BLOOD AND MARROW
TRANSPLANT
CLINICAL TRIALS NETWORK

Continued, Long-Term Follow-Up and Lenalidomide Maintenance Therapy for Patients Who Have Enrolled on BMT CTN 0702

(ClinicalTrials.gov Number: NCT02322320)

BMT CTN PROTOCOL 0702 – Long-Term Follow-Up Version 2.0

Study Chairpersons

Amrita Krishnan, MD[1*], George Somlo, MD[1], Edward Stadtmauer, MD[2]

Protocol Team

Brianne Allison [3]
Pam Budnick[3]
Angela Dispenzieri, MD[4]
Nancy Geller, PhD[6]
Sergio Giralt, MD[7]
John Koreth, MBBS, DPhil[10]
Adam Mendizabal, PhD[5]
Phil McCarthy, MD[9]
Courtney Nelson[5]
Hari Parameswaran, MD, MS[11]
Marcelo C. Pasquini, MD, MS[11]
Muzaffar Qazilbash, MD[8]
David Vesole, MD[12]

Sponsored by the National Institutes of Health
National Heart, Lung, and Blood Institute
National Cancer Institute

[1] City of Hope National Medical Center
[2] University of Pennsylvania Cancer Center
[3] National Marrow Donor Program
[4] Mayo Clinic Rochester
[5] The EMMES Corporation
[6] National Heart, Lung, and Blood Institute
[7] Memorial Sloan-Kettering Cancer Center
[8] University of Texas, MD Anderson Cancer Center
[9] Roswell Park Cancer Institute
[10] Dana Farber Cancer Institute
[11] Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin
[12] Hackensack University Medical Center
[*] Corresponding Chairperson

Approval Signature (Protocol Chair/Officer)

Approval Signature (Protocol Chair/Officer)

Core Study Participants:

BMT Program at Northside Hospital
Case Western Reserve University Consortium
Oregon Health & Sciences University
University Hospitals of Cleveland
City of Hope National Medical Center, Duarte, CA
Dana Farber/Partners Cancer Center
Brigham & Women's Hospital
Duke University Medical Center
Fred Hutchinson Cancer Research Center
Memorial Sloan-Kettering Cancer Center
Ohio State Consortium
Ohio State
Roswell Park Cancer Institute
University of North Carolina Hospital at Chapel Hill
Stanford Hospital and Clinics
University of Florida College of Medicine
University of Michigan Consortium
University of Michigan
Vanderbilt University
University of Minnesota
University of Nebraska Consortium
University of Kansas
University of Nebraska Medical Center
University of Pennsylvania Cancer Center
University of Texas, MD Anderson Cancer Center
Washington University, Barnes Jewish Hospital

Affiliate and Cooperative Group Study Participants:

Arizona Cancer Center
Colorado Blood Cancer Institute
H. Lee Moffitt Cancer Center
Hackensack University Medical Center
Jewish Hospital BMT Program
Karmanos Cancer Institute/BMT
Louisiana State University Health Sciences Center
Medical College of Wisconsin
Mount Sinai Medical Center
North Shore University Hospital
Penn State College of Medicine
Rush University
Sarah Cannon BMT Program
Texas Transplant Institute
UCSD/SCRIPPS School of Medicine
University of Illinois
University of Kentucky
University of Miami
University of Oklahoma
University of Texas Southwestern Medical Center
University of Wisconsin Hospital
Wake Forest University Health Sciences
West Virginia University Hospital

PROTOCOL SYNOPSIS – BMT CTN 0702 LONG-TERM FOLLOW-UP PROTOCOL

Continued, Long-Term Follow-Up and Lenalidomide Maintenance Therapy for Patients Who Have Enrolled on BMT CTN 0702

Co-Principal Investigators: Amrita Krishnan, MD, George Somlo, MD, and Edward Stadtmauer, MD

Study Design: The study is designed to provide continued, long-term follow-up on patients enrolled on BMT CTN 0702 who have not experienced progression, as well as to offer optional long-term lenalidomide maintenance therapy to those BMT CTN 0702 patients who have completed 3 years of protocol-defined maintenance therapy without evidence of disease progression.

Primary Objective: The primary objective is to compare progression-free survival (PFS) as a time to event analysis between the three randomized treatment arms from the BMT CTN 0702 protocol as a pairwise comparison. The analysis will be conducted once all surviving patients have been followed for at least 5-years post randomization on the BMT CTN 0702 protocol.

Secondary Objectives: Secondary objectives include the cumulative incidence of second primary malignancies (SPM), probability of overall survival (OS), probability of event-free survival (EFS) and Health Quality of Life (QOL) on all patients, including those not receiving long-term lenalidomide maintenance therapy.

Eligibility Criteria: Patients eligible for long-term follow-up are those who were enrolled and randomized on the BMT CTN 0702 protocol and who are alive at the end of the BMT CTN 0702 protocol-defined follow-up period without progression. Patients eligible for long-term lenalidomide maintenance therapy include patients who have completed 3 years of BMT CTN 0702 protocol-defined lenalidomide maintenance therapy with no evidence of disease progression.

Treatment/Follow-Up: All patients who consent to the long-term follow-up protocol will undergo study assessments every 6-months. Patients eligible to continue with lenalidomide maintenance therapy will continue with the last tolerated dose of lenalidomide that was documented upon completion of BMT CTN 0702 maintenance therapy.

Accrual Objective:	It is anticipated that approximately 450 patients will be enrolled on this protocol based on assumed estimates of PFS from the BMT CTN 0702 study. The total sample size may be as low as 417 if the observed 3-year PFS on the BMT CTN 0702 is 55% but may be as high as 569 if the 3-year PFS is 75%.
Study Duration:	Patients will be followed until death, progression, withdrawal from the study, or through the end of 2018.
Interim Analysis:	No formal interim analyses are planned.

Figure 1: Study Schema

Outline of Study Schema for Long-Term Follow-Up and Lenalidomide Maintenance

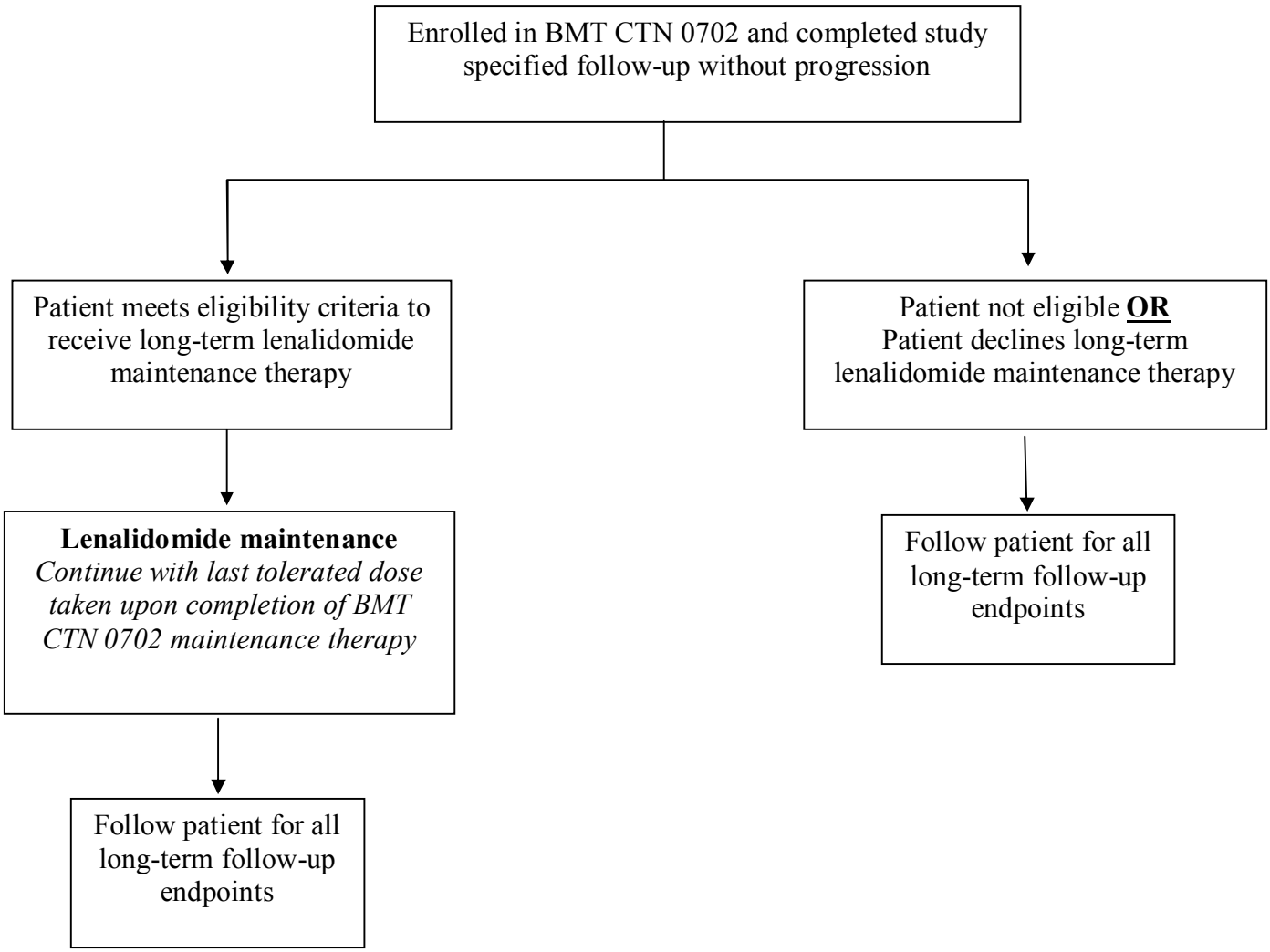


TABLE OF CONTENTS

LIST OF APPENDICES

CHAPTER 1

1. BACKGROUND AND RATIONALE

1.1. Background

Therapeutic advances in multiple myeloma (MM) have resulted in substantially improved survival. Similarly, in a large population-based study of 45,595 MM patients, myeloma-specific 5-year median overall survival (OS) improved from 36% to 68% under age 50, and from 34% to 58% among patients of ages 51-65 years between 1973 and 2009.

Post-transplant consolidation and maintenance strategies have also yielded improved progression-free survival (PFS) and OS. The BMT CTN 0702 study randomized patients to receive two autologous hematopoietic cell transplants (HCT), or one autologous HCT and post transplant consolidation, or one autologous HCT with maintenance. Of note, all patients receive a total of 3 years of maintenance therapy using lenalidomide. Since the implementation of BMT CTN 0702, the experience with maintenance has broadened, and at least two large phase III clinical trials that continued lenalidomide maintenance for longer periods were associated with longer survival, compared to placebo. This long-term follow-up protocol focuses on extending the follow-up period for all patients on BMT CTN 0702 to assess long-term outcomes such as PFS and incidence of SPMs. A secondary objective is to provide patients with lenalidomide maintenance therapy free of charge until there is evidence of disease progression.

1.2. Lenalidomide Maintenance in Multiple Myeloma

There are three phase III studies that examined lenalidomide maintenance therapy versus placebo following autologous hematopoietic stem cell transplant (AHSCT)[1,2,3] (Table 1.2). The CALGB/ECOG 100104 (BMT CTN 0704) study randomized MM patients after induction therapy and single AHSCT to lenalidomide versus placebo until progression. The induction regimens varied, with 74% of patients receiving a thalidomide- or lenalidomide-based induction regimen. The median time to progression (TTP) was 46 months for the lenalidomide group and 27 months for the placebo group ($P<0.001$). The 3-year PFS was 66% for the lenalidomide group and 39% for the placebo group ($P<0.001$). At a median follow-up of 34 months, the 3 year OS rates were 88% for the lenalidomide group and 80% for the placebo group ($P=0.028$). The study was updated in 2013 and with a median follow-up of 48 months, the OS was 80% for the lenalidomide group and 70% for the placebo group ($P=0.008$)[4]. The study was un-blinded at a median follow-up of 26 months because the primary endpoint (TTP) had been met and 67% of eligible placebo patients crossed over to receive lenalidomide. A TTP and OS benefit for the lenalidomide arm remains despite the cross-over.

The IFM 05-02 study treated MM patients after induction with a single (79%) or tandem AHSCT (21%) followed by a 2 cycle consolidation with lenalidomide before randomization to lenalidomide maintenance, originally until progression[5]. The induction regimens were vincristine, doxorubicin and dexamethasone (VAD) or bortezomib and dexamethasone (VD). Approximately 25% of patients received consolidation with dexamethasone, cyclophosphamide,

etoposide and cisplatin before AHSCT. The median PFS was 41 months for the lenalidomide group and 23 months for the placebo group respectively (P<0.001). The 4 year PFS was 43% for the lenalidomide group and 22% for the placebo group (P<0.001). At 45 months of median follow-up, the OS was 74% for the lenalidomide group and 76% for the placebo group. The 4 year OS rate was 73% for the lenalidomide group and 75% for the placebo group respectively (P=0.7). The study was un-blinded at median follow-up of approximately 30 months and all maintenance was stopped at a median time of 32 months for the lenalidomide arm due to concern regarding second primary malignancy (SPM) development (Section 1.3). At a median follow-up of 60 months from randomization, lenalidomide maintenance improved PFS (42%) when compared to placebo (18%) (P<0.0001). The 5 year OS is 68% in the lenalidomide group and 67% in the placebo group (HR=1) and the median survival after first progression is 29 months for the lenalidomide group and 48 months in the placebo group (P<0.0001).

Table 1.2: Lenalidomide Maintenance after Autologous Hematopoietic Cell Transplantation for Multiple Myeloma

Study	Number of Patients	Initial Dose (mg)	Maintenance versus no Maintenance	
			EFS or PFS	**OS**
McCarthy et al NEJM 2012	460	10	TTP **46 vs 27months** (P<0.001)	Median followup 34 m **85 vs 77%** (P=0.028)
			3-year PFS rate **66%** (95% CI, 59 to 73) vs **39%** (95% CI, 33 to 48)	3 year OS rate **88 %** (95% CI, 84 to 93) vs **80 %** (95% CI, 74 to 86)
			EFS **43 vs 27 months** (P<0.001)	
McCarthy et al Clin Lym Myelom Leuk 2013 (Update)				Median followup 48 m **80 vs 70%** (P=0.008)
Attal et al NEJM 2012	614	10	PFS **41 vs 23 months** (P<0.001)	Median followup 45 m **74 vs 76%** (P=0.7)
			4 year PFS **43 vs 22%** (P<0.001)	4 year OS **73 vs75%** (NS)
			EFS **40 vs 23 months** (P<0.001)	
Attal et al ASH 2013 abst 206			5 year PFS **42% vs 18%** (P<0.001)	Median followup 70 m 5 year OS **68 vs 67%** (NS)
Boccadoro et al JCO 2013	202 (NIT) 200 (IT)	10 (3 of 4 weeks monthly)	Median PFS (combining NIT and IT groups) **37 vs 26 months**(P <0.001)	5 year OS (combining NIT and IT groups) **75 versus 58%** (P=0.02)

Study	Number of Patients	Initial Dose (mg)	Maintenance versus no Maintenance	
			EFS or PFS	**OS**
Palumbo et al ASH 2013 abst 763	194 (NIT) 195 (IT)	10: days 1 to 21 of 28 days +/- **P** 50: every other day	3 year PFS (combining NIT and IT groups) RP: 60% vs 38% for R alone (P=0.003)	31 month median followup (combining NIT and IT groups) 3 year OS (NIT and IT) ND

EFS: Event-free survival includes deaths, progressions and second cancers; IT: Intensive Therapy: NIT: Non-intensive therapy; ND: No difference, NS: Not significant; OS: Overall Survival; P: Prednisone, PFS: Progression-Free Survival, R: Lenalidomide. Adapted with permission from McCarthy PL. Part I: the role of maintenance therapy in patients with multiple myeloma undergoing autologous hematopoietic stem cell transplantation. J Natl Compr Canc Netw. 2013 Jan 1;11(1):35-42.

Another lenalidomide maintenance study following chemotherapy versus tandem autologous HCT has been reported; RV-MM-PI-209[3]. At a median follow-up of 49 months from chemotherapy versus tandem autologous HCT and a median follow-up of 35 months from randomization to lenalidomide maintenance versus no maintenance, the median PFS for lenalidomide maintenance was 37 months (including autologous HCT and non-HCT patients received maintenance) versus 26 months for patients not receiving maintenance (P<0.0001). The 5 year OS estimates were 75% and 58% for the lenalidomide maintenance and no maintenance groups respectively (P=0.02). A meta-analysis of IFM 05 02, CALGB 100104, RV-MM-PI-209 (MPR vs Mel200) and MM 015 (a non-transplant trial) found that lenalidomide maintenance when compared to placebo improves PFS and OS[5].

In another study by the GIMEMA (Gruppo Italiano Malattie EMatologiche dell'Adulto) Multiple Myeloma Working Group, newly diagnosed patients received lenalidomide and dexamethasone (RD) induction followed by randomization to cyclophosphamide/ lenalidomide/dexamethasone (CRD) or tandem autologous HCT with melphalan, and a second randomization occurred to lenalidomide/prednisone versus lenalidomide maintenance until progression[6]. There was as superior PFS for the lenalidomide/prednisone maintenance arm when compared to lenalidomide alone: 62% versus 38%, (p=0.003).

