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EAA171

Optimizing Prolonged Treatment In Myeloma Using MRD Assessment (OPTIMUM)

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Addendum #1 (Pre-Activation)
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Addendum #5

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Rev. Add3

Agents	IND#	NSC#	Supply
Ixazomib/Placebo		767907	NCI supplied
Lenalidomide	N/A	703813	Commercially available

IND Sponsor: DCTD, NCI

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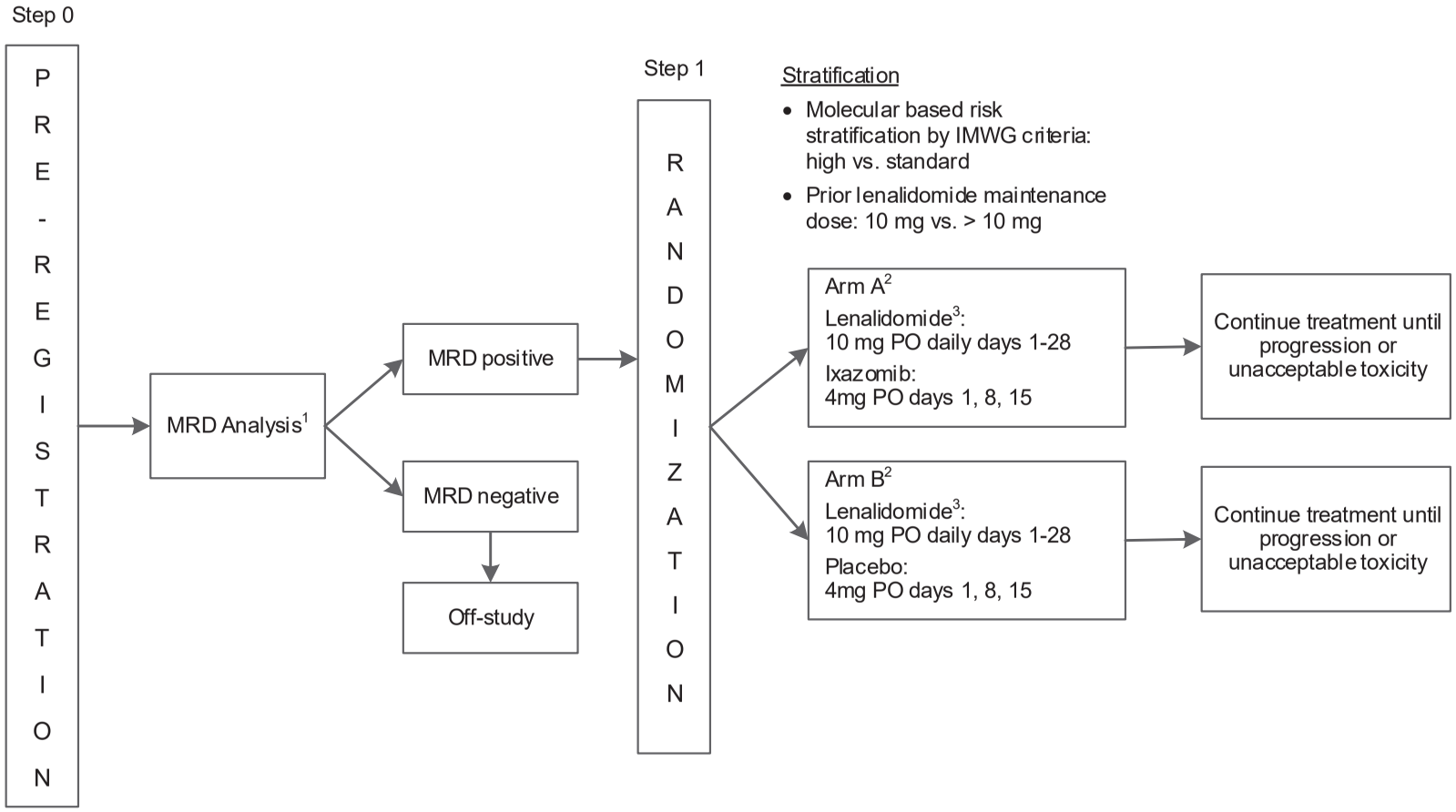
CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

Rev. Add1

For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory > Regulatory Submission) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878) for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions by phone or email : 1-888-823-5923, or ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).		
For clinical questions (i.e., patient eligibility or treatment-related) Contact the Study PI of the Coordinating Group.		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		

Rev. Add1
Rev. Add3

Schema



1 cycle = 28 days

Accrual Goal: Step 0 = 840 patients, Step 1 = 510 MRD positive patients

1. Eligibility status for Step 1 randomization will be determined by either central MRD assessment at Mayo Clinic or local immunofixation test results.
2. Treatment is blinded. Confirmation of randomization will indicate that patient is on Arm X.
3. For patients with creatinine clearance 30-60 mL/min lenalidomide dose will be reduced to 5 mg PO daily.

1. Introduction

1.1 Background

The treatment approaches for myeloma have undergone dramatic transformation over the past decade with the introduction of several new classes of effective drugs, often used in combination to achieve the maximum response. Prior treatment approaches in transplant-eligible patients consisted of a defined duration of induction therapy with a doublet followed by a single stem cell transplant (SCT) and observation, yielding a median of 2-3 years of myeloma disease control. The current approach typically includes an induction therapy utilizing a triplet combination that includes a proteasome inhibitor and an immunomodulatory drug (IMiD), followed by a single SCT and post-transplant maintenance with or without a brief consolidation phase.[1-3] This change in strategy has led to a near doubling of the progression free survival (PFS) in this patient group. Sequential approaches as well as newer drug combinations also have led to unprecedented depth of response in myeloma, with a substantial majority of patients achieving a complete response (CR) or better to therapy. However, patients continue to relapse despite reaching a CR, reflecting the inadequacy of this measurement in detecting a substantial burden of residual tumor cells. As a result, it became apparent that newer, more sensitive approaches to tumor burden assessment are needed and this led to the development of flow cytometry or Next-Generation Sequencing based approaches, which can detect tumor burden to a sensitivity of 1 in 10^5 to 10^6 cells.

New International Myeloma Working Group (IMWG) response criteria: Given the impact of minimal residual disease (MRD) results on the outcomes in myeloma and more importantly, the relative lack of sensitivity of conventional electrophoretic methods of protein measurement, the IMWG recently updated the response criteria to include MRD assessment (Table 1).[4] The revised criteria, including either one of the two most prevalent methods as equally acceptable, instead focuses on the level of tumor burden that defines MRD negativity. While there is early data showing that 10^{-6} provides a better outcome compared with 10^{-5}, the latter was selected for the definition given the importance of having access to techniques that can be used everywhere. The revised criteria also incorporated imaging, given that disease can be present outside the marrow space and this can have an impact on the outcomes as shown by the French trial (IFM2009), where both PET negativity and marrow MRD negativity at 10^{-5} had a better outcome than either being positive. Finally, the concept of sustained MRD as an additional measure of response stability has been introduced as part of the MRD criteria.

Table 1. Revised IMWG Response Criteria		
Response subcategory		**Revised IMWG Response criteria**
MRD negativity criteria requires conventional CR	**Sustained MRD negative**	MRD negative in the marrow and by imaging as defined below, confirmed one year apart. Subsequent evaluations can be used to further specify the duration of negativity (e.g., MRD negative @ 5 years etc.)
	Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by next-generation flow cytometry on bone marrow aspirates with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
	Sequencing MRD negative	Absence of clonal plasma cells by next generation sequencing on bone marrow aspirates with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
	Imaging MRD-negative	MRD negative as defined by Next-generation flow or Next-generation sequencing **PLUS** Disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT

The value of MRD negativity has been studied in multiple phase II and III studies and a table summarizing the results is shown below. These studies clearly demonstrate a prognostic value for this measurement (Table 2).

Table 2: Studies utilizing MRD detection and outcomes based on MRD status			
Study/ Design	**N**	**MRD (-)**	**Outcomes**
Paiva et al[5]: Newly diagnosed MM patients from GEM2000 (VBMCP/VBAD induction plus ASCT]). MRD status by MFC was determined at day 100 after SCT.	295	42%	PFS (median 71 vs 37 months, P < .001) and OS (median not reached vs 89 months, P = .002) were longer in patients who were MRD negative at day 100 after SCT.
Rawstron et al[6]: MRC IX trial of newly diagnosed MM: Intensive pathway with CTD vs. CVAD followed by SCT	397	62%	Median PFS for MRD (+) of 15.5 months vs. 28.6 months for MRD (-) patients (P<0.001). Median OS of 59.0 months in MRD (+) vs. 80.6 months in MRD (-) patients (P = 0.02)
Rawstron et al[6]: MRC IX trial of newly diagnosed MM: non-intensive pathway (MP vs. CTDa)	245	15%	MRD (+) at end of induction associated with non-significantly inferior PFS (7.4 vs. 10.5 months).
Puig et al[7]: GEM2000 (VBMCP/VBADx6 followed by SCT), GEM05 (transplant-	102	51%	MRD (-) had significantly longer PFS, both in intensively treated patients (45 vs 27 months, P=0.02) and in non-intensively treated patients (NR

Table 2: Studies utilizing MRD detection and outcomes based on MRD status			
Study/ Design	**N**	**MRD (-)**	**Outcomes**
eligible patients: VBMCP/VBAD plus Btz in the last two cycles, thal/dex or btz/thal/dex; elderly patients: six induction cycles with VMP or VTP).			vs 27 months P=0.002)
Sarasquete et al[8]: MM patients who had achieved CR after SCT	24	53%	Improved PFS for MRD (-) (27 vs. 10months, P=0.05).
Paiva et al[9]: Transplant-ineligible MM patients who had achieved >75% reduction in the M-component after induction	102	30%	Achieving MRD-negativity translated into superior PFS and TTP compared with conventional CR or stringent CR (without clonality assessment on trephine biopsy).
Paiva et al[10]: Newly diagnosed MM patients from GEM2000 and GEM2005MENOS65 achieving CR at day 100 after SCT.	241	64%	The presence of baseline high-risk cytogenetics and persistent MRD at day 100 after ASCT were the only independent factors that predicted unsustained CR
Roussel[11]: Phase II study with three induction cycles followed by SCT, consolidation, and 1-year lenalidomide maintenance	31	68%	Estimated 100% relapse-free survival at 3-years for MRD-negative patients
Puig et al[7]: GEM2000 (VBMCP/VBADx6 followed by ASCT), GEM05 (transplant-eligible patients: VBMCP/VBAD plus Btz in the last two cycles, thal/dex or btz/thal/dex; elderly patients: six induction cycles with VMP or VTP).	102 (241)	47%	MRD (-) patients had significantly longer PFS, both in the intensively treated patient group (54 vs 27 months, P=0.001) and in the non-intensively treated cases (NR vs. 31 months, P=0.029)
Korthals et al[12]: Induction: 2 to 4 cycles of idarubicin and dex followed by ASCT	53 (70)	49%	Median EFS in the low-MRD group was significantly longer than in the high-MRD group (35 vs. 20 months; P = .001). OS was significantly longer for the low-MRD group (70 vs. 45

Table 2: Studies utilizing MRD detection and outcomes based on MRD status

Study/ Design	N	MRD (-)	Outcomes
			mos; P = 0.04).
Putkonen et al[13]: Patients with myeloma who had achieved CR/near-to-CR after autologous or allogeneic stem cell transplantation	30 (37)	57%	Low/negative MRD after SCT was a significant predictive factor for the prolongation of PFS (70 vs. 19 months; P = 0.003)
Martinez Lopez et al[14]: Patients enrolled in the GEM2000 protocol: six cycles of VBCMP/VBAD followed by SCT.	53 (88)	53%	PFS of 68% in MRD (-) vs. 28% for MRD (+) patients; P = 0.001
Ladetto et al[15]: 4 cycles of bortezomib, thalidomide and dexamethasone consolidation after SCT	39	18%	Improved PFS; 100% vs. 77% at 6 months (grouped by median tumor load median as detected by ASO RQ-PCR (P=0.02)
Sarasquete et al[8]: MM patients who had achieved CR after SCT	24 (32)	29%	Improved PFS for MRD (-) (34 vs. 15 months, P=0.04)
Martinelli et al[16]: Patien[17]ts in CR following autologous or allogeneic SCT	44 (50)	27%	MRD (-) patients had a significantly lower relapse rate (41% v 16%; P <0.05) and longer relapse-free survival than MRD+ cases (35 v 110 months; P <0.005).

In addition, a recent meta-analysis of several studies highlights the impact of MRD negativity on PFS and overall survival (OS), both in all patients as well as in those patients in a conventional CR.[18] In this analysis of published literature (1990-2016), 14 studies (n = 1273) provided data on the impact of MRD on PFS, and 12 studies (n = 1100) provided data on the impact of MRD on OS. Results were reported specifically in patients who had achieved conventional CR in 5 studies for PFS (n = 574) and 6 studies for OS (n = 616). Achievement of MRD-negative status following treatment was associated with a significant improvement in progression-free survival (hazard ratio [HR], 0.41; 95% CI, 0.36-0.48; N = 1273). Overall survival was also significantly prolonged in MRD-negative patients (HR, 0.57; 95% CI, 0.46-0.71; N = 1100). In looking specifically at CR patients, there was improvement in PFS (HR, 0.44; 95% CI, 0.34-0.56; P < .001) as well as OS (HR, 0.47; 95% CI, 0.33-0.67; P < .001).

All these studies clearly show the prognostic value of achieving MRD negativity with the current therapies. Based on this prognostic potential, the FDA has recently approved the next-generation sequencing (NGS) assay to detect MRD, in patients with multiple myeloma (MM). However, it remains unclear if MRD

should be the target of therapy and if therapeutic decisions can be based on the MRD status of individual patients. The continuing improvements in therapy and consequent deep responses has led to an urgency in defining the role of MRD in myeloma.

1.2 Rationale for the Trial

The mainstream adoption of MRD represents years of work demonstrating the clinical relevance of achieving an MRD state after any given therapy. The available data demonstrate the prognostic value of this response state and its potential for a regulatory endpoint given the long period of time required to reach median progression and overall survival with the new therapies used in MM. So, two important questions with respect to MRD in MM have been answered: First, for a given patient achieving MRD negative status with therapy will translate to better outcomes and can be used for prognostication. Second, and for a group of patients, a higher proportion of patients achieving MRD will translate to better survival thus allowing for comparisons of different types of therapy, lending itself to be a valid regulatory endpoint. The most significant question for the patient and the physician in the clinic, however, is to determine what to do with the MRD result for a given patient, as the achievement of MRD is a composite outcome of the therapy employed and the disease biology for a given patient. Our goal is to prove that if a patient is MRD positive, changing therapy to convert this patient to MRD negative status will translate to a better outcome for the given patient, thus taking biology out of the equation. This requires carefully designed phase III trials, as is the case with the current trial design. The current trial will be able to ask critical questions as to whether acting on the MRD status will improve the depth of response, prolong disease control and most importantly overall survival for a given patient.

Also, this trial design will give us a unique opportunity to study the kinetics of relapse from MRD in patients with MM. This information is crucial as we make progress in the field. Once we achieve a high proportion of MRD negative state with the improved therapies, the question which will need to be addressed is the timing of retreatment for disease recurrence: whether this should be started at the reemergence of MRD positivity or at the time of biochemical relapse? This study by virtue of the design and serial MRD assessment and imaging assessment will provide the necessary information that will drive the design of future studies. It is possible that early intervention in these patients, at the time of MRD conversion, may have a better long-term impact, akin to the hypothesis currently being studied in smoldering multiple myeloma (SMM).

The fundamental question that this trial is designed to address can be stated very clearly - Does escalating therapy based on the MRD positive status after a defined duration of therapy alter the outcomes in patients with myeloma? This is the most important question we face in this disease today.[4,19] If the MRD is negative, do we stop therapy? If the MRD is positive, do we escalate therapy? The former question is going to be addressed through a clinical trial of daratumumab and lenalidomide vs. lenalidomide maintenance that is being planned through the cooperative groups. The study that we propose will complement this trial and help answer the second question. In order to answer this question with certainty, we require a homogenous group of patients who have received similar treatments, in whom we can test the MRD status using a well-defined method, and who can then be randomized to either continue with the

same treatment or alter the treatment approach. The control arm treatment should be considered the standard of care (SOC) in the population being studied. Among patients with myeloma who are eligible to undergo autologous peripheral blood stem cell transplant, the current SOC is to initiate therapy with a triplet combination (typically an IMiD and a proteasome inhibitor containing combination) and continue for three to four cycles, followed by autologous SCT and lenalidomide maintenance, typically continued until progression.[1-3,20,21]

Lenalidomide maintenance as SOC: Maintenance approaches have become SOC in myeloma, both in the transplant and non-transplant setting. While the maintenance approach in the non-transplant setting remains less well defined, multiple phase III trials as well as a meta-analysis of the three largest trials have clearly shown OS and PFS improvement with lenalidomide maintenance post-autologous stem cell transplant.[1-3,20,21] Lenalidomide was recently approved by FDA for use in the maintenance setting based on these data.

Unanswered question regarding duration of maintenance: However, significant confusion remains in terms of the ideal duration of maintenance in this setting. The original French trial limited the duration to 2 years due to concerns about second primary malignancies. The US trial continued until progression– this is one of the reasons often quoted for the difference in the survival outcomes. An ongoing clinical trial (E1A11, ENDURANCE) is asking this question in the non-transplant setting. Understanding the impact of MRD negativity on the outcomes and how that interacts with the duration of maintenance will be critical to improve our understanding of this question.

Assessing for MRD status at the end of 1 year of maintenance and randomizing the patients to either continuing the current therapy or intensifying the therapy by adding another drug class to lenalidomide will provide a clean design to answer this clinically important question.

We elected to utilize next generation flow cytometry (NGF) using the Euroflow approach for MRD assessment.[4,22] The main reason for selecting this approach, instead of an NGS based approach for this trial, is the ability to interpret the assay without having a baseline specimen, which we believe will be difficult given that the patient is enrolled on trial at around the end of 12-18 months of therapy (induction, SCT and 6-12 months of maintenance) and marrow will have small numbers of plasma cells.

The proposed design has several unique strengths. The natural history of patients receiving lenalidomide maintenance for one year or indefinitely is well known based on several large clinical trials. The expected MRD status at the end of one year of maintenance has been defined recently in a large French randomized trial of VRD induction followed by transplant and one year of lenalidomide maintenance, where MRD assessment was systematically undertaken in a majority of patients. The control arm of indefinite lenalidomide maintenance is fully supported by the available data from phase III trials as well as a recent meta-analysis of the phase III trials which demonstrated an overall survival outcome improvement with the maintenance approach compared with observation. A similar study in the US (IFM/DFCI) essentially replicates the design of the French trial with a crucial difference being lenalidomide maintenance is indefinite until progression (NCT01208662). Evaluation of the OS benefit for escalating therapy in patients with persistent MRD will immediately

make the results highly relevant for clinical practice, and will transform MRD assessment from a prognostic tool to an important clinical tool.

Finally, we will use a double blind, placebo-controlled design, allowing for an unbiased estimate of the clinical benefit and the impact on PRO metrics.

We plan to evaluate multiple secondary endpoints in this trial including several exploratory approaches. In addition to standard response rates and PFS, we will explore the ability of an additional agent to produce MRD negativity in patients who have not been able to achieve MRD negativity while taking a single drug for 12 months. This will provide important information regarding the clonal heterogeneity and the differential effect of two classes of drugs on two clones, as can be learned from the accompanying genetic studies. This trial will prove to be a rich resource in asking some important future exploratory questions regarding the biology of the disease.

1.3 Choice of Intervention

Ixazomib in myeloma: Ixazomib is the first oral proteasome inhibitor to enter clinical practice and is currently approved for use in combination with lenalidomide in patients with relapsed myeloma. Ixazomib citrate (MLN9708), which has been formulated for oral (PO) administration, is a small molecule proteasome inhibitor.[23-25] It is the citrate ester of the biologically active boronic acid form, ixazomib (MLN2238). In water or aqueous systems, ixazomib citrate rapidly hydrolyzes to ixazomib. Similar to bortezomib, ixazomib potently, reversibly, and selectively inhibits the 20S proteasome. However, in contrast to bortezomib, it has a shorter dissociation half-life (t1/2) that may contribute to increased tissue distribution. Bortezomib has a slowly reversible dissociation rate from the red blood cell proteasome, while ixazomib demonstrates a more rapidly reversible dissociation rate from the blood but sustained effects on bone marrow and tumor proteasomes suggesting better tissue distribution. Ixazomib has been studied in several phase I and phase I/II studies evaluating both twice-weekly and weekly dosing schedules. In the twice-weekly dosing schedule, ixazomib is given on Days 1, 4, 8, and 11 of a 21-day cycle; in the weekly dosing schedule, the drug is given on Days 1, 8, and 15 of a 28-day cycle. To date, the development of oral ixazomib has focused on multiple myeloma [relapsed and/or refractory and newly diagnosed] and a related plasma cell dyscrasia, systemic light chain (AL) amyloidosis.

In Study C16005, ixazomib was given weekly (Days 1, 8, and 15), in combination with lenalidomide (Days 1-21), and dexamethasone (Days 1, 8, 15, and 22) in a 28-day cycle.[26] Patients with newly diagnosed MM were enrolled and treated with oral ixazomib (days 1, 8, and 15) plus lenalidomide 25 mg (days 1-21) and dexamethasone 40 mg (days 1, 8, 15, 22) for up to twelve 28-day cycles, then maintenance therapy with ixazomib (same schedule) every 28 days until progression. Patients could undergo stem cell collection after three cycles and discontinue for autologous stem cell transplant (ASCT) after six cycles. Overall, 65 patients were enrolled, 15 in Phase I and 50 in Phase II. Patients received a median of six cycles (range 1-19) with 27 (42%) remaining on treatment as of November 2012. Of those who have undergone stem cell mobilization, a median yield was 11.3 x 10^6 CD34+ cells/Kg (range 5-28). Ixazomib maximum tolerated dose (MTD) was established as 2.97 mg/m^2 and RP2D was selected as 2.23 mg/m^2; RP2D translates to a 4.0 mg fixed dose based on population PK results. Among the 64 evaluable patients, the overall response rate was 92%, including

55% Very Good Partial Response (VGPR) and 23% CR. Median time to first response was 0.92 months (range 0.89-6.44). Importantly, in this trial, 25 patients continued on maintenance ixazomib with no additional toxicity or toxicity-related discontinuation, but with increasing depth of response with time. Given the data on proteasome inhibitor –IMiD combinations in myeloma, adding ixazomib to lenalidomide allows us to utilize an effective agent, and allows us to do a double-blind study which is critical for evaluation of patient reported outcomes.

The combination of ixazomib and lenalidomide has been studied as maintenance therapy post autologous SCT.[27] This phase II trial enrolled 64 patients with a median age of 60 (range 39-74); 34 remained on therapy as of May 2017 having received a median of 28 cycles (range 1-51). Best overall response included stringent Complete Response (sCR 7.8%), CR (26.5%), VGPR (53%) and PR (10.9%). 29 patients had an improvement in their best overall response from their baseline response. The median PFS had not been reached with a median follow up of 37.8 months; estimated 2-year PFS is 81%. 30 patients are off study: 16 due to progressive disease (PD), 3 at PI discretion, and 11 due to consent withdrawal. 22 patients had G1/2 peripheral neuropathy (PN); 6 patients had G3 PN. 16 patients required a dose reduction to 2.4 mg for PN (8), neutropenia (3), hearing loss (2), rash (1), thrombocytopenia (1) and 4 patients discontinued ixazomib for neuropathy (2), neutropenia (1), and thrombocytopenia (1). 15 patients had a dose reduction of Len to 10 mg for 21 days of a 28-day cycle, while 9 patients had a dose reduction to 5 mg for 28 days.

