MSK PROTOCOL COVER SHEET

A Single Arm Open-Label Pilot Study of Prophylactic Romiplostim Use Compared to Benchmark Rate in the Prevention of Chemotherapy Induced Thrombocytopenia in Pediatric Solid Tumors Patients Undergoing Myelosuppressive Chemotherapy

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Current Version Date: October 18, 2021

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Chemotherapy induced thrombocytopenia (CIT) is a significant toxicity of high dose chemotherapy, causing bleeding, requiring platelet transfusions, and often resulting in delays in planned therapy. Romiplostim, a thrombopoeitin mimetic, has been shown to stimulate platelet recovery and reverse CIT in adult oncology patients and has been extensively studied for children treated for immune thrombocytopenia purpura. Given its promising efficacy in treating CIT in adults and safety in pediatric studies, we describe a study of a single-arm, open-label, phase II study of prophylactic romiplostim in pediatric patients at high risk for developing CIT due to being treated with the EFT (Ewing's Family of Tumors), MAP (Methotrexate, Adriamycin, cisPlatin), or D9803 regimens, 3 highly myelosuppressive pediatric oncology treatment regimens. Patients will begin treatment at the start of the 'regimen-specific' identified cycle number with romiplostim at 10 mcg/kg subcutaneously once weekly until completion of high dose chemotherapy. The primary goal of the study is to reduce the number of platelet transfusions compared to the benchmark rate. Secondary goals include reducing the number of chemotherapy delays and dose reductions due to CIT, as well as monitoring for adverse events.

TARGET PATIENTS

Patients ≤ 21 years old with solid tumors undergoing induction chemotherapy with the EFT regimen for solid tumors (e.g. Ewing Sarcoma, malignant rhabdoid tumors, other rare sarcomas), the MAP regimen for Osteosarcoma, or the D9803 regimen for Rhabdomyosarcoma.

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INTERVENTION

Romiplostim starting at 10 mcg/kg SC once weekly beginning Cycle 5 Day 1 of EFT regimen, MW0 Day 1 of MAP regimen, or Cycle 7 Day 1 of D9803 regimen.

- Throughout this protocol, to allow for patient scheduling limitations and needs, treatment of romiplostim will be every 7 days +/- 3 days which we will interchangeably call 'weekly'
- Romiplostim dose may need to be adjusted based on the platelet count.
- Laboratory assessments include weekly CBCs and CMPs approximately every 3 weeks.

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ENDPOINTS

Primary:

1. Total number of platelet transfusions administered during the studied portions of the EFT, MAP or D9803 cycles.

Secondary:

1. Number and duration of chemotherapy delays and/or chemotherapy dose reductions due to inadequate platelet recovery (platelets ≤75,000 /mcL) during the treated EFT, MAP or D9803 cycles.
2. Number of patients who develop grade IV thrombocytopenia during the studied EFT, MAP or D9803 cycles.
3. Number of adverse events particularly thrombosis, marrow toxicity, or organ dysfunction observed in patients who receive romiplostim.

2.1 OBJECTIVES AND SCIENTIFIC AIMS

Primary objective:

- To evaluate whether romiplostim administration can decrease the total number of platelet transfusions required during the treatment courses of EFT, MAP, or D9803 when compared to the benchmark rate.

Secondary objectives:

- To evaluate whether romiplostim administration can decrease the number and severity of chemotherapy modifications (chemotherapy dose reductions and/or delays) during treatment course of EFT, MAP or D9803 secondary to thrombocytopenia compared to the benchmark rate.
- To evaluate the incidence of CTCAE grade IV thrombocytopenia in patients who receive romiplostim compared to the benchmark rate.
- To assess the safety profile of romiplostim administration in pediatric patients with solid tumors receiving EFT, MAP, or D9803.

Exploratory objective:

- Describing the transfusion rate at different age groups.

3.0 BACKGROUND AND RATIONALE

INTRODUCTION

Thrombocytopenia has long been recognized as a significant complication of pediatric cancer treatment. Standard induction chemotherapy regimens for many pediatric solid tumors are highly myelosuppressive and result in chemotherapy induced thrombocytopenia (CIT). [1-3] Profound CIT increases the risk of bleeding, need for platelet transfusions, and can cause interruptions and modifications in planned cancer therapy. The actual incidence of CIT can vary significantly depending on the: (i) individual chemotherapy agents, (ii) dosing of chemotherapy, and (iii) combinations of agents used. [4, 5]

Curative treatment of most childhood solid tumors is based on the administration of multiple cycles of intensively dosed chemotherapy. [6, 7] Pediatric chemotherapy regimens are particularly intensive and myelosuppressive. It is common practice to reduce the dosage or delay the next cycle of chemotherapy in response to hematologic toxicity or inadequate count recovery from prior cycle, however this reduces the overall dose intensity of treatment.[8] It has been shown that reduced dose intensity correlates with worse survival outcome in both retrospective and prospective clinical studies in numerous cancer types. [8-12] Therefore, the practice of reducing dose intensity may achieve reduction in toxicity, but may also decrease the therapeutic effect of the treatment and impact the likelihood of cure.

In a retrospective series of 609 adult patients with solid tumors who exhibited CIT (as defined by platelets of <50,000/mcL), a delay in subsequent chemotherapy occurred during 6% of cycles, a reduction in chemotherapy occurred in 15% of patients with CIT, and the CIT cohort used more resources when compared to those who did not experience CIT. [13] In an additional retrospective review of 254 adult solid tumor patients, the incidence of clinicially significant CIT was found to be 10.1%. In this study, clinically significant CIT was defined as platelet count <75,000/mcL and presence of bleeding, dose reduction/delay, platelet transfusion or therapy cessation.[14] Unfortunately, pediatric literature is sparse regarding the incidence of dose reductions and delays of chemotherapy and the transfusion burden of CIT. [15]

MSKCC HISTORICAL COHORT

Based on review of MSKCC data, three of the most severely myelosuppressive regimens utilized in newly diagnosed pediatric solid tumor patients were EFT, MAP and D9803 regimens, most commonly used for Ewing's sarcoma, Osteosarcoma and Rhabdomyosarcoma respectively (Table 1). These regimens differ in the their treatment length but similarly, consist of myelosuppressive high doses of cyclophosphamide (EFT, D9803), Ifosfamide (EFT), Cisplatin (MAP) and Doxorubicin (EFT, MAP).

