MSK PROTOCOL COVER SHEET

An Open-Label, Pilot Study of Romiplostim for Conditioning Regimen-Related Thrombocytopenia after High-Dose Therapy and Autologous Hematopoietic Cell Transplantation

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

TARGET PATIENTS

Adult patients ≥ 18 years old undergoing high-dose therapy and autologous hematopoietic cell transplantation (HDT-AHCT) for : Multiple myeloma (MM), Hodgkin lymphoma (HL) or non-Hodgkin lymphoma (NHL).

INTERVENTION

- Romiplostim 3.0 mcg/kg SC on Day +1 and Romiplostim 2.0 mcg/kg SC on Day +8 after HDT-AHCT. Beyond Day +8, patients will be treated weekly until platelet count is >50,000/mcL, without any platelet transfusions in the prior 48 hours. All doses after the second Romiplostim dose will be titrated as per Table 3, based on weekly CBC/platelet counts. Patients will receive a maximum of six weekly doses of romiplostim.
  - Romiplostim doses after Day +8 may have a +2 day window
- Lab assessments:
  - CBC, CMP, and Immature Platelet Fraction every day from day of AHCT (Day 0) until Day +15. All patients will get at least weekly (+/- 3 days) labs until day +30. Patients who need 3 or more doses of romiplostim will get weekly (+/- 3 days) labs as long as their platelet count is ≥25,000. For patients who need 3 or more doses of romiplostim they will receive labs every second day until their platelets are ≥25,000.
  - LDH, PT/INR, APTT every 7 days (+/-2 days) from Day +1 until Day +15.
  - CBC, CMP, Immature Platelet Fraction, LDH, PT/INR, and APTT will be done at days +30 (+/- 7 days), +60 (+/- 7 days) and at +100 (+/- 14 days) from AHCT.

2.1 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective

1) To evaluate whether receiving romiplostim after HDT-AHCT decreases the number of days requiring platelet transfusions or grade 4 CTCAE thrombocytopenia following HDT-AHCT

Secondary Objectives

1) To evaluate whether romiplostim can reduce the number of platelet transfusions issued during the AHCT admission

2) To evaluate whether romiplostim can reduce the time to platelet engraftment after HDT-AHCT Platelet engraftment is defined as the first day of seven consecutive days with a platelet count of ≥20 K/mcL without transfusion support.

3) To evaluate whether romiplostim can reduce the length of stay of AHCT

4) The safety profile of romiplostim will be assessed in this patient population during the course of the study as per Section 11.0 Toxicities/Side Effects.

3.0 BACKGROUND AND RATIONALE

HDT-AHCT and Chemotherapy-Induced Thrombocytopenia (CIT)

High-dose therapy and autologous hematopoietic cell transplantation (HDT-AHCT) remains a standard of care consolidation strategy for patients with multiple myeloma (MM) that provides prolonged disease-free survival.[1,2] The standard conditioning regimen for MM is monotherapy with high-dose melphalan.[2] HDT-AHCT is also a potentially curative modality for patients with relapsed, chemosensitive Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL).[3,4] For HL and the majority of NHL subtypes, the most commonly used conditioning regimen is BEAM [carmustine, etoposide, cytarabine, and melphalan] followed by CBV [cyclophosphamide, carmustine, and etoposide].[4–6] In recent years, for patients with central nervous system lymphoma (CNSL), our group and others have successfully utilized an intensive conditioning regimen, TBC [thiotepa, busulfan, and cyclophosphamide.][7–9]

The HDT-AHCT platform is built upon myeloablative conditioning, which consists of single agent or combination chemotherapies aimed at overcoming potential residual disease and any possible chemoresistance.[4] In doing so, the normal hematopoietic cell compartment of the bone marrow is also eliminated, after which an infusion of autologous stem cells is required to restore normal hematopoiesis roughly 2 weeks after AHCT. There are profound cytopenias following AHCT prior to engraftment, notably thrombocytopenia. Currently, the management of chemotherapy-induced thrombocytopenia (CIT) is supportive with platelet transfusions per the discretion of the treating medical oncologist.[10] Most patients undergoing HDT-AHCT require multiple platelet transfusions during their AHCT hospitalization. Platelet transfusions are generally given to non-bleeding patients with severe thrombocytopenia. For inpatient stem cell transplantations, the standard platelet transfusion threshold is to transfuse if platelets are < 10,000/mcL. For outpatient stem cell transplantations, the standard platelet transfusion threshold is to transfuse if platelets are < 20,000/mcL. Patients may also be transfused for any platelet count if necessary for clinical reasons, if deemed appropriate by the treating physician. Even after neutrophil engraftment, thrombocytopenia often delays hospital discharge and increases the risk of bleeding complications.[11,12] Table 1 presents the MSKCC historic thrombocytopenia data in patients undergoing HDT-AHCT from 2014 through 2016. The key parameters presented are platelet transfusions issued (mean, median, range), day to platelet engraftment, day to neutrophil engraftment, and length of stay. Neutrophil engraftment after transplantation is defined as an absolute neutrophil count

(ANC) ≥ 500 K/mcL for 3 consecutive days. The first of these 3 consecutive days is considered the day of neutrophil engraftment. Platelet engraftment is defined as the time after transplantation needed to achieve a platelet count exceeding 20,000/mcL without transfusion support for 7 consecutive days. The first of those 7 consecutive days is considered the day of platelet engraftment.

