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Phase II Trial of Daratumumab for Transplant-Eligible Multiple Myeloma Patients

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Mayo Clinic Cancer Center

MC1785: Phase II Trial of Daratumumab for Transplant-Eligible Multiple Myeloma Patients

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√Study contributor(s) not responsible for patient care

Drug Availability
Commercial Agents: Daratumumab, Lenalidomide
Drug Company Supplied: None

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Amendment 9	Pending

Protocol Resources

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*No waivers of eligibility

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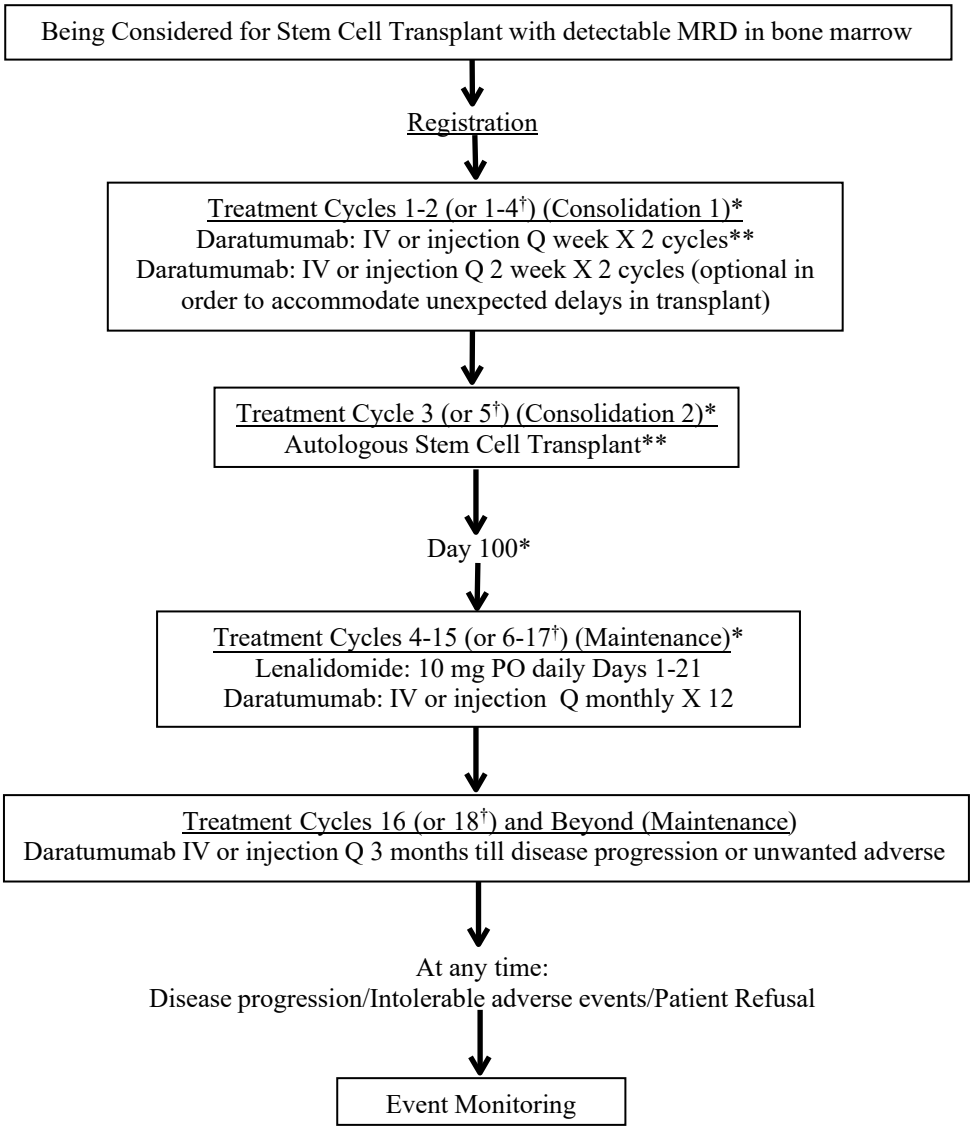
Study Schema



If a patient is deemed ineligible or a cancel, please refer to Section 13 for follow-up information.

*MRD Assessment (Day 100 or before the start of Maintenance if patient receives optional consolidation treatments) :
Peripheral Blood (Next Generation Sequencing; NGS): Prior to cycle 1, 3 (or 5 in case cycles 3 and 4 given), at Day 100, prior to cycle 8, 12, 16, 18, 20 (or cycle 10, 14, 18, 20, 22 in case cycles 3 and 4 given)
Bone Marrow (Multiparameter Flow Cytometry; MPF and NGS): Prior to cycle 1, 3 (or 5 in case cycles 3 and 4 given), at Day 100, prior to cycle 16 (or 18 in case cycles 3 and 4 given)

****Cycle 1 (to 3, as the case may be for that patient)** = 28 days (4 weeks)
Cycle 2 (or 4, as the case may be for that patient) = Up to 84 days (4 weeks treatment + window period up to 8 weeks between Consolidation 1 and ASCT)
Cycle 3 =Up to 124 days (Day 100 visit of ASCT occurs 90-110 days after ASCT + window period up to 14 days between Day 100 visit and start of Maintenance)
Cycles 4-15 (or 6-17, as the case may be for that patient) = 28 days (4 weeks)
Cycles 16 and beyond (or 18 and beyond as the case may be) = 90 days (3 months)
†In case patient given cycle 3 and 4 optional treatment in consolidation 1, the subsequent cycle numbers will be adjusted accordingly.

Confirmation of PD is not required. However, treatment may be discontinued for progressive disease that is unconfirmed per physician discretion. In this case, an objective status of PD should be entered on the measurement form and progressive disease should be reported on the event monitoring form.

Generic name: Daratumumab Brand name(s): Darzalex® Mayo Abbreviation: Dara Availability: Commercial	Generic name: Lenalidomide Brand name(s): Revlimid® Mayo Abbreviation: REVLIMID Availability: Commercial

1.0 Background

1.1 Multiple Myeloma

Multiple myeloma (MM) is a malignant disorder of the plasma cells, characterized by uncontrolled and progressive proliferation of a plasma cell clone. The disease leads to progressive morbidity and eventual mortality by lowering resistance to infection and causing significant skeletal destruction (with bone pain, pathological fractures, and hypercalcemia), anemia, renal failure, neurological complications and hyper viscosity syndrome.

The majority of patients with MM produce a monoclonal protein, also called paraprotein, M-protein or M-component, which is an immunoglobulin (Ig) or a fragment of one that has lost its function.[1,2] Normal immunoglobulin levels are compromised, leading to susceptibility of infections. The proliferating MM cells displace the normal bone marrow leading to dysfunction in normal hematopoietic tissue and destruction of the normal bone marrow architecture, which is reflected by clinical findings such as anemia, paraprotein in serum or urine, and bone resorption seen as diffuse osteoporosis or lytic lesions shown in radiographs.[3] Furthermore, hypercalcemia, renal insufficiency or failure, and neurological complications are frequently seen.[4] A small minority of patients with MM are non-secretory.

At the time of diagnosis, multiple myeloma is a heterogeneous disease, with a course that varies on the basis of both disease- and host-related factors (e.g., age, renal function, stage, chromosomal abnormalities). Multiple myeloma causes significant morbidity and mortality. It accounts for approximately 1% of all malignancies and 13% of hematologic cancers. Approximately 50,000 patients per year are diagnosed with multiple myeloma in the EU and US, and 30,000 patients per year die due to multiple myeloma.

1.2 Treatment for Multiple Myeloma

Treatment choices for MM vary with age, performance status, comorbidity, the aggressiveness of the disease, and related prognostic factors.[5] Newly diagnosed patients with MM are typically categorized into 2 subpopulations usually defined by their age and suitability for the subsequent approach to treatment. Younger patients will typically receive an induction regimen followed by consolidation treatment with high-dose chemotherapy and autologous stem cell transplantation (ASCT). For those not considered suitable for high-dose chemotherapy and ASCT, longer-term treatment with multi-agent combinations including alkylators, high-dose steroids, and novel agents are currently considered as standards of care.

Over the past few years several novel treatments (immunomodulatory drugs; IMiDs and proteasome inhibitors) have become available for patients with MM. Although higher percentages of patients are achieving remission, all patients eventually relapse and become resistant to therapy. Novel agents and new combinations regimens are needed for improved outcome in this disease. There is an increasing body of evidence suggesting that clinical or laboratory parameters may be important in selecting specific treatment options for patients with MM.[5] This is further important since the novel agents being used for the treatment of MM have their own inherent side effect profiles that are unique and need specific management as against the more expected adverse events from conventional chemotherapeutic agents. This is especially true in elderly patients who may

have other comorbidities, since the median age at diagnosis for MM is 70 years. Thus, there is a constant need to develop newer, better-tolerated agents/regimens that can keep the disease controlled for prolonged durations as well as be safe with respect to low cumulative toxicities.

1.3 Role of Daratumumab in Multiple Myeloma

Daratumumab is an immunoglobulin G1 kappa (IgG1k) human monoclonal antibody (mAb) that binds to a unique CD38 epitope on CD38-expressing cells with high affinity. It was developed by the immunization of human immunoglobulin transgenic mice with recombinant CD38 protein.[6] CD38 is a 46-kDa type II transmembrane glycoprotein that is highly expressed on MM cells.[7] CD38 has various mechanisms including ectoenzymatic activity, receptor-mediated regulation of cell adhesion and signal transduction.[8] Preclinical studies have shown that daratumumab induces MM cell death through several mechanisms, including complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and FcR mediated-crosslinking inducing apoptosis.[6] In a combined analysis of GEN501 and SIRIUS studies including 148 patients, the Overall Response Rate (ORR) was 31 %, and at a median follow-up of 14.8 months, the estimated Overall Survival (OS) was 19.9 months.[9] These trials demonstrated that daratumumab is active as monotherapy in patients with heavily pre-treated and relapsed/refractory myeloma (RRMM) alongside maintaining its anti-myeloma activity in previously treatment refractory patients as evident by ORR 33 and 29.7 % in GEN501and SIRIUS, respectively.[9] Preclinical studies have shown that Daratumumab in combination with other agents enhances the antimyeloma activity and now there are reported multiple phase II /III trials to study the same. These include data from the CASTOR and POLLUX trials of the combination of daratumumab and dexamethasone with bortezomib and lenalidomide, respectively, showing enhanced efficacy of these regimens in patients with early relapsed MM (2^{nd} or 3^{rd} line) and low minimal residual disease (MRD) states leading to the FDA approval of these regimens.[10,11]

1.4 Role of ASCT and Post-ASCT Maintenance Therapy in Multiple Myeloma

ASCT is the standard of care in transplant-eligible MM patients based on several phase III trials and meta-analyses depicting significant improvement in progression free Survival (PFS), CR, and OS.[12] Attal et al in IFM-90 trial reported superior outcomes of high-dose chemotherapy (HDC) followed by ASCT compared to conventional chemotherapy alone, with improved OS (57%), CR (22%) and event-free survival (EFS) (16%), and median OS 57 months versus 44 months.[13] The majority of post-ASCT patients relapse with median PFS around 36 months. Relapses are harder to treat and prognosis gets worse with each relapse. Multiple studies have suggested a survival advantage from attaining a deeper response to induction chemotherapy and ASCT, and sustained CR was shown to be a surrogate for OS in MM population.[13,14] The clinical significance of MRD negativity using highly sensitive methods has been reviewed and goal of MRD is to stratify the risk and evaluate the response to novel agents.[15] Despite remarkable improvement in treatment outcome in MM with the use of IMiDs and novel agents, it remains an incurable disease. Multiple studies in the last few years have examined the role of consolidation and/or maintenance to eliminate MRD after HDC-ASCT in MM. Post-ASCT consolidation and/or maintenance strategies have been studied in multiple trials including single and combination agents including interferon-alpha,

glucocorticoids, thalidomide, lenalidomide, bortezomib and combination regimens to determine compare PFS and OS to improve long term outcomes.[16]

1.5 Minimal Residual Disease (MRD) in Multiple Myeloma

CR is defined as disappearance of clonal plasma cells in the bone marrow, and absence of paraprotein in urine and serum by immunofixation. Stringent CR (sCR) as defined by International Myeloma Workshop includes above mentioned paramenters along with a normal kappa/lambda free light chain ratio.[17] Molecular CR (mCR) defined as absence of detectable disease by polymerase chain reaction (PCR) for Ig gene rearrangement was associated with prolonged PFS and OS in allogeneic transplant patients and this extent of response was not achieved in autologous transplant patients.[17] With the use of novel therapies, there was necessity to develop sensitive assays to detect and monitor MRD that will have prognostic implication in PFS and OS to compare between different consolidation and/or maintenance agents. Various methods include allele-specific oligonucleotide PCR (ASO-PCR), next-generation sequencing (NGS) and multiparameter flow cytometry (MPF) capable of detecting 1 clonal cell in 10^6 and 1 clonal cell in 10^4 normal cells, respectively.[17] In a study of 102 MM patients, a comparison of CR detection by negative immunofixation (CR), normal serum free light chain ratio (sCR), and undetectable myeloma cells by MPF (immunophenotyping CR-iCR) treated with novel agents showed that 43% patients achieved CR, 30% achieved sCR, and 30% achieved iCR. Patients in iCR showed significantly improved PFS and TTP as compared to sCR versus CR with no significant survival difference between sCR versus CR patients.[18] In this study ASO-PCR and MPF were able to detect MRD in 17 and 11 patients, respectively. PFS for those patients without versus with MRD detected by ASO-PCR was 34 versus 15 months, respectively (P=.04) and by MPF was 27 versus 10 months, respectively (P=.05). In order to predict unsustained CR, a study was conducted in 241 patients in CR at Day-100 after ASCT.[19] It was found that presence of baseline high-risk cytogenetics by fluorescent in situ hybridization (HR 17.3; P<.01), and persistent MRD by MPF at day-100 after ASCT (HR 8.0; P<.01) were the only independent factors that predicted for unsustained CR and a poor outcome with a median OS of 39 months. Another study assessed MRD using MPF in post-induction and at day-100 post SCT as well as post-induction in transplant ineligible patients.[20] This study demonstrates clinical utility of MPF as the patients with MRD had inferior outcomes as compared to those without detectable MRD. The same study also showed that maintenance therapy benefits the patients with MRD negativity and also can convert patients to MRD negative status. MRD may serve as a biomarker to inform MM therapy and MRD negativity becomes a goal of future studies.

