September 26, 2019

Martha Kruhm, MS RAC
Head, Protocol and Information Office
Quality Assurance Section
CTEP, DCT, NCI
6130 Executive Blvd, EPN Room 7000
Bethesda, MD 20892

Dear Ms. Kruhm:

Enclosed is Addendum #14 to E3A06, *Randomized Phase III Trial of Lenalidomide Versus Observation Alone in Patients with Asymptomatic High-Risk Smoldering Multiple Myeloma.*

This addendum is in response to a Lenalidomide request for amendment from Dr. Streicher, August 13, 2019.

There are no revisions to the case report forms as a result of this amendment.

Please replace your current copy of the protocol and Informed Consent document with these updated versions. We recommend that each institution maintain a file containing the original protocol, Informed Consent, and all subsequent revisions/versions.

IRB Review Requirements:

Full IRB review of this addendum is **recommended**, however, ECOG-ACRIN will accept the method of review determined by the standard operating procedures for the IRB of record for this protocol. *[If changes have been made to the consent, insert the following sentence here:* It is the decision of the local IRB whether or not subjects are to be re-consented]. This addendum must be submitted and reviewed by your IRB within 90 days of receipt of this notice, unless your local IRB has different written SOPs, which must be available at future ECOG-ACRIN audits.

Sites using the CIRB as their IRB of record: The protocol and/or informed consent form changes have been approved by the CIRB and must be activated within 30 days of the CIRB posting of this notice.

Sites not using the NCI CIRB: Per CTMB Guidelines, the protocol updates and/or informed consent changes must be approved by local IRBs within 90 days of distribution of this notice. If your local IRB has different SOPs, they must be available at future E-A audit.

I. Recommendations:

#	Section	Comments
1.	5.5.2.3	Please replace the 2 remaining mentions of “LCP” with “CPPCP”. Response: **This has been completed**
2.	Appendix VI	1) Please delete “sexually mature” from the definition of FCBP. 2) In section 1.3.1, the italicized paragraph regarding dexamethasone-containing lenalidomide regimens can be deleted. Response: **This has been completed**

28 State Street, Suite 1100, Boston, MA 02109 p: 857.504.2900 f: 617. 589.0914 ecog-acrin.org

#	Section	Comments
3.	Appendix VII	1) Please delete “sexually mature” from the definition of FCBP. 2) Please add back the following text in red in the “male” section: Do not donate blood, semen or sperm Response: **This has been completed**
4.	9.9	NCI and the CTSU would be happy to have a call with the E-A to brainstorm strategies to increase awareness of the importance of outreach to Black or African American patients and physicians to consider participation in this trial given their higher incidence rates of multiple myeloma . Contact Andrea Denicoff at: denicofa9@mail.nih.gov' Response: **This is no longer applicable to the study**
5.	9 Accrual	The investigators state that the plan is to increase accrual of Black or African American patients and operationally close the trial to non-AA patients when they reach 150 non-AA patients. A revised plan that changes the study number to 150 should be included in the statistical section, study design, and consent An explanation of why this is being done should be included in the background section. Section 9.8.3 indicates accrual will continue to 180 patients. Which would seem to include 150 patients and 30 AA patients. These numbers however do not include the AA patients included in the first 150. Is the intent to include 30 additional randomized patients, to complete a total of 30 patients, or to a total of 21 as indicated in the table 9.9. The intent to increase the total AA accrual to 21 needs to be clarified described if in fact the study will remain open to accrue these patients. Will this continue in a randomized fashion? Will an analysis plan be included? The total number of participants in the consent 224 does not match any of these numbers. Please clarify. Response: **This is no longer applicable to the study**

The following revisions to E3A06 protocol have been made in this addendum:

	Section	Change
1.	Cover Page	Updated Version Date
2.	Contacts Page	Updated Madhav Dhodapkar, MD contact information
3.	5.2.3	Updated the AE team at ECOG-ACRIN and NCI fax phone numbers
4.	5.3	Updated the Lenalidomide CAEPR list with version 2.8, June 27, 2019.
5.	5.5.2.3	Replaced the 2 remaining mentions of “LCP” with “CPPCP”.
6.	Appendix VI	Deleted “sexually mature” from the definition of FCBP. The italicized paragraph regarding dexamethasone-containing lenalidomide regimens has been deleted.
7.	Appendix VII	Deleted “sexually mature” from the definition of FCBP. Added back the following text in red in the “male” section: Do not donate blood, semen or sperm
8.	Appendix XIII	Clarified what needs to be reported in female patients and CTEP’s phone number

The following revisions to E3A06 Informed Consent Document have been made in this addendum:

	Section	Change
1.	Cover Page	Updated Version Date
2.	Risks and side effects related to the lenalidomide include:	Updated Lenalidomide risk list to version 2.8 from June 27, 2019.

If you have any questions regarding this addendum, please contact Camilla Abreu at cabreu@ecog-acrin.org or 857-504-2900.

We request review and approval of this addendum to E3A06, so ECOG-ACRIN may activate it promptly. Thank you.

Sincerely,

Pamela Cogliano

Senior Director, Protocol Development Enclosure

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ECOG-ACRIN
cancer research group
Reshaping the future of patient care

E3A06

Randomized Phase III Trial of Lenalidomide Versus Observation Alone in Patients with Asymptomatic High-Risk Smoldering Multiple Myeloma

STUDY CHAIR:	Sagar Lonial MD
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QOL CO-CHAIR:	Matthias Weiss, MD
SWOG CO-CHAIR:	Madhav Dhodapkar, MD
LABORATORY CO-CHAIRS:	Joshua Epstein, D.Sc. Rafael Fonesca, MD Madhav V. Dhodapkar, MD

Rev. 8/11
Rev. 7/13

Version Date: September 26, 2019
NCI Update Date: February 3, 2016

STUDY PARTICIPANTS

ALLIANCE / Alliance for Clinical Trials in Oncology
NRG / NRG Oncology Foundation, Inc
SWOG / SWOG

NOTE: This study is supported by the NCI Cancer Trials Support Group (CTSU). Institutions not aligned with ECOG-ACRIN will participate through the CTSU mechanism (please see Section 4 for details).

ACTIVATION DATE

October 5, 2010
Addendum #1: Incorporated prior to activation
Addendum #2: 6/11
Addendum #3: 8/11
Addendum #4: 10/11
Addendum #5: 2/12
Addendum #6: 9/12
Addendum #7: 7/13
Addendum #8: 12/13
Addendum #9: 7/14
Addendum #10: 10/14

Addendum #11: 1/16
Update #1: 2/16
Addendum #12: 7/16
Addendum #13
Addendum #14

Agents	IND#	NSC#	Supply
Lenalidomide		NSC 703813	NCI-supplied

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NOTE: Please refer to Section 4 for CTSU registration guidelines.

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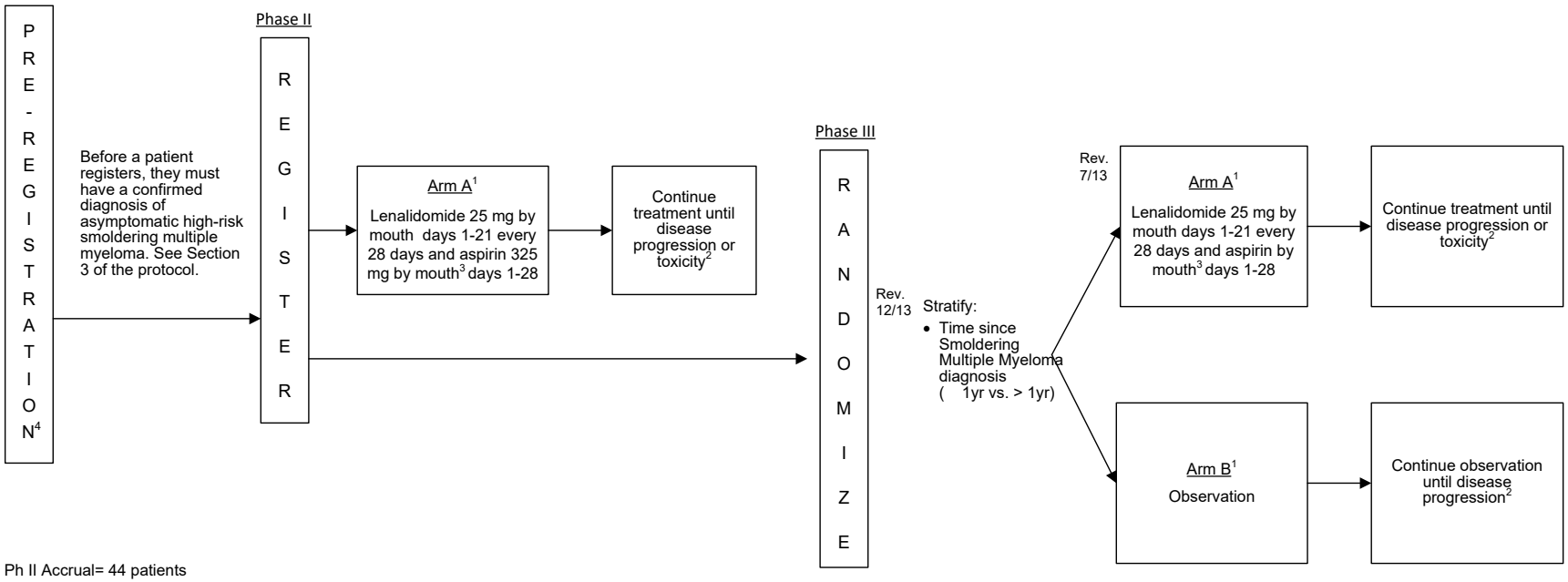
CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206 Email: CTSURegulatory@ctsu.coccg.org (for submitting regulatory documents only)	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 at ctsucontact@westat.com.	ECOG-ACRIN Operations Office - Boston, FSTRF, 900 Commonwealth Avenue Boston, MA 02215 (ATTN: DATA). Phone # 617-632-3610 Fax # 617-632-2990 Data should be sent via postal mail (preferred), however fax is accepted. Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
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' websiteis 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.		
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.		
For detailed information on the regulatory and monitoring procedures for CTSU sites please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' website https://www.ctsu.org > education and resources tab > CTSU Operations Information >CTSU Regulatory and Monitoring Policy		
The CTSU Web site is located at https://www.ctsu.org		

Schema



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Rev.7/13 Ph II Accrual= 44 patients
Rev.11/15 Ph III Accrual= 180 patients
Accrual = 224 patients
Cycle= 28 days

Rev. 7/13
1. Enrollment will be suspended for a phase II safety analysis when the phase II accrual goal is met. Once that has happened, the randomized portion of the trial will begin.
2. Mobilize stem cells following 4-6 cycles of therapy. While stem cell collection following 4-6 cycles of therapy is suggested strongly, it is not required for protocol participation.

Rev. 2/12, 7/13
3. Patients are to receive aspirin or an alternative as outlined in Sections 5.1.1 and 5.5.2.1. The suggested dose is 325 mg/day however the dose is at the discretion of the treating physician. Alternative dosing of 75 mg/day or higher is acceptable provided the patient is at low risk of thrombosis.

Rev.6/14
4. Submission of pre-study specimens per patient consent.

1. Introduction

1.1 Multiple Myeloma (MM)

Multiple myeloma (MM) accounts for 10% of all hematologic malignancies (1-3). For many years, autologous stem cell transplantation (ASCT), alkylator-based chemotherapy, and corticosteroids had been the mainstay of therapy for the disease. Recently, thalidomide, bortezomib, and lenalidomide have emerged as effective single-agents, demonstrating significant clinical activity in relapsed and refractory MM (4-6). The discovery of these drugs has been accompanied by a growing awareness of the importance of bone marrow microenvironmental changes such as induction of angiogenesis, suppression of cell-mediated immunity, and expression of various adhesion molecules and cytokines in disease progression (7,8). The present challenge is to determine how best to incorporate thalidomide, bortezomib and lenalidomide into the therapeutic strategy for myeloma. ECOG has conducted randomized phase III trials incorporating thalidomide and lenalidomide as part of the initial therapy for newly diagnosed symptomatic MM.

1.2 Smoldering Multiple Myeloma (SMM)

Approximately 15-20% of patients with MM are asymptomatic at presentation (9-12). These patients are usually referred to smoldering multiple myeloma (SMM) (2). They are to be distinguished from patients with monoclonal gammopathy of undetermined significance (MGUS) (13, 14). The current definitions of these disorders are described in the Table below.

Criteria for the diagnosis of MGUS, SMM and MM (15-17)

MGUS Serum monoclonal protein < 3 g/dl and bone marrow plasma cells < 10% and absence of anemia, renal failure, hypercalcemia and lytic bone lesions
SMM Serum monoclonal protein ≥ 3 g/dl and/or bone marrow plasma cells ≥ 10% and absence of anemia, renal failure, hypercalcemia and lytic bone lesions
MM Presence of a serum/urine monoclonal protein, bone marrow plasmacytosis and anemia, renal failure, hypercalcemia, or lytic bone lesions; patients with primary systemic amyloidosis and 30% bone marrow plasma cells are considered to have both multiple myeloma and amyloidosis
Abbreviations: MGUS, monoclonal gammopathy of undetermined significance; SMM, smoldering multiple myeloma; MM, multiple myeloma.

Patients with SMM have a much higher risk of transformation to overt symptomatic myeloma than patients with MGUS. Most patients with SMM progress eventually to symptomatic MM, and the risk of progression is substantially higher than with MGUS (10-20% per year for SMM versus 1% per year from MGUS) (9). The time to progression (TTP) to symptomatic disease is approximately 2-4 years, but differs greatly depending on the definition used for SMM (18). In SMM patients having bone marrow plasma cells (BMPC) ≥ 10%, the median time to progression is approximately 2-3 years (19). In a large study by Kyle and colleagues, using the current criteria for SMM the risk of progression was approximately 10% per year, a rate much higher than observed with MGUS (12).

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1.3 Targeted Patient Population

The above points support the use of lenalidomide as the experimental arm. The current standard of care for SMM is observation alone with no therapy (1), justifying observation as the control arm. Additionally, in the current trial, we propose to evaluate those patients with SMM who have the highest risk of progression to symptomatic MM. Based upon published data by Kyle et al (12)and Dispenzieri et al (23), we propose to limit eligibility to the highest risk smoldering myeloma patients. Kyle's study cohort (12) is classified into three prognostic groups as follows: high-risk ≥ 10% BMPC and serum M-protein ≥ 3 gm/dl, intermediate-risk ≥ 10% BMPC and serum M-protein < 3 gm/dl and low-risk < 10% BMPC and serum M-protein < 3 gm/dl.

Dispenzieri et al (23) further divided patients based on the free light chain (FLC) ratio. The normal reference range for FLC ratio is 0.26-1.65. In the Dispenzieri study, 90% of patients were abnormal based on this definition. To discern whether the extent to which FLC ratio was abnormal had an impact, they evaluated the prognostic effect of continuous FLC ratio and found an optimal breakpoint of the FLC ratio was < 0.125 or > 8.0. With this range, 60% of patients were abnormal. Risk of progression was approximately 35% at 2 years and 60% at 5 years. This is slightly higher than the risk of progression using the < 0.26 or > 1.65 of 32.5% and 52.6%, respectively. They then constructed a risk

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stratification model including three risk factors: ≥ 10% bone marrow plasma cells, serum M-protein ≥ 3 gm/dl and FLC ratio less than 0.125 or greater than 8. For our trial, high- and intermediate-risk patients based on the Kyle stratification are eligible for entry in the study if they also have an abnormal free light chain ratio defined as < 0.26 or > 1.65. Given the published natural history of these patients, it will be easier to show benefit for these patients, and they have the highest risk of progression to symptomatic myeloma.

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1.4 Lenalidomide

Single agent lenalidomide has shown responses in approximately one-third of patients with advanced MM, even if patients had previously failed thalidomide (36). In combination with dexamethasone, lenalidomide was active in approximately 60% of patients with advanced relapsed MM (37, 38), and over 90% of patients with newly diagnosed symptomatic MM (30-32). Thus, the drug is likely to have significant activity in patients with asymptomatic MM who are at an earlier stage the disease. This hypothesis has been previously tested with thalidomide, where the activity observed with thalidomide in relapsed MM did translate into significant activity in the asymptomatic stage (25,39). Lenalidomide is a safer and more potent analog of thalidomide, and there is no reason to believe that the drug will fail to act in the asymptomatic stage. Additionally, for patients who achieve long lasting and deep responses to lenalidomide based therapy, there is a history of chronic administration of lenalidomide for periods far longer than other therapies in the setting of relapsed and newly diagnosed myeloma. The net result of these observations is that lenalidomide is an active agent with a good safety profile in the acute and chronic administration setting, and is an ideal agent to test in a patient population that is at high risk of progression to symptomatic myeloma, yet to date has not proven to benefit from early therapy.

In a phase II trial of 122 patients with relapsed myeloma, approximately 25% responded to single-agent lenalidomide therapy (40). This trial included several patients who had earlier failed thalidomide. Typical dosing for lenalidomide is 25 mg per day on days 1-21 of a 28 day cycle. The most common adverse effects are thrombocytopenia and neutropenia. Side effects such as sedation, constipation, and neuropathy appear to be less common with lenalidomide.

The clinical efficacy of lenalidomide was established in two recent phase III trials, where patients with relapsed refractory MM had superior response rates, TTP and overall survival with lenalidomide plus dexamethasone compared to dexamethasone/placebo (37,38).

In a trial among newly diagnosed MM patients, the combination of lenalidomide plus dexamethasone has shown remarkable activity with responses in more than 90% of patients (30,31).

Additional rationale for the current trial was generated when the closely related analogue thalidomide was shown to improve TTP in another trial of SMM, but its use was limited by the development of peripheral neuropathy (25).

The risk of deep vein thrombosis (DVT) with lenalidomide is one concern; however this risk appears to be limited to patients receiving high dose dexamethasone plus lenalidomide;(41) the risk does not seem to be increased when lenalidomide is used as a single-agent (42) or when the drug is used in combination with lower doses of dexamethasone (41).

Lenalidomide has anti-angiogenic and immunomodulatory properties (43). Therapy targeted against angiogenesis presents an exciting, new and possibly less toxic way to treat malignant disease. There is evidence that increased bone marrow angiogenesis occurs in myeloma and is correlated with the plasma cell labeling index (PCLI; a measure of plasma cell proliferative activity) (44,45). Angiogenesis has also been shown to be a powerful prognostic factor in newly diagnosed MM, and it increases as patients progress from asymptomatic to symptomatic disease (24,46,47).

To better study the risks of lenalidomide in this asymptomatic patient population, we have built in a pilot phase prior to the start of the randomized phase of the trial.