1.3.Second Primary Malignancies

The lenalidomide group in CALGB/ECOG 100104 (BMT CTN 0704) had an increased incidence of hematologic toxicities (primarily neutropenia) and an increase in second primary malignancies (SPM). There were 8/231(3.5%) hematologic malignancies, primarily Acute Myeloid Leukemia/Myelodysplastic Syndrome (AML/MDS) in lenalidomide group patients versus 1/229 (0.4%) in placebo group patients. There were 10/231 (4.3%) versus 5 (2.1%) solid tumors in lenalidomide group and placebo group patients respectively, and 4/231 (1.7%) versus 3/229 (1.3%) non-melanoma skin cancers. In the 2013 update, one AML was reported in the lenalidomide arm (total 9/231 hematologic malignancies) and one case of ALL and MDS in two placebo arm patients who crossed over to lenalidomide[6]. One solid tumor (renal cell carcinoma) was reported in another cross over patient and 4 non-melanoma skin cancers were reported; 3 in

the lenalidomide arm and one in a cross over placebo patient. The cumulative incidence risk (CIR) for the development of SPM was greater for the lenalidomide group when compared to the placebo group ($p<0.008$). The CIR of progressive disease ($p<0.001$) or death ($p<0.002$) were greater for the placebo group when compared to the lenalidomide group. When including deaths, progressions and SPMs as events, the median EFS was 43 months for the lenalidomide group and 27 months for the placebo group ($P<0.001$).

The placebo group patients in the IFM 05-02 study did not cross over to receive lenalidomide at un-blinding. The lenalidomide group had an increased incidence of hematologic toxicities (primarily neutropenia) and an increase in SPMs. There were 13/306 (4.2%) hematologic malignancies, (primarily Acute Lymphoblastic Leukemia (ALL) and Hodgkin Lymphoma and AML/MDS) in lenalidomide group patients versus 5/302 (primarily AML/MDS only) in placebo group patients. There were 10/306 (3.3%) versus 4/302 (1.3%) solid tumors in the lenalidomide group and placebo group patients respectively and 5/306 (1.6%) versus 3/302 (1.0%) non-melanoma skin cancers. When including deaths, progressions and SPMs as events, the median EFS was 40 months for the lenalidomide group and 23 months for the placebo group ($P<0.001$). An updated analysis was recently presented[7].

The SPM rate was approximately 4.5% in both maintenance arms (AHSCT and non-AHSCT).
The risk factors for SPM development are not fully defined. A meta-analysis was undertaken of 6383 NDMM patients treated on Phase III transplant and non-transplant clinical trials, 3218 receiving lenalidomide maintenance and 3165 receiving no maintenance[8]. The CI of hematologic SPMs was higher for patients receiving lenalidomide maintenance when compared to placebo arm patients (HR: 3.8; 95% CI 2.11-6.86; $p<0.001$). The CI of death was death at 60 months was 26.2 (95% CI 22.4 -28.8) for the lenalidomide arm and 36.3 (95% CI 25.9-46.6) for the no maintenance arm. There was a higher incidence of hematologic SPMs with oral melphalan when compared to IV melphalan (HR 3.3; 95% CI 1.46-7.46 $p=0.004$). Previous work has demonstrated that monoclonal gammopathy of unknown significance (MGUS) and MM have both been associated with the development of AML/MDS[9]. It is uncertain as to what the bone marrow defect is in MGUS and MM patients (not having received anti-MM therapy) that predisposes them to AML/MDS development.

1.4. Rationale for Study

This current protocol has the objective to compare long-term outcomes based on the randomized treatment groups from the BMT CTN 0702 protocol. All consenting patients will continue to be monitored for the development of long-term complications with emphasis on second primary malignancies. Patients who do not consent to the long-term follow-up mechanism or who have experienced progression on the BMT CTN 0702 study will be followed through the standard CIBMTR long-term follow-up mechanism. Additionally, the protocol will extend the duration of lenalidomide maintenance for all patients enrolled in the BMT CTN 0702 study who have completed 3 years of maintenance and have not experienced disease progression.

CHAPTER 2

2. STUDY DESIGN

2.1. Study Overview

This study is designed to compare long-term outcomes among patients randomized on the BMT CTN 0702 protocol. All patients who consent will be followed for death, progression, SPMs and QOL. Patients who do not consent to the long-term follow-up mechanism or who have experienced progression on the BMT CTN 0702 study will be followed through the standard CIBMTR long-term follow-up mechanism. Additionally, patients who are eligible and are willing to continue with lenalidomide as maintenance therapy will be provided lenalidomide free of charge. These patients will continue to receive lenalidomide as maintenance therapy until disease progression or discontinuation due to toxicity, death, or withdrawal from the study. The endpoints assessed will include progression-free survival (PFS), overall survival (OS), event-free survival (EFS), incidence of second primary malignancies (SPM) and health quality of life (QOL).

2.2. Hypothesis and Specific Objectives

2.2.1. Hypothesis

Use of novel anti-myeloma agents will improve long-term PFS after high-dose melphalan followed by autologous hematopoietic cell transplantation (HCT) as compared to a second autologous transplantation.

2.2.2. Study Objectives

The primary objective of this long-term follow-up protocol is to compare the PFS as a time to event analysis from randomization on the BMT CTN 0702 protocol between the three randomized treatment arms as a pairwise comparison. The analysis will be conducted once all alive patients have been followed for 5-years post randomization on the BMT CTN 0702 protocol.

2.2.3. Secondary objectives include:

- Overall survival from randomization on the BMT CTN 0702 protocol;
- Event-free survival from randomization on the BMT CTN 0702 protocol;
- Incidence from randomization on the BMT CTN 0702 protocol of second primary malignancies in long-term use of lenalidomide as maintenance therapy.
- Health Quality of Life

2.3. Patient Eligibility

Patients must meet specified eligibility criteria to be enrolled on the study. All questions regarding eligibility criteria should be directed to the BMT CTN 0702 Long-Term Follow-Up Protocol Coordinator at 301-251-1161.

2.3.1. Initial Patient Eligibility Criteria for Long-Term Follow-Up Only

Patients fulfilling the following criteria will be eligible to provide continued long-term follow-up data as part of this study:

1. Enrolled and randomized on the BMT CTN 0702 protocol
2. Alive at the completion of BMT CTN 0702 protocol specified follow-up defined as 4 years post-randomization
3. Patients without evidence of disease progression at the completion of BMT CTN 0702 protocol specified follow up. (see Section 3.1 for disease progression definition)
4. Signed Informed Consent Form
5. Patients with the ability to speak English or Spanish are eligible to participate in the HQL component of this trial.

2.3.2. Patient Eligibility Criteria for Optional Long-term Lenalidomide Maintenance Therapy

Patients fulfilling the following criteria will be eligible to provide continued long-term follow-up data AND receive long-term lenalidomide maintenance therapy as part of this study:

1. Enrolled and randomized to BMT CTN 0702
2. Completion of 3 years of maintenance therapy on BMT CTN 0702
3. Registered in the mandatory Revlimid REMS® program (formerly the RevAssist® for Study Participants (RASP) program), and be willing and able to comply with the requirements of the Revlimid REMS® program, including counseling, pregnancy testing, and phone surveys.
4. Signed informed consent form.
5. Patients with the ability to speak English or Spanish are eligible to participate in the HQL component of this trial.

2.3.3. Patient Exclusion Criteria for Long-term Lenalidomide Maintenance Therapy

Patients who meet any of the following criteria will be ineligible to receive long-term lenalidomide maintenance therapy as part of this study*:

1. Patients who have evidence of disease progression prior to enrollment (see Section 3.1 for disease progression definition).

---

* All patients will be followed for long-term outcomes.

2. Patients who were discontinued from BMT CTN 0702 lenalidomide maintenance therapy, for any reason, prior to the completion of the 3 years of 0702 maintenance.
3. Female patients who are pregnant (positive -BetaHCG) or breastfeeding.
4. Females of childbearing potential (FCBP) or men who have sexual contact with FCBP unwilling to use contraceptive techniques (Appendix B) during the length of lenalidomide maintenance therapy.
5. Patients who experienced thromboembolic events while on full anticoagulation during prior therapy with lenalidomide.
6. Patients unwilling to take DVT prophylaxis.
7. Patients who developed a second primary malignancy, excluding non-melanoma skin cancers after initiation of lenalidomide maintenance therapy on BMT CTN 0702.

2.4. Study Treatments

2.4.1. Lenalidomide

Lenalidomide will be administered initially at the patient's last documented dose prior to discontinuation of BMT CTN 0702 lenalidomide maintenance therapy. Cycle duration is 28 days. Patients will continue lenalidomide until disease progression, or discontinuation due to toxicity, death, or withdrawal from the study. Patients who discontinue lenalidomide due to any reason other than death, or withdrawal of consent will continue to be followed per Section 4.4.1

2.4.2. Suggested Treatment Modification Guidelines for Maintenance Therapy

In the presence of lenalidomide-related non-hematologic toxicities (Table 2.4.2a), the study drug will be held until the toxicity resolves, then restarted at a reduced dose as described in Table 2.4.2b. Dose modifications for hematologic toxicities are described in Table 2.4.2c. If the patient is on DVT/PE prophylaxis or treatment, discontinuation or modifications of anticoagulation should be considered by the treating physician.

Table 2.4.2a – Suggested Treatment Modification Guidelines for Long-Term Lenalidomide

Grade by NCI CTCAE# [1]	Action
Non-blistering rash **Grade 2- 3** (Generalized rash ≥ 25% BSA)	Hold lenalidomide: Follow weekly. If the toxicity resolves to ≤ grade 1 restart lenalidomide at next lower dose level.
Non-blistering rash **Grade 4**	Discontinue lenalidomide.
Desquamating (blistering) rash **any Grade**	Discontinue lenalidomide.
Erythema multiforme **≥ Grade 3** (Severe (e.g., generalized rash or painful stomatitis); IV fluids, tube feedings, or TPN indicated)	Discontinue lenalidomide. If toxicity resolves to < grade 1 restart at next lower dose level.

Grade by NCI CTCAE# [1]	Action
Sinus bradycardia/ other cardiac arrhythmia **Grade 2** (Non urgent, medical intervention indicated OR Moderate)	Hold lenalidomide. If the toxicity resolves to ≤ grade 1 restart lenalidomide at next lower dose level .
≥ Grade 3 (Incompletely controlled or controlled with device- e.g. pacemaker or Severe)	Discontinue lenalidomide. If toxicity resolves to < grade 1 restart at next lower dose level.
Allergic reaction or hypersensitivity **Grade 2-3** (flushing; urticaria; dyspnea; drug fever≥ 38ºC – symptomatic bronchospasm; parenteral meds indicated)	Hold lenalidomide If the toxicity resolves to ≤ grade 1 restart lenalidomide at next lower dose level.
Grade 4 (anaphylaxis)	Discontinue lenalidomide
Venous thrombosis/embolism **≥ Grade 3** (DVT or cardiac thrombosis; intervention indicated)	Hold (interrupt) lenalidomide and start anticoagulation. Restart therapy per institutional guidelines.
Glomerular filtration rate (Creatinine Clearance) **≥ Grade 3** (≤ 25%LLN, chronic dialysis not indicated)	Hold (interrupt) lenalidomide. If creatinine clearance has improved to ≤ grade 2 restart at next lower dose level.
Other non-hematologic toxicity assessed as Lenalidomide-related **≥ Grade 3**	Hold (interrupt) lenalidomide. If the toxicity resolves to ≤ grade 2 restart lenalidomide at next lower dose level.
Hyperthyroidism or Hypothyroidism	Hold lenalidomide. Evaluate etiology, and initiate appropriate therapy. Restart lenalidomide at next lower dose level.
Peripheral Neuropathy Grade 2 with pain or Grade 3	Hold lenalidomide. If the toxicity resolves to <Grade 1 restart therapy at next lower dose level.
Peripheral Neuropathy Grade 4	Discontinue lenalidomide.
Constipation Grade 1-2	Initiate bowel regimen and maintain dose level.
Constipation ≥ Grade 3	Hold lenalidomide. If the toxicity resolves to ≤Grade 1 restart therapy at next lower dose level.
Pregnancy[3]	Discontinue lenalidomide study drug.

[1]Please consult NCI CTCAE version 3.0 http://ctep.cancer.gov/reporting/ for complete **Grade** descriptions. The **"≥ Grade 3"** descriptions listed above are minimums

[3]If a subject, or the partner of a male study subject, misses her period or if her pregnancy test or her menstrual bleeding is abnormal, pregnancy testing and counseling must be performed (Section 4.4.5).

Table 2.4.2b – Lenalidomide Dose Reduction Steps During Long-Term Maintenance Therapy

Lenalidomide Dose Reduction Steps for Non-Hematologic Toxicity	
Dose at Time of Toxicity	**Dose reduction**
15 mg daily	10 mg daily
10 mg daily	5 mg daily
5 mg daily	5 mg daily for 21 days every 28 days
5 mg daily for 21 days every 28 days	Discontinue lenalidomide

Table 2.4.2c – Lenalidomide Dose Modifications for Hematologic Toxicities

Lenalidomide Dose Modifications for Hematologic Toxicities	
Dose at Time of Toxicity	**Action**
15 mg per day	If ANC is < 1000/μL or the platelet count is < 50,000/μL, then lenalidomide will be held for up to 8 weeks. Lenalidomide drug may be re-instituted at 10 mg per day once the ANC is ≥ 1000/μL and the platelet count is ≥ 50,000/μL. If, however, after an 8 week treatment delay, the ANC remains < 1000/μL or the platelet count < 50,000/μL, maintenance therapy will be discontinued.
10 mg per day	If ANC is < 1000/μL or the platelet count is < 50,000/μL, then lenalidomide will be held for up to 8 weeks. Lenalidomide may be re-instituted at 5 mg per day once the ANC is ≥ 1000/μL and the platelet count is ≥ 50,000/μL. If however, after an 8 week treatment delay, the ANC remains < 1000/μL or the platelet count < 50,000/μL, maintenance therapy will be discontinued.
5 mg per day	If ANC is < 1000/μL or the platelet count is < 50,000/μL, then lenalidomide will be held for up to 8 weeks. Once the ANC is ≥ 1000/μL and the platelet count is ≥ 50,000/μL, then lenalidomide may be re-instituted at 5 mg per day for 21 days of a 28-day cycle. If, however, after an 8 week treatment delay, the ANC remains < 1000/μL or the platelet count < 50,000/μL, maintenance therapy will be discontinued.
5 mg per day for 21 of 28 days	If ANC is < 1000/μL or the platelet count is < 50,000/μL, then maintenance therapy will be discontinued.

2.4.3. Lenalidomide Maintenance Dose Re-escalation:

If a dose reduction has occurred and ANC ≥ 1000/μL and platelet count is ≥ 75,000/μL, the study drug dose may be re-escalated as shown in Table 2.4.2b, one step per cycle to a maximum of 15 mg daily.

2.5. Supportive Care

2.5.1. Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) Prophylaxis

Patients receiving dexamethasone and thalidomide as remission induction therapy for MM have an increased risk of developing DVT/PE. This risk may be as high as 10%. It is unclear whether the risk is the same in patients receiving lenalidomide as a single agent and as maintenance therapy after autologous transplantation. Treating physicians should be aware of this risk and have heightened vigilance regarding this possible toxicity. Aspirin should be administered per institutional guidelines during lenalidomide maintenance therapy unless the patient is treated with alternate prophylaxis of either low molecular weight heparin or coumadin.

2.6. Participant Risks

2.6.1. Lenalidomide

Common toxicities described for lenalidomide include:

- Neurologic: Somnolence, dizziness, headache, confusion, tremor, loss of co-ordination, asthenia, paresthesia, numbness, and leukoencephalopathy (radiographic findings).
- Hematologic: anemia, neutropenia, leucopenia, lymphopenia and thrombocytopenia; thromboembolic events (deep vein thrombosis and pulmonary embolism).
- Gastrointestinal: Constipation, dehydration, dry mouth, diarrhea, dyspepsia, nausea, vomiting and stomatitis.
- Constitutional: Weakness, insomnia, rigors, chills, sweating, weight loss and fever.
- Reproductive: teratogenicity and miscarriage.
- Musculoskeletal: arthralgia, back/neck pain, joint pain, muscle cramp and weakness.
- Cardiac: hypotension.
- Dermatologic: rash, dry skin, itching.
- Endocrine: hypothyroidism.
- Infection.
- Pulmonary: cough, dyspnea.
- Metabolic: hypokalemia, liver damage.
- Renal: increased creatinine, renal failure.

Pregnancy reporting:
See Section 4.2.3, Adverse Event Reporting.

Other instructions related to lenalidomide:
Only one cycle of therapy may be dispensed to the patient each month. During long-term lenalidomide maintenance, a maximum 28-day supply may be dispensed. Lenalidomide capsules should be swallowed whole, and should not be broken, chewed or opened. If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up. Patients taking more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

2.7.Study Drug Supply

2.7.1. Lenalidomide (NSC 703813)

Lenalidomide will be provided by Celgene and distributed by Biologics, Incorporated. Patients must be registered in the Revlimid REMS® program (formerly RevAssist® for Study Participants (RASP) program) in order to receive lenalidomide through the program (please see Appendix C).

NOTE:
Before lenalidomide is dispensed, patients must 1) have a negative pregnancy test (if applicable) and 2) be counseled by a trained counselor. BMT CTN 0702 Long-Term Follow-Up Study patients must be counseled through the Revlimid REMS® program. A maximum 28-day supply may be dispensed to a patient at one time.

Chemical Name: 3-(4'-amino-1,3-dihydro-1-oxo-2*H*-isoindol-2-yl)-2,6-piperidinedione

Other Names: CC-5013, Revlimid®, CDC-501

Classification: Immunomodulatory Agent

CAS Registry Number: 191732-72-6

Molecular Formula: $C_{13}H_{13}N_3O_3$ **M.W.:** 259.25

Mechanism of Action:
Lenalidomide, a thalidomide analog, is an immunomodulatory agent with a spectrum of activity that is still under investigation. Some of its effects include inhibition of inflammation, inhibition of angiogenesis, inhibition of hematopoietic tumor cell proliferation, modulation of stem cell differentiation and up regulating responses of T cells and NK cells.