1.6 Rationale of Daratumumab as a Consolidation Therapy before SCT and Maintenance Therapy in Post-SCT Settings for MRD Assessment

Our primary endpoint is to determine the percentage of patients with MRD negativity at Day 100 post SCT and at post-maintenance treatment for 1 year. Phase II multicenter single arm study was conducted in 10 IFM centers in France in 2009 to evaluate response after lenalidomide, bortezomib and dexamethasone (RVD) induction followed by SCT followed by 2 RVD consolidations and 1-year lenalidomide maintenance in 31 untreated transplant eligible MM patients.[21] At the time of consolidation, 97% achieved PR, 87% at least VGPR, including 50% who achieved CR and among 26 evaluable patients, 15 (58%) were MRD negative. They evaluated MRD by bone marrow aspirate at post-induction/pre-ASCT, post-ASCT, post-consolidation and end of treatment regardless of

response. With lenalidomide, 5 patients experienced MRD improvement and after all treatment sequences, 21 patients (68%) achieved MRD negativity. Overall, there were high response rates and depth of response increased over the course of the transplantation program. Rate of VGPR increased from 58% after induction to 70% and 87% after transplant and consolidation, respectively. 1-year lenalidomide maintenance further improved MRD negativity. 3-year PFS was 100% for MRD negative patients. Further studies evaluated that MRD negativity is a major prognostic factor for clinical outcome and MRD negativity should be the goal for treatment of ASCT eligible patients in MM.[21-24] Another study was conducted in 241 MM patients in 2 PETHEMA/GEM trials, GEM2000 (VBMCP [vincristine, carmustine, doxorubicin and dexamethasone followed by HDT/SCT and 2-year IFN and prednisone maintenance; n=140) and GEM-2005 <65 y (randomized induction with the same chemotherapy plus bortezomib in the last 2 cycles or thalidomide/dexamethasone or bortezomib/thalidomide/dexamethasone followed by HDT/SCT and 3-year maintenance with IF-2alphab or thalidomide or thalidomide/bortezomib; n= 101).[19] TTP (median 71 months) and OS (71% at 5 years) were longer in CR patients than in less than CR patients at Day-100 after HDT/SCT (TTP; median 47 months and OS: 60% at 5 years). Multivariate analysis showed that the best predictive parameters for TTP were immunophenotypic CR status (MRD by MFC) and FISH cytogenetics. 16% of CR patients had high-risk disease and showed a significantly inferior TTP (3 years, 40% vs. 80%) and borderline OS (3 years, 73% vs. 96%) compared with standard risk patients. Persistent MRD in 87 (36%) out of 241 CR patients showed significantly inferior TTP (3 years 58% vs. 86%) and OS (3 years 80% vs. 90%). They further explored clinical impact of the immunophenotypic CR in standard and high-risk disease. Best prognosis was for patients with both standard-risk cytogenetics and achievement of immunophenotypic CR (3 years: TTP 94%, OS 100%), whereas worse outcome occurred in both high-risk disease and persistent MRD (3 years: TTP 0%, OS 32%). Of 241 patients, 29 (12%) were in unsustained CR within 1 year had persistent MRD by MFC (66% vs. 32%) as compared with the remaining patients.

1.7 Trial Design

This will be a phase II, open label, prospective clinical trial in MM patients with any induction treatment, who are considered eligible for an SCT and have detectable MRD. So far there have not been any clinical trials to determine the effect of daratumumab on MRD as a consolidation therapy in pre-ASCT setting and as maintenance therapy in post-ASCT setting. The reason to include patients with MM who have received any induction is that the aim of this trial is to assess the efficacy of daratumumab in the pre- and post-ASCT settings in improving the MRD-status of patients. Treatment dose in the maintenance portion (daratumumab+lenalidomide) will be fixed based on other prior clinical trials using this combination.

2.0 Goals

2.1 Primary Objective:

To determine the percentage of patients achieving MRD negativity by MPF after autologous stem cell transplant (SCT) (at Day 100) using pre-SCT daratumumab consolidation.

2.2 Secondary Objectives:

2.21 To determine percentage of patients achieving MRD negativity by MPF after 1 year of daratumumab+lenalidomide-based maintenance therapy.

2.22 To determine progression-free survival (PFS) for peri-SCT treatment with daratumumab.

2.23 To determine percentage of MRD negativity by MPF after pre-SCT consolidation with daratumumab.

2.24 To determine safety profile of peri-SCT daratumumab with lenalidomide.

2.25 To determine the overall response rate (ORR) of patients receiving peri-SCT daratumumab for MM.

2.26 To determine the overall survival (OS) for patients receiving peri-SCT daratumumab for MM.

3.0 Patient Eligibility

3.1 Inclusion Criteria

3.11 Age ≥18 years and considered transplant eligible.

3.12 Diagnosis: Pathologically confirmed diagnosis of multiple myeloma who are transplant eligible and have received any prior induction therapy (with or without maintenance).

3.13 Measurable MRD in bone marrow within 28 days prior to registration (MPF method)

3.14 ECOG Performance Status (PS) 0, 1, or 2 (Appendix I) at registration.

3.15 The following laboratory values obtained ≤14 days prior to registration:

- Absolute neutrophil count (ANC) ≥1,000 cell/mm^3 without growth factor support
- Platelets ≥50,000 cells/mm^3 for patients who have bone marrow plasmacytosis <50% or ≥30,000 cells/mm^3 for patients who have bone marrow plasmacytosis of ≥50%
- Calculated or measured creatinine clearance ≥30 ml/min (see Appendix II)
- Total bilirubin ≤1.5 x upper limit of normal (ULN) unless due to Gilbert's syndrome, in which case the direct bilirubin must be ≤1.5 X ULN.
- Aspartate aminotransferase (AST)/SGOT and alanine aminotransferase (ALT)/SGPT ≤3 x ULN
- PT/INR ≤1.5 X ULN
- Negative Urine or serum pregnancy test for women of childbearing potential. NOTE: Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program.

3.16 Provide informed written consent.

3.17 Measureable disease of multiple myeloma as defined in section 11.1 at the time specified by one of the following:

- If no relapse prior to transplant, values obtained at the time of diagnosis
- If disease relapse prior to transplant and the patient did not have treatment for the relapsed disease prior to transplant, the values obtained at the time of relapse immediately prior to the transplant.
- If disease relapse prior to transplant and the patient did have treatment for the relapsed disease prior to transplant, the values obtained prior to this therapy, ie, the time of relapse.

3.2 Exclusion Criteria

3.21 Any previous ASCT for MM. **EXCEPTION**: Patient had autologous stem cell transplant > 3 years ago without any related adverse events. (**NOTE**: Patient may have had prior stem cell collection before registration on the study)

3.22 Any prior therapy with daratumumab

3.23 Non-secretory MM or known AL amyloidosis

3.24 Clinically significant active infection requiring intravenous antibiotics (≤14 days prior to registration).

3.25 ≥Grade 3 neuropathy and/or POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes).

3.26 Other prior malignancy.
EXCEPTIONS:
- Adequately treated basal cell or squamous cell skin cancer
- Any *in situ* cancer
- Adequately treated Stage I or II cancer from which the patient is currently in complete remission, or
- Any other cancer from which the patient has been disease free for at least three years

3.27 Concurrent therapy considered investigational.
NOTE: Patients must not be planning to receive any radiation therapy (except localized radiation for palliative care that must be completed prior to starting Cycle 1, Day 1).

3.28 Any of the following because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown:
- Pregnant women
- Nursing women (lactating females are eligible provided that they agree not to breast feed while taking lenalidomide)
- Men or women of childbearing potential who are unwilling to employ adequate contraception

3.29a Major surgery ≤4 weeks prior to registration.

3.29b History of stroke/intracranial hemorrhage ≤6 months prior to registration.

3.29c Clinically significant cardiac illness including New York Heart Association (NYHA) Class III or Class IV heart failure (Appendix III), unstable angina pectoris, myocardial infarction within the past 6 months, or ≥Grade 3 cardiac arrhythmias noted ≤ 14 days prior to registration.

3.29d Known HIV+ patients

3.29e Known Hepatitis B or Hepatitis C infection.

3.29f Exhibiting clinical signs of meningeal involvement of multiple myeloma.

3.29g Known severe chronic obstructive pulmonary disease or asthma defined as forced expiratory volume (FEV1) in 1 second less than <60% of expected.

4.0 Test Schedule

4.1 Test schedule[a]

Tests and Procedures	≤28 days prior to registration	≤14 days prior to registration	Cycle 1, Day 1	Cycle 1, Day 15	Cycle 2 (to 4†), Day 1	Cycle 2 (or 4†): ≤14 days prior to ASCT	Cycle 3 (or 5†): Day 100 visit of ASCT (occurs 90-110 days after ASCT)	Cycle 4 (or 6‡) and beyond (end of each cycle)	End of Treatment
Complete medical and disease history		X			X	X	X	X	
Physical examination[b]		X			X	X	X	X	
Electrocardiogram (ECG)		X							
Performance status (ECOG scale)(Appendix 1)		X			X	X	X	X	
CBC with differential		X	X[c]	X	X	X	X	X	X
Type and Screen			X						
Prothrombin time (PT) and INR		X	X[c]	X	X	X	X		
Blood chemistries: sodium, chloride, potassium, magnesium, phosphate, uric acid, BUN, glucose, ALT/AST (SGPT/SGOT), alkaline phosphatase, total protein, Direct bilirubin, total bilirubin, albumin, serum creatinine, and estimated creatinine clearance (Appendix II), calcium and lactate dehydrogenase (LDH)		X	X[c]	X	X	X	X	X	X

Tests and Procedures	≤28 days prior to registration	≤14 days prior to registration	Cycle 1, Day 1	Cycle 1, Day 15	Cycle 2 (to 4[†]), Day 1	Cycle 2 (or 4[†]): ≤14 days prior to ASCT	Cycle 3 (or 5[†]): Day 100 visit of ASCT (occurs 90-110 days after ASCT)	Cycle 4 (or 6[‡]) and beyond (end of each cycle)	End of Treatment
Bone marrow aspirate/biopsy with standard testing (including but not limited to myeloma FISH and flow cytometry) [d]	X					X[d]	X	X	
Bone marrow MRD Assessment by MPF[, d]	X					X	X	X	
Peripheral blood MRD testing[e]	X					X	X	X	
Electrophoresis of serum and urine (SPEP/UPEP)		X			X[l]	X[l]	X[l]	X[l]	X*
*Serum immunoglobulins[d]		X			X	X	X	X	X*
*Immunofixation serum and urine (IF)		X			X	X	X	X	X*
*Immunoglobulin free light chain (FLC)		X			X	X	X	X	X*
*Serum β2-microglobulin		X							
Skeletal bone survey		X							
PET scan[g]	X							X	
Adverse Event monitoring[f]		X			X	X	X	X	X
Pregnancy test[e]		X						X	
Registered in the REVLIMID REMS™ program[h]							X		
Pill Diary[i]								X	

Cycle 1 (to 3, as the case may be for that patient) = 28 days (4 weeks)
Cycle 2 (or 4, as the case may be for that patient) = Up to 84 days (4 weeks treatment + window period up to 8 weeks between Consolidation 1 and ASCT)
Cycle 3 (or 5, as the case may be for that patient) = Up to 124 days (Day 100 visit of ASCT occurs 90-110 days after ASCT + window period up to 14 days between Day 100 visit and start of Maintenance)
Cycles 4-15 (or 6-17, as the case may be for that patient) = 28 days (4 weeks)
Cycles 16 and beyond (or cycle 18 and beyond, as the case may be for that patient) = 90 days (3 months)

†In case patient given cycle 3 and 4 optional treatment in consolidation 1, the subsequent cycle numbers and Day 100 ASCT visit will be adjusted accordingly.

