANALYSES

5.1. Determination of Sample Size

A hazard ratio (HR) of 0.667, likely corresponding to a 50% improvement in PFS, would be considered to be clinically meaningful in this relapsed/refractory locally advanced or metastatic TNBC patient population. Four hundred and eighty-eight patients (488) patients are anticipated to be enrolled. The population of patients with brain metastases will be capped at 15 % (N=74) of the trial population. The primary PFS analysis will be performed when 425 investigator defined PFS events have occurred in all patients randomized as long as 315 or more PFS events have also occurred, according to Independent Review Committee (IRC) review, in the primary analysis population of patients without brain metastases (BM-ve population). Assuming at most 15% of patients have brain metastases and there are 13% or fewer IRC events compared to investigator review, it would be expected that there would be at least 315 IRC events in the BM-ve population at the time 425 investigator PFS events have been observed amongst all patients randomized. If the true HR is 0.667 in the IRC review of the BM-ve population, the study will have at least 95% power to detect a statistically significant improvement in PFS, with a two-sided type 1 error rate of 5%, if data are analyzed after 315 IRC PFS. PFS estimates in this patient population vary from 1.7 to 4.2 months (3 months average). For an estimate of median PFS of 3 months in the control TPC group, and assuming a 24 month enrollment period, it is expected the primary PFS analysis will be performed after a minimum follow-up of approximately 4 months. Overall survival will be analyzed at the time of the PFS analysis and also after 330 deaths have occurred in the primary analysis population of randomized patients without brain metastases. The study will have approximately 89.5% power to detect an improvement in overall survival in the BM-ve population, with a two-sided 5% type 1 error rate, assuming that 72% of the planned number of deaths in BM-ve population have occurred at the time of the interim analysis (i.e., 238 deaths), and the true HR for OS is 0.7. Assuming a 10 month median in the control arm, a HR of 0.7 would likely correspond to a 4.3 month improvement. The final analysis of OS is predicted to occur after a minimum follow-up of 17 months, 13 months after the primary analysis of PFS.

5.2. Interim analysis

The originally planned interim analysis for futility based on progression free survival included in the Protocol (Amendment 1-4) is canceled and communicated to the FDA and thus excluded from this analysis plan.

There will be an interim analysis of overall survival at the time of the final PFS analysis. A Lan-DeMets spending function that approximates O'Brien-Fleming stopping boundaries will be applied to the interim OS analysis, where the 2-sided significance level applied is determined by $\alpha(t) = 2-2\Phi(-z_{\alpha/2}/\sqrt{t})$. In the equation, t is the number of OS events occurring at the interim divided by the number expected at the final analysis (i.e., 330) of the BM-ve population. If the final number of events differs from expected, the final significance level will be adjusted so that the overall alpha is controlled given the significance level applied at the first analysis.

5.3. Overview of General Approaches

Continuous data will be summarized using descriptive statistics: n, mean, median, standard deviation, minimum and maximum. Categorical data will be summarized using counts and percentages. For summary statistics, the tables will be presented by treatment arm, and additionally by an overall column unless otherwise specified. In general, a data listing will be provided for reference on endpoints to which summary or analyses are conducted.

All statistical analyses will be performed using a two-sided hypothesis test at the overall

5% level of significance. *P*-values will be rounded to three decimal places. The multiple comparisons procedure described in Section 5.11.1 will be used to control Type I error rate.

Each category of analyses will be conducted in respective analysis populations according to Table 4 unless otherwise specified.

Endpoints and analyses pertaining to the study's primary and secondary objectives will be conducted as prescribed in respective sections of this SAP. CCI [redacted]

5.4. Patient Accrual and Eligibility

Number and percentage of subjects enrolled and randomized will be summarized and listed for the Screened Population by country and by site.

Screen failures will be summarized for the Screened Population by the Inclusion/Exclusion criteria that were not met.

A listing will be provided for each subject including informed consent date, randomization date, first dosing date, country and site for the Screened Population.

5.5. Demographics

Demographic characteristics will be summarized using descriptive statistics, including but not limited to: age, age group, sex, race, ethnicity, height, weight, body mass index (BMI) and baseline creatinine clearance.

A listing of demographic information will be provided for the ITT population.

