IMMUNOMEDICS®, INC.

PROTOCOL: IMMU132-05

Phase III Study of Sacituzumab Govitecan (Immu-132) In Relapsed/Refractory Triple-Negative Breats Cancer

Protocol Title: **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**

IND #: **122694**

EudraCT Number: **2017-003019-21**

Sponsor: Immunomedics, Inc.
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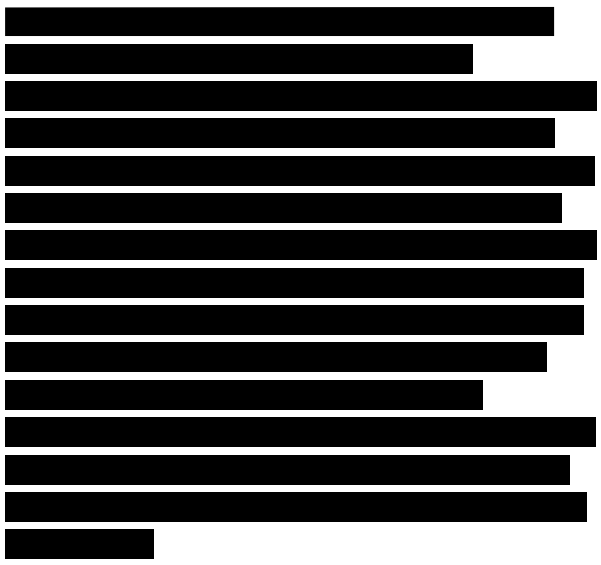
Release Date: **November 18, 2015**

Revision Date: **August 26 2019 (Includes Amendments 1- 6)**

SUMMARY OF CHANGES

Protocol Sections	Change	Rationale
Protocol	Minor typographical, grammatical and formatting corrections were made throughout the protocol.	Formatting and grammar consistency
IN THE EVENT OF EMERGENCY	**Delete page:** ~~IN THE EVENT OF EMERGENCY~~ ~~Any death, serious* adverse experience, or unexpected (and severe) adverse experience undergone by the patient while receiving or within 30 days of receiving test drug, even though the event may not appear to be drug-related, must be promptly reported (within 24 hours) by telephone or facsimile to the Sponsor's designee. Reports should be made to:~~ ~~Synteract~~ ~~Telephone*:~~ ~~PPD~~ ~~Facsimile*:~~ ~~PPD~~ ~~E-mail:~~ ~~PPD~~ ~~*additional toll free country specific phone or fax lines will be provided to sites~~	Removed page to be consistent with protocol template
Synopsis Scope of Study	**Old Text:** Four hundred and eighty-eight patients (488) are anticipated to be enrolled. Up to approximately 150 institutions will participate in this study, including sites in North America, Europe ~~and potentially elsewhere.~~ **New Text**: Approximately four hundred and eighty-eight patients (488) are anticipated to be enrolled. Up to approximately 150 institutions will participate in this study, including sites in North America, and Europe.	Update to reflect enrollment

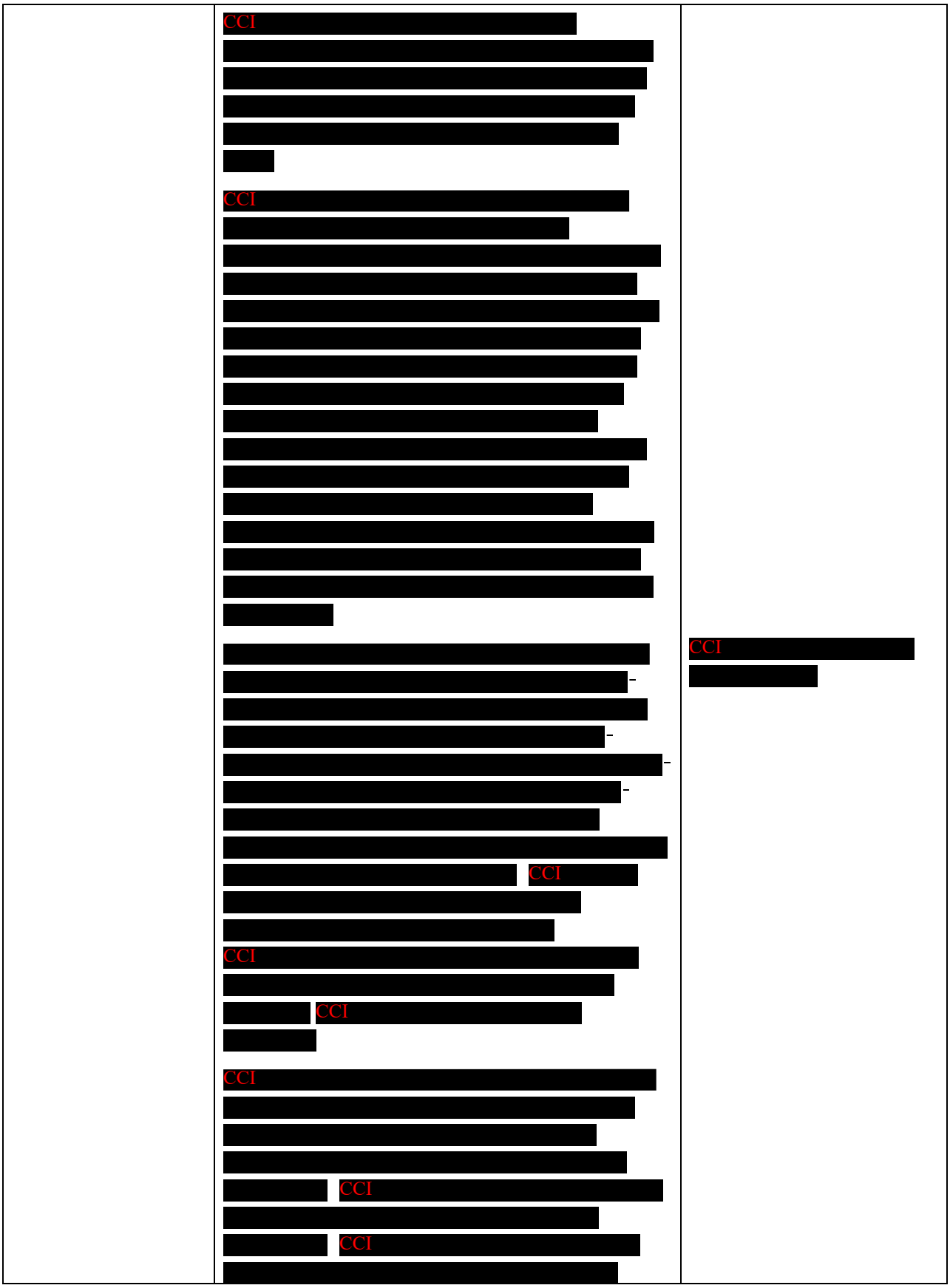
Synopsis Study Design	CCI [redacted]	CCI [redacted]
Synopsis Study Procedure	CCI [redacted] CCI [redacted] **Added Text:** CCI [redacted] **Deleted Text:** CCI [redacted]	CCI [redacted] CCI [redacted] CCI [redacted]

	CCI CCI CCI 	
Sample Size	**Old Text:** 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). **New Text** Approximately four hundred and eighty-eight patients (488) patients are anticipated to be enrolled. The population of	Updated for clarification

	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 IRC review, as defined for the primary analysis in the primary analysis population of patients without brain metastases (BM-ve population).	
Centralized Procedures	**Deleted Text:** The DSMC reviews will include one planned interim futility analysis of data on progression-free survival (based on the central assessment) at 50% (approximately 213events) of the required 425 progressions or deaths for final analysis. For this interim futility analysis, the DSMC will be guided by the pre-specified futility monitoring boundaries based on a fixed boundary of HR=0.999 applied to the brain metastasis negative population. The DSMC will consider all available safety and efficacy data prior to formulating its recommendations regarding continuation or termination of the trial. If futility is not demonstrated for the primary endpoint of PFS, the trial will continue. **New Text:** The DSMC will consider all available safety and efficacy data prior to formulating its recommendations regarding continuation or termination of the trial.	Interim analysis for futility was not performed due to rapid enrollment
Data Analysis	**Old Text:** CCI [redacted] CCI [redacted]	CCI [redacted]

	New Text: CCI [redacted] CCI [redacted]	
LIST OF ABBREVIATIONS	**Added Text:** IMMU-132 Company Code for sacituzumab govitecan	For consistency
3.1 Study Overview	**Old Text:** Four-hundred eighty-eight (488) patients from up to 150 centers, including sites in North America, Europe and potentially elsewhere will be randomized 1:1 to the following treatment arms: **New Text**: Approximately four hundred eighty-eight (488) patients from up to approximately 150 centers, including sites in North America, and Europe will be randomized 1:1 to the following treatment arms:	For consistency with synopsis
3.2 Data Safety Monitoring Committee (DSMC)	**Old Text:** An independent DSMC will be convened at regular intervals to assess the progress of this study, and review safety and progression data, per an adopted DSMC charter. In the absence of unexpected safety concerns, ~~or futility at the time of interim analysis for meeting the primary PFS endpoint,~~ the study will continue. **New Text:** An independent DSMC will be convened at regular intervals to assess the progress of this study, and review safety and progression data, per an adopted DSMC charter. In the absence of unexpected safety concerns, the study will continue.	Interim analysis for futility was not performed due to rapid enrollment

5 STUDY PROCEDURES	CCI [redacted]	CCI [redacted]
5.3 Pre-Study/Baseline Evaluations	CCI [redacted] CCI [redacted]	CCI [redacted]
5.4 Procedures During Treatment	**Old Text:** Anti-drug antibody sample (~~hRS7,SN38~~frozen immediately, to be shipped to Sponsor's designee for analysis) *[For IMMU-132, required Day 1 of even cycles. For TPC, not applicable]* **New Text**: Anti-drug antibody sample (frozen immediately, to be shipped to Sponsor's designee for analysis) *[For IMMU-132, required Day 1 of even cycles. For TPC, not applicable]*	Clarification
CCI [redacted]	CCI [redacted]	CCI [redacted]



	CCI CCI [redacted]	
5.9 End of Study	**Deleted Text:** ~~As at the end of study, in the event the Investigator believes a patient is continuing to receive clinical benefit, the Sponsor will discuss options with the Investigator in order to ensure the potential for continuing supply of sacituzumab govitecan.~~ **Added Text:** At the completion of the trial, subjects who are deriving benefit from sacituzumab govitecan may continue to receive treatment in a rollover study, if one is available. This rollover study may be designed to provide continued access to sacituzumab govitecan for eligible subjects who have previously participated in Immunomedics sponsored parent study, who are tolerating sacituzumab govitecan, have no evidence of progressive disease or are still deriving clinical benefit despite progression (as assessed by the investigator). Subjects will receive the dose ofsacituzumab govitecan currently receiving in the parent study at the time of consenting to participate in the rollover study, if applicable.	
6.3 Study Drug Preparation	**Added Text: Please use Pharmacy Binder as primary source for study drug preparation.** **Deleted Text:** ~~For patient dose preparation, IMMU-132 is to be reconstituted with normal saline for use **within 8 hours** after preparation. Appropriate use of aseptic technique should be employed in preparing the dose. Allow the IMMU-132 vials to warm to room temperature to allow faster dissolution. The 200 mg of lyophilized powder in each vial should be reconstituted using 20 mL of 0.9% sterile sodium chloride (normal saline). The reconstituted solution should be gently shaken and allowed to dissolve for up to 15 minutes. Calculate the prescribed dose in mg based on the patient's body weight at the beginning of EACH cycle (or more frequently for > 10%~~	Clarification and to be consistent with Pharmacy manual

	~~change in body weight or if required by institutional policy). The appropriate calculated amount should then be withdrawn from the supplied vials of study medication. Inject the solution into a glass or plastic infusion container slowly to minimize foaming and do not shake the contents. Adjust the volume in the infusion container as needed with normal saline to obtain a concentration of 1.1 3.4 mg/mL (total volume should not exceed 500 mL). Only normal sterile saline should be used since the stability of the reconstituted product has not been determined with other infusion based solutions. A sample drug preparation chart for a 70 kg patient is provided in **Table 3** with 200 mg/vials and 250 mL bags of normal saline as the infusion container. The prepared study drug is stable for up to 8 hours at room temperature~~	
Table 6	**Deleted Text :** ~~(refer to table 9 A) and (refer to table 9B)~~	No table 9A or 9B
7 STUDY EVALUATIONS	CCI [redacted] [redacted] CCI [redacted] CCI [redacted]	CCI [redacted]

8.2 Reporting AE's/SAE's	**Old Text:** Disease progression is a worsening of a patient's condition attributable to the disease for which the study medication is being given. This may be an increase in severity of the disease or an increase in the symptoms of the disease. New or increasing symptoms related to disease progression should be reported as an AE; unless death occurs within 30 days of the patient's last dose of study medication. **Added Text:**. In this protocol, disease progression is an efficacy endpoint and should not be reported as an AE. It is important to differentiate expected disease progression from an AE. Events that are clearly consistent with the expected pattern of disease progression should not be considered AEs. Expected disease progression refers to an event that is unequivocally related to disease progression, and that the clinical course is consistent with what would be expected for the patient's disease. A clinical event in the setting of disease progression would be considered an AE if it could not be unequivocally attributed to or consistent with expected disease progression.	Clarification of text
8.2 Reporting AEs/SAEs	**Deleted Text:** ~~For SAEs, the Sponsor designated contact is to be notified by the Investigator, using the designated form, **within 24 hours of the site becoming aware of the event**. The initial report is to be followed by submission of more detailed SAE information within 5 calendar days of the event.~~ **Added Text**: All SAEs and pregnancies must be reported to the Sponsor or the Sponsor's designee immediately, and no later than 24 hours of becoming aware of the event. All SAEs and pregnancies should be reported to the Sponsor's designee as per the reporting instructions provided on the SAE Form Completion Guidelines and as stated on the SAE Form.	Update to safety language to be consistent with protocol template

8.2 Reporting AEs/SAEs	**Deleted Text:** ~~Synteract~~ ~~Telephone*:~~ PPD ~~Facsimile*:~~ PPD ~~E-mail:~~ PPD ~~*additional toll free country specific phone or fax lines will be provided to sites~~	Removal of Synteract information
8.7 Expedited Reporting	**Old Text:** In this trial, ~~Synteract~~ is responsible for expedited reporting of any SAE considered to be SUSAR (Suspected Unexpected Serious Adverse Reaction). A SUSAR is any adverse event which meets the following 3 criteria • Serious Adverse Event. An event meeting the SAE criteria in Section 8.1. • Suspected Adverse Reaction. An event for which there is a reasonable possibility that there is a causal relationship between the study treatment and the event • Unexpected Adverse Reaction. An event for which the nature or severity is not consistent with the applicable product information (*e.g.* Investigator's Brochure for an unapproved investigational product ~~or package insert/summary of product characteristics for an approved product).~~ ~~Expedited reporting of SUSARs is only required for events related to sacituzumab govitecan. Events otherwise meeting the definition of SUSAR but related to TPC do not require expedited reporting but will be reported to the respective product manufacturers.~~ ~~Synteract~~ will report all relevant information about suspected serious unexpected adverse reactions (SUSARs) to all applicable	Removal of Synteract information

	regulatory authorities in all participating countries, and via the Eudravigilance database (EVCTM), as required. SUSARs determined to be fatal or life-threatening must be submitted not later than 7 calendar days after initial report of the information to ~~Synteract~~ (follow-up within an additional 8 days); otherwise SUSARs must be submitted within 15 calendar days. The ~~Synteract~~ will also report all SUSARs to the governing Ethics Committees and will inform all investigators, as required. **New Text:** In this trial, the Sponsor's designee is responsible for expedited reporting of any SAE considered to be SUSAR (Suspected Unexpected Serious Adverse Reaction). A SUSAR is any adverse event which meets the following 3 criteria • Serious Adverse Event. An event meeting the SAE criteria in Section 8.1. • Suspected Adverse Reaction. An event for which there is a reasonable possibility that there is a causal relationship between the study treatment and the event • Unexpected Adverse Reaction. An event for which the nature or severity is not consistent with the applicable product information (*e.g.* Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product). The Sponsor's designee will report all relevant information about suspected serious unexpected adverse reactions (SUSARs) to all applicable regulatory authorities in all participating countries, and via the Eudravigilance database (EVCTM), as required. SUSARs determined to be fatal or life-threatening must be submitted not later than 7 calendar days after initial report of the	

	information to the Sponsor's designee (follow-up within an additional 8 days); otherwise SUSARs must be submitted within 15 calendar days. The Sponsor's designee will also report all SUSARs to the governing Ethics Committees and will inform all investigators, as required.	
9.1 Determination of Sample size	**Old Text:** in the primary analysis population of patients without brain metastases (BM-ve population). **New Text:** as defined for the primary analysis in the primary analysis population of patients without brain metastases (BM-ve population).	Updated for clarification
9.2 Interim analysis	**Deleted Text:** ~~The DSMC reviews will include one planned interim analysis for futility of data on progression-free survival (based on the central assessment) at 50% (approximately 213 events) of the required 425 PFS events for the final analysis. For the interim analysis, the DSMC will be guided by the pre-specified futility monitoring boundaries based on a fixed boundary of HR=0.999 applied to the brain metastasis-negative population. There is only a 0.6% probability that the study would falsely stop for futility if the true PFS HR is 0.667. The DSMC will consider all available safety and efficacy data prior to formulating its recommendations regarding continuation or termination of the trial. If futility is not indicated for the primary endpoint of PFS brain metastasis-negative population, the trial will continue.~~ **Old Text:** where the ~~1~~-sided significance level applied is determined by α^{1}~~(t)~~ = 2-2Φ(- z ~~0.5*0.025~~/√t). **New Text:** where the 2-sided significance level applied is determined by α(t) = 2-2Φ(- $z_{\alpha/2}$/√t).	Interim analysis for futility was not performed due to rapid enrollment **Typo correction:** 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.
	Deleted Text: ~~If OS in the ITT population is only tested at the final OS analysis, a 2-sided significance level of 0.05 will be applied to this endpoint.~~ **Added Text:** 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.	Change to the analysis plan as required by the FDA
9.3 Efficacy Analysis	**Old Text:** The primary analysis population consists of all ITT patients without brain metastases labelled throughout as the BM-ve population, defined as all randomized patients who have been identified by the IRC as not having brain lesions at baseline. **New Text:** The primary analysis population consists of all ITT patients without brain metastases labeled 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.	Primary analysis population of BM-ve population as defined by randomization strata: IRC does not identify subjects who have no brain lesions at baseline.
	Old Text: where the ~~1~~-sided significance level applied is determined by $\alpha^{1}(t) = 2\text{-}2\Phi(-z_{0.5*0.025}/\sqrt{t})$. **New Text:** where the 2-sided significance level applied is determined by $\alpha(t) = 2\text{-}2\Phi(-z_{\alpha/2}/\sqrt{t})$.	**Typo correction:** 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.
	Old Text: If OS in the ITT population is only tested at the final OS analysis, a 2-sided significance level of 0.05 will be applied to this endpoint. **New Text:** 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.	OS significance level: Change to the analysis plan as required by the FDA
	Old Text: FDA definitions and guidance as described in Guidance for Industry: Clinical Trials Endpoints for the Approval of Cancer Drugs and Biologics ~~(May 2007)~~ will be used. **New Text:** FDA definitions and guidance as described in Guidance for Industry: 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) will be used.	Reference to FDA guidelines Clinical Trials Endpoints for the Approval of Cancer Drugs and Biologics are updated according to the latest version along with Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics (April 2015).
	Old Text: or the appearance of new non-target lesions. **New Text:** or the appearance of new lesions or unequivocal progression of non-target lesions.	Clarified reference of progression according to RECIST 1.1
	Old Text: Patients that progress following more than one missed scheduled visit will be censored at the last date of radiographic assessment without documented progressive	Modified censoring rule in the IR response per the FDA's request.

