Clinical Protocol CA139387

Rollover Study of weekly Paclitaxel (BMS-181339) in Patients with Breast Cancer

[redacted]

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[redacted]

[redacted]

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SYNOPSIS

Clinical Protocol CA139387

Title of Study: Protocol CA139387: Rollover Study of Weekly Paclitaxel (BMS-181339) in Patients with Advanced Breast Cancer.
Estimated Number of Study Centers and Countries/Regions: 5 sites/Japan
Study Phase: II
[redacted]
Primary Objective: The primary objective is to provide an access to Paclitaxel therapy to all subjects who have completed previous [redacted] and are deemed to be benefiting from this treatment (and should continue on this therapy) as assessed by the treating investigator(s). Cond study (CA 139-387) will also evaluate the frequency and the severity of observed adverse events in treated study subjects.
Study Design: This study is a rollover study designed to provide an access to Paclitaxel therapy to breast cancer subjects who have completed previous [redacted] and are believed to be benefiting from this treatment as assessed by the treating investigator(s). Only breast cancer patients who have participated in a previous [redacted] can enroll in this rollover weekly Paclitaxel trial (CA139387) provided that they meet all eligibility criteria. Study subjects will receive weekly Paclitaxel at the dose consistent with their last dose in the previous Phase II weekly Paclitaxel trial. Paclitaxel will be given as a one hour intravenous (iv) infusion on Days 1, 8 15,22, 29, 36 followed by 2 weeks of no treatment (observation). One treatment course will consist of 49 days. Safety assessment required in the protocol should be done at each of these weekly visits. Tumor response will be assessed at the completion of at least every 7 weeks.
Number of Subjects per Group: Approximately 10 subjects.
Study Population: Patients with advanced breast cancer that have completed therapy in a previous [redacted] and are proven to be benefiting from it with recommendation of continuation of this treatment, as assessed by the treating investigator(s).
Test Product, Dose and Mode of Administration, Duration of Treatment: Paclitaxel will be administered intravenously by a 1-hour infusion for the first week of each treatment course. All patients will receive premedication with Paclitaxel given at the last dose that each individual patient was receiving on the previous [redacted] The day of the initial drug dose administration on the given course is defined as Day 1 of the treatment course. Subsequent Paclitaxel administrations will be given on Days 8, 15, 22, 29 and 36 followed by two weeks of rest (i.e. until Day 49). One treatment course consists of 49 days total.
Reference Therapy, Dose and Mode of Administration, Duration of Treatment: Not applicable.
Criteria for Evaluation: Every adverse event shall be evaluated and its severity be graded according to the NCI- Common Toxicity Criteria (NCI-CTC) Ver.2.0 (see Appendix 10; It also includes Japanese-language version translated by the JCOG.). Responses will be assessed according to the "Evaluation Criteria on the Therapeutic Effects in Patients with Advanced or Recurrent Breast Cancer "(Extract) and RECIST criteria (See Appendix 7).
Statistical Methods: Demographic data and safety will be summarized using descriptive statistics.

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[redacted]

[redacted]

[redacted]

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary study objectives are as follow:

1) To provide the access to Paclitaxel therapy to breast cancer subjects who have completed at least 2 course on the previous [redacted] conducted in Japan and are believed to be benefiting from this treatment, as assessed by the treating investigator(s).

2) To evaluate the frequency and the severity of observed adverse reactions in treated subjects.

2.2 Secondary Objectives

The secondary objective is to obtain additional data on the response rate and duration of responses to complement information collected on the previous [redacted].

3 STUDY DESIGN AND EVALUATION

3.1 Study Design

Only subjects who participated in the previous Phase II study may enroll in this rollover study provided that they meet all specified in this protocol inclusion and exclusion criteria. Subjects will receive weekly Paclitaxel at the dose that was their last dose on the previous [redacted] delivered as a one hour iv infusion on Days 1,8,15,22,29,36 followed by 2 weeks of rest (no therapy). One course of therapy consists of 49 days. The range of doses on this study are expected to be decided based on dose reductions seen in [redacted]. Safety assessment required in the protocol should be done at each of these weekly visits. Response to therapy will be assessed at least every 7 weeks, if clinically indicated.

3.2 Study Population

Patients with advanced breast cancer who have completed weekly Paclitaxel dosing in previous [redacted] and are believed to benefit from this treatment with recommendation to continue this regimen, as assessed by the treating investigator(s).

3.3 Criteria for Evaluation

Observed responses should be evaluated according to the "Evaluation Criteria on the Therapeutic Effects in Patients with Advanced or Recurrent Breast Cancer "(Extracts) and the "RECIST" criteria (See Appendix 7).

Every observed adverse event shall be evaluated according to the NCI Common Toxicity Criteria (NCI-CTC) Ver.2.0 (see Appendix 10, translated by the JCOG Japanese language version will also be available). For any toxicity not defined by the NCI-CTC criteria, it must be classified into the category of "Other toxicity" with detailed description on the toxicity observed and be graded according to the following criteria:

Grade 0: Normal, normal/within normal range, no toxicity
Grade 1: Minor/Mild toxicity
Grade 2: Medium/Moderate toxicity
Grade 3: Severe/High-grade toxicity
Grade 4: Life-threatening toxicity
Grade 5: Death due to toxicity

3.4 Sample Size Determination

Sample size will be determined by the number of appropriate subjects who have completed previous [redacted] and are eligible to participate in this rollover (CA139387) study. At the present time 9 patients remain on [redacted]. It is estimated that less than 10 patients will be rolled over to this study from [redacted].

3.5 Interim Analyses

There are no planned interim analyses. If requested by Japanese regulatory agencies, an interim analysis of this trial may be performed to support the Japanese regulatory filing.

4 STATISTICAL METHODOLOGY

4.1 Data Set Descriptions

Subjects who receive at least one dose of weekly Paclitaxel treatment will be included in the baseline, dosing and safety summaries. Data from the previous [redacted] will be utilized for the demographic data and baseline values in enrolled patients for this rollover trial. To obtain an additional data on a response rate and duration of responses, efficacy data will be collected in this rollover CA139387 study.

4.2 Analyses

4.2.1 Demographics and Baseline Characteristics

Demographic data, performance status, diagnosis, stage, disease locations, prior treatment(s), and selected baseline laboratory results will be summarized using

descriptive statistics for all patients who received at least one dose of study medication.

Baseline laboratory measurements will be collected from the data obtained for the participation in a previous [redacted]

4.2.2 Efficacy Analyses

Duration of response will be summarized using descriptive statistics for all responders among response-evaluable patients.

4.2.3 Safety Analyses

All patients who received at least one dose of study medication will be included in the safety analysis. Worst toxicity grades per patient will be tabulated for adverse events and laboratory measurements.

[redacted].

4.2.5 Other Analyses

Not applicable.

5 SUBJECT SELECTION CRITERIA

For entry into the study, the following criteria MUST be met.

5.1 Inclusion Criteria

Only patients enrolled in the previous [redacted] who have completed [redacted] dosing and are believed to be benefiting from this treatment with advice to continue this regimen, as assessed by the treating investigator(s), may be considered for this rollover study after meeting study eligibility criteria as listed below.

Signed written informed consent

1) Give written and voluntary informed consent.

Target population

2) Patients should receive at least 2 courses, or more, of [redacted] in the previous study ([redacted])and the efficacy evaluation should be completed and confirmed by the treating investigator(s).
3) Patients who maintain bone marrow function and meet the following standards at the time of laboratory test obtained prior to the 1st Paclitaxel administration in this rollover study;

- WBC count of 3,000/μL or higher, or absolute neutrophile count (ANC) of 1,500/μL or above.
- Platelet count of 75,000/μL or above.

4) Performance Status (PS) of 0 - 2 (according to Classification Criteria of Performance Status by the Eastern Cooperative Oncology Group-ECOG. (See Appendix 8).

Age and Sex

5) Women, ages 20 or older.

Women of childbearing potential (WOCBP) must be using an adequate method of contraception to avoid pregnancy throughout the study and for up to 2 weeks after the study in such a manner that the risk of pregnancy is minimized.

WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal [defined as amenorrhea ≥ 12 consecutive months; or women on hormone replacement therapy (HRT) with documented serum follicle stimulating hormone (FSH) level > 35mIU/mL]. Even women who are using oral, implanted or injectable contraceptive hormones or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy or practicing abstinence or where partner is sterile (e.g., vasectomy), should be considered to be of child bearing potential.

WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to the start of study medication.

[redacted]

[redacted]

[redacted]

5.2 Exclusion Criteria

Sex and Reproductive Status

1) WOCBP who are unwilling or unable to use an acceptable method to avoid pregnancy for the entire study period and for up to 2 weeks after the study.
2) WOCBP using a prohibited contraceptive method (however, prohibited contraceptive methods are not specified in this protocol).
3) Women who are pregnant or breastfeeding
4) Women with a positive pregnancy test on enrollment or prior to study drug administration.

Target Disease Exceptions

5) Patients with cerebral metastasis that are associated with clinical symptoms, and/or are associated with surrounding edema, or that require ongoing therapy with steroids or anti-convulsants.

Medical History and Concurrent Diseases

6) Patients with serious uncontrolled medical illness despite optimal therapy i.e. uncontrolled cardiac disease, unstable angina, cerebrovascular disorder, diabetes mellitus etc; active infection, active gastric ulcer etc.

Allergies and Adverse Drug Reactions

7) Patients with previous history of serious hypersensitivity reaction to Paclitaxel.

Prohibited Therapies and/or Medications

8) Patients who following their last dose of [redacted] given on the previous [redacted] study received chemotherapy other than [redacted], surgical procedure, hormonal therapy, immunotherapy, radiotherapy, physiotherapy and/or other therapies against their cancer that may prohibit appropriate evaluation of the efficacy and safety of Paclitaxel on this rollover study.

Other Exclusion Criteria

9) Subjects who are compulsorily detained for legal reasons or treatment of either a psychiatric or physical (e.g., infectious disease) illness must not be enrolled into this study.
10) Patients whose final efficacy evaluation is judged as Progressive Disease (PD) by the treating investigator(s) based on the CT or any other images taken within 4 weeks prior to the enrollment in this study.
11) Patients with grade 2 or higher peripheral neuropathy and/or grade 2 or higher arthralgia/myalgia despite optimal medical therapy that, in the opinion of treating investigator(s), will make unsafe to continue further Paclitaxel therapy.
12) Any serious, clinically unmanageable by standard medical therapy (i.e. G-CSF for neutropenia, blood transfusion for anemia, etc.) adverse event(s), subjective/objective findings, abnormal laboratory values etc. that occur prior to initiation of Paclitxel therapy on this rollover study that, in the opinion of treating investigator(s), will make unsafe to continue further Paclitaxel therapy.

[redacted]

6 STUDY CONDUCT

6.1 Ethics

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and will be consistent with International Conference on Harmonization Good Clinical Practice (ICH GCP), Japan GCP and regulatory requirements.

The study will be conducted in compliance with the protocol. The protocol and any Amendments and the subject informed consent will receive Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval/favorable opinion prior to initiation of the study.

Freely given written informed consent must be obtained from every subject prior to clinical trial participation, including informed consent for any screening procedures conducted to establish subject eligibility for the trial.

Subjects unable to give their written consent (e.g., stroke patients, or subjects with severe dementia) may only be enrolled in the study with the consent of their legally acceptable representatives. The subject must also be informed about the nature of the study to the extent compatible with the subject's understanding, and should they become capable, personally sign and date the consent form as soon as possible.

For further details on informed consent, see Section 10.2.

The rights, safety and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

Study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s).

This trial will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment).

Systems with procedures that assure the quality of every aspect of the study will be implemented.

Study site personnel involved in this study must bear in mind that study subjects are at a risk of experiencing adverse events as a result of administration of the investigational product and study-related procedures. Anticipated benefits of the investigational products and anticipated disadvantages to the subjects must be described in the informed consent form and explained to subjects prior to enrollment in this study. During and following a subject's participation in the trial, the head of the medical institution or the investigator should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the clinical trial.

When serious unexpected events occur in a subject during the course of this study, the investigators should promptly evaluate whether the study should be discontinued, in collaboration with the Sponsor.

All study site and sponsor personnel involved in this study must take the necessary actions to ensure that all information collected about study subjects throughout the study appropriately protects subjects' privacy according to the requirements specified in the criminal law and the pharmaceutical affairs law. This applies, but is not limited to, information collected on the written informed consent, CRFs, source documents,

and publication of study results. Consequently, study subjects should, wherever possible, be identified by subject number.

A detailed summary of the applicable regulatory requirements is provided in Appendix 2.

6.2 Study Therapy

[redacted]

6.2.2 Treatment Group Assignment

Every potential study patient shall, when she/he fully meets all the eligibility criteria and submits a signed freely given informed consent, be eligible for this study registration. For each study participant, an Investigator/Sub-investigator is required to fill in all necessary items on a case registration form and send it to the Case Registration Center via facsimile as specified below. The Case Registration Center shall confirm that the data described in a registration card sent by an Investigator/Sub-investigator fulfills all inclusion criteria and does not meet any of the exclusion criteria before a case registration. The Case Registration Center shall inform an Investigator/Sub-investigator of the registration number for a registered case by telephone or facsimile. If the data described in a registration card does not fulfill the inclusion criteria or does meet any of the exclusion criteria, the Case Registration Center shall confirm the data in question by discussing it with an Investigator/Sub-investigator and, if the case is ineligible for the study, inform an Investigator/Sub-investigator of this decision by telephone and facsimile.

[redacted]

6.2.3 Treatment Administration

6.2.3.1 Method

The firs Paclitaxel dose on a given course is defined as Day 1 of therapy with subsequent drug administrations being given on Days 8, 15, 22, 29 and 36 followed by 2 weeks of rest (no drug given). One course of treatment will therfore consist of total of 49 days.

1) Pre-medications (also see Section 6.5.1)

The following premedications must be given before each paclitaxel infusion

- Dexamethasone 8 mg i.v.(*: Dose can be reduced to 4mg → 2mg → 1mg) administered 1 hour before and completed 30 minutes prior to the initiation of the paclitaxel infusion
- Ranitidine 50 mg i.v.- administered 1 hour before and completed 30 minutes prior to the initiation of the paclitaxel infusion
- Diphenhydramine 50 mg p.o.

(*): Dexamethasone:

Dexamethasone dose at the initial administration day (Day 1) shall be the same as the last dose in the previous [redacted]. If any hypersensitivity reaction was observed at the last dose in the previous Phase II study, a dosage of dexamethasone shall be double of the last dose. During the observation period (Days 1 – 7), **if there are no specific clinical problems,** dexamethasone dose for the subsequent week (Day 8) would be allowed to be decreased by half the dose from the previous week (i.e.4mg), if necessary. Consequently, if no clinically significant hypersensitivity reaction is observed in a week following the drug administration, it would be possible to use again a half of the previous dexamethasone dose (i.e. 2mg), if necessary. The minimum dexamethasone dosage however, can not be less then 1 mg). If clinically significant hypersensitivity reaction develops, and it is judged that further continuation of weekly Paclitaxel is in the best patient's interest, dexamethasone dose shall be double the previous dose (e.g. if 8 mg was given and there was an event observed then, the next dexamethasone should be 16 mg) for the subsequent Paclitaxel administrations.

2) Paclitaxel (Day1, 8, 15, 22, 29, 36) (see Section 6.5.1)

After administration of the pre-medications, the patient should receive Paclitaxel dose that is consistent with the last dose(*) of Paclitaxel that the given patient has received in the previous study [redacted]). This Paclitaxel dose shall be mixed with 250 mL of a saline solution or 5% glucose solution for intravenous infusion given over 1-hour.

(*) weekly Paclitaxel dose should be reduced, if appropriate, according to the severity of adverse effect(s) observed at the last Paclitaxel treatment in the previous Phase II study according to the "Dose Modification" criteria (See Section 6.2.3)".

Administration of weekly Paclitaxel dose should be given on the expected date of treatment ± one day.

	course 1							course 2	
Days	Day1	Day8	Day15	Day22	Day29	Day36	Day43	Day50	+++
Paclitaxel	O	O	O	O	O	O	~	O	+++

6.2.3.2 Criteria for re-treatment within the course of therapy

(Days: 8, 15, 22, 29, 36 of a therapy course)

An in-course repeated dosing could be allowed only when the laboratory test values and clinical assessments in the previous week or immediately before Paclitaxel administration meet the following requirements;

- WBC count of 2,000/μL or above, or absolute neutrophile count (ANC) of 1,000/μL or above.
- Platelet count of 75,000/μL or above.
- No Grade 2 or higher peripheral neuropathy and/or Grade 2 arthralgia/myalgia despite optimal medical therapy which, in the opinion of treating investigator(s), will make further Paclitaxel therapy unsafe.
- Any serious, clinically unmanageable by standard medical therapy (i.e. G-CSF for neutropenia, blood transfusion for anemia, etc.) adverse event(s), subjective/objective findings, abnormal laboratory values etc. occur that, in the opinion of treating investigator(s), will make unsafe to continue further Paclitaxel therapy.

If the patient does not meet above requirements or if the investigator/sub-investigator judges that, it is in the best patient's interest to delay Paclitaxel dosing, the drug administration shall be postponed by one week. Reasons for this decision should be described in a case report form. A dose modification, if appropriate, should be

performed for a successive in-course dosing. (See Section 6.2.3 “Dose Modification").

The study should be discontinued if more than two consecutive Paclitaxel administrations or more than three out of six doses total within the given treatment course are not delivered. However, in patients with evidence of Paclitaxel anti-tumor effects, as judged by the treating investigator(s), subsequent Paclitaxel therapy following longer than allowed suspension of treatment may be allowed. The reasons for this decision shall be described in a case report form and all safety precautions should be observed.

6.2.3.3 Re-treatment Criteria for Course 2 and thereafter

The second and consequent courses of therapy should be started after confirmation that the following criteria are all met prior to the drug administration.

- WBC count of 3,000/μL or above, or ANC of 1,500/μL or above.
- Platelet count of 75,000/μL or above.
- No Grade 2 or higher peripheral neuropathy and/or Grade 2 arthralgia/myalgia despite optimal medical therapy which, in the opinion of treating investigator(s), will make further Paclitaxel therapy unsafe.
- Any serious, clinically unmanageable by standard medical therapy (i.e. G-CSF for neutropenia, blood transfusion for anemia, etc.) adverse event(s), subjective/objective findings, abnormal laboratory values etc. occur that, in the opinion of the treating investigator(s), will make unsafe to continue further Paclitaxel therapy.
- No Grade 3 or higher non-hematological toxicity despite optimal medical therapy.

When any one of the criteria is not met, administration should not be started (a dose modification should be performed for a successive in-course repeated dosing. See Section 6.2.3 “Dose Modification"). Paclitaxel therapy should be started as soon as the laboratory test values and the symptoms are recovered to the acceptable level. However, if the re-treatment criteria are not met following 2 weeks after the scheduled initiation date of the given treatment course, the study therapy shall be discontinued in a given patient. When the initiation of the treatment course is delayed, the delayed initiation date shall be set as Day 1 of the given course with the subsequent treatment schedule adjusted accordingly.

However, in the given patient (i.e. in case of electrolytes abnormalities, etc.), if in the opinion of the treating investigator(s) it is still safe and in the best patient’s interest to

continue Paclitaxel therapy (with dose adjustment, if clinically indicated), the treatment may continue but the reasons for this decision must be described in the case report form.

6.2.4 Dose Modifications

Paclitaxel dose shall be reduced according to the severity of an adverse event using criteria listed below. Paclitaxel dose should be decreased by the increment of 20mg/m^2 /dose. Patients who require a decrease below the total of 60mg/m^2 /dose will be discontinued from treatment..

- WBC count: less than 1000/μL (*1)
- Grade 3 neutropenia (neutrophils count <1000/μL but ≥ 500//μL) or higher, neutropenia associated with fever (≥38°C) or infection
- Grade 3 or higher non-hematological toxicity (*2)
- Development of Grade 2 or higher peripheral neuropathy and/or Grade 2 arthralgia/myalgia despite optimal medical therapy which, in the opinion of treating investigator(s), will make further Paclitaxel therapy clinically difficult.
- When an investigator/sub-investigator judges to be clinically appropriate to skip a scheduled drug administration and/or to require a dose reduction.
- In the opinion of the treating investigator/sub-investigator there is a need for dose modification. Reasons for this decision should be described in a case report form.

(*1) Dose reduction based on the WBC count being less than 1,000/μL shall depend on a decision of treating investigator/sub-investigator (taking into consideration the time of bone marrow recovery, clinical scenario for a given patient, etc.).

(*2): For the given patient, if in the opinion of the treating investigator/sub-investigator it is not clinically necessary to reduce the Paclitaxel dose (including Grade 3 or higher electrolyte abnormality, etc.) the dose may stay the same however, the reason for this decision must be described in a case report form.