5.6. Baseline Disease Characteristics

Summaries of baseline disease characteristics will include but not limited to the following variables: stratification factors employed in the randomization(number of prior treatments for metastatic or locally advanced disease, presence of known baseline brain metastases, and region), documented histology review of ER, PR and HER2 status as required by eligibility criteria, original diagnosis and time from diagnosis, UGT1A1 status, BRCA1 and BRCA 2 mutational status, baseline ECOG score. Prior treatment history including whether the patients have received prior breast-cancer related surgery and type of surgery, location and type of prior

radiotherapy will also be summarized. Presence of metastasis from baseline tumor scans will be categorized by location. Patients' hepatic function will be categorized by baseline serum bilirubin: (1) Normal (<= ULN) (2) >1-1.5 ULN (>1 and <=1.5 x ULN) and (3) >1.5 ULN (> 1.5 x ULN).

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.

Baseline disease characteristics and medical history listings will be provided for the ITT population.

5.7. Patient Disposition

The numbers and percentages of patients who are included in each analysis population will be summarized by treatment arm. The number and percentages of patients who discontinue from the study and the reason for discontinuation will also be presented. The summary will also include the number of treatment cycles patients received. The length of follow-up in each treatment arm will be summarized descriptively and the survival status during follow-up will be presented.

A listing will be generated reflecting treatment group, date of randomization, date of first dose, date of last dose, date and reasons of treatment and study discontinuation, survival follow-up status and information for each patient will be provided for the ITT Population.

A listing of randomization scheme will be provided along with stratification factors after study unblinding at final analysis.

5.8. Protocol Deviation

Protocol deviations including violations of Inclusion and Exclusion Criteria will be summarized by importance and categories of deviation and listed for the ITT Population.

5.9. Prior Anticancer Therapy, Prior and Concomitant Medications

Prior anticancer systemic therapies (as entered on the Prior Systemic Therapy CRF), prior and concomitant medications (as entered on the Prior and Concomitant Medication CRF) 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 therapy. Concomitant medications include medications that were taken at any time while on study treatment, including medication that were started before first administration of study therapy but ongoing at the time of first study therapy, or that were initiated on or after first administration but prior to 30 days after last administration of study therapy. If an end date is missing or the medication is ongoing during study treatment, the medication will be included as concomitant medication.

Prior anticancer systemic therapies will be summarized according to WHO Drug Anatomical Therapeutic Chemical (ATC) Classification, and listed additionally with treatment setting, best response and reason for ending the treatment, start and end date, and date of progressive disease from the treatment.

Prior medications and concomitant medications will be summarized according to WHO Drug Anatomical Therapeutic Chemical (ATC) Classification.

Prior anticancer therapy, prior and concomitant medications listings will be provided for the ITT Population.

5.10. Exposure to Study Therapies

Treatment exposure to study therapies will be summarized for treatment duration, number of doses received, and number of treatment cycles received. Number and percentage of subjects who had a dose reduction and reasons for dose reduction, number and percentage of subjects with 0, 1, 2, 3 and >3 dose reductions, time to the first dose reduction, number and percentage of subjects who had dose interruptions, or infusion terminated prematurely will be summarized for subjects who received IMMU-132, and for subjects on the TPC arm to the extent that such drug exposure information were collected on CRF by each respective treatment of physician choice.

Duration of treatment (in months) will be summarized and number of subjects with treatment duration longer than or equal to 6 months, 12 months, 24 months and 36 months will be summarized.

For subjects who received IMMU-132, 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 <50%, 50% to < 70%, 70% to <90%, 90% to <110%, >=110%.

Delivered dose (in 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 (in 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 (in mg/kg) received for each subject is defined as the sum of all delivered doses (in mg/kg) of all infusions the subject received in the study. Total assigned dosage (in mg/kg) for each subject is defined as the product of the assigned dose of IMMU-132 (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.

CCI [redacted]

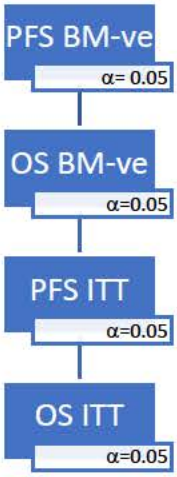
Treatment exposure will be summarized by the Safety Population and CCI [redacted] and listed for the Safety Population.

