STATISTICAL ANALYSIS PLAN

A Phase I/II Study of IMMU-132 (hRS7-SN38 Antibody Drug Conjugate) in Patients with Epithelial Cancer

Protocol Number:	IMMU-132-01
Protocol Version and Date:	24 April 2017 (includes Amendments #1 through #11)
Name of Test Drug:	Sacituzumab Govitecan (IMMU-132)
Phase:	Phase I/II
Sponsor:	Immunomedics, Inc. 300 The American Road Morris Plains, 004EJ 07950 PPD
Analysis Plan Date:	February 27, 2019
Analysis Plan Version:	Version 3.0

APPROVAL SIGNATURE PAGE

Protocol Title:	A Phase I/II Study of IMMU-132 (hRS7-SN38 Antibody Drug Conjugate) in Patients with Epithelial Cancer
Protocol Number:	IMMU-132-01
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Date: 27 Feb 2019

Sponsor Approval:

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report.

Sponsor Signatory:

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Date: 27 FEB 2019

REVISION HISTORY

Version Number	Version Date	Summary and Rational of Revision(s)
First draft (V0.1)	13Jul2017	
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Fourth draft (V0.4)	07Sep2017	
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V1.0	24Oct2017	
V2.0	14Mar2018	• Final SAP was amended after clinical database lock updated to version 2.0. SAP section 1. • Sample size for the Target mTNBC Population has been revised and updated to 108. SAP section 3.4. • Sample size for patients who received at least 2 lines of prior standard chemotherapy for metastatic disease (ie, excluding hormonal or other investigational treatment) updated to 94. SAP section 3.4. • Per-Protocol Population definition has been reworded. SAP section 4.3. • Data listing for the efficacy population has been updated to 108. SAP section 4.1. • Patients Disposition category screened/entered into the study has been excluded. SAP section 5.1. • A separate listing of patients registered but did not receive study drug has been excluded. SAP section 5.1. • New text has been added to Percentage of patients with dose reduction. SAP section 5.5. • Planned dose intensity definition has been updated. SAP section 5.5. • Response assessment dates derivation has been corrected. SAP section 6. • Objective response rate definition has been reworded. SAP section 6.2. • Clinical benefit rate definition has been updated and corrected. SAP section 6.3. • Guidelines and specification for Progression Assessment and Censoring for Analysis of PFS has been updated. SAP section 6.4. • Duration of Response definition has been updated. SAP section 6.6. • Sensitivity analyses text has been modified. SAP section 6.9. • Treatment-related Grade 3 or higher AEs by SOC and PT was removed and on treatment deaths definition has been updated. SAP section 7.1. • Lab baseline definition has been updated. SAP section 7.3.

		• New text has been added for the eDISH figures, defining the Horizontal and Vertical lines for 3xULN and 2XULN. SAP section 7.3. • Informed Consent major protocol violation category has been removed. SAP section 8. • New text has been added to clarify derivation of Radiation during treatment violation category under prohibited medications category of major protocol violation. SAP section 8. • Best Overall Response with Confirmation of CR and PR Required table has been updated for the patients missing subsequent response. Appendix 12.
V3.0	01Feb2019	• Added analyses populations other than the Target mTNBC Population based on cancer histology and associated efficacy and safety analyses. • Added additional subgroup analyses for selected efficacy and safety endpoints. • Added safety analyses and definitions of AE of special interest. • Added some additional safety analyses for the Overall Safety Population. • Dose intensity and relative dose intensity definitions are clarified and updated. • The study drug name sacituzumab govitecan is added to the SAP. Where IMMU-132 is referred to, in keeping consistent with the Protocol, is identical to sacituzumab govitecan that may be used in other documents. • Added operational dates and characteristics such as data planned data cut-off date, last patient enrolment date and total number of subjects enrolled for final CSR analyses. • Changed the programming spec for swimmer plot. • CCI [redacted] • Moved data handling rules of missing dates from the SAP into separate documentation.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ADC	Antibody-drug conjugate
AE	Adverse event
ALT	Alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
CCI	[redacted]
BMI	Body mass index
BOR	Best overall response
CAP	College of American Pathologists
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology for Adverse Events
DILI	Drug-induced liver injury
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eDISH	Evaluation of drug-induced serious hepatotoxicity
FDA	Food and Drug Administration
HAHA	Human anti-human antibody
HR	Heart rate
ICR	Independent central review
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
mTNBC	Metastatic Triple-Negative Breast Cancer
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival

Abbreviation	Definition
PK	Pharmacokinetic
popPK	Population Pharmacokinetics
PP	Per-protocol
PR	Partial response
PT	Preferred term
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SCLC	Small cell lung cancer
SD	Stable disease
SOC	System organ class
TBL	Total bilirubin level
TEAE	Treatment-emergent adverse event
TNBC	Triple Negative Breast Cancer
TTR	Time to response
UC	Urothelial Cancer
UGT1A1	Uridine diphosphate glucuronosyltransferase 1A1
ULN	Upper limit of normal
US	United States
WHO	World Health Organization

1. INTRODUCTION

This document is the Statistical Analysis Plan (SAP) for Protocol IMMU-132-01 "A Phase I/II Study of IMMU-132 (hRS7-SN38 Antibody Drug Conjugate) in Patients with Epithelial Cancer," which was issued on 24 April 2017 (includes Amendments #1 through #11).

This SAP provides a comprehensive and detailed description of the strategy, rationale, and statistical techniques used to evaluate the specified efficacy and safety endpoints.

Safety and efficacy data will be presented separately for the metastatic Triple-Negative Breast Cancer (mTNBC) Target Population, metastatic non-triple-negative Breast Cancer (mBC) population and metastatic Urothelial Cancer (mUC) including urinary bladder as specifically defined in Section 4, Analyses Population. In addition, safety data will also be presented on all patients, irrespective of tumor type or IMMU-132 dose received; this population will for the remainder of the SAP be referred to as the Overall Safety Population. Whereas patients populations with cancer type Small-cell lung cancer (SCLC), Non-small-cell lung cancer (NSCLC), Colorectal (CRC), Esophageal cancer (EGC), Endometrial cancer (EMC), and Pancreatic ductal adenocarcinoma (PDC) will be analyzed separately only for the selected efficacy endpoints.

CCI [redacted]

Subsequently, the SAP is amended (Version 3.0) to include efficacy and safety analyses for patient populations (as defined by underlying malignancy) other than the Target mTNBC Population, and additional safety analyses for the Overall Safety Population, to be based on data from final database lock (DBL) with planned data cut-off date of 1 March 2019, in support of the clinical study report (CSR). Separate pharmacokinetic (PK) analysis, popPK and immunogenicity plans will detail the PK, popPK and immunogenicity analyses.

