BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

**BMT CTN PROTOCOL 1203**

**A Multi-center Phase II Trial Randomizing Novel Approaches for Graft-versus-Host Disease Prevention Compared to Contemporary Controls**

**Summary of Proposed Changes to Version 3.0**

The key proposed changes are summarized below followed by the detailed changes. Note: deletions to the protocol are indicated in ~~strike-out text~~; additions are noted in underlined text.

- Added Hodgkin's Lymphoma as an inclusion criterion
- Added use of post-transplant therapy as an exclusion criteria
- Added the inability to withhold agents that may interact with hepatic cytochrome P450 enzymes (CYP3A4) or glutathione S-transferases involved in bortezomib and/or busulfan metabolism during day -5 through day +7as an exclusion criterion
- Added secondary AML arising from myeloproliferative disease (e.g. CMML) as exclusion criteria
- Added guidance on timing of infusion and Bortezomib dosing
- Removed immune reconstitution studies
- Clarified patient enrollment requirements so that pre-transplant assessments are completed within 21 days prior to randomization, and for conditioning to begin within 14 days after randomization.
- Added requirement to repeat bone marrow biopsy if not within 35 days of conditioning for patients with acute leukemia, CML, or MDS.
- Added requirement for imaging studies to be within 56 days of conditioning for patients with lymphomas.
- Replacedthe definition of "adverse event" with the one approved by the FDA.
- Updated adverse event language in Chapter 4 and Appendix J to include special reporting requirements for Bortezomib and Maraviroc.

***Cover page****:*
- Clinicaltrials.gov number added
- Protocol team members updated

***Page i:*** The list of participating Core and Affiliate centers was updated

***Page ii (Protocol Synopsis)****:* added Interim Analysis and Stopping Guidelines summaries

***Study Schema*** *(page v)*: Diagram modified according to proposed changes in section 2.3

***§2.3.1 Inclusion Criteria***

- ***#1***: Age 18 – 75 years (patient is at least 18.0 years and less than 76.0 years at time of enrollment)
- ***#3***: Patients with chronic lymphocytic leukemia/small lymphocytic lymphoma, follicular, marginal zone, diffuse large B-cell, Hodgkin's Lymphoma, or mantle cell lymphoma with chemosensitive disease at time of transplantation
- ***#5b***: Unrelated donor must be willing to donate peripheral blood stem cells and be medically ~~eligible~~ cleared to donate stem cells according to NMDP criteria
- ***#6***: Cardiac function: Ejection fraction at rest greater than or equal to 45%

***§2.3.2 Exclusion Criteria***

- **#6**: Patients with transformed lymphoma (e.g., Richters transformation arising in follicular lymphoma or chronic lymphocytic leukemia)
- ***#14***: … Cancer treated with curative intent greater than or equal to 5 years previously will be allowed…
- ***#16*** *(NEW)*: Planned post-transplant therapy (including use of TKIs)
- ***#17*** *(NEW):* Inability to withhold agents that may interact with hepatic cytochrome P450 enzymes (CYP3A4), or glutathione S-transferases involved in bortezomib and/or busulfan metabolism during day -5 through day +7. It is acceptable to use alternative non-interacting medications during this period, and then resume prior medications
- ***#18*** *(New):* Patients with secondary acute myeloid leukemia arising from myeloproliferative disease, including CMML, with evidence of active myeloproliferative features or myelofibrosis in the background.

***§2.4.2 Hematopoietic Stem Cell Transplantation:***

PBSC will be administered on Day 0 to all patients according to individual institutional guidelines after appropriate processing and quantification has been performed by the local laboratory. Stem cells are administered through an indwelling central venous catheter. If infusion occurs over two days, Day 0 is the day the last infusion is completed. Sites should avoid infusion after 4pm because this complicates the administration of Bortezomib if dose modifications are required due to toxicity. If modifications are required, late infusion of the stem cell source could alter the calendar schedule and result in either a missed dose or a protocol violation. ~~If infusion occurs over two days, Day 0 is the day the last infusion is completed.~~

***§2.4.3 Tacrolimus/Methotrexate/Bortezomib*:**

*Tacrolimus*: Dose reductions should be made if toxicity is present or whole blood levels are above the recommended range, in the absence of toxicity. Patients with severe intolerance of tacrolimus may be placed on cyclosporine (trough level of 200-400 ng/mL) or sirolimus (trough level of 3-8 ng/mL).

***§2.4.4 Tacrolimus/Methotrexate/Maraviroc***:

*Tacrolimus*: Tacrolimus will be given per institutional practices, orally at a dose of 0.05 mg/kg or intravenously at a dose of 0.03 mg/kg starting Day -3. The dose of tacrolimus may be rounded to the nearest 0.5 mg for oral formulations. Subsequent dosing will be based on blood levels. The dose should be adjusted accordingly to maintain a suggested level of 5-15 ng/mL. If patients are on medications which alter the metabolism of tacrolimus (e.g. azoles), the initial starting dose and subsequent doses should be altered as per institutional practices. Tacrolimus taper can be initiated at a minimum of 90 days post HSCT if there is no evidence of active GVHD. The rate of tapering will be done according to institutional practices but patients should be off tacrolimus by Day 180 post HSCT if there is no evidence of active GVHD.

Dose reductions should be made if toxicity is present or whole blood levels are above the recommended range, in the absence of toxicity. Patients with severe intolerance of tacrolimus may be placed on cyclosporine (trough level of 200-400 ng/mL) or sirolimus (trough level of 3-8 ng/mL).