6.2.5 Discontinuation of Therapy

Study therapy MUST be immediately discontinued for the following reasons:

- If the clinical efficacy evaluation reveals progressive disease (PD).
- Withdrawal of informed consent (subject's decision to withdraw for any reason).
- Any clinical adverse event, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued treatment with study therapy is not in the best interest of the subject.

- Pregnancy.
- Termination of the study by BPKK.
- The compulsory detention for legal reasons or for treatment of either a psychiatric or physical (e.g., infectious disease) illness.
- If a patient becomes ineligible after registration for the study.

Also, the study subject should be discontinued from the study therapy for the following reasons:

- A treatment delay of > 2-weeks because of paclitaxel related toxicity
- If in the opinion of the treating investigator(s) further continuation of Paclitaxel therapy is judged to be unsafe or clinically inappropriate based on the development of new or worsening of previous symptoms.
- If any clinical findings consistent with the Grade 1 or higher interstitial pneumonia, pneumonia, pulmonary fibrosis or severe infection develops.
- If there is a need for dose reduction below the total of 60mg/m^2/dose which violates the dose-reduction criteria.
- If an alternative systemic or local anti-cancer therapy is initiated.
- If the patient has moved away from the area during the study participation that makes the continuation of the study therapy no longer feasible.
- If the treating investigator/sub-investigator judges that the discontinuation of study therapy is in the best patient's interest..

For discontinuation of the study see Section 6.6.

6.2.6 Treatment Compliance

Each study drug administration must be conducted under the supervision of an investigator/sub-investigator and the following data must be described in the case report form (CRF); date of paclitaxel administration, dosage, infusion time, body weight, and the pre-medications given.

6.2.7 Other Guidance

Not applicable.

6.3 Blinding/Unblinding

Not applicable.

6.3.1 Blinding

Not applicable.

6.3.2 Unblinding

Not applicable.

[redacted]

[redacted]

6.5 Non-therapy Precautions and Restrictions

6.5.1 Precautions

1) Pre-medication drugs:

Based on the foreign literature, prolonged use of dexamethasone as pre-medication for the weekly Paclitaxel regimen appears is utilized. Compared with the dosing method for every 3 weeks Paclitaxel schedule, the total volume of steroids administered with the weekly regimen(s) appears to be fairly large. Therefore, it is considered highly likely that this may cause suppression of the adrenocortical function hence, lower doses of dexamethasone are permitted based on tolerance of the individual patient.

A clinical study reported by [redacted] using decreasing doses of dexamethasone demonstrated that the dose of 20mg of dexamethasone (administered twice: 12 hours and 6 hours before Paclitaxel infusion) was gradually decreased to 2mg and only 1/22 patients developed skin rash but others tolerated Paclitaxel therapy well. Another report by [redacted] revealed following results: 16mg of dexamethasone was administered as pre-medication to 43 patients. There was one patient with apnea that resolved without treatment but other 42 patients had no evidence of any hypersensitivity reaction.

Based on these reports, in the Japanese Phase I weekly Paclitaxel study, dexamethasone was initially administered at the 16mg dose, which was lower than the approved 20 mg dose, with subsequent decrease to a total of 2 mg. During this study dexamethasone dosing was further changed to the initial dose of 8 mg with subsequent dose decrease to a total of 1mg. With this last dexamethasone pre-medication regimen there were no hypersensitivity reaction observed.

Based on these data, the pre-medication regimen shall be used as described in the Section 6.2.2.1 (1).

2) Paclitaxel

2-1) Preparation and i.v. infusion time

Immediately prior to the infusion, Paclitaxel shall be mixed with 250 ml of a saline solution or 5% glucose solution and administered as a 1-hour IV infusion.

Containers for the solution MUST be made of glass, polyethylene or polypropylene. Paclitaxel is known to dissolve the container if it is made of polyvinyl chloride (PVC) and the plasticizer, DEHP[di-(2-ethylhexyl)phthalate], in the container may cause leaching.

2-2) Injection kit

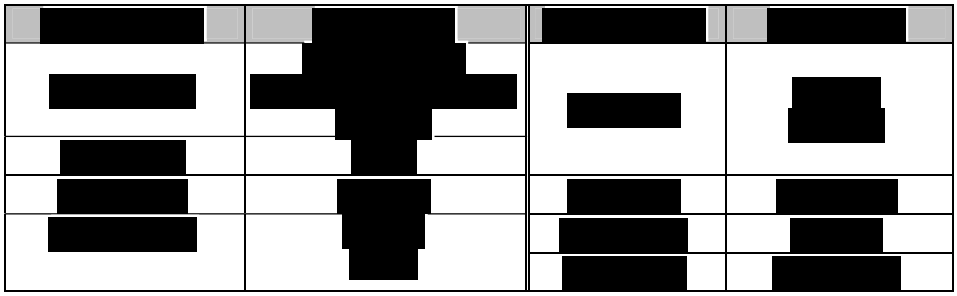
An injection kit made of PVC should NOT be used because of a possible leaching caused by plasticizer (DEHP). For the Paclitaxel injection, an in-line filter must be used.

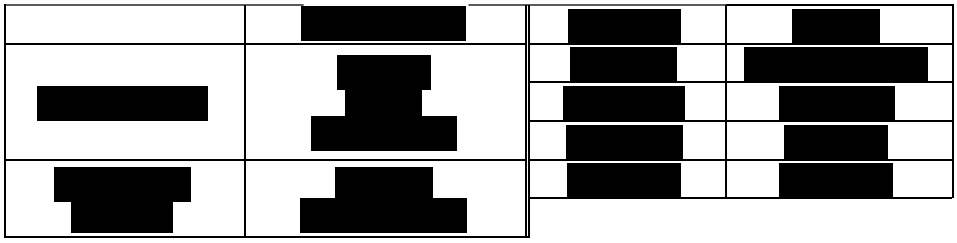
2-3) Other Caution Items

Paclitaxel is reconstituted with ethanol as a solvent. For any patient with alcoholic sensitivity, administration shall be made with full care. Upon administration, a patient's subjective and objective symptoms shall be carefully monitored and a patient should be carefully monitored during the time-points specified below;

a) First-at 30 minutes following initiation of IV infusion for possible development of immediate allergy-like symptom or arrhythmia
b) Subsequently- during and immediately after completion of IV infusion for possible hypotension.

   For treatment of immediate allergy-like symptoms, arrhythmia or hypotension, refer to Appendix 9.





6.6 Withdrawal of Subjects from Study

Subjects MUST be discontinued from the study therapy AND withdrawn from the study participation for the reasons described in Section 6.2.5.

7 STUDY PROCEDURES AND OBSERVATIONS

7.1 Flow Chart/Time and Events Schedule

Clinical laboratory testing and monitoring during the study period shall be conducted at every appropriate time-point as detailed in Table 1. For those tests conducted after the final course of treatment on a previous [redacted] please follow instructions shown in Table 1.

Any adverse event that does not recover to a baseline level by the 14th day of observation a follow-up shall be done, as much as possible, until the recovery to baseline or symptoms stabilization.

Table.7.1: X: required measurement point, XX: Conduct, if possible, at the time of clinic visit.

Procedure	[redacted]		Rollover study (CA139387)					
	As needed after 2nd course		1st course					2nd- course
	Last dose	Obser-vation	1st week (Day1)			Day8, 15,22, 29,36	7w Day43 (off)	1w Day1
			Pre-dose[a]	Infusion	Post-infusion			
Patient background	X							
Body weight (BW), Height, and BSA			X					X
Subjective/objective findings and P.S.	X	X	X			X	X	X
Blood Test (clinical laboratory)	X	X	X			X	X	X
Ca[b]			X					X[b]
Chest CT-scan[c]	Conduct when acute lung disorder or interstitial pneumonia were suspected							
Chest X-ray[d]	Conduct if necessary							
PaO_2[e]	Conduct if necessary							
ECG[f]	Conduct if necessary							
Blood pressure[g]			X		X	X		X
Urine test[h]			X					X[h]
Pregnancy test[i]			X					XX
[redacted] Observation of lesion for efficacy evaluation[j]	Conduct at least every 7 weeks[j]							

* A day that a study drug is administered is Day 1.

* Each laboratory test (except for tumor marker test) must be completed prior to administration of each weekly drug administration.

* Administration of weekly Paclitaxel doses and initiation of successive treatment courses must be done within an expected date of treatment + one day.

[a] Each required examination before the administration of a 1st course shall be conducted within 2 days before the first dose. Tumor status evaluation (tumor measurements, tumor markers) could be conducted within one month prior to the scheduled 1st Paclitaxel dose.

[b] Once a course evaluation is required.

[c] Conduct when acute lung disorder or interstitial pneumonia is suspected.

[d] Can be done for evaluation of clinical symptoms such as fever, cough, shortness of breath or dyspnea. Can be repeated as clinically indicated.

[e] Conduct if clinically indicated i.e. if any respiratory symptoms such as cough or shortness of breath develops.

[f] Done for patients with suspected cardiac-related toxicity. ECG monitoring during subsequent treatments shall be done when clinically indicated. with strong consideration given to safety of further Paclitaxel therapy.

[g] Frequent monitoring shall be performed. Patients should be closely monitored during and after the study drug infusion. Patients who will be going home following completion of Paclitaxel infusion (outpatient clinic practice) should be thoroughly evaluated for any side effects including vital signs and performance status.

[h] Should be done once prior to each treatment course. If the drug safety can be adequately judged from other evaluation(s) i.e. serum creatinine, etc., this test may not have to be done routinely.

[i] A pregnancy test shall be conducted within 72 hours prior to Day 1 of a 1st course for a WOCBP (WOCBP must have a negative serum or urine pregnancy test which has minimum sensitivity 25 IU/L or equivalent units of HCG). For successive treatment courses, it will be conducted prior to a Day 1 of each treatment course(as much as possible).

[j] To objectively evaluate the anti-tumor effect , an identical imaging diagnostic method shall be utilized for the individual patient More than one diagnostic method could be applied, if clinically indicated. In addition, lesion(s) that can be evaluated only clinically i.e. skin or chest wall lesions , should be, as much as possible, photographed and lesion measurements should be documented.

* A day that a study drug is administered is Day 1.

* Each laboratory test (except for tumor marker test) must be completed prior to administration of each weekly drug administration.

* Administration of weekly Paclitaxel doses and initiation of successive treatment courses must be done within an expected date of treatment + one day.

7.2 Procedures by Visit

7.2.1 Screening evaluation

The following tests should be performed within 14 days prior to a first dose of study drug administration. If data (i.e. laboratory test values, etc.) from the time prior to obtaining the informed consent is used for study enrollment, the study subject shall agree to this herself/himself.

- Subjective/objective findings(including Performance Status-PS)
- Clinical efficacy from [redacted]
- ECG (see Table 1)
- Blood test (Hb, WBC, ANC, Plt, T-Bil, AST(GOT), ALT(GPT), BUN, S-Cr, Ca)
- Serum or Urine pregnancy test: in case of WOCBP(minimum sensitivity 25IU/L or equivalent units of HCG)

7.2.2 Day 1 of the first therapy course (before infusion)

The following evaluation shall be conducted on Day1 of the 1st treatment course prior to a study drug administration;

- Body weight and height. Body Surface Area (BSA)

- Subjective/objective findings(including PS)
- Blood test and urine test (see Section 7.3.3for details)
- Blood pressure (pre-dose and post- infusion)
- Serum or Urine pregnancy test: in case of WOCBP (minimum sensitivity 25IU/L or equivalent units of HCG within 72 hours prior to the start of study medication. However, if a pregnancy test is already conducted within 72 hours prior to the study drug administration during the enrollment period the repeated test is not needed.

7.2.3 Evaluations during each therapy course (on Days 8, 15, 22, 29, 36, 43 of each course)

The following items shall be examined;

- Subjective/objective findings (including PS)
- Blood test and urine test (see Section 7.3.3 for details)
- Blood pressure (pre-dose and post- infusion)

See Table 1 for details of evaluation on day 43 (7^{th} week of each course of treatment)

7.2.4 Evaluations on Day 1 of Course 2 and thereafter (excluding the first course)

Following evaluation should be done on Day1 of the second therapy course and each subsequent treatment course(excluding the first course).

- Body weight, BSA.

Serum calcium and urine test shall be conducted at least once a course. When safety of further Paclitaxel therapy is adequately judged from i.e. serum creatinine values, etc., the urine test may not to be done routinely.

Tumor status evaluation should be done after completion of each treatment course (i.e. every 4~ 7 weeks or sooner, if clinically indicated)

- Measurements of lesion(s) for efficacy evaluation should be done using the same imagining method for each tumor status evaluation i.e. CT and/or MRI and/or bone scan etc. Lesions that can be evaluated only clinically i.e. skin and/or chest wall lesions should be photographed and measurement(s) of such lesions should be documented (as much as possible)

- Tumor marker (at least one type regardless of marker type)

7.2.5 Discharge evaluations

When the patient is discontinued from the study therapy (taken off the study) either due to a progressive disease or toxicity, or other (please see Section 6.2.5 for details), the following evaluation shall be done at the 14th day from the last dose (it may also be done on the 15th day or later, if necessary i.e. subject's personal matters or unexpected inconvenience at a study site,etc).

- Subjective/objective findings (including PS)
- Blood test, urine test (see Section 7.3.3)

7.3 Details of Procedures

7.3.1 Study Materials

The Sponsor will provide the Paclitaxel(BMS-181339) Investigator Brochure, any relevant safety addendum, protocol and any amendments to the protocol, Case Report Forms(CRF), instructions for completing CRFs, case registration forms and Severe Adverse Reaction (SAE) forms etc.

7.3.2 Safety Assessments

7.3.2.1 Subjective/objective findings

It shall be conducted weekly on a day of the drug administration and, if possible, during the week when therapy is suspended (during the patient visit at the clinic or in the hospital). Instruct all patients to inform the investigator immediately if the patient develops fever, dry cough, shortness of breath for early detection and diagnosis of acute lung disorder or interstitial pneumonia. Investigator must evaluate carefully each study patient (i.e.auscultation, etc) even without clinical symptoms. Conduct chest CT-scan immediately, if clinically indicated, for proper diagnosis and treatment.. Conduct A-aDO2 or DLCO, if necessary.

7.3.2.2 Blood Pressure

It should be measured pre-dose and post-dose on every drug administrations. Frequent monitoring should be performed, fully observing the patients during and after the study drug IV infusion. If the patient is treated in the outpatient clinic settings, she/he should be thoroughly evaluated (i.e. for any side effects, performance status, vital signs, etc) prior to discharge to home.

7.3.2.3 Chest X-ray and PaO2

Monitor carefully for the clinical symptoms such as fever, cough, shortness of breath or dyspnea, and if any of these symptoms develop, chest x-ray and/or PaO_2 may be conducted, if clinically indicated. If acute lung disorder or interstitial pneumonia is suspected, a chest CT-scan and, if necessary, additional A-aDO_2 or DL_{CO} can be done (cf. 6.2.4 and Appendix 9). Consider consult with experts on respiratory diseases, if needed.

7.3.3 Laboratory Test Assessments

The following laboratory tests shall be conducted at the time of registration and prior to the scheduled Paclitaxel administration at each study site (corrected Ca test shall be conducted at least once a course);

1) Hematology
   RBC count, hemoglobin, WBC count, neutrophil count, and platelet count.
2) Serum Chemistry
   Total protein, albumin, total bilirubin, ALP, AST, ALT, LDH, BUN, S-Cr, Na, K, Cl and Ca.
3) Others
   CRP (C-reactive protein)
   The following tests will be done at least once for each course prior to Paclitaxel administration.
4) Urine test: urine protein, urine sugar, urobilinogen
   The following obligatory evaluation should be done prior to the administration of a first drug dose on the first treatment course and subsequently, every ~ 7 weeks.
5) Tumor marker
   Appropriate type (at least one type regardless of marker type)
   For WOCBP, a pregnancy test must be conducted within 72 hours prior to an initial study drug administration on a 1st course and prior to the1st dose on subsequent treatment courses (as much as possible).

6) Pregnancy test

Appropriate test (Serum or Urine pregnancy test [minimum sensitivity 25 IU/L or equivalent units of HCG]).

Results of all laboratory tests required by this protocol must be recorded on the laboratory pages of the CRF or by another method as agreed upon between the Investigator/Sub-investigator and this, too must be recorded in the CRF (see Section 9.8 Laboratory Test Abnormalities).

The following evaluation should be conducted if any respiratory symptoms such as cough or shortness of breath develop.

7) PaO_2

7.3.4 Efficacy Assessments

7.3.4.1 Primary Efficacy Assessments

The primary efficacy endpoint will not be set in this study.

7.3.4.2 Secondary Efficacy Assessments

Not applicable.

8 INVESTIGATIONAL PRODUCT

Investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in the study, whether blinded or unblinded.

8.1 Investigational Product Identification

The sponsor will provide Paclitaxel and pre-medication drugs as study drugs.

Study Drug:

Code name: BMS-181339

Generic name: Paclitaxel

Dosage form/content: Each vial (16.7 mL) contains 100 mg of paclitaxel.

 # Premedications:

Drug Name	Formulation	Contents	Packaging
Dexamethasone	vial	One vial (2 mL) contains 8 mg dexamethasone sodium phosphate (6.6 mg as dexamethasone)	50 vials/box
Diphenhydramine	tablet	One tablet contains 10 mg diphenhydramine hydrochloride	500 tablets/bottle
Ranitidine	ampule	One ampule contains 50 mg ranitidine	10 ampules/box

8.2 Packaging and Labeling

A label bearing the following information will be placed on the container or the package of the investigational product (see Appendix 3):

- The fact that the drug is for clinical study use
- Name of the investigational product (code name)
- Lot number
- Dosage form and content
- Storage condition
- Name and address of the sponsor
- Use date, if necessary

8.3 Handling and Dispensing of Investigational Product

After study contract between the sponsor and the medical institution is finalized, the sponsor will supply the investigational drug to the investigational product storage manager designated by the head of the medical institution. The investigational product storage manager will store and manage the investigational product appropriately, according to the written procedures prepared and provided by the sponsor, and follow up the status of dispensing by keeping the record of the investigational product management sheet.

Investigational product should be stored in a secure area according to local regulations. It is the responsibility of the Investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

8.4 Investigational Product Records at Investigational Site(s)

It is the responsibility of the investigational product storage manager designated by the head of the medical institution to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received and placed in storage area.
- Amount currently in storage area.
- Label ID number or batch number.
- Dates and initials of person responsible for each investigational product inventory entry/movement.
- Amount dispensed to and returned by each subject, including unique subject identifiers.
- Amount transferred to another area for dispensing or storage.
- Non-study disposition (e.g., lost, wasted, broken).
- Amount returned to Sponsor.

Sponsor will provide forms to facilitate inventory control if the staff at the investigational site does not have an established system that meets these requirements.

Sponsor should also provide procedures stipulating instructions for the handling, storage and management of investigational products and recording thereof.

8.5 Return and Destruction of Investigational Product

8.5.1 Return of Investigational Product

Upon completion or termination of the study, all unused and/or partially used investigational product must be returned to BMKK, if not authorized by BMKK to be destroyed at the site.

All investigational products returned to BMKK must be accompanied by the appropriate documentation and be clearly identified by protocol number and study site name. Empty containers should not be returned to BMKK. It is the responsibility of the medical institution to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable local

and institutional guidelines and procedures. The return of unused investigational product(s) should be arranged by the responsible Study Monitor.

Upon completion or termination of the study, all unused and/or partially used investigational product must be returned to BMKK, if not authorized by BMKK to be destroyed at the site.

All investigational products and empty containers returned to BMKK must be accompanied by the appropriate documentation and be clearly identified by protocol number and study site name. The return of unused investigational product(s) should be arranged by the responsible Study Monitor.

8.5.2 Destruction of Investigational Product

All unused investigational products must be returned to BMKK and therefore, the product can not be destroyed at the site without appropriate reasons. The investigational product storage manager must provide a detailed explanation to BMKK if the drug is destroyed at the site. BMKK will ensure appropriate destruction of investigational product.

8.6 Retained Samples for Bioavailability/Bioequivalence Studies

Not Applicable.

9 ADVERSE EVENT REPORTING IN CLINICAL TRIALS

9.1 Importance of Adverse Event Reporting

Timely and complete reporting of safety information assists BMS/BMKK in identifying any untoward medical occurrence, thereby allowing: (1) protection of safety of study subjects; (2) a greater understanding of the overall safety profile of the investigational product; (3) recognition of dose-related investigational product toxicity; (4) appropriate modification of study protocols; (5) improvements in study design or procedures; and (6) adherence to worldwide regulatory requirements.

9.2 Collection of Safety Information

In BMS/BMKK clinical trials, an ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered a medicinal product and which

does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational or marketed) product, whether or not considered related to the medicinal (investigational or marketed) product.

During clinical trials, adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, patients should not be questioned regarding the specific occurrence of one or more adverse events.)

Following the subject's written consent to participate in the study, all serious AEs should be collected. The collection of non-serious AE information should begin at initiation of investigational product. Non-serious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the patient.

