# CLINICAL STUDY PROTOCOL

**X16047**
**UC IRB# 14-0899**

Phase II Randomized Trial of Continuation of Post-Transplant Maintenance with Single-Agent lenalidomide vs. Consolidation/Maintenance with Ixazomib-lenalidomide-Dexamethasone in Patients with Residual Myeloma

**Indication:** Post-transplant maintenance

**Phase:** Phase II

| **Protocol History** | |
|---|---|
| Original | 01 JUL 2014 |
| Version 1.1 | 09 JUN 2015 |
| Version 1.2 | 10 SEP 2015 |
| Version 2 | 14 DEC 2015 |
| Version 2.1 | 4 APR 2016 |
| Version 2.2 | 26 OCT 2016 |
| Version 2.3 | 19 JUN 2017 |
| Version 2.4 | 14 JUN 2019 |
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| **Version 2.6** | **25Sept2019** |

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This is a multi-institution investigator-initiated study. The principal investigator **Dr. Andrzej Jakubowiak** (who may also be referred to as the sponsor-investigator) is conducting the study and acting as the sponsor. Therefore, the legal/ethical obligations of the principal investigator include both those of a sponsor and those of an investigator.

PROTOCOL SUMMARY

**Study Title:** Phase II Randomized Trial of Continuation of Post-Transplant Maintenance with Single-Agent lenalidomide vs. Consolidation/Maintenance with Ixazomib-lenalidomide-Dexamethasone in Patients with Residual Myeloma

**Phase:** II

**Number of Patients:** 60

**Study Objectives**

**Primary**

- To determine the rate of MRD-negative disease by multiparameter flow cytometry (MFC) for patients enrolled based on MFC-positivity or by next generation sequencing (NGS) for patients enrolled based on NGS-positivity (with MRD-negative disease by MFC at screening), at 12 months after randomization

**Secondary**

- Evidence of response as demonstrated by the improvement of the depth of response by at least one category according to IMWG response criteria. (For example, an improvement from very good partial response (VGPR) to near complete response (nCR) or better than nCR including conversion from CR to MRD negative disease [overall response]) at 6 and 12 months.
- Estimate of progression free survival
- Estimate of overall survival
- Estimate of duration of MRD-negative disease
- Safety and tolerability of experimental arm vs. control

**Tertiary/Exploratory** ***(if applicable)***

- Determination of markers of response based on pre-treatment characteristics using methods described in correlative research, protocol section 8.
- Evaluation of MRD by gene sequencing method using the Adaptive Biotechnologies platform (clonoSEQ®) in parallel with multi-parameter flow cytometry (MFC)

**Overview of Study Design:**

This is a phase 2, open-label, randomized study in which subjects are enrolled 1:1 control to experimental arm stratified by 1) level of response at study entry (in accordance with the IMWG uniform response criteria) and 2) risk factors:

1) Level of response including transplant; response is assessed at study screening for this protocol:
    i. <VGPR
    ii. ≥VGPR
2) Risk Factors at the time of diagnosis:
    i. At least one of the following poor prognostic risk factors (Yes/No):
        1. del-13 (by karyotyping)
        2. hypodiploidy (by karyotyping)
        3. t(4;14) (by FISH)
        4. t(4;16) (by FISH)
        5. t(14;20) (by FISH)
        6. del17p (by FISH)
        7. 1q21 gain (by FISH)

**Dose Schedule**

Each cycle is 28 days for both the Control arm and Experimental Arm.

| **Cycle** | **CONTROL** | **EXPERIMENTAL** | | |
|---|---|---|---|---|
| | **Lenalidomide** | **Lenalidomide** | **Ixazomib** | **Dex[b]** |
| **Cycle 1 - 4** | Last best tolerated dose of either 10 or 15 mg. If the 10 mg dose is tolerated for 3 cycles, either **off or on protocol**, it can be escalated to 15 mg per dose | 25 mg daily | First cycle 3 mg per dose; can be escalated to 4 mg per dose in cycle 2 | Initially 40 mg weekly (or last best tolerated dose prior to transplant) |
| **Cycle 5 - 12** | Best tolerated dose | Best tolerated dose | Best tolerated dose | STOP* |
| **Treatment Days** | 1 – 28 | 1 - 21 | 1, 8, 15 | 1, 8, 15, 22 |

1) * A total of 20 mg of dexamethasone weekly or prednisone equivalent will be permitted to improve/prevent toxicities (ex. rash or GI side effects)

**Study Population:** Post-Transplant Multiple Myeloma on Lenalidomide Maintenance

**Key Inclusion Criteria:**

1) Patients who completed induction treatment followed by autologous stem cell transplant as initial therapy for symptomatic myeloma as per IMWG criteria and are considered for single agent Lenalidomide maintenance or initiated single agent Lenalidomide maintenance
    a. Patients will be eligible for enrollment in the first 0-6 months of lenalidomide maintenance provided that lenalidomide maintenance has been initiated within 6 months after transplant as per standard of care.
        i. Patients do not have to be on Lenalidomide at the time of study consent.
    b. Patients already in lenalidomide must be receiving lenalidomide 10 mg or 15 mg (as per CALGB trial, McCarthy et al., N Eng J Med, 2012) and be able to tolerate dose escalation to 25 mg daily.
    c. Patients receiving off protocol lenalidomide maintenance cannot exceed6 months post-transplant
    d. A one week break from off protocol lenalidomide is suggested, prior to initiating treatment on the study
        i. Any delays >7 days to align treatment with the start of Cycle 1 Day 1, of either arm, must be discussed with the PI.
    e. Patients who completed tandem transplantation will be eligible for enrollment
2) No evidence of progressive disease on lenalidomide
3) Evidence of minimal residual disease at the time of screening defined as at least MRD-positive disease
    a. A primary method of evaluation of MRD is Multi-parameter Flow Cytometry (MFC) performed at University of Chicago
    b. Patients who have negative MRD by Multi-Parameter Flow Cytometry (MFC) but have residual original monoclonal protein by serum or urine immunofixation may be eligible if they are found to have MRD-positive disease by Next Generation Sequencing (NGS).
    c. If patient is receiving lenalidomide, any delays required to align treatment with the start of Cycle 1 of either arm, must be discussed with the PI.
4) Bone marrow specimen will be required at study entry; available DNA sample will be used for calibration step for MRD evaluation by gene sequencing
5) Males and females ≥ 18 years of age
6) Life expectancy of more than 3 months
7) ECOG performance status of 0-2
8) Adequate hepatic function, with bilirubin ≤1.5 x ULN and aspirate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 xULN
9) ANC ≥1.0 x $10^9$/L, hemoglobin ≥8 g/dL, platelet count ≥75 x 109/L.
10) Calculated creatinine clearance (by Cockcroft-Gault) ≥50 ml/min or serum creatinine below 2 g/dL (section 13.2)
11) Voluntary written consent must be given before performance of any study related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
12) Female patients who:
    a. Are postmenopausal for at least 1 year before the screening visit, OR
    b. Are surgically sterile, OR

c. If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form through 90 days after the last dose of study drug, OR
d. Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, sympto-thermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

13) Male patients, even if surgically sterilized (i.e., status post-vasectomy), must agree to one of the following:
    a. Agree to practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study drug, OR
    b. Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

**Exclusion**

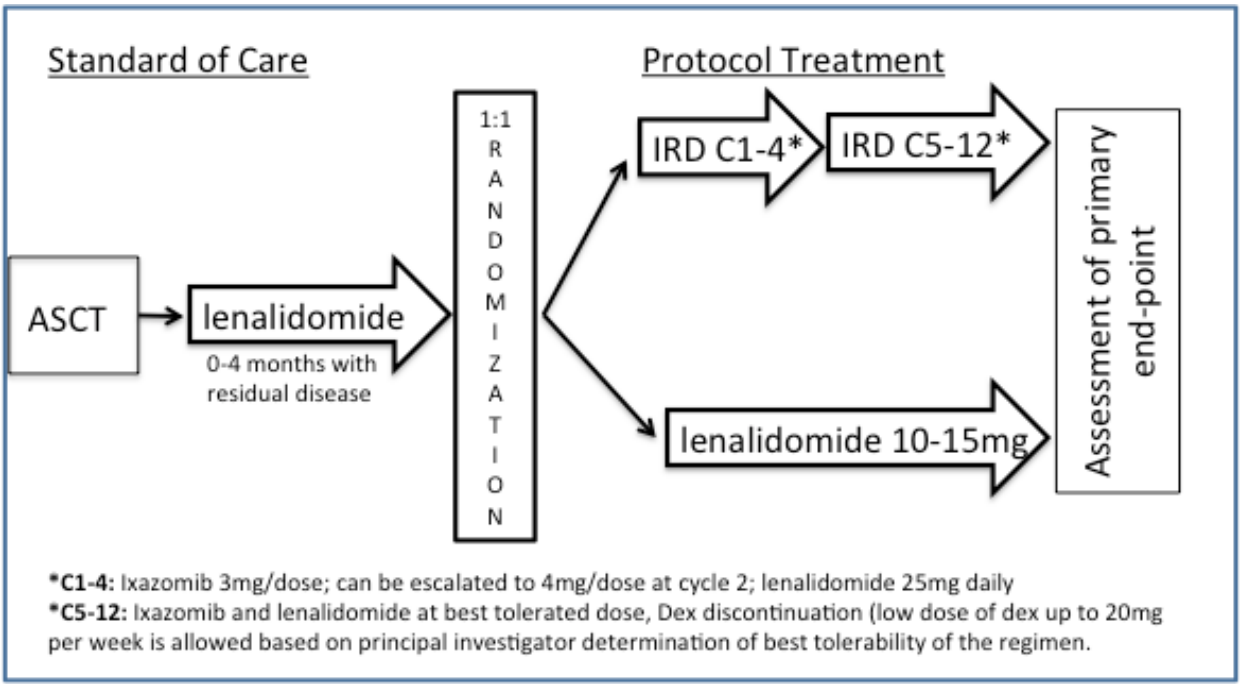
14) Evidence of progressive disease on lenalidomide maintenance as per IMWG criteria
15) Patients who have already started or received multi-drug consolidation regimen post-transplant except for patients receiving up to 6 months of single agent lenalidomide maintenance
16) Longer than 12 months since the initiation of induction therapy at the of start of lenalidomide maintainance
17) Prior progression after initial therapy.
    a. Subjects, whose therapy changed due to suboptimal response, intolerance, etc., remain eligible, provided they do not meet criteria for progression.
    b. No more than two regimens will be allowed excluding dexamethasone alone.
18) Diarrhea > Grade 1 in the absence of anti-diarrheals
19) Central Nervous System involvement
20) Female patients who are lactating or have a positive serum pregnancy test during the screening period.
21) History of allergy to mannitol
22) Major surgery within 14 days before enrollment.
23) Radiotherapy within 14 days before randomization. If the involved field is small, 7 days will be considered a sufficient interval between treatment and administration of the ixazomib.
24) Evidence of current uncontrolled cardiovascular conditions such as hypertension, cardiac arrhythmias, symptomatic congestive heart failure or New York Heart Association Stage III and IV, or unstable angina, or myocardial infarction within the past 6 months.
25) Rate-corrected QT interval of electrocardiograph (QTc) > 470 msec on a 12-lead ECG during screening
26) Uncontrolled diabetes
27) Acute infection requiring systemic anti-infectives, antivirals, or antifungals within two weeks prior to first dose
28) Systemic treatment, within 14 days before the first dose of ixazomib, with strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's wort.
29) Ongoing or active systemic infection, active hepatitis B or C virus infection, or known human immunodeficiency virus (HIV) positive.
30) Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
31) Known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent.

32) Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of ixazomib including difficulty swallowing.
33) Diagnosed or treated for another malignancy within 2 years before study enrollment or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with non-melanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.
34) Patient has ≥ Grade 3 peripheral neuropathy or Grade 2 with pain on clinical examination during the screening period.
35) Participation in other clinical trials, with other investigational agents not included in this trial, within 30 days of the start of this trial and throughout the duration of this trial.

**Duration of Study:**

Subjects will be treated on protocol for 12 months or until disease progression or if lenalidomide and/or ixazomib are permanently discontinued due to intolerance before the end of 1year. Patients who complete 12 months of protocol treatment will be taken off protocol with management as per PI discretion and standards of care but will continue to be followed for progression, if the patient did not progress on study treatment, and survival.

## STUDY OVERVIEW DIAGRAM



SCHEDULE OF EVENTS

| Assessment | Screening[2] | Cycles 1-12 | | | | EOT | Long-term follow-up |
|---|---|---|---|---|---|---|---|
| **Day** | **-42 to -1** | **1** | **8** | **15** | **22** | | |
| Informed Consent+♥ | X | | | | | | |
| Medical History / Treatment History[1] | X | | | | | | |
| Skeletal Survey | X | | | | | | |
| ECG[3] | X | | | | | X | |
| Physical Exam / ECOG[4, 5] | X | X | | | | X | |
| Vital Signs[6] | X | X | | | | X | |
| Height[7], Weight, BSA | X | X | | | | X | |
| 24-hour urine[8] | X | X | | | | X | |
| Urinalysis | X | | | | | X | |
| C- Reactive Protein | X | | | | | | |
| Hematology[9] | X | X | [X] | [X] | | X | |
| Serum Chemistry[10] | X | X | [X] | [X] | | X | |
| Pregnancy Test[11, 12] | X | X | | | | X | |
| **Disease Assessment** | | | | | | | X[20] |
| β2-microglobulin | X | | | | | | |
| SPEP, UPEP[13] | X | X | | [X] | | X | |
| BM Aspirate/biopsy, cytogenetics, FISH[14] | X | | | | | X | |
| Quantitative Immunoglobulins | X | X | | [X] | | X | |
| SFLC | X | X | | [X][15] | | X | |

| Assessment | Screening[2] | Cycles 1-12 | | | | EOT | Long-term follow-up |
|---|---|---|---|---|---|---|---|
| **Day** | **-42 to -1** | **1** | **8** | **15** | **22** | | |
| Neurological Assessment[16] | X | X | | | | X | |
| QOL Assessment[16] | X | X | | | | X | |
| Correlative Samples[17] | X | X | | | | X | |
| Sample for MRD Analysis[18, ∞] | X | | | | | X | |
| Adverse Events[19] | X | | | | | | |
| **Control Arm** | | | | | | | |
| Lenalidomide[21,22, 28] | | Continuous Days 1-28 | | | | X[26] | X[26] |
| **Experimental Arm** | | | | | | | |
| Lenalidomide[21,23, 28] | | Continuous Days 1-21 | | | | X[26] | X[26] |
| Ixazomib[24] | | X | X | X | | | |
| Dexamethasone[25] | | X | X | X | X | | |
| Survival and Evaluation of Second Primary malignancies | | | | | | | X[27] |

\+ Documented informed consent must be obtained prior to any screening procedures but can be obtained prior to the screening window of 42 days

♥ Informed consent is valid for 42 days – if the patient has not been enrolled/randomized within the screening window, re-consent must be obtained prior to submitting the registration packet for review

* Variations of ± 3 days of the scheduled visit are permitted

∞ Using diagnostic bone marrow samples for the Adaptive ID (calibration) testing is preferred as these will have the highest disease burden. If the calibration is successful, please submit the screening bone marrow samples to determine MRD status prior to study entry. If DNA identification from the diagnostic sample fails, procure additional slides from the screening marrow as these can be used for both calibration and MRD tracking. Contact the UC Multi-Site Coordinator prior to submitting additional samples, if the initial ID test fails.

[X] Only as clinically indicated

2) Includes neuropathy history and documentation of the CTCAE grade if peripheral neuropathy is present at baseline.

| Assessment | Screening[2] | Cycles 1-12 | | | | EOT | Long-term follow-up |
|---|---|---|---|---|---|---|---|
| Day | -42 to -1 | 1 | 8 | 15 | 22 | | |

3) May be within 42 days of planned treatment start. Includes: lateral radiograph of the skull, anteroposterior and lateral views of the spine, and anteroposterior views of the pelvis, ribs, femora, and humeri. Skeletal surveys performed outside of the 42-day window may be considered for inclusion 6 or 8 weeks prior to randomization. Please contact the Lead Principal Investigator and/or/CRA on a case-by-case basis.
4) 12-lead ECG, including QTc interval completed on local machine.
5) For Day 1 of cycle 1, screening results may be used if within 7 days of treatment start.
6) Complete physical exam (including vital signs [systolic and diastolic blood pressure, respiration, pulse, and oral temperature], weight, calculation of body surface area [BSA] & ECOG score) required at screening & Day 1 of each cycle.
7) Systolic and diastolic blood pressure, pulse, respiration, temperature day 1 of each cycle, EOT visit and as clinically indicated.
8) Height required at screening only
9) 24 hour urine total protein, urine protein electrophoresis (UPEP), and urine protein immunofixation. For subjects whose disease is being monitored through UPEP, additional post baseline 24-hour urine collections are required as indicated
10) On day 1 of each cycle and EOT visit is required, and as clinically indicated at other time-points. Hemoglobin, WBC with complete differential, platelet count, absolute lymphocyte and absolute neutrophil counts. Results must be reviewed before dosing.
11) On day 1 of each cycle and EOT visit is required, and as clinically indicated at other time-points. Full serum chemistry panel at screening, day 1 of each cycle and at EOT visit: sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, total protein, albumin, calcium, total bilirubin, alkaline phosphatase, ALT, AST, LDH, and CRP. Abbreviated serum chemistry panel should be included as necessary.
12) Pregnancy tests for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not had a hysterectomy or bilateral oophorectomy; or 2) has not been naturally post-menopausal for at least 24 consecutive months (i.e., menses within the preceding 24 months) See Appendix F of protocol for details.
13) Pregnancy tests must occur within 10-14 days and again within 24 hours prior to prescribing lenalidomide (prescriptions must be filled within 7 days. 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 13.6).
14) Serum protein electrophoresis and urine protein electrophoresis (the latter only for those whose disease is being followed by UPEP). Subjects with baseline urine protein greater than 200 mg/24 hours must have a UPEP to confirm VGPR or better. Obtain blood for M-protein levels measured by SPEP or quantitative immunoglobulins for those subjects in whom SPEP/UPEP are felt to be unreliable (IgA type multiple myeloma), depending upon which studies were positive at baseline. Response will be assessed comparing day 1 of each cycle values to the respective baseline (pre-induction treatment) values for each subject.

| Assessment | Screening[2] | Cycles 1-12 | | | | EOT | Long-term follow-up |
|---|---|---|---|---|---|---|---|
| Day | -42 to -1 | 1 | 8 | 15 | 22 | | |