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1.5 Rationale and Hypothesis for Current Study

Over the years due to lack of effective therapy, patients with SMM have been observed without therapy. However, with the discovery of new active agents, the time has come to test therapeutic intervention in asymptomatic MM with the goal of delaying progression to symptomatic MM because of the following reasons:

i) Once symptomatic, MM is incurable, and symptoms from MM such as bone fractures can be debilitating. Patients with asymptomatic MM who will be considered for this study will be at high risk of progression to symptomatic MM. The median time to progression is approximately 18 months in patients who have no bony lesions.(19) The presence of bone lesions on skeletal survey or magnetic resonance imaging greatly increases the risk of progression in asymptomatic MM.(9, 20-22) Patients with abnormal peripheral blood monoclonal plasma cell studies defined as an increase in the number or proliferative rate of circulating plasma cells by immunofluorescent

assays are at higher risk for earlier progression to myeloma. In a study of 57 patients, we found the median time to progression was 9 months for those with abnormal peripheral blood monoclonal plasma cell studies versus 30 months for those with normal studies.(*P* <0.01)) (19). More recently, the serum free light chain (FLC) ratio has been shown to be a significant adverse predictor of outcome, and the test is widely available. Patients with bone marrow plasma cells 10% or more and an abnormal FLC ratio have a median progression free survival (PFS) of 2.3 years, and a 2 year PFS rate of 58.5% (23).

ii) As discussed later, progression to symptomatic MM likely involves an angiogenic switch, similar to the progression of in-situ carcinomas to an invasive phenotype (8, 24). Thus there is mechanistic rationale for anti-angiogenic agents such as lenalidomide to delay progression.

iii) There is strong preliminary data from a phase II trial at Mayo Clinic that the related agent thalidomide is effective in asymptomatic MM with evidence suggesting a delay in time to progression based on historical controls (25).

iv) Single agent lenalidomide is an attractive new option that is ideally suited for testing in asymptomatic MM (6, 26). The drug does not appear to have much of the non-hematologic side-effects that have been a problem with the use of thalidomide in this population such as peripheral neuropathy (6,27,28). It has shown remarkable activity in relapsed and newly diagnosed MM (29,30). Lenalidomide is orally administered making it convenient for long term therapy in an asymptomatic population. Incidentally, there is remarkable interest in this agent as initial therapy as evidenced by the rapid accrual to ECOG E4A03 trial with lenalidomide in newly diagnosed MM.

v) There is evidence from Mayo and ECOG studies that therapy with lenalidomide does not adversely affect stem cell collection (30-32). Some reports have found problems with stem cell mobilization with growth factors alone (33), which is resolved with the use of growth factor plus cyclophosphamide (34). This appears to be an effect of lenalidomide on adhesion molecules, rather than toxicity to stem cells since patients can successfully mobilize with cyclophosphamide (34, 35).

vi) Given the toxicity of stem cell transplantation and current MM therapy, and given the destructive bone lesions that characterize MM, there is a strong patient demand for novel therapeutic options that would delay progression to symptomatic MM, rather than observation without therapy.

Patients and physicians alike desire a way to delay progression in patients with SMM. Currently, such patients are observed without therapy even though the risk of progression is high. Symptomatic MM has a median survival of 3–4 years and is associated with significant morbidity from destructive bone lesions, renal failure, and infections. Therapy includes aggressive chemotherapy regimens including stem cell transplantation, but is not curative. With the advent of new, non-cytotoxic agents with novel mechanisms of action that target critical steps in MM pathogenesis, there is a great need for clinical trials using these agents. There is little question whether lenalidomide can induce responses in patients with SMM. The more important end-point is demonstration of a superior PFS with lenalidomide compared to observation, especially considering the costs and possible side-effects of therapy. Therefore, a randomized, phase III trial is

necessary. Overall survival differences between lenalidomide and observation need to be studied; however, overall survival as a primary end-point has become unrealistic given the rapid advances in new therapeutic options available to patients at the time of relapse, and the protracted time it would take to complete in patients with SMM in which the median overall survival is likely to be in excess of seven years.

We are confident that this phase III trial will be successful in improving progression-free survival of SMM (the primary endpoint), and further, will have the potential to effect a paradigm shift in the treatment of early stage MM. If the endpoints of the trial are successfully met, the benefits of therapy far outweigh the risks. There is strong preliminary data supporting a role for use of lenalidomide in this setting, a therapy that overcomes much of the limitations previously seen with agents like thalidomide, melphalan, or corticosteroids. In sum, per detailed discussions with NCI/CTEP and various cooperative groups, this trial is felt to be of major importance and will be done collaboratively by ECOG-ACRIN and SWOG.

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1.5.1 Modifications in Addendum #8:

In Addendum #8, we are modifying the inclusion criteria in response to emerging data in the smoldering MM arena. The first modification is to relax the free light entry criteria. We are continuing to exclude patients with a normal free light ratio as they have a very low risk of conversion. However, we are now amending to allow any free light chain abnormality (abnormal ratio) to enroll. This change is being made to allow further exploration of the potential benefit of early treatment among patients with abnormal but not at the extremes free light chain ratio. The second change is to allow for patients diagnosed with smoldering MM to be enrolled if within 5 years of diagnosis of smoldering MM as opposed to 1 year. This modification is to bring our trial into more alignment with what is being reported by the PETHEMA group in their current high risk smoldering clinical trial. Research on the natural history of SMM published by Kyle et al (12) in an unselected SMM cohort show the risk of progression over the first 5 years is 10% per year, approximately 3% per year for the next 5 years and 1% per year for the last 10 years. This suggests that broadening eligibility by years since diagnosis from 1 to 5 likely will not have a significant impact on PFS estimates. Additionally, patients will be stratified at randomization according to time since diagnosis of SMM: (1 year vs. > 1 year).

1.6 Quality of Life Assessment

1.6.1 Background and Significance

The Quality of Life (QOL) of MM patients is determined by disease specific symptoms and treatment specific side-effects. Patients with SMM participating in E3A06 are required to be asymptomatic from disease and must be MM specific treatment naive. Patient reported outcome (PRO) assessment as part of E3A06 is designed to describe symptoms of MM specific disease progression as well as potential side-effects from treatment intervention. The PRO instrument chosen

consists of the Functional Well Being (FWB) and Physical Well Being (PWB) components of the Functional Assessment of Cancer Therapy - General (FACT-G) (48). This instrument has been validated extensively and has been incorporated into our ongoing E1A05 and E1A06 phase III MM treatment trials. For the purpose of a comprehensive, disease specific QOL assessment in symptomatic MM patients we will also utilize the Multiple Myeloma Subscale (MMS). This MM specific novel instrument, as described in detail in 6.3.1, has been developed by interviewing MM patients, describing and quantifying their disease and treatment specific symptoms as well as by incorporating the cumulative experience of MM expert physicians.

1.6.2 Hypothesis

We hypothesize that the combination of the functional well-being (FWB) and physical well-being (PWB) components of the FACT-G (14 questions) will assess the overall functional and physical well-being and serious toxicities experienced by SMM patients and correlate with the impact of a specific treatment intervention in terms of progression free survival. The primary endpoint for this quality of life assessment is best assessed at the end of cycle 24 treatment since at this point patients will have experienced both acute and chronic toxicities, if any, and beyond two years, more and more patients will drop out due to disease progression.

1.7 Correlative Studies

1.7.1 Background

Samples will be collected as in previous studies (E1A00 and E4A03) using the ECOG-ACRIN myeloma tumor biology kit at time of study entry and at time patient goes off-study. Further samples will be collected by SWOG (University of Arkansas and Yale University). Since laboratory correlative studies and sample submission are routinely done with ECOG-ACRIN and SWOG myeloma studies, we have a well organized system for sample submission and processing. Studies will be supported by existing ECOG-ACRIN R01 grants to Drs. Rajkumar and Fonseca, and existing SWOG laboratory grants. Correlative studies will be headed by Madhav Dhodapkar and Joshua Epstein from SWOG (immune function studies and GEP studies), and Rafael Fonseca from ECOG-ACRIN (IgH translocations). As discussed earlier, we have shown that certain biologic characteristics such as angiogenesis are increased in MM,(8, 46) and decreases with response following thalidomide therapy (49). We have shown myeloma cells express the various cytokines such as basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) (50,51). We have also found that response to thalidomide may be determined by underlying specific cytogenetic abnormalities (primary IgH translocations) (52). We have expertise with the assays planned including GEP studies, studies of immune function, detecting IgH translocations and other cytogenetic abnormalities, MRI studies, estimating level of expression of various cytokines by

immunohistochemistry, quantitative RT-PCR and Western blotting, and FISH (8, 46, 50, 51, 53-59).

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The slide based bone marrow plasma cell labeling index (PCLI) is now being determined by a cytometric flow procedure (PCPRO). This technique provides identification of clonal plasma cells and cells in S-phase of the cell cycle.

Circulating plasma cells will be assessed by a CD38/CD45 immunofluorescence flow cytometry assay.

The Beta-2-Microglobulin levels are ascertained using an automated system based on nephelometry.

1.7.2 Gene Expression Profiling

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Studies from the Epstein lab have shown that GEP of tumor cells can provide valuable insights into the genetic heterogeneity in MM. Three aspects of these studies are of particular interest in this trial (57,58,60):

- GEP based Molecular subtypes of MM (60)
- MGUS-Like versus non-MGUS-Like subtype of MM (58)
- MM associated microenvironment genes (58)

Preliminary studies from Little Rock have identified genes differentially expressed in the microenvironment between MGUS and MM, and differential response to therapy based on baseline GEP subtype. The GEP obtained at baseline will be used to assess whether specific subtypes of MM are more or less likely to achieve clinical response to lenalidomide therapy.

1.7.3 Immune Function

This trial provides an important opportunity to evaluate the changes in immune function as a result of lenalidomide therapy in early myeloma. Lenalidomide was developed in part due to its capacity to mediate greater co-stimulation of T cells compared to the parent compound, thalidomide. Several groups have now documented that progression of MGUS to MM is associated with changes in the function of both innate as well as adaptive immune effector cells. The underlying hypothesis is that lenalidomide will favorably impact these responses and this will correlate with clinical benefit in terms of PFS. Analyses of immune function will be carried out in the Dhodapkar lab, which has considerable experience with such studies. Certain aspects of immune response are of particular interest in this trial:

- Changes in NK and NKT number and activation
- Changes in effector (Th1, Th17), and regulatory (FOXP3+ tregs) T cells
- Changes in antigen specific immunity, particularly against stem cell associated antigens (e.g., SOX-2), shown to correlate with favorable outcome in these patients
- Changes in dendritic cell subsets

1.7.4 Radiologic Studies (MRI)

Historical experience dictates the use of skeletal surveys as baseline radiological evaluation for patients with plasma cell disorders. While these studies are useful in some patients, their overall sensitivity is not as good as that seen with CT scans, MRI, or PET scans. Because one of the criteria for having symptomatic myeloma is based upon the presence of bone disease, more sensitive testing may be of value. Additionally, it is important to distinguish between patients that have bone marrow involvement from SMM or MM vs. bone involvement from MM. Data from the Arkansas group has demonstrated that the presence of focal MRI lesions that harbor residual disease has independent prognostic implications. However, an analysis from Dimopolus et al demonstrated that even if the bone marrow signal was evaluated (focal vs. diffuse involvement) there were prognostic implications for patients with symptomatic myeloma. These observations suggest that there may be clinical utility to evaluating the role of MRI in predicting outcome among a group of asymptomatic myeloma patients.

1.7.5 Cytogenetic Abnormalities

It is our hypothesis that the different genetic subtypes of the disease will be associated with differential risk of progression from SMM to MM. In general, the high-risk genetic categories in MM fall into one of three genetic subtypes: t(4;14)(p16;q32), t(14;16)(q32;q23), and those having 17p deletions. These three groups we have collectively called “High-Risk MM” (HR-MM). Patients with HR-MM tend to be slightly younger in age and present with less bone disease, and more frequently IgA subtype MM (a known predictor of progression from MGUS to MM). It is then that we believe that HR-MM genetic changes, when present in MGUS or SMM, will dictate a slightly higher risk of progression per year. Over the course of several years, this might dictate that HR-MM genetic lesions in SMM dictate progression earlier in life, and hence the younger age of presentation for MM with HR-MM genetic features.

2. Objectives

2.1 Phase II

2.1.1 Primary Objective

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2.1.1.1 To study the risk of grade 3 adverse events that effect vital organ function (such as cardiac, hepatic or thromboembolic) or any grade 4 or higher non-hematologic adverse events among patients receiving lenalidomide as treatment for high-risk asymptomatic, smoldering multiple myeloma.

2.1.2 Secondary Objectives

2.1.2.1 To assess the response to therapy of patients treated with lenalidomide as treatment for asymptomatic, smoldering multiple myeloma.

2.1.3 Correlative Objectives

2.1.3.1 To describe the cohort in terms of GEP and cytogenetic risk classification and evaluate baseline immune and MRI parameters.

2.2 Phase III

2.2.1 Primary Objectives

2.2.1.1 To compare progression free survival where failure is defined as death or the development of symptomatic myeloma indicating treatment between patients receiving lenalidomide versus observation alone in high-risk asymptomatic, smoldering multiple myeloma.

2.2.2 Secondary Objectives

2.2.2.1 To determine and compare the response rate, time to progression, 1-year progression-free survival probability, and overall survival between patients randomized to receive lenalidomide or observation in the setting of asymptomatic myeloma.

2.2.2.2 To estimate the incidence of adverse events in patients receiving lenalidomide therapy for early-stage multiple myeloma.

2.2.3 Correlative Objectives

2.2.3.1 To evaluate the impact of therapy within GEP-defined risk groups and GEP as a prognostic marker.

2.2.3.2 To study the effects of lenalidomide on laboratory markers of immune function.

2.2.3.3 To study the prognostic value of MRI detected asymptomatic bone disease on clinical outcome.

2.2.3.4 To evaluate the prognostic effect of baseline high-risk cytogenetic abnormalities on clinical outcome.

2.3 Quality of Life Assessment Objectives

2.3.1 To compare QOL change between treatment and observation arms based on the functional (FWB) and physical (PWB) well-being components of the FACT-General (G) patient-reported outcome (PRO) measure from registration (prior to initiation of treatment) up to cycle 24.

2.3.2 To examine the impact of differential treatment response (PFS), if observed, on QOL based on the FACT FWB+PWB up to cycle 48.

2.3.3 To obtain prospective data on Myeloma specific QOL attributes, utilizing and evaluating the Multiple Myeloma Subscale (MMS).

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: All questions regarding eligibility should be directed to the study chair or study chair liaison.

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.

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NOTE: This study involves pre-registration (see Section 4). Bone marrow and peripheral blood specimens are to be submitted for defined laboratory research studies and future undefined research studies as outlined in Section 10 per patient consent.

3.1 Eligibility Criteria

_____ 3.1.1 Age ≥ 18 years.

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_____ 3.1.2 Patients must be diagnosed with asymptomatic high-risk smoldering multiple myeloma (SMM) within the past 60 months, as confirmed by both of the following:

1) Bone marrow plasmacytosis with ≥ 10% plasma cells or sheets of plasma cells at any time before initiating study treatment, including a marrow which must be obtained by bone marrow aspiration and/or biopsy within 4 weeks prior to randomization.

   If plasmacytosis, % plasma cells: _____ Date: _____

   If sheets of plasma cells, Date: _____

2) Abnormal serum free light chain ratio (< 0.26 or > 1.65) by serum FLC assay. FLC assay must be performed within 28 days of randomization.

   Serum Free Light Chain Ratio _____ Date of Test _____

_____ 3.1.3 Patients must have measurable levels of monoclonal protein (M-protein): ≥ 1g/dL on serum protein electrophoresis or ≥ 200 mg of monoclonal protein on a 24 hour urine protein electrophoresis which must be obtained within 4 weeks prior to randomization.

Both SPEP and UPEP are required to be performed within 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.

_____3.1.4 Patients must have no lytic lesions on skeletal surveys and no hypercalcemia (i.e., ≥ 11 mg/dL).

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_____3.1.5 The following laboratory levels must be obtained within four weeks prior to randomization:

_____ 3.1.5.1 Hemoglobin ≥ 11 g/dL.

Hemoglobin: _____Date:_____

_____ 3.1.5.2 Platelet count ≥ 100,000 cells/mm^3.

Platelet:_____ Date:_____

_____ 3.1.5.3 Absolute neutrophil count ≥ 1500 cells/mm^3.

ANC:_____ Date:_____

_____ 3.1.5.4 Calculated creatinine clearance ≥ 30 mL/min.

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Creatinine clearance:_____ Date:_____

_____ 3.1.5.5 Bilirubin 1.5 mg/dL.

Bilirubin:_____ Date:_____

_____ 3.1.5.6 SGPT (ALT) and SGOT (AST) 2.5 times the upper limit of normal.

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

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

_____ 3.1.6 No prior or concurrent systemic or radiation therapy for the treatment of myeloma.

_____ 3.1.7 Concurrent use of bisphosphonates is not permitted. However, prior bisphosphonates or once-a-year intravenous bisphosphonate given for the treatment of osteoporosis is permitted.

_____ 3.1.8 Prior or concurrent use of erythropoietin is disallowed.

_____ 3.1.9 Prior glucocorticosteroid therapy for the treatment of multiple myeloma is not permitted.

_____ 3.1.10 Prior systemic glucocorticosteroid use for the treatment of non-malignant disorders is permitted; concurrent use after registration on the study should be restricted to the equivalent of prednisone 10 mg per day.

_____ 3.1.11 Prior or concurrent topical or localized glucocorticosteroid therapy to treat non-malignant comorbid disorders is permitted.

_____3.1.12 Patients must not have active, uncontrolled seizure disorder. Patients must have had no seizures in the last 6 months.

_____ 3.1.13 Patients must not have uncontrolled intercurrent illness including uncontrolled hypertension, symptomatic congestive heart failure, unstable angina, uncontrolled cardiac arrhythmia, uncontrolled psychiatric illness or social situation that would limit compliance with the study, or a prior history of Stevens Johnson Syndrome.

_____ 3.1.14 ECOG performance status 0, 1, or 2.

_____ 3.1.15 Patients must not have baseline bone lesions or plasmacytomas.

_____ 3.1.16 Patients with monoclonal gammopathy of undetermined significance are not eligible.

_____ 3.1.17 Patients must not have Grade 2 or higher peripheral neuropathy.

_____ 3.1.18 Patients must not have active, uncontrolled infection.

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_____ 3.1.19 Patients may have a history of current or previous deep vein thrombosis or pulmonary embolism but are required to take some form of anti-coagulation as prophylaxis if they are not currently on full-dose anticoagulation.

_____ 3.1.20 Patients should not have New York Heart Association classification III or IV heart failure.

_____ 3.1.21 Patients with a history of prior malignancy are eligible provided they were treated with curative intent and have been free of disease for the time period considered appropriate for cure of the specific cancer. For most diseases this time frame is 5 years.

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_____ 3.1.22 Patients should not be felt to have an immediate need for chemotherapy.

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_____ 3.1.23 Females of childbearing potential (FCBP) must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10 – 14 days prior to and again within 24 hours of starting cycle 1 of lenalidomide and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking lenalidomide. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy.

A FCBP is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months). All patients must be counseled by a trained counselor every 28 days about pregnancy precautions and risks of fetal exposure. (See **Appendix VI**: Risks Associated with Pregnancy and also **Appendix VII**: Lenalidomide Education and Counseling Guidance Document).

Female of childbearing potential (Y/N)? _____

Date of Test: _____

_____3.1.24 HIV infection is not excluded. HIV+ patients must meet the following criteria:

- CD4 cell count ≥ 350/mm^3
- No history of AIDS-related illness
- Not currently prescribed zidvoudine or stavudine

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4. Registration Procedures

CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed *Statement of Investigator Form* (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed *Supplemental Investigator Data Form* (IDF)
- a completed *Financial Disclosure Form* (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>. For questions, please contact the CTEP Investigator Registration Help Desk by email at <pmbregpend@ctep.nci.nih.gov>.

CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the CTEP Associate Registration Help Desk by email at <ctepreghelp@ctep.nci.nih.gov>.