5.11. Efficacy Analysis

5.11.1. Multiplicity Control

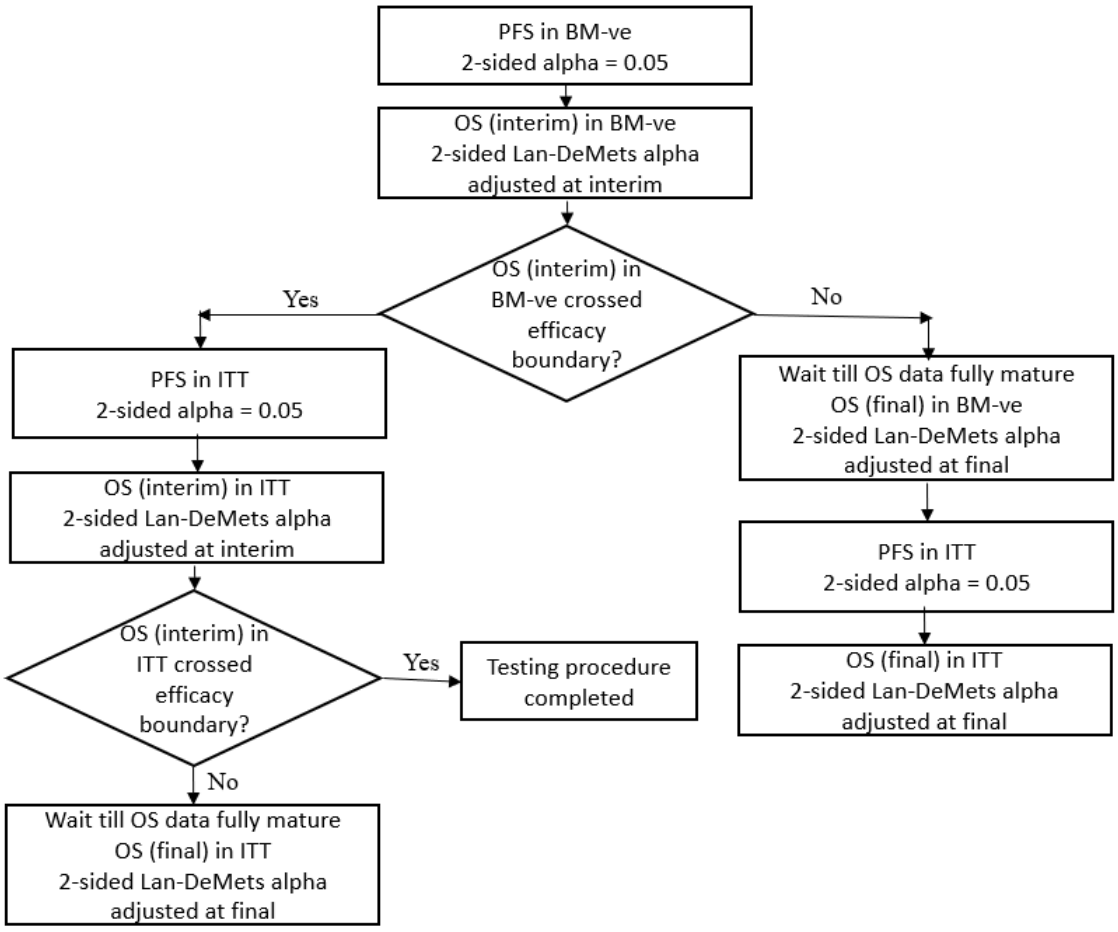
The overall Type I error rate is strictly controlled at a two-sided alpha of 0.05, by a hierarchical testing strategy. The primary endpoint of IRC assessed PFS will be analyzed and tested first in the ITT Population Without Brain Metastases (BM-ve Population), and if the primary analysis test is significant, subsequent key secondary endpoints (OS in BM-ve Population, IRC-assessed

PFS in the ITT Population, OS in the ITT Population) will be tested in a sequential manner as depicted in the diagram below, where a given hypothesis can only be declared statistically significant if all hypotheses above it in the hierarchy are also statistically significant. If fewer than 30 patients with brain metastases are recruited, analyses in the ITT population will be removed from the hierarchy.



Overall survival will be analyzed both at the time of the primary PFS analysis (referred to as Interim OS analysis hereafter) and, if not statistically significant at this time, then later when a total of 330 deaths have occurred in the primary analysis population of randomized patients without brain metastases. A Lan-DeMets spending function that approximates O'Brien/Fleming stopping boundaries will be applied to the interim OS analysis, where the 2-sided significance level applied is determined by $\alpha(t) = 2\text{-}2\,\Phi(-z_{\alpha/2}/\sqrt{t})$. In the equation, t is the number of OS events occurring at the interim divided by the number expected at the final analysis (i.e., 330) of the BM-ve population. If the final number of events differs from expected, the final significance level will be adjusted so that the overall alpha is controlled given the significance level applied at the first analysis.