<u>We selected ixazomib as the intervention in this trial for several reasons:</u>

1. Ixazomib appears to be at least as effective when used in combination with lenalidomide and dexamethasone in newly diagnosed myeloma, when comparing the results of the C16005 trial with the published data with VRd. Patients coming on this trial would have received on average four cycles of bortezomib containing regimen (VRd or VCd) as induction prior to stem cell transplantation, and hence would be relatively PI naïve. To further allay the concerns of the steering committee, we have now excluded any patient who progressed on a bortezomib-containing regimen pre-SCT or were primary refractory. This is likely to be a small population considering the high response rate with VRd and VCd.[24]
2. Ixazomib has the added advantage of being taken orally, and making it more convenient and acceptable for a patient who has been on oral maintenance for a year and now may be hesitant to come back in weekly for an injectable medication. An integrated analysis of ixazomib maintenance across 4 different studies was presented recently demonstrating a continued increase in depth of response with continued treatment, with excellent tolerability.[28] The phase III trial of ixazomib maintenance versus placebo was recently announced to show a PFS benefit for ixazomib.
3. The oral nature of the medication also allows us to do a placebo-controlled trial (Takeda has agreed to provide this), which will allow us to make a true estimate of the impact of therapy escalation on quality of life and patient reported outcomes.
4. The combination of ixazomib and lenalidomide as maintenance was studied in a phase II trial by investigators at MD Anderson and the results presented recently points toward this regimen being effective and well-tolerated in the setting of post-transplant maintenance.[27]

5. Most importantly, this design will nicely complement the SWOG maintenance trial, which is examining a de-escalation of a daratumumab + lenalidomide-based maintenance in the setting of no residual disease. This study will evaluate a PI and IMiD combination asking an equally relevant question of escalating therapy in face of residual disease. Given the three important therapeutic classes of current therapies, examining both a PI and IMiD combination as well as a monoclonal antibody (MoAb) + IMiD in this MRD guided treatment setting is important.
6. Finally, use of ixazomib as the add-on for escalating treatment will also keep other important classes of drugs, especially daratumumab (or anti-CD38 MoABs), in reserve for use at the time of the first relapse.

1.4 Patient Reported Outcomes Component

1.4.1 Background

Patient-reported outcomes (PRO) that measure the impact of disease and treatment on well-being from a physical, functional, emotional and social perspective are an important part of the benefit equation. Health-related quality of life (QOL) assessments have been incorporated into prior phase III multiple myeloma clinical trials and have been very useful in putting the results of these phase III trials in perspective. In fact, one of the earliest studies to address this was the phase III trial comparing an early SCT to a delayed SCT.[43] It was concluded that an early SCT was preferable based on the QOL estimates analyzed, which was defined as the time without symptoms and toxicity (Q-TWiST). More recently, there has been increased interest in assessing QOL among patients with MM given significant improvement in survival observed as well as the availability of different treatment options. A phase III trial of thalidomide maintenance evaluated QOL using the EORTC QLQ-C30 instrument in combination with a disease specific module. Assessments were performed every 2 months to 6 months then Q3 monthly to 5 years. A change score of 10 points from baseline was defined as clinically relevant. While PFS was prolonged with maintenance therapy, there was significant worsening of all the QOL parameters studied.[35] In another phase III trial comparing three different bortezomib combinations as upfront therapy for transplant ineligible patients (bortezomib-dexamethasone, bortezomib-thalidomide-dexamethasone, bortezomib-melphalan-prednisone, followed by bortezomib maintenance therapy), patient-reported QOL was recorded also using the EORTC QLQ-C30 questionnaire.[44] Decline in QOL parameters were observed in the early phases of therapy in all groups with recovery over time. These results demonstrate the feasibility of conducting health-related QOL assessments in the context of multicenter clinical trials as well as its value in reaching the eventual conclusions. Intensifying therapy and/or prolonging duration of therapy comes at a price economically due to patient financial burden and clinically due to sub-optimal tolerability, both of which may impact QOL. Research exploring factors contributing to medication adherence and the impact of side effects and symptom burden from the patient perspective, however, is limited.

1.4.2 Rationale

Patients and physicians often decide to alter therapy based on a variety of factors including patient age, patient and physician preference, response status, and toxicity from ongoing therapy. As we explore the concept of increasing the rate of MRD negativity by intensifying the therapy, it is important to assess the impact that the intervention has on PROs. With a comprehensive PRO evaluation, we will elucidate potential advantages and expand understanding at key clinical decision points. We hypothesize that adding ixazomib will not be associated with significantly worse treatment-related QOL compared with continuing on lenalidomide monotherapy given the oral, intermittent nature of ixazomib therapy. Furthermore, we hypothesize that longerperiods of ixazomib therapy will lower risk of disease progression and will may yield improved QOL. For this trial, we have chosen specific time points for primary comparison between arms, however, with limited QOL research in this setting we have yet to determine whether these are appropriate. Towards that end, it is also important to assess timing of QOL changes afforded with relatively frequent longitudinal QOL assessment. Beyond comparing treatment arms, we will evaluate the relationship between conversion from MRD-positive to MRD-negative status and change in QOL with the hypothesis that responders have comparatively better QOL than non-responders, a favorable outcome for the intervention arm. This assessment will have clinical translational value, as this will be one of the considerations as we move towards an MRD directed strategy in the clinic. Lastly, poor medication adherence as well as increased incidence and/or severity of patient reported adverse events are expected to be associated with lower QOL.

QOL assessments performed every three months during the first year post randomization will provide valuable longitudinal data to quantify the impact of the different maintenance approaches on patient QOL. Similar measurements during year 2 will provide an insight into the effects of disease recurrence on QOL measurements, as there will be an increasing proportion of patients on the control arm who will start to demonstrate biochemical recurrences. To interpret these maintenance QOL analyses, we will capture actual treatment received over the given period and monitor patient-specific barriers to medication adherence. As well, we will measure the impact of symptom burden and treatment-related side effects from a patient perspective. Assessing PROs during maintenance will, therefore, be of critical importance to the evaluation of the overall benefit of this therapeutic strategy and its clinical utility. PRO metrics, unfortunately, depend heavily on patient perspective that can be altered in different ways by the burden of therapy and the response to therapy. A placebo-controlled design such as the one proposed, however, enables an unbiased assessment of the true impact of altering therapy based on the MRD status.

1.4.3 Design

Chosen PRO instruments are designed to capture potential side-effects from treatment intervention, the impact of disease recurrence,

behavior towards taking treatment, and health-related quality of life. The Functional Assessment of Chronic Illness Therapy (FACIT) (http://www.facit.org) and the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) (https://healthcaredelivery.cancer.gov/pro-ctcae/) measurement systems will be utilized. Specifically, general health-related quality of life will be assessed with the Functional Assessment of Cancer Therapy – General (FACT-G) including 2 subscales [physical well-being (PWB) and functional well-being (FWB)].[39] We will add a treatment-specific tool to evaluate neurotoxicity along with the disease-specific multiple myeloma assessment.[40,70] These instruments have been validated and have been incorporated into our prior phase III MM treatment trials (E1A05, E1A06) as well as current phase III trials (E1A11, E3A06).[31,41] More recently, data from E1A05 showed the FACT-MM was feasible for use in clinical trials to measure myeloma-related functions and demonstrated acceptable psychometric properties.

NCI PRO-CTCAE items will evaluate treatment-emergent side effects expected with ixazomib and lenalidomide. This will be coupled with routine provider initiated and protocol specific interval toxicity assessment to inform a more comprehensive assessment, both as it concerns intensity and frequency, of perceived and experienced side effects from therapy. Furthermore, side effects from prolonged therapy with lenalidomide and ixazomib perceived by a patient and captured with the NCI PRO-CTCAE may be different than when assessed by a provider, an analysis that has not been performed yet in former clinical trials involving these agents. Considering the importance of reliable compliance with prescribed oral therapy as it concerns therapeutic benefit, understanding treatment adherence is important. Aside from tabulating compliance with continuous, protocol specific lenalidomide and ixazomib therapy based on patient medication calendars, medication taking behavior will be evaluated with the Adherence Starts with Knowledge (ASK-12).[42,43] The timing of PRO measurements will be consistent with office visits primarily during treatment, and will vary based on the instrument.

1.5 Imaging Component

1.5.1 Background

Advanced imaging modalities have contributed significantly to our understanding of disease biology in multiple myeloma and is an integral component of the diagnostic criteria, differentiating asymptomatic precursor stages from active disease. Multiple different modalities have been used in myeloma studies and provide complementary information. ^{18}F-FDG PET/CT allows simultaneous assessment of the bone, as well as presence of extramedullary lesions. MRI allows better assessment of the soft tissue and marrow involvement, especially with the use of diffusion-weighted images. Both baseline assessments, as well as follow-up imaging, also have an important prognostic role and appear to be associated with the survival of patients with MM. Myeloma cells, while they tend to be

primarily marrow-based, can be found in the extramedullary compartment, including the peripheral blood. As a result, imaging plays an important role in assessing response to therapy as well as identifying disease progression, both inside and outside the marrow. In fact, functional imaging assessment using ^{18}F-FDG PET/CT is an integral part of minimal residual disease assessment in myeloma in addition to following foci of extramedullary disease identified prior to start of treatment. Ongoing studies continue to explore new modalities as well as novel tracers to better identify the tumor cells.

1.5.2 Rationale

There is much to be learned in terms of the added value of imaging to the assessment of disease response and outcomes using traditional protein-based disease assessments. The value of PET-CT and MRI as tools for assessment of MRD has been assessed in the IFM2009 trial (IMAJEM).[25] That study was able to demonstrate an inferior survival outcome associated with persistent positivity even in the presence of MRD negativity in the marrow. While MRI changes were observed with therapy, PET-CT appeared to be more useful in the setting of response assessment. Other large retrospective studies have also examined the value of PET-CT. This trial provides a unique opportunity to assess the prognostic impact of PET positive lesions at the end of a year of maintenance, and how that may be impacted by the randomized intervention. It also provides a unique opportunity to examine the incremental value of PET-CT to marrow-based MRD testing and the impact of discrepant findings in the marrow and the extramedullary compartment. Another area that has not been studied well is the kinetics of relapse, especially in the extramedullary compartment. This trial, which will be enriched in a group of patients at higher-than-average risk of relapse (MRD-positive), will allow us to study the kinetics of extramedullary relapse in the context of biochemical relapse. Importantly, this will give us a unique opportunity to validate the currently proposed criteria for PET-CT assessment.[29]

1.5.3 Design

^{18}F-FDG PET/CT is currently considered a standard imaging modality for initial assessment, as part of MRD assessment and for identification of relapsed disease. Patients in this trial will undergo baseline ^{18}F-FDG PET/CT, as well as ^{18}F-FDG PET/CT at 12 and 24 cycles from study entry, in addition to those done for MRD confirmation. The serial imaging studies will be centrally reviewed, allowing us to complete the aims proposed.

2. Objectives

2.1 Primary Objective

2.1.1 To evaluate whether escalating maintenance therapy with the addition of ixazomib to lenalidomide improves overall survival (OS) among patients who are MRD positive after approximately 1 year of lenalidomide maintenance following an early stem cell transplant (≤ 12 months from diagnosis).

2.2 Secondary Objectives

2.2.1 To establish whether progression-free survival (PFS) is superior with the addition of ixazomib to lenalidomide maintenance.

2.2.2 To evaluate best response on treatment and compare response rates between arms.

2.2.3 To evaluate the safety profile of ixazomib added to lenalidomide and compare toxicity rates between arms.

2.3 Exploratory Objectives

2.3.1 To measure treatment exposure and adherence.

2.3.2 To estimate treatment duration, duration of response and time to progression.

2.4 Patient-Reported Outcomes (PRO) Objectives

2.4.1 Primary PRO Objectives

2.4.1.1 To quantify the extent to which the addition of ixazomib to lenalidomide maintenance contributes to neuropathy and associated physical and functional impairments.

2.4.1.2 To assess the impact of the addition of ixazomib to lenalidomide maintenance on disease control and associated physical and functional well-being.

2.4.2 Secondary PRO Objectives

2.4.2.1 To evaluate time to worsening and recovery rate related to neuropathy.

2.4.2.2 To evaluate time to improvement and response rate related to disease control.

2.4.3 Exploratory PRO Objectives

2.4.3.1 To evaluate attributes of select patient reported treatment-emergent symptomatic adverse events (PRO-CTCAE) longitudinally and compare responses with provider-reported adverse events.

2.4.3.2 To measure the likelihood of medication adherence and examine the relationship with treatment exposure.

2.4.3.3 To assess correlation among patient reported outcome measures and association with clinical outcomes.

2.4.3.4 To tabulate PRO compliance and completion rates.

2.5 Imaging Objectives

2.5.1 To evaluate the association between baseline ^{18}F-FDG PET/CT and patient outcomes.

2.5.2 To compare overall survival (OS) with the addition of ixazomib to lenalidomide among baseline ^{18}F-FDG PET/CT-positive and ^{18}F-FDG PET/CT -negative subgroups.

2.5.3 To compare the change in quantitative ^{18}F-FDG PET/CT parameters over time with the addition of ixazomib to lenalidomide.

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: CTEP Policy does not allow for the issuance of waivers to any protocol specified criteria (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm). Therefore, all eligibility criteria listed in Section 3 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 3 can result in the participant being censored from the analysis of the study, and the citation of a major protocol violation during an audit. All questions regarding clarification of eligibility criteria must be directed to the Group's Executive Officer (EA.ExecOfficer@jimmy.harvard.edu) or the Group's Regulatory Officer (EA.RegOfficer@jimmy.harvard.edu).

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

NOTE: This study involves pre-registration and randomization. Bone marrow specimen must be submitted for central MRD assessment and results will determine Step 1 eligibility. Patients will not be randomized without MRD results.

3.1 Step 0 Pre-Registration

_____ 3.1.1 Patient must be ≥ 18 years of age.

Rev. Add3 _____ 3.1.2 Patient must be previously diagnosed with multiple myeloma (MM) and be on lenalidomide maintenance with ≥ 5mg daily for at least 6 months and no more than 18 months after an early autologous stem cell transplantation (SCT ≤ 12 months of diagnosis). Patient must not be off lenalidomide maintenance therapy for more than 30 days prior to start of treatment on Step 1 of this protocol.

Rev. Add3 _____ 3.1.3 Patient must be able to undergo a diagnostic bone marrow aspirate following pre-registration to Step 0.

NOTE: A bone marrow aspirate specimen must be submitted to Mayo Clinic Hematology Laboratory for central assessment of Minimal Residual Disease (MRD) status to confirm patient's eligibility for Step 1 randomization.

Mayo Clinic will forward results to the submitting institution within three (3) business days of receipt of the bone marrow specimen.

Rev. Add3 _____ 3.1.4 Patient must have an ECOG performance status 0, 1, or 2.

_____ 3.1.5 Patient must not have primary refractory or progressive disease on a proteasome inhibitor-based regimen during induction therapy prior to stem cell transplant.

_____ 3.1.6 Patient must not be on other concurrent chemotherapy, or any ancillary therapy considered investigational.

NOTE: Bisphosphonates are considered to be supportive care rather than therapy and are allowed while on protocol treatment.

_____ 3.1.7 Patient must not have uncontrolled psychiatric illness or social situations that would limit compliance with study requirements.

_____ 3.1.8 Patient must not have another malignancy requiring treatment or have received treatment within two years before pre-registration or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with non-melanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.

Rev. Add3 _____ 3.1.9 Patient must have been able to maintain at least 5mg daily dose of lenalidomide without growth factor support.

_____ 3.1.10 Patient must not have known gastrointestinal (GI) disease or GI procedure that could interfere with the oral absorption or tolerance of ixazomib or lenalidomide including difficulty swallowing.

_____ 3.1.11 Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

_____ 3.1.12 Patient must not have known hepatitis B surface antigen-positive status or known or suspected active hepatitis C infection, but testing specifically for the trial is not required.

_____ _____

Physician Signature Date

Rev. Add3 **OPTIONAL:** This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

3.2 Step 1 Randomization

Rev. Add3 _____ 3.2.1 Patient must meet all eligibility criteria in Section 3.1 at the time of Step 1 randomization.

_____ 3.2.2 Patient must not be off lenalidomide maintenance therapy for more than 30 days prior to start of treatment on Step 1 of this protocol.

_____ 3.2.3 Patient must have evidence of residual disease by central MRD testing or by presence of monoclonal protein in serum or urine.

_____ 3.2.4 Patient must have SPEP, UPEP, and serum FLC performed ≤ 28 days prior to randomization.

Serum M-protein by SPEP _____ (g/dL)

Date of Test: _____

Urine M-protein light chain excretion by UPEP_____ (mg/24hr)

Date of Test: _____

NOTE: UPEP (on a 24-hour collection) is required, no substitute method is acceptable. Urine must be followed monthly if the baseline urine M-spike is ≥ 200 mg/24 hr. Please note that if both serum and urine M-components are present, both must be followed in order to evaluate response.

Serum Free Light Chain

Kappa FLC _____ (mg/dL) or _____ (mg/L);

Lambda FLC _____ (mg/dL) or _____ (mg/L);

Kappa/lambda ratio _____

Date of Test: _____

_____ 3.2.5 Patient must have the following laboratory levels obtained ≤ 14 days prior to randomization:

_____ 3.2.5.1 Hemoglobin ≥ 8 g/dL

Hemoglobin:_____ Date:_____

_____ 3.2.5.2 Untransfused platelet count ≥ 75,000 cells/mm^3

Platelet:_____ Date:_____

_____ 3.2.5.3 Absolute neutrophil count (ANC) ≥ 1000 cells/mm^3

ANC:_____ Date:_____

_____ 3.2.5.4 Calculated creatinine clearance ≥ 30 mL/min

Creatinine clearance:_____ Date:_____

_____ 3.2.5.5 Total bilirubin ≤ 1.5 times the upper limit of normal (ULN)

Total bilirubin:_____ ULN:_____ Date:_____

_____ 3.2.5.6 SGPT (ALT) and SGOT (AST) ≤ 3 times the upper limit of normal (ULN)

SGPT (ALT):_____ ULN:_____ Date:_____

SGOT (AST):_____ ULN:_____ Date:_____

_____ 3.2.6 Patient must not have Grade 2 or higher peripheral neuropathy or grade 1 peripheral neuropathy with pain per CTCAE.

_____ 3.2.7 Patient must not have uncontrolled intercurrent illness.

_____ 3.2.8 Patient must not have Grade 2 or higher diarrhea per CTCAE in the absence of antidiarrheals.

_____ 3.2.9 Patient must not have been on systemic treatment, within 14 days before the first dose of ixazomib, with strong CYP3A inducers (such as rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of St. John's wort.

Rev. Add3 _____ 3.2.10 Patient must agree to register into the mandatory Revlimid REMS® program and be willing and able to comply with the requirements of Revlimid REMS®. Refer to Section 8.2.8 of the protocol for more information on the Revlimid REMS® Program.

Rev. Add3 _____ 3.2.11 Patient must not be pregnant due to potential harm to the fetus from ixazomib and lenalidomide. All patients of childbearing potential must have a blood test or urine study with a sensitivity of at least 25 mIU/mL within 10-14 days prior to the first dose of lenalidomide and again within 24 hours prior to the first dose of lenalidomide. Patients of childbearing potential must also agree to ongoing pregnancy testing while on treatment. A patient of childbearing potential is defined as anyone, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy, or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months). Please see Appendix VI: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.

Patient of childbearing potential (Y/N)? _____

Date of blood test or urine study: _____

Result (positive/negative): _____

Rev. Add3 _____ 3.2.12 Patients of childbearing potential must either abstain from sexual intercourse for the duration of their participation in the study or agree to use TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME for 1) at least 28 days before starting study treatment; 2) while participating in the study; 3) during dose interruptions; and 4) for at least 90 days after the last dose of protocol treatment. Patients must also agree to not breastfeed during this same time period. Men must agree to either abstain from sexual intercourse for the duration of their participation in the study or use a latex condom during sexual contact with a partner of childbearing potential while participating in the study and for 90 days after the last dose of protocol treatment even if they have had a successful vasectomy. Patients must also agree to abstain from donating sperm while on study treatment and for 28 days after the last dose of protocol treatment even if they have had a successful vasectomy. All patients must agree to abstain from donating blood during study participation and for at least 28 days after the last dose of protocol treatment.

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

4. Registration and Randomization Procedures

Cancer Therapy Evaluation Program Investigator Registration Procedures

Rev. Add3

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✔	✔			
Financial Disclosure Form	✔	✔	✔		
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔		
GCP training	✔	✔	✔		
Agent Shipment Form (if applicable)	✔				
CV (optional)	✔	✔	✔		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL)

In addition, all investigators act as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the

DTL must be rostered at the enrolling site with a participating organization. Additional information can be found on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR ***Help Desk*** by email at RCRHelpDesk@nih.gov.

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Cancer Trials Support Unit Registration Procedures

Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

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IRB Approval:

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRB Manager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an active CTEP status;
- Active status at the site(s) on the IRB/REB approval (*applies to US and Canadian sites only*) on at least one participating organization's roster;
- If using NCI CIRB, active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Includes the IRB number of the IRB providing approval in the FDA Form 1572 in the RCR profile;
- Lists all sites on the IRB/REB approval as Practice Sites in the FDA Form 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements:

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number; and
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO).

- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all protocol-specific requirements (PSRs).

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Downloading Site Registration Documents:

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and its associated investigators and staff on a participating roster. To view/download site registration forms:

- Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of the screen
  - Enter the protocol #number in the search field at the top of the protocol tree; or
  - Click on the By Lead Organization folder to expand then select ECOG-ACRIN, and protocol number EAA171.
- Click on *Documents*, *Protocol Related Documents*, and use the *Document Type* filter and select *Site Registration*, to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

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Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal, log in to the CTSU members' website, go to the Regulatory section and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: at 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org in order to receive further instruction and support.

Delegation of Tasks Log (DTL)

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Each site must complete a protocol-specific Delegation of Tasks Log (DTL) using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an Approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and include a Master Task List, which describes DTL task assignments, CI signature, and CTEP registration requirements.

Checking Your Site's Registration Status:

Site's registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration*; and
- Enter the site's 5-character CTEP Institution Code and click on Go

- Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

NOTE: The status given only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

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Patient Enrollment

Patients must not start protocol treatment prior to Step 1 randomization.

Treatment should start within fourteen (14) days after Step 1 randomization.

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their FDA Form 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and HIPAA authorization form.

NOTE: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.1 Step 0 Pre-Registration

To proceed to randomization, patients must have central MRD testing performed by Mayo Clinic.

NOTE: Patients who are only pre-registered must not begin treatment.

The following information is to be provided at the time of pre-registration to the trial:

4.1.1 Protocol Number

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4.1.2 Site/Investigator Identification

- Institution CTEP ID
- Treating Investigator
- Consenting Person
- Site Registrar
- Network Group Credit
- Credit Investigator

4.1.3 Patient Identification

- Patient's initials (first and last)
- Patient's Hospital ID and/or Social Security number
- Patient demographics
  - Gender
  - Birth date (mm/dd/yyyy)
  - Race
  - Ethnicity
  - Nine-digit ZIP code
  - Method of payment
  - Country

4.1.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.1.

4.1.5 Additional Requirements

4.1.5.1 Patients must provide a signed and dated, written informed consent form.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office – Boston.

4.1.5.2 Bone marrow aspirate must be submitted to Mayo Clinic following pre-registration as indicated in Section 10 for determination of MRD status. Mayo Clinic will forward results to the submitting institution within three (3) business days of receipt of the bone marrow.

4.2 Step 1 Randomization

The following information is to be provided at the time of randomization to the trial:

4.2.1 Protocol Number

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4.2.2 Site/Investigator Identification

- Institution CTEP ID

- Treating Investigator
- Consenting Person
- Site Registrar
- Network Group Credit
- Credit Investigator

4.2.3 Patient Identification

- Patient's initials (first and last)
- Patient's Hospital ID and/or Social Security number
- Patient demographics
  - Gender
  - Birth date (mm/dd/yyyy)
  - Race
  - Ethnicity
  - Nine-digit ZIP code
  - Method of payment
  - Country

4.2.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.2.