Table 1. Historical Data on Platelet Transfusions (Based on MSKCC experience from 2017 through 2020)

Cohort	No. of Patients	Median No. Platelets Issued Per Patient (Range)	Mean No. Platelets Issued Per Patient (IQR)	Median No. days with Transfusions or Grade 4 Thrombocytopenia (Range)	Mean No. days with Transfusions or Grade 4 Thrombocytopenia (IQR)
MM					
Melphalan	485	2 (0-19)	2.65 (1-3)	5 (0-53)	6.8 (3-8)
NHL and HL					
BEAM/CBV	296	4 (0-44)	5 (3-6)	8 (2-68)	9.5 (6-10)
TBC	73	5 (2-32)	6.3 (4-7)	10 (5-38)	11.9 (8-13)

MM: multiple myeloma; NHL: non-Hodgkin lymphoma; HL: Hodgkin lymphoma; BEAM: carmustine, etoposide, cytarabine, and melphalan; CBV: cyclophosphamide, carmustine, and etoposide; TBC: thiotepa, busulfan, and cyclophosphamide.

Romiplostim – Mechanism of Action and Clinical Activity

Romiplostim (Nplate®) is a thrombopoietin (TPO) mimetic that binds to the TPO receptor (Mpl).[13] It is a 'peptibody' formed by the fusion of the Fc portion of an IgG1 monoclonal antibody with four TPO mimetic peptides. It binds the distal cytokine homology region of the TPO receptor leading to the activation of the JAK/STAT pathyway.[14] In addition, it has been shown to activate the MAP kinase pathway leading to activation of anti-apoptotic pathways resulting in increased platelet production. Romiplostim is FDA approved for use in chronic immune thrombocytopenia (ITP), and it has been shown to increase and maintain platelet counts in splenectomized and non-splenectomized patients with few adverse effects.[15,16] To date, no anti-TPO antibody formation of clinical significance has been reported. In several trials of patients with ITP, the mean therapeutic dose of romiplostim to achieve a platelet count of 50-200,000/mcL was 3-4 mcg/kg.[10,14]

At MSKCC, our Hematology Service has extensive experience using romiplostim for chemotherapy-induced thrombocytopenia (CIT), in patients with advanced stage solid tumor malignancies.[18] The goal of romiplostim therapy was improvement and maintenance of platelet counts to >100,000/mcL in order to allow for the resumption and continuation of cancer-directed therapy. The results of an investigator-initiated, phase II, open-label clinical

trial of romiplostim for CIT in patients with advanced stage solid tumors versus observation control were recently reported.[19] The observation-control patients who did not correct their platelet counts were eligible to crossover to the romiplostim arm. A total of 40 patients were enrolled, with 32 patients receiving up-front romiplostim and 8 observation patients. 27 of the 32 (84%) of the romiplostim-treated patients corrected their platelets to target goal within 3 weeks. After correction of their platelet count, 25 of these patients resumed chemotherapy, and all but one were able to maintain their scheduled chemotherapy treatments without recurrence of CIT. The mean effective romiplostim dose was 2.5 mcg/kg (range 1.8-4.1). Importantly, there were no observed adverse effects on the bone marrow. Four patients (12.5%) of the 32 treated patients had a non-fatal thrombotic event. It is important to note that all of these patients were at high risk of thrombosis based on their underlying malignancy, and this incidence of thrombosis is considered within a typical range in patients with advanced solid tumors on chemotheray.[19]

An unmet need exists for an alternative to platelet transfusions for patients undergoing HDT-AHCT. Blood product transfusions are costly and there are risks of short-term and long-term transfusion complications. Further, responses to platelet transfusions are short-lived, typically 12 hours or less. Enhancing platelet engraftment with romiplostim, post HDT-AHCT would be a highly attractive.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

We are proposing a single-center, open-label, pilot study of romiplostim for patients undergoing HDT-AHCT. We will enroll a total of 63 patients within 18 months of opening of the study to reach a sample size of 60 patients. Patients will have (A) MM undergoing high-dose melphalan and AHCT, (B) HL or NHL undergoing BEAM- or CBV-AHCT or (C) CNSL undergoing TBC-AHCT.

Further:

- At least 20 will have MM undergoing high-dose melphalan and AHCT
- At least 20 will have HL or NHL undergoing BEAM- or CBV-AHCT.
- Remaining patients with MM or HL/NHL as available to reach final sample size of 60 patients

Patients will be enrolled prior to admission for HDT-AHCT, and they will undergo their planned HDT-AHCT for their respective hematologic malignancy as per institutional standards as follows:

We hypothesize that the use of romiplostim after HDT-AHCT will: (A) Reduce the number of days requiring platelet transfusions or grade 4 CTCAE thrombocytopenia following HDT-AHCT; (B) Reduce the number of platelet transfusions issued during the AHCT admission;

(C) Reduce the time to platelet engraftment after AHCT; (D) Reduce the length of stay for the AHCT as compared to historical data.

4.3 Intervention

Patients will be enrolled prior to admission for HDT-AHCT, and they will undergo their planned HDT-AHCT for their respective hematologic malignancy as per institutional standards as detailed in Section 9.0 Treatment/Intervention Plan.