All tests and procedures are clinically indicated, unless noted with an R to indicate funding by research

a) All scheduled visits will have a window of ±3 days, Cycle 1, Day 1, unless otherwise stated, all procedures to be completed within 3 days prior to commencing subsequent treatment cycle. (±3 days does not apply to daratumumab treatment in cycles 1-4; consolidation 1)
b) To include blood pressure, pulse rate, temperature, weight. Height to be documented ≤14 days prior to registration
c) Labs are not required to be repeated if done ≤14 days prior to registration.
d) Standard of care procedure: Prior to Cycle 1, pre-ASCT, at Day 100, prior to Cycle 16 or if considered clinically indicated at any other time during the study. Bone marrow biopsy during cycle 2 can be done any tiem between days 28 and 84.
e) To coincide with standard of care blood sample collection at: Prior to Cycle 1, pre-ASCT, at Day 100, prior to cycles 8, 12, 16, 18, and 20. NOTE: To coincide with the day of MRD testing by bone marrow biopsy, if occurring at that time point.
f) Serum immunoglobulins to include IgG, IgA and IgM for all patients and IgD or IgE where clinically indicated. NOTE: bone marrow testing prior to registration must be after the last anti-myeloma treatment but ≤ 28 days of registration.
g) A PET scan should be done within 28 days prior to registration, prior to Cycle 16 treatment and whenever else considered clinically necessary. PET scan done when CR considered to assess imaging response.
h) During treatment period, at end of treatment visit. The patient should be contacted by a nurse 30 days after the last dose of study treatment (or at the time of initiation of subsequent treatment if started before 30 days) to check if the patient has experienced any late adverse events. Grade 3 or higher adverse events at least possibly related to study treatment and deaths due to any cause should be reported as a late adverse event on the Survival and Disease Status Follow-Up/Event Monitoring form if they were not already reported on the Adverse Event form for the last cycle and they occurred prior to any subsequent treatment and 30 days post-end of treatment
i) For females of childbearing potential, a negative pregnancy test (urine or serum) must be documented within 14 days of starting treatment on the study and for patients starting Cycle 4 (daratumumab+lenalidomide) in accordance with the REVLIMID REMSTM program. A female of childbearing potential (FCBP) 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).
j) Patients starting Cycle 4 treatment (daratumumab+lenalidomide) prior to starting treatment with REVLIMID
k) To be collected at the end of every cycle of maintenance therapy while the patient is receiving lenalidomide
l) UPEP testing required at baseline only. Subsequent testing will be as needed per physician discretion.

*Repeat Electrophoresis of serum and urine, Serum immunoglobulins, Immunofixation serum and urine, and Immunoglobulin free light chain only if the assessments were not completed 14 days prior to End of Treatment visit.

4.2 Event Monitoring/Survival Follow-up

	Event Monitoring Phase[1]				
	Q 3 months until PD or subsequent treatment	At PD or subsequent therapy	After PD or subsequent therapy Q 6 months	Death	New Primary
Event Monitoring	X	X	X	X	At each occurrence

1. If a patient is still alive 3 years after registration, no further follow-up is required

5.0 Grouping Factor:

None

6.0 Registration/Randomization Procedures

6.1 Registration Procedures

6.11 To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the MCCC Registration Office at (507) 284-2753 between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the MCCC web page (http://ccswww.mayo.edu/training/) and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and a MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the MCCC Registration Office (507) 284-2753. If the patient was fully registered, the MCCC Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about A Registered Subject."

6.12 Prior to accepting the registration, registration/randomization application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.13 Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office (fax: 507-284-0885). If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

6.14 Treatment on this protocol must commence at Mayo Clinic under the supervision of a medical oncologist/hematologist.

6.15 Treatment cannot begin prior to registration and must begin ≤ 28 days after registration.

6.16 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.17 All required baseline symptoms (see Section 10.6) must be documented and graded.

6.18 Study drug is available on site.

7.0 Protocol Treatment

Daratumumab may be administered within ±1 day of the scheduled dose if there are any logistical challenges (holiday, patient transport or other logistics, scheduling availability, etc.)

7.1 Treatment Schedule

7.11 Consolidation 1 (Cycles 1-2 or 1-4, as the case may be for that patient)

Agent	Dose	Route	Day	Cycles
Daratumumab	16 mg/Kg* (IV) 1,800 mg (Injection)	IV or injection	1, 8, 15, 22	Cycle 1-2
Daratumumab	16 mg/Kg* (IV) 1,800 mg (injection)	IV or injection	1, 15	Cycle 3-4

Cycle 1 (to 3, as the case may be for that patient) length = 28 days;
Cycle 2 (or 4, as the case may be for that patient) length = up to 84 days (4 weeks treatment + window period up to 8 weeks between Consolidation 1 and ASCT)
Treatment Window (for patients receiving treatment through a local medical doctor)= ±5 days
*Any dose-adjustments will be made as per the prescriber information. Daratumumab administration as per prescriber information and institutional guidelines.

7.12 Consolidation 2 (Cycle 3 or 5, as the case may be for that patient)

- All patients enrolled in the trial after completing consolidation 1 treatment will proceed to a SCT with Day 0 of SCT within 8 weeks of completing cycle 2 (or 4, as the case may be for that patient), Day 28 of consolidation 1.
- Stem cell collection could have been completed prior to initiating consolidation 1 or may be performed within the up to 8-week period between completion of Cycle 2 (or 4, as the case may be for that patient), Day 28 and Day 0 of SCT.
- Consolidation 1 should not be interrupted for the purpose of stem cell collection.
- SCT procedures should be completed as per institutional standards.
- Consolidation 2 period will be considered up until the Day 100 visit (±10 days as per institutional BMT program scheduling).
- Cycle 3 (or 5, as the case may be for that patient) length = Up to 124 days (Day 100 visit of ASCT occurs 90-110 days after ASCT + window period up to 14 days between Day 100 visit and start of Maintenance)

7.13 Maintenance (Cycles 4 and Beyond, or cycle 6 and beyond as the case may be for that patient)

- All patients will be initiated on maintenance therapy as below within 14 days of completing Day 100 visit post-SCT.

Agent	Dose	Route	Day	Cycles
Daratumumab	16 mg/Kg* (IV) 1,800 mg (Injection)	IV or Injection	1	Cycle 4-15 (or 6-17)
Lenalidomide	10 mg*	PO	1-21	Cycle 4-15

				(or 6-17)

Cycles 4-15 (or 6-17) length = 28 days
*Any dose-adjustments will be made as per the prescriber information. Daratumumab administrations as per prescriber information and institutional guidelines.
Note: Thromboprophylaxis is required as standard of care (see Section 9.3) for all patients on maintenance treatment.

- **NOTE:** Prior to Cycle 16 (or 18), patients who are still maintaining response will proceed to maintenance with single-agent daratumumab every 3 months till disease progression or unwanted adverse events, if any. Cycles 16 and beyond length = 90 days (3 months).
- In the event of disease progression, intolerable adverse event or patient refusal for continued therapy, they will proceed to event monitoring without any additional anti-MM therapy.
- Considering that there are newer immunotherapy compounds being made available for the treatment of multiple myeloma, based on the initial results of this clinical trial, amendments may be put in place to add more arms to the study with newer, proven safe combination regimens, especially for maintenance treatment.

7.2 Treatment by a local medical doctor (LMD) allowed.

When it has been determined that a patient's malignant disease is stable and the patient is tolerating therapy without excessive toxicity at a stable dose level, the patient may continue treatment via the patient's Local Medical Doctor (LMD). The patient will be required to return to Mayo Clinic for all study visits.

7.3 Overdose

Any dose of study drug in excess of that specified in this protocol is considered to be an overdose. Signs and symptoms of an overdose that meet any Serious Adverse Event criterion must be reported as a Serious Adverse Event in the appropriate time frame and documented as clinical sequelae to an overdose.

There has been no experience of overdosage with daratumumab in clinical studies. Doses up to 24 mg/kg have been administered intravenously in a clinical study without reaching the maximum tolerated dose. There is no known specific antidote for daratumumab overdose. In the event of an overdose, the subject should be monitored for any signs or symptoms of adverse effects and appropriate symptomatic treatment be instituted immediately.

Refer to Section 10 for further information regarding AE reporting.

8.0 Dosage Modification Based on Adverse Events

Any adverse event noted in the study and its resultant dose-modifications should be managed as per the prescribing information of daratumumab and/or lenalidomide as per which of these two drugs the adverse event is attributable to.

ALERT: ADR reporting may be required for some adverse events (See Section 10)

8.1 General Considerations:

a) Missed doses for lenalidomide are to be omitted rather than made up, unless the dose was forgotten and remembered on the same day, in which case the dose can be taken

that day. Any doses missed on a particular day are not to be made up the next day. Doses that are considered to be vomited are not to be made up and a mention about the time of dose and time of vomiting episode should be made in the pill diary.

b) Daratumumab may be administered within ±1 day of the scheduled dose if there are any logistical challenges (holiday, patient transport or other logistics, scheduling availability, etc.)

c) If multiple toxicities are experienced, dose modifications will be based on the toxicity requiring the largest dose reduction.

d) Reductions are based on the dose given in the preceding cycle and are based on toxicities with an attribution of possible, probable, or definite that were observed since the prior toxicity evaluation.

e) If a drug is omitted due to specific adverse events and the patient is on combination therapy (maintenance therapy), the other agents, considered unrelated to the adverse event may be continued.

f) If a patient cannot be administered a dose of daratumumab during Consolidation 1 (Cycles 1-2 or 1-4, as the case may be for that patient) for >28 days due to adverse events or any other reason, the patient should be removed from the study treatment and go to event monitoring. (NOTE: Patients on maintenance therapy (cycles 4 and beyond, or cycle 6 and beyond as the case may be for that patient) may be continued on treatment with single-agent daratumumab or lenalidomide in case the other agent has to be permanently discontinued in absence of disease progression. If a patient on maintenance treatment must discontinue both, lenalidomide and daratumumab, they should be removed from the protocol therapy and proceed to event monitoring.

8.2 Lenalidomide Dose Modifications

Lenalidomide (Days 1-21)	
Starting dose	10mg
-1	5 mg
-2	Discontinue

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified ← ←

CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION**
Investigations	Platelet count decreased Grade 4	Lenalidomide	*Omit dose until AE has resolved to Grade 1 or better • Follow CBC weekly • If thrombocytopenia <30,000/mm^3 recurs, reduce dose by one dose level (by 5 mg) and continue therapy when platelet count ≥30,000/mm^3 If, after lenalidomide has been omitted, and the AE does not return to ≤Grade 1 within 4 weeks, then the patient may continue on single-agent daratumumab till the completion of maintenanceand then proceed to Event Monitoring
	Neutrophil count decreased Grade 4		*Omit dose until AE has resolved to Grade 2 or better • Follow CBC weekly * If neutropenia has resolved to ≤Grade 2, resume dose at one level lower *If, after lenalidomide has been omitted, and the AE does not return to ≤Grade 1 within 4 weeks, then the patient may continue on single-agent daratumumab till the completion of maintenance and then proceed to Event Monitoring
Blood and lymphatic system disorders	Anemia Grade 4		*Omit dose until AE has resolved to Grade 2 or better • Follow CBC weekly * If anemia has resolved to ≤Grade 2, resume dose at one level lower *If, after lenalidomide has been omitted, and the AE does not return to ≤Grade 1 within 4 weeks, then the patient may continue on single-agent daratumumab till the completion of maintenance and then proceed to Event Monitoring
	Febrile neutropenia ≥Grade 3		• Omit dose and follow CBC weekly • If neutropenia has resolved to ≤Grade 2, resume dose at same level with GCSF support (See Section 9.6)

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION**
Cardiac disorders	Sinus bradycardia/ other cardiac arrhythmia Grade 2	Lenalidomide	Omit dose and follow at least weekly until resolution • If AE resolves to ≤Grade 1, reduce dose by one dose level (by 5mg) and continue therapy
	≥ Grade 3		• Discontinue study treatment and go to event monitoring
Vascular disorders	Thromboembolic event ≥ Grade 3		• Omit dose and start anticoagulation; restart at investigator's discretion (maintain dose level)
Immune system disorders	Allergic reaction Grade 2-3		• Omit dose and follow at least weekly until resolution • If AE resolves to ≤Grade 1, reduce dose by 5 mg and continue therapy
	Anaphylaxis Grade 4		• Discontinue study treatment and go to event monitoring
Skin and subcutaneous tissue disorders	Erythema multiforme ≥Grade 3		Discontinue study treatment and go to event monitoring
	Skin ulceration ≥Grade 2		Discontinue study treatment and go to event monitoring
	Other: Non-blistering rash Grade 3		• If Grade 3 omit dose and follow weekly until resolution • If AE resolves to ≤Grade 2 continue therapy
	Other: Non-blistering rash Grade 4		• Discontinue study treatment and go to event monitoring
Other AEs	Non-hematologic AE assessed as related to lenalidomide ≥Grade 3		• Omit dose and follow at least weekly until resolution • If the AE resolves to ≤Grade 2, implement one dose reduction step and continue therapy (per Table 8.2)

* Located at http:/ctep.cancer.gov/protocolDevelopment/electronic_applications.ctc.htm

** Use the following to describe actions in the Action column:

- Omit = The current dose(s) for the specified drug(s) during a cycle is skipped. The patient does not make up the omitted dose(s) at a later time
- Hold/Delay = The current dose(s) of all drugs during a cycle is delayed. The patient does make up the delayed dose(s) when the patient meets the protocol criteria to restart drugs.
- Discontinue = The specified drug(s) are totally stopped.