	disease **New Text**: Patients that progress or die following more than one missed scheduled visit will be censored at the last date of radiographic assessment without documented progressive disease	
	Old Text: The primary analysis of PFS will be based on the assessment of the central reviewer; additional sensitivity analyses will be performed based the site assessment of PFS. **New Text:** The primary analysis of PFS will be based on the assessment of the central reviewer; additional sensitivity analyses will be performed based on definitions of PFS as defined in the Statistical Analysis Plan including the investigator's assessment.	Multiple sensitivity analyses of PFS were defined in the SAP, which were clarified in the SAP and provided reference to it in the protocol.
	Old Text: Prognostic factors included in the analyses will be finalized prior to database lock and included ~~in an addendum~~ to the Statistical Analysis Plan. **New Text:** Prognostic factors included in the analyses will be finalized prior to database lock and included in the Statistical Analysis Plan.	Clarification of SAP
CCI [redacted]	CCI [redacted]	CCI [redacted]
15 References	**New Text:** Bardia A, Mayer IA, Diamond JR et al. Efficacy and Safety of Anti-Trop-2 Antibody Drug Conjugate Sacituzumab Govitecan (IMMU-132) in Heavily Pretreated Patients With Metastatic Triple-Negative Breast Cancer. J Clin Oncol. 2017 35:2141-2148.	Updated missing references

15 References	**New Text:** Lipscomb J et al. Patient-reported outcomes in cancer: a review of recent research and policy initiatives. CA Cancer J Clin. 2007; 57(5):278-300.	Updated missing references
15 References	**Deleted Text:** ~~Hammond MEH, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol. 2010;28:2784-95.~~	Deleted unreferenced reference
15 References	**Deleted Text:** ~~Mantel, N Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemotherapy Reports. 1966;50:163-170.~~	Deleted unreferenced reference
Appendix 4 Study Calendar	**Old Text:** For patients receiving TPC, required prior to, once during, and at the end of each infusion, or if administered orally, once at each study visit; *otherwise as per local standard of care*. **New Text**: For patients receiving TPC, required prior to, once during, and at the end of each infusion, (Vinorelbine vital signs are required prior to and at the end of each infusion due to short infusion time) or if administered orally, once at each study visit; *otherwise as per local standard of care*. **Old Text:** [12]Anti-drug antibodies required from all patients receiving IMMU-132 with serum samples obtained at baseline (may be taken at C1D1 provided it is before study drug administration), at Day 1 of even cycles, and at final study visit. ~~Two additional monthly samples for anti-drug antibodies will be collected in the event of positive results at the final study visit.~~ **New Text**: [12]Anti-drug antibodies required from all patients receiving IMMU-132 with serum samples obtained at baseline (may be taken at C1D1 provided it is before study drug administration), at Day 1 of even cycles, and at final study visit.	Clarification Clarification

9.3. Efficacy Analyses	The wording of the bottom right box of the diagram was changed to "OS (final) in ITT, 2-sided Lan-DeMets alpha adjusted at final" per FDA feedback	Updated on August 26, 2019 per FDA feedback

SYNOPSIS

Protocol Title	**An International, Multi-Center, Open-Label, Randomized, Phase III Trial of Sacituzumab Govitecan (IMMU-132) versus Treatment of Physician Choice in Patients with Metastatic Triple-Negative Breast Cancer Who Received at Least Two Prior Treatments**
Sponsor	Immunomedics, Inc., 300 The American Road, Morris Plains, NJ 07950
Study Drug	Sacituzumab govitecan (IMMU-132) is an antibody-drug conjugate (ADC) composed of the humanized monoclonal antibody, hRS7 IgG1κ, which binds to Trop-2 (trophoblast cell-surface antigen-2); the camptothecin-derived agent, SN-38, a topoisomerase I inhibitor; and CL2A, a linker, which couples SN-38 to hRS7 IgG1κ.
Background	Patients with triple-negative breast cancer (TNBC) who have failed approved or accepted treatments in the 1st and 2nd line setting remain in dire need of additional therapeutic approaches. The Trop-2 antigen is highly expressed on most solid epithelial cancers, including TNBC. Sacituzumab govitecan was developed by Immunomedics to treat these cancers by binding to Trop-2 for targeted delivery of SN-38 directly to the tumor cell while minimizing systemic exposure of SN-38 to decrease host toxicity. A phase I/II trial in heavily treated patients with a variety of solid cancers, including TNBC, demonstrated that sacituzumab govitecan was therapeutically active when given on days 1 and 8 of repeated 21-day cycles, with neutropenia being the main toxicity followed by a low incidence of severe diarrhea. Since 10 mg/kg was the maximum dose that allowed multiple cycles to be given repeatedly with acceptable toxicity, this dose of sacituzumab govitecan was selected for further clinical development with this treatment schedule, including this Phase III study.
Objectives	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 metastatic TNBC previously treated with at least two systemic chemotherapy regimens, and without brain metastasis at baseline. The secondary objectives of the study are to compare between the two treatment groups for: • Progression Free Survival (PFS) in the ITT population • Overall Survival (OS) in the ITT population and in the subpopulation of patients with brain metastasis • Independently-determined Objective Response Rate (ORR), duration of response (DoR) and time to onset of response per RECIST 1.1 criteria

- Quality of life
- Safety (adverse events, safety laboratories, incidence of dose delays and dose reductions, treatment discontinuations due to adverse events)

CCI [redacted]

Treatment

Sacituzumab govitecan (10 mg/kg intravenously on Days 1 and 8 of a 21-day cycle) or (TPC) selected from one of the following 4 monotherapy treatment regimens, and administered for metastatic breast cancer, as per label or NCCN guidelines as per below and with dose modifications as provided in the protocol if too toxic

- 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)
- Capecitabine (1000-1250 mg/m^2 orally twice daily on Days 1-14 of a 21-day cycle)
- Gemcitabine (800-1200 mg/m^2 intravenously on Days 1, 8 and 15 of a 28-day cycle)
- Vinorelbine (25 mg/m^2 intravenously on Day 1 weekly). (Note: eligible patients with Grade 2 peripheral neuropathy should not be prescribed vinorelbine as TPC)

Scope of Study

Approximately four hundred and eighty-eight patients (488) are anticipated to be enrolled. Up to approximately 150 institutions will participate in this study, including sites in North America, and Europe

Study Duration

Enrollment is expected to be completed in approximately 24 months. The screening period is up to 28 days (4 weeks). Patients will be treated until progression, death, study withdrawal, or unacceptable toxicity. After discontinuation of treatment, all patients will be followed every 4 weeks for survival follow-up. This may be by telephone, and will include documentation of any further active therapy administered for their breast cancer.

Study Design

This is an international, multi-center, open-label, randomized, Phase III study in patients with either locally advanced or metastatic TNBC refractory or relapsing after at least 2 prior standard-of-care 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 and 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 12-months of adjuvant therapy. Patients with brain metastasis that have been treated and are stable by MRI for at least 4 weeks are eligible provided they are off high-dose steroids (>20 mg prednisone or equivalent) for at least 2 weeks prior to randomization. (Low dose steroids of ≤ 20 mg daily are allowed provided dose has been stable for 4 weeks). All patients should 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.

Clinical sites will use standard ASCO/CAP criteria for the pathological diagnosis of TNBC, defined as negative for estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2). Receptor results will be based on local assessment of the most recent biopsy findings (or other pathology reports). HER2 negative is defined as one of the following: 0 or 1+ by immunohistochemistry (IHC), or if IHC 2+, then fluorescence in situ hybridization (FISH) ratio of *HER2* gene: chromosome 17 being less than 2, as per standard guidelines. ER- and PR-negative is defined as < 1% of cells expressing hormonal receptors by IHC, as per standard guidelines.

CCI [redacted] A single whole-blood sample will be also collected from all patients for determination of *UGT1A1* genotype for retrospective assessment predicting of toxicity.

CCI [redacted].

Patients meeting eligibility will be randomized 1:1 to receive either sacituzumab govitecan or treatment of physician choice (TPC), which needs to be selected prior to randomization from one of the 4 allowed regimens. Randomization will be stratified by number of prior chemotherapies for locally advanced or metastatic disease (2-3 vs >3), geographical location (North America vs rest of world) and known brain metastasis at baseline (yes or no).

Patients will be treated until progression requiring discontinuation of further treatment, unacceptable toxicity, study withdrawal, or death,

whichever comes first. Tumor progression leading to treatment withdrawal will be assessed by the investigator. Starting with the initial dose of sacituzumab govitecan or TPC, CT or MRI scans will be obtained every 6 weeks for 36 weeks, then every 9 weeks thereafter, until the occurrence of progression of disease or unacceptable toxicity requiring discontinuation of further treatment. For each patient, the same imaging technique should be used throughout the trial. All images will be evaluated locally at the study site for tumor status as per RECIST1.1. Additional CT or MRI scans may be performed at the discretion of the physician to assess disease status as medically indicated. In case of progression on clinical grounds, the investigator will make every effort to document progression objectively/radiographically, so that documentation can be reviewed by the IRC. Patients on either treatment arm who have progression of disease assessed for the first time during the study but, who, in the opinion of the treating physician are deriving continued clinical benefit from IMMU-132 or TPC treatment, relative to other available treatment options, may continue to be treated based on physician discretion as long as they continue to meet eligibility criteria. Other study procedures during treatment include quality of life questionnaires, physical examination and vital signs, CBC (with differential and platelet counts), routine serum chemistries, serum samples for levels of sacituzumab govitecan, CCI , concomitant medications, and adverse events. (*See Study Procedures*)

A final study visit will be conducted within 4 weeks after the last dose of sacituzumab govitecan or TPC for patients discontinuing study participation unless an earlier termination is required. Patients who discontinue for reasons other than progression should have a CT/MRI scan performed. Patients who discontinue treatment due to toxicity will continue with radiologic response assessments at the protocol-required schedule, until progression of disease or initiation of new therapy. The reason for study discontinuation will be documented and any adverse events or abnormal laboratories at that time will be followed until resolution or stabilization.

No crossover to sacituzumab govitecan treatment will be allowed after discontinuing treatment in the TPC arm, but otherwise there is no restriction on subsequent therapies that a patient may receive after discontinuing the study.

All patients, including those prematurely terminating study participation, will be followed every 4 weeks for survival follow-up. This may be by telephone and will include documentation of any further anti-cancer therapy they may receive. Survival status may be also documented from public databases (e.g., Social Security database), as allowed by local regulations.

Population	Female or male patients, ≥18 years of age, must be able to give signed, written informed consent. They must have histological or cytological confirmation of TNBC according to ASCO/CAP criteria as determined by local institution according to ASCO/CAP criteria, with locally advanced or metastatic disease documented by CT or MRI imaging, and currently have measurable disease by CT or MRI. Patients with brain metastases are eligible only if treated and stable by MRI for at least 4 weeks prior to randomization provided they are off high-dose steroids (≥20 mg prednisone or equivalent) for at least 2 weeks. (Low dose steroids of ≤ 20 mg daily are allowed provided the dose is stable for 4 weeks). They must be refractory to, or relapsed after, at least two prior standard-of-care 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 chemotherapies for locally advanced or metastatic disease. Adjuvant or neoadjuvant therapy for early stage 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 of adjuvant therapy. 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. Patients must have an ECOG performance score of 0 or 1, a 3-month life expectancy, adequate hematology without transfusion support (hemoglobin > 9 g/dL, ANC > 1,500 per mm^3, platelets > 100,000 per mm^3), adequate renal and hepatic function (creatinine clearance of > 60 ml/min, may be calculated using Cockcroft-Gault equation), bilirubin ≤ 1.5 IULN, AST and ALT ≤ 2.5 x IULN or ≤ 5 x IULN if known liver metastases), serum albumin ≥ 3.0 mg/dL and least 2 weeks beyond prior anti-cancer treatment (chemotherapy, radiotherapy and/or major surgery) or at least 3 weeks beyond prior antibody treatment for cancer and, with exception of alopecia and neuropathy (≤ Grade 2), recovered from all acute toxicities to Grade 1 or less. *See Protocol for additional entry requirements.*
Concomitant Medications and Procedures	Premedication for prevention of infusion reaction with antipyretics, H_1 and H_2 blockers should be administered before sacituzumab govitecan infusions. Corticosteroids (50 mg hydrocortisone or equivalent P.O. or I.V.) may be added if necessary, and were used in approximately two-thirds of the patients in the phase 2 trial. Premedication according to

established guidelines with a two or three drug combination regimen (e.g. dexamethasone with either a 5-HT3 receptor antagonist or a NK_1 receptor antagonist, as well as other drugs as indicated) for prevention and treatment of chemotherapy-induced nausea and vomiting (CINV) is strongly recommended. Additional antiemetics, sedatives, and other supportive measures may be employed as clinically indicated. All patients should be given medications for nausea and vomiting to take home after each infusion and instructed on use as needed. At the onset of diarrhea, promptly initiate loperamide, 4 mg initially followed by 2 mg with every episode of diarrhea for a maximum of 16 mg daily. Discontinue loperamide 12 hours after diarrhea resolves. Additional supportive measures (e.g. fluid and electrolyte substitution) may also be employed as clinically indicated. All patients should be given take-home medications with clear instructions for treatment of diarrhea. Patients who exhibit an excessive cholinergic response to treatment with sacituzumab govitecan (e.g., abdominal cramping, diarrhea, salivation, etc.) can receive appropriate premedication (e.g., atropine) for subsequent treatments.

The use of such medications for patients receiving TPC is at the discretion of the treating physician, but must be recorded.

All patients on study will receive aggressive medical management for toxicity and best supportive care, which includes the use of growth factors or blood transfusions, continuing or initiating the use of corticosteroids, other palliative medications for complications of disease (including medications for pain and dietary support), treatment of any active infections, and palliative external radiation therapy for bone metastases, or medications for other ongoing medical conditions. These must be recorded.

The use of other anti-cancer treatment (besides IMMU-132 or TPC) is not permitted during this study. However, palliative and/or supportive medications such as bone-modifying medications (bisphosphonates or denosumab), and/or procedures such as radiation and surgery will be allowed at the investigator's discretion.

After discontinuing the study, the patient may not receive any more sacituzumab govitecan; otherwise, there is no restriction on subsequent therapies or interventions that a patient may receive. Any further anti-cancer therapy should be documented.

Study Procedures

Baseline evaluations that must be performed within 28 days of first study treatment include patient medical and surgical history, including all prior treatments for breast cancer (with best RECIST response, where available, and time to progression for last therapy), histology or cytology documentation confirming triple-negative breast cancer according to ASCO/CAP criteria, BRCA 1&2 mutational status, if known, CT or MRI imaging (chest, abdomen, pelvis, other areas of known/suspected involvement, with contrast as appropriate) confirming locally advanced or

metastatic disease, patients with brain metastasis must have a brain MRI, (target and non-target lesions must be determined by the clinical site at time of randomization), physical examination with vital signs, concomitant medications, standard 12-lead ECG, CBC including platelet count (with WBC differential in absolute cell counts), routine serum chemistries, hepatitis B and C testing, serum sample for human anti-drug antibodies (hRS7 and SN-38) (to be frozen for shipment to Sponsor's designee for analysis), whole blood sample for determination of *UGT1A1* genotype, and quality of life assessments. CBC including platelet count (with WBC differential in absolute cell counts) and serum chemistries must be repeated within 72 hours of cycle 1, day 1 to reconfirm eligibility. A negative urine or serum pregnancy test in women of childbearing potential is required within 7 days prior to starting treatment.

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Before randomization, the managing physician must select a treatment choice (TPC) for each patient from one of the 4 drugs. No combination of the four choices is permitted. Patients then will be randomized 1:1 by IWRS (interactive web-based response system) to receive either sacituzumab govitecan (10 mg/kg on Days 1 and 8 of a 21-day cycle) or the preselected TPC, with stratification by number of prior treatments for metastatic or locally advanced disease (2-3 vs >3), geographical location (North America vs Rest of World), and known, baseline brain metastasis (yes or no). The population of patients with brain metastases will be capped at 15 % (N=74) of the trial patient's population.

Patients will be treated until progression requiring discontinuation of further treatment, unacceptable toxicity, study withdrawal, or death, whichever comes first. All patients will receive best supportive care during the study, which includes continuing or initiating the use of corticosteroids, other palliative medications for complications of breast cancer (including medications for pain and dietary support), treatment of any active infections, and procedures such as stenting for obstructions, palliative external radiation therapy for bone metastases, or medications for other ongoing medical conditions. Patients who discontinue treatment due to toxicity will continue with radiologic response assessments at the protocol-required schedule, until progression of disease or initiation of new therapy. Prior to discontinuation of study treatment, patients may not receive other investigational antitumor agents or antineoplastic chemotherapy, or immunotherapy for their breast cancer.

NCI-CTCAE v4.03 toxicity grades will be used to classify safety evaluations and adverse events, including serious adverse events (SAEs). Adverse event reporting will begin with patient number assignment at time of randomization and continue to 30 days after last administration of study

drug. SAEs must be reported to the Sponsor's designee within 24 hours of the event, and treatment-related AEs and SAEs will be followed until recovery or stabilization in the event of residual effects.

In the event of an administration reaction to IMMU-132, the infusion is to be permanently discontinued if severe or life-threatening (Grade 3 or 4); otherwise, the infusion should be slowed for mild toxicity (Grade 1), and for moderate toxicity (Grade 2) temporarily stopped for at least 15 minutes or until symptoms resolve, and then resumed at the slowed rate, if the patient is stable. In the event of hematological or other toxicity to sacituzumab govitecan, patient doses may be reduced, held or permanently discontinued following guidelines provided in Section 6.4.4 of the protocol. Use of growth factors for maintenance of dose intensity will be used for IMMU-132 following guidelines provided in Section 6.4.6 of the protocol. Use of prophylactic medications, transfusions, or other supportive medications are allowed as medically indicated, as best supportive care, at physician discretion. Once dose-reduced for toxicity in spite of adequate use of supportive medications, dosing cannot be re-escalated after resolution of toxicity.

In case of any administration reaction or other toxicity to TPC, patient doses may be reduced, held or permanently discontinued following guidelines provided in Section 6.4.4 of the protocol. Use of prophylactic medications, including growth factors, transfusions, or other supportive medications are allowed as required, as best supportive care, at physician discretion.

For routine safety analysis, all patients will have adverse events and concomitant medications (continued, changed) recorded each study visit. A physical examination will be obtained the first treatment day of each repeated treatment cycle (every 3 weeks for TPC if given weekly [e.g. vineorelbine]), and a pregnancy test, urinalysis and ECG will be obtained the first treatment day of even cycles (every 6 weeks for TPC given weekly [e.g. vinorelbine]) except for Gemcitabine where pregnancy testing will be obtained the first treatment day of each cycle. Vital signs will be obtained on each treatment day if administered intravenously or once at every study visit if administered orally. CCI [redacted]

CBC and serum chemistries will be obtained each treatment day for patients receiving IMMU-132 or TPC given intravenously (eribulin, gemcitabine, vinorelbine). For patients receiving TPC given orally (capecitabine), CBC and serum chemistries will be obtained at least the first treatment day of each cycle and as per standard of care on other treatment days or study visits. In the event of ≥ Grade 3 hematological toxicity, CBC will subsequently be obtained more frequently at the discretion of the managing physician until toxicity recovers to baseline or

Grade 1 levels.

Quality of life (EORTC QLQ-C30 questionnaires) will be evaluated in all patients at baseline, the beginning of every cycle, and the final study visit.

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CT or MRI imaging of the chest, abdomen and pelvis (along with brain MRI in all patients with known baseline brain mets and other areas of disease previously imaged) with contrast as appropriate will be obtained in all patients every 6 weeks for 36 weeks, then every 9 weeks thereafter, and for each patient, the same imaging technique should be used throughout the trial. Responses identified prior to 36 weeks on study require confirmatory scans, which will be performed at the next scheduled scanning time-point (6 weeks later). For responses after 36 weeks, confirmatory scans will be done within 4-6 weeks of scan showing the onset of response. Imaging results will be evaluated locally at each study site for tumor status as per RECIST1.1. Disease progression per RECIST1.1 leading to treatment withdrawal will be assessed by the investigator. Clinical progression leading to patient discontinuation should be documented also by CT/MRI scan of target lesions, if possible. Patients who discontinue for other reasons other than progression should have a CT/MRI scan performed within 4 weeks from treatment discontinuation so that documentation can be reviewed by the IRC. Patients on either treatment arm who have progression of disease assessed for the first time during the study but who, in the opinion of the treating physician are deriving clinical benefit from IMMU-132 or TPC treatment relative to other available treatment options, may continue to be treated.

Final study visit will be conducted 4 weeks after the last treatment dose for all patients discontinuing study participation, unless an early termination visit is required. Patients who discontinue treatment due to toxicity will continue with radiologic response assessments at the protocol-required schedule, until progression of disease or initiation of new therapy. The reason for study discontinuation will be documented and any adverse events or abnormal laboratories at that time will be followed until

resolution or stabilization.