Table 1: Chemotherapy Schematic EFT, MAP, D9803

Regimen	Cycle order and duration		Doses of chemotherapy		Local control
EFT	7 cycles: 21 days each	Cycles 1-3, 7: CAV Cycles 4-6: IE	**CAV**: VCR 2mg/m2 Doxo 75mg/m2 CPM 2100 mg/m2	**IE:** Ifosfamide 14,000mg/m2 Etoposide 500mg/m2	For Ewing Sarcomas, tumor resection +/- radiation usually after cycle 3; Other tumors treated with this regimen may have local control at different times.
MAP	28 weeks: Induction 9 weeks; Maintenance 19 weeks	IW0, IW5, MW0, MW5: CDDP/Doxo, MW10, MW15: Doxo only Remaining weeks: HD-MTX	**CDDP/Doxo**: CDDP 120mg/m2 Doxo 75mg/m2	**HD-MTX:** MTX 12,000 mg/m2	For Osteosarcoma, tumor resection after Induction week 9
D9803	12-14 cycles VAC every 21 days		**VAC:** VCR: 2mg/m2 AMD: 0.045mg/kg if >/=1yo, 0.025mg/kg if <1yo CPM: 2200 mg/m2 if >/= 1yo, 36 mg/kg if <1yo		For Rhabdomyosarcoma, tumor resection + radiation usually between cycle 5-7

CAV: Cyclophosphamide/doxorubicin/vincristine. IE: Ifosfamide/etoposide. VCR: vincristine. CPM: Cyclophosphamide. Doxo: Doxorubicin. CDDP: Cisplatin. VAC: Vincristine/dactinomycin/cyclophosphamide. AMD: Dactinomycin

Charts were obtained from a query of all patients < 21 years old treated on MSK IRB 13-068 (EFT), our up-front regimen for patients with Ewing Sarcoma, on IRB 03-074 (MAP), our upfront regimen for patients with Osteosarcoma, and on D9803, the COG regimen for intermediate-risk Rhabdomyosarcoma patients from 1/1/2013 through 1/1/2020. These charts were reviewed to

determine the number of platelet transfusions and chemotherapy dose reductions and delays. A chemotherapy dose reduction was defined as ≥ 20% reduction in the intended dose for the next cycle and a treatment delay was defined as a start date ≥ 25 days (for 21 day cycles) or ≥ 10 days (for 1 week cycles) from start of prior chemotherapy cycle.

Seventy nine patients (EFT N=28, MAP N=44, D9803 N=7) were treated with the above regimens during this period. Platelet transfusion requirements increase with cycle number (Table 2). For EFT/Cycle 1 there was a mean of 0.2 (range 0-2) transfusions given. For EFT/Cycle 7, the mean increased to 2.6 (range 0-7). For the MAP cohort, 22/44 patients received at least one transfusion during the first 9 induction weeks. Those patients who required a transfusion during the induction stage, continued to require notably more transfusions throughout their post-operative maintenance therapy than those who did not require transfusions during induction suggesting a particular susceptibility to CIT in this cohort. Given the preferential need in this select group, further analysis was performed. For the CDDP/Doxo weeks of MAP highlighed in Table 2, there was a mean of 0.1 (range 0-2) transfusions during IW0, but for MW5, the mean increased to 1.7 (range 0-4). For D9803/Cycle 1 there was a mean of 0, but by D9803/Cycle 10, the mean increased to 2.8 (range 0-16). The total platelet transfusions per full regimen were a mean of 8.0 (IQR 5-12) for EFT, mean of 6.0 (IQR 5-7) for MAP, and mean of 4.0 (IQR 2-8) for D9803.

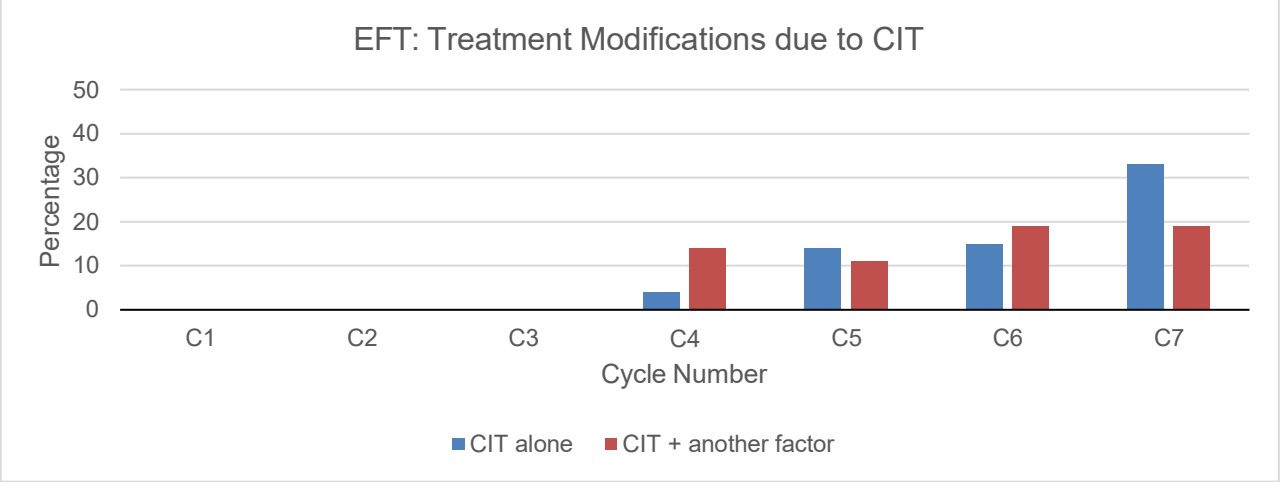
Table 2: Platelet Transfusion Requirements Per Cycle