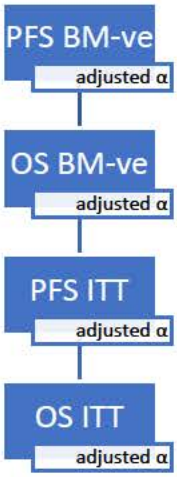
The PFS ITT analysis will only be declared as statistically significant if both the PFS BM-ve and OS BM-ve analyses have also been declared as statistically significant. However, given the PFS ITT analysis will not be updated at the final OS analysis, a 2-sided significance level of 0.05 will be applied to this endpoint if and when both PFS and OS are statistically significant in the BM-ve population. In addition, OS in the ITT population will only be tested once PFS in the ITT population has been declared statistically significant. If this occurs at the time of the interim analysis, OS in the ITT population will be tested at the same adjusted alpha level computed for the analysis of OS in the BM-ve population. The significance level for the final analysis of OS in the ITT population will be determined by the Lan-DeMets spending function to ensure alpha is controlled at a 2-sided alpha of 0.05 at the final OS analysis, if OS analyses in the ITT population is also conducted at the time of PFS analysis. The testing procedures and corresponding alpha levels for type I error rate control are depicted in the following diagram.



The primary outcome in this study is PFS; the secondary outcome is OS. The actual rates of occurrence of PFS events and deaths have been lower than the rates assumed in the study protocol. This reduction implies that the study will last much longer than anticipated if it continues until it reaches the targeted 315 PFS events in the primary BM-ve population. Therefore, on a recommendation from the DSMC and in consultation with the FDA, the Sponsor has elected to initiate the process of conducting the final primary analyses before the study reaches the protocol-specified 315 PFS events in the BM-ve population. In view that the recommendation was made prior to the 315 PFS events is reached, an adjustment will be imposed on the primary PFS analysis, according to the actual number of PFS events included in the database for this analysis, based on the Lan-DeMets alpha spending function that approximates O'Brien-Fleming stopping boundaries. If 302 of the 315 (or 96%) targeted PFS events are available, the 2-sided significant level to be applied will be 0.0443. Moreover, the number of deaths in the primary BM-ve population is close to reaching full maturity (316 of the 330, or 96% of the deaths the protocol specified in the primary BM-ve population for the final OS analysis), thus this analysis will also serve as the final analysis for the secondary endpoint of OS.

The original protocol and SAP specified two analyses of OS. The first was to occur at the time of the final PFS analysis when 72% of the planned number of deaths was expected. The second OS analysis was to occur when all 330 deaths had occurred in the BM-ve population. Instead, only a

single, and therefore final, analysis of the study will occur. This analysis will serve as the final analysis for PFS, as described above, as well as the final analysis for OS for both the BM-ve and ITT populations. The 2-sided significance level for OS will be 0.0443(as illustrated above), as well as for the subsequent testing steps, inherited from the primary PFS test. This strategy preserves that hierarchical testing strategy described in the SAP previously. Below is the updated diagram with the adjusted alpha level.



5.11.2. Primary Analysis for Progression-Free Survival (PFS, primary endpoint)

The primary analysis of PFS in the BM-ve Population for comparison between sacituzumab govitecan 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 and its associated 95% CIs are determined by the Brookmeyer and Crowley method with log-log transformation. Milestone PFS rates at time points including 6 months, 9 months, and 12 months will be derived from KM estimates.

5.11.3. Sensitivity Analysis of PFS

Sensitivity analyses of PFS in the BM-ve Population and ITT Population will be generated following the FDA Guidance of Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics(December 2018) and Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics (April 2015). The differences between the primary analysis PFS definition and comparisons of their censoring rules are illustrated in Table 5.

Sensitivity Analysis 1

In the first sensitivity analyses of PFS (based on the central review), objectively documented progression or death will not be censored, regardless of the timing of the events.

Sensitivity Analysis 2

A second sensitivity analysis (Sensitivity Analysis 2, corresponding to Table D1 in Appendix D of Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics, April 2015) of PFS will be performed by assigning the dates for censoring and events only at scheduled assessment dates.