If lenalidomide has been omitted and the toxicity does not return to ≤Grade 2 within 28 days during Consolidation 1 (Cycles 1-2), may continue on single-agent daratumumab till the completion of maintenance and then proceed to Event Monitoring.

8.21 Lenalidomide dose adjustment for renal function

Lenalidomide dose will be adjusted as per standard of care guidelines in the prescribing information of lenalidomide for multiple myeloma patients.

8.3 Daratumumab Dose Modifications (**NOTE:** Only if any of the following criteria are met and the event cannot be ascribed to lenalidomide or to any other concurrent medication that the patient may be on, the daratumumab administration must be held/omitted as specified below to allow for recovery from toxicity).

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specied ← ←

CTCAE System/Organ/ Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
Investigations	Neutrophil count decreased Grade 4 lasting >7 days Platelet count decreased Grade ≥3 with bleeding	Daratumumab	Hold (Day 1) or Omit (Days 8, 15, or 22) Daratumumab** until recovery to Grade ≤2 or baseline May restart at same dose at the next planned dosing date.
Blood and lymphatic system disorders	Febrile neutropenia ≥Grade 3 Neutropenia with infection, of any grade		Hold (Day 1) or Omit (Days 8, 15, or 22) Daratumumab** until recovery to Grade ≤2 or baseline May restart at same dose at the next planned dosing date.
Gastrointestinal disorders	Nausea Grade 2 (if persistent for >7 days despite optimal antiemetic therapy) Vomiting ≥Grade 3 (if persistent for >7 days despite optimal antiemetic therapy) Diarrhea ≥Grade 3 (if persistent for >7 days despite optimal anti-diarrheal therapy)		Hold (Day 1) or Omit (Days 8, 15, or 22) Daratumumab** until recovery to Grade ≤1 or baseline May restart at same dose at the next planned dosing date.
Other (Non-hematologic)****	Any other Grade 4 AE or any unmanageable Grade 3 AE that was present at baseline or lasts for >7 days after the last administration of daratumumab		Hold (Day 1) or Omit (Days 8, 15, or 22) Daratumumab** until recovery to Grade ≤1 or baseline May restart at same dose at the next planned dosing date.

Additional Adverse Events:

** If Daratumumab is omitted in the middle of the cycle and the toxicity resolves, patient can re-start the drug but the days of drug treatment missed do not need to be caught-up and can be omitted in order to maintain the cycle schedule.

- Dose omission: Daratumumab may be omitted for adverse event considerations for a maximum of 28 consecutive days during Consolidation 1 (Cycle 1-2 or 1-4, as the case may be for that patient). Patients on maintenance therapy may be continued on treatment with single-agent daratumumab or lenalidomide in case the other agent has to be permanently discontinued in absence of disease progression. If a patient on maintenance treatment must discontinue both,

lenalidomide and daratumumab, they should be removed from the protocol therapy and proceed to event monitoring.

- If multiple adverse events are seen, administer dose based on the greatest reduction required by any single adverse event observed.
- Dose modifications are for adverse events attributed to study treatment only. Dose modifications are not required for adverse events if they are deemed unrelated and/or unlikely related to study treatment.
- Reductions apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

**** If cough, dyspnea, and other pulmonary symptoms occur, a chest x-ray and high-resolution chest CT scan should be obtained. Incentive spirometry studies (to include DLCO) should be considered. Consider Pneumocystis pneumonia or viral pneumonitis. Patients who experience a deep vein thrombosis (DVT), pulmonary embolus (PE), or other clotting event should have all study drugs temporarily omitted while full-dose anticoagulation is initiated (other than warfarin or other Vitamin K antagonist). There should not be a delay of more than 28 days in reinitiating the study treatment.

NOTE: If the patient experiences a significant adverse event requiring a dose reduction at the start of the next cycle, then the dose will remain lowered for that entire remaining length of the study treatment.

NOTE: In the event patient is benefitting from treatment and the delay was unrelated to treatment toxicity, patient may remain on study with approval of study PI.

9.0 Ancillary Treatment/Supportive Care

9.1 Full Supportive Care

Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

9.2 Bisphosphonates

Patients may receive concurrent treatment with a bisphosphonate.

9.3 Thrombophylaxis

Due to the increased risk of deep vein thrombosis (DVT) for multiple myeloma patients, thromboprophylaxis is to be used as standard of care on this regimen according to the International Myeloma Working Group guidelines (http://jco.ascopubs.org/content/32/6/587.full).[25]

9.4 Prohibited medications

The following medications are not permitted during the trial:

- Any other investigational treatment
- Any cytotoxic chemotherapy

- Any other systemic anti-neoplastic therapy including, but not limited to, immunotherapy, hormonal therapy or monoclonal antibody therapy.
- Any external beam radiotherapy. **NOTE:** Radiation therapy administered with palliative intent to control localized symptoms from MM is permitted provided the symptoms are not considered due to disease progression.

9.5 Anti-emetics

Anti-emetics may be used at the discretion of the attending physician

9.6 Blood products and growth factors

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology (42) Update of Recommendations for the Use of Hematopoietic Colony-Stimulating Factors: Evidence-Based, Clinical Practice Guidelines.[26]

9.7 Diarrhea

Diarrhea could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).

In the event of Grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.

If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting **should be hospitalized** for intravenous hydration and correction of electrolyte imbalances.

9.8 Concomitant medications

Any systemic, anti-myeloma therapy or steroids other than those prescribed by the protocol are prohibited while on protocol therapy. Guidelines for selection and use of other concomitant medications should be derived from the lenalidomide and daratumumab prescribing information. Other than study medications, administration of any therapeutic or diagnostic investigational agent (for any indication) is prohibited while on study.

10.0 Adverse Event (AE) Reporting and Monitoring

The site principal investigator is responsible for reporting any/all serious adverse events to the sponsor as described within the protocol, regardless of attribution to study agent or treatment procedure.

The sponsor/sponsor-investigator is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:

- Any suspected adverse reaction that is both serious and unexpected.
- Any findings from laboratory animal or *in vitro* testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.

- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug

- Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).

Summary of SAE Reporting for this study
(please read entire section for specific instructions):

WHO:	WHAT form:	WHERE to send:
All sites	Pregnancy Reporting http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportFormUpdated.pdf	Mayo Sites – attach to MCCC Electronic SAE Reporting Form
Mayo Clinic Sites	Mayo Clinic Cancer Center SAE Reporting Form http://livecycle2.mayo.edu/workspace/?startEndpoint=MC4158-56/Processes/MC4158-56-Process.MC4158-56 AND attach MedWatch 3500A: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf	Will automatically be sent to CANCERCROSAFETYIN@mayo.edu

Definitions

Adverse Event
Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction
Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Expedited Reporting
Events reported to sponsor within 24 hours, 5 days or 10 days of study team becoming aware of the event.

Routine Reporting
Events reported to sponsor via case report forms

Events of Interest
Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

Unanticipated Adverse Device Event (UADE)
Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

a. Identify the grade and severity of the event using the CTCAE version 4.0.

b. Determine whether the event is expected or unexpected (see Section 10.2).

c. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).

d. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).

e. Determine if other reporting is required (see Section 10.5).

f. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

NOTE: A severe AE is NOT the same as a serious AE, which is defined in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events - are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure, (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.
An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.
NOTE: *The consent form may contain study specific information at the discretion of the Principal Investigator; it is possible that this information may NOT be included in the protocol or the investigator brochure. Refer to protocol or IB for reporting needs.

10.3 Attribution to agent(s) or procedure

When assessing whether an adverse event (AE) is related to a medical agent(s) medical or procedure, the following attribution categories are utilized:

Definite - The AE *is clearly related* to the agent(s)/procedure.
Probable - The AE *is likely related* to the agent(s)/procedure.
Possible - The AE *may be related* to the agent(s)/procedure.
Unlikely - The AE *is doubtfully related* to the agent(s)/procedure.
Unrelated - The AE *is clearly NOT related* to the agent(s)/procedure.

10.31 **AEs Experienced Utilizing Investigational Agents and Commercial Agent(s) on the SAME (Combination) Arm**

NOTE: When a commercial agent(s) is (are) used on the same treatment arm as the investigational agent/intervention (also, investigational drug, biologic, cellular product, or other investigational therapy under an IND), the **entire combination (arm) is then considered an investigational intervention for reporting.**

- An AE that occurs on a combination study must be assessed in accordance with the guidelines for **investigational** agents/interventions.

- An AE that occurs prior to administration of the investigational agent/intervention must be assessed as specified in the protocol. In general, only Grade 4 and 5 AEs that are unexpected with at least possible attribution to the commercial agent require an expedited report, unless hospitalization is required. Refer to Section 10.4 for specific AE reporting requirements or exceptions.

An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent)

occurs with a higher degree of severity or specificity, expedited reporting is required.

- An increased incidence of an expected adverse event (AE) is based on the patients treated for this study at their site. A list of known/expected AEs is reported in the package insert or the literature, including AEs resulting from a drug overdose.

- Commercial agent expedited reports must be submitted to the FDA via MedWatch 3500A for Health Professionals (complete all three pages of the form).

  http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

  or

  http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/ListFormsAlphabetically/default.htm

  Instructions for completing the MedWatch 3500A:
  http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/UCM387002.pdf

10.32 EXPECTED Serious Adverse Events: Protocol Specific Exceptions to Expedited Reporting

For this protocol only, the following Adverse Events/Grades are expected to occur within this population and do not require Expedited Reporting. These events must still be reported via Routine Reporting (see Section 10.6).*
*Report any clinically important increase in the rate of a serious suspected adverse reaction (at your study site) over that which is listed in the protocol or investigator brochure as an expedited event.

*Report an expected event that is greater in severity or specificity than expected as an expedited event.

System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not be expeditedly reported[1]
Blood and lymphatic system disorders	Anemia	≤Grade 4
Gastrointestinal Disorders	Diarrhea	≤Grade 3
	Nausea	≤Grade 3
	Vomiting	≤Grade 3
General disorders and administration site conditions	Fatigue	≤Grade 3
Investigations	Lymphocyte count decreased	≤Grade 4
	Neutrophil count decreased	≤Grade 4

System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not be expeditedly reported[1]
	Platelet count decreased	≤Grade 4
	White blood cell count decreased	≤Grade 4

[1] These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.
Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (*i.e.*, there is no untoward medical occurrence) associated with the hospitalization:
- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for elective procedures unrelated to the current disease and/or treatment on this trial
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (*e.g.*, battery replacement) that was in place before study entry
- Hospitalization, or other serious outcomes for signs and symptoms of progression of the cancer.]

10.4 Expedited Reporting Requirements for IND/IDE Agents

10.41 Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the sponsor within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥24 hrs	7 Calendar Days	24-Hour 3 Calendar Days
Not resulting in Hospitalization ≥24 hrs	Not required	

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

NOTE: Refer to Section 10.32 for exceptions to Expedited Reporting

10.42 General reporting instructions

The Mayo IND Coordinator will assist the sponsor-investigator in the processing of expedited adverse events and forwarding of suspected unexpected serious adverse reactions (SUSARs) to the FDA and IRB.

Submit the Medwatch form and the CIOMS 1 form via email AEintakeCT@pcyc.com or fax ((408) 215-3500) to Pharmacyclics Drug Safety, or designee, within 15 days of the event. Pharmacyclics may request follow-up and other additional information from the Sponsor Investigator.

10.43 Reporting of re-occurring SAEs

ALL SERIOUS adverse events that meet the criteria outlined in table10.41 MUST be immediately reported to the sponsor within the timeframes detailed in the corresponding table. This reporting includes, but is not limited to SAEs that re-occur again after resolution.

10.5 Other Required Reporting

10.51 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS)

Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS) in general, include any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs.

Note: If there is no language in the protocol indicating that pregnancy is not considered an adverse experience for this trial, and if the consent form does not indicate that subjects should not get pregnant/impregnate others, then any pregnancy in a subject/patient or a male patient's partner (spontaneously reported) which occurs during the study or within 120 days of completing the study should be reported as a UPIRTSO.

Mayo Clinic Cancer Center (MCCC) Institutions:

If the event meets the criteria for IRB submission as a Reportable Event/UPIRTSO, provide the Reportable Event coversheet and appropriate documentation to CANCERCROSAFETYIN@mayo.edu. The Mayo Regulatory Affairs Office will review and process the submission to the Mayo Clinic IRB.

10.52 Death

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Reportable categories of Death

- Death attributable to a CTCAE term.

- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.

- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.

- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.

- Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (including cysts and polyps) – Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.53 Secondary Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

- All secondary malignancies that occur following treatment with an agent under an IND/IDE will be reported. Three options are available to describe the event:

  - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])

  - Myelodysplastic syndrome (MDS)

  - Treatment-related secondary malignancy

- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.54 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting unless otherwise specified.