Note: Serum samples collected for IMMU-132 levels or anti-drug antibodies must be immediately frozen for storage until shipment to the Sponsor's designee for analysis.

Follow-Up

After discontinuation of study treatment, all patients, including those patients prematurely terminating study treatment, will be followed every 4 weeks for survival follow-up. This may be by telephone, and will include documentation of any further active therapy administrated for their breast cancer. Adverse event reporting will continue for 30 days after the last dose of study treatment.

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. Approximately 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 IRC review, as defined for the primary analysis 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 analysed 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. OS will be analysed 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.

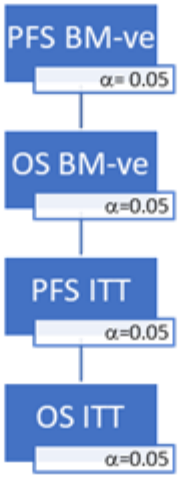
Centralized Procedures

Stratified randomization will be by means of an interactive web-based response system (IWRS). An independent centralized blinded assessment of progression-free survival will be conducted for determination of the study primary endpoint. An independent Drug Safety and Monitoring Committee (DSMC) will be convened at regular intervals to assess the progress of this study, and review safety and progression data, per an approved DSMC charter. The DSMC will consider all available safety and efficacy data prior to formulating its recommendations regarding continuation or termination of the trial.

Data Analysis

The primary analysis population consists of all patients without brain metastases, labelled throughout as the BM-ve population. Analyses will also be performed amongst all randomized patients, regardless of whether they have brain metastases, labelled throughout as the ITT population.

To strongly control Type I Error across populations and the two key endpoints of IRC PFS and overall survival (OS), a hierarchical testing strategy will be performed as displayed below, where a given hypothesis can only be declared statistically significant if all previous hypotheses in the hierarchy are also statistically significant. If fewer than 30 patients with brain metastases are recruited, analyses in the ITT population will not be performed.



Imaging evidence of efficacy will be obtained from CT or MRI scans using RECIST 1.1 criteria to classify tumor response, time to onset of objective response, duration of objective response, and time to progression. Using descriptive statistics, these metrics will be tabulated and compared between the two treatment arms. A stratified log-rank test stratified by randomization strata will be used to compare the treatment groups for the time-to-event endpoints of Progression-Free Survival (PFS) and Overall Survival (OS). Estimates of hazard ratios and 95% confidence intervals of

PFS and OS will be based on stratified Cox proportional hazard regression model with treatment arm as the only covariate.

Descriptive statistics will be used to characterize quality of life (QOL) questionnaire responses [EORTC QLQ C-30].

All patients administered at least one dose of IMMU-132 or TPC will be included in the evaluation of safety. Safety and tolerability will be evaluated from adverse events, standard safety laboratories (CBC with differential and platelet count, serum chemistries, and urinalysis), physical examination, ECG and vital signs. Adverse events will be classified according to the MedDRA systems of preferred terms and system organ class, and all adverse events and abnormal laboratories will be classified for severity using NCI CTCAE v4.03 toxicity grades. Descriptive statistics will be used to characterize adverse events, and abnormal laboratories.

The frequency of AEs will be tabulated by MedDRA System Organ Class (SOC) and Preferred Term for each treatment group. AEs leading to death or to discontinuation from treatment, as well as all SAEs will be summarized separately. The reasons for discontinuation will also be summarized for each treatment group using frequency distributions. Both actual and change-from-baseline data on vital signs will be summarized using descriptive statistics by treatment group for each study time-point. Routine safety laboratories, based on hematology and serum chemistry data, will be listed by patient and summarized by descriptive statistics for each treatment group, if appropriate. Laboratory test results will be graded according to CTCAE severity grade when applicable. The frequency distribution of the worst CTCAE grade observed will be tabulated for each parameter by treatment group. For parameters for which a CTCAE scale does not exist, the proportion of patients with abnormal values will be summarized by treatment group. Similarly, data on anti-drug antibody responses will be listed and summarized by descriptive statistics. Furthermore, the *UGT1A1* genotype will be determined for patients receiving sacituzumab govitecan at baseline and compared to hematological toxicity and incidence of diarrhea.

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serum concentration data.

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LIST OF ABBREVIATIONS

AE	adverse event
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
CFR	Code of Federal Regulation
CNS	central nervous system
CR	complete response
CRF	case report form
CT	computed tomography imaging
CTCAE	common terminology criteria for adverse events
DNA	deoxyribonucleic acid
DLT	dose-limiting toxicity
DSMC	Drug Safety and Monitoring Committee
ECG	electrocardiogram
EORTC	European Organization for Research and Treatment of Cancer
FDA	Food and Drug Administration
GCP	good clinical practice
GI	gastrointestinal
HAHA	human anti-human antibody
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
IATA	International Air Transport Association
ICH	International Committee on Harmonization
IEC	independent ethics committee
IgG	immunoglobulin G
IND	Investigational New Drug
IRB	Institutional Review Board
IRC	Independent Review Committee
IULN	institutional upper limit of normal
IMMU-132	Company Code for sacituzumab govitecan
LA	Locally advanced
LDH	lactate dehydrogenase
mAb	monoclonal antibody
MRI	magnetic resonance imaging

MTD	maximum tolerated dose
NSAE	non-serious adverse event
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
NSAID	non-steroidal anti-inflammatory drug
OR	Objective Response, OR = CR + PR
ORR	Objective (overall) response rate
OS	overall survival
PBS	phosphate-buffered saline
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
QLQ-30	quality of life questionnaire version 30
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RBC	red blood cell
SAE	serious adverse event
SCLC	small cell lung cancer
SD	stable disease
TNBC	Triple-Negative Breast Cancer
TPC	treatment of physician's choice
Trop-2	Trophoblastic cell-surface antigen
TTP	time to progression
WBC	white blood cells

1. INTRODUCTION

1.1. Description of the Investigational Product

SN-38, a topoisomerase I inhibitor, is the active metabolite of irinotecan, which is approved as a single agent for colorectal cancer and included in treatment regimens such as FOLFIRI (Zaanan 2011). Only 5% of irinotecan is converted to the active SN-38 form by esterase activity residing primarily in the liver, albeit there are esterases in the tumor that can cleave irinotecan to SN-38 (Mathijsen 2001). Its catabolism in the liver results in its transport through the bile duct into the intestines, resulting in GI toxicity.

In an attempt to improve the bioavailability of SN-38, Immunomedics, Inc. developed a procedure for coupling SN-38 to an antibody that retains the antibody molecular integrity and specific binding (Govindan 2009; Moon 2010). In murine models bearing human tumor xenografts, one particular linker with an SN-38 release half-life of 1.0 to 1.5 days was found to have the best therapeutic response. Importantly, significant anti-tumor effects were possible at doses that were completely non-toxic to the mice.

Sacituzumab govitecan (Company Code: IMMU-132) is an antibody-drug conjugate (ADC) composed of the following three compounds:

1. The humanized monoclonal antibody, hRS7 IgG1κ, binds to Trop-2 (trophoblastic cell-surface antigen, also known as EGP-1, epithelial glycoprotein-1). It is a cell surface, transmembrane calcium signal transducer glycoprotein belonging to the *TACSTD* gene family that is highly expressed in many epithelial cancers, particularly metastatic sites (Alberti 2007), with much lower expression in normal tissues (Trerotola 2010). Trop-2 has been implicated in oncogenesis, often being found in more aggressive tumors (Fang 2009). The antibody was initially developed as a murine monoclonal antibody by the immunization of mice with a fresh specimen of a human lung cancer. The properties of the parent murine antibody have been extensively described (Basu 1995; Stein 1994; Shih 1995; Stein 1993; Stein 1995; Stein 1997).
2. The camptothecin-derived agent, SN-38, a topoisomerase 1 inhibitor.
3. A linker, with the company designation, CL2A, which binds SN-38 to the antibody.

IMMU-132 is prepared at a ratio of 7 to 8 molecules of SN-38 per molecule of the anti-Trop-2 antibody, hRS7 (Goldenberg 2015). For clinical use, 10 mg/mL are formulated in 25 mM MES buffer, pH 6.5, together with the other excipients (25 mM trehalose, 0.01% Polysorbate 80). It is then lyophilized at 200 mg/vial. IMMU-132 is supplied in 50-mL clear glass vials to be stored under refrigerated conditions (2-8ºC) until used. Since the formulated drug product contains no preservative, vials should be used only once and within eight hours of reconstitution.

Each 200 mg vial of IMMU-132 is reconstituted with 20 ml of saline and then further diluted with saline for intravenous administration so that the final concentration of IMMU-132 is in the 1.1-3.4 mg/ml range.

IMMU-132 should be administered at a starting dose of 10 mg/kg on days 1 and 8 of a 21-day cycle. Dose reductions and dose delays are linked to certain toxicity.

1.2. Summary of Non-Clinical and Clinical Findings

1.2.1. Non-Clinical Studies

The anti-tumor activity of the hRS7-SN-38 conjugate was examined in mice bearing a variety of human epithelial cancer xenografts, where it was shown to have significant anti-tumor effects compared to free SN-38, irinotecan, or an irrelevant IgG-SN-38 conjugate (Cardillo 2011; Goldenberg 2015; Cardillo 2015). There were significant changes in liver transaminases that were returning to normal levels 2 weeks after treatment in mice (Cardillo 2011).

While Trop-2 is highly conserved among various species, the hRS7 antibody does not bind to murine Trop-2, but an immunohistology study of cynomolgus monkey tissues showed hRS7 bound to Trop-2 and had a similar distribution as found in humans (Cardillo 2011). Thus, a toxicology study was performed with IMMU-132 in monkeys with the purpose to assess the dose-limiting toxicity and to determine if Trop-2 expressing normal tissues would limit the use of this conjugate. Two doses were administered within one week (3 days apart) at a cumulative amount of 120 and 240 mg/kg (1.92 and 3.84 mg/kg of SN-38; human equivalent dose of the conjugate was 38.7 and 77.4 mg/kg). Pharmacokinetic analysis of the clearance of the hRS7 IgG and SN-38 (as free SN-38, total SN-38, and a derived IgG-bound SN-38) showed the IgG cleared at what appeared to be an expected rate (e.g., 30% cleared over 1 day, terminal half-life ~5 days). The clearance parameters for the total and IgG-bound SN-38 were very similar, with a half-life of ~13 h, which reflects the clearance of the IgG and the fact that the SN-38 is released from the conjugate at a rate of ~50% every 20 h. As expected, the AUC for the total and IgG-bound SN-38 was nearly 15-times higher than the free SN-38, which had a half-life of ~25 h, similar to the rate reported for SN-38 released from irinotecan. Thus, the conjugate is capable of liberating low concentrations of SN-38 in the serum at a slow and sustained rate.

In cynomolgus monkeys administered the cumulative dose of 120 mg/kg, there was evidence of myelosuppression within 3 days, but the decrease in counts did not achieve gradable levels and were completely restored within 10-14 days. No significant change in serum chemistries or tissue pathology was noted. At the 240 mg/kg, severe gastrointestinal (GI) and hematological toxicities occurred; therefore, the maximum tolerated dose had been exceeded. The conjugate displayed a similar toxicity profile as irinotecan, with major GI and hematological toxicity. Importantly, there were no serious histopathological changes to tissues with known hRS7 binding in the monkey, with the exception of mild to moderate hemorrhage of the endometrium and atrophy of the endometrial glands that were showing recovery at the time the study was terminated. ***(See Investigator Brochure for additional information on IMMU-132)***

In vitro studies in 2 triple-negative breast cancer cell lines, one expressing Trop-2 and another being Trop-2-negative, showed that double-stranded DNA breaks only occurred in the Trop-2-expressing cell line after a brief exposure (1 h) with IMMU-132 (Goldenberg 2015). This study confirmed that SN-38 delivery by the specific IMMU-132 conjugate was necessary for the therapeutic effect, with a non-targeting conjugate having nearly 3-fold less double-stranded DNA breaks than IMMU-132-treated Trop-2-expressing cells. In mice bearing Trop-2-expressing human tumor xenografts that were given irinotecan or IMMU-132, SN-38 levels in the tumors exposed to IMMU-132 were as much as 130-fold more than in the irinotecan-treated animals, illustrating the superior targeting of the conjugate to deliver SN-38 to tumors (Sharkey 2015). In

addition, these studies showed that the SN-38 was protected from glucuronidation while coupled to the IgG, and since the linker was coupled to SN-38's lactone ring, this also preserves SN-38 in its most active form until it is released from the conjugate. This reduced glucuronidation is believed to explain the low incidence of severe diarrhea found in the clinical trials. Thus, IMMU-132 appears to be a more effective vehicle for delivering SN-38 than irinotecan, and potentially less toxic in terms of severe diarrhea.

1.2.2. Clinical Study

Study IMMU-132-01 entitled "A Phase I/II Study of IMMU-132 (hRS7-SN38 Antibody-Drug Conjugate) in Patients with Epithelial Cancer," conducted under IND 115621 (ClinicalTrials.gov identifier, NCT01631552), is the only ongoing clinical investigation of the safety and efficacy of IMMU-132 in patients with cancer. This is a Phase I/II, open-label multi-center, US-only, study of IMMU-132 in previously-treated patients with advanced, metastatic, epithelial tumors. The primary objective of this study is to 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 cancer. The secondary objectives are to obtain initial data concerning pharmacokinetics, immunogenicity, and efficacy with this dosing regimen.

Briefly, the study population is constituted of males or non-pregnant, non-lactating, females ≥ 18 years of age, able to give written informed consent, if they have documented epithelial cancer that involves any of the following tumor types: ovarian, cervical, endometrial, breast (triple-negative and non-triple-negative), prostate (hormone refractory), lung [non-small cell (NSCLC) and small cell (SCLC)], head and neck (squamous cell), esophageal, colorectal, gastric, pancreas, renal (clear cell), urothelial, hepatocellular, glioblastoma multiforme and thyroid (follicular) cancers. There is no Trop-2 selection for enrollment. Patients must have metastatic disease and have either relapsed after receiving or were refractory to at least one standard chemotherapy regimen for their disease, with measurable disease by CT or MRI at the time of treatment, but no single lesion ≥ 7 cm in diameter.

1.2.2.1. Phase I

In the completed Phase I portion of Study IMMU-132-01, doses as high as 18 mg/kg were given on day 1 and 8 of a 21-day treatment cycle (Starodub 2015). Neutropenia was the dose-limiting toxicity at this level, with the MTD declared to be 12 mg/kg. Most of the other adverse events at all dose levels were Grade 2 or lower. Fatigue, alopecia and occasional mild to moderate diarrhea were some of the more common non-hematological toxicities, with two patients reporting a rash. While 12 mg/kg was considered the MTD, there was tendency for patients treated at this level to have delays in their dose schedule, as well as dose reductions. Therefore, in order to continue treatment with minimal delays or reductions, IMMU-132 treatment starting at either 8 or 10 mg/kg (days 1 and 8 of a 21-day cycle) was selected for evaluation in the Phase II portion of this study, with particular emphasis to enroll patients with triple-negative breast, small and non-small cell lung cancers, and secondarily patients with esophageal and urothelial cancers.

Table 1 below indicates the incidence of drug-related grade 3+ adverse events observed at 10 mg/kg in all patients/all tumors enrolled at the 10 mg/kg dose level. Most frequent drug-related

grade 3+ adverse events were neutropenia (18%), diarrhea (6%), febrile neutropenia (5%), fatigue (5%), leukopenia (5%) and anemia (4%).

Table 1: Incidence of Drug-Related Grade 3+ Adverse Events at 10 mg/kg IMMU-132

	10 mg/kg (N = 109)
Neutropenia	18%
Diarrhea	6%
Febrile neutropenia	5%
Fatigue	5%
Leukopenia	5%
Anemia	4%

1.2.2.2. Phase 2

As of June 30, 2017, 110 patients with relapsed/refractory TNBC were treated with sacituzumab govitecan 10 mg/kg on days 1 and 8 every 21 days until progression or unacceptable toxicity. The age range of all patients was from 31 to 81 years old with a median age of 55 years old. The patient population were heavily pre-treated; 59% of patients were treated in the 4th line setting and beyond. Some patients received up to 10 prior therapies and 75% of patients had received prior platinum agents.

The most common adverse events were neutropenia, nausea, and diarrhea (see Table 2). Most adverse events were managed with supportive medication or dose modifications. Majority of patients were able to continue at the 10 mg/kg dose, 25% of patients had dose modifications, predominantly to 7.5 mg/kg. Only two patients discontinued treatment due to adverse events (grade 3 transient infusion reaction and grade 2 fatigue). There were no treatment-related deaths.

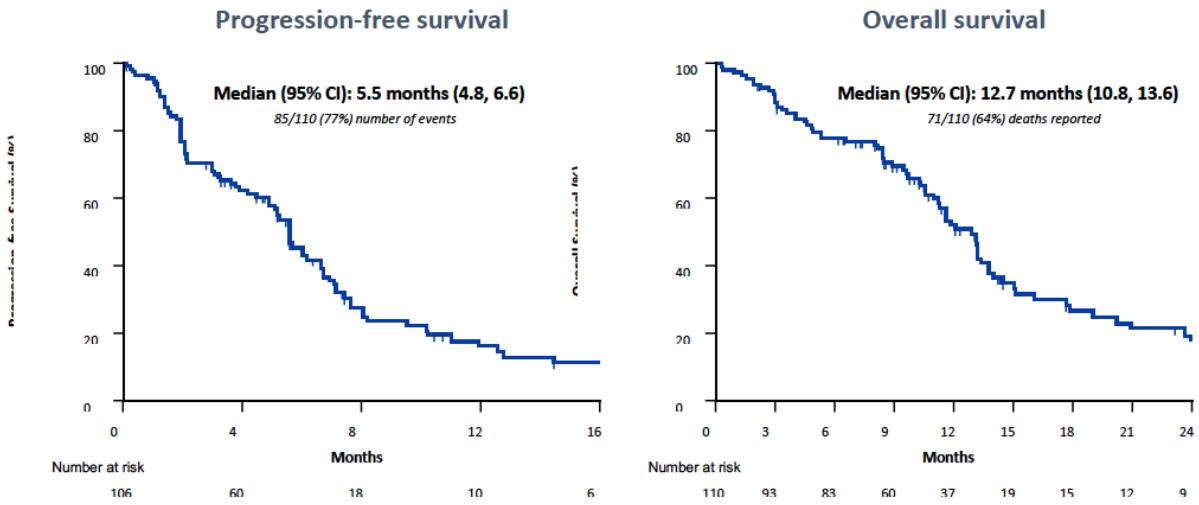
Table 2: Drug-related adverse events in TNBC patients.

Body system	Adverse event (AE)	All grades	Grade 3 or 4
Hematologic	Neutropenia	63%	41%
	Febrile neutropenia	8%	7%
	Anemia	52%	10%
	Leukopenia	24%	14%
Gastrointestinal	Nausea	63%	5%
	Diarrhea	56%	8%
	Vomiting	46%	5%
	Constipation	32%	1%
Other	Fatigue	50%	7%
	Alopecia	36%	NA
	Decreased appetite	30%	0%
	Hyperglycemia	23%	4%
	Hypomagnesemia	21%	1%
	Hypophosphatemia	15%	8%

Interim Summary of Efficacy (Bardia 2015, Bardia 2017)

Out of 110, 102 patients were assessable. Three patients achieved complete responses and 34 partial responses, for an objective response rate of 34% by the investigator (RECIST 1.1). Six patients achieved CR and 28 patients achieved PR by the blinded independent central review, for an objective response rate of 31%. Clinical benefit rate (CR+PR+SD ≥6 months) was 45% (50/110). 74% (75/102) of patients experienced a reduction of target lesions (sum of diameters). 8 patients withdrew prior to assessment (4 PD, 4 MRI brain metastases). The median time to onset of response was 2 months with a median duration of response of 7.6 months. Importantly, 9 patients were progression free for more than 1 year from start of treatment including 4 patient for 2 to 3 years and 12 patients were continuing treatment as of June 30, 2017 data cut-off. The median PFS was 5.5 months and the median OS was 12.7 months at the data cutoff date of June 30, 2017. Patients benefit from sacituzumab govitecan treatment irrespective of age, onset of metastatic disease, or number of prior regimens.