~~For patients randomized to the Tac/MTX/ Maraviroc arm, the doses and schedule of tacrolimus and methotrexate will be same described in Section 2.4.3~~

Maraviroc
Maraviroc will be dosed at 300 mg orally twice a day and will start on Day -3 *prior* to hematopoietic stem cell infusion, and continue until Day 30 post HSCT. If the patient requires a two-day stem cell infusion, maraviroc treatment will end 30 days after the first infusion day (on day 29). There are no food restrictions.

***§2.4.5 Tacrolimus/Mycophenolate Mofetil/Cyclophosphamide***

*Tacrolimus*: Dose reductions should be made if toxicity is present or whole blood levels are above the recommended range, in the absence of toxicity. Patients with severe intolerance of tacrolimus may be placed on cyclosporine (trough level of 200-400 ng/mL) or sirolimus (trough level of 3-8 ng/mL).

*Cyclophosphamide:* It is crucial that no immunosuppressive agents are given prior to transplant, or until 24 hours after the completion of the post-transplant cyclophosphamide. This includes corticosteroids as anti-emetics.

***§2.5.3 Prophylaxis Against Infections – Antifungal Therapy -*** **CMV:** CMV monitoring ~~through nucleic acid amplified testing (NAAT)~~ will be done according to institutional guidelines.

***§2.7.2 Bortezomib and Maraviroc Administration:***

*MARAVIROC:* Tablets ~~must~~ should be swallowed whole. However, if necessary they may be crushed and administered to the patient in a liquid or pudding. ~~Do not break or chew the tablets.~~

***§3.2.9 Infections:*** The cumulative incidence of CMV ~~and EBV reactivation by nucleic acid amplification test (NAAT)~~ in the first 100 days post HSCT will be described.

~~***§3.2.10 Immune Reconstitution:*** Quantitative assessments of peripheral blood CD3, CD4, CD8, CD19 and CD56 positive lymphocytes will be done through flow cytometric analysis at Days 35, 100, 180 and 365 after transplant~~.

***§4.1Approaching Patients, Eligibility Screening and Obtaining Consent:*** Subjects will be approached for this study after the decision to proceed with transplantation is made and a suitable HLA-matched PBSC donor is identified. Patients willing to participate in the trial will sign an Institutional Review Board approved consent form. Transplant physicians will evaluate the patient eligibility for randomization onto this study (see Section 2.2). Eligibility criteria will be verified and ineligible patients will proceed off study and no further follow-up will be obtained. ~~Eligible patients willing to participate in the trial will sign an Institutional Review Board approved consent form.~~ Transplant center personnel will record the documentation of patient consent in EMMES AdvantageEDC$^{SM}$ (Electronic Data Capture, an Internet-based data entry system) and patients will be registered through AdvantageEDC.

***§4.3 Randomization:*** Once the subject is deemed eligible and has given written informed consent, and the transplant center has confirmed patient eligibility and registered the patient's conditioning regimen, randomization occurs. Patients should be randomized as close as possible to the initiation of the conditioning regimen, and preferably within 7 days of and not more than 14 days from the ~~planned~~ initiation of conditioning. If there is a delay in conditioning, certain pre-transplant evaluations will have to be repeated. Refer to section 4.6.1 Patient Assessments-pre-transplant evaluations.

***§4.5 Patient Evaluation***: The patient pre-transplant evaluation must be completed within ~~six weeks of conditioning~~ three weeks (≤21 days) of randomization ~~for transplantation~~. If an unexplained delay in treatment occurs and the initiation of conditioning is greater than 14 days after randomization, some pre-transplant evaluations may need to be repeated. See Section 4.6.1 Patient Assessments-pre-transplant evaluations.

***§Table 4.6b: Patient Clinical Assessments***

Footnote #1: CBC with differential performed three times weekly…

Footnote #7: GVHD assessments performed weekly from Day 7 until Day 63 post-transplant, and then at Days 100, 120, 150, 180, 270, and 365. The GVHD assessment will include a review of all abnormalities experienced during the entire assessment period and the highest grade for each abnormality (whether attributed to GVHD or not) during the assessment period will be recorded on the Acute GVHD form, ~~and/or~~ the Follow-up GVHD form, and the Chronic GVHD Provider Survey in AdvantageEDC.

***§4.6.1 Patient Assessments - Pre-transplant evaluations***
The following observations must be completed within three weeks (≤21 ~~42~~ days) ~~prior to~~ of patient ~~enrollment~~ randomization, and within (≤) 35 days of conditioning. If the initiation of conditioning is greater than 14 days from randomization then pre-transplant evaluations must be completed according to institutional practice, unless otherwise indicated.