2. STUDY OBJECTIVES

This is a first-in-man clinical study with the antibody-drug conjugate (ADC), IMMU-132, which uses the humanized antibody hRS7 to deliver the topoisomerase I inhibitor, SN-38, directly to Trop-2-expressing epithelial tumors. The study has been conducted in 2 Phases. Dose escalation in Phase I was designed to determine a maximum acceptable dose and to select cancer types for further study in the Phase II expansion cohorts. Phase II continued enrollment with dose levels and cancers selected based upon Phase I results and preliminary efficacy results.

2.1. Primary Objective

The primary objective in Phase I is to identify the maximum acceptable dose and evaluate the safety and tolerability of IMMU-132 as a single agent administered in 3-week treatment cycles, in previously treated patients with advanced epithelial cancers. The primary objective in Phase II is the evaluation of the safety and efficacy of IMMU-132 administered in 3-week treatment cycles, at a dose selected in Phase I.

2.2. Secondary Objectives

In Phase I, the secondary objectives are to obtain initial data concerning PK, immunogenicity, and efficacy with this dosing regimen. In Phase II, secondary objectives also include PK and immunogenicity.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

IMMU-132-01 is a Phase I/II, open-label, basket design study of IMMU-132 in adult patients with epithelial cancers expressing Trop-2. The allowed cancer types include ovarian, endometrial, cervical, breast (Triple-Negative Breast Cancer [TNBC] and non-TNBC), prostate (hormone refractory), lung (non-small cell and small-cell lung [NSCLC and SCLC], head and neck (squamous cell), esophageal, gastric, hepatocellular, renal (clear cell), thyroid, glioblastoma multiforme, colorectal, pancreatic, and urothelial cancers (UC). Eligible patients were required to have metastatic (Stage IV) disease at the time of study entry (except for glioblastoma multiforme) and be refractory to or have relapsed after at least 1 prior standard therapeutic regimen for their disease. All patients received IMMU-132 administered IV as a single agent in 3-week treatment cycles (Days 1 and 8 of 21-day cycles). Patients were to continue treatment until disease progression requiring discontinuation of treatment or unacceptable toxicity. A protocol-defined dose reduction scheme was in place to manage patients with selected AEs.

The primary objective of Phase I is to evaluate the safety and tolerability of IMMU-132 in patients with advanced epithelial cancers, using a dose escalation design to determine the maximum acceptable dose. The secondary objective of Phase I is to evaluate the PK, immunogenicity, and preliminary efficacy of IMMU-132. The primary objective of Phase II is the evaluation of the safety and efficacy of IMMU-132 at a dose selected in Phase I, while the secondary objectives of Phase II also include evaluation of PK and immunogenicity.

Screening/baseline procedures include patient history, physical examination with vital signs and performance status evaluation, local histology/pathology review to confirm 1 of the epithelial cancers listed above, safety laboratory assessments, and electrocardiogram (ECG). Tumor imaging was performed using contrast enhanced computed tomography (CT) or magnetic resonance imaging (MRI). Baseline imaging was obtained within 4 weeks of study entry. Blood/samples were collected to test for human anti-human antibody (HAHA), and uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) genotype CCI [redacted]

During the study, imaging was performed at baseline (ie, within 4 weeks of study entry) and thereafter in 8 weekly intervals from the start of treatment onwards, with confirmatory CT/MRI scans obtained 4 to 6 weeks after an initial partial response (PR) or complete response (CR), until permanent treatment discontinuation. Response assessment was performed according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Response assessment was performed locally, but independent central review (ICR) of the tumor scans was additionally obtained for mTNBC patients who had at least 2 prior therapies for metastatic disease, were being treated at the 10 mg/kg dose level, and whose local scans demonstrated at least 20% decrease. ICR of tumor scans was performed by Intrinsic Imaging (Bolton, Massachusetts; San Antonio, Texas, US). The details of the independent review were provided in an imaging charter for the study.

After treatment discontinuation, patients were to be followed until resolution or stabilization of any treatment-related AEs. All patients were followed for survival every month, which may be by telephone with patient or caregiver.

CCI [redacted]

The safety of patients is assessed based on occurrence of AEs, clinical laboratory assessments, vital signs, and ECGs.

3.2. Phase I Dose-Escalation

Phase I dose-escalation used a standard 3+3 dose escalation design. Three to 6 patients per cohort were to be enrolled in up to 4 planned dose levels, for a planned total number of 24 patients. Based on preclinical studies, 8 mg/kg was selected as the starting dose.

3.3. Phase II

In Phase II, after initially enrolled patients were evaluated in each cancer indication selected by the Sponsor in up to 2 dose levels to provide additional safety and efficacy data, indications showing a promising tumor response were considered adequate evidence of activity for further clinical development, which included TNBC, NSCLC, SCLC and UC. After initial review of patients treated at both IMMU-132 doses of 8 and 10 mg/kg, 10 mg/kg was selected for further clinical development. This dose has been received by the majority of patients in this study, including the majority of patients with mTNBC.

CCI [redacted]

The enrollment of patients of the target mTNBC population was stopped on 14 February 2017 since the enrollment goals were met after a total of 148 mTNBC patients had been entered, but the enrollment of patients in other cancer indications continued. Subsequently, in June 2017, the Sponsor notified the sites of the decision to stop further enrollment of patients into the study, and the last patient enrolled occurred on 22 June 2017.

CCI [redacted]

4. ANALYSIS POPULATIONS

Given that this study was conducted as a Phase I/Phase II and included a diverse population comprised of patients with different tumor types, it is necessary to define specific patient populations. The following sections outline the populations to be included for the evaluation of efficacy and safety. The patient populations to be used are:

- Target mTNBC Population: Patients with relapsed/refractory mTNBC who have received at least 2 prior therapies for metastatic disease and who received IMMU-132 at a dose of 10 mg/kg.
- Per-Protocol (PP) Population (specific to the Target mTNBC Population): This will include patients of the Target mTNBC Population who received at least 1 complete cycle of IMMU-132 and had data available from at least 1 response assessment.
- Overall Safety Population: This will include all patients who received at least 1 dose of IMMU-132, irrespective of dose, tumor type, or number of prior therapies.

At the time of final SAP (version 3.0), the following patient populations are added for safety and efficacy analyses:

- Metastatic, non-triple-negative breast cancer (mBC) Population: This will include all patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) metastatic breast cancer (mBC) who progressed on at least 1 prior hormonal therapy in the metastatic setting and who received at least 1 dose of IMMU-132 at a dose of 10 mg/kg.
- Metastatic Urothelial cancer including urinary bladder (mUC) Population: This will include all mUC patients who had relapsed after or were refractory to at least 1 prior standard therapeutic regimen and who received at least 1 dose of IMMU-132 at a dose of 10 mg/kg.