15) Bone marrow aspirate and biopsy – quantify % myeloma cell involvement; bone marrow sample for cytogenetics and fluorescent in situ hybridization (FISH). Please note that cytogenetic profile at the time of diagnosis will be used for patient stratification at study entry. Bone marrow aspirate and biopsy should be performed at screening, end of 12 cycles/end of treatment and at any time that a bone marrow is performed as standard of care. If CR is recorded between screening and EOT, a Bone Marrow Biopsy can be indicated as per standards of care to be performed at 6 months from randomization (with acceptable window 3-9 months; for 6 months response assessment). However, if CR is suspected within 3 months of EOT, it is acceptable to wait for the EOT BM biopsy. Repeat bone marrow biopsy/aspirate if CR is suspected and as appropriate to confirm achievement of sCR, CR, or nCR (aspirate only—biopsy not required). If institution has established flow-based multi-color study for minimal residual disease (MRD), this evaluation should include MRD evaluation. Bone marrow biopsy/aspirate performed outside of the 42-day window may be considered for inclusion. Please contact the Lead Principal Investigator and/or the CRA on a case-by-case basis.
16) Serum Free Light Chains repeated only to confirm response.
17) Screening and Day 1 of every cycle. Includes neurologic exam (to detect peripheral neuropathy and/or changes in pre-existing neuropathy) and examination of clinical AEs indicative of neuropathy. Collect FACT/GOG neurotoxicity questionnaire and QOL assessment at each time point above.
18) For patients who sign additional consent: peripheral blood and bone marrow aspirate samples collected at screening, end of treatment, and any time after randomization that CR or better is suspected. Buccal mucosa swab will be collected at screening only.
19) All patients are required to have a sample for MRD collected at screening, at the End of Treatment visit, and at any other time a Bone Marrow biopsy/aspirate is collected as SOC. Additionally, FFPE or BMA slides from diagnosis will be required for calibration of MRD by NGS for all patients. If CR is recorded between screening and EOT, a Bone Marrow Biopsy can be indicated. However, if CR is suspected within 3 months of EOT, it is acceptable to wait for the EOT BM biopsy. It is expected that samples will be collected at a minimum of two time-points for each patient. Refer to lab manual for collection and shipping instructions. Central analysis includes MRD by multi-parameter flow cytometry and MRD by gene sequencing.
20) AEs will be collected from the time of signing informed consent to 30 days following the last dose of treatment. Please refer to section 9 for specific collection requirements.
21) Assessment for disease progression in subjects who did not progress during treatment. At least every 3 months (+/- 30 days) for 2 years from safety follow-up visit (which must be 28days (+/- 3 days) post-last study treatment).
22) lenalidomide must be prescribed through and in compliance with the lenalidomide REMS™ program of Celgene Corporation. Prescriptions must be filled within 7 days. Consideration should be given to prescribing lenalidomide 5 to 7 days in advance of Day 1 of each cycle to allow time for required patient and prescriber surveys, and drug shipment to patient. Any unusedlenalidomide will be counted and documented by each site.
23) Control Arm: Lenalidomide should continue at best tolerated dose of either 10 mg or 15 mg on days 1-28. If the 10 mg dose is tolerated for three cycles, it can be escalated to 15 mg per dose.

| Assessment | Screening[2] | Cycles 1-12 | | | | EOT | Long-term follow-up |
|---|---|---|---|---|---|---|---|
| Day | -42 to -1 | 1 | 8 | 15 | 22 | | |

24) Experimental Arm: lenalidomide dosing Days 1-21. Cycle 1-4 lenalidomide will be administered at 25 mg daily. Cycles 5-12 lenalidomide will continue at best tolerated dose days 1-21. lenalidomide should be taken in the evening at approximately the same time each day.
25) Cycles 1-4: Ixazomib at 3-4 mg Days 1, 8, 15. Cycles 5+ Ixazomib at best tolerated dose on Days 1, 8, 15. Ixazomib should be taken on an empty stomach or at least 1 hour before or 2 hours after a meal.
26) Days 1, 8, 15 and 22, dexamethasone should be taken with a meal, and approximately 2 hours before Ixazomib on days they coincide. At Cycles 1-4, dexamethasone will be administered at 40 mg. Dexamethasone will be discontinued at the end of cycle 4.
27) Single-agent lenalidomide maintenance therapy is recommended using last tolerated dose of lenalidomide for 21 days in 28 day cycles after completion of protocol treatment.
28) Patients will be followed for survival and development of any new cancers, at least every 3 months for 2 years form last treatment. Reports of any death should include date of death and specific cause (disease under study or specify other cause).
29) If patient is currently receiving lenalidomide, any delays required to align treatment with the start of Cycle 1 of either arm, must be discussed with the PI

# TABLE OF CONTENTS

# LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

| Abbreviation | Term |
|---|---|
| $5\text{-}HT_3$ | 5-hydroxytryptamine 3 serotonin receptor |
| AE | adverse event |
| ALL | acute lymphoblastic leukemia |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| AML | acute myelogenous leukemia |
| ANC | absolute neutrophil count |
| API | active pharmaceutical ingredient |
| aPTT | activated partial thromboplastin time |
| Ara-C | Cytarabine |
| ASCO | American Society of Clinical Oncology |
| AST | aspartate aminotransferase |
| AUC | area under the plasma concentration versus time curve |
| $AUC_{24\ hr}$ | area under the plasma concentration versus time curve from zero to 24 hours |
| $AUC_{inf}$ | area under the plasma concentration versus time curve from zero to infinity |
| $AUC_{\tau}$ | area under the plasma concentration versus time curve from zero to next dose |
| BCRP | breast cancer resistance protein |
| βhCG | beta-human chorionic gonadotropin |
| BID | bis in die; twice a day |
| BM | bone marrow |
| BSA | body surface area |
| BUN | blood urea nitrogen |
| BZD | Benzodiazepines |
| CBC | complete blood count |
| CCTO | Cancer Clinical Trials Office (University of Chicago) |
| CFR | Code of Federal Regulations |
| CL | clearance, IV dosing |
| $CL_P$ | plasma clearance |
| $CL_{Total}$ | total clearance |
| $C_{max}$ | single-dose maximum (peak) concentration |
| CNS | central nervous system |
| $CO_2$ | carbon dioxide |
| CR | complete response |

| Abbreviation | Term |
|---|---|
| CRM | continual reassessment method |
| CRP | C-reactive protein |
| CSF-1R | colony-stimulating factor 1 receptor |
| CT | computed tomography |
| $C_{trough}$ | single-dose end of dosing interval (trough) concentration |
| CV | coefficient of variation |
| CYP | cytochrome $P_{450}$ |
| DDI | drug-drug interaction |
| DLT | dose-limiting toxicity |
| DME | drug metabolizing enzymes |
| DNA | deoxyribonucleic acid |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| ELISA | enzyme-linked immunosorbent assay |
| EOS | End of Study (visit) |
| EOT | End of Treatment (visit) |
| EU | European Union |
| FDA | United States Food and Drug Administration |
| GCP | Good Clinical Practice |
| G-CSF | granulocyte colony stimulating factor |
| GGT | gamma glutamyl transferase |
| GI | Gastrointestinal |
| GLP | Good Laboratory Practices |
| GM-CSF | granulocyte macrophage-colony stimulating factor |
| GMP | Good Manufacturing Practice |
| Hb | Hemoglobin |
| Hct | Hematocrit |
| HDPE | high-density polyethylene |
| hERG | human ether-à-go-go related gene |
| HIV | human immunodeficiency virus |
| HNSTD | highest nonseverely toxic dose |
| IB | Investigator's Brochure |
| $IC_{50}$ | concentration producing 50% inhibition |

| Abbreviation | Term |
|---|---|
| ICF | informed consent form |
| ICH | International Conference on Harmonisation |
| IEC | independent ethics committee |
| IRB | institutional review board |
| ITT | intent-to-treat |
| IV | intravenous; intravenously |
| IVRS | interactive voice response system |
| $K_i$ | inhibition constant |
| KPS | Karnofsky Performance Status |
| LDH | lactate dehydrogenase |
| LFT | liver function test(s) |
| MedDRA | Medical Dictionary for Regulatory Activities |
| Millennium | Millennium Pharmaceuticals, Inc., and its affiliates |
| MRI | magnetic resonance imaging |
| MRU | medical resource utilization |
| MTD | maximum tolerated dose |
| MUGA | multiple gated acquisition (scan) |
| NCCN | National Comprehensive Cancer Network |
| NCI | National Cancer Institute |
| NCI CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| NPO | nothing by mouth |
| NYHA | New York Heart Association |
| PBMC | peripheral blood mononuclear cell |
| PCR | polymerase chain reaction |
| PD | progressive disease (disease progression) |
| Pgp | P-glycoprotein |
| PK | pharmacokinetic(s) |
| PO | *per os*; by mouth (orally) |
| PR | partial response |
| PRO | patient-reported outcome |
| PSA | prostate-specific antigen |
| QD | *quaque die*; each day; once daily |
| QID | *quater in die;* 4 times a day |
| QOD | *quaque altera die*; every other day |
| QOL | quality of life |

| Abbreviation | Term |
|---|---|
| QTc | rate-corrected QT interval (millisec) of electrocardiograph |
| RBC | red blood cell |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| SAE | serious adverse event |
| SC | Subcutaneous |
| SD | stable disease |
| SmPC | Summary of Product Characteristics |
| $t_{1/2}$ | terminal disposition half-life |
| TGI | tumor growth inhibition |
| $T_{max}$ | single-dose time to reach maximum (peak) concentration |
| UK | United Kingdom |
| ULN | upper limit of the normal range |
| US | United States |
| $V_z$ | volume of distribution in the terminal phase |
| WBC | white blood cell |
| WHO | World Health Organization |

# 1. BACKGROUND AND STUDY RATIONALE

## 1.1 Scientific Background

### 1.1.1 Disease under Treatment

Multiple myeloma is a clonal neoplastic proliferation of plasma cells affecting 19,900 US patients each year [1]. Multiple myeloma is characterized by anemia, bone destruction, monoclonal gammopathy, renal failure, hypercalcemia and increased susceptibility to infections. The disease is systemic, and chemotherapy is indicated for management of symptomatic myeloma. Current front-line treatments include combination chemotherapy with regimens using melphalan (Alkeran®), bortezomib (Velcade®), thalidomide (Thalomid®), and lenalidomide and their combinations with and without corticosteroids. In addition, two agents, pomalidomide (Pomalyst®) and carfilzomib (Kyprolis®), have been recently approved in the treatment of relapsed disease. Younger patients are consolidated with high-dose therapy (ablative chemotherapy or radiation) with autologous stem cell transplantation (ASCT). Although improvements in progression free survival and overall survival have occurred in the past 5 years, even with the best available approved agents, 10-30% of patients fail to respond to the primary therapy, and almost all subjects eventually relapse, with a median overall survival of 44.8 months. [2]

### 1.1.2 Ixazomib (MLN9708)

## 1.2 Preclinical Experience

Please refer to the current ixazomib Investigator's Brochure (IB) and Safety Management Attachment (SMA).

## 1.3 Clinical Experience

Ixazomib has been evaluated as an oral single agent in Phase 1 studies that have included patients with advanced solid tumors, lymphoma, relapsed/refractory MM (RRMM), and relapsed or refractory light-chain (AL) amyloidosis, with demonstrated early signs of activity. Ongoing studies continue to investigate both single-agent ixazomib and  ixazomib in combination with standard treatments. Based on encouraging preliminary data observed in patients with MM requiring systemic treatment, 2 Phase III trials in newly diagnosed MM (NDMM) (C16014) and RRMM (C16010) patient populations are currently evaluating ixazomib in combination with lenalidomide and Dexamethasone (Rd) versus placebo/R/d. Both trials compare ixazomib at a weekly dose of 4.0 mg on Days 1, 8, and 15 in a 28-day cycle to a standard dose of lenalidomide with a weekly dexamethasone dose of 40 mg. In addition, ongoing clinical pharmacology studies

include evaluation of drug-drug interactions with ketoconazole and rifampin, effect of food, and oral bioavailability. Studies evaluating the safety and pharmacokinetics (PK) of ixazomib alone (in Japanese patients) and in combination with lenalidomide and dexamethasone in Asian adult patients (including Japanese patients) with a diagnosis of NDMM are ongoing.

As of 27 March 2013, preliminary clinical data is available for a total of 653 patients across 13 studies. The emerging safety profile indicates that ixazomib is generally well tolerated. The adverse events (AEs) are consistent with the class-based effects of proteasome inhibition and are similar to what has been previously reported with Velcade though the severity of some, for example peripheral neuropathy, is less. While some of these potential toxicities may be severe, they can be managed by clinical monitoring and standard medical intervention, or, as needed, dose modification or discontinuation.

Fatigue was the most common AE reported among 384 patients treated in the oral (PO) studies (47%). Other common AEs reported in the pooled intravenous (IV) and PO safety populations include nausea, thrombocytopenia, diarrhea, and vomiting. Rash is also a commonly reported treatment-emergent event; however, there is some variety in its characterization and causality resulting in different preferred terms to describe it. A high-level term outline of rash events includes rashes, eruptions and exanthemas NEC; pruritus NEC; erythemas; papulosquamous conditions; and exfoliative conditions. The dose escalation phases of most trials reported in the IB have now completed enrollment, and gastrointestinal (GI) symptoms were the common dose-limiting toxicities (DLTs) when the use of prophylactic anti-emetics was not permitted per protocol. In the expansion cohorts or phase 2 cohorts (as per each study), the incidence and severity of GI symptoms was mitigated by the use of the lower maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) (as per each study) and standard clinical usage of anti-emetics and/or antidiarrheal medications as deemed appropriate. Prophylactic use of anti-emetics has not been required as with other agents but (as outlined in Section 6.7) has been used according to standard practice and are effective.

The most frequent (at least 20%) treatment-emergent adverse events (TEAEs) reported with the PO formulation pooled from single-agent studies (n = 201) irrespective of causality to ixazomib, include nausea (53%), fatigue (51%), diarrhea (44%), thrombocytopenia (34%), vomiting (38%), decreased appetite (32%), fever (21%), and anemia (21%). The most frequent (at least 20%) TEAEs reported with the PO formulation pooled from combination trials (irrespective of the combination) (n = 173), irrespective of causality to ixazomib, include diarrhea (47%), fatigue (44%), nausea (38%), peripheral edema (35%), constipation (33%), insomnia (29%),

thrombocytopenia (28%), anemia (26%), vomiting (26%), neutropenia (25%), back pain (24%), pyrexia (23%), peripheral edema (21%, each), fever (20%), cough (20%), hypokalemia (20%), neutropenia (20%), and upper respiratory tract infection (20%). Overall rash of all grades is reported in approximately 50% of patients and is more common when ixazomib is given in combination with lenalidomide where rash is an overlapping toxicity.

Additional detailed information regarding the clinical experience of ixazomib may be found in the IB, including information on the IV formulation.

### 1.4 Pharmacokinetics and Drug Metabolism

Clinical IV and PO PK data shows that ixazomib citrate (measured as the biologically active boronic acid form of ixazomib [MLN2238]) has multi-exponential disposition with a rapid initial phase that is largely over by 4 hours. Oral ixazomib citrate is rapidly absorbed with a median single-dose first time of occurrence of maximum (peak) concentration ($T_{max}$) of approximately 0.5 to 2.0 hours and a terminal disposition half-life ($t_{1/2}$) after multiple dosing of approximately 5 to 7 days [3]. Results of a population PK analysis (n = 137) show that there is no relationship between body surface area (BSA) or body weight and clearance (CL). Also, based on stochastic simulations for fixed dose, exposures are independent of the individual patient's BSA [4]. Based on these data, a recommendation was made for fixed dosing in clinical trials. An absolute bioavailability of 67% was determined for ixazomib using the population PK analysis. Please refer to the current ixazomib IB and Safety Management Attachment (SMA) for information on the PK for IV doses of ixazomib.

Metabolism appears to be the major route of elimination for ixazomib, and urinary excretion of the parent drug is negligible (< 5% of dose). In vitro studies indicate that ixazomib is metabolized by multiple cytochrome P450s (CYPs) and non-CYP enzymes/proteins. The rank order of relative biotransformation activity of the 5 major human CYP isozymes was 3A4 (34.2%) > 1A2 (30.7%) > 2D6 (14.7%) > 2C9 (12.1%) > 2C19 (< 1%). Ixazomib is not an inhibitor of CYPs 1A2, 2C9, 2C19, 2D6, or 3A4 nor a time-dependent inhibitor of CYP3A4/5. The potential for ixazomib treatment to produce drug-drug interactions (DDIs) via CYP inhibition is inferred to be low. However, there may be a potential for DDIs with a concomitant strong CYP3A4 or CYP1A2 inhibitor or inducer because of the potential for first-pass metabolism when ixazomib is administered via the PO route and because of the moderate contribution of CYP3A4- and CYP1A2-mediated metabolism of ixazomib in human liver microsomes. Ixazomib may be a weak substrate of P-glycoprotein (Pgp), breast cancer resistance protein (BCRP), and multidrug resistance associated protein (MRP2) efflux pump transporters.

Ixazomib is not an inhibitor of Pgp, BCRP, and MRP2. The potential for DDIs with substrates or inhibitors of Pgp, BCRP, and MRP2 is, therefore, inferred to be low. Clinical Study C16009 (Arm 1) with ketoconazole, a strong CYP3A4 inhibitor, showed a 2-fold increase in area under the plasma concentration versus time curve (AUC) in the presence of ketoconazole. This resulted in the continued exclusion of strong CYP3A4 inhibitors in ongoing/planned clinical studies.

Further details on these studies are provided in the IB.

### 1.5 Clinical Trial Experience Using the Oral Formulation of Ixazomib

As of 27 March 2013, a total of 507 patients with differing malignancies (multiple myeloma, AL amyloidosis, non-hematologic cancers, and lymphoma) have been treated in studies evaluating the oral ixazomib formulation. These patients have been treated with differing doses of ixazomib either as a single-agent treatment (in 201 patients) or in combination with clinically available treatments (in 306 patients). Information regarding the ongoing studies, patient populations, and doses investigated is included in Table 1-1.