10.55 Pregnancy, Fetal Death, and Death Neonatal

Pregnancy reporting for Celgene/Revlimid REMS™ program

Females of reproductive potential must adhere to scheduled pregnancy testing as required in the Revlimid REMS™ program.

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on lenalidomide, or within 28 days of the subject's last dose of lenalidomide, are considered immediately reportable events. Lenalidomide is to be discontinued

immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile or other appropriate method using the Pregnancy Initial Report Form. The female subject should be referred to an obstetrician-gynecologist (not necessarily one with reproductive toxicity experience) or another appropriate healthcare professional for further evaluation.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form or equivalent form.

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form or approved equivalent form.

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 the IP should also be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

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 their healthcare provider immediately.

Pregnancy reporting Mayo Clinic

If a female subject (or female partner of a male subject) taking investigational product becomes pregnant, the subject taking should notify the Investigator, and the pregnant female should be advised to call her healthcare provider immediately. The patient should have appropriate follow-up as deemed necessary by her physician. If the baby is born with a birth defect or anomaly, a second expedited report is required.

Prior to obtaining private information about a pregnant woman and her infant, the investigator must obtain consent from the pregnant woman and the newborn infant's parent or legal guardian before any data collection can occur. A consent form will need to be submitted to the IRB for these subjects if a pregnancy occurs. If informed consent is not obtained, no information may be collected.

In cases of fetal death, miscarriage or abortion, the mother is the patient. In cases where the child/fetus experiences a serious adverse event other than fetal death, the child/fetus is the patient.

NOTE: When submitting Mayo Expedited Adverse Event Report reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section. Include any available medical documentation. Include this form: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportFormUpdated.pdf

10.551 Pregnancy

Pregnancy should be reported in an expedited manner as **Grade 3 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy)"** under the Pregnancy, puerperium and perinatal conditions SOC. Pregnancy should be followed until the outcome is known.

10.552 Fetal Death

Fetal death is defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation."

Any fetal death should be reported expeditiously, as **Grade 4 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy loss)"** under the Pregnancy, puerperium and perinatal conditions SOC.

10.553 Death Neonatal

Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention, should be reported expeditiously.

A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration - Other (neonatal loss)"** under the General disorders and administration SOC.

10.6 Required Routine Reporting

10.61 **Baseline and Adverse Events Evaluations**
Pretreatment symptoms/conditions to be graded at baseline and adverse events to be graded at each evaluation.
Grading is per CTCAE v4.0 **unless** alternate grading is indicated in the table below:

System Organ Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation
Blood and lymphatic system disorders	Anemia		X
Skin and subcutaneous tissue disorder	Rash Maculo-papular		X*
General disorders and administration site conditions	Infusion related reaction		X
	Injection site reaction		X
	Fatigue	X	X
Investigations	Neutrophil count decreased		X
	Platelet count decreased		X

*Only for evaluations during cycles 4-15

10.62 Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.6:

10.621 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.622 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.623 Grade 5 AEs (Deaths)

10.6231 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.6232 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.7 Late Occurring Adverse Events

Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

10.8 Adverse Events of Special Interest (AESI)

Specific adverse events, or groups of adverse events, will be followed as part of standard safety monitoring activities. These events (regardless of seriousness) will be reported to Pharmacyclics Drug Safety per SAE reporting timelines.

10.81 Major Hemorrhage

Major hemorrhage is defined as any of the following:

- Any treatment-emergent hemorrhagic adverse events of Grade 3 or higher*. Any treatment-emergent serious adverse events of bleeding of any grade
- Any treatment-emergent central nervous system hemorrhage/hematoma of any grade

*All hemorrhagic events requiring transfusion of red blood cells should be reported as grade 3 or higher AE per CTCAE v4.0.

Events meeting the definition of major hemorrhage will be captured as an event of special interest according to Section 10.8 above.

11.0 Treatment Evaluation - The International Myeloma Working Group (IMWG) uniform response criteria (Kumar et al, 2016[17]) will be used to assess response to therapy

11.1 Terms and definitions

- **M-protein:** synonyms include M-spike, monoclonal protein and myeloma protein, paraprotein, M-component.

  Serum M-protein level is quantitated using densitometry on SPEP except in cases where the SPEP is felt to be unreliable.
  - M-proteins migrating in the β-region (usually IgA M-proteins)
  - Cases in which the M-protein is so large and narrow on agarose (some specimens >4 g/dL) that they underestimate the actual immunoglobulin level (by greater than 1500 mg/dL) due to technical staining properties of the agarose gel.
  - Cases in which there are multiple peaks of same M-protein (aggregates or dimers)

  If SPEP is not available or felt to be unreliable (above examples) for routine M-protein quantitation, then quantitative immunoglobulin levels derived from nephelometry or turbidometry can be accepted, with the exception that quantitative IgG may not be used. However, this must be explicitly reported at baseline, and only nephelometry can be used for that patient to assess response. SPEP derived M-protein values and quantitative nephelometric immunoglobulin values cannot be used interchangeably.

  Urine M-protein measurement is estimated using 24-h UPEP only. Random or 24 h urine tests measuring kappa and lambda light chain levels are not

reliable and are not recommended.

FLC estimation is currently carried out using the serum FLC assay (Freelite, The Binding Site Limited, UK). Patients with kappa/lambda FLC ratio <0.26 are defined as having monoclonal lambda FLC and those with ratios >1.65 as having a monoclonal kappa FLC. The monoclonal light chain isotype is considered the involved FLC isotype, and the opposite light chain type as the uninvolved FLC type.

- **Response terms:** The following response terms will be used: stringent Complete Response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), Minimal Response (MR), stable disease (SD), and progressive disease (PD).

  In addition, for each response category, there will be an "unconfirmed" response category, which will be for internal use, for the purpose of guiding decision making and test ordering. These designations will be applied at the time of the first measurement at which the quantitative aspect of the response category has been satisfied without the confirmation step having been satisfied. The designation "u" will precede the standard abbreviations, and will include usCR, uCR, uVGPR, uPR, uMR, uPD.

- **Measurable disease:** Patients who have a measurable serum or urine M-protein.

  - Serum M-protein ≥1 g/dl
    NOTE: Quantitative IgG may not be used for defining measurable disease
  - Urine M-protein ≥ 200 mg/24 h
  - Serum FLC assay: Involved FLC level ≥ 10 mg/dl provided serum FLC ratio is abnormal
  - Bone marrow plasma cells ≥ 30%

The serum free light chain (FLC) assay is of particular use in monitoring response to therapy in patients who have oligo-secretory or non-secretory disease and **should be used in assessing response only if the baseline serum and/or urine M proteins are not "measurable" as above, and the baseline level of the involved FLC is "measurable."** When using this assay, it is important to note that the FLC levels vary considerably with changes in renal function and in patients with renal insufficiency, the levels of both the kappa and lambda may remain elevated, but the ratio normalizes with achievement of CR. Thus, both the level of the involved and the uninvolved FLC isotype (i.e., the involved/uninvolved ratio or involved-uninvolved difference) should be considered in assessing response. ***Patients included on the study on the basis of FLC alone (i.e., no measurable serum/urine M-protein) should be the only ones who are evaluated using FLC response criteria. The others should follow usual criteria and ignore FLC results*** with the exception of defining stringent complete

response.

- **Evaluable disease**: Patients who do not have a "measurable" serum M-protein, serum free light chain, or urine M-protein.

- **Oligosecretory myeloma:** Patient with multiple myeloma who has NEVER had "measurable" serum M-protein or urine M-protein, but has had a detectable M-protein in his/her serum and/or urine and/or measurable serum free light chain.

- **Non-secretory myeloma:** Patient with multiple myeloma who has NEVER had a detectable M-protein in his/her serum and/or urine.

11.2 Clarification of test indications

Listed below are the minimal required tests required to assess response based on the characteristics of their disease at on study.

Table 11.2

Tests Required To Assess Response (Must Be Done At Each Disease Measurement Visit except as indicated[1,2])

On Study Baseline Value	SPEP[4]	24 hr UPEP[2]	Ig FLC	BM Bx
Serum M-protein ≥1 g/dl, and urine M-protein≥ 200 mg/24 hrs	X	X		
Serum M-protein ≥ 1 g/dl, but urine M-protein < 200 mg/24 hrs	X			
Serum M-protein <1 g/dl, and urine M-protein≥ 200 mg/24 hrs		X		
Serum M-protein < 1 g/dl, urine M-protein < 200 mg/24 hrs, but involved Ig FLC is ≥10 mg/dL			X	
Serum M-protein < 1 g/dl, urine M-protein< 200 mg/24 hrs, involved Ig FLC is <10 mg/dL, bone marrow ≥30% plasma cells				X[3]

[1] ***SPEP, UPEP, Immunofixation studies of both serum and urine, and Bone marrow biopsy*** *are required to document CR regardless of registration values, and in addition* ***FLC*** *measurement and* ***bone marrow immunophenotyping*** *is required to document sCR. SPEP and UPEP are required to document VGPR regardless of registration values.*

[2] *For serum measurable patients, 24 hour urine does not need to be confirmed (i.e. repeated after documented response) for any response category*

[3] *At a minimum, a bone marrow biopsy should be repeated every 3 months until documented response. Bone marrow biopsy results do not need to be repeated after documented response.*

[4] *If serum M-protein is being followed by quantitative immunoglobulin levels derived from nephelometry or turbidometry, quantitative immunoglobulins are required. SPEP is only required to document CR or VGPR.*

11.3 Confirmed response

In order to be classified as a hematologic response, confirmation of serum M-protein, serum immunoglobulin free light chain (when primary determinant of response) and urine M- protein (when primary determinant of response) results must be made by verification on two consecutive determinations.

- Bone marrow aspirate and biopsy are **only** required to document CR or sCR, except for patients with evaluable disease **only**, where a bone marrow is required to document all response categories including progression. However, a second confirmatory bone marrow is **not** required to confirm response in any case.
- Radiographic studies are not required to satisfy these response requirements; however, if radiographic studies were performed there should be no evidence of progressive or new bone lesions.

Appropriate tests required to document and confirm response are listed in Table 11.2

11.4 Bone progression

Caution must be exercised to avoid rating progression on the basis of variation of radiologic technique alone. Compression fracture does not exclude continued response and may not indicate progression. When progression is based on skeletal disease alone, it should be discussed with the Study Chair before removing the patient from the study.

11.5 Response and Progression

Criteria for response and progression are listed in Table 11.5. Progressive disease for all patients as defined in Table 11.5.

Baseline values for disease assessment: All disease response measurements will be based on the values obtained at the time of diagnosis if there has been no relapse prior to transplant. If patients had a disease relapse prior to transplant, the baseline values will be those obtained at the time of relapse immediately prior to the transplant. If patient had treatment for the relapsed disease prior to transplant, the values will be from prior to this therapy, ie, the time of relapse.

Table 11.5	
IMWG MRD NEGATIVITY CATEGORY	**RESPONSE CRITERIA [a]**
Flow MRD [k]	Absence of phenotypically aberrant clonal plasma cells by MPF on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Imaging + MRD-negative	MRD negative as defined by MPF or NGS PLUS Disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to < mediastinal blood pool Standard uptake value or decrease to less than that of surrounding normal tissue
STANDARD IMWG RESPONSE CATEGORY	**RESPONSE CRITERIA [a]**
Stringent Complete Response (sCR) [b]	CR as defined *plus* Normal FLC ratio *and* • Absence of clonal PCs by immunohistochemistry or 2- to 4-color flow cytometry [i]
Complete Response (CR) [b]	• Negative immunofixation of serum and urine [c] *and* • Disappearance of any soft tissue plasmacytoma *and* • <5% PCs in Bone Marrow *and* • If the only measurable disease is FLC, a normal FLC ratio [d]
Very Good Partial Response (VGPR)	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis [c] *or* • ≥90% reduction in serum M-protein and urine M-protein <100 mg/24 h [c] • If the only measurable disease is FLC, a >90% reduction in the difference between involved and uninvolved FLC levels
Partial Response (PR)	• If present at baseline, ≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥90% or to <200 mg/24hrs [c] • If the only measurable disease is FLC, a ≥50% reduction in the difference between involved and uninvolved FLC levels • If the only measurable disease is BM, a ≥ 50% reduction in BM PCs (provided the baseline PCs was ≥ 30%) • If present at baseline, ≥ 50% reduction in the size (SPD) of soft tissue plasmacytomas [j]
Minor Response (MR)	• If present at baseline, ≥25% but ≤ 49% reduction of serum M protein *and* reduction in 24-hour urine M-protein by 50-89% which still exceeds 200mg/24 hours [c] *and* • If present at baseline, ≥50% reduction in the size (SPD) of soft tissue plasmacytoma [j]

Stable Disease (SD)	• Not meeting criteria for sCR, CR, VGPR, PR, MR or PD
Progressive Disease (PD) [b, h]	Increase of 25% from lowest value in any of the following [f, g]: • Serum M-protein (absolute increase must be ≥ 0.5 g/dL) *and/or* • Urine M-protein (absolute increase must be ≥ 200 mg/24 hrs) *and/or* • If the only measurable disease is FLC, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL) *and/or* • If the only measurable disease is BM, bone marrow PC percentage (absolute increase must be ≥ 10%) [e] Or any one or more of the following: • Development of new bone lesion or soft tissue plasmacytoma or ≥50% increase from nadir in the size (SPD) of existing bone lesions or soft tissue plasmacytoma or ≥ 50% increase in the longest diameter of a previous lesion >1 cm in short axis [j] • 50% increase in circulating plasma cells (minimum of 200 cells per L) if this is the only measure of disease
Clinical Relapse	One or more of the following direct indicators of increasing disease and/or end-organ dysfunction that are considered related to the underlying plasma cell proliferative disorder: 1. Development of new soft tissue plasmacytomas or bone lesions on skeletal survey, magnetic resonance imaging, or other imaging 2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion 3. Hypercalcemia (>11.5 mg/dL; >2.875mM/L) 4. Decrease in hemoglobin of more than 2 g/dL (1.25mM) or to less than 10 g/dL 5. Rise in serum creatinine by more than or equal to 2 mg/dL (≥177mM/L) 6. Hyperviscosity

[a] All response categories require two consecutive assessments (sCR, CR, VGPR, PR, MR, PD) made at any time before the institution of any new therapy. MRD tests should be done as specified per the test schedule. sCR, CR, VGPR, PR, MR and SD categories and MRD require no known evidence of progressive or new bone lesions or extramedullary plasmacytomas if radiographic studies were performed. However, radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. Each category, except for stable disease, will have a working subcategory of "unconfirmed" [prefix 'u"] to designate first time point at which response category MAY have been achieved if confirmed. The date of the initial test is considered as the date of response for evaluation of time dependent outcomes such as duration of response.