And the following patient populations are added for limited efficacy analyses:

- Small-cell lung cancer (SCLC) Population: This will include all SCLC patients as enrolled in the study in accordance with the eligibility criteria and who received at least 1 dose of IMMU-132.
- Non-small-cell lung cancer (NSCLC) Population: This will include all NSCLC patients as enrolled in the study in accordance with the eligibility criteria and who received at least 1 dose of IMMU-132.
- Colorectal (CRC) Population: This will include all CRC patients as enrolled in the study in accordance with the eligibility criteria and who received at least 1 dose of IMMU-132.
- Esophageal cancer (EGC) Population: This will include all EGC patients as enrolled in the study in accordance with the eligibility criteria and who received at least 1 dose of IMMU-132.
- Endometrial cancer (EMC) Population: This will include all EMC patients as enrolled in the study in accordance with the eligibility criteria and who received at least 1 dose of IMMU-132.

- Pancreatic ductal adenocarcinoma (PDC) Population: This will include all PDC patients as enrolled in the study in accordance with the eligibility criteria and who received at least 1 dose of IMMU-132.

For the mTNBC target population of 108 patients, it was ensured that all patients had a minimum of 4 months follow-up. This allowed to include at least 2 post-baseline assessments (except for patients who died or discontinued study treatment prior to their second post-baseline scan).

CCI [redacted] At the time of final analyses, because of the additional enrollment up until 22 June 2017, the Overall Safety Population increased to approximately 495.

CCI [redacted] Subsequently, for the final data analyses to support CSR, the targeted data cut-off date is planned on 01 March 2019. If different, the actual data cut-off will be stated in the CSR. The cut-off date applies to both the Overall Safety Population and individual cancer populations.

4.1. Efficacy Populations

The analysis populations for efficacy analyses include cancer specific populations as defined in Section 4. Only patients who received at least one dose of IMMU-132 will be included in the analysis.

CCI [redacted] CCI [redacted]

For other cancer-specific analysis populations, efficacy analysis and listings will be conducted where applicable. No per-protocol populations or sensitivity analyses are planned for cancer types other than mTNBC.

Data listing will in general be performed on the Overall Safety Population and where applicable, also on the cancer specific analysis population.

4.2. Safety Populations

For the purposes of summarizing safety data, there will be 4 populations, as follows:

- Target mTNBC Population, as defined in Section 4.
- Metastatic, non-triple-negative breast cancer (mBC) Population, as defined in Section 4.
- Metastatic Urothelial cancer including urinary bladder (mUC) Population, as defined in Section 4.
- Overall Safety Population, as defined in Section 4 which includes all patients regardless of cancer type, regardless of number of prior cancer therapies, and regardless of IMMU-132 dose as long as the patient received at least 1 dose of IMMU-132.

4.3. Per-Protocol Population

The Per-Protocol Population is defined as the subset of Target mTNBC patients who received at least 1 cycle of IMMU-132 and had available data from at least 1 response assessment. The Per-Protocol Population is specific to the mTNBC patients and mainly used for sensitivity analyses of efficacy, and no other cancer specific populations has a similarly defined per-protocol population.

4.4. Analyses Population Overview

Analysis populations will be summarized in this study for relevant safety and efficacy endpoint. CCI [redacted] an overview of the analyses conducted is shown in Table 1. At the time of final analyses to support CSR, requisite analyses CCI [redacted] for the Target mTNBC Population will be repeated based on the updated data based on the final DBL data cut-off date (the sample size of the Target mTNBC Population still remained the same in the updated data). In addition, additional analyses will be conducted for analysis populations other than mTNBC, along with analyses for the Overall Safety Population, an overview of the analyses is shown in Table 2.

Table 1: Overview of Analyses and Populations CCI [redacted]

	Target mTNBC Population	Overall Safety Population (N=420 CCI [redacted])	Per-Protocol Population
Disposition	X	X	
Demographics	X	X	
Prior anticancer therapy	X	X	
Concomitant medication and medical history	X	X	
Efficacy (ORR, PFS, OS, DOR, TTR)	X		X (only ORR; PFS; OS)
Sensitivity efficacy (ORR, PFS, OS)	X		
Exposure	X	X	
AEs	X	X	
Deaths	X	X	
Laboratory	X	X	
Vital signs	X	X	
ECG	X	X	
Subgroups efficacy	X		
Subgroups exposure	X	X	
Subgroups safety	X	X	
Major protocol deviations	X	X	

Abbreviations: AE = Adverse event, DOR = Duration of response, ECG = Electrocardiogram, mTNBC = Metastatic Triple Negative Breast Cancer, ORR = Objective response rate, OS = Overall survival, PFS = Progression-free survival, TTR = Time to response.

Table 2: Overview of Analyses and Populations for Final Analyses

	mBC	mUC	SCLC, NSCLC, CRC, EGC, EMC, PDC	Overall Safety Population (N=approximately 495 at final DBL)
Disposition	X	X		X
Demographics	X	X		X
Prior anticancer therapy	X	X		X
Concomitant medication and medical history	X	X		X
Efficacy (ORR, CBR, PFS, OS, DOR, TTR)	X	X	X	
Exposure	X	X		X
AEs	X	X		X
Deaths	X	X		X
Laboratory	X	X		X
Vital signs	X	X		X
ECG	X	X		X
Subgroups analyses *	X	X		X
Major protocol deviations	X	X		X

* Overview of subgroup analyses is provided in Section 6.10, Subgroup Analyses and Section 7.1, Adverse Events.
Abbreviations: AE = Adverse event, DOR = Duration of response, ECG = Electrocardiogram, mTNBC = Metastatic Triple Negative Breast Cancer, ORR = Objective response rate, OS = Overall survival, PFS = Progression-free survival, TTR = Time to response.

5. STATISTICAL ANALYSES

Throughout this SAP, efficacy data will be summarized for the Target mTNBC Population, mBC, mUC, SCLC, NSCLC, CRC, EGC, EMC and PDC Population, with all patients in the respective population combined, while safety data will be summarized for the Target mTNBC Population, mBC Population, mUC Population and the Overall Safety Population. For the Overall Safety Population, data will be summarized by dose group (defined as assigned dose) and overall.

All data will be listed for the Overall Safety Population and where applicable, in the cancer-specific analysis population, as specified.

Screen failures and entered-but-not-dosed patients will be excluded from all analyses.