Figure 1: Progression-free survival and overall survival



1.3. Summary of Potential Risks

In patients with TNBC, the following adverse events (AEs), all grades and regardless of relationship to IMMU-132, have been observed at the following rates (by order of frequency in each category):

- **Very likely: (≥ 40%):** nausea, vomiting, diarrhea, neutropenia, anemia, fatigue
- **Likely (20%-39%):** alopecia, constipation, decreased appetite, leukopenia hyperglycemia, hypomagnesemia
- **Less Likely (10%-<20%):** hypophosphatemia, febrile neutropenia

1.4. Description of Study Population

TNBC is a serious disease, with an annual incidence estimated to be about 40,000 people (20,000 for metastatic TNBC) in the United States, and with a median survival of 10-13 months for metastatic TNBC (Andre 2012). This incidence is based upon the estimate that between 10%

and 20% of women with breast cancer have TNBC, since their tumors do not express estrogen receptor, progesterone receptor, or HER2/neu (Mancini 2014). Therefore, metastatic TNBC is insensitive to most of the available targeted therapies for breast cancer treatment, including HER2-directed therapy (such as trastuzumab), and endocrine therapies (such as tamoxifen or the aromatase inhibitors).

There is currently no single standard chemotherapy to treat patients with relapsed/refractory metastatic TNBC. Duration of response is usually short, with rapid relapse, and visceral and brain metastases being very common.

In TNBC patients treated with capecitabine, median PFS was 1.7 months (Perez 2010), and it was 2.9 months for gemcitabine combined with carboplatin in patients treated with up to 2 prior chemotherapies (O'Shaughnessy 2014).

In a small cohort of 22 second-line TNBC patients (33% chemotherapy-naïve and one median prior chemotherapy regimen) treated with nab-paclitaxel, median PFS was 3.7 months (Forero-Torres 2015).

Median PFS was 2.9 months in 86 metastatic TNBC patients treated with cisplatin or carboplatin, and who received no more than one prior chemotherapy (Isakoff 2015).

1.5. Rationale for Dose Regimen

Most patients in IMMU-132-01 study have been treated with 8 or 10 mg/kg doses. There was no major difference in safety between these two doses, but there was a trend for better efficacy with 10 mg/kg dosing, which was therefore selected for this study.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of this study is to compare the efficacy of sacituzumab govitecan to the TPC as measured by independently-reviewed IRC 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.

2.2. Secondary Objectives

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

- PFS for the ITT population
- 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. STUDY DESIGN

3.1. Study Overview

This is a Phase III, randomized, open-label, multicenter (up to 100 centers) study of IMMU-132 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. A table of approved or standard therapeutic regimens for TNBC is included in Appendix 1. 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, and Europe will be randomized 1:1 to the following treatment arms:

- Sacituzumab govitecan (10 mg/kg on Days 1 and 8 of 21-day cycles)
- TPCdetermined before randomization from only one of the following 4 treatment regimens, and administered for metastatic breast cancer as per label or NCCN guidelines below or with dose modifications if too toxic (see Section 6.5). No combination of the four choices is permitted.
  - Eribulin (1.4 mg/m^2 intravenously on Days 1 and 8 of a 21-day cycle for North America sites, 1.23mg/m^2 intravenously on Days 1 and 8 of a 21-day cycle for European sites)
  - Capecitabine (1000-1250 mg/m^2 orally twice daily on Days 1-14 of a 21-day cycle)
  - Gemcitabine (800-1200 mg/m^2 intravenously on Days 1, 8 and 15 of a 28-day cycle)
  - Vinorelbine (25 mg/m^2 intravenously on Day 1 weekly (Note: eligible patients with Grade 2 peripheral neuropathy should not be prescribed vinorelbine as TPC)

Patients will be stratified at randomization by:

- Number of prior treatments for advanced disease (2-3 vs >3)
- North America vs Rest of World
- Known, baseline brain metastasis (yes or no)

Patients will be treated until progression requiring discontinuation of further treatment, unacceptable toxicity, study withdrawal, or death, whichever comes first. Tumor progression leading to treatment withdrawal will be assessed by the investigator. Patient who discontinue treatment for other reasons than PD should a MRI/CT scan performed within 4 weeks of study treatment discontinuation. No crossover to IMMU-132 treatment will be allowed at time of progression in the TPC arm.

Clinical sites will use standard ASCO/CAP criteria for the pathological diagnosis of TNBC, defined as negative for estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2). Receptor results will be based on local assessment of the most recent analyzed biopsy (or other pathology specimen). HER2 negative is defined as one of the following: 0 or 1+ by immunohistochemistry (IHC), or if IHC 2+, then fluorescence *in situ* hybridization (FISH) ratio of *HER2* gene: chromosome 17 being less than 2, as per standard guidelines (Wolff 2013). ER- and PR-negative is defined as < 1% of cells expressing hormonal receptors by IHC, as per standard guidelines (Hammond 2010).

CCI [redacted]

This study will utilize an intent-to-treat analysis.

Screening evaluations within 28 days of the scheduled start of treatment include signature of informed consent, patient eligibility determination, BRCA 1&2 mutational status, if known, medical/surgical history, physical examination with vital signs and performance evaluation, prior and concomitant medications, local histology review to confirm TNBC diagnosis, CT or MRI scans (chest, abdomen, pelvis, with contrast as appropriate) with additional imaging of other involved/suspected areas. Patients with known or suspected brain metastasis must have a brain MRI and must be documented to have had stable CNS disease for at least 4 weeks Target and non-target lesions must be determined by the clinical site at time of randomization. CBC (including platelet count, with WBC differential in absolute cell counts), routine serum chemistries, urinalysis, ECG and serum samples for anti-drug antibodies will be also performed. In women of childbearing potential, a urine or serum βHCG is also required within one week of treatment. CBC (including platelet count, with WBC differential in absolute cell counts), routine serum chemistries will be repeated within 72 hours of cycle 1, day 1 to ensure eligibility.

IMMU-132 (10 mg/kg) is administered in 21-day treatment cycles with once-weekly dosing the first two weeks (days 1 and 8) and no dosing the third week. Dosing is based on patient's body weight on Day1 of each cycle (or at each dosing day if change in body weight is > 10% or if

required by institutional policy). TPC dosing is based upon body surface area as per local standard of care. Treatment of all patients may continue until subsequent imaging documents disease progression from the pre-study assessment requiring discontinuation. NCI CTCAE v4.03 is used to grade all adverse events and to provide dose reduction, delay or cessation guidelines in the event of treatment-related toxicity. Growth factors and other supportive care are allowed and are strongly encouraged to be used aggressively including for prophylaxis when medically necessary any time during treatment with IMMU-132 or the TPC. Refer to guidelines in Section 6.4.6 and Table 6.

Toxicity guidelines for patients receiving TPC should follow local standard of care. If a patient randomized to receive IMMU-132 experiences ≥ Grade 2 neutropenia or ≥ Grade 2 GI toxicity prior to starting on the first treatment day (Cycle 1 Day 1), the treatment initiation should be withheld until resolved to ≤ Grade 1. If recovery to ≤ Grade 1 requires more than a 3-week delay, the patient should come off the study. In subsequent treatment cycles, if a patient experiences ≥ Grade 3 neutropenia or ≥ Grade 3 GI toxicity, IMMU-132 should be withheld until resolved to ≤ Grade 1 and patients will be assessed at least weekly (biweekly for Grade 4 toxicities). If recovery to ≤ Grade 1 requires more than a three-week delay, the patient should come off the study. IMMU-132 will be permanently discontinued for a patient in the event of any ≥ Grade 3 infusion reactions which occurs after pre-medication with antihistamines, H2 blockers and steroids. In the event of other ≥ Grade 3 treatment-related toxicity at the time of a scheduled treatment day, IMMU-132 will be held and patients will be assessed at least weekly (biweekly for Grade 4 toxicities). If recovery to ≤ Grade 1 delays the next dose by only one week, treatment may resume without dose reduction; however, patients should be administered growth factor support such as gCSF. If recovery of non-hematologic toxicity to ≤ Grade 1 delays the next dose by 2 or 3 weeks, treatment must be resumed at a reduced dose (see Table 6). If recovery to ≤ Grade 1 requires more than three weeks delay, treatment must be permanently discontinued. If recovery of hematologic toxicity (neutropenia) to ≤ Grade 1 delays the next dose by 1 week, growth factors should be added as per Section 6.4.6, or as medically necessary to prevent dose delays and dose reduction.

Patients who exhibit an excessive cholinergic response to IMMU-132 or TPC treatment (e.g., abdominal cramping, diarrhea, salivation, etc.) can receive appropriate premedication (e.g., atropine) for subsequent treatments.

Study procedures during treatment include physical examination and vital signs, CBC (with differential and platelet count), routine serum chemistries, urinalysis, serum samples for CCI ECG, anti-drug antibody response, concomitant medications, and adverse events. Starting with the initial dose of IMMU-132 or TPC, CT or MRI examinations are to be obtained every 6 weeks for 36 weeks, then every 9 weeks thereafter, until the occurrence of progression of disease requiring discontinuation of further treatment. Responses identified prior to 36 weeks on study require confirmatory scans, which will be performed at the next scheduled scanning time-point (6 weeks later). For responses after 36 weeks, confirmatory scans will be done within 6 weeks of the scan showing the onset of response. For each patient, the same imaging technique should be used throughout for tumor assessment. The decision to discontinue the patient for tumor progression will be made by the investigator based on local imaging scan results. Patients on either treatment arm who have progression of disease assessed for the first time during the study but who, in the opinion of the treating physician are deriving continued clinical benefit from IMMU-132 or TPC treatment, relative to other available treatment options, may continue to

be treated based on physician discretion as long as they continue to meet eligibility criteria. Clinical progression leading to patient discontinuation should be documented also by imaging scan of target lesions if possible. Patients who discontinue for other reasons than PD should a MRI/CT scan performed within 4 weeks from study treatment discontinuation so that documentation can be reviewed by the IRC. Patients who discontinue treatment due to toxicity will continue with radiologic response assessments according to the protocol-required schedule, until progression of disease or initiation of new therapy. Additional CT or MRI may be performed at the discretion of the physician to assess disease status as medically indicated.

Quality of life questionnaires will need to be completed at baseline, the beginning of every cycle, and at the final study visit.

Within four weeks after discontinuing treatment, the patient will undergo an end-of-study evaluation. All patients, including those prematurely terminating study participation, will be followed every 4 weeks for survival follow-up. This may be by telephone and will include documentation of any further anti-cancer therapy they may receive. Survival status may be also documented from public databases (e.g., Social Security database), as allowed by local regulations.

3.2. Data Safety Monitoring Committee (DSMC)

An independent DSMC will be convened at regular intervals to assess the progress of this study, and review safety and progression data, per an adopted DSMC charter. In the absence of unexpected safety concerns, , the study will continue.

4. PATIENT POPULATION

The study population comprises previously-treated patients with relapsed/refractory metastatic TNBC. Eligible patients must satisfy the following entry criteria at time of randomization:

4.1. Inclusion Criteria

1. Female or male patients, ≥18 years of age, able to understand and give written informed consent.
2. Histologically or cytologically confirmed TNBC per ASCO/CAP criteria, based on the most recent analyzed biopsy or other pathology specimen. Triple negative is defined as <1% expression for estrogen receptor (ER) and progesterone receptor (PR) and negative for human epidermal growth factor receptor 2 (HER2) by in-situ hybridization.
3. Metastatic disease documented by CT or MRI imaging.
4. Measurable disease by CT or MRI as per RECIST 1.1. Bone-only disease is not **permitted.**
5. **Brain MRI must be done for patients with brain metastasis and patient must have** had stable* CNS disease for at least 4 weeks.* A maximum of 15% (N=74) of patients with brain metastases will be included in this trial.

   *"Stable" brain mets may be defined as:

- Prior local treatment by radiation, surgery, or stereotactic surgery
- Imaging – stable or decreasing size after such local treatment
- Clinically stable signs and symptoms
- ≥2 weeks from discontinuation of anti-seizure medication.

Corticosteroid (if needed) - dose should be stable, or decreasing for at least 2 weeks before randomization. Steroid dose should be 20 mg or less of prednisone/prednisolone daily, or equivalent of a different steroid.

6. At least 2 weeks beyond high dose systemic corticosteroids (however, low dose corticosteroids ≤ 20 mg prednisone or equivalent daily are permitted provided the dose is stable for 4 weeks).
7. Refractory to or relapsed after at least two prior standard of care chemotherapy regimens for unresectable, locally advanced or metastatic breast cancer (Appendix 1). (These regimens will qualify regardless of triple-negative status at the time they were given. There is no cap on the number of prior chemotherapies for locally advanced or metastatic disease and earlier adjuvant or neoadjuvant therapy 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).
    a. 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.
    ~~b.~~ All patients must have been previously treated with a 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.
8. Eligible for one of the chemotherapy options listed as TPC (Eribulin, capecitabine, gemcitabine, or vinorelbine) as per investigator assessment.
9. ECOG performance score of 0 or 1 (Appendix 2).
10. Adequate hematology without transfusional support (hemoglobin > 9 g/dL, ANC > 1,500 per mm^3, platelets > 100,000 per mm^3). Blood transfusion or growth factor support is not allowed within 14 days prior to screening labs.
11. Adequate renal and hepatic function (creatinine clearance of > 60 ml/min, may be calculated using Cockcroft-Gault equation; bilirubin ≤ 1.5 IULN, AST and ALT ≤ 2.5 x IULN or ≤ 5 x IULN if known liver metastases and serum albumin ≥3 g/dL).
12. Recovered from all toxicities to Grade 1 or less by NCI CTCAE v4.03 (except alopecia or peripheral neuropathy that may be Grade 2 or less) at the time of randomization. Patients with Grade 2 neuropathy are eligible but may not receive vinorelbine as TPC.
13. Patients must have completed all prior cancer treatments at least 2 weeks* prior to randomization including chemotherapy (includes also endrocrine treatment), radiotherapy

and major surgery. **Prior antibody treatment for cancer must have been completed at least 3 weeks prior to randomization*.

14. Prior investigational agents are permitted, provided completion according to the timeframes above.
15. Patients must have a life expectancy of 3-months or greater, in the opinion of the investigator.

4.2. Exclusion Criteria

1. Women who are pregnant or lactating.
2. Women of childbearing potential or fertile men unwilling to use highly effective* contraception during study and up to three months after treatment discontinuation in women of child-bearing potential and six months in males post last study drug.
3. Patients with Gilbert's disease.
4. Patients with non-melanoma skin cancer or carcinoma *in situ* of the cervix are eligible, while patients with other prior malignancies must have had at least a 3-year disease-free interval.
5. Patients known to be HIV positive,
6. Patients with hepatitis B positive, or hepatitis C positive infection**.
7. Known history of unstable angina, MI, or CHF present within 6 months of randomization or clinically significant cardiac arrhythmia (other than stable atrial fibrillation) requiring anti-arrhythmia therapy.
8. Known history of clinically significant active COPD, or other moderate-to-severe chronic respiratory illness present within 6 months of randomization.
9. Prior history of clinically significant bleeding, intestinal obstruction, or GI perforation within 6 months of randomization.
10. Infection requiring antibiotic use within one week of randomization.
11. Patients with active chronic inflammatory bowel disease (ulcerative colitis, Crohn disease) and patients with a history of bowel obstruction
12. Patients who have received a live vaccine within 30 days of randomization
13. Patients who previously received irinotecan.
14. Rapid deterioration during screening prior to randomization, e.g. significant change in performance status, ≥ 20% decrease in serum albumin levels, unstable pain symptoms requiring modifications in analgesic management.
15. Other concurrent medical or psychiatric conditions that, in the Investigator's opinion, may be likely to confound study interpretation or prevent completion of study procedures and follow-up examinations.

*Highly effective is defined as i.e. Combined (estrogen and progestogen containing) hormonal contraception: oral, intravaginal, transdermal, progestin -only hormonal

contraception associated with inhibition of ovulation: oral, injectable, implantable, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomized partner, sexual abstinence). Abstinence refers to 'True abstinence' which means it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptotherma, post-ovulation methods), declaration of abstinence for the duration of exposure to study treatment, and withdrawal are not acceptable methods of contraception.

** In patients with a history of HBV, hepatitis B core antibody (HBcAb) testing is required and if positive, then HB DNA testing will be performed and if positive the patient will be excluded.

4.3. Concomitant Medications and Procedures

- No anti-cancer therapies, aside the study drug (IMMU-132)/TPC are permitted during this study. However, palliative and/or supportive medications, such as bone-modifying medications (bisphosphonates or denosumab), and/or procedures such as radiation and surgery will be allowed at the investigator's discretion. If a patient requires palliative radiotherapy for brain metastases, IMMU-132 or TPC should be interrupted one week before the procedure and reinstated two weeks after the procedure, provided that palliative radiotherapy is not indicated for tumor progression, in which case the patient will have to be discontinued for the trial.
- Premedication for prevention of infusion reaction with antipyretics, H_1 and H_2 blockers are strongly recommended before sacituzumab govitecan infusions. Corticosteroids (50 mg hydrocortisone or equivalent P.O. or I.V.) may be added if necessary and were used in approximately two-thirds of patients from the phase 2 trial. Premedication according to established guidelines with a two or three drug combination regimen (e.g. dexamethasone with either a 5-HT3 receptor antagonist or a NK_1 receptor antagonist, as well as other drugs as indicated) for prevention and treatment of chemotherapy-induced nausea and vomiting (CINV) is strongly recommended (see below for information on medication affecting QT interval).
- Additional antiemetics, sedatives, and other supportive measures may also be employed as clinically indicated. In addition, all patients should be given medications for use at home for prevention and treatment of nausea, vomiting and diarrhea. Patients should be instructed as to how to aggressively treat nausea and vomiting with these out-patient medications.
- At the onset of diarrhea, promptly initiate loperamide, 4 mg initially followed by 2 mg with every episode of diarrhea for a maximum of 16 mg daily. Discontinue loperamide 12 hours after diarrhea resolves. Additional supportive measures (e.g. fluid and electrolyte substitution) may also be employed as clinically indicated. All patients should be given take-home medications with clear instructions for treatment of diarrhea.
- Patients who exhibit an excessive cholinergic response to sacituzumab govitecan treatment (e.g., abdominal cramping, diarrhea, salivation, etc.) can receive appropriate premedication (e.g., atropine) for subsequent treatments.

- Patients receiving IMMU-132 who experience neutropenia will be prescribed growth factors as per Section 6.4.6 as clinically indicated, including prophylactically. Other hematopoietic growth factors or blood transfusions are allowed at physician's discretion. Patients on TPC may receive G-CSF, other hematopoietic growth factors or blood transfusions per physician discretion.
- High dose systemic corticosteroids are not allowed within 2 weeks of randomization. Low dose, stable doses of corticosteroids ≤ 20 mg prednisone or equivalent daily are permitted if patient entered the study on low dose steroids for their treated brain metastasis, or if medically indicated as part of their premedications for infusions. (topical steroids and corticosteroid inhalers are allowed).
- Antiemetics, anti-diarrheal medications, cytokines or blood transfusions should be administered as clinically necessary.
- Other supportive and palliative care is allowed as medically warranted.

CYP3A4 inducers and inhibitors

There is a potential for altered toxicity profile from common medications and foods with possible potent effects on liver metabolism of drugs, such as irinotecan and SN-38. As such, all patients should be advised to avoid the following medications while on study:

CYP 3A4 Inhibitors		**CYP 3A4 Inducers**	
Amiodarone	Imatinib	Aminoglutethimide	Oxcarbazepine
Amprenavir	Indinavir	Bexarotene	Phenobarbital
Aprepitant	Isoniazid	Bosentan	Phenytoin
Atazanavir	Itraconazole	Carbamazepine	Primidone
Chloramphenicol	Ketoconazole	EfavirenzFosphenytoin	Rifabutin
Clarithromycin	Lapatinib	Griseofulvin	Rifampin
Conivaptan	Miconazole	Modafinil	Rifapentine
Cyclosporine	Nefazodone	Nafcillin	St. John's wort
Darunavir	Nelfinavir	Nevirapine	
Dasatinib	Posaconazole		
Delavirdine	Ritonavir		
Diltiazem	Quinupristin		
Erythromycin	Saquinavir		
Fluconazole	Tamoxifen		
Fluoxetine	Telithromycin		
Fluvoxamine	Troleandomycin		
Fosamprenavir	Verapamil		
Grapefruit juice	Voriconazole		

4.4. Patients receiving anticoagulants

As irinotecan and SN-38 may affect CYP2C9, patients receiving Coumadin or warfarin may be at risk and those patients should be more intensively monitored for their Coumadin/warfarin during study treatment.