Drug Supply and Storage:
Celgene supplies and Biologics, Inc. distributes lenalidomide 5 mg (size 2) hard gelatin capsules in tamper-evident, child-resistant, opaque, high density polyethylene (HDPE) bottles with HDPE caps.

The capsules also contain anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

Lenalidomide (Revlimid®) will be provided to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers. Lenalidomide will be provided in accordance with the Revlimid REMS® program of Celgene Corporation. Per standard Revlimid REMS® requirements all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in and must comply with all requirements of the Revlimid REMS® program. Prescriptions must be filled within 7 days.

All study participants must be registered into the mandatory Revlimid REMS® program, and be willing and able to comply with the requirements of the Revlimid REMS® program including counseling and phone surveys.

Any unused lenalidomide supplies distributed through the Revlimid REMS® program must be returned as instructed through the Revlimid REMS® program.

Administration:
Take lenalidomide by mouth with or without food. Do not crush, chew or open capsules.

Dispensing:
Only enough lenalidomide for one cycle may be dispensed at one time. The drug will be mailed directly to the patient through the Revlimid REMS® program.

Patient Care Implications and Counseling:
Risks Associated with Pregnancy
Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. The teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed.

Definition of female of childbearing potential (FCBP)
This protocol defines a female of childbearing potential as a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Before starting study drug:

Female Subjects:

- FCBP must have two negative pregnancy tests (minimum sensitivity of 50 mIU/mL) prior to starting study drug. The first pregnancy test must be performed within 10-14

days prior to the start of study drug and the second pregnancy test must be performed within 24 hours prior to the start of study drug (prescriptions must be filled within 7 days as required by Revlimid REMS®). The subject may not receive study drug until the Investigator has verified that the results of these pregnancy tests are negative.

- FCBP must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 4 weeks before starting lenalidomide. FCBP must also agree to ongoing pregnancy testing.

Male Subjects:

- Must agree to use a latex condom during sexual contact with females of childbearing potential while participating in the study and for at least 28 days following discontinuation from the study even if he has undergone a successful vasectomy.

All Subjects:

- Only enough lenalidomide for one cycle of therapy may be dispensed with each cycle of therapy.
- If pregnancy or a positive pregnancy test does occur in a study subject or the partner of a male study subject during study participation, lenalidomide must be immediately discontinued.

Counseling Requirements for the Revlimid REMS® program:

- This program provides education and counseling on the risks of fetal exposure, blood clots and reduced blood counts. Counseling will be provided by Biologics, Inc. prior to drug distribution please refer to Appendix C (Revlimid REMS® Program). Patients will be required to receive counseling every 28 days during treatment with lenalidomide, follow the pregnancy testing and birth control requirements of the program that are appropriate and take telephone surveys regarding compliance with the program.

Potential Drug Interactions:
Periodic monitoring of digoxin levels is recommended during co-administration with lenalidomide.

Monitor patients receiving concomitant warfarin per standard practice guidelines.

Lenalidomide is not a substrate of human CYP enzymes, nor is it an inhibitor or inducer.

Drug Ordering and Accountability:
The Revlimid REMS® program provides education and counseling on the risks of fetal exposure, blood clots and reduced blood counts. Counseling will be provided by Biologics, Inc. prior to drug distribution. Please refer to Appendix C (Revlimid REMS® Program). The patient will be required to receive counseling every 28 days during treatment with lenalidomide, follow the pregnancy testing and birth control requirements of the program that are appropriate in order to take the telephone surveys regarding compliance with the program. All physicians must be registered prescribers of Revlimid® in the Revlimid REMS® program. Physician registration

allows access to the Revlimid REMS® software to enroll patients in the Revlimid REMS® program. Please reference Appendix E (Revlimid REMS® Program) and follow the directions for submitting the registration. Biologics, the distributor of the lenalidomide, will not dispense or ship Revlimid® prior to Celgene's receipt of registration. Prescription information MUST BE entered using the Revlimid REMS® study specific electronic prescription form found in Appendix C (Revlimid REMS® Program). An authorization **number** must be on the prescription form at the time of faxing. A maximum of a 28-day supply of Revlimid® may be dispensed per cycle sent to the actual address noted on the Revlimid REMS® electronic prescription form. Biologics will verify the authorization number and complete the patient counseling. Patients will be provided with instructions from Biologics with each new dispense on the procedures for return of any un-used Revlimid® capsules.

CHAPTER 3

3. STUDY ENDPOINTS AND DEFINITIONS

3.1. Definition of Disease Progression

Disease progression will be evaluated as defined below and will be evaluated relative to the patient's best response on BMT CTN 0702

Disease Progression (PD) from CR or sCR requires one or more of the following:

- A reappearance of serum monoclonal paraprotein, with a level of at least 0.5 g/dL.
- 24-hour urine protein electrophoresis with at least 200 mg paraprotein/24 hours.
- Abnormal FLC levels of >10 mg/dl, only in patients without measurable paraprotein in the serum and urine.
- At least 10% plasma cells in a bone marrow aspirate or on trephine biopsy.
- Definite increase in the size of existing bone lesions or soft tissue plasmacytomas.
- Development of new bone lesions or soft tissue plasmacytomas.
- Development of hypercalcemia (corrected serum Ca >11.5 mg/dL or >2.8 mmol/L) not attributable to any other cause.

Progressive Disease (PD) for patients <u>not</u> in CR or sCR, progressive disease requires one or more of the following:

- >25% increase in the level of the serum monoclonal paraprotein, which must also be an absolute increase of at least 0.5 g/dL.
- >25% increase in 24-hour urine protein electrophoresis, which must also be an absolute increase of at least 200 mg/24 hours.
- Absolute increase in the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dl), only in patients without measurable paraprotein in the serum and urine.
- >25% increase in plasma cells in a bone marrow aspirate or on trephine biopsy, which must also be an absolute increase of at least 10%.
- Definite increase in the size of existing bone lesions or soft tissue plasmacytomas.
- Development of new bone lesions or soft tissue plasmacytomas.
- Development of hypercalcemia (corrected serum Ca >11.5 mg/dL or >2.8 mmol/L) not attributable to any other cause.
- NOTE: Development of a compression fracture does not exclude continued response and may not indicate progression.

3.2. Primary Endpoint

3.2.1. Progression-Free Survival

The primary objective is to compare progression-free survival (PFS) as a time to event analysis between the three randomized treatment arms from the BMT CTN 0702 protocol as a pairwise comparison. The analysis will be conducted once all alive patients have been followed for 5-years post randomization on the BMT CTN 0702 protocol. Patients are considered a failure of the primary endpoint if they die or suffer from disease progression. The time to this event is the time from randomization on the BMT CTN 0702 protocol until progression, death, or initiation of non-protocol anti-myeloma therapy. Patients will be censored at loss to follow-up or end of 2018, whichever comes first.

3.3. Secondary Endpoints

3.3.1. Overall Survival

The event is death from any cause. Overall survival time will be calculated as the time from randomization on the BMT CTN 0702 protocol until death, loss to follow-up or the end of the study, whichever comes first. Patients alive at the time of last observation or lost to follow-up will be censored at the date of last contact. Overall survival will be compared between treatment arms once all alive patients have been followed for 5-years post randomization on the BMT CTN 0702 protocol.

3.3.2. Event-free Survival

Event-free survival (EFS) time will be calculated as the time from randomization on the BMT CTN 0702 protocol until death from any cause, disease progression, or second primary malignancy, whichever comes first. Patients alive at the time of last observation or lost to follow-up will be censored at the date of last contact. Event-free survival will be compared between treatment arms once all alive patients have been followed for 5-years post randomization on the BMT CTN 0702 protocol.

3.3.3. Incidence of Second Primary Malignancies

The event is development of a second malignancy, excluding non-melanoma skin cancers, after randomization on the BMT CTN 0702 protocol. The cumulative incidence of SPMs will be described for all patients enrolled in this long-term follow-up study treating death as a competing risk and censoring patients alive at the time of last observation or lost to follow-up. Incidence of second primary malignancies will be compared between treatment arms once all alive patients have been followed for 5-years post randomization on the BMT CTN 0702 protocol. SPMs will also be described by histologic type.

3.3.4. Unexpected Grades 3-5 Adverse Events

Unexpected grades 3-5 adverse events will be tabulated and compared by treatment arm.

3.3.5. Health Quality of Life

The FACT-BMT version 4.0 instrument is comprised of a general core questionnaire, the FACT-G, which evaluates the health-related quality of life (HQL) of patients receiving treatment for cancer, and a specific module, BMT Concerns, which addresses disease and treatment-related questions specific to bone marrow transplant. The FACT-G consists of four subscales developed and normed in cancer patients: Physical Well-being, Social/Family Well-being, Emotional Well-being, and Functional Well-being. Each subscale is positively scored, with higher scores indicating better functioning. The FACT-BMT Total, which is the grand total of all items in the FACT-G and BMT modules, will be used as the outcome measure in summarizing the FACT-BMT data.

The MOS SF-36 instrument is a general assessment of health quality of life with eight components: Physical Functioning, Role Physical, Pain Index, General Health Perceptions, Vitality, Social Functioning, Role Emotional, and Mental Health Index. Each domain is positively scored, indicating that higher scores are associated with positive outcome. This scale has been widely applied in a variety of outcome studies and is being used in this protocol as a generic measure of quality of life. To facilitate comparison of the results with published norms, the Physical Component Summary (PCS) and Mental Component Summary (MCS) will be used as the outcome measures in summarizing the SF-36 data.

HQL will be described and compared between all treatment arms utilizing the FACT-BMT self report, transplant specific questionnaire and the generic quality of life tool (SF-36). The questionnaires will be scored according to standard procedures. The self report questionnaires will be completed yearly until disease progression. Only English and Spanish speaking patients are eligible to participate in the HQL component of this study.

CHAPTER 4

4. PATIENT ENROLLMENT AND EVALUATION

4.1. Enrollment Procedures

4.1.1. Eligibility and Enrollment

All BMT CTN 0702 patients who are alive and progression-free at the completion of the BMT CTN 0702 protocol specified follow-up period are eligible to be followed for long-term outcomes in this protocol. Patients who do not consent to the long-term follow-up mechanism or who have experienced progression on the BMT CTN 0702 study will be followed through the standard CIBMTR long-term follow-up mechanism. Patients who have completed 3 years of 0702 lenalidomide maintenance without evidence of disease progression are also eligible to receive continued, long-term lenalidomide maintenance therapy. Once the study has been described to the patient and informed consent has been obtained, an authorized user at the clinical center completes the 0702 Long Term Follow Up protocol Enrollment form in the Advantage Electronic Data Capture (AdvantageEDC^{SM}) system.

4.1.2. Revlimid REMS® Lenalidomide Counseling

Lenalidomide counseling will be provided through the Revlimid REMS® program for patients who will receive long-term lenalidomide as part of this study. Biologics Inc. will supply all counseling prior to drug distribution. Requirements are outlined in the Study Drug Supply Section 2.7.

4.2. Study Monitoring

4.2.1. Follow-up Schedule

Follow-up visits will occur every 6 months for all patients, beginning from the date of study entry on the long-term follow-up protocol, until death, progression, withdrawal of consent, or the end of the study.

4.2.2. Data Reporting

Criteria for Forms Submission
Criteria for timeliness of submission for all study forms are detailed in the Data Management Handbook. Forms that are not entered into the web-based data entry system within the specified time will be considered delinquent. A missing form will continue to be required either until the form is entered into the web based data entry system and integrated into the Data and Coordinating Center's (DCC's) master database, or until an exception is granted and entered into the Missing Form Exception File, as detailed in the Data Management Handbook.

4.3. Adverse Event Reporting

4.3.1. Unexpected, Grades 3-5 Adverse Events

Reporting of Adverse Events (AE) in the long-term follow-up protocol will follow the same mechanism as the BMT CTN 0702 parent clinical trial for patients receiving long-term lenalidomide maintenance therapy. AEs will be reported according to the BMT CTN Manual of Procedures. The BMT CTN Data and Safety Monitoring Board (DSMB) will be responsible for the safety and oversight of this long-term follow-up protocol. Unexpected, grades 3-5 adverse events will be reported through the expedited AE reporting system in AdvantageEDC using NCI's Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Unexpected, grade 4-5 AEs must be reported within 24 hours of knowledge of the event. Unexpected, grade 3 AEs must be reported within three business days of knowledge of the event.
The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 will be utilized for AE reporting and can be found at http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

Selected expected serious AEs (Appendix F - Table F-1) require expedited reporting with an Individual Case Safety Report (ICSR). Additionally, selected AEs of interest (Appendix F - Table F-2) will require expedited reporting through an ICSR, if they fulfill serious criteria according to the Code of Federal Regulations Title 21 (21 CFR 312.32) and occur after the administration of lenalidomide and up to 30 days after the permanent discontinuation of lenalidomide. See Appendix F for additional details on expedited reporting.

The aforementioned adverse event reporting criteria are for patients who receive long-term lenalidomide maintenance therapy. Patients not eligible for receiving long-term lenalidomide maintenance therapy or patients who have permanently discontinued lenalidomide maintenance will not require reporting of unexpected grades 3-5 adverse events or ICSRs with the exception of second primary malignancies as noted in 4.3.2. All patients will be required to report deaths as noted in section 4.3.3.

4.3.1.1. Adverse Event Reporting Following Progression

- If a patient meets the protocol defined definition of progression (Chapter 3), Unexpected Grade 3-5 Adverse Events and events listed in Appendix K are no longer required to be reported on the Adverse Event Form once the patient is more than 28 days from their last dose of lenalidomide. However, SPMs should continue to be reported within three business days of the knowledge of the event through the end of the study follow up period.

4.3.2. Reporting Second Primary Malignancies

All second primary malignancies (SPM), excluding non-melanoma skin cancers, experienced by patients enrolled on the long-term follow-up study will be reported using the Adverse Event forms (AE1-AE6) in AdvantageEDC and must be reported within three business days of knowledge of the event. The Event Description of the Adverse Event forms should include

histologic type. Patients who do not consent or who have progressed on the BMT CTN 0702 protocol will have SPMs reported through the standard CIBMTR reporting mechanism.

4.3.2.1. Adverse Event Reporting Following an SPM

Adverse Event reporting following an SPM is dependent on the treatment received for the reported SPM.

- If a patient experiences an SPM resulting in permanent discontinuation of lenalidomide and initiation of non-protocol systemic therapy, Unexpected Grade 3-5 Adverse Events and events listed in Appendix K will are no longer required to be reported on the Adverse Event Form once the patient is more than 28 days from their last dose of lenalidomide.
- If a patient experiences an SPM that does *not* result in permanent discontinuation of lenalidomide, Adverse Events will continue to be reported as per section 4.2.3 and appendix K of the protocol.
- Requests to discontinue Adverse Event Reporting for events that do not meet the criteria above will be considered on a case by case basis.

4.3.3. Reporting Patient Deaths

Recipient Death Information must be entered into AdvantageEDC within 24 hours of knowledge of the patient's death for patients who are enrolled in the long-term follow-up protocol. If the cause of death is unknown at that time, it need not be recorded at that time. However, once the cause of death is determined, the form must be updated in the web-based data entry system. Patients who do not consent or who have progressed on the BMT CTN 0702 protocol will have deaths reported through the standard CIBMTR reporting mechanism.

4.3.4. Pregnancy Reporting

Pregnancies occurring while the subject is on lenalidomide or within four weeks after the subject's last dose of lenalidomide are considered expedited reportable events. If the subject is on lenalidomide, it is to be discontinued immediately and the subject is to be instructed to return any unused portion of lenalidomide to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported within 24 hours of the Investigator's knowledge of the pregnancy using the Adverse Event Forms in AdvantageEDC.

The Investigator will follow the subject until completion of the pregnancy, and must report the outcome of the pregnancy and neonatal status as specified below. The Investigator will provide this information as a follow-up to the initial report.

If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures to report the event within 24 hours of the Investigator's knowledge of the event).

Any suspected fetal exposure to lenalidomide must be reported within 24 hours of being made aware of the event. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the *in utero* exposure to lenalidomide should also be reported.

In the case of a live "normal" birth, the outcome should be reported as soon as the information is available.

Male Subjects
If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking lenalidomide should notify the Investigator, and the pregnant female partner should be advised to call her healthcare provider immediately.

4.4. Patient Assesssments

Data collection is designed around the following three scenarios:

- Patients who enroll on the long-term follow-up protocol but who do not receive long-term lenalidomide for maintenance (see section 4.4.1)
- Patients who enroll on the long-term follow-up protocol and who receive long-term lenalidomid for maintenance (see section 4.4.2)
- Patients who progress prior to or during the long-term follow-up protocol (see section 4.4.3)

4.4.1. Long-Term Follow-Up Only- Assessment Schedule

Table 4.4.1 summarizes patient clinical assessments over the course of the study for patients who have not progressed prior to enrollment on this study and who are **not** receiving long-term lenalidomide.

The following evaluations will be performed at initiation of long-term follow-up, and then every 6 months (+/-30 days, unless otherwise noted) until progression, death, or withdrawal from the study, unless otherwise noted below:

1. History and physical exam, including height and weight
2. Evaluation for the occurrence of progression every 6 months
3. Evaluation for the occurrence of second primary malignancies
4. Health Quality of Life (HQL) instruments will be completed yearly after randomization on BMT CTN 0702 until disease progression or the end of 2018.
5. *Optional* blood samples for future research will be collected prior to the initiation of long-term follow-up, and at disease progression.