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4.2.5 Stratification Factors

- Molecular-based risk: high vs. standard
- Prior lenalidomide maintenance dose: 5 mg, 10 mg, > 10 mg

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- < 12 months maintenance and ≥ 12 months maintenance

4.3 Additional Requirements

4.3.1 Quality of life forms are to be submitted as indicated in Section 6.3.

4.3.2 Revlimid REMS Program

Lenalidomide will be provided in accordance with the Revlimid REMS® program of Celgene Corporation. Per standard Revlimid REMS® requirements all physicians who prescribe lenalidomide for research patients enrolled into this trial, and all research patients must be registered in and comply with all requirements of the Revlimid REMS® program. Refer to Section 8.2.8 of the protocol for more information on the Revlimid REMS® Program.

4.3.3 Medidata Rave

Medidata Rave is a clinical data management system being used for data collection for this l trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and

- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

  Rave role requirements:

  Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;

  - Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
  - Rave Read Only role must have at a minimum an Associates (A) registration type

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

This study has a Delegation of Tasks Log (DTL). Therefore, those requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. To accept the invitation, site staff must either click on the link in the email or log in to iMedidata via the CTSU members' website under Data Management > Rave Home and click to accept the invitation in the Tasks pane located in the upper right corner of the iMedidata screen. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the Tasks pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the Studies pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com.

4.3.4 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

4.3.5 Imaging Submission Using Transfer of Images and Data

Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- A valid CTEP-IAM account.
- Registration and Credential Repository (RCR) registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR) registration type. Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR.
- TRIAD Site User role on an NCTN or ETCTN roster.

All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

TRIAD Installation:

To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at https://triadinstall.acr.org/triadclient/.

This process can be done in parallel to obtaining your CTEP-IAM account and RCR registration.

For questions, contact TRIAD Technical Support staff via email TRIAD-Support@acr.org or 1-703-390-9858.

Image Submission and Quality Assurance Review:

Standard of Care (SOC) ^{18}F-FDG Whole Body PET/CT imaging should ideally use the same scanner and should be used consistently across all imaging time points for the same patient if possible. If the same scanner is not available, equipment that most closely approximates the baseline scanner should be used.

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For ^{18}F FDG PET CT imaging time from ^{18}F-FDG injection to beginning of PET CT acquisition will be 60 minutes +/- 10 minutes. This is to be adhered to for all PET CT scanners and study time points.

Upon arrival at the PET facility for their ^{18}F-FDG Whole Body scan, confirm that the patient is properly prepared for the imaging study per institutional guidelines including but not limited to:

The patient is fasting for at least 4 hours but should be hydrated with plain water.

The time between injection of ^{18}F-FDG and imaging should be 60 minutes +/- 10 minutes.

The patient's weight and height are measured and recorded (not verbally relayed by the subject).

The pre-injection blood glucose level is in accordance with institutional guidelines (typically < 200 mg/dL, measured ideally within one hour of ^{18}F-FDG injection). If the serum glucose is out of the expected range, the study should be rescheduled. The referring physician or primary physician of the subject should be contacted to optimize blood glucose control.

In diabetic patients, insulin injection is not administered for at least 6 hours before the injection of ^{18}F-FDG. In patients on oral anti-diabetic medications, these drugs must be taken as planned before the injection of ^{18}F-FDG.

The patient should be off steroids for at least 24 hours and if on intravenous glucose/dextrose, they should be stopped for 6 hours.

All imaging time points for repeat PET imaging should ideally use the same scanner and the same imaging parameters as used for the baseline PET study.

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There are several sources for SOC guidelines for ^{18}F-FDG Whole Body PET/CT scans. For this study, the following should serve as the minimum requirement to be used locally: http://jnm.snmjournals.org/content/47/6/1059.long.

All imaging time points should be submitted to the ACR Core Laboratory via TRIAD for Image Quality Assurance (IQA) review. **Imaging should be submitted within three (3) business days from the time of acquisition to ensure rapid review and prompt feedback of any discrepancies from the Core Lab.**

Upon image receipt, a Core Lab Imaging Technologist will perform an IQA review of the image data to ensure that all imaging is intact and has been submitted in its entirety (i.e., primary PET AC, PET NAC and CTAC series), the recommended imaging parameters were followed, and the exam is of adequate image quality. In the event that an exam is deemed non-compliant or is missing critical DICOM tags used for SUV analysis (i.e., weight, height and time of injection), a Core Lab Imaging Technologist will issue a query within the Medidata

Rave data management system. Sites are expected to resolve data queries within seven (7) business days.

NOTE: **Please refrain from anonymizing the DICOM header of any exam prior to uploading into the TRIAD application.** Custom DICOM editing can exclude an exam from the final analysis, due to the omission of technical data elements. These elements include, but are not limited to, the study date, scanner station name, scanner serial number, patient height and weight and any scan acquisition parameter. TRIAD has been uniquely configured to locate and scrub all PHI from the exam's DICOM header, during the image transfer to ensure the anonymity of our trial patients.

4.4 Emergency Unblinding

The information provided below is for the use by a physician, nurse, CRA or pharmacist treating the patient. These contact numbers should not be used by patients. Patients should be instructed to call their doctor's office in the event of an emergency or adverse event that may result in the need to unblind the patient.

In the event of an emergency or severe adverse reaction necessitating identification of the medication for the welfare of the patient, please contact the EA Drug Team at DrugOrder@ecog-acrin.org during business hours (9am-4pm M-F Eastern Time) or AnswerConnect at 1-866-296-8940 outside of those hours. The request will require the protocol number (i.e., EAA171), the patient ID number (5-digit number), patient initials, patient step, your contact information, as well as the reason for unblinding. ECOG-ACRIN staff may contact you for further details in-order to determine the validity of the request and will work to obtain the required approvals to unblind the patient. Once approved, a staff member will provide the unblinded treatment identity. Note that if a patient is unblinded, they must discontinue protocol treatment.

NCI CTEP should also be notified of a request for unblinding.

4.5 Instructions for Patients Who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted through Medidata Rave according to the schedule in the EAA171 Forms Completion Guidelines. However, laboratory, patient reported outcomes, and imaging correlatives beyond baseline will not be collected.

5. Treatment Plan

5.1 Administration Schedule

NOTE: All patients should be on at least 81 mg acetylsalicylic acid (ASA) daily while receiving lenalidomide. Please see Section 5.6.16 for additional information regarding thromboprophyaxis.

5.1.1 Arm X (Arms A and B)

NOTE: Patients are randomized to Arm A (lenalidomide and ixazomib) or Arm B (lenalidomide and placebo) but will be identified as on Arm X as this is a blinded trial.

Lenalidomide: 10 mg PO daily days 1-28

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NOTES: For patients with creatinine clearance 30-60 mL/min lenalidomide dose will be reduced to 5 mg PO daily.

Lenalidomide may be taken with or without food. Capsules must not be crushed, chewed, or opened.

Please refer to Section 8.2 for additional Lenalidomide administration details.

Ixazomib/Placebo: 4 mg PO days 1, 8, and 15

Repeat cycle every 28 days until disease progression or unacceptable toxicity.

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NOTES: Ixazomib/Placebo capsule(s) must be taken on an empty stomach, 1 hour before or 2 hours after food. Capsule(s) must be swallowed whole with water. Do not open or break capsules.

Missed or delayed doses can be taken only if the next scheduled dose is ≥ 72 hours away. A missed dose should not be taken within 72 hours of the next scheduled dose. If vomiting occurs after taking a dose, the patient should not repeat the dose. Resume dosing at the time of the next scheduled dose.

Please refer to Section 8.1 for additional Ixazomib/Placebo administration details.

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5.2 Lenalidomide Fertility Instructions

NOTE: Please also see Appendix VI "Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods."

Before starting study drug:

All study participants must be registered into the mandatory Revlimid REMS® program, and be willing and able to comply with the requirements of Revlimid REMS®. Patients of childbearing potential must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10 to 14 days prior to the first dose of lenalidomide and again within 24 hours of starting each new cycle. Patients of childbearing potential must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of

birth control, one highly effective method and one additional effective method AT THE SAME TIME, 1) at least 28 days before starting lenalidomide; 2) while participating in the study; 3) during dose interruptions; and 4) for at least 28 days after the last dose of lenalidomide.

Patients of childbearing potential must also agree to ongoing pregnancy testing as outlined in Appendix VI. Patients must also agree to not breastfeed during this same time period. Male patients must agree to either abstain from sexual intercourse for the duration of their participation in the study or use a latex condom during sexual contact with a partner of childbearing potential while participating in the study and for 28 days after the last dose of protocol treatment even if they have had a successful vasectomy.

Patients must also agree to abstain from donating sperm while on study treatment and for 28 days after the last dose of protocol treatment even if they have had a successful vasectomy. All patients must agree to abstain from donating blood during study participation and for at least 28 days after the last dose of protocol treatment.

5.3 Adverse Event Reporting Requirements

All adverse events described throughout this protocol and all reportable adverse events on this protocol will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

Clinician graded CTCAE is the AE (adverse event) safety standard. PRO-CTCAE items are to complement CTCAE reporting. Patients will respond to PRO-CTCAE items but no protocol directed action will be taken. PRO-CTCAE is not intended for expedited reporting, real time review or safety reporting.

5.3.1 Purpose

Adverse event (AE) data collection and reporting, which are a required part of every clinical trial, are done so investigators and regulatory agencies can detect and analyze adverse events and risk situations to ensure the safety of the patients enrolled, as well as those who will enroll in future studies using similar agents.

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5.3.2 Routine Reporting of Adverse Events (Medidata Rave)

Adverse events are reported in a routine manner at scheduled times during a trial using the Medidata Rave clinical data management system. Please refer to Section 4.3.3 of the protocol for more information on how to access the Medidata Rave system and the EAA171 forms packet for instructions on where, when and what adverse events are to be reported routinely on this protocol.

Symptomatic Adverse Events reported by patients through PRO-CTCAE are not safety reporting and may be presented with other routine AE data.

5.3.3 Expedited Reporting of Adverse Events (CTEP-AERS)

In addition to routine reporting, certain adverse events must be also reported in an expedited manner for timelier monitoring of patient safety and care. The remainder of this section provides information and instructions regarding expedited adverse event reporting.

5.3.4 Terminology

- **Adverse Event (AE):** Any untoward medical occurrence associated with the use of an agent in humans, whether or not considered agent related. Therefore, an AE can be **ANY** unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- **Attribution:** An assessment of the relationship between the adverse event and the protocol treatment, using the following categories.

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ATTRIBUTION	DESCRIPTION
Unrelated	The AE is *clearly NOT related* to protocol treatment.
Unlikely	The AE is *doubtfully related* to protocol treatment.
Possible	The AE *may be related* to protocol treatment.
Probable	The AE is *likely related* to protocol treatment.
Definite	The AE is *clearly related* to protocol treatment.

- **CAEPR (Comprehensive Adverse Events and Potential Risks List):** An NCI generated list of reported and/or potential AEs associated with an agent currently under an NCI IND. Information contained in the CAEPR is compiled from the Investigator's Brochure, the Package Insert, as well as company safety reports.
- **CTCAE:** The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term.
- **Hospitalization (or prolongation of hospitalization):** For AE reporting purposes, a hospitalization is defined as an inpatient hospital stay equal to or greater than 24 hours.
- **Life Threatening Adverse Event:** Any AE that places the patient at immediate risk of death from the AE as it occurred.
- **Serious Adverse Event (SAE):** Any adverse event occurring at any dose that results in **ANY** of the following outcomes:
  - Death
  - A life-threatening adverse event
  - Inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours).
  - A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
  - A congenital anomaly/birth defect.

- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

- **SPEER (Specific Protocol Exceptions to Expedited Reporting):** A subset of AEs within the CAEPR that contains a list of events that are protocol specific exceptions to expedited reporting. If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ONLY be reported expeditiously if the grade being reported exceeds the grade listed in the parentheses next to the event.

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5.3.5 Expedited Adverse Event Reporting Procedure

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) Integration enables evaluation of Adverse Events (AE) entered in Rave to determine whether they require expedited reporting and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting. Sites must initiate all AEs for this study in Medidata Rave.

Sites must initiate all AEs for this study in Medidata Rave.

Pre-treatment AEs: AEs that occur after informed consent is signed and prior to start of treatment are collected in Medidata Rave using the Pre-treatment Adverse Event form. Pre-existing medical conditions (formerly referred to as baseline AEs) identified during baseline assessment are not considered AEs and therefore should not be reported on the Pre-treatment Adverse Event form. If these pre-existing conditions worsen in severity, the investigator must reassess the event to determine if an expedited report is required. Whether or not an expedited report is required, the worsened event should be reported as a routine AE.

Treatment-emergent AEs: All AEs that occur after start of treatment are collected in Medidata Rave, using the Adverse Event form, which is available for entry at each treatment course or reporting period and is used to collect AEs that start during the period or persist from the previous reporting period. AEs that occur 30 Days after the Last Administration of the Investigational Agent/Intervention are collected using the Late Adverse Event form.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct and
- AEs are recorded and complete (no missing fields) and the form is query free.

NOTE: The CRA reports AEs in Rave at the time the Investigator learns of the event.

NOTE: If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form. Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form. Contact the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com if you have any issues submitting an expedited report in CTEP-AERS.

In the rare occurrence that internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at:

- (301-897-7497).

Once internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the direct link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU members' website:

- Study specific documents: Protocols > Documents> Protocol Related Documents> Adverse Event Reporting; and
- Additional resources: Resources > CTSU Operations Information> User Guides & Help Topics.

NCI requirements for SAE reporting are available on the CTEP website.

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

5.3.6 Steps to determine if an adverse event is to be reported in an expedited manner – Arms A and B (Note: Since this is a blinded study, the treatment arm code (TAC) will appear as Arm X in the CTEP-AERS system.)

Guidelines for reporting adverse events **OCCURRING WHILE ON PROTOCOL TREATMENT AND WITHIN 30 DAYS** of the last administration of the investigational agent(s).

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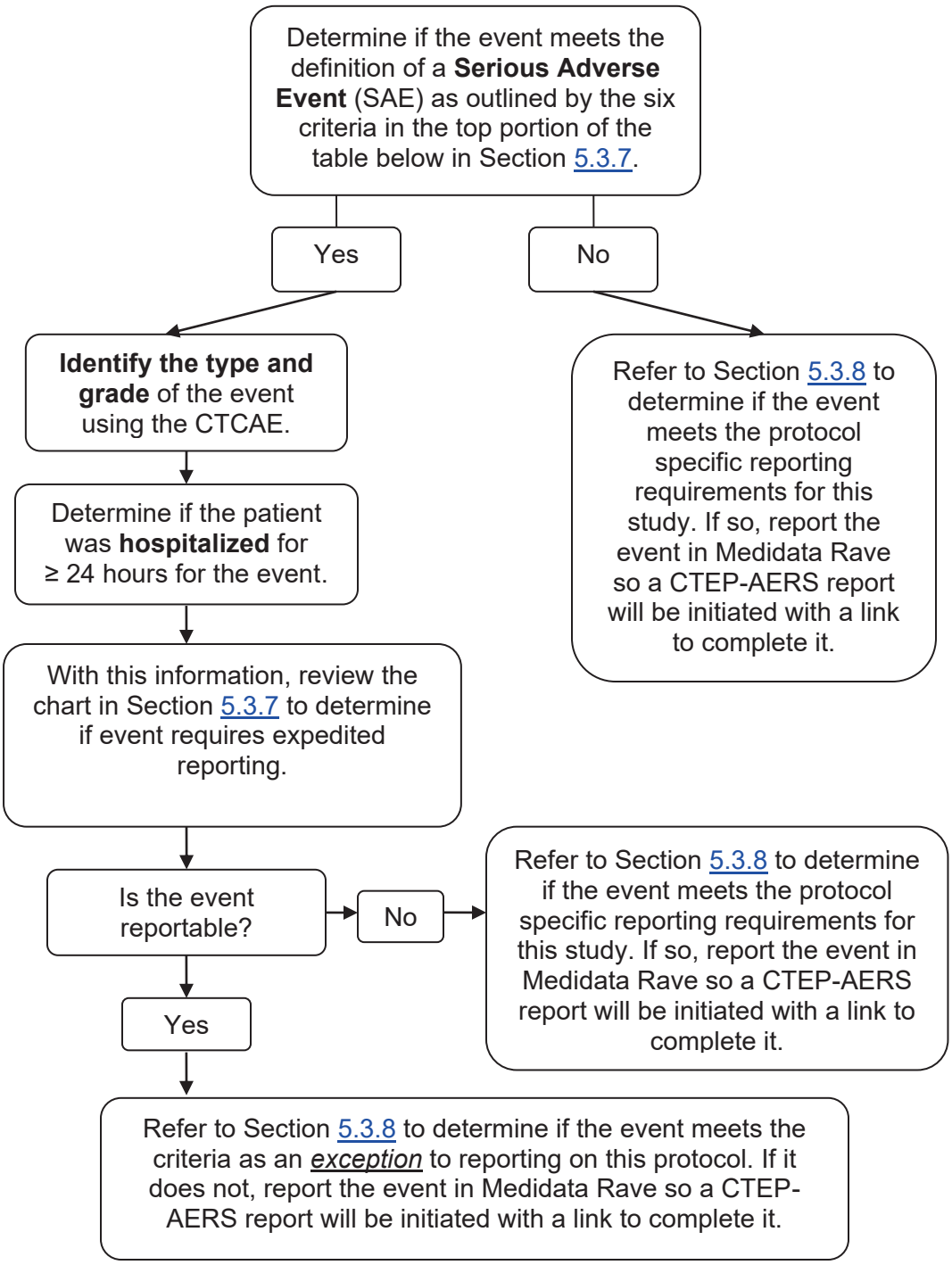
- Site must determine if an event meets expedited reporting requirements so that the AE will be entered into Medidata Rave, triggering a CTEP-AERS report, within the mandated timeframes outlined in Section 5.3.7.
- Do not initiate the CTEP-AERS report via the CTEP-AERS website.
- We encourage all sites to confirm the Rules Engine assessment with the charts and tables below.
- Once the CTEP-AERS is completed, ECOG-ACRIN, the NCI, and all appropriate regulatory agencies will be notified of the event in an expeditious manner.


Determine if the event meets the definition of a **Serious Adverse Event** (SAE) as outlined by the six criteria in the top portion of the table below in Section 5.3.7.
Yes
No
Identify the type and grade of the event using the CTCAE.
Refer to Section 5.3.8 to determine if the event meets the protocol specific reporting requirements for this study. If so, report the event in Medidata Rave so a CTEP-AERS report will be initiated with a link to complete it.
Determine if the patient was **hospitalized** for ≥ 24 hours for the event.
With this information, review the chart in Section 5.3.7 to determine if event requires expedited reporting.
Is the event reportable?
No
Refer to Section 5.3.8 to determine if the event meets the protocol specific reporting requirements for this study. If so, report the event in Medidata Rave so a CTEP-AERS report will be initiated with a link to complete it.
Yes
Refer to Section 5.3.8 to determine if the event meets the criteria as an *exception* to reporting on this protocol. If it does not, report the event in Medidata Rave so a CTEP-AERS report will be initiated with a link to complete it.

5.3.6.1 Guidelines for reporting adverse events **OCCURRING GREATER THAN 30 DAYS** after the last administration of the investigational agent(s).

If the adverse event meets the definition of a **Serious Adverse Event (SAE)** as outlined by the six criteria in the top portion of the table below in Section 5.3.7, OR the protocol specific requirements in Section 5.3.8, AND has an attribution of possible, probably or definite, the following events require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4 and Grade 5 AEs

NOTE: Any death occurring greater than 30 days after the last dose of investigational agent with an attribution of possible, probable or definite must be reported in CTEP-AERS accessed via Medidata Rave even if the patient is off study.

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

5.3.7 Expedited Reporting Requirements for Arm X (Arms A and B) on protocol EAA171

Investigational Agents: Ixazomib/Placebo

Commercial Agents: Lenalidomide

When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered to be investigational and expedited reporting of adverse events follow the guidelines for investigational agents.

Late Phase II and Phase III Studies

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND *within 30 Days of the Last Administration of the Investigational Agent/Intervention*.[1]

NOTE: Footnote 1 instructs how to report serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention.

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **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 NCI in CTEP-AERS accessed via Medidata Rave within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol-specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" – The AE must initially be reported in CTEP-AERS accessed via Medidata Rave within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" – A complete expedited report on the AE must be submitted within 10 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 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

5.3.8 Additional instructions, requirements and exceptions for protocol EAA171

Additional Instructions

- For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events in CTEP-AERS accessed via Medidata Rave, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.
- **Reporting a death on study**: A death occurring while on study treatment or within 30 days of the last dose of study treatment requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

  NOTE: A death due to progressive disease should be reported as a Grade 5 "*Disease progression*" under the System Organ Class (SOC) "*General disorder and administration site conditions*". 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.

EAA171 specific expedited reporting requirements:

- **Pregnancies:** Pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test, regardless of age or disease state) occurring while the female patient is on ixazomib/placebo or lenalidomide, or within 28 days of the female patient's last dose of ixazomib/placebo or lenalidomide, are considered immediately reportable events. The pregnancy, suspected pregnancy, or positive/ inconclusive pregnancy test must be reported in CTEP-AERS accessed via Medidata Rave within 24 hours of the Investigator's knowledge. Please refer to Appendix V for detailed instructions on how to report the occurrence of a pregnancy as well as the outcome of all pregnancies.

EAA171 specific expedited reporting exceptions:

For study Arm X (Arms A and B), the adverse events listed below **do not** require expedited reporting:

- If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported expeditiously if the grade being reported exceeds the grade listed in the parentheses next to the event.

5.3.9 Other recipients of adverse event reports and supplemental data

DCTD/NCI will notify ECOG-ACRIN/pharmaceutical collaborator(s) of all AEs reported to the FDA. Any additional written AE information requested MUST be submitted to BOTH the NCI and ECOG-ACRIN.

Adverse events determined to require expedited reporting must also be reported by the institution, according to the local policy and procedures, to the Institutional Review Board responsible for oversight of the patient.

5.3.10 Second Primary Cancer Reporting Requirements

All cases of second and secondary malignancies including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), regardless of attribution, that occur following treatment on NCI-sponsored trials utilizing the agent Lenalidomide must be reported as follows:

1. Complete a Second Primary Form in Medidata Rave within 14 days.
2. Report the diagnosis expeditiously by initially reporting it PROMPTLY upon learning of the secondary malignancy on the Adverse Event Form or Late Adverse Event Form in the appropriate Treatment Cycle or Post Registration folder in Medidata Rave. Once the adverse event is entered into Rave, the Rules Engine on the Expedited Reporting Evaluation Form will confirm whether or not the second primary requires expedited reporting. The CTEP-AERS report must then be initiated directly from the Expedited Reporting Evaluation Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website.

   Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, c.) treatment related secondary malignancy or d) Neoplasms Other, malignant (grade 3 or 4)

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   NOTE: When reporting attribution on the AE form, assess the relationship between the secondary malignancy and the current protocol treatment ONLY (and NOT relationship to anti-cancer agent received either before or after protocol treatment).

   NOTE: We encourage all sites to confirm the Rules Engine assessment with the Second Primary reporting requirements outlined in this section.

3. Report the diagnosis via http://ctep.cancer.gov.
4. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
5. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP

NOTE: All new malignant tumors must be reported in CTEP-AERS accessed via Medidata Rave whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported including solid tumors (including non-melanoma skin malignancies), hematologic malignancies, Myelodysplastic Syndrome (MDS)/Acute Myelogenous Leukemia (AML), and in situ tumors.

Whenever possible, the CTEP-AERS report should include the following:

- Tumor pathology
- History of prior tumors
- Prior treatment/current treatment including duration
- Any associated risk factors or evidence regarding how long the tumor may have been present
- When and how the tumor was detected
- Molecular characterization or cytogenetics or the original tumor (if available) and of any new tumor
- Tumor treatment and outcome (if available).