- EKG and LVEF (may be performed ≤ 56 ~~84~~ days prior to patient ~~enrollment~~ randomization).
- Pulmonary function tests, including DLCO and FEV1 (may be performed ≤ 56 ~~84~~ days prior to patient ~~enrollment~~randomization).
- Disease evaluation for patients with acute leukemia, CML or MDS includes a bone marrow aspirate and biopsy for pathology and cytogenetics. **A bone marrow biopsy must be performed ≤21 days prior to randomization and must be repeated if not within 35 days prior to the initiation of the transplant conditioning regimen.**
- Disease evaluation for patients with lymphomas includes imaging studies for matters of comparison post-transplant., the types of which may be determined according to the center's institutional practices. **Imaging studies must be done within (≤) 42 days prior to patient randomization, and if the initiation of conditioning is greater than 14 days from**

**randomization (or ≥ 56 days from last imaging) then should be repeated according to the center's standard requirements.**

- ~~Disease evaluation of the malignant disease: For acute leukemia, CML and MDS this includes a bone marrow aspirate and biopsy for pathology and cytogenetics. For lymphomas this includes imaging studies, which will be done according to institutional practices for matter of comparison post-transplant.~~

***§4.6.1 Patient Assessments - Post-transplant evaluations***

- CBC with differential performed at least three times a week from Day 0 until ANC > 500/□BC with differential performed at least three times a week from Day 0 until ANC > 500/des a bone marrow asThereafter, CBC weekly until Day 63 post-transplant, then every other week through Day 100 post-transplant, and then at Days 180, 270 and 365 post-transplant.~~CBC at least three times a week from Day 0 until ANC > 500/□BC at least three times a week from Da00/□BC at least three times a week from Da00/ until ANC > 500/ from Day 0 until ANC > 500/des a bone marrow asThereafter, CBC weekly until Day 63 post-transplant, then every other week through Day 100 post-transplant, and then at Days 180, 270 and 365 post-transplant.~~

***§4.7 Adverse Event Reporting Requirements***: Reporting of adverse events on the BMT CTN 1203 trial has unique requirements due to the addition of bortezomib and maraviroc as part of this protocol. Adverse event reporting requirements are summarized below and further described in Appendix J.

***§4.7.1 Definitions***

**Adverse Event**: ~~An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study. Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.~~ An Adverse Event (AE) is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease aconsidered related to the medical treatment or procedure.

***§4.7.2 BMT CTN Adverse Event Reporting Guidelines***

It is BMT CTN policy that AEs must be reported even if the investigator is unsure whether a relationship exists between the adverse event and the use of the study treatment. Reporting of AEs for BMT CTN 1203 will be consistent with the BMT CTN Manual of Procedures. Additional requirements specific to this protocol are outlined below an in Appendix J.

Unexpected, grades 3-5 AEs, irrespective of the attribution of the event to the study drug ~~/device~~/procedure/treatment, will be reported through the expedited AE reporting system via AdvantageEDC, and will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. The BMT CTN 1203 protocol has three distinct interventions to which patients are randomized. Determination of expectedness for events occurring on each treatment arm will be at the discretion of the investigator as described in Appendix J, section J.3.

***§4.7.3 Additional Adverse Event Reporting Requirements for Patients Randomized to the Tacrolimus/ Methotrexate/Bortezomib Arm***

Millennium Pharmaceuticals, Inc. (MPI) is supplying bortezomib for this study and a description of additional adverse event reporting requirements for this study, detailed in Appendix J apply to any patient who is randomized to receive bortezomib as part of the GVHD prophylaxis regimen. The additional adverse event reporting period for ~~these patients~~ bortezomib begins with the first dose ~~of study drug~~ (Day +1) and continues until 30 days after the last dose of ~~study drug~~ bortezomib (Day +7 plus 30 days = Day +37). Along with the additional adverse event reporting requirements, any adverse event reported through

the expedited AE reporting system will include the investigator's assessment of relationship to bortezomib (unrelated, unlikely, possible, probable, or definite).

***§4.7.4 Adverse Event Reporting for Patients Randomized to the Tacrolimus/Methotrexate/Maraviroc Arm:*** Patients randomized to the maraviroc arm will have all unexpected grade 3-5 AEs reported throughout the course of the study, which will include the investigator's assessment of relationship to maraviroc (unrelated, unlikely, possible, probable, or definite).

***§5.1.3 Primary Endpoint:*** The primary endpoint is time to GRFS from the time of transplant. All transplanted patients will be followed for the primary endpoint for at least one year; however the primary endpoint will be analyzed as a time to event endpoint. The primary analysis will be performed using a modified intent-to-treat principle and will be performed among transplanted patients only.

***TABLE 5.2: OPERATING CHARACTERISTICS OF STUDY DESIGN***
Column C of GRFS corrected to read 0.23 instead of 0.38

| GRFS at 1 Year | | | |
|---|---|---|---|
| Control | A | B | C |
| 0.23 | 0.23 | 0.23 | 0.23 |
| 0.23 | 0.38 | 0.23 | 0.23 |
| 0.23 | 0.38 | 0.38 | 0.38 |
| 0.23 | 0.38 | 0.38 | ~~0.38~~0.23 |
| 0.23 | 0.38 | 0.33 | 0.33 |
| 0.23 | 0.38 | 0.28 | 0.28 |
| 0.35 | 0.35 | 0.35 | 0.35 |
| 0.35 | 0.50 | 0.35 | 0.35 |
| 0.35 | 0.50 | 0.50 | 0.35 |
| 0.35 | 0.50 | 0.50 | 0.50 |
| 0.35 | 0.50 | 0.45 | 0.45 |
| 0.35 | 0.50 | 0.40 | 0.40 |

***§5.5 Analysis of Primary Endpoint***: Kaplan-Meier curves along with 90% confidence intervals will be constructed to estimate GRFS probabilities for each treatment group as well as the control. The primary analysis will consist of a comparison of GRFS among transplanted patients for each treatment arm to the control group, based on a multivariate Cox regression model.