Table 4.4.1 – Evaluations During Long-Term Follow-Up

Study Assessments	Long-term follow-up Assessment Timepoints										
	0	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**R5Y**	**R6Y**	**R7Y**
History and Physical Examination	X	X	X	X	X	X	X	X			
HQL Instruments[1]									X	X	X
Optional Blood Samples for Research[2]	X	Event-driven – at disease progression									

[1]HQL assessments at R5Y, R6Y, and R7Y are a continuation of HQL on BMTCTN 0702. These instruments should be completed yearly from randomization on BMT CTN 0702. There is a +/- 6 month window on HQL assessments to allow for capture at the scheduled 6 month patient visits.
[2] Optional blood samples will be collected from patients who provided consent prior to the initiation of long-term follow-up and again at disease progression (where applicable).

4.4.2. Long-Term Follow-Up and Long-Term Lenalidomide Maintenance Assessment Schedule

Table 4.4.2 summarizes patient clinical assessments over the course of the study for patients who elect to receive long-term lenalidomide maintenance therapy as part of this study.

The following evaluations will be performed at initiation of long-term lenalidomide maintenance therapy, and then every 6 months (+/-30 days, unless otherwise noted) until progression, death, or withdrawal from the study unless otherwise noted below:

1. History and physical exam;
2. Required evaluation for Lenalidomide: Pregnancy test, serum HCG (sensitivity of at least 50 mIU/mL) for female of childbearing potential (FCBP):
    a. FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days and then every 28 days while on lenalidomide maintenance therapy (including breaks in therapy); at discontinuation of lenalidomide and at Day 28 post the last dose of lenalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on therapy (including breaks in therapy), at discontinuation of lenalidomide and at Day 14 and Day 28 post the last dose of lenalidomide.
    b. The subject must follow the requirements of the Revlimid REMS® program of the Celgene Corporation. This program provides education and counseling on the risks of fetal exposure, blood clots and reduced blood counts. The patient will be required to receive counseling every 28 days during treatment with lenalidomide, follow the pregnancy testing and birth control requirements of the program that are appropriate in order to take the telephone surveys regarding compliance with the program.
    c. Patients will require CBC with differential prior to the monthly supply of lenalidomide. These laboratory tests may be done remotely and sent to the transplant center.
3. Evaluation for the occurrence of progression every 6 months
4. Evaluation for the occurrence of second primary malignancies

5. Health Quality of Life (HQL) instruments will be completed yearly after randomization on BMT CTN 0702 until disease progression or the end of 2018.
6. *Optional* blood samples for future research will be collected prior to the initiation of maintenance therapy and at disease progression.

Table 4.4.2 – Evaluations During Long-Term Maintenance Therapy

Study Assessments	Long-term Maintenance Assessment Timepoints										
	0	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**R5Y**	**R6Y**	**R7Y**
History and Physical Examination	X	X	X	X	X	X	X	X			
HQL Instruments[1]									X	X	X
Optional Blood Samples for Research[2]	X	Event-driven – at disease progression									

[1] HQL assessments at R5Y, R6Y, and R7Y are a continuation of HQL on BMTCTN 0702. These instruments should be completed yearly from randomization on BMT CTN 0702. There is a +/- 6 month window on HQL assessments to allow for capture at the scheduled 6 month patient visits.
[2] Optional blood samples will be collected from patients who provided consent prior to the initiation of long-term follow-up and again at disease progression (where applicable).

4.4.3. Long-Term Follow-Up Assessment Schedule (Post-Progression)

Patients who progress prior to enrollment on this study or patients who progress while on the long-term follow-up protocol will have outcomes collected through the standard CIBMTR long-term follow-up mechanism.

CHAPTER 5

5. STATISTICAL CONSIDERATIONS

5.1. Study Design and Objectives

The primary motivation of this long-term follow-up protocol is to provide a mechanism to follow patients randomized on BMT CTN 0702 who have not experienced progression prior to enrollment on the long-term follow-up protocol for long-term outcomes including PFS, OS, EFS, incidence of SPMs and QOL. Patients who do not consent to the long-term follow-up mechanism or who have experienced progression on the BMT CTN 0702 study will be followed through the standard CIBMTR long-term follow-up mechanism. The primary objective is to compare PFS as a time to event analysis across the 3 different randomized treatment arms from the BMT CTN 0702 protocol. The analysis will be conducted once all living patients have been followed for 5-years post randomization on the BMT CTN 0702 protocol. The secondary objective is to provide lenalidomide as maintenance therapy to eligible patients until progression.

5.2. Accrual, Registration and Follow-up

It is anticipated that approximately 450 patients will be enrolled on this protocol based on assumed estimates of PFS estimates from the BMT CTN 0702 study. The total sample size may as low as 417 if the observed 3-year PFS on the BMT CTN 0702 is 55% but may be as high as 569 if the 3-year PFS is 75%. Follow-up on this protocol will continue through December 31, 2018.

5.3. Analysis of the Primary Endpoint

The primary analysis will include all randomized subjects from the BMT CTN 0702 protocol, classified according to their randomized treatment allocation, irrespective of treatment actually received [intent-to-treat]. The time to this event is the time from randomization on the BMT CTN 0702 protocol to progression, initiation of non-protocol anti-myeloma therapy, or death from any cause. Patients will be censored at loss to follow-up or end of 2018, whichever comes first. Deaths without progression are treated as failures no matter when they occur. The analysis will be conducted once all living patients have been followed for 5-years post randomization on the BMT CTN 0702 protocol.

Data for patients not enrolled on the long-term follow-up protocol will be included from the BMT CTN 0702 protocol. Additionally, patients who do not consent to the long-term follow-up or who have progressed on the BMT CTN 0702 protocol will be followed according to the standard CIBMTR long-term follow-up mechanism. The treatment arms will be compared with a two-sided log-rank test stratified on risk status. Tests will be performed pair-wise at the .01667 level in order to maintain study-wide type I error at 0.05. PFS will be compared between treatment arms as a time to event analysis. A secondary analysis of PFS will be conducted using Cox regression, adjusting for demographic and baseline characteristics which are statistically

different between treatment arms ($p<0.1$). Additionally, discontinuation of lenalidomide maintenance will be considered as a time-varying covariate in the Cox regression model.

5.4. Analysis of the Secondary Endpoints

Overall Survival
The event is death from any cause. Overall survival (OS) time will be calculated as the time from randomization on the BMT CTN 0702 protocol to death, loss to follow-up or the end of the study, whichever comes first. Patients alive at the time of last observation or lost to follow-up will be censored at the date of last contact. The Kaplan-Meier estimate of survival will be estimated at 5 years post randomization on the BMT CTN 0702 protocol along with corresponding 95% confidence intervals. Overall survival will be compared between treatment arms using a two-sided log-rank test once all alive patients have been followed for 5-years post randomization on the BMT CTN 0702 protocol.

Event-Free Survival
Event-free survival (EFS) time will be calculated as the time from randomization on the BMT CTN 0702 protocol to death, progression, second primary malignancy, loss to follow-up or the end of the study, whichever comes first. Patients alive at the time of last observation or lost to follow-up will be censored at the date of last contact. The Kaplan-Meier estimate of EFS will be estimated at 5 years post randomization on the BMT CTN 0702 protocol along with corresponding 95% confidence intervals. Overall survival will be compared between treatment arms using a two-sided log-rank test once all alive patients have been followed for 5-years post randomization on the BMT CTN 0702 protocol.

Second Primary Malignancies
The event is the development of any SPMs, excluding non-melanoma skin cancers, as described in Chapter 3. Death without SPMs will be considered a competing risk for this event. Cumulative incidence function will be used to calculate this endpoint and time of randomization on the BMT CTN 0702 protocol will be the starting point for the analysis. Estimates at 5 years will be described along with 95% confidence intervals. The cumulative incidence of SPMs will be compared between treatment arms using a two-sided Gray's test once all alive patients have been followed for 5-years post randomization on the BMT CTN 0702 protocol. SPMs will also be described by histologic type.

Unexpected Grades 3-5 Adverse Events
Unexpected grades 3-5 adverse events will be tabulated and compared across treatment arms. AEs will be described using the Medical Dictionary for Regulatory Activities (MedDRA) and classified according to the system organ class and preferred term. Summaries by type and severity by treatment arm will be provided.

Health Quality of Life
Health quality of life (HQL) will be compared between all treatment groups utilizing the FACT-BMT self report, transplant specific questionnaire and the generic quality of life tool, the SF-36. Only English and Spanish speaking patients are eligible to participate in the HQL component of

this trial. Outcomes of the HQL assessments will be described once all alive patients have been followed for five years post randomization on the BMT CTN 0702 protocol.

5.5. Safety Oversight

The BMT CTN DSMB will monitor the accruing safety and efficacy data on an approximate 6-month basis as per the DSMB charter. The DSMB will make recommendations to the NHLBI regarding release of data to investigators and the general public.

APPENDIX A

PATIENT INFORMED CONSENT

Informed Consent to Participate in Research

Your Name: _____

Study Title: Continued, Long-Term Follow-Up and Lenalidomide Maintenance Therapy for Patients Who Have Enrolled on BMT CTN 0702

Protocol: BMT CTN 0702 Long-Term Follow-Up

Principal Investigator: *Insert local PI information*

Sponsor: The National Institutes of Health (NIH) is sponsoring this study by providing financial support for the coordination of this study through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN). Celgene is supplying the study drug lenalidomide.

1. Introduction

We invite you to join this clinical trial, also known as a research study. You are being asked to join because:

1. You took part in the study, A Trial of Single Autologous Transplant with or without Consolidation Therapy versus Tandem Autologous Transplant with Lenalidomide Maintenance for Patients with Multiple Myeloma, also called **BMT CTN 0702**

2. After your autologous transplant, you finished 3 years of maintenance treatment for the BMT CTN 0702 study

3. Your disease did not return or worsen (this is also called **disease progression**) during the BMT CTN 0702 study.

Because there's no cure for Multiple Myeloma (MM), **maintenance treatment (chemotherapy)** is given to slow the return of your disease after an **autologous transplant**. We are doing this study to learn how well maintenance treatment works to control your disease long-term (more than 3 years after transplant).

For this study, the type of maintenance treatment you will get is **lenalidomide**. Lenalidomide is the same medication you have received for the first 3 years as maintenance following your autologous transplant. Lenalidomide is a chemotherapy drug used to slow down relapse.

This study will include 450 participants. You participation on this study is expected to last until your disease returns or progresses.

This Consent Form will tell you about the purpose of the study, the possible risks and benefits, other options available to you, and your rights as a participant in the study.

Everyone who takes part in research at [*insert facility name*] should know that:

- Being in any research study is voluntary.
- You may or may not benefit from being in the study. Knowledge we gain from this study may benefit others.
- If you join the study, you can quit the study at any time.
- If you decide to quit the study, it will not affect your care at [insert name of facility or institution].

- Please ask the study staff questions about anything that you do not understand, or if you would like to have more information.
- You can ask questions now or any time during the study.
- Please take the time you need to talk about the study with your doctor, study staff, and your family and friends. It is your decision to be in the study. If you decide to join, please sign and date the end of the Consent Form.

You and your doctor will discuss other follow-up treatment choices if you do not want to participate in this study.

2. Study Background

The National Institutes of Health (NIH), through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), are providing staff support and money for this research study. The BMT CTN and the NIH will make decisions about how to manage the study.

Celgene will supply the drug, lenalidomide, for this study.

For this study, we will give you maintenance treatment (lenalidomide) to slow down the relapse of your disease. We will watch your health closely (this is also called follow-up) after your autologous transplant.

There's no cure for multiple myeloma (MM). After transplant, the disease will almost always return, or relapse. Even with maintenance treatment, MM will relapse. Your doctor doesn't know how long it will take for the disease to return.

3. Study Purpose

We are inviting you to take part in this study because you finished the BMT CTN 0702 study and your disease did not return or worsen. We are doing this study to learn more about ways to prevent or delay relapse of multiple myeloma (MM). We also want to know how well you do long-term (more than 3 years) after transplant.

You will get maintenance treatment and have a physical evaluation (test) every 6 months to see if you still have MM in your body. This study will help doctors make the best choice about long-term treatment after autologous transplant for patients with MM.

4. Rights to Ask Questions and/or Withdraw

You have the right to ask questions about the study at any time. If you have questions about your rights as a participant or you want to leave the study, please contact:

[*insert contact info*]

Being in this study is voluntary. You can choose not to be in this study or leave this study at any time. If you choose not to take part or leave this study, it will not affect your regular medical care in any way.

Your study doctor and study staff will be available to answer any questions that you may have about taking part in or leaving this study.

5. Study Tests

We will check (test) your health every 6 months until the end of the study. This is called long-term follow-up maintenance treatment, after transplant. We will stop the study tests if your disease returns or relapses.

Before You Start Maintenance Treatment

You will need to have several check-ups and tests before you begin maintenance therapy. These tests include:

- Physical exam, including height and weight
- A pregnancy test using a blood sample (if you are a woman able to have children). This test will be done about 2 weeks before you start maintenance treatment. If you are pregnant or breastfeeding, you can't take part in this study.
- Tests to check for cancer as decided by your doctors. These tests would normally be done even if you were not on a research study and may include:
    - Bone marrow aspiration and biopsy (see **Section 6: Risks and Discomforts**)
    - Blood tests (up to 4 – 5 tablespoons)
    - Urine tests
- Optional blood samples for future research (**see Section 17: Blood Samples for Future Research**).

We will also ask you to take a quality of life survey. The survey will ask about:

- Any side effects of your treatment
- Any health problems
- How well you can do things that are important to you
- How you relate to other people
- Your feelings.

An interviewer will contact you to take the survey. These interviews will take about 30 minutes and will be done at a time that works for you. You may skip any questions you wish.

During Your Maintenance Treatment

You will keep taking lenalidomide during long-term maintenance treatment. If you stopped taking lenalidomide for the BMT CTN 0702 study, you will start taking it again. You will stay on maintenance treatment until your cancer returns, or relapses. If your cancer does not relapse during the study, you will keep taking lenalidomide until the study ends.

We will give you the same dose of lenalidomide that you were taking when you finished the BMT CTN 0702 study. We will give you lenalidomide as a pill to take once a day.

- Swallow the lenalidomide pills whole, with water, at the same time each day. Don't break, chew or open the pills. If you take more lenalidomide than you were prescribed, you should seek emergency medical care and contact the study staff immediately.
- If you miss a dose of lenalidomide, take it as soon as you remember on the same day. If you miss taking your dose for the entire day, take your regular dose the next scheduled day. Don't take 2 doses to make up for the missed dose.

We will watch your health closely during maintenance treatment, including how well your organs work (function). We will lower your dose or stop the treatment if your organs don't handle the treatment well. We will raise your dose or re-start the treatment when your organs start to work well again.

We will modify the dose and/or may stop the maintenance treatment if you:

- Have a serious side effect, like severe diarrhea or skin rash
- Have low blood cell counts

We will stop the maintenance treatment if you:

- Are a woman and become pregnant, or there is a chance that you are pregnant
- Don't follow the study directions, or
- Choose to leave the study.

You'll get lenalidomide for this study through the RevAssist for Study Participants (REVLIMID REMS™ Program. You will only get a 28-day supply of lenalidomide at a time. Because you took part in the BMT CTN 0702 study, you are already registered for the program.

Return all leftover lenalidomide pills through the REVLIMID REMS™ Program. Your doctor will tell you how to return the pills.

Females that are pregnant or can become pregnant shouldn't touch the lenalidomide pills or pill bottles, unless they wear gloves.

Health Evaluations (tests)

You will visit the clinic every 6 months. At each clinic visit you will have:

- Physical exam, including height and weight
- A pregnancy test using a blood sample (if you are a woman able to have children). If you are pregnant or breastfeeding, you must leave the study. We will give you a pregnancy test:
    - 24 or less hours before your first dose of lenalidomide
    - Next, once a week for 4 weeks
    - Then, once every 4 weeks until the study ends. If you have irregular periods (the number of days in your menstrual cycle is different each month), you will take a pregnancy test once every 2 weeks until the study ends.
    - Last, 4 weeks after you stop taking lenalidomide.
- Counseling once every 4 weeks on the risks of lenalidomide including:
    - Reasons not to share lenalidomide or donate blood
    - Risks to the unborn
    - Risk of changes in numbers of blood cells and blood clots

- Reminder not to break, chew or open the lenalidomide pills.

This counseling is part of the Revlimid REMS™ education program for the study drug. You get the Lenalidomide Information Sheet for Patients Enrolled in Clinical Research Studies with each new supply of lenalidomide.

- Tests to check for cancer as decided by your doctors. These tests would normally be done even if you were not on a research study and may include:
  - Bone marrow aspiration and biopsy (see **Section 6: Risks and Discomforts**)
  - Blood tests (up to 4 – 5 tablespoons)
  - Urine tests
- Optional blood samples for future research (see **Section 17: Blood Samples for Future Research**).

You can do these tests at a clinic near your home. Your clinic will send your test results to the study doctor.

We will also ask you to take a quality of life survey once per year (see **Before You Start Maintenance Treatment**).

6. Risks and Discomforts

You will have side effects while on the study. Side effects can range from mild to serious. The risks and discomforts of long-term maintenance treatment after transplant are the same if you join this study, or if you don't join this study.

Your healthcare team may give you medicines to help with side effects like nausea (feeling sick to your stomach). In some cases, side effects can last a long time or may never go away.

Risks of Medications

The risks of the chemotherapy drugs you get as part of the treatment are listed below. How often patients get each of the side effects are shown in **Table 1**. **Risks and Side Effects**.