4.5. Patients receiving QT prolonging drugs

Patients receiving QT prolonging drugs should be carefully monitored as some of the study medications may further increase the QT interval. When possible, the investigator should consider avoiding the following medications and using alternative medications that do not affect the QT interval. While 5-HT_3 receptor antagonist compounds can prolong the QT interval, they have been found to be effective in treatment/prophylaxis of nausea associated with sacituzumab govitecan and investigators are advised to monitor patients closely when used.

Medications affecting QT interval	
Amantadine	Methadone
Amiodarone	Moxifloxacin
Azithromycon	Nilotinib
Chloroquine	Ondansetron
Chlorpromazine	Pentamidine
Cisapride	Procainamide
Clarithromycin	Quetiapine
Clozapine	Quinidine
Disopyramide	Resperidone
Dofetilide	Roxithromycin
Dolasteron	Sertinodole
Domperidone	Sotalol
Erythromycin	Tamoxifen
Escitalopram	Telithromycin
Granisetron	Terfaenadine
Haloperidol	Venlaxafine
Lapatinib	Zisprasidone
Lithium	

Guidance for Industry, E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) October 2005, ICH.

Geoffrey K Isbister and Colin B Page. Drug induced QT prolongation: the measurement and assessment of the QT interval in clinical practice. Br J Clin Pharmacol. 2013 Jul; 76(1): 48–57.

5. STUDY PROCEDURES

Unless otherwise specified, collection windows for study time points are within ± 2 days for the treatment schedule and ± 5 business days for response assessments. Planned deviations in treatment schedule are allowable up to 7 days due to holidays, vacation or personal reasons.

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Serum and whole blood samples obtained for anti-drug antibodies, CCI [redacted] and *UGT1A1* levels are to be shipped to the Sponsor's designee who will perform these assays. Instructions for shipping these blood samples are given in Appendix 3. Otherwise, all procedures are to be performed locally at each study site.

5.1. Informed Consent

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

A table of approved or standard therapeutic regimens is included in Appendix 1. *Patients must be informed that alternatives to receiving IMMU-132 are available prior to consenting to participate in this trial.*

If the patient agrees to participate, the informed consent form must be signed, dated, and witnessed, with a copy given to the subject.

5.2. Patient Registration

At such time as a patient has been deemed eligible for the study and all required screening evaluations have been completed the patient can be randomized. This will be done via an interactive web-based response system.

Randomization must occur on or before Cycle 1 Day 1, such that dosing commences within 5 days after randomization.

5.3. Pre-Study/Baseline Evaluations (see Study Calendar, Appendix 4)

Baseline and screening evaluations conducted to establish eligibility will be performed within 28 days prior to first study treatment:

- Signed informed consent
- Urine or serum βHCG, in women of childbearing potential *(required within 7 days prior to treatment)*
- Histology review to confirm TNBC diagnosis
- BRCA 1&2 mutational status, if known

- Medical/surgical history review with treatment history to include treatment response and also time to progression for last therapy regimen
- ECOG Performance evaluation
- Prior/Concomitant medications review
- Physical examination with vital signs, defined as heart rate, blood pressure, respiratory rate, body weight and body temperature
- Standard 12-lead electrocardiogram (ECG)
- CBC including platelet count, with WBC differential in absolute cell counts, to be repeated within 72 hours of cycle 1, day 1 to confirm eligibility
- Routine serum chemistries (glucose, creatinine, BUN, total bilirubin, AST, ALT, LDH, alkaline phosphatase, serum albumin, total protein, Na, K, calcium, Cl, CO_2, magnesium and phosphorus)
- Hepatitis B surface antigen test, hepatitis C antibody test.
- Creatinine clearance (may be calculated using Cockcroft-Gault equation)
- Baseline serum sample prior to receiving sacituzumab govitecan for anti-drug antibody (hRS7 and SN-38) response (frozen, to be shipped to Sponsor's designee for analysis)
- Urinalysis
- CT or MRI with contrast as appropriate (chest, abdomen, pelvis, other regions of known/suspected involvement)*
- Brain MRI in patients with known brain metastases
- Quality of life patient questionnaire (EORTC QLQ C30)
- [redacted]
- A single whole-blood sample to be collected from each patient prior to receiving IMMU-132, for determination of *UGT1A1* genotype

**CT and MRI of the chest, abdomen and pelvis (CAP) must be of diagnostic quality and include appropriate use of contrast for the region being imaged.*

5.4. Procedures During Treatment (see Study Calendar, Appendix 4)

- Dosing (*IMMU-132 dosing is based on patient's body weight on Day 1 of each cycle (or at each dosing day if change in body weight is >10% or if required by institutional policy. TPC dosing is based upon body surface area as per local standard of care.*)

- Vital signs* *(For IMMU-132, prior to first infusion and every 15 minutes for the first hour then every 30 minutes until completing IV administration, at completion, and 30 minutes post infusion). In absence of significant changes, may be reduced with subsequent doses to prior to infusion, at 30 minutes, and then at completion. For TPC, at least before, once during and after IV administration and once at study visits for oral treatment; otherwise as per local standard of care).* *heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature. Timepoints can be ± 1-2 min.
- Blood samples prior to infusion:
  - CBC (with differential in absolute cell counts and including platelet count). *For IMMU-132 or TPC given intravenously (eribulin, gemcitabine, vinorelbine), required every treatment day. For TPC given orally (capecitabine), required at start of each cycle and on other treatment days and study visits as per local standard of care. In event of ≥ Grade 3 hematologic toxicity, to be obtained more frequently at the discretion of the managing physician until recovery to ≤ Grade 2 levels.*
  - Serum chemistry panel (glucose, creatinine, BUN, total bilirubin, AST, ALT, LDH, alkaline phosphatase, serum albumin, total protein, Na, K, calcium, Cl, CO_2, magnesium and phosphorus). *For IMMU-132 or TPC given intravenously (eribulin, gemcitabine, vinorelbine), required every treatment day. For TPC given orally (capecitabine), required at start of each cycle and on other treatment days and study visits as per local standard of care. To be obtained more frequently at the discretion of the managing physician if abnormal results warrant follow-up.*
- Urinalysis, pregnancy test (if applicable), and ECG. *For IMMU-132, required only on Day 1 of even cycles (cycle 2, 4, 6, 8, etc.). For TPC, required at the start of even cycles (every 6 weeks if given weekly [e.g. vinorelbine]). For patients receiving Gemcitabine, pregnancy test will be performed at the start of every cycle (every 4 weeks).*
- Physical examination. *Required on Day 1 of all cycles for IMMU-132 and at start of each cycle for TPC (every 3 weeks if given weekly [e.g. vinorelbine])*
- Adverse event reporting, *all patients at every study visit*
- Concomitant medications (continued, changed), *all patients at every study visit*
- Serum samples for Exposure-Response *(For IMMU-132, required on both Days 1 and 8 of Cycle 1 only, prior to infusion and 30 minutes afterwards; frozen immediately, to be shipped to Sponsor's designee for analysis; For TPC, not applicable)*
- Anti-drug antibody sample (frozen immediately, to be shipped to Sponsor's designee for analysis) *[For IMMU-132, required Day 1 of even cycles. For TPC, not applicable]*

CT or MRI examinations. Starting with the initial dose of IMMU-132 or TPC, CT or MRI scans are to be obtained in all patients after the first treatment dose every 6 weeks for 36 weeks,

then every 9 weeks thereafter until the occurrence of progression of disease requiring discontinuation of further treatment. Patients on either treatment arm who have progression of disease assessed for the first time during the study but, who, in the opinion of the treating physician are deriving continued clinical benefit from IMMU-132 or TPC treatment, relative to other available treatment options, may continue to be treated. Patients who discontinue treatment due to toxicity will continue with radiologic response assessments at the protocol-required schedule, until progression of disease or initiation of new therapy. CT or MRI imaging will include chest, abdomen, pelvis, other areas of known/suspected involvement, with contrast as appropriate. Patients with known brain metastasis must have a brain MRI. Target and non-target lesions must be determined by the clinical site at time of randomization. Responses identified prior to 36 weeks on study require confirmatory scans, which will be performed at the next scheduled scanning time-point (6 weeks later). For responses after 36 weeks, confirmatory scans will be done within 6 weeks of scan showing the onset of response. For each patient, the same imaging technique should be used throughout for tumor assessment. Clinical progression leading to patient discontinuation should be documented also by CT or MRI scan of target lesions if possible. Patients who discontinue treatment for other reasons than PD should a MRI/CT scan performed within 4 weeks from study treatment discontinuation so that documentation can be reviewed by the IRC. Additional CT or MRI studies may be performed at the discretion of the physician to assess disease status as medically indicated.

Note: A qualifying CT or MRI scan of the chest, abdomen, or pelvis must be of diagnostic quality, including use of appropriate contrast for the region being imaged.

Quality of life questionnaires (EORTC QLQ-C30; **see** Appendix 5) will need to be completed in all patients at baseline, at Day 1 of each cycle, and at the final study visit.

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5.6. Final Study Evaluation or Unscheduled/Early Termination Visit

To be conducted within 4 weeks after the last dose of IMMU-132 or TPC or in the event of premature study termination:

- Physical examination (complete)
- Pregnancy test, if applicable
- Vital signs defined as heart rate, systolic and diastolic blood pressure, respiratory rate, body weight and body temperature.
- CT or MRI with contrast as appropriate (chest, abdomen, pelvis, other regions of known/suspected involvement)*
- Blood samples
  - CBC (with differential and platelet count)
  - Serum chemistry panel
  - Serum sample for anti-drug antibodies (In patients receiving IMMU-132 only, frozen immediately, to be shipped to Sponsor's designee for analysis)
- Urinalysis
- ECG
- Concomitant medications (continued, changed)
- Adverse event reporting
- Quality of Life (EORTC QLQ-C30)

**CT and MRI of the chest, abdomen and pelvis (CAP) must be of diagnostic quality and include appropriate use of contrast for the region being imaged.*

5.7. Long-Term Follow-Up

All patients will be followed every 4 weeks thereafter for survival, which may be by telephone and will include documentation of any further therapy administrated for their breast cancer.

5.8. Criteria for Removal from Protocol Treatment

Patients may be removed from protocol treatment under the following conditions:

- First documentation of progressive disease or symptomatic deterioration indicating treatment failure in the absence of clinical benefit.
- Unacceptable toxicity
- Treatment delay for any reason >3 weeks
- Pregnancy
- Physician decision (non-compliance of the patient (to treatment or protocol-specified procedures), or continuing treatment not in the best interests of the patient)

- Withdrawal of consent at any time for any reason

Patients will end the study under any of the following conditions:

- Death
- Withdrawal of consent for the study at any time for any reason
- Lost to follow-up
- Sponsor decision

5.9. End of Study

End of study is defined as the point in time when the number of progression events required for the primary analysis have been reached or if the Sponsor terminates the study, whichever comes first. The primary analysis is expected to occur minimally 9 months after the last patient is randomized to the study. Survival data may continue to be collected after End of Study.

At the completion of the trial, subjects who are deriving benefit from sacituzumab govitecan may continue to receive treatment in a rollover study, if one is available. This rollover study may be designed to provide continued access to sacituzumab govitecan for eligible subjects who have previously participated in Immunomedics sponsored parent study, who are tolerating sacituzumab govitecan, have no evidence of progressive disease or are still deriving clinical benefit despite progression (as assessed by the investigator). Subjects will receive the dose of sacituzumab govitecan currently receiving in the parent study at the time of consenting to participate in the rollover study, if applicable.

6. STUDY DRUG INFORMATION

6.1. Description of Study Drug

hRS7 is a CDR-grafted, humanized monoclonal IgG_1 anti-Trop-2 antibody. The antibody is prepared using cell culture methods in accordance with Food and Drug Administration (FDA) guidelines for the manufacture and testing of monoclonal antibody products for human use. SN-38 (7-ethyl-10-hydroxy-camptothecin) is a small molecule and the active metabolite of the chemotherapeutic agent, irinotecan.

IMMU-132 is an antibody drug-conjugate prepared by Immunomedics, Inc. (Morris Plains, NJ). The conjugation uses a spacer containing a cleavable-carbonate bond to attach SN-38 to reactive cysteine thiols present on the hRS7 antibody. For clinical use, 10 mg/mL IMMU-132 is formulated in 25 mM MES, pH 6.5, together with the other excipients (25 mM trehalose, 0.01% Polysorbate 80), which is then lyophilized. Glass vials containing 200 mg of IMMU-132 as a sterile, non-pyrogenic, lyophilized powder are to be stored under refrigerated conditions (2-8ºC) until used. Each vial is labeled “For Investigational Use Only” and identified by study drug name, lot number, and dose. Since the formulated drug product contains no preservative, vials should be used only once.

6.2. Drug Accountability

All vials of study drug must be stored under refrigeration (monitored at 2-8ºC) in a locked room that can be accessed only by the pharmacist, the study Investigator, or another duly authorized study/site personnel. The study medications must not be used outside of the context of this protocol. Under no circumstances should the Investigator or other site personnel supply study drug to other Investigators, patients, or clinics, or allow supplies to be used other than as directed by this protocol without prior written authorization from Immunomedics, Inc.

Adequate records documenting receipt, use, return, loss, or other disposition of study drug vials must be kept. A complete drug accountability record, supplied by Immunomedics (or its designee or NCI drug accountability forms), or computer records used by the pharmacy at the investigational site, can be used to provide drug accountability. In all cases, information describing study medication supplies and their disposition, patient-by-patient, must be provided and signed by the Investigator (or the pharmacist or other person who dispensed the drug) and collected by the Study Monitor. Requisite data include relevant dates, quantities, batches or code numbers, and patient identification for patients who received trial product.

At the end of the study, following authorization by study management, study medication may be destroyed at the site as dictated by the appropriate standard operating procedures at the participating institutions. Destruction must be documented with signature by institution's pharmacist or delegate. Alternatively, after notification, all unused products will be collected by the Study Monitor and returned to Immunomedics, Inc., or designee.

6.3. Study Drug Preparation

Please use Pharmacy Binder as primary source for study drug preparation.

Table 3: IMMU-132 Preparation for 10 mg/kg Dosing (Assumes 70-kg Patient)

Total Dose Needed	**700 mg (200 mg/vial)**
a. Vials Required	4
b. Volume of saline to be used for reconstitution	20 mL
c. Volume after reconstitution of each vial with USP saline	80 mL
d. Volume Withdrawn for Scheduled Dose	70 mL
e. Dilute with Normal Saline	180 mL
f. Total Volume Dispensed	250 mL
g. Final Concentration (mg/mL)	2.8

6.4. IMMU-132 Treatment

Note: This section specifically provides guidance for IMMU-132 administration and toxicity management, including guidelines for infusion reactions, dose delay, dose reduction and treatment discontinuation. For similar information regarding the 4 TPCs in this study, please see Section 6.5.

6.4.1. Preventative Medications

Premedication for prevention of infusion reaction with antipyrectis, H_1 and H_2 blockers should be administered before sacituzumab govitecan infusions. Corticosteroids (hydrocortisone 50 mg or equivalent P.O. or I.V.) may be added if necessary and were used in approximately two-thirds of the patients in the Phase 2 trial. Premedication according to established guidelines with a two or three drug combination regimen (e.g. dexamethasone with either a 5-HT3 receptor antagonist or a NK_1 receptor antagonist, as well as other drugs as indicated) for prevention and treatment of chemotherapy-induced nausea and vomiting (CINV) is strongly recommended. Additional antiemetics, sedatives, and other supportive measures may also be employed as indicated per investigator discretion. All patients should be given medications to take home for prevention and treatment of nausea and vomiting. At the onset of diarrhea, promptly initiate loperamide, 4 mg initially followed by 2 mg with every episode of diarrhea for a maximum of 16 mg daily. Discontinue loperamide 12 hours after diarrhea resolves. Additional supportive measures (e.g. fluid and electrolyte substitution) may also be employed as clinically indicated. All patients should be given take-home medications with clear instructions for treatment of diarrhea. Patients who exhibit an excessive cholinergic response to treatment with sacituzumab govitecan (e.g., abdominal cramping, diarrhea, salivation, etc.) can receive appropriate premedication (e.g., atropine) for subsequent treatments.

6.4.2. Vital Signs

Vital signs (heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature)

for IMMU-132 will be assessed prior to the first infusion of cycle 1 and every 15 ± 5 minutes for the first hour and then every 30 minutes until completing IV administration, at completion, and then 30 minutes post infusion. In absence of significant changes, may be reduced with subsequent doses to prior to infusion, at 30 minutes, and then at completion. Timepoints can be ± 1-2 min.

6.4.3. Intravenous Administration of IMMU-132

Do not administer as an IV push or bolus. IMMU-132 is administered intravenously as a slow infusion as described below.

Intravenous access must be well established prior to initiating infusion. At the time of dosing, the IV line will be connected to an infusion container containing the prepared volume of IMMU-132. Either gravity or an infusion pump may be used. Only normal saline should be used as the infusion base solution, since the Sponsor has not examined the compatibility of IMMU-132 with other infusion diluents.

The initial infusion should proceed **slowly.** If vital signs remain stable and in the absence of infusion reactions, the infusion rate can be incrementally advanced following suggested guidelines given in Table 4, and following completion, the intravenous line should be flushed slowly with 20 mL normal saline and the end of infusion time recorded. In the event of infusion reactions or vital sign changes, the infusion rate may be slowed, interrupted or terminated, as considered appropriate by the managing physician (See Section 6.4.4).

Table 4: Infusion Rate Guidelines For Patients Remaining Stable in Absence of Hypersensitivity or Infusion-Related Events

Infusion Rate	Infusion #1	Subsequent Infusions
Initial Rate (first 15 min.)	50 mg/hr, or less	100 - 200 mg/hr
Incremental Rate (advance every 15-30 min.)	50 mg/hr	100 - 200 mg/hr
Maximum Recommended Rate	500 mg/hr	1000 mg/hr

6.4.4. Managing IMMU-132 Infusion Toxicity

The Sponsor's designee should be notified within 24 hours in the event of any serious infusion reaction occurring with IMMU-132 or one of the TPC drugs.

NCI CTCAE version 4.03 is used to grade all adverse events and to provide management guidelines for infusion toxicity.

For a serious infusion reaction considered severe or life threatening (NCI toxicity Grade 3 or higher) the infusion must be permanently terminated.

- Examples of such events include: serious or clinically significant cardiopulmonary events, severe allergic (symptomatic bronchospasm) or anaphylactic reactions, or other severe reactions.
- The occurrence of Grade 3 infusion-related reactions (e.g., prolonged infusion related reactions not rapidly responsive to symptomatic medication and/or brief interruption of infusion) also require the infusion to be permanently terminated.

Otherwise, for moderate infusion toxicity (Grade 2 events), the infusion should be temporarily stopped for at least 15 minutes or until symptoms resolve, and then resumed at the slowed infusion rate, if the patient is stable. Recommended actions for mild toxicity (Grade 1 events) include slowing the remaining infusion rate. Any infusion toxicity must have resolved to ≤ Grade 1 prior to a patient receiving the next scheduled infusion.

Additional Medications

Patients may be medicated during treatment as indicated in the judgment of the treating physician to control potential infusion or hypersensitivity responses. For anaphylactic reactions, appropriate medical measures (e.g., epinephrine, antihistamines, hydrocortisone, and IV fluids) should be taken. Such a subject should not receive additional study drug and should be discontinued from the study.

Nausea, Vomiting and Diarrhea

Gastrointestinal toxicity may be dose-limiting with IMMU-132. Premedication according to established guidelines with a two or three drug combination regimen (e.g. dexamethasone with either a 5-HT3 receptor antagonist or a NK_1 receptor antagonist, as well as other drugs as indicated)for prevention and treatment of chemotherapy-induced nausea and vomiting (CINV) is recommended.

At the onset of diarrhea, promptly initiate loperamide, 4 mg initially followed by 2 mg with every episode of diarrhea for a maximum of 16 mg daily. Discontinue loperamide 12 hours after diarrhea resolves. Additional supportive measures (e.g. fluid and electrolyte substitution) may also be employed as clinically indicated. All patients should be given take-home medications with clear instructions for treatment of diarrhea.