[b] CR patient will need to progress at the same level as VGPR and PR patients to be considered a PD. A positive immunofixation alone is not sufficient. If a patient has already achieved a complete response prior to registration as a result of the induction therapy, the patient will be considered a continued complete response if they continue to meet the complete response criteria at the next assessment. Reconfirmation of complete response is not required.

[c] If more than one M protein spike meets the criteria for measurable disease at baseline, then both need to be followed for response. Otherwise, only follow the measurable M protein spike for response.

[d] In patients in whom the only measurable disease is by serum FLC levels: CR in such patients indicates a normal FLC ratio of 0.26-1.65 in addition to the CR criteria listed above.

[e] Bone marrow criteria for PD are only to be used in patients without measurable disease by M protein and by FLC;

[f] A "25% increase" refers to M protein, FLC and bone marrow results and does not refer to bone lesions, soft tissue plasmacytoma or hypercalcemia. The lowest value does not need to be a confirmed value. If the lowest serum M-protein is ≥ 5 g/dL, an increase in serum M-protein of ≥ 1 g/dL is sufficient to define disease progression.

[g] In the case where a value is felt to be a spurious result per physician discretion (for example, a possible lab error), that value will not be considered when determining the lowest value.

[h] Progressive disease should be confirmed on two consecutive evaluations, where the timing of confirmation is per the treating physician and can be done immediately within the same cycle or on the next cycle. However, treatment may be discontinued for progressive disease that is unconfirmed per physician discretion. In this case, an objective status of PD should be entered on the measurement form and progressive disease should be reported on the event monitoring form.

[i] Presence/absence of clonal cells is based upon the k/l ratio. An abnormal k/l ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is k/l of 4:1 or 1:2.

[j] Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the sum of the products of the maximal perpendicular diameters of measured lesions (SPD).

[k] Requires a complete response as defined in the table. MRD tests should be done as specified per the test schedule. MRD requires no known evidence of progressive or new bone lesions if radiographic studies were performed. However, radiographic studies are not required to satisfy these response requirements. **NOTE: An objective status of MRD negative should be reported on the treatment measurements form only when flow MRD by bone marrow is negative.**

11.6 Criteria for engraftment (for hematopietic stem cell transplant studies only)

Engraftment is defined as:

- The first day of three consecutive days on which the absolute neutrophil count (ANC) >500/mm^3 and
- The first of three consecutive days with an untransfused platelet count >20,000/mm^3.

12.0 Descriptive Factors

12.1 Depth of Response at registration: MRD positive sCR vs. MRD positive CR vs. VGPR vs PR vs SD

12.2 MM risk categories (As per Appendix IV): High vs. standard/intermediate vs. unknown.

12.3 Immediately prior treatment was maintenance: yes vs. no

12.4 Prior number of anti-myeloma regimens: 1 vs. >1 (NOTE: Any maintenance therapy given after an induction regimen is considered a part of that induction therapy and thus, 1 regimen)

12.5 Parameters followed for hematologic response (pick one) as per the time specified in section 3.18 : serum M-spike ≥1 g/dL and urine M-spike ≥200 mg/24 hours vs. serum M-spike ≥1g/dL only vs. urine M-spike ≥200 mg/24 hours only vs. serum immunoglobulin free light chain ≥10 mg/dL vs. bone marrow cells ≥30%. Distinguish between SPEP measurements versus quantitative IgA measurements versus quantitative IgD measurements for serum M-spike.

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Patients who are responding

Patients who are sCR, CR, VGPR, PR, MR, or SD (or usCR, uCR, uVGPR, uPR, uMR) will continue treatment per protocol. Treatment may continue until disease progression as long as the patient continues to respond and does not have any unacceptable toxicity.

13.3 Criteria for Initiation of Event Monitoring

Patients who go off protocol treatment for the following reasons will go to the event-monitoring phase per Section 4.2:

- Progressive multiple myeloma at any time on the clinical trial
- Patient requests to discontinue study treatment
- Patient develops an intercurrent illness that precludes further participation, or requires a prohibited concomitant treatment
- The Investigator withdraws the patient in the patient's best interests
- Administrative reasons (e.g., the patient is transferred to hospice care)
- An adverse event, which in the opinion of the Investigator, precludes further trial participation
- A dose omission of more than 28 days beyond the scheduled date of retreatment for daratumumab or lenalidomide

All attempts should be made to complete the End of Study procedures if a patient goes off treatment early.

13.4 Criteria for Study Discontinuation

The study may be temporarily or permanently discontinued at any site and at any time. Reasons for study discontinuation may include, but are not limited to, the following:

- Safety concerns
- Poor enrollment

- Non-compliance with the protocol, Good Clinical Practice guidances or other regulatory requirements by the Investigator(s)
- Request to discontinue the trial by a regulatory or health authority or an IRB
- Manufacturing difficulties/concerns

All Investigators and the requisite regulatory authorities will be notified if the study is suspended or terminated for safety reasons. In the case of such termination, the Investigator will notify the IRB.

13.5 Ineligibles

A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will go directly to the event-monitoring phase of the study (or off study, if applicable).

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per the protocol.
- If the patient never received treatment, on-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

13.6 Major violation

A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the event-monitoring phase of the study. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. Event monitoring will be required per Section 4.2 of the protocol.

13.7 Cancel

A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

14.0 Body Fluid Biospecimens

None.

15.0 Drug Information

15.1 Daratumumab (**Darzalex Faspro™,** Darzalex™, JNJ-54767414)

15.11 **Background**: Daratumumab is an antineoplastic agent that is an antibody against the CD-38 antigen expression on cells including multiple myeloma.

SQ formulation: Daratumumab and hyaluronidase-fihj injection is a sterile, preservative-free, colorless to yellow, and clear to opalescent solution supplied in a single-dose vial for subcutaneous administration. Each 15 mL single-dose vial contains 1800 mg daratumumab and 30,000 units hyaluronidase, L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 20, sorbitol, and Water for Injection, USP.

IV formulation: Daratumumab drug product is a colorless to yellow liquid concentrate. It is presented at a target concentration of 20 mg/mL in a 6R or 25R vial with a nominal fill volume of 5 mL or 20 mL, respectively. It is administered by the intravenous (IV) route after dilution in a sterile, pyrogen-free physiological saline solution (0.9% NaCl) provided by the investigation site. The diluent is a commercially available product approved by the competent authority of the relevant country.

Daratumumab drug product is formulated as a concentrate of 20.0 mg/mL ± 2.0 mg/mL in an isotonic buffer consisting of sodium acetate, sodium chloride, mannitol and polysorbate 20 at pH 5.5.

15.12 **Storage and handling**:

The daratumumab vials should be stored in the original carton in a refrigerator at 2ºC to 8ºC and must not be utilized after the expiry date printed on the label. The product must be protected from light and must not be frozen. Since daratumumab does not contain preservatives, any unused portion remaining in the vial must be discarded.

IV: Daratumumab will be diluted in a sterile, pyrogen-free physiological saline solution (0.9% NaCl) prior to IV administration.

SQ: Daratumumab and hyaluronidase-fihj SC injection is directly drawn from the vial into a syringe and is compatible with polypropylene or polyethylene syringe material; polypropylene, polyethylene, or polyvinyl chloride (PVC) subcutaneous infusion sets; and stainless steel transfer and injection needles. After the solution is withdrawn into the syringe, replace the transfer needle with a syringe cap. To avoid needle clogging, attach the hypodermic injection needle or subcutaneous infusion set to the syringe immediately prior to injection.

15.13 **Administration:**

- IV Administration: Administer the diluted solution by intravenous infusion using an infusion set fitted with a flow regulator and with an in-line, sterile, non-pyrogenic, low protein-binding polyethersulfone (PES) filter (pore size 0.22 or 0.2 micrometer). Polyurethane (PU), polybutadiene (PBD), PVC, PP or PE administration sets must be used.
  - Infusion should be completed within 15 hours
  - Refer to the Infusion rates in the table below
  - Do not store any unused portion of the infusion solution for reuse. Any unused product or waste material should be disposed of in accordance with local requirements.
  - Do no infuse daratumumab concomitantly in the same intravenous line with other agents

- SQ administration: Utilizing a hypodermic injection needle or subcutaneous infusion set, inject 15 mL of the daratumumab and hyaluronidase-fihj solution into the subcutaneous tissue of the abdomen approximately 3 inches to the right or left of the navel over approximately 3-5 minutes. No data are available on performing the injection at other sites of the body.

Daratumumab has been administered as monotherapy at doses up to 24 mg/kg and as combination therapy at doses up to 16 mg/kg. The daratumumab infusion should be intravenously administered at the appropriate initial infusion rate, as presented in the table below. Incremental escalation of the infusion rate should be considered only if the previous infusion of daratumumab was well tolerated as defined in the table below.**Infusion Rates for Daratumumab Administration via IV**

	Dilution Volume	**Initial Infusion Rate (first hr)**	**Increments of Infusion Rate**	**Maximum Infusion rate**
First Infusion	1000 ml	100 mL/hr	50 mL/hr every hr	200 mL/hr
Second infusion[a]	500 ml	50 mL/hr	50 mL/hr every hr	200 mL/hr
Subsequent infusions[b]	500 ml	50 mL/hr	50 mL/hr every hr	200 mL/hr

[a]Modified rates should only be used if the first infusion of daratumumab was well-tolerated as defined by an absence of > Grade 1 IRRs during the first 3 hours.
[b]Modified rates should only be used if the first 2 infusions of daratumumab were well-tolerated as defined by an absence of > Grade 1 IRRs during a final infusion rate of ≥ 100 mL/hr.

15.14 **Pharmacokinetic information**:

Pharmacokinetic (PK) data are available from GEN501, MMY2002 and MMY1002 monotherapy studies. Doses across these studies ranged from 0.005 to 24 mg/kg. The PK profile was consistent with target-mediated disposition with rapid target-related clearance at low doses and slower clearance at higher doses. Preliminary PK data from Study GEN503 show that following both the first dose and multiple repeated doses, the PK profile of daratumumab in combination with lenalidomide and dexamethasone is similar to what was observed in Study GEN501 following the same dose and schedule. The data suggest that lenalidomide and dexamethasone do not affect the PK profile of daratumumab.

Overall, biomarker assessments evaluated to date provided evidence of NK cell reduction with daratumumab single agent or combination treatment. Increases in T-cell counts and clonality were observed providing preliminary evidence of the immunomodulatory effects of daratumumab that needs further investigation. No significant changes in other immune subsets were observed with daratumumab treatment. A large overlap in baseline CD38 expression was observed between responders and non-responders along with its reduction with daratumumab treatment irrespective of response.

Following the administration of the recommended dose of 1,800 mg daratumumab and 30,000 units hyaluronidase subcutaneously once weekly for 8 weeks, the mean ± standard deviation (SD) maximum trough concentrations (Ctrough following the 8th dose) were 593±306 µg/mL compared to 522±226 µg/mL for daratumumab 16 mg/kg administered intravenously, with a geometric mean ratio of 108% (90% CI: 96, 122). The estimated median daratumumab area under the concentration-time curves (AUC0-7 days) and daratumumab peak concentration (Cmax) following the 8th dose were comparable between subcutaneous and intravenous daratumumab (4017 µg/mL•day vs. 4,019 µg/mL•day for AUC0-7 days and 592 µg/mL vs. 688 µg/mL for Cmax). The absolute bioavailability of daratumumab-hyaluronidase is 69%, with peak concentrations occurring around 3 days (Tmax). The estimated mean (coefficient of variation, CV) volume of distribution for the central compartment is 5.2 L (37%) and peripheral compartment was 3.8 L with the daratumumab-hyaluronidase formulation. Daratumumab is cleared by parallel linear and nonlinear saturable target mediated clearances. The estimated mean (CV%) linear clearance of daratumumab is 119 mL/day. The estimated mean (CV%) elimination half-life associated with linear clearance is 20 days (22%).