~~***§5.6.12 Immune Reconstitution:*** Quantitative assessment of peripheral blood CD#… will be tabulated for each randomized treatment arm…~~

***APPENDIX B, CONSENT FORMS – Patient Informed Consent***

- ***§5 Study Treatment and Tests – Before the Transplant*** *(page B-4):* A ~~blood~~ pregnancy test if you are a woman able to have children. If you are pregnant, you will not be able to take part in this study.

- ***§6 Study Treatment*—Table 1- Risks and Side Effects**: Combined 'loss of appetite' bullet with 'anorexia' bullet under likely side effects for Bortezomib (Velcade®).

***APPENDIX C, LABORATORY PROCEDURES***:

| Windows for Submitting Optional Research Samples | | | | |
|---|---|---|---|---|
| **Day 0 (Prior to Initiation of Conditioning)** | **Day 35 (±2)** | **Day 100 (±7)** | **Day 180 (±14)** | **Day 365 (±14)** |

***APPENDIX J, ADVERSE EVENT REPORTING REQUIREMENTS ~~for PATIENTS RANDOMIZED to RECEIVE TACROLIMUS/METHOTREXATE/BORTEZOMIB as GVHD PROPHYLAXIS~~***

***§J.1 Adverse Event Reporting:*** Adverse events (AEs) will be collected on calendar-driven forms and event-driven forms in AdvantageEDC.

The calendar-driven forms are those that appear in the AdvantageEDC Forms Grid for each enrolled patient at designated time points (e.g., Day 28 post transplant) throughout the course of the study. Completion of a calendar-driven form is expected by the Target Date for the given assessment period.

Calendar-driven forms for the BMT CTN 1203 study are as follows:

- **Toxicity Form**: this form documents all expected toxicities for the BMT CTN 1203 study; each toxicity is also assigned a grade, based on the NCI CTCAE Version 4.0.
- **Hematology/Chemistry Form**: this form documents selected hematology (CBC/differential) and blood chemistry results.
- **Follow-Up Status Form**: this form documents the status of each patient at various intervals on the study.

Event-driven forms must be completed when a certain event triggers the appearance of the form in the AdvantageEDC Forms Grid. Most often the event-driven form is triggered by information entered on the Follow-up Status Form. Event-driven forms for the BMT CTN 1203 study are as follows:

- **Re-Admission/Hospitalization Form**: this form documents all hospital admissions, *including* the admission for transplant for this study.
- **Infection Form**: this form documents infections from the Day 0 (date of transplant) through the 1-year post-transplant follow-up period.
- **Secondary Graft Failure Form**: this form captures the details associated with secondary graft failure. DO NOT report secondary graft failure as an Unexpected, Grade 3-5 Adverse Event.
- **Progression/Relapse Form**: the form captures detailed information associated with progression or relapse of the primary disease. DO NOT report progression or relapse as an Unexpected, Grade 3-5 Adverse Event.
- **Death Form**: this form documents the death of a patient from the time of study enrollment and randomization through the 1-year post-transplant follow-up period.
- **Bortezomib SAE Screening Form**: this form captures basic information on all SAEs only for patients randomized to the bortezomib arm from the first dose of bortezomib through 30 days after the last dose.
- **Adverse Event Forms**: this series of forms captures details on adverse events that are *both* unexpected and grades 3-5, based on the NCI CTCAE Version 4.0, regardless of attribution to any of the study interventions. These forms are also used to collect information on any SAE event required by the additional adverse event reporting requirements. These events will be reviewed by the Medical Monitor at the BMT CTN Data and Coordinating Center (DCC) within 2 business days of receiving the summary of the adverse event from the transplant center. If the Medical

Monitor requires additional information to make his/her assessment, the transplant center will have 4 business days to respond to the request for additional information.

***§J.2 Reporting Expected Toxicities:*** Expected toxicities for all patients enrolled on BMT CTN 1302 will be collected on the BMT CTN 1203 Calendar-Driven Toxicity Form.

***§J.3 Reporting Unexpected, Grade 3-5 Adverse Events:*** **All Unexpected, Grade 3-5 Adverse Events should be reported for every patient enrolled on the study from the time of enrollment until 1 years post transplant**. Additional Adverse Event reporting applies to patients dependent on the treatment received on the study. Determination of the expectedness of adverse events should be differentiated between the arms at the discretion of the investigator. For example, sweat gland disturbances would be an expected risk associated with maraviroc, but the investigator should assess the expectedness for a patient experiencing sweat gland disturbances randomized to the bortezomib arm.

***§J.4 Additional Reporting Requirements for Patients Randomized to the Tacrolimus/Methotrexate/ Bortezomib from the 1st dose of Bortezomib thorugh 30 Days After the Last Dose***

This section outlines the adverse event reporting requirements for all patients randomized to the Tacrolimus/Methotrexate/Bortezomib from the first dose through 30 days after the last dose.

**In addition to the standard BMT CTN guidelines for reporting adverse events** (see ~~Chapter 4,~~ Section 4.7), MPI is requiring the reporting of **all** Serious Adverse Events (SAEs) that occur **after the initial dose** of study bortezomib (Day +1), **during treatment**, and **within 30 days of the last dose** of study bortezomib (Day +7 plus 30 days).