NOTE: The ECOG-ACRIN Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the ECOG-ACRIN Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted in CTEP-AERS or by the ECOG-ACRIN Second Primary Form.

5.4 Comprehensive Adverse Events and Potential Risks Lists

5.4.1 Comprehensive Adverse Events and Potential Risks list (CAEPR) for MLN9708 (Ixazomib citrate, NSC 767907)

Rev. Add3

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 1122 patients.* Below is the CAEPR for MLN9708 (Ixazomib citrate).

NOTE: Report AEs on the SPEER ONLY IF they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.1, March 26, 2022[1]

Adverse Events with Possible Relationship to MLN9708 (Ixazomib citrate) (CTCAE 5.0 Term) [n= 1122]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		
		Thrombotic thrombocytopenic purpura	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation		
Diarrhea			***Diarrhea (Gr 2)***
Nausea			***Nausea (Gr 2)***
Vomiting			***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
		Edema limbs	
Fatigue			***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
HEPATOBILIARY DISORDERS			
		Hepatobiliary disorders - Other (hepatotoxicity)[2]	
INFECTIONS AND INFESTATIONS			
	Upper respiratory		***Upper respiratory infection (Gr 2)***

Adverse Events with Possible Relationship to MLN9708 (Ixazomib citrate) (CTCAE 5.0 Term) [n= 1122]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
	infection		
INVESTIGATIONS			
	Neutrophil count decreased		***Neutrophil count decreased (Gr 2)***
	Platelet count decreased		***Platelet count decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		
NERVOUS SYSTEM DISORDERS			
	Headache		
	Nervous system disorders - Other (peripheral neuropathies NEC, peripheral neuropathy, peripheral motor neuropathy)		***Nervous system disorders - Other (peripheral neuropathies NEC, peripheral neuropathy, peripheral motor neuropathy) (Gr 2)***
	Peripheral sensory neuropathy		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
	Dyspnea		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Drug-induced liver injury, hepatocellular injury, hepatic steatosis, hepatitis cholestatic and hepatotoxicity have each been reported in <1% of patients treated with MLN9708. Events of liver impairment have been reported. Monitor hepatic enzymes regularly and adjust dosing for Grade 3 or 4 symptoms.

Adverse events reported on MLN9708 (Ixazomib citrate) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that MLN9708 (Ixazomib citrate) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia

CARDIAC DISORDERS - Myocardial infarction

EYE DISORDERS - Blurred vision; Retinal detachment

GASTROINTESTINAL DISORDERS - Enterocolitis

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Disease progression; Flu like symptoms; Malaise

HEPATOBILIARY DISORDERS - Bile duct stenosis

INFECTIONS AND INFESTATIONS - Bronchial infection; Fungemia; Infections and infestations - Other (Parainfluenza Infection); Lung infection; Pharyngitis; Sepsis; Shingles; Sinusitis

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall; Injury, poisoning and procedural complications - Other (femoral neck fracture); Spinal fracture

INVESTIGATIONS - Aspartate aminotransferase increased; Lymphocyte count decreased; White blood cell decreased

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypokalemia; Hyponatremia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Muscle weakness lower limb; Myalgia; Pain in extremity

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (non-Hodgkin's lymphoma); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (plasma cell myeloma); Tumor pain

NERVOUS SYSTEM DISORDERS - Dizziness; Dysgeusia

PSYCHIATRIC DISORDERS - Insomnia

RENAL AND URINARY DISORDERS - Acute kidney injury

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchial obstruction

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Erythema multiforme; Pruritus

VASCULAR DISORDERS - Hypotension

VASCULAR DISORDERS - Hypotension; Vasculitis

NOTE: MLN9708 (Ixazomib citrate) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

5.4.2 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Lenalidomide (Revlimid, NSC 703813)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. Refer to the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. Frequency is provided based on 4081 patients. Below is the CAEPR for lenalidomide (CC-5013).

Rev. Add1

Version 2.8, June 27, 2019[1]

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 5.0 Term) [n= 4081]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia		
	Blood and lymphatic system disorders - Other (pancytopenia)	
	Febrile neutropenia	
	Hemolysis	
CARDIAC DISORDERS		
		Atrial fibrillation
		Heart failure
		Myocardial infarction[2]
EAR AND LABYRINTH DISORDERS		
	Vertigo	
ENDOCRINE DISORDERS		
		Hyperthyroidism
	Hypothyroidism	
EYE DISORDERS		
	Blurred vision	
	Cataract	
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
Constipation		
Diarrhea		
	Dry mouth	
	Dyspepsia	
	Nausea	
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Chills	
	Edema limbs	

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 5.0 Term) [n= 4081]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
Fatigue		
	Fever	
	Generalized edema	
	Non-cardiac chest pain	
	Pain	
HEPATOBILIARY DISORDERS		
		Hepatic failure
		Hepatobiliary disorders - Other (cholestasis)
IMMUNE SYSTEM DISORDERS		
		Allergic reaction
		Anaphylaxis
		Immune system disorders - Other (angioedema)
		Immune system disorders - Other (graft vs. host disease)[3]
INFECTIONS AND INFESTATIONS		
	Infection[4]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
	Bruising	
	Fall	
INVESTIGATIONS		
	Alanine aminotransferase increased	
	Alkaline phosphatase increased	
	Aspartate aminotransferase increased	
	Blood bilirubin increased	
	GGT increased	
	Investigations - Other (C-Reactive protein increased)	
		Lipase increased
	Lymphocyte count decreased	
Neutrophil count decreased		
Platelet count decreased		
	Weight loss	
	White blood cell decreased	
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
	Dehydration	
	Hyperglycemia	
	Hyperuricemia	
	Hypocalcemia	
	Hypokalemia	

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 5.0 Term) [n= 4081]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Hypomagnesemia	
	Hyponatremia	
	Hypophosphatemia	
	Iron overload	
		Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	
	Back pain	
	Bone pain	
	Generalized muscle weakness	
	Muscle cramp	
	Myalgia	
	Pain in extremity	
		Rhabdomyolysis[5]
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
		Leukemia secondary to oncology chemotherapy[6]
		Myelodysplastic syndrome[6]
		Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor flare)[7]
		Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (second primary malignancies)
		Treatment related secondary malignancy[6]
NERVOUS SYSTEM DISORDERS		
	Dizziness	
	Depressed level of consciousness	
	Dysesthesia	
	Dysgeusia	
	Headache	
	Paresthesia	
	Peripheral motor neuropathy	
	Peripheral sensory neuropathy	
		Stroke[2]
	Syncope	
	Tremor	
PSYCHIATRIC DISORDERS		
	Depression	
	Insomnia	

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 5.0 Term) [n= 4081]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Psychiatric disorders - Other (mood altered)	
RENAL AND URINARY DISORDERS		
		Acute kidney injury
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Cough	
	Dyspnea	
	Epistaxis	
		Pneumonitis
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Dry skin	
		Erythema multiforme
	Hyperhidrosis	
	Pruritus	
	Rash maculo-papular	
		Skin and subcutaneous tissue disorders - Other (drug reaction with eosinophilia and systemic symptoms [DRESS])
	Skin and subcutaneous tissue disorders - Other (pyoderma gangrenosum)	
		Stevens-Johnson syndrome
		Toxic epidermal necrolysis
SURGICAL AND MEDICAL PROCEDURES		
		Surgical and medical procedures - Other (impaired stem cell mobilization)[8]
VASCULAR DISORDERS		
	Hematoma	
	Hypertension	
	Hypotension	
	Peripheral ischemia	
	Thromboembolic event[9]	
	Vasculitis	

[1] This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2] Myocardial infarction and cerebrovascular accident (stroke) have been observed in multiple myeloma patients treated with lenalidomde and dexamethasone.

[3] Graft vs. host disease has been observed in subjects who have received lenalidomide in the setting of allo-transplantation.

[4] Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[5] The rare adverse event of rhabdomyolysis has been observed with lenalidomide. The reports of rhabdomyolysis were confounded by concurrent use of statins and dexamethasone, concurrent viral and bacterial infections, trauma, and serotonin syndrome. Statins, infections, trauma, and serotonin syndrome are known risk factors for rhabdomyolysis.

[6] There has been an increased frequency of secondary malignancies (SPM) including ALL, AML, and MDS, and certain other types of cancers of the skin and other organs in multiple myeloma (MM) patients being treated with melphalan, prednisone, and lenalidomide post bone marrow transplant. The use of lenalidomide in cancers other than MM, shows that invasive SPMs occurred in a small number of patients. Patients treated with lenalidomide should be closely followed for the occurance of SPMs.

[7] Serious tumor flare reactions have been observed in patients with chronic lymphocytic leukemia (CLL) and lymphoma.

[8] A decrease in the number of stem cells (CD34+ cells) collected from patients treated with >4 cycles of lenalidomide has been reported.

[9] Significantly increased risk of deep vein thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis has been observed in patients with multiple myeloma receiving lenalidomide with dexamethasone.

[10] Gastrointestinal hemorrhage includes: Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[11] Gastrointestinal obstruction includes: Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Obstruction gastric, Rectal obstruction, and Small intestinal obstruction under the GASTROINTESTINAL DISORDERS SOC.

[12] Osteonecrosis of the jaw has been seen with increased frequency when lenalidomide is used in combination with bevacizumab, docetaxel (Taxotere®), prednisone, and zolendronic acid (Zometa®).

NOTE: While not observed in human subjects, lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study similar to birth defects caused by thalidomide in humans. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death. Pregnancy must be excluded before start of treatment. Prevent pregnancy during treatment by the use of two reliable methods of contraception.

NOTE: In a trial of first line treatment of patients with chronic lymphocytic leukemia (CLL), single agent lenalidomide (CC-5013) increased the risk of death as compared to control arm (chlorambucil).

NOTE: In two randomized trials of patients with multiple myeloma (MM), the addition of MK-3475 (pembrolizumab) to a thalidomide analog plus dexamethasone, resulted in increased mortality. Treatment of patients with MM with a PD-1 or PD-L1 blocking antibody, such as MK-3475 (pembrolizumab), in combination with a thalidomide analog, such as lenalidomide, is not recommended outside of controlled clinical trials.

NOTE: In a clinical trial in patients with Mantle cell lymphoma (MCL), there was an increase in early deaths (within 20 weeks); 12.9% in the lenalidomide (CC-5013) arm vs. 7.1% in the control arm.

Adverse events reported on lenalidomide (CC-5013) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that lenalidomide (CC-5013) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (monocytosis); Disseminated intravascular coagulation; Eosinophilia

CARDIAC DISORDERS - Atrial flutter; Atrioventricular block first degree; Cardiac arrest; Cardiac disorders - Other (cardiovascular edema); Cardiac disorders - Other (ECG abnormalities); Chest pain - cardiac; Left ventricular systolic dysfunction; Palpitations; Pericarditis; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia; Ventricular tachycardia

EAR AND LABYRINTH DISORDERS - Tinnitus

ENDOCRINE DISORDERS - Cushingoid

EYE DISORDERS - Dry eye; Flashing lights; Retinopathy

GASTROINTESTINAL DISORDERS - Abdominal distension; Anal mucositis; Ascites; Colonic perforation; Dysphagia; Flatulence; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (Crohn's disease aggravated); Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (pale feces); Gastrointestinal hemorrhage[10]; Gastrointestinal obstruction[11]; Ileus; Mucositis oral; Pancreatitis; Rectal mucositis; Small intestinal mucositis

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Malaise; Multi-organ failure

HEPATOBILIARY DISORDERS - Cholecystitis

INFECTIONS AND INFESTATIONS - Conjunctivitis; Infections and infestations - Other (opportunistic infection associated with >=Grade 2 Lymphopenia); Myelitis

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fracture; Hip fracture; Vascular access complication

INVESTIGATIONS - Activated partial thromboplastin time prolonged; Cholesterol high; Creatinine increased; Electrocardiogram QT corrected interval prolonged; INR increased; Investigations - Other (hemochromatosis)

METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperkalemia; Hypoglycemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Chest wall pain; Joint effusion; Muscle weakness lower limb; Neck pain; Osteonecrosis of jaw[12]

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain

NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Dysphasia; Edema cerebral; Encephalopathy; Intracranial hemorrhage; Ischemia cerebrovascular; Leukoencephalopathy; Memory impairment; Nervous system disorders - Other (hyporeflexia); Spinal cord compression; Seizure; Somnolence; Transient ischemic attacks

PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Psychosis

RENAL AND URINARY DISORDERS - Urinary frequency; Urinary incontinence; Urinary tract pain

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Reproductive system and breast disorders - Other (hypogonadism); Vaginal hemorrhage

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Allergic rhinitis; Atelectasis; Bronchopulmonary hemorrhage; Hypoxia; Laryngeal mucositis; Pharyngeal mucositis; Pleural effusion; Pulmonary hypertension; Respiratory failure; Tracheal mucositis; Voice alteration

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Nail loss; Photosensitivity; Rash acneiform; Skin and subcutaneous tissue disorders - Other (Sweet's Syndrome); Urticaria

VASCULAR DISORDERS - Hot flashes; Phlebitis; Vascular disorders - Other (hemorrhage NOS)

NOTE: Lenalidomide (CC-5013) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

5.5 Dose Modifications

NOTE: Dose modifications are based on adverse events, which are possibly, probably or definitely related to drug. More than one dose reduction per cycle may occur.

Patients experiencing grade 3 or 4 AE's that are possibly, probably or definitely related to a particular agent(s) requiring dose modifications as per the tables below will have that particular agent(s) held until resolution of the AE. If AE improves to baseline or ≤ grade 1 prior to next scheduled dose, treatment should be restarted with a one dose level reduction for the causative drug for the remainder of the cycle. The next cycle will then continue with this reduced dose level. Patients experiencing grade 3 or 4 AEs that are possibly, probably or definitely related to a particular agent(s) which occur on or after the last treatment day of a cycle, will have that particular agent(s) reduced by one dose level beginning with the next cycle.

NOTE: If the AE is attributed to a specific drug, only that drug needs dose reduction. If the AE is possibly attributed to more than one agent, the more likely agent can be first reduced, and then the other drug if the toxicity recurs. If both drugs are equally likely to have contributed to the toxicity, reduce the ixazomib/placebo first.

Once a patient's dose has been reduced, no dose-re-escalation is permitted unless it is clear that the drug was not responsible for the toxicity that led to the dose reduction.

Rev. Add3

A delay of up to 14 days is allowed between cycles. Any delay beyond 14 days should be discussed with the study chair. If treatment has been delayed for > 8 weeks due to treatment related toxicity, the patient will go off study treatment. A treatment delay of greater than 14 days, but no longer than 60 days, is allowed if the delay is unrelated to study treatment.

If ixazomib/placebo is held for toxicity, the patient may restart drug during the same cycle provided there are additional doses left in the cycle.

If there is a delay in obtaining lenalidomide for start of a new cycle, the cycle can be delayed until it is available in order to allow all drugs to be started at the same time. However, if the cycle has already started, treatment may continue and lenalidomide should be started when it becomes available and continue for the remaining days of lenalidomide as per cycle.

PRO-CTCAE data should not be used for determining dose delays or dose modifications or any other protocol directed action.

5.5.1 Ixazomib/Placebo Treatment Adjustment

See table below for ixazomib/placebo treatment adjustment steps

Ixazomib/Placebo Treatment Adjustment Steps	
Starting Dose	**4 mg days 1, 8, 15 every 28 days**
Dose Level -1	3 mg days 1, 8, 15 every 28 days
Dose Level -2	2.3 mg days 1, 8, 15 every 28 days
Dose Level -3	Discontinue

5.5.2 Lenalidomide Treatment Adjustment

See table below for lenalidomide treatment adjustment steps

Lenalidomide (CC-5013) Treatment Adjustment Steps		
Starting Dose	**(For CrCl 30-60 ml/min) 5 mg daily for 28 days**	**10 mg daily for 28 days**
Dose Level -1	5 mg daily for 21 days every 28 days	10 mg daily for 21 days every 28 days
Dose Level -2	2.5 mg daily for 28 days	5 mg daily for 28 days
Dose Level -3	2.5 mg every other day for 28 days	2.5 mg daily for 28 days
Dose Level -4	Discontinue	2.5 mg every other day for 28 days

5.5.3 Dose Modifications for Ixazomib/Placebo and Lenalidomide Based on Toxicity

	At retreatment and Day 2-21 of Cycle	
NCI CTCAE Grade	**If attributed to Lenalidomide**	**If attributed to Ixazomib/Placebo**
Sustained (≥ 7 days) ≥ Grade 3 neutropenia or ≥ Grade 3 neutropenia associated with fever (temperature ≥ 38.5º C) or Grade 4 neutropenia	Hold (interrupt dose) and follow CBC on days of scheduled ixazomib/placebo doses. If the toxicity resolves to baseline or ≤ grade 2 prior to Day 14 restart lenalidomide at next lower dose level and continue the cycle until Day 14. Start next cycle at the reduced dose level. If neutropenia is the only toxicity for which a dose reduction is required, G-CSF may be used and the lenalidomide dose maintained.	Hold (interrupt dose) and follow CBC on days of scheduled ixazomib/placebo doses. If the toxicity resolves to baseline or ≤ grade 2, restart ixazomib/placebo at next lower dose level and continue for rest of cycle as per protocol. Start next cycle at the reduced dose level.
Sustained (≥ 7 days) ≥ Grade 3 thrombocytopenia or ≥ Grade 3 thrombocytopenia with bleeding or grade 4 thrombocytopenia	Hold (interrupt dose) and follow CBC on days of scheduled ixazomib/placebo doses. If the toxicity resolves to baseline or ≤ grade 2 prior to Day 14 restart lenalidomide at next lower dose level and continue the cycle until Day 14. Start next cycle at the reduced dose level.	Hold (interrupt dose) and follow CBC on days of scheduled ixazomib/placebo doses. If the toxicity resolves to baseline or ≤ grade 2, restart ixazomib/placebo at next lower dose level and continue for rest of cycle as per protocol. Start next cycle at the reduced dose level.

	At retreatment and Day 2-21 of Cycle	
NCI CTCAE Grade	**If attributed to Lenalidomide**	**If attributed to Ixazomib/Placebo**
Infection ≥ grade 2 (with normal neutrophil count)	Hold (interrupt dose) and observe. If the toxicity resolves to baseline or ≤ grade 1 prior to Day 14 restart lenalidomide at next lower dose level and continue the cycle until Day 14. Start next cycle at the reduced dose level.	Hold (interrupt dose) and follow CBC on days of scheduled ixazomib/placebo doses. If the toxicity resolves to baseline or ≤ grade 1, restart ixazomib/placebo at next lower dose level and continue for rest of cycle as per protocol. Start next cycle at the reduced dose level.
Non-blistering rash Grade 2-3 Grade 4	Hold (interrupt dose) and observe. If the toxicity resolves to baseline or ≤ grade 1 prior to Day 14 restart lenalidomide at next lower dose level and continue the cycle until Day 14. Start next cycle at the reduced dose level. Discontinue lenalidomide and do not resume.	Hold (interrupt dose) and observe. If the toxicity resolves to baseline or ≤ grade 1, restart ixazomib/placebo at next lower dose level and continue for rest of cycle as per protocol. Start next cycle at the reduced dose level.
Desquamating (blistering) rash - any Grade	Discontinue lenalidomide.	Start next cycle at the reduced dose level.
Erythema multiforme ≥ Grade 3	Discontinue lenalidomide.	Start next cycle at the reduced dose level.
Sinus bradycardia/ other cardiac Arrhythmia Grade 2 Grade 3-4	Hold (interrupt dose) and observe. If the toxicity resolves to baseline or ≤ grade 1 prior to Day 14 restart lenalidomide at next lower dose level and continue the cycle until Day 14. Start next cycle at the reduced dose level. Discontinue lenalidomide.	No dose modifications required
Allergic reaction or Hypersensitivity Grade 2-3	Hold (interrupt dose) and observe. If the toxicity resolves to baseline or ≤ grade 1 prior to Day 14 restart lenalidomide at next lower dose level and continue the cycle until Day 14. Start next cycle at the reduced dose level.	Hold (interrupt dose) and follow on days of scheduled ixazomib/placebo doses. If the toxicity resolves to baseline or ≤ grade 1, restart ixazomib/placebo at next lower dose level and continue for rest of cycle as per protocol. Start next cycle at the reduced dose level.

	At retreatment and Day 2-21 of Cycle	
NCI CTCAE Grade	**If attributed to Lenalidomide**	**If attributed to Ixazomib/Placebo**
Grade 4	Discontinue lenalidomide.	Discontinue ixazomib/placebo and do not resume.
Constipation Grade 1-2 ≥ Grade 3	Initiate bowel regimen and maintain dose level. Hold (interrupt dose) and observe. If the toxicity resolves to baseline or ≤ grade 1 prior to Day 14 restart lenalidomide at next lower dose level and continue the cycle until Day 14. Start next cycle at the reduced dose level.	Initiate bowel regimen and maintain dose level.
Renal Function CrCl < 30 mL/min*	Hold (interrupt dose) and observe. If the toxicity resolves to baseline or ≤ grade 1 prior to Day 14 restart lenalidomide at next lower dose level and continue the cycle until Day 14. Start next cycle at the reduced dose level.	No dose modifications required
Venous Thrombosis/embolism ≥ Grade 3	Hold (interrupt) dose and start anticoagulation; restart at investigator's discretion after adequate anticoagulation (maintain dose level).	No dose modifications required.
Nervous system toxicity Peripheral neuropathy Grade 1 or 2 without pain		Reduce dose of ixazomib/placebo to the next lower dose level. If a patient is already at the lowest drug level, go off treatment.
Grade >2 or grade 2 with pain	Reduce dose of lenalidomide to the next lower dose level. If a patient is already at the lowest drug level, go off treatment.	Discontinue ixazomib/placebo until toxicity resolves or returns to baseline. When toxicity resolves, re-initiate ixazomib/placebo at the next lower dose level. If a patient is already at the lowest drug level, go off treatment.
Grade 4	Reduce dose of lenalidomide to the next lower dose level. If a patient is already at the lowest drug level, go off treatment.	Discontinue ixazomib/placebo
Hyperthyroidism or Hypothyroidism	Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. Restart lenalidomide next cycle (decrease dose by one dose level).	No dose modifications required

	At retreatment and Day 2-21 of Cycle	
NCI CTCAE Grade	**If attributed to Lenalidomide**	**If attributed to Ixazomib/Placebo**
Any other ≥ grade 3 non-hematologic toxicity assessed as at least possibly related to the drugs (nausea, emesis and diarrhea included only if the grade persists despite maximal supportive care)	Hold (interrupt dose) and observe if toxicity is thought to be at least possible related to lenalidomide. If the toxicity resolves to baseline or ≤ grade 2 prior to Day 14 restart lenalidomide at next lower dose level and continue the cycle until Day 14. Start next cycle at the reduced dose level.	Hold (interrupt dose) if toxicity is thought to be at least possible related to ixazomib/placebo. If the toxicity resolves to baseline or ≤ grade 2, restart ixazomib/placebo at next lower dose level and continue for rest of cycle as per protocol. Start next cycle at the reduced dose level.

* Creatinine clearance calculation can be made using standard methods, but the same method should be used for the entire duration of the study.

5.6 Supportive Care

5.6.1 All supportive measures consistent with optimal patient care will be given throughout the study.

5.6.2 Oral hydration

Patients are encouraged to drink at least 6 to 8 cups of liquid per day.

5.6.3 Disallowed concurrent treatment

The following treatments are not permitted during the trial:

- Any other investigational treatment
- Any other systemic anti-neoplastic therapy including, but not limited to, immunotherapy, hormonal therapy or monoclonal antibody therapy
- Any external beam radiotherapy

5.6.4 Nausea and/or vomiting

Standard anti-emetics including 5-hydroxytryptamine 3 serotonin receptor antagonists are recommended for emesis if it occurs once treatment is initiated; prophylactic anti-emetics may also be considered at the physician's discretion. Dexamethasone should not be administered as an anti-emetic. Fluid deficit should be corrected before initiation of study drug and during treatment.