Table 1. Risks and Side Effects

Likely	What it means: This type of side effect is expected in more than 20% of patients. This means that 21 or more patients out of 100 might get this side effect.
Less Likely	What it means: This type of side effect is expected in 20% of patients or fewer. This means that 20 patients or fewer out of 100 might get this side effect.
Rare, but Serious	What it means: This type of side effect is expected in fewer than 3% of patients. This means that 3 patients (or fewer) out of 100 might get this side effect. It doesn't happen very often, but is serious when it does.

Lenalidomide (Revlimid®)

Likely (May happen in more than 20% of patients)	**Less Likely** (May happen in 20% of patients or less)	**Rare, but Serious** (May happen in less than 3% of patients)
▪ Low number of white blood cells (neutrophil/granulocyte) ▪ Low number of platelets in the blood with increased risk of bleeding ▪ Feeling tired ▪ Itchy skin ▪ Skin rash with flaky, bumpy skin ▪ Constipation ▪ Diarrhea ▪ Nausea (feeling sick to your stomach)	▪ Anemia (low number of red blood cells) ▪ Low number of white blood cells (leukocytes) ▪ Cough ▪ Fever, with chills ▪ Trouble sleeping ▪ Excessive sweating ▪ Weight loss because not feeling hungry ▪ Belly pain ▪ Vomiting (throwing up) ▪ Low amount of thyroid hormone in the blood ▪ Swelling and redness of the skin with sores ▪ Sores in the mouth, intestines, and anus ▪ Infection ▪ Feeling dizzy ▪ Headache ▪ Swelling, pain and ache in	▪ Allergic reactions (swelling of the skin, face or throat) that can cause you to pass out (faint) or lead to death ▪ Rash with skin peeling and mouth sores that can lead to death ▪ Outer layer of skin (epidermis) comes apart from the middle layer (dermis), which can lead to death ▪ Pancreatitis (swelling of the intestines, stomach, or pancreas) ▪ High number of enzymes in the blood ▪ Fast death of cancer cells that can hurt organs like the kidneys ▪ Temporary growth in tumor or worsening of tumor-related problems ▪ Reversible damage to brain tissue that can lead to coma ▪ Kidney damage that could require dialysis

Likely (May happen in more than 20% of patients)	**Less Likely** (May happen in 20% of patients or less)	**Rare, but Serious** (May happen in less than 3% of patients)
	joints and muscles of back, arms and legs ▪ Trouble breathing ▪ Blood clots (clumps of solid blood in your vein) that can lead to death	▪ Second cancers

We don't know if second cancers are caused by lenalidomide or other drugs. Other research looked at the number of patients who got second cancers after taking lenalidomide for:

- Diseases other than multiple myeloma, AND
- Relapsed multiple myeloma.

In these studies, no difference was shown in the number of patients who got second cancers.

Researchers for other studies of lenalidomide are still watching patients to see if they get second cancers. We will give you any new information that we learn about second cancers.

Risk to the Unborn

The treatments in this study haven't been proven to be safe at any stage of pregnancy or nursing (breast feeding). If you are pregnant or nursing, you can't join this study. **If lenalidomide is taken during pregnancy, it may cause birth defects or death to an unborn baby.**

Women and men must refrain from all acts of vaginal sex (abstinence) or use **2 types** of effective birth control while receiving maintenance treatment. You must use effective birth control during the entire study and for 28 days after stopping maintenance treatment. Effective birth control is defined as the following:

1. Refraining from all acts of vaginal sex (abstinence)
2. Consistent use of birth control pills
3. Injectable birth control methods (Depo-Provera, Norplant)

4. Tubal sterilization or male partner who has undergone a vasectomy

5. Placement of an IUD (intrauterine device)

6. Use of a diaphragm with contraceptive jelly and/or condoms with contraceptive foam every time you have sex.

Females taking lenalidomide have blood clots more often. Because of this, you should talk to your doctor about birth control pills and hormone replacement therapy, and the risks and benefits.

You do not need to use effective birth control only if you are a woman and cannot have children because you:

- Had a hysterectomy (your ovaries and uterus were removed), OR
- Had a bilateral oophorectomy (your ovaries were removed), OR
- Went through menopause (post-menopausal).

Reproductive Risks

The drugs used in this research study may damage your reproductive organs, affect your ability to have children, or cause birth defects if you take them while you are pregnant or nursing.

Both women who can become pregnant and their male partners should use birth control while on this study and for 28 days after maintenance treatment is stopped. **If you or your partner becomes pregnant during this study, you must tell the study doctor immediately.**

Your doctor will discuss the risks to your unborn child and options with you.

It is important that females who aren't pregnant or nursing don't become pregnant while part of the study. If you are a woman and become pregnant while on this study, we will stop the maintenance treatment drug right away.

Your study doctor will watch your health closely while you are pregnant and for 30 days after the pregnancy ends.

- **Females who join the study**

If you are female and can become pregnant, you will need to take a pregnancy test before you start the study. You should discuss ways to prevent pregnancy while you're in the study. Women who have gone through puberty might experience irregular menstrual cycles or their cycle might stop forever. This doesn't mean that you can't become pregnant. You must still use 2 effective

forms of birth control during the study and continue with it for 28 days after you finish maintenance treatment.

Be sure to talk with your doctor about options for fertility planning, like storing your eggs, before starting chemotherapy treatment.

- **Males who join the study**

If you are male, your body may not be able to produce sperm (become sterile). Be sure to talk with your doctor about options for fertility planning, like banking your sperm, before starting chemotherapy treatment.

Damage to the vital organs in your body

Your vital organs include your heart, lungs, liver, intestines, kidneys, bladder and brain. The chemotherapy and GVHD drugs may hurt these organs. You may develop lung problems from chemotherapy or an infection.

Some patients can have veno-occlusive disease (VOD) of the liver. Patients with VOD become jaundiced (yellow skin), have problems with their liver, retain too much water (feel swollen and uncomfortable), and have stomach swelling and pain.

If there is serious damage to your vital organs, you may have to stay in the hospital longer or return to the hospital after your transplant. Many patients get better, but these complications can cause permanent damage to your organs or death.

Serious infections

It may take many months for your immune system to recover from the chemotherapy, GVHD and maintenance therapy drugs. There is an increased risk of infection during this time when your body is healing. We will give you drugs to reduce the chance of infection, but they may not work. If you have an infection, you may have to stay in the hospital longer or return to the hospital after transplant. Many patients get better, but some infections can cause death.

Relapse (return) of disease or a new blood cancer

Your disease may come back even if the transplant was successful at first. In rare cases, a new blood cancer may develop from your cells. If cancer develops in your blood cells, you may need more chemotherapy or another transplant.

Other Treatments or Medicines

Some medicines react with each other, and it is important that you tell the study doctor or staff about any other drugs, treatments, or medicines you are taking. This includes non-prescription or over-the-counter medicines, vitamins, and herbal treatments.

It is also important that you tell the study staff about any changes to your medicines while you're in the study.

Risks of Blood Draws

The risks and side effects of having blood taken from your arm with a needle include:

- Pain, like a pinch
- Swollen, red and sore skin where the needle went
- Bruising
- Feeling faint or dizzy

Risks of Bone Marrow Aspiration and Biopsy

The risks and side effects of anesthesia drug injection include:

- Pain, like a pinch
- Burning feeling in your skin and hip bone

The risks and side effects of a bone marrow aspiration and biopsy include:

- Pressure and pain in hip
- Bleeding
- Bruising
- Ache in hip bone and muscles
- Infection (this is rare)

Unforeseen Risks

New risks might appear at any time during the study. These risks might be different from what is listed in this Consent Form. We will promptly tell you about new information that may affect your decision to take part in the study.

For more information about risks and side effects, ask your study doctor.

Statement that You Understand the Study Drug Risks and Side Effects

Females Who Can Become Pregnant

Please read each statement carefully. Next to each statement that you agree with, write your initials in the space provided.

_____ My doctor discussed the risks and side effects of lenalidomide with me. I understand that if I am pregnant or become pregnant while taking lenalidomide, my unborn baby may have birth defects or could die.

_____ I understand that effective birth control includes:

- Refraining from all acts of vaginal sex (abstinence)
- Consistent use of birth control pills
- Injectable birth control methods (Depo-Provera, Norplant)
- Tubal sterilization or male partner who has undergone a vasectomy
- Placement of an IUD (intrauterine device)
- Use of a diaphragm with contraceptive jelly and/or condoms with contraceptive foam every time you have sex.

_____ I must not take lenalidomide if I am pregnant or can become pregnant and am not using **2 types** of effective birth control. Also, I must not take lenalidomide if I am nursing.

_____ I understand that I can become pregnant if:

- I have vaginal sex,
- My uterus and/or ovaries haven't been removed (no hysterectomy),
- I've had one or more menstrual periods in the last 2 years, and
- I haven't gone through menopause.

_____ I must refrain from all acts of vaginal sex **(abstinence)** or use **2 types** of effective birth control:

- For 28 or more days before starting lenalidomide
- While taking part in the study, even if you stop taking lenalidomide

- For 28 or more days after you stop taking lenalidomide.

_____ I understand that I must have pregnancy tests done at my clinic at:

- About 2 weeks before starting lenalidomide
- 24 or less hours before my first dose of lenalidomide
- Once a week for 4 weeks
- Once every 4 weeks until the study ends. If I have irregular periods, I will take a pregnancy test once every 2 weeks until the study ends.
- When I have been taken off lenalidomide
- 4 weeks after I stop taking lenalidomide.

_____ I will immediately stop taking lenalidomide and tell my doctor if I become pregnant or think I might be pregnant during the study. I must talk to my doctor if I stop using 2 types of effective birth control or before changing types of birth control.

_____ I am not pregnant now, and I will not try to become pregnant for 28 days or longer after I finish the study.

_____ I understand that lenalidomide will be prescribed only for me. I will not share it with anyone, not even someone that has symptoms like mine. I will keep it out of reach of children. I will never give it to females who are pregnant or able to have children.

_____ I will return all leftover study drugs through the Revlimid REMS™ Program.

_____ I understand that I can't donate blood while taking lenalidomide. Also, I can't donate blood for 28 days after I stop taking lenalidomide.

Females Who Can't Become Pregnant

Please read each statement carefully. Next to each statement that you agree with, write your initials in the space provided.

_____ My doctor discussed the risks and side effects of lenalidomide with me. I understand that if a female is pregnant or becomes pregnant while taking lenalidomide, her unborn baby may have birth defects or could die.

_____ I am not pregnant now and I'm not able have children because:

- I went through menopause 2 years ago or longer (no periods or spotting)

- I had my uterus removed (hysterectomy) and/or both ovaries removed (bilateral oophorectomy).

_____ I understand that lenalidomide will be prescribed only for me. I will not share it with anyone, not even someone that has symptoms like mine. I will keep it out of reach of children. I will never give it to females who are pregnant or able to have children.

_____ I will return all leftover study drugs through the Revlimid REMS™ Program.

_____ I understand that I can't donate blood while taking lenalidomide. Also, I can't donate blood for 28 days after I stop taking lenalidomide.

Males

Please read each statement carefully. Next to each statement that you agree with, write your initials in the space provided.

_____ My doctor discussed the risks and side effects of lenalidomide with me. I understand that if a female is pregnant or becomes pregnant while taking lenalidomide, her unborn baby may have birth defects or could die.

_____ I understand that effective birth control includes:

- Refraining from all acts of vaginal sex (abstinence)
- Consistent use of birth control pills
- Injectable birth control methods (Depo-Provera, Norplant)
- Tubal sterilization or male partner who has undergone a vasectomy
- Placement of an IUD (intrauterine device)
- Use of a diaphragm with contraceptive jelly and/or condoms with contraceptive foam every time you have sex.

_____ I understand that I must never have vaginal sex without **2 types** of effective birth control, even if I had a vasectomy. I must use 2 types of effective birth control while I take lenalidomide and for 28 days after I stop taking lenalidomide.

_____ I will tell my doctor if I have vaginal sex with a female and don't use **2 types** of effective birth control. I will tell my doctor if I think that my sexual partner might be pregnant. I will tell my sexual partner to tell her doctor immediately if she becomes pregnant or thinks she might be pregnant.

_____ I understand that lenalidomide will be prescribed only for me. I will not share it with anyone, not even someone that has symptoms like mine. I will keep it out of reach of children. I will never give it to females who are pregnant or able to have children.

_____ I will return all leftover study drugs through the Revlimid REMS™ Program.

_____ I understand that I can't donate blood while taking lenalidomide. Also, I can't donate blood for 28 days after I stop taking lenalidomide.

7. Alternative Treatments

Participation in this study is optional. If you choose not to take part, you may still receive long-term follow-up after your transplant. The evaluations you would have could be very similar to what would have if you join this study.

Your study doctor will talk with you about your options. If you decide not to participate in this study, your medical care will not be affected in any way.

8. Possible Benefits

Taking part in this study will not make your health better. The information from this study will help doctors learn more about ways to treat multiple myeloma.

This information could help people with multiple myeloma who may need a transplant in the future.

9. New Information Available During the Study

During this research study, the study doctors may learn about new information about the risks and benefits of the study. If this happens, they will tell you about the new information. The new information may mean that you can no longer participate in the study, or that you may not want to continue in the study.

If this happens, the study doctor will stop your participation in the study and will offer you all available care to suit your needs and medical conditions.

10. Privacy, Confidentiality and Use of Information

Your confidentiality is one of our main concerns. We will do our best to make sure that the personal information in your medical record is kept private. However, we cannot guarantee total privacy.

All your medical and demographic information (such as race and ethnicity, gender and household income) will be kept private and confidential. *(Name of Transplant Center)* and the organizations listed below will not disclose your participation by any means of communication to any person or organization, except by your written request, or permission, or unless required by federal, state or local laws, or regulatory agencies.

Individuals authorized by the organizations below will have access to your research and medical information. They may use this information for inspections or audits to study the outcomes of your treatment. In agreeing to participate, you consent to such inspections and to the copying of parts of your records, if required by these organizations.

We may give out your personal information if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Information about your transplant from your original medical records may be seen or sent to national and international transplant registries, including:

- /Institution/
- The Center for International Blood and Marrow Transplant Research (CIBMTR)
- The National Marrow Donor Program (NMDP)
- The Food and Drug Administration (FDA)
- The National Institutes of Health (NIH), which include the National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI)
- Data and Coordinating Center of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN)
- Data and Safety Monitoring Board (DSMB), not part of /Institution/
- Study investigators.

We will not identify you by name in any publications or reports that come from these organizations or groups.

Information that does not include personally identifiable information about this study has been or will be submitted, at the appropriate and required time, to the government-operated clinical trial registry data bank, which contains registration, results, and other information about registered studies.

This data bank can be accessed by you and the general public at www.ClinicalTrials.gov. Federal law requires clinical trial information for certain studies to be submitted to the data bank.

For questions about access to your medical records, please contact /name/ at /number.

11. Ending Your Participation

The study doctor or the study sponsor may stop the study at any time, and we may ask you to leave the study. We may ask you to leave the study if you do not follow directions or if you suffer from side effects of the tests. If we ask you to leave the study, the reasons will be discussed with you. Possible reasons to end your participation in this study include:

- Your disease returns or worsens during the study.
- You need a medical treatment not allowed in this study.
- The study doctor decides that it would be harmful to you to stay in the study.
- You are having serious side effects.
- You cannot keep appointments as directed.
- The study is stopped for any reason.

We ask that you talk with the research doctor and your regular doctor before you leave the study. Your doctors will tell you how to stop safely and talk with you about other treatment choices.

Even if you leave the study, the information collected from your participation will be included in the study evaluation, unless you specifically ask that it not be included.

12. Physical Injury as a Result of Participation

It is important that you tell your doctor, _____ *[investigator's name(s)]* or study staff if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number]*.

You will get all available medical treatment if you are injured from taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

In case you are injured in this study, you do not lose any of your legal rights to ask for or receive payment by signing this form.

13. Compensation or Payment

You will not be paid for taking part in this study. You will not be paid or reimbursed for any extra costs (for example, travel and meals) from taking part in this study.

You will have no rights to any patents or findings from this study. You will not be compensated for any patents or findings from this study.

14. Costs and Reimbursements

Most of the visits for this research study are standard medical care after your autologous transplant and will be billed to your insurance company. You and/or your health plan/insurance company will need to pay for some or all of the costs of standard treatment in this study.

You will get the study drug, lenalidomide, for free from Celgene. You and your health insurance plan will not be charged for the drug.

You or your insurance will not be charged for optional blood samples for research on this study. You will not pay for any extra tests that are being done for the study.

Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out if they will pay.

For questions about your costs, financial responsibilities, and/or medical insurance coverage for your transplant and this study, please contact /Center/ Financial Counselor at /Number/.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

15. For More Information

If you need more information about this study, or if you have problems while taking part in this study, you can contact the study doctor or his/her staff.

They can be reached at the telephone numbers listed here:

[*Insert name and contact details*]

16. Contact Someone about Your Rights

If you wish to speak to someone not directly involved in the study, or if you have any complaints about any aspect of the project, the way it is being conducted or any questions about your rights as a research participant, then you may contact:

[*Insert appropriate contact details*]

The ethical aspects of this study have been reviewed and approved by *[name of IRB]*.

17. Blood Samples for Future Research (Optional)

This section of the informed consent form is about future research studies that will use blood samples from people who are taking part in the main study. You may choose to give samples for these future research studies if you want to. You can still be a part of the main study even if you say 'no' to give samples for future research studies.

Researchers are trying to learn more about how the human body processes the drugs used for transplant and how the body recovers after transplant. This research is meant to gain knowledge that may help people in the future and make transplants even more successful.