## Table 1-1 Clinical Studies of Oral Ixazomib

| Trial/ Population | Description | Doses Investigated |
|---|---|---|
| **C16003**<br>RRMM<br>N = 60 | PO, TW, single agent | 0.24-2.23 mg/m$^2$ TW<br>MTD: 2.0 mg/m$^2$<br>DLT: rash, thrombocytopenia<br>Closed to enrollment |
| **C16004**<br>RRMM<br>N = 60 | PO, W, single agent | 0.24-3.95 mg/m$^2$ W<br>MTD: 2.97 mg/m$^2$<br>DLT: rash, nausea, vomiting, diarrhea<br>Closed to enrollment |
| **C16005**<br>NDMM<br>N = 65 | PO, W, combination with Rd 28-day cycle | 1.68-3.95 mg/m$^2$ W<br>MTD: 2.97 mg/m$^2$<br>DLT: nausea, vomiting, diarrhea, syncope<br>RP2D[a]: 4.0 mg fixed (switched to fixed dosing in phase 2, equivalent to 2.23mg/m$^2$)<br>Closed to enrollment |
| **C16006**<br>NDMM<br>N = 20 | PO, TW (Arm A- 42 day cycle) and W (Arm B- 28 day cycle), combination with Melphalan and Prednisone | Arm A[a]: 3-3.7-mg fixed dose TW<br>DLT: rash, thrombocytopenia, subileus<br>Arm B[a]: 3-5.5-mg fixed dose, W<br>DLT: Esophageal ulcer nausea, vomiting, hematemesis, thrombocytopenia, ileus, neurogenic bladder<br>MTD = 3.0 mg |
| **C16007**<br>RRAL<br>N = 27 | PO, W, single agent | 4-5.5-mg fixed dose[a] W<br>DLT: thrombocytopenia, diarrhea, dyspnea, acute rise in creatinine, cardiac arrest<br>MTD: 4.0 mg W |
| **C16008**<br>NDMM<br>N = 64 | PO, TW, combination with Rd 21-day cycle | 3.0-3.7-mg fixed dose[a] W<br>MTD: 3.0 mg<br>Closed to enrollment |
| **C16009**<br>Solid tumors, Lymphomas<br>N = 54 | PO, W, single agent | 5.5-mg fixed dose[a] W |
| **C16010**<br>RRMM<br>N = 200 | PO, W, with Rd versus placebo-Rd | 4.0 mg W |
| **C16011**<br>RRAL<br>N = 4 | PO, W, with Dex versus physician's choice of a Dex-based regimen | 4.0 mg W |
| **C16013**<br>RRMM<br>N = 9 | PO, W, with Rd | 4.0 mg W |

## Table 1-1 Clinical Studies of Oral Ixazomib

| Trial/ Population | Description | Doses Investigated |
|---|---|---|
| **C16014** Symptomatic MM N=701 | PO, combination with Rd | ixazomib 4.0 mg or matching placebo on Days 1, 8, and 15, plus Rev 25 mg on Days 1-21 (10 mg if low creatinine clearance, with escalation to 15 mg if tolerated) and Dex 40 mg (or 20 mg if >75 years old) on Days 1, 8, 15, and 22 |
| **C16015** Symptomatic MM with normal renal function or severe renal impairment N=28 | PO, combination with Dex | Part A: ixazomib 3.0 mg on Day 1<br>Part B: ixazomib 4.0 mg on Days 1, 8, and 15, plus Dex 40 mg (or 20 mg if >75 years old) on Days 1, 8, 15 and 22 of a 28-day cycle |
| **C16017** RR follicular lymphoma N=58 | PO, W | 4.0, 5.3, and 7.0 mg, W<br>Treatment at RP2D once determined. |
| **C16018** Advanced solid tumors or hematologic malignancies with varying degrees of liver dysfunction N=45 | Part A: PO, Day 1 of 15-day cycle<br>Part B: PO, W | 1.5 mg (severe hepatic impairment), 2.3 mg (moderate hepatic impairment), or 4.0 mg (normal hepatic function) |
| **TB-MC010034** RRMM N = 10 | PO, W | 4.0 mg, W<br>Single agent: 4.0 mg<br>Combination with Rd |

Abbreviations: RRAL = Relapsed and/or refractory Primary systemic light chain (AL) amyloidosis; BSA = body surface area; Dex=dexamethasone; DLT = dose-limiting toxicity; IV = intravenously; Rd = lenalidomide plus dexamethasone; MTD = maximum tolerated dose; NDMM = newly diagnosed multiple myeloma; PO = orally; RR= relapsed and/or refractory; RRAL= relapsed and/or refractory systemic light chain amyloidosis RRMM = relapsed and/or refractory multiple myeloma; TBD = to be determined; TW = twice weekly; W = weekly; RP2D= recommended phase 2 dose.

Note that blinded data from pivotal Studies C16010 and C16011 are not included.

a Approximate BSA and fixed dosing equivalence: 3 mg~ equivalent to 1.68 mg/m$^2$ BSA dosing; 4.0 mg ~ equivalent to 2.23 mg/m$^2$ BSA dosing; and 5.5 mg~ equivalent to 2.97 mg/m$^2$ BSA dosing.

**Overview of the Oral Formulation of Ixazomib**

The emerging safety profile indicates that ixazomib is generally well tolerated. The adverse events (AEs) are consistent with the class-based effects of proteasome inhibition and are similar to what has been previously reported with Velcade though the severity of some, for example peripheral neuropathy, is less. While some of these potential toxicities may be severe, they can be managed by clinical monitoring and standard medical intervention, or, as needed, dose modification or discontinuation.

In the 4 ongoing studies (C16003, C16004, C16007, and C16009) investigating single-agent oral ixazomib in patients with differing malignancies (multiple myeloma, AL amyloidosis, non-hematologic cancers, and lymphoma), a total of 201 patients have been treated as of 27 March 2013. These patients have been treated with different doses of ixazomib as they are all phase 1 trials. An overview of the most frequent (at least 10%) AEs, occurring in the pooled safety population from single-agent oral ixazomib Studies (C16003, C16004, C16007, and C16009), are shown in Table 1-2.

**Table 1-2 Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events in Oral Single-Agent Studies**

| Primary System Organ Class<br>Preferred Term | Oral Single Agent<br>Total<br>n = 201<br>n (%) |
|---|---|
| Subjects with at Least One Adverse Event | 197 (98) |
| Gastrointestinal disorders | 160 (80) |
| Nausea | 106 (53) |
| Diarrhea | 88 (44) |
| Vomiting | 77 (38) |
| Constipation | 46 (23) |
| Abdominal pain | 33 (16) |
| General disorders and administration site conditions | 151 (75) |
| Fatigue | 103 (51) |
| Pyrexia | 51 (25) |
| Edema peripheral | 27 (13) |
| Asthenia | 31 (15) |
| Nervous system disorders | 92 (46) |
| Headache | 29 (14) |
| Dizziness | 26 (13) |

**Table 1-2 Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events in Oral Single-Agent Studies**

| Primary System Organ Class<br>Preferred Term | Oral Single Agent<br>Total<br>n = 201<br>n (%) |
|---|---|
| Neuropathy peripheral | 21 (10) |
| Metabolism and nutrition disorders | 107 (53) |
| Decreased appetite | 64 (32) |
| Dehydration | 37 (18) |
| Blood and lymphatic system disorders | 98 (49) |
| Thrombocytopenia | 68 (34) |
| Anemia | 42 (21) |
| Neutropenia | 29 (14) |
| Lymphopenia | 20 (10) |
| Skin and subcutaneous tissue disorders | 90 (45) |
| Rash macular[a] | 23 (11) |
| Musculoskeletal and connective tissue disorders | 93 (46) |
| Back pain | 24 (12) |
| Arthralgia | 28 (14) |
| Respiratory, thoracic and mediastinal disorders | 78 (39) |
| Cough | 28 (14) |
| Dyspnea | 30 (15) |
| Infections and infestations | 89 (44) |
| Upper respiratory tract infection | 31 (15) |

Source: Ixazomib Investigator's Brochure Edition 7

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, version 15.0.

Subject Incidence: A subject counts once for each preferred term. Percentages use the number of treated subjects as the denominator.

a Note that rash maculopapular and rash macular represent the 2 most common terms used to describe rash.

As of 27 March 2013, there are 5 studies actively enrolling patients with multiple myeloma to investigate oral ixazomib in combination with standard combination regimens.

The most frequent (at least 10%) AEs occurring in the pooled safety population from Studies C16005, C16006, C16008, and C16013 are shown for all grades (Table 1-3). Note that in combination trials "related" is defined as related to any study drug in the combination regimen.

## Table 1-3 Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events in Oral Combination Studies

| Primary System Organ Class<br>Preferred Term | Total Oral Combo Agent (5/6/8/13)<br>n = 173<br>n (%) |
|---|---|
| Subjects with at Least One Adverse Event | 163 (94) |
| Gastrointestinal disorders | 139 (80) |
| Nausea | 65 (38) |
| Diarrhea | 81 (47) |
| Vomiting | 51 (29) |
| Constipation | 57 (33) |
| General disorders and administration site conditions | 132 (76) |
| Fatigue | 76 (44) |
| Pyrexia | 39 (23) |
| Edema peripheral | 61 (35) |
| Asthenia | 20 (12) |
| Nervous system disorders | 115 (66) |
| Headache | 28 (16) |
| Dizziness | 34 (20) |
| Neuropathy peripheral | 45 (26) |
| Metabolism and nutrition disorders | 91 (53) |
| Decreased appetite | 25 (14) |
| Hypokalemia | 34 (20) |
| Blood and lymphatic system disorders | 88 (51) |
| Thrombocytopenia | 49 (28) |
| Anemia | 45 (26) |
| Neutropenia | 43 (25) |
| Lymphopenia | 20 (12) |
| Skin and subcutaneous tissue disorders | 102 (59) |
| Rash maculopapular[a] | 29 (17) |
| Rash macular[a] | 22 (13) |
| Musculoskeletal and connective tissue disorders | 99 (57) |
| Back pain | 42 (24) |
| Pain in extremity | 31 (18) |
| Arthralgia | 22 (13) |
| Respiratory, thoracic and mediastinal disorders | 80 (46) |
| Cough | 36 (21) |
| Dyspnea | 26 (15) |

**Table 1-3 Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events in Oral Combination Studies**

| Primary System Organ Class<br>Preferred Term | Total Oral Combo Agent (5/6/8/13)<br>n = 173<br>n (%) |
|---|---|
| Infections and infestations | 92 (53) |
| Upper respiratory tract infection | 35 (20) |
| Psychiatric disorders | 73 (42) |
| Insomnia | 50 (29) |

Source: Ixazomib Investigator's Brochure Edition 7

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, version 15.0.

Subject Incidence: A subject counts once for each preferred term. Percentages use the number of treated subjects as the denominator.

Data from ongoing blinded pivotal trials (C16010) are not included.

a. Note that rash maculopapular and rash macular represent the 2 most common terms used to describe rash.

The clinical experience with ixazomib also shows early signs of antitumor activity as evidenced by at least a 50% reduction in disease burden in some patients and prolonged disease stabilization in others across all ongoing trials. The antitumor activity has been seen with single-agent ixazomib, when combined with established therapies, and across the malignancies studied (advanced solid tumors [5], non-Hodgkin's disease, Hodgkin's disease [6], relapsed and/or refractory multiple myeloma [RRMM; 7; 8], relapsed or refractory systemic light chain amyloidosis [RRAL; 9], and newly diagnosed multiple myeloma [NDMM; 10; 11; 12]) to date.

Though additional data are needed to characterize the clinical benefit of this drug, the emerging data supports the ongoing development of ixazomib.

### 1.6 Relapsed and/or Refractory Multiple Myeloma

The early development of ixazomib in patients with RRMM involved 2 studies (C16003 and C16004) with similar objectives, but each investigated 1 of the 2 dosing schedules commonly used with the first-in-class proteasome inhibitor, Velcade.

Study C16003 is an open-label, dose escalation, phase 1 study of ixazomib dosing on a twice-weekly schedule on Days 1, 4, 8, and 11 of a 21-day cycle in adult patients with RRMM.[13, 14] Study C16004 is an open-label, dose escalation, phase 1 study of ixazomib dosing on a weekly schedule on Days 1, 8, and 15 of a 28-day cycle in adults patients with RRMM.[15, 16,17]Both studies have now completed enrollment. The DLTs in Study C16003 were rash macular and

thrombocytopenia and the DLTs in C16004 were nausea, diarrhea, vomiting, and erythema multiforme.

In the dose escalation component of both studies, patients had multiple myeloma that had relapsed following at least 2 lines of therapy that must have included bortezomib, thalidomide (or lenalidomide), and corticosteroids. In both studies, when the MTD was established, cohorts of patients representing the heterogeneous patient population seen in clinical practice were to be enrolled into 1 of 4 expansion cohorts, including a relapsed and refractory cohort, a carfilzomib cohort, a proteasome inhibitor-naïve cohort, and a Velcade-relapsed cohort.

Final study results are being analyzed, but preliminary data suggest that ixazomib has anti-tumor activity in heavily pretreated MM patients, with durable responses/disease control, and is generally well tolerated. Please refer to the ixazomib IB and SMA for further information.

### 1.7 Newly Diagnosed Multiple Myeloma (NDMM)

Multiple research paths are being explored in patients with NDMM with a focus on evaluating ixazomib in combination with agents commonly used across treatment settings. The development of ixazomib in combination with lenalidomide with dexamethasone (Rd) in patients with NDMM who are transplant eligible or ineligible involves 2 studies (C16005 and C16008) with similar study designs except for a few key differences, namely the schedules of ixazomib and dexamethasone. Ixazomib is also being evaluated in combination with melphalan and prednisone (MP) for patients who are not transplant eligible due to age or coexisting morbidity (in Study C16006).

All 3 studies are phase 1/2, with phase 1 focusing on safety and phase 2 on efficacy (and further characterization of safety). Please refer to the ixazomib IB and SMA for further information.

### 1.8 Clinical Trial Experience Using the Intravenous Formulation of Ixazomib

See the IB for descriptions of the 2 studies that investigated IV ixazomib in advanced solid tumors and advanced lymphoma (Studies C16001 and C16002, respectively).

### 1.9 Study Rationale

In the recent years, emerging evidence demonstrates that increased control of multiple myeloma, and possibly a functional cure in some patients, may be achieved if we deliver extended treatment to patients with newly diagnosed disease. In addition, as more sensitive methods for the assessment of minimal residual disease (MRD) have been developed, including allele-specific oligonucleotide polymerase chain reaction (ASO-PCR), multiparameter flow cytometry

(MFC), and more recently gene sequencing, MRD negativity is evolving as the new goal of therapy and possibly a new surrogate marker for progression free survival (PFS) and overall survival (OS). For example, in a multivariate analysis of 295 newly diagnosed MM patients, MRD negativity at 100 days post-transplant was the most important, independent prognostic factor for PFS and OS. [19]

In addition, there is vast data demonstrating that post-transplant maintenance improves outcomes. Most recently, two studies have shown that post-transplant maintenance with single-agent lenalidomide improves PFS and in one of these two studies OS. [20,21] Based on these results, post-transplant maintenance with lenalidomide has now been incorporated into the MM treatment algorithm in the United States. Improved outcomes in the maintenance phase have been also shown with single agent thalidomide and bortezomib. [22, 23, 24] Furthermore, there is also emerging evidence that two- or three-drug regimens are active in post-transplant setting. For example, bortezomib, thalidomide, dexamethasone (VTD) when given every 3 months, was reported to prolong PFS when compared to thalidomide alone, with surprisingly significant benefit for standard risk but not poor risk patients. [25] In addition, there is also mounting evidence that post-transplant consolidation, given in addition to or prior to maintenance, deepens the response and likely contributes to improved PFS, particularly with 3-drug regimens including proteasome inhibitor (PI) and immunomodulatory drug (IMiD). [26, 27]

Extended treatment with bortezomib, lenalidomide, dexamethasone (RVD) and carfilzomib, lenalidomide, dexamethasone (CRd) resulted in deeper responses over time and likely contributed to the excellent results with CR+nCR rate of 57% and 67%, respectively (phase II) and an estimated 18-month and 24-month PFS of 75% and 92%, respectively. In a recently presented follow-up of the CRd study, the rate of MRD negativity improved by about 20% between 8 and 16 months of CRd maintenance. [28] Furthermore, it was demonstrated that extended, 2-year treatment with three drug combinations (CRd and RVd), which included low-dose dexamethasone is well tolerated, with limited and mostly mild toxicity, including limited dexamethasone-related toxicity. [28]

Taken together, these studies shows that combinations of a PI and IMiD may be superior compared to single agents in the consolidation/maintenance phase and results in improved depth of response and prolonged PFS and OS. The advent of active oral PIs, and, in particular, the proven efficacy of ixazomib (MLN9708) in combination with lenalidomide and low dose dexamethasone [10, 11]), yields the possibility of exploring this strategy without the limitations that chemotherapy infusions pose over extended treatment both in convenience and increased toxicity.

Lenalidomide maintenance is most commonly used in the post-transplant setting and considered standard of care in the United States. Approximately 30% of patients who initiate lenalidomide maintenance are in CR post-transplant (McCarthy et al, N Eng J Med, 2012). Of these patients, approximately 70% would be expected to have MRD negative status. [19] However, a significant proportion of patients are not in CR, and consequently with residual MRD and therefore at higher risk for earlier relapse and shorter survival. [19] Based on this observation, we propose to evaluate the impact of consolidation and extended maintenance with an all oral combination of ixazomib, lenalidomide, and low dose dexamethasone (IRD) in patients who are already on single agent lenalidomide maintenance but who have persistent residual disease, a population that is in need of further improvement in their disease outcome. [19] The aim of this proposal is to provide preliminary evidence that IRD will statistically improve the rate of MRD-negative disease and the depth of response in the post-transplant setting compared to the rate observed in patients who continue single agent lenalidomide. Since there is vast evidence that the rate of CR and in particular the rate of MRD-negative disease translates into longer PFS, the study is anticipated to generate preliminary information for further, more definite exploration of this strategy.

The rationale for adding a PI (ixazomib) to lenalidomide in this subset of patients is discussed above. The rationale for adding low dose dexamethasone is three-fold: (1) 3-drug combinations of PI, IMiD, and low dose dexamethasone, and in particular IRD have a proven track record of efficacy, while only limited information is available for combination of lenalidomide with PI, with evidence that it could have inferior efficacy without dexamethasone [29]; (2) low dose dexamethasone has previously been shown to be well tolerated with long term use [30]; (3) dexamethasone appears to improve the tolerability of ixazomib, particularly by reducing the incidence of rash and gastrointestinal symptoms that are associated with this agent [10, 16].

Subjects are randomized in a 1:1 ratio between IRd vs. R with both arms undergoing 12 months of treatment to balance the study objectives and risk of toxicities. This duration of treatment is supported by prior observations that the median time to the achievement sCR and MRD-negative status is approximately12-13 months of treatment and that the plateau of sCR and MRD is reached at about 16-18 months from the start of the treatment. [28] All subjects enrolled into the trial will already be on a post-transplant lenalidomide maintenance regimen such that the protocol period of 12 months will prove to be sufficient for determination of the primary objective and for the duration that limits increased risks of toxicities.

An extended treatment with lenalidomide in post-transplant setting may raise concerns for increased risk of second primary malignancies (SPM). While the risk of SPM has been reported with lenalidomide maintenance, in a recent large meta-analysis by Palumbo et al, the risk of

SPM was greatest in patients in the context of recent melphalan, particularly in patients who received oral melphalan in addition to lenalidomide. Moreover, in the post-transplant setting, mostly initial exposure to lenalidomide accounted for SMPs, and there is no evidence to date that an extended treatment with lenalidomide beyond an initial period of 1 year increases this rate. [21] In addition, the overall cumulative risk of death due to myeloma was much greater compared to risk of death from SPM, suggesting a positive benefit/risk profile in patients receiving lenalidomide [31], supporting further the proposed duration of treatment on this protocol.

Because of the emergence of a correlation between minimal residual disease (MRD) and PFS/OS, the rate of MRD negativity will be used as a surrogate marker for PFS and exploration of the primary objective. MRD-negative status will be determined by multiparameter flow cytometry (MCF) and next generation sequencing (NGS). We hypothesize that the IRD combination will increase the rate of MRD-negative disease by 20% in the experimental versus control arm within 12 months from the date of randomization as specified in the statistical section. If the results meet statistical endpoints for a promising outcome, future phase III clinical trials will be warranted to expand on this hypothesis.

### 1.10 Potential Risks and Benefits

Please refer to the current ixazomib IB and SMA.

The clinical benefit of ixazomib continues to be studied in a comprehensive and global development plan that involves studies sponsored by Millennium. Ixazomib appears to show early signs of anti-tumor activity as evidenced by at least 50% reduction in disease burden in some patients, including patients that have been heavily pretreated as well as those with newly diagnosed MM, and prolongs stabilization of the underlying disease in other patients across all ongoing trials. The preliminary findings are favorable when considering historical and available therapies for the patient populations evaluated. Though additional data are needed to characterize the clinical benefit of this drug, the emerging data supports expanded development of ixazomib for the treatment of patients with advanced malignancy.