CTSU Registration Procedures

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

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at https://www.ctsu.org. For sites under the CIRB initiative, IRB data will automatically load to RSS.Submitting Regulatory Documents

Downloading Site Registration Documents:

Site registration forms may be downloaded from the **E3A06** protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Click on the **ECOG-ACRIN** link to expand, then select trial protocol **E3A06**
- Click on the Site Registration Documents link

Requirements for **E3A06** site registration:

- CTSU IRB Certification (for sites not participating via the NCI CIRB)
- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)

Submitting Regulatory Documents

Submit completed forms along with a copy of your IRB Approval and Model Informed Consent to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-866-651-2878
FAX: (215) 569-0206
E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

Required Protocol Specific Regulatory Documents

1. CTSU Regulatory Transmittal Form.

2. Copy of IRB Informed Consent Document.

NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

3. A. CTSU IRB Certification Form.
Or
B. Signed HHS OMB No. 0990-0263.
Or
C. IRB Approval Letter

NOTE: The above submissions must include the following details:

- **Indicate all sites approved for the protocol under an assurance number.**
- **OHRP assurance number of reviewing IRB**
- **Full protocol title and number**
- **Version Date**
- **Type of review (full board vs. expedited)**

- **Date of review.**
- **Signature of IRB official**

Checking Your Site's Registration Status:
Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Patient Enrollment

Patients must not start protocol treatment prior to registration.

Treatment should start within seven working days after registration.

Patient registration can occur only after pre-treatment evaluation is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at <https://eapps-ctep.nci.nih.gov/iam/index.jsp>) and a 'Registrar' role on either the LPO or participating organization roster.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

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

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

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4.1 Pre-Registration

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

The following information will be requested at time of randomization:

4.1.1 Protocol Number

4.1.2 Investigator Identification

4.1.2.1 Institution and affiliate name (Institution CTEP ID)

4.1.2.2 Investigator's name (NCI number)

4.1.2.3 Cooperative Group Credit

4.1.2.4 Credit Investigator

4.1.2.5 Protocol specific contact information

4.1.3 Patient Identification

4.1.3.1 Patient's initials (first and last)

4.1.3.2 Patient's Hospital ID and/or Social Security number

4.1.3.3 Patient demographics

4.1.3.3.1 Gender

4.1.3.3.2 Birth date

4.1.3.3.3 Race

4.1.3.3.4 Ethnicity

4.1.3.3.5 Nine-digit ZIP code

4.1.3.3.6 Method of payment

4.1.3.3.7 Country of residence

4.1.3.4 Additional Requirements

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

4.1.3.4.2 Bone marrow and peripheral blood specimens are to be submitted at pre-registration for defined laboratory research studies and future undefined research studies as outlined in Section 10 per patient consent.

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4.2 Registration

The following information will be requested at the time of registration.

4.2.1 Protocol Number

4.2.2 Investigator Identification

4.2.2.1 Institution and affiliate name (Institution CTEP ID)

4.2.2.2 Investigator's name (NCI number)

4.2.2.3 Cooperative Group Credit

4.2.2.4 Credit Investigator

4.2.2.5 Protocol specific contact information

4.2.3 Patient Identification

4.2.3.1 Patient's initials (first and last)

4.2.3.2 Patient's Hospital ID and/or Social Security number

4.2.3.3 Patient demographics

4.2.3.3.1 Gender

4.2.3.3.2 Birth date

4.2.3.3.3 Race

4.2.3.3.4 Ethnicity

4.2.3.3.5 Nine-digit ZIP code

4.2.3.3.6 Method of payment

4.2.3.3.7 Country of residence

4.3 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.0. A registration worksheet has been appended to the protocol. A confirmation of registration and patient labels will be forwarded by the ECOG-ACRIN Operations Office - Boston.

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4.4 Additional Requirements

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

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4.4.2 Peripheral blood and bone marrow should be submitted for correlative studies and/or banking as indicated in Section 10 per patient consent.

NOTE: ECOG-ACRIN requires that biological samples submitted from patients participating in E3A06 be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS). See Section 10.5.

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NOTE: Institutions outside of the United States and Canada must confer with the receiving laboratory and the ECOG-ACRIN Operations Office - Boston regarding logistics for submission of fresh samples.

4.5 Stratification Factors

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4.5.1 Time Since Smoldering Multiple Myeloma Diagnosis: 1 year vs. > 1 year.

4.6 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 according to the instructions in the E3A06 Forms Packet. Document the reason for not starting protocol treatment on the off treatment form. Also report the date and type of the first non-protocol treatment that the patient receives.

5. Treatment Plan

5.1 Administration Schedule

5.1.1 Arm A Lenalidomide*

Lenalidomide 25 mg by mouth days 1-21 every 4 weeks (28 days).

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Aspirin (or alternative prophylaxis) days 1-28 for each treatment cycle. Suggested dose is 325 mg/day, however the dose is at the discretion of the treating physician. Alternative dosing of 75mg/day or higher is acceptable provided the patient is at low risk of thrombosis.

All patients on Arm A are required to receive prophylaxis against thrombosis. For patients in Arm A, physicians should consider prophylaxis with aspirin alone as studies with single agent lenalidomide in the setting of relapsed disease show a relatively low incidence of thrombosis (< 5%). See Section 5.5.2.1 for acceptable alternative prophylaxis.

Treatment continues until progression to symptomatic myeloma or discontinuation due to toxicity.

For patients with CrCl 30-60 mL per minute, lenalidomide dose is 10 mg per day for days 1-21 every 28 days. Creatinine clearance (CLcr) can either be measured CLcr or estimated by the Cockcroft-Gault method: {[140 – age (yrs)] × [lesser of IBW (kg) or actual weight (kg)]} / [72 × serum creatinine (mg/dL)]; multiply by another factor of 0.85 if female.

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* **NOTE:** The first 44 patients to accrue will be placed on Arm A without randomization (Phase II).

5.1.2 Arm B Observation

Observation continues until progression to symptomatic myeloma.

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5.2 **Adverse Event Reporting Requirements**

NOTE: Effective April 1, 2018 all expedited adverse event reporting done via CTEP-AERS will use CTCAE version 5.0 terminology and grading. Routine adverse event reporting and dose modifications guidelines for this study will continue to be based on CTCAE version 4.0 terminology and grading.

5.2.1 Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial (please refer to the E3A06 Forms Packet for the list of forms with directions for routine adverse event reporting). Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. The following sections provide information about expedited reporting.

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5.2.2 Determination of reporting requirements

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the grade (severity), the relationship to the study therapy (attribution), and the prior experience (expectedness) of the adverse event; 3) the phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

An investigational agent is a protocol drug administered under an Investigational New Drug Application (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Steps to determine if an adverse event is to be reported in an expedited manner:

Step 1: *Identify the type of event*: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized until March 31, 2018 for AE reporting. Effective April 1, 2018 all expedited adverse event reporting done via CTEP-AERS will use CTCAE version 5.0 terminology and grading. 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).

Step 2: Grade the event using the NCI CTCAE version 5.0.

Step 3: *Determine whether the adverse event is related to the protocol therapy (investigational or commercial).* Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

Step 4: *Determine the prior experience of the adverse event*. *Expected* events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered *unexpected*, for expedited reporting purposes only, when either the type of event or the severity of the event is **NOT** listed in:

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- **Arm A** – the current NCI Specific Protocol Exceptions to Expedited Reporting (SPEER) for Lenalidomide

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NOTE: The NCI SPEER for Lenalidomide is included in Section 5.3 of the protocol.

- **FOR THIS PROTOCOL**, events listed in the **SPEER** for Lenalidomide should be considered EXPECTED if the grade being reported is the same or lower than the grade noted in the parentheses next to the AE in the

SPEER. Events listed in the SPEER column should be considered UNEXPECTED if the grade being reported exceeds the grade noted in parentheses next to the AE in the SPEER.

- The SPEER is presented in the last column of the CAEPR and identified with ***bold*** and ***italicized*** text.

Step 5: Review the "Additional instructions, requirements, and exceptions for protocol E3A06" table in Section 5.2.6 for protocol and/or ECOG-ACRIN specific requirements for expedited reporting of specific adverse events that require special monitoring.

NOTE: For general questions regarding expedited reporting requirements, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497.

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5.2.3 Reporting procedure

This study requires that expedited adverse event reporting use CTEP's Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted electronically to ECOG-ACRIN and the appropriate regulatory agencies via the CTEP-AERS Web-based application located at http://ctep.cancer.gov.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to

- the AE Team at ECOG-ACRIN (857-504-2900) and
- the NCI (301-897-7497)

An electronic report MUST be submitted immediately upon re-establishment of internet connection.

Supporting and follow up data: Any supporting or follow up documentation must be faxed to ECOG-ACRIN (617-632-2990), Attention: AE within 48-72 hours. In addition, supporting or follow up documentation must be faxed to the NCI (301- 897-7404) in the same timeframe.

NCI Technical Help Desk: For any technical questions or system problems regarding the use of the CTEP-AERS application, please contact the NCI Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457.

5.2.4 When to Report an Event in an Expedited Manner

Some adverse events require 24-hour notification (refer to Section 5.2.6). Please complete a 24-Hour Notification Report via the CTEP-AERS website (http://ctep.cancer.gov) within 24 hours of learning of

the event. The full CTEP-AERS report must be completed and submitted via CTEP-AERS within 5 calendar days.

If the CTEP-AERS system is down, a 24-hour notification call must be made to ECOG-ACRIN (857-504-2900) and to NCI (301-897-7497). Once the system is restored, a 24-hour Notification Report must be entered into the CTEP-AERS system by the original submitter of the report at the site.

When an adverse event requires expedited reporting, submit a full CTEP-AERS report within the timeframes outlined in Section 5.2.6.

NOTE: Adverse events that meet the reporting requirements in Section 5.2.6 and occur within 30 days of the last dose of protocol treatment must be reported on an expedited adverse event report form (using CTEP-AERS). For any adverse events that occur more than 30 days after the last dose of treatment, only those that have an attribution of possibly, probably, or definitely AND meet the reporting requirements in Section 5.2.6 must be reported on an expedited adverse event report form (using CTEP-AERS).

5.2.5 Other Recipients of Adverse Event Reports

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

Adverse events determined to be reportable 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.

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5.2.6 Expedited reporting for investigational agents

Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND: CTEP-AERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days[1] of the Last Dose of Investigational Agent (CC-5013/Lenalidomide) in this Study (Arm A) OR Within 30 Days of the Last Dose of Any Protocol Treatment.

Attribution	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]	Grades 4 & 5[2]
				Unexpected		Expected			
	Unexpected and Expected	Unexpected	Expected	with Hospitalization	without Hospitalization	with Hospitalization	without Hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur <u>greater</u> than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:**

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

- Grade 4 and Grade 5 unexpected events

CTEP-AERS 10 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

[2] Although a CTEP-AERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table. See NOTE below regarding how to report a death due to progressive disease.

Please see additional information below under section entitled "Additional instructions, requirements, and exceptions for protocol E3A06"

March 2005

NOTE: All deaths on study or within 30 days of the last dose of treatment require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should 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.

NOTE: A death that occurs > 30 days after the last dose of treatment and is attributed possibly, probably, or definitely to the treatment must be reported within 10 calendar days of learning of the event.

- Expedited AE reporting timelines:
  - **24 Hours; 5 calendar days** – The investigator must initially report the AE via CTEP-AERS within <u>24 hours</u> of learning of the event followed by a complete CTEP-AERS report within <u>5 calendar days</u> of the initial 24-hour report.
  - **10 calendar days** – A complete CTEP-AERS report on the AE must be submitted within <u>10 calendar days</u> of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates **hospitalization* (or prolongation of existing hospitalization)** must be reported regardless of attribution and designation as expected or unexpected

with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in **persistent or significant disability/incapacity, congenital anomaly, or birth defect** must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

*Hospitalizations are defined as lasting 24 hours or longer and these events must be reported via CTEP-AERS.

Additional instructions, requirements and exceptions for protocol E3A06

1. Additional Instructions:

- With respect to determining the specific day by which the event must be reported, the day the reporter learns of the adverse event constitutes "Day 0"
- For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events via CTEP-AERS, 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.

2. ECOG-ACRIN and Protocol Specific expedited reporting requirements:

The adverse events listed below also require expedited reporting for this trial:

ECOG-ACRIN specific expedited reporting requirements:

- **Hospitalizations:** Any grade 1 or 2 adverse event with precipitates a hospitalization lasting ≥ 24 hours (or prolongs hospitalization) must be reported via CTEP-AERS within 10 calendar days of learning of the event regardless of the attribution and designation as expected or unexpected.
- **Grade 3 expected events:** Any grade 3 expected **non-hematologic** event, with an attribution of possible, probable of definite, must be reported via CTEP-AERS within 10 calendar days of learning of the event, regardless of whether hospitalization is required.

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- **Pregnancies**

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

3. Protocol specific expedited reporting exceptions:

For study arm A, the adverse events listed below **do not** require expedited reporting via CTEP-AERS:

- Grade 4 expected myelosuppresion (unless it results in a hospitalization, in which case, a CTEP-AERS report is required).

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5.2.7 Reporting Secondary AML/MDS/ALL

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-sponsred trials must be reported as follows:

1. Submit a completed Second Primary Form within 30 days to ECOG-ACRIN at:

   ECOG-ACRIN Operations Office - Boston
   FSTRF
   900 Commonwealth Avenue
   Boston, MA 02215

2. Report the diagnosis via CTEP-AERS, regardless of attribution, at http://ctep.cancer.gov

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

3. Submit a copy of the pathology report to ECOG-ACRIN and NCI/CTEP confirming the diagnosis.

4. If the patient has been diagnosed with AML/MDS, submit a copy of the cytogenetics report (if available) to ECOG-ACRIN and NCI/CTEP.

NOTE: All new malignant tumors must be reported through CTEP-AERS 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). ng 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:

NOTE: The 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 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 via CTEP-AERS or by the Second Primary Form.

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Rev. Add13
Rev. Add14
Rev. 7/13

5.3 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Lenalidomide (CC-5013, 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. 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 4081 patients.* Below is the CAEPR for lenalidomide (CC-5013).

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NOTE: FOR THIS PROTOCOL, events listed in the SPEER column should be considered EXPECTED if the grade being reported is the same or lower than the grade noted in the parentheses next to the AE in the SPEER. Events listed in the SPEER column should be considered UNEXPECTED if the grade being reported exceeds the grade noted in parentheses next to the AE in the SPEER.

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Version 2.8, June 27, 2019[1]

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 5.0 Term) [n= 4081]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 3)***
	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		***Hypothyroidism (Gr 3)***
EYE DISORDERS			
	Blurred vision		
	Cataract		

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 5.0 Term) [n= 4081]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
Constipation			***Constipation (Gr 3)***
Diarrhea			***Diarrhea (Gr 3)***
	Dry mouth		
	Dyspepsia		
	Nausea		***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		***Chills (Gr 2)***
	Edema limbs		***Edema limbs (Gr 3)***
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 3)***
	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]		***Infection[4] (Gr 3)***
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Bruising		
	Fall		
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		
	Blood bilirubin increased		

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 5.0 Term) [n= 4081]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	GGT increased		
	Investigations - Other (C-Reactive protein increased)		
		Lipase increased	
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***
Neutrophil count decreased			***Neutrophil count decreased (Gr 4)***
Platelet count decreased			***Platelet count decreased (Gr 4)***
	Weight loss		***Weight loss (Gr 2)***
	White blood cell decreased		***White blood cell decreased (Gr 4)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 3)***
	Dehydration		
	Hyperglycemia		
	Hyperuricemia		
	Hypocalcemia		
	Hypokalemia		
	Hypomagnesemia		
	Hyponatremia		
	Hypophosphatemia		
	Iron overload		
		Tumor lysis syndrome	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		
	Bone pain		
	Generalized muscle weakness		
	Muscle cramp		***Muscle cramp (Gr 2)***
	Myalgia		***Myalgia (Gr 2)***
	Pain in extremity		
		Rhabdomyolysis[5]	

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 5.0 Term) [n= 4081]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
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		***Insomnia (Gr 2)***
	Psychiatric disorders - Other (mood altered)		
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 3)***
	Epistaxis		
		Pneumonitis	

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 5.0 Term) [n= 4081]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Dry skin		
		Erythema multiforme	
	Hyperhidrosis		***Hyperhidrosis (Gr 2)***
	Pruritus		***Pruritus (Gr 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr 3)***
		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]		***Thromboembolic event[9] (Gr 3)***
	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.

5.4 Dose Modifications

Dose modifications are based on adverse events which are possibly, probably or definitely related to drug.

All toxicity grades below are described using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

Lenalidomide Treatment Adjustment

See Table below for Lenalidomide Treatment Adjustment Steps

Lenalidomide (CC-5013) Treatment Adjustment Steps	
Starting Dose	**25 mg daily for 21 days every 28 days**
Dose Level -1	15 mg daily for 21 days every 28 days
Dose Level -2	10 mg daily for 21 days every 28 days
Dose Level -3	5 mg daily for 21 days every 28 days

Subjects experiencing ≥ grade 3 adverse events will have their study drug held until resolution of the AE. Subjects experiencing grade 3/4 AEs prior to Day 15 of a cycle will need to hold lenalidomide. If AE improves to grade 1 or less prior to Day 21, lenalidomide should be restarted with a one dose level reduction for the remainder of the cycle. The next cycle will then continue with this reduced dose level. For grade 3 or 4 AEs which occur on or after Day 15 of a cycle, the subject's study drug is to be held for the remainder of the cycle and will be reduced by one dose level beginning with the next cycle. Once a subject's dose has been reduced, no dose-re-escalation is permitted.

Lenalidomide (CC-5013) Dose modifications based on adverse events (Arm A)

NCI CTC AE Grade	At retreatment* and Day 2-14 of Cycle	≥ Day 15 of Cycle
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 weekly. If the toxicity resolves to baseline or g rade 1 prior to Day 21 restart at next lower dose level and continue the cycle until Day 21.	Omit lenalidomide for remainder of cycle. If toxicity resolves, restart lenalidomide next cycle with a decrease in dose by one dose level.
Thrombocytopenia ≥ Grade 3 (platelet count < 50,000/mm³)	Hold (interrupt dose) and follow CBC weekly. If the toxicity resolves to baseline or g rade 1 prior to Day 21 restart at next lower dose level and continue the cycle until Day 21.	Omit lenalidomide for remainder of cycle. If toxicity resolves, restart lenalidomide next cycle with a decrease in dose by one dose level.
Non-blistering rash Grade 2-3	Hold (interrupt) dose and follow. If the toxicity resolves to grade 1 prior to Day 21 restart at next lower dose level and continue the cycle until Day 21.	Omit lenalidomide for remainder of cycle. If toxicity resolves, restart lenalidomide next cycle with a decrease in dose by one dose level.
Grade 4	Discontinue lenalidomide and do not resume.	Discontinue lenalidomide and do not resume.
Desquamating (blistering) rash - any Grade	Discontinue lenalidomide.	Discontinue lenalidomide and do not resume.
Erythema multiforme ≥ Grade 3	Discontinue lenalidomide.	Discontinue lenalidomide and do not resume.
Sinus bradycardia/ other cardiac Arrhythmia Grade 2	Hold (interrupt) dose and follow. If the toxicity resolves to grade 1 prior to Day 21 restart at next lower dose level and continue the cycle until Day 21.	Omit lenalidomide for the reminder of the cycle. If toxicity resolves, restart lenalidomide next cycle with a decrease in dose by one dose level.
Grade 3-4	Discontinue lenalidomide.	Discontinue lenalidomide and do not resume.
Allergic reaction or Hypersensitivity Grade 2-3	Hold (interrupt) dose and follow. If the toxicity resolves to grade 1 prior to Day 21 restart at next lower dose level and continue the cycle until Day 21.	Omit lenalidomide for the remainder of the cycle. If toxicity resolves, restart lenalidomide next cycle with a decrease in dose by one dose level.
Grade 4	Discontinue lenalidomide.	Discontinue lenalidomide and do not resume.
Constipation Grade 1-2	Initiate bowel regimen and maintain dose level.	Initiate bowel regimen and maintain dose level.
≥ Grade 3	Hold (interrupt) dose and follow. If the toxicity resolves to grade 1 prior to Day 21 restart at next lower dose level and continue the cycle until Day 21.	Omit lenalidomide for the remainder of the cycle. If toxicity resolves, restart lenalidomide next cycle with a decrease in dose by one dose level.