All identified AEs must be recorded and described on the appropriate Non-serious or Serious AE page of the CRF. If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms. The following information should be captured for all AEs: date (and time) of onset and resolution, severity of the event (see definitions), investigator's opinion of the relationship to investigational product (see definitions), treatment required for the AE (see categories), cause of the event (if known), and information regarding resolution/outcome (see definitions).

Severity will be graded according to the... NCI-CTC

The following categories and definitions of severity should be used for AEs in this clinical trial:

- Mild (Grade I) - Awareness of event but easily tolerated
- Moderate (Grade II) - Discomfort enough to cause some interference with usual activity
- Severe (Grade III) - Inability to carry out usual activity
- Very Severe (Grade IV) - Debilitating, significantly incapacitates subject despite symptomatic therapy

The following categories and definitions of causal relationship to study drug should be used for all BMS/BMKK clinical trial AEs:

- Certain: There is a reasonable causal relationship between the study drug and the AE. The event responds to withdrawal of study drug (dechallenge), and recurs with rechallenge when clinically feasible.
- Probable: There is a reasonable causal relationship between the study drug and the AE. The event responds to dechallenge. Rechallenge is not required.
- Possible: There is reasonable causal relationship between the study drug and the AE. Dechallenge information is lacking or unclear.
- Not likely: There is a temporal relationship to study drug administration, but there is not a reasonable causal relationship between the study drug and the AE.
- Unrelated: There is not a temporal relationship to study drug administration (too early, or late, or study drug not taken), or there is a reasonable causal relationship between another drug, concurrent disease, or circumstance and the AE.

The adverse event will be regarded as related to study drug if the causal relationship is assessed as either "1. Certain ","2. Probable" or "3. Possible".

If a causal relation of an adverse event is assessed as "4. Not likely" or "5. Unrelated," reasons for the evaluation are to be described.

The following categories and definitions of outcome /resolution should be used for all BMS/BMKK clinical trial AEs

1) Did not resolve (Persisted or Aggravated)
2) Resolved (Recovered)
3) Resolved, but residual effects(s) persist (Relieved)
4) Unknown
5) Subject Died*

* "Subject Died" category applies to reporting of Serious AEs only.

The following categories and definitions on action taken with respect to investigational product administration should be used for all BMS/BMKK clinical trial AEs

1) None
2) Dose reduced*
3) Interrupted
4) Discontinued
5) Dose Increased*

* "Dose reduced" and "dose increased" should be deleted if not applicable

The following categories on treatment required should be used for all BMS/BMKK clinical trial AEs

1) No
2) Yes (If Yes, comment on the treatment.)

A detailed explanation of the categories and definitions applicable to AEs due to laboratory abnormalities is provided in Appendix 5.

9.3 Adverse Events Related to Study Conditions

If the investigator believes that an SAE is not related to the investigational product, but is potentially related to the conditions of the study, (such as withdrawal of previous therapy, or complication of a diagnostic procedure), the relationship should be specified in the narrative section of the SAE page of the CRF.

9.4 Overdose

An overdose is defined as the accidental or intentional ingestion of any dose of a product that is considered both excessive and medically important. For reporting purposes, BMS considers an overdose, regardless of adverse outcome, as an important medical event (see Serious Adverse Events).

9.5 AE Follow-up

AEs should be followed to resolution or stabilization, and reported as SAEs if they become serious. This also applies to subjects experiencing AEs that cause interruption or discontinuation of investigational product, or those experiencing AEs that are present at the end of their participation in the study; such subjects should receive post-treatment follow-up as appropriate. If an ongoing AE changes in its severity or in its perceived relationship to study drug, a new AE entry for the event should be completed.

9.6 Reporting of AE Information Following Study Completion

Collection of safety information following the end of investigational product administration is important in assisting in the identification of possible delayed toxicities or withdrawal effects. In BMS/BMKK trials, all SAEs must be collected which occur within 30 days of discontinuation of dosing or completion of the patient's participation in the study if the last scheduled visit occurs at a later time. In

addition, the investigator should notify BMS/BMKK of any SAE which may occur after this time period which they believe to be certainly, probably or possibly related to investigational product.

9.7 Handling of Serious Adverse Events (SAEs)

A ***serious AE*** is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening (defined as an event in which the subject or patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe),
- requires inpatient hospitalization or causes prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a cancer,
- is a congenital anomaly/birth defect,
- results in the development of drug dependency or drug abuse,
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient/subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) For reporting purposes, BMS/BMKK also considers the occurrences of pregnancy or overdose (regardless of adverse outcome) as events which must be reported as important medical events.

Adverse events classified as "serious" must be recorded on the SERIOUS AE (SAE) page of the CRF and require expeditious handling and reporting to BMKK as well as to the head of the medical institutions to comply with regulatory requirements.

All serious AEs whether related or unrelated to investigational product, must be immediately reported to BMKK as well as to the head of the medical institution (or designee) by confirmed facsimile transmission. A documented telephone call may be used in lieu of a facsimile. If only limited information is initially available, follow-up reports are required. The original BMKK SAE form must be kept on file at the sponsor. In selected circumstances, the protocol may specify conditions which require additional telephone reporting.

Cases of pregnancy must be reported on Pregnancy Surveillance Forms in lieu of SAE pages (see Section 9.10).

Collection of complete information concerning SAEs is extremely important. Thus, follow-up information which becomes available as the SAE evolves, as well as supporting documentation (e.g., hospital discharge summaries and autopsy reports), should be collected subsequently, if not available at the time of the initial report, and immediately sent using the same procedure as the initial SAE report.

As required, BMKK will notify Investigators and the heads of the medical institutions of all AEs that are serious, unexpected, and certainly, probably, or possibly related to the investigational product. This notification will be in the form of a Safety Update.

Upon receiving such notices, the Investigator must review and retain the notice with the Investigator Brochure. At the same time sponsor will immediately submit a copy of this information to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) according to local regulations, via the head of the medical institution. The Investigator and IRB/IEC will determine if the informed consent requires revision. The Investigator should also comply with the IRB/IEC procedures

for reporting any other safety information. Where required, submission of Safety Updates by the Investigator to Health Authorities, should be handled according to local regulations.

Serious adverse events whose causal relationship to the investigational product cannot be ruled out (adverse drug reactions) and that meet the criteria as specified in Article 273 of the Enforcement Regulations of the Pharmaceutical Affairs Law are to be reported on an expedited basis. The sponsor will report the adverse drug reactions to the regulatory authority. The time limit of reporting varies according to whether the reported adverse drug reactions are expected or unexpected.

i. Unexpected "Death" or "cases which might result in death": within 7 days
ii. Unexpected events other than those listed above: within 15 days
iii. Expected "Death" or "Cases which might result in death": within 15 days

When necessary, the sponsor will consult with the medical expert on the actions to be taken regarding the conduct of the study, including whether this study is to be continued or not. Procedures for termination or suspension of this study are described in Section 10.7.

Reporting of Serious Adverse Events Seen in the Other Studies

When serious adverse events possibly related to the investigational product (adverse drug reactions) are reported in other studies, the sponsor will take the following actions.

For an unexpected serious adverse drug reaction, the sponsor will consult with the medical expert, if necessary, and the sponsor will notify Investigator and the head of the medical institution promptly. Any serious adverse drug reactions specified in Section 9.7 Serious Adverse events (SAEs) will be reported to the regulatory authority on an expedited basis within the specified time limits.

Periodically, according to the Investigator Brochure SOP, the Investigator Brochure will be updated to include new and relevant safety information. Until such time that

an AE becomes identified in the Investigator Brochure, it will continue to be reported to Investigators and to health authorities in line with local regulations.

9.8 Laboratory Test Abnormalities

All laboratory test values captured as part of the study should be recorded on the appropriate laboratory test results pages of the CRF, or be submitted electronically from a central lab. In addition, in order for BMKK to collect additional information about clinically important laboratory abnormalities, at a minimum, the following laboratory abnormalities should be captured on the non-serious or serious AE pages of the CRF as appropriate:

- Any laboratory test result that meets the criteria for a Serious Adverse Event
- Any laboratory abnormality that required the patient to have investigational product discontinued or interrupted
- Any laboratory abnormality that required the patient to receive specific corrective therapy.

It is expected that wherever possible, the clinical, rather than the laboratory term would be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

A detailed definition of abnormal laboratory changes and outcome is provided in Appendix 5.

9.9 Other Safety Considerations

Any clinically significant changes noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded on the appropriate AE page of the CRF (i.e., NON-SERIOUS or SERIOUS).

9.10 Pregnancy

Sexually active women of childbearing potential must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized. (See Section 5.1 for definition of WOCBP).

Before enrolling women of childbearing potential (WOCBP) in this clinical trial, Investigators must review the guideline about study participation for WOCBP which can be found in the GCP Manual for Investigators. The topics include the following:

- General Information
- Informed Consent Form
- Pregnancy Prevention Information Sheet
- Drug Interactions with Hormonal Contraceptives
- Contraceptives in Current Use
- Guidelines for the Follow-up of a Reported Pregnancy

Prior to study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent form documenting this discussion.

All WOCBP MUST have a **negative** pregnancy test within 72 hours **prior** to receiving investigational product. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG. If the pregnancy test is positive, the subject must not receive investigational product and must not be enrolled in the study.

Pregnancy testing must also be performed throughout the study as specified in Section 7.3.3 and the results of all pregnancy tests (positive or negative) recorded on the case report form.

In addition, all WOCBP should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

If following initiation of study treatment, it is subsequently discovered that a trial subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for subject safety). Exceptions to investigational product discontinuation may be considered for life-threatening conditions only after consultation with the BMKK Medical Monitor or as otherwise specified in this protocol. The Investigator must immediately notify the BMKK Medical Monitor of this event and record the pregnancy on the Pregnancy Surveillance Form. Pregnancy Surveillance Forms are forwarded to BMKK as described in Section 9.7 (SAEs).

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the Investigator must report to BMKK, on the appropriate BMKK pregnancy surveillance forms(s), follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants should be followed for a minimum of eight weeks.

10 ADMINISTRATIVE SECTION

10.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMKK. The Investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an Amendment, except where necessary to eliminate an immediate hazard(s) to study subjects. Any significant deviation must be documented in the CRF or in the specific sheet provided to record these deviations.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC, via the head of the medical institution, for review and approval/favorable opinion;
- **Bristol-Myers K.K.**;
- The head of the medical institution;
- Regulatory Authority(ies), if required by local regulations.

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMKK.

If the revision is an Administrative Letter, the Sponsor must inform their IRB(s)/IEC(s) via the head of the medical institution.

If an Amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to

obtain consent from subjects currently enrolled in the study if they are affected by the Amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

10.2 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate.

10.2.1 Informed Consent Procedures

Preparation of the consent form is the responsibility of the Investigator and must include all elements required by ICH, GCP and applicable regulatory requirements, and must adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form must also include a statement that BMKK and regulatory authorities have direct access to subject records. Prior to the beginning of the study, the Investigator must have the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects.

The Investigator must provide the subject with a copy of the consent form and written information about the study in the language in which the subject is most proficient. The language must be non-technical and easily understood. The Investigator should allow time necessary for subject to inquire about the details of the study, then informed consent must be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The subject should receive a copy of the signed informed consent and any other written information provided to study subjects prior to subject's participation in the trial.

10.2.2 Subjects Unable to Give Informed Consent

10.2.2.1 Miscellaneous Circumstances

Subjects who are compulsorily detained for legal reasons or treatment of either a psychiatric or physical (e.g., infectious disease) illness must not be enrolled into this study.

In circumstances where a subject's only access to treatment is through enrollment in a clinical trial, e.g., for subjects in developing countries with limited resources or for

subjects with no marketed treatment options, the investigator must take special care to explain the potential risks and benefits associated with the trial and ensure that the subject is giving informed consent.

When a subject may be in a dependent relationship with the investigator, a subinvestigator who is completely independent of the relationship between the subject and investigator should obtain the subject's informed consent.

10.2.3 Illiterate Subjects

If the subject is unable to read, a reliable and independent witness should be present during the entire informed consent discussion. The choice of the witness must not breach the subject's rights to confidentiality. A reliable independent witness is defined as one not affiliated with the institution or engaged in the investigation. A family member or acquaintance are appropriate independent witnesses. After the subject orally consents and has signed, if capable, the witness should sign and personally date the consent form attesting that the information is accurate and that the subject has fully understood the content of the informed consent agreement and is giving true informed consent.

10.2.4 Update of Informed Consent

The informed consent and any other information provided to subjects, should be revised whenever important new information becomes available that is relevant to the subject's consent, and should receive IRB/IEC approval/favorable opinion prior to use. The Investigator, or a person designated by the head of the medical institution, should fully inform the subject of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

During a subject's participation in the trial, any updates to the consent form and any updates to the written information will be provided to the subject.

10.3 Monitoring for Protocol Compliance

Representatives of BMKK/BMS must be allowed to visit all study site locations periodically to assess the data, quality and study integrity. On site they will review study records and directly compare them with source documents and discuss the conduct of the study with the Investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by BMS/BMKK internal auditors and government inspectors who must be allowed access to CRFs, source documents and other study files. BMS/BMKK audit reports will be kept confidential.

THE HEAD OF THE MEDICAL INSTITUTION MUST NOTIFY BMKK PROMPTLY OF ANY INSPECTIONS SCHEDULED BY REGULATORY AUTHORITIES, AND PROMPTLY FORWARD COPIES OF INSPECTION REPORTS TO BMKK.

10.4 Records and Reports

An Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the investigational product or entered as a control in the investigation. Data reported on the CRF, that are derived from source documents, must be consistent with the source documents or the discrepancies must be explained.

The CRF must be completed legibly in ink. Subjects are to be identified by birth date and subject number, if applicable. All requested information must be entered on the CRF in the spaces provided. If an item is not available or is not applicable, it must be documented as such; do not leave a space blank.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The Investigator will maintain a copy of the Signature Sheet to document signatures and seals of all persons authorized to make entries and/or corrections on CRFs. The original of this sheet will be kept by the sponsor. A correction must be made by striking through the incorrect entry with a single or double line and entering the correct information adjacent to the incorrect entry. The correction must be dated, signed or sealed and explained (if necessary) by the person making the correction and must not obscure the original entry.

The completed CRF must be promptly reviewed, signed or sealed, and dated by a qualified physician who is an Investigator or Subinvestigator. The Investigator must retain a copy of the CRFs including records of the changes and corrections.

10.5 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

Before study initiation, the Sponsor must have written and dated approval/favorable opinion from the IRB/IEC, via the head of the medical institution, for the protocol, consent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects. The Sponsor should also provide the IRB/IEC, via the head of the medical institution, with a copy of the Investigator Brochure or product labeling, information to be provided to subjects and any updates.

The Investigator and Sponsor should provide the IRB/IEC, via the head of the medical institution, with reports, updates, and other information (e.g., Safety Updates, Amendments, Administrative Letters) according to regulatory requirements or Institution procedures.

10.6 Records Retention

The head of the medical institution must retain investigational product disposition records, copies of CRFs (or electronic files), and source documents for the maximum period required by applicable regulations and guidelines, or Institution procedures, or for the period specified by the Sponsor, whichever is longer. The head of the medical institution must contact BMKK prior to destroying any records associated with the study.

BMKK will notify the head of the medical institution when the trial records are no longer needed.

10.7 Study Completion, Termination and Suspension Study Completion

10.7.1 Study Completion

When this study is completed, the investigator will notify the head of the medical institution in writing of the completion and provide a written overview of the study results.

The head of the medical institution will in turn notify the Sponsor and the IRB in writing of the completion and send a copy of the written overview of the study results.

10.7.2 Termination or Suspension of an Entire Study

For an event that may require termination of this study, the sponsor will consult with the medical expert before deciding on the termination or suspension of this study. The sponsor will provide to the medical expert any relevant safety, efficacy or other available information that may justify the need for terminating or suspending the study. The termination or suspension of this study will be decided by the sponsor, taking in consideration the advice given by the medical expert.

When the termination of this study is decided, the sponsor will promptly notify the investigator and the head of the medical institution in writing of the decision and reasons for the termination.

10.7.3 Termination or Suspension of the Study at the Medical Institution

When the investigator considers it necessary to terminate or suspend this study, the investigator will promptly report the fact and reasons in writing to the head of the medical institution to which the investigator belongs.

The head of the medical institution will in turn promptly notify the Sponsor and the IRB in writing of the fact and explain in detail the events and rationale which required the termination or suspension of the study.

11 GLOSSARY OF TERMS AND LIST OF ABBREVIATIONS

11.1 Glossary of Terms

Not applicable.

11.2 List of Abbreviations

Term	Definition
d.i.v.	drip infusion in vein
3w1q	3 weeks administration, 1week quit
6w1q	6 weeks administration, 1week quit
6w2q	6 weeks administration, 2week quit
°C	degrees centigrade
µL	microliters
µm	micrometers
A-aDO_2	Alveolar to arterial oxygen gradient
ADM	doxorubicin
AE(s)	adverse event(s)
Alb	Albumin
ALP	alkaline phosphatase
ALT (GOT)	alanine aminotransferase (Glutamic Oxaloacetic Transaminase)
ANC	Absolute Neutrophil Count
AST (GPT)	aspartate aminotransferase (Glutamin Pyruvic Transaminase)
A-V	atrioventricular
BMKK	Bristol Myers K.K.
BRM	biological response modifiers
BUN	blood urea nitrogen
Ca	Calcium
CAP	cyclophosphamide, doxorubicin, cisplatin
CHF	congestive heart failure
Cl	Chloride
cm3	centimeters cubed
CPA	cyclophosphamide
CR	complete response
CRF	case report form
CRP	C-reactive protein
CT	computed tomography
DL_{CO}	Diffusing capacity of the lung for carbon monoxide

Term	Definition
DLT	dose-limiting toxicity
ECG	electrocardiogram
ER	estrogen receptor
GCP	Good Clinical Practice
Hb	Hemoglobin
IC_{50}	50% inhibitory concentration
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IV	intravenous
K	potassium
LDH	lactosedehydrogenase
mg/m^2	milligrams per square meter
mL	mililiters
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
Na	sodium
NCI	National Cancer Institute
ng/mL	nanograms per milliliter
NSCLC	Non-small cell lung cancer
PaO_2	Partial pressure oxygen
PD	progressive disease
PgR	Progesterone receptor
Plt	Platelet
PO, p.o.	orally
PR	partial response
PS	performance status
PVC	polyvinyl chloride
RBC	red blood cells
SAE(s)	serious adverse event(s)
S-Cr	Serum Creatinine
SD	stable disease
T-Bil	Total Bilirubin
TP	Total Protein
WBC	white blood cells

[redacted]

[redacted]

APPENDIX 1 INFORMED CONSENT ELEMENT

The informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following mandatory topics:

1	That the study involves research.
2	The purpose of the study.
3	The expected duration of the subject's participation in the study.
4	The study treatment(s) and the probability for random assignment to each treatment.
5	The study procedures to be followed, including all invasive procedures.
6	Those aspects of the study that are experimental.
7	The reasonably foreseeable risks or inconveniences to the subject, and when applicable, to an embryo, fetus, or nursing infant.
8	The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
9	The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.
10	That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the study are published, the subject's identity will remain confidential.
11	That the BPKK/BMS monitor and/or BPKK/BMS representative, IRB/IEC, and regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing and dating a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
12	The subject's responsibilities.

13	The compensation and/or treatment available to the subject in the event of study-related injury.
14	The anticipated prorated payment, if any, to the subject for participating in the study.
15	The person(s) to contact for further information regarding the study and the rights of study subject's, and whom to contact in the event of study-related injury.
16	That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the study, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
17	The foreseeable circumstances and/or reasons under which the subject's participation in the study may be terminated.
18	The anticipated expenses, if any, to the subject for participating in the study.
19	The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
20	That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
21	The approximate number of subjects involved in the study.
22	The name, title and address of the Investigator or the subinvestigator to contact.

Additional mandatory topics for inclusion in the informed consent of studies enrolling Women of Child Bearing Potential (WOCBP):

1 General Statement

The subject must not be, and should not become pregnant during exposure to the investigational product. Subjects should be instructed to contact the Investigator if they plan to change their pregnancy avoidance method or if they need to take any prescription drug or other medication not prescribed by Investigator. Sexually active subjects must use an effective method of pregnancy avoidance during the course of the study, in a manner such that risk of failure is minimized. The informed consent must indicate that information on pregnancy prevention for women of child-bearing potential has been reviewed with the subject by the Investigator or study designee.

2 Laboratory & Animal Reproductive Toxicology

A statement addressing what is known about the investigational product from laboratory and animal reproductive toxicity studies concerning possible mutagenic and/or teratogenic effects should be included in the consent. The consent should indicate that this information has limited predictive value for humans.

3 Unforeseeable Risks

The consent must indicate that exposure to the investigational product may involve currently unforeseeable risks to the subject (or embryo or fetus, if the subject is or may become pregnant).