Per the FDA guidance, this second type of sensitivity analysis may be biased if the progression occurred closer to the last assessment.

Sensitivity Analysis 3

A third sensitivity analysis (Sensitivity Analysis 3, corresponding to Table D2 in Appendix D of Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics, April 2015) of PFS will be performed using a conservative approach by assigning the dates of discontinuation, change of treatment, or the 2nd missed scheduled assessment as an event date.

Sensitivity Analysis 4

A fourth sensitivity analysis (Sensitivity Analysis4, corresponding to Table D3 in Appendix D of Clinical Trial Endpoints for the Approval of Non Small Cell Lung Cancer Drugs and Biologics, April 2015) of PFS based on the investigator's assessment. Clinical progression without documented radiographical progression will be considered as an event.

Sensitivity Analysis 5

The fifth sensitivity analyses will be done using the same primary definition of PFS but will be conducted in the corresponding Safety Population subjects who received study therapies, instead of the ITT and BM-ve Population.

Table 5: Sensitivity Analyses of PFS and Corresponding Censoring Rules

Case	Primary Analysis PFS definition	Sensitivity Analysis 1	Sensitivity Analysis 2	Sensitivity Analysis 3	Sensitivity Analysis 4 (Based on investigator assessed PFS)	Sensitivity Analysis 5
No adequate response assessment after randomization						Use the same censoring rule of Primary Analysis PFS definition but in Safety Population. For sensitivity analysis of PFS analysis in the ITT population, use Safety Population instead; for sensitivity analysis of PFS in the BM-ve Population, use Safety Population without Baseline Brain Metastasis instead.
Died prior to second scheduled assessment	Date of Death	Date of Death	Date of Death	Date of Death	Date of Death	
Did not die or died after missing 2 or more scheduled assessments	Censored at Randomization	Progressed at date of Death if died; or censored at date of randomization if did not die	Censored at Randomization	Censored at randomization if did not die, progressed on the date of 2nd missed scheduled assessment	Censored at Randomization	
Continued scheduled response assessments until objective PD or death						
PD at scheduled assessment, or prior to missing 2 scheduled successive assessments	Date of PD	Date of PD	Date of PD if at scheduled assessment; Date of next scheduled assessment if PD between scheduled assessments or prior to missing 2 scheduled successive assessments. (including PD that occurred at End of Treatment/Early Withdrawal visits)	Date of PD	Date of PD if at scheduled assessment; Date of next scheduled assessment if PD between scheduled assessments or prior to missing 2 scheduled successive assessments.	
Clinical PD indicated between scheduled assessments or prior to missing 2 scheduled	N/A	N/A	N/A	N/A	Date of next scheduled assessment	

successive assessments					
Death between scheduled assessments, or prior to missing 2 scheduled successive assessments	Date of Death	Date of death	Date of death	Date of Death	Date of death
PD or death after missing 2 or more scheduled assessments	Censored at Date of last adequate response assessment before missed assessments	Date of PD or Death	Censored at Date of last adequate response assessment before missed assessments	Progressed at 2nd missed scheduled assessment	Censored at Date of last adequate response assessment before missed assessments
Treatment discontinuation for undocumented progression, toxicity or other reason	Included in other scenario	Included in other scenario	Included in other scenario	Progressed at the time of discontinuation	Included in other scenario
Continued scheduled response assessments without objective PD or death					
Initiated other anti-cancer treatment	Censored at Date of last adequate response assessment with documented non-progression prior to starting other anti-cancer treatment	Date of documented progression or death if occurred	Censored at Date of last adequate response assessment with documented non-progression prior to starting other anti-cancer treatment	Progressed on the date of start of anti-cancer treatment	Censored at Date of last adequate response assessment with documented non-progression prior to starting other anti-cancer treatment
No objective PD or death	Censored at Date of last adequate response assessment	Censored at Date of last adequate response assessment	Censored at Date of last adequate response assessment	Censored at Date of last adequate response assessment	Censored at 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 endpoint of PFS will be indicated censored if explicitly stated as censored and calculated at the specified time description ; otherwise PFS will be indicated as an event at the specified time description.

5.11.4. Overall Survival

OS will be analyzed by the same method as the primary PFS analysis.

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

5.11.5. Time to Progression

The Time to Progression will be analyzed by the same method as the primary PFS analysis.