Regardless of the conditioning regimen received, all patients will receive romiplostim 3.0 mcg/kg SC on Day +1 and romiplostim 2.0 mcg/kg SC on Day +8 after HDT-AHCT. Beyond Day +8, patients will be treated until platelet count is >50,000/mcL, without any platelet transfusions in the prior 48 hours. All doses after the second romiplostim dose will be titrated as per Table 3, based on weekly CBC/platelet counts. No patient will receive more than six doses of romiplostim, even if platelets have not corrected by Day +42.

If there is a medical circumstance wherein the platelets decrease to <20,000/mcL, romiplostim can be resumed during hospitalization at the discretion of the treating physician for medical necessity. Throughout the study, all patients will receive weekly doses of romiplostim.

Table 3. Individualized Treatment Dose Adjustment by Platelet Count for 3rd – 6th Romiplostim Doses

Platelet Count	Romiplostim Dose
PLT < 20,000 mcL	3.0 mcg/kg
20,000 ≤ PLT ≤ 35,000 mcL	2.0 mcg/kg
35,000 < PLT ≤ 50,000 mcL	1.0 mcg/kg

5.1 THERAPEUTIC/DIAGNOSTIC AGENTS & NON-THERAPEUTIC ASSESSMENTS

Romiplostim, a TPO mimetic, is an Fc-peptide fusion protein (peptibody) that activates intracellular transcriptional pathways leading to increased platelet production via the TPO receptor (known as cMpl). The peptibody molecule contains two identical single-chain subunits, each consisting of human immunoglobulin IgG1 Fc domain, covalently linked at the C-terminus to a peptide containing two thrombopoietin receptor-binding domains. Romiplostim has no amino acid sequence homology to endogenous TPO. Romiplostim is produced by recombinant DNA technology in *Escherichia coli (E coli)*.[14,15]

Romiplostim is approximately 59 kilodalton and is comprised of 4 Mpl-binding domains and an Fc fragment. The peptibody is produced by recombinant DNA technology in Escherichia coli (E coli). Though it has no amino acid sequence homology to endogenous thrombopoietin (eTPO), romiplostim is an agonist of the thrombopoietin (TPO) receptor and signals and activates intracellular transcriptional pathways to increase platelet production.

Romiplostim is supplied as a sterile, preservative-free lyophilized white powder ready for reconstitution. It is supplied for single use in 5 cc Type I glass vials containing 625 µg of

romiplostim, 500 µg deliverable drug product. When reconstituted with the appropriate volume of sWFI, romiplostim is at a concentration of 0.5 mg/mL in 10 mM histidine, 4% (w/v) mannitol, 2% (w/v) sucrose, and 0.004% (w/v) polysorbate 20 at a pH of 5.0. The product, when reconstituted, is a clear colorless solution practically free from particles.

Prior to administration, romiplostim is reconstituted in the vial to 0.5 mg/mL (1.2 ml of sWFI is added to vials containing 625 µg (500 µg) of romiplostim), and drawn into a syringe for subcutaneous injection.

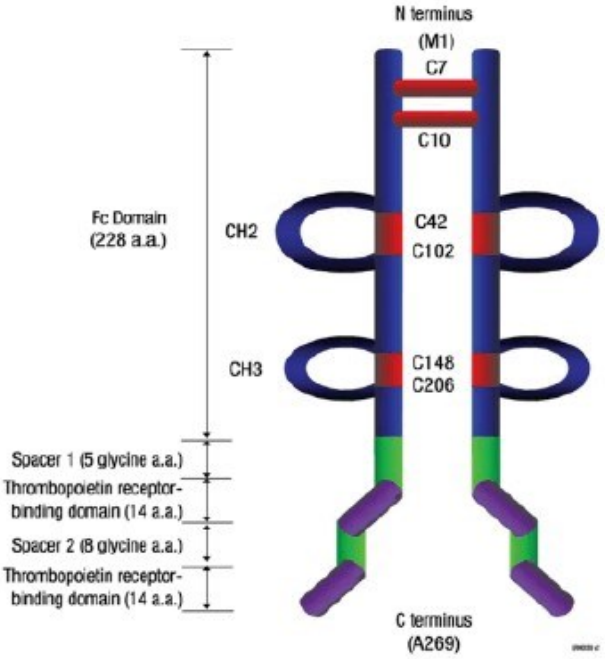
Romiplostim vials will be stored in their carton to protect from light until the time of use. Keep romiplostim vials refrigerated at 2°to 8°C (36° to 46°F). Do not freeze.

A. Romiplostim is an FDA approved drug, approved for the indication of chronic immune (idiopathic) thrombocytopenic purpura (ITP). The investigators brochure, provided by Amgen, is attached as Appendix A.

B. Relevant statements from the Product Insert:

   1. INDICATIONS AND USAGE: “Romiplostim is a thrombopoietin receptor agonist indicated for the treatment of thrombocytopenia in patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.”

- Active Ingredients: Romiplostim
- Pharmacological Class: Thrombopoietin receptor agonist
- Structural Formula:



- Dose Formulation: Romiplostim is supplied in a 5-mL single-use vial as a sterile, white, preservative-free, lyophilized powder containing a protein concentration of 0.5

mg/mL of 10 mM histidine, 4.0% mannitol, 2.0% sucrose, 0.004% polysorbate 20, and a pH 5.0 when reconstituted with 1.2 mL of sterile water for injection.