Renal Function CrCl 30-60 mL/min CrCl <30 mL/min	Hold (interrupt) dose and follow. If the toxicity resolves to < grade 1 prior to Day 21 restart at next lower dose level and continue the cycle until Day 21. Discontinue lenalidomide.	Omit lenalidomide for remainder of cycle. Reduce dose of lenalidomide by one dose level for next cycle. Discontinue lenalidomide.
Venous Thrombosis/embolism ≥ Grade 3	Hold (interrupt) dose and start anticoagulation; restart at investigator's discretion after adequate anticoagulation (maintain dose level).	Omit lenalidomide for remainder of cycle and start anticoagulation. Restart at investigator's discretion after adequate anticoagulation (maintain dose level).
Hepatic or other Non-hematologic toxicity Assessed as lenalidomide- Related ≥ Grade 3	Hold (interrupt) dose and follow. If the toxicity resolves to grade 1 prior to Day 21 restart at next lower dose level and continue the cycle until Day 21.	Omit lenalidomide for remainder of cycle.
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).	Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. Restart lenalidomide next cycle (decrease dose by one dose level).

As noted in the table above, lenalidomide can be introduced after resolution of certain toxicities, midway through the cycle, provided the toxicity resolves prior to day 21. If drug needs to be held at the time of retreatment for adverse events, then the date of when treatment is resumed is considered day 1 of new treatment cycle. Patients requiring a treatment delay beyond 6 weeks will end protocol treatment.

If lenalidomide is held for an entire cycle and toxicity resolution does not occur within this time, lenalidomide dosing should be permanently stopped.

5.5 Supportive Care

5.5.1

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

5.5.2 Thrombosis Prophylaxis

5.5.2.1 Arm A

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All patients on Arm A are to receive prophylaxis against thrombosis. For patients in Arm A, physicians should consider prophylaxis with aspirin alone as studies with single agent lenalidomide in the setting of relapsed disease show a relatively low incidence of thrombosis (<5%).

If the participant is on full-dose anticoagulation and it is anticipated that the course of therapy with full-dose anticoagulation is to be completed during participation in

this trial, the participant must then be placed on some form of anti-coagulation as prophylaxis.

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Arm	DVT prophylaxis	Acceptable alternative prophylaxis**
A	Aspirin each day of treatment cycle*	Lovenox 40 mg once a day subcutaneously or equivalent OR full dose coumadin targeting a therapeutic INR 2-3. For patients unable to tolerate 325 mg aspirin, 0 to 81 mg may be given.

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* Suggested dose of Aspirin is 325 mg/day, however the dose is at the discretion of the treating physician. Alternative dosing of 75mg/day or higher is acceptable provided the patient is at low risk of thrombosis.

** Aspirin should not be given if patients are treated with alternative prophylaxis.

5.5.2.2 Prior or concurrent use of erythropoietin is disallowed.

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5.5.2.3 Each site must have two trained counselors available for counseling all patients receiving lenalidomide supplied by the Division of Cancer Treatment and Diagnosis. Trained counselors must complete training using the online program provided free by Celgene, the Celgene Pregnancy Prevention Counseling Program (CPPCP) Registration for CPPCP is done by completing the form found in Appendix XII and following the directions provided in the email notification. After the training is complete, the counselors must generate a training certificate and provide it to the CTSU for documentation. Sites may not order lenalidomide until documentation for two trained counselors is provided to the appropriate office. The CPPCP forms can be faxed to the CTSU at 1-888-691-8039.

5.6 Duration of Therapy

- Patients who progress to symptomatic myeloma at any time are discontinued from participation.
- Patients on Arm A of therapy are strongly encouraged to undergo growth factor based stem cell collection following 4-6 cycles of therapy.
- Patients are not permitted to undergo cyclophosphamide or other chemotherapy administration while on study for any reason, and specifically not for stem cell mobilization.

5.6.1 Extraordinary Medical Circumstances

Patients will receive protocol therapy unless:

If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued.

5.6.2 Patient withdraws consent.

5.6.3 Patient experiences progression of disease.

5.6.4 Patient experiences unacceptable toxicity.

5.6.5 Non-Protocol therapies are administered.

5.7 Duration of Follow Up

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

6. Measurement of Effect

Definitions of Stringent Complete Response, Complete Response, Very Good Partial Response, Partial Response, and Stable Disease are based on International Uniform Response Criteria for Multiple Myeloma and the American Society of Hematology/Food and Drug Administration consensus panel recommendations for the assessment of disease progression.(64)

6.1 Response Considerations

6.1.1 Terms and Definitions

6.1.1.1 M-Protein

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

6.1.1.2 Response Terms

The following response terms will be used: stringent complete response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), stable disease (SD), and progression (PD).

See Sections 6.2.1-6.2.6 for definitions.

6.1.1.3 Measurable Disease

Defined by at least one of the following three measurements

- Serum M protein ≥ 1 g/dL (≥ 10gm/L)(10 g/L)
- Urine M protein ≥ 200 mg/24 hours
- Serum free light chain (FLC) assay: Involved free light chain level ≥ 10 mg/dL (≥ 100 mg/L) provided serum FLC ratio is abnormal

6.1.1.4 Evaluable Disease

Patients who do not have a “measurable” serum or urine M-spike.

6.1.1.5 Oligosecretory Myeloma

Patient with Multiple Myeloma who has NEVER had “measurable” disease, but has had a detectable monoclonal protein in his/her serum and/or urine.

6.1.1.6 Non-Secretory Myeloma

Patient with Multiple Myeloma who has NEVER had a detectable monoclonal protein in his/her serum and/or urine.

6.1.1.7 Response Evaluation and Confirmation

Except for assessment of sCR, CR, or VGPR patients with measurable disease restricted to the SPEP will need to be

followed only by SPEP; correspondingly, patients with measurable disease restricted to the UPEP will need to be followed only by UPEP.

Patients with measurable disease in either SPEP or UPEP or both will be assessed for response only based on these two tests and not by the FLC assay. FLC response criteria are only applicable to patients without measurable disease in the serum or urine.

To be considered CR, both serum and urine immunofixation must be carried out and be negative regardless of the size of baseline M-protein in the serum or urine.

In order to be classified as a sCR, CR, PR, or VGPR, confirmation of serum and urine monoclonal protein results is required and must be made at anytime before the institution of any new therapy. Confirmation is mandatory for sCR, CR, PR and VGPR documentation.

Bone marrow biopsy is required for CR; however, a repeat bone marrow biopsy is not needed for confirmation.

Bone radiographs are not required to document response. If bone radiographs are obtained, their findings must be consistent with the bone response criteria.

6.1.1.8 Oligosecretory and Non-secretory Myeloma

Patients with oligosecretory myeloma who have measurable levels on the serum FLC assay, are assessed for response using the FLC assay instead of serum and urine M-protein levels. All other requirements as outlined in each response category must be met. Patients with oligosecretory myeloma who do not have measurable levels on the serum FLC assay and patients with non-secretory myeloma may be assessed for response using bone marrow plasma cell involvement provided baseline bone marrow plasma cell percentage was ≥30%.

6.1.1.9 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 such as in patients with IgA monoclonal proteins migrating in the beta region. IF SPEP is not available or felt to be unreliable for routine M-protein quantitation during therapy, then quantitative immunoglobulin levels on nephelometry or turbidometry can be accepted. However, this must be explicitly reported; and only nephelometry can be used for that patient to assess response and SPEP and nephelometric 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

NOTE: For this protocol, patients will only have measurable serum and/or urine M-protein.

6.2.1 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, immunofluorescence, flow cytometry, or any other clonality determination method.[a]

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

6.2.2 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 at two consecutive times, and
- Disappearance of any soft tissue plasmacytomas *and*
- < 5% plasma cells in bone marrow

6.2.3 Very Good Partial Response (VGPR)

- Serum and urine M-component detectable by immunofixation but not on electrophoresis *or*
- 90% or greater reduction in serum M-component plus urine M-component < 100 mg per 24 hours (by SPEP and UPEP)
- If the serum and urine M protein are unmeasurable and the immunoglobulin free light chain parameter is being used to measure response, a ≥ 90% decrease in the difference between

involved and uninvolved free light chain (FLC) levels is required in place of the M protein criteria.

6.2.4 Partial Response (PR)

- Patients who have measurable disease in the serum at baseline require ≥ 50% reduction in the level of serum M-protein (by SPEP).
- Patients who have measurable disease in the urine at baseline require ≥ 90% reduction in the level of urine M-protein or the urine M-protein must be < 200mg/24hr (by 24 hr UPEP).
- If the serum and urine M-protein are unmeasurable and the immunoglobin free light chain parameter is being used to measure response, a ≥ 50% decrease in the difference between involved and uninvolved free light chain (FLC) levels is required in place of the M-protein criteria.
- If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30%.
- In addition to above listed criteria, if present at baseline, a ≥ 50% reduction in size of soft tissue plasmacytomas is also required.

6.2.5 Stable Disease (SD)

Failure to meet response criteria outlined above.

6.2.6 Progression (PD)

The investigation that qualified as progression should be repeated and verified on a subsequent occasion only if treating physician deems it clinically necessary. Patients will be considered to have progression if both of the following criteria are met.(64)

1. Any one or more of the following:
    - Increase in serum M-protein to ≥ 25% above the lowest response level, which must also be an absolute increase of at least 0.5g/dl to qualify as “progression.”
    - Increase in urine M-protein to ≥ 25% above the lowest response level for 24-hour excretion, which also must be an absolute increase of at least 200mg/24 hours of urine M-protein to qualify as “progression.”
    - Increase in bone marrow plasma cell percentage to ≥ 25% from lowest response value (the absolute % increase must be ≥ 10%).

AND

2. Any one or more of the following felt related to the underlying clonal plasma cell proliferative disorder:
    - Hypercalcemia (> 11 mg/dL)
    - Decrease in hemoglobin of ≥ 2 gms/dL

- Serum creatinine level ≥ 2mg/dL
- Development of myeloma bone lesions or soft tissue plasmacytoma.

If subsequent verification is done, progression should be recorded as the date when the abnormality was first detected, not the date when it was confirmed.

6.3 Quality of Life Measurement

6.3.1 QOL Instruments

For the primary quality of life endpoint we will use a combined scale comprised of the well established and validated functional well-being (FWB) and physical wellbeing (PWB) components of FACT-G version 4 (14 questions), which will address the physical and functional well-being of SMM patients.

In addition, a new MM specific subscale (MMS) (14 questions) will be evaluated as a secondary endpoint. The MM subscale was developed in a three-step process using both expert and patient input. First, a pool of potential items was generated from the literature to create an item rating survey. These items were reviewed by thirteen health care providers with expertise in the diagnosis and treatment of Multiple Myeloma recruited through ECOG-ACRIN Myeloma Committee as well as from Mayo Clinic in Scottsdale, AZ, Mayo Clinic in Rochester, MN, and Marshfield Clinic in Marshfield, WI. Items were rated according to how common and how important they are when occurring in patients with this condition. Finally, experts were asked to circle up to 20 of the most important items (including self-nominated items) affecting patients with Multiple Myeloma. Expert input was compiled and ten additional items nominated during the surveys were added to the item rating survey. This survey was then formatted to be a semi-structured, self-administered, web-based interview that was conducted with a sample of forty-one MM patients. Identification and enrollment of eligible patients was performed using the International Myeloma Foundation website. Further candidate items were then generated by these patients using this semistructured interview designed to elicit personal experiences about how Multiple Myeloma and its treatment may affect physical status, emotional well-being, functional well-being, family/social issues, sexuality/intimacy, work status, and future orientation. Patients were also asked to complete the same item rating survey administered to the experts (with the additional ten questions) as well as answer basic disease and treatment questions. Patients were also given the opportunity to provide comments on items as well as additional feedback. Second, a team of CORE staff with extensive experience in QOL research, assessment and scale construction followed a standard process of item review and reduction as well as scale construction creating a final list of 14 items. Third, this final list of items was then reviewed by the Multi-Lingual Translation Team to screen for potential translation issues and to correct item wording in problematic instances.

6.3.2 Timing of QOL Assessments

The QOL assessment utilizing the FACT PWB+FWB and the MMS instruments will first be administered at registration (+ 7days) prior to initiation of treatment or observation. During the treatment or observation period, QOL will be measured every 6 cycles (day end + 7 days) up to cycle 48 and at the end of treatment (+ 14 days). For patients who discontinue protocol therapy or go off observation early not due to disease progression, QOL will also be assessed at the next quarterly Long Term follow-up visit (+ 14 days). After this, these patients will not be followed further for QOL.

7. Study Parameters for Arm A and Arm B

7.1 Therapeutic Parameters (for both arms of the study)

1. Prestudy scans and x-rays used to assess all measurable or non-measurable sites of disease must be done within **4 weeks** (28 days) prior to randomization/registration.
2. Prestudy CBC (with differential and platelet count) should be done **4 weeks** (28 days) before randomization/ registration.
3. All required prestudy chemistries, as outlined in Section 3, should be done **4 weeks** (28 days) before randomization/registration unless specifically required on Day 1 as per protocol.

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Procedure	Prior to registration (≤ 28 days) [1]	10-14 days prior to starting Treatment or Observation	< 24 hours prior to starting Treatment or Observation	Induction- At the end of each Treatment or Observation cycle	Day 1 of each cycle	Studies needed to confirm sCR or CR	Periodically during Treatment or Observation	At study discontinuation or progression (whichever comes first)	28 Days after discontinue-ation of treatment	Post treatment to 10 years from study entry[11]
History and exam[6]	X			X				X		X
Bone Marrow Aspirate and Biopsy[9]	X					X				
ECOG Performance Status	X			X				X		X
NYHA Classification	X									
Chemistry labs[3]	X			X				X		X
CBC with differential[4]	X			X				X		X
Serum light chain assay	X			X		X		X		X
Serum immunoglobin G, A, M	X			X				X		X
QOL[7]	X			X				X		X

	SPEP	X			X				X		X
	Serum M-protein immunofixation	X					X				
	24 hr UPEP	X			X[2,10]				X[2,10]		X[2,10]
	Urine M-protein immunofixation	X					X				
	Metastatic bone survey	X						X[12]	X		X[12]
	ECG (12-lead)	X									
	Serum Pregnancy test for FCBP[5]	X	X[5]	X[5]	X[5]				X[5]	X[5]	
Rev. 8/11	Patient Education and Counseling[14]	X		X	X	X			X	X	
	Serum Beta-2 microglobulin	X							X		
	C-reactive protein	X									
	LDH	X									
Rev. 8/11	Dispense lenalidomide[15]			X		X					
Rev. 7/14	TSH (ARM A ONLY)[16]	X									X[13]
	Ultrasound[8]				X						
	Documentation of oral drug				X						
	MRI (spine and pelvis)	X									
Rev. 12/13	Biological Sample Submissions	See Section 7.2									

1. Registration test results can be used for cycle 1 if less than 7 days before starting cycle 1.

2. If serum and urine M-components are measurable, both must be followed in order to evaluate response. Measurable levels of monoclonal protein (M-protein) are defined as ≥ 1.0 g/dL on serum protein electrophoresis or ≥ 200 mg 24hr of monoclonal light chain on a 24-hour urine protein electrophoresis; results must be obtained with 4 weeks prior to randomization.

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3. Chemistry includes sodium, potassium, calcium, magnesium, phosphorus, blood urea nitrogen (BUN), creatinine, creatinine clearance, glucose, alkaline phosphatase, total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT). Magnesium and phosphorus is not required but should be tested as clinically indicated.
4. Hematology (CBC with differential) includes WBC, ANC, Platelets, Hgb, and Hct required for protocol therapy must be done < 24 hours prior to the treatment cycle.
5. Pregnancy tests for females of childbearing potential for patients on Arm A only. A female of childbearing potential (FCBP) is a sexually mature female, regardless of sexual orientation or whether they have undergone tubal ligation, who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months). Pregnancy tests (sensitivity of 25 mIu/mL) must occur within 10 – 14 days and again within 24 hours prior to initiation of lenalidomide. FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days and then every 28 days while on therapy (including breaks in therapy); at discontinuation of lenalidomide and at Day 28 post the last dose of lenalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on therapy (including breaks in therapy), at discontinuation of lenalidomide and at Day 14 and Day 28 post the last dose of lenalidomide (see Appendix VI.

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6. Clinical exam should look for plasmacytoma.
7. QOL timepoints: At registration (+ 7 days) prior to initiation of treatment or observation; the last day (+ 7) of cycles 6, 12, 18, 24, 30, 36, 42, and 48; and at the end of treatment or observation (+14 days). For patients that discontinue protocol therapy or go off observation early not due to disease progression, QOL will also be assessed at the next quarterly Long Term follow-up visit (+ 14 days). After this, patients will not be followed further for QOL.
8. If leg swelling or pain is present in legs, an ultrasound of the legs will be done for deep vein thrombosis.
9. Bone marrow biopsy or aspirate performed to evaluate plasma cells %, presence of sheets of plasma cells and presence of plasma cell clonality. Absence of plasma cell clonality required for sCR.
10. Needed if urine M-spike at study entry was ≥ 200 mg/24 hr or if VGPR needs to be documented.
11. Patients will be followed for progression every 3 months if patient is < 2 years from study entry, every 6 months if patient is 2-5 years from study entry, every 12 months if patient is 6-10 years from study entry. No specific requirements if patient is more than 10 years from study entry. Patients will be followed for survival only once progression occurs and study treatment ends.
12. To be repeated every year or if clinically indicated for progression or symptoms.
13. To be assessed every 4 months.
14. All patients must be counseled about pregnancy precautions, risks of fetal exposure and other risks. The counseling must be done on Day 1 of each cycle (or at a minimum of every 28 days) and at drug discontinuation. The Lenalidomide Education and Counseling Guidance Document (Appendix VII) must be completed and signed by a trained counselor at the participating site prior to each dispensing of lenalidomide treatment. A copy of this document must be maintained in the patient records. A Lenalidomide Information Sheet (Appendix VIII) will be supplied to each patient receiving lenalidomide treatment. The patient must read this document prior to starting lenalidomide study treatment and each time they receive new supply of study drug.

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15. Only enough lenalidomide for 28 days or one cycle of study treatment may be provided to the patient each cycle.

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16. TSH should be tested for Arm A ONLY and then only when clinically indicated by the Principal Investigator.

7.2 Biological Sample Submissions

1. Bone marrow and peripheral blood samples should be submitted as outlined in Section 10 of E3A06 for correlative studies and/or banking per patient consent. Kits are being provided for the collection and shipment of the samples, please refer to Section 10 and Appendices III and IV for instructions.

NOTE: Institutions outside of the United States and Canada must confer with the receiving laboratory and the ECOG-ACRIN Operations Office - Boston regarding logistics for submission of fresh samples.

Rev. 7/14

NOTE: It is required that biological sample submissions be logged into the ECOG-ACRIN Sample Tracking System (STS) (see Section 10.5) for purposes of monitoring compliance.

Rev. 2/12

NOTE: An informed consent must be signed prior to the submission of any samples for laboratory studies and/or banking. Samples for the optional laboratory studies and/or banking should be submitted only from patients who have given written consent for the use of their samples for these purposes.