5.1. Patient Disposition

Disposition in terms of number of patients treated, permanently discontinued treatment, and reasons for treatment discontinuation will be summarized for the Target mTNBC Population, mBC Population, mUC Population and the Overall Safety Population.

A by-patient listing for disposition will be provided, including whether the patient is included in each of the analysis sets, treatment status, date of stopping treatment, date of stopping study participation, reason for treatment discontinuation, reason for study discontinuation, and survival follow-up status (ie, date of death, indicator of death during study, and cause of death).

Patient disposition will also be summarized for the subgroups for selected analyses populations as identified and defined in Section 6.10 and Section 7.1.

5.2. Demographics and Baseline Characteristics

Demographics and baseline disease characteristics for the Target mTNBC Population, mBC Population, mUC Population and the Overall Safety Population will be summarized using descriptive statistics. Continuous data will be summarized by mean, standard deviation, minimum, median, maximum and number of patients. Categorical variables will be summarized by frequency tabulations (count, percent) with a separate cell summarizing any missing data where applicable.

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

5.2.1. Demographics

Baseline demographic data summaries will include age, age group, sex, race, ethnicity, height, weight, body mass index (BMI), and number of subjects with renal impairment and hepatic impairment.

Patient demographic data will also be summarized for the subgroups as identified and defined in Section 6.10 and Section 7.1.

Age will be calculated as: Age = Integer ≤ [(Informed Consent Date – Date of Birth + 1) / 365.25].

Body mass index will be calculated as: BMI (kg/m^2) = weight in kg / (height in m^2).

5.2.2. Baseline Disease Characteristics

Baseline disease characteristics will be provided for the target mTNBC Population, mBC Population, mUC Population and Overall Safety Population and will include Eastern Cooperative Oncology Group (ECOG) performance status, CCI UGT1A1 status, tumor stage at initial diagnosis and at screening. In addition, the time since diagnosis of initial cancers will also be displayed.

5.3. Prior Anticancer Therapy

Prior systemic anticancer therapy will be summarized for the target mTNBC Population, mBC Population and mUC Population. For the Target mTNBC Population, the number of prior anticancer therapies for metastatic disease (2 prior lines vs >2 prior lines) and number of prior chemotherapies for metastatic disease (categories: 0, 1, 2, >2) will also be summarized categorically. In addition, time since last prior therapy (calculated from the end date of last prior therapy to the first dose of IMMU-132) and the duration of last line of prior therapy will be summarized. A frequency table will also be produced summarizing chemotherapy, hormonal therapy and investigational therapy products separately. For the target mTNBC Population, the number of prior anticancer therapies and of prior chemotherapies (excluding investigational and hormonal treatments) will also be summarized by the median, minimum and maximum number of therapies, and the number of patients. The number of patients receiving each individual therapy will also be summarized.

For mUC Population, the number of prior anticancer therapies, chemotherapies, cisplatin, platinum-based chemotherapies, immune check point inhibitors (CPI) including anti-PD1/PDL-1 therapies will be summarized descriptively and by categories of number of lines of each type of therapies. In addition, time since last prior therapy and the duration of last line of prior therapy will be summarized.

For mBC Population, the number of prior anticancer therapies, chemotherapies, CDK4/6 inhibitors, mTOR inhibitors, hormonal therapies, endocrine therapies, and immune CPIs will be summarized similarly descriptively and by number of lines of each type of therapies, along with summaries of time since last prior therapy and the duration of last line of prior therapy.

Additional analyses of prior anticancer therapies of particular interest, if warranted, may be generated.

5.4. Concomitant Medications and Medical History

5.4.1. Medical History

Medical history will be summarized for the Target mTNBC Population, mBC Population, mUC Population and the Overall Safety Population, and listed by patient. 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.

5.4.2. Concomitant Medications

Previous and concomitant medications will be summarized for the Target mTNBC Population, mBC Population, mUC Population and the Overall Safety Population and coded using the World Health Organization (WHO) Drug Dictionary (WHO Drug Dictionary B3 Enhanced March 2017). Medications in this section are distinct from the anticancer medications described

previously. These medications will be recorded on the "Pre-infusion medications" case report form (CRF) and the "Prior and concomitant medications" CRF rather than the "Prior Treatments" CRF. Concomitant medications are those medications that were ongoing at the time of first IMMU-132 dose or that were initiated after first dose but prior to last dose. If an end date is missing or the medication is ongoing during IMMU-132 treatment, the medication will be included as concomitant medication. Reporting of pre-treatment and concomitant medications will be by WHO Drug Anatomical Therapeutic Chemical (ATC) Classification.

Concomitant medical/surgical procedures are defined as therapies that were initiated on/after the date of the first dose of study drug and on/before the end of the study treatment period. The number (%) subjects who had concomitant medical/surgical procedures will be summarized separately in frequency tabulations.

Additional analyses or listing of concomitant medication of specific interest, if warranted in the course of safety review, may be generated.

5.5. Exposure to Study Drug and Compliance

Treatment exposure will be summarized for the Target mTNBC Population, mBC Population, mUC Population and the Overall Safety Population using the following measures:

- Number of doses administered
- Duration of treatment (months)
- Number of patients remaining on the same dose
- Number of IMMU-132 treatment cycles
- Percentage of patients with treatment delays
- Percentage of patients with dose reduction (separately for each category: Any, 1, 2 and 3 dose reductions)
- Time to first dose reduction
- Percentage of patients with permanent treatment discontinuations
- Percentage of patients with infusion interruptions but completed (based on CRF tick box information)
- Percentage of patients with infusions prematurely discontinued (based on CRF tick box information)
- Duration of patient follow-up (from start of treatment to death, last follow up, study discontinuation or data cut-off date)

Duration of treatment (in days) will be calculated as (date of the last dose – date of the first dose + 1) before being converted to months by dividing it by 30.4375. For patients who are still on treatment at the data cut-off date, the date of the last dose will be the latest dosing record end date.

Dose reductions will be calculated by taking the assigned dose level infused for each infusion (from the dose administered CRF). From this it will be possible to calculate when a dose reduction has occurred and the amount by which the dose was reduced. This will enable the dose

reduction, time to dose reduction, and number of patients with a 25% and 50% dose reduction, as outlined above to be derived.

Dose intensity is calculate by the following algorithm:

Delivered dose (in mg) for each infusion is provided per CRF form.

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 dosage (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 (in 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.

Patients with treatment delays longer than the 3 weeks permitted in the protocol will be summarized by number and percentage of patients. A treatment delay will have been considered to have occurred if there are >28 days between Dose 1 and Dose 2 of the same cycle, or >35 days between Dose 2 of Cycle n and Dose 1 of Cycle n+1.