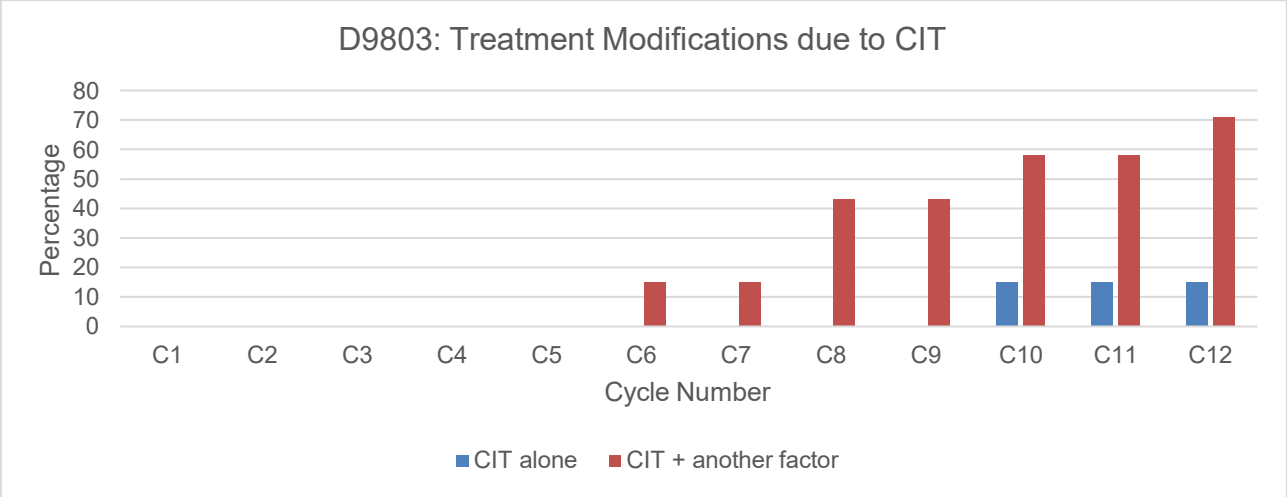
	Cycle	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**Total in Target Cycles**
EFT	Mean	0.2	0.7	1.9	1.3	1.2	1.7	2.6						5.0
	Range	0-2	0-3	0-6	0-7	0-3	0-8	0-7						0-14
	N	28	28	28	27	25	25	26						
D9803	Mean	0	0	0.5	0.2	0.3	0.4	0.5	0.9	0.8	2.7	0.4	0	4.6
	Range	0	0	0-2	0-1	0-1	0-1	0-2	0-4	0-2	0-16	0-2	0	0-19
	N	7	7	6	6	7	7	6	7	6	6	5	5	
MAP (CDDP/ Doxo only cycles)	**Weeks**	IW0	IW5	MW0	MW5	MW10	MW15							
	Mean	0.1	1.1	1.3	1.7	0.7	1.0							4.9
	Range	0-2	0-3	0-4	0-5	0-4	0-3							1-9
	N	21	22	22	22	21	21							

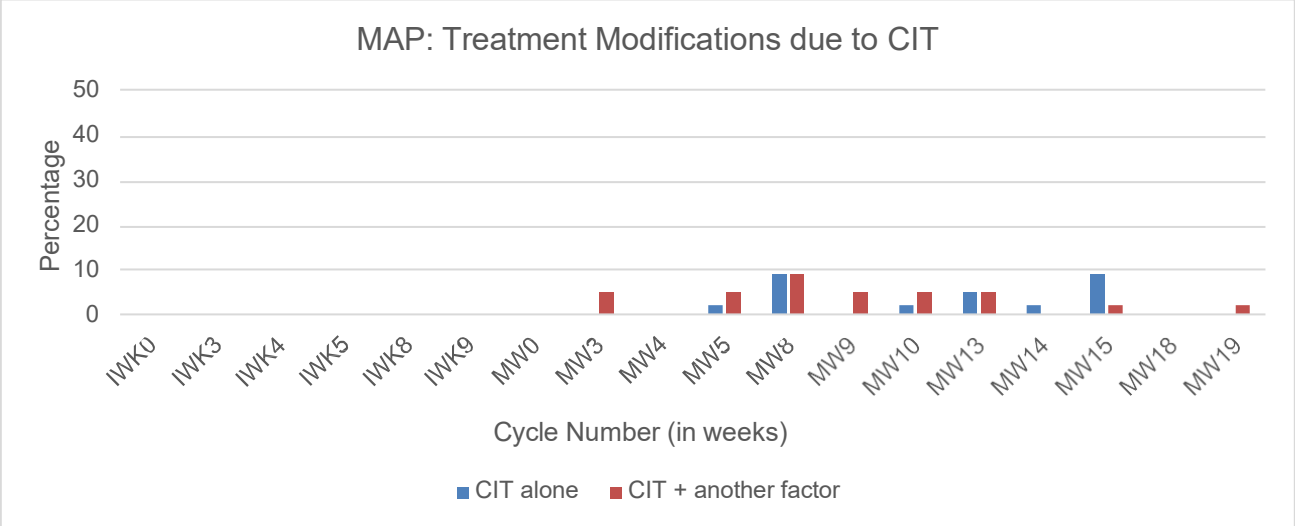
Dose reduction and/or delay of chemotherapy due to CIT similarly increased over the course of therapy (Figure 1). For EFT, at cycle 2, no patient had reduction and/or delay of chemotherapy due to isolated CIT, however by the last cycle, 32% experienced reduction and/or delay of treatment due to isolated CIT. In aggregate for the EFT cohort during cycles 4-7, 25% (n=21/82) of cycles were delayed/modified due to thrombocytopenia alone and an additional 10% (n=8/82) of cycles were delayed/modified due to thrombocytopenia and another factor. For D9803, at cycle 2, no patient had

reduction and/or delay of treatment due to CIT, however by the second half of the regimen (C7-C12), 15-70% experienced reduction and/or delay due to CIT +/- another factor. For MAP, during the first 9 induction weeks, no patient had reduction and/or delay of chemotherapy due to CIT, but during the following 19 maintenance weeks, up to 10% of patients experienced reduction and/or delay due to CIT +/- another factor.

Figure 1: CIT Related Treatment Modifications







It is clear that CIT is a serious sequela of myelosuppressive chemotherapy in pediatrics, requiring frequent platelet transfusions and chemotherapy modifications which worsen as treatment progresses. CIT treatment remains a serious unmet need.

PLATELET TRANSFUSION RISKS

The therapeutic introduction of recombinant granulocyte colony stimulating factor (G-CSF) in 1988 revolutionized supportive care for chemotherapy. [16, 17] G-CSF diminishes the severity and complications from chemotherapy-induced neutropenia. However, there are no current FDA-approved medications to reduce the risk of developing CIT. Currently, the standard of care includes platelet transfusions for active bleeding or prophylactic transfusions for severe thrombocytopenia (platelet count <10-20,000/mcL). However, the response to platelet transfusion is unreliable and the effect is short-lived, therefore platelet transfusions are not practical to maintain platelet counts through cycles of chemotherapy nadir. [18, 19] Further, up to 20-30% of platelet transfusions can result in febrile or allergic reactions, and more rare but serious complications include septic reactions from contaminated blood and transfusion related acute lung injury, estimated at 1 in 50,000 and 1 in 5000 transfusions, respectively. [1] Platelets are also a limited resource frequently in high demand. Platelets are obtained from a single donor via apheresis or pooled from 5-6 donors, the shelf life is only five days, and the transfused platelets only last in the body for a maximum of approximately five days. In addition, there is the serious problem of platelet refractoriness, which has a reported incidence of 15%-25% in patients with hematologic or oncologic diagnoses utilizing leukocyte-reduced blood products. [20] Pathogen-reduced platelet products have come into favor recently but studies are showing individuals who receive pathogen-reduced platelets have an even higher risk of developing platelet refractoriness and require more platelet transfusions then those receiving standard platelet transfusions. [21] Platelet-reactive antibodies, directed against the HLA and HPA present on the platelet surface, are more likely to develop with repeated blood product exposure and are frequently associated with accelerated platelet destruction and transfusion failure. Platelet refractoriness

becomes especially concerning when a patient develops a clinically significant bleed as it can be nearly impossible to increase their platelet count to a hemostatic level. [20]