4 Occurrence of Pregnancy or Suspected Pregnancy

The informed consent must include study contact name(s) and telephone number(s) for the subject to call if she becomes pregnant or suspects pregnancy, has missed her period or it is late, or she has a change in her usual menstrual cycle (e.g., heavier bleeding during her period or bleeding between periods).

5 Discontinuation from the Study

Any subject who becomes pregnant during the course of the study will be immediately withdrawn (unless allowed or stated differently in the protocol) and referred for obstetrical care. All financial aspects of obstetrical, child or related care are the responsibility of the subject.

6 Pregnancy Follow-up

If a subject becomes pregnant, BMS will seek access to the subject's and/or infant's clinic/hospital records through the pregnancy, and for a minimum of 8 weeks following delivery.

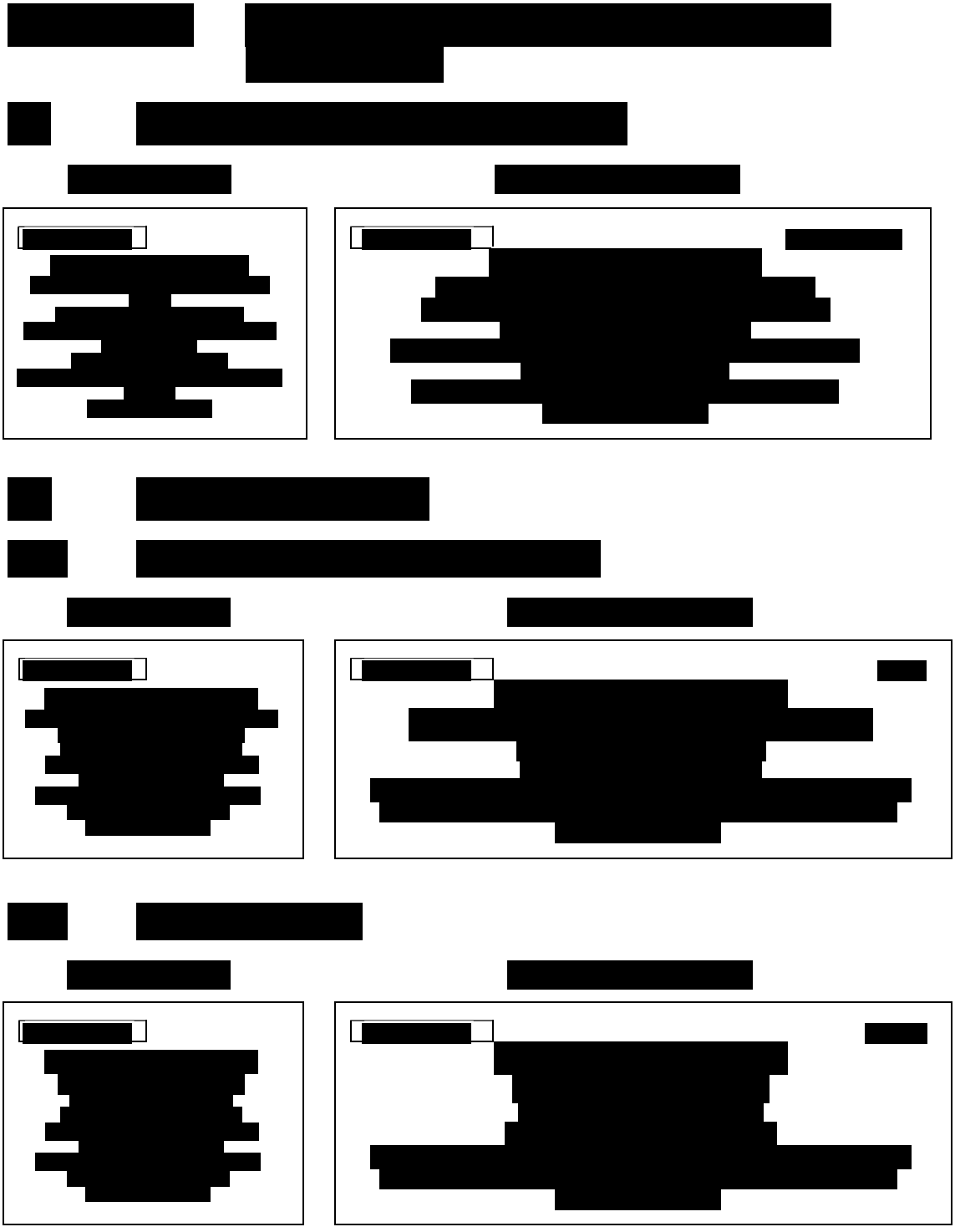
7 Use of a Study-prohibited Contraceptive Method

When applicable, the informed consent should clearly indicate if a contraceptive method is prohibited (e.g., when hormonal contraceptive interaction with the investigational product(s) is known or suspected). In this situation, a study participant should be instructed to notify the Investigator or study designee if a prohibited contraceptive method is initiated during the course of the study so that additional precautions can be taken or the subject discontinued from the study.

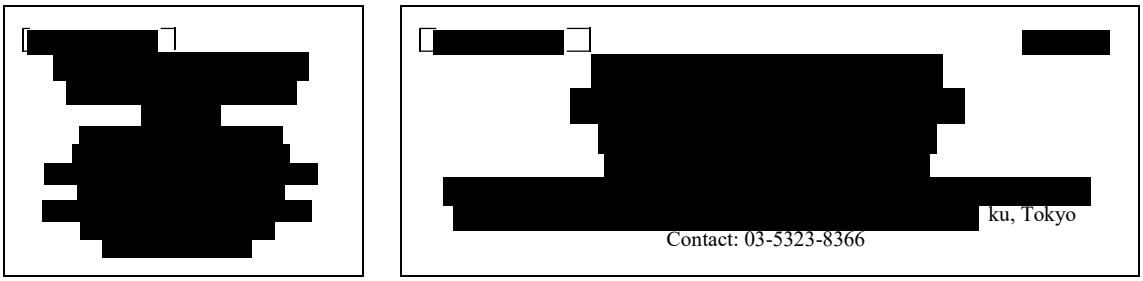
8 Non-investigational product Interactions with Hormonal Contraceptives

Women using a hormonal method of contraception (oral contraceptives, implantable or injectable agents) must be instructed to notify the Investigator or study designee of the need to take any prescription drug or other medication not prescribed by the Investigator. The purpose of this statement is to identify any potential non-investigational product interaction with the contraceptive which might reduce the effectiveness of the contraceptive method.

[redacted]



[redacted]



APPENDIX 4 ROLES AND RESPONSIBILITIES OF STUDY RELATED PERSONNEL AND STUDY PERIOD

The study system is described below.

4.1 SPONSOR

4.1.1 Sponsor

[redacted]

4.1.2 Study Director

Taku Seriu, M.D., Director

[redacted]

4.1.3 Medical Expert and Roles Thereof

[redacted]

Roles

The medical expert will, as occasion demands, advise about the following matters etc. from a medical point of view:

- Examination of the Protocol
- Preparation for and participation, if necessary, at KIKO Consultations
- Examination of the Case Report Form (CRF)
- Examination of the informed consent form and explanatory document
- Examination of investigator's brochure
- Examination of handling for adverse events (AEs) and safety information
- Examination of continuation, change, termination and suspension of the study
- Review of the clinical study report

4.1.4 Monitor

[redacted]

4.1.5 Auditor

[redacted]

4.1.6 Biostatistics Analyst

[redacted]

4.2 PK/PD ANALYST

Not applicable.

4.3 COORDINATING INVESTIGATOR AND ROLES THEREOF

[redacted]

[Roles]

- Coordinate the details of the protocol between the study sites.
- Coordinate troubles on interpretations of the protocol occurring during the study.
- Opinion co-adjustment between the study coordinating investigators and investigators at Evaluation Committee Meeting and other occasions.
- Advise about the preparation and revision of the protocol and others.

4.4 COORDINATION COMMITTEE AND ROLES THEREOF

Not applicable

4.5 EFFICACY AND SAFETY COMMISSIONER

[redacted]

[Roles]

1) The efficacy/safety evaluation commissioner shall evaluate the progress of the study, safety information and others, when appropriate, and advise the sponsor about continuation, change and termination or suspension of the study. The efficacy/safety evaluation committee consists of members independent of the sponsor and the investigator.

2) At the request of the sponsor, the efficacy/safety evaluation committee shall conduct the following tasks;

- The committee shall advise the sponsor about the appropriateness of study plan concerning safety assurance and others. The committee shall examine whether the protocol is to be revised or not and, if required, advise the sponsor about the revision.
- When a serious adverse event possibly affecting the conduct of the entire study is reported by the sponsor (see 8.2), the committee shall hold a meeting (or handed-round decision-making system*) and advise about continuation of the study, changes of the study plan and termination or suspension of the study.

- Each committee member shall review the minutes of the meeting (if a handed-round decision-making system is used, replies from each committee member are handled as the minutes) and affix his or her signature or seal.

Supplemental information on the handed-round decision-making system. The chairman shall decide whether handed-round decision-making is to be required or not. When it is considered necessary to use a handed-round decision-making system from the standpoint of the items of discussion or because of expedited nature of discussion, the chairman shall ask each member to deliberate the matters in writing, and each member shall report the results of deliberation to the chairman in writing. The sponsor shall receive the report of each member from the chairman and retain the report as the minutes of the committee meeting.

4.6 INVESTIGATORS

Refer to an Attachment, "List of Clinical Trial Sites and Investigators"

4.7 ASSIGNMENT MANAGER AND ROLES THEREOF

Not applicable.

4. 8 STUDY PERIOD

June/2005- Approval

APPENDIX 5 DEFINITION OF ABNORMAL CHANGES AND OUTCOME OF LABORATORY TESTS

Laboratory values will be monitored, and their significance will be evaluated by the investigator/subinvestigator taking in consideration how they evolve throughout the study. Any abnormal change observed, per the definition below, shall be recorded in the appropriate form as an "Adverse Event", together with its severity, actions taken and causal relationship to study drug, to be evaluated as described Section 9 in this protocol For details on the follow-up of AEs please refer to Section 9 in this protocol.

On laboratory test values: The abnormal values shall be evaluated according to the NCI Common Toxicity Criteria (NCI-CTC) ver.2.0 (Translated version into Japanese

by the JCOG will also be available in Appendix 10) . For the item that is not listed in the NCI-CTC, a normal value at each study site shall be applied).

1) Definition of abnormal changes

For laboratory test parameters, an "abnormal value" is defined as a value deviated from the normal range specified at the medical institution. When a laboratory value is initially "normal" and becomes "abnormal" during the treatment period or is initially "abnormal" and further "aggravates," such a change in laboratory values, if it is clinically significant (adverse event), is considered to be an "abnormal change."

If the investigator/subinvestigator did not assess such a change in laboratory values as an "abnormal change," the investigator/subinvestigator must provide details of and reasons for the assessment in column "Comment" on the laboratory pages of the CRF.

2) Outcome

The outcome of an abnormal change will be recorded according to the following criteria:

1) Did not resolve: The value remained outside the normal range and continued to be clinically significant (or worsened with a consequent increase in severity)
2) Resolved: The value was reversed to the pretreatment level or returned to a normal range
3) Resolved, but residual effect(s) persist: The value was not reversed to a normal range but improved to a clinically insignificant level
4) Unknown: Use of an alternative therapeutic method or failure of following-up (the reasons should be described)

APPENDIX 6 DIRECT ACCESS TO SOURCE DOCUMENTS AND DEFINITION THEREOF

The head of the medical institution and the investigator must permit monitoring and auditing to be performed by the sponsor, reviews by the IRB, and inspection by the regulatory authorities. Direct access to all the study-related records such as source documents should be provided upon request by the monitors and the auditors of the sponsor, the IRB, or the regulatory authorities. In this particular study, source documents, and the CRF data deemed as source data are defined as follows:

1) Source documents

- Subject identification code sheet
- Medical records
- Written consent
- Study drug management sheet
- Laboratory examination data
- Electrocardiography (ECG) charts
- Image that can identify the lesion (MRI, CT, etc.).

2) CRF data deemed as source data

Of the data directly recorded in the CRFs, the following data are deemed as source data: various comments described in the CRFs, study drug relation to abnormal laboratory test finding, comments of adverse events (event, severity, date of onset, actions taken regarding study drug, treatment required for event, outcome, causal relationship to study drug, comments), comments of discontinuation or drop-outs due to any safety problem, comments of protocol compliance status). The data directly described in the margin area of CRF, they are also deemed as source data.

APPENDIX 7 CRITERIA FOR RESPONSE

7.1 Evaluation Criteria on Therapeutic Effects in Patients with Advanced or Recurrent Breast Cancer(Extracts)

7.1.1 Measurement of a Lesion

1-1 Tumor lesion sites are divided into 13, as shown in Table 1, and individually measured site-by-site. These lesions include the 3 categories; 1) bi-directional measurable lesions, 2) one-directional measurable lesions and 3) immeasurable (evaluable) lesions. However, if two or more categories of lesions co-exist in one identical lesion site, these lesions shall independently be measured for records. The measurement shall in principle be made every 4 weeks.

1-2 A bi-directional lesion represents a product multiplying the largest diameter by its vertical counterpart diameter. (cm2) If a plural number of lesions exist in one identical lesion site, a product for each lesion must separately be figured out. In case only one directional measurement could be available in a front view image by X-ray, etc., a measured value of lateral view that is assumed to be vertical to the front view could be allowable for use.

1-3 One directional lesion measurement must always be done on one identical site. (cm) If a plural number of lesions exist in one identical lesion site, a product for each lesion must separately be figured out.

1-4 In an immeasurable (evaluable) lesion, an evaluation must be made as much as possible on a dose-response reaction using various parameters (radiography, diagnostic imaging methods and other useful means to trace the post-dose progresses) before and during the therapeutic period.

1-5 An efficacy evaluation on radiotherapy shall be applied only to the limited area of irradiated lesion.

7.1.2 Definition of Objective Effects

2-1 CR(Complete Response): A disappearance of all tumor lesions confirmed lasts at lest 4 weeks or longer.

2-1-1 For each skeletal (osseous) lesion, a definition shall be made as follows;

1) In osteolytic lesions prior to this study drug therapy, it shall be defined as a fluoroscopically completely hardened or a recovered back-to-normal.

2) In osteogenic lesions prior to this study drug therapy, it shall be defined as a fluoroscopically significant decrease in concentration level.

Note 1:Bone scintigraphy findings could be available for use as an auxiliary tool for diagnostics.

Note 2:For the spinal bones, a diagnosis by CT or MRI is better.

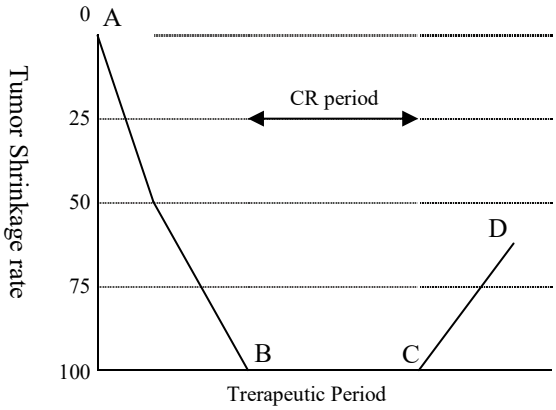
2-2 Partial Response(PR): defined as a decrease by 50% or more in a total product of measurable lesions. In an immeasurable (evaluable) lesion, defined as a clear improvement. As for any bone metastasis, defined as a calcification of bone-soluble lesion or a decrease in concentration of an osteogenic lesion. These phenomena must last at least 4 weeks or longer. During the course, either one of the lesions (secondary lesions included) shall not be increased by 25% or more and not bear any new lesion.

2-3 No Change (NC): defined as a decrease by 50% or less or as an increase by 25% or more in a total product of measurable lesions. In immeasurable (evaluable) and secondary lesions, neither clear improvement nor clear increase is shown and no new lesion appears in either case. These phenomena must last at least 4 weeks or longer, and for a bone lesion 8 weeks or more.

2-4 Progressive Disease(PD): defined as an increase by 25% or more in a total product of measurable lesions; a significant increase of measurable (evaluable) and secondary lesions, or a development of new lesion. However, in case of bone metastasis, a pathological fracture or necrosis (or weakness) will not always be interpreted as an evidence for progressive disease.

2-4-1 Though an improvement seen in some lesions and a total product of lesions reveals a shrinkage, if any one of the lesions that shows an increase by 25% or more at the time of the most shrunken compared with the baseline value, it shall be defined as PD. However, even if any one of the lesions that shows an increase by 25% or more at the time of the most shrinkage compared with the baseline value in patients with PR, it shall be interpreted as PR as long as thr shrinkage rate stays at 50% or lower compared with the baseline values. (Actual cases seen below)

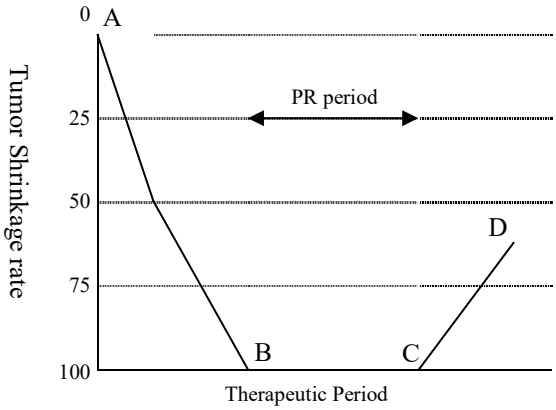
Figure 1. the case of CR



A: Day of study therapy initiation
B: Day that CR is first confirmed
C: Day that CR is last confirmed
D: Day that PD is confirmed
B-C: CR period

Note: Though Point D shows a shrinkage of 50% or more, compared with Point A, but since it shows 25% or more increase in the value at start of study therapy compared with Point C, it shall be interpreted as PD.

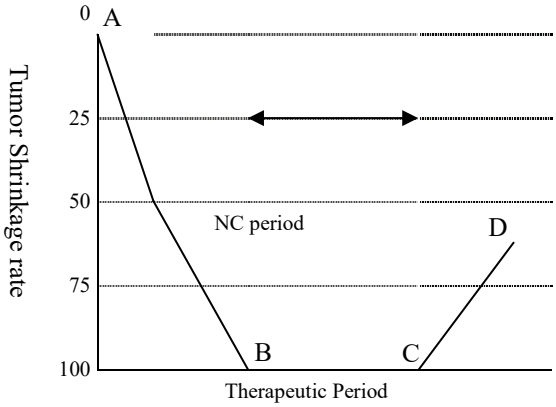
Figure 2. the case of PR



A: Day of study therapy initiation
B: Day that PR is first confirmed
C: Day that PR is last confirmed
D: Day that PD is confirmed
B-C: PR period

Note: Points C & D show 25% or more increase in the value at start of study therapy compared with Point B. However, since Point C shows 50% or more in shrinkage compared with Point A, it will be PR; in the same manner, Point D 50% or less in shrinkage compared with Point D, be interpreted as PD.

Figure 3. the case of NC



A: Day of study therapy initiation
B: Day that the most tumor shrinkage is first confirmed
C: Day that NC is last confirmed
D: Day that PD is confirmed
A-C: NC period
Note: Point D shows an increase of 25% or less compared with Point A, but
it shows 25% or more increase in baseline values compared with Point B, be interpreted as PD.

Note 1: CR: Complete Response(Complete or significant response), PR: Partial Response(partial or responsed), NC: No Change (Not any changed), PD: Progressive Disease

Note 2: A total product of lesions means a total product of the largest diameter and its vertical largest diameter multiplied (cm2) for bi-directional lesions and a product of measured values for one-directional lesions in plural number of lesions of one identical site.

Note 3: When a progressive disease stays as NC for long (24 weeks or longer) by the study drug therapy, it will be recorded separately as long NC in efficacy. However, it will not be added to "9. Calculation of Response Rate".

Note 4: Cases that a decrease of 50% or more in a total product of measurable lesions lasts for 4 weeks or less and those that a decrease of 25% or more to 50% or less lasts for 4 weeks or longer could be recorded separately as

MR(Minor Response). However, it will not be added to "9. Calculation of Response Rate"

Note 5: Upon evaluating the effects in a therapeutic plan that a minimum dosage or a minimum dosing period is specified, it requires a regulated observation period of 4 weeks or more and that of 8 weeks or more for bone lesions. However, for a clarified PD, it will not be applied.

Note 6: Evaluations for radiotherapy, they will be recorded immediately after, 4 weeks and 12 weeks after radiotherapy.

Note 7: For successively planned surgery, etc., an evaluation of objective effects in case of not enough observation period given after study therapy(topical arterial injection therapy, etc.) could well be made by only changes of concerned lesions according to the specifications, regardless of duration. However, it must be described separately to other treatment methods.