5.6.5 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 Journal of Clinical Oncology, Vol 24, No 18 (June 20), 2006: pp. 2932-2947. Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as estrogen containing therapies, should be

used with caution after making a benefit-risk assessment in patients receiving lenalidomide.

5.6.6 Diarrhea

Diarrhea should be managed according to clinical practice, including the administration of antidiarrheals such as loperamide once infectious causes are excluded. Fluid intake should be maintained to avoid dehydration. Fluid deficit should be corrected before initiation of treatment and during treatment. Additional doses of loperamide at 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. Please monitor patients carefully for development of ileus.

5.6.7 Herpes Zoster prophylaxis

Patients may be at an increased risk of infection including reactivation of herpes zoster and herpes simplex viruses. Prophylaxis with acyclovir 400 mg PO BID should be used for all patients while on study therapy and for 3 months beyond the end of therapy.

5.6.8 Prohibited medications

Prohibited enzyme inducers

- Systemic treatment with any of the following metabolizing enzyme inducers should be avoided, unless there is no appropriate alternative medication for the patient's use. (Rationale: If there were to be a drug-drug interaction with an inducer, ixazomib/placebo exposure would be decreased)

Strong CYP3A inducers

- Including Rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, and phenobarbital

Additional strong CYP3A inducers can be found at: https://drug-interactions.medicine.iu.edu/main-table.aspx

Excluded foods and dietary supplements include St. John's wort.

5.6.9 Erythematous Rash with or without Pruritus

Rash with or without pruritus has been reported with ixazomib, primarily at the higher doses tested and when given with agents where rash is an overlapping toxicity. The rash may range from limited erythematous areas, macular and/or small papular bumps that may or may not be pruritic over a few areas of the body, to a more generalized eruption that is predominately on the trunk or extremities. Rash has been most commonly characterized as maculopapular or macular. To date, when it does occur, rash is most commonly

reported within the first three cycles of therapy. The rash is often transient, self-limiting, and is typically Grade 1 to 2 in severity. Rash can also be seen with lenalidomide, and usually responds to dose interruption and dose decrease.

Symptomatic measures such as antihistamines or corticosteroids (oral or topical) have been successfully used to manage rash and have been used prophylactically in subsequent cycles. The use of a topical, IV, or oral steroid (e.g., prednisone ≤10 mg per day or equivalent) is permitted. Management of a Grade 3 rash may require intravenous antihistamines or corticosteroids. Administration of ixazomib/placebo (and/or other causative agent if given in combination) should be modified per protocol and re-initiated at a reduced level from where rash was noted (also, per protocol).

In line with clinical practice, dermatology consult and biopsy of Grade 3 or higher rash or any SAE involving rash is recommended. Prophylactic measures should also be considered if a patient has previously developed a rash (e.g., using a thick, alcohol-free emollient cream on dry areas of the body or oral or topical antihistamines). A rare side effect is Stevens-Johnson Syndrome, a severe and potentially life-threatening rash marked by skin peeling and mouth sores, which should be managed symptomatically according to standard medical practice. Punch biopsies for histopathological analysis are encouraged at the discretion of the investigator.

5.6.10 Thrombocytopenia

Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Thrombocytopenia may be severe but has been manageable with platelet transfusions according to standard clinical practice. Ixazomib/placebo and lenalidomide administration should be modified as noted as per dose modification recommendations in the protocol when thrombocytopenia occurs (see Section 5.5). Therapy can be reinitiated at a reduced level upon recovery of platelet counts. A rare risk is thrombotic thrombocytopenic purpura (TTP), a rare blood disorder where blood clots form in small blood vessels throughout the body characterized by thrombocytopenia, petechiae, fever, or possibly more serious signs and symptoms. TTP should be managed symptomatically according to standard medical practice.

5.6.11 Neutropenia

Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Neutropenia may be severe but has been manageable. Growth factor support is not required but may be considered according to standard clinical practice. Ixazomib/placebo administration should be modified as noted as per dose modification recommendations in the protocol when neutropenia occurs. Therapy can be reinitiated at a reduced level upon recovery of ANCs.

5.6.12 Fluid deficit

Dehydration should be avoided since ixazomib may cause vomiting, diarrhea, and dehydration. Patients should be encouraged to maintain adequate fluid intake. Acute renal failure has been reported in patients treated with ixazomib, commonly in the setting of the previously noted gastrointestinal toxicities and dehydration. Fluid deficit should be corrected before initiation of study drug and as needed during treatment to avoid dehydration.

5.6.13 Hypotension

Symptomatic hypotension and orthostatic hypotension with or without syncope have been reported with ixazomib. Blood pressure should be closely monitored while the patient is on study treatment and fluid deficit should be corrected as needed, especially in the setting of concomitant symptoms such as nausea, vomiting, diarrhea, or anorexia. Patients taking medications and/or diuretics to manage their blood pressure (for either hypo- or hypertension) should be managed according to standard clinical practice, including considerations for dose adjustments of their concomitant medications during the course of the trial. Fluid deficit should be corrected before initiation of study drug and as needed during treatment to avoid dehydration.

5.6.14 Posterior Reversible Encephalopathy Syndrome

One case of posterior reversible encephalopathy syndrome, which ultimately resolved, has been reported with ixazomib. This condition is characterized by headache, seizures and visual loss, as well as abrupt increase in blood pressure. Diagnosis may be confirmed by magnetic resonance imaging (MRI). If the syndrome is diagnosed or suspected, symptom-directed treatment should be maintained until the condition is reversed by control of hypertension or other instigating factors.

5.6.15 Transverse Myelitis

Transverse myelitis has also been reported with ixazomib. It is not known if ixazomib causes transverse myelitis; however, because it happened to a patient receiving ixazomib, the possibility that ixazomib may have contributed to transverse myelitis cannot be excluded.

5.6.16 Thromboprophylaxis

All patients should be on at least 81 mg ASA daily while receiving lenalidomide. If they are unable to take ASA or are at high risk of VTE per investigator assessment, full dose anticoagulation is recommended.

5.7 Duration of Therapy

Patients will receive protocol therapy unless:

- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the instructions in the EAA171 Forms Completion Guidelines.

- Patient withdraws consent.
- Patient experiences unacceptable toxicity.
- Non-protocol therapies are administered.
- Patient experiences disease progression.

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5.8 Duration of Follow-up

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for response until progression, even if non-protocol therapy is initiated, and for survival for 10 years from the date of randomization. All patients must also be followed through completion of all protocol therapy.

6. Measurement of Effect

6.1 Response Considerations

The International Myeloma Working Group (IMWG) uniform response criteria will be adapted to assess response to therapy in this trial.[4,44] Since patients are entering the study at end of defined duration of therapy, and baseline disease parameters may not be known, we will limit the assessments to categories that are independent of baseline values (i.e., MRD negative, sCR, CR, and VGPR as defined below).

6.1.1 Terms and Definitions

6.1.1.1 M-Protein

Synonyms include M-spike, monoclonal protein, myeloma protein, monoclonal paraprotein, M-component.

6.1.1.2 Free Light Chain (FLC) Estimation

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.

6.1.1.3 Response Terms:

Only the following response terms will be used in this study: Sustained MRD negative (MRD-), Flow MRD-, Sequencing MRD-, Imaging Plus MRD-, stringent complete response (sCR), complete response (CR), very good partial response (VGPR), and progression (PD). Partial response or stable response categories are not being used in the current study.

See Section 6.2 for definitions.

6.1.1.4 Response Evaluation and Confirmation

In order to assess hematologic response categories of sCR, CR and VGPR, assessment of serum M-protein, serum immunoglobulin free light chain and urine M-protein will need to be performed as applicable. Confirmation of these results must be made by verification on two consecutive determinations.

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.

6.1.1.5 Bone Progression

Caution must be exercised to avoid rating progression or relapse 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.

6.1.2 Monoclonal Protein Considerations

Serum M protein level is quantitated using densitometry on serum protein electrophoresis (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. 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-hour urine protein electrophoresis (UPEP) only. Random or 24-hour urine tests measuring kappa and lambda light chain levels are not reliable and are not allowed.

6.2 Response Categories

6.2.1 IMWG MRD Negativity Category

Requires a complete response as defined in Section 6.2.2. MRD tests should be initiated only at the time of suspected complete response. 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 except for the requirement of ^{18}F-FDG PET if imaging MRD-negative status is reported.

6.2.1.1 Sustained MRD Negative

MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (e.g., MRD-negative at 5 years)

6.2.1.2 Flow MRD Negative

Absence of phenotypically aberrant clonal plasma cells by NGF 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

6.2.1.3 Sequencing MRD Negative

Absence of clonal plasma cells by NGS on bone marrow aspirates in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the ClonoSEQ platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher

6.2.1.4 Imaging Plus MRD Negative

MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less than mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue

6.2.2 Standard IMWG Response Category

6.2.2.1 Stringent Complete Response (sCR)

CR as defined below plus all of the following:

- Normal serum FLC ratio at two consecutive times and
- Absence of clonal cells in bone marrow by immunohistochemistry or 2- to 4- color flow cytometry.[a]
- Presence/absence of clonal cells is based upon the κ/λ ratio. An abnormal κ/λ ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ ratio of 4:1 or 1:2.

6.2.2.2 Complete Response (CR)

Patients who have complete disappearance of an M-protein and no evidence of myeloma in the bone marrow are considered to have complete response. To be considered CR, patients must meet all of the following criteria:

- Negative immunofixation on the serum and urine
- Disappearance of any soft tissue plasmacytomas
- ≤ 5% plasma cells in bone marrow
- If the only measurable disease is FLC, a normal FLC ratio of 0.26-1.65

6.2.2.3 Very Good Partial Response (VGPR)

- Serum M-protein detectable by immunofixation but not quantifiable on electrophoresis AND

- Urine M-protein < 100 mg/24 hours

6.2.2.4 Progression (PD)

Patients will be considered to have met progression if one of the following criteria is met. The investigation that qualified as progression should be repeated and verified on a subsequent occasion only if treating physician deems it clinically necessary.

Increase of ≥ 25% from lowest value reported in

- Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dL).
- Urine M-component and/or (the absolute increase must be ≥ 200 mg/ 24 hours.
- Only in patients without measurable serum and urine M protein levels: the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL.
- If the only measurable disease is bone marrow, bone marrow plasma cell percentage: the absolute % must be ≥ 10%.
- Development of new bone lesions or soft tissue plasmacytomas 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 > 1cm in short axis. 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).

6.2.2.5 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 with no alternate explanation:

- Development of new soft tissue plasmacytomas or bone lesions on skeletal survey, magnetic resonance imaging, or other imaging
- 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
- Hypercalcemia (>11.5 mg/dL; >2.875mM/L)

- Decrease in hemoglobin of more than 2 g/dL (1.25mM) or to less than 10 g/dL
- Rise in serum creatinine by more than or equal to 2 mg/dL (≥177mM/L)

6.3 Patient Reported Outcomes Measurement

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Patient reported outcomes assessments are required for English-speaking patients.

6.3.1 PRO Instruments

FACT

Health-related QOL will be assessed with three instruments: 1) the FACT-General (G) functional well-being (FWB) and physical well-being (PWB) subscales.[39] Each FACT-G subscale has 7 items. The 14 items are based on a 5-point Likert scale (0-4) resulting in a score ranging from 0 to 56 points with a higher score indicating better health-related QOL; 2) The FACT/GOG-Neurotoxicity Trial Outcomes Index (FACT/GOG-Ntx TOI) comprised of the FWB and PWB subscales plus the neurotoxicity subscale which has 11 items, summing to a score of 0-100;[70] and 3) the FACT-Multiple Myeloma Trial Outcomes Index (FACT-MM TOI) comprised of the FWB and PWB subscales plus the multiple myeloma subscale which has 14 items, summing to a score of 0-112 for the instrument.[40] The anticipated time to complete is roughly 8-10 minutes.

NCI PRO-CTCAE

NCI PRO-CTCAE items will be administered to allow patients to self-report symptomatic adverse events experienced on treatment. In its current version (dated 6/22/2018), there are 80 symptomatic AE terms included in the PRO-CTCAE item library which draw directly from the CTCAE, the standardized safety assessment lexicon for cancer clinical trials. Items correspond to 5 attributes measured [frequency (F), severity (S), interference (I), presence/absence (P) and amount (A)] based on multiple choice questions. Response for each attribute except P which is binary is on a 5-point Likert scale with 5 indicating ‘almost constantly’ frequency, ‘very severe’ severity, ‘very much’ amount or ‘very much’ interference. For each attribute, recall is the past 7 days. Attributes measured for each symptomatic AE varies and comprise the PRO-CTCAE item library.

For this study, 23 symptomatic AEs summing to 38 items have been selected as presented below. There are 10 symptomatic AEs which are assessed using one item, 11 symptomatic AEs which are assessed using two items, and 6 symptomatic AEs which are assessed using three items. The types of items in order of prevalence include severity (n=18 symptomatic AEs), interference (n=9 symptomatic AEs), frequency (n=7 symptomatic AEs), present/not present (n=4 symptomatic AE), and amount (none). The anticipated time to complete should be approximately 10 minutes.

PRO-CTCAE Symptomatic AE (Attributes)	CTCAE Term – System Organ Class
Dry Mouth (S)	Dry mouth - Gastrointestinal disorders
Taste Changes (S)	Dysgeusia - Nervous system disorders
Nausea (FS)	Nausea - Gastrointestinal disorders
Vomiting (FS)	Vomiting - Gastrointestinal disorders
Heartburn (FS)	Dyspepsia - Gastrointestinal disorders
Bloating (FS)	Bloating - Gastrointestinal disorders
Constipation (S)	Constipation - Gastrointestinal disorders
Diarrhea (F)	Diarrhea - Gastrointestinal disorders
Swelling (FSI)	Edema limbs - General disorders and administration site conditions
Rash (P)	Rash maculo-papular - Skin and subcutaneous tissue disorders
Skin Dryness (S)	Dry skin - Skin and subcutaneous tissue disorders
Itching (S)	Pruritus - Skin and subcutaneous tissue disorders
Hives (P)	Urticaria - Skin and subcutaneous tissue disorders
Sensitivity to Light (P)	Photosensitivity - Skin and subcutaneous tissue disorders
Numbness and Tingling (SI)	Peripheral sensory neuropathy - Nervous system disorders
Dizziness (SI)	Dizziness - Nervous system disorders
Blurred Vision (SI)	Blurred vision - Eye disorders
Concentration (SI)	Concentration Impairment - Nervous system disorders
Memory (SI)	Memory impairment - Nervous system disorders
Muscle Pain (FSI)	Myalgia - Musculoskeletal and connective tissue disorders
Insomnia (SI)	Insomnia - Psychiatric disorders
Fatigue (SI)	Fatigue - General disorders and administration site conditions
Bruising (P)	Bruising - Injury, poisoning and procedural complications

Adherence Starts with Knowledge Scale

The Adherence Starts with Knowledge Scale (ASK-12) will be used to assess the likelihood that a patient is taking oral medications per protocol.[43] The 12-item questionnaire was derived from the predecessor ASK-20 using a study population of 112 patients with

asthma, congestive heart failure or diabetes.[42] In this study, the ASK-12 had good internal consistency (Cronbach's coefficient alpha=0.75), and test-retest reliability (intraclass correlations (ICC)=0.79). The ASK-12 which elicits the same type of information as the Morisky Medication Adherence Scale (MMAS) also demonstrated convergent validity through strong correlation with MMAS-4 (Spearman correlation r = 0.74; p < 0.001). The ASK-12 titled 'Taking Medicine-What Gets in the Way?' is segmented into three sections: inconvenience/forgetfulness (3 items), treatment beliefs (4 items) and behavior (5 items). Response for each item is on a 5-point Likert scale (1-5) with the total score ranging from 12-60 and a higher score representing less likelihood of medication adherence. The anticipated time to complete is roughly 3-4 minutes.

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6.3.2 Patient-Reported Outcomes Assessment Schedule

PRO time-points overlap with protocol-specified clinic visits. The NCI PRO-CTCAE will be assessed at baseline and the beginning of each cycle on study therapy up to two-years. The FACT-G (PWB+FWB), Ntx and MM are first administered at baseline prior to starting treatment for evaluation of change longitudinally. The FACT-G (PWB+FWB), Ntx and MM then will be administered every three cycles for the first 24 cycles (beginning of cycles 4, 7, 10, 13, 16, 19, 22 and 25) and every six cycles thereafter up to completion of 48 cycles (beginning of cycles 31, 37, 43, 49), and at treatment discontinuation prior to completing 48 cycles. During long-term follow-up, there will be 4 quarterly assessments for one year. The ASK-12 will be assessed every six cycles on treatment up to completion of 48 cycles (beginning of cycles 7, 13, 19, 25, 31, 37, 43, and 49).

Assessment Timepoint[1,2]	**Questionnaires to be Administered**		
Study Cycle	**FACT-G, Ntx and MM[3]**	**PRO-CTCAE**	**ASK-12**
Baseline			
Within 28 days prior to Step 1 registration	X	X	
On Treatment			
Cycles 2-3		X	
Cycle 4	X	X	
Cycles 5-6		X	
Cycle 7	X	X	X
Cycles 8-9		X	
Cycle 10	X	X	
Cycles 11-12		X	
Cycle 13	X	X	X

Assessment Timepoint[1,2]	Questionnaires to be Administered		
Study Cycle	**FACT-G, Ntx and MM[3]**	**PRO-CTCAE**	**ASK-12**
Cycles 14-15		X	
Cycle 16	X	X	
Cycles 17-18		X	
Cycle 19	X	X	X
Cycles 20-21		X	
Cycle 22	X	X	
Cycles 23-24		X	
Cycle 25	X	X	X
Cycle 31	X		X
Cycle 37	X		X
Cycle 43	X		X
Cycle 49	X		X
Long Term Follow-Up[4]			
3 months post-tx	X		
6 months post-tx	X		
9 months post-tx	X		
1-year post-tx	X		

[1] +/- 7 days if appointments on the scheduled date are missed, the questionnaires will be mailed electronically to participants who will be asked to complete the questionnaires and return answers by electronic mail to the clinic. After 7 days, clinic or research staff may contact participants by telephone and ask participants to complete the questionnaire over the telephone reading their answers to the staff person. This approach will approximate the completion of PROs in clinic as closely as possible.

[2.] Assessments to be completed at beginning of the cycle +/- 7 days.

[3] FACT-G, Ntx and FACT-MM measures are included on one paper form. FACT-G, Ntx and MM will also be assessed at treatment discontinuation prior to 48 cycles

[4] Months post-treatment with respect to the date of discontinuation of treatment.

6.3.3 Patient-Reported Outcomes Additional Instructions

All questionnaires will be administered as a paper survey, with the aim that the patient completes questionnaires at the time of scheduled study clinic visits.

The patient should be instructed to respond to the questionnaires in terms of his or her experience during the timeframe specified on each questionnaire.

The patient should be asked to read the instructions at the beginning of each questionnaire and complete all the items. It is permissible to assist the patient with the questionnaires as long as the staff person does not influence the patient's responses.

The questionnaires must be reviewed by the protocol nurse or research coordinator as soon as the patient completes them to ensure all items were marked appropriately. If more than one answer was marked, the patient should be asked to choose the answer which best reflects how he or she is feeling. If a question was not answered, the patient should be asked if he or she would like to answer it. The patient should always have the option to refuse. If the patient cannot complete a questionnaire, or if the patient refuses to complete a questionnaire, the reason should be noted according to the instructions in the EAA171 Forms Completion Guidelines.

If appointments on the scheduled date are missed, the questionnaires will be mailed electronically to participants who will be asked to complete the questionnaires and return answers by electronic mail to the clinic. After 7 days, clinic or research staff may contact participants by telephone and ask participants to complete the questionnaire over the telephone reading their answers to the staff person. This approach will approximate the completion of PROs in clinic as closely as possible.

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NOTE: When delivering questionnaires to patients by electronic mail or over the telephone, please document the process of distribution and completion carefully and thoroughly in the medical record in case of an audit review.

PRO-CTCAE items will be administered sometimes coincident with other study PRO measures following procedures for PRO administration as described above. PRO-CTCAE items will be administered prior to clinic visits, or prior to participant's discussion of disease status and treatment side effects with health-care professionals. This is modeled after NCI PRO-CTCAE study procedures employed in other clinical trial validation studies. Clinicians will be instructed to complete clinician-rated treatment toxicities (CTCAE) prior to reviewing PRO-CTCAE ratings. This will minimize the extent to which PRO-CTCAE responses introduce a bias to clinician CTCAE ratings. PRO-CTCAE are currently undergoing validation and thus exploratory in nature, therefore, at this point should not be used to inform clinician CTCAE ratings. Clinicians will be instructed to review PRO-CTCAE items after clinician toxicity ratings have been completed to identify any patient-reported symptoms and toxicities that warrant clinical attention. Supportive care measures to manage treatment toxicities are described in Section 5.6.

7. Study Parameters

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7.1 Therapeutic Parameters (for both arms of the study)

1. Pre-study scans and x-rays used to assess all measurable or non-measurable sites of disease must be done ≤ 4 weeks prior to randomization.
2. Pre-study CBC (with differential and platelet count) must be done ≤ 14 days prior to randomization.
3. All required pre-study chemistries, as outlined in Section 3, must be done ≤ 14 days prior to randomization – unless specifically required on Day 1 as per protocol.

Schedule of events

Biological Specimen Submission: MANDATORY for Minimal Residual Disease Assessment		
	Following Pre-Registration	**Submit to:**
Bone Marrow Aspirate (1) 6mL ACD (yellow top) tube[10]	**X**	**Mayo Clinic**

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Study Parameters						
Tests and Procedures	**Prior to randomization (≤ 28 days unless otherwise noted)**	**At the end of each cycle**	**Annually**	**At study discontinuation or progression (whichever comes first)**	**28 days after discontinuation of treatment**	**Post Treatment to 10 years from study entry[9]**
History and Exam, Performance Status, Height[16] and Weight	X	X		X		
CBC with Differential[1]	X	X		X		
Chemistry Labs[2]	X	X		X		
Beta-2 Microglobulin	X					
LDH	X					
SPEP[3]	X	X		X		X
Serum M-protein Immunofixation	X[13]	X[7]				X[7]

Study Parameters						
Tests and Procedures	**Prior to randomization (≤ 28 days unless otherwise noted)**	**At the end of each cycle**	**Annually**	**At study discontinuation or progression (whichever comes first)**	**28 days after discontinuation of treatment**	**Post Treatment to 10 years from study entry[9]**
24 hr UPEP[3]	X	X		X		X
24 hr Urine M-protein Immunofixation	X[13]	X[7]				X[7]
Serum Free Light Chain Assay	X	X[7]		X		X[15]
Serum Immunoglobulin G, A, M	X	X		X		X
Bone Marrow Aspirate and/or Biopsy	X		X[11]			
^{18}F-FDG PET/CT	X[8]	X[12]				
Serum or Urine Pregnancy Test[4]	X	X		X	X	
Adverse Event Assessment	X	X			X	
PRO Assessment[5]	See Section 6.3.2					
MRD	See above: Biological Specimen Submission table					
Registration to Revlimid REMS®[14]	X					
Patient Medication Calendar[6]		X				

1. Baseline CBCs (with differential and platelet count) which includes WBC, ANC, Platelets, and Hgb must be done ≤ 14 days prior to randomization. CBCs required for protocol therapy must be done < 4 days prior to the treatment cycle.
2. Chemistry includes sodium, potassium, calcium, blood urea nitrogen (BUN), creatinine, creatinine clearance, glucose, alkaline phosphatase, total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT). Magnesium and phosphorus are not required but should be tested as clinically indicated.
3. Assessment is required if used to assess disease response. To confirm VGPR or higher response, both serum and urine M-components must be evaluated.