ROMIPLOSTIM MECHANISM OF ACTION and PHARMACOKINETICS

Thrombopoietin (TPO) is the main regulator of platelet production. Recombinant TPO entered clinical trials in 1995. A full length recombinant human TPO (rhTPO) and a non-glycosylated, recombinant protein comprised of a partial TPO peptide sequence coupled to a polyethylene glycol moiety (PEG-rHuMGDF) were studied and both raised the platelet counts in test subjects. [22] In a study in lymphoma, PEG-rHuMGDF allowed for improved chemotherapy dose-intensity, reduced the rate of grade IV thrombocytopenia, and reduced the need for platelet transfusion. [23] Further, there was a trend towards improved survival with PEG-rHuMGDF support. However, therapeutic development of both forms of recombinant TPO was halted following the development of anti-drug antibodies that cross-reacted with endogenous TPO in some healthy volunteers, causing thrombocytopenia. [22] More recently, new drugs have been developed that are TPO receptor agonists. Romiplostim (Nplate) is a thrombopoietin (TPO) mimetic that binds to the distal cytokine homology region of the TPO receptor (Mpl) leading to the activation of the JAK/STAT and MAP kinase pathways, resulting in increased platelet production. [24] Romiplostim stimulates megakaryocyte colony growth and maturation. The stimulation of the MAP kinase pathway leads to activation of anti-apoptotic pathways, also resulting in increased platelet production. Romiplostim also works in synergy with cytokines, such as erythropoietin and stem cell factor, to stimulate megakaryocyte growth and expansion and though it works through its its interaction with Mpl receptor, it does no inhibit native TPO. [25] As romiplostim bears no structural or biochemical resemblance to TPO, there is no risk of developing TPO antibodies, unlike the first generation of TPO mimetics.[26] Following romiplostim administration, platelet production peaks between 8-15 days. [27] Romiplostim is known to cause a dose-dependent rise in platelet counts, with a rise being seen 4-9 days after subcutaneous administration and peak platelet counts occurring approximately 10-16 days from administration. [25, 27, 28]. Romiplostim is already FDA-approved for use in adult and pediatric patients with chronic immune thrombocytopenia (ITP) and has a very favorable side effect profile. [29-31] The current dosing range of romiplostim for both pediatrics and adults is 1-10 mcg/kg, and in the initial pediatric ITP trials, it was seen that serum concentrations in pediatrics is no different then in adults.[29, 30] In the ITP trials the starting dose of romiplostimn was 1 mcg/kg with weekly dose adjustments of 1 mcg/kg with goal of obtaining platelet counts of 50-200,000/mcL. In the randomized phase 3 trial, median effective dose during the trial was 5.5 mcg/kg (IQR 3-10 mcg/kg) and in key adult ITP trials the mean therapeutic romiplostim dose was 3-4 mcg/kg [30, 32] Further studies and collection of real world clinical practice have shown safety with starting at doses >1 mcg/kg without any increase adverse effects. [33-37]

TPO RECEPTOR and CANCER CELLS

During development of recombinant TPO, studies were done to determine if there was thrombopoietin receptor (c-mpl) expression in human cancer cell lines and primary tissues. In one study, no primary tumors types studied were found to express c-mpl. [38] In another study, expression of *MPL* (TPO-R) mRNA was examined in tumor cell lines, patient tumor samples and normal tissues and found to be either very low or undetectable in tumor and normal tissue samples. [39] C-mpl appears to have

restricted expression that is primarily related to megakaryocytopoiesis and suggests that thrombopoietin/thrombopoetin mimetic use is unlikely to have direct effects on malignant or normal tissue when used for treatment of CIT. Further, there has been no evidence of tumor progression or increased relapse rates with either first generation or second generation TPO mimetic use in human studies. [37, 40-43]

ONCOLOGY CLINICAL STUDIES

At MSKCC, we have successfully used romiplostim to treat adult solid tumor patients with CIT, including a recently completed randomized Phase II trial. [37] In this trial, 44/52 (85%) of patients treated with romiplostim for prolonged CIT corrected their platelet counts within three weeks. Further, once these patients went on to resume chemotherapy, only 6.8% had recurrent CIT while on romiplostim. Of the 44 patients who resumed chemotherapy, 28 (64%) where able to resume the same chemotherapy that had led to the CIT and 16 (36%) resumed a different regimen. Additonally, 11/19 (58%) patients who had prior reductions in the chemotherapy dosing due to CIT, where able to resume full or increased dosing. Of the 44 patients who resumed chemotherapy, 28 (64%) continued on romiplostim for >6 months [37] This study demonstrated that there was a clear benefit of romiplostim maintenance therapy, allowing adult patients who had previously developed CIT to more consistently receive chemotherapy with fewer treatment delays due to thrombocytopenia. There were no new safety signals in this patient population. An additional retrospective study assessing romiplostim use in adult solid tumor patients with CIT, found that 13/17(76%) patients treated with romiplostim achieved platelet counts >100,000/mcL by three weeks of treatment and only 1/17 (6%) never had resolution of CIT. [40] In this study, romiplostim plus chemotherapy was also assessed and 18/22 (82%) patients were able to tolerate chemotherapy at or above the dose intensity prior to romiplostim initiation and the mean duration of chemotherapy delays due to CIT decreased from 4 weeks to 1 weeks. Romiplostim statistically significantly reduced chemotherapy delays and dose-reductions due to thrombocytopenia.[40] There is, however, limited experience in pediatric patients with CIT, with two case series demonstrating efficacy of romiplostim for treatment of CIT. [36, 44] In the one case series with five pediatric solid tumor patients with CIT, all patients had resolution of CIT between 2-3 doses of romiplostim and were able to resume chemotherapy with only 1/5 patients having any further chemotherapy delays while on romiplostim. [36] In the other pediatric cancer case series, romiplostim was used in the setting of secondary thrombocytopenia after allogeneic transplants. In this case series, 6/7 (86%) of patients became transfusion independent by week 2 of treatment and no patients developed adverse events from romiplostim. [44]

ROMIPLOSTIM DOSING RATIONALE

None of the literature involving romiplostim use in cancer patients has shown any new or alarming safety signals, including no increased risk of thrombosis and no evidence of development of myelodysplastic syndrome or a hematologic malignancy. [36, 37, 40, 44] It also appears that for CIT, starting doses higher then 1 mcg/kg were safe and the majority of patients required dosing at or above 3 mcg/kg. In the MSKCC randomized phase II CIT study, the mean romiplostim dose to correct CIT was 2.6 (2.4-2.8, 95% CI) and the mean dose to maintain platelets >100,000 during resumption of chemotherapy was 3.3 (2.7-3.8 95% CI). [37] In the retrospective adult CIT study, the median

romiplostim starting dose with 3 mcg/kg (range 1-10 mcg/kg). [40] In the pediatric solid tumor CIT case series, the median starting dose was 3 mcg/kg with maximum doses ranging from 3-10 mcg/kg and in the pediatric transplant case series with secondary thrombocytopenia, patients required doses ranging from 3-7 mcg/kg. Notably however, the dose of chemotherapy used on these studies are quite high and, in the initial set of patients treated on this study prior to this amendment, the low doses used for adult CIT and pediatric ITP are likely too low and therefore we recommend starting at the upper end of the dosing range (10 mcg/kg) and de-escalating only if needed. This will not only increase the likelihood of achieving maximum efficacy with preservation of safety but also greatly simplify the algorithm without requiring the provider to follow a complicated escalation protocol.