Table 1: Total Evaluation of Objective Effects for Lesions										
Cate-gory		Sites	Disease Type		bi-directionally measurable		one-directionally measurable		immea-surable	Total Evaluation
					measured values	Judg-ments	measured values	Judg-ments		
Soft tissues	1	Primary breast and opposite side of breast	a. tumor							
			b. diffuse infiltration							
	2	Dermal(Skin) and Subcutaneous	topical	a. node						
				b. disperse						
				c. diffuse infiltration						
			d. distal							
	3	lymphatic node	a. topical/local							
			b. distal							
	4	mediastinal hilar tumor								
bone	5	bone	a. bone							
			b. bone marrow							
Viscera	6	lung	a. node type							
			b. disperse type							
			c. funicular type							
	7	pleura	a. node/thickness							
			b. pleural effusion							
	8	pericardial humor								
	9	hepatic								
	10	intra-abdominal tumor								
	11	ascites								
	12	central nervous system(CNS, brain, eyes, etc.)								
	13	Others ( )								

Note 1: Topical area for skin and subcutaneous tissue means an anterior ipsilateral thorax and others distal.

Note 2: A topical/local area of lymphatic node includes ipsilateral axilla, supra- and sub-clavicular and parasternal, and others distal.

Note 3: For pleural effusion, pericardial humor and ascites, it requires to be sytologically diagnosed as positive. A cytological negativity without use of diuretics and complete disappearance of lesion with no humoral retention; this is the only one case for PR.

Note 4: For hepatic and cerebral tests, lesions must be identified by angiography, scintigraphy, echography and CT, etc. Measurement for hepatic hypertrophy shall be made vertically from the costal end in identical site.

Note 5: See Text 2-1,2 and 4.

Note 6:No CR evaluation will be made in these lesions.

7.2 Response Evaluation Criteria in Solid Tumors (RECIST;Outlines)

7.2.1 Measurability of Tumor Lesions at Baseline

At baseline, tumor lesions will be categorized as:

measurable lesions: lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as 20 mm with conventional techniques or as 10 mm with spiral CT scan.

non- measurable lesions: all other lesions, including small lesions (longest diameter 20 mm with conventional techniques or 10 mm with spiral CT scan) and truly non-measurable lesions.

All measurements should be recorded in metric notation, using a ruler or calipers.

All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Lesions that are considered as truly non-measurable include the following:

- bone lesions;
- leptomeningeal disease;
- ascites;
- pleural/pericardial effusion;
- inflammatory breast disease;
- lymphangitis cutis/pulmonis;
- abdominal masses that are not confirmed and followed by imaging techniques;
- cystic lesions;

7.2.2 Tumor response evaluation

7.2.2.1 Baseline Documentation of "Target" and "Non-Target" Lesions

All measurable lesions up to a maximum of 10 lesions representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as “Present” or “Absent”.

7.2.2.2 Response Criteria

7.2.2.2.1 Evaluation of Target Lesions

Complete Response CR	disappearance of all target lesions.
Partial response PR	at least a 30% decrease in the sum of LD of target lesions taking as reference the baseline sum LD.
Progression PD	at least a 20% increase in the sum of LD of target lesions taking as references the smallest sum LD recorded since the treatment started or the appearance of one and more new lesions.
Stable Disease SD	neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum LD since the treatment started.

7.2.2.2.2 Evaluation of non target lesions

Complete Response CR	disappearance of all non-target lesions and normalization of tumor marker level.
Non-Complete Response CR/	

Non-Progression(non-PD):	persistence of one and more non-target lesion or/and maintenance of tumor marker level above the normal limits.
Progression PD	appearance of one and more new lesions. Unequivocal progression of existing non-target lesions.

7.2.2.2.3 Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence. The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria (see Section 9.2.3)

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Non-CR/Non-PD	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

7.2.3 Confirmation Criteria

To be assigned a status of PR or CR, the size changes in tumor measurements must be confirmed by repeat studies that should be performed no less than 4 weeks after the criteria for response are first met.

In the case of SD, the follow-up measurements conducted at least 6 weeks and longer after registration must have met the SD criteria at least once.

APPENDIX 8 PERFORMANCE STATUS

CLASSIFICATION OF PERFORMANCE STATUS (GENERAL CONDITIONS) SPECIFIED BY THE EASTERN COOPERATIVE ONCOLOGY GROUP

Grade	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 walking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of walking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair

APPENDIX 9 THERAPEUTIC ACTIONS FOR ACUTE ALLERGIC SYMPTOMS, ARRHYTHMIA, HYPOTENSION OR INTERSTITIAL PNEUMONIA

Careful monitoring should be made, especially during the first 30 minutes after initiation of infusion when hypersensitivity reactions (immediate type allergy-like symptoms) or arrhythmia possibly appear, during, and after, the infusion when hypotension may appear.

[Hypersensitivity Reactions (Immediate type Allergy-like Symptoms)]

In the U.S. clinical studies, the reported hypersensitivity reactions (immediate type allergy-like symptoms) attributed to paclitaxel administration included dyspnea, bronchospasm, decreased blood pressure, increased blood pressure, angioedema (laryngeal stridor, epiglottic swelling, periorbital edema, etc.), urticaria, flushing, erythematous rash, abdominal pain, pain of extremities, vomiting, fever, and rigidity.

In the event of clear evidence of hypersensitivity reaction (immediate type allergy-like reactions), paclitaxel should immediately be discontinued, and the following actions should be taken while close cardiopulmonary monitoring:

1) Diphenhydramine-calcium bromide (5 ml; containing 20 mg of diphenhydramine) should be intravenously administered (the dose should be adjusted appropriately according to the patient™s status).

2) Epinephrine (not greater than 0.25 mg) should be diluted with saline or other solvents and administered intravenously as slowly as possible. This course should be repeated at 5- to 15-minute intervals at its need (alternatives are dobutamine and dopamine preparations).

    a) Hypotension not responding to epinephrine: Central venous pressure and other cardiovascular parameters should be monitored, and intravenous fluid should be given, if necessary.

    b) Stridor not responding to epinephrine: bronchodilators such as salbutamol sulfate (1.5 - 2.5 mg of salbutamol or equivalent doses of other drugs) should be given by inhalation, using a nebulizer.

3) It is known that corticosteroids are effective in blocking allergic reactions of delayed type due to various antigens. Sodium methylprednisolone succinate

125 mg may be administered intravenously for prevention of recurrence or allergic symptoms.

[Arrhythmia]

The following therapeutic actions may be taken for arrhythmia:

1) Asymptomatic bradycardia: paclitaxel may be continued.

2) Symptomatic bradycardia: paclitaxel should be discontinued.

3) Marked sinus bradycardia: paclitaxel should be discontinued, and atropine should be administered intravenously at 5-minute intervals (0.5 mg per administration) until the total dose reaches 2.0 mg.

4) Atrioventricular block: paclitaxel should be discontinued. Class I block and block of Mobitz Type I will usually disappear spontaneously. Atropine produces transient improvement of atrioventricular conduction. For severe bradycardia and others (block of Mobitz Type II or complete atrioventricular block), pacing therapy should be used.

5) Marked ventricular ectopy (PVC, non-sustained VT, etc.) and marked tachycardia: paclitaxel should be discontinued, and lidocaine should be used. Intravenous lidocaine therapy should be started with 1 - 2 mg/kg/min and, if effective, followed by drip infusion of 1 - 2 mg/min.

[Hypotension]

The following therapeutic actions may be taken for hypotension:

1) Mild: Fluid therapy should be used, if necessary, for keeping blood pressure.

2) Moderate or severe: Persistent intravenous infusion of dopamine should immediately be started. Doses (5 - 15 ∝g/kg/min) should be adjusted according to the severity. The infusion should be continued until blood pressure is stabilized. If necessary, norepinephrine should be administered. After confirming that blood pressure remains stable, the dose of dopamine should be reduced, or the use of this drug should be discontinued.

[Interstitial pneumonia]

The following therapeutic measures may be taken for interstitial pneumonia diagnosed with clinical symptoms and diagnostic imaging after failure of antibiotics treatment:

It is reported that following treatment is effective: Discontinue the drug therapy, and apply corticosteroid pulse therapy (methylprednisolone 1000mg in 5% glucose solution or saline solution 200mL for intravenous over 1-hour for consecutive three days (1 course). Repeat 3 courses at maximum with an interval of 1 to 2 week. Following prednisolon 40-60 mg/day p.o. with dose reduction every 1 to 2 weeks).

Consult with doctors who are expert in respiratory disease in time of need.

APPENDIX 10 NATIONAL CANCER INSTITUTE CTC VERSION 2

PDF file can be found at

[redacted]

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COMMON TOXICITY CRITERIA (CTC)

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
ALLERGY/IMMUNOLOGY					
Allergic reaction/ hypersensitivity (including drug fever)	none	transient rash, drug fever <38°C (<100.4°F)	urticaria, drug fever ≥38°C (≥100.4°F), and/or asymptomatic bronchospasm	symptomatic bronchospasm, requiring parenteral medication(s), with or without urticaria; allergy-related edema/angioedema	anaphylaxis
Note: Isolated urticaria, in the absence of other manifestations of an allergic or hypersensitivity reaction, is graded in the DERMATOLOGY/SKIN category.					
Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	none	mild, not requiring treatment	moderate, requiring treatment	-	-
Autoimmune reaction	none	serologic or other evidence of autoimmune reaction but patient is asymptomatic (e.g., vitiligo), all organ function is normal and no treatment is required	evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism), requiring treatment other than immunosuppressive drugs	reversible autoimmune reaction involving function of a major organ or other adverse event (e.g., transient colitis or anemia), requiring short-term immunosuppressive treatment	autoimmune reaction causing major grade 4 organ dysfunction; progressive and irreversible reaction; long-term administration of high-dose immuno-suppressive therapy required
Also consider Hypothyroidism, Colitis, Hemoglobin, Hemolysis.					
Serum sickness	none	-	-	present	-
Urticaria is graded in the DERMATOLOGY/SKIN category if it occurs as an isolated symptom. If it occurs with other manifestations of allergic or hypersensitivity reaction, grade as Allergic reaction/hypersensitivity above.					
Vasculitis	none	mild, not requiring treatment	symptomatic, requiring medication	requiring steroids	ischemic changes or requiring amputation
Allergy/Immunology - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
AUDITORY/HEARING					
Conductive hearing loss is graded as Middle ear/hearing in the AUDITORY/HEARING category.					
Earache is graded in the PAIN category.					
External auditory canal	normal	external otitis with erythema or dry desquamation	external otitis with moist desquamation	external otitis with discharge, mastoiditis	necrosis of the canal soft tissue or bone
Note: Changes associated with radiation to external ear (pinnae) are graded under Radiation dermatitis in the DERMATOLOGY/SKIN category.					

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	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Inner ear/hearing	normal	hearing loss on audiometry only	tinnitus or hearing loss, not requiring hearing aid or treatment	tinnitus or hearing loss, correctable with hearing aid or treatment	severe unilateral or bilateral hearing loss (deafness), not correctable
Middle ear/hearing	normal	serous otitis without subjective decrease in hearing	serous otitis or infection requiring medical intervention; subjective decrease in hearing; rupture of tympanic membrane with discharge	otitis with discharge, mastoiditis or conductive hearing loss	necrosis of the canal soft tissue or bone
Auditory/Hearing - Other (Specify, _____)	normal	mild	moderate	severe	life-threatening or disabling
BLOOD/BONE MARROW					
Bone marrow cellularity	normal for age	mildly hypocellular or ≤25% reduction from normal cellularity for age	moderately hypocellular or >25 - ≤50% reduction from normal cellularity for age or >2 but <4 weeks to recovery of normal bone marrow cellularity	severely hypocellular or >50 - ≤75% reduction in cellularity for age or 4 - 6 weeks to recovery of normal bone marrow cellularity	aplasia or >6 weeks to recovery of normal bone marrow cellularity
Normal ranges:					
children (≤18 years)	*90% cellularity average*				
younger adults (19-59)	60 - 70% cellularity average				
older adults (≥60 years)	50% cellularity average				
Note: Grade Bone marrow cellularity only for changes related to treatment not disease.					
CD4 count	WNL	<LLN - 500/mm^3	200 - <500/mm^3	50 - <200/mm^3	<50/mm^3
Haptoglobin	normal	decreased	-	absent	-
Hemoglobin (Hgb)	WNL	<LLN - 10.0 g/dL <LLN - 100 g/L <LLN - 6.2 mmol/L	8.0 - <10.0 g/dL 80 - <100 g/L 4.9 - <6.2 mmol/L	6.5 - <8.0 g/dL 65 - <80 g/L 4.0 - <4.9 mmol/L	<6.5 g/dL <65 g/L <4.0 mmol/L
For leukemia studies or bone marrow infiltrative/ myelophthisic processes, if specified in the protocol.	WNL	10 - <25% decrease from pretreatment	25 - <50% decrease from pretreatment	50 - <75% decrease from pretreatment	≥75% decrease from pretreatment
Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis, other)	none	only laboratory evidence of hemolysis [e.g., direct antiglobulin test (DAT, Coombs') schistocytes]	evidence of red cell destruction and ≥2gm decrease in hemoglobin, no transfusion	requiring transfusion and/or medical intervention (e.g., steroids)	catastrophic consequences of hemolysis (e.g., renal failure, hypotension, bronchospasm, emergency splenectomy)
Also consider Haptoglobin, Hemoglobin.					

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Adverse Event	0	Grade 1	2	3	4
Leukocytes (total WBC)	WNL	<LLN - 3.0 x 10^9 /L <LLN - 3000/mm^3	≥2.0 - <3.0 x 10^9 /L ≥2000 - <3000/mm^3	≥1.0 - <2.0 x 10^9 /L ≥1000 - <2000/mm^3	<1.0 x 10^9 /L <1000/mm^3
For BMT studies, if specified in the protocol.	WNL	≥2.0 - <3.0 X 10^9/L ≥2000 - <3000/mm^3	≥1.0 - <2.0 x 10^9 /L ≥1000 - <2000/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	<0.5 x 10^9 /L <500/mm^3
For pediatric BMT studies (using age, race and sex normal values), if specified in the protocol.		*≥75 - <100% LLN*	*≥50 - <75% LLN*	*≥25 - 50% LLN*	*<25% LLN*
Lymphopenia	WNL	<LLN - 1.0 x 10^9 /L <LLN - 1000/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	<0.5 x 10^9 /L <500/mm^3	-
For pediatric BMT studies (using age, race and sex normal values), if specified in the protocol.		*≥75 - <100%LLN*	*≥50 - <75%LLN*	*≥25 - <50%LLN*	*<25%LLN*
Neutrophils/granulocytes (ANC/AGC)	WNL	≥1.5 - <2.0 x 10^9 /L ≥1500 - <2000/mm^3	≥1.0 - <1.5 x 10^9 /L ≥1000 - <1500/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	<0.5 x 10^9 /L <500/mm^3
For BMT studies, if specified in the protocol.	WNL	≥1.0 - <1.5 x 10^9 /L ≥1000 - <1500/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	≥0.1 - <0.5 x 10^9 /L ≥100 - <500/mm^3	<0.1 x 10^9 /L <100/mm^3
For leukemia studies or bone marrow infiltrative/ myelophthisic process, if specified in the protocol.	WNL	10 - <25% decrease from baseline	25 - <50% decrease from baseline	50 - <75% decrease from baseline	≥75% decrease from baseline
Platelets	WNL	<LLN - 75.0 x 10^9 /L <LLN - 75,000/mm^3	≥50.0 - <75.0 x 10^9 /L ≥50,000 - <75,000/mm^3	≥10.0 - <50.0 x 10^9 /L ≥10,000 - <50,000/mm^3	<10.0 x 10^9 /L <10,000/mm^3
For BMT studies, if specified in the protocol.	WNL	≥50.0 - <75.0 x 10^9 /L ≥50,000 - <75,000/mm^3	≥20.0 - <50.0 x 10^9 /L ≥20,000 - <50,000/mm^3	≥10.0 - <20.0 x 10^9 /L ≥10,000 - <20,000/mm^3	<10.0 x 10^9 /L <10,000/mm^3
For leukemia studies or bone marrow infiltrative/ myelophthisic process, if specified in the protocol.	WNL	10 - <25% decrease from baseline	25 - <50% decrease from baseline	50 - <75% decrease from baseline	≥75% decrease from baseline
Transfusion: Platelets	none	-	-	yes	platelet transfusions and other measures required to improve platelet increment; platelet transfusion refractoriness associated with life-threatening bleeding. (e.g., HLA or cross matched platelet transfusions)
For BMT studies, if specified in the protocol.	none	1 platelet transfusion in 24 hours	2 platelet transfusions in 24 hours	≥3 platelet transfusions in 24 hours	platelet transfusions and other measures required to improve platelet increment; platelet transfusion refractoriness associated with life-threatening bleeding. (e.g., HLA or cross matched platelet transfusions)
Also consider Platelets.					

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Adverse Event	Grade 0	1	2	3	4
Transfusion: pRBCs	none	-	-	yes	-
For BMT studies, if specified in the protocol.	none	≤2 u pRBC in 24 hours elective or planned	3 u pRBC in 24 hours elective or planned	≥4 u pRBC in 24 hours	hemorrhage or hemolysis associated with life-threatening anemia; medical intervention required to improve hemoglobin
For pediatric BMT studies, if specified in the protocol.	*none*	*≤15mL/kg in 24 hours elective or planned*	*>15 - ≤30mL/kg in 24 hours elective or planned*	*>30mL/kg in 24 hours*	*hemorrhage or hemolysis associated with life-threatening anemia; medical intervention required to improve hemoglobin*
Also consider Hemoglobin.					
Blood/Bone Marrow - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
CARDIOVASCULAR (ARRHYTHMIA)					
Conduction abnormality/ Atrioventricular heart block	none	asymptomatic, not requiring treatment (e.g., Mobitz type I second-degree AV block, Wenckebach)	symptomatic, but not requiring treatment	symptomatic and requiring treatment (e.g., Mobitz type II second-degree AV block, third-degree AV block)	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Nodal/junctional arrhythmia/dysrhythmia	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Palpitations Note: Grade palpitations only in the absence of a documented arrhythmia.	none	present	-	-	-
Prolonged QTc interval (QTc >0.48 seconds)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Sinus bradycardia	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Sinus tachycardia	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment of underlying cause	-
Supraventricular arrhythmias (SVT/atrial fibrillation/ flutter)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Syncope (fainting) is graded in the NEUROLOGY category.					
Vasovagal episode	none	-	present without loss of consciousness	present with loss of consciousness	-

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	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Ventricular arrhythmia (PVCs/bigeminy/trigeminy/ ventricular tachycardia)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Cardiovascular/ Arrhythmia - Other (Specify, _____)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic, and requiring treatment of underlying cause	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
CARDIOVASCULAR (GENERAL)					
Acute vascular leak syndrome	absent	-	symptomatic, but not requiring fluid support	respiratory compromise or requiring fluids	life-threatening; requiring pressor support and/or ventilatory support
Cardiac-ischemia/infarction	none	non-specific T - wave flattening or changes	asymptomatic, ST - and T - wave changes suggesting ischemia	angina without evidence of infarction	acute myocardial infarction
Cardiac left ventricular function	normal	asymptomatic decline of resting ejection fraction of ≥10% but <20% of baseline value; shortening fraction ≥24% but <30%	asymptomatic but resting ejection fraction below LLN for laboratory or decline of resting ejection fraction ≥20% of baseline value; <24% shortening fraction	CHF responsive to treatment	severe or refractory CHF or requiring intubation
CNS cerebrovascular ischemia is graded in the NEUROLOGY category.					
Cardiac troponin I (cTnI)	normal	-	-	levels consistent with unstable angina as defined by the manufacturer	levels consistent with myocardial infarction as defined by the manufacturer
Cardiac troponin T (cTnT)	normal	≥0.03 - <0.05 ng/mL	≥0.05 - <0.1 ng/mL	≥0.1 - <0.2 ng/mL	≥0.2 ng/mL
Edema	none	asymptomatic, not requiring therapy	symptomatic, requiring therapy	symptomatic edema limiting function and unresponsive to therapy or requiring drug discontinuation	anasarca (severe generalized edema)
Hypertension	none	asymptomatic, transient increase by >20 mmHg (diastolic) or to >150/100* if previously WNL; not requiring treatment	recurrent or persistent or symptomatic increase by >20 mmHg (diastolic) or to >150/100* if previously WNL; not requiring treatment	requiring therapy or more intensive therapy than previously	hypertensive crisis
**Note: For pediatric patients, use age and sex appropriate normal values >95th percentile ULN.*					