**Serious Adverse Event**: A serious adverse event (SAE) is any adverse event that results in one of the following outcomes, regardless of causality and expectedness:

~~*Adverse events that are commonly observed after hematopoietic cell transplantation including neutropenia, thrombocytopenia, anemia, minor bleeding episodes (i.e. epistaxis), graft versus host disease (GVHD), graft failure, hepatic veno occlusive disease (VOD), and thrombotic microangiopathy (TMA) will be reported according to Chapter 4, Section 4.7.2 and will not be reported as SAEs, even if they fulfill SAE criteria (as defined above) in the reporting period, however will be reported to Millennium on a monthly basis by the BMT CTN Data and Coordinating Center.*~~

***§J.4.1 Reporting Timelines for Events Occuring During Bortezomib Reporting Period***

- **Fatal and Life-Threatening** events must be reported in AdvantageEDC within 24 hours, ~~but no later than 4 calendar days,~~ of the investigator's observation or awareness of the event.
- **All Other Serious** events (non-fatal/non-life-threatening) must be reported in AdvantageEDC within ~~4~~3 calendar days of the investigator's observation or awareness of the event.

***§J.4.2 How to Report Serious Adverse Events During Bortezomib Reporting Period***

All SAEs from the first dose of bortezomib through 30 days after the last dose will be reported in AdvantageEDC by completing the Bortezomib SAE Screening Form ~~Unexpected, Grades 3-5 Adverse Event forms (AE1-AE6).~~ All SAEs also require completion of the Adverse Event Forms (AE1-AE6), unless any of the following SAEs are determined to be unrelated or unlikely related to the bortezomib, then the Adverse Event Forms are not required:

- Neutropenia
- Thrombocytopenia
- Anemia
- Minor bleeding episodes (i.e. epistaxis)

- Graft-verus-host disease (GVHD)
- Graft failure
- Hepatic veno-occlusive disease (VOD)
- Thrombotic microangiopathy (TMA)

Accurate completion of the Bortezomib SAE and/or Adverse Event ~~se~~ forms will allow the DCC to provide MPI with the details they require to fully understand each event, so it is *critical* that all fields are filled in and comprehensive supporting source documents for the event (PHI redacted) are uploaded to the appropriate forms.

If an adverse event does not meet the criteria of an SAE, it will require reporting on the Adverse Event form if it is both unexpected and grade 3-5 based on the BMT CTN standard reporting guidelines.

~~Although these forms are designated for capturing only unexpected events with a grade 3-5 severity level, this study will utilize this set of forms for MPI's reporting requirements.~~

***§J.4.3 Frequently Asked Questions***

Below are some examples of anticipated questions with regard to the reporting requirements detailed above. These questions do not cover all possible scenarios, therefore it is important to contact the BMT CTN Adverse Event or 1203 ~~DCC~~ Protocol Coordinator should there be any questions or concerns regarding the reporting of an event and whether the event meets the MPI reporting requirements.

- **Since hospitalization is considered an SAE, should the patient's admission for transplant be reported as an SAE?** *NO. Admissions that are scheduled to occur during the study period, bu planned prior to study entry are not considered SAEs given the disease existed before the person was enrolled in the trial and provided that it did not deteriorate in an unexpected manner during the trial. The~~se~~ SAE reporting requirements also begin with the first dose of study drug (bortezomib on Day +1), so the~~. The~~ admission for transplant will occur before this reporting begins. Among patients who undergo the transplant procedure as outpatients and have scheduled hospitalization at time they become neutropenic in the absence of fever, an SAE report is not required, unless the neutropenia prolongs the scheduled hospitalization.*
- **A patient is discharged from the hospital post-transplant on Day +32, and is then re-admitted 2 days later for diarrhea and nausea. Should this re-admission be reported as an SAE?** *Possibly. Even though the subsequent hospitalization falls within the reporting period (Day +7 plus 30 days) the reason for admission is likely GVHD. If the GVHD is determined to be unrelated or unlikely related to the bortezomib, only the Bortezomib SAE screening form is required. If the GVHD is determined to be possibly, probably or definitely related to bortezomib, then an SAE should be reported on both the Bortezomib SAE screening form and the Adverse Event forms. If the work up is negative for GVHD of the gastrointestinal tract, then an SAE should be reported.*

**~~REPORTING INSTRUCTIONS ACCORDING TO AE~~**

~~Adverse events (AEs) will be collected on calendar-driven forms and event-driven forms in AdvantageEDC.~~

~~The calendar-driven forms are those that appear in the AdvantageEDC Forms Grid for each enrolled patient at designated time points (e.g., Day 28 post transplant) throughout the course of the study. Completion of a calendar-driven form is expected by the Target Date for the given assessment period.~~

~~Calendar-driven forms for the BMT CTN 1203 study are as follows:~~

- ~~**Toxicity Form**: this form documents all expected toxicities for the BMT CTN 1203 study; each toxicity is also assigned a grade, based on the NCI CTCAE Version 4.0.~~
- ~~**Hematology/Chemistry Form**: this form documents selected hematology (CBC/differential) and blood chemistry results.~~

~~Event-driven forms must be completed when a certain event triggers the appearance of the form in the AdvantageEDC Forms Grid. Most often the event-driven form is triggered by information entered on the Follow-up Status Form. Event-driven forms for the BMT CTN 1203 study are as follows:~~