- Storage: Lyophilized product should be stored refrigerated at 2°C to 8°C (36°F to 46°F); vials should be kept in the carton to protect from light until time of use. Do not freeze. Alternatively, the romiplostim lyophilized product can be kept at room temperature up to 25°C (77°F) in the original carton; however, under these conditions, the romiplostim lyophilized product must be used within 30 days. If not used within 30 days, discard romiplostim. Protect romiplostim from direct light and do not expose to temperatures above 25°C (77°F).
- Source of Supply: Drug will be supplied by Amgen Inc.

6.1 CRITERIA FOR PARTICIPANT ELIGIBILITY

6.2 Participant Inclusion Criteria

1. Adult patients ≥ 18 years old diagnosed with multiple myeloma (MM), any subtype of Hodgkin lymphoma (HL), or any subtype of non-Hodgkin lymphoma (NHL).
    - For MM, the conditioning regimen used will be high-dose melphalan.
    - For HL and NHL, the conditioning will be one of the following high-dose regimens: BEAM, CBV, or TBC.
    - Other conditioning regimens not listed above, or variations of the above conditioning regimens, may be allowed at the discretion of the principal investigator if the regimen is considered myeloablative.
2. Adequate organ function is required, defined as follows:
    - Serum bilirubin ≤ 2 mg/dL, unless benign congenital hyperbilirubinemia.
    - AST, ALT, and alkaline phosphatase < 3 times the upper limit of normal.
    - Creatinine clearance ≥ 40 ml/min (calculated by Cockcroft Gault)
    - LVEF ≥ 45% by MUGA or resting echocardiogram.
    - Pulmonary function (FEV1 and corrected DLCO) ≥ 45% predicted.
    - Adequate performance status ECOG ≤ 2.
3. Ability to provide written informed consent.
4. Patients undergoing HDT-AHCT.

6.3 Participant Exclusion Criteria

1. Patients with a previous diagnosis of a myeloid malignancy.
2. Patients for whom the treating oncologist will be using a non-standard platelet transfusion threshold during the AHCT.
3. Patients with a history of a prior symptomatic or incidental venous thromboembolic event (such as DVT or pulmonary embolism) within the prior 6 months are eligible if they are on and tolerating anti-coagulation, or greater than 6 months ago are eligible if they completed or are on and tolerating anti-coagulation.
    - A venous thrombotic event associated with a central venous catheter will not make the patient ineligible.

4. Patients with a history of symptomatic arterial thrombotic events such as myocardial infarction, ischemic cerebral vascular accident or transient ischemic attack in the past 6 months are ineligible.
5. Patients who had been diagnosed with Immune Thrombocytopenic Purpura (ITP) at any time prior to the AHCT are ineligible.
6. Patients with a serious concomitant medical condition that could interfere with the conduct of the clinical trial, such as unstable angina, renal failure requiring hemodialysis, or active infection requiring IV antibiotics.
7. Previous use of romiplostim, PEGylated recombinant human megakaryocyte growth and development factor, eltrombopag, recombinant human TPO, any other TPO receptor agonist, or any investigational platelet producing agent.
8. Females who are pregnant or breastfeeding or planning to become pregnant or breastfeed during treatment and for an additional 30 days after treatment discontinuation or longer if required by prescribing information for chemotherapy received during the study.
9. Patients unwilling to use highly effective contraception during the study period and for the duration required by prescribing information for chemotherapy(ies) administered during the study.

7.0 RECRUITMENT PLAN

This study will be conducted at MSKCC. Potential research subjects will be identified by members of the Adult Bone Marrow Transplant (BMT) and Hematology Services. After consultation with the Adult BMT attending physician, eligible patients will be asked to participate in the study. If consent is offered, the risks and benefits will be presented to the patient by an investigator prior to the patient consenting. If the patient consents, they will be enrolled/registered by a clinical research coordinator.

This study does not compete with any existing or planned other studies for conditioning-regimen induced thrombocytopenia, and therefore, we anticipate a high percent of the appropriate patients who are undergoing HDT-AHCT will be referred and enrolled.

7.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

7.2 Randomization

There will be no randomization in this study.

8.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

9.1 PRE-TREATMENT/INTERVENTION

Documentation of tests resulted and/or verification will be completed within the following guidelines before enrolling on trial:

<u>Within 28 days prior to enrollment:</u>

- Complete Blood Count (CBC) with differential.
- Comprehensive Metabolic Panel (CMP) (must include: BUN, Creatinine, sodium, potassium, chloride, CO2, calcium, glucose, total Bilirubin, total protein, albumin, alkaline phosphatase, AST, ALT)
- Lactate Dehyrogenase (LDH)
- Prothrombin Time (PT), International Normalized Ratio (INR)
- Activated Partial Thromboplastin Time (APTT)
- If patients have not had prior cytogenetic testing with FISH panel for MDS from a bone marrow aspirate and/or biopsy or peripheral blood testing, this will be performed during screening.
- Pulmonary Function Test
- MUGA or resting echocardiogram

<u>Within 48 hours of enrollment,</u>

- Complete Blood Count (CBC) with differential.