If you agree to provide blood samples, here is what will happen:

- We will collect two extra blood samples at the same time you have routine blood tests done. The amount of blood collected from you is about 6 teaspoons (31 ml) each time.

  We will collect blood samples at two times during the study:

  - First clinic visit after you join the study
  - Last clinic visit at the end of the study

- The blood samples will be sent to the BMT CTN Repository for processing and storage. A repository is a place that protects, stores and sends out samples for approved research studies. All research samples will be given a bar code that cannot be linked to you by future researchers testing your samples.

- Materials stored in the Repository will be used mainly by clinicians and researchers in the BMT CTN network. In the future, the unused research samples and clinical data will be made available outside of this network.

- Researchers can apply to study the materials stored in the Repository. The BMT CTN Steering Committee and/or the BMT CTN Executive Committee must approve each request before they will share samples or information with researchers. This is to make sure that the investigators requesting the samples are qualified, and that the research is of high quality.

- DNA from your stored blood samples might be used in genome-wide association (GWA) studies for a future project either done or supported by the National Institutes of Health (NIH). Genome-wide association studies are a way for scientists to find genes that have a role in human disease or treatment. Each study can look at hundreds of thousands of genetic changes at the same time.

  If your coded samples are used in such a study, the researcher is required to add your test results and sample information into a shared, public research database. This public database is called the NIH Genotype and Phenotype Database and it is managed by the National Center for Biotechnology Information (NCBI). The NCBI will never have any information that would identify you, or link you to your information or research samples.

Some general things you should know about letting us store your blood samples for research are:

- We will only store samples from people who give us permission.

- Research is meant to gain knowledge that my help people in the future. You will not get any direct benefit from taking part. Additionally, you or your doctor will not be given results and they will not be added to your medical record.

- A possible risk is the loss of confidentiality about your medical information. We will use safety measures with both your samples and clinical information to make sure that your personal information will be kept private. The chance that this information will be given to someone else is extremely small.

- Your blood will be used only for research and will not be sold. The research done with your blood may help to develop new products in the future. You will not get paid for any samples or for any products that may be developed from current or future research.

You can change your mind at any time about allowing us to use your samples and health information for research.

We ask that you contact [Principal Investigator] in writing and let him/her know you do not want us to use your research samples or health information for research. His/her mailing address is on the first page of this form. However, samples and information that have already been shared with other researchers cannot be taken back or destroyed.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, please indicate your choice below. If you have any questions, please talk to your doctor or nurse, or call our research review board at _____.

No matter what you decide to do, it will not affect your care.

Statement of Consent for Research Samples

The purpose of storing blood samples, the procedures involved, and the risks and benefits have been explained to me. I have asked all the questions I have at this time and I have been told whom to contact if I have more questions. I have been told that I will be given a signed copy of this consent form to keep.

I understand that I do not have to allow the use of my blood for research. If I decide to not let you store research samples now or in the future, it will not affect my medical care in any way.

I voluntarily agree that my blood and information can be stored indefinitely by the BMT CTN and/or NHLBI Repositories for research to learn about, prevent, or treat health problems. I also understand that my DNA and health information may or may not be used in genome-wide association studies.

Blood

❑ I agree to allow my blood samples to be stored for research.

❑ I do not agree to allow my blood samples to be stored for research.

_____ _____

Signature Date

Health Insurance Portability and Accountability Act 1 (HIPAA2) Authorization to use and disclose individual health information for research purpose

A. Purpose:

As a research participant, I authorize the Principal Investigators and the researcher's staff to use and disclose my individual health information for the purpose of conducting the research study:

Continued, Long-Term Follow-Up and Lenalidomide Maintenance Therapy for Patients Who Have Enrolled on BMT CTN 0702

B. Individual Health Information to be Used or Disclosed:

My individual health information that may be used or disclosed to do this research includes:

- Demographic information (for example, date of birth, sex, weight)
- Medical history (for example, diagnosis, complications with prior treatment)
- Findings from physical exams
- Laboratory test results obtained at the time of work up and after transplant (for example, blood tests, biopsy results)

C. Parties Who May Disclose My Individual Health Information:

The researcher and the researcher's staff may collect my individual health information from:

[*List hospitals, clinics or providers from which health care information can be requested*]

D. Parties Who May Receive or Use My Individual Health Information:

The individual health information disclosed by parties listed in item c and information disclosed by me during the course of the research may be received and used by the following parties:

- Dr. Amrita Krishnan, Study Chairperson and staff/laboratories at City of Hope National Medical Center
- Dr. George Somlo, Study Chairperson and staff/laboratories at City of Hope National Medical Center

2 HIPAA is the Health Insurance Portability and Accountability Act of 1996, a federal law related to privacy of health information

- Dr. Edward Stadtmauer, Study Chairperson and staff/laboratories at University of Pennsylvania Cancer Center.

Study Sponsors

- National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI), both of the National Institutes of Health (NIH),

1. Blood and Marrow Transplant Clinical Trials Network (BMT CTN) Data and Coordinating CenterU.S. government agencies that are responsible for overseeing research such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP)

2. U.S. government agencies that are responsible for overseeing public health concerns such as the Centers for Disease Control (CDC) and federal, state and local health departments

3. Celgene (the manufacturer of lenalidomide)

4. Biologics, Inc (the distributor of lenalidomide).

E. Right to Refuse to Sign this Authorization:

I do not have to sign this Authorization. If I decide not to sign the Authorization, I will not be allowed to participate in this study or receive any treatment related to research that is provided through the study.

My decision not to sign this authorization will not affect any other treatment, payment, or enrollment in health plans or eligibility for benefits.

F. Right to Revoke:

I can change my mind and withdraw this authorization at any time by sending a written notice to the Principal Investigator to inform the researcher of my decision.

If I withdraw this authorization, t he researcher may only use and disclose the protected health information already collected for this research study. No further health information about me will be collected by or disclosed to the researcher for this study.

G. Potential for Re-disclosure:

My individual health information disclosed under this authorization may be subject to re-disclosure outside the research study and no longer protected. Examples include potential

disclosures for law enforcement purposes, mandated reporting or abuse or neglect, judicial proceedings, health oversight activities and public health measures.

H. Genetic Information Nondiscrimination Act (GINA)

A new federal law (2009), called the Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and employers of 15 or more persons to discriminate against you based on your genetic information.

Health insurance companies and group health plans may not request your genetic information that we get from this research. This means that they must not use your genetic information when making decisions regarding insurability. Be aware that this new federal law will not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

I. This authorization does not have an expiration date.

TITLE: Continued, Long-Term Follow-Up and Lenalidomide Maintenance Therapy for Patients Who Have Enrolled on BMT CTN 0702

PROTOCOL NUMBER: BMT CTN #0702 Long-term Follow-Up Study

PRINCIPAL INVESTIGATOR:

Name:

Address:

Email:

Phone:

Fax:

I have read and understood this Consent Form. The nature and purpose of the research study has been explained to me.

- I have had the chance to ask questions, and understand the answers I have been given. I understand that I may ask questions at any time during the study.
- I freely agree to be a participant in the study.
- I understand that I may not directly benefit from taking part in the study.
- I understand that, while information gained during the study may be published, I will not be identified and my personal results will stay confidential.
- I have had the chance to discuss my participation in this research study with a family member or friend.
- I understand that I can leave this study at any time, and doing so will not affect my current care or prevent me from receiving future treatment.
- I understand that I will be given a copy of this signed consent form.

_____ _____

Participant Name Date

_____ _____

Signature Date

I certify that I have provided a verbal explanation of the details of the research study, including the procedures and risks. I believe the participant has understood the information provided.

_____ _____

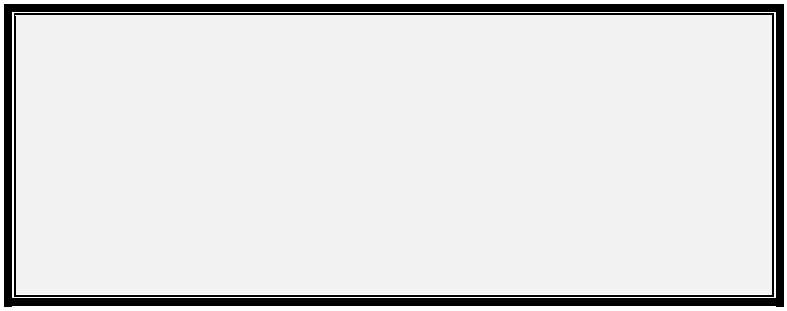
Name of Counseling Physician Date

_____ _____

Signature of Counseling Physician Date

PATIENT INFORMED CONSENT FORM

Informed Consent to Participate in Long-Term Follow-Up Research



Your Name: _____

Study Title: Continued, Long-Term Follow-Up and Lenalidomide Maintenance Therapy for Patients Who Have Enrolled on BMT CTN 0702

Protocol: BMT CTN 0702 Long-Term Follow-Up

Principal Investigator: *Insert local PI information*

Sponsor: The National Institutes of Health (NIH) is sponsoring this study by providing financial support for the coordination of this study through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN). Celgene is supplying the study drug lenalidomide.

1. Introduction

We invite you to join this clinical trial, also known as a research study. You are being asked to join because:

- You took part in the study, A Trial of Single Autologous Transplant with or without Consolidation Therapy versus Tandem Autologous Transplant with Lenalidomide Maintenance for Patients with Multiple Myeloma, also called **BMT CTN 0702**
- Your disease did not return or worsen (this is also called **disease progression**) during the BMT CTN 0702 study.

Because there's no cure for Multiple Myeloma (MM), the disease almost always returns or worsens. We are doing this study to learn how well patients do more than 3 years after autologous transplant.

This study will include 450 participants. Your participation on this study is expected to last until your disease returns or progresses.

This Consent Form will tell you about the purpose of the study, the possible risks and benefits, other options available to you, and your rights as a participant in the study.

Everyone who takes part in research at [*insert facility name*] should know that:

- Being in any research study is voluntary.
- You may or may not benefit from being in the study. Knowledge we gain from this study may benefit others.
- If you join the study, you can quit the study at any time.
- If you decide to quit the study, it will not affect your care at [insert name of facility or institution].
- Please ask the study staff questions about anything that you do not understand, or if you would like to have more information.
- You can ask questions now or any time during the study.
- Please take the time you need to talk about the study with your doctor, study staff, and your family and friends. It is your decision to be in the study. If you decide to join, please sign and date the end of the Consent Form.

You and your doctor will discuss other follow-up treatment choices if you do not want to participate in this study.

This consent form tells you about the study. The Principal Investigator (the person in charge of this research) or a co-worker of the Principal Investigator will also describe this study to you and answer all of your questions. Furthermore, throughout your follow up questions will be answered as needed. Before you decide whether or not to take part, read the information below and ask questions about anything you do not understand. Taking part in this follow-up study is entirely your choice.

2. Study Background

The National Institutes of Health (NIH), through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), are providing staff support and money for this research study. The BMT CTN and the NIH will make decisions about how to manage the study.

For this study, we will watch your health closely (this is also called follow-up) after your autologous transplant.

There's no cure for MM. After transplant, the disease will almost always return, or relapse. Some patients may keep getting treatment after transplant called maintenance treatment. Maintenance treatment is given to slow down relapse. Even with maintenance treatment, MM will relapse. Your doctor doesn't know how long it will take for the disease to return.

3. Study Purpose

We are inviting you to take part in this study because you completed the BMT CTN 0702 study and your disease did not return or worsen. We are doing this study to learn more about ways to prevent or delay relapse of multiple myeloma (MM). We also want to know how well you do long-term (more than 3 years) after transplant.

You will have a physical evaluation (test) every 6 months to see if you still have Multiple Myeloma (MM) in your body. This study will help doctors make the best choice about long-term treatment after autologous transplant for patients with MM.

4. Rights to Ask Questions and/or Withdraw

You have the right to ask questions about the study at any time. If you have questions about your rights as a participant or you want to leave the study, please contact:

[*insert contact info*]

Being in this study is voluntary. You can choose not to be in this study or leave this study at any time. If you choose not to take part or leave this study, it will not affect your regular medical care in any way.

Your study doctor and study staff will be available to answer any questions that you may have about taking part in or leaving this study.

5. Study Tests

We will check (test) your health before you enter the study and every 6 months after that. This is called long-term follow-up after transplant. We will stop the study tests if your disease returns or relapses.

You will need to have several check-ups and tests for this study. You will visit the clinic every 6 months. At each clinic visit you will have:

- Physical exam, including height and weight
- Tests to check for cancer as decided by your doctors. These tests would normally be done even if you were not on a research study. These tests may include:
    - Bone marrow aspiration and biopsy (see **Section 6: Risks and Discomforts**)
    - Blood tests (up to 4 – 5 tablespoons)
    - Urine tests
- Optional blood samples for future research (**see Section 17: Blood Samples for Future Research**).

You can do these tests at a clinic near your home. Your clinic will send your test results to the study doctor.

We will also ask you to take a quality of life survey each year. The survey will ask about:

- Any side effects of your treatment
- Any health problems
- How well you can do things that are important to you
- How you relate to other people
- Your feelings.

An interviewer will contact you before you start long-term follow-up. These interviews will take about 30 minutes and will be done at a time that works for you. You may skip any questions you wish.

6. Risks and Discomforts

You will have side effects while on the study. Side effects can range from mild to serious. The risks and discomforts of long-term follow-up after transplant are the same if you join this study, or if you don't join this study.

Risks of Blood Draws

The risks and side effects of having blood taken from your arm with a needle include:

- Pain, like a pinch
- Swollen, red and sore skin where the needle went
- Bruising
- Feeling faint or dizzy

Risks of Bone Marrow Aspiration and Biopsy

The risks and side effects of anesthesia drug injection include:

- Pain, like a pinch
- Burning feeling in your skin and hip bone

The risks and side effects of a bone marrow aspiration and biopsy include:

- Pressure and pain in hip
- Bleeding
- Bruising
- Ache in hip bone and muscles
- Infection (this is rare)

Unforeseen Risks

New risks might appear at any time during the study. These risks might be different from what is listed in this Consent Form. We will promptly tell you about new information that may affect your decision to take part in the study.

For more information about risks and side effects, ask your study doctor.

7. Alternative Treatments

Participation in this study is optional. If you choose not to take part, you may still receive long-term follow-up after your transplant. The evaluations you would have could be very similar to whatyou would have if you join this study.

Your study doctor will talk with you about your options. If you decide not to participate in this study, your medical care will not be affected in any way.

8. Possible Benefits

Taking part in this study will not make your health better. The information from this study will help doctors learn more about ways to treat multiple myeloma.

This information could help people with multiple myeloma who may need a transplant in the future.

9. New Information Available During the Study

During this research study, the study doctors may learn about new information about the risks and benefits of the study. If this happens, they will tell you about the new information. The new information may mean that you can no longer participate in the study, or that you may not want to continue in the study.

If this happens, the study doctor will stop your participation in the study and will offer you all available care to suit your needs and medical conditions.

10. Privacy, Confidentiality and Use of Information

Your confidentiality is one of our main concerns. We will do our best to make sure that the personal information in your medical record is kept private. However, we cannot guarantee total privacy.

All your medical and demographic information (such as race and ethnicity, gender and household income) will be kept private and confidential. *(Name of Transplant Center)* and the organizations listed below will not disclose your participation by any means of communication to any person or organization, except by your written request, or permission, or unless required by federal, state or local laws, or regulatory agencies.

Individuals authorized by the organizations below will have access to your research and medical information. They may use this information for inspections or audits to study the outcomes of your treatment. In agreeing to participate, you consent to such inspections and to the copying of parts of your records, if required by these organizations.

We may give out your personal information if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Information about your transplant from your original medical records may be seen or sent to national and international transplant registries, including:

- /Institution/
- The Center for International Blood and Marrow Transplant Research (CIBMTR)
- The National Marrow Donor Program (NMDP)
- The Food and Drug Administration (FDA)
- The National Institutes of Health (NIH), which include the National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI)
- Data and Coordinating Center of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN)
- Data and Safety Monitoring Board (DSMB), not part of /Institution/
- Study investigators.

We will not identify you by name in any publications or reports that come from these organizations or groups.

Information that does not include personally identifiable information about this study has been or will be submitted, at the appropriate and required time, to the government-operated clinical trial registry data bank, which contains registration, results, and other information about registered studies.

This data bank can be accessed by you and the general public at www.ClinicalTrials.gov. Federal law requires clinical trial information for certain studies to be submitted to the data bank.

For questions about access to your medical records, please contact /name/ at /number.

11. Ending Your Participation

The study doctor or the study sponsor may stop the study at any time, and we may ask you to leave the study. We may ask you to leave the study if you do not follow directions or if you suffer from side effects of the tests. If we ask you to leave the study, the reasons will be discussed with you. Possible reasons to end your participation in this study include:

- Your disease returns or worsens during the study.
- You need a medical treatment not allowed in this study.
- The study doctor decides that it would be harmful to you to stay in the study.
- You are having serious side effects.
- You cannot keep appointments as directed.
- The study is stopped for any reason.

We ask that you talk with the research doctor and your regular doctor before you leave the study. Your doctors will tell you how to stop safely and talk with you about other treatment choices.

Even if you leave the study, the information collected from your participation will be included in the study evaluation, unless you specifically ask that it not be included.

12. Physical Injury as a Result of Participation

It is important that you tell your doctor, _____ *[investigator's name(s)]* or study staff if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number]*.

You will get all available medical treatment if you are injured from taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

In case you are injured in this study, you do not lose any of your legal rights to ask for or receive payment by signing this form.