Clinical benefit and safety of ixazomib in combination with lenalidomide and dexamethasone has been established, based on the results of studies listed in Table 1-1 above. Two ongoing randomized trials with Ixazomib and lenalidomide and dexamethasone reflect the confidence of safety of the combination and dexamethasone in newly diagnosed and relapsed myeloma. In addition, the combination of Ixazomib and lenalidomide was well tolerated as maintenance in post-transplant setting (Shah et al, ASH 2013, Abstract 1983) and is providing rationale for randomized trial in cooperative groups.

This study will be conducted in compliance with the protocol, good clinical practice (GCP), applicable regulatory requirements, and International Conference on Harmonisation (ICH) guidelines.

## 2. STUDY OBJECTIVES

### 2.1 Primary Objectives

- To determine the rate of MRD-negative disease by multiparameter-flow cytometry (MFC) for patients enrolled based on MFC-positivity or by next generation sequencing (NGS) in patients enrolled based on NGS-positivity (patients with MRD-negative disease by MFC at screening), at 12 months after randomization

### 2.2 Secondary Objectives

- Evidence of response as demonstrated by the improvement in the depth of response by at least one category according to IMWG response criteria. (For example, an improvement from very good partial response (VGPR) to near complete response (nCR) or better than nCR including conversion from CR to MRD negative disease [overall response]) at 6 and 12 months
- Progression free survival (PFS)
- Overall survival (OS)
- Duration of MRD-negative disease
- Safety and tolerability of experimental arm (IRd) vs. control arm (R)

### 2.3 Tertiary/Exploratory Objectives *(if applicable)*

- Determination of markers of response based on pre-treatment characteristics using methods described in correlative research, protocol section 8.
- Evaluation of MRD by gene sequencing method using the Adaptive Biotechnologies platform (clonoSEQ® assay) in parallel with multi-parameter flow cytometry (MFC)

## 3. STUDY ENDPOINTS

### 3.1 Primary Endpoints

Rate of MRD negativity after 12 months of treatment with Ixazomib in combination with lenalidomide and dexamethasone compared to MRD negativity rate after 12 months of lenalidomide alone. For the majority of patients, where MRD positivity at screening will be determined by Multi-parameter Flow Cytometry (MFC), an improvement will be defined as a

conversion from MRD-positive to MRD-negative disease by MFC. Additionally, in the fraction of patients with MRD-negative disease by MFC at screening, who were MRD-positive by Next

Generation Sequencing (NGS), an improvement will be defined as a conversion from MRD-positive to MRD-negative disease by NGS

### 3.2 Secondary Endpoints

- The assessment of other measures of response including rate of VGPR, CR, sCR
- The assessment of duration of MRD-negative disease
- Estimates of PFS and OS
- Estimate of correlation between MRD status and PFS
- The assessment of safety and tolerability of IRd arm compared to R arm

### 3.3 Tertiary/Exploratory Endpoints

- Correlation of MRD results obtained by MCF with MRD results by gene sequencing method
- Feasibility of MRD evaluations in the multi-site setting
- Identification of biologic markers that may predict which patients are likely to benefit from to IRd maintenance

## 4. STUDY DESIGN

### 4.1 Overview of Study Design

This is a phase 2, open-label, randomized study in which subjects are enrolled 1:1 control to experimental arm stratified by 1) level of response at study entry and 2) risk factors:

1. Level of response to first line therapy including transplant; response is assessed at study screening
    a. <VGPR
    b. ≥VGPR
2. Risk Factors at the time of diagnosis
    a. At least one of the following poor prognostic risk factors:
        i. del-13 (by karyotyping)
        ii. hypodiploidy (by karyotyping)
        iii. (4;14) ( by FISH)
        iv. t(14;16) (by FISH)

v. t(14;20) (by FISH)

vi. del17p (by FISH)

vii. 1q21 gain (by FISH)

b. No risk factors

### 4.2 Study Procedures

Refer to the Study Schedule of Events for an overview. After screening, eligibility determination, enrollment & randomization, subjects will receive treatment in either control or experimental arm in 28-day cycles for 12 cycles or until progression, unacceptable toxicity or subject withdraws consent.

A subject is considered to be off-treatment following a 30-day safety follow-up period after the last treatment. Long-term follow-up for survival will be 2 years from End of Treatment visit.

#### 4.2.1 Screening Procedures

The screening period is 42 days in length. Screening can only start after the patient has signed the Informed Consent Form.

| | |
|---|---|
| Signed written informed consent | Obtained prior to performing any study specific assessments |
| Demographics and medical history | • Age, gender, ethnic background<br>• Details on myeloma diagnosis prior cancer therapy, including start and stop dates, transplant regimen, lenalidomide maintenance regimen<br>• Previous and concurrent relevant diseases<br>• Current symptoms and/ or residual toxicities |
| Pregnancy test (if applicable) (Day - 7 to -1) | A serum pregnancy test will be performed in pre-menopausal women and women who are post-menopausal for < 2 years. In case the sampling date for the serum pregnancy test exceeds 7 days before treatment start, a urine test is required for confirmation |
| Physical examination and vital signs | • Body height and weight<br>• BSA<br>• ECOG Performance Status<br>• Blood pressure, pulse, temperature<br>• Physical examination |

| | |
|---|---|
| Cardiac evaluation | 12-lead ECG required at screening (local machine) |
| Urinalysis | Urine bilirubin, glucose, hemoglobin, ketones, pH, protein. |
| Hematology (CBC) | Hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell (WBC) count, WBC differential, red blood cell count, lymphocytes, monocytes, neutrophils, band neutrophils, eosinophils, basophils, platelets. WBC differential may be automated or manual as per institutional standards. Reticulocytes may be done only when clinically indicated |
| Clinical chemistry | Sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, phosphate, magnesium, ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin, uric acid, LDH, and CRP |
| CRP & β2 microglobulin | Required at screening only |
| Myeloma Disease Assessment - laboratory | M-protein determination:<br>• Serum Protein Electrophoresis (SPEP) and immunofixation<br>• Urine Protein Electrophoresis (UPEP) and immunofixation<br>• Serum Free Light Chains (SFLC)<br>• Serum quantitative immunoglobulins (Igs)<br>All of the above assessments are required at screening regardless of the disease classification. |
| Bone Marrow Biopsy | Quantify percent myeloma cell involvement, and obtain bone marrow aspirate for conventional cytogenetics and fluorescent *in situ* hybridization. Required specimen for calibration step for MRD evaluation by gene sequencing. For subjects who sign consent for correlative samples, an additional aspirate sample should be collected at screening (Section 8). Bone marrow biopsy/aspirate performed outside of the 42 day window may be considered for inclusion. Please contact the Lead Principal Investigator and/or the CRA on a case-by-case basis. |
| Plasmacytoma Evaluation | May be performed by physical exam or imaging, whichever is clinically indicated and at the treating investigator's discretion. |

| | |
|---|---|
| Skeletal Survey | May be within 42 days of planned treatment start (does not need to be repeated if within 42 days). Includes: lateral radiograph of the skull, anteroposterior and lateral views of the spine, and anteroposterior views of the pelvis, ribs, femora, and humeri. |
| Neurotoxicity Assessment | Includes Neurotoxicity Questionnaire (Appendix 13.4) |
| QOL Assessment | Patient reported survey (Appendix 14.5) |
| Adverse Events | Only SAEs considered related to study procedure need to be reported. |
| Correlative Samples | Peripheral blood and bone marrow aspirate samples collected at screening. Buccal mucosa swab will be collected at screening only |

### 4.2.2 Treatment Phase Procedures

Following randomization, these assessments should be performed on Day 1 of each cycle unless otherwise noted.

| | |
|---|---|
| Complete Physical examination and vital signs | • Body weight<br>• BSA<br>• ECOG Performance Status<br>• Blood pressure, pulse, temperature<br>• Pulse oximetry |
| Hematology<br>(Day 1 of every cycle and when clinically indicated) | Hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell (WBC) count, WBC differential, red blood cell count, lymphocytes, monocytes, neutrophils, band neutrophils, eosinophils, basophils, platelets. WBC differential may be automated or manual as per institutional standards. Reticulocytes may be done only when clinically indicated |

| | |
|---|---|
| Complete clinical chemistry<br>(Day 1 of every cycle and when clinically indicated) | Sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, phosphate, magnesium, ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin, uric acid, LDH, CRP. |
| Pregnancy Test | Day 1 of every cycle in accordance with the lenalidomide REMS™ program for FCBP (Appendix 13.6) |
| Myeloma Disease Assessment – laboratory<br>(Day 1 of every cycle) | M-protein determination:<br>• Serum Protein Electrophoresis (SPEP) and immunofixation<br>• Urine Protein Electrophoresis (UPEP) and immunofixation<br>• Serum Free Light Chains<br>• Serum quantitative immunoglobulins (Igs)<br>Only those assessments used to follow the myeloma disease are required past screening. All assessments are required for confirmation of response. |
| Neurotoxicity Assessment | Including Neurotoxicity Questionnaire (Appendix 13.4) |
| QOL Assessment | Patient reported survey (Appendix 14.5) |
| Adverse events | Assessed on an ongoing basis |

| | |
|---|---|
| Study Treatment – Experimental Arm | Ixazomib on Days 1, 8, 15. lenalidomide on Days 1-21. Dexamethasone 1, 8, 15, 22 (Cycle 1-4). **Refer to Schedule of Events Table and Section 7.2.1** |
| Study Treatment – Control Arm | lenalidomide on Days 1-28. **Refer to Schedule of Events Table and Section 7.2.2** |
| Correlative Samples | For patients who give consent, peripheral blood and bone marrow aspirate samples collected at any time after randomization that CR or better is suspected. |

### 4.2.3 End of Treatment Procedures

Patients who discontinue therapy for any reason must have and end of treatment (EOT) visit completed 30 days (± 7 days) after the last application of study drug. Following the end of treatment, subjects will be followed for survival for 2 years.

| | |
|---|---|
| Physical examination and vital signs | • Body weight<br>• Blood pressure, pulse, temperature<br>• Physical examination<br>• Pulse oximetry |
| Cardiac evaluation | 12-lead ECG |
| Urinalysis | Urine bilirubin, glucose, hemoglobin, ketones, pH, protein |
| Hematology | Hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell (WBC) count, WBC differential, red blood cell count, lymphocytes, monocytes, neutrophils, band neutrophils, eosinophils, basophils, platelets. WBC differential may be automated or manual as per institutional standards. Reticulocytes may be done only when clinically indicated |
| Clinical chemistry | Sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, phosphate, magnesium, ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin, uric acid, LDH, CRP |

| | |
|---|---|
| Pregnancy test (if applicable) | A serum pregnancy test will be performed in pre-menopausal women and women who are post-menopausal for < 2 years to exclude that a pregnancy occurred under treatment and in accordance with lenalidomide REMS™ (Appendix 13.6) |
| Myeloma Disease Assessment–laboratory | M-protein determination:<br>• Serum Protein Electrophoresis (SPEP) and immunofixation<br>• Urine Protein Electrophoresis (UPEP) and immunofixation<br>• Serum Free Light Chains<br>• Serum quantitative immunoglobulins (Igs) |
| Bone Marrow Biopsy | Quantify percent myeloma cell involvement, and obtain bone marrow aspirate for conventional cytogenetics and fluorescent in situ hybridization. A sample for MRD evaluation is required to be collected. For subjects who sign consent for correlative samples, an additional aspirate sample should be collected at screening (Section 8) |
| Correlative Samples | For patients who give consent, peripheral blood and bone marrow aspirate samples collected at End of Treatment |
| Neurotoxicity Assessment | Including Neurotoxicity Questionnaire (Appendix 5) |
| QOL Assessment | Patient reported survey |
| Adverse events | Record through 30-days after last treatment. All SAEs considered related to treatment must be followed until resolution. |

### 4.3 Number of Patients

A total of 60 patients will be enrolled in a 1:1 ratio into one of two arms: IRd or lenalidomide alone. Enrollment is defined as the time of randomization. **Protocol treatment must start within 2 days of randomization**.

### 4.4 Duration of Study

The study is planned to start in Q3 2014 with respect to first patient in (FPI). The enrollment period is expected to be 12-14 months across 8 centers for a total enrollment of 60 subjects. The maximum length of treatment period will be 12 months not accounting for dose delays or

interruptions. Subjects will be followed after the end of treatment visit for up to 2 years. The accrual end date will be by 3/31/2020.

### 4.5 Response Evaluation

Response will be evaluated based on IMWG criteria (Appendix 13.3). The first evaluation will be completed at the end of Cycle 1 and the M-spike value will be compared to baseline (pre-induction treatment) M-spike to determine response. If M-spike is not available, the respective pre-treatment immunoglobulin level and for light-chain-disease-only subjects, involved free light chain level or 24-hr total protein level, will be used to assess response.

If at any time throughout the treatment a complete response or better is suspected, a complete disease assessment should be performed to confirm response according to IMWG criteria (Appendix 13.3).

## 5. STUDY POPULATION

### 5.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

1. Patients who completed induction treatment followed by autologous stem cell transplant as initial therapy for symptomatic myeloma as per IMWG criteria and are considered for single agent lenalidomide maintenance or initiated single agent lenalidomide maintenance.
    a) Patients will be eligible for enrollment in the first 0-6 months of lenalidomide maintenance provided that lenalidomide maintenance has been initiated within 6 months post transplant as per standard of care.
        i. Patients do not have to be on Lenalidomide at the time of study consent.
    b) Patients already in lenalidomide maintenance must be received lenalidomide 10 mg or 15 mg and be able to tolerate dose escalation to 25 mg daily.
    c) Patients receiving off protocol lenalidomide maintenance cannot exceed 6 months post-transplant
    d) A one week break from off protocol lenalidomide is suggested, prior to initiating treatment on the study
        i. Any delays >7 days to align treatment with the start of Cycle 1 Day 1, of either arm, must be discussed with the PI.

e) Patients who completed tandem transplantation will be eligible for enrollment

2. No evidence of progressive disease on lenalidomide
3. Evidence of minimal residual disease at the time of screening defined as at least MRD-positive disease.
    a) The primary method of evaluation of MRD is Multi-parameter Flow Cytometry (MFC) performed at the University of Chicago.
    b) Patients who have negative MRD by Multi-Parameter Flow Cytometry (MFC) but have residual original monoclonal protein by serum or urine immunofixation may be eligible if they are found to have MRD-positive disease by Next Generation Sequencing (NGS)
    c) If patient is receiving lenalidomide, any delays required to align treatment with the start of Cycle 1 of either arm, must be discussed with the PI.
4. Bone marrow specimen from diagnosis (or pre-induction) will be required at study entry; available DNA sample will be used for calibration step for MRD evaluation by gene sequencing
5. Males and females ≥ 18 years of age
6. Life expectancy of more than 3 months
7. ECOG performance status of 0-2
8. Adequate hepatic function, with bilirubin ≤1.5 x ULN and aspirate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 xULN
9. ANC ≥1.0 x $10^9$/L, hemoglobin ≥8 g/dL, platelet count ≥75 x $10^9$/L.
10. Calculated creatinine clearance (by Cockcroft-Gault) ≥50 ml/min or serum creatinine below 2 g/dL (section 13.2)
11. Voluntary written consent must be given before performance of any study related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
12. Female patients who:
    - Are postmenopausal for at least 1 year before the screening visit, OR
    - Are surgically sterile, OR

- If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form through 90 days after the last dose of study drug, OR
- Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

13. Male patients, even if surgically sterilized (i.e., status post-vasectomy), must agree to one of the following:
    - Agree to practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study drug, OR
    - Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

### 5.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Evidence of progressive disease on lenalidomide maintenance as per IMWG criteria
2. Patients who have already started or received multi-drug consolidation regimen post-transplant except for patients receiving up to 6 months of single agent lenalidomide maintenance.
3. Longer than 12 months since the initiation of induction therapy at the time of start lenalidomide maintainance
4. Prior progression after initial therapy.
    a) Subjects, whose therapy changed due to suboptimal response, intolerance, etc., remain eligible, provided they do not meet criteria for progression.
    b) No more than two regimens will be allowed excluding dexamethasone alone.
5. Diarrhea > Grade 1 in the absence of anti-diarrheals
6. Central Nervous System involvement of the disease under study.
7. Female patients who are lactating or have a positive serum pregnancy test during the screening period.

8. History of allergy to mannitol
9. Major surgery within 14 days before enrollment.
10. Radiotherapy within 14 days before randomization. If the involved field is small, 7 days will be considered a sufficient interval between treatment and administration of the ixazomib.
11. Evidence of current uncontrolled cardiovascular conditions, including uncontrolled cardiac conditions such as hypertension, or cardiac arrhythmias, or New York Heart Association Stage III and IV congestive heart failure, or unstable angina or myocardial infarction within the past 6 months.
12. Rate-corrected QT interval of electrocardiograph (QTc) > 470 msec on a 12-lead ECG during screening
13. Uncontrolled diabetes
14. Acute infection requiring systemic anti-infectives, antivirals, or antifungals within two weeks prior to first dose
15. Systemic treatment, within 14 days before the first dose of ixazomib, with strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's wort.
16. Ongoing or active systemic infection, active hepatitis B or C virus infection, or known human immunodeficiency virus (HIV) positive.
17. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
18. Known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent.
19. Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of ixazomib including difficulty swallowing.
20. Diagnosed or treated for another malignancy within 2 years before study enrollment or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with non-melanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.
21. Patient has ≥ Grade 3 peripheral neuropathy or Grade 2 with pain on clinical examination during the screening period.

22. Participation in other clinical trials with other investigational agents not included in this trial, within 30 days of the start of this trial and throughout the duration of this trial.

## 6. REGISTRATION PROCESS

When a potential patient has been identified, notify the CRA via phone or email to ensure a reservation on the study (contact information listed on enrollment form). Reservations for potential subjects will only be held for subjects who have signed consent for that particular study.

When registering a subject, the following must occur:

- Confirm that the institution has a current IRB approval letter for the correct version of protocol/consent and has an annual update on file, if appropriate.
- Submit all required materials (Eligibility Checklist, Source documentation, & signed consent form) to confirm eligibility and required pre-study procedures to the CRA a minimum of 48 hours prior to the subject's scheduled therapy start date.
- Source documentation includes copies of all original documents that support each inclusion/exclusion criteria. The eligibility checklist does not serve as source documentation but rather as a checklist that original source documentation exists for each criterion.
- Communicate with the CRA to ensure all necessary supporting source documents are received and the potential subject is eligible to start treatment on schedule. If there are questions about eligibility, the CRA will discuss it with the PI. PI may clarify, but not overturn, eligibility criteria.
- Affiliate sites must confirm registration of subjects by obtaining a subject study ID number from the CRA via phone, fax or email.
- If a subject does not start on the scheduled day 1 treatment date, promptly inform the CRA as the delay in start may deem the subject ineligible and/or require further or repeat testing to ensure eligibility.
- The date the patient is randomized if randomization is involved or receives treatment for the first time will be considered the patient's "On Study Date." The patient's subject ID will be assigned and a confirmation of registration will be issued by the CRA on this date. Subjects that sign consent and do not go "On Study" will be recorded in the database with the date they signed consent and the reason for not going "On Study" (e.g., Ineligible, Screen Failure or Withdrawn Consent).