- Comprehensive Metabolic Panel (CMP) (must include: BUN, Creatinine, sodium, potassium, chloride, CO2, calcium, glucose, total Bilirubin, total protein, albumin, alkaline phosphatase, AST, ALT)
- Lactate Dehyrogenase (LDH)
- Prothrombin Time (PT), International Normalized Ratio (INR)
- Activated Partial Thromboplastin Time (APTT)
- Immature Platelet Fraction
- Negative pregnancy test (serum hCG or urine) result in women of child bearing potential (must be done only once within 48 hours of enrollment)

Prior to enrollment:

- Bone marrow and/or lymph node biopsy confirming a diagnosis of MM, HL, or NHL at any time prior to HDT-AHCT.

10.1 TREATMENT/INTERVENTION PLAN

Patients will be enrolled prior to admission for HDT-AHCT, and they will undergo their planned AHCT for their respective hematologic malignancy as per institutional standards.

A. Regardless of the conditioning regimen received, all patients will receive romiplostim 3.0 mcg/kg SC on Day +1 and romiplostim 2.0 mcg/kg SC on Day +8 after HDT-AHCT. Beyond Day +8, patients will be treated until platelet count is >50,000/mcL, without any platelet transfusions in the prior 48 hours. All doses after the second romiplostim dose will be titrated as per Table 3, based on weekly CBC/platelet counts. Patients will receive a maximum of six weekly doses of romiplostim.
B. Laboratory Assessments
    a. CBC, CMP, and Immature Platelet Fraction every day from day of AHCT (Day 0) until Day +15. All patients will get at least weekly (+/- 3 days) labs until Day +30. Patients who need 3 or more doses of romiplostim will get weekly (+/- 3 days) labs as long as their platelet count is ≥25,000. For patients who need 3 or more doses of romiplostim and whose platelet counts are <25,000 they will receive labs every second day until their platelets are ≥25,000.
    b. LDH, PT/INR, APTT every 7 days (+/-2 days) from Day +1 until Day +15.
    c. CBC with differential, CMP, Immature Platelet Fraction, LDH, PT/INR, and APTT will be done at days +30 (+/- 7 days), +60 (+/- 7 days) and at +100 (+/-14 days) from AHCT.
C. If there is a medical circumstance wherein the platelets decrease to <20,000/mcL, romiplostim can be resumed during hospitalization at the discretion of the treating physician for medical necessity. However, a patient will not exceed six total doses of romiplostim.
D. If there is a medical circumstance (e.g. prolonged infection, sepsis, pneumonia) wherein a subject remains admitted for more than 30 days post-AHCT, which inhibits platelet recovery and platelet engraftment, daily labs will be discontinued and will instead be collected at least once weekly until discharge from hospital.
E. Toxicity assessments will be done weekly until 7 days after the last dose of Romiplostim (Days +1, +8, +15, +22, +29, … +/- 2 days), and Days +30 (+/-7 days), +60 (+/-7 days), and +100 (+/- 14 days) from AHCT.

11.1 EVALUATION DURING TREATMENT/INTERVENTION

The following assessments will be made during the study to assess efficacy and safety. See Table 4 Schedule of Assessments.

Laboratory Assessments

a. CBC with differential, CMP, and Immature Platelet Fraction every day from day of AHCT (Day 0) until day +15 All patients will get at least weekly (+/- 3 days) labs until day +30. Patients who need 3 or more doses of romiplostim will get weekly (+/- 3 days) labs as long as their platelet count is ≥25,000. For patients who need 3 or more doses of romiplostim and whose platelet counts are <25,000 they will receive labs every second day until their platelets are ≥25,000.
b. LDH, PT/INR, APTT every 7 days (+/-2 days) from Day +1 until Day +15.
c. CBC with differential, CMP, Immature Platelet Fraction, LDH, PT/INR, and APTT will be done at days +30 (+/- 7 days), +60 (+/- 7 days) and at +100 (+/- 14 days) from AHCT.
d. For women of childbearing potential, a pregnancy test (negative serum or urine hCG) must be done at the end of treatment visit, 7 days after the last dose of romiplostim.

Safety endpoints will include change in typical neutrophil engraftment kinetics, venous or arterial thrombosis, evidence of marrow toxicity, and evidence of organ dysfunction.

12.1 CRITERIA FOR REMOVAL FROM STUDY

Treatment will continue until the occurrence of any of the following events:

- Continuation is no longer in the patient's best interest as determined by the patient's treating oncologist.
- Patient withdraws consent
- Death
- Lost to follow-up
- Major violation of study protocol, such as non-compliance.
- Adverse event(s) that, in the judgment of the Investigator or treating oncologist, may cause severe or permanent harm or which rule out continuation of the trial.

Discontinuation of Romiplostim:

If a patient develops a Grade 3/4 adverse event, attributable to romiplostim, based on the Common Terminology Criteria for Adverse Events (CTCAE version 5), the Romiplostim will be discontinued.

If a patient develops an asymptomatic deep vein thrombosis and/or pulmonary embolism, or a symptomatic deep vein thrombosis and/or pulmonary embolism, not associated with hemodynamic instability, and not considered life-threatening, the romiplostim may be continued if there is consensus of judgment of the treating oncologist and study investigator.