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Biological Materials[3,4]		**Pre-Registration[1]**	**At Study Discontinuation or Progression[2]**	**Ship To:**
From Patients Who Answer "YES" to "*I agree to participate in the laboratory research studies that are being done as part of this clinical trial.***"**				
Peripheral Blood	Two (2) ACD tubes (yellow top), 14mL	X	X	Mayo Clinic Myeloma Reference Laboratory
Rev. 2/12 Peripheral Blood	Four (4) 10mL Green Top tubes (sodium heparin)	X	X	Yale University
Bone Marrow Core Biopsy	Five (5) Unstained Slides	X	X	Mayo Clinic Myeloma Reference Laboratory
Rev. 2/12 Bone Marrow Core Biopsy	Snap Frozen	X	X	University of Arkansas
Rev. 7/13 Bone Marrow Aspirate	[Deleted in Addendum #7]			Mayo Clinic Myeloma Reference Laboratory
Rev. 7/13 Bone Marrow Aspirate	One (1) ACD tube (yellow top), 7mL	X	X	
Rev. 2/12 Bone Marrow Aspirate	5-10mL Sodium Heparin (green top tube)	X	X	Yale University
Rev. 2/12 Bone Marrow Aspirate	EDTA tube (purple top), 10-20mL	X	X	University of Arkansas
From Patients Who Answer "YES" to "*I agree to provide additional blood for research.***"**				
Rev. 2/12 Peripheral Blood	One (1) SST tube (red top), 5-7mL	X	X	Mayo Clinic Myeloma Reference Laboratory

1. Prior to treatment.
2. Whichever comes first. Biopsies performed at time of suspected progression are requested.
3. Submissions are optional based on patient consent to the correlative studies and/or banking as outlined in Section 10.
4. Kits are available for the collection and shipment of the samples. See Section 10.3.

8. Drug Formulation and Procurement

8.1 Lenalidomide (NSC 703813), (IND)

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NOTE: Before lenalidomide is dispensed, patients must 1) have a negative pregnancy test (if applicable) and 2) be counseled by a trained counselor. Pharmacists may be trained counselors (see Lenalidomide Counselor Program Site Counselor Identification Form in the protocol). The counseling requirements for investigational-use lenalidomide are separate from the RevAssist program. Only a 28-day supply may be dispensed to a patient at one time.

8.1.1 Other names

Revlimid® (formerly Revimid®), CDC-501, CC-5013

8.1.2 Classification

Immunomodulatory drug.

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8.1.3 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 upregulating responses of T cells and NK cells.

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8.1.4 How Supplied

Celgene supplies and CTEP, NCI, DCTD distributes lenalidomide 5 mg (size 2) and 25 mg (size 0) hard gelatin capsules in tamper-evident, child-resistant, opaque, high density polyethylene (HDPE) bottles with HDPE caps. Bottles contain 100 capsules per container.

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

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8.1.5 Storage and Stability

Storage: The capsules should be stored at room temperature (15-30°C) away from moisture and direct sunlight.

Stability: Refer to the package labeling for expiration date. Lenalidomide stability is adequate for at least 28 days after transferring to a pharmacy vial.

NOTE: Per FDA guidelines for prevention of pregnancy that only one month supply of lenalidomide may be dispensed to the patient at one time.

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Dispensing

Only a 28-day supply may be dispensed at one time. Sites may not mail lenalidomide to patients.

8.1.6 Dose Specifics

For Arm A patients, lenalidomide is initiated on Day 1 of Cycle 1 at a dose of 25 mg orally and will be taken days 1-21 for each 28 day cycle.

Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.

Lenalidomide capsules should be swallowed whole, and should not be broken, chewed, or opened.

If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up.

Patients who take more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

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8.1.7 Route of Administration

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

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8.1.8 Patient Care Implications and Counseling

Risks Associated with Pregnancy

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

Definition of female of childbearing potential (FCBP)

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

Before starting study drug:

Female Subjects:

- FCBP must have two negative pregnancy tests (minimum sensitivity of 25 mIU/mL) prior to starting study drug. The first pregnancy test must be performed within 10-14 days prior to the start of study drug and the second pregnancy test must be performed within 24 hours prior to the start of study drug. The subject may not receive study drug until the Investigator has verified that the results of these pregnancy tests are negative.

Male Subjects:

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

All Subjects:

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

Counseling

- In investigational studies where lenalidomide is supplied by the NCI, patients will be counseled by a qualified healthcare professional (including but not limited to, nurses, pharmacists and physicians). Two healthcare professionals at each site will be trained by Celgene in requirements specific to counseling of subjects (investigators cannot counsel patients as part of this requirement). Refer to specific protocol sections for more information about training requirements.
- Once trained, these healthcare staff will counsel subjects prior to medication being dispensed to ensure that the subject has complied with all requirements including use of birth control and pregnancy testing (FCBP) and that the subject understands the risks associated with lenalidomide. This step will be documented with a completed Lenalidomide Education and Counseling Guidance Document (Appendix VII) and no drug will be dispensed until this step occurs. Counseling includes verification with the patient that required pregnancy testing was performed and results were negative. A Lenalidomide Information Sheet (Appendix VIII) will be supplied with each medication dispense.

8.1.9 Potential Drug Interactions

Periodic monitoring of digoxin levels is recommended during coadministration with lenalidomide. Digoxin levels were slightly higher when digoxin was administered with lenalidomide in a clinical study. There was no effect on lenalidomide pharmacokinetics.

Warfarin and lenalidomide may be co-administered without additional monitoring. No pharmacokinetic or pharmacodynamic interactions were observed between lenalidomide and warfarin.

Nonclinical in vitro metabolism studies suggest that lenalidomide is not likely to result in metabolic drug interactions in humans. In vitro, lenalidomide did not significantly inhibit marker enzyme activities for CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4. In rats, no induction of any CYP450 enzymes was observed.

Administration of lenalidomide in monkeys showed no effects on the activities of CYP1A, CYP2B, CYP2C, CYP2E, CYP3A, or CYP4A.

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8.1.10 Availability

Available as a 5 mg and 25 mg hard gelatin capsule.

Drug Ordering: Maintenance of NCI drug accountability records is required. Lenalidomide may be requested by the Principal Investigator (or their authorized designees) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained - see general information).

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NCI SUPPLIED AGENT(S) - GENERAL INFORMATION

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Ordering Processing (OAOP) application (http://eapps-ctep.nci.nih.gove/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password.

For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBDAfterHours@mail.nih.gov anytime.

Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the NCI Investigational Agent Accountability Record available on the NCI home page (http://ctep.cancer.gov) or by calling the PMB at 240-276-6575.

8.1.11 Side Effects

See CAEPR (Section 5.3)

8.1.12 Nursing/ Patient Implications

Please refer to Appendix VI: Risk Associated with Pregnancy and Appendix VII: Education and Counseling Guidance Document.

1. Ensure women of childbearing age are not pregnant and sexually active women and men are abstaining or are using an effective form of contraception while taking lenalidomide.
2. Caution patient not to drive or use hazardous machinery until the potential sedative effects of the drug are known in the patient.
3. Caution patient to report leg swelling or shortness of breath, because of the risk of thrombosis/embolism

4. Counsel patient to report abnormal sensations in hands or feet, such as decreased sensation or dysesthesia. Paresthesias are often noted early before neuropathy develops.
5. Advise patient to immediately report rashes or fever.
6. Advise patient to take dose at the same time each day.

8.1.13 References

1. Richardson PG, Schlossman RL, Weller E, et al. Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed Multiple Myeloma. Blood 2002; 100:3063-7.
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3. Zangari M, Tricot G, Zeldis J, Eddlemon P, Saghafifar F, Barlogie B. Results of Phase I Study of CC-5013 for the Treatment of Multiple Myeloma (MM) Patients Who Relapse after High Dose Chemotherapy (HDCT). Blood 2001:775a (A3226).
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9. Statistical Considerations

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9.1 Introduction

This revised statistical considerations section reflects observed accrual and updated results of the Spanish SMM trial at ASH 2014 (Mateos et al. Blood 2014).

As of the end of June 2015, 93 patients have enrolled over the 26 months since accrual began on the Phase III study (Feb 2013). The accrual rate over this time was approximately 3.5 patients per month, which approximates 50% of the anticipated accrual rate (7 patients per month). Accrual over the last 6 months has averaged 4.5 patients per month. Following the recommendation of the Data Safety Monitoring Committee, the anticipated accrual rate is revised in addendum #11 to reflect the current actual accrual.

At the same time, the expected median PFS on observation (Obs) arm is revised in addendum #11 to reflect results from the Spanish SMM trial reported at ASH 2014 (Mateos et al. Blood 2014). In this study, 119 patients were randomized to receive induction lenalidomide (25 mg/day d1-21)-dexamethasone (20 mg/day d1-4, d12-15) (Rd) for 9 cycles and then maintenance lenalidomide (10 mg/day) up to 2 years total treatment versus watchful waiting. Long-term follow-up results showed a survival hazard ratio (watchful waiting/Rd) of 4.35 [95% CI (1.5-13.0)]. Time-to-progression (TTP) hazard ratio was 6.21 [95% CI (3.1-12.7)]. When E3A06 was originally designed, the median progression free survival (PFS) on observation was expected to be 31 months, and it was considered that patients treated with lenalidomide (Revlimid; R) would have comparatively longer PFS (60 months). However, the recent update showed that the median time to progression (TTP) on the watchful waiting arm (akin to the E3A06 observation arm) was 21 months which suggests that the median PFS on the Obs arm might be shorter than we had originally expected. Thus, in this addendum, in addition to the anticipated accrual rate, the expected median PFS on the Obs arm is also revised. The total accrual, the total information time and the interim analysis plan are also amended, accordingly.

Before this amendment (addendum #11), the trial was designed to have 95% power, at the one-sided 0.025 significance level, to reject the null hypothesis of no difference between Obs and R arms, given a true PFS Obs/R hazard ratio of 2.0 or more with 336 patients (accrued over 48 months and followed an additional 6 months) and 124 PFS events. The design incorporated 5 interim analyses and one final analysis for the PFS comparison. No interim analysis has been performed prior to this amendment.

9.2 Accrual

Accrual to E4A03, an ECOG study of newly diagnosed patients looking at treatment with lenalidomide and dexamethasone, reached a rate of 300 patients per year. For every 10 newly diagnosed myeloma patients, the study team feels there are 2 newly diagnosed SMM patients, equating to 60 newly diagnosed SMM patients per year. Of these newly diagnosed SMM patients, approximately 90% fall into intermediate and high risk class based on Kyle's definition which provides for 54 patients per year. Approximately 90% of these have abnormal

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free light chain (< 0.26 or > 1.65), however, we will conservatively estimate 65% enrollment. Therefore, the ECOG-ACRIN accrual rate to this study is expected to be 36 patients per year, or 3 patients per month. SWOG and other collaborative groups' contribution to accrual is estimated at 4 patients per month or 48 patients per year. Given an estimated accrual rate of 7 patients per month, we will accrue for 48 months to obtain 336 patients (168 on each arm) for the Phase III study.

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Based on observed accrual as of June 2015, the accrual rate is revised to 3-4 patients per month. With a new accrual target of 180 patients and approximately 87 patients remaining to be enrolled, it is anticipated enrollment will be completed in 24 months.

9.3 Phase II Study

A phase II group of patients will be enrolled all receiving lenalidomide at a fixed dose of 25 mg days 1-21 every 28 days to evaluate the early toxicity and tolerance of this dosing. Patients will be treated until progression or excessive

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toxicity. While all toxicities and dose modifications will be monitored, the primary endpoint for the phase II study will be grade 3 toxicity effecting vital organ function (such as cardiac, hepatic or thromboembolic) or any grade 4 or higher non-hematologic toxicity observed within 6 cycles of treatment. Toxicities

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evaluated will be based on CTEP-AERS expedited reporting. An acceptable toxicity rate is 15% and a toxicity rate of 30% or greater is considered unacceptable. 34 patients will be enrolled in the phase II cohort. If 9 or more patients experience toxicity as defined then the study will not continue. With this design, the probability of stopping early is 73.2% if the true but unknown toxicity rate is 30%, and 5.9% if the true rate is 15%. Accrual is expected to take approximately 5 months and the toxicity expected to be analyzed approximately 2-3 months after the last patient has completed 6 cycles of treatment.

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Thirty-six patients enrolled in the phase II study. Due to an error in the registration system, 8 additional patients were directly assigned to lenalidomide treatment. These 8 patients will be analyzed with the phase II cohort in the final analysis of study results, and in particular will be included in the final adverse event analyses. They may also be included in some correlative analyses. The final phase II cohort thus includes 44 patients.

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9.4 Primary Clinical Endpoint

The most clinically relevant endpoint for this high-risk SMM population is progression free survival (PFS) as defined by the ASH FDA consensus panel, where failure is defined as death or the appearance of symptomatic myeloma indicating treatment.(64) Following the ASH/FDA consensus, symptomatic MM is present or imminent end-organ damage characterized by hypercalcemia, renal insufficiency, anemia or bone disease related to the plasma cell proliferative process.(64) Our primary analysis is the comparison of progression-free survival (PFS) of high risk SMM patients treated with lenalidomide to those given no treatment. Patients will be randomized in equal proportions to R or Obs. Treatment will be assigned using permuted blocks within strata with dynamic balancing within main institution and their affiliate networks. PFS in each of the arms will be estimated using the method of Kaplan and Meier.(65) PFS between the two arms will be compared using a stratified log-rank test.(66)

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It is expected that the median PFS of patients on the Obs arm will be 24.8 months (hazard rate of 0.0279). The study is designed to detect a 60% reduction in hazard rate to 0.011. If PFS follows an exponential distribution, this difference corresponds to a 150% improvement in PFS to a median of 62 months. These rates are derived from studies cited earlier (more specifically a 2-yr progression rate of 41.5% for the obs arm based on the Dispenzieri study)(23),an NIH funded phase III trial of thalidomide plus zoledronic acid versus zoledronic acid alone at

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the Mayo Clinic and the Spanish SMM study (Mateos et al. Blood 2014). The primary analysis will be intention-to-treat analysis. Accrual duration is estimated at 45 months in order to obtain 180 patients (90 on each arm), and follow patients for an additional 9 months after closure to accrual. At this point, full information which is considered to be when 76 patients have progressed or died will be obtained.

With the expected accrual and failure rates above, the trial will have 96% power, at the one-sided 0.025 significance level, to detect a hazard ratio of 2.5 or more (for Obs versus R). By starting with such high power, the study is designed to accommodate potential treatment non-adherence. For example, if (a random) 5% of the patients on each arm cross over to the opposite treatment, then the ITT hazard ratio would be expected to be about 2.2 (when the true Obs vs R ratio for the full population is 2.5), and the design would still have about 91.1% power, and if 10% of the patients on each arm cross over to the opposite treatment, then the ratio would be decreased to about 1.97, and the ITT analysis would still have at least 78% power.

This design incorporates 5 interim analyses and one final analysis for the PFS comparison. The final analysis will occur at full information (76 patients progressed/died). This study incorporates a group sequential monitoring plan to adjust for sequential testing to stop early in favor of the alternative hypothesis. Once the trial reaches approximately 25% information, one analysis will be performed every 6 months to correspond with the scheduled Data Monitoring Committee (DMC) meeting. Critical values will be determined using a truncated version of the Lan-Demets error spending rate function corresponding to the O'Brien-Fleming boundary.(67) At each interim analysis, the null hypothesis of equal PFS rates on the two arms will be tested against the one-sided alternative

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of increased PFS on the R arm. The p-value from a one-sided stratified log-rank test will be compared to the critical value. At any of the interim analyses, if the null hypothesis is rejected, the DMC may consider closing the study. The table below gives the expected timing of the analyses and the critical values for rejecting the null hypothesis.

Repeated analysis	Time from Study Start (Months)	Information Time (%)	Failures under the Alternative Hypothesis	Nominal Significance level for Rejecting the Null Hypothesis
1	24	26	20	0.0005
2	30	39	29	0.0005
3	36	53	40	0.0015
4	42	69	52	0.0061
5	48	86	65	0.0130
6	54	100	76	0.0199

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In addition to monitoring the study for early stopping in favor of the alternative hypothesis of increased PFS on the R arm, the study will also be monitored for early stopping in favor of the null hypothesis of no significant increase in PFS on the R arm using the repeated confidence interval methodology similar to that described by Jennison and Turnbull.(68) At each interim analysis, a nominal one-sided (1-alpha) confidence interval around the hazard ratio (Obs over R) produced by the Cox proportional hazards model will be computed.(69) The alpha used to compute the confidence interval is the nominal significance level of the use function boundary at the information fraction at the particular analysis time. The target hazard ratio will be adjusted for observed treatment non-adherence. If at any of the analyses the confidence interval does not contain the target hazard ratio, the DMC may consider stopping the trial early for lack of treatment difference.

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9.5 Secondary Clinical Endpoints

Secondary endpoints for this study include response rate and duration of response among responders. Response rate (CR+PR) on the R arm will be calculated and a 95% confidence interval will be computed around the response rate. The maximum width of a 95% confidence interval around response rate would be 21.5%. Duration of response among responders will be estimated using the Kaplan-Meier method.(65) Cox proportional hazards model will be used to assess PFS outcome in multiple regression analyses of established prognostic factors.(69) Adverse events will be monitored on all patients and summarized by arm. The difference in rates of all Grade 3 or higher toxicities will be evaluated for all randomized patients using the Fisher's Exact Test.

Overall Survival (OS) in each of the arms will be estimated using the method of Kaplan and Meier.(65) OS between the two arms will be compared using stratified log-rank test. (66) Cox proportional hazards model will be used to estimate the hazard rate between arms (69). OS will be evaluated at month 90/ year 7.5 when there is adequate power. The estimated 3-year survival probability on the R arm is supposed to parallel the probability for the general population of persons aged over 65 years (93%). The 3-year survival probability for an untreated high-risk SMM population is estimated at 83%.(23) Assuming exponential distributions, these probabilities correspond to a median OS of 28.7 and 11.2 years. For this analysis, we assume the R treated high-risk SMM population has a slightly inferior hazard of death than the general population: 3-year survival probability of 91% (hazard rate=0.0315). This estimate is

unchanged although the Spanish study reported 93% survival after approximately 5 years of follow-up (Mateos et al. Blood 2014). In the first report (Mateos et al. NEJM 2013), the 3-year survival on the watchful waiting arm of the Spanish study was 80%. In the long-term update, 5-year survival was 67% corresponding to a median OS of 9.2y on the watchful waiting arm. In this redesign, the 3-year OS estimate for the Obs arm was thus reduced to 79%. If OS follows an exponential distribution, this corresponds to medians of 22 years (R) and 8.8 years (Obs). There is 81% power to detect this difference assuming a one-sided 0.025 significance level and 47 events out of n=180 patients at the time of analysis.

Overall Survival (OS) in each of the arms will be estimated using the method of Kaplan and Meier.(65) OS between the two arms will be compared using
Rev. 12/13 stratified log-rank test. (66) Cox proportional hazards model will be used to estimate the hazard rate between arms (69). OS will be evaluated at month 90/ year 7.5 when there is adequate power. The estimated 3-year survival probability on the R arm is supposed to parallel the probability for the general population of persons aged over 65 years (93%). The 3-year survival probability for an untreated high-risk SMM population is estimated at 83%.(23) Assuming exponential distributions, these probabilities correspond to a median OS of 28.7 and 11.2 years. For this analysis, we assume the R treated high-risk SMM population has a slightly inferior hazard of death than the general population: 3-year survival probability of 91% (hazard rate=0.0314). This estimate is unchanged and was confirmed with results from the Spanish study [ref]. The 3-year survival probability on the watchful waiting arm of the Spanish study, however, was 67%. Given the Spanish study was comprised of higher risk patients, a 3-year probability of 79% is assumed. If OS follows an exponential distribution, this corresponds to medians of 22 years (R) and 8.8 years (Obs). There is 81% power to detect this difference assuming a one-sided 0.025 significance level and 47 events out of n=180 patients at the time of analysis

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9.6 Stem Cell Mobilization

Patients are recommended to undergo stem cell mobilization with growth factors following 4 to 6 cycles of therapy. Successful mobilization defined as collection of $5x10^6$ cd34 cells per kilogram weight is an important outcome for patients treated with lenalidomide treatment. A growth factor mobilization failure rate of 10% is considered acceptable and a rate of 25% or less is unacceptable. Assuming 60% of patients on the lenalidomide arm opt for stem cell growth factor mobilization then there will be approximately 54 evaluable patients. An early stopping rule on the first 13 evaluable patients will be imposed. With 13 evaluable patients, if 3 or more patients fail, the study team will consider stopping this trial for an unacceptable growth factor mobilization failure rate. With this design based on exact binomial distribution, the probability of stopping early is 67% if the true but unknown failure rate is 25%, and 13% if the true rate is 10%.