# 7.STUDY DRUG

## 7.1 Description of Investigational Agents

### Ixazomib Capsules

The ixazomib drug product is provided in strengths of 4.0-, 3.0-, and 2.3-mg and 2.0-, 0.5-, and 0.2 mg capsules as the active boronic acid. The different dose strengths are differentiated by both capsule size and color as described below:

| Dose Strength | Capsule Size | Capsule Color |
|---|---|---|
| 4.0 mg | Size 4 | Ivory |
| 3.0 mg | Size 3 | Light gray |
| 2.3 mg | Size 2 | Light pink |
| 2.0 mg | Size 2 | Swedish orange |
| 0.5 mg | Size 3 | Dark green |
| 0.2 mg | Size 4 | White opaque |

For additional details, please see the ixazomib IB.

### Lenalidomide

Lenalidomide, a thalidomide analogue, is an immunomodulatory agent with anti-angiogenic and anti-neoplastic properties. The chemical name is 3-(4-amino-1-oxo 1,3-dihydro-2H-isoindol-2-yl) piperidine-2,6-dione. The empirical formula for lenalidomide is C13H13N3O3, and the gram molecular weight is 259.3.

Lenalidomide is off-white to pale-yellow solid powder. It is soluble in organic solvent/ water mixtures, and buffered aqueous solvents. Lenalidomide is more soluble in organic solvents and low pH solutions. Solubility was significantly lower in less acidic buffers, ranging from about 0.4 to 0.5 mg/mL. Lenalidomide has an asymmetric carbon atom and can exist as the optically active forms S(-) and R(+), and is produced as a racemic mixture with a net optical rotation of zero. Lenalidomide is available in 5mg, 10mg, 15mg and 25mg capsules for PO administration. Each capsule contains lenalidomide as the active ingredient and the following inactive ingredients: lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The 5 mg and 25 mg capsule shell contains gelatin, titanium dioxide and black ink. The 10 mg capsule shell contains gelatin, FD&C blue #2, yellow iron oxide, titanium dioxide and black ink. The 15 mg capsule shell contains gelatin, FD&C blue #2, titanium dioxide and black ink.

**Dexamethasone**

Dexamethasone is a commercially available PO drug, supplied as 2 and 4 mg tablets. It is a synthetic adrenocortical steroid and occurs as a white to off-white, odorless, crystalline powder. It is stable in air and practically insoluble in water.

## 7.2 Study Drug Administration

All protocol-specific criteria for administration of study drug must be met and documented before drug administration. Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified sub-investigator(s). Patients should be monitored for toxicity, as necessary, and doses of ixazomib should be modified as needed to accommodate patient tolerance to treatment; this may include symptomatic treatment, dose interruptions, and adjustments of ixazomib dose (see Section 7.3).

### 7.2.1 Experimental Arm

All Cycles are 28 days long.

Ixazomib Administration

Capsules of ixazomib will also be referred to as study drug. Study drug will be supplied by Millennium as capsules of 0.2-, 0.5-, and 2.0 mg, or as capsules of 2.3-, 3.0- and 4.0 mg ixazomib.

Subjects randomized to the experimental arm will receive Ixazomib as follows:

- Cycles 1-4: Ixazomib will be administered on Days 1, 8, and 15.
    - Cycle 1 will started at 3 mg. If 3 mg Ixazomib is well tolerated, the dose may be increased to 4 mg at the start of Cycle 2
- Cycles 5-12: Ixazomib will be administered on Days 1, 8, and 15 at the best tolerated dose established for the individual patient during Cycles 1-4.

Patients should be instructed to swallow ixazomib capsules whole, with water, and not to break, chew, or open the capsules. Ixazomib should be taken on an empty stomach (no food or drink) at least 1 hour before or 2 hours after a meal or any other medication. Each capsule should be swallowed separately with a sip of water. A total of approximately 8 ounces (240 mL) of water should be taken with the capsules.

Missed doses can be taken as soon as the patient remembers, if the next scheduled dose is 72 hours or more away. A double dose should not be taken to make up for a missed dose. If the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose.

Site staff will oversee the study subject taking day 1 doses of every cycle of all medications (IRd or R) during the visits to ensure proper administration. Site staff should not provide any study drug until dosing is to begin. Additionally, site staff will ensure that the study subject is adequately informed and understands dosing instructions for all medications. The site staff might consider asking the subject to repeat the dosing instructions to ensure his/her understanding, and allow the opportunity to ask questions. Dosing instructions should be repeated before a new dose of study drug is provided to the study subject.

Finally, dosing diaries will be completed by the site personnel including dates of doses to be taken, # of capsules to be taken/dosing day. In addition, where applicable, the site staff will cross out non-dosing days on the study subject's dosing diary at each dispensation visit.

Ixazomib Destruction

Investigational ixazomib (expired or end of study) should be destroyed on site according to the institution's standard operating procedure. Be sure to document removal and destruction on drug accountability logs.

Lenalidomide Administration

Lenalidomide will be provided in accordance with the lenalidomide REMS® program of Celgene Corporation. Per standard lenalidomide REMS® requirements, all physicians who prescribe lenalidomide for research subjects enrolled into this trial must be registered in must comply with all requirements of the lenalidomide REMS® program. Prescriptions must be filled within 7 days. Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle. Unused lenalidomide will be counted and documented by each site.

Subjects randomized to the experimental arm will receive lenalidomide as follows:

- Cycles 1-4: Lenalidomide will be administered on Days 1-21 at a dose of 25 mg.
- Cycles 5-12: Lenalidomide will be administered on Days 1-21 at the best tolerated dose.

Lenalidomide should be taken in the evening at approximately the same time each day. Lenalidomide is taken with water on a full or empty stomach. Subjects should not break, chew

or open capsules. Missed doses can be taken as soon as the patient remembers as long as it is less than 12 hours since the scheduled time. If it has been more than 12 hours, the dose should be skipped. Vomited doses will not be made up. Subjects should be instructed to never take lenalidomide past Day 21 of each cycle.

Dexamethasone Administration

Dexamethasone will ideally be best administered in the morning with a meal 2 hours before Ixazomib. If this is not possible, dexamethasone will be administered with a meal and at least 1 hour after ixazomib dose on days that they coincide (Days 1, 8, 15), as follows:

- Cycles 1-4: 40 mg PO per dose Days 1, 8, 15 and 22
    - Dexamethasone may administered as a split schedule of 20 mg PO or IV (pre-ixazomib during weeks 1-3 when ixazomib is administered) on Days 1, 2, 8, 9, 15, 16, 22, and 23 after discussion with the Lead Principal Investigator.
- Cycles 5-12: Dexamethasone discontinuation
    - Low dose of dexamethasone up to 20 mg per dose weekly on days 1, 8, 15, and 22 is allowed based on investigator determination of best tolerability of regimen.

Dexamethasone given on days without ixazomib and lenalidomide (Days 22) may be self-administered by the subject on an outpatient basis. Missed doses of dexamethasone will not be made up.

### 7.2.2 Control Arm

Lenalidomide Administration

Lenalidomide will be provided in accordance with the Lenalidomide REMS® program of Celgene Corporation. Per standard lenalidomide REMS® requirements, all physicians who prescribe lenalidomide for research subjects enrolled into this trial must be registered in must comply with all requirements of the lenalidomide REMS® program. Prescriptions must be filled within 7 days. Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle. Unused lenalidomide will be counted and documented by each site.

Subjects randomized to the control arm will receive lenalidomide as follows:

- Cycles 1-12: Lenalidomide will be continuously administered on Days 1-28 at a dose of either 10 mg or 15 mg.

- Lenalidomide administration may be given at 5 mg only if it is documented that this was the best last tolerated dose. 5 mg dosing requires Lead Principal Investigator approval.
- If the 10 mg dose is tolerated for 3 cycles – **off or on protocol** – the dose can be escalated to 15 mg.

Lenalidomide should be taken at approximately the same time each day. Lenalidomide is taken with water on a full or empty stomach. Subjects should not break, chew or open capsules. Late doses of lenalidomide should if possible be taken on the assigned day but should not be made up the next day. Vomited doses will not be made up.

### 7.3 Dose-Modification Guidelines

The following sections summarize dosing modifications for ixazomib, lenalidomide, and dexamethasone. Dose modifications different from those stated in the protocol must be discussed with the Lead Principal Investigator. Administration of ixazomib and/or lenalidomide will be discontinued in the event of any toxicity that, in the opinion of the Lead or Treating Investigator, warrants discontinuation.

In addition to dose reductions, administration of ixazomib and/or lenalidomide will be held temporarily in the event of a treatment-related toxicity, at the Treating Investigator's discretion. Study treatment may be re-introduced, if the event resolves back to the patient's baseline value or to ≤ Grade 1 within 21 days; otherwise, study drug will be permanently discontinued. Any deviations from this plan must be approved by the Lead Principal Investigator.

Experimental Arm:

**Table 7-1 Ixazomib Dose Adjustments**

| Nominal Ixazomib Dose | Dose -1 | Dose -2 | Dose -3 |
|---|---|---|---|
| 4 mg Days 1, 8, 15 ***(if escalated after Cycle 1)*** | 3 mg | 2.3 mg | Discontinue |
| 3 mg Days 1,8,15 | 2.3mg | Discontinue | N/A |

**Table 7-2 Lenalidomide Dose Adjustments**

| Nominal Lenalidomide Dose | Dose -1 | Dose -2 | Dose -3 | Dose -4 | Dose -5 |
|---|---|---|---|---|---|
| 25 mg Days 1-21 | 20mg | 15 mg | 10 mg | 5 mg | 5 mg every other day |

| | | | | | |
|---|---|---|---|---|---|
| 15 mg Days 1-21 | 10 mg | 5 mg | 5 mg every other day | Discontinue | N/A |
| 1 mg Days 1-21 | 5 mg | 5 mg every other day | Discontinue | N/A | N/A |

**Table 7-3 Dexamethasone Dose Adjustments***

| Nominal Dexamethasone Dose | Dose -1 | Dose -2 | Dose -3 | Dose -4 |
|---|---|---|---|---|
| 40 mg | 20 mg | 12 mg | 8 mg | 4 mg |

*Split dosing of dexamethasone on days 1, 2, 8, 9, 15, 16, 22, and 23 may be implemented to control toxicities that do not require a dose reduction. Split dosing requires Lead Principal Investigator approval before implementing

Control Arm

**Table 7-4 Lenalidomide Dose Adjustments**

| Nominal Lenalidomide Dose | Dose -1 | Dose -2 | Dose -3 | Dose -4 |
|---|---|---|---|---|
| 15 mg Days 1-28 | 10 mg | 5 mg | 5 mg Days 1-21 | 5 mg every other day Days 1-21 |
| 10 mg Days 1-28 | 5 mg | 5 mg Days 1-21 | 5 mg every other day Days 1-21 | Discontinue |

### 7.3.1 Recommended Criteria for Beginning or Delaying a Subsequent Treatment Cycle & Dose Modifications for Treatment Associated Toxicity

All treatment cycles are 28 days. For a new cycle of treatment to begin, the patient must meet the following criteria:

- ANC must be ≥ 1,000/mm$^3$.
- Platelet count must be ≥ 75,000/mm$^3$.
- All other non-hematologic toxicity (except for alopecia) must have resolved to ≤ Grade 1 or to the patient's baseline condition

If the patient fails to meet the above-cited criteria for initiation of the next cycle of treatment, dosing should be delayed for 1 week. At the end of that time, the patient should be re-evaluated to determine whether the criteria have been met. If the patient continues to fail to meet the above-cited criteria, delay therapy and continue to reevaluate. The maximum delay before treatment should be discontinued will be 3 weeks or at the discretion of the Principal Investigator. Any delay greater than 21 days must be reviewed with the Lead Principal Investigator if the treating investigator believes that continued treatment is in the subject's best interest and confirmation of clinical benefit (absence of disease progression).

The following tables outline dosing recommendations for Ixazomib, lenalidomide and Dexamethasone.

**Dosage adjustments for hematologic toxicity are outlined in Table 6-5**

**Table 7-5 Ixazomib and Lenalidomide Dose Adjustments for Hematologic Toxicities[a, b]**

| Criteria | Action |
|---|---|
| If platelet count decreased to Grade 3 with clinically significant bleeding or Grade 4 < 25 × $10^9$/L on any dosing day (other than Day 1) | |
| Within-Cycle Dose Modifications | • Ixazomib dose and lenalidomide should be withheld.<br>• Complete blood count (CBC) with differential should be repeated at least twice weekly until the platelet counts have exceeded the pre-specified values (see Section 6.3.1) on at least 2 occasions.<br>• Once resolved to Grade ≤1:<br>o 1st occurrence – decrease lenalidomide by 1 dose level; ixazomib may be reinitiated without dose reduction on the first occurrence.<br>o 2nd occurrence - decrease ixazomib 1 dose level and resume len at its most recent dose<br>o 3rd occurrence – decrease len 1 dose level from previous dose<br>o 4th occurrence – decrease ixazomib 1 dose level from previous dose |
| Day 1 of Cycle Dose Modifications | • 1st occurrence – decrease lenalidomide 1 dose level<br>• 2nd occurrence – decrease ixazomib 1 dose level<br>• 3rd occurrence – decrease lenalidomide by 1 additional dose level<br>• 4th occurrence – decrease ixazomib by 1 additional dose level |
| Neutrophil count (ANC) decreased Grade 3 (ANC 500-1000/$mm^3$) or > Grade 3 with fever (temperature >38.5°C) | |

**Dosage adjustments for hematologic toxicity are outlined in Table 6-5**

**Table 7-5 Ixazomib and Lenalidomide Dose Adjustments for Hematologic Toxicities[a, b]**

| Criteria | Action |
|---|---|
| Within-Cycle Dose Modifications | • Ixazomib dose and lenalidomide should be withheld.<br>• Complete blood count (CBC) with differential should be repeated at least twice weekly until the ANC has exceeded the pre-specified values (see Section 6.3.1) on at least 2 occasions.<br>• If neutropenia resolved to <Grade 2:<br>o Lenalidomide decrease 1 dose level<br>o Ixazomib – resume at its most recent dose if ANC recovered prior to next planned dose and resume planned treatment cycle |
| Day 1 of Cycle Dose Modifications | • If neutropenia is the only toxicity for which a dose reduction is required, G-CSF may be used prophylactically, as per ASCO guidelines, for the subsequent cycle and dose maintained<br>• For each subsequent occurrence of the same level of neutrophil count decrease, hold lenalidomide treatment and upon recovery of ANC to >1,000/mm3 resume as follows:<br>o 1st occurrence – decrease lenalidomide 1 dose level<br>o 2nd occurrence – decrease ixazomib 1 dose level<br>o 3rd occurrence – decrease lenalidomide by 1 additional dose level; do not dose below 5mg daily |
| Grade 4 neutropenia (<500/mm$^3$) | |
| Within Cycle Dose Modifications | • Ixazomib dose and lenalidomide should be withheld.<br>• Complete blood count (CBC) with differential should be repeated at least twice weekly<br>• If neutropenia resolved to <Grade 2 within the cycle:<br>o Lenalidomide decrease 1 dose level below current dose level<br>o Ixazomib if prior to next planned dose, decrease 1 dose level |

**Dosage adjustments for hematologic toxicity are outlined in Table 6-5**

**Table 7-5 Ixazomib and Lenalidomide Dose Adjustments for Hematologic Toxicities[a, b]**

| Criteria | Action |
|---|---|
| Day 1 of Cycle Dose Modifications | • Use of G-CSF as above<br>• For each subsequent drop <1,000/mm$^3$ and recovery to >1,000/mm$^3$, decrease lenalidomide one dose level less than the previous dose, but do not dose below 5 mg daily |

a) Both drugs may be reduced at the same time at the investigator's discretion
b) Doses held during a treatment cycle are not to be replaced

**Treatment modifications due to ixazomib-related AEs are outlined in Table 6-6.**

**Table 7-6 Ixazomib Treatment Modification (Delays, Reductions, and Discontinuations) Due to Adverse Events (Non-Hematologic Toxicities)**

| Adverse Event (Severity) | Action on ixazomib | Further Considerations |
|---|---|---|
| **Peripheral Neuropathy:** | | |
| Grade 1 peripheral neuropathy without pain | • No action | Grade 1 signs and symptoms: asymptomatic; without pain or loss of function; clinical or diagnostic observations only [14] |
| New or worsening Grade 1 peripheral neuropathy with pain or Grade 2 | • Hold ixazomib until resolution to Grade ≤ 1 without pain or baseline<br>• Reduce ixazomib 1 dose level | Grade 2 signs and symptoms: Moderate symptoms; limiting instrumental activities of daily living (ADL) [14] |
| New or worsening Grade 2 peripheral neuropathy with pain or Grade 3 | • Hold ixazomib until resolution to Grade ≤ 1 without pain or baseline<br>• Reduce ixazomib to next lower dose upon recovery | Grade 3 signs and symptoms: severe symptoms; limiting self-care ADL; assistive device indicated [14] |
| New or worsening Grade 4 peripheral neuropathy | • Discontinue ixazomib | |

**Table 7-6 Ixazomib Treatment Modification (Delays, Reductions, and Discontinuations) Due to Adverse Events (Non-Hematologic Toxicities)**

| Adverse Event (Severity) | Action on ixazomib | Further Considerations |
|---|---|---|
| Grade 2 Rash | • Follow at least weekly<br>• Symptomatic recommendations as per section 6.6 | The investigator and project clinician may discuss considerations for dose modifications and symptom management. |
| Grade 3 non-hematologic toxicity judged to be related to ixazomib except for the following toxicity:<br>• > Grade 3 nausea and/or emesis in the absence of optimal anti-emetic prophylaxis (section 6.7)<br>• > Grade 3 diarrhea that occurs in the absence of optimal supportive therapy (section 6.7)<br>• Grade 3 fatigue | • Hold ixazomib until resolution to Grade < 1 or baseline<br><br>*Subsequent recurrence Grade 3 that does not recover to < Grade 1 reduce ixazomib 1 dose level* | Symptomatic recommendations noted in Section 6.7<br>Monitor closely, take appropriate medical precautions, and provide appropriate symptomatic care |
| Grade 4 non-hematologic toxicities judged to be related to ixazomib | • Consider permanently discontinuing ixazomib | Exceptions are cases in which the investigator determines the patient is obtaining a clinical benefit |
| Delay of >2 weeks in the start of a subsequent cycle due to lack of toxicity recovery related to ixazomib | Hold ixazomib until resolution<br><br>Reduce ixazomib 1 dose level | The maximum delay before treatment should be discontinued will be 3 weeks. If the maximum delay has been exceeded, resuming treatment can be considered after discussion with overall PI if clinical benefit is determined |

Once ixazomib, lenalidomide, and/or dexamethasone are reduced for any toxicity, the dose may not be re-escalated.

Lenalidomide dose adjustments are allowed based on clinical and laboratory findings. Sequential lenalidomide dose reductions to 15 mg daily, 10 mg daily, and 5 mg daily are recommended for toxicity as indicated in Table 6-7.