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	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Hypotension	none	changes, but not requiring therapy (including transient orthostatic hypotension)	requiring brief fluid replacement or other therapy but not hospitalization; no physiologic consequences	requiring therapy and sustained medical attention, but resolves without persisting physiologic consequences	shock (associated with acidemia and impairing vital organ function due to tissue hypoperfusion)
Also consider Syncope (fainting). Notes: Angina or MI is graded as Cardiac-ischemia/infarction in the CARDIOVASCULAR (GENERAL) category. *For pediatric patients, systolic BP 65 mmHg or less in infants up to 1 year old and 70 mmHg or less in children older than 1 year of age, use two successive or three measurements in 24 hours.*					
Myocarditis	none	-	-	CHF responsive to treatment	severe or refractory CHF
Operative injury of vein/artery	none	primary suture repair for injury, but not requiring transfusion	primary suture repair for injury, requiring transfusion	vascular occlusion requiring surgery or bypass for injury	myocardial infarction; resection of organ (e.g., bowel, limb)
Pericardial effusion/ pericarditis	none	asymptomatic effusion, not requiring treatment	pericarditis (rub, ECG changes, and/or chest pain)	with physiologic consequences	tamponade (drainage or pericardial window required)
Peripheral arterial ischemia	none	-	brief episode of ischemia managed non-surgically and without permanent deficit	requiring surgical intervention	life-threatening or with permanent functional deficit (e.g., amputation)
Phlebitis (superficial)	none	-	present	-	-
Notes: Injection site reaction is graded in the DERMATOLOGY/SKIN category. Thrombosis/embolism is graded in the CARDIOVASCULAR (GENERAL) category.					
Syncope (fainting) is graded in the NEUROLOGY category.					
Thrombosis/embolism	none	-	deep vein thrombosis, not requiring anticoagulant	deep vein thrombosis, requiring anticoagulant therapy	embolic event including pulmonary embolism
Vein/artery operative injury is graded as Operative injury of vein/artery in the CARDIOVASCULAR (GENERAL) category.					
Visceral arterial ischemia (non-myocardial)	none	-	brief episode of ischemia managed non-surgically and without permanent deficit	requiring surgical intervention	life-threatening or with permanent functional deficit (e.g., resection of ileum)
Cardiovascular/ General - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling

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Adverse Event	Grade 0	1	2	3	4
COAGULATION					
Note: See the HEMORRHAGE category for grading the severity of bleeding events.					
DIC (disseminated intravascular coagulation) Also consider Platelets. Note: Must have increased fibrin split products or D-dimer in order to grade as DIC.	absent	-	-	laboratory findings present with no bleeding	laboratory findings and bleeding
Fibrinogen	WNL	≥0.75 - <1.0 x LLN	≥0.5 - <0.75 x LLN	≥0.25 - <0.5 x LLN	<0.25 x LLN
For leukemia studies or bone marrow infiltrative/ myelophthisic process, if specified in the protocol.	WNL	<20% decrease from pretreatment value or LLN	≥20 - <40% decrease from pretreatment value or LLN	≥40 - <70% decrease from pretreatment value or LLN	<50 mg
Partial thromboplastin time (PTT)	WNL	>ULN - ≤1.5 x ULN	>1.5 - ≤2 x ULN	>2 x ULN	-
Phlebitis is graded in the CARDIOVASCULAR (GENERAL) category.					
Prothrombin time (PT)	WNL	>ULN - ≤1.5 x ULN	>1.5 - ≤2 x ULN	>2 x ULN	-
Thrombosis/embolism is graded in the CARDIOVASCULAR (GENERAL) category.					
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura/TTP or hemolytic uremic syndrome/HUS)	absent	-	-	laboratory findings present without clinical consequences	laboratory findings and clinical consequences, (e.g., CNS hemorrhage/ bleeding or thrombosis/ embolism or renal failure) requiring therapeutic intervention
For BMT studies, if specified in the protocol. Also consider Hemoglobin, Platelets, Creatinine. Note: Must have microangiopathic changes on blood smear (e.g., schistocytes, helmet cells, red cell fragments).	-	evidence of RBC destruction (schistocytosis) without clinical consequences	evidence of RBC destruction with elevated creatinine (≤3 x ULN)	evidence of RBC destruction with creatinine (>3 x ULN) not requiring dialysis	evidence of RBC destruction with renal failure requiring dialysis and/or encephalopathy
Coagulation - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
CONSTITUTIONAL SYMPTOMS					
Fatigue (lethargy, malaise, asthenia) Note: See Appendix III for performance status scales.	none	increased fatigue over baseline, but not altering normal activities	moderate (e.g., decrease in performance status by 1 ECOG level or 20% Karnofsky or *Lansky*) or causing difficulty performing some activities	severe (e.g., decrease in performance status by ≥2 ECOG levels or 40% Karnofsky or *Lansky*) or loss of ability to perform some activities	bedridden or disabling

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Adverse Event	Grade 0	1	2	3	4
Fever (in the absence of neutropenia, where neutropenia is defined as AGC <1.0 x 10^9/L) Also consider Allergic reaction/hypersensitivity. Note: The temperature measurements listed above are oral or tympanic.	none	38.0 - 39.0°C (100.4 - 102.2°F)	39.1 - 40.0°C (102.3 - 104.0°F)	>40.0°C (>104.0°F) for <24hrs	>40.0°C (>104.0°F) for >24hrs
Hot flashes/flushes are graded in the ENDOCRINE category.					
Rigors, chills	none	mild, requiring symptomatic treatment (e.g., blanket) or non-narcotic medication	severe and/or prolonged, requiring narcotic medication	not responsive to narcotic medication	-
Sweating (diaphoresis)	normal	mild and occasional	frequent or drenching	-	-
Weight gain Also consider Ascites, Edema, Pleural effusion (non-malignant).	<5%	5 - <10%	10 - <20%	≥20%	-
Weight gain associated with Veno-Occlusive Disease (VOD) for BMT studies, if specified in the protocol. Also consider Ascites, Edema, Pleural effusion (non-malignant).	<2%	≥2 - <5%	≥5 - <10%	≥10% or as ascites	≥10% or fluid retention resulting in pulmonary failure
Weight loss Also consider Vomiting, Dehydration, Diarrhea.	<5%	5 - <10%	10 - <20%	≥20%	-
Constitutional Symptoms - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
DERMATOLOGY/SKIN					
Alopecia	normal	mild hair loss	pronounced hair loss	-	-
Bruising (in absence of grade 3 or 4 thrombocytopenia) Note: Bruising resulting from grade 3 or 4 thrombocytopenia is graded as Petechiae/purpura and Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia in the HEMORRHAGE category, not in the DERMATOLOGY/SKIN category.	none	localized or in dependent area	generalized	-	-
Dry skin	normal	controlled with emollients	not controlled with emollients	-	-
Erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)	absent	-	scattered, but not generalized eruption	severe or requiring IV fluids (e.g., generalized rash or painful stomatitis)	life-threatening (e.g., exfoliative or ulcerating dermatitis or requiring enteral or parenteral nutritional support)
Flushing	absent	present	-	-	-
Hand-foot skin reaction	none	skin changes or dermatitis without pain (e.g., erythema, peeling)	skin changes with pain, not interfering with function	skin changes with pain, interfering with function	-
Injection site reaction	none	pain or itching or erythema	pain or swelling, with inflammation or phlebitis	ulceration or necrosis that is severe or prolonged, or requiring surgery	-

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	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Nail changes	normal	discoloration or ridging (koilonychia) or pitting	partial or complete loss of nail(s) or pain in nailbeds	-	-
Petechiae is graded in the HEMORRHAGE category.					
Photosensitivity	none	painless erythema	painful erythema	erythema with desquamation	-
Pigmentation changes (e.g., vitiligo)	none	localized pigmentation changes	generalized pigmentation changes	-	-
Pruritus	none	mild or localized, relieved spontaneously or by local measures	intense or widespread, relieved spontaneously or by systemic measures	intense or widespread and poorly controlled despite treatment	-
Purpura is graded in the HEMORRHAGE category.					
Radiation dermatitis	none	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation ≥1.5 cm diameter and not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include bleeding not induced by minor trauma or abrasion
Note: Pain associated with radiation dermatitis is graded separately in the PAIN category as Pain due to radiation.					
Radiation recall reaction (reaction following chemotherapy in the absence of additional radiation therapy that occurs in a previous radiation port)	none	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation ≥1.5 cm diameter and not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include bleeding not induced by minor trauma or abrasion
Rash/desquamation	none	macular or papular eruption or erythema without associated symptoms	macular or papular eruption or erythema with pruritus or other associated symptoms covering <50% of body surface or localized desquamation or other lesions covering <50% of body surface area	symptomatic generalized erythroderma or macular, papular or vesicular eruption or desquamation covering ≥50% of body surface area	generalized exfoliative dermatitis or ulcerative dermatitis
Also consider Allergic reaction/hypersensitivity.					
Note: Stevens-Johnson syndrome is graded separately as Erythema multiforme in the DERMATOLOGY/SKIN category.					
Rash/dermatitis associated with high-dose chemotherapy or BMT studies.	none	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation ≥1.5 cm diameter and not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include spontaneous bleeding not induced by minor trauma or abrasion
Rash/desquamation associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol.	None	macular or papular eruption or erythema covering <25% of body surface area without associated symptoms	macular or papular eruption or erythema with pruritus or other associated symptoms covering ≥25 - <50% of body surface or localized desquamation or other lesions covering ≥25 - <50% of body surface area	symptomatic generalized erythroderma or symptomatic macular, papular or vesicular eruption, with bullous formation, or desquamation covering ≥50% of body surface area	generalized exfoliative dermatitis or ulcerative dermatitis or bullous formation
Also consider Allergic reaction/hypersensitivity.					
Note: Stevens-Johnson syndrome is graded separately as Erythema multiforme in the DERMATOLOGY/SKIN category.					

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	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Urticaria (hives, welts, wheals)	none	requiring no medication	requiring PO or topical treatment or IV medication or steroids for <24 hours	requiring IV medication or steroids for ≥24 hours	-
Wound-infectious	none	cellulitis	superficial infection	infection requiring IV antibiotics	necrotizing fasciitis
Wound-non-infectious	none	incisional separation	incisional hernia	fascial disruption without evisceration	fascial disruption with evisceration
Dermatology/Skin - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
ENDOCRINE					
Cushingoid appearance (e.g., moon face, buffalo hump, centripetal obesity, cutaneous striae)	absent	-	present	-	-
Also consider Hyperglycemia, Hypokalemia.					
Feminization of male	absent	-	-	present	-
Gynecomastia	none	mild	pronounced or painful	pronounced or painful and requiring surgery	-
Hot flashes/flushes	none	mild or no more than 1 per day	moderate and greater than 1 per day	-	-
Hypothyroidism	absent	asymptomatic,TSH elevated, no therapy given	symptomatic or thyroid replacement treatment given	patient hospitalized for manifestations of hypothyroidism	myxedema coma
Masculinization of female	absent	-	-	present	-
SIADH (syndrome of inappropriate antidiuretic hormone)	absent	-	-	present	-
Endocrine - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
GASTROINTESTINAL					
Amylase is graded in the METABOLIC/LABORATORY category.					
Anorexia	none	loss of appetite	oral intake significantly decreased	requiring IV fluids	requiring feeding tube or parenteral nutrition
Ascites (non-malignant)	none	asymptomatic	symptomatic, requiring diuretics	symptomatic, requiring therapeutic paracentesis	life-threatening physiologic consequences
Colitis	none	-	abdominal pain with mucus and/or blood in stool	abdominal pain, fever, change in bowel habits with ileus or peritoneal signs, and radiographic or biopsy documentation	perforation or requiring surgery or toxic megacolon
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Melena/GI bleeding, Rectal bleeding/hematochezia, Hypotension.					
Constipation	none	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon

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	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Dehydration	none	dry mucous membranes and/or diminished skin turgor	requiring IV fluid replacement (brief)	requiring IV fluid replacement (sustained)	physiologic consequences requiring intensive care; hemodynamic collapse
Also consider Diarrhea, Vomiting, Stomatitis/pharyngitis (oral/pharyngeal mucositis), Hypotension.					
Diarrhea patients without colostomy:	none	increase of <4 stools/day over pre-treatment	increase of 4-6 stools/day, or nocturnal stools	increase of ≥7 stools/day or incontinence; or need for parenteral support for dehydration	physiologic consequences requiring intensive care; or hemodynamic collapse
patients with a colostomy:	none	mild increase in loose, watery colostomy output compared with pretreatment	moderate increase in loose, watery colostomy output compared with pretreatment, but not interfering with normal activity	severe increase in loose, watery colostomy output compared with pretreatment, interfering with normal activity	physiologic consequences, requiring intensive care; or hemodynamic collapse
Diarrhea associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol.	None	>500 - ≤1000mL of diarrhea/day	>1000 - ≤1500mL of diarrhea/day	>1500mL of diarrhea/day	severe abdominal pain with or without ileus
For pediatric BMT studies, if specified in the protocol.		*>5 - ≤10 mL/kg of diarrhea/day*	*>10 - ≤15 mL/kg of diarrhea/day*	*>15 mL/kg of diarrhea/day*	-
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Pain, Dehydration, Hypotension.					
Duodenal ulcer (requires radiographic or endoscopic documentation)	none	-	requiring medical management or non-surgical treatment	uncontrolled by outpatient medical management; requiring hospitalization	perforation or bleeding, requiring emergency surgery
Dyspepsia/heartburn	none	mild	moderate	severe	-
Dysphagia, esophagitis, odynophagia (painful swallowing)	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly pureed, soft, or liquid diet	dysphagia, requiring IV hydration	complete obstruction (cannot swallow saliva) requiring enteral or parenteral nutritional support, or perforation
Note: If the adverse event is radiation-related, grade either under Dysphagia-esophageal related to radiation or Dysphagia-pharyngeal related to radiation.					
Dysphagia-esophageal related to radiation	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly pureed, soft, or liquid diet	Dysphagia, requiring feeding tube, IV hydration or hyperalimentation	complete obstruction (cannot swallow saliva); ulceration with bleeding not induced by minor trauma or abrasion or perforation
Also consider Pain due to radiation, Mucositis due to radiation. Note: Fistula is graded separately as Fistula-esophageal.					
Dysphagia-pharyngeal related to radiation	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly pureed, soft, or liquid diet	dysphagia, requiring feeding tube, IV hydration or hyperalimentation	complete obstruction (cannot swallow saliva); ulceration with bleeding not induced by minor trauma or abrasion or perforation
Also consider Pain due to radiation, Mucositis due to radiation. Note: Fistula is graded separately as Fistula-pharyngeal.					
Fistula-esophageal	none	-	-	present	requiring surgery
Fistula-intestinal	none	-	-	present	requiring surgery

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	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Fistula-pharyngeal	none	-	-	present	requiring surgery
Fistula-rectal/anal	none	-	-	present	requiring surgery
Flatulence	none	mild	moderate	-	-
Gastric ulcer (requires radiographic or endoscopic documentation)	none	-	requiring medical management or non-surgical treatment	bleeding without perforation, uncontrolled by outpatient medical management; requiring hospitalization or surgery	perforation or bleeding, requiring emergency surgery
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia.					
Gastritis	none	-	requiring medical management or non-surgical treatment	uncontrolled by out-patient medical management; requiring hospitalization or surgery	life-threatening bleeding, requiring emergency surgery
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia.					
Hematemesis is graded in the HEMORRHAGE category.					
Hematochezia is graded in the HEMORRHAGE category as Rectal bleeding/hematochezia.					
Ileus (or neuroconstipation)	none	-	intermittent, not requiring intervention	requiring non-surgical intervention	requiring surgery
Mouth dryness	normal	mild	moderate	-	-
Mucositis Notes: Mucositis not due to radiation is graded in the GASTROINTESTINAL category for specific sites: Colitis, Esophagitis, Gastritis, Stomatitis/pharyngitis (oral/pharyngeal mucositis), and Typhlitis; or the RENAL/GENITOURINARY category for Vaginitis. Radiation-related mucositis is graded as Mucositis due to radiation.					
Mucositis due to radiation	none	erythema of the mucosa	patchy pseudomembranous reaction (patches generally ≤1.5 cm in diameter and non-contiguous)	confluent pseudomembranous reaction (contiguous patches generally >1.5 cm in diameter)	necrosis or deep ulceration; may include bleeding not induced by minor trauma or abrasion
Also consider Pain due to radiation. Notes: Grade radiation mucositis of the larynx here. Dysphagia related to radiation is also graded as either Dysphagia-esophageal related to radiation or Dysphagia-pharyngeal related to radiation, depending on the site of treatment.					
Nausea	none	able to eat	oral intake significantly decreased	no significant intake, requiring IV fluids	-
Pancreatitis	none	-	-	abdominal pain with pancreatic enzyme elevation	complicated by shock (acute circulatory failure)
Also consider Hypotension. Note: Amylase is graded in the METABOLIC/LABORATORY category.					
Pharyngitis is graded in the GASTROINTESTINAL category as Stomatitis/pharyngitis (oral/pharyngeal mucositis).					

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	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Proctitis	none	increased stool frequency, occasional blood-streaked stools or rectal discomfort (including hemorrhoids) not requiring medication	increased stool frequency, bleeding, mucus discharge, or rectal discomfort requiring medication; anal fissure	increased stool frequency/diarrhea requiring parenteral support; rectal bleeding requiring transfusion; or persistent mucus discharge, necessitating pads	perforation, bleeding or necrosis or other life-threatening complication requiring surgical intervention (e.g., colostomy)
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Pain due to radiation. Notes: Fistula is graded separately as Fistula-rectal/anal. Proctitis occurring more than 90 days after the start of radiation therapy is graded in the RTOG/EORTC Late Radiation Morbidity Scoring Scheme. (See Appendix IV)					
Salivary gland changes	none	slightly thickened saliva; may have slightly altered taste (e.g., metallic); additional fluids may be required	thick, ropy, sticky saliva; markedly altered taste; alteration in diet required	-	acute salivary gland necrosis
Sense of smell	normal	slightly altered	markedly altered	-	-
Stomatitis/pharyngitis (oral/pharyngeal mucositis)	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema, or ulcers, but can eat or swallow	painful erythema, edema, or ulcers requiring IV hydration	severe ulceration or requires parenteral or enteral nutritional support or prophylactic intubation
For BMT studies, if specified in the protocol.	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema or ulcers but can swallow	painful erythema, edema, or ulcers preventing swallowing or requiring hydration or parenteral (or enteral) nutritional support	severe ulceration requiring prophylactic intubation or resulting in documented aspiration pneumonia
Note: Radiation-related mucositis is graded as Mucositis due to radiation.					
Taste disturbance (dysgeusia)	normal	slightly altered	markedly altered	-	-
Typhlitis (inflammation of the cecum)	none	-	-	abdominal pain, diarrhea, fever, and radiographic or biopsy documentation	perforation, bleeding or necrosis or other life-threatening complication requiring surgical intervention (e.g., colostomy)
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Hypotension, Febrile neutropenia.					
Vomiting Also consider Dehydration.	none	1 episode in 24 hours over pretreatment	2-5 episodes in 24 hours over pretreatment	≥6 episodes in 24 hours over pretreatment; or need for IV fluids	requiring parenteral nutrition; or physiologic consequences requiring intensive care; hemodynamic collapse
Weight gain is graded in the CONSTITUTIONAL SYMPTOMS category.					
Weight loss is graded in the CONSTITUTIONAL SYMPTOMS category.					
Gastrointestinal - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling

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Adverse Event	Grade 0	1	2	3	4
HEMORRHAGE					
Notes: Transfusion in this section refers to pRBC infusion. For any bleeding with grade 3 or 4 platelets (<50,000), always grade Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia. Also consider Platelets, Transfusion: pRBCs, and Transfusion: platelets in addition to grading severity by grading the site or type of bleeding. If the site or type of Hemorrhage/bleeding is listed, also use the grading that incorporates the site of bleeding: CNS Hemorrhage/bleeding, Hematuria, Hematemesis, Hemoptysis, Hemorrhage/bleeding with surgery, Melena/lower GI bleeding, Petechiae/purpura (Hemorrhage/bleeding into skin), Rectal bleeding/hematochezia, Vaginal bleeding. If the platelet count is ≥50,000 and the site or type of bleeding is listed, grade the specific site. If the site or type is not listed and the platelet count is ≥50,000, grade Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia and specify the site or type in the OTHER category.					
Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia	none	mild without transfusion		requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Also consider Platelets, Hemoglobin, Transfusion: platelets, Transfusion: pRBCs, site or type of bleeding. If the site is not listed, grade as Hemorrhage-Other (Specify site, _____). Note: This adverse event must be graded for any bleeding with grade 3 or 4 thrombocytopenia.					
Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia	none	mild without transfusion		requiring transfusion	catastrophic bleeding requiring major non-elective intervention
Also consider Platelets, Hemoglobin, Transfusion: platelets, Transfusion: pRBCs, Hemorrhage - Other (Specify site, _____). Note: Bleeding in the absence of grade 3 or 4 thrombocytopenia is graded here only if the specific site or type of bleeding is not listed elsewhere in the HEMORRHAGE category. Also grade as Other in the HEMORRHAGE category.					
CNS hemorrhage/bleeding	none	-	-	bleeding noted on CT or other scan with no clinical consequences	hemorrhagic stroke or hemorrhagic vascular event (CVA) with neurologic signs and symptoms
Epistaxis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hematemesis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hematuria (in the absence of vaginal bleeding)	none	microscopic only	intermittent gross bleeding, no clots	persistent gross bleeding or clots; may require catheterization or instrumentation, or transfusion	open surgery or necrosis or deep bladder ulceration
Hemoptysis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hemorrhage/bleeding associated with surgery	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Note: Expected blood loss at the time of surgery is not graded as an adverse event.					
Melena/GI bleeding	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention