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4. Patients of childbearing potential must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10 to 14 days prior to starting lenalidomide. It is recommended to perform the pregnancy test as close to the date of randomization as possible in case there are drug shipment and treatment start date delays. A negative serum or urine pregnancy test must be repeated within 24 hours of starting lenalidomide and with each new cycle. Patients must also commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, for 1) at least 28

days before starting study treatment; 2) while participating in the study; 3) during dose interruptions; and 4) for at least 90 days after the last dose of protocol treatment. Patients of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at study discontinuation, and at day 28 following discontinuation from the study. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study discontinuation, and at days 14 and 28 following discontinuation from the study. Men must agree to use a latex condom during sexual contact with a partner of childbearing potential while participating in the study and for 90 days after the last dose of protocol treatment even if they have had a successful vasectomy. See Appendix VI: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods

Rev. Add3 5. Please refer to Section 6.3.2 for the PRO assessment schedule.

6. The Patient Medication Calendar must be completed for each cycle of treatment to record ixazomib/placebo and lenalidomide capsules taken. Please see Appendix II: Patient Medication Calendar.

7. Serum and urine immunofixation and serum FLC only need to be repeated to confirm sCR or CR.

Rev. Add3 8. Within 8 weeks of pre-registration Step 0.

Rev. Add3 9. Follow-up post-treatment till progression. After progression, follow for survival for a maximum of 10 years. Every 3 months if patient is < 2 years from randomization, every 6 months if patient is 2-5 years from randomization, every 12 months if patient is 5 years or more from randomization. No specific requirements if patient is more than 10 years from randomization.

10. All specimens must be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS). See Section 10.3

11. End of cycles 12, 24, 36 and 60 (± 6 weeks) only

12. End of cycles 12 and 24 (± 6 weeks) only

13. Institutions must upload immunofixation test results via Medidata Rave to determine eligibility status for Step 1 randomization.

14. Please refer to Section 8.2.8 and www.celgeneriskmanagement.com for information about the Revlimid REMS® program.

15. As clinically indicated.

Rev. Add3 16. Height is only required at baseline (prior to randomization) and does not need to be repeated.

8. Drug Formulation and Procurement

Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status, a "current" password and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

8.1 MLN9708 (Ixazomib citrate)

8.1.1 Other Names

Ixazomib ML0070120, MLN2238 citrate ester, Ninlaro®

8.1.2 Classification

Proteasome inhibitor

8.1.3 Mode of Action

Ixazomib/placebo is a reversible proteasome inhibitor. Ixazomib/placebo preferentially binds and inhibits the chymotrypsin-like activity of the beta 5 subunit of the 20S proteasome. It induced apoptosis of multiple myeloma cell lines in vitro.

8.1.4 Storage and Stability

Storage: Store ixazomib/placebo capsules between 2º – 30ºC (36º – 86ºF). Ixazomib/placebo should remain in the blister and carton provided until use. Do not freeze or store above 30°C.

If a storage temperature excursion is identified, promptly return ixazomib/placebo capsules to 2º – 30ºC (36º – 86ºF) and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Stability studies are ongoing.

8.1.5 Dose Specifics

Ixazomib/placebo will be administered at a dose of 4 mg on days 1, 8, and 15 of each cycle.

8.1.6 Preparation

No specific preparation is required.

NOTE: Ixazomib/placebo is an anticancer drug. As with other potentially toxic compounds, caution should be exercised when handling ixazomib/placebo. It is recommended to wear gloves and protective garments during preparation when dispensed in clinic. Please refer to published guidelines regarding the proper handling and disposal of anticancer agents.

8.1.7 Route of Administration

Ixazomib/placebo will be administered orally.

8.1.8 Method of Administration

Take capsule(s) on an empty stomach, 1 hour before or 2 hours after food. Swallow whole capsules with water. Do not open or break capsules.

Missed or delayed dose can be taken only if the next scheduled dose is ≥ 72 hours away. A missed dose should not be taken within 72 hours of the next scheduled dose. If vomiting occurs after taking a dose, the patient should not repeat the dose. Resume dosing at the time of the next scheduled dose.

8.1.9 Availability

Clinical Supplies: Ixazomib (NSC 767907) and matching placebo will be provided free of charge by Takeda and distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI).

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Ixazomib and matching placebo will be supplied in blister cards containing 3 capsules each.

Each blinded, patient-specific blister card will be labeled with:

- the protocol number (i.e., “EAA171”)
- the blister card number (i.e., “blister card 1 of 2” or “blister card 2 of 2”)
- the number of capsules (i.e., “3 capsules”)
- the patient ID number (e.g.,"99999", which represents the unique patient identifier assigned at registration)
- the patient initials (i.e., first initial, middle, last initial [e.g., "FML"])
- the agent identification (i.e., “Ixazomib 4 mg or placebo capsule”, “Ixazomib 3 mg or placebo capsule” or “Ixazomib 2.3 mg or placebo capsule”)

- a blank line for the pharmacist to enter the patient's name
- administration instructions (i.e., "Take one capsule on days 1, 8 and 15 of each 28-day cycle.")
- storage instructions [i.e., "Store between 2º – 30º C (36º – 86º F)."]
- emergency contact instructions
- a Julian date

The Julian date indicates the day the bottle was labeled and shipped and is composed of the last two digits of the calendar year (e.g., 2019 = 19, 2020 = 20) and a day count (e.g., January 1 = 001, December 31 = 365). For example, a bottle labeled and shipped on January 1, 2019 would have a Julian date of '19001' and a bottle labeled and shipped on December 31, 2019 would have a Julian date of '19365'. The Julian date will be used by PMB for recalls. When a lot expires, PMB will determine the last date the expired lot was shipped and will recall all bottles (i.e., both Ixazomib and Placebo) shipped on or before that date thus eliminating any chance of breaking the blind. **The Julian Date – Order number (e.g., 21352-0003) from the patient-specific label must be used as the Lot number on the NCI Oral DARF.**

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BLINDED AGENT ORDERS: No blinded starter supplies will be available for this study.

Patients will be registered and randomized through OPEN and assigned patient ID number. This number must recorded by the registering institution at the time of registration for proper clinical supply dispersion. Once a patient has been registered, ECOG-ACRIN will electronically transmit a clinical drug request for that patient to the PMB. This request will be entered and transmitted by ECOG-ACRIN the day the patient is registered and will be processed by PMB the next business day and shipped the following business day. If a patient is registered on Monday, ECOG-ACRIN would enter a clinical drug request for that patient on Monday and PMB would process that request on Tuesday and ship the drug on Wednesday. Sites could expect to receive their order approximately Thursday or Friday. Shipments to United States sites can be expedited (i.e., receipt on Thursday in example above) by the provision of an express courier account name and number to ECOG-ACRIN at the time the patient is registered/randomized.

The initial patient-specific supply will be enough to complete 8 weeks of treatment (2 x 3-capsule blister cards). The supplies will be sent to the registering investigator / drug shipment investigator at the time of registration and should arrive within 5 to 7 business days. Subsequent orders for blinded, patient-specific supplies must be requested by the Principal Investigator (or his/her authorized designee[s]) for EAA171 at each participating institution using the PMB On-line Agent Order Processing (OAOP) program. The assigned patient ID number (e.g., 999999) and the patient initials (e.g., "FML") should be entered in the "Patient or Special Code" field. A separate order is required for each patient ID number (e.g., 999999) being ordered. All drug orders should

be shipped directly to the physician responsible for treating the patient. Requests can be placed **6 weeks after the last shipment is received.**

DOSE ADJUSTMENTS: ***Starter supplies for dose reductions will not be provided.*** If the patient is dose reduced from the original 4 mg or placebo dose, an agent request must be submitted by the site through the OAOP application. Ixazomib/placebo 3 mg and 2.3 mg dose adjustments will be ordered through OAOP only at the time of the dose reduction. The patient-specific blister cards of the dose adjusted supplies will be enough to complete 8 weeks of treatment (2 x 3-capsule blister cards). Requests for additional supplies can be placed **6 weeks after the last shipment is received.**

Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. The CTEP-assigned protocol number and patient ID must be used for ordering all CTEP-supplied investigational agents for this study. The responsible investigator must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI BioSketch, Agent Shipment Form (ASF), and Financial Disclosure Form (FDF).

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees must submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an “active” account status and a “current” password. For questions about drug orders, transfers, returns, or accountability, call or email PMB at any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

Transfer of Ixazomib/Placebo: Ixazomib/placebo may ***not*** be transferred from one patient to another patient or from one protocol to another protocol. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). Ixazomib/placebo supplied for this study may not be used outside the scope of this protocol. To obtain an approval for transfer, investigators should complete and submit to the PMB (PMBAfterHours@mail.nih.gov) a Transfer Investigational Agent Form available on the NCI home page (http://ctep.cancer.gov) or call the PMB at 240-276-6575. The participating institution should also inform the ECOG-ACRIN of the transfer by transferring the patient in TUMS.

Return of Ixazomib/Placebo: At the completion of accrual and treatment, all unused (unopened) blister packs of ixazomib/placebo must be returned to the PMB. When it is necessary to return study drug (e.g., unused blister packs remaining when the protocol is closed to accrual and treatment at a participating clinical site, unopened expired blister packs, or supplies remaining after a patient goes off of protocol treatment), investigators should return the ixazomib/placebo to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov).

Supplies remaining from dispensed blister cards should be documented on the patient-specific NCI Investigational Agent Accountability Record Form for Oral Agents. On the correct dispensing row, document the date returned and the quantity, then destroy on site in accordance with institutional policy.

Agent Inventory Records: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each patient, agent, strength, formulation and ordering investigator on this protocol. **Please note that the Julian Date – Order number (e.g., 21352-0003) from the patient-specific label must be used as the Lot number on the NCI Oral DARF.**

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Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling (240) 276-6575 Monday through Friday between 8:30am and 4:30pm Eastern Time. You may also contact the PMB via e-mail at PMBAfterHours@mail.nih.gov.

8.1.10 Side Effects

See Section 5.4.1 for the Comprehensive Adverse Event and Potential Risks (CAEPR) list.

8.1.11 Potential Drug Interactions

Ixazomib/placebo is metabolized by CYP3A4 (42.3%), 1A2 (26.1%), 2B6 (16%), 2C8 (6%), 2D6 (4.8%), 2C19 (4.8%), and 2C9 (<1%). Co-administration of ixazomib/placebo with clarithromycin did not result in a clinically significant change in the systemic exposure of ixazomib/placebo. Co-administration of ixazomib/placebo with rifampin decreased ixazomib/placebo Cmax by 54% and AUC by 74%. Therefore, avoid concomitant administration of ixazomib/placebo with strong CYP3A4 inducers (such as rifampin, phenytoin, carbamazepine, and St. John's Wort).

Ixazomib/placebo is neither a time-dependent nor a reversible inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5. Ixazomib/placebo did not induce CYP1A2, CYP2B6, and CYP3A4/5 activity or corresponding immunoreactive protein levels. Ixazomib/placebo is not expected to produce drug-drug interactions via CYP inhibition or induction.

Ixazomib/placebo is a low affinity substrate of P-gp. Ixazomib/placebo is not a substrate of BCRP, MRP2 or hepatic OATPs. Ixazomib/placebo is not an inhibitor of P-gp, BCRP, MRP2, OATP1B1, OATP1B3, OCT2, OAT1, OAT3, MATE1, or MATE2-K. Hence, ixazomib/placebo is not expected to cause transporter-mediated drug-drug interactions.

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8.1.12 Patient Implications

There are no human data available regarding the potential effect of ixazomib/placebo on pregnancy or development of the embryo or

fetus. Based on clinical data, ixazomib/placebo caused embryo-fetal toxicity in pregnant rats and rabbits at doses resulting in exposures that were slightly higher than those observed in patients receiving the recommended dose. Patients should avoid becoming pregnant while being treated with ixazomib/placebo. Patients of childbearing potential and patients who are sexually active with a partner of childbearing potential must use effective contraceptive measures during and for 90 days following treatment.

It is not known whether ixazomib/placebo or its metabolites are present in human milk. Many drugs are present in human milk and as a result, there could be a potential for adverse events in nursing infants. Patients should discontinue nursing while receiving ixazomib/placebo.

8.2 Lenalidomide

Please refer to the commercial package insert for complete drug and toxicity information.

8.2.1 Other Names

CC-5013, Revlimid™, CDC-501

8.2.2 Classification

Immunomodulatory Agent

8.2.3 Mode of Action

Lenalidomide, a thalidomide analog, is an immunomodulatory agent with a spectrum of activity that is still under investigation. Some of its effects include inhibition of inflammation, inhibition of angiogenesis, inhibition of hematopoetic tumor cell proliferation, modulation of stem cell differentiation and upregulation of T cell and NK cell responses.

8.2.4 Storage and Stability

Storage: Store capsules at room temperature (25°C). Excursions are permitted (to 15-30°C).

Stability: Refer to the package labeling for expiration date.

8.2.5 Dose Specifics

Lenalidomide will be administered at a dose of 10 mg on days 1-28.

8.2.6 Preparation

No preparation is required.

Only a one cycle (28-day) supply may be dispensed at one time.

8.2.7 Route of Administration

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

8.2.8 Availability

Lenalidomide will be provided in accordance with Celgene Corporation's Revlimid REMS® program. Per standard Revlimid

REMS® program requirements, all physicians who prescribe lenalidomide for research patients enrolled into this trial, and all research patients enrolled into this trial, must be registered in, and must comply with, all requirements of the Revlimid REMS® program.

Further information about the Revlimid REMS® program is available at www.celgeneriskmanagement.com.

Celgene distributes lenalidomide 2.5 mg and 5 mg hard gelatin capsules in tamper-evident, child-resistant, opaque, high density polyethylene (HDPE) bottles with HDPE caps.

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

8.2.9 Side Effects

See Section 5.4.2 for the Comprehensive Adverse Event and Potential Risks (CAEPR) list.

8.2.10 Potential Drug Interactions

Periodic monitoring of digoxin levels is recommended during coadministration with lenalidomide.

Monitor patients receiving concomitant warfarin per standard practice guidelines.

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

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8.2.11 Nursing/Patient Implications

Risks Associated with Pregnancy

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

Definition of patient of childbearing potential

A patient of childbearing potential is anyone, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy, or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Before starting study drug:

Patients of Childbearing Potential:

- Patients of childbearing potential must have two negative pregnancy tests (minimum sensitivity of 25 mIU/mL) prior to

starting study drug. The first pregnancy test must be performed within 10 to 14 days prior to the start of study drug and the second pregnancy test must be performed within 24 hours prior to the start of study drug. The patient may not receive study drug until the Investigator has verified that the results of these pregnancy tests are negative.

Male Patients:

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

All Patients:

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

9. Statistical Considerations

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9.1 Study Design

This is a randomized phase III study with the primary aim to evaluate whether intensifying maintenance therapy based on MRD positive status after approximately 1 year post early stem cell transplant lenalidomide maintenance results in prolonged overall survival (OS). OS will be compared between patients with MRD positive status (n=510) randomized to either ixazomib-lenalidomide (Arm A) or placebo-lenalidomide (Arm B).

9.2 Study Endpoints

9.2.1 Clinical Outcomes

9.2.1.1 Primary Endpoint

- Overall survival defined as the time from randomization to death due to any cause, or censored at date last known alive

9.2.1.2 Secondary Endpoints

- Progression-free survival defined as the time from randomization until the earlier of progression or death due to any cause, or censored at date of last disease evaluation (Note: Only deaths that occur within 3 months of the last disease evaluation are considered events.)
- Best response on treatment for eligible patients based on standard IMWG criteria as described in Section 6; Response rates for eligible patients including very good partial response (VGPR), complete response (CR) and stringent CR (sCR) at 12-, 24-, 36- and 60-cycles post-randomization
- Incidence of adverse events by worst grade and type for treated patients determined using CTCAE; Rates of worst grade 3 or higher non-hematologic toxicity and overall worst grade 3 or higher toxicity on treatment

9.2.1.3 Exploratory Endpoints

- Time to progression (TTP) defined as the time from randomization to progression, or censored at date of last disease evaluation
- Duration of response (DOR) defined as the time of observed response (VGPR or better) to the time of progression in the respective group of responders
- Treatment duration calculated as the time from randomization to date off treatment, or censored at the date of last treatment
- Cumulative dose calculated as the sum of all doses taken across all cycles

- Dose intensity calculated as cumulative dose received divided by treatment duration
- Relative dose intensity calculated as the dose intensity divided by planned dose intensity

9.2.2 Patient-Reported Outcomes

9.2.2.1 Primary Endpoint

- Change in FACT/GOG-Ntx TOI score calculated as the difference after completion of 12 cycles of study therapy from baseline
- Change in FACT-MM TOI score calculated as the difference after completion of 24 cycles of study therapy from baseline

9.2.2.2 Secondary Endpoints

- Levels and changes from baseline of all instruments
- Time to worsening of FACT/GOG-Ntx TOI defined as the time from baseline to a decrease of 8 points (MID), respectively, or censored at the date of last assessment
- FACT/GOG-Ntx TOI recovery rate in the patients experiencing a MID decrease, the proportion of patients with the FACT/GOG-Ntx TOI score returning to baseline level
- Time to improvement of the FACT-MM TOI defined as the time from baseline to an increase of 10 points (MID), respectively, or censored at the date of last assessment
- FACT-MM TOI response rate defined as the proportion of patients experiencing a MID improvement since baseline at each assessment time point

9.2.2.3 Exploratory Endpoints

- Presence, frequency, interference, amount and/or severity of select PRO-CTCAEs tabulated at each cycle
- ASK-12 scores at each assessment time point
- PRO compliance rate defined as the proportion of patients who submit the given PRO instrument among those eligible at each time point which excludes those missing by design (due to death or disease progression, early treatment discontinuation)
- PRO completion rate defined as the proportion of patients who complete given PRO instrument based on the instrument's scoring system among those eligible at each time point

9.3 Statistical Analysis Plan

9.3.1 Primary Clinical Analysis

The primary analysis will be on an intention to treat (ITT) basis considering the randomized treatment assignment irrespective of treatment received. OS will be estimated using the Kaplan-Meier (KM) method and compared using a stratified log-rank test. Stratified cox proportional hazards regression will produce a treatment hazard ratio (HR) estimate (ixazomib-lenalidomide/placebo-lenalidomide). Interim analyses for efficacy will be conducted. The design incorporates a group sequential monitoring plan with 6 interim analyses (IA) and one final analysis for the OS comparison between arms. Based on accrual and failure rate assumptions in the sample size calculation (Section 9.4), interim analyses are expected to occur from 3y to 5.5y after randomization and the final analysis at full information (179 deaths) is expected to occur after 6y of follow-up. Critical values as presented below in Table 1 are based on the Lan-DeMets error spending rate function corresponding to the truncated version of O'Brien-Fleming boundaries to preserve the overall type I error rate. At each interim analysis, the null hypothesis of equal OS on the two arms will be tested against the 1-sided alternative of increased OS on the ixazomib-lenalidomide arm. The p-value from a 1-sided stratified log-rank test will be compared to the level of nominal significance associated with these critical values. If the boundary is crossed at an IA, there is sufficient evidence of efficacy to stop the study in favor of the alternative hypothesis. The DSMC then would consider stopping the study early.

Table 1

Analysis	Study Time (years)	Information Time (%)	Failures under Alternative	Critical Value	Nominal Significance
1	3.0	35%	63	3.2905	0.0005
2	3.5	47%	84	3.1768	0.0007
3	4.0	59%	105	2.7443	0.0030
4	4.5	70%	126	2.4984	0.0062
5	5.0	81%	145	2.3232	0.0101
6	5.5	91%	162	2.1904	0.0142
7	6.0	100%	179	2.0858	0.0185

Coupled with the interim analysis for early stopping for superiority of ixazomib-lenalidomide (Arm A), the study will be monitored for harm and inefficacy. At 35% information, the DSMC may consider stopping the study early for harm if the lower bound of a 95% confidence interval for the HR is above 1.0. Interim inefficacy monitoring is planned to start after approximately 47% of full information becomes available with repeated analysis at each semi-annual DSMC meeting. The Linear 20% Inefficacy Boundary (LIB20), an approach described by Freidlin et al, will be used.[71] The study may be stopped if there is

not at least a small trend in favor of the alternative hypothesis starting at this time. Specifically, at each interim analysis, if the estimated HR is larger than the cutoff value given in the LIB20 boundary (Table 2), the DSMC then would consider stopping the study early for lack of efficacy.

Table 2

Information Proportion	Cutoff Hazard Ratio
47%	1.004
59%	0.984
70%	0.965
81%	0.947
91%	0.931
100%	0.917

9.3.2 Secondary Clinical Analyses

Progression-Free Survival (PFS)

An important secondary aim is to evaluate whether a response-adapted strategy translates into superior progression-free survival for patients switching to more-intensive treatment. PFS will be estimated using the KM method and compared using the stratified log-rank test. Median PFS on the control arm is assumed to be 18 months based on results from recent clinical trials. Assuming exponential distribution of failures, this study is design to detect a 44% increase in median PFS to 26 months on the experimental arm. This corresponds to a treatment HR approximating 0.70 [monthly hazard rate 0.0385 versus 0.0267]. At 1-sided 2.5% type I error, there is approximately 90% power using a log-rank test to detect this HR given 510 patients uniformly accrued over 3.5y with full information of 319 PFS events at 4.5y (accrual end plus one year). The actual timing of this PFS analysis will depend on accrual. The analysis will not be done before one year after the last patient is randomized. No interim analyses for the PFS comparison will be conducted. The study team will also not consider or declare the experimental arm to be a success based on the PFS endpoint alone.

Response

Response will be tabulated by category. Response rates (sCR, CR, VGPR) will be compared using the chi-squared test for proportions. It is hypothesized that the ixazomib-lenalidomide arm will have higher response rates. Ineligible patients are excluded from the analysis and unevaluable patients are counted in the denominator. Sensitivity analyses will exclude unevaluable patients from the rate calculations. Given 255 patients per arm, there is over 90% to detect a difference of 15% in VGPR rates at 1-sided 2.5% significance assuming a 52.5% overall VGPR rate.

Toxicity

We will monitor the toxicities experienced by all treated patients. Interim analyses of toxicity are performed twice yearly for all ECOG-ACRIN studies. Expedited reporting of certain adverse events is required, as described in Section 5.3. We are specifically interested in comparing the rates of worst grade 3 or higher non-hematologic treatment-related events using the chi-squared test for proportions. It is likely that the ixazomib-lenalidomide arm will have moderately higher toxicity rates than the placebo-lenalidomide arm. The grade 3 or higher treatment-related non-hematologic rate on the placebo-lenalidomide arm is estimated to be around 36% based on reported toxicity rates on the lenalidomide arm of the CALGB maintenance trial. Assuming 1-sided 2.5% significance, there is 84% power to detect a difference in grade 3 or higher treatment-related non-hematologic rates of 13% (ixazomib-lenalidomide arm 49% rate) with all enrolled patients treated. The maximum width of a 95% CI for a rate of a given toxicity on either treatment arm is 13%. As exploratory, global grade 3 or higher treatment-related non-hematologic rates will be evaluated within age subgroups dichotomized at 65 years. We also plan to examine comprehensively adverse events experienced by study participants using the Tox-T method which has been validated as a tool to assess adverse events in other NCTN trials.[46]

9.3.3 Exploratory Clinical Endpoints

Time to Progression and Duration of Response

TTP and DOR in each arm will be estimated using the Kaplan-Meier method.

Treatment Exposure

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Treatment exposure to the oral medications lenalidomide and ixazomib will be quantified using patient medication calendars. Cumulative dose, dose intensity, and relative dose intensity will be calculated overall and by cycle. Data will be summarized by treatment arm with descriptive statistics and graphically over time. Treatment duration in each arm will be estimated using the Kaplan-Meier method. Patients will be classified into dichotomous groups based on a 75% relative dose intensity cutoff (< 75% vs ≥ 75% represents poor vs good treatment adherence). The proportion of patients with poor lenalidomide treatment adherence will be compared between arms using the chi-squared test for proportions. In addition, multivariable logistic regression analysis will be conducted to identify the baseline factors associated with calculated good treatment adherence. We will conduct one interim analysis to monitor treatment adherence to ixazomib. Specifically, the treatment adherence rate at 18 months will be measured by ixazomib relative dose intensity at or exceeding 75% (“good” treatment adherence). This analysis is expected to occur at 2.5 years from randomization when 72 patients (29% of target accrual) have reached potentially 18 months of assigned ixazomib therapy. If the treatment adherence rate is at least 80% we would consider this acceptable while a treatment adherence rate of 65% is considered evidence that adherence to ixazomib is unacceptable. If

54 or more patients achieve target treatment adherence exceeding 75% over 18 months, then the study will continue. If the true treatment adherence rate is 65%, the probability of concluding treatment adherence is acceptable is 0.05 (type I error). If the true treatment adherence rate is 80%, the probability of concluding treatment adherence is acceptable is 0.88 (power).