13.0 CRITERIA FOR OUTCOME ASSESSMENT AND ENDPOINT EVALUABILITY

13.1 Criteria for Therapeutic Response/Outcome Assessment

Primary Endpoint

1) The number of days requiring platelet transfusions or grade 4 CTCAE thrombocytopenia following HDT-AHCT

Secondary Endpoints

1) The number of platelet transfusions issued during the AHCT admission

2) The time to platelet engraftment after HDT-AHCT Platelet engraftment is defined as the first day of seven consecutive days with a platelet count of ≥20 K/mcL without transfusion support.

3) The length of stay of AHCT

4) The safety profile of romiplostim as per Section 11.0 Toxicities/Side Effects.

Platelet transfusions will be at the discretion of the treating BMT attending at will not be specified in the protocol. However, a member of the investigator team will review the medical record to determine the reason for the transfusion, specified as (a) thrombocytopenia alone, (b) bleeding attributed, at least in part to thrombocytopenia, and/or (c) need for interventional procedure while thrombocytopenia is present.

13.2 Criteria for Study Endpoint Evaluability

All patients who enroll, and receive at least two dose of romiplostim, will be evaluable for primary and secondary endpoints. If a patient has enrolled, but does not receive two doses of romiplostim due to death, or change in medical status, they will not be evaluable and they will be replaced on the study.

14.0 BIOSTATISTICS

This pilot study will investigate whether romiplostim reduces the number of days requiring platelet transfusions or grade 4 CTCAE thrombocytopenia following HDT-AHCT. The study includes patients with (1) MM undergoing high-dose melphalan and AHCT, (2) HL or NHL undergoing BEAM- or CBV-AHCT or (3) CNSL undergoing TBC-AHCT. Further, at least 20 will have MM undergoing high-dose melphalan and AHCT, and at least 20 will have HL or NHL undergoing BEAM-, CBV-, or TBC-AHCT. The primary endpoint along with the secondary endpoints will be evaluated in cohorts (1) MM and (2) HL or NHL separately. Due to anticipated low numbers, patients with CNSL receiving TBC-conditioning will be considered exploaratory only.

The primary endpoint is the number of days post HDT-AHCT requiring transfusions or grade 4 CTCAE thrombocytopenia. The study does not include a formal hypothesis test for the primary endpoint or corresponding decision rule. Instead the median and interquartile range

(IQR) of the number of days will be used to describe the number of days post HDT-AHCT requiring transfusions or grade 4 CTCAE thrombocytopenia for each cohort separately. The mean number of days along with a 95% confidence interval will additionally be reported. These summary statistics will be compared to the summary statistics of the historical data from patients transplanted from 2014-2016, presented in Table 1. For Cohort 1 (MM), the associated standard deviation for the mean of days post HDT-AHCT requiring transfusions or grade 4 CTCAE thrombocytopenia is 3.5. With 20 or more patients, the half width of the 95% confidence interval for the mean number of days for patients treated with romiplostim is +/- 1.6 or less if a similar standard deviation is observed. For Cohort 2 (HL/NHL), the standard deviation is 4.7, corresponding to a half width of +/- 2.1 or less. While not formally comparing these data to the historical MSKCC data, observed improvements in the mean number of days requiring transfusions or grade 4 CTCAE thrombocytopenia will help design a larger phase II study to formally evaluate romiplostim in the HDT-AHCT setting. If the mean number of days requiring platelet transfusions decreases by at least 1.5 days for Cohort 1, and/or at least 2 days for Cohorts 2, this study will be considered sufficiently promising. We will then proceed with a phase II trial for the cohort or cohorts that reached the above criteria (i.e. the specified decrease in days requiring platelet transfusion).

Evaluability criteria for both the primary and secondary endpoints are provided in Section 13.2.

In addition to the primary endpoint, the pilot study includes a number of secondary objectives.

1. To estimate the median and mean number of platelet transfusions issued during AHCT admission. In addition to the mean, the 95% confidence interval will be reported.This will be reported separately for each cohort.

2. To estimate the median and mean time to platelet engraftment after AHCT. In addition to the mean, the 95% confidence interval will be reported.This will be reported separately for each cohort.

3. To estimate the median and mean AHCT length of stay. In addition to the mean, the 95% confidence interval will be reported.This will be reported separately for each cohort.

4. To describe the safety and toxicity profile of romiplostim in this patient population. Toxcitiy will be described by grade and will be reported separately for each cohort.

15.1 TOXICITIES/RISKS/SIDE EFFECTS

Based on our initial experience, we have not observed treatment-related toxicities in our patients treated with romiplostim for CIT. Based on the romiplostim Prescribing Information, the most common adverse reactions (≥ 5% higher patient incidence in romiplostim versus placebo) are arthralgia, dizziness, insomnia, myalgia, pain in extremity, abdominal pain, shoulder pain, dyspepsia, and paresthesia.

Individual cases of thrombosis and been reported in patients receiving romiplostim, but in one recent review of long-term use of romiplostim, “The thrombotic adverse event rate

across all studies was 0.09 events per 100 patient-weeks on romiplostim therapy," markedly lower than would expected in patients with active cancer receiving chemotherapy. We have not observed an increased thrombosis rate compared with expected rates in patients with metastatic cancer, on chemotherapy, however, we will monitor any clinical evidence of thrombosis as well as hemorrhage.