Body Weight (BW): After administration of 1,800 mg daratumumab and 30,000 units hyaluronidase subcutaneously once weekly for 8 weeks, the mean maximum C_{trough} was 12% lower in the higher body weight group (>85 kg) while the mean maximum C_{trough} was 81% higher in the lower BW group (≤ 50 kg) compared to the corresponding BW groups in the intravenous daratumumab arm.

15.15 **Known potential toxicities**:

- **Very Common (≥10%):**
  Blood and lymphatic system disorders: neutropenia, thrombocytopenia, anemia, lymhopenia
  Gastrointestinal disorders: nausea, vomiting, diarrhea, constipation
  Infections and infestations: upper respiratory tract infection, bronchitis, pneumonia, nasopharyngitis
  Injury, poisoning and procedural complications: infusion related reaction
  Metabolism and nutrition disorders: hypokalemia, hyperglycemia, decreased appetite
  Musculoskeletal and connective tissue disorder: muscle spasms, back pain, arthralgia, pain in extremity, bone pain, musculoskeletal chest pain
  Nervous system disorders: dizziness, headache, tremor
  Psychiatric disorders: Insomnia, anxiety

Respiratory, thoracic and ediastinal disorders: cough, dyspnea, nasal congestion
Vascular disorders: hypertension
General disorders and administration site conditions: fatigue, pyrexia, chills, peripheral edema, asthenia, non-cardiac chest pain, pain

- **Common (1 to <10%):**
  General disorders and administration site conditions: injection site reaction, peripheral edema
  Infections and infestations: respiratory tract infection, influenza, lower respiratory tract infection, sepsis, sinusitis, rhinitis, pharyngitis, viral respiratory tract infection, nasopharyngitis, respiratory syncytial virus infections, laryngitis, tonsillitis, lung infection, herpes zoster
  Blood and lymphatic disorders: febrile neutropenia
  Cardiac disorders: atrial fibrillation
  Respiratory, thoracic, and mediastinal disorders: pulmonary edema, hypoxia, laryngeal edema, pneumonitis, bronchospasm

- **Uncommon and rare known potential toxicities, <1%:**
  Infections and infestations: metapneumovirus infection, tracheitis, acute sinusitis, bronchiolitis, epiglottitis, oropharyngeal candidiasis, rhinovirus infection, tracheobronchitis, upper respiratory tract bacterial infection, infectious bronchitis, infectious laryngitis, infectious pharyngitis, viral rhinitis, respiratory syncytial virus, infectious pneumonia
  Blood and Lymphatic Disorders: neutropenic sepsis, neutropenic infection

Please refer to the prescribing information or package insert for a more complete comprehensive list of treatment-related adverse events

15.16 **Drug procurement:** Drug will be procured from the commercial supply of daratumumab.

15.17 **Special populations:**

- **Geriatric use:** Of the 237 subjects treated with daratumumab monotherapy in clinical studies, 44% were 65 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out. Based on population PK analysis, age (range: 31 to 84 years) had no clinically important effect on the PK of daratumumab, and the exposure of daratumumab was similar between younger (age <65 years, n=127) and older patients (age ≥65 years, n=96). No dose adjustments are considered necessary.
- **Renal impairment:** No formal studies of daratumumab in subjects with renal impairment have been conducted. Changes in renal function are unlikely to have an effect on the elimination of daratumumab since daratumumab is not excreted via renal pathways. Based on a population pharmacokinetic (PK) analysis no dosage adjustment is necessary for subjects with renal impairment. Daratumumab has not been studied in

subjects with severe renal impairment (creatinine clearance <20 mL/min) or on hemodialysis.

- **Hepatic Impairment:** No formal studies of daratumumab in subjects with hepatic impairment have been conducted. Changes in hepatic function are unlikely to have any effect on the elimination of daratumumab since IgG1 molecules such as daratumumab are not metabolized through hepatic pathways. Based on a population PK analysis, no dosage adjustments are necessary for subjects with mild hepatic impairment (Total Bilirubin [TB] 1.0× to 1.5× upper limit of normal [ULN] or aspartate aminotransferase [AST] >ULN). Daratumumab has not been studied in subjects with moderate to severe hepatic impairment (TB >1.5× ULN and any AST).

15.18 **Nursing Guidelines**

- Daratumumab can cause severe infusion reactions, usually during the first infusion. Patients who have experience a reaction may experience further reactions with subsequent infusions. Most reactions occur during or within 4 hours of infusion, however, may occur up to 48 hourse after an infusion. Warn patient of this possibility. Monitor patient throughout infusion for bronchospasm, hypoxia, SOB, and hypertension. Patients may also experience symptoms of anaphylaxis. Administer emergency medication as ordered.
- Patients may experience infections, including URI and pneumonia. Patients who have an ongoing infection should not receive agent.
- Patients may experience gastrointestinal side effects including diarrhea and nausea. Treat sympotomatically and monitor for effectiveness.
- Warn patients about the possibility of peripheral neuropathy, dizziness, and insomnia.
- Fatigue is common. Instruct patient in energy conserving lifestyle.
- Rarely patients may experience cardia issues including, atrial-fibrillation, peripheral edema, and hypertension. Instruct patient to report any chest pain, heart palpitations, and swelling to the study team.
- Monitory CBC w/diff as cytopenias (thrombocytopenia, neutropenia, anemia, and lymphopenia) have been seen. Instruct patient to report any unusual, bruising, bleeding, and/or infections/fever to the study team.

15.2 Lenalidomide for Oral Administration (Revlimid®)

15.21 **Background**: Lenalidomide has antineoplastic, immunomodulatory and antiangiogenic characteristics via multiple mechanisms. Lenalidomide selectively inhibits secretion of proinflammatory cytokines (potent inhibitor of tumor necrosis factor-alpha secretion); enhances cell-mediated immunity by stimulating proliferation of anti-CD3 stimulated T cells (resulting in increased IL-2 and interferon gamma secretion); inhibits trophic signals to angiogenic factors in cells. Lenalidomide inhibits the growth of myeloma cells by inducing cell cycle arrest and cell death.

15.22 **Formulation and Dispensing**: Commercially available for oral administration as: Capsules: 5 mg, 10 mg, 15 mg and 25 mg

Lenalidomide is approved for marketing only under a FDA approved, restricted distribution program called Revlimid REMS. Physicians, pharmacies, and patients must be registered; a maximum 28-day supply may be dispensed; a new

prescription is required each time it is filled; pregnancy testing is required for females of childbearing potential.

15.23 **Preparation, storage, and stability**: Store oral capsules at controlled room temperature between 15ºC and 30ºC (59 ºF and 86 ºF). Refer to labeling on the bottle for expiration date of the commercial tablets.

15.24 **Administration:** Refer to the treatment section for specific administration instructions. Administer with water. Swallow capsule whole; do not break, open, or chew.

15.25 **Pharmacokinetic information**:
Absorption: Rapid
Metabolism: Approximately two-thirds of Lenalidomide is eliminated unchanged through urinary excretion.
Protein binding: ~30%
Time to peak, plasma: Healthy volunteers: 0.6-1.5 hours; Myeloma patients: 0.5-4 hours
Half-life elimination: ~3 hours
Excretion: Urine (~67% as unchanged drug)

15.26 **Potential Drug Interactions**:
Increased Effect/Toxicity: Abatacept and Anakinra may increase the risk of serious infection when used in combination with Lenalidomide. Lenalidomide may increase the risk of infections associated with vaccines (live organism).
Decreased Effect: Lenalidomide may decrease the effect of vaccines (dead organisms).
Herb/Nutraceutical Interactions: Avoid echinacea (has immunostimulant properties; consider therapy modifications).

15.27 **Known potential adverse events:** Consult the package insert for the most current and complete information.

Boxed Warnings:
1. Potential for human birth defects
2. Hematologic toxicity (neutropenia and thrombocytopenia)
3. Deep Venous Thrombosis and Pulmonary Embolism

Common known potential toxicities, >10%:
Cardiovascular: Peripheral edema
Central nervous system: Fatigue, pyrexia, dizziness, headache
Dermatologic: Pruritus, rash, dry skin
Endocrine & metabolic: Hyperglycemia, hypokalemia
Gastrointestinal: Diarrhea, constipation, nausea, weight loss, dyspepsia, anorexia, taste perversion, abdominal pain
Genitourinary: Urinary tract infection
Hematologic: Thrombocytopenia, neutropenia, anemia, myelosuppression is dose-dependent and reversible with treatment interruption and/or dose reduction
Neuromuscular & skeletal: Muscle cramp, arthralgia, back pain, tremor, weakness, paresthesia, limb pain

Ocular: Blurred vision
Respiratory: Nasopharyngitis, cough, dyspnea, pharyngitis, epistaxis, upper respiratory infection, pneumonia

Less common known potential toxicities, 1% - 10%:
Cardiovascular: Edema, deep vein thrombosis, hypertension, chest pain, palpitation, atrial fibrillation, syncope
Central nervous system: Insomnia, hypoesthesia, pain, depression
Dermatologic: Brusing, cellulitis, erythema
Endocrine & metabolic: Hypothyroidism, hypomagnesemia, hypocalcemia
Gastrointestinal: Vomiting, xerostomia, loose stools
Genitourinary: Dysuria
Hematologic: Leukopenia, febrile neutropenia, Lymphopenia
Hepatic: ALT increased
Neuromuscular & skeletal: Myalgia, rigors, neuropathy
Respiratory: Sinusitis, rhinitis, bronchitis, pulmonary embolism
Miscellaneous: Night sweats, diaphoresis

Rare known potential toxicities, <1% (Limited to important or life-threatening):
Angioedema, Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis
Tumor Lysis Syndrome

15.28 **Drug procurement:** As a requirement of the REMS program, access to Lenalidomide is restricted. Lenalidomide is approved for marketing only under a FDA approved, restricted distribution program called REVLIMID REMS (www.REVLIMIDREMS.com) formerly known as the RevAssist program. Physicians, pharmacies, and patients must be registered; a maximum 28-day supply may be dispensed; a new prescription is required each time it is filled; pregnancy testing is required for females of childbearing potential.

15.29 **Nursing Guidelines:**

- Myelosuppression is dose-dependent and reversible with treatment interruption and/or dose reduction. Monitor CBC w/diff regularly. Instruct patient to report any unusual bruising or bleeding (thrombocytopenia); signs and symptoms of infection (neutropenia); and energy conserving lifestyle (anemia).
- Lenalidomide can have thrombotic adverse events (i.e DVT and PE). Instruct patient to report any limb swelling or pain, and to seek medical attention for shortness of breath or chest pain.
- Because of the potential for birth defects patients should be instructed in effective methods of birth control. Female patients should use 2 forms of birth control during treatment and for 4 weeks after discontinuing therapy. Males must be instructed to use a latex condom during any sexual contact with a woman of child bearing potential (even if they have had a vasectomy), because it is unknown if lenalidomide is present in semen.
- Patents may experience pruritus, rash and dry skin. Because of the rare risk of Steven's Johnson Syndrome, patients should immediately report any rash to their provider.
- Drug may cause hyperglycemia. Patients with diabetes or impaired fasting glucose may need to have their glucose levels monitored more closely.

- Gastrointestinal side effects (diarrhea, constipation, nausea, dyspepsia, anorexia, etc) are commonly seen. Manage patient symptomatically and monitor for effectiveness.
- Patients may experience myalgias, arthralgias, and other generalized pain. Administer analgesics as ordered and monitor for their effectiveness.
- Upper respiratory symptoms (nasopharyngitis, cough, epistaxis, etc.) can be seen. Manage symptomatically and monitor for effectiveness.

16.0 Statistical Considerations and Methodology

16.1 Overview

This is a phase II study of Daratumumab for transplant eligible multiple myeloma patients. This study is designed to assess the rate of minimal residual disease (MRD) negativity using a one stage phase II study design with an interim analysis in patients with transplant eligible multiple myeloma.

16.11 Primary Endpoint: The primary endpoint of this study is the rate of MRD negative response after ASCT. MRD negative response after ASCT is defined as achievement of MRD negative status in the bone marrow by flow cytometry (MPF) at the day 100 post ASCT visit. All patients meeting the eligibility criteria, who have signed a consent form and have begun treatment will be evaluable for response, unless they are determined to be a major violation.

16.12 Sample Size: The one stage study design with an interim analysis to be used is fully described below. A minimum of 20 and a maximum of 45 evaluable patients will be accrued total onto this phase II study unless undue toxicity is encountered. We anticipate accruing an additional 5 patients to account for ineligibility, cancellation, major treatment violation, or other reasons for a total of 50 patients overall.

16.13 Accrual Rate and Study Duration: The anticipated accrual rate is 2 evaluable multiple myeloma patients per month. Therefore, the accrual period for this phase II study is expected to be about 2 years. The maximum total study duration is expected to be approximately 5 years, or until the last patient accrued has been observed at least for 3 years after registration.