Additional antiemetics, sedatives, and other supportive measures may also be employed as clinically indicated. All patients should be given take home medications for prevention and treatment of nausea, vomiting and diarrhea. Hospital or institutional guidelines may exist and should be consulted for recommended treatment of these conditions in patients received cancer therapy. A partial list of the major medications is provided below in Table 5 but the hospital/institution guidelines or the references below should be consulted for more detailed information as to management of these conditions.

Patients who exhibit an excessive cholinergic response to IMMU-132 treatment (e.g., abdominal cramping, diarrhea, salivation, etc.) can receive appropriate premedication (e.g., atropine) for subsequent treatments.

Chemotherapy Induced Nausea Vomiting (CINV) guidelines			
High risk	Not applicable		
Moderate risk	IMMU-132		
Low risk	Vinorelbine, eribulin, gemcitabine, capecitabine		
Minimal risk	Not applicable		
Suggested anti-emetic regimen			
	Anti-emetic regimen	**Delayed CINV**	**Anti-emetic regimen**
High risk	$5HT_3$ antagonist + dexamethasone+ aprepitant	High risk	Dexamethasone (days 2-4) + Aprepitant (days 2-3) + lorazepam in selected patients
Moderate risk	$5HT_3$ antagonist + dexamethasone+ aprepitant in selected cases	Moderate risk	Dexamethasone (days 2-4) + aprepitant day 2-3 (if used on day 1) + lorazepam in selected patients
Low risk	Dexamethasone or metoclopramide or prochlorperazine	Low risk	No anti-emetics
Minimal risk	No anti-emetics	Minimal risk	No anti-emetics

Table 5: Recommended Medications for Nausea, Vomiting and Diarrhea*

Agent	**Dose/Frequency**	**Route of administration**
For Prevention of Acute Emesis:		
Palonosetron	0.075mg	
Decadron	10-20 mg	PO or IV
	10 mg every 12 hours	PO or IV
Granisetron	1 mg or 0.01 mg/kg	IV
	1-2 mg daily	PO

Table 5: Recommended Medications for Nausea, Vomiting and Diarrhea*

Agent	Dose/Frequency	Route of administration
Ondansetron	8 mg or 0.15 mg/kg	IV
	16-24 mg daily	PO
Lorazepam	0.5-2 mg every 4-6 hours	PO or sublingual
Alprazolam	0.5-2 mg every 4-6 hours	PO or sublingual
For Delayed Emesis:		
Fosaprepitant	150 mg day 1 only	IV
For Diarrhea:		
Loperamide	4 mg initially followed by 2 mg with every episode for a maximum of 16 mg daily. Discontinue 12 hours after diarrhea resolves and normal diet is resumed.	PO
Octreotide	100-150 mcg three times daily	Subcutaneously
Fluoroquinolones (for diarrhea persisting > 24 hrs, ANC < 500 or fever with diarrhea)	(e.g., ciprofloxacin 250-750 mg every 12 hours for 7 days)	PO

* Based on Benson 2004; Kris 2006.

6.4.5. IMMU-132 Dosing Schedule

All patients receive IMMU-132 to be administered weekly for 2 consecutive weeks (2 weekly doses plus 1 week without treatment represents a single 3-week cycle). Treatment cycles can be continued without a rest period in the absence of progression of disease or unacceptable toxicity. Patients on either treatment arm who have progression of disease assessed for the first time during the study but, who, in the opinion of the treating physician are deriving continued clinical benefit from IMMU-132 or TPC treatment, may continue to be treated. Planned deviations in treatment schedule are allowable up to 7 days due to holidays, vacations or personal reasons.

6.4.6. IMMU-132 Dose Reduction and Termination Guidelines

An overview of dose reduction and discontinuation is provided in the table below. The protocol allows aggressive medical management of patients in order to avoid dose reduction and dose delay as much as possible. Growth factors should be initiated according to guidelines in Section 6.4.6 and Table 6 and may be used prophylactically as clinically indicated. In patients who would be considered high risk for neutropenia (those who experienced febrile neutropenia or Grade 3-4 neutropenia with prior treatments), use of growth factors may be initiated early on and used prophylactically as early as cycle 1.

Table 6: IMMU-132

Dose	10 mg/kg IV on day 1 and 8 of a 21-day cycle			
When dose reduce	Infusion reaction	**Grade 2**: stop for 15 min or until resolution then resume at a slower rate **Grade 1**: slow infusion rate		
		Any infusion reaction must have resolved to < grade 1 before the next scheduled infusion		
	Hematologic toxicity-Use growth factors at any time as clinically indicated, including prophylactically	If patient experience grade ≥ 2 neutropenia on **cycle 1 day 1**, treatment initiation should be withheld until ≤ Grade 1. If delay more than 3 weeks, discontinue		
		If patient experience Grade ≥ 3 neutropenia **in subsequent treatment cycles**, treatment initiation should be withheld until ≤ grade 1 and growth factors should be used as clinically indicated. Patient will be assessed weekly for Grade 3 and bi-weekly for grade 4. If delay more than 3 weeks, discontinue		
		In the event of neutropenia Grade ≥ 3 on the time of scheduled treatment day: Resume treatment without dose reduction if delay is 1 week only Resume treatment without dose reduction **with addition of growth factors** if delay is 2 or 3 weeks (as is also recommended for delays greater than 1 week) Resume treatment with a dose reduction if patients is already receiving growth factors		
		Dose reduction scheme		
		Grade 4 neutropenia ≥ 7 days, Grade 3 febrile neutropenia	First occurrence	Add growth factors
			Second occurrence	25% dose reduction
			Third occurrence	50% dose reduction
			Fourth occurrence	Discontinue
	GI toxicity	If patient experience Grade ≥ 2 GI toxicity on **cycle 1 day 1**, treatment initiation should be withheld until ≤ Grade 1. If delay more than 3 week, discontinue		
		If patient experience Grade ≥ 3 GI toxicity **in subsequent treatment cycles**, treatment initiation should be withheld until ≤ Grade 1. Patient will be assessed weekly for grade 3 and bi-weekly for Grade 4. If delay more than 3 week, discontinue		
		In the event of GI toxicity Grade ≥ 3 on the time of scheduled treatment day: Resume treatment without dose reduction if delay is 1 week only Resume treatment without dose reduction if delay is 2 or 3 week		
	Non-hematologic toxicity	**Dose reduction scheme**		
		-Grade 4 non-hematological toxicity of any duration -Any Grade > 3 nausea, vomiting or diarrhea not controlled by antiemetics and antidiarrheal agents -Grade >3 non-hematologic toxicity > 48h despite optimal medical treatment -Grade 3 non-hematologic toxicity which delays dose by 2-3 weeks for recovery to < grade 1	First occurrence	25 % reduction
			Second occurrence	50 % reduction
			Third occurrence	discontinue
Discontinuation	Grade 3-4 infusion reaction Any delay more than 3 weeks			

The major toxicities of IMMU-132 are expected to be gastrointestinal symptoms and hematologic suppression. All patients will be closely monitored over the course of their treatment and aggressively medically managed in order to prevent dose reductions and delays where possible, with NCI-CTCAE v4.03 used to grade all adverse events and to provide dose reduction, delay or cessation guidelines in the event of toxicity.

If a patient experiences ≥ Grade 2 neutropenia or ≥ Grade 2 GI toxicity on the first treatment day (Cycle 1, Day 1), growth factors should be administered and treatment initiation should be withheld until resolved to ≤ Grade 1. If recovery to ≤ Grade 1 requires more than three-week delay, the patient should be withdrawn from the study. In subsequent treatment cycles, if a patient experiences ≥ Grade 3 neutropenia or ≥ Grade 3 GI toxicity, the treatment should be withheld until resolved to ≤ Grade 1 and patients will be assessed at least weekly (biweekly for Grade 4 toxicities). If recovery to ≤ Grade 1 requires more than a 3-week delay, the patient should come off the study.

Treatment will be permanently discontinued for a patient in the event of any ≥ Grade 3 infusion reactions which occur after pre-medication with antihistamines, H2 blockers and steroids.

In the event of ≥ Grade 3 treatment-related neutropenia at the time of a scheduled treatment day, the dose will be held and patients will be assessed at least weekly. Growth factors should be initiated. If recovery to ≤ Grade 1 delays the next dose by only one week, treatment may resume then without dose reduction with growth factor support as per Section 6.4.6 and Table 6. If recovery to ≤ Grade 1 delays the next dose by 2 or 3 weeks, treatment may be resumed at the same dose with the addition of growth factors. If a patient is already receiving growth factors support and the next treatment is delayed by 2 or 3 weeks, treatment must be resumed at a reduced dose (Table 6). If recovery to ≤ Grade 1 requires more than a three-week delay, treatment must be permanently discontinued.

In the event of other ≥ Grade 3 treatment-related non-hematologic toxicity at the time of a scheduled treatment day, the dose will be held and patients will be assessed at least weekly. If recovery to ≤ Grade 1 delays the next dose by only one week, treatment may resume then without dose reduction. If recovery to ≤ Grade 1 delays the next dose by 2 or 3 weeks, treatment must be resumed at a reduced dose (Table 6). If recovery to ≤ Grade 1 requires more than a three-week delay, treatment must be permanently discontinued.

The development of any of the following severe toxicities due to treatment requires permanent dose reduction for that patient by 25% of the assigned dose for first occurrence, 50% of the initial assigned dose for second occurrence, and with treatment discontinued entirely in the event of a third occurrence (Table 6).

6.5. Treatment of Physician Choice (TPC)

Treatment of Physician's Choice (TPC) determined before randomization from only one of the following 4 single-agent treatment regimens and administered for locally advanced, unresectable or metastatic breast cancer as per NCCN guidelines (https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.) No combination of the four choices is permitted.

- Eribulin (1.4 mg/m^2 IV 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). See Section 6.5.1
- Capecitabine (1000-1250 mg/m^2 orally twice daily on Days 1-14 of a 21-day cycle). See Section 6.5.2
- Gemcitabine (800-1200 mg/m^2 IV on Days 1, 8 and 15 of a 28-day cycle). See Section 6.5.3
- Vinorelbine (25 mg/m^2 IV on Day 1 weekly). See Section 6.5.4 (Note: eligible patients with Grade 2 neuropathy should not be prescribed vinorelbine as TPC).

An overview of dose, dose reduction , discontinuation is provided in the 2 tables below (North America and EU).

	Capecitabine				Eribulin		Gemcitabine					Vinorelbine	
Dose	1000-1250mg/m² twice in a day on day 1 and 14 of 21 day cycle				1.4 mg/m² on day 1 and day 8 of a 21 day cycle		800-1200 mg/m² on day 1, day 8 day, day 15 of 28 day cycle					25 mg/m² weekly	
When dose reduce?	**Any NCIC grade 2 toxicity**				**On day 1 or 8:** **Hematological toxicity** **Grade 3-4 non hematological toxicity**		**Hematological toxicity:** Grade 3 **ANC**: reduce to 75% - Grade 4 **ANC**: Hold Grade 1-2 **PLT**: reduce to 75% - Grade 3 **PLT**: Hold **Grade 3-4 non hematological toxicity**					**Granulocytopenia** **Hepatic toxicity** (bilirubin)	
Dose reductions			During cycle	Cycle +1 dose	**Do not give day 1 or day 8 if:** ANC < 1,000/mm³ PLT < 75,000/mm³ Grade 3-4 non hem AE		Recommended dose modifications for myelosuppression on day of treatment:					Dose adjustement based granulocytes	
	Grade 2	1st occ	Hold until gr 0-1	100%			**D**	**ANC**	**&**	**PLT**	**Dose**	**Granul**	**Dose**
		2nd occ.		75%	**Dose day 8 may be delayed** on for 8 days max; omit dose if not resolved <2. If resolved to <2, then dose on day 15 and restart next cycle on day 28 with one dose reduction		1	≥1500	&	≥100,000	100%	≥1500	100%
		3rd occ		50%				<1500	or	<100,000	Hold	1,000-1499	50%
		4th occ	**Discontinue**		**Reduce dose if:**		8	≥1200	&	≥75,000	100%	<1,000	Hold and repeat count weekly discontinue if < 1,000 for > 3 weeks
	Grade 3	1st occ	Hold until gr 0-1	75%	1. ANC < 1000/mm³ or ANC <1000/mm³ with fever and infection			1000–1199	or	50,000-75,000	75%		
		2nd occ		50%	2. Plt < 25,000 or < 50,000/mm³ requiring PLT transfusions			700-999	&	≥50,000	50%	**Tot Bili (mg/dl)**	**Dose**
		3rd occ	**Discontinue**		3. grade 3-4 Non hematological AE 4. dose omitted or delayed on day 8 at previous cycle			< 700	or	<50,000	Hold	≤2.0	100%
					Dose reduce to 0.7 mg/m² for any AE requiring dose reduction while at 1.1 mg/m²		Day 15: Same as day 8					2.1-3.0	50%
							Hold or reduce by 50% for grade 3-4 **non hematological** toxicity until resolved					>3.0	25%
												Hematologic and hepatic toxicity: use the lowest dose **Neuropathy:** discontinue if gr. ≥ 2	
Discontin.	**Discontinue if grade 4** or hold until grade 0-1 if patient best interest				**Discontinue** for any AE requiring dose reduction while at 0.7 mg/m²		**Discontinue** if unexplained dyspnea or evidence of severe pulmonary toxicity, severe hepatic toxicity, hemolytic uremic, capillary leak syndromes or PRES syndrome						
Start. dose adjustment	**For renal failure (Cockroft-Gault equation)**				**For renal failure**		**Gemcitabine should be administered with caution in patients with renal impairment**					**No dose adaptation for renal failure**	
	Calc. creat clear.		Starting dose		Calc. creat. Clear.	Starting dose							
	50-120 ml/min		100%		50-120 ml/m	1.4 mg/m²							
	30-50 m/min		75%		30-50ml/m	1.1 mg/m²							
Start. dose adjustment					**For hepatic impairment**		**Gemcitabine should be administered with caution in patients with hepatic impairment**					(see above)	
					Child-Pugh A	1.1 mg/m²							
					Child-Pugh B	0.7 mg/m²							

Overview of Dose, dose reduction and discontinuation for TPC (Europe)

	Capecitabine				Eribulin		Gemcitabine					Vinorelbine	
Dose	1000-1250mg/m² twice in a day on day 1 and 14 of 21 day cycle				1.23 mg/m² on day 1 and day 8 of a 21 day cycle		800-1200 mg/m² on day 1, day 8 day, day 15 of 28 day cycle					25 mg/m² weekly	
When dose reduce?	**Any NCIC grade 2 toxicity**				**On day 1 or 8:** **Hematological toxicity** **Grade 3-4 non hematological toxicity**		**Hematological toxicity:** Grade 3 **ANC**: reduce to 75% - Grade 4 **ANC**: Hold Grade 1-2 **PLT**: reduce to 75% - Grade 3 **PLT**: Hold **Grade 3-4 non hematological toxicity**					**Granulocytopenia** **Hepatic toxicity** (bilirubin)	
Dose reductions			During cycle	Cycle +1 dose	**Do not give day 1 or day 8 if:** ANC < 1,000/mm³ PLT < 75,000/mm³		Recommended dose modifications for myelosuppression on day of treatment:					Dose adjustement based granulocytes	
	Grade 2	1st occ	Hold until gr 0-1	100%	Grade 3-4 non hem AE		**D**	**ANC**	**&**	**PLT**	**Dose**	**Granul**	**Dose**
		2nd occ.		75%	**Dose day 8 may be delayed** on for 8 days max; omit dose if not resolved <2. If resolved to <2, then dose on day 15 and restart next cycle on day 28 with one dose reduction		1	≥1500	&	≥100,000	100%	≥1500	100%
		3rd occ		50%				<1500	or	<100,000	Hold	1,000-1499	50%
		4th occ	**Discontinue**		**Reduce dose if:**		8	≥1200	&	≥75,000	100%	<1,000	Hold and repeat count weekly discontinue if < 1,000 for > 3 weeks
	Grade 3	1st occ	Hold until gr 0-1	75%	1. ANC < 1000/mm³ or ANC <1000/mm³ with fever and infection			1000–1199	or	50,000-75,000	75%		
		2nd occ		50%	2. Plt < 25,000 or < 50,000/mm³ requiring PLT transfusions			700-999	&	≥50,000	50%	**Tot Bili (mg/dl)**	**Dose**
		3rd occ	**Discontinue**		3. grade 3-4 Non hematological AE 4. dose omitted or delayed on day 8 at previous cycle			< 700	or	<50,000	Hold	≤2.0	100%
					Dose reduce to 0.67 mg/m² for any AE requiring dose reduction while at 0.97 mg/m²		Day 15: Same as day 8					2.1-3.0	50%
							Hold or reduce by 50% for grade 3-4 **non hematological** toxicity until resolved					>3.0	25%
												Hematologic and hepatic toxicity: use the lowest dose **Neuropathy:** discontinue if gr. ≥ 2	
Discontin.	**Discontinue if grade 4** or hold until grade 0-1 if patient best interest				**Discontinue** for any AE requiring dose reduction while at 0.67 mg/m²		**Discontinue** if unexplained dyspnea or evidence of severe pulmonary toxicity, severe hepatic toxicity, hemolytic uremic, capillary leak syndromes or PRES syndrome						
Start. dose adjustment	**For renal failure (Cockroft-Gault equation)**				**For renal failure**		**Gemcitabine should be administered with caution in patients with renal impairment**					**No dose adaptation for renal failure**	
	Calc. creat clear.		Starting dose		Calc. creat. Clear.	Starting dose							
	50-120 ml/min		100%		50-120 ml/m	1.23 mg/m²							
	30-50 m/min		75%		30-50ml/m	0.97 mg/m²							
Start. dose adjustment					**For hepatic impairment**		**Gemcitabine should be administered with caution in patients with hepatic impairment**					(see above)	
					Child-Pugh A	0.97 mg/m²							
					Child-Pugh B	0.67 mg/m²							

6.5.1. Eribulin (Halaven)

Eribulin (1.4 mg/m^2 for North America sites, 1.23 mg/m^2 for EU sites) is to be administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle undiluted or diluted in 100 mL of 0.9% Sodium Chloride Injection, USP; do not dilute in or administer through an intravenous line containing solutions with dextrose. The recommended dose in patients with mild hepatic impairment (Child-Pugh A) is 1.1 mg/m^2 for North American sites, 0.97 mg/m^2 for EU sites administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle The recommended dose in patients with moderate hepatic impairment (Child-Pugh B) is 0.7 mg/m^2 for North America, 0.67 mg/m^2 for EU administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle. (*See* Appendix 7 *for Child-Pugh scores in patients with hepatic impairment.*) Assess for peripheral neuropathy and obtain complete blood cell counts prior to each dose.

Recommended dose delays*

Do not administer eribulin on Day 1 or Day 8 for any of the following:

- ANC < 1,000/mm^3
- Platelets < 75,000/mm^3
- Grade 3 or 4 non-hematological toxicities

The Day 8 dose may be delayed for a maximum of 1 week.

- If toxicities do not resolve or improve to ≤ Grade 2 severity by Day 15, omit the dose.
- If toxicities resolve or improve to ≤ Grade 2 severity by Day 15, administer eribulin at a reduced dose and initiate the next cycle no sooner than 2 weeks later.

Recommended dose reductions

- If a dose has been delayed for toxicity and toxicities have recovered to Grade 2 severity or less, resume eribulin at a reduced dose as set out below.
- Do not re-escalate eribulin dose after it has been reduced.
- Permanently reduce the 1.4 mg/m^2 eribulin dose to 1.1 mg/m^2 (0.97mg/m^2 for EU sites) for any of the following:
  - ANC <500/mm^3 for >7 days
  - ANC <1,000/mm^3 with fever or infection
  - Platelets <25,000/mm^3
  - Platelets <50,000/mm^3 requiring transfusion
  - Non-hematologic Grade 3 or 4 toxicities
  - Omission or delay of Day 8 eribulin dose in previous cycle for toxicity
  - Dose reduce to 0.7 mg/m^2 (0.67 mg/m^2 for EU sites) for any event requiring permanent dose reduction while receiving 1.1 mg/m^2 (0.97 mg/m^2 for EU sites)

- Discontinue eribulin for any occurrence of any event requiring permanent dose reduction while receiving 0.7 mg/m^2 (0.67 mg/m^2 for EU sites)

*ANC = absolute neutrophil counts; Toxicities as per NCI-CTCAE version 3.0

6.5.2. Capecitabine (Xeloda)

Capecitabine (1000-1250 mg/m^2) is to be administered orally twice daily for 2 weeks followed by one-week rest period given as a 21-day cycle. Capecitabine dose modification scheme described below is recommended for the management of adverse reactions.