- ~~**Re-Admission/Hospitalization Form**: this form documents all hospital admissions, *including* the admission for transplant for this study. DO NOT report a hospital admission as an Unexpected, Grade 3-5 Adverse Event.~~
- ~~**Infection Form**: this form documents infections from the Day 0 (date of transplant) through the 1-year post-transplant follow-up period. DO NOT report an infection as an Unexpected, Grade 3-5 Adverse Event.~~
- ~~**Secondary Graft Failure Form**: this form captures the details associated with secondary graft failure. DO NOT report secondary graft failure as an Unexpected, Grade 3-5 Adverse Event.~~
- ~~**Progression/Relapse Form**: the form captures detailed information associated with progression or relapse of the primary disease. DO NOT report progression or relapse as an Unexpected, Grade 3-5 Adverse Event.~~
- ~~**Death Form**: this form documents the death of a patient from the time of study enrollment and randomization through the 1-year post-transplant follow-up period. DO NOT report a death as an Unexpected, Grade 3-5 Adverse Event.~~
- ~~**Unexpected, Grades 3-5 Adverse Event Forms**: this series of forms captures details on adverse events that are *both* unexpected and grades 3-5, based on the NCI CTCAE Version 4.0, regardless of attribution to any of the study interventions. These events will be reviewed by the Medical Monitor at, or associated with the BMT CTN Data and Coordinating Center (DCC) within 2 business days of receiving the summary of the adverse event from the transplant center. If the Medical Monitor requires additional information to make his/her assessment, the transplant center will have 4 business days to respond to the request for additional information.~~

### ***J.5 Reporting Requirements for Patients Randomized to Tacrolimus/Methotrexate/Bortezomib Beginning 30 days After the Last Dose of Bortezomib***

This section outlines the adverse event reporting requirements for all patients beginning 30 days after the final dose of bortezomib until 1 year post transplant.

**Replaced *TABLE J-1: ADVERSE EVENTS FOR BMT CTN 1203 BY ORGAN SYSTEM* with *TABLE J-1: ADVERSE EVENTS FOR BMT CTN 1203 BEGINNING 30 DAYS AFTER THE LAST DOSE OF BORTEZOMIB BY ORGAN SYSTEM***

| Adverse Event | Collection Type | Collection Form[1] |
|---|---|---|
| **AUDITORY DISORDERS** | | |
| **Hearing loss** | **Calendar-Driven** | **Toxicity** |
| **BLOOD AND LYMPHATIC DISORDERS** | | |
| **Anemia** | **Calendar-Driven** | **Toxicity** |
| **Neutropenia** | **Calendar-Driven** | **Toxicity** |
| **Thrombocytopenia** | **Calendar-Driven** | **Toxicity** |
| **Thrombotic thrombocytopenic purpura/ Thrombotic microangiopathy** | **Calendar-Driven** | **Toxicity** |
| **CARDIAC DISORDERS** | | |

| Adverse Event | Collection Type | Collection Form[1] |
|---|---|---|
| **Cardiac arrhythmia** | **Calendar-Driven** | **Toxicity** |
| **Hypertension** | **Calendar-Driven** | **Toxicity** |
| **Hypotension** | **Calendar-Driven** | **Toxicity** |
| **Left ventricular systolic dysfunction** | **Calendar-Driven** | **Toxicity** |
| **Myocardial infarction** | **Calendar-Driven** | **Toxicity** |
| **New or worsening heart failure** | **Calendar-Driven** | **Toxicity** |
| **Pericardial effusion** | **Calendar-Driven** | **Toxicity** |
| **Pericarditis** | **Event-Driven** | **Adverse Event Form** |
| **Peripheral edema** | **Calendar-Driven** | **Toxicity** |
| **Restrictive cardiomyopathy** | **Calendar-Driven** | **Toxicity** |
| **GASTROINTESTINAL DISORDERS** | | |
| **Abdominal pain** | **Calendar-Driven** | **Toxicity** |
| **Anorexia** | **Calendar-Driven** | **Toxicity** |
| **Constipation** | **Calendar-Driven** | **Toxicity** |
| **Diarrhea** | **Calendar-Driven** | **Toxicity** |
| **Dysgeusia (taste alteration)** | **Calendar-Driven** | **Toxicity** |
| **Dyspepsia (heartburn)** | **Calendar-Driven** | **Toxicity** |
| **Gastroenteritis** | **Calendar-Driven** | **Toxicity** |
| **Intestinal obstruction** | **Event-Driven** | **Adverse Event Form** |
| **Nausea** | **Calendar-Driven** | **Toxicity** |
| **Oral mucositis** | **Calendar-Driven** | **Toxicity** |
| **Vomiting** | **Calendar-Driven** | **Toxicity** |
| **GENERAL DISORDERS** | | |
| **Fatigue** | **Calendar-Driven** | **Toxicity** |
| **Fever** | **Calendar-Driven** | **Toxicity** |
| **HEPATOBILIARY/PANCREAS DISORDERS** | | |
| **Abnormal liver function tests** | **Calendar-Driven** | **Toxicity** |
| **Hepatitis** | **Event-Driven** | **Adverse Event Form** |
| **Liver failure** | **Event-Driven** | **Adverse Event Form** |
| **Pancreatitis** | **Calendar-Driven** | **Toxicity** |
| **HEMORRHAGIC DISORDERS** | | |
| **Intracranial** | **Event-Driven** | **Adverse Event Form** |
| **Gastrointestinal** | **Calendar-Driven** | **Toxicity** |
| **Genitourinary** | **Calendar-Driven** | **Toxicity** |
| **Pulmonary/Upper respiratory** | **Calendar-Driven** | **Toxicity** |
| **IMMUNE SYSTEM DISORDERS** | | |
| **Allergic reaction** | **Event-Driven** | **Adverse Event Form** |
| **Anaphylaxis (swelling of the skin and/or swelling of the face or throat)** | **Event-Driven** | **Adverse Event Form** |
| **INFECTIONS** | | |
| **Fungal infections of the mouth and throat** | **Event-Driven** | **Infection** |
| **Herpes virus/shingles** | **Event-Driven** | **Infection** |
| **Infections of the bladder, sinuses, throat, stomach and intestines, and skin** | **Event-Driven** | **Infection** |
| **Sepsis** | **Event-Driven** | **Infection** |
| **METABOLISM AND NUTRITION DISORDERS** | | |
| **Hypercalcemia** | **Calendar-Driven** | **Toxicity** |