The existing safety profile of romiplostim in children with ITP, encouraging efficacy data in adult solid tumor patients, and limited safety concerns in children with cancer supports the development of a rigorous clinical investigation to evaluate the safety and efficacy of romiplostim for the prevention of CIT in children with solid malignancies.

STUDY RATIONALE

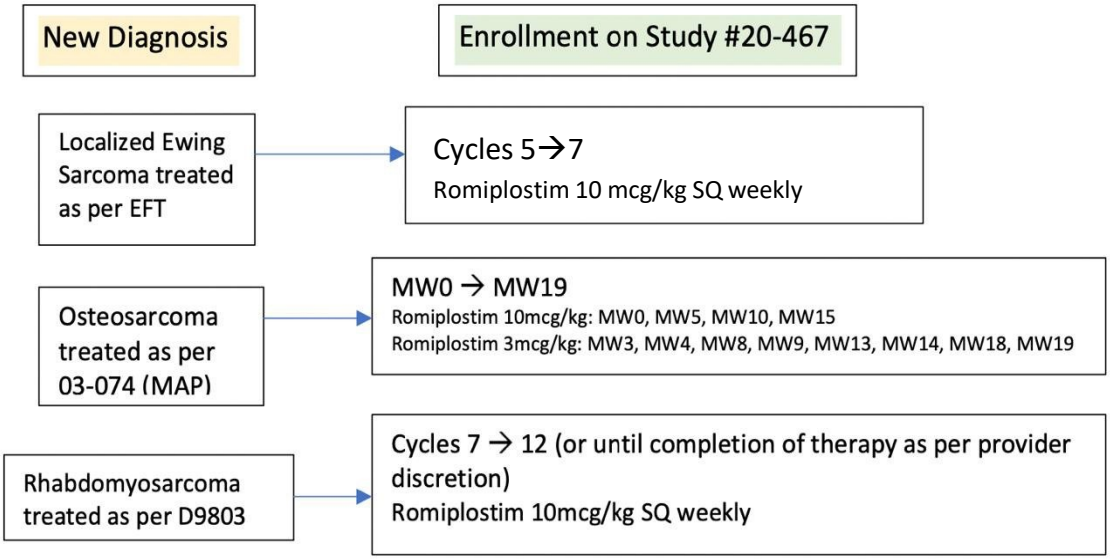
Based on our prior experience and preliminary data, we are proposing a single arm prospective study of romiplostim in pediatric cancer patients undergoing EFT, D9803 or MAP chemotherapy. Further for EFT, since we have demonstrated that the major burden of platelet transfusion and reduced relative dose intensity (RDI) of chemotherapy occur after cycle 4, we will target our intervention at cycles 5, and later. For the D9803 regimen, since both our institutional historical data as well as the data from the COG D9803 trial data published in 2009 [45] have demonstrated that hematologic toxicities contribute to both the platelet transfusion burden as well as reduced RDI generally after the time of local control, we will target our intervention at cycle 7, and later (after surgery and radiation therapy is complete). For the MAP regimen, our historical institutional data illustrates the impact of treatment-related thrombocytopenia in a select ‘high-risk cohort’ (individuals who received >/= 1 transfusion during Induction) and mainly during the weeks consisting of Cisplatin and Doxorubicin. Given this, we propose to initiate treatment starting at MW0 in individuals who have received >/= 1 transfusion during induction and continue treatment through the end of maintenance. All study patients will receive romiplostim. The endpoints will be: (Primary) reduction in platelet transfusions, and (Secondary) improved RDI. We will use our institutional historical experience as the benchmark rates.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

Phase II single-center, single arm study of romiplostim for pediatric patients at risk for CIT undergoing treatment with EFT, MAP, or D9803 compared to the benchmark rate. The benchmark rate was obtained by reviewing patients with solid tumors ages 1-21 years old treated with EFT, MAP, or D9803 regimens by MSKCC Pediatric Sarcoma teams during 2013-2020. Study patients will receive weekly doses of romiplostim. The initial romiplostim dose will be 10 mcg/kg, and subsequent doses will vary based on chemotherapy regimen (see section 10.0) for a target of platelet count > 75,000-200,000/mcL. Patients will continue romiplostim until completion of EFT, MAP, or D9803, as defined

above. Maximum romiplostim dose is 10 mcg/kg. Patients will be followed until 6 months after the last dose of romiplostim.



We hypothesize that prophylactic use of romiplostim during the myelosuppressive regimens of EFT, MAP, and D9803 for pediatric solid tumor patients will stimulate platelet recovery resulting in (1) a decreased number of platelet transfusions and (2) fewer chemotherapy modifications due to CIT compared to the current standard of care.

4.3 Intervention

Romiplostim Treatment: Patients will be enrolled any time: from Cycle 3 Day 1 until the receipt of chemotherapy on Cycle 5 Day 1 for EFT, from Induction week 8 until receipt of chemotherapy on Maintenance week 0 for MAP, and from Cycle 5 Day 1 until the receipt of chemotherapy on Cycle 7 Day 1 for D9803. They will then receive weekly (+/- 3 days) subcutaneous romiplostim injections beginning with Cycle 5 Day 1 for EFT, MW0 Day 1 for MAP or Cycle 7 Day 1 for D9803. Starting dose of romiplostim will be 10 mcg/kg (with the exception of MAP HD-MTX weeks for which dose will be 3mcg/kg), with adjustments per updated protocol (section 10.0) to target platelet count of 100,000 - 200,000/mcL. All doses of romiplostim will be held for a platelet count >/= 400,000/mcL. Romiplostim will stop upon platelet count recovery after final cycle of chemotherapy. Patients will be followed until 6 months after the last dose of romiplostim.

Control: No control arm. We will use institutional benchmark rates from our EFT, MAP, and D9803 patients from 2013-2020.

5.0 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)*.[22, 24]

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.