Toxicity NCIC Grades*	**During a Course of Therapy**	**Dose Adjustment for Next Treatment (% of starting dose)**
Grade 1	Maintain dose level	Maintain dose level
Grade 2		
1st appearance	Interrupt until resolved to Grade 0-1	100%
2nd appearance		75%
3rd appearance		50%
4th appearance	Discontinue treatment permanently	-
Grade 3		
1st appearance	Interrupt until resolved to Grade 0-1	75%
2nd appearance		50%
3rd appearance	Discontinue treatment permanently	-
Grade 4		
1st appearance	Discontinue permanently OR If physician deems it to be in the patient's best interest to continue, interrupt until resolved to Grade 0-1	50%

*National Cancer Institute of Canada Common Toxicity Criteria were used except for the hand-and-foot syndrome. In patients with moderate renal impairment (baseline creatinine clearance = 30 to 50 mL/min), a dose reduction to 75% of the XELODA starting dose l (from 1250 mg/m2 to 950 mg/m2 twice daily) is recommended.

6.5.3. Gemcitabine (Gemzar)

Gemcitabine (800-1200 mg/m^2) is to be administered intravenously diluted with 0.9% sodium chloride injection over 30 minutes on Days 1, 8, and 15 of each 28-day cycle. Recommended dose modifications for gemcitabine for myelosuppression on day of treatment are described below.

Treatment Day	**Absolute neutrophil count (x 10^6/L)**		**Platelet count (x 10^6/L)**	**% of full dose**
Day 1	≥1500	and	≥100,000	100%
	less than 1500	or	less than 100,000	Hold
Day 8 and Day 15	≥1200	and	>75,000	100%
	1000-1199	or	50,000-75,000	75%
	700-999	and	≥50,000	50%
	<700	or	<50,000	Hold

Dose Modifications for Non-Hematologic Adverse Reactions

- Withhold Gemzar or reduce dose by 50% for other severe (Grade 3 or 4) non-hematological toxicity until resolved.
- No dose modifications are recommended for alopecia, nausea, or vomiting.

Permanently discontinue Gemzar for any of the following:

- Unexplained dyspnea or other evidence of severe pulmonary toxicity
- Severe hepatic toxicity
- Hemolytic-uremic syndrome
- Capillary leak syndrome
- Posterior reversible encephalopathy syndrome

6.5.4. Vinorelbine (Navelbine)

Vinorelbine (25 mg/m^2 weekly) is to be administered as IV injection over 6-10 min. vinorelbine Injection must be diluted in either a syringe or IV bag using one of the recommended solutions. The diluted vinorelbine should be administered over 6 to 10 minutes into the side port of a free-flowing IV closest to the IV bag followed by flushing with at least 75 to 125 mL of one of the solutions.

Syringe: The calculated dose of vinorelbine should be diluted to a concentration between 1.5 and 3.0 mg/mL. The following solutions may be used for dilution:

- 5% Dextrose Injection, USP
- 0.9% Sodium Chloride Injection, USP

IV Bag: The calculated dose of vinorelbine should be diluted to a concentration between 0.5 and 2 mg/mL. The following solutions may be used for dilution:

- 5% Dextrose Injection, USP
- 0.9% Sodium Chloride Injection, USP
- 0.45% Sodium Chloride Injection, USP
- 5% Dextrose and 0.45% Sodium Chloride Injection, USP

Dose Modifications for Hematologic Toxicity: Neutrophil counts should be $\geq$ 1,000 cells/mm^3 prior to the administration of NAVELBINE. Adjustments in the dosage of vinorelbine should be based on neutrophil counts obtained on the day of treatment according to the following table.

Dose Adjustments Based on Neutrophil Counts	
Neutrophils on Day of Treatment (cells/mm^3)	**Percentage of Starting Dose of vinorelbine**
≥1,500	100%
1,000 to 1,499	50%
< 1,000	Do not administer. Repeat neutrophil count in 1 week. If 3 consecutive weekly doses are held because neutrophil count is <1,000 cells/mm^3,discontinue NAVELBINE.
Note: For patients who, during treatment with vinorelbine, experienced fever and/or sepsis while neutropenic or had 2 consecutive weekly doses held due to neutropenia, subsequent doses of NAVELBINE should be:	
≥1,500	75%
1,000 to 1,499	37.5%
<1,000	See above

Dose Modifications for Hepatic Insufficiency: vinorelbine should be administered with caution to patients with hepatic insufficiency. In patients who develop hyperbilirubinemia during treatment with vinorelbine, the dose should be adjusted for total bilirubin (see below).

Dose Modification Based on Total Bilirubin	
Total Bilirubin (mg/dL)	Percentage of Starting Dose of vinorelbine
≤2.0	100%
2.1 to 3.0	50%
>3.0	25%

Dose Modifications for Concurrent Hematologic Toxicity and Hepatic Insufficiency*:* In patients with both hematologic toxicity and hepatic insufficiency, the lower ofthe doses based on the corresponding starting dose of vinorelbine determined from Tables above should be administered.

Dose Modifications for Renal Insufficiency: No dose adjustments for vinorelbine are required for renal insufficiency.

Dose Modifications for Neurotoxicity: If Grade ≥2 neurotoxicity develops, vinorelbine should be held until the toxicity resolves to < grade 1 and then restarted at a 50% of the starting dose of navelbine. If ≥ Grade 2 neurotoxicity reoccurs after dose reduction to 50%, navelbine should be held until the toxicity resolves to < Grade 1 and then restarted at a 25% of the starting dose of navelbine. If ≥ Grade 2 neurotoxicity reoccurs after dose reduction to 25%, navelbine should be discontinued

Permanently reduce the navelbine dose to 50% of the starting dose for any of the following:

- Non-hematologic Grade 3 or 4 toxicities

6.6. Management of Nausea and Vomiting for the TPC arm

The management of nausea and vomiting as per the table below is recommended for patients in the TPC arm.

Chemotherapy Induced Nausea Vomiting (CINV) guidelines			
High risk	Not applicable		
Moderate risk	IMMU-132		
Low risk	Vinorelbine, eribulin, gemcitabine, capecitabine		
Minimal risk	Not applicable		
Suggested anti-emetic regimen			
	Anti-emetic regimen	**Delayed CINV**	**Anti-emetic regimen**
High risk	$5HT_3$ antagonist + dexamethasone+ aprepitant	High risk	Dexamethasone (days 2-4) + Aprepitant (days 2-3) + lorazepam in selected patients
Moderate risk	$5HT_3$ antagonist + dexamethasone+ aprepitant in selected cases	Moderate risk	Dexamethasone (days 2-4) + aprepitant day 2-3 (if used on day 1) + lorazepam in selected patients
Low risk	Dexamethasone or metoclopramide or prochlorperazine	Low risk	No anti-emetics
Minimal risk	No anti-emetics	Minimal risk	No anti-emetics

7. STUDY EVALUATIONS

Safety and tolerability will be evaluated from adverse events, standard safety laboratories (CBC with differential and platelet count, serum chemistries, and urinalysis), physical examination, and vital signs. Adverse events will be classified according to the MedDRA system of preferred terms and system organ class, and all adverse events and abnormal laboratories will be classified for severity using NCI-CTCAE v4.03 toxicity grades. Descriptive statistics will be used to characterize adverse events, cytopenias, and other abnormal laboratories.

Efficacy will be evaluated from CT scans or MRI studies, using RECIST 1.1 criteria given in Appendix 6 to classify tumor response, time to onset of objective response, duration of objective response, and time to progression. For each patient, the same imaging technique should be used throughout the trial. Overall survival will be determined.

CCI [redacted]

[redacted]

CCI [redacted]

CCI [redacted]

Patient-reported outcomes (PROs) provide a means of evaluating the subjective effect treatments have on patients and their quality of life (QOL) (Lipscomb *et al*, 2007). EORTC QLQ-C30 (Appendix 5) will be completed at baseline, the beginning of every cycle, and the final study visit.

8. ADVERSE EVENTS

All patients must be carefully monitored for Adverse Events (AEs), including clinical laboratory tests. AEs should be assessed in terms of their seriousness, intensity, and relationship to the study drug. For consistency, events are to be graded using the NCI-CTCAE version 4.03.

An AE is any untoward medical occurrence; the event does not necessarily have a causal relationship with that treatment or usage. AEs include the following: An exacerbation, or an unexpected increase in frequency or intensity of a pre-existing condition (other than condition under investigation), including intermittent or episodic conditions.

1. Significant or unexpected worsening or exacerbation of the condition/indication under investigation
2. A suspected drug interaction
3. An intercurrent illness
4. Any clinically-significant laboratory abnormality

An AE does not include:

1. Anticipated day-to-day fluctuations of any pre-existing conditions, including the disease under study
2. Signs and symptoms of the disease under study that do not represent a significant worsening or exacerbation
3. Expected progression of the disease under investigation

8.1. Serious Adverse Events (SAEs)

An AE that meets one or more of the following criteria/outcomes is classified as serious:

1. Fatal
2. Life-threatening
3. Disabling/incapacitating
4. Results in hospitalization or prolongs a hospital stay
5. A congenital abnormality

6. Other serious medical events may also be considered SAEs if they require medical or surgical intervention to prevent one of the outcomes listed above (e.g., allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions not resulting in hospitalization, development of drug dependency or drug abuse)

An SAE does not include:

1. Progression of disease.
2. Hospitalization for a routine clinical procedure as stipulated by the protocol. Hospitalization for non-medical reasons (i.e., social admissions, hospitalizations for social, convenience or respite care).

8.2. Reporting AEs/SAEs

The Investigator is to report all AEs directly observed or spontaneously reported by patients using concise medical terminology. Each patient will be questioned about AEs at each clinic or evaluation visit, asking, for example, "Since your last clinic visit, have you had any health problems?"

All AEs will be reported following the first dose of study treatment through 30 days following the last day of administration of study treatment. Only treatment-related AEs will be captured from End of Treatment through the Safety Follow-up visit. All treatment-related AEs/SAEs that are ongoing at the time of the Safety Follow-up visit will be followed until resolution, return to baseline, or until they are Grade ≤ 1 (and following consultation and agreement by the Medical Monitor). During Follow-up visits in patients who discontinued therapy for reasons other than progression, any SAE determined by the Investigator to be potentially related to study treatment must also be reported. Whenever possible, a diagnosis should be given when signs and symptoms are due to common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection").

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

A clinical laboratory AE is any laboratory value that is considered clinically significant by the Investigator and has caused a medical intervention, dose hold, dose reduction or schedule change. Laboratory abnormalities that have not required medical intervention should not be recorded as AEs (they will be analyzed and reported in the laboratory section of the clinical study report).

All SAEs and pregnancies must be reported to the Sponsor or the Sponsor's designee immediately, and no later than 24 hours of becoming aware of the event.

All SAEs and pregnancies should be reported to the Sponsor's designee as per the reporting instructions provided on the SAE Form Completion Guidelines and as stated on the SAE Form.

Reporting requirements for AEs are summarized in the following table (Table 7)

Table 7: Reporting Requirements For Adverse Events

	Reporting Time	Type of Report
SERIOUS	Within 24 hours	Initial report on designated SAE form
	Within 5 calendar days	Follow-up/Final report on designated form
NON-SERIOUS	Per CRF submission procedure	Appropriate CRF pages

8.3. Recording Information on AEs

All AEs, whether observed by the Investigator, elicited from, or volunteered by the patient, will be recorded including: duration, severity, relationship to the study medication, treatment, action taken with respect to the study medication and outcome. When possible, all events should be reported in diagnostic terms or the most acceptable medical terms in order to interpret safety information accurately.

The investigator must review all laboratory and test data and record any adverse events. The same format will be used as for other adverse events, regardless whether related to study therapy or not, including event severity grading, attribution, and resolution. A summary listing of all adverse events occurring during the past year on this study will be provided in progress reports reported to regulatory authorities.

The Investigator will notify the Sponsor's designee if he/she becomes aware at any time, during or following the study, of the occurrence of death or new malignancy involving the participant of a clinical trial, even though the event may not appear to be drug-related.

8.4. Grading of AE Severity

The severity of AEs will be graded using the NCI-CTCAE Version 4.03. For each event, the highest severity grade should be reported. If a CTCAE criterion does not exist, the Investigator should use the grade or adjectives as described in Table 8.

Table 8: Grading Of Adverse Event Severity

Grade	Adjective	Description
Grade 1	Mild	Does not interfere with patient's usual function
Grade 2	Moderate	Interferes to some extent with patient's usual function
Grade 3	Severe	Interferes significantly with patient's usual function
Grade 4	Life-Threatening	Results in a threat to life or in an incapacitating disability
Grade 5	Death	Results in death (should be reported as a SAE)

A severe reaction (e.g., a severe headache) would not be classified as serious unless it met one of the criteria for SAE(s) listed above.

8.5. Pregnancy

The Sponsor's designated contact must be notified of any patient becoming pregnant during the study, or of any spontaneous abortion or of any therapeutic abortion and any pregnancy must be followed until completion or termination of pregnancy. The notification should be performed on the pregnancy form and be handled in the same manner as for SAEs. In the case of a live birth, the "normality" of the newborn can be assessed at the time of birth. The "normality" of an aborted fetus can be assessed by gross visual inspection unless pre-abortion laboratory findings are suggestive of a congenital anomaly.

8.6. Follow-up of Unresolved AEs

Only AE and SAE possibly or probably related to study treatment will be followed-up beyond the 30-day period following the study treatment discontinuation. Such events should be followed until they resolve or are grade ≤1. Follow-up of these AE will reported in the CRF.

8.7. Expedited Reporting

In this trial, the Sponsor's designee is responsible for expedited reporting of any SAE considered to be SUSAR (Suspected Unexpected Serious Adverse Reaction).

A SUSAR is any adverse event which meets the following 3 criteria

- Serious Adverse Event. An event meeting the SAE criteria in Section 8.1.
- Suspected Adverse Reaction. An event for which there is a reasonable possibility that there is a causal relationship between the study treatment and the event
- Unexpected Adverse Reaction. An event for which the nature or severity is not consistent with the applicable product information (*e.g.* Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

The Sponsor's designee will report all relevant information about suspected serious unexpected adverse reactions (SUSARs) to all applicable regulatory authorities in all participating countries, and via the Eudravigilance database (EVCTM), as required. SUSARs determined to be fatal or life-threatening must be submitted not later than 7 calendar days after initial report of the information to the Sponsor's designee (follow-up within an additional 8 days); otherwise SUSARs must be submitted within 15 calendar days.

The Sponsor's designee will also report all SUSARs to the governing Ethics Committees and will inform all investigators, as required.

8.8. Reporting death

Death is an outcome of a serious adverse event and not a serious adverse event in itself. When death is an outcome, the event(s) resulting in death should be reported (e.g. "pulmonary embolism" with a fatal outcome).

The appropriate diagnosis or term should be recorded and assigned severity Grade 5;

- In instances of death due to "Disease Progression" the cause of death should be indicated as the event or condition resulting in death to the extent possible (e.g. "respiratory failure" due to progressive TNBC).
- Deaths that occur later than 30 days after the last study drug administration should be reported as SAEs only if assessed as related to the study treatment.

8.9. Reporting to IRB/Ethics Committee (EC)

SAEs will be reported to the local (or contract) Institutional Review Board (IRB)/Ethics Committee (EC) by the Investigator according to the IRB's/EC's policy and procedures. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the Health Competent Authorities and concerned Ethics Committees (ECs)/Institutional Review

Boards (IRBs) in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries. For the purpose of SUSARs reporting, only possibly or probably related SAEs (i.e., there is a reasonable possibility of causality) will be considered serious adverse drug reactions.

8.10. Reporting to Health Authorities

The Sponsor's designee will be responsible for reporting all AEs and SAEs to the appropriate regulatory authorities (e.g., U.S. FDA), Investigators, and central IRB in accordance with all applicable regulations and guidance documents.

9. STATISTICAL CONSIDERATIONS

9.1. 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, as defined for the primary analysis 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 analysed 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. OS 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.

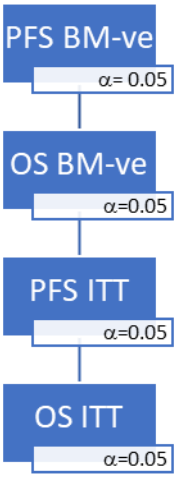
9.2. Interim analysis

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. 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.

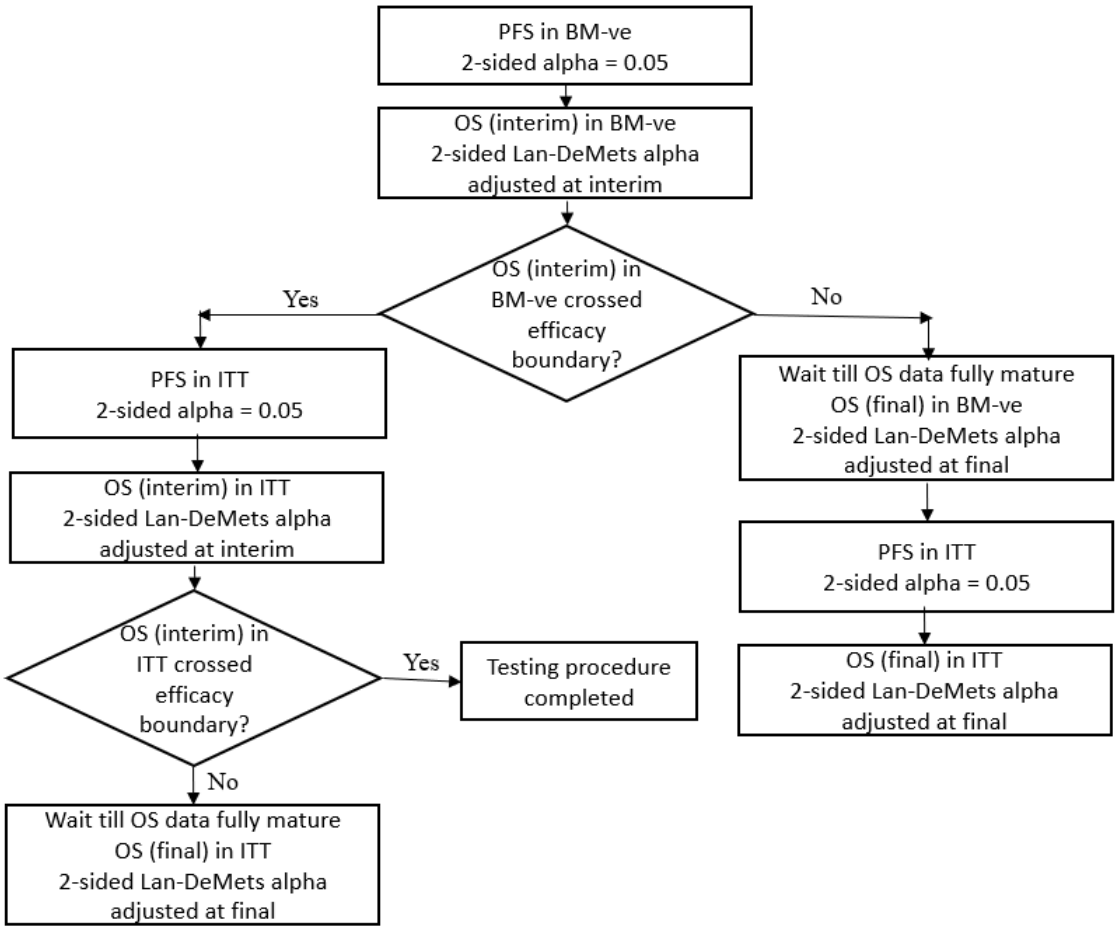
9.3. Efficacy Analyses

The primary analysis population consists of 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. Analyses will also be performed amongst all randomized patients, regardless of whether they have brain metastases, labelled throughout as the ITT population.

To strongly control type I error across populations and the two key endpoints of IRC PFS and overall survival (OS), a hierarchical testing strategy will be performed as displayed 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 analysed both at the time of the primary PFS analysis and, if not statistically significant at this time, 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.



Efficacy analyses will be performed on an intent-to-treat basis so that all patients randomized in the relevant population will be included. As a sensitivity analysis, efficacy will be also analyzed based on the Efficacy-Analyzable population, defined as all eligible, randomized and treated patients with at least one cycle of IMMU-132 or TPC and available follow-up radiological assessment data.