| Adverse Event | Collection Type | Collection Form[1] |
|---|---|---|
| **Hyperglycemia** | **Calendar-Driven** | **Toxicity** |
| **Hypoglycemia** | **Calendar-Driven** | **Toxicity** |
| **Hypokalemia** | **Calendar-Driven** | **Toxicity** |
| **Hyponatremia** | **Calendar-Driven** | **Toxicity** |
| **Tumor lysis syndrome** | **Event-Driven** | **Adverse Event Form** |
| **MUSCULOSKELETAL AND TISSUE DISORDERS** | | |
| **Arthralgia** | **Calendar-Driven** | **Toxicity** |
| **Myalgia** | **Calendar-Driven** | **Toxicity** |
| **Muscle weakness (generalized or specific area)** | **Calendar-Driven** | **Toxicity** |
| **NERVOUS SYSTEM DISORDERS** | | |
| **Anxiety** | **Calendar-Driven** | **Toxicity** |
| **Confusion** | **Calendar-Driven** | **Toxicity** |
| **Depression** | **Calendar-Driven** | **Toxicity** |
| **Dizziness** | **Calendar-Driven** | **Toxicity** |
| **Encephalopathy** | **Event-Driven** | **Adverse Event Form** |
| **Headache** | **Calendar-Driven** | **Toxicity** |
| **Insomnia** | **Calendar-Driven** | **Toxicity** |
| **Neuropathy** | **Calendar-Driven** | **Toxicity** |
| **Reversible posterior leukoencephalopathy syndrome (PRES)** | **Calendar-Driven** | **Toxicity** |
| **Seizure** | **Calendar-Driven** | **Toxicity** |
| **Severe muscle weakness/paralysis** | **Event-Driven** | **Adverse Event Form** |
| **Somnolence** | **Calendar-Driven** | **Toxicity** |
| **Syncope (fainting)** | **Calendar-Driven** | **Toxicity** |
| **OCULAR/VISUAL DISORDERS** | | |
| **Blurred vision** | **Calendar-Driven** | **Toxicity** |
| **Conjunctivitis** | **Calendar-Driven** | **Toxicity** |
| **Sudden loss of vision** | **Event-Driven** | **Adverse Event Form** |
| **RENAL DISORDERS** | | |
| **Cystitis Non-infective** | **Calendar-Driven** | **Toxicity** |
| **Acute kidney injury** | **Calendar-Driven** | **Toxicity** |
| **Chronic kidney disease** | **Calendar-Driven** | **Toxicity** |
| **RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS** | | |
| **Bronchitis** | **Calendar-Driven** | **Infection** |
| **Cough** | **Calendar-Driven** | **Toxicity** |
| **Dyspnea** | **Calendar-Driven** | **Toxicity** |
| **Hypoxia** | **Calendar-Driven** | **Toxicity** |
| **Pleural effusion** | **Calendar-Driven** | **Toxicity** |
| **Pneumonia** | **Calendar-Driven** | **Infection** |
| **Sinusitis** | **Calendar-Driven** | **Toxicity** |
| **Sore throat** | **Calendar-Driven** | **Toxicity** |
| **SKIN AND SUBCUTANEOUS TISSUE DISORDERS** | | |
| **Pruritis** | **Calendar-Driven** | **Toxicity** |
| **Rash** | **Calendar-Driven** | **Toxicity** |
| **Hyperhidrosis (excessive sweating)** | **Calendar-Driven** | **Toxicity** |
| **VASCULAR DISORDERS** | | |
| **Capillary leak syndrome** | **Calendar-Driven** | **Toxicity** |

| Adverse Event | Collection Type | Collection Form[1] |
|---|---|---|
| **Thromboembolic event** | **Calendar-Driven** | **Toxicity** |
| **OTHER** | | |
| **Pregnancy** | **Event-Driven** | **Adverse Event Form** |
| **Other unexpected grade 3-5 AE** | **Event-Driven** | **Adverse Event Form** |

[1]Events determined to be at least possibly related to bortezomib that occur more than 30 days from the last dose may be reported via the Bortezomib SAE Screening Form and Adverse Event Form at the discretion of the investigator.