9.7 Quality of Life

9.7.1 Primary QOL Endpoints

Quality of life assessment is performed in an identical fashion in both arms A and B and will be administered to both arms on the same schedule and frequency. The QOL assessment utilizing the FACT-

FWB+PWB and MMS instruments will first be administered at registration (+ 7 days) prior to initiation of treatment or observation. During the treatment or observation period, QOL will be measured every 6 cycles (day end + 7 days) and at the end of treatment or observation (+ 14 days). For patients that discontinue protocol therapy or go off observation early not due to disease progression, QOL will also be assessed at the next quarterly Long Term follow-up visit (+ 14 days). After this, these patients will not be followed further for QOL. Patients will be asked to complete the QOL questionnaire just prior to meeting with health care providers at scheduled visits. This should reduce the impact of health care related information upon perceived QOL.

The FACT-FWB+PWB PRO instrument has 14 items and the score ranges from 0-56. The primary endpoint for the QOL study will be defined as the mean change of the FACT-FWB+PWB score from registration (prior to randomization) to cycle 24. The null hypothesis is that the FACT-FWB+PWB mean change score between the two groups is the same over this time period. Based on the length of this PRO instrument, a minimal absolute difference in means change scores of the two arms of 4-6 is considered clinically significant between two groups.(70) Nevertheless, for this analysis the difference in drug-related QOL must be much greater to overcome a significant PFS benefit. The FACT- FWB+PWB domains are reported to have a standard deviation (SD) of 11. (Personal Correspondence with K. Yost dtd 12.26.08)

Differences in FACT-FWB+PWB mean change scores between the treatment arms from time of registration to cycle 24 that can be detected with 80% power are presented in following table. The expected hazard rates on each arm served to establish patients alive without PD at the end of the interval. Sensitivity for the % of patients alive without PD (n=55 patients given expected hazard rates) assumed to complete the questionnaire at the end of cycle 24 (compliance rates of 55%, 70%, 85%), allowing for slightly more variability in the instrument (11.0, 12.0) and assuming different correlation (0.4, 0.6, 0.8) between repeated measures was performed. For example, assuming a SD of 11.0 for the FACT-FWB+PWB, a correlation between repeated measures of 0.6 and using a two-sided t-test with a 0.05 significance level, there is sufficient power to detect a true difference in the FACT-FWB+PWB mean change score between the two arms of 7.3-9.2. Given our chosen interval for the primary endpoint and the reduced sample size with the redesign, we will only be able to detect large differences in mean change score between arms at expected compliance rate (70%).

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Differences detected with 80% power between Treatment Arms in Mean Change Score from Registration to end of Cycle 24: FACT-FWB+PWB

standard deviation (SD)	correlation	SD of change	55% compliance n=30	70% compliance n=38	85% compliance n=56
11.0	0.4	12.05	11.2	9.9	9.0
	0.6	9.84	9.2	8.1	7.3
	0.8	6.96	6.5	5.7	5.2
12.0	0.4	13.15	12.2	10.8	9.8
	0.6	10.73	10.0	8.8	8.0
	0.8	7.59	7.1	6.2	5.7

9.7.2 Secondary QOL Endpoints

We will also explore the impact of the differential treatment survival (PFS) on the quality of life at certain clinically meaningful time points. More specifically, we will first evaluate the difference in the FACT-FWB+PWB mean scores between patients that experience disease progression (PD) and patients who do not experience PD using mixed effects model, where the longitudinal scores were collected from the following eight intervals:

- Interval 1: (registration prior to randomization – end cycle 6)
- Interval 2: (beg cycle 7 - end cycle 12)
- Interval 3: (beg cycle 13 - end cycle 18)
- Interval 4: (beg cycle 19 - end cycle 24)
- Interval 5: (beg cycle 25 - end cycle 30)
- Interval 6: (beg cycle 31 - end cycle 36)
- Interval 7: (beg cycle 37 - end cycle 42)
- Interval 8: (beg cycle 43 - end cycle 48)

Patients are included in the analysis of an interval if they have not failed up to the beginning of the interval. During an interval, for those patients that experience PD or discontinue treatment due to other reasons, the QOL assessment at the time of progression/ discontinuation will be used and for those who survive the interval, the QOL assessment at the end of the interval is used. We will also perform sensitivity for patients that did experience PD during the interval with respect to change in QOL status since last QOL assessment. Given the expected high level of missingness in the QOL data, we will analyze that data according to the methods described in Schluchter and in Schluchter, Greene and Beck.(71, 72)

These methods take into account the possibility of informative missingness by jointly modeling the longitudinal response (here, QOL scores) and the time to dropout.

9.7.3 Exploratory QOL Endpoints

For both the PACT-FWB+PWB and MMS subscales, we will provide descriptive statistics and calculate Chronbach's alpha to assess reliability. Further we will assess the differences in the MMS between the two arms at cycle 24 visit. We also are interested in the relationships between individual elements of the FACT-PWB+FWB and the MMS instrument and important clinical measures in an effort to discern criterion validity. We will segment patients into clinical groups such as ECOG performance status 0-1 vs 2 that we expect to have significantly different scores and analyze these relationships with 1-way multivariate analysis of variance (MANOVA). When MANOVA is significant then a univariate analysis of variance is done on each dependent variable.

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9.8 Correlative Studies

Phase II correlative samples will be used for descriptive stats, assay validation, and for preliminary feasibility purposes.

9.8.1 Gene Expression Profiling

GEP will be evaluated at baseline and post-treatment at time of progression (or at off-study if patients discontinue protocol therapy for reasons other than progression). For patients randomized to the lenalidomide arm, comparisons will be made of their baseline GEP versus their post-treatment sample drawn as described above at the time of progression or off-study. Data preprocessing is the first step in microarray data analysis. This entails background adjustment, normalization (e.g., scaling and quantile normalization), and summarization. These tasks can be accomplished using various software such as MAS 5.0 from Affy, or the R packages affy, affycomp, gcrma, and affyPLM. Exploratory analyses will then be performed to examine the underlying distributions using box plots, density plots, scatter plots, etc. Next differential expression analysis of the two groups (baseline vs. off-study) will be performed. Since statistical tests will be conducted upon tens of thousands of genes simultaneously, the false discovery rate (FDR) will be used to control the percentages of false positives among selected genes.(73) Relevant tools for differential expression analysis include permutation procedures, SAM,(74) empirical Bayes methods, q-value, etc.(75, 76) Once significant genes have been identified, hierarchical clustering analysis will be performed to investigate any relation among the selected genes.(77) In this context we will also evaluate the role of DKK1 expression.

All of our calculations for the GEP correlative endpoints assume samples are obtained from all patients. To evaluate GEP as a prognostic marker, we will evaluate the difference in PFS outcome by GEP-defined risk group (high-risk vs standard-risk) within each arm (R and Obs) and overall. The table below presents the PFS hazard ratios with GEP-defined high risk being an unfavorable subtype that can be detected with 80% power assuming a 5% level of significance and

exponential distribution of events under various scenarios of high-risk subtype prevalence, sample size (overall vs. single arm) and PFS event estimates. The event count (n=123 PFS events) assumes the GEP analysis is done at 7.5 years from activation parallel with the timing of the overall survival analysis. For example, comparing patients with a high-risk sub-type to those with standard risk in the entire cohort of patients, the log rank test will have 80% power to detect a HR of 1.91 or greater if prevalence of high-risk subgroup is 15%. The HR narrows to 1.67 or greater if the prevalence is as high as 35%. Within a single arm, the number of PFS events is estimated as half the expected PFS information (n=62 events), 30% less (n=43 events) or 30% more (n=80 events). For example, comparing patients with a high-risk sub-type to those with standard-risk in the a single arm and a prevalence of 25%, there is 80% power assuming 0.05 significance to detect a hazard ratio ranging from 2.02-2.42 depending on the events estimate. This improves with greater prevalence.

Hazard Ratios: GEP Risk Group			
Scenario	**High-Risk subgroup prevalence**	**N events**	**Hazard Ratio (high-risk vs. standard-risk) alpha 0.05/0.10**
n=180 (all patients)			
	10%	123	2.11/1.96
	15%	123	1.91/1.78
	20%	123	1.80/1.69
	25%	123	1.73/1.63
	30%	123	1.69/1.60
	35%	220	1.67/1.58
n=90 (R or Obs arm)			
	25%	43	2.42/2.21
	25%	62	2.15/1,98
	25%	80	2.02/1.87

We will also explore the treatment effect within each GEP-defined risk group but will only be able to detect large treatment effects. The table below outlines the hazard ratios (Obs:R) that can be detected with 80% power assuming 5% significance and exponential distribution of events under different prevalence and event scenarios. For example, if the high-risk group has a prevalence of 15% and if 90% of patients in that group experience a PFS event (13% of total events) then the HR is 4.72. If 60% of patients in that group experience a PFS event (20% of total events) then the HR is 3.60.

Hazard Ratios: Treatment Effect				
Scenario	High-Risk subgroup prevalence	N patients	% Total events	Hazard Ratio (Obs vs R) alpha 0.05/0.10
High-Risk				
	15%	27	13%	4.72/3.83
	15%	27	20%	3.16/2.78
	25%	45	22%	3.13/2.72
	25%	45	33%	2.41/2.18
	35%	63	31%	2.57/2.30
	35%	63	46%	2.11/1.94
Standard-Risk				
	85%	286	87%	1.73/1.62
	85%	286	80%	1.77/1.66
	75%	252	78%	1.78/1.68
	75%	252	67%	1.87/1.74
	65%	218	69%	1.85/1.72
	65%	218	54%	2.03/1.87

9.8.2 Immune Function

In a recent SWOG study, immune function as measured by SOX-2 has been studied. In that patient population, a large difference in progression-free survival for SOX-2 positive versus SOX-2 negative patients was found. SOX-2 positive patients experience much longer progression-free survival (HR=0.15, p=0.01). In this study, we will evaluate whether this observation can be generalized. At baseline, approximately 2/3 of patients will be SOX-2 negative versus 1/3 of patients being SOX-2 positive. Given 33% prevalence of SOX-2 positive, analysis at 7.5y, and full sample yield, this study has 80% power to detect HR of 0.33, 0.43, and 0.50 or lower if the number of events in the R-treated arm are n=43 events, n=62 events, and n=80 events, respectively given 5% significance (0.38, 0.48 and 0.54 with 10% significance). Changes in immune expression with R therapy will be evaluated only by descriptive statistics for hypothesis generation.

9.8.3 Radiologic Studies (MRI)

The presence of focal lesions on MRI has emerged as an important predictor of outcome in MM. (11) All consenting patients will undergo an MRI scan at baseline in order to evaluate the number of focal lesions. The data about the presence of focal lesions on baseline MRI studies will be analyzed and correlated with clinical outcome. We will analyze the difference in response rates (CR/PR) between R only patients with abnormal versus normal MRI using the Fisher's exact test assuming a target overall response rate of 30% and 5% level of significance. The Fisher's exact test will have approximately 89% power to detect a difference in response of at least 31% between those with abnormal MRI and those without abnormal MRI if the prevalence of MRI abnormality is 40% and power of 78% with prevalence of 20%.

9.8.4 Cytogenetic Abnormalities

Based on Dr. Fonseca's research, patients with t(4;14) or t(14;16) or 17p13 deletion will be classified as High Risk ("HR-SMM"). In symptomatic MM, the prevalence of these cytogenetic abnormalities is approximately 25%. Since these abnormalities are believed to occur at the onset of disease course, the prevalence in a SMM population should also be 25%. The remainder of the population is classified as Standard Risk ("SR-SMM"), with a prevalence of 75%. The primary analysis will center on the comparison of HR-SMM to SR-SMM. Full event information for the primary PFS endpoint is n=76 events given 45 months of accrual and 6 months of follow up. Assuming overall lab sample submission yield of 55% to full event information, we will have approximately n=42 events. There will be 80% power with the logrank test to detect a hazard ratio (HR) comparing High-Risk vs. Standard-Risk cytogenetic groups of 2.43 and 2.21 with significance of 5% and 10%, respectively. The increased risk conferred on the HR-SMM population is within expectations. Additionally, distributions by High- and Standard-Risk cytogenetic groups will be estimated using the method of Kaplan and Meier. Post-treatment samples are collected since unlike t4;14 and t14;16, the deletion of 17p- can be late event and may be captured only at the time of disease progression. We will provide descriptive statistics on data from post-treatment samples.

9.9 Gender and Ethnicity

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Based on previous data from E4A03 the anticipated accrual in subgroups defined by gender and race is (phase III only):

Ethnic Category	**Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	1	4	5
Not Hispanic or Latino	84	91	175
Ethnic Category: Total of all subjects	85	95	180
Racial Category			
American Indian or Alaskan Native	1	0	1
Asian	2	0	2
Black or African American	12	9	21
Native Hawaiian or other Pacific Islander	0	0	0
White	70	86	156
Racial Category: Total of all subjects	85	95	180

9.10 Study Monitoring

This study will be monitored by the ECOG-ACRIN Data Monitoring Committee (DMC). The DMC meets twice each year. For each meeting, all monitored studies are reviewed for safety and progress toward completion. When appropriate, the DMC will also review interim analyses of outcome data. Copies of the toxicity reports prepared for the DMC meetings are included in the study

reports prepared for the ECOG-ACRIN group meeting. These group meeting reports are made available to the local investigators, who may provide them to their IRBs. Only the study statistician and the DMC 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 DMC. Any DMC 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 DMC Policy can be obtained from the ECOG-ACRIN Operations Office - Boston.

10. Correlative Studies

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NOTE: An informed consent must be signed prior to the submission of any samples for any laboratory studies and/or banking. Samples for the optional laboratory studies and/or banking should be submitted only from patients who have given written consent for the use of their samples for these purposes.

NOTE: Institutions outside of the United States and Canada must confer with the receiving laboratory and the ECOG-ACRIN Operations Office - Boston regarding logistics for submission of fresh samples.

NOTE: ECOG-ACRIN requires that all biological samples submitted be entered and tracked via the online ECOG-ACRIN Sample Tracking System. An STS shipping manifest form must be generated and shipped with the sample submissions. See Section 10.5.

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10.1 Bone Marrow and Peripheral Blood for Laboratory Studies at Mayo Clinic

The goal of the planned laboratory correlative studies is to better understand the impact of certain cytogenetic characteristics with differential risk of progression given respective treatments. Specifically, we will evaluate the impact of the high-risk cytogenetics which includes patients with t(4;14)(p16;q32), t(14;16)(q32;q23), and those having 17p deletions, all of which we hypothesize will adversely affect the risk of progression.

Biologic features of patients will be performed by assessing the molecular cytogenetic category by FISH. This analysis will be performed at the Mayo Clinic – Arizona, under the direction of Dr. Rafael Fonseca.

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The slide based bone marrow plasma cell labeling index (PCLI) is now being determined by a cytometric flow procedure (PCPRO). This technique provides identification of clonal plasma cells and cells in S-phase of the cell cycle.

Circulating plasma cells will be assessed by a CD38/CD45 immunofluorescence flow cytometry assay.

The Beta-2-Microglobulin levels are ascertained using an automated system based on nephelometry.

These studies will be performed at the ECOG-ACRIN Myeloma Reference Core Laboratory at Mayo Clinic.

10.1.1 Sample Submission Schedule

Collect samples of peripheral blood, bone marrow aspirates and bone marrow core biopsy slides at:

Rev. 7/14

- Preregistration
- At study discontinuation or progression, whichever comes first

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NOTE: Pre-study samples for research should be collected at the same time as the diagnostic blood and bone marrow studies that are required to establish the diagnosis of myeloma and determine eligibility. Additional procedures to collect the research specimens should not be required.

10.1.2 Sample Preparation Guidelines

Rev. 2/12, 12/13

Myeloma Tumor Biology Kits are available to order, and will include materials necessary for the preparation and shipment of samples. Three separate kits will be provided per time point for the samples being sent to Mayo Clinic, University of Arkansas, and Yale University.

Rev. 2/12

Kits should be ordered at least 24 hours in advance of each sample time point. To order kits call Kim Henderson - Mayo Myeloma Clinic Reference Laboratory at (507) 284-3805 or e-mail henderson.kimberly@mayo.edu.

Any questions concerning sample collection and shipments can be directed to Kim Henderson - Mayo Reference Laboratory at (507) 284-3805.

10.1.2.1 Peripheral Blood

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Draw 14 mL of peripheral blood into two (2) ACD Vacutainer tubes (yellow top). Provided in the kit. Ship day of collection.

Collect 5-7 mL of peripheral blood into red top serum separator tube (e.g., SST®; Becton-Dickinson). Tubes must be centrifuged at 1000g for 10 minutes.

10.1.2.2 Bone Marrow Aspirate

This redirect bone marrow aspirate should be drawn at the same time that a 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 sample was obtained.

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Draw one (1) 7mL of redirect bone marrow aspirate into an ACD vacutainer tube (yellow top).

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10.1.2.3 [Deleted in Add#7]

10.1.2.4 Bone Marrow Core Biopsy Slides

5 air-dried, unstained “charged” slides from the paraffin block of the bone marrow core biopsy. **EXCEPTION:** Core biopsy slides can be mailed later if they are not available at the time of shipping.

Rev. 2/12

10.1.3 Shipping Guidelines

Log the samples into the ECOG-ACRIN Sample Tracking System (STS) the day of shipment. If the STS is unavailable, an Generic Specimen Submission Form (#2981) must be submitted with the samples, along with the Patient Information Form (Appendix III). Once STS is available, retroactively log the shipment into STS using the actual collection and shipping dates.

Rev. 7/14

If your shipment was not logged into the ECOG-ACRIN STS please call Kim Henderson at (507) 284-3805 or e-mail Henderson.Kimberly@mayo.edu to notify the laboratory when

samples are being shipped. Indicate the ECOG-ACRIN protocol number, the FedEx tracking number, and name and phone number of the contact person.

Samples are to be shipped day of collection. The specimens from multiple patients may be shipped together, but must be placed in separately labeled tubes and bags. All specimens must be clearly labeled with the protocol number E3A06, the patient's initials (last name, first name), ECOG-ACRIN patient ID number, date of collection, and type of sample (PB or BM). **A current white blood count and differential** should be included with each submission, entered via the Sample Tracking System.

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Specimens should be mailed the day they are obtained and shipped overnight to arrive during normal working hours. Follow packing guidelines listed in the kits. If samples are sent late in the week and will arrive on the weekend, please note "Saturday Delivery" on the Federal Express form.

FRIDAY AND PRE-HOLIDAY SHIPMENTS SHOULD BE AVOIDED.

It is requested that the bone marrow core biopsy slides be sent with the other samples in the Myeloma Tumor Biology Kit. However, they may be shipped separately, within one month of the collection, if they cannot be prepared on the same day as the other samples are collected.

Complete the specimen ID label on each tube. Each tube must be clearly labeled. Each sample should be labeled with the protocol number E3A06, the patient's initials (last name, first name), ECOG-ACRIN patient ID number and sample type (peripheral blood (PB) or bone marrow (BM)).