## Table 7-7 Lenalidomide Lenalidomide Dose Modifications Due to Non-Hematologic Toxicities

| Adverse Event (Severity) | Action |
|---|---|
| Other Grade 3/4 toxicities | • Hold lenalidomide treatment until toxicity has resolved to ≤ Grade 1 or patient's baseline; restart at the next lower dose level (5mg less than the previous dose)<br>○ *Do not dose below 5 mg daily* |
| Rash | |
| • Non-blistering Rash, Grade 3 | • Hold lenalidomide and follow weekly. If the toxicity resolves to ≤ Grade 1 prior to Day 21 of the current cycle, restart at 1 dose decrement and continue the cycle until Day 21 of the current cycle. |
| • Non-blistering Rash, Grade 4 | • Discontinue lenalidomide treatment |
| • Desquamating (blistering rash) – Any grade | • Discontinue Lenalidomide treatment |
| Erythema multiforme ≥ Grade 3 | • Discontinue lenalidomide treatment |
| Sinus Bradycardia / other new onset cardiac arrhythmia not present at baseline or deterioration of pre-existing cardiac arrhythmia | |
| • ≤ Grade 2 | • Hold lenalidomide, follow at least weekly. If the toxicity resolves to ≤ Grade 1 prior to Day 21, restart at 1 dose decrement and continue the cycle until Day 21. |
| • ≥ Grade 3 | • Discontinue lenalidomide treatment |
| Allergic Reaction / Hypersensitivity | |
| • Grade 2-3 | • Hold Lenalidomide, follow at least weekly. If the toxicity resolves to ≤ Grade 1 prior to Day 21, restart at 1 dose decrement and continue the cycle until Day 21. |
| • Grade 4 | • Discontinue lenalidomide treatment |
| Infection Grade 3-4 | Hold lenalidomide, ixazomib, and dexamethasone until systemic treatment for infection is completed. If no neutropenia, restart all three drugs at same dose. If neutropenic, follow neutropenic instructions. |
| Herpes Zoster or simplex of any grade | Hold Lenalidomide, ixazomib , and dexamethasone until lesions are dry. Resume at same doses. |
| Renal Dysfunction | Dose reduce per lenalidomide package insert for impaired renal function; monitor renal function regularly |
| Venous Thrombosis/Embolism ≥ Grade 3 | Hold lenalidomide dose and adjust anticoagulation regimen; re-start at Treating Investigator's discretion at same dose |
| Hyperthyroidism or hypothyroidism | Omit lenalidomide for remainder of cycle, evaluate, and initiate appropriate therapy. Restart lenalidomide next cycle at 1 dose decrement |
| Congestive heart failure (CHF) | Any subject with NYHA stage III or IV CHF, whether or not lenalidomide related, must have the dose held until resolution or return to baseline. If CHF was felt to be lenalidomide related, reinstate by one dose decrement after return to baseline. If no resolution of CHF after 2 weeks, the subject will be withdrawn from the study. |

**Table 7-8 Treatment Guidelines for Toxicity Related to Dexamethasone**

| Body System | Symptom | Recommended Action |
|---|---|---|
| Gastrointestinal | Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1-2 (requiring medical management) | Treat with $H_2$ blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level. |
| Gastrointestinal | ≥ Grade 3 (requiring hospitalization or surgery) | Hold dexamethasone until symptoms adequately controlled. Restart at 1 dose decrement along with concurrent therapy with $H_2$ blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, discontinue dexamethasone permanently. |
| Gastrointestinal | Acute pancreatitis | Discontinue dexamethasone permanently. |
| Cardiovascular | Edema ≥ Grade 3 (limiting function and unresponsive to therapy or anasarca) | Diuretics as needed, and restart dexamethasone at 1 dose decrement; if edema persists despite above measures, decrease dose another level. Discontinue dexamethasone permanently if symptoms persist despite second reduction |
| Neurology | Confusion or mood alteration > Grade 2 (interfering with function +/- interfering with activities of daily living) | Hold dexamethasone until symptoms resolve. Restart at 1 dose decrement. If symptoms persist despite above measures, discontinue dexamethasone permanently. |
| Musculoskeletal | Muscle weakness > Grade 2 (symptomatic and interfering with function +/- interfering with activities of daily living) | Decrease dexamethasone by 1 dose level. If weakness persists, decrease dose by 1 more dose level. Discontinue dexamethasone permanently if symptoms persist. |
| Metabolic | Hyperglycemia ≥ Grade 3 | Treatment with insulin or PO hypoglycemic agents as needed. If uncontrolled despite above measures, decrease dose by 1 dose level until levels are satisfactory. |

#### 7.3.1.1 Conditions Not Requiring Dose Reduction

The following conditions are exceptions to the above guidelines.

- Grade 3 nausea, vomiting, or diarrhea (unless persisting more than 3 days with adequate treatment of antiemetics or antidiarrheal agents)
- Grade 3 dexamethasone-related hyperglycemia (see Table 6-8 for guidelines and treatment)

- Grade 1-2 lenalidomide and/or ixazomib-induced rash
- Grade 3 fatigue (unless persisting for > 14 days)
- Alopecia

## 7.4 Mandatory Concomitant Medications

### 7.4.1 Recommended Concomitant Medications

- Aspirin for VTE prophylaxis.
    - Note: If a subject is allergic to aspirin, low-molecular-weight heparin or clopidogrel may be used. In subjects with a prior history of venous thrombosis, low-molecular-weight heparin or therapeutic doses of warfarin (target INR 2-3) are required (or follow most current guidelines for DVT prophylaxis).
- Acyclovir 400 mg orally twice a day for HZV prophylaxis (or equivalent)

### 7.4.2 Excluded Concomitant Medications

Concurrent therapy with a marketed or investigational anticancer therapeutic is not allowed.

Corticosteroids for non-malignant conditions (e.g., asthma, inflammatory bowel disease) equivalent to a dexamethasone dose ≥ 4 mg/day or prednisone ≥ 20 mg/day are not permitted.

Other investigational agents are not to be used during the study.

The following medications and procedures are prohibited during the study.

Systemic treatment with any of the following metabolizing enzyme inducers should be avoided, unless there is no appropriate alternative medication for the patient's use (Rationale: If there were to be a DDI with an inducer, ixazomib exposure would be less; therefore, there would be a reduced chance of an AE. However, there may be less chance for an antitumor effect, but that is not an absolute reason to be taken off ixazomib):

- Strong CYP3A inducers: rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, and phenobarbital
- Excluded foods and dietary supplements include St. John's wort and Ginkgo biloba

The following procedures are prohibited during the study.

- Any antineoplastic treatment with activity against MM, other than study drugs
- Radiation therapy (note that, in general, the requirement for local radiation therapy indicates disease progression)
- Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days prior to study drug dosing for any dosing day

### 7.4.3 Permitted Concomitant Medications and Procedures

The following medications and procedures are permitted during the study:

- Antiemetics, including 5-HT3 serotonin receptor antagonists, may be used at the discretion of the investigator.
- Loperamide or other antidiarrheal should be used for symptomatic diarrhea at discretion of the investigator. The dose and regimen will be according to institutional guidelines. IVF should be given to prevent volume depletion.
- Growth factors (e.g., granulocyte colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF], recombinant erythropoietin) are permitted. Their use should follow published guidelines and/or institutional practice. Erythropoietin will be allowed in this study. Their use should follow published guidelines and/or institutional practice.
- Patients should be transfused with red cells and platelets as clinically indicated and according to institutional guidelines however screening platelet count must be independent of platelet transfusions for at least 2 weeks.
- Antiviral therapy such as acyclovir may be administered if medically appropriate.
- Concomitant treatment with bisphosphonates will be permitted, as appropriate.
- Patients who experience worsening neuropathy from baseline may be observed for recovery and have dose reductions/delays as indicated in the protocol, and any supportive therapy or intervention may be initiated as appropriate at the discretion of the investigator.
- Supportive measures consistent with optimal patient care may be given throughout the study.

- Radiation therapy to a localized mass is acceptable with prior approval of the Lead Principal Investigator.

- Prophylactic proton pump inhibitor or an H2 antagonist are recommended but NOT required and considered optional medications.

- Vaccines that are required post-transplant.

### 7.5 Precautions and Restrictions

- Fluid deficit should be corrected before initiation of treatment and during treatment.

- Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided with impaired renal function given reported NSAID-induced renal failure in patients with decreased renal function.

**Pregnancy**

It is not known what effects ixazomib has on human pregnancy or development of the embryo or fetus. The use of lenalidomide in pregnant females and nursing mothers has not been studied nor has the effect of the lenalidomide on human eggs and sperm. Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryo/fetal 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.

Female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Non-sterilized female patients of reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, or

- Surgically sterile, or

- If they are of childbearing potential, agree to practice 2 effective methods of contraception from the time of signing of the informed consent form through 90 days after the last dose of study drug, or

- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

Male patients, even if surgically sterilized (i.e., status post-vasectomy) must agree to 1 of the following:

- Practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study drug, or

- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)

All study participants must be registered into the mandatory lenalidomide REMS® program and be willing and able to comply with the requirements of lenalidomide REMS®. Before starting lenalidomide, FCBP must have 2 negative pregnancy tests (sensitivity of at least 50 mIU/mL) prior to initiating lenalidomide. The first pregnancy test must be performed within 10-14 days before, and the second pregnancy test must be performed within 24 hours before prescribing lenalidomide (prescriptions must be filled within 7 days). The subject may not receive lenalidomide until the investigator has verified that the results of these pregnancy tests are negative.

### 7.6 Management of Clinical Events

Adverse drug reactions such as thrombocytopenia, diarrhea, fatigue, nausea, vomiting, and rash have been associated with ixazomib treatment. Management guidelines regarding these events are outlined below. Further details of management of ixazomib AEs are described in Section 6 of the ixazomib IB.

**Prophylaxis Against Risk of Reactivation of Herpes Infection**

Patients may be at an increased risk of infection including reactivation of herpes zoster and herpes simplex viruses. Antiviral therapy such as acyclovir, valacyclovir, or other antivirals will be mandatory (see section 7.4.1). Other antivirals are also acceptable.

**Nausea and/or Vomiting**

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

**Diarrhea**

Prophylactic antidiarrheals will not be used in this protocol. However, diarrhea should be managed according to clinical practice, including the administration of antidiarrheals once infectious causes are excluded. Fluid intake should be maintained to avoid dehydration. Fluid deficit should be corrected before initiation of treatment and during treatment.

**Erythematous Rash With or Without Pruritus**

As with bortezomib, rash with or without pruritus has been reported with ixazomib, primarily at the higher doses tested and when given with agents where rash is an overlapping toxicity. The rash may range from limited erythematous areas, macular and/or small papular bumps that may or may not be pruritic over a few areas of the body, to a more generalized eruption that is predominately on the trunk or extremities. Rash has been most commonly characterized as maculopapular or macular. To date, when it does occur, rash is most commonly reported within the first 3 cycles of therapy. The rash is often transient, self-limiting, and is typically Grade 1 to 2 in severity.

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

In line with clinical practice, dermatology consult and biopsy of Grade 3 or higher rash or any SAE involving rash is recommended. Prophylactic measures should also be considered if a

patient has previously developed a rash (e.g., using a thick, alcohol-free emollient cream on dry areas of the body or oral or topical antihistamines). A rare risk is Stevens – Johnson Syndrome, a severe and potentially life-threatening rash with skin peeling and mouth sores, which should be managed symptomatically according to standard medical practice. Punch biopsies for histopathological analysis are encouraged at the discretion of the investigator.

**Thrombocytopenia**

Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Thrombocytopenia may be severe but has been manageable with platelet transfusions according to standard clinical practice. Ixazomib administration should be modified as noted as per dose modification recommendations in the protocol when thrombocytopenia occurs (see Table 6-2). Therapy can be reinitiated at a reduced level upon recovery of platelet counts. A rare risk is thrombotic thrombocytopenic purpura (TTP), a rare blood disorder where blood clots form in small blood vessels throughout the body characterized by thrombocytopenia, petechiae, fever, or possibly more serious signs and symptoms. TTP should be managed symptomatically according to standard medical practice.

**Neutropenia**

Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Neutropenia may be severe but has been manageable. Growth factor support is not required but may be considered according to standard clinical practice. Ixazomib administration should be modified as noted as per dose modification recommendations in the protocol when neutropenia occurs (see Table 6-2). Therapy can be reinitiated at a reduced level upon recovery of ANCs.

**Fluid Deficit**

Dehydration should be avoided since ixazomib may cause vomiting, diarrhea, and dehydration. Acute renal failure has been reported in patients treated with ixazomib, commonly in the setting of the previously noted gastrointestinal toxicities and dehydration.

Fluid deficit should be corrected before initiation of study drug and as needed during treatment to avoid dehydration.

**Hypotension**

Symptomatic hypotension and orthostatic hypotension with or without syncope have been reported with ixazomib. Blood pressure should be closely monitored while the patient is on study treatment and fluid deficit should be corrected as needed, especially in the setting of

concomitant symptoms such as nausea, vomiting, diarrhea, or anorexia. Patients taking medications and/or diuretics to manage their blood pressure (for either hypo- or hypertension) should be managed according to standard clinical practice, including considerations for dose adjustments of their concomitant medications during the course of the trial. Fluid deficit should be corrected before initiation of study drug and as needed during treatment to avoid dehydration.

**Posterior Reversible Encephalopathy Syndrome**

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

**Transverse Myelitis**

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

## 7.7 Investigational Product

### 7.7.1 Ixazomib Preparation, Reconstitution, and Dispensing

Ixazomib is an anticancer drug and as with other potentially toxic compounds caution should be exercised when handling ixazomib capsules.

#### 7.7.1.1 Ixazomib Packaging and Labeling

The study drug ixazomib capsules will be provided by Millennium. The study drug will be labeled and handled as open-label material, and packaging labels will fulfill all requirements specified by governing regulations.

The capsules are individually packaged using cold-form foil-foil blisters that are in a child-resistant carton. There are 3 capsules in each wallet/carton.

#### 7.7.1.2 Ixazomib Storage, Handling, and Accountability

Upon receipt at the investigative site, ixazomib should remain in the blister and carton provided until use or until drug is dispensed. The container should be stored at the investigative site refrigerated (36°F to 46°F, 2°C to 8°C). Ensure that the drug is used before the retest expiry date

provided by Millennium. Expiry extensions will be communicated accordingly with updated documentation to support the extended shelf life.

In countries where local regulations permit, ixazomib capsules dispensed to the patient for take-home dosing should remain in the blister packaging and refrigerated as noted above until the point of use. The investigative site is responsible for providing the medication to the patient in the correct daily dose configurations. Comprehensive instructions should be provided to the patient in order to ensure compliance with dosing procedures. Patients who are receiving take-home medication should be given only 1 cycle of medication at a time. Patients should be instructed to store the medication refrigerated (36°F to 46°F, 2°C to 8°C) for the duration of each cycle. Patients should be instructed to return their empty blister packs to the investigative site, rather than discarding them. Reconciliation will occur accordingly when the patient returns for their next cycle of take-home medication. Any extreme in temperature should be reported as an excursion and should be dealt with on a case-by-case basis.

Because ixazomib is an investigational agent, it should be handled with due care. Patients should be instructed not to chew, break, or open capsules. In case of contact with broken capsules, raising dust should be avoided during the clean-up operation. The product may be harmful by inhalation, ingestion, or skin absorption. Gloves and protective clothing should be worn during cleanup and return of broken capsules and powder to minimize skin contact.

The area should be ventilated and the site washed with soap and water after material pick-up is complete. The material should be disposed of as hazardous medical waste in compliance with federal, state, and local regulations.

In case of contact with the powder (e.g., from a broken capsule), skin should be washed immediately with soap and copious amounts of water for at least 15 minutes. In case of contact with the eyes, copious amounts of water should be used to flush the eyes for at least 15 minutes. Medical personnel should be notified. Patients are to be instructed on proper storage, accountability, and administration of ixazomib, including that ixazomib is to be taken as intact capsules.

After cycle 1 and with approval of the treating investigator, subjects may take ixazomib at home. Research center personnel will review the dosing instructions with subjects. Subjects will be asked to maintain a diary to record drug administration. Subjects will be asked to bring any unused drug and empty drug containers to the research center at their next visit. Research personnel will count and record the number of used and unused drug at each visit and reconcile with the patient diary.

### 7.7.2 Lenalidomide

#### 7.7.2.1 Lenalidomide Dispensing

Commercially available (lenalidomide) capsules are supplied through the lenalidomide REMS® program as the drug is approved for indications in this study. Lenalidomide is for PO (oral) administration only.

Lenalidomide will be provided in accordance with the lenalidomide REMS® program of Celgene Corporation. Per standard lenalidomide REMS® requirements, all physicians who prescribe lenalidomide for research subjects enrolled into this trial must be registered in must comply with all requirements of the lenalidomide REMS® program. Prescriptions must be filled within 7 days. Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle. Unused lenalidomide will be counted and documented by each site. See appendix 14.7 for lenalidomide Prescribing Information.

#### 7.7.2.2 Lenalidomide Storage, Handling and Accountability

Store lenalidomide at 25°C (77 °F) away from direct sunlight; excursions permitted to 15-30°C (59-86 °F). Bottles of lenalidomide will contain a sufficient number of capsules to last for one cycle of dosing. Sites will be required to record and document subject compliance regarding lenalidomide dosing.

Research center personnel will review the dosing instructions with subjects. Subjects will be asked to maintain a diary to record drug administration. Subjects will be asked to bring any unused drug and empty drug containers to the research center at their next visit. Research personnel will count and record the number of used and unused drug at each visit and reconcile with the patient diary.

### 7.7.3 Dexamethasone

Dexamethasone, a synthetic adrenocortical steroid, is a white to practically white, odorless, crystalline powder. It is stable in air. It is practically insoluble in water.

#### 7.7.3.1 Dexamethasone Dispensing

Dexamethasone is a commercially available PO drug, supplied as 2 and 4 mg tablets.

#### 7.7.3.2 Dexamethasone Storage, Handling and Accountability

Store dexamethasone at controlled room temperature 20ºC to 25ºC (68ºF to 77ºF). Sites will be required to record and document subject compliance regarding dexamethasone dosing. Subjects may take oral dexamethasone at home. Research center personnel will review the dosing instructions with subjects. Subjects will be asked to maintain a diary to record drug administration.

### 7.8 Study Compliance

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified sub-investigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing.

### 7.9 Treatment Assignment

Subjects who are deemed eligible for enrollment into the trial will be randomized to the experimental arm (IRd) vs. the control arm (single-agent lenalidomide) in a 1:1 ratio. Two factors will be considered during randomization:

a. Level of overall response including transplant from the pre-induction level of disease; response is assessed at study screening 3 months following initiation of lenalidomide maintenance at the time of screening for this protocol:
   ii. <VGPR
   iii. ≥VGPR

2) Risk Factors at the time of diagnosis
   iv. At least one of the following poor prognostic risk factors:
      1. del-13 (by karyotyping)
      2. hypodiploidy (by karyotyping)
      3. (4;14) ( by FISH)
      4. t(14;16) (by FISH)
      5. t(14;20) (by FISH)
      6. del17p (by FISH)
      7. 1q21 gain (by FISH)
   v. No risk factors

### 7.10 Termination of Treatment and/or Study Participation

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The investigator also has the right to withdraw patients from the study for any of the following reasons:

- Adverse event
- Protocol violation / subject non-compliance
- Lost to follow-up
- Progressive disease
- Study terminated
- Subject no longer consents to participate in the study
- Pregnancy or suspected pregnancy
- Delay in treatment >21 days due to unrecovered toxicity unless treating investigator considers continued therapy to be in the subject's best interest and approval is granted by the Lead Principle Investigator
- Other

The Lead Principal Investigator must be contacted to discuss any impending discontinuation of a study subject/patient prior to withdrawal from the study. If withdrawal occurs prior to discussion with the Lead Principal Investigator, they must be notified within 24 hours via email with a copy to the University of Chicago CRA.