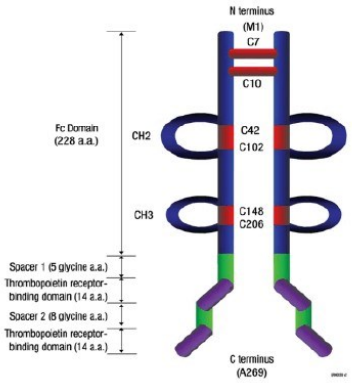
Romiplostim vials will be stored in their carton to protect from light until the time of use. Keep romiplostim vials refrigerated at 2°to 8°C (36° to 46°F). Do not freeze.

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 included.

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 Nplate lyophilized product can be kept at room temperature up to 25°C (77°F) in the original carton; however, under these conditions, the Nplate lyophilized product must be used within 30 days. If not used within 30 days, discard Nplate. Protect Nplate 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

- Documented diagnosis of a primary solid tumor. Patients must have histological verification of malignancy at MSKCC.
- Male and female patients aged 1-21 years with a primary solid tumor undergoing treatment with the pre-defined chemotherapy regimens of EFT, MAP, D9803. Prior to enrollment patient could have been undergoing induction therapy with a similarly myelosuppressive regimen as long as they will be continuing with EFT, MAP, D9803 at the time of study enrollment.
- Patients undergoing treatment with MAP chemotherapy who have had ≥ 1 platelet transfusion during induction stage of treatment.
- Total Bilirubin (sum of conjugated + unconjugated) ≤ 3 times institutional upper limit of normal (ULN) for age and ALT/AST ≤ 3 times institutional ULN for age.
- Normal cardiac function:
    - Shortening fraction greater than or equal to 28% by echocardiogram OR Left ventricular ejection fraction (LVEF) greater than or equal to 50% on technetium- 99m pertechnetate radionuclide cineangiography (MUGA) or echocardiogram.
    - Screening ECG with corrected QT (QTc) interval of < 470 msec.
    - Timing of cardiac assessment: We will utilize the most recent EKG/ECHO when assessing cardiac function. See section 9.0 for additional details.

- Adequate renal function, defined as an estimated Creatinine Clearance or GFR >40ml/min or an normal creatine for age (see below)

  Serum Creatine by age:

	Maximum Serum Creatinine (mg/dL)	
Age (years)	Male	Female
< 6	0.8	0.8
6 to <10	1	1
10 to < 13	1.2	1.2
13 to <16	1.5	1.4
≥ 16	1.7	1.4

These threshold creatine values were derived from the Scwartz formula estimating GFR, utilizing child length and statured published by the CDC.

6.3 Participant Exclusion Criteria

- Patients with history of hematologic malignancies or allogenic/autogenic stem cell transplant.
- Patients with a currently known predisposition to a myeloid stem cell disorder, myeloid leukemia, and/or bone marrow failure syndrome including, but not limited to:
  - Aplastic anemia
  - Ataxia telangiectasia
  - Bloom syndrome
  - Congenital amegakaryocytic thrombocytopenia
  - Cyclic neutropenia
  - Diamond Blackfan anemia
  - Dyskeratosis congenita
  - Familial AML/MDS syndromes (including *ANKRD26*, *CEBPA*, *DDX41*, *ETV6*, *GATA2*, *RUNX1*, *SRP72*)
  - Fanconi anemia
  - Kostmann disease
  - Li-Fraumeni syndrome
  - Neurofibromatosis
  - Nijmegen breakage syndrome
  - Noonan syndrome
  - Paroxysmal nocturnal hemoglobinuria
  - Pearson syndrome
  - Poland syndrome
  - Rothmund-Thomson syndrome
  - Severe congenital neutropenia
  - Thrombocytopenia absent radii syndrome
  - Trisomy 8
  - Trisomy 21
  - WHIM syndrome
  - Wiskott Aldrich syndrome
  - Xeroderma pigmentosa

- Secondary malignancy in the past 5 years.
- Patients who have previously undergone up-front chemotherapy and have relapsed or progressed through therapy.
- Patients who have received 4 or more cycles of induction chemotherapy for their current malignancy prior to time of enrollment.
- Previous use of romiplostim, eltrombopag, recombinant human TPO, or any other TPO receptor agonist, or any investigational platelet producing agent.
- Patients receiving other investigational agents are not eligible for study entry.
- History of uncontrolled arrhythmias, clinically significant electrocardiogram (ECG) abnormalities, active heart failure or pericardial disease.
- Patients with current or prior venous thrombotic event or arterial thrombotic event at time of enrollment will be ineligible for this study.
- Pregnant women/lactating mothers.
- Patients unwilling to use effective contraception method, which includes abstinence.
- Patients with an inability to return for follow-up visits or obtain follow-up studies required to assess toxicity to therapy.

7.0 RECRUITMENT PLAN

All consecutive eligible patients will be offered participation in this study by their attending physician in the Department of Pediatrics at Memorial Sloan Kettering Cancer Center. No patients will be identified by chart review or direct advertising. The consenting professional will be responsible for explaining the study, obtaining written informed consent, and registering the patient on study. Participation of women and minority groups will be encouraged.

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:

As per standard of care prior to enrollment:

- Histological verification of primary solid tumor any time prior to enrollment
- EKG
- ECHO

As part of standard of care, all patients will have a baseline echocardiogram and EKG as part of their pre EFT and MAP assessment since both of these regimens include doxorubicin. The timing of the start of treatment on EFT, MAP, D9803 to enrollment on this romiplostim/CIT study should be less than 4 months. Generally, there is also surveillance echocardiograms after 2 cycles of doxorubicin, that is, after 150 mg/m2, so most patients would also have an updated ECHO/EKG closer to time of enrollment.

Within 28 days prior to enrollment:

- History and Physical Exam, including medication review
- Height, weight, and body surface area
- 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)
- Prothrombin Time (PT), International Normalized Ratio (INR)
- Activated Partial Thromboplastin Time (APTT)

Within 48 hours of treatment start:
- 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)
- Negative pregnancy test (serum or urine hCG) result in women of child bearing potential
- Prothrombin Time (PT), International Normalized Ratio (INR)
  Activated Partial Thromboplastin Time (APTT)

10.0 TREATMENT/INTERVENTION PLAN

Patients will be enrolled any time: from Cycle 3 Day 1 until the receipt of chemotherapy on Cycle 5 Day 1 for EFT, from Induction week 8 until receipt of chemotherapy on Maintenance week 0 for MAP, and from Cycle 5 Day 1 until the receipt of chemotherapy on Cycle 7 Day 1 for D9803. Chemotherapy administration, monitoring and cancer evaluations will continue as planned per institutional standards.