5.11.6. Objective Response Rate and Clinical Benefit Rate

The objective response rate (ORR) and Clinical Benefit Rate (CBR) will be summarized based on both IRC assessment and investigator assessments, along with number and percentage of subjects with a best overall response of complete response (CR), Partial response (PR), Stable Disease (SD), SD with a duration of 6 months or longer, Progressive Disease (PD), and Not Evaluable (NE). For subjects who were assessed as without measurable disease at baseline by IRC, the additional category of Non-CR/Non-PD will be added. 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.

A sensitivity analysis of ORR and CBR will be conducted in an "Efficacy Analyzable Population", defined as randomized and treated patients who received at least one cycle of IMMU-132 or TPC and at least two post-baseline radiological assessment data.

5.11.7. Time to Response (TTR) and Duration of Response (DOR)

Only patients achieving CR or PR will be included in the calculation for Time to Response and Duration of Response (DOR) analyses. TTR will be summarized by descriptive statistics, and by the number of percentage of responders whose TTR is within 3 months, 6 months and 12 months. DOR in each treatment arm will be estimated using the Kaplan-Meier method, and analyzed by the same method as the primary PFS analysis. The number and percentage of responders with a DOR greater than or equal to a timeline including 3 months, 6 months, 9 months and 12 months will be estimated.

5.11.8. Patient Reported Outcome

Descriptive statistics and summaries of the EORTC-QLQC30 physical functioning subscale will be presented by treatment group. As EORTC QLQ C30 are completed by patients on Day 1 of each cycle, and at final study visit. If patients did not receive dosing, they will lack this measurement on Day 1 of each treatment cycle, therefore, this analysis will be conducted in the Safety Population only.

5.11.9. Other Analyses and Listings

For the primary endpoint of PFS in the ITT Population and BM-ve Population, a summary table will be provided for the number and frequency of events vs. subjects whose PFS is censored. For events, PFS will be further summarized by the type of events of whether it is Progression or

death, and for censored subjects, according to the reason of censoring according to the censoring rule Table 1.

A summary of baseline tumor assessment will be provided for target lesions and non-target lesions and target lesion/non-target lesion combined according to anatomical location for the ITT population and BM-ve Population.

For the ITT Population, the following listings will be provided for IRC assessed and investigator assessed tumor response, respectively: 1) a listing of all tumor assessments including tumor assessment results (target, non-target and new lesions) 2) a listing of tumor response at each assessment time point and best overall response for the subject, 3) a listing for all responders (CR and PR) with their best overall response, time to response and duration of response; 4) a listing of the magnitude of tumor burden reduction in target lesions.

A plot of target-lesion tumor burden (spider plot) will be provided and a plot of maximum tumor burden reduction (waterfall plot) will be provided for the ITT population and BM-ve Population, for IRC-assessed and investigator assessed results.

Concordance between IRC assessed and investigator assessed tumor response will be summarized by a contingency table of responders (CR+PR), non-responders (SD + PD for investigator-assessed, SD + PD + non-CR/non-PD for IRC-assessed) and NE, for ITT Population and BM-ve Population.

For the ITT Population, a listing will be provided for subsequent anti-cancer therapies including drug name, start and stop date (and study day relative to date of randomization), progression date if radiographically progressed, end-of-treatment date and reason (including clinical or radiographical progression if progressive disease is listed as reason), and death date if known.

For the ITT Population, a listing of PFS and OS will be provided including PFS time and OS time, radiographical progression date if the subject had a radiographical progression, death date if known, censoring information for PFS and OS, and reasons for censoring of PFS and OS, respectively.

The outbreak of the COVID-19 pandemic in early 2020 has affected the clinical operations of the trial and consequently the collection of clinical data. Some protocol-specified data points may not be collected on schedule or even at all for subjects who still remain on treatment or for those who have stopped treatment but are still being followed. Some sensitivity analyses will be performed excluding data collected that are impacted by COVID-19 to explore the extent to which COVID-19 may have affected inference from the study.

5.11.10. Subgroup Analyses

Subgroup analyses including but not limited to the following demographic, disease characteristics and prognostic factors will be applied to the ITT Population and BM-ve Population, for the primary endpoint of PFS, secondary endpoints of OS and ORR. A Forest plot of treatment effect on these endpoints in the subgroups will be generated.