In addition, exposure data will also be summarized for the subgroups as identified and defined in Section 6.10 and Section 7.1.

6. EFFICACY ANALYSIS

Efficacy results will be summarized for the target mTNBC Population, mBC Population and mUC Population. In addition, selected efficacy data will be summarized separately for each cancer type populations including SCLC, NSCLC, CRC, EGC, EMC and PDC. Formal statistical hypothesis testing will not be performed. Descriptive statistics, data summaries and graphical methods will be used to assess the efficacy of IMMU-132.

The primary endpoint will be the objective response rate (ORR) [PR+CR], with responders requiring a confirmatory response assessment no sooner than 4 weeks after the criteria for response are first met. Assessment of tumor response is based upon on-site readings by local radiologists, using RECIST 1.1 for all populations. Response rates will be additionally provided for the Target mTNBC Population and Per-Protocol Population (specific to mTNBC).

CCI [redacted] tumor scans were additionally assessed by independent central review (ICR) for mTNBC patients; however, this is not done for other cancer populations. For mTNBC population, an ICR was conducted for tumor scans from patients who achieved an objective response by local radiologists or at least 20% reduction of their locally determined target lesions. Local vs ICR assessments at each response time point and overall will be compared to determine concordance of local vs ICR best overall results. An imaging scans time point will be presented graphically for the Target mTNBC Population, whether tumor CT scans results were collected within allowed time windows at each of the imaging time points (based on 8 weekly imaging allowed by protocol and collection windows for study time points that were nominally within ±10%), based on available data.

Secondary efficacy endpoints will include time to response (TTR), duration of response (DOR), clinical benefit rate (CR+PR+SD [stable disease] ≥6 months), progression-free survival (PFS), and overall survival (OS). DOR, PFS, and OS data will be analyzed via Kaplan-Meier method and 95% CI from Brookmeyer and Crowley method with log-log transformation. TTR will be summarized by descriptive statistics, whilst clinical benefit rate will be presented as a response rate along with ORR.

6.1. Best Overall Response

Response will be determined using RECIST 1.1 criteria, and summarized by the best overall response (BOR) using the following hierarchical order: CR, PR, SD, PD, Not evaluable and Not assessed. CR or PR will require a confirmation scan.

6.2. Objective Response Rate

The ORR is defined as the rate of the overall best response as CR or PR. All patients in the applicable analysis population will be included in the denominator in the calculation of the percentage for each response category and ORR. ORR will be summarized by the percentage of responses with 2-sided exact binomial 95% CI.

6.3. Clinical Benefit Rate

Clinical benefit rate (CR+PR+[SD ≥6 months]) is defined as those patients with best response as CR or PR or else SD with a duration of at least 6 months. SD for 6 months duration is defined as the time from the first dose to the first documentation of PD or to the last adequate response assessment prior to data cut-off date, whichever is earlier. Clinical benefit rate will be summarized by the percentage of responses with 2-sided exact binomial 95% CI.

6.4. Progression-Free Survival

Progression-free survival is defined as the interval from the first dose start date to the date of disease progression defined as documented PD or death from any cause, whichever occurs first. Death was considered an end point only while the patient was on study and receiving treatment or undergoing response assessments. Patients otherwise without adequate response assessments or without radiologic evidence of progression were censored. Clinical PD was not considered as a PFS event. PFS = (Earliest Date of Disease Progression/ Death – First Dose Start Date + 1) / 30.4375.

The approach regarding handling of assessments, dates, and censoring presented in Table 3 is based upon RECIST1.1 guidelines (Eisenhauer et al., EJC, 2009). CCI

Table 3: Guidelines for Response Assessment and Censoring for Analysis of Progression-Free Survival

Guidelines for Progression Assessment and Censoring for Analysis of PFS		
Case	Outcome	Date of Event/Censoring[1]
No adequate response assessment after start of treatment		
Died prior to second scheduled assessment	PD	Date of death
Did not die prior to second scheduled assessment	Censor	Date of first dose
Continued study until objective PD or death		
At scheduled assessment	PD	Date of objective PD
Between scheduled assessments	PD	Date of objective 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		
Discontinued for undocumented PD, toxicity, other reasons	Censor	Date of last adequate response assessment
Lost to follow-up	Censor	Date of last adequate response assessment
Initiated other treatment	Censor	Date of last adequate response assessment prior to starting other treatment
No objective PD at final assessment	Censor	Date of last adequate response assessment

Abbreviations: CT = Computed tomography, MRI = Magnetic resonance imaging, PD = Progressive disease, PFS = Progression-free survival.

If the onset of response required evaluations at different times (ie, chest CT on 1 day, abdomen and pelvic MRI several days later) the last measurement date was to be used. For PD based on the sum of target lesion measurements at different times, the last measurement date was to be used. For PD based on new or non-target lesions, if these were equivocal at 1 assessment and later considered unequivocal PD, the earliest date when progression was suspected was to be used.

[1] *Adequate response assessment was defined as a response assessment other than 'not assessed' or 'not evaluable'. As progression was based on the sum of target lesion measurements at different time points, the last measurement date was to be used. For progression based on new or non-target lesions which ware equivocal at 1 assessment but later considered unequivocal PD, the earliest date when progression was suspected was to be used.*

6.5. Overall Survival

Overall survival is defined as the time from the date of the first dose start date to the date of death due to any cause. Patients without documentation of death at the time of the data cutoff for analysis will be censored at the date the patient was last known to be alive or the data cutoff date, whichever is earlier. The last known alive date is the last record in the study database. This date may be the maximum of the last visit date or last contact date, including telephone follow-up where the patient is known to be alive.

6.6. Duration of Response

Among responders (patients who have a best response of PR or CR), DOR will be calculated as the date of the first evaluation showing documented PR, or CR to the date of the first PD or Death . DOR = (Earliest Date of Progression or Death – Date of First PR/CR + 1) / 30.4375. For patients not progressing, censoring rules apply. DOR censoring rules are presented in Table 4.