All enrolled patients will receive **Romiplostim 10 mcg/kg subcutaneous on Day 1** (unless platelet count is > 400,000/mcL). Patients will then continue to receive weekly (+/- 3 days) romiplostim throughout the remainder of their EFT, MAP, D9803 regimens. For many patients, cycle 7 (EFT) will be the last dose of romiplostim that they receive, however if a patient has persistent thrombocytopenia (i.e. Plts < 75k), they can continue to receive weekly romiplostim at the same dose until count recovery. Also, as described in “Alterations to Chemotherapy Cycles”, below there are unique circumstances in which patients will be allowed to continue romiplostim for 1 additional cycle; these additional cycles will be separately analyzed as described later.

Interim analysis of study protocol performed after enrollment of 2 patients who received chemotherapy as per EFT showed that the romiplostim dosing algorithm was both complex and inefficient. Therefore, we propose a simplified dosing adjustment table to be utilized moving forward. As previously stated, **Romplostim will always be held for platelet counts > 400,000/mcL**. On the day of a schedule dose, if the platelet count is >400,000/mcL, that specific weekly dose will be held. Other than this unique situation of thrombocytosis, **the dose of romiplostim should remain at 10 mcg/kg (or 3 mcg/kg on HD-MTX weeks as per MAP regimen)**. Given 10 mcg/kg is the maximum tolerated dose, no dosing escalations will occur beyond this.

PEDIATRIC ROMIPLOSTIM DOSING TABLE

Regimen	Starting Dose	Modification if Thrombocytosis (>400,000/mcL)	Specific regimen considerations
EFT	**10 mcg/kg**	HOLD dose and repeat CBC in week. If <400,000/mcL okay to resume at 8mcg/kg	If continues to have thrombocytosis, continue to decrease dose weekly by 2mcg/kg.
MAP	For CDDP/DOXO weeks: **10 mcg/kg** For HD-MTX weeks: **3mcg/kg**	HOLD dose and repeat CBC in week. If <400,000/mcL okay to resume at 8mcg/kg HOLD dose and repeat CBC in week. If <400,000/mcL okay to resume at 1mcg/kg	If continues to have thrombocytosis, continue to decrease dose weekly by 2mcg/kg. If continues to have thrombocytosis, HOLD dose until next CDDP/Doxo week.
D9803	**10 mcg/kg**	HOLD dose and repeat CBC in week. If <400,000/mcL okay to resume at 8mcg/kg	If continues to have thrombocytosis, continue to decrease dose weekly by 2mcg/kg.

General Romiplostim Dosing Guidelines

- Assess platelet counts at least weekly (+/- 3 days) starting with day 1 of each study treatment cycle.
- Romiplostim is not to be administered on any day in which the platelet count is > 400,000/mcL. This rule takes priority over all other recommendations.
- The maximum dose of romiplostim is 10 mcg/kg.
- The dose of romiplostim for a given cycle is determined using the dosing table on day 1 of that cycle or week.

Treatment Delays and Special Considerations

- For patients who begin a cycle early, platelet count will be considered the count on which chemotherapy starts this cycle.
- If patients have multiple platelet counts on the day determined to be the planned start of this cycle, providers should use their discretion as to which platelet count is most appropriate to utilize for dosing romiplostim.
- If patients have a recent platelet transfusion within 3 days of the planned start of this cycle, providers can use their discretion as to whether the platelet count has been transiently elevated as a result of the transfusion and may consider adjusting romiplostim dose accordingly.

There may be clinical circumstances for which a provider may choose to dose romiplostim outside of the recommended table. In such cases, the rationale for dosing outside of this range should be documented.

On Protocol Lab Assessments:

- CBCs weekly and CMPs, PT/PTT, and pregnancy test at the start of each cycle (q3 weeks) (+/- 3 days).
- Completion of romiplostim: CBC, CMP, PT/PTT, and pregnancy test 1 week after final dose of romiplostim administered (+/- 3 days).
- Post romiplostim monitoring: CBC and CMP 30 days after the completion of romiplostim evaluation (+/- 14 days).

ALTERATIONS to CHEMOTHERAPY CYCLES

Patients receiving EFT almost always receive 7 cycles of therapy, although if extreme toxicity or there is progression on chemotherapy, then these patients would possibly change regimens. If any patient does not receive cycles 4-7 of EFT, they will be evaluated separately. Based on historical data, we do not expect this to occur in more than 1-2 patients total.

Institutionally, patients receiving D9803 almost always receive only 12 cycles. But given COG protocol builds in up to 14 cycles, if there are circumstances that a patient continues chemotherapy past 12 cycles, they may continue weekly Romiplostim until the point of count recovery following their final cycle.

CONFIRMATION OF DOSING STRATEGY

As this is the first trial utilizing prophylactic romiplostim for CIT, the first 2 patients have completed romiplostim on this updated study and so we reviewed these cases to adjust the dosing strategy. We will re-assess the patients' platelet responses to romiplostim and will continue to consider adjusting the prophylactic romiplostim dosing algorithm if necessary (for example, determining if the starting dose of 10mcg/kg is well tolerated).

11.1 EVALUATION DURING TREATMENT/INTERVENTION

Study Assessments and Testing	Within 28 days Prior to Enrollment	Day 1 of Study Cycles[2]	Weekly During Study Cycles[3]	End of Treatment (7 days after the last dose of romiplostim +/- 3 days) [3]	Post Therapy Assessment[4]	Study Completion[5]
Confirmation of Solid Tumor Diagnosis	X[1]					
EKG	X[1]					
ECHO	X[1]					
History and Physical Exam	X	X	X	X	X	
Vital Signs	X	X	X	X	X	
CBC with differential	X	X	X	X	X	
CMP	X	X		X	X	
PT/PTT	X	X		X		
Serum/Urine HCG		X		X		
Adverse Event Assessments		X	X	X	X	X

1. Confirmation of solid tumor diagnosis, EKG and ECHO may be completed any time prior to enrollment as per standard of care.
2. Labs prior to treatment start may occur within 48 hours of Day 1.
3. Weekly lab assessments may occur q 7 d +/- 3 days from prior testing.
4. Post therapy assessment may occur 30 days +/- 14 days from end of treatment evaluation.
5. Study Completion: 6 months (+/- 14 days) after the last dose of romiplostim, the study team will contact the patient to evaluate their clinical condition, including adverse events and disease status.

12.0 CRITERIA FOR REMOVAL FROM STUDY

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

- Patient/Patient's guardian withdraws consent
- Death
- Lost to follow-up
- Patient is taken off of the chemotherapy regimens EFT/MAP/D9803 for any reason.
- 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 will occur if any of the following events happen:

- If a patient develops a Grade 3/4 adverse event, attributable to romiplostim, based on the Common Terminology Criteria for Adverse Events (CTCAE version 5.0).
- If a patient develops any venous thromboembolism or arterial thrombus, including deep vein thrombosis and/or pulmonary embolism.
- If the patient becomes pregnant and/or is breastfeeding.