If the reason for withdrawal is the occurrence of an AE, the subject will be followed until such events resolve, stabilize, and, according to the Treating Investigator's judgment, there is no need of further follow-up. The reason for withdrawal from the study will be documented in the case report form.

At the time of withdrawal, all study procedures outlined for the End of Study visit should be completed. The primary reason for patient's withdrawal from the study should be recorded in the source documents and CRF.

# 8. STATISTICAL AND QUANTITATIVE ANALYSES

## 8.1 Statistical Methods

A total of 60 patients will be enrolled in a 1:1 ratio stratified according to level of response (<VGPR vs ≥ VGPR) and presence or absence of at least one poor prognostic risk factor (Yes to at least one cytogenetic risk factor including del-13 or hypodiploidy by karyotyping, or any of t(4;14), t(14;16), t(14;2), del17p, 1q21 gain by FISH. The primary objective of this study is to compare the rate of MRD at 12 months between the two arms. Because this is a proof of concept trial rather than a confirmatory trial, the comparison will be made using one--sided test at 80% power and at most 10% type I error. The outcome will be considered promising and warrant evaluation with phase III trial if MRD negative disease is 20% higher in the experimental arm vs. the control arm. This assumption is based on the following data:

1) While it is well established that CR rate may increase over time post-transplant, even without any maintenance (in the IFM study, at randomization to lenalidomide maintenance or placebo 5% and 8% of patients were in CR, but ultimately 29% and 27%, respectively achieved CR; Attal et al, N Eng J Med, 2012), the conversion to CR on lenalidomide maintenance in patients with established persistent measurable disease is expected to be less than 5%

2) CR rate to lenalidomide alone is estimated < 5% in newly diagnosed myeloma (Rajkumar et al, Blood 2005).

3) While there is not published data on the rate of conversion from less than MRD-negative to MRD-negative disease while on lenalidomide maintenance, it is estimated that only a small proportion of patients on lenalidomide arm (which we estimate to be < 5% and/or not to be clinically significant) will convert to MRD-negative status because of delayed effect of transplant and/or lenalidomide treatment.

4) Based on experience from the CRd trial (Jakubowiak et al, ASCO 2013), approximately 20% of patients have a potential to convert from less than MRD-negative to MRD-negative disease between 8 and 20 months (1-year) of the CRd treatment.

Together, these observations provided rationale for 12 months of duration of treatment and statistical design: an increase of the rate of MRD-negative disease by 20% - 28% in the experimental arm versus control arm was used for calculation of sample size (as for example 26.7 % rate in the experimental arm and 5% in control arm).

In addition, Kaplan-Meier analysis of PFS will be conducted at time points with 95% confidence intervals with Cox proportional hazard regression models (exploratory). For these secondary analyses, conventional, p-values from statistical tests at or below 5% (two-sided) will be considered significant.

### 8.1.1 Determination of Sample Size

A total of 60 patients (30 per arm) is based on the assumption that the rate of MRD negative disease that is approximately 20% higher in the experimental arm vs. the control arm will be considered promising for further evaluation. Because this is a proof of concept phase II randomized trial rather than a confirmatory trial, the comparison will be made using a one-sided test at 80 % power and at most 10% type I error. Table 8.1 below shows the detectable difference depending on the control rate. Boldfaced figures are values assumed most likely based on the literature and previous studies. Calculations are based on a Cochran-Mantel-Haenszel test with continuity correction.

**Table 8-1 Detectable increases in the rate of MRD with 80 %power (one-sided α=0.10)**

| Control Arm | Experimental Arm | Difference |
|---|---|---|
| 2.5% | 21.8 % | 19.3 % |
| **5.0%** | **26.7 %** | **21.7 %** |
| 10.0% | 35.5 % | 25.5% |
| 15.0% | 42.4% | 27.4% |
| 20.0% | 48.1 % | 28.1 % |

### 8.1.2 Randomization and Stratification

Patients will be randomized 1:1 and stratified based on criteria outlined in section 6.9 (VGPR status and risk factors vs. no risk factors). Randomization will occur between Day +70 and +120 post-transplantation. Initiation of maintenance therapy with study drug will begin between day +80 and +130. Prior to randomization, subjects must undergo disease re-staging, must have adequate organ function (ANC ≥1000µL, platelet count ≥75,000µL, creatinine clearance ≥ 30mL/min, bilirubin ≤2mg/dL, AST ≤3 x ULN, and Alk. Phos.≤ 3 x ULN), and must have no evidence of progressive disease.

### 8.1.3 MRD Evaluations

#### 8.1.3.1 MRD Evaluations by MCF

The primary end-point analysis will be performed by the Department of Pathology at the University of Chicago. Bone marrow aspirate for MRD analysis by 10-color multiparameter flow cytometry will be collected for all patients at the time of enrollment and during all subsequent bone marrow biopsies, including at the end of treatment (a minimum of two samples per patient). All samples collected at participating sites will be shipped and processed at the University of Chicago laboratories. Instructions detailing the collection method, processing, and shipment of these samples will be provided in a separate manual.

#### 8.1.3.2 MRD Evaluations by gene sequencing

**8.1.4As part of an additional MRD evaluation, all bone marrow aspirates collected for MRD analysis will also be analyzed using the. Clono SEQ® platform. The collection time points will be as described above: at the time of enrollment, at any time during a suspected CR or better, and at 12 months/end of treatment. The samples will be part of the same aspirate collected for multiparameter flow cytometry and the details of this collection will be described in a separate manual. All samples will be sent to the University of Chicago Multiple Myeloma Program Coordinator. Processing of samples including DNA isolation, storage, and shipment to Adaptive Biotechnologies will be performed by the University of Chicago laboratory. Samples processing at the University of Chicago will be supported by separate grants and funds from the University of Chicago investigators. Adaptive Biotechnologies will provide funding for Clono SEQ® analysis. Populations for Analysis**

The Intent-to Treat (ITT) population of patients will be defined as all patients who receive at least one dose of treatment in either of the arms (ixazomib or lenalidomide or dexamethasone in the experimental arm or lenalidomide in the control arm). “A secondary, evaluable population will also be analyzed that will include all patients in the ITT population with the following exceptions:

(1) Patients who discontinued the trial for reasons other than toxicity or progressive disease, and

(2) Patients who met eligibility for MRD positive disease but the MRD testing at the 12-month timepoint is either not successful (by NGS) or the sample is not available (pt withdraws consent, sample is a dry tap, etc).

Patients in categories (1) or (2) will be rendered “non-evaluable.” Additionally, in the situation that a patient is rendered non-evaluable, a new patient will be randomized into the trial to preserve the sample size for primary endpoint analysis. Additionally, in the situation that a

patient is rendered non-evaluable, a new patient will be randomized into the trial to preserve the sample size for primary endpoint analysis. Patients enrolled in this trial will be patients who completed initial induction followed by autologous stem cell transplant for symptomatic myeloma (per IMWG criteria) and in the first 0-6 months of Lenalidomide maintenance provided that was initiated within 6 months after transplant as per standard of care and with at least MRD-positive residual myeloma. The study's primary endpoint, attainment of MRD-negative disease by MFC will be assessed at the completion of the 12 cycle of protocol treatment (both arms). In patients that were enrolled based on their MRD-positivity by MFC, an improvement will be counted when these patients switch to MRD-negative disease by MFC at the 12-month time-point. Patients that were enrolled per their MRD-positivity by NGS will require NGS analysis to determine their MRD status at 12 months of treatment. In this patient population, only a switch from MRD-positivity to negativity by NGS will be counted as an improvement. We anticipate that no more than 10% of patients will be enrolled who are MFC negative but NGS positive. If there is an imbalance between the two treatment arms in this variable we will adjust by post-hoc stratification or covariate analysis. All patients enrolled and receiving any IRD or R treatment will be evaluable for this endpoint, with the exception of patients that decline to receive treatment for reasons unrelated to toxicity and/or efficacy. Patients in that category will be replaced. All other patients who discontinue treatment before receiving 12 cycles of protocol treatment will be considered treatment failures for assessment of the study's primary endpoint. The proportion of MRD-negative patients will be reported along with 95% confidence intervals.

### 8.1.5 Demographic and Baseline Characteristics

Baseline characteristics will be summarized in Baseline Characteristic summary table for two treatment arms

### 8.1.6 Efficacy Analysis

The primary objective of this study is to compare the rate of MRD at 12 months between the two arms. Because this is a proof of concept trial rather than a confirmatory trial, the comparison will be made using a one sided test at the 10% significance level. This comparison will be performed using (i) a chi-square or Fisher's exact test comparing the two treatment arms, and (ii) a Cochran Mantel-Haenszel (CMH) test stratified by VGPR status and risk factors vs. no risk factors. We anticipate 20-30% of pts will be high risk and 20-40% will be in less than a VGPR at study entry. Therefore, in the event of small stratum sizes (<5 per stratum in either treatment arm), we will conduct an exact logistic regression analysis in place of the CMH test (Hirji, Mehta, and Patel, et al., 1987).

Secondary objectives include the overall response rate, defined as at least a partial response to therapy (>PR), at least VGPR (>VGPR) and at least nCR rate (>nCR), CR, and sCR rates, time to progression, duration of response, and progression-free and overall survival. The rate of overall response will be reported along with its exact 95% binomial confidence interval. Time to event endpoints will be estimated using the product-limit method of Kaplan and Meier. Follow-

up time for these endpoints will be calculated from the date of randomization. For time to progression, patients that do not experience progression during follow-up will be censored on the date of their last clinical examination. Duration of response will be assessed conditional upon achieving at least a partial response. Follow-up time for this endpoint will be calculated from the date of the clinical examination, which confirmed the response, until the date of disease progression, or censoring at the date of last clinical follow-up. For progression-free survival, follow-up time will continue from the date of randomization until the date of documented disease progression or death. Patients who do not reach either milestone during follow-up will be censored on their date of last clinical assessment.

Correlative biomarkers will be assessed for association with response in the experimental arm using nonparametric tests given the relatively small number of responders anticipated (20%). A Wilcoxon rank-sum test will be used to compare baseline (pre-treatment) biomarker levels in the responders vs. non-responders.

### 8.1.7 Safety Analysis

Safety analysis will be based on the incidence, intensity, and type of adverse events, and clinically significant changes in the patient's physical examination, vital signs, and clinical laboratory results. Safety variables will be tabulated and presented for all patients in the study. Exposure to study drug and reasons for discontinuation of study treatment will be tabulated. Group comparisons will be performed using chi-square or Fisher's exact test.

All adverse events occurring on study will be listed in by-patient data listings. Treatment emergent events will be tabulated, where treatment emergent is defined as any adverse event that occurs after administration of the first dose of study drug and through the End of Study visit or up through 30 days after the last dose of study drug, any event that is considered drug-related regardless of the start date of the event, or any event that is present at baseline but worsens in intensity or is subsequently considered drug-related by the Treating investigator and/or Lead Principal Investigator. Events that are considered related to treatment (possibly, probably or definitely drug-related) will also be tabulated. Deaths, serious adverse events and events resulting in study discontinuation will be tabulated.

Change from baseline in clinical laboratory parameters will be summarized across time on study, and the frequency of clinically significant abnormal laboratory values will be tabulated. Similarly, changes in vital sign parameters will be summarized over time, and any abnormal values will be tabulated.

# 9. CORRELATIVE SAMPLES

In addition to the required bone marrow aspirate sample for MRD analysis collected at screening and time of response, for patients who consent, we will collect samples including bone marrow core biopsy and aspirate, peripheral blood, and buccal swabsPeripheral blood and bone marrow samples will also be collected at the time of achievement of at least CR, or better, at 1 year after randomization (providing that the patient is at least in CR and no recent bone marrow evaluation within 1-2 months). Correlative samples should be collected at any time that bone marrow is performed as SOC outside of these time points. Additional evaluations may include proteomics, gene expression profiling, microRNA, SNP analysis, analysis of genetic variants

**Table 8-1 Correlative Sample Schema**

| Visit | Bone Marrow Aspirate | Peripheral Blood | Plasma | Serum | Buccal Mouth Swab |
|---|---|---|---|---|---|
| **Screening** | X | X | X | X | X |
| **At any time after randomization after achievement of CR or better*** | X | X | X | X | |
| **End of Treatment** | X | X | X | X | |

Refer to the laboratory manual for collection procedures, processing, and shipments

# 10. ADVERSE EVENTS

## 10.1 Adverse Event Definition

Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

An unexpected AE is any adverse drug event, the specificity or severity of which is not consistent with the current IB or prescribing information for a marketed compound. Also, reports which add significant information on specificity or severity of a known, already documented AE constitute unexpected AEs. For example, an event more specific or more severe than described in the IB would be considered "unexpected".

### 10.2 Causality

Using the following criteria, the relationship of the AE to the study drug should be assessed as follows: Definite, Probably, Possible, Unlikely, Unrelated.

### 10.3 Adverse Event Reporting Procedures

Information about all AEs, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory tests or other means, will be collected and recorded and followed as appropriate.

All AEs (e.g., any new event or worsening in severity or frequency of a pre-existing condition or laboratory finding) with an onset date on or after the first dose of treatment through 30-days after the last treatment dose must be promptly documented on the appropriate CRF in eVelos. Any SAE (Section 10.4) which is considered related to study procedures and occurs after informed consent but before Cycle 1 Day 1 must be reported. Details of the event must include severity, relationship to study drug, duration, action taken, and outcome. All AEs must be followed to resolution or stabilization regardless of relationship to study drug.

All AEs that are considered related to study drug must be followed to resolution or stabilization if improvement is not expected.

AEs must be reported from the date of the first dose of treatment through 30 days post-last dose of study treatment or initiation of a new anti-cancer therapy, whichever occurs first. If a subject is enrolled but discontinues study prior to receiving any study drug, only SAEs that are considered related to study procedures must be reported through the end-of-study visit. AEs which completely resolve and then recur should be recorded as a new AE. For subjects who complete the end of study visit less than 30 days following their last dose of study drug, a follow up of ongoing AEs should be attempted by telephone, and documented in the subject's source.

AEs continuing at 30 days post-last dose should have a comment in the source by the Treating Investigator that the event has stabilized or is not expected to improve. SAEs continuing at 30 days post-last dose should be followed until resolution or stabilization.

Whenever possible, the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 should be used to describe the event and for assessing the severity of AEs. Any events representing a change in the CTCAE Grade need to be reported on the AE case report form. This includes any change in laboratory values.

For AEs not adequately addressed in the CTCAE, the severity table below may be used:

| Severity | Description |
|---|---|
| GRADE 1 – Mild | Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required. |
| GRADE 2 – Moderate | Mild to moderate limitation in activity—some assistance may be needed; no or minimal medical intervention/therapy required. |
| GRADE 3 – Severe | Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible. |
| GRADE 4 – Life-threatening | Extreme limitation in activity, significant assistance required; life-threatening (immediate risk of death); significant medical intervention/therapy required, hospitalization or hospice care probable. |
| GRADE 5 – Fatal | Death |

Any condition, laboratory abnormality, or physical finding with an onset date prior to the subject signing consent for study participation is considered to be pre-existing in nature and part of the subject's medical history.

The Treating Investigator is responsible for evaluating all AEs for relationship to study drug and for seriousness, obtaining supporting documents, and determining that documentation of the event is adequate. The Site or Lead Principal Investigator may delegate these duties to Sub-investigators and must ensure that these Sub-investigators are qualified to perform these duties under the supervision of the Principal Investigator and that they are listed on the FDA Form 1572 and delegation log.

### 10.4 Serious Adverse Event

#### 10.4.1 Serious Adverse Event Definition

Serious AE (SAE) means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph below on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (e.g., prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

Any death occurring within 30 days of the subject receiving study drug, regardless of the subject having discontinued from the study must be reported to the Lead Principal Investigator as an SAE.

In addition, new primary malignancies that occur during the follow-up periods must be reported, regardless of causality to study regimen, for a minimum of three years after the last dose of the investigational product, starting from the first dose of study drug.

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned).

Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcomes or action criteria described above, and are usually associated with events that pose a threat to a patient's life or ability to function. A severe AE ((Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/$mm^3$ to less than 2000 is considered a Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

### 10.4.2 Serious and Unexpected Suspected Adverse Reaction (SUSAR)

A serious adverse event is considered to be a suspected adverse reaction if there is evidence to suggest a causal relationship to the study agent. This may include a single occurrence of an event strongly associated with drug exposure (e.g. Stevens Johnson Syndrome), one or more occurrence of an event otherwise uncommon in the study population, or an aggregate analysis of specific events occurring at greater frequency than expected from historical controls.

Unexpected events are those not listed at the observed specificity or severity in the protocol, consent, investigator brochure, FDA approved package insert, or elsewhere in the current IND application. This includes adverse events listed in the protocol, consent or IND as occurring within the class of drugs or otherwise expected from the drug's pharmacological properties but which have not been previously observed with this investigational agent. **ALL serious and unexpected suspected adverse reactions (SUSARs) occurring on this clinical trial must be reported to the FDA. Refer to section 10.4.3 for reporting guidelines.**

The lead institution (University of Chicago) is responsible for notifying the appropriate Regulatory Agencies, when required, and in accordance with applicable laws and regulations of any Expedited Safety Reports.

**ALL Serious Adverse Events, whether or not they are considered related to the study agent MUST be reported to the Lead Principal Investigator and to the University of Chicago**

**Comprehensive Cancer Center (via paper submission via fax or email). Refer to Section 10.4.3 for reporting guidelines.**

### 10.4.3 Procedures for Reporting Serious Adverse Events

Use the UC CCC protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Information about all serious adverse events (SAE) from the start of treatment through 30 days after the last dose of study drug will be collected and recorded on the appropriate SAE form. The responsible Research Nurse or other designated individual at the treating site should report the SAE to the Study Lead Investigator, the University of Chicago CRA and the CCTO by the end of the business day when s/he becomes aware of the event. Events occurring after business hours should be reported to the CCTO by 12 pm (noon) the next business day. Reports should be made using the 'Serious Event Report' Form. Please scan and send via email (preferred) or fax to the following:

**University of Chicago Phase II CRA General**:
PhaseIICRA@medicine.bsd.uchicago.edu
Phone: 773-834-3095
Fax: 773-702-4889

**UC CCC Cancer Clinical Trials Office Quality Assurance**:
qaccto@bsd.uchicago.edu

All unexpected adverse reactions must be reported to the IND holder so the University of Chicago CCTO can inform the FDA. The responsible Research Nurse or other designated individual at the treating site should provide a complete written report using the FDA MedWatch 3500A form. The completed form should be sent to the CCTO (qaccto@bsd.uchicago.edu) and the Phase II CRA (PhaseIICRA@medicine.bsd.uchicago.edu) within the specified timelines below regardless of whether all information regarding the event is available. If applicable, a follow-up report should be provided to the CCTO when additional information on the event becomes available.

Participating sites should not forward any adverse event reports directly to the FDA. The CCTO will report all events to the FDA as per the current FDA guidelines.

***Fatal or Life-threatening Events***: within 4 calendar days from treating investigator knowledge of the event.

***All Other Reportable Events****:* within 10 calendar days of treating investigator knowledge of the event.

AEs may be spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. For SAEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration. For serious pretreatment events, the investigator must determine both the intensity of the event and the relationship of the event to study procedures. If a subject is permanently withdrawn from the study because of a SAE, this information must be included in the initial or follow-up SAE report as well as the appropriate form for Study Discontinuation.