Table 4: Guidelines for Response Assessment and Censoring for Analysis of Duration of Response

Guidelines for Progression Assessment and Censoring for Analysis of Duration of Response			
Condition	Case	Outcome	Date of Progression or Censoring
Objective PD or Death occurred	At or between scheduled assessments or prior to missing 2 scheduled successive assessments	PD / Death	Date of objective PD or Death
	Progression or Death after missing 2 or more scheduled successive assessments	Censor	Date of last adequate response assessment
No objective PD or Death occurred	Initiated other treatment	Censor	Date of last adequate response assessment prior to starting other treatment
	Lost to follow-up	Censor	Date of last adequate response assessment
	Data cutoff	Censor	Date of last adequate response assessment

Abbreviations: CT = Computed tomography, MRI = Magnetic resonance imaging, PD = Progressive disease.
If the onset of response requires evaluations at different times (ie, chest CT on 1 day, abdomen and pelvic MRI several days later) the last measurement date should be used. For progression based on the sum of target lesion measurements at different times (ie, chest CT on 1 day, abdomen and pelvic MRI several days later) the last measurement date should be used. For progression based on new or nontarget lesions, if these are equivocal at 1 assessment and later considered unequivocal progression, the earliest date when progression was suspected should be used. If progression occurred after 2 or more scheduled successive response assessments were missed or inadequate, the outcome will be censored at the last prior adequate assessment. Adequate response assessment is defined as a response assessment other than "not assessed" or "not evaluable" for the determination of duration of response. If objective evidence of progression has not occurred and the patient is either lost to follow-up, died, a new treatment is initiated, or data cut-off occurs, then the outcome will be censored at the last prior adequate assessment.

6.7. Time to Response

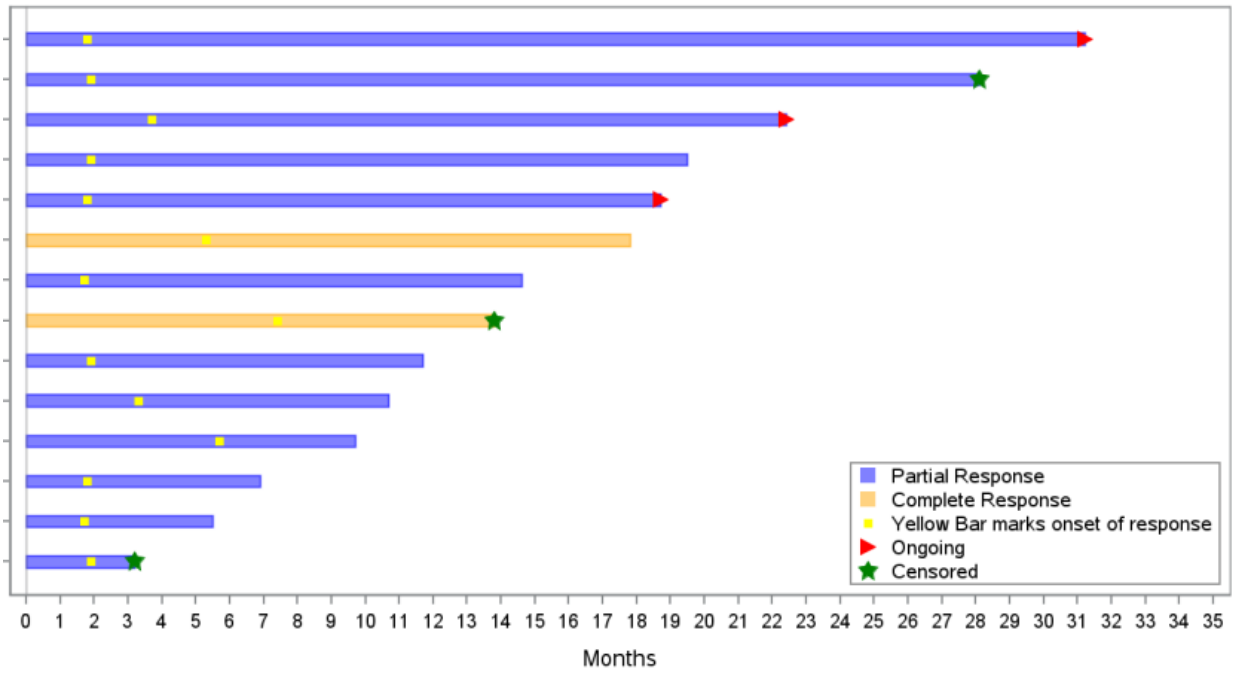
Time to response is defined as the time from the first dose to the first documentation of response (PR or CR).

6.8. Other Analyses Related to Efficacy

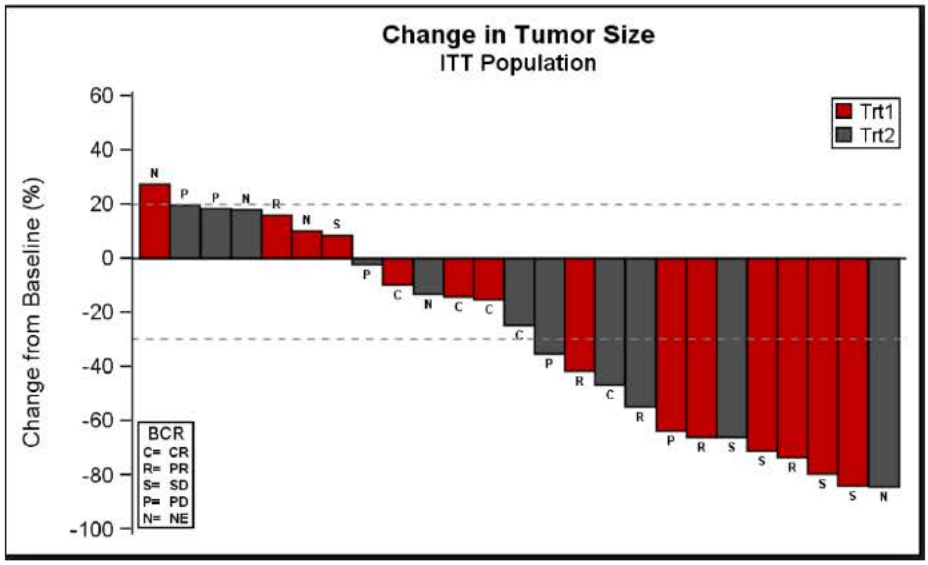
Waterfall plots of the percent change from baseline in target lesion measurement will be presented.

Swimmer plots of onset to response and duration of response will be presented. The plot will include only CR and PR patients distinctly color coded; onset of response, response ongoing status will be marked at the end of the plot indicating 1) DOR is stopped by PD or death, 2) DOR is censored due to missing 2 or more scheduled, initiated of other treatment or loss to follow-up; and 3) DOR is ongoing (censored but not due to reasons listed in 2).

Example of swimmer plot:



Example of waterfall plot:



6.9. Sensitivity Analyses

CCI [redacted]

Analyses based on the Per-Protocol Population will be performed for ORR, PFS, and OS for the Target mTNBC Population.

Sensitivity analyses will only be conducted for the Target mTNBC Population, but not planned for other cancer-specific analysis population.