- Age group (<65 vs >=65)
- Race (White, Black, Asian, Other);

- Prior therapies: (2, 3, 2-3, and >3);
- Brain metastases (Yes, No; ITT only);
- Region (North America, Rest of World);
- Original diagnosis TNBC (Yes, No);
- UGT1A1 status
- BRCA 1 status (Positive, Negative)
- BRCA 2 status (Positive, Negative)
- Trop-2 Status
- Presence of liver metastasis at baseline (Yes, No)

CCI [redacted]

5.12. Safety Analyses

Safety analyses will be conducted in the Safety Population.

5.12.1. 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). 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 by treatment group and overall using MedDRA Preferred Term and System Organ Class (SOC). An AE that occurs more than once within each patient 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 only be counted 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 NCI-CTCAE **Grade 3 or Higher** Treatment-Emergent Adverse Events by SOC and PT
- Summary of **Treatment-related** Treatment-Emergent Adverse Events by SOC and PT
- Summary of NCI-CTCAE **Grade 3 or Higher Treatment-related** Treatment-Emergent 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 Treatment-Emergent **Serious** Adverse Events by SOC and PT
- Summary of **Treatment-related** Treatment-Emergent **Serious** Adverse Events by SOC and PT
- Summary of Treatment-Emergent Adverse Events by SOC and PT in Patients by **UGT1A1** Result
- [redacted]
- Summary of Treatment-Emergent **Serious** Adverse Events by SOC and PT in Patients by **UGT1A1** Results

- Summary of Treatment-Emergent Adverse Events **Leading to Dose Reduction** 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 Drug Discontinuation** by SOC and PT
- Summary of Treatment-Emergent Adverse Events Reported **by >=10% Patients** in Any Treatment Arm by Preferred Term
- Summary of NCI-CTCAE **Grade 3 or Higher** Treatment-Emergent Adverse Events Reported by **>=5%** Patients in Any Treatment Arm by Preferred Term
- Summary of Treatment-Emergent **Serious** Adverse Events Reported **by >=2%** Patients in Any Treatment Arm by Preferred Term
- Summary of Treatment-Emergent **Serious** Adverse Events **Leading to Death** by SOC and PT

The following AE listings will be provided:

- Listing of All Adverse Events.
- Listing of Serious Treatment-Emergent Adverse Events
- Listing of Treatment-Emergent Adverse Events Leading to Death
- Listing of Treatment-Emergent Adverse Events Leading to Dose Reduction
- Listing of Treatment-Emergent Adverse Events Leading to Study Drug Interruption
- Listing of Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation

All TEAEs by SOC/PT and the overall TEAE summary table for the following subgroups will be provided:

- Age group (<65 vs >=65)
- Race (White, Black, Asian, Other)
- Ethnicity
- Brain metastases (Yes, No)
- [redacted]
- Patients' hepatic function by baseline serum bilirubin: (1) Normal (<= ULN) (2) >1-1.5 ULN (>1 and <=1.5 x ULN) and (3) >1.5 ULN (> 1.5 x ULN).

In addition, treatment-related TEAEs and Serious TEAEs will be provided by subgroups according to CCI [redacted] and hepatic functioning.

5.12.2. Adverse Events of Special Interest (AEOSI)

In addition to analyses of AEs, adverse events of special interest (AEOSI) will be assessed. Definitions of AEOSI, as currently defined, are provided in Table 6, including but not limited to listed. For AEOSI, frequency tables will be generated, showing overall summary of AEOSI, Summary of AEOSI by SOC and PT, Serious AEOSI by SOC and PT, AEOSI leading to discontinuation by SOC and PT, AEOSI leading to treatment interruption by SOC and PT, Grade 3 or higher AEOSI by SOC and PT, treatment-related AEOSI (by a worst CTCAE grade of 3, 4, or 5, >=3 and any grade) by SOC 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: diarrhea
Nausea	Preferred term: nausea
Vomiting	Preferred term: vomiting
Neutropenia+	Preferred terms: neutropenia, neutrophil count decreased, febrile neutropenia
Febrile neutropenia+	Preferred term: febrile neutropenia
Infections	SOC: infections and infestations
Anemia+	Preferred terms: anemia; hemoglobin decreased
Thrombocytopenia+	Preferred terms: thrombocytopenia; platelet count decreased
Fatigue	Preferred term: fatigue and asthenia
Neuropathy+	Preferred term: gait disturbance, hypoesthesia, muscular weakness, neuropathy peripheral, paresthesia, and peripheral sensory neuropathy

Abbreviation: SMQ=Standard MedDRA Query
All definitions based on MedDRA vs 20.0
+ Grouped AE terms

5.12.3. 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. A listing of all death information will be generated.