9.3.4 Patient-Reported Outcomes (PRO) Endpoints

PRO compliance and completion rates will be tabulated at each collection time point and overall separately for the FACT-G (FWB and PWB subscales), FACT-Ntx, FACT-MM, ASK-12 and PRO-CTCAE instruments.

Health-Related Quality of Life (QOL)

To assess the impact of treatment and disease on health-related QOL, there are two co-primary endpoints: change in FACT/GOG-Ntx TOI from baseline to end of cycle 12 post-randomization (beginning of cycle 13 assessment) and change in FACT-MM TOI from baseline to end of cycle 24 (beginning of cycle 25 assessment) post randomization. The FACT-G (FWB and PWB subscales), Ntx and MM will be administered at the beginning (day 1)of every 3 cycles for the first 24 cycles (beginning of cycles 4, 7, 10, 13, 16, 19, 22 and 25) and every 6 cycles thereafter (up to completion of 48 cycles of therapy (beginning of cycles 31, 37, 43, and 49), or at treatment discontinuation prior to completion of 48 cycles of therapy. During long-term follow-up/post-treatment end, there will be four quarterly assessments for 1 year. We hypothesize that treatment with ixazomib will not result in a significant difference in the FACT/GOG-Ntx TOI over the first 12 cycles and that improved PFS will result in higher FACT-MM TOI scores by end of 24 cycles. All patients who receive at least one dose of study drug and complete the QOL assessment at both time points are eligible. Power calculations are based on t-tests comparing the two treatment arms for the change in score with a 2-sided 0.05 alpha split between these comparisons. In an unselected group of MM patients being treated with oral therapy (n=118), the FACT-MM TOI had a standard deviation (SD) of approximately 21 points. The FACT-Ntx TOI has a reported SD of 14-16.[70] We propose using a general effect size measure of half standard deviation to establish the minimally important difference (MID).[47,69] We therefore will establish a MID of 10 for the FACT-MM TOI and 8 for the FACT-Ntx TOI. We assume 90% and 81% of patients are alive by year 1 and 2, respectively, as well as a 10% drop-out rate resulting in potential patients of n=414 and n=373 for each analysis. Sensitivity for the proportion assumed to submit the questionnaire at both time points (compliance rates of 60% and 80%), allowing for a range of instrument variability and assuming different correlation (0.6, 0.4) between repeated measures was performed (Table 3). The difference in the FACT-Ntx TOI mean change score over 12 cycles of treatment between the ixazomib-lenalidomide arm and the placebo-lenalidomide arm that can be detected with 80% power at 2-sided 0.025 significance level ranges from 3.7-6.9 points as shown below. The difference in the FACT-MM TOI mean change score over 24 cycles of

treatment between the ixa-lenalidomide arm and the placebo-lenalidomide arm that can be detected with 80% power at 2-sided 0.025 significance level ranges from 5.8-10.0 points. All of the scenarios show the target MID for each comparison or smaller can be detected with satisfactory power and thus we will be able to show a significant difference in QOL if it occurs.

Table 3

Standard Deviation (SD)	Correlation	SD of change	Differences in FACT-Ntx TOI Subscale Mean Change Score (power=80%, 2-sided alpha=0.025) 60% compliance (n=124/arm)	80% compliance (n=164/arm)
From Baseline to 12 Cycles Post Randomization				
12.0	0.6	10.7	4.2	3.7
	0.4	13.1	5.2	4.5
14.0	0.6	12.5	4.9	4.3
	0.4	15.3	6.0	5.3
16.0	0.6	14.3	5.6	4.9
	0.4	17.5	6.9	6.0
Standard Deviation (SD)	**Correlation**	**SD of change**	**Differences in FACT-MM TOI Mean Change Score (power=80%, 2-sided alpha=0.025) 60% compliance (n=112/arm)**	**80% compliance (n=148/arm)**
From Baseline to 24 Cycles Post Randomization				
18.0	0.6	16.1	6.7	5.8
	0.4	19.7	8.2	7.1
20.0	0.6	17.9	7.4	6.4
	0.4	21.9	9.1	7.9
22.0	0.6	19.7	8.2	7.1
	0.4	24.1	10.0	8.7

Sensitivity analysis will be conducted to retain patients who discontinued treatment early and missing their FACT-Ntx TOI score after 12 cycles of treatment (beginning of cycle 13 assessment) using their QOL score at early treatment discontinuation for the analysis. For the FACT-MM TOI analysis after 24 cycles of treatment (beginning of cycle 25 assessment) the long-term follow-up assessment closest to 2 years from randomization will be used if patients are not on treatment. Descriptive statistics (mean, SD, median, range) will be used to evaluate the distribution of levels and

changes for the set of health-related QOL evaluations including the FACT/GOG-Ntx TOI, FACT-MM TOI and FACT-G (FWB and PWB subscales). Levels and changes will also be assessed graphically. Linear mixed effects models will be used to perform repeated measured regression analysis with the assumed covariance matrix maximizing Akaike information criteria. Models with treatment, assessment time, and treatment by assessment time interaction with and without other predictors will be fit. If there is substantial missingness, we will analyze the data according to the methods described in Schluchter and Schluchter, Greene and Beck. These methods consider missingness informative by jointly modeling longitudinal QOL score and survival time to dropout.

There are two key secondary health-related QOL analysis comparing treatment arms: Time to worsening of the FACT/GOG-Ntx TOI and time to improvement of the FACT-MM TOI. Time to worsening of the FACT/GOG-Ntx TOI and time to improvement of the FACT-MM TOI will be analyzed with the KM method and compared using the log-rank test. We will establish significance as alpha=1.67% based on Bonferroni adjustment (5% divided over 3 comparisons). We will provide rates on each arm including exact binomical 95% confidence intervals for the FACT/GOG-Ntx TOI recovery rate and FACT-MM TOI response rate.

As exploratory, correlation between time to worsening of symptoms with PFS and OS will be assessed with Kendall's Tau adjusted for censored observations.

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Finally, we will evaluate whether patients with poor treatment adherence based on medication calendars and lower likelihood of medication adherence based on ASK-12 scores have lower QOL scores [the FACT/GOG-Ntx TOI, FACT-MM TOI and FACT-G (FWB and PWB subscales)] after 12- and 24-cycles of treatment. Linear regression analysis at these 2 time points separately will be conducted with QOL score as outcome and treatment adherence group as the main effect adjusting for baseline QOL score along with other disease and demographic characteristics.

PRO-CTCAE

Analyses related to the PRO-CTCAE are exploratory. Descriptive statistics will be used to summarize selected PRO-CTCAEs tabulated at each cycle overall and by arm. We will map PRO-CTCAEs with provider reported AEs and evaluate differences in incidence and worst severity. PRO-CTCAE ratings will further be evaluated in relation to patient bother by treatment side effects (FACT-GP5 item, "I am bothered by treatment side effects") to identify the toxicities that are most highly associated with treatment tolerability issues.

Medication Adherence Scale

Analyses related to the ASK-12 are exploratory. Descriptive statistics will be used to summarize ASK-12 scores tabulated every 6 cycles on study therapy. The ASK-12 is reported to have a mean (standard deviation) of 27.5 (7.2). Differences between arms will be evaluated

based on the t-test (or Wilcoxon rank sum test). Patients will also be classified into high versus low likelihood of medication adherence groups according to tertile distributions (lowest tertile vs second and top). The relationship between likelihood of medication adherence and calculated treatment adherence dichotomous groups will be evaluated in 2x2 tables. In addition, multivariable logistic regression analysis will be conducted to identify the baseline factors associated with low likelihood of medication adherence over 12- and 24-cycles of treatment.

9.4 Sample Size Considerations

OS will be estimated based on the KM method and compared between arms using the stratified log-rank test. All survival estimates are from randomization,
Rev. Add1 which would be ~18 months from start of initial therapy. Median OS for the control arm was estimated to be 5.5 years (y) considering expectations in this setting for an unselected cohort as well as results from the previously mentioned meta-analysis according to post-treatment MRD status.[3] Based on the log-rank test, there is approximately 80% power at 1-sided 2.5% significance to detect a difference in 4y OS from 60.4% to 72.2% reflecting an approximate 35% reduction in hazard [treatment HR=0.65] assuming 510 patients uniformly accrued over 3.5y and 179 deaths at full information (6y).

9.5 Projected Accrual

This study aims to screen 840 patients to pre-registration Step 0 at an accrual rate of 20 patients per month/240 patients per year for an accrual duration of 3.5y. With an allowance of 15% for patients not yielding high quality specimens for MRD analysis, it is expected that 714 patients will have MRD measured. MRD status is anticipated to be split 75% positive/25% negative resulting in 536 MRD positive patients and 178 MRD negative patients. Some drop-out (5%) between marker evaluation and enrollment to Step 1 treatment is also anticipated resulting in an estimated 510 patients randomized to Arm A or Arm B with 1:1 allocation. Patients with MRD negative disease status based on NGF and immunofixation results will not be registered to the treatment phase.

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9.6 Randomization Scheme

Patients are randomized in equal allocation to ixazomib-lenalidomide or placebo-lenalidomide and stratified by molecular risk status by International Myeloma Working Group (IMWG) criteria: standard or high risk, prior lenalidomide maintenance dose: 5 mg,10 mg, or >10 mg, prior maintenance duration: < 12 months or ≥ 12 months. Treatment will be assigned using permuted blocks within strata with dynamic balancing by main ECOG-ACRIN institution.[33]

9.7 Gender and Ethnicity

Based on observed data from E1A11 the anticipated accrual in subgroups defined by gender and race is expected to parallel the newly diagnosed setting as follows:

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DOMESTIC PLANNED ENROLLMENT REPORT (TREATMENT)					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	2	4	0	0	**6**
Asian	6	4	0	0	**10**
Native Hawaiian or Other Pacific Islander	2	0	0	0	**2**
Black or African American	27	29	0	0	**56**
White	147	255	17	17	**437**
More Than One Race	0	0	0	0	**0**
Total	**184**	**292**	**17**	**17**	**510**

The accrual targets in individual cells are not large enough for definitive treatment comparisons to be made within these subgroups. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.

Study Monitoring

This study will be monitored by the ECOG-ACRIN Data Safety Monitoring Committee (DSMC). The DSMC meets twice each year. For each meeting, all monitored studies are reviewed for safety and progress toward completion. When appropriate, the DSMC will also review interim analyses of outcome data. Copies of the toxicity reports prepared for the DSMC meetings are included in the study reports prepared for the ECOG-ACRIN group meeting (except that for double blind studies, the DSMC may review unblinded toxicity data, while only pooled or blinded data will be made public). These group meeting reports are made available to the local investigators, who may provide them to their IRBs. Only the study statistician and the DSMC members will have access to interim analyses of outcome data. Prior to completion of this study, any use of outcome data will require approval of the DSMC. Any DSMC recommendations for changes to this study will be circulated to the local investigators in the form of addenda to this protocol document. A complete copy of the ECOG-ACRIN DSMC Policy can be obtained from the ECOG-ACRIN Operations Office – Boston.

10. Specimen Submissions

Following pre-registration (Step 0), diagnostic bone marrow aspirates must be submitted to Mayo Clinic Hematology Laboratory for the central Minimal Residual Disease (MRD) assessment as described in Sections 1.1 and 11. The institution will be notified of the results within three (3) business days of receipt of the bone marrow specimen.

All specimens must be clearly labeled with the ECOG-ACRIN protocol number (EAA171), the patient's initials (last name, first name) and ECOG-ACRIN patient sequence number, the collection date, and specimen type.

It is required that all specimens submitted on this trial be entered and tracked via the ECOG-ACRIN Sample Tracking System (STS) [Section 10.3]. An STS shipping manifest form is to be included with every submission.

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10.1 Submissions to the Mayo Clinic Myeloma Reference Laboratory

Myeloma Tumor Biology Kits are available to order and will include materials necessary for the preparation and shipment of the specimens. To order kits contact Stacey Lehman at the Mayo Clinic Myeloma Reference Laboratory at (507) 284-3805 or email Lehman.Stacey@mayo.edu. Include the name of the contact person, phone number, address where kits should be shipped, ECOG-ACRIN protocol number (EAA171), the number of kits needed, and if the kits need to be shipped priority overnight. Otherwise kits will arrive in three to four working days.

Any questions concerning specimen collection and shipment can be directed to Stacey Lehman at (507) 284-3805 or Lehman.Stacey@mayo.edu.

10.1.1 Sample Submission Schedule

Bone marrow specimens are to be submitted as indicated below:

Biological Materials[1]	Following Pre-registration
MANDATORY for Minimal Residual Disease Assessment	
Bone Marrow Aspirate (1) 6mL ACD (yellow top) tube	X

1. Kits are being provided for the collection and shipment of the bone marrow specimens.

10.1.2 Sample Preparation Guidelines

Bone Marrow Aspirate

This redirect bone marrow aspirate should be drawn at the same time that the bone marrow aspiration/biopsy is being done for clinical and diagnostic purposes and should be done through the same skin puncture site that the clinical specimen was obtained.

- Draw 6mL of "redirect" bone marrow aspirate into **one (1) ACD (yellow top) vacutainer tube** provided in the Myeloma Tumor Biology Kit. Please use the first or second pull for these tubes. Ship the day of collection.

10.1.3 Shipping Procedures

If your shipment was not logged into the ECOG-ACRIN STS, please call Stacey Lehman at (507) 284-3805 or email Lehman.Stacey@mayo.edu to notify the laboratory when specimens are being shipped. Indicate the ECOG-ACRIN protocol number (EAA171), the FedEx tracking number, and name and phone number of the contact person.

Bone marrow aspirates should be sent fresh, the day of collection, at ambient temperature (do not freeze) and shipped overnight to arrive during normal working hours. Specimens from multiple patients may be shipped together, but must be placed in separately labeled tubes and bags.

Follow the packing guidelines listed in the kit. If specimens are sent late in the week and will arrive on the weekend, please note "Saturday Delivery" on the Federal Express form.

FRIDAY AND PREHOLIDAY SHIPMENTS SHOULD BE AVOIDED.

Packing instructions:

- Place the slightly thawed Kool-PAK in the bottom of Styrofoam container (Kool-PAK should be frozen at least 24 hours in advance). Allow the frozen ice pack to thaw at room temperature for 2–3 hours before preparing the specimens for shipment.
- Place absorbent toweling on top of the Kool-PAK.
- Place specimens in their individual plastic bags provided, wrap in paper toweling and place them in the Styrofoam container and close the lid. Do not place the specimens directly on the ice pack.
- Place the Styrofoam container and the Sample Tracking System Shipping Manifest Form within the cardboard mailing sleeve.
- Prepare the package for shipping, applying packing tape as needed. Complete the sender portion of the return FedEx air bill and adhere to the exterior lid of the box. Ship specimens via priority overnight delivery the same day collected.
- Notify Federal Express for pick-up and/or leave package at the designated FedEx drop-off location.

  The specimens in prepared kits should be shipped to the following address:

  Stacey Lehman
  Mayo Foundation
  221 4th Avenue SW
  613 Stabile
  Rochester, MN 55905

  An STS shipping manifest form must be generated and shipped with all specimen submissions.

10.2 Use of Specimens in Research

Specimens will be distributed to investigators at Mayo Clinic Hematology Laboratory for the laboratory research studies defined in Section 11.

Specimens from patients who consented to allow their specimens to be used for future approved research studies will be retained in an ECOG-ACRIN designated central repository.

Specimens submitted will be processed to maximize their utility for current and future research projects.

If future use is denied or withdrawn by the patient, the specimens will be removed from consideration for use in any future research study. Specimens will be destroyed per guidelines of the respective repository.

10.3 ECOG-ACRIN Sample Tracking System

It is **required** (barring special circumstances) that all specimens submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). As of June 2007, the software will allow the use of either 1) an ECOG-ACRIN user-name and password previously assigned (for those already using STS), or 2) a CTSU username and password.

When you are ready to log the collection and/or shipment of the specimens required for this study, please access the Sample Tracking System software by clicking https://webapps.ecog.org/Tst.

Important: Please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link: http://www.ecog.org/general/stsinfo.html. Please take a moment to familiarize yourself with the software prior to using the system.

An STS generated shipping manifest must be generated and shipped with all specimen submissions.

Please direct your questions or comments pertaining to the STS to ecog.tst@jimmy.harvard.edu.

Study Specific Notes

Generic Specimen Submission Form (#2981v3), along with the Mayo Clinic Patient Information Form (Appendix VII), will be required only if STS is unavailable at time of specimen submissions. Notify the laboratory of the shipment by faxing a copy of the completed form to the laboratory.

Retroactively enter all specimen collection and shipping information when STS is available.

10.4 Sample Inventory Submission Guidelines

Inventories of all specimens submitted from institutions will be tracked via the ECOG-ACRIN STS and receipt and usability verified by the receiving laboratory. Inventories of specimens forwarded and utilized for the approved laboratory research studies will be submitted by the laboratory to the ECOG-ACRIN Operations Office - Boston on a monthly basis in an electronic format defined by the ECOG-ACRIN Operations Office - Boston.

11. Laboratory Research Studies

These analyses will be performed at the Hematology Laboratory at Mayo Clinic Rochester, MN under the direction of Dr. Shaji Kumar.

11.1 Assessment of Minimal Residual Disease

11.1.1 MRD – Next Generation Flow Cytometry Methods

Next generation flow cytometry (NGF) MRD assessment is conducted with multiparameter flowcytometry. The reagents for the MRD assessment will utilize the MM MRD kit (cytognos # MM-MRD, Salamanca). Analysis will follow the Euroflow approach using Infinicyt software as outlined by Flores-Montero et al. [22] The methodology has been described before and will be used without additional modification. Briefly, it utilizes an 8-color flow approach using two tubes, one with cytoplasmic light chains assessment on permeabilized cells. Four milliliters (ml) BM aspirate will be lysed using a fixative free erythrocyte lysing solution (# CYT-BL (10X), Cytognos, Salamanca, Spain). Per manufacturers guidelines, up to two ml of marrow will be suspended in 50 ml of freshly made 1X lyse and gently mixed for 15 minutes. After centrifugation, the supernant is aspirated and the pellet resuspended in 2 ml of Staining Buffer (SB - PBS /0.09% Azide /0.5% BSA). The tube is then filled to 50 ml with staining buffer and centrifuged. Two ml of SB are used to resuspend one pellet and combined with the pellet in the second tube. The cell suspension is transferred to a 12 X 75 tube. After centrifugation, the supernant is aspirated and the pellet is resuspended in 0.5 ml of SB. The suspension is diluted with SB not to exceed 10^7 per ml. Up to 10 million cells are added to tube 1 and tube 2. Both tubes are stained for 30 minutes at room temperature, in the dark with multi epitope CD38 FITC/CD138 V450/CD45 Percp 5.5 /CD19 PE-Cy7 in both tubes for plasma cell (PC) gating. To determine PC phenotype both tube 1 and 2 contain CD27-BV510 and CD56-PE; tube 1 also includes CD117 APC and CD81 APC C750. After incubation, tube 1 is resuspended for 10 minutes in BD FACs Lyse. The pellet is resuspended in 0.5 ml SB and held until run on the flow cytometer. Tube 2 is further processed for cytoplasmic light chain staining (Kappa APC /Lambda APC-C750) with a fix and perm step. After centrifugation, the pellet is resuspended in 0.5 ml SB and held until run on the flow cytometer. The bone marrow quality will be determined by assessing for expected normal marrow cells. Normal and neoplastic plasma cells will be reported as percentage of all CD38/138/45 gated cells. The report will include the total number of cells analyzed, PC immunophenotype (including clonality), and plasma cell (normal and abnormal) percentages and event (abnormal plasma cell) count to determine MRD negative or positive status.

11.2 Lab Data Transfer Guidelines

The data collected on the above-mentioned laboratory research studies will be submitted electronically using a secured data transfer to the ECOG-ACRIN

Operations Office - Boston by the investigating laboratories on a quarterly basis or per joint agreement between ECOG-ACRIN and the Investigator.

12. Imaging Correlative Studies

12.1 ^{18}Fluorodeoxyglucose (FDG) PET/CT

Advanced imaging modalities are playing an increasingly important role in the diagnosis, risk stratification and response assessment of myeloma. ^{18}F-FDG PET/CT allows simultaneous assessment of the bone marrow, as well as presence of extramedullary lesions. Both baseline assessments as well as follow up imaging have an important prognostic role and appear to be associated with survival. Myeloma cells, while they tend to be primarily marrow based, can be found in the extramedullary compartment, including the peripheral blood. As a result, imaging plays an important role in assessing response to therapy, as well as in identifying disease progression, both inside and outside the bone marrow. In fact, functional imaging assessment using ^{18}F-FDG PET/CT is an integral part of minimal residual disease assessment in myeloma, in addition to following foci of extramedullary disease identified prior to start of treatment.

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12.1.1 Imaging Schedule

All registered patients from both the ixazomib/lenalidomide arm and the placebo/lenalidomide arm are expected to undergo ^{18}F-FDG PET/CT as SOC at the following time points:

- Prior to initiation of randomized study mandated therapy [referred to as the baseline scan]. The baseline scan can be done prior to study registration, as long as it is within 8 weeks of pre-registration step 0
- After completion of 12 cycles of study mandated therapy (± 6 weeks) [referred to as the year 1 scan]
- After completion of 24 cycles of study mandated therapy (± 6 weeks) [referred to as the year 2 scan]

All ^{18}F-FDG PET/CT images are to be submitted via TRIAD as outlined in Section 4.3.5.

12.1.2 Criteria for defining abnormal ^{18}F-FDG PET/CT

The primary ^{18}F-FDG PET/CT reading will be performed using IMWG PET criteria, where a negative PET is described as disappearance of every area of increased tracer uptake found at disease sites on the baseline ^{18}F-FDG PET/CT, or a preceding ^{18}F-FDG PET/CT, or decrease to less than that seen in mediastinal blood pool SUV.[4]

However, other criteria including IMPETUS and IMAJEM trial criteria will also be applied as exploratory analyses to determine if a better reading scheme can be established with respect to accuracy in the prediction of patient outcome.[29,45]

12.1.3 Imaging Aims and Statistics

There are three imaging aims in this correlative study, which will be based on central review of the acquired ^{18}F-FDG PET/CT scans, and which are distinguished into primary and secondary.

Imaging aims which involve patient outcomes (overall survival or progression-free survival) will be conducted at full information. In

addition, reporting of imaging aims will not be done prior to reporting of the respective primary or secondary therapy endpoints.

12.1.3.1 Primary imaging aim

[1] To evaluate the association between baseline ^{18}F-FDG PET/CT and patient outcomes.

The primary imaging aim consists of evaluating the association between baseline ^{18}F-FDG PET/CT and patient outcomes, and seeks to address the question of whether abnormal ^{18}F-FDG PET/CT findings at baseline (i.e., after approximately 1 year of lenalidomide maintenance following an early stem cell transplant) are prognostic of poorer progression-free survival (PFS) and overall survival (OS). The potential association will be analyzed using both quantitative and qualitative ^{18}F-FDG PET/CT parameters.