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	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Petechiae/purpura (hemorrhage/bleeding into skin or mucosa)	none	rare petechiae of skin	petechiae or purpura in dependent areas of skin	generalized petechiae or purpura of skin or petechiae of any mucosal site	-
Rectal bleeding/ hematochezia	none	mild without transfusion or medication	persistent, requiring medication (e.g., steroid suppositories) and/or break from radiation treatment	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Vaginal bleeding	none	spotting, requiring <2 pads per day	requiring ≥2 pads per day, but not requiring transfusion	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hemorrhage - Other (Specify site, _____)	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
HEPATIC					
Alkaline phosphatase	WNL	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Bilirubin	WNL	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
Bilirubin associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol.	normal	≥2 - <3 mg/100 mL	≥3 - <6 mg/100 mL	≥6 - <15 mg/100 mL	≥15 mg/100 mL
GGT (γ - Glutamyl transpeptidase)	WNL	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Hepatic enlargement	absent	-	-	present	-
Note: Grade Hepatic enlargement only for treatment related adverse event including Veno-Occlusive Disease.					
Hypoalbuminemia	WNL	<LLN - 3 g/dL	≥2 - <3 g/dL	<2 g/dL	-
Liver dysfunction/ failure (clinical)	normal	-	-	asterixis	encephalopathy or coma
Portal vein flow	normal	-	decreased portal vein flow	reversal/retrograde portal vein flow	-
SGOT (AST) (serum glutamic oxaloacetic transaminase)	WNL	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
SGPT (ALT) (serum glutamic pyruvic transaminase)	WNL	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Hepatic - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
INFECTION/FEBRILE NEUTROPENIA					
Catheter-related infection	none	mild, no active treatment	moderate, localized infection, requiring local or oral treatment	severe, systemic infection, requiring IV antibiotic or antifungal treatment or hospitalization	life-threatening sepsis (e.g., septic shock)

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Adverse Event	Grade 0	1	2	3	4
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC <1.0 x 10^9/L, fever ≥38.5°C) Also consider Neutrophils. Note: Hypothermia instead of fever may be associated with neutropenia and is graded here.	none	-	-	Present	Life-threatening sepsis (e.g., septic shock)
Infection (documented clinically or microbiologically) with grade 3 or 4 neutropenia (ANC <1.0 x 10^9/L) Also consider Neutrophils. Notes: Hypothermia instead of fever may be associated with neutropenia and is graded here. In the absence of documented infection grade 3 or 4 neutropenia with fever is graded as Febrile neutropenia.	none	-	-	present	life-threatening sepsis (e.g., septic shock)
Infection with unknown ANC Note: This adverse event criterion is used in the rare case when ANC is unknown.	none	-	-	present	life-threatening sepsis (e.g., septic shock)
Infection without neutropenia Also consider Neutrophils.	none	mild, no active treatment	moderate, localized infection, requiring local or oral treatment	severe, systemic infection, requiring IV antibiotic or antifungal treatment, or hospitalization	life-threatening sepsis (e.g., septic shock)
Wound-infectious is graded in the DERMATOLOGY/SKIN category.					
Infection/Febrile Neutropenia - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
LYMPHATICS					
Lymphatics	normal	mild lymphedema	moderate lymphedema requiring compression; lymphocyst	severe lymphedema limiting function; lymphocyst requiring surgery	severe lymphedema limiting function with ulceration
Lymphatics - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
METABOLIC/LABORATORY					
Acidosis (metabolic or respiratory)	normal	pH <normal, but ≥7.3	-	pH <7.3	pH <7.3 with life-threatening physiologic consequences
Alkalosis (metabolic or respiratory)	normal	pH >normal, but ≤7.5	-	pH >7.5	pH >7.5 with life-threatening physiologic consequences
Amylase	WNL	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN
Bicarbonate	WNL	<LLN - 16 mEq/dL	11 - 15 mEq/dL	8 - 10 mEq/dL	<8 mEq/dL

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	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
CPK (creatine phosphokinase)	WNL	>ULN - 2.5 x ULN	>2.5 - 5 x ULN	>5 - 10 x ULN	>10 x ULN
Hypercalcemia	WNL	>ULN - 11.5 mg/dL >ULN - 2.9 mmol/L	>11.5 - 12.5 mg/dL >2.9 - 3.1 mmol/L	>12.5 - 13.5 mg/dL >3.1 - 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Hypercholesterolemia	WNL	>ULN - 300 mg/dL >ULN - 7.75 mmol/L	>300 - 400 mg/dL >7.75 - 10.34 mmol/L	>400 - 500 mg/dL >10.34 - 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Hyperglycemia	WNL	>ULN - 160 mg/dL >ULN - 8.9 mmol/L	>160 - 250 mg/dL >8.9 - 13.9 mmol/L	>250 - 500 mg/dL >13.9 - 27.8 mmol/L	>500 mg/dL >27.8 mmol/L or acidosis
Hyperkalemia	WNL	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L	>7.0 mmol/L
Hypermagnesemia	WNL	>ULN - 3.0 mg/dL >ULN - 1.23 mmol/L	-	>3.0 - 8.0 mg/dL >1.23 - 3.30 mmol/L	>8.0 mg/dL >3.30 mmol/L
Hypernatremia	WNL	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
Hypertriglyceridemia	WNL	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 10 x ULN	>10 x ULN
Hyperuricemia	WNL	>ULN - ≤10 mg/dL ≤0.59 mmol/L without physiologic consequences	-	>ULN - ≤10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L
Also consider Tumor lysis syndrome, Renal failure, Creatinine, Hyperkalemia.					
Hypocalcemia	WNL	<LLN - 8.0 mg/dL <LLN - 2.0 mmol/L	7.0 - <8.0 mg/dL 1.75 - <2.0 mmol/L	6.0 - <7.0 mg/dL 1.5 - <1.75 mmol/L	<6.0 mg/dL <1.5 mmol/L
Hypoglycemia	WNL	<LLN - 55 mg/dL <LLN - 3.0 mmol/L	40 - <55 mg/dL 2.2 - <3.0 mmol/L	30 - <40 mg/dL 1.7 - <2.2 mmol/L	<30 mg/dL <1.7 mmol/L
Hypokalemia	WNL	<LLN - 3.0 mmol/L	-	2.5 - <3.0 mmol/L	<2.5 mmol/L
Hypomagnesemia	WNL	<LLN - 1.2 mg/dL <LLN - 0.5 mmol/L	0.9 - <1.2 mg/dL 0.4 - <0.5 mmol/L	0.7 - <0.9 mg/dL 0.3 - <0.4 mmol/L	<0.7 mg/dL <0.3 mmol/L
Hyponatremia	WNL	<LLN - 130 mmol/L	-	120 - <130 mmol/L	<120 mmol/L
Hypophosphatemia	WNL	<LLN -2.5 mg/dL <LLN - 0.8 mmol/L	≥2.0 - <2.5 mg/dL ≥0.6 - <0.8 mmol/L	≥1.0 - <2.0 mg/dL ≥0.3 - <0.6 mmol/L	<1.0 mg/dL <0.3 mmol/L
Hypothyroidism is graded in the ENDOCRINE category.					
Lipase	WNL	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN
Metabolic/Laboratory - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
MUSCULOSKELETAL					
Arthralgia is graded in the PAIN category.					
Arthritis	none	mild pain with inflammation, erythema or joint swelling but not interfering with function	moderate pain with inflammation, erythema, or joint swelling interfering with function, but not interfering with activities of daily living	severe pain with inflammation, erythema, or joint swelling and interfering with activities of daily living	disabling

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Adverse Event	Grade 0	1	2	3	4
Muscle weakness (not due to neuropathy)	normal	asymptomatic with weakness on physical exam	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	bedridden or disabling
Myalgia [tenderness or pain in muscles] is graded in the PAIN category.					
Myositis (inflammation/damage of muscle) Also consider CPK. Note: Myositis implies muscle damage (i.e., elevated CPK).	none	mild pain, not interfering with function	pain interfering with function, but not interfering with activities of daily living	pain interfering with function and interfering with activities of daily living	bedridden or disabling
Osteonecrosis (avascular necrosis)	none	asymptomatic and detected by imaging only	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	symptomatic; or disabling
Musculoskeletal - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
NEUROLOGY					
Aphasia, receptive and/or expressive, is graded under Speech impairment in the NEUROLOGY category.					
Arachnoiditis/meningismus/ radiculitis Also consider Headache, Vomiting, Fever.	absent	mild pain not interfering with function	moderate pain interfering with function, but not interfering with activities of daily living	severe pain interfering with activities of daily living	unable to function or perform activities of daily living; bedridden; paraplegia
Ataxia (incoordination)	normal	asymptomatic but abnormal on physical exam, and not interfering with function	mild symptoms interfering with function, but not interfering with activities of daily living	moderate symptoms interfering with activities of daily living	bedridden or disabling
CNS cerebrovascular ischemia	none	-	-	transient ischemic event or attack (TIA)	permanent event (e.g., cerebral vascular accident)
CNS hemorrhage/bleeding is graded in the HEMORRHAGE category.					
Cognitive disturbance/ learning problems	*none*	*cognitive disability; not interfering with work/school performance; preservation of intelligence*	*cognitive disability; interfering with work/school performance; decline of 1 SD (Standard Deviation) or loss of developmental milestones*	*cognitive disability; resulting in significant impairment of work/school performance; cognitive decline >2 SD*	*inability to work/frank mental retardation*

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	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Confusion	normal	confusion or disorientation or attention deficit of brief duration; resolves spontaneously with no sequelae	confusion or disorientation or attention deficit interfering with function, but not interfering with activities of daily living	confusion or delirium interfering with activities of daily living	harmful to others or self; requiring hospitalization
Cranial neuropathy is graded in the NEUROLOGY category as Neuropathy-cranial.					
Delusions	normal	-	-	present	toxic psychosis
Depressed level of consciousness	normal	somnolence or sedation not interfering with function	somnolence or sedation interfering with function, but not interfering with activities of daily living	obtundation or stupor; difficult to arouse; interfering with activities of daily living	coma
Note: Syncope (fainting) is graded in the NEUROLOGY category.					
Dizziness/lightheadedness	none	not interfering with function	interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling
Dysphasia, receptive and/or expressive, is graded under Speech impairment in the NEUROLOGY category.					
Extrapyramidal/ involuntary movement/ restlessness	none	mild involuntary movements not interfering with function	moderate involuntary movements interfering with function, but not interfering with activities of daily living	severe involuntary movements or torticollis interfering with activities of daily living	bedridden or disabling
Hallucinations	normal	-	-	present	toxic psychosis
Headache is graded in the PAIN category.					
Insomnia	normal	occasional difficulty sleeping not interfering with function	difficulty sleeping interfering with function, but not interfering with activities of daily living	frequent difficulty sleeping, interfering with activities of daily living	-
Note: This adverse event is graded when insomnia is related to treatment. If pain or other symptoms interfere with sleep do NOT grade as insomnia.					
Irritability (children <3 years of age)	*normal*	*mild; easily consolable*	*moderate; requiring increased attention*	*severe; inconsolable*	-
Leukoencephalopathy associated radiological findings	none	mild increase in SAS (subarachnoid space) and/or mild ventriculomegaly; and/or small (+/- multiple) focal T2 hyperintensities, involving periventricular white matter or <1/3 of susceptible areas of cerebrum	moderate increase in SAS; and/or moderate ventriculomegaly; and/or focal T2 hyperintensities extending into centrum ovale; or involving 1/3 to 2/3 of susceptible areas of cerebrum	severe increase in SAS; severe ventriculomegaly; near total white matter T2 hyperintensities or diffuse low attenuation (CT); focal white matter necrosis (cystic)	severe increase in SAS; severe ventriculomegaly; diffuse low attenuation with calcification (CT); diffuse white matter necrosis (MRI)
Memory loss	normal	memory loss not interfering with function	memory loss interfering with function, but not interfering with activities of daily living	memory loss interfering with activities of daily living	amnesia

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	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Mood alteration-anxiety, agitation	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	suicidal ideation or danger to self
Mood alteration-depression	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	suicidal ideation or danger to self
Mood alteration-euphoria	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	danger to self
Neuropathic pain is graded in the PAIN category.					
Neuropathy-cranial	absent	-	present, not interfering with activities of daily living	present, interfering with activities of daily living	life-threatening, disabling
Neuropathy-motor	normal	subjective weakness but no objective findings	mild objective weakness interfering with function, but not interfering with activities of daily living	objective weakness interfering with activities of daily living	paralysis
Neuropathy-sensory	normal	loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	objective sensory loss or paresthesia (including tingling), interfering with function, but not interfering with activities of daily living	sensory loss or paresthesia interfering with activities of daily living	permanent sensory loss that interferes with function
Nystagmus	absent	present	-	-	-
Also consider Vision-double vision.					
Personality/behavioral	normal	change, but not disruptive to patient or family	disruptive to patient or family	disruptive to patient and family; requiring mental health intervention	harmful to others or self; requiring hospitalization
Pyramidal tract dysfunction (e.g., ↑ tone, hyperreflexia, positive Babinski, ↓ fine motor coordination)	normal	asymptomatic with abnormality on physical examination	symptomatic or interfering with function but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling; paralysis
Seizure(s)	none	-	seizure(s) self-limited and consciousness is preserved	seizure(s) in which consciousness is altered	seizures of any type which are prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)
Speech impairment (e.g., dysphasia or aphasia)	normal	-	awareness of receptive or expressive dysphasia, not impairing ability to communicate	receptive or expressive dysphasia, impairing ability to communicate	inability to communicate
Syncope (fainting)	absent	-	-	present	-
Also consider CARDIOVASCULAR (ARRHYTHMIA), Vasovagal episode, CNS cerebrovascular ischemia.					

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	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Tremor	none	mild and brief or intermittent but not interfering with function	moderate tremor interfering with function, but not interfering with activities of daily living	severe tremor interfering with activities of daily living	-
Vertigo	none	not interfering with function	interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling
Neurology - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
OCULAR/VISUAL					
Cataract	none	asymptomatic	symptomatic, partial visual loss	symptomatic, visual loss requiring treatment or interfering with function	-
Conjunctivitis	none	abnormal ophthalmologic changes, but asymptomatic or symptomatic without visual impairment (i.e., pain and irritation)	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Dry eye	normal	mild, not requiring treatment	moderate or requiring artificial tears	-	-
Glaucoma	none	increase in intraocular pressure but no visual loss	increase in intraocular pressure with retinal changes	visual impairment	unilateral or bilateral loss of vision (blindness)
Keratitis (corneal inflammation/ corneal ulceration)	none	abnormal ophthalmologic changes but asymptomatic or symptomatic without visual impairment (i.e., pain and irritation)	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	unilateral or bilateral loss of vision (blindness)
Tearing (watery eyes)	none	mild: not interfering with function	moderate: interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	-
Vision-blurred vision	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision-double vision (diplopia)	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision-flashing lights/floaters	normal	mild, not interfering with function	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-

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	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Vision-night blindness (nyctalopia)	normal	abnormal electro-retinography but asymptomatic	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision-photophobia	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Ocular/Visual - Other (Specify, _____)	normal	mild	moderate	severe	unilateral or bilateral loss of vision (blindness)
PAIN					
Abdominal pain or cramping	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Arthralgia (joint pain)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Arthritis (joint pain with clinical signs of inflammation) is graded in the MUSCULOSKELETAL category.					
Bone pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Chest pain (non-cardiac and non-pleuritic)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Dysmenorrhea	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Dyspareunia	none	mild pain not interfering with function	moderate pain interfering with sexual activity	severe pain preventing sexual activity	-
Dysuria is graded in the RENAL/GENITOURINARY category.					
Earache (otalgia)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Headache	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling

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	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Hepatic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Myalgia (muscle pain)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Neuropathic pain (e.g., jaw pain, neurologic pain, phantom limb pain, post-infectious neuralgia, or painful neuropathies)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Pain due to radiation	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Pelvic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Pleuritic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Rectal or perirectal pain (proctalgia)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Tumor pain (onset or exacerbation of tumor pain due to treatment)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Tumor flare is graded in the SYNDROME category.					
Pain - Other (Specify, _____)	none	mild	moderate	severe	disabling
PULMONARY					
Adult Respiratory Distress Syndrome (ARDS)	absent	-	-	-	present
Apnea	none	-	-	present	requiring intubation

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Adverse Event	Grade 0	1	2	3	4
Carbon monoxide diffusion capacity (DL_{CO})	≥90% of pretreatment or normal value	≥75 - <90% of pretreatment or normal value	≥50 - <75% of pretreatment or normal value	≥25 - <50% of pretreatment or normal value	<25% of pretreatment or normal value
Cough	absent	mild, relieved by non-prescription medication	requiring narcotic antitussive	severe cough or coughing spasms, poorly controlled or unresponsive to treatment	-
Dyspnea (shortness of breath)	normal	-	dyspnea on exertion	dyspnea at normal level of activity	dyspnea at rest or requiring ventilator support
FEV_1	≥90% of pretreatment or normal value	≥75 - <90% of pretreatment or normal value	≥50 - <75% of pretreatment or normal value	≥25 - <50% of pretreatment or normal value	<25% of pretreatment or normal value
Hiccoughs (hiccups, singultus)	none	mild, not requiring treatment	moderate, requiring treatment	severe, prolonged, and refractory to treatment	-
Hypoxia	normal	-	decreased O_2 saturation with exercise	decreased O_2 saturation at rest, requiring supplemental oxygen	decreased O_2 saturation, requiring pressure support (CPAP) or assisted ventilation
Pleural effusion (non-malignant)	none	asymptomatic and not requiring treatment	symptomatic, requiring diuretics	symptomatic, requiring O_2 or therapeutic thoracentesis	life-threatening (e.g., requiring intubation)
Pleuritic pain is graded in the PAIN category.					
Pneumonitis/pulmonary infiltrates	none	radiographic changes but asymptomatic or symptoms not requiring steroids	radiographic changes and requiring steroids or diuretics	radiographic changes and requiring oxygen	radiographic changes and requiring assisted ventilation
Pneumothorax	none	no intervention required	chest tube required	sclerosis or surgery required	life-threatening
Pulmonary embolism is graded as Thrombosis/embolism in the CARDIOVASCULAR (GENERAL) category.					
Pulmonary fibrosis	none	radiographic changes, but asymptomatic or symptoms not requiring steroids	requiring steroids or diuretics	requiring oxygen	requiring assisted ventilation
Note: Radiation-related pulmonary fibrosis is graded in the RTOG/EORTC Late Radiation Morbidity Scoring Scheme-Lung. (See Appendix IV)					
Voice changes/stridor/larynx (e.g., hoarseness, loss of voice, laryngitis)	normal	mild or intermittent hoarseness	persistent hoarseness, but able to vocalize; may have mild to moderate edema	whispered speech, not able to vocalize; may have marked edema	marked dyspnea/stridor requiring tracheostomy or intubation
Notes: Cough from radiation is graded as cough in the PULMONARY category. Radiation-related hemoptysis from larynx/pharynx is graded as Grade 4 Mucositis due to radiation in the GASTROINTESTINAL category. Radiation-related hemoptysis from the thoracic cavity is graded as Grade 4 Hemoptysis in the HEMORRHAGE category.					
Pulmonary - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling

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Adverse Event	Grade 0	1	2	3	4
RENAL/GENITOURINARY					
Bladder spasms	absent	mild symptoms, not requiring intervention	symptoms requiring antispasmodic	severe symptoms requiring narcotic	-
Creatinine	WNL	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 6.0 x ULN	>6.0 x ULN
Note: Adjust to age-appropriate levels for pediatric patients.					
Dysuria (painful urination)	none	mild symptoms requiring no intervention	symptoms relieved with therapy	symptoms not relieved despite therapy	-
Fistula or GU fistula (e.g., vaginal, vesicovaginal)	none	-	-	requiring intervention	requiring surgery
Hemoglobinuria	-	present	-	-	-
Hematuria (in the absence of vaginal bleeding) is graded in the HEMORRHAGE category.					
Incontinence	none	with coughing, sneezing, etc.	spontaneous, some control	no control (in the absence of fistula)	-
Operative injury to bladder and/or ureter	none	-	injury of bladder with primary repair	sepsis, fistula, or obstruction requiring secondary surgery; loss of one kidney; injury requiring anastomosis or re-implantation	septic obstruction of both kidneys or vesicovaginal fistula requiring diversion
Proteinuria	normal or <0.15 g/24 hours	1+ or 0.15 - 1.0 g/24 hours	2+ to 3+ or 1.0 - 3.5 g/24 hours	4+ or >3.5 g/24 hours	nephrotic syndrome
Note: If there is an inconsistency between absolute value and dip stick reading, use the absolute value for grading.					
Renal failure	none	-	-	requiring dialysis, but reversible	requiring dialysis and irreversible
Ureteral obstruction	none	unilateral, not requiring surgery	-	bilateral, not requiring surgery	stent, nephrostomy tube, or surgery
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis)	none	asymptomatic, not requiring treatment	mild, reversible and manageable with oral replacement	reversible but requiring IV replacement	irreversible, requiring continued replacement
Also consider Acidosis, Bicarbonate, Hypocalcemia, Hypophosphatemia.					
Urinary frequency/urgency	normal	increase in frequency or nocturia up to 2 x normal	increase >2 x normal but <hourly	hourly or more with urgency, or requiring catheter	-
Urinary retention	normal	hesitancy or dribbling, but no significant residual urine; retention occurring during the immediate postoperative period	hesitancy requiring medication or occasional in/out catheterization (<4 x per week), or operative bladder atony requiring indwelling catheter beyond immediate postoperative period but for <6 weeks	requiring frequent in/out catheterization (≥4 x per week) or urological intervention (e.g., TURP, suprapubic tube, urethrotomy)	bladder rupture

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Adverse Event	Grade 0	1	2	3	4
Urine color change (not related to other dietary or physiologic cause e.g., bilirubin, concentrated urine, hematuria)	normal	asymptomatic, change in urine color	-	-	-
Vaginal bleeding is graded in the HEMORRHAGE category.					
Vaginitis (not due to infection)	none	mild, not requiring treatment	moderate, relieved with treatment	severe, not relieved with treatment, or ulceration not requiring surgery	ulceration requiring surgery
Renal/Genitourinary - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
SECONDARY MALIGNANCY					
Secondary Malignancy - Other (Specify type, _____) excludes metastasis from initial primary	none	-	-	-	present
SEXUAL/REPRODUCTIVE FUNCTION					
Dyspareunia is graded in the PAIN category.					
Dysmenorrhea is graded in the PAIN category.					
Erectile impotence	normal	mild (erections impaired but satisfactory)	moderate (erections impaired, unsatisfactory for intercourse)	no erections	-
Female sterility	normal	-	-	sterile	-
Feminization of male is graded in the ENDOCRINE category.					
Irregular menses (change from baseline)	normal	occasionally irregular or lengthened interval, but continuing menstrual cycles	very irregular, but continuing menstrual cycles	persistent amenorrhea	-
Libido	normal	decrease in interest	severe loss of interest	-	-
Male infertility	-	-	oligospermia (low sperm count)	azoospermia (no sperm)	-
Masculinization of female is graded in the ENDOCRINE category.					
Vaginal dryness	normal	mild	requiring treatment and/or interfering with sexual function, dyspareunia	-	-
Sexual/Reproductive Function - Other (Specify, _____)	none	mild	moderate	severe	disabling
SYNDROMES (not included in previous categories)					
Acute vascular leak syndrome is graded in the CARDIOVASCULAR (GENERAL) category.					
ARDS (Adult Respiratory Distress Syndrome) is graded in the PULMONARY category.					