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- Place the slightly thawed Kool-PAK in 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 specimen 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 specimen(s) directly on the ice pack.
- Place the Styrofoam container and the Sample Tracking System Shipping Manifest Form within the cardboard mailing sleeve.

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- 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 priority overnight delivery the same day collected.
- Notify Federal Express for pick-up and/or leave package at the designated FedEx drop-off location.

Please call Kim Henderson at (507) 284-3805 or email henderson.kimberly@mayo.edu to notify the Mayo Clinic Myeloma

Reference Laboratory when specimen(s) are being shipped. The samples in the Myeloma Tumor Biology kit should be shipped to the following:

Kim Henderson
Mayo Clinic Myeloma Reference Laboratory
613 Stabile
200 First Street Southwest
Rochester, MN 55905

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

Rev. 2/12

Samples shipped to the Mayo Clinic Myeloma Reference Laboratory will be used for studies done at the Tumor Biology Laboratory.

10.2 Bone Marrow for Gene Expression Profiling (GEP) – University of Arkansas

Molecular testing is important in a variety of ways for patients with myeloma. *(1-6)* Gene expression profiling (GEP) has revealed important underlying biology such as DKK-1 expression. *(1)* In addition, GEP patterns have allowed the identification of 7 molecular subgroups of disease (Zhan et al., 2006) and identified both high and low risk disease in these subgroups as well as localizing critical genes to particular segments of chromosome 1q and 1p *(2-6)*

GEP analysis of CD138 purified plasma cells will be performed to determine the disease subtype and risk category patients fall into using the molecular classification model as well as the 70-gene risk model developed by Dr. Shaughnessy. Multivariate Cox-regression will then be used to determine whether the risk-category as determined by the 70-gene model can be validated in the cooperative-group setting.

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New unpublished data from Dr. Epstein's laboratory have now also identified genes expression patterns in whole bone biopsies that are predictive of outcome that is capable of detecting more high risk than identified with the 70-gene model on purified plasma cells. This is a potentially important advance in the use of GEP in the clinical management of the disease as biopsies do not require extensive processing as bone marrow biopsies do not require the extensive processing required for isolating tumor cells from bone marrow aspirates and can be flash frozen at the time of procurement and shipped to the core facility. Thus, GEP of tumor cells and whole bone biopsies in the intergroup setting will be performed with the following sub-aims:

1) To determine whether GEP signatures, i.e. 7-group model, DKK1, high-risk as defined by a validated 70-gene GEP model, of tumor cells isolated from bone marrow aspirates taken at enrollment exhibit significant associations with EFS/OS in the lenalidomide arm and/or rate progression in the observational arm.

Rev. 2/12

2) To determine whether GEP signatures of the bone microenvironment derived from whole bone biopsies can be related to EFS/OS on the lenalidomide arm and/or progression in the observational arm.
3) Determine whether a 20-gene risk signature derived from whole biopsies from patients on TT3 can be predictive of outcome following lenalidomide

treatment and if the same score is related to risk of progression in the observational arm

4) Once in CR or n-CR, use GEP of whole bone biopsies to determine whether the "normalization" of GEP signatures can be used as an indication of profound tumor cytoreduction with durable EFS.

Gene expression profiling has emerged as a powerful means of disease classification and risk stratification in multiple myeloma. Dr. Shaughnessy and the University of Arkansas Medical Sciences have previously identified and validated the existence of 7 distinct subtypes of myeloma each exhibiting distinct clinical features and survival times. They have also recently defined and validated in numerous trial settings, the existence of a high risk entity present in approximately 15-20% of newly diagnosed disease, that is not benefiting from any of the current treatment strategies employed. In a comparison of the outcomes of these various molecular entities in newly diagnosed disease treated on the clinical trials Total Therapy 2 versus Total Therapy 3, they have shown that while high risk disease within each of the 8 molecular entities does not benefit from the changes in protocol design in Total Therapy 3, e.g. addition of Velcade upfront and throughout therapy and shorted induction and consolidation time frames, the low risk form of the MS or t(4;14)-positive disease is experiencing a dramatic benefit in both EFS and OS (Pineda et al., 2007 or 8). Moreover, exciting new data is emerging that suggests that GEP signatures of the tumor and its microenvironment, as seen in the analyses of whole biopsies, can be a strong prognostic variable in TT3 trials at UAMS. Thus this study is interested in whether the combination of lenalidomide with other new agents will have an effect on molecularly defined subgroups and risk groups defined by GEP of the tumor cell alone and tumor-host microenvironment, with the hope that its inclusion will benefit high-risk disease. Finally, unpublished data emerging from the S0120 trial suggests that elevated expression of the gene coding for *DKK1* is significantly correlated with the risk of progression of MGUS/SMM to symptomatic MM. Expression of *DKK1* mRNA in tumor cells and DKK1 protein in BM serum isolated from **E3A06** will be correlated with bone disease and outcome.

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This analysis will be performed at the University of Arkansas, under the direction of Dr. Joshua Epstein.

10.2.1 Sample Submission Schedule

Collect samples of bone marrow aspirate and bone marrow biopsy core at:

Rev. 7/14

- Preregistration
- At study discontinuation or progression, whichever comes first

Rev. 7/14

NOTE: Pre-study samples for research should be collected at the same time as the diagnostic blood and bone marrow studies that are required to establish the diagnosis of myeloma and determine eligibility. Additional procedures to collect the research specimens should not be required.

To obtain a high quality sample not affected by dilution effects from PBL contamination, the gene array sample should be taken as part of diagnostic marrow. *Making sure*

that the sample is taken with diagnostic sample will increase the likelihood that sufficient number of malignant CD138-positive tumor cells will be isolated and therefore preclude a request for another sample. If there are insufficient plasma cells in the sample to perform gene array, an additional bone marrow pull may be requested.

10.2.2 Sample Preparation Guidelines

All submitted specimens must be labeled with the ECOG-ACRIN protocol number (E3A06), ECOG-ACRIN patient ID number, patient's initials (last name, first name), and date of specimen collection, also note on label "for separation for GEP."

Kits are available to order for the collection and shipment of the samples, please refer to Section 10.1.2 for guidelines and Appendix IV "Bone Marrow Aspirate Kit University of Arkansas" and Appendix XI "Bone Marrow Core Biopsy Kit University of Arkansas" for specimen checklist and shipping instructions.

10.2.2.1 Bone Marrow Aspirate

Bone Marrow (BM) should be drawn from iliac crest so that it is immediately diluted in EDTA anticoagulant. BM, 10-20mL, should be drawn at a ratio of 4:1 - BM to EDTA. Sample should be gently mixed and immediately stored on ice. BM should be tightly packed with wet ice in Styrofoam cooler. The samples should be in the center of cooler volume so that ice is on all sides. Sample should be shipped priority overnight. **Because of shipping and receiving requirements, bone marrow aspirates should not be taken on Fridays, Saturdays or Sundays. All specimens should be drawn and shipped Monday - Thursday.**

10.2.2.2 Bone Marrow Biopsy Core

A portion of the bone marrow biopsy core should be submitted for research genomic evaluation studies. Bone marrow biopsy core of sufficient length (1-2cm) should be taken **prior to the aspirate**. PBL is removed by touching to sterile swab and placed in 1.5 ml chilled eppendorf cyrotube. Bone marrow biopsy cores must be snap-frozen immediately after resection by dropping into liquid nitrogen (if possible) or placed in dry ice. The frozen cores should then be transferred into a tube that has been kept on dry ice to prevent thawing of the core, and either immediately shipped on dry ice or stored at -70°C and batch shipped at a later date on dry ice via Federal Express.

10.2.3 Shipping Guidelines

Log the samples into the ECOG-ACRIN Sample Tracking System (STS) the day of shipment. If the STS is unavailable, an Generic Specimen Submission Form (#2981) must be submitted with the

samples. Once STS is available, retroactively log the shipment into STS using the actual collection and shipping dates.

Samples are to be shipped day of collection. The specimens from multiple patients may be shipped together, but must be placed in separately labeled tubes and bags.

Specimens should be mailed the day they are obtained and shipped overnight to arrive during normal working hours. Specimens must be mailed Sunday through Wednesday using Federal Express or other overnight priority delivery to arrive on Monday through Thursday (no later than 12:00 p.m. on Thursday) Follow packing guidelines listed in the kits.

Aspirate sample should be shipped overnight courier on wet ice ensuring that enough ice or cold packs are present so that the sample will never go to room temperature.

Biopsies must be shipped by overnight courier with sample buried in dry ice.

FRIDAY AND PRE-HOLIDAY SHIPMENTS SHOULD BE AVOIDED.

1. The specimen must be wrapped in an absorbable material.
2. The specimen must be placed in an AIRTIGHT container (like a re-sealable bag).
3. Pack the re-sealable bag and specimen in a Styrofoam shipping container.
4. Pack the Styrofoam shipping container in a cardboard box.
5. The cardboard box must be marked as "BIOHAZARD".

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Please contact Shayu Deshpande at sdeshpande@uams.edu or (501) 526-6990 ext. 8941 to notify them when specimen(s) are being shipped.

Bone marrow specimens for GEP should be shipped to the following address:

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University of Arkansas for Medical Sciences
Attn: Shayu Deshpande
Rockefeller Cancer Institute, Room 940
4301 W Markham, Slot 724
Little Rock, AR 72205-7199
Phone: (501) 526-6990 ext. 8941

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

10.3 Specimens for Immunology Testing – Yale University

Studies from the Dhodapkar lab and others have extensively characterized the changes in immune effector cells in MM. Immune system is currently thought to be a major target of these “immune modulatory drugs”, although the precise mechanism of the effects and their correlation with clinical outcome remains unclear. Most studies with revlimid in MM now utilize combination therapies. Therefore the effects of the drug are difficult to ascertain. As discussed

previously, this trial therefore provides an unprecedented opportunity to prospectively evaluate this issue in the context of a controlled study with single agent revlimid. Two aspects are of particular interest in this trial.

- Changes in antigen specific T cell function, particularly those against stem cell associated antigens such as SOX2, and selected cancer-testis antigens *(7-9)*. T cell immunity will be analyzed using overlapping peptide libraries using methods as described previously.
- Changes in number and activation status of natural killer and natural killer T (NKT) cells, analyzed using flow cytometry, using methods as described previously by the Dhodapkar lab. *(10,11)*

The presence of spontaneous T cell immunity to SOX2, an embryonal stem cell antigen that marks putative stem cells in MM, correlates with risk of progression. We hypothesize that these features will correlate with response to Revlimid and risk of disease progression. Finally, this trial also provides an unprecedented opportunity to evaluate the changes in immune effector cells as well as changes in gene expression in response to single agent Revlimid in patients with early MM.

This analysis will be performed at Yale University, under the direction of Dr. Madhav Dhodapkar.

10.3.1 Sample Submission Schedule

Collect samples of peripheral blood and bone marrow aspirate at:

Rev. 7/14

- Preregistration
- At study discontinuation or progression (whichever comes first)

Rev. 7/14

NOTE: Pre-study samples for research should be collected at the same time as the diagnostic blood and bone marrow studies that are required to establish the diagnosis of myeloma and determine eligibility. Additional procedures to collect the research specimens should not be required.

10.3.2 Sample Preparation Guidelines

All submitted specimens must be labeled with the ECOG-ACRIN protocol number (E3A06), ECOG-ACRIN patient ID number, patient's initials, and date of specimen collection.

Kits are available to order for the collection and shipment of the samples, please refer to Section 10.1.2 for guidelines and Appendix X "Bone Marrow Aspirate and Peripheral Blood Kit-Yale University" for specimen checklist and shipping instructions.

- Peripheral blood: Collect four (4) 10mL green top tubes (sodium heparin anti-coagulant).
- Bone marrow aspirate: Collect 5-10mL of bone marrow aspirate in one (1) sodium heparin coagulant (green top tube).

Questions regarding immunology specimens/shipment should be directed to Lin Zhang at (203) 737-5176 or lin.zhang@yale.edu.

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10.3.3 Shipping Guidelines

Log the samples into the ECOG-ACRIN Sample Tracking System (STS) the day of shipment. If the STS is unavailable, an Generic Specimen Submission Form (#2981) must be submitted with the samples. Once STS is available, retroactively log the shipment into STS using the actual collection and shipping dates.

The specimens should be shipped the same day as collection. The specimens from multiple patients may be shipped together, but must be placed in separately labeled tubes and bags. Follow packing guidelines listed in the kits.

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Specimens must be mailed on Sunday through Wednesday using EshipGlobal to arrive on Monday through Thursday (no later than 12:00 p.m. on Thursday). Avoid Friday or preholiday shipments. **Tubes should be sent at room temperature (NOT frozen).**

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Please contact Lin Zhang at the Dhodapkar lab at (203) 737-5176 or lin.zhang@yale.edu prior to sending the shipment as she will need to print the shipping label and either fax or e-mail to the person sending the samples to the lab.

Specimens should be submitted to:

Madhav Dhodapkar, M.D. – Yale University
Dhodapkar Lab
Nathan Smith Bldg, Room NSB-287B
Yale School of Medicine
333 Cedar Street
New Haven, CT 06510

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

10.4 Banking

The residuals and/or derivatives of samples collected for this study will be retained at the Mayo Tumor Biology Laboratory for possible use in future ECOG-ACRIN approved studies. If future use is denied or withdrawn by the patient, the samples will be removed for consideration for use in any future study.

10.5 ECOG-ACRIN Sample Tracking System

It is **required** (barring special circumstances) that all samples submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). 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 samples required for this study, please access the Sample Tracking System software by clicking https://webapps.ecog.org/Tst

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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.

Rev. 12/13 A shipping manifest form must be generated and shipped with all sample submissions.

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

10.5.1 Study Specific Notes

10.5.1.1 An Generic Specimen Submission Form (#2981) will be required only if STS is unavailable at time of sample submission. Indicate the appropriate Lab ID # on the submission form:

- 0005 = ECOG-ACRIN Myeloma Core Laboratory
- Rev. 2/12 159 = University of Arkansas
- Rev. 2/12 158 = Yale University

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

Rev. 2/12 10.6 Sample Inventory Submission Guidelines

Inventories of all samples collected, aliquoted, and used on the above mentioned laboratory correlative studies will be submitted electronically by secure web application to the ECOG-ACRIN Operations Office - Boston on a monthly basis, or upon request by any laboratory holding and/or using any specimens associated with this study.

Rev. 2/12 10.7 Lab Data Transfer Guidelines

The data collected or generated on the above mentioned laboratory correlative studies will be submitted electronically via secure data portal to the ECOG-ACRIN Operations Office - Boston by the central laboratories on a quarterly basis. The quarterly cut-off dates are March 31, June 30, September 30 and December 31.

11. Records to Be Kept

Please refer to the E3A06 Forms Packet for the forms submission schedule and copies of all forms. The E3A06 Forms Packet may be downloaded by accessing the ECOG World Wide Web Home Page (http://www.ecog.org). Forms must be submitted to the ECOG-ACRIN Operations Office - Boston, FSTRF, 900 Commonwealth Avenue, Boston, MA 02215 (ATTN: DATA).

This study will be monitored by the CTEP Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly from the ECOG-ACRIN Operations Office - Boston to CTEP by electronic means.

11.1 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.

12. Patient Consent and Peer Judgment

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

13. References

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Randomized Phase III Trial of Lenalidomide Versus Observation Alone in Patients with Asymptomatic High-Risk Smoldering Multiple Myeloma

Appendix I

Informed Consent Template for Cancer Treatment Trials (English Language)
[Deleted in Addendum #7]

INFORMED CONSENT INTENTIONALLY REMOVED FROM PROTOCOL DOCUMENT

Appendix I was removed from the protocol document in Addendum #7 and is posted as a separate document on the ECOG website. This was removed from the protocol to comply with NCI formatting guidelines.

Randomized Phase III Trial of Lenalidomide Versus Observation Alone in Patients with Asymptomatic High-Risk Smoldering Multiple Myeloma

Rev. 7/14

Appendix II

Patient Thank You Letter

[PATIENT NAME] [DATE]
[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important clinical trial. Trials like this offer a chance to get the best care while helping us make better care available for all patients. Many questions remain unanswered in myeloma. With the participation of people like you in clinical trials, we will improve treatment and quality of life for those with your type of cancer.

We believe this program will provide you with high quality, thorough care. Your physician and research staff will maintain very close contact with you. This is important to allow your physician to provide you with the best care while learning as much as possible to help you and other patients.

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

Sincerely,

[PHYSICIAN NAME]

Randomized Phase III Trial of Lenalidomide Versus Observation Alone in Patients with Asymptomatic High-Risk Smoldering Multiple Myeloma

Appendix III

Myeloma Tumor Biology Kit

Specimen Checklist and Shipping Instructions

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

Kit Contents:

- 5 lb Styrofoam box and cardboard mailing sleeve
- Patient Information Form
- FedEx Airbill with pre-printed return address
- 7mL ACD (yellow top) collection tubes
- SST (serum separator tube) collection tube

Rev. 7/13
- [Deleted in Addendum #7]
- Four (4) zip lock specimen bags labeled for bone marrow and peripheral blood

Rev. 2/12
- (1) Ice pack. 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 specimens for shipment.

Packing and Shipping Instructions:

1. Collect the following specimens:

Rev. 2/12
- Peripheral blood – Draw two (2) 7mL ACD tubes (yellow top).

Rev. 2/12
- Peripheral blood – Draw one (1) 7mL SST tube. Centrifuge tube at 1000g for 10 minutes.

Rev. 2/12, 7/13
- Bone Marrow aspirate - Draw 7mLs of a 'redirect' bone marrow aspirate in one (1) ACD tube (yellow top).

Rev. 7/13
- [Deleted in Addendum #7]

Rev. 2/12
- Bone marrow core biopsy slides– 5 air-dried, unstained biopsy slides. Exception: Unstained core biopsy slides can be mailed later if they are not available at the time of shipping the bone marrow aspirate and peripheral blood.

2. Place the slightly thawed Kool-PAK in bottom of Styrofoam container.
3. Place absorbent toweling on top of Kool-PAK.
4. 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 specimen(s) directly on the ice pack.

Rev. 2/12
5. Place the Styrofoam container and the Sample Tracking System Shipping Manifest Form within the cardboard mailing sleeve.
6. Prepare the package for shipping, applying packing tape as needed. Complete the sender portion of the return FedEx Airbill and adhere to the exterior lid of the box. Ship specimens via overnight delivery the same day collected.
7. Notify Federal Express for pick-up and/or leave package at the designated FedEx drop-off location.

Rev. 7/14 **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 Kim Henderson at (507) 284-3805 or e-mail Henderson.Kimberly@mayo.edu to notify the laboratory when samples are being shipped.** Indicate the ECOG-ACRIN protocol number, the FedEx tracking number, and name and phone number of the contact person. The blood samples in prepared kits should be shipped to the following:

The samples in this prepared kit should be shipped to the following:

Kim Henderson
Mayo Clinic Myeloma Reference Laboratory
613 Stabile
200 First Street Southwest
Rochester, MN 55905

Patient Information Form

It is required that samples submitted from patients participating in E3A06 be entered and tracked via the online ECOG-ACRIN Sample Tracking System (see Section 10.2). 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: _____/_____/_____

Institution/Affiliate: _____

Physician: _____

Patient Initials (last name, first name): _____

Rev. 7/14 ECOG-ACRIN Parent Protocol #: E3A06

ECOG-ACRIN Patient Sequence #: _____

Contact Person: _____

Institution: _____

Address: _____

City _____ State _____ Zip _____

Phone #: _____

Fax #: _____

PLEASE INCLUDE A CURRENT WHITE BLOOD COUNT AND DIFFERENTIAL

WBC: _____

% of Lymphocytes: _____

% of Monocytes: _____

Please indicate which samples are being shipped at this time:

Rev. 7/14
1. Preregistration
2. At study discontinuation or progression; whichever comes first

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

Kim Henderson
Mayo Clinic Myeloma Reference Laboratory
(507) 284-3805
henderson.kimberly@mayo.edu

Affiliates who anticipate participating in this study should please call in advance for kits.