13.0 CRITERIA FOR OUTCOME ASSESSMENT AND ENDPOINT EVALUABILITY

13.1 Criteria for Therapeutic Response/Outcome Assessment

Primary endpoint is number of platelet transfusions (typically, prophylactic for platelet count <10,000/ mcL when admitted and <20,000/mcL when outpatient; and on demand for active bleeding) required during the treated cycles until end of high dose chemotherapy.

Secondary endpoints:

1. Number and severity of chemotherapy modifications (chemotherapy dose reductions and/or delays) during treatment course of EFT, MAP, D9803 secondary to thrombocytopenia compared to the benchmark rate.
2. CTCAE grade IV thrombocytopenia in patients who receive romiplostim compared to the benchmark rate.
3. Safety profile of romiplostim administration in pediatric patients with solid tumors receiving N8 or EFT as graded by CTCAE v5.

13.2 Criteria for Study Endpoint Evaluability

Patients evaluable for efficacy (including the primary endpoint) are all patients who received at least one dose of romiplostim and completed their planned cycles of therapy (7 cycles of EFT, 12 cycles of D9803, 28 weeks of MAP). Patients who do not complete the planned therapy will be replaced, but will be evaluated for safety. Thus, patients evaluable for safety are all patients who received at least one dose of romiplostim. Not more than 1 or 2 patients are expected to interrupt their treatment early. If a patient has enrolled, but does not receive romiplostim they will not be evaluable and they will be replaced on the study.

14.0 BIOSTATISTICS

14.1 Populations for Analyses

- Efficacy set: All enrolled patients who receive at least one dose of romiplostim, and receive Cycles 5-7 of EFT, Cycles 7-12 of D9803, and MW0-MW19 of MAP.
- Safety set: participants who receive at least one dose of romiplostim.

14.2 2 Primary endpoint and Sample size

This is a one-arm study aiming at estimating the number of platelet transfusions associated with the use of romiplostim, and compare this estimate to a benchmark data. We obtained an historic mean of by averaging EFT, D9803 and MAP mean transfusions. The number of platelet transfusions during treatment is assumed to follow a Poisson distribution. Although our historical means revealed more platelet transfusions per cycle for EFT (thus a higher lambda parameter), the average number of platelet transfusions per treatment duration (last cycles) was comparable. We thus assumed a common Poisson distribution for the number of observed transfusions.

EFT cycles 5-7: Total platelet transfusions = 5.0
D9803 cycles 7-12: Total platelet transfusions = 4.6
MAP MW0 to MW19: Total platelet transfusions = 4.9

We will include 30 patients in total (across all treatment regimens) in the study. A sample size of 29 patients gives us 80% power to detect a 20% decrease in the mean number of platelet transfusions (from 4.9 to 3.9), using a one-sample test for single Poisson rate with a one-sided 0.05 significance level. We therefore plan to enroll a total of 30 patients to account for potential drop outs.

The number of platelets transfusions will be average over the patients in the Efficacy set, and a one-sided one-sample test will be used to compare the estimated rate to the benchmark of 4.9, using 0.05 as a threshold for significance. In addition, the probability to observe between 0 and 5 (included) transfusions with those regimens will be estimated.

As a sensitivity analysis, the rate of platelets transfusions with 95% confidence interval will also be assessed for each therapy regimen separately.

14.3 3 Secondary endpoints

Chemotherapy modifications are defined as chemotherapy dose reductions and/or delays. Thrombocytopenia caused chemotherapy dose reductions and/or delays occured in 37% of cycles 5-7 in the EFT cohort, 52% of cycles 7-12 of the D9803 cohort, and 6% of the maintenance cycles in the MAP cohort. The proportion of cycles with chemotherapy modifications will be described for each therapy regimen separately and estimated over the patients in the Safety set, and one-sided one-sample z-test will be used to compare it to each regimen benchmark, using 0.05 as a threshold for significance. The cumulative number of delayed days is the total number of days that therapy was delayed due to inadequate platelet recovery. The cumulative number of delayed days will be described for each therapy regimen separately.

The incidence of cycles with grade IV thrombocytopenia will be estimated overall in the patients in the Safety set. It will be described for each regimen separatemly and compared to the benchmark of each regimen (0.86 for EFT, 0.41 for D9803, and 0.84 for MAP) using a one-sided one-sample z-test using 0.05 as a threshold for significance.

Adverse events will be graded using CTCAE v5.0. All events will be tabulated by grade, overall and by cycle of N8 and EFT, using patients in the Safety set.

For both primary and secondary endpoints, complete case analyses will be done in case of missing data, and not adjustment will be done to correct for the multiplicity of tests.

14.4 Exploratory endpoints

The transfusion rate will additionally be estimated separately in patients aged <12, 12-18, >18 using a Poisson distribution.

15.0 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 pediatric adverse reactions (≥ 5% incidence and ≥ 5% more frequent in the romiplostim arm across the two placebo-controlled trials) were contusion, upper respiratory tract infection, oropharyngeal pain, pyrexia, diarrhea, rash, upper abdominal pain, ear infection, gastroenteritits, sinusitits, purpura, urticaria, and peripheral swelling. For adult patients, the most common adverse reactions (≥ 5% incidence and ≥ 5% more frequent in the romiplostim arm across the two placebo-controlled trials) were arthralgia, dizziness, insomnia, myalgia, pain in extremity, abdominal pain, shoulder pain, dyspepsia and paresthesia.

Individual cases of thrombosis in the adult population have been reported in patients receiving romiplostim however, in the MSKCC Phase II Trial of Romiplostim for Chemotherapy Induced Thrombocytopenia, there was no observed increase in thrombosis rate compared with expected rates in patients with metastatic cancer, on chemotherapy [37]. Additionally, in both the initial phase III, randomized double blind, placebo-controlled study of romiplostim in children with ITP and the pediatric long-term treatment extension trial, no thrombosis events were observed [30, 31]. We will however monitor for 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 once per cycle from start of romiplostim. The study will report all attributable toxicities from the time a patient signs consent until 6 months after the last dose of romiplostim. All toxicities meeting these criteria should be reported to MSKCC as a toxicity with supporting source documentation.

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 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. and the FDA 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.

16.0 PROTECTION OF HUMAN PARTICIPANTS

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 Associate (CRA) and/or Clinical Research Coordinator (CRC) will be assigned to the study at MSKCC. The responsibilities of the CRA/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

A Clinical Research Associate (CRA) and/or Clinical Research Coordinator (CRC) from the Department of Pediatrics will assist the PI in data quality assurance. The CRA/CRC will confirm up-front registration of all subjects, check eligibility, review records to confirm that informed consent is properly obtained and procedures are performed according to study protocol, and monitor protocol accrual. Paper copies of medical records, where used, will be compared to electronic records to ensure accuracy. Investigator meetings will be held to discuss issues and educate and train all investigators to maintain compliance to the protocol.

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 once 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.

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18.0 APPENDICES

Not applicable