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	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Autoimmune reactions are graded in the ALLERGY/IMMUNOLOGY category.					
DIC (disseminated intravascular coagulation) is graded in the COAGULATION category.					
Fanconi's syndrome is graded as Urinary electrolyte wasting in the RENAL/GENITOURINARY category.					
Renal tubular acidosis is graded as Urinary electrolyte wasting in the RENAL/GENITOURINARY category.					
Stevens-Johnson syndrome (erythema multiforme) is graded in the DERMATOLOGY/SKIN category.					
SIADH (syndrome of inappropriate antidiuretic hormone) is graded in the ENDOCRINE category.					
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura/TTP or hemolytic uremic syndrome/HUS) is graded in the COAGULATION category.					
Tumor flare	none	mild pain not interfering with function	moderate pain; pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain; pain or analgesics interfering with function and interfering with activities of daily living	Disabling
Also consider Hypercalcemia. Note: Tumor flare is characterized by a constellation of symptoms and signs in direct relation to initiation of therapy (e.g., anti-estrogens/androgens or additional hormones). The symptoms/signs include tumor pain, inflammation of visible tumor, hypercalcemia, diffuse bone pain, and other electrolyte disturbances.					
Tumor lysis syndrome	absent	-	-	present	-
Also consider Hyperkalemia, Creatinine.					
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) is graded in the RENAL/GENITOURINARY category.					
Syndromes - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling

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Appendix I
Adverse Event Module

To be implemented at the request of the study sponsor or principal investigator in the protocol or by protocol amendment when more detailed information is considered pertinent.

Adverse Event:	Date of Treatment:		Course Number:
Date of onset:			Grade at onset:
Date of first change in grade:			Grade:
Date of next change in grade:			Grade:
Date of next change in grade:			Grade:
Date of next change in grade:			Grade:
Date of next change in grade:			Grade:
Date of next change in grade:			Grade:
Did adverse event resolve? If so, date of resolution of adverse event:	Yes_____	No_____	
Date of last observation (if prior to recovery):			
Reason(s) observations stopped (if prior to recovery):			
Was patient retreated?	Yes_____	No_____	
If yes, was treatment delayed for recovery?	Yes_____	No_____	
Date of next treatment?			
Dose reduced for next treatment?	Yes_____	No_____	

Additional Comments:

_____

_____

If module is being activated for new adverse event not currently in CTC, please provide definitions for adverse event grading:

Grade 0 = _____

Grade 1 = _____

Grade 2 = _____

Grade 3 = _____

Grade 4 = _____

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Appendix II
Infection Module

To be implemented at the request of the study sponsor or principal investigator in the protocol or by protocol amendment when more detailed information is considered pertinent.

1. Use the Common Toxicity Criteria definitions to grade the severity of the infection.
2. Specify type of infection from the following (CHOOSE ONE):

   BACTERIAL FUNGAL PROTOZOAL VIRAL UNKNOWN
3. Specify site of infection from the following (CHOOSE ALL THAT APPLY):

   BLOOD CULTURE POSITIVE
   BONE INFECTION
   CATHETER (intravenous)
   CATHETER (intravenous), tunnel infection
   CENTRAL NERVOUS SYSTEM INFECTION
   EAR INFECTION
   EYE INFECTION
   GASTROINTESTINAL INFECTION
   ORAL INFECTION
   PNEUMONIA
   SKIN INFECTION
   UPPER RESPIRATORY INFECTION
   URINARY TRACT INFECTION
   VAGINAL INFECTION
   INFECTION, not otherwise specified (Specify site, _____)
4. Specify organism, if known: _____.
5. Prophylactic antibiotic, antifungal, or antiviral therapy administration

   Yes_____ No_____

   If prophylaxis was given prior to infection, please specify below:

   Antibiotic prophylaxis _____

   Antifungal prophylaxis _____

   Antiviral prophylaxis _____

   Other prophylaxis _____

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Appendix III
Performance Status Scales/Scores

PERFORMANCE STATUS CRITERIA

Karnofsky and Lansky performance scores are intended to be multiples of 10.

ECOG (Zubrod)		Karnofsky		Lansky*	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
		90	Able to carry on normal activity; minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
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 his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

*The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.

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Appendix IV

RTOG/EORTC Late Radiation Morbidity Scoring Scheme

Use for adverse event occurring greater than 90 days after radiation therapy.

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Bladder- Late RT Morbidity Scoring	No change from baseline	Slight epithelial atrophy/minor telangiectasia (microscopic hematuria)	Moderate frequency/ generalized telangiectasia/ intermittent macroscopic hematuria	Severe frequency and dysuria/severe generalized telangiectasia (often with petechiae); frequent hematuria; reduction in bladder capacity (<150 mL)	Necrosis/contracted bladder (capacity <100 mL)/severe hemorrhagic cystitis
Bone- Late RT Morbidity Scoring	No change from baseline	Asymptomatic; no growth retardation; reduced bone density	Moderate pain or tenderness; growth retardation; irregular bone sclerosis	Severe pain or tenderness; complete arrest of bone growth; dense bone sclerosis	Necrosis/ spontaneous fracture
Brain- Late RT Morbidity Scoring	No change from baseline	Mild headache; slight lethargy	Moderate headache; great lethargy	Severe headaches; severe CNS dysfunction (partial loss of power or dyskinesia)	Seizures or paralysis; coma
Esophagus- Late RT Morbidity Scoring	No change from baseline	Mild fibrosis; slight difficulty in swallowing solids; no pain on swallowing	Unable to take solid food normally; swallowing semi-solid food; dilation may be indicated	Severe fibrosis; able to swallow only liquids; may have pain on swallowing; dilation required	Necrosis/ perforation; fistula
Eye- Late RT Morbidity Scoring	No change from baseline	Asymptomatic cataract; minor corneal ulceration or keratitis	Symptomatic cataract; moderate corneal ulceration; minor retinopathy or glaucoma	Severe keratitis; severe retinopathy or detachment; severe glaucoma	Panophthalmitis; blindness
Heart- Late RT Morbidity Scoring	No change from baseline	Asymptomatic or mild symptoms; transient T wave inversion and ST changes; sinus tachycardia >110 (at rest)	Moderate angina on effort; mild pericarditis; normal heart size; persistent abnormal T wave and ST changes; low QRS	Severe angina; pericardial effusion; constrictive pericarditis; moderate heart failure; cardiac enlargement; EKG abnormalities	Tamponade/severe heart failure/severe constrictive pericarditis
Joint- Late RT Morbidity Scoring	No change from baseline	Mild joint stiffness; slight limitation of movement	Moderate stiffness; intermittent or moderate joint pain; moderate limitation of movement	Severe joint stiffness; pain with severe limitation of movement	Necrosis/complete fixation
Kidney- Late RT Morbidity Scoring	No change from baseline	Transient albuminuria; no hypertension; mild impairment of renal function; urea 25 - 35 mg%; creatinine 1.5 - 2.0 mg%; creatinine clearance >75%	Persistent moderate albuminuria (2+); mild hypertension; no related anemia; moderate impairment of renal function; urea >36 - 60 mg%; creatinine clearance >50 - 74%	Severe albuminuria; severe hypertension; persistent anemia (<10 g%); severe renal failure; urea >60 mg%; creatinine >4 mg%; creatinine clearance <50%	Malignant hypertension; uremic coma/urea >100%
Larynx- Late RT Morbidity Scoring	No change from baseline	Hoarseness; slight arytenoid edema	Moderate arytenoid edema; chondritis	Severe edema; severe chondritis	Necrosis

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Appendix IV (continued)

RTOG/EORTC Late Radiation Morbidity Scoring Scheme

Use for adverse event occurring greater than 90 days after radiation therapy.

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Liver- Late RT Morbidity Scoring	No change from baseline	Mild lassitude; nausea; dyspepsia; slightly abnormal liver function	Moderate symptoms; some abnormal liver function tests; serum albumin normal	Disabling hepatic insufficiency; liver function tests grossly abnormal; low albumin; edema or ascites	Necrosis/hepatic coma or encephalopathy
Lung- Late RT Morbidity Scoring	No change from baseline	Asymptomatic or mild symptoms (dry cough); slight radiographic appearances	Moderate symptomatic fibrosis or pneumonitis (severe cough); low grade fever; patchy radiographic appearances	Severe symptomatic fibrosis or pneumonitis; dense radiographic changes	Severe respiratory insufficiency/ continuous O_2/assisted ventilation
Mucous membrane- Late RT Morbidity Scoring	No change from baseline	Slight atrophy and dryness	Moderate atrophy and telangiectasia; little mucus	Marked atrophy with complete dryness; severe telangiectasia	Ulceration
Salivary glands- Late RT Morbidity Scoring	No change from baseline	Slight dryness of mouth; good response on stimulation	Moderate dryness of mouth; poor response on stimulation	Complete dryness of mouth; no response on stimulation	Fibrosis
Skin- Late RT Morbidity Scoring	No change from baseline	Slight atrophy; pigmentation change; some hair loss	Patchy atrophy; moderate telangiectasia; total hair loss	Marked atrophy; gross telangiectasia	Ulceration
Small/Large intestine- Late RT Morbidity Scoring	No change from baseline	Mild diarrhea; mild cramping; bowel movement 5 x daily; slight rectal discharge or bleeding	Moderate diarrhea and colic; bowel movement >5 x daily; excessive rectal mucus or intermittent bleeding	Obstruction or bleeding, requiring surgery	Necrosis/perforation fistula
Spinal cord- Late RT Morbidity Scoring	No change from baseline	Mild Lhermitte's syndrome	Severe Lhermitte's syndrome	Objective neurological findings at or below cord level treatment	Mono-, para-, quadriplegia
Subcutaneous tissue- Late RT Morbidity Scoring	No change from baseline	Slight induration (fibrosis) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic; slight field contracture; <10% linear reduction	Severe induration and loss of subcutaneous tissue; field contracture >10% linear measurement	Necrosis
Radiation - Other (Specify, _____)	None	Mild	Moderate	Severe	Life-threatening or disabling

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Appendix V

BMT-Specific Adverse Events

Summary of BMT-Specific Adverse Events that may be used **if specified by the protocol**. These differ from the standard CTC and may be more relevant to the transplant setting. They are listed here for the convenience of investigators writing transplant protocols. They are also included in the CTC document.

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Bilirubin associated with graft versus host disease for BMT studies .	normal	≥2 - <3 mg/100 mL	≥3 - <6 mg/100 mL	≥6 - <15 mg/100 mL	≥15 mg/100 mL
Diarrhea associated with graft versus host disease (GVHD) for BMT studies.	none	>500 - ≤1000mL of diarrhea/day	>1000 - ≤1500mL of diarrhea/day	>1500mL of diarrhea/day	severe abdominal pain with or without ileus
Diarrhea for pediatric BMT studies.		*>5 - ≤10 mL/kg of diarrhea/day*	*>10 - ≤15 mL/kg of diarrhea/day*	*>15 mL/kg of diarrhea/day*	-
Hepatic enlargement	absent	-	-	present	-
Leukocytes (total WBC) for BMT studies.	WNL	≥2.0 - <3.0 X 10^9 /L ≥2000 - <3000/mm^3	≥1.0 - <2.0 x 10^9 /L ≥1000 - <2000/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	<0.5 x 10^9 /L <500/mm^3
Leukocytes (total WBC) for pediatric BMT studies (using age, race and sex normal values).		*≥75 - <100% LLN*	*≥50 - <75% LLN*	*≥25 - 50% LLN*	*<25% LLN*
Lymphopenia for pediatric BMT studies (using age, race and sex normal values).	mm^3	*≥75-<100%LLN*	*≥50-<75%LLN*	*≥25-<50%LLN*	*<25%LLN*
Neutrophils/granulocytes (ANC/AGC) for BMT studies.	WNL	≥1.0 - <1.5 x 10^9 /L ≥1000 - <1500/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	≥0.1 - <0.5 x 10^9 /L ≥100 - <500/mm^3	<0.1 x 10^9 /L <100/mm^3
Platelets for BMT studies.	WNL	≥50.0 - <75.0 x 10^9 /L ≥50,000 - <75,000/mm^3	≥20.0 - <50.0 x 10^9 /L ≥20,000 - <50,000/mm^3	≥10.0 - <20.0 x 10^9 /L ≥10,000 - <20,000/mm^3	<10.0 x 10^9 /L <10,000/mm^3
Rash/dermatitis associated with high-dose chemotherapy or BMT studies.	none	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation, ≥1.5 cm diameter, not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include spontaneous bleeding not induced by minor trauma or abrasion
Rash/desquamation associated with graft versus host disease (GVHD) for BMT studies.	none	macular or papular eruption or erythema covering <25% of body surface area without associated symptoms	macular or papular eruption or erythema with pruritus or other associated symptoms covering ≥25 - <50% of body surface or localized desquamation or other lesions covering ≥25 - <50% of body surface area	symptomatic generalized erythroderma or symptomatic macular, papular or vesicular eruption, with bullous formation, or desquamation covering ≥50% of body surface area	generalized exfoliative dermatitis or ulcerative dermatitis or bullous formation

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Appendix V (Continued)

BMT-Specific Adverse Events

Summary of BMT-Specific Adverse Events that may be used **if specified by the protocol**. These differ from the standard CTC and may be more relevant to the transplant setting. They are listed here for the convenience of investigators writing transplant protocols. They are also included in the CTC document.

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Stomatitis/pharyngitis (oral/pharyngeal mucositis) for BMT studies.	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema or ulcers but can swallow	painful erythema, edema, or ulcers preventing swallowing or requiring hydration or parenteral (or enteral) nutritional support	severe ulceration requiring prophylactic intubation or resulting in documented aspiration pneumonia
Transfusion: Platelets for BMT studies.	none	1 platelet transfusion in 24 hours	2 platelet transfusions in 24 hours	≥3 platelet transfusions in 24 hours	platelet transfusions and other measures required to improve platelet increment; platelet transfusion refractoriness associated with life-threatening bleeding. (e.g., HLA or cross matched platelet transfusions)
Transfusion: pRBCs for BMT studies.	none	≤2 u pRBC in 24 hours elective or planned	3 u pRBC in 24 hours elective or planned	≥4 u pRBC in 24 hours	hemorrhage or hemolysis associated with life-threatening anemia; medical intervention required to improve hemoglobin
Transfusion: pRBCs for pediatric BMT studies.	*none*	*≤15mL/kg in 24 hours elective or planned*	*>15 - ≤30mL/kg in 24 hours elective or planned*	*>30mL/kg in 24 hours*	*hemorrhage or hemolysis associated with life-threatening anemia; medical intervention required to improve hemoglobin*
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura/TTP or hemolytic uremic syndrome/HUS) for BMT studies.	-	evidence of RBC destruction (schistocytosis) without clinical consequences	evidence of RBC destruction with elevated creatinine (≤3 x ULN)	evidence of RBC destruction with creatinine (>3 x ULN) not requiring dialysis	evidence of RBC destruction with renal failure requiring dialysis and/or encephalopathy
Weight gain associated with Veno-Occlusive Disease (VOD) for BMT studies.	<2%	≥2 - <5%	≥5 - <10%	≥10% or as ascites	≥10% or fluid retention resulting in pulmonary failure

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Appendix VI

BMT Complex/Multicomponent Events

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Note: The grading of Complex/Multicomponent Events in bone marrow transplant will be defined in the protocol. The grading scale must use the CTC criteria for grading the specific component events (adverse events).					
Failure to engraft	absent	mild	moderate	severe	life-threatening
Also consider Hemoglobin, Neutrophils/granulocytes (ANC/AGC), Neutrophils/granulocytes (ANC/AGC) for BMT studies, if specified in the protocol, Platelets, Platelets for BMT studies, if specified in the protocol					
Graft versus host disease	absent	mild	moderate	severe	life-threatening
Also consider Fatigue, Rash/desquamation, Rash/desquamation associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol, Diarrhea for patients without colostomy, Diarrhea for patients with colostomy, Diarrhea associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol, Diarrhea for pediatric BMT studies, if specified in the protocol, Bilirubin, Bilirubin associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol					
Stem cell infusion complications	absent	mild	moderate	severe	life-threatening
Also consider Allergic reaction/hypersensitivity, Conduction abnormality/Atrioventricular heart block, Nodal/junctional arrhythmia/dysrhythmia, Prolonged QTc interval (QTc >0.48 seconds), Sinus bradycardia, Sinus tachycardia, Supraventricular arrhythmias (SVT/atrial fibrillation/flutter), Vasovagal episode, Ventricular arrhythmia (PVCs/bigeminy/trigeminy/ventricular tachycardia), Cardiovascular/Arrhythmia - Other (Specify, _____), Hypertension, Hypotension, Fever (in the absence of neutropenia, where neutropenia is defined as AGC <1.0 x 10^9/L), Rigors/chills, Sweating (diaphoresis), Rash/desquamation, Rash/desquamation associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol, Urticaria (hives, welts, wheals), Diarrhea for patients without colostomy, Diarrhea for patients with colostomy, Diarrhea associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol, Diarrhea for pediatric BMT studies, if specified in the protocol, Nausea, Vomiting, Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Hemoptysis, Alkaline phosphatase, Bilirubin, Bilirubin associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol, GGT, SGOT (AST), SGPT (ALT), Infection (documented clinically or microbiologically) with grade 3 or 4 neutropenia (ANC <1.0 x 10^9/L), Infection without neutropenia, Hyperkalemia, Hypernatremia, Hypokalemia, Depressed level of consciousness, Seizures, Abdominal pain, Headache, Creatinine, Hemoglobinuria					
Veno-Occlusive Disease (VOD)	absent	mild	moderate	severe	life-threatening
Also consider Weight gain associated with Veno-Occlusive Disease (VOD) for BMT studies, if specified in the protocol, Bilirubin, Bilirubin associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol, Depressed level of consciousness, Hepatic pain, Renal failure, Hepatic enlargement					