Imaging evidence of efficacy will be obtained from CT or MRI scans using RECIST 1.1 criteria to classify tumor response, time to onset of objective response, duration of objective response, and time to progression. Starting with the initial dose of sacituzumab govitecan or TPC, CT or MRI scans will be obtained every 6 weeks for 36 weeks, then every 9 weeks thereafter, until the occurrence of progression of disease requiring discontinuation of further treatment. For each patient, the same imaging technique should be used throughout the trial. Using descriptive statistics, these metrics will be tabulated and compared between the two treatment arms.

A stratified log-rank test stratified by randomization strata will be used to compare the treatment groups for the time-to-event endpoints of PFS and Overall Survival Estimates of hazard ratios and 95% confidence intervals of PFS and OS will be based on a stratified Cox proportional hazard regression model with treatment arm as the only covariate.

The PFS, OS, ORR, duration of response, and time to onset of response will be tabulated and compared between the two treatment groups.

PFS will be measured by an independent centralized and blinded group of radiology experts who will be assessing tumor response using RECIST 1.1 criteria. FDA definitions and guidance as described in Guidance for Industry: 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) will be used.

Target lesions will be assessed by CT scans or MRIs according to the same schedule in both treatment arms. 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 (see Appendix 6). 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, compared to the previous minimum, or the appearance of new lesions or unequivocal progression of 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 that progress or die following more than one missed scheduled visit 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.

The primary analysis of PFS will be based on the assessment of the central reviewer; additional sensitivity analyses will be performed based on definitions of PFS as defined in the Statistical Analysis Plan including the investigator's assessment.

OS will be measured from the date of randomization to death from any cause. Patients not known to have died at last follow-up are censored on the date they were last known to be alive. Patients are censored at the date of initiation of therapy (Day 1) if no additional data are obtained.

All statistical analyses will be performed using SAS® (SAS Institute, Version 9.2 or later, Cary, NC). Summary tables and listings will also be prepared using SAS.

All summaries will present analyses by treatment arm and overall. 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.

In an exploratory analysis of PFS, a Cox proportional hazard regression analysis (Cox 1972) stratified by the randomization strata will be performed to determine which factors are significantly associated with PFS. Univariate and multivariate Cox regression analyses will be performed including treatment arm and selected prognostic factors. Univariate prognostic factors that are significant at the 0.10 level will be included in the multivariate model. The resulting hazard ratios for each prognostic factor, associated 95% confidence intervals, and *p* values will be reported for the univariate and multivariate models. Prognostic factors included in the analyses will be finalized prior to database lock and included in the Statistical Analysis Plan. In addition, subgroup analyses of PFS will be performed based on each level of the stratification factors, and important baseline demographics and disease characteristic factors.

All analyses and descriptive summaries will be based on observed data. Unless otherwise specified missing data will not be imputed or "carried-forward".

Quality of life assessment

Descriptive statistics (mean, standard error, minimum, and maximum) will be used to evaluate the changes from baseline in EORTC QLQ-C30 scores for each visit by treatment arm.

Based on the labelling of capecitabine, gemcitabine, eribulin and vinorelbine, as well the known toxicities of IMMU-132 in the Phase I/II study, the major expected toxicities in this study are summarized below (Table 9).

Table 9: Anticipated toxicities of IMMU-132 and control drugs

	IMMU-132	Capecitabine	Vinorelbine	Gemcitabine	Eribulin
Cutaneous					
Rash		X		X	
Hair loss	X				X
Hand-foot syndrome		X			
Cardio-Circulatory					
Swelling		X		X	
Heart palpitations		X			
Pain					
Muscle pain					X
Joint pain					X
Gastrointestinal					
Decrease appetite					X
Nausea	X	X	X	X	X
Vomiting	X	X	X	X	X
Constipation			X		X
Diarrhea	X	X	X		
Abdominal pain	X	X			
Fecal incontinence	X	X	X		
Sleep/Wake					
Fatigue	X	X	X		X
Respiratory					
Shortness of breath	X	X	X	X	X
Neurological					
Numbness & tingling		X	X		X
Miscellaneous					
Chills	X	X		X	X
Nose bleed		X		X	
Oral					
Difficulty swallowing		X			
Mouth/throat sores		X			

9.4. Safety Analyses

All patients administered at least one dose of IMMU-132 or TPC will be included in the evaluation of safety.

The total amount of study drug and number of cycles and doses received will be summarized by treatment group.

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, ECG, and vital signs (heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature).

The frequency and severity of adverse events (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, using the worst NCI-CTCAE grade and relationship category. AEs will be consolidated using the worst NCI-CTCAE grade and relationship category observed for classification into each MedDRA SOC summary.

AEs leading to death or to discontinuation from treatment, as well as all SAEs will be summarized separately. A listing of all death information will be generated. The reasons for study discontinuation will also be summarized for each treatment group.

Both actual and change-from-baseline data on vital signs and ECG intervals (with particular emphasis on corrected QT interval) will be summarized using descriptive statistics by treatment group for each study time-point. Percentages with abnormal ECGs will be presented at each scheduled time point.

Routine safety laboratories, based on hematology and routine serum chemistry data (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. Laboratory test results for platelets, neutrophils, white blood count, lymphocytes and hemoglobin will be graded according to NCI-CTCAE severity grade. 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 NCI-CTCAE scale does not exist, the proportion of patients with abnormal values will be summarized by treatment group.

Data on anti-drug antibody responses will be listed and summarized by descriptive statistics.

CCI [redacted]

[redacted]

[redacted]

CCI [redacted]

CCI [redacted]

[redacted]

10. TREATMENT COMPLIANCE

IMMU-132 will be administered at scheduled study centers under the supervision of the Investigator or sub-investigator(s). The pharmacist will maintain records of study drug receipt, preparation, and dispensing, including the applicable lot numbers, patient's height, weight and total drug administered in milligrams. Any discrepancy between the calculated dose and dose administered and the reason for the discrepancy must be recorded in the source documents and on appropriate CRF.

11. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

12. DATA HANDLING AND RECORD KEEPING

12.1. Electronic Case Report Forms (eCRFs)

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

It is the Investigator's responsibility to ensure completion and to review and approve all eCRFs. eCRFs must be signed by the Investigator or by an authorized staff member. These signatures serve to attest that the information contained on the CRFs is true. At all times, the Investigator has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the eCRFs. Patient source documents are the physician's patient records maintained at the study site. In most cases, the source documents will be the hospital's or the physician's chart. In cases where the source documents are the hospital or the physician's chart, the information collected on the eCRFs must match those charts. In some cases, a portion of the source documents for a given study site may be the eCRFs. The Investigator must agree which items will be recorded in the source documents and for which items the eCRF will stand as the source document.

Corrections to the eCRF must be initialed and dated by the person making the correction (ICH E6 4.9.3).

12.2. Record Retention

Records and documents pertaining to the conduct of this study, including eCRFs, source documents, consent forms, laboratory test results, and medication inventory records must be retained by the Investigator for at least 15 years. No study records shall be destroyed without prior authorization from Immunomedics. For studies conducted outside the United States under a US IND, the Investigator must also comply with US FDA IND regulations, ICH guidelines, and with the regulations of the relevant national and local health authorities. Current US federal law requires an Investigator to maintain such records for a period of two years following approval of a Biologic License Application, or, if the Biologic License Application is not approved, until two years following notification by Immunomedics that the clinical investigations have been discontinued.

13. ADMINISTRATIVE REQUIREMENTS

13.1. Good Clinical Practice

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

13.2. Ethical Considerations

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

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

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

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

13.3. Patient Information and Consent

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

The written patient information must not be changed without prior approval by Immunomedics or its designee and the IRB/IEC.

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

13.4. Protocol Compliance

The Investigator will conduct the study in compliance with the protocol provided by Immunomedics or its designee, and given approval by the IRB/IEC and the appropriate regulatory authorities. Modifications to the protocol should not be made without agreement of both the Investigator and Immunomedics or its designee. Changes to the protocol will require written IRB/IEC approval prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to the patient. The IRB/IEC may provide, if applicable, regulatory authorities permit, expedited review and approval for minor change(s) in ongoing studies that have the approval of the IRB/IEC. The Sponsor's designee will submit all protocol modifications to the regulatory authorities in accordance with the governing regulations.

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

13.5. Site Monitoring and On-Site Audits

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

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

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

13.6. Patient Data Protection

Privacy Act Compliance. Information collected in this clinical trial is subject to the Health Insurance Portability and Accountability Act of 1996 (HIPAA) as described in 45 CFR 160 and 45 CFR 164. The study Investigator is responsible for informing patients of their rights under HIPAA, and obtaining any necessary HIPAA authorizations. In compliance with the provisions of that policy, Immunomedics or designee will not collect any protected health information, and will only collect de-identified health information. Any clinical study information referred to in this section is understood to be compliant with the provisions of the Privacy Act.

The information obtained during the conduct of this clinical study is confidential, and disclosure to third parties other than those noted below is prohibited. Information obtained during the

conduct of this study will be used by Immunomedics or designee in connection with the development of the study drug. The study Investigator is obliged to provide Immunomedics or designee with complete test results and all data developed in this study. This information may be disclosed to other physicians participating in the study, to the FDA, or to national and local health authorities. To ensure compliance with all current Federal Regulations and the ICH/GCP guidelines, data generated by this study must be available for inspection upon request by representatives of the FDA, national and local health authorities, Immunomedics, designee, and the IRB/EC for each study site.

13.7. Financial Disclosure

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

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

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

13.8. Sponsor Discontinuation Criteria

Immunomedics, Inc. reserves the right to discontinue the trial prior to inclusion of the intended number of patients, but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the Investigator must contact all participating patients within a time period set by the Sponsor. In the unlikely event of premature termination or discontinuation of the study, in the event the Investigator believes a patient is continuing to receive clinical benefit, the Sponsor will discuss options with the Investigator in order to ensure continuing supply of sacituzumab govitecan.

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

14. DISSEMINATION AND PUBLICATION OF RESULTS

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

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APPENDIX 1. LIST OF STANDARD TREATMENTS FOR TNBC

Refractory to or relapsed after at least two chemotherapy regimens containing one or more of the following agents: Doxorubicin, Epirubicin, Pegylated liposomal Doxorubicin, Docetaxel, Paclitaxel, Albumin-bound Paclitaxel (Abraxane), Gemcitabine, Vinorelbine, Vinblastine, Capecitabine, Ixabepilone (Ixempra) Eribulin, Platinum and TDM-1. CCI [redacted]

Note: The list includes regimens recommended by the NCCN guidelines as well as used in documented clinical trials. Patients who received other treatment combinations may also be eligible for enrollment after obtaining approval from the medical monitor.

APPENDIX 2. PERFORMANCE STATUS EVALUATION

by the Eastern Cooperative Oncology Group, PPD , Group Chair.*

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

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655.

ECOG PERFORMANCE STATUS	KARNOFSKY PERFORMANCE STATUS
0—Fully active, able to carry on all pre-disease performance without restriction	100—Normal, no complaints; no evidence of disease 90—Able to carry on normal activity; minor signs or symptoms of disease
1—Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	80—Normal activity with effort, some signs or symptoms of disease 70—Cares for self but unable to carry on normal activity or to do active work
2—Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours	60—Requires occasional assistance but is able to care for most of personal needs 50—Requires considerable assistance and frequent medical care

3—Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours	40—Disabled; requires special care and assistance 30—Severely disabled; hospitalization is indicated although death not imminent
4—Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	20—Very ill; hospitalization and active supportive care necessary 10—Moribund
5—Dead	0—Dead

*Karnofsky D, Burchenal J, The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod C, ed. Evaluation of Chemotherapeutic Agents. New York, NY: Columbia University Press; 1949:191–205.
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APPENDIX 3. PROCEDURE FOR COLLECTION, STORAGE, AND SHIPMENT OF SAMPLES

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

- **Serum samples for exposure response and anti-drug antibodies**
- **Whole-blood samples for UGT1A1 genotyping**
- [redacted]

APPENDIX 4. STUDY CALENDAR

PRETREATMENT		TREATMENT*†	POST TREATMENT	
Study Procedures	≤28 days of C1D1	IMMU-132 or TPC cycles to continue until disease progression warranting discontinuation or unacceptable toxicity	Final Visit††	Long Term Follow-up
Signed Informed Consent	X			
Patient Eligibility	X			
Histology[1]	X			
Medical/Surgical History[2]	X			
CCI				
IMMU-132 Only *UGT1A1* Genotype	X			
BRCA 1&2 Status, if available	X			
Creatinine clearance	X			
MRI Brain if known brain metastasis	X	Every 6 weeks through 36 weeks (week 6, 12, 18, 24, 30, 36), then every 9 weeks		
AE reporting		Each study visit	X	
Concomitant Medications	X	Each study visit	X	
Vital Signs[4]		Each Infusion (IV) or study visit (oral)	X	
CBC (with platelets and WBC diff. in absolute cell counts)[5]	X	Every cycle: Day 1 & 8 (IMMU-132), each infusion (IV TPCs), or Day 1, then per SOC (oral TPC)	X	
ECOG Performance Status	X	Every cycle: Day 1	X	
Quality of Life[6]	X	Every cycle: Day 1	X	
Serum Chemistries[7]	X	Every cycle: Day 1 & 8 (IMMU-132), each infusion (IV TPCs), or Day 1, then per SOC (oral TPC)	X	
Hepatitis B surface antigen test, hepatitis C antibody test	X			
Pregnancy Test, if applicable[8]	X	Even cycles: Day 1 Gemcitabine:day 1 of every cycle	X	
Physical Examination	X	Every cycle: Day 1	X	
Urinalysis	X	Even cycles: Day 1	X	
12-lead ECG	X	Even cycles: Day 1	X	
IMMU-132 only[9] • Exposure-Response[10] [redacted] CCI • Anti-Drug Antibodies[12]	X	First cycle: Day 1 & 8 See Schedule Even cycles: Day 1 and Day 8	X	
CT/MRI[13]	X	Every 6 weeks through 36 weeks (week 6, 12, 18, 24, 30, 36), then every 9 weeks	X[13 bis]	
Survival Status, Post-Study Therapy[14]				X

*IMMU-132 administered at dose of 10 mg/kg IV on day 1 & 8 of 21-day cycles; TPC dose and dosing cycles as per NCCN guidelines
†For TPC agents dosed weekly (e.g. vineorelbine), a cycle is defined as every 3 weeks (21 days)

[††] Last study visit 4 weeks after the last treatment dose or in event of premature study termination.
[1]Documented confirmation of TNBC diagnosis
[2]Treatment history to include treatment response and also time to progression for last therapy regimen.
CCI [redacted]
[4]Vital signs (heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature) for patients receiving IMMU-132 required on Day 1 of cycle 1 prior to infusion, during infusion every 15 minutes for the first hour then every 30 minutes, at completion, and then additionally 30 minutes later. In absence of significant changes, may be reduced with subsequent doses to prior to infusion, at 30 minutes, and then at completion. For patients receiving TPC, required prior to, once during, and at the end of each infusion, (Vinorelbine vital signs are required prior to and at the end of each infusion due to short infusion time) or if administered orally, once at each study visit; *otherwise as per local standard of care*. Vital signs are required in all patients at final study visit. Timepoints can be ± 1-2 min.
[5] To be repeated within 72 hours of cycle 1, day 1 to confirm eligibility. CBC for patients receiving IMMU-132, required at baseline, Day 1 & 8 of each cycle, and final study visit. For patients receiving TPC, required at baseline, Day 1 of each cycle, and final study visit, and as required by SOC on other treatment days or other study visits. Note, is not required to be repeated at C1D1 (IMMU-132 and TPC) if baseline sample collected within 72 hours prior). In the event of ≥ Grade 3 hematological toxicity, CBC will be obtained more frequently at the discretion of the managing physician until toxicity recovers to Grade 2 levels and then weekly until recovery to baseline or Grade 1 levels.
[6]QOL (EORTC QLQ C30) questionnaire to be completed by all patients at baseline, on Day 1 of each cycle, and at final study visit.
[7]Serum chemistries include glucose, creatinine, BUN, total bilirubin, AST, ALT, LDH, alkaline phosphatase, serum albumin, total protein, Na, K, calcium, Cl, CO_2, magnesium and phosphate. Serum chemistries are required in all patients at baseline, Day 1 of every cycle (not required to be repeated at C1D1 if baseline sample collected within 72 hours prior), and final study visit. To be obtained more frequently at the discretion of the managing physician if abnormal results warrant follow-up
[8]Pregnancy test required in patients (if applicable) within 7 days prior to start of treatment, Day 1 of even cycles (2, 4, 6, 8, etc.), and final study visit. For patients receiving Gemcitabine, pregnancy test will be performed on day 1 of every cycles (every four weeks).
[9]Serum samples to be frozen immediately and stored for shipment to the Sponsor's designee to perform the assays.
[10]Serum samples for exposure-response required from all patients receiving IMMU-132, prior to infusion and 30 minutes afterwards on both Days 1 and 8 of Cycle 1 only.
CCI [redacted]
[12]Anti-drug antibodies required from all patients receiving IMMU-132 with serum samples obtained at baseline (may be taken at C1D1 provided it is before study drug administration), at Day 1 of even cycles, and at final study visit.
[13]CT or MRI (chest, abdomen, pelvis; other if needed) is required in all patients after the start of treatment at 6-week intervals through 36 weeks, then every 9 weeks until the occurrence of progression of disease requiring discontinuation of further treatment. For each patient, the same imaging technique should be used throughout the trial. Responses identified prior to 36 weeks on study require confirmatory scans, which will be performed at the next scheduled scanning time-point (6 weeks later). For responses after 36 weeks, confirmatory scans will be done within 6 weeks of scan showing the onset of response. Additional CT/MRI can be performed at the discretion of the physician to assess disease status as medically indicated. Clinical progression leading to patient discontinuation should be documented also by CT or MRI scan of target lesions if possible. Patients who discontinue treatment due to toxicity will continue with radiologic response assessments at the protocol-required schedule, until progression of disease or initiation of new therapy.
[13 bis]: if PD not yet confirmed
[14]All patients will be followed every 4 weeks thereafter for survival, which may be by telephone and will include documentation of any further therapy administrated for their breast cancer.

NOTE: Unless otherwise specified, collection windows for study time points are within ± 2 days for the treatment schedule and ± 5 business days for response assessments. Planned deviations in treatment schedule are allowable up to 7 days due to holidays, vacation or personal reasons.

APPENDIX 5. EORTC QLQ-C30 (VERSION 3)

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

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

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

15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

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

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

APPENDIX 6. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) 1.1

New Response evaluation criteria in Solid tumors: Revised RECIST criteria [*EJC* 4 (2): 228-247, 2009] are summarized below.

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

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

Special considerations regarding lesion measurability:

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment: Bone lesions: • Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions. • Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are non-measurable. Cystic lesions: • Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. • 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

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

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

Evaluation Criteria Used for Categorizing Treatment Response of Target Lesions	
Response Category	**Definition**
Complete Response (CR)	Disappearance of all target lesions
Partial Response (PR)	> 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD)	> 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

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

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

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

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

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

*When evaluation of possible CR depends on distinguishing residual disease from normal tissue, fine needle aspirate/biopsy is recommended before confirming the complete response status.
**Patients without objective evidence of disease progression, but with globally deteriorated health status requiring discontinuation of treatment should be classified as having "symptomatic deterioration" at that time, with every effort made to document the objective progression, even after discontinuation of treatment.

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

APPENDIX 7. CHILD-PUGH SCORE IN PATIENTS WITH HEPATIC IMPAIRMENT

Modified Child-Pugh Score			
Manifestation	**One point**	**Two points**	**Three points**
Encephalopathy[a]	None	Grade I–II	Grade III–IV
Ascites	Absent	Nontense	Tense
Bilirubin (mg/dl)			
Noncholestatic	<2	2–3	>3
Cholestatic	<4	4–10	>10
Albumin (g/dl)	>3.5	2.8–3.5	<2.8
INR (International normalized ratio)	<1.7	1.7–2.3	>2.3
[a]Encephalopathy: I, mild confusion or slowing, no asterixis; II, drowsy, asterixis present; III, marked confusion, somnolence, asterixis present; IV, unresponsive or responsive only to painful stimuli, no asterixis.			
Class A, 5– 6 points Class B, 7–9 points Class C, >10 points			

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

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