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Quantitatively, the association between baseline SUV-based quantitative ^{18}F-FDG PET/CT parameters (SUVmax, SUVpeak, MTV, TLG) and PFS will be analyzed through Cox regression. PFS will be defined as the time from randomization until the earlier of progression or death due to any cause. SUV-based quantitative ^{18}F-FDG PET/CT (qPET) parameters will be analyzed as continuous covariates, and adjustment will be made for potential confounders, including patient age and the randomization stratification factors. In addition, we will formally test whether this association differs by study arm through a statistical interaction term between the qPET parameter and study arm. If this interaction is not significant at the 0.05 level, then a single overall hazard ratio will be estimated for the entire study cohort. We assume that up to 10% of patients may not receive the ^{18}F-FDG PET/CT at baseline or may have an uninterpretable scan. Standardizing each qPET parameter to have mean 0 and standard deviation 1, and assuming the R-square of each qPET parameter with other covariates is no more than 0.4, the proposed sample size of 510 patients (459 evaluable) has power of 82% to detect a hazard ratio as low as 1.25 per standard deviation increase in the qPET parameter, when the progression event rate is 0.6. If the observed progression event rate over the duration of the trial is higher than 0.6, the power will correspondingly increase (e.g., power=85% for a progression event rate of 0.65). A two-sided Cox regression with a type I error rate of 0.05 was used for this computation (PASS 16). In addition, for further clinical utility, we will explore estimating an optimal threshold for each baseline qPET parameter using recursive partitioning in a conditional inference framework, with 95% confidence interval derived using the bootstrap technique.[50] Finally, since a marker displaying an independent, strong association may not necessarily contribute meaningfully to improved classification, we will

also examine the ability of each baseline qPET parameter to serve as a prognostic marker in discriminating patients which progress within 2 years and 3 years of the start of study mandated therapy using time-dependent (cumulative sensitivity/dynamic specificity) ROC analysis.[51,52] Area under the time-dependent ROC curve [AUC(t)] will be estimated using the NNE method proposed by Heagerty.[53,54]

Qualitative criteria are described in protocol Section 12.1.2. These criteria will be used to dichotomize the baseline ^{18}F-FDG PET/CT scans as either negative or positive, where analyses using the IMPETUS and IMAJEM criteria are considered exploratory. The association between a positive/abnormal baseline ^{18}F-FDG PET/CT scan and PFS will be assessed through Kaplan-Meier curves with the log-rank test. An adjusted analysis will also be conducted using a Cox regression model, with adjustment for potential confounders, including patient age and the randomization stratification factors. In addition, we will formally test whether this association differs by study arm through a statistical interaction term between ^{18}F-FDG PET/CT positivity and study arm. If this interaction is not significant at the 0.5 level, then a single overall hazard ratio will be estimated for the entire study cohort. It is anticipated that between 50-70% of patients will have a positive ^{18}F-FDG PET/CT scan at baseline. Assuming 60% of patients have a positive ^{18}F-FDG PET/CT scan at baseline, the proposed sample size of 510 patients (459 evaluable) yields 87% power at a type I error rate of 0.05 to detect a difference in median PFS between ^{18}F-FDG PET/CT-positive and ^{18}F-FDG PET/CT-negative patients as low as 7 months (19 vs. 26 months, respectively, assuming 3 years of accrual time and 4.5 years of patient follow-up; PASS 16).

Similar analyses will be conducted for the OS outcome. OS will be defined as the time from randomization until death or the date last known alive.

The ^{18}F-FDG PET/CT images will be collected centrally and archived for future research analysis. All data and results will be anonymized.

12.1.3.2 Secondary imaging aims

[2] To compare overall survival (OS) with the addition of ixazomib to lenalidomide among baseline ^{18}F-FDG PET/CT-positive and ^{18}F-FDG PET/CT-negative subgroups.

This secondary imaging aim consists of a subgroup analysis of the trial primary endpoint, and will assess for heterogeneity of treatment effect by baseline ^{18}F-FDG PET/CT status. If such heterogeneity is detected, this

would suggest that the effectiveness of ixazomib treatment could be increased by targeting patients with the appropriate baseline ^{18}F-FDG PET/CT status.[55]

Heterogeneity of treatment effect will be assessed at full information, using a two-sided statistical test for interaction between study arm (ixazomib/lenalidomide vs. placebo/lenalidomide) and baseline ^{18}F-FDG PET/CT status (positive/abnormal vs. negative) in a Cox regression model.[56,57] If the statistical test for interaction is not significant at the 0.05 level, we will conclude that there is not sufficient evidence for heterogeneity of treatment effect; if the statistical test for interaction is significant, estimated treatment hazard ratios for OS (ixazomib arm vs. placebo arm) will be reported separately for baseline ^{18}F-FDG PET/CT-positive and ^{18}F-FDG PET/CT-negative subgroups, along with the corresponding 95% confidence intervals. OS will be defined as the time from randomization until death or the date last known alive.

We anticipate between 50-70% of patients will have a positive ^{18}F-FDG PET/CT scan at baseline. Sensitivity of the findings will be examined by adjusting the Cox model for patient age and the randomization stratification factors.

[3] To compare the change in quantitative ^{18}F-FDG PET/CT parameters over time with the addition of ixazomib to lenalidomide.

This secondary imaging aim consists of comparing the change in ^{18}F-FDG PET/CT parameters over time across study arms and seeks to address the question of whether adding ixazomib to lenalidomide results in sharper decreases in ^{18}F-FDG uptake (as measured by ^{18}F-FDG PET/CT) compared to lenalidomide plus placebo, thus giving evidence of greater disease control.

The difference in qPET parameters from the baseline ^{18}F-FDG PET/CT to the year 1 ^{18}F-FDG PET/CT will be reported by study arm. An analysis of covariance (ANCOVA) model will be used to test for a treatment effect on each qPET parameter, where the baseline qPET parameter value and an indicator for study arm are included as covariates, with the qPET parameter at year 1 as the model outcome.[59-61] Sensitivity of the findings will be examined by additionally adjusting the ANCOVA model for the randomization stratification factors (, as this would be expected to further improve precision of the study arm comparison.[62]

In addition, longitudinal profiles of each qPET parameter from the baseline ^{18}F-FDG PET/CT through the year 2 ^{18}F-FDG PET/CT will be compared across study arm through an appropriately constructed linear mixed model.[63]

Assuming that up to 15% of patients may not have either the baseline ^{18}F-FDG PET/CT scan performed or the year 1 ^{18}F-FDG PET/CT scan performed, or may have one or more of these scans uninterpretable, the proposed sample size of 510 patients (434 evaluable, 217 per study arm) has power of 80% using ANCOVA at a type I error rate of 0.05 to detect a difference in year 1 mean SUVmax between arms as low as 2.0, with only moderate correlation between the baseline and year 1 SUVmax (R-squared=0.45) and common standard deviation as large as 10.0 (PASS 16). Larger correlation between baseline and year 1 SUVmax and/or smaller standard deviation of SUVmax would result in greater power.

13. Electronic Data Capture

Please refer to the EAA171 Forms Completion Guidelines for the forms submission schedule. Data collection will be performed in Medidata Rave and TRIAD.

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Data for this study will be submitted via the Data Mapping Utility (DMU). Cumulative protocol- and patient-specific data will be submitted weekly to CTEP electronically via the DMU. DMU Light reporting consists of Patient Demographics, On/Off Treatment Status, Abbreviated Treatment and Course information, and Adverse Events as applicable. Instructions for setting up and submitting data via DMU are available on the CTEP Website: https://ctep.cancer.gov/protocolDevelopment/dmu.htm.

NOTE: All adverse events (both routine and serious) that meet the protocol mandatory reporting requirements must be reported via DMU in addition to expedited reporting of serious adverse events via CTEP-AERS.

13.1 Records Retention

FDA regulations (21 CFR 312.62) require clinical investigators to retain all trial-related documentation, including source documents, long enough to allow the sponsor to use the data to support marketing applications.

This study will be used in support of a US marketing application (New Drug Application), all records pertaining to the trial (including source documents) must be maintained for:

- two years after the FDA approves the marketing application, or
- two years after the FDA disapproves the application for the indication being studied, or
- two years after the FDA is notified by the sponsor of the discontinuation of trials and that an application will not be submitted.

Please contact the ECOG-ACRIN Operations Office – Boston prior to destroying any source documents.

14. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

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Optimizing Prolonged Treatment In Myeloma Using MRD Assessment (OPTIMUM)

Appendix I

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the web site at http://www.ecog.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the participation of people like you in clinical trials, we hope to improve treatment and quality of life for those with your type of cancer.

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of ***[INSTITUTION]*** and ECOG-ACRIN, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

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Appendix II

Patient Medication Calendar

Medication Calendar Directions

1. Take your scheduled dose of each medication.
2. Ixazomib/Placebo: Take capsule(s) on an empty stomach, 1 hour before or 2 hours after food. Swallow whole capsules with water. Do not break or open the capsules.
3. Lenalidomide: Take capsule by mouth with or without food. Do not crush, chew or open the capsules.
4. Missed or delayed doses can be taken only if the next scheduled dose is ≥ 72 hours away. A missed dose should not be taken within 72 hours of the next scheduled dose. If vomiting occurs after taking a dose, do not repeat the dose. Resume dosing at the time of the next scheduled dose.
5. Please bring the empty carton or any leftover medication and your medication calendar to your next clinic visit.

Patient Medication Calendar

This is a calendar on which you are to record the time and number of capsules you take each day. You should take your scheduled dose of each capsule. **Note the times and the number of capsules that you take each day.** If you develop any side effects, please record them and anything you would like to tell the doctor in the space provided. Bring any unused capsules and your completed medication calendar to your doctor's visits.

Patient Initials (L, F): _____ Patient Study ID: _____ Cycle #: _____

DAY	DATE	TIME	# CAPSULES TAKEN		Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
			Ixazomib/Placebo Capsules	Lenalidomide Capsules	
1					
2					
3					
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Optimizing Prolonged Treatment In Myeloma Using MRD Assessment (OPTIMUM)

Appendix III

CRADA/CTA

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.
2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements , the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data."):
    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.
    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.
3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected , used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.
4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.
6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

   ncicteppubs@mail.nih.gov

   The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

Appendix IV

ECOG Performance Status

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

Appendix V

Instructions for Reporting Pregnancies on a Clinical Trial

What needs to be reported?

All pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test regardless of age or disease state) of a female patient while she is on ixazomib/placebo or lenalidomide, or within 28 days of the female patient's last dose of ixazomib/placebo or lenalidomide must be reported in an expeditious manner. The outcome of the pregnancy and neonatal status must also be reported.

How should the pregnancy be reported?

For this study, a pregnancy, suspected pregnancy (including a positive or inconclusive pregnancy test) must be initially reported on the Adverse Event Form or Late Adverse Event Form in the appropriate Treatment Cycle or Post Registration folder in Medidata Rave. Once the adverse event is entered into Rave, the Rules Engine on the Expedited Reporting Evaluation Form will confirm whether or not the pregnancy requires expedited reporting. The CTEP-AERS report must then be initiated directly from the Expedited Reporting Evaluation Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website.

When does a pregnancy, suspected pregnancy or positive/inconclusive pregnancy test need to be reported?

An initial report must be done within 24 hours of the Investigator's learning of the event, followed by a complete expedited CTEP-AERs report within 5 calendar days of the initial 24-hour report.

What other information do I need in order to complete the CTEP-AERs report for a pregnancy?

- The pregnancy (fetal exposure) must be reported as a Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)" under the System Organ Class (SOC) "Pregnancy, puerperium and perinatal conditions"
- The pregnancy must be reported within the timeframe specified in the Adverse Event Reporting section of the protocol for a grade 3 event.
- The start date of the pregnancy should be reported as the calculated date of conception.
- 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 of the CTEP-AERs report.

What else do I need to know when a pregnancy occurs to a patient?

- The Investigator must follow the female patient until completion of the pregnancy and must report the outcome of the pregnancy and neonatal status in CTEP-AERs accessed via Medidata Rave.
- The decision on whether an individual female patient can continue protocol treatment will be made by the site physician in collaboration with the study chair and ECOG-ACRIN Operations Office – Boston. Please contact the ECOG-ACRIN Operations Office – Boston to ask for a conference call to be set up with the appropriate individuals.

- *It is recommended the female patient be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.*

How should the outcome of a pregnancy be reported?

The outcome of a pregnancy should be reported as an *amendment* to the initial CTEP-AERs report if the outcome occurs on the same cycle of treatment as the pregnancy itself. However, if the outcome of the pregnancy occurred on a subsequent cycle, a *new* and separate CTEP-AERs report should be initiated (via Medidata Rave) reporting the outcome of the pregnancy.

What constitutes an abnormal outcome?

An abnormal outcome is defined as any pregnancy that results in the birth of a child with persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies, or birth defects. For assistance in recording the grade or category of these events, please contact the CTEP AEMD Help Desk at 301-897-7497 or aemd@tech-res.com, for it will need to be discussed on a case by case basis.

Reporting a Pregnancy Loss

A pregnancy loss is defined in CTCAE as "*A death in utero.*"

For this study, it must be initially reported on the Adverse Event Form or Late Adverse Event Form in the appropriate Treatment Cycle or Post Registration folder in Medidata Rave. Once the adverse event is entered into Rave, the Rules Engine on the Expedited Reporting Evaluation Form will confirm whether or not the adverse event requires expedited reporting. The CTEP-AERS report must then be initiated directly from the Expedited Reporting Evaluation Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website. The pregnancy loss must be reported as a Grade 4 "*Pregnancy loss*" under the System Organ Class (SOC) "*Pregnancy, puerperium and perinatal conditions"*.

A pregnancy loss should **NOT** be reported as a Grade 5 event as currently CTEP-AERs recognizes this event as a patient's death.

Reporting a Neonatal Death

A neonatal death is defined in CTCAE as "*A newborn death occurring during the first 28 days after birth*" that is felt by the investigator to be at least possibly due to the investigational agent/intervention. However, for this protocol, any neonatal death that occurs within 28 days of birth, without regard to causality, AND any infant death after 28 days that is suspected of being related to the *in utero* exposure to ixazomib/placebo or lenalidomide, must be initially reported on the Adverse Event Form or Late Adverse Event Form in the appropriate Treatment Cycle or Post Registration folder in Medidata Rave. Once the event is entered into Rave, the Rules engine on the Expedited Reporting Evaluation Form will confirm whether or not the event requires expedited reporting. The CTEP-AERS report must then be initiated directly from the Expedited Reporting Evaluation Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website. The neonatal death must be reported as a Grade 4 "*Death neonatal*" under the System Organ Class (SOC) "General disorder and administration site conditions".

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A neonatal death should **NOT** be reported as a Grade 5 event as currently CTEP-AERs recognizes this event as a patient's death.

Additional Required Forms:

When submitting CTEP-AERs reports for pregnancy, pregnancy loss, or neonatal loss, the **CTEP *'Pregnancy Information Form'*** must be completed and faxed along with any additional medical information to CTEP (301-897-7404). This form is available on CTEP's website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf)

Appendix VI

Rev. Add3

Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods

1.1. Risks Associated with Pregnancy

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. A teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a pregnancy prevention program must be followed.

1.1.1. Definition of a Patient of Childbearing Potential

A patient of childbearing potential is anyone who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

1.1.2. Definition of a Patient Not of Childbearing Potential

Patients who do not meet the above definition of a patient of childbearing potential should be classified as Patient Not of Childbearing Potential.

1.2. Counseling

1.2.1. Patients of Childbearing Potential

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

- Patients understand the potential teratogenic risk to the unborn child
- Patients understand the need for effective contraception, without interruption, 28 days before starting lenalidomide, throughout the entire duration of lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide
- Patients understand and agree to inform the Investigator if a change or stop of method of contraception is needed
- Patients must be capable of complying with effective contraceptive measures
- Patients are informed and understand the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- Patients understand the need to commence lenalidomide as soon as it is dispensed following a negative pregnancy test
- Patients understand and accept the need to undergo pregnancy testing based on the frequency outlined in this plan (Section 1.4 below) and in the Informed Consent

- Patients acknowledge that they understand the hazards lenalidomide can cause to an unborn fetus and the necessary precautions associated with the use of lenalidomide.

The Investigator must ensure that a patient of childbearing potential:

- Complies with the conditions of the pregnancy prevention plan, including confirmation that they have an adequate level of understanding
- Acknowledges the aforementioned requirements.

1.2.2. Patients Not of Childbearing Potential

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

- Patients acknowledge they understand the hazards lenalidomide can cause to an unborn fetus and the necessary precautions associated with the use of lenalidomide.

1.2.3. Males

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

- Male patients understand the potential teratogenic risk if engaged in sexual activity with a pregnant partner or a partner of childbearing potential.
- Male patients understand the need for the use of a condom even if they have had a vasectomy, if engaged in sexual activity with a pregnant partner or a partner of childbearing potential.
- Understand the potential teratogenic risk if the patient donates semen or sperm.

1.3. Contraception

1.3.1. Patients of Childbearing Potential

Patients of childbearing potential enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence [e.g., calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact during the following time periods related to this study: 1) for at least 28 days before starting lenalidomide; 2) while taking lenalidomide; 3) during dose interruptions; and 4) for at least 28 days after the last dose of lenalidomide.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. If the below contraception methods are not appropriate for the patient of childbearing potential, they must be referred to a qualified provider of contraception methods to determine the medically effective contraception method appropriate to the patient. The following are examples of highly effective and additional effective methods of contraception:

- Examples of highly effective methods:
  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [e.g., desogestrel])
  - Tubal ligation
  - Partner's vasectomy
- Examples of additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

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

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

1.3.2. Male Patients

Male patients must practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence [e.g., calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant partner or a partner of childbearing potential while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide, even if they have undergone a successful vasectomy.

1.4. Pregnancy Testing

Medically supervised pregnancy tests with a minimum sensitivity of 25mIU/mL must be performed for patients of childbearing potential.

Patients of childbearing potential must have two negative pregnancy tests (sensitivity of at least 25mIU/mL) prior to starting lenalidomide. The first pregnancy test must be performed within 10 to 14 days prior to the start of lenalidomide and the second pregnancy test must be performed within 24 hours prior to the start of lenalidomide. The patient may not receive lenalidomide until the study doctor has verified that the results of these pregnancy tests are negative.

Patients of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while taking lenalidomide, at study discontinuation, and at Day 28 following the last dose of lenalidomide.

Patients of childbearing potential with irregular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 14 days while taking lenalidomide, at study discontinuation, and at Days 14 and 28 following the last dose of lenalidomide.

1.5. Pregnancy Precautions for Lenalidomide Use

1.5.1. Before Starting Lenalidomide

1.5.1.1 Patients of Childbearing Potential

Patients of childbearing potential must have two negative pregnancy tests (sensitivity of at least 25mIU/mL) prior to starting lenalidomide. The first pregnancy test must be performed within 10 to 14 days prior to the start of lenalidomide and the second pregnancy test must be performed within 24 hours prior to the start of lenalidomide. The patient may not receive lenalidomide until the study doctor has verified that the results of these pregnancy tests are negative.

Patients of childbearing potential must use two reliable forms of contraception simultaneously, or practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence [e.g., calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact for at least 28 days before starting lenalidomide.

1.5.1.2. Male Patients

Male patients must agree to practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence [e.g., calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant partner or a partner of childbearing potentialwhile taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide, even if he has undergone a successful vasectomy.

1.5.2. During and After Study Participation

1.5.2.1 Patients of Childbearing Potential

- Patients of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while taking lenalidomide, at study discontinuation, and at Day 28 following the last dose of lenalidomide.
- Patients of childbearing potential with irregular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 14 days while taking lenalidomide, at study discontinuation, and at Days 14 and 28 following the last dose of lenalidomide.
- At each visit, the Investigator must confirm with the patient of childbearing potential that they are continuing to use two reliable

methods of birth control if not committing to complete abstinence, or confirm commitment to complete abstinence.

- If a patient of childbearing potential considers the need to change or to stop a method of contraception, the Investigator must be notified immediately.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in a patient, lenalidomide must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a patient misses their period or if her pregnancy test or their menstrual bleeding is abnormal. Lenalidomide must be discontinued during this evaluation.
- Patients must agree to abstain from breastfeeding while taking lenalidomide and for at least 28 days after the last dose of lenalidomide.

1.5.2.2. Male Patients

- Must practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence [e.g., calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or use a condom during sexual contact with a pregnant partner or a partner of childbearing potential while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide, even if he has undergone a successful vasectomy.
- Must not donate semen or sperm while receiving lenalidomide, during dose interruptions or for at least 28 days after the last dose of lenalidomide.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in the partner of a male patient while taking lenalidomide, the Investigator must be notified immediately.

1.5.3. Additional Precautions

- Patients should be instructed to never give lenalidomide to another person.
- Patients should be instructed to return any unused capsules to the study doctor.
- Patients should not donate blood while receiving lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.
- No more than a 28-day lenalidomide supply may be dispensed with each cycle of lenalidomide.

Optimizing Prolonged Treatment In Myeloma Using MRD Assessment (OPTIMUM)

Appendix VII

Myeloma Tumor Biology Kit

Specimen Checklist and Shipping Instructions

****PLEASE AVOID DRAWING OR SENDING SPECIMENS ON FRIDAYS AND HOLIDAYS****

Kit Contents:

- 5lb Styrofoam box and cardboard mailing sleeve
- Patient Information Form
- FedEx air bill with pre-printed return address
- 6mL ACD (yellow top) collection tubes
- Absorbent tube holder
- Zip lock biohazard specimen bags
- (1) Kool-PAK. Place the ice pack in the freezer for at least 24 hours prior to specimen shipment. Allow the frozen ice pack to thaw at room temperature for 2-3 hours **before** preparing the specimen for shipment.

Packing and Shipping Instructions:

1. Collect the following specimens:
    1. Bone marrow aspirate - Draw 6mL of 'redirect' bone marrow aspirate into one (1) 6mL ACD tube.
2. All specimens are to be clearly labeled with the ECOG-ACRIN protocol number EAA171, the patient's initials (last name, first name), ECOG-ACRIN patient sequence number, specimen type (BM/PB) and date of collection.
3. Place the slightly thawed Kool-PAK in bottom of Styrofoam container.
4. Place absorbent toweling on top of Kool-PAK.
5. Place specimens in the plastic bags provided, wrap in paper toweling and place them in the Styrofoam container and close the lid. Do not place the specimens directly on the ice pack.
6. Place the Styrofoam container and the Sample Tracking System shipping manifest form within the cardboard mailing sleeve.
7. Prepare the package for shipping, applying packing tape as needed. Complete the sender portion of the return FedEx air bill and adhere to the exterior lid of the box. Ship specimens via priority overnight delivery the same day collected.
8. Notify Federal Express for pick-up and/or leave package at the designated FedEx drop-off location.

The ECOG-ACRIN Sample Tracking System will automatically contact the Myeloma Reference Laboratory. If you did not use the ECOG-ACRIN Sample Tracking System please call Stacey Lehman at (507) 284-3805 or email Lehman.Stacey@mayo.edu to notify the laboratory when specimens are being shipped. Indicate the ECOG-ACRIN protocol number, the FedEx tracking number, and name and phone number of the contact person.

The specimens in prepared kits should be shipped to the following:

Stacey Lehman
Mayo Foundation
221 4th Avenue SW
613 Stabile
Rochester, MN 55905

Patient Information Form

It is required that specimens submitted from patients participating in EAA171 be entered and tracked via the online ECOG-ACRIN Sample Tracking System (see Section 10.3). This form is used only in the event that the STS is inaccessible and then the shipments are to be logged in retroactively, indicating the actual dates of collection and shipment.

Specimen Date: / /

Patient Initials (last name, first name):

ECOG-ACRIN Protocol #: EAA171

ECOG-ACRIN Patient Sequence #:

Contact Person:

Institution:

Address:

City State Zip

Phone #:

FAX #:

Please indicate which specimens are being shipped at this time:

1. Pre-Registration

Any questions concerning these specimens or to obtain a Myeloma Tumor Biology kit, please contact:

Stacey Lehman
Mayo Clinic Myeloma Reference Laboratory
Lehman.Stacey@mayo.edu
(507) 284-3805