13. Compensation or Payment

You will not be paid for taking part in this study. You will not be paid or reimbursed for any extra costs (for example, travel and meals) from taking part in this study.

You will have no rights to any patents or findings from this study. You will not be compensated for any patents or findings from this study.

14. Costs and Reimbursements

Most of the visits for this research study are standard medical care after your autologous transplant and will be billed to your insurance company. You and/or your health plan/insurance company will need to pay for some or all of the costs of standard treatment in this study.

You or your insurance will not be charged for optional blood samples for research on this study. You will not pay for any extra tests that are being done for the study.

Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out if they will pay.

For questions about your costs, financial responsibilities, and/or medical insurance coverage for your transplant and this study, please contact /Center/ Financial Counselor at /Number/.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

15. For More Information

If you need more information about this study, or if you have problems while taking part in this study, you can contact the study doctor or his/her staff.

They can be reached at the telephone numbers listed here:

[*Insert name and contact details*]

16. Contact Someone about Your Rights

If you wish to speak to someone not directly involved in the study, or if you have any complaints about any aspect of the project, the way it is being conducted or any questions about your rights as a research participant, then you may contact:

[*Insert appropriate contact details*]

The ethical aspects of this study have been reviewed and approved by *[name of IRB]*.

17. Blood Samples for Future Research (Optional)

This section of the informed consent form is about future research studies that will use blood samples from people who are taking part in the main study. You may choose to give samples for these future research studies if you want to. You can still be a part of the main study even if you say 'no' to give samples for future research studies.

Researchers are trying to learn more about how the human body processes the drugs used for transplant and how the body recovers after transplant. This research is meant to gain knowledge that may help people in the future and make transplants even more successful.

If you agree to provide blood samples, here is what will happen:

- We will collect two extra blood samples at the same time you have routine blood tests done. The amount of blood collected from you is about 6 teaspoons (31 ml) each time.

  We will collect blood samples at two times during the study:

  - First clinic visit after you join the study
  - Last clinic visit at the end of the study

- The blood samples will be sent to the BMT CTN Repository for processing and storage. A repository is a place that protects, stores and sends out samples for approved research studies.

All research samples will be given a bar code that cannot be linked to you by future researchers testing your samples.

- Materials stored in the Repository will be used mainly by clinicians and researchers in the BMT CTN network. In the future, the unused research samples and clinical data will be made available outside of this network.

- Researchers can apply to study the materials stored in the Repository. The BMT CTN Steering Committee and/or the BMT CTN Executive Committee must approve each request before they will share samples or information with researchers. This is to make sure that the investigators requesting the samples are qualified, and that the research is of high quality.

- DNA from your stored blood samples might be used in genome-wide association (GWA) studies for a future project either done or supported by the National Institutes of Health (NIH). Genome-wide association studies are a way for scientists to find genes that have a role in human disease or treatment. Each study can look at hundreds of thousands of genetic changes at the same time.

  If your coded samples are used in such a study, the researcher is required to add your test results and sample information into a shared, public research database. This public database is called the NIH Genotype and Phenotype Database and it is managed by the National Center for Biotechnology Information (NCBI). The NCBI will never have any information that would identify you, or link you to your information or research samples.

Some general things you should know about letting us store your blood samples for research are:

- We will only store samples from people who give us permission.

- Research is meant to gain knowledge that my help people in the future. You will not get any direct benefit from taking part. Additionally, you or your doctor will not be given results and they will not be added to your medical record.

- A possible risk is the loss of confidentiality about your medical information. We will use safety measures with both your samples and clinical information to make sure that your personal information will be kept private. The chance that this information will be given to someone else is extremely small.

- Your blood will be used only for research and will not be sold. The research done with your blood may help to develop new products in the future. You will not get paid for any samples or for any products that may be developed from current or future research.

You can change your mind at any time about allowing us to use your samples and health information for research.

We ask that you contact [Principal Investigator] in writing and let him/her know you do not want us to use your research samples or health information for research. His/her mailing address is on the first page of this form. However, samples and information that have already been shared with other researchers cannot be taken back or destroyed.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, please indicate your choice below. If you have any questions, please talk to your doctor or nurse, or call our research review board at _____.

No matter what you decide to do, it will not affect your care.

Statement of Consent for Research Samples

The purpose of storing blood samples, the procedures involved, and the risks and benefits have been explained to me. I have asked all the questions I have at this time and I have been told whom to contact if I have more questions. I have been told that I will be given a signed copy of this consent form to keep.

I understand that I do not have to allow the use of my blood for research. If I decide to not let you store research samples now or in the future, it will not affect my medical care in any way.

I voluntarily agree that my blood and information can be stored indefinitely by the BMT CTN and/or NHLBI Repositories for research to learn about, prevent, or treat health problems. I also understand that my DNA and health information may or may not be used in genome-wide association studies.

Blood

❑ I agree to allow my blood samples to be stored for research.

❑ I do not agree to allow my blood samples to be stored for research.

_____ _____

Signature Date

Health Insurance Portability and Accountability Act 1 (HIPAA3) Authorization to use and disclose individual health information for research purpose

A. Purpose:

As a research participant, I authorize the Principal Investigators and the researcher's staff to use and disclose my individual health information for the purpose of conducting the research study:

Continued, Long-Term Follow-Up and Lenalidomide Maintenance Therapy for Patients Who Have Enrolled on BMT CTN 0702

B. Individual Health Information to be Used or Disclosed:

My individual health information that may be used or disclosed to do this research includes:

- Demographic information (for example, date of birth, sex, weight)
- Medical history (for example, diagnosis, complications with prior treatment)
- Findings from physical exams
- Laboratory test results obtained at the time of work up and after transplant (for example, blood tests, biopsy results)

C. Parties Who May Disclose My Individual Health Information:

The researcher and the researcher's staff may collect my individual health information from:

[*List hospitals, clinics or providers from which health care information can be requested*].

D. Parties Who May Receive or Use My Individual Health Information:

The individual health information disclosed by parties listed in item c and information disclosed by me during the course of the research may be received and used by the following parties:

- Dr. Amrita Krishnan, Study Chairperson and staff/laboratories at City of Hope National Medical Center
- Dr. George Somlo, Study Chairperson and staff/laboratories at City of Hope National Medical Center

3 HIPAA is the Health Insurance Portability and Accountability Act of 1996, a federal law related to privacy of health information

- Dr. Edward Stadtmauer, Study Chairperson and staff/laboratories at University of Pennsylvania Cancer Center.

Study Sponsors

- National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI), both of the National Institutes of Health (NIH),
- Blood and Marrow Transplant Clinical Trials Network (BMT CTN) Data and Coordinating Center
- U.S. government agencies that are responsible for overseeing research such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP)
- U.S. government agencies that are responsible for overseeing public health concerns such as the Centers for Disease Control (CDC) and federal, state and local health departments
- Celgene (the manufacturer of lenalidomide)
- Biologics, Inc (the distributor of lenalidomide).

E. Right to Refuse to Sign this Authorization:

I do not have to sign this Authorization. If I decide not to sign the Authorization, I will not be allowed to participate in this study or receive any treatment related to research that is provided through the study.

My decision not to sign this authorization will not affect any other treatment, payment, or enrollment in health plans or eligibility for benefits.

F. Right to Revoke:

I can change my mind and withdraw this authorization at any time by sending a written notice to the Principal Investigator to inform the researcher of my decision.

If I withdraw this authorization, t he researcher may only use and disclose the protected health information already collected for this research study. No further health information about me will be collected by or disclosed to the researcher for this study.

G. Potential for Re-disclosure:

My individual health information disclosed under this authorization may be subject to re-disclosure outside the research study and no longer protected. Examples include potential

disclosures for law enforcement purposes, mandated reporting or abuse or neglect, judicial proceedings, health oversight activities and public health measures.

H. Genetic Information Nondiscrimination Act (GINA)

A new federal law (2009), called the Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and employers of 15 or more persons to discriminate against you based on your genetic information.

Health insurance companies and group health plans may not request your genetic information that we get from this research. This means that they must not use your genetic information when making decisions regarding insurability. Be aware that this new federal law will not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

I. This authorization does not have an expiration date.

TITLE: Continued, Long-Term Follow-Up and Lenalidomide Maintenance Therapy for Patients Who Have Enrolled on BMT CTN 0702

PROTOCOL NUMBER: BMT CTN #0702 Long-term Follow-Up Study

PRINCIPAL INVESTIGATOR:

Name:

Address:

Email:

Phone:

Fax:

I have read and understood this Consent Form. The nature and purpose of the research study has been explained to me.

- I have had the chance to ask questions, and understand the answers I have been given. I understand that I may ask questions at any time during the study.
- I freely agree to be a participant in the study.
- I understand that I may not directly benefit from taking part in the study.
- I understand that, while information gained during the study may be published, I will not be identified and my personal results will stay confidential.
- I have had the chance to discuss my participation in this research study with a family member or friend.
- I understand that I can leave this study at any time, and doing so will not affect my current care or prevent me from receiving future treatment.
- I understand that I will be given a copy of this signed consent form.

_____ _____

Participant Name Date

_____ _____

Signature Date

I certify that I have provided a verbal explanation of the details of the research study, including the procedures and risks. I believe the participant has understood the information provided.

_____ _____

Name of Counseling Physician Date

_____ _____

Signature of Counseling Physician Date

APPENDIX B

LENALIDOMIDE RISKS OF FETAL EXPOSURE, PREGNANCY TESTING GUIDELINES AND ACCEPTABLE BIRTH CONTROL METHODS

APPENDIX B

LENALIDOMIDE RISKS OF FETAL EXPOSURE, PREGNANCY TESTING GUIDELINES AND ACCEPTABLE BIRTH CONTROL METHODS

Risks Associated with Pregnancy
Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. The teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed.

The use of lenalidomide in pregnant females and nursing mothers has not been studied nor has the effect of the lenalidomide on human eggs and sperm. The risks to a fetus are not known. However, because lenalidomide is related to thalidomide, and thalidomide is known to cause severe birth defects, the following requirements must be observed.

Females of childbearing potential (FCBP)[†] must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual intercourse during the following time periods related to this study: 1) for at least 28 days before starting study drug; 2) while participating in the study; and, 3) for at least 28 days after discontinuation from the study. The two methods of reliable contraception must include one highly effective method (i.e. intrauterine device (IUD), hormonal [birth control pills, injections, or implants], tubal ligation, partner's vasectomy) and one additional effective (barrier) method (i.e. latex condom, diaphragm, cervical cap). FCBP must be referred to a qualified provider of contraceptive methods if needed.

Criteria for females of childbearing potential (FCBP)
This protocol defines a female of childbearing potential as a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Counseling
All counseling will be conducted through the Revlimid REMS® program.

For a female of childbearing potential, lenalidomide is contraindicated unless all of the following are met (i.e., all females of childbearing potential must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

[†] A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or, 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 28 days before starting study treatment, throughout the entire duration of study treatment, dose interruption and 28 days after the end of study treatment
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She understands the need to commence the study treatment as soon as study drug is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing based on the frequency outlined in this protocol
- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide

The investigator must ensure that for females of childbearing potential:

- Complies with the conditions for pregnancy risk minimization, including confirmation that she has an adequate level of understanding
- Acknowledge the aforementioned requirements

For a female NOT of childbearing potential, lenalidomide is contraindicated unless all of the following are met (i.e., all females NOT of childbearing potential must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide

Traces of lenalidomide have been found in semen. Male patients taking lenalidomide must meet the following conditions (i.e., all males must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a female of childbearing potential
- Understand the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a pregnant female or a female of childbearing potential.

<u>Contraception</u>

Females of childbearing potential (FCBP) enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual contact during the following time periods related to this study: 1) for at least 28 days before starting study drug; 2) while participating in the study; 3) during dose interruptions; and, 4) for at least 28 days after study treatment discontinuation.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. FCBP must be referred to a qualified provider of

contraceptive methods if needed. T he following are examples of highly effective and additional effective methods of contraception:

Highly effective methods:

- Intrauterine device (IUD)
- Hormonal (birth control pills, injections, implants)
- Tubal ligation
- Partner's vasectomy

Additional effective methods:

- Male condom
- Diaphragm
- Cervical Cap

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking lenalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception the patient should switch to one of the effective method listed above. The risk of venous thromboembolism continues for 4 to 6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia.

Pregnancy testing

Medically supervised pregnancy tests with a minimum sensitivity of 50 mIU/mL must be performed for females of childbearing potential, including females of childbearing potential who commit to complete abstinence, as outlined below.

Before starting study drug

Female Patients:

FCBP must have two negative pregnancy tests (minimum sensitivity of 50mIU/mL) prior to starting study drug. The first pregnancy test must be performed within 10 to 14 days prior to the start of study drug and the second pregnancy test must be performed within 24 hours prior to the start of study drug (prescriptions must be filled within 7 days as required by the Revlimid REMS® program). The patient may not receive study drug until the study doctor has verified that the results of these pregnancy tests are negative.

Male Patients:

Must practice complete abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during

dose interruptions and for at least 28 days following study drug discontinuation, even if he has undergone a successful vasectomy.

During study participation and for 28 days following study drug discontinuation

Female Patients:

- FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at study discontinuation, and at day 28 following study drug discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study discontinuation, and at days 14 and 28 following study drug discontinuation.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in a study patient, study drug must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a patient misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Study treatment must be discontinued during this evaluation.
- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after study drug discontinuation.

Male Patients:

- Counseling about the requirement for complete abstinence or condom use during sexual contact with a pregnant female or a female of childbearing potential and the potential risks of fetal exposure to lenalidomide must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in the partner of a male study patient during study participation, the investigator must be notified immediately.

<u>Additional precautions</u>

- Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to the study doctor at the end of treatment.
- Female patients should not donate blood during treatment and for at least 28 days following discontinuation of lenalidomide.
- Male patients should not donate blood, semen or sperm during treatment or for at least 28 days following discontinuation of lenalidomide.
- Only enough study drug for 28 days or one cycle of therapy (whichever is shorter) may be dispensed with each cycle of therapy.

APPENDIX C

REVLIMID REMS® PROGRAM

APPENDIX C

Revlimid Overview

Revlimid REMS® for Study Participants

Revlimid REMS® description:
A program that allows patients enrolled in authorized clinical trials access to free Revlimid® through the Revlimid REMS® program.

Access to the Revlimid REMS® Program:

1. **All physicians must be registered prescribers of Revlimid® in the Revlimid REMS® Program All clinical sites must have access to the Revlimid REMS® software to enroll patients in the Revlimid REMS® program**
   1) Prescriber submits Registration Form via fax or RevAssist® Online ***(RAO*** for Revlimid) to Celgene Customer Care.
   2) Prescriber is registered within 15 minutes.
   3) Registration confirmation fax is sent to prescriber's office via fax. (For RAO, the confirmation notification is displayed on the screen immediately)
   4) Starter Kit is sent to prescriber's office (overnight). The starter kit will contain the following:
      - Instructions For Prescribers
      - Patient Resource Packs
      - Guide to English and Non-English Materials
      - Computer software used to generate Patient-Physician Agreement Forms (PPAF)

2. **All studies must have an FDA letter of IND exemption or an active IND, active IRB approval and Celgene required regulatory documents.**

3. **Patients must sign the research specific IRB-approved informed consent and be enrolled in a Celgene-approved Medical Affairs clinical trial using Revlimid®**

4. **Celgene Customer Care Center must be contacted to confirm if a patient needs to be registered by calling 1-888-423-5436.**

5. **Patients must also sign the appropriate PPAF form and follow all the procedures of the Revlimid REMS® Program**
   1) Patient and Prescriber complete the PPAF together.
   2) The form is faxed to Celgene Customer Care or submitted electronically through ***RAO***.
   3) Patient is registered within 15 minutes.
   4) Confirmation fax is sent to prescribing office notifying them that the patient is now registered. For RAO, the confirmation notification is displayed on the screen immediately.

6. **Patients and prescribers must take the phone surveys as required by the Revlimid REMS® Program (The PPAF generated for the patient determines which phone survey**

questions will be asked.) An authorization number is provided at the completion of the phone survey, the authorization number should be noted on the prescription form.
Patient Survey requirements:

- For men: Do not need to call Celgene the first month but must call monthly starting the second month.
- For females of non - child bearing potential: Must call for the first month and then call every 6 months after.
- For females of child bearing potential: Must call for the first month and then every month after.

Prescribing Revlimid® in the Revlimid REMS® program

- Celgene Medical Affairs Operations will activate the study with Biologics upon receipt of all required regulatory documents.
- Biologics will not dispense or ship Revlimid® prior to Celgene's notification of activation.
- Prescription information MUST BE entered using **the BMT CTN 0702 Revlimid REMS® study specific electronic prescription form.** This form can be found on the BMT CTN SharePoint website (https://bmtctnsp.net)
- **An authorization number** must be on the prescription form at the time of faxing.
- Prescriptions for Revlimid® must be sent to Biologics Clinical Trial Division at the following FAX number: 919-256-0794
- Only a 28-day supply of Revlimid® may be provided per cycle sent to the actual address noted on the **Revlimid REMS® electronic prescription form.**
- **Biologics will verify the authorization number** and complete the patient counseling.