Assessment of potential toxicity will be based on the Common Terminology Criteria for Adverse Events (CTCAE) Version 5. We will monitor for evidence of marrow toxicity, with weekly CBC (CBC must include: WBC, Hgb, platelet, MCV, cell differential) and lab toxicities of grade 3/4 will be adjudicated on a regular basis by the PI or Co-PI of the study.

Toxicity assessments will be done weekly (+/- 3 days while COVID restrictions remain in place) until 7 days after the last dose of Romiplostim, and Days +30 (+/-7 days), +60 (+/-7 days), and +100 (+/- 14 days) from AHCT. If a patient is discontinuing chemotherapy/treatment and going to hospice/ comfort care, the final toxicity assessments will be omitted if toxicities were managed regularly.

The study will report all toxicities from the time a patient signs consent until 30 days after the last dose of treatment, unless they are at least possible related to the protocol, in which case they will be reported beyond the 30-day period. All toxicities meeting these criteria should be reported to MSKCC as a toxicity in CRDBi-Multicenter with supporting source documentation.

Longterm safety follow up for secondary malignancy is not planned within this protocol because the patients enrolled will be followed as part of their standard of care on the Adult Bone Marrow Transplant Service at MSKCC.

15.1 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All patients will be followed for safety and toxicity related to the study drug (romiplostim). Potentially serious toxicities are an expected part of autologous stem cell transplantation. The reportable adverse events (AEs) and serious adverse events (SAEs) associated with autologous stem cell transplantation will be defined according to the Adult Bone Marrow Transplant (ABMT) Adverse Event (AE) and Serious Adverse Event (SAE Guide). The ABMT AE and SAE Guide is posted as a Standard Working Procedure (SWP) on the Clinical Research Policies and Regulations page:

https://one.mskcc.org/sites/pub/clinresearch/Policies/Departmental%20SOPs/Adult%20BMT%20AE%20and%20SAE%20Guide.pdf

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

15.2. External SAE Reporting

The MSKCC research staff must inform Amgen, Inc. of any Suspected Unexpected Serious Adverse Reaction (SUSAR) as soon as possible but no later than 5 calendar days of the MSKCC principal investigator becoming aware of the event. All SUSARs will be reported up to 30 days after the last dose of treatment, unless they are at least possibly related to the protocol, in which case they will be reported beyond the 30-day period.

The MSKCC research staff must also inform Amgen, Inc. of any pregnanacy or exposure to drug through lactation and the associated reports and outcomes (i.e. unexpected pregnancy, pregnancy of partner, spontaneous abortion, congenital abnormality etc.). This report must be sent to Amgen Safety within 1 business day of MSKCC research staff awareness for reports meeting serious criteria, and is not to exceed 15 calendar days of MSKCC research staff awareness for non-serious reports.

16.1 PROTECTION OF HUMAN PARTICIPANTS

Inclusion of Children in Research:

This protocol/project does not include children because the number of children is limited and the majority are already accessed by a nationwide pediatric cancer research network. This statement is based on exclusion 4b of the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.

Incentives/Costs/Benefits:

No incentives will be offered to patients/subjects for participation in this study. Participation is voluntary. The potential benefits of participation in the study will be weighed against other treatment options (see below) including supportive care. The patient/subject or their health insurance provider will be responsible for the costs of standard medical care including MD visits, routine blood tests, administration of the study drug, and bone marrow biopsies and aspirates. The patient/subject or their health insurance provider will not be charged for the study drug romiplostim.

Alternative treatment of patients: Usual care with transfusion of platelets when necessary as deemed by treating oncologist.

16.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals/entities described in the Research Authorization form. A Research Authorization form must be approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with others at the time of study publication.

16.2 Data Management

A Clinical Research Coordinator (CRC) will be assigned to the study at MSKCC. The responsibilities of the CRC include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into a secure database, Medidata Rave. Source documentation will be available to support the computerized patient record.

Investigators will permit study-related audits by the sponsor, IRB review, and regulatory inspection(s) (e.g., FDA, EMEA, TPP), providing direct access to the facilities where the study took place, to the source documents, and to all other study documents.

Final data sets for publication are required to be locked and stored centrally for potential future access requests from outside entities.

16.3 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates, the extent and accuracy of evaluations and follow-ups will be monitored periodically throughout the study period for potential problems, which will be brought to the attention of the study team for discussion and action.

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, or more frequently if indicated.

16.4 Data and Safety Monitoring

The Data and Safety Monitoring Plan utilized for this study must align with the MSK DSM Plan, where applicable.

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering were approved by the National Cancer Institute in August 2018. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials."

There are several different mechanisms by which clinical studies are monitored for data, safety and quality. At a departmental/PI level there exists procedures for quality control by the research team(s). Institutional processes in place for quality assurance include protocol monitoring, compliance and data verification audits, staff education on clinical research QA and two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Deputy Physician-in-Chief, Clinical Research.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required.