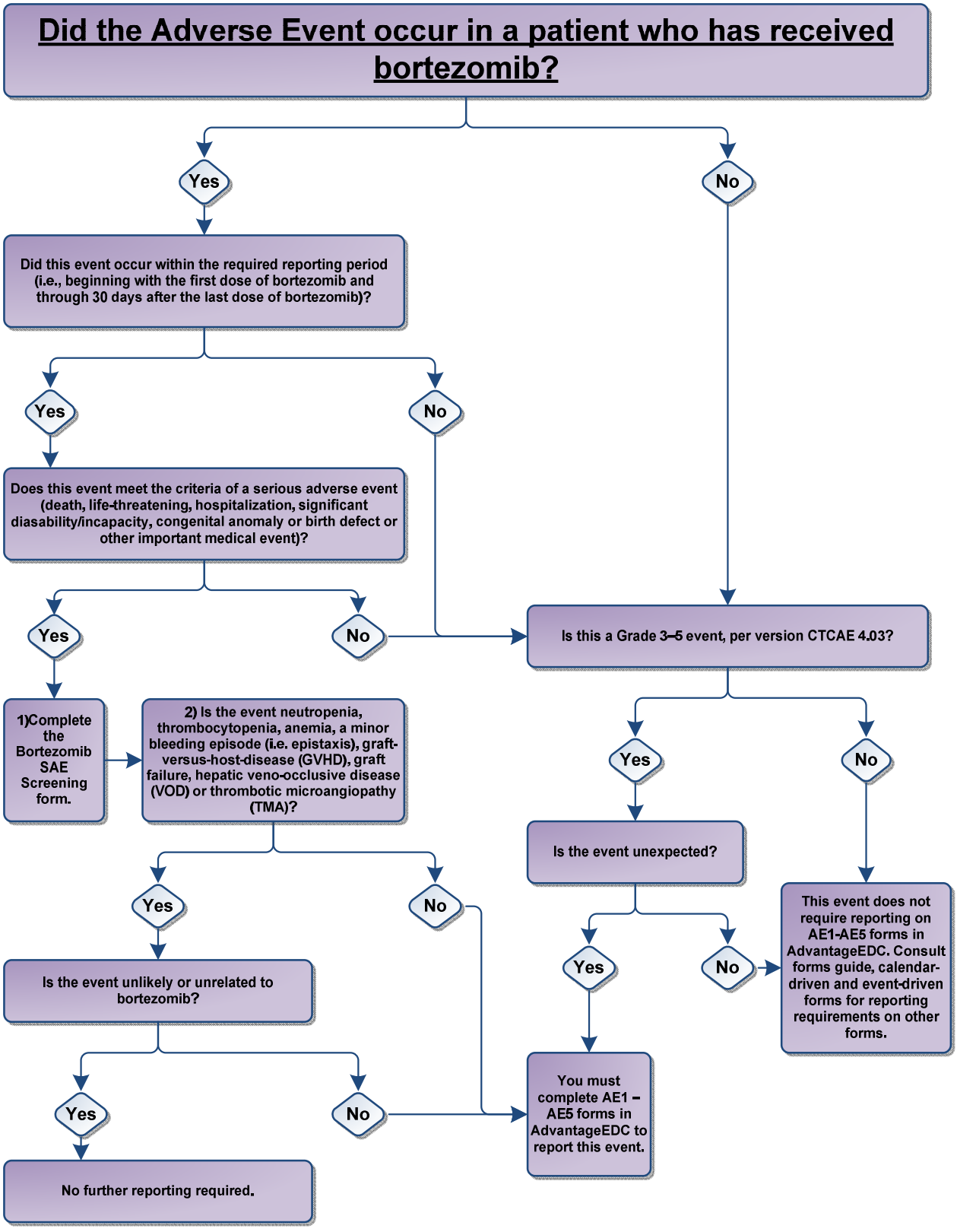
***§J.6 Reporting Requirements for All BMT CTN 1203 Participants***

This section outlines the reporting requirements for all participants enrolled on BMT CTN 1203 from enrollment through 1 year post transplant..

For patients randomized to Tacrolimus/Methotrexate/Bortezomib and Tacrolimus/MMF/Maraviroc, an assessment of relationship to Bortezomib and Maraviroc is required in addition to an assessment of relationship to transplant.

Figure J-2 provides a decision tree for any adverse event that occurs on a patient randomized to any of the 3 treatment arms.

***FIGURE J-2: DECISION TREE FOR ADVERSE EVENTS FOR BMT CTN 1203*** - see last page


Did the Adverse Event occur in a patient who has received bortezomib?
Yes
No
Did this event occur within the required reporting period (i.e., beginning with the first dose of bortezomib and through 30 days after the last dose of bortezomib)?
Yes
No
Does this event meet the criteria of a serious adverse event (death, life-threatening, hospitalization, significant diasability/incapacity, congenital anomaly or birth defect or other important medical event)?
Yes
No
1)Complete the Bortezomib SAE Screening form.
2) Is the event neutropenia, thrombocytopenia, anemia, a minor bleeding episode (i.e. epistaxis), graft-versus-host-disease (GVHD), graft failure, hepatic veno-occlusive disease (VOD) or thrombotic microangiopathy (TMA)?
Yes
No
Is the event unlikely or unrelated to bortezomib?
Yes
No
No further reporting required.
Is this a Grade 3–5 event, per version CTCAE 4.03?
Yes
No
Is the event unexpected?
Yes
No
You must complete AE1 – AE5 forms in AdvantageEDC to report this event.
This event does not require reporting on AE1-AE5 forms in AdvantageEDC. Consult forms guide, calendar-driven and event-driven forms for reporting requirements on other forms.