CCI [redacted]

CCI [redacted]

CCI

CCI

[redacted]

7. SAFETY ANALYSIS

Safety will be assessed for the Target mTNBC Population, mBC Population, mUC Populations and the Overall Safety Population. Data will be presented in terms of AEs, laboratory data, ECG data, and vital signs.

7.1. 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) Version 20.0 unless otherwise specified. The severity will be graded based on the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. All AEs will be listed. Only TEAEs will be summarized and will be referred to as AEs hereafter. Timing of AEs and concomitant medications will take account of the date and the time of the AE or concomitant medication.

The frequency and severity of AEs will be tabulated by MedDRA SOC and PT. For this purpose, an AE that occurs more than once within each patient will be counted only once (at the worst CTCAE grade and relationship category). Adverse event tables will be sorted by SOC frequency and within each SOC, the PTs will be sorted by decreasing frequency for the total IMMU-132 treated patients' column reported in each table.

Additional by-patient listings will be provided for AEs leading to on-treatment death, serious AEs (SAEs), and AEs leading to discontinuation of treatment (excluding AEs leading to death).

Tables summarizing the incidence of AEs will be generated for each of the following:

1. Overall summary of AEs
2. All AEs by SOC and PT
3. Most common AEs (defined as ≥10% of the total number of patients) by PT
4. Grade 3 or higher AEs by SOC and PT
5. AEs by SOC, PT, and grade; columns for: any grades; grade 3, grade 4, grade 5
6. Treatment-related AEs by SOC and PT
7. Treatment-related grade 3 or higher AEs
8. SAEs by SOC and PT
9. Treatment-related SAEs by SOC and PT
10. AEs leading to permanent treatment discontinuation by SOC and PT
11. AEs leading to dose interruption by SOC and PT
12. AEs leading to on-treatment death by SOC and PT, where AEs leading to death is defined as any event of grade 5 and/or outcome equal to fatal, and on-treatment death is defined as date of death within 30 days of last dose

All TEAEs by SOC/PT and the overall TEAE summary table for the following subgroups will be provided when the numbers of patients are deemed sufficient for the Target mTNBC Population and for the Overall Safety Population:

- Age (<50, 50-65, >65 years)
- Sex (male and female) - only for the Overall Safety Population
- Race
- Ethnicity
- Types of Malignancy according to patient's eligibility criteria CRF - only for the Overall Safety Population
- ECOG Performance Score
- Renal Impairment (creatinine >ULN; creatinine ≤ULN)
- Hepatic Impairment, as defined by baseline serum bilirubin:
    - Normal (<=ULN)
    - >1-1.5ULN (> 1 and <= 1.5 x ULN)
    - >1.5ULN (> 1.5 x ULN)
- UGT1A1 (including but not limited to: *1/*1; *1/*28; *28/*28; not done or missing combined in 1 group)

For the mUC and mBC populations, subgroup analyses of all TEAEs by SOC/PT summary table and the overall TEAE summary table will be done for hepatic impairment and UGT1A1 subgroups, respectively, as defined above.

For the Overall Safety Population, additional subgroup safety analyses including treatment-related AEs and SAEs will be summarized by SOC and PT for hepatic impairment and UGT1A1 subgroups.

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, including but not limited to listed. For AESI, frequency tables will be generated, showing overall summary of AESI, Summary of AESI by SOC and PT, Serious AESI by SOC and PT, AESI leading to discontinuation by SOC and PT, AESI leading to treatment interruption by SOC and PT, Grade 3 or higher AESI by SOC and PT, treatment-related AESI (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

In addition, AESI will be summarized for neutropenia, diarrhea, anemia, nausea and vomiting. For each type of AESI, the following will be generated based on the Overall Safety Population:

- Summary of Subjects with the concerned AESI (by a worst CTCAE grade of 3, 4, or 5, >=3 and any grade)
- Summary of subjects who permanently discontinued treatment due to AESI
- Time to onset of 1st event of AESI from the 1st dose of study drug and of 1st event of AESI or to the 1st event of AESI of Grade 3 or higher; time to onset of event of AESI from the time of the dose that is immediately prior to the onset of the AESI event
- Duration of AESI of any grade, and duration of AESI of grade 3 or higher

Additional analyses of AEs in general or of specific interest, if warranted in the course of safety review, may be generated.

7.2. Death

All-cause deaths will be summarized (including presentation of death due to PD, AE, or other reason) and listed, and deaths within 30 days of the last dose of study drug will be summarized for the Target TNBC Population, mBC Population, mUC Population and Overall Safety Population. In addition, a listing of death based on patient death report CRF will be provided.

7.3. Clinical Laboratory Evaluations

Clinical laboratory data results will be reported in standard international units and US conventional units. Baseline is defined as the last observation occurring prior to the first treatment administration of IMMU-132. Observations occurring on the same day as first

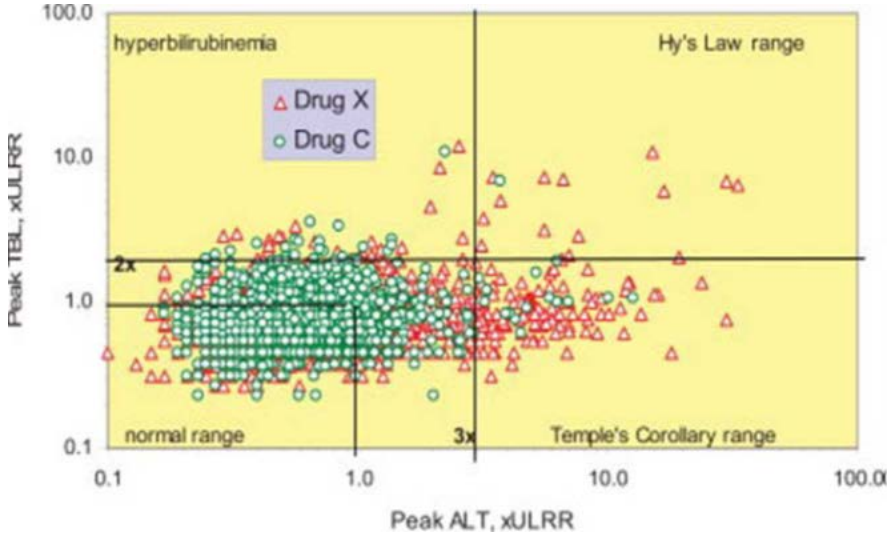
treatment day will be the baseline assessment as they are assumed to have occurred prior to the time of treatment according to study schedule.

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.

Hematology and serum chemistry data will be listed by patient and summarized by study visit. Actual values by visit and change-from-baseline will be summarized by mean, median, standard deviation, minimum, maximum and number of patients.