Protocol compliance and drug return

- Patients will be provided with instructions from Biologics with each new dispense on the procedures for return of any un-used Revlimid® capsules. (Patients will be instructed to call the 1-800 number to request a prepaid return envelope as per the commercial drug return procedures)
- Sites may request that patients maintain a diary and/or to bring their bottles in for a pill count at each visit in order to review "**patient compliance."** However, they are not responsible for "**drug accountability.**"

IMPORTANT INFORMATION ABOUT RevAssist®

- To avoid fetal exposure REVLIMID®(lenalidomide) is only available under a special restricted distribution program called Revlimid REMS®
- Only prescribers registered with Revlimid REMS® can prescribe REVLIMID®(lenalidomide)
- Only Revlimid REMS®contract pharmacies can dispense REVLIMID®(lenalidomide)
- In order to receive REVLIMID® (lenalidomide), patients must enroll in Revlimid REMS®and agree to comply with the requirements of the Revlimid REMS® program
- Information about REVLIM®(lenalidomide) and the Revlimid REMS® program can be obtained by calling the Celgene Customer Care Center toll-free at 1-888-423-5436, or at www. REVLIMID.com

How to Fill a REVLIMID® (lenalidomide) Prescription

1. Healthcare provider (HCP) instructs patient to complete patient survey
2. HCP completes survey
3. HCP completes patient prescription form
4. HCP obtains Revlimid REMS®authorization number
5. HCP provides authorization number on patient prescription form
6. HCP faxes form, including prescription
7. HCP advises patient that a representative from a Revlimid REMS® contract pharmacy will contact them
8. Revlimid REMS® contract pharmacy conducts patient education
9. Revlimid REMS® contract pharmacy calls for confirmation number
10. Revlimid REMS® contract pharmacy ships REVLIMID® to patient with the FDA-approved MEDICATION GUIDE

APPENDIX D

LENALIDOMIDE INFORMATION SHEET

APPENDIX D

LENALIDOMIDE INFORMATION SHEET

This information sheet is current as of June 24, 2009. A current information sheet will be given with your supply of lenalidomide. **FOR PATIENTS ENROLLED IN CLINICAL RESEARCH STUDIES**

Please read this Lenalidomide Information Sheet before you start taking lenalidomide and each time you get a new supply, since there may be new information. This Lenalidomide Information Sheet does not take the place of an informed consent to participate in clinical research or talking to your study doctor or healthcare provider about your medical condition or your treatment.

What is the most important information I should know about lenalidomide?

1. **Lenalidomide may cause birth defects (deformed babies) or death of an unborn baby.** Lenalidomide is similar to the medicine thalidomide. It is known thalidomide causes life-threatening birth defects. Lenalidomide has not been tested in pregnant women but may also cause birth defects.

   If you are a female who is able to become pregnant:

   - **Do not take lenalidomide if you are pregnant or plan to become pregnant**
     - for 28 days before starting lenalidomide
     - while taking lenalidomide
     - during dose interruptions of lenalidomide
     - for 28 days after stopping lenalidomide
   - **Stop taking lenalidomide if you become pregnant during lenalidomide treatment**
   - **Do not breastfeed while taking lenalidomide**
   - **You must have pregnancy testing done at the following times**
     - within 10 – 14 days and again 24 hours prior to the first dose of lenalidomide
     - weekly for the first 28 days
     - every 28 days after the first month or every 14 days if you have irregular menstrual periods
       - if you miss your period or have unusual menstrual bleeding
       - 28 days after the last dose of lenalidomide (14 and 28 days after the last dose if menstrual periods are irregular)
   - **You must practice complete abstinence or use two reliable, separate forms of effective birth control at the same time:**
     - for 28 days before starting lenalidomide
     - while taking lenalidomide

- during dose interruptions of lenalidomide
- and for 28 days after stopping lenalidomide

- Female partners of males taking lenalidomide should be advised to call their own physician right away if they get pregnant.
- Study doctors, healthcare providers and patients should report all cases of pregnancy to the National Cancer Institute and the pharmaceutical collaborator, Celgene Corporation at 1-888-423-5436.

If you are a male:
It is not known if lenalidomide passes into semen.

- Male patients, including those who have had a vasectomy, must use a latex condom during sexual intercourse with a pregnant female or a female that can become pregnant:
  - While you are taking lenalidomide
  - for 28 days after you stop taking lenalidomide
- **Male patients should not donate sperm or semen** while taking lenalidomide and for 28 days after stopping lenalidomide.

2. **Lenalidomide may cause a reduction in the number of white blood cells and platelets.** This can lead to increased risk of infection and bleeding. You may need a blood transfusion or certain medicines if your blood counts drop too low. You will have blood tests done as part of the clinical research trial in which you are participating. This is discussed in the informed consent document.

3. **Lenalidomide may cause an increased chance for blood clots in the veins and in the lungs.** Call your study doctor or get emergency medical care right away if you get the following signs or symptoms:
   - shortness of breath
   - chest pain
   - arm or leg swelling

4. **Lenalidomide restrictions in sharing lenalidomide and donating blood:**

- **Do not share lenalidomide with other people**
- **Do not give blood** while you take lenalidomide and for 28 days after stopping lenalidomide
- You will get no more than a 28-day supply of lenalidomide at one time

Additional information is provided in the informed consent form and you can ask your study doctor for more information.

APPENDIX E

RESEARCH SAMPLES

OPTIONAL **RESEARCH SPECIMENS**

Patients consenting to the optional future research will have blood samples collected for future research supporting this protocol. All research sample aliquots will be given unique bar code designations that cannot be linked back to the participant's name or other identifying information. Laboratory test results, clinical information, etc., associated with the coded samples are provided to the Investigator only after completion of the protocol. Samples sent to researchers cannot be linked with any remaining samples at the repository.

Patient samples will be collected both prior to the initiation of long-term follow-up and at disease progression. All research samples will be collected and shipped same-day to the BMT CTN Repository for processing and sample aliquot storage. Sample collection and shipping procedures are detailed in the BMT CTN 0702 Long-Term Follow-Up Laboratory Sample Guide.

Under current guidelines of the BMT CTN, any request to utilize samples from the biorepository is first reviewed by the protocol team. Upon approval, the request is then reviewed by the BMT CTN Biomarkers Committee, which advises the Executive or Steering Committee. Following approval by these boards, samples are then released from the BMT CTN biorepository.

	Type of Sample	Type of Processing	Dates Samples Obtained	Shipping Specifications	Storage Location
Patient Research Peripheral Blood Specimen (Serum)	6 mL peripheral blood	Collect blood sample in a Red/Gray Top BD SST™ Tube with Silica Clot Activator & Polymer Gel. Let sample sit upright in rack for 30 minutes. Centrifuge for 10 minutes. Gel barrier will form separating the serum specimen from clot. Prepare tube for transport along with other research samples.	Prior to initiation of long-term follow-up and at disease progression.	Serum blood tube will be shipped at ambient temperature on the day of collection, to the BMT CTN Research Repository by priority overnight FED EX delivery for processing and final frozen storage of serum aliquots. Guidelines for specimen handling and shipment to the BMT CTN Central Processing Laboratory/BMT CTN Research Repository are detailed in the 0702 Long-Term Follow-Up Laboratory Sample Guide	BMT CTN Research Repository
Patient Research Peripheral Blood Specimen (Plasma)	5 mL peripheral blood	Collect blood sample in a 5 mL fill, white top plastic Greiner Vacuette ® PST tube. Gently mix sample with EDTA by inverting the tube 8-10 times. Centrifuge for 10 minutes. Gel barrier will form separating the plasma specimen from cells. Prepare tube for transport along with other research samples.	Prior to initiation of long-term follow-up and at disease progression..	Plasma blood tube will be shipped at ambient temperature on the day of collection, to the BMT CTN Research Repository by priority overnight FED EX delivery for processing and final frozen storage of serum aliquots. Guidelines for specimen handling and shipment to the BMT CTN Central Processing Laboratory/ Research Repository is detailed in the 0702 Long-TermFollow-Up Laboratory Sample Guide	BMT CTN Research Repository

	Type of Sample	Type of Processing	Dates Samples Obtained	Shipping Specifications	Storage Location
Patient Research Peripheral Blood Specimen (PBMC)	20 mL peripheral blood	Collect peripheral blood sample in two 10 mL fill, green top plastic BD Vacutainer® tube, containing Sodium-Heparin anticoagulant. Gently mix sample by inversion 8-10 times to mix sample well with heparin anticoagulant. No additional sample processing is required.	Prior to initiation of long-term follow-up therapy and at disease progression.	Peripheral blood tubes will be shipped at ambient temperature on the day of collection, to the BMT CTN Research Repository by priority overnight FED EX delivery for processing and final frozen storage of isolated viable PBMC aliquots. Guidelines for specimen handling and shipment to the BMT CTN Central Processing Laboratory/BMT CTN Research Repository is detailed in the 0702 Long-Term Follow-Up Laboratory Sample Guide	BMT CTN Research Repository

APPENDIX F

ADVERSE EVENTS

APPENDIX F

ADVERSE EVENTS

Selected expected serious AEs (Table F-1) and grade 3-5 unexpected AEs according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 require expedited reporting with an Individual Case Safety Report (ICSR) through completion of the Adverse Event Forms. Additionally, selected AEs of interest (Table F-2) will require expedited reporting through an ICSR, if they fulfill serious criteria and occur after the administration of lenalidomide. Refer to Chapter 4 regarding reporting of SPMs and other reporting requirements.

TABLE F-1: SERIOUS ADVERSE EVENTS THAT REQUIRE EXPEDITED REPORTING BY INDIVIDUAL CASE SAFETY REPORTS (ICSR)[1]

Adverse Event	Seriousness or Capture Method[1]	Collection Form
ALLERGY/IMMUNOLOGY		
Anaphylactic reaction	SAE	ICSR
CARDIAC		
Asystole	SAE	ICSR
Atrial Ventricular Block	SAE	ICSR
Congestive Heart Failure	SAE	ICSR
Myocardial Infarction	SAE	ICSR
Pericarditis	SAE	ICSR
Pericardial disease	SAE	ICSR
Pericardial effusion (including tamponade)	SAE	ICSR
Prolongation of QTc interval	SAE	ICSR
Sinus Bradycardia	SAE	ICSR
Supraventricular Tachycardia	SAE	ICSR
Ventricular Tachycardia	SAE	ICSR
Pulmonary hypertension	SAE	ICSR
COAGULATION		
Disseminate intravascular coagulation (DIC)	SAE	ICSR
DERMATOLOGY		
Erythema multiforme (toxic epidermal necrolysis)	SAE	ICSR
Sweet's Syndrome (acute neutrophilic dermatosis)	SAE	ICSR

Adverse Event	Seriousness or Capture Method[1]	Collection Form
Pyoderma gandrenosum	SAE	ICSR
Vasculitis	SAE	ICSR
ENDOCRINE		
Hyperthyroidism	SAE	ICSR
GASTROINTESTINAL		
Ileus (functional obstruction of bowel, i.e., neuroconstipation)	SAE	ICSR
GI Perforation	SAE	ICSR
Diverticulitis	SAE	ICSR
Ischemic bowel	SAE	ICSR
HEMORRHAGE		
Central Nervous system	SAE	ICSR
HEPATOBILIARY/PANCREAS		
Liver dysfunction/failure (Clinical - CTCAE)	SAE	ICSR
Pancreatitis	SAE	ICSR
NEUROLOGY		
Neurology – Peripheral neuropathy	SAE	ICSR
Neuropathy: Motor	SAE	ICSR
Neuropathy: Sensory	SAE	ICSR
Syncope (fainting)[2]	SAE	ICSR
CNS ischemia	SAE	ICSR
Coma	SAE	ICSR
Cranial palsy	SAE	ICSR
Seizure	SAE	ICSR
Spinal cord compression	SAE	ICSR
Brain Edema	SAE	ICSR
Encephalopathy	SAE	ICSR
Leukoencephalopathy syndrome including reversible posterior leukoencephalopathy syndrome [RPLS]) or (Leukoencephalopathy radiographic findings)	SAE	ICSR
PULMONARY/UPPER RESPIRATORY		
Acute Respiratory Distress Syndrome	SAE	ICSR
Alveolar Hemorrhage	SAE	ICSR
Pleural effusion (non-malignant)	SAE	ICSR
Pneumonitis/Pulmonary Infiltrates (absence of infection)	SAE	ICSR
Pulmonary Hypertension	SAE	ICSR

Adverse Event	Seriousness or Capture Method[1]	Collection Form
RENAL/GENITOURINARY		
Renal failure	SAE	ICSR
SYNDROMES		
Tumor flare	SAE	ICSR
Tumor lysis syndrome	SAE	ICSR
VASCULAR		
Acute vascular leak syndrome	SAE	ICSR
DEATH		
Sudden death	SAE	ICSR
OTHER		
Second malignancies	SAE	ICSR

[1] Serious Adverse events are defined by the 21 CFR (312.32a): AE that results in death, requires hospitalization, persistent or significant disability or incapacity, congenital anomaly, that is life threatening or considered as medically important.

TABLE F-2: EXPECTED ADVERSE EVENTS OF INTEREST THAT WILL REQUIRE EXPEDITED REPORTING IF THEY MEET SERIOUS ADVERSE EVENT CRITERIA AND OCCUR AFTER THE INITIATION OF LENALIDOMIDE AND THROUGH 28 DAYS AFTER THE DISCONTINUATION OF LENALIDOMIDE

Adverse Event	Seriousness or Capture Method[1]	Collection Form
AUDITORY/EAR		
Hearing loss	SAE	ICSR
CARDIAC		
Atrial fibrillation	SAE	ICSR
Atrial flutter	SAE	ICSR
COAGULATION		
Deep vein thrombosis	SAE	ICSR
Pulmonary emboli[3]	SAE	ICSR
HEMORRHAGE		
Hemorrhage, Gastrointestinal	SAE	ICSR
Hemorrhage, Pulmonary	SAE	ICSR
METABOLIC/LABORATORY		
Elevation of ALT ≥ 2.5x ULN	SAE	ICSR
Elevation of AST ≥2.5x ULN	SAE	ICSR
Elevation of Bilirubin ≥ 3x ULN	SAE	ICSR
MUSCULOSCELETAL/SOFT TISSUE		
Muscular weakness	SAE	ICSR
NEUROLOGY		
Neurology – Peripheral neuropathy	SAE	ICSR

Adverse Event	Seriousness or Capture Method[1]	Collection Form
Neuropathy: Motor	SAE	ICSR
Neuropathy: Sensory	SAE	ICSR
Syncope (fainting)	SAE	ICSR
OCULAR/VISUAL		
Vision – Blurred vision	SAE	ICSR
PAIN		
Pain – Neuralgia	SAE	ICSR
INFECTION		
Febrile neutropenia	SAE	ICSR
DEATH		
Sudden death	SAE	ICSR
OTHER		
Second malignancies	SAE	ICSR

[1] Serious Adverse events as defined by the 21 CFR (312.32a): AE that results in death, requires hospitalization, persistent or significant disability or incapacity, congenital anomaly, that is life threatening or considered as medically important.

APPENDIX G

REFERENCES

APPENDIX G

REFERENCES

[1] Boccadoro M, Cavallo F, Gay FM, Raimondo FD, Nagler A, Montefusco V *et al.* Melphalan/prednisone/lenalidomide (MPR) versus high-dose melphalan and autologous transplantation (MEL200) plus lenalidomide maintenance or no maintenance in newly diagnosed multiple myeloma (MM) patients. *Journal of Clinical Oncology* 2013; 31(suppl:8509a).

[2] McCarthy PL, Owzar K, Hofmeister CC, Hurd DD, Hassoun H, Richardson PG *et al.* Lenalidomide after stem-cell transplantation for multiple myeloma. *The New England journal of medicine* 2012; 366(19): 1770-81.

[3] Attal M, Lauwers-Cances V, Marit G, Caillot D, Moreau P, Facon T *et al.* Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. *The New England journal of medicine* 2012; 366(19): 1782-91.

[4] McCarthy P, Owzar K, Hofmeister CC, Richardson PG, Hassoun H, Stadtmauer EA *et al.* Analysis of Overall Survival (OS) in the Context of Cross-Over from Placebo to Lenalidomide and the Incidence of Second Primary Malignancies (SPM) in the Phase III Study of Lenalidomide Versus Placebo Maintenance Therapy Following Autologous Stem Cell Transplant (ASCT) for Multiple Myeloma (MM) CALGB (Alliance) ECOG BMTCTN. *Clinical Lymphoma Myeloma and Leukemia* 2013; 13(Supplement 1): S28,S15-5.

[5] Singh PP, Kumar S, LaPlant BR, Gertz MA, Dispenzieri A, Leif Bergsagel P *et al.* Lenalidomide Maintenance Therapy In Multiple Myeloma: A Meta-Analysis Of Randomized Trials. *Blood* 2013; 407a.

[6] Palumbo A, Gay F, Spencer A, Raimondo FD, Zdenek A, Larocca A *et al.* A phase III study of ASCT vs cyclophosphamide-lenalidomide-dexamethasone and lenalidomide-prednisone maintenance vs lenalidomide alone in newly diagnosed myeloma patients. *Blood* 2013; 763a.

[7] Attal M, Lauwers-Cances V, Marit G, Caillot D, Facon T, Hulin C *et al.* Lenalidomide Maintenance After Stem-Cell Transplantation For Multiple Myeloma: Follow-Up Analysis Of The IFM 2005-02 Trial. *Blood* 2013; 406a.

[8] Palumbo A, Bringhen S, Rajkumar SV, Lupparelli G, Usmani S, Waage A *et al.* Second primary malignancies (SPM) in newly diagnosed myeloma (MM) patients treated with lenalidomide (Len): Meta-analysis of 6,383 individual patient data (IPD). *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2013; 31(suppl; abstr 8517).

[9] Mailankody S, Pfeiffer RM, Kristinsson SY, Korde N, Bjorkholm M, Goldin LR *et al.* Risk of acute myeloid leukemia and myelodysplastic syndromes after multiple myeloma and its precursor disease (MGUS). *Blood* 2011; 118(15): 4086-92.