5.12.4. Vital Sign

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.

5.12.5. Electrocardiograms

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

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

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

The proportion of patients who have a maximum post-baseline increase from baseline in QTcF/QTcB 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 and by overall.

5.12.6. Clinical Laboratory Evaluations

Routine safety laboratories, based on hematology and routine serum chemistry data (including but not limited to glucose, creatinine, BUN, total bilirubin, AST, ALT, LDH, alkaline phosphatase, serum albumin, total protein, Na, K, calcium, Cl, CO_2, magnesium and phosphate), will be summarized using values at each visit and change from baseline using descriptive statistics for each treatment group and overall. 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 severity grade. A shift table of the worst NCI-CTCAE grade observed on-treatment will be tabulated for each lab parameter and presented in a frequency table by baseline grade. For parameters for which a CTCAE scale does not exist, the proportion of patients with abnormal values will be summarized by dose group.

5.12.7. Physical Exam and Pregnancy Test

Physical exam results are listed according to body system and presented for any abnormal findings from the physical examination.

Pregnancy test results will be listed.

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

5.15. Data Handling Rules

Data and programming specification and rules, including but not limited to the following, are described below.

5.15.1. Conversions from Days to Years, Months or Weeks

Years = # of days / 365.25 (use of SAS function) Months = # of days / 30.4375 (i.e. 365.25/12) Weeks = # of days / 7

Values based on the above computations will be rounded to tenths.

Age will be calculated using the following formula in SAS, where birthdate is the SAS date corresponding to birth date and icdate is the date of informed consent:

Age=intck('YEAR', birthdate, icdate (_),'C');

5.15.2. Computation of Duration

Duration for time variables based on two dates, e.g., Start Date and End Date, will be calculated as (End Date – Start Date + 1) (in days) unless otherwise specified.

5.15.3. 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.

5.15.4. Non-Numeric Laboratory Results and Calculation of Normal Ranges

Laboratory values including symbols ("<" or ">", for example) will not be used in summary analyses. These values will be reflected in listings of the data. When there are potential conflicts between local lab normal ranges and ranges used in CTC grading, CTC normal ranges will be used.

5.15.5. Imputation of Missing or Incomplete Dates

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

1. 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.
2. Missing day and month
   - The year is the same as the year of the first dose date: use December 31.
3. Missing year

   Uncertain: unable to impute.
4. 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.

5. Missing month and year

   Uncertain: unable to impute

6. Missing day and year

   Uncertain: unable to impute

7. 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 after the start date of the AE or medication, then make end date equals to start date.

5.16. Statistical Software used in data analysis

All statistical analyses will be performed using SAS® (SAS Institute, 2010) Version 9.2 or later

6. REFERENCES

Cox, D.R. (1972). Regression models and life tables (with discussion). Journal of the Royal Statistical Society, B34:187-220.

E.A. Eisenhauer, et,al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). EJC 45(2009) 228 – 247.

Hosmer, D.W., and Lemeshow, S. (2000). Applied logistic regression, second edition.Hoboken: John Wiley & Sons, Inc.

Kaplan, E.L., and Meier P. (1958). Nonparametric estimation from incomplete observations. J Am Stat Assoc, 53:457-481.

Klein JP, Logan B, Harhoff M, Andersen PK. (2007). Analyzing survival curves at a fixed point in time. Stat Med. 2007 Oct 30; 26(24):4505-19.

Mantel, N. (1966). Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemotherapy Reports, 50:163-170.

Mantel, N., and Haenszel, W. (1959). Statistical aspects of the analysis of data from retrospective studies of disease. J National Cancer Inst., 22:719-748.

Pocock, S., and Simon, R. (1975). Sequential treatment assignments with balancing for prognostic factors in the controlled clinical trial. Biometrics 31: 103-115.

SAS Institute Inc. (2010). SAS/STAT® 9.2 User's guide. Cary, NC: SAS Institute Inc.

US Dept. Health and Human Services, FDA (Jan.2017) Multiple Endpoints in Clinical Trials, Guidance for the Industry

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