Shift tables from baseline to worst CTCAE grade on treatment and from worst to last CTCAE grade on treatment will be presented where CTCAE grade is available. Shift tables will be presented based on CTCAE v4.03 criteria, using the grades 1 through 4 as well as a grade 0 indicating no abnormality. These shift tables will report the shift from baseline CTCAE grade to worst grade on treatment and from worst to last on-treatment visit.

For liver function tests, summaries of maximum alanine aminotransferase (ALT), maximum aspartate aminotransferase (AST), and maximum total bilirubin level (TBL) will be produced to evaluate for possible drug-induced liver injury (DILI), including presentation of Hy's law/evaluation of drug-induced serious hepatotoxicity (eDISH) figures (see figure below). For the eDISH figures the horizontal and vertical lines for 2ULN and 3ULN will be selected based on the lowest available reference range for each parameter. In addition, tables will be produced summarizing the number and percentage of patients with multiples of the upper limit of normal (ULN) for AST and ALT (≤3 ULN, >3 ULN) and bilirubin (≤2 ULN and >2 ULN) and for patients who fulfil either AST or ALT >3 ULN in conjunction with bilirubin >2 ULN.



Patients with elevated ALT or AST (>3 ×ULN) or bilirubin (>2 ×ULN) will be flagged on the relevant listing of laboratory data.

7.3.1. Pregnancy Tests

Pregnancy test results will be listed.

7.4. Physical Examination

A by-patient listing will be presented for any clinically significant findings from the physical examination.

7.5. Vital Signs

The actual value and change from baseline (most recent evaluation within 28 days prior to beginning study therapy) to each on-study evaluation, including baseline and end of treatment, will be summarized for vital signs.

Vital sign measurements will be presented for each patient in a by-patient data listing.

7.6. Electrocardiograms

Descriptive statistics for the actual values and changes from baseline over time will be summarized for the ECG parameters including heart rate (HR) measured in beats per minute, QTcB and QTcF is not recorded on the CRF page and will be calculated in the following way: QTcB = QT/sqrt (RR) and QTcF is calculated as QTcF = QT/cube root of RR interval where RR = 60/HR.

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 the final evaluation on treatment will also be provided.

As ECG comments were collected in a free text field; a listing will also be produced with ECG investigator comments in the output (as well as a listing with any investigator comments).

8. MAJOR PROTOCOL DEVIATIONS

A by-patient listing with major study protocol violations and deviations will be provided for patients in the Overall Safety Population, and major protocol deviations as identified will be summarized for the Target mTNBC, mUC, mBC, and Overall Safety Population.

Protocol Violations to be Programmed

- Inclusion/Exclusion Criteria
  - <2 weeks between previous treatment, immune therapy, chemotherapy, or investigational therapy for metastatic disease and start of treatment with IMMU-132.
- Prohibited Medication
  - Anticancer therapy during treatment with IMMU-132 (fulvestrant; Gemzar; letrozole; nivolumab; paclitaxel; temozolomide).
  - Radiation during treatment with IMMU-132 was not allowed except for pain palliation or prophylaxis.
  - Prophylactic medication of hematopoietic growth factors or blood transfusions before Cycle 1.

9. INTERIM ANALYSIS

Analyses based on data from the 30 June 2017 cut-off conducted under SAP version 2.0 CCI [redacted] Various administrative interim analyses had been conducted to support clinical development decisions or public data disclosures or publications. The final analyses are conducted under SAP version 3.0 based on the planned data cut-off date of 01 March 2019.

10. METHODS FOR HANDLING MISSING DATA

Data handling rules, such as imputation rules for missing or partial dates of AE and concomitant medication as conventionally applied, and other data handling or programming specifications as applied in programming will be specified and documented by a data handling and programming specifications document.

11. CHANGES TO THE PLANNED ANALYSES OR THE STATISTICAL ANALYSIS SECTION FROM THE PROTOCOL

CCI [redacted]

12. APPENDIX

Eisenhauer EA, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47. doi: 10.1016/j.ejca.2008.10.026.

Tumor Response Rules

Objective Response: Objective responses are evaluated according to RECIST1.1 (Eisenhauer et al., Eur J Cancer, 228-247, 2009). Study IMMU-132-01 requires measurable radiologic disease at baseline by CT or MRI. Target lesions may include up to 5 measurable lesions (at most 2 per organ) selected at baseline and may include pathologic lymph nodes with short axis ≥15 mm. The sum of diameters of target lesions uses the longest diameter for lesions that are not lymph nodes and the shortest diameter for lesions that are pathologic lymph nodes. Objective tumor response for target lesions at each assessment are defined as:

- Complete Response (CR): Disappearance of all target lesions. Any pathologic lymph node must have reduction in short axis to <10 mm.
- Partial Response (PR): ≥30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): ≥20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (which includes the baseline sum if the smallest on study). In addition to a relative increase of ≥20%, the sum must also demonstrate an absolute increase of ≥5 mm. (Note: the appearance of 1 or more new lesions is also considered progression).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Non-target lesions are other measurable or non-measurable lesions at baseline including pathologic lymph nodes with short axis ≥10 mm. Objective tumor response for non-target lesions at each assessment are defined as:

- Complete Response (CR): Disappearance of all non-target lesions. All pathologic lymph nodes must be non-pathologic in size (<10 mm short axis).
- Non-CR/Non-PD: Persistence of 1 or more non-target lesions.
- Progressive Disease (PD): Unequivocal progression of existing non-target lesions (note: the appearance of 1 or more new lesions is also considered progression).

The overall response at each assessment is based on the response of the target and non-target lesions, as well as the appearance of any new lesions, as follows:

Overall Response at Each Assessment			
Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE (inevaluable)
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
Abbreviations: CR = Complete response, PR = Partial response, SD = Stable disease, NE = Not evaluable.			

This study requires confirmation of an overall assessment of CR or PR at least 4 weeks after the criteria for response are first met. The BOR across all assessments is determined as follows:

Best Overall Response with Confirmation of CR and PR Required		
Overall Response		BEST Overall Response
Initial	Subsequent	
CR	CR	CR
CR	PR	SD, PD or PR*
CR	SD	SD if minimum criteria for SD duration met, otherwise PD
CR	PD	SD if minimum criteria for SD duration met, otherwise PD
CR	Missing	SD if minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD if minimum criteria for SD duration met, otherwise PD
PR	Missing	SD if minimum criteria for SD duration met, otherwise NE
Abbreviations: CR = Complete response, NE = Not evaluable, PD = Progressive disease, PR = Partial response, SD = Stable disease.		
** If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.*		