The MSK DSMB monitors phase III trials and the DSMC monitors non-phase III trials. The DSMB/C have oversight over the following trials:

- MSK Investigator Initiated Trials (IITs; MSK as sponsor)
- External studies where MSK is the data coordinating center

- Low risk studies identified as requiring DSMB/C review

The DSMC will initiate review following the enrollment of the first participant/or by the end of the year one if no accruals and will continue for the study lifecycle until there are no participants under active therapy and the protocol has closed to accrual. The DSMB will initiate review once the protocol is open to accrual.

The MSKCC research staff will submit to Amgen, Inc. annual safety reports. These reports will include SUSARs and pregnancy and lactation exposure (and any associated reports/outcomes). The reports will be sent to the NASCR Manager once per year and at the end of the study. Any other report containing safety data generated during the course of the study will also be sent to Amgen, Inc. at the time of submission to any body governing research conduct. A final end of study safety report will be sent to Amgen, Inc. at the time of submission to any body governing but no later than 1 calendar year past study completion.

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18.0 APPENDICES

Appendices will be stored in a separate file and will be submitted in electronic and/or paper format.

Appendix A: Investigators Brochure

19.0 MSK MULTICENTER TRIAL ADDENDUM

Data analysis being performed by the site(s): "Clinical, laboratory and radiographic data will be shared with SYLVESTER COMPREHENSIVE CANCER CENTER, including but not limited to: cancer therapy, COVID-19 treatment, demographic information, and assessment values."

Dr. Gerald A Soff MD (Clinical Director, Hemostasis, Thrombosis and Transfusion Services, University of Miami Health System/Sylvester Comprehensive Cancer Center) will serve as a Data Collaborator for this study. In this capacity, he will participate in analysis, presentation, and publication of the data and findings of the study. He will also contribute to the language for amendments to the protocols, if necessary.

Dr. Soff will not have access to any Protected Health Information (PHI) on any patient. He will have access to aggregated data only. All correspondences between the MSKCC investigators and Dr. Soff will be conducted via secure email. Data will be made available to Dr. Soff throughout the performance of the study, as well as during the period when the data are analyzed and written up for presentation and publication.

Table 4. Schedule of Study Assessments

Study Assessments/ Testing	**Screening** Within 28 days of AHCT Admission	Day of AHCT Admission	**Day 0** Day of AHCT	**Daily** from Day 0 until Day +15[7].	**Weekly** from Day +1 until last doseof Romiplostim[8].	**End of Treatment** 7 Days after last doseof Romiplostim (+/- 3d)	**Day (d) Post-AHCT**			
							d +21 (+/- 3d)	**d +30 (+/- 7d)**	**d +60 (+/- 7d)**	**d+100 (+/- 14d)**
Consultation with Adult BMT Physician	X									
Sign informed consent	X									
History,	X									
Physical Exam	X				X	X		X		
Vital Signs	X	X	X	X				X		
ECOG performance status	X				X[11]	X		X		
Confirmation of diagnosis[1]	X									
CBC	X	X	X	X	X	X	X	X	X	X
CMP	X	X	X	X	X	X	X	X	X	X
LDH	X				X[9]	X		X	X	X
PT/INR and APTT	X				X[10]	X		X	X	X
Immature Platelet Fraction	X	X	X	X	X	X	X	X	X	X
Cytogenetics[2]	X									X[3]
Romiplostim injection[4]					X					
Adverse Event Assessments	X				X	X		X	X	X
Pregnancy Test[5]	X[6]					X		X	X	X
Pulmonary Function Test	X									
MUGA or Resting Echocardiogram	X									

[1] Bone marrow and/or lymph node and/ortissue biopsy confirming a diagnosis of MM, HL, or NHLatany time prior to HDT-AHCT.

[2] If never previously done, a baseline cytogenetics will be drawn during screening. The cytogenetic testing will include the FISH panel for MDS froma bone marrow aspirate and/orbiopsy or peripheral bloodtesting.

[3] A repeat cytogenetics will be drawn on Day +100 (+/-14 days) from AHCT only if there is evidence of romiplostim toxicity tothe bone marrow. Appearance of leukoerythroblastosis on the peripheral blood, will be considered a surrogate for possible romiplostim toxicity tothe bone marrow. Leukoerythroblastic changes consist of immature white cells, nucleated red blood cells, orincrease inteardrop cells (dacrocytes).

[4] All patients will receive romiplostim 3.0 mcg/kg SC on Day +1 and romiplostim 2.0 mcg/kg SC on Day +8 after HDT-AHCT. Beyond Day +8 patients will be treateduntil platelet countis >50,000/mcL, without any platelettransfusions inthe prior 48 hours. All doses after the secondromiplostimdose will be titrated as per Table 3, based on weekly CBC/platelet counts. Patients will receive a maximum of six weeklydoses of romiplostim. Romiplostim doses after Day +8 may have a +2 day window

[5] For women of childbearing potential, a negative pregnancy test (serum orurine b-HCG) mustbe done atthe timepoints specified inthe calendar.

[6] The screening pregnancy testmust be done within 48 hours of AHCT

[7] For patients who need 3 ormore doses of romiplostim and whose platelet counts are <25,000 they will receive labs every second day beyond Day +15 until their platelets are ≥25,000.

[8] While COVID restrictions remainin place, weekly physicianvisits will have a windowing of +/- 3 days.

[9] LDH only needed weekly until Day +15.

[10] PT/INR and APTT only neededweekly until Day +15.

[11] ECOG only requiredfor outpatient visits.