Randomized Phase III Trial of Lenalidomide Versus Observation Alone in Patients with Asymptomatic High-Risk Smoldering Multiple Myeloma

Appendix IV

Bone Marrow Aspirate Kit – University of Arkansas

Specimen Checklist and Shipping Instructions

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

Kit Contents:

- Styrofoam box and cardboard mailing sleeve
- FedEx Airbill with pre-printed return address
- 10mL EDTA (purple top) collection tubes
- Zip lock specimen bags

Packing and Shipping Instructions:

1. Collect the following specimens:
   - Bone Marrow Aspirate - Draw 10-20 ml of a 're-direct' bone marrow aspirate and place in EDTA (purple top) tubes. **Samples should be gently mixed and immediately stored on ice.**
2. Specimens should be labeled with ECOG-ACRIN protocol number (E3A06), ECOG-ACRIN patient ID number, patient's initials (last name, first name), and date of specimen collection.
3. Place specimens in their individual plastic bags and place in the Styrofoam cooler tightly packed with wet ice OR with cold packs. **Samples should be in the center of the cooler so ice is on all sides.**
4. Place the Styrofoam container and the Sample Tracking System Shipping Manifest Form within the cardboard mailing sleeve.
5. Prepare the package for shipping, applying packing tape as needed. Complete the sender portion of the return FedEx Airbill and adhere to the exterior lid of the box. Ship specimens via overnight delivery the same day collected.
6. Notify Federal Express for pick-up and/or leave package at the designated FedEx drop-off location.

Rev. 2/12, 2/16 **Please contact Shayu Deshpande at sdeshpande@uams.edu or (501) 526-6990 ext. 8941 to notify them when specimen(s) are being shipped.**

The samples in this prepared kit should be shipped to the following:

University of Arkansas for Medical Sciences
Rockefeller Cancer Institute, Room 940
Rev. 2/16 Attn: Shayu Deshpande
4301 West Markham, Slot 724
Little Rock, AR 72205-7199

Randomized Phase III Trial of Lenalidomide Versus Observation Alone in Patients with Asymptomatic High-Risk Smoldering Multiple Myeloma

Appendix V

Patient Pill Diary

Please use this diary to record your daily protocol medication. Use the space below marked "Comments" 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.)

Rev.7/13

Day	Date	# of 5 mg Lenalidomide capsules taken	# of 25 mg Lenalidomide capsules taken	Aspirin daily or other recommended prophylaxis	Comments
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					
23					
24					
25					
26					
27					
28					

Patient/Administrator Signature:_____ Date: _____

Randomized Phase III Trial of Lenalidomide Versus Observation Alone in Patients with Asymptomatic High-Risk Smoldering Multiple Myeloma

Rev. 8/11, 1/16

Appendix VI

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.

Criteria for females of childbearing potential (FCBP)

Rev. Add14 This protocol defines a female of childbearing potential as a woman 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).

Counseling

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

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 4 weeks before starting study treatment, throughout the entire duration of study treatment, dose interruption and 28 days after the end of study treatment
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She understands the need to commence the study treatment as soon as study drug is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing based on the frequency outlined in this protocol
- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide

The investigator must ensure that for females of childbearing potential:

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

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

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

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

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

Contraception

Females of childbearing potential (FCBP) 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 subject. Periodic abstinence [eg 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 study drug; 2) while participating in the study; 3) during dose interruptions; and 4) for at least 28 days after study treatment discontinuation.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. FCBP must be referred to a qualified provider of contraceptive methods if needed. The following are examples of highly effective and additional effective methods of contraception:

- 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
- Additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

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

Pregnancy testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for females of childbearing potential, including females of childbearing potential who commit to complete abstinence (true abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception), as outlined below.

Before starting study drug

Female Patients:

FCBP 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 study doctor has verified that the results of these pregnancy tests are negative.

Male Patients:

Must practice complete abstinence (true abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg 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 female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 28 days following study drug discontinuation, even if he has undergone a successful vasectomy.

During study participation and for 28 days following study drug discontinuation

Female Patients:

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

Male Patients:

- Counseling about the requirement for complete abstinence (true abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception) or condom use during sexual contact with a pregnant female or a female of childbearing potential and the potential risks of fetal exposure to lenalidomide must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in the partner of a male study patient during study participation, the investigator must be notified immediately.

Additional precautions

- Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to the study doctor at the end of treatment.
- Female patients should not donate blood during treatment, during dose interruptions, and for at least 28 days the last dose of lenalidomide.
- Male patients should not donate blood, semen or sperm during treatment, during dose interruptions, and for at least 28 days after stopping lenalidomide.

Only enough study drug for 28 days or one cycle of therapy (whichever is shorter) may be dispensed with each cycle of therapy.

Randomized Phase III Trial of Lenalidomide Versus Observation Alone in Patients with Asymptomatic High-Risk Smoldering Multiple Myeloma

Appendix VII

Rev. 8/11, 1/16

Lenalidomide Education and Counseling Guidance Document

To be completed prior to each dispensing of study drug.

Protocol Number: _____

Patient Name (Print): _____ DOB: _____/_____/_____ (mm/dd/yyyy)

(Check the appropriate box to indicate risk category)

Female: □

If female, check one:

Rev. Add14

□ FCBP (Female of childbearing potential): a female who: 1) has achieved menarche at some point 2) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) 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 during the preceding 24 consecutive months)

□ NOT FCBP

Male: □

Do Not Dispense study drug if:

- **The patient is pregnant.**
- **No pregnancy tests were conducted for a FCBP.**
- **The patient states she did not use TWO reliable methods of birth control (unless practicing complete abstinence of heterosexual contact) [at least 28 days prior to treatment, during treatment and during dose interruption].**
- **The subject stated that he or she has or does not want to adhere to pregnancy precautions outlined within this Pregnancy Prevention Plan (PPP).**

FCBP:

1. I verified that the required pregnancy tests performed are negative.
2. I counseled FCBP regarding the following:
   - Potential risk of fetal exposure to lenalidomide: If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females are advised to avoid pregnancy while taking lenalidomide. The teratogenic potential of lenalidomide in humans cannot be ruled out. FCBP must agree not to become pregnant while taking lenalidomide.
   - Using TWO reliable methods of birth control at the same time or complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle

of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.)from heterosexual contact [at least 28 days prior to treatment, during treatment, during dose interruption and 28 days after discontinuation of lenalidomide].

That even if she has amenorrhea she must comply with advice on contraception

- Use of one highly effective method and one additional method of birth control AT THE SAME TIME. The following are examples of highly effective and additional effective methods of contraception:
  - 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
  - Additional effective methods:
    - Male condom
    - Diaphragm
    - Cervical Cap

- Pregnancy tests before, during, and after treatment, even if the patient agrees not to have reproductive heterosexual contact. Two pregnancy tests will be performed prior to receiving study drug, one within 10 to 14 days and the second within 24 hours of the start of study drug.
- Frequency of pregnancy tests to be done:
  - Every week during the first 28 days of this study and a pregnancy test every 28 days during the patient's participation in this study if menstrual cycles are regular or every 14 days if cycles are irregular.
  - If the patient missed a period or has unusual menstrual bleeding.
  - When the patient is discontinued from the study and at day 28 after study drug discontinuation if menstrual cycles are regular. If menstrual cycles are irregular, pregnancy tests will be done at discontinuation from the study and at days 14 and 28 after study drug discontinuation.
  - Stop taking study drug immediately in the event of becoming pregnant and to call their study doctor as soon as possible.
  - NEVER share study drug with anyone else.
  - Do not donate blood while taking study drug, during breaks (dose interruptions), and for at least 28 days after stopping the last dose of the study drug.
  - Do not breastfeed while taking lenalidomide and for at least 28 days after the last dose of lenalidomide.
  - Do not break, chew, or open study drug capsules.
  - Return unused study drug to the study doctor.

Provide Lenalidomide Information Sheet to the patient.

FEMALE NOT OF CHILDBEARING POTENTIAL (NATURAL MENOPAUSE FOR AT LEAST 24 CONSECUTIVE MONTHS, A HYSTERECTOMY, OR BILATERAL OOPHORECTOMY):

I counseled the female NOT of child bearing potential regarding the following:

- Potential risks of fetal exposure to lenalidomide (Refer to item #2 in FCBP)
- NEVER share study drug with anyone else.
- Do not donate blood while taking study drug, during breaks (dose interruptions), and for at least 28 days after the last dose of the study drug.
- Do not break, chew, or open study drug capsules
- Return unused study drug capsules to the study doctor.

3. Provide Lenalidomide Information Sheet to the patient.

MALE:

Rev. Add14 4. I counseled the Male patient regarding the following:

- Do not donate blood, semen or sperm
- Potential risks of fetal exposure to lenalidomide (Refer to item #2 in FCBP).
- To engage in complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or use a condom when engaging in sexual contact (including those who have had a vasectomy) with a pregnant female or a female of childbearing potential, while taking study drug, during dose interruptions and for 28 days after stopping study drug.
- Should not impregnate his female partner while in the study.
- Males should notify their study doctor when their female partner becomes pregnant and female partners of males taking study drug should be advised to call their healthcare provider immediately if they get pregnant.
- NEVER share study drug with anyone else.
- Do not donate blood while you take lenalidomide, during breaks (dose interruptions), and for at least 28 days after stopping study drug the last dose of lenalidomide.
- Do not break, chew, or open study drug capsules.
- Return unused study drug capsules to the study doctor.

5. Provide Lenalidomide Information Sheet to the patient.

Counselor Name (Print): _____

Counselor Signature: _____ Date: _____/_____/_____

Maintain a copy of the Lenalidomide Education and Counseling Guidance Document in the patient records.

Randomized Phase III Trial of Lenalidomide Versus Observation Alone in Patients with Asymptomatic High-Risk Smoldering Multiple Myeloma

Appendix VIII

Rev. 8/11, 1/16

Lenalidomide Information Sheet

FOR PATIENTS ENROLLED IN CLINICAL RESEARCH STUDIES

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

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

Lenalidomide may cause birth defects (deformed babies) or death of an unborn baby. Lenalidomide is similar to the medicine thalidomide. It is known that thalidomide causes life-threatening birth defects. Lenalidomide has not been tested in pregnant women but may also cause birth defects. Findings from a monkey study indicate that lenalidomide caused birth defects in the babies of female monkeys who received the drug during pregnancy.

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

Do not take study drug if you are pregnant or plan to become pregnant

Either do not have sexual intercourse at all or use two reliable, separate forms of effective birth control at the same time:

- for 28 days before starting lenalidomide
- while taking lenalidomide
- during dose interruptions of lenalidomide
- for 28 days after stopping lenalidomide

You must have pregnancy testing done at the following times:

- within 10 to 14 days and again 24 hours prior to the first dose of lenalidomide
- weekly for the first 28 days
- every 28 days after the first month or every 14 days if you have irregular menstrual periods
- if you miss your period or have unusual menstrual bleeding
- 28 days after the last dose of lenalidomide (14 and 28 days after the last dose if menstrual periods are irregular)

Stop taking study drug if you become pregnant during treatment

- If you suspect you are pregnant at any time during the study, you must stop lenalidomide immediately and immediately inform your study doctor. Your study doctor will report all cases of pregnancy to the National Cancer Institute and the pharmaceutical collaborator, Celgene Corporation.

Do not breastfeed while taking lenalidomide and for at least 28 days after the last dose of lenalidomide.

The study doctor will be able to advise you where to get additional advice on contraception.

If you are a female not of childbearing potential:

In order to ensure that an unborn baby is not exposed to lenalidomide, your study doctor will confirm that you are not able to become pregnant.

If you are a man:

Lenalidomide is detected in trace quantities in human semen. The risk to the fetus in females of child bearing potential whose male partner is receiving lenalidomide is unknown at this time.

Men (including those who have had a vasectomy) must either abstain from sexual intercourse or use a condom during sexual contact with a pregnant female or a female that can become pregnant:

- While you are taking lenalidomide
- During dose interruptions of lenalidomide
- For 28 days after you stop taking lenalidomide

Men should not donate sperm or semen while taking lenalidomide, during breaks (dose interruptions), and for at least 28 days after stopping lenalidomide.

If you suspect that your partner is pregnant any time during the study, you must immediately inform your study doctor. The study doctor will report all cases of pregnancy to the National Cancer Institute who will report the cases to the pharmaceutical collaborator, Celgene Corporation. Your partner should call their healthcare provider immediately if she gets pregnant.

Restrictions in sharing lenalidomide and donating blood:

Do not share lenalidomide with other people. It must be kept out of the reach of children and should never be given to any other person.

Do not donate blood while you take lenalidomide, during breaks (dose interruptions), and for at least 28 days after stopping the last dose of lenalidomide.

Do not break, chew, or open study drug capsules.

You will get no more than a 28-day supply of lenalidomide at one time.

Return unused study drug capsules to your study doctor.

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

Randomized Phase III Trial of Lenalidomide Versus Observation Alone in Patients with Asymptomatic High-Risk Smoldering Multiple Myeloma

Appendix IX

Cooperative Research and Development Agreement (CRADA/CTA)

The agent lenalidomide supplied by CTEP, DCTD, NCI used in this protocol is provided to the NCI under a Collaborative Agreement (CRADA, Agent-CRADA, CTA, CSA) between Celgene (hereinafter referred to as a "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/default.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. 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:

   Regulatory Affairs Branch, CTEP, DCTD, NCI
   Executive Plaza North, Suite 7111
   Bethesda, Maryland 20892
   FAX 301-402-1584
   Email: 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.

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Appendix X

Bone Marrow Aspirate and Peripheral Blood Kit — Yale University

Specimen Checklist and Shipping Instructions

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

Kit Contents:

- Styrofoam box and cardboard mailing sleeve
- Rev. 12/13 10ml Sodium Heparin (green top) collection tubes
- Zip lock specimen bag

Packing and Shipping Instructions:

1. Collect the following specimens:
   - Peripheral blood – Draw four (4) 10ml Sodium Heparin tubes (green top).
   - Bone Marrow Aspirate - Draw 5-10ml of a 're-direct' bone marrow aspirate in one (1) Sodium Heparin tube (green top).
2. Specimens should be labeled with ECOG-ACRIN protocol number (E3A06), ECOG-ACRIN patient ID number, patient's initials (last name, first name), and date of specimen collection.
3. Place specimens in zip lock plastic bag, wrap with absorbent material and place in the Styrofoam cooler. **Tubes should be sent at room temperature.**
4. Place the Styrofoam container and the Sample Tracking System Shipping Manifest within the cardboard mailing sleeve.
5. Rev. 12/13 Prepare the package for shipping, applying packing tape as needed. Ship specimens via overnight delivery the same day collected.
6. Rev. 12/13 Please contact Lin Zhang at (203) 737-5176 or lin.zhang@yale.edu prior to sending the shipment as she will need to print the shipping label and either fax or e-mail to the person sending the samples to the lab.

Rev. 12/13 The samples in this prepared kit should be shipped using EshipGlobal to the following:

Dhodapkar Laboratory
Nathan Smith Building
Room NSB-287B
Yale School of Medicine
333 Cedar Street
New Haven, CT 06510
Tel: (203) 737-5176

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Appendix XI

Bone Marrow Core Biopsy Kit—University of Arkansas

Specimen Checklist and Shipping Instructions

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

Kit Contents:

- Styrofoam box and cardboard mailing sleeve
- FedEx Airbill with pre-printed return address
- Zip lock specimen bag

Packing and Shipping Instructions:

8. Collect the following specimen:
    - Bone Marrow Core Biopsy – Snap-freeze immediately after resection by dropping into liquid nitrogen or dry ice.
9. Transfer the frozen core into a tube that has been kept on dry ice to prevent thawing of the core.
10. Immediately ship on **dry ice OR store at 70°C and batch ship at a later date**.
11. Specimens should be labeled with ECOG-ACRIN protocol number (E3A06), ECOG-ACRIN patient ID number, patient's initials (last name, first name), and date of specimen collection.
12. Place specimens in their individual plastic bags and place in the Styrofoam cooler tightly packed with dry ice.
13. Place the Styrofoam container and the Sample Tracking System Shipping Manifest Form within the cardboard mailing sleeve.
14. Prepare the package for shipping, applying packing tape as needed. Complete the sender portion of the return FedEx Airbill and adhere to the exterior lid of the box. Ship specimens via overnight delivery.
15. Notify Federal Express for pick-up and/or leave package at the designated FedEx drop-off location.

Rev. 2/12, 2/16 **Please contact Shayu Deshpande at sdeshpande@uams.edu or (501) 526-6990 ext. 8941 to notify them when specimen(s) are being shipped.**

The samples in this prepared kit should be shipped to the following:

University of Arkansas for Medical Sciences
Rockefeller Cancer Institute, Room 940
Rev. 2/16 Attn: Shayu Deshpande
4301 West Markham, Slot 724
Little Rock, AR 72205-7199

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Rev. 8/11, 1/16

Appendix XII

Celgene Pregnancy Prevention & Counseling Program Site Counselor Identification Form

Celgene Corporation	Celgene Pregnancy Prevention & Counseling Program Site Counselor Identification Form NCI Protocol #:_____

- Please identify at least two (2) counselors and fax back to 888-314-2392
- Use one form per counselor.
- Identified counselors must be licensed healthcare professionals (e.g. RN, PA, RPh, PhD, LPN, CNP, or MD) and must not be the principal investigator.
- If you have any questions, please email (coop_ma@celgene.com)

General Information

Principal Investigator:_____ Institution Name:_____

Counselor Information

CTEP person ID:_____ CTEP site ID:_____

First Name:_____ Middle Initial:_____ Last Name:_____

License Type: (circle one) MD PhD PA CNP RN LPN RPh Other:_____

Email Address:_____

Phone:_____ Fax:_____

Institution Street Address:_____

City:_____ State/Region:_____

Zip/Post Code:_____ Country:_____

Which training will you require? □Adult □Pediatric

Were you previously approved as a Counselor? □No □Yes (Previous training) □Adult □Pediatric

If no, please list all the protocols #(s), corresponding CTEPsiteID(s) and institution names(s) that you *plan to provide* counseling for:

If yes, please list the protocols #(s), corresponding CTEPsiteID(s) and institution names(s) *for protocols Celgene has already associated you with*:

Protocol#:	CTEPsiteID	Institution

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Rev. Add13
Rev. Add14
Rev. 7/14

Appendix XIII

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 Lenalidomide, or within 28 days of the female patient's last dose of 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?

The pregnancy, suspected pregnancy, or positive/inconclusive pregnancy test must be reported via CTEP's Adverse Event Reporting System (CTEP-AERS)

(http://ctep.cancer.gov)

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 via CTEP-AERS.
- 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 Operations Office - Boston. Please contact the ECOG Operations Office - Boston to ask for a conference call to be set up with the appropriate individuals.
- It is recommended the female subject 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* CTEP-AERS report should be initiated 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.*"

It must be reported via CTEP-AERS as Grade 4 "*Pregnancy loss*" under the System Organ Class (SOC) "*Pregnancy, puerperium and perinatal conditions"*.

A fetal death 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 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, must be reported via CTEP-AERS AND any infant death after 28 days that is suspected of being related to the *in utero* exposure to Lenalidomide must also be reported via CTEP-AERS.

It must be reported via CTEP-AERS as Grade 4 "*Death Neonatal*" under the System Organ Class (SOC) "General disorder and administration site conditions".

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)