16.3 Statistical Design:

16.31 Decision Rule:

Previous studies of evaluation of minimal residual disease in multiple myeloma have been limited and have included small numbers of patients. In one previous study of lenalidomide, bortezomib and dexamethasone (RVD) induction followed by ASCT followed by 2 cycles of RVD consolidation and 1-year Lenalidomide maintenance in 31 untreated transplant eligible MM patients, an MRD negative response rate of 54% by flow cytometry was seen post ASCT in 26 evaluable patients tested. A MRD negative response rate of 65% by bone marrow flow cytometry would be of interest for this study.

The largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 45%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 65%. The following one–stage design with an interim analysis is based on a two-stage Simon optimum design[28] and requires 45 evaluable patients to test the null hypothesis that the true success proportion in this patient population is at most 45%.

16.311 Interim Analysis: Enter 20 evaluable patients into the study. If 9 or fewer successes are observed in the first 20 evaluable patients, we will consider this regimen ineffective in this patient population and terminate the

study. Otherwise, if the number of successes is at least 10, we will continue accrual.

16.312 Final Decision Rule: Enter an additional 25 evaluable patients into the study. If 24 or fewer successes are observed in the first 45 evaluable patients, we will consider this regimen ineffective in this patient population and terminate this study. Otherwise, if the number of successes is at least 25, this will be considered evidence of promising activity and the treatment may be recommended for further testing in subsequent studies in this population.

16.313 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making process.

16.314 NOTE: We will not suspend accrual at the interim analysis to allow the first 20 patients to become evaluable, unless undue toxicity is observed. Given the limited overall sample size and the inclusion of an adverse events stopping rule, we feel it is ethical to not halt accrual for the interim analysis. However, if accrual is extremely rapid, we may temporarily suspend accrual in order to obtain safety data on these patients before re-opening accrual to further patients.

16.32 Power and Significance Level: Assuming that the number of successes is binomially distributed, the significance level is .09, i.e. there is a 9% chance of finding the drug to be effective when it truly is not. The probability of declaring that this regimen warrants further study (i.e. statistical power) and the probability of stopping at the interim analysis under various success proportions can be tabulated as a function of the true success proportion as shown in the following table.

If the true success proportion is...	0.45	0.50	0.55	0.60	0.65
Then the probability of declaring that the regimen warrants further study is…	0.09	0.25	0.49	0.74	0.90
And the probability of stopping at the interim analysis is…	0.59	0.41	0.25	0.13	0.05

16.33 Other considerations: Adverse events, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study.

16.4 Analysis Plan

The analysis for this trial will commence at planned time points (see 16.2) and at the time the patients have become evaluable for the primary endpoint. The Statistician and Study Chair will make the decision, in accord with CCS Standard Operating Procedures, availability of data for secondary endpoints (e.g., laboratory correlates), and the level of data maturity. It is anticipated that the earliest date in which the results will be made available via manuscript, abstract, or presentation format is all patients have been

followed at least through the day 100 post ASCT visit (approximately 8 months) or have discontinued study treatment prior to ASCT.

16.41 Primary Outcome Analysis:

16.411 Definition: The primary endpoint of this trial is the rate of MRD negative response after ASCT. MRD negative response after ASCT is defined as achievement of MRD negative status in the bone marrow by flow cytometry (MPF) at the day 100 post ASCT visit. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response, unless they are determined to be a major violation.

16.412 Estimation: The proportion of successes will be estimated by the number of successes divided by the total number of evaluable patients. Ninety-five percent confidence intervals for the true success proportion will be calculated according to the approach of Duffy and Santner.

16.413 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making processes; however, they will be included in final point estimates and confidence intervals

16.42 Secondary Outcome Analyses

The rate of MRD negative response after pre-SCT consolidation with Daratumumab will be estimated by the number of patients who achieve MRD negative status by flow cytometry (MPF) in the bone marrow afterpre-SCT consolidation with Daratumumab divided by the total number of evaluable patients. Exact binomial 95% confidence intervals for the true rate of MRD negative response after pre-SCT consolidation with Daratumumab will be calculated.

The rate of MRD negative response after 1 year (12 cycles) of Daratumumab and lenalidomide maintenance will be estimated by the number of patients who achieve MRD negative status by flow cytometry(MPF) in the bone marrow after 1 year of maintenance therapy divided by the total number of evaluable patients. Exact binomial 95% confidence intervals for the true rate of MRD negative response after 1 year of maintenance will be calculated.

Progression-free survival time is defined as the time from registration tothe time of progression or death due to any cause. Patients who are aliveand progression-free will be censored on the date of their last disease assessment. Patients who receive subsequent treatment for myeloma before disease progression will be censored on the date of their last disease assessment prior to initiation of the subsequent treatment. The distribution of progression-free survival will be estimated using the method of Kaplan-Meier.

Survival time is defined as the time from registration to death due to any cause. The distribution of survival time will be estimated using the method of Kaplan-Meier.

The overall response rate at day 100 post ASCT will be estimated by the number of patients with an objective status of sCR, CR, VGPR, or PR at the day 100 post ASCT assessment divided by the total number of evaluable patients. Response assessment will be in comparison to values obtained at the disease assessment at the time registration. Exact binomial 95% confidence intervals for the true overall response rate at day 100 post ASCT will be calculated.

Adverse Events: All eligible patients that have initiated treatment will be considered evaluable for assessing adverse event rate(s). The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed to determine patterns. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration.

16.43 Exploratory Outcomes Analyses

16.431 To evaluate the correlation of MRD assessment between blood and bone marrow, patients will be categorized as positive vs. negative MRD for each measure. The number of patients who have agreement between the 2 measures (both positive or both negative) will be assessed.

16.432 To evaluate the correlation of MRD assessment between flow cytometry (MPF) and NGS, patients will be categorized as positive vs. negative MRD for each measure. The number of patients who have agreement between the 2 measures (both positive or both negative) will be assessed.

16.433 Immune repertoire profiling (Section 1.74) will be assessed as continuous variables and their mutual change over time as assessed on the pre-specified time points will be correlated with response category to the treatment.

16.434 ADCP and ADCC (Section 1.75) will be assessed as continuous variables and their mutual change over time as assessed on the pre-specified time points will be correlated with response category to the treatment

16.5 Data and Safety Monitoring:

16.51 The principal investigator(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

16.52 Adverse Event Stopping Rules:

The stopping rules specified below are based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e. an adverse event with attribute specified as "possible," "probable," or "definite") that satisfy one of the following:

- If 5 or more patients in the first 15 treated patients experience a grade 4 or higher non-hematologic adverse event at least possibly related to treatment.
- If after the first 15 patients have been treated, 30% of all patients experience a grade 4 or higher non-hematologic adverse event at least possibly related to treatment.

We note that we will review grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.6 Results Reporting on ClinicalTrials.gov

At study activation, this study will have been registered within the "ClincialTrails.gov" website. The Primary and Secondary Endpoints along with other required information for this study will be reported on www.ClinicalTrials.gov. For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 3 years after the study opens to accrual. The definition of "Primary Endpoint Completion Date" (PECD) for this study is at the time all patients registered have been followed at least through the day 100 post ASCT visit (approximately 8 months) or have discontinued study treatment prior to ASCT.

16.7 Inclusion of Women and Minorities:

16.71 This study will be available to all eligible patients, regardless of race, gender, or ethnic origin.

16.72 There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

16.73 The geographical region served by MCCC has a population which includes approximately 5% minorities. Based on prior MCCC studies involving similar disease sites, we expect about 5-7% of patients will be classified as minorities by race and about 40% of patients will be women. Expected sizes of racial by gender subsets are shown in the following table:

Accrual Estimates by Gender/Ethnicity/Race

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	0	1	1
Not Hispanic or Latino	20	29	49
Ethnic Category: Total of all subjects	20	30	50
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	0	0	0
Black or African American	1	1	2
Native Hawaiian or other Pacific Islander	0	0	0
White	19	29	48
Racial Category: Total of all subjects	20	30	50

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens: None.

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Data submission instructions for this study can be found in the Data Submission Schedule.

18.2 Event monitoring

See Section 4.2 and data submission table for the event monitoring/survival follow-up schedule.

18.3 CRF completion

This study will use Medidata Rave for remote data capture (rdc) of all study data.

18.4 Site responsibilities

Each site will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.5 Supporting documentation

This study requires supporting documentation for diagnosis prior to study entry as well as for evidence of response to study therapy and progression after study therapy. For patients with any previous ASCT for MM, provide a clinic note including ASCT history or transplant records (E.g. central registry records) . Supporting documentation for diagnosis will include either a pathology report or a laboratory report demonstrating multiple myeloma (including SPEP, UPEP, FLC, Serum and Urine Immunofixation, Bone Marrow Biopsy and Aspirate, skeletal bone survey, PET scan, Plasma Cell Proliferation and Assessment and FISH). These reports should be uploaded into the Supporting Documentation: Baseline form within 14 days of registration.

For progression of disease prior to study entry, supporting documentation includes the evidence needed to determine the patient's progression prior to enrollment. These documents should be uploaded into the Supporting Documentation: Baseline form within 14 days of registration.

For response to treatment, supporting documentation may include SPEP, UPEP, FLC, Serum and Urine Immunofixation, Bone Marrow Biopsy and aspirate, skeletal bone survey, and PET scan. These documents should be uploaded into the Supporting Documentation form.

For patients who progress after study therapy supporting documentation may include any of the following: SPEP, UPEP, FLC, serum and urine immunofixation, bone marrow biopsy and aspirate, skeletal bone survey, and PET scan. These documents should be uploaded into the Supporting Documentation form.

18.6 Labelling of materials

Each site will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.7 Incomplete materials

Any data entered into a form will result in that form being marked as "received." However, missing data will be flagged by edit checks in the database.

18.8 Overdue lists

A list of overdue materials is automatically available to each site at any time. The appropriate co-sponsor/participant will be responsible to obtain the overdue material.

18.9 Correction forms

If a correction is necessary the QAS will query the site. The query will be sent to the appropriate site to make the correction in the database and respond back to the QAS.

19.0 Budget

19.1 Costs charged to patient: All routine clinical care. Lenalidomide and daratumumab procurement.

19.2 Tests to be research funded: None.

19.3 Other budget concerns: Protocol administration, study coordinator time, data management, and statistical analysis efforts will be funded by the Division of Hematology-Oncology.

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Appendix I ECOG Performance Status Scale

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead

*As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

The ECOG Performance Status is in the public domain therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

From http://www.ecog.org/general/perf_stat.html

Appendix II Creatinine Clearance (CrCl) Calculation

Cockcroft-Gault Equation:

Creatinine clearance for males = $\frac{(140 - \text{age})(\text{weight in kg})}{(72)(\text{serum creatinine in mg/dL})}$

Creatinine clearance for females = $\frac{(140 - \text{age})(\text{weight in kg})(0.85)}{(72)(\text{serum creatinine in mg/dL})}$

Appendix III New York Heart Association Classification of Congestive Heart Failure

NYHA Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. no shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while *at rest*. Mostly bedbound patients.

Adapted from Dolgin M, Association NYH, Fox AC, Gorlin R, Levin RI, New York Heart Association. Criteria Committee. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, MA: Lippincott Williams and Wilkins; March 1, 1994. Original source: Criteria Committee, New York Heart Association , Inc. Diseases of the Heart and Blood Vessels. Nomenclature and Criteria for diagnosis, 6th edition Boston, Little, Brown and Co. 1964, p 114.

Appendix IV Mayo Risk Stratification

High Risk

FISH deletion 17p

FISH t(14; 16)

FISH t(14; 20)

GEP (if done) High-risk signature

Intermediate Risk

FISH t(4:14)

Metaphase cytogenetic del 13

Hypodiploidy

Standard Risk

All others including:

FISH t(11; 14)

FISH t(6; 14)

Appendix V Patient Medication Diary

PATIENT MEDICATION DIARY

Please complete this diary on a daily basis. Write in the amount of the dose of lenalidomide, that you took in the appropriate "Day" box.

On the days that you do not take any study drug, please write in "0". If you forget to take the drug but remember on the same day, it is ok to take the drug at that time. If you forget to take your daily dose and do not remember on the same day, please write in "0" and do not make up this missed dose. Remember to take your prescribed dose at the next regularly scheduled time. If you experience a vomiting episode in the same day after taking lenalidomide, do not make up this dose. Please indicate the time you took the drug and the time you vomited.

If you experience any health/medical complaints or take any medication other lenalidomide, please record this information.

Take the lenalidomide with water at about the same time every day (with or without food). Swallow the capsules whole; do not open, break, or chew the capsules.

Week of: _____

Study Drug	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Lenalidomide							

Week of: _____

Study Drug	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
Lenalidomide							

Week of: _____

Study Drug	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21
Lenalidomide							

Week of: _____

Study Drug	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
Lenalidomide							

Patient Signature: _____

My next scheduled visit is: _____

If you have any questions, please call: _____

HEALTH/MEDICAL COMPLAINTS

Please record all health/medical complaints you may have experienced below.

Please describe what you experienced	Date started	Date stopped

OTHER MEDICATION

Record only medication (prescription and/or over-the-counter, including herbal medications and vitamins) taken other than_____.

Name of Medication	Why did you take the medication?	Dose	Frequency

Study Coordinator Use Only

Verified by _____ Date_____