The Treating Investigator is responsible for notifying their respective Institutional Review Board (IRB) or Independent Ethics Committee (IEC) in accordance with local regulations of all SAEs. Events occurring at a participating site may be reported to the University of Chicago IRB if they meet current reporting criteria.

The University of Chicago will be responsible for notifying the Regulatory Agencies where required as described in section 10.4.3.2.

#### 10.4.3.1 Expedited Reporting by the University of Chicago to Millennium

AEs which are serious must be reported to Millennium Pharmacovigilance (or designee) from the first dose of study drug through 30 days after administration of the last dose of ixazomib. Any SAE that occurs at any time after completion of ixazomib treatment or after the designated follow-up period that the sponsor-investigator and/or sub-investigator considers to be related to any study drug must be reported to Millennium Pharmacovigilance (or designee). In addition, new primary malignancies that occur during the follow-up periods must be reported, regardless of causality to study regimen, for a minimum of three years after the last dose of the investigational product, starting from the first dose of study drug. All new cases of primary malignancy must be reported to Millennium Pharmacovigilance (or designee).

Reporting to Millennium will be done exclusively by the University of Chicago using MedWatch Form 3500A and submit by facsimile or email according to the following timelines:

**Fatal and Life Threatening SAEs** within 24 hours but no later than 4 calendar days of the sponsor-investigator's observation or awareness of the event

**All other serious (non-fatal/non-life threatening) events** within 4 calendar days of the sponsor-investigator's observation or awareness of the event

The MedWatch Form 3500A used for SAE reporting must include at minimum:

- **Event term(s)**
- **Serious criteria**
- **Intensity of the event(s):** Sponsor-investigator's or sub-investigator's determination. Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version specified in the protocol, as a guideline, whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.
- **Causality of the event(s):** Sponsor-investigator's or sub-investigator's determination of the relationship of the event(s) to study drug administration.

Follow-up information on the SAE may be requested by Millennium.

SAE grades and relationship to all study drugs will be determined by the investigator or sub-investigator according to sections 10.2 and 10.3.

Sponsor-investigator must also provide Millennium Pharmacovigilance with a copy of all SAE communications with applicable regulatory authorities related to the study product(s), as soon as possible but no later than 4 calendar days of such communication.

**SAE and Pregnancy Reporting Contact Information**

Fax Number: 1-800-963-6290
Email: TakedaOncoCases@cognizant.com

#### 10.4.3.2 Expedited Reporting By the University of Chicago to the FDA

It is the responsibility of the University of Chicago coordinator on behalf of the Lead Principal Investigator to notify all participating sites of all serious unexpected suspected adverse reactions that occur on this clinical trial and which are reported to the FDA as an IND Safety Report (21 CFR 312.32). A copy of the completed Form 3500A (MedWatch) will be provided to the responsible Regulatory Manager by the IND coordinator for distribution to all participating sites.

This study will be conducted under an IND held by Andrzej Jakubowiak at the University of Chicago. The University of Chicago CCTO will be responsible for facilitating all communications with the FDA on behalf of the IND holder. Participating sites should not communicate directly with the FDA.

Current FDA regulations require that all SUSARs (see definition in section 10.4.2 occurring on this trial, other findings that suggest a significant risk to humans exposed to the investigational drug (e.g. information from pooled analysis of multiple studies), and any clinically significant increase in the rate of an expected serious adverse reaction be reported as an IND Safety Report.

In order to meet these requirements, the lead principal investigator will review all reported serious adverse events as they occur to determine if FDA reporting is required and will conduct a literature search to seek new safety information and review and analyze all safety information from this clinical trial at least annually and more frequently as appropriate.

Individual Event Reports: FDA Form 3500A (MedWatch) will be completed for all SAEs that require FDA reporting. Serious Adverse Event Reports for fatal or life-threatening events must be returned to the Lead Investigator/ University of Chicago CRA within 4 calendar days. The University of Chicago is responsible for completing the MedWatch Form 3500A and reporting to the FDA. All other events must be received within 10 calendar days.

Other findings that suggest significant risks to the subject: A narrative description summarizing all relevant findings will be provided by the lead principal investigator along with a copy of any relevant publications (if applicable).

Clinically Significant Increase in Frequency of Events: A narrative description summarizing all relevant findings will be provided by the lead principal investigator along with details of individual cases (if applicable).

All MedWatch reports are due to the designated University of Chicago CRA (and will be forwarded to the University of Chicago Clinical Trials Office IND coordinator) according to the specified timeline regardless of whether or not all information regarding this event is available. If applicable, a follow-up report should be provided to the University of Chicago CRA/ IND coordinator once additional information on the event is available.

The completed MedWatch 3500A form will be forwarded to the FDA as appropriate by the University of Chicago Comprehensive Cancer Center – Cancer Clinical Trials Office (CCTO) on behalf of the IND Holder within the appropriate timeframes as designated in 21 CRF 312.32.

### 10.5 Procedures for Reporting Drug Exposure during Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor-investigator must immediately fax a completed Pregnancy Form provided by Millennium to the Millennium Department of Pharmacovigilance or designee (see Section 10.4.3.1). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor-investigator must also immediately fax a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 10.4.3.1). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

If the outcome of the pregnancy meets a criterion for immediate classification as an SAE—spontaneous abortion (any congenital anomaly detected in an aborted fetus is to be documented), stillbirth, neonatal death, or congenital anomaly—the Investigator should repeat the procedures for expedited reporting of SAEs as outlined above.

### 10.6 Procedures for Reporting Drug Exposure during Pregnancy and Birth Events

Millennium shall notify the Treating Investigator via an IND Safety Report of the following information:

- Any AE associated with the use of the drug in this study or other studies that is both serious and unexpected
- Any findings from tests in laboratory animals that suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity or carcinogenicity.

The Treating Investigator shall notify his/her IRB/IEC promptly of these new serious and unexpected AEs or significant risks to subjects in accordance with their policies.

The Lead Principal Investigator must keep copies of all AE information, including correspondence with Millennium and the IRB/IEC on file (see Section 11.7 for records retention information).

# 11. ADMINISTRATIVE REQUIREMENTS

## 11.1 Product Complaints

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact MedComm Solutions (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium Quality representative.

| **For Product Complaints Call:** |
|---|
| MedComm Solutions at |
| 877-674-3784 (877 MPI DRUG) |
| (US and International) |

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to Millennium Pharmacovigilance (refer to Section 10.4.3.1).

# 12. REGULATORY OBLIGATIONS

## 12.1 Informed Consent

No Investigator may involve a human being as a subject in research unless the Investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An Investigator shall seek such consent only under circumstances that provide the prospective subject or the subject's legally authorized representative sufficient opportunity to consider whether or not to participate, and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in a language understandable to the subject or representative.

The University of Chicago will provide the Site Principal Investigator with a sample consent form developed by the University of Chicago. Local and/or institutional requirements may require disclosure of additional information in the informed consent. Any changes to the consent form must be submitted to the University of Chicago for approval, prior to submission to the participating site IRB/IEC. The participating site IRB/IEC will review the consent form for approval. A copy of the IRB/IEC approval form must be submitted to the University of Chicago prior to initiation of the study at the participating site.

Before implementing any study procedure, informed consent shall be documented by the use of a written consent form approved by the IRB/IEC and signed and dated by the subject or the subject's legally authorized representative at the time of consent. A copy of the signed informed consent will be given to the subject or subject's legally authorized representative. The original signed consent must be maintained by the Site Principal Investigator and available for inspection at any time.

The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

### 12.2 Compliance with Laws and Regulations

The study will be conducted in accordance with U.S. Food and Drug Administration (FDA) and International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), the Declaration of Helsinki, Health Canada, any applicable local health authority, and Institutional Review Board (IRB) or Ethics Committee requirements.

This study must have the approval of a properly constituted IRB or Ethics Committee. Before the investigational drug is shipped to the Lead or Site Principal Investigator, the Lead Investigator or designee will provide Millennium with a copy of the IRB or Ethics Committee approval letter stating that the study protocol and any subsequent amendments and informed consent form have been reviewed and approved.

The Lead and Site Principal Investigator or designee will be responsible for obtaining annual IRB or Ethics Committee re-approval throughout the duration of the study. Copies of the Investigator's annual report to the IRB or Ethics Committee and copies of the IRB or Ethics Committee continuance of approval must be provided to Millennium.

### 12.3 Pre-Study Documentation Requirements

Before study can be initiated at a given site, the following documents must be on file with the University of Chicago for that site:

- A U.S. Form FDA 1572 signed by the Site Principal Investigator
- Current Curriculum Vitae (CV) for the Site Principal Investigator and all Sub-Investigators
- Current IRB/IEC membership list
- IRB/IEC approved informed consent and approval letter
- IRB/IEC approval of any advertising materials to be used for study recruitment, if applicable (also to be approved by the University of Chicago)
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Investigational drug accountability standard operating procedures
- Additionally, before the study can be initiated at a site, the required executed research contract/subcontract must be on file with the University of Chicago.

### 12.4 Annual IRB Renewals, Continuing Review and Final Reports

A continuing review of the protocol will be completed by the University of Chicago IRB and the participating institutions' IRBs at least once a year for the duration of the study. The annual IRB renewal approvals for participating institutions should be forwarded promptly to the UCCCC Regulatory Manager. If the institution's IRB requires a new version of the consent form with the annual renewal, the consent form should be included with the renewal letter.

### 12.5 Subject Confidentiality

Subject medical information obtained as part of this study is confidential, and must not be disclosed to third parties, except as noted below. The subject may request in writing that medical information be given to his/her personal physician.

The Investigator/Institution will permit direct access to source data and documents by the University of Chicago, Millennium, and its designee, the FDA and/or other applicable regulatory authority. The access may consist of trial-related monitoring, audits, IRB or Ethics Committee reviews, and FDA inspections.

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 CFR 164.508.

### 12.6 Protocol Amendments and Study Termination

All protocol amendments will be implemented by the University of Chicago and must receive IRB/IEC approval before implementation, except where necessary to eliminate an immediate hazard to subjects. Amendments should only be submitted to the IRB/IEC after consideration by Millennium. Only the Lead Investigator can authorize any modifications, amendments, or termination of the protocol. Once a protocol amendment has been approved by the University of Chicago IRB, the Regulatory Manager will send the amended protocol and consent form to the affiliate institutions electronically for submission to the affiliate institution's IRB. The Site Principal Investigator or designee must send a copy of the approval letter from the IRB for the amendment, along with the revised Informed Consent form (as applicable), to the University of Chicago. The University of Chicago version date and/or amendment number must appear on the affiliate consent form and on the affiliate IRB approval letter (the version date can be found on the footer of every page of the protocol and consent form, and the amendment number can be found on the University of Chicago IRB amendment approval letter sent with the amendment).

The University of Chicago jointly with the study supporters and the Lead Principal Investigator reserves the right to terminate the study according to the study contract. The Site and Lead Principal Investigator or designee should notify jointly the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to the regulatory affairs manager at the University of Chicago Cancer Clinical Trials Office.

### 12.7 Study Documentation and Archive

#### 12.7.1 Source Documentation

Source records are original documents, data, and records (e.g., medical records, raw data collection forms, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical trial. The Site and Lead Principal Investigators will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each subject enrolled in this clinical trial. Source records must be adequate to reconstruct all data transcribed onto the case report forms.

### 12.7.2 Record Retention

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

### 12.7.3 Case Report Form Completion

The data collected for this study will be entered into a secure database Velos eResearch. The University of Chicago will provide you with the applicable user registration information. Source documentation must be available to support the computerized patient record. Source records are original documents, data, and records (e.g., medical records, raw data collection forms, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical trial. Each site will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each subject enrolled in this clinical trial. Source records must be adequate to reconstruct all data transcribed onto the case report form. Upon registration, source documentation including demographics, screening labs, subject demographics, physician's notes for confirmation of concurrent conditions, and confirmation of disease status and treatment history. Additional information may be requested on a case-by case basis.

AEs are to be entered in real time. SAEs are to be reported to the University of Chicago within 24 hours of the site's knowledge of the event. All other data is to be entered within 30 days of source acquisition.

### 12.7.4 Archival of Records

According to 21 CFR 312.62I, the Site and Lead Principal Investigators shall retain records required to be maintained under this part for a period of 2 years following the date a marketing

application is approved for the drug for the indication for which it is being investigated. If no application is to be filed or if the application is not approved for such indication, the Site and Lead Principal Investigator shall retain these records until 3 years after the investigation is discontinued and the FDA or applicable regulatory authorities are notified.

The Site and Lead Principal Investigator must retain protocols, amendments, IRB/IEC approvals, copies of the Form FDA, signed and dated consent forms, medical records, case report forms, drug accountability records, all correspondence, and any other documents pertaining to the conduct of the study.

### 12.7.5 Clinical Monitoring Procedures

Clinical studies coordinated by The University of Chicago must be conducted in accordance with the ethical principles that are consistent with Good Clinical Practices (GCP) and in compliance with other applicable regulatory requirements.

This study will be remotely monitored by the designated University of Chicago Medicine Clinical Research Associate (CRA). Monitoring will be conducted to verify the following:

- Adherence to the protocol
- Completeness and accuracy of study data and samples collected
- Compliance with regulations
- Submission of required source documents

Sites will be required to submit source documentation via fax or email to the University of Chicago. Source documentation required at screening includes but is not limited to medical history, treatment history, screening note for eligibility, and screening lab assessments. The University of Chicago will alert the sites to schedule a remote monitoring visit and to request source documentation.

Prior to subject recruitment, a participating site will undergo site initiation teleconference to be conducted by the designated University of Chicago Medicine CRA and Lead Principal Investigator. The site's principal investigator and his or her study staff should make every effort in attending the site initiation meeting. Study-related questions or issues identified during the site initiation meeting will be followed-up by the appropriate UCM personnel until they have been answered and resolved.

Participating sites will also undergo a site close-out teleconference upon completion, termination or cancellation of a study to ensure fulfillment of study obligations during the conduct of the study, and that the Site Principal Investigator is aware of his/her ongoing responsibilities.

### 12.7.6 Obligations of Study Site Investigators

The Study Site Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Study Site Principal Investigator is responsible for personally overseeing the treatment of all study patients. He/she must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Study Site Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered into the CRFs. Periodically, monitoring visits or audits will be conducted and he/she must provide access to original records to permit verification of proper entry of data.

### 12.7.7 Protocol Deviations

Protocol deviations must be recorded using the Protocol Deviation Form and sent via email to PhaseIICRA@medicine.bsd.uchicago.edu. Deviations that are considered major because they impact subject safety or alter the risk/benefit ratio, compromise the integrity of the study data, and/or affect subjects' willingness to participate in the study must be reported into the Velos system within 7. Please contact the University of Chicago CRA (PhaseIICRA@medicine.bsd.uchicago.edu) if you have questions about how to report deviations. Major protocol deviations should be reported to the local IRB according to the treating site's regulations.

### 12.7.8 Data Safety and Monitoring

The University of Chicago Medical Center is responsible for data and safety monitoring for this study, including reviewing and monitoring the study's scientific progress, accrual rate and any serious adverse events. This protocol will undergo weekly review at the University of Chicago multi-institutional data and safety monitoring teleconference as per procedures specified by the UCCCC NCI-approved Data and Safety Monitoring Plan.

The study will conduct teleconferences at a rate determined by the Lead Principal Investigator to review the following:

- Enrollment rate relative to expectations, characteristics of participants
- Safety of study participants (Serious Adverse Event & Adverse Event reporting)
- Adherence to protocol (protocol deviations)
- Completeness, validity and integrity of study data
- Retention of study subjects

### 12.7.9 Quality Assurance & Auditing

In addition to the clinical monitoring procedures, the University of Chicago Cancer Clinical Trials Office (CCTO) will perform routine Quality Assurance Audits of investigator-initiated clinical trials as described in the NCI-approved UC CCC DSM Plan. Audits provide assurance that trials are conducted and study data are collected, documented and reported in compliance with the protocol. Further, they ensure that study data are collected, documented and reported in compliance with Good Clinical Practices (GCP) Guidelines and regulatory requirements by performing annual quality assurance audits. The CCTO will review subjects enrolled at the University of Chicago in accordance with audit procedures specified in the Data and Safety Monitoring plan.

Auditing procedures for participating sites must be specified and approved by the UC CCC Clinical Research Advisory Committee. In general, auditing responsibility will be delegated to the participating center, with the annual audit report forwarded to the University of Chicago for review.

A regulatory authority (e.g. FDA) may also wish to conduct an inspection of the study, during its conduct or even after its completion. If an inspection has been requested by a regulatory authority, the site investigator must immediately inform the University of Chicago Cancer Clinical Trials Office and Regulatory Manager that such a request has been made.

## 13. REFERENCES

1. Etchin J, Sun Q, Kentisis A, Farmer A, Zhang ZC, Sanda T, Mansour MR< Barcelo C, McCauley D, Kauffman M, Shacham S, Christie AL, Kung AL, Rodig SJ, Chook YM, Look AT. Antileukemia activity of nuclear export inhibitors that spare normal hematopoietic cells. Leukema 2013 Jan;27(1):66-74

2. Ranganathan P, Yu X, Na C, Santhanam R, Shacham S, Kauffman M, Walker A, Klisovic R, Blum W, Caligiuri M, Croce CM, Marucci G, Garzon R. Preclinical activity of a novel CRM1 inhibitor in acute myeloma leukemia. Blood. 2012 Aug 30;120(9):1765-73.

3. Gupta, N., et al., Clinical Pharmacokinetics of Intravenous and Oral MLN9708, An Investigational Proteasome Inhibitor: An Analysis of Data From Four Phase 1 Monotherapy Studies. in 52nd ASH Annual Meeting and Exposition, 2010. 116(21): p. abstr 1813.

4. Gupta, N., M. Saleh, and K. Venkatakrishnan. Flat-Dosing Versus BSA-Based Dosing for MLN9708, An Investigational Proteasome Inhibitor: Population Pharmacokinetic (PK) Analysis of Pooled Data From 4 Phase-1 Studies in 53rd ASH Annual Meeting and Exposition. 2011. San Diego, CA; p. abstr 1433

5. Chow, L.Q., et al. MLN9708, an investigational proteasome inhibitor, in patients with solid tumors; Updated phase 1 results in Head and Neck Symposium. 2012. Phoenix, AZ

6. Assouline, S., et al. Once-weekly MLN9708, an investigational proteasome inhibitor, in patients with relapsed/refractory lymphoma: results of a phase 1 dose-escalation study in 17th EHA Annual Congress. 2012. Amsterdam, the Netherlands.

7. Lonial, S., et al. Phase I study of twice-weekly dosing of the investigational oral proteasome inhibitor MLN9708 in patients (pts) with relapsed and/or refractory multiple myeloma (MM) in ASCO Annual Meeting. 2012. Chicago, Illinois.

8. Kumar S, et al. Weekly Dosing of the Investigational Oral Proteasome Inhibitor MLN9708 in Patients with Relapsed and/or Refractory Multiple Myeloma: Results From a Phase 1 Dose- Escalation Study In 53rd ASH Annual Meeting and Exposition; 2011 10-13 Dec; San Diego, CA; p. abstr 816..

9. Merlini, G., et al. MLN9708, a Novel, Investigational Oral Proteasome Inhibitor, in Patients with Relapsed or Refractory Light-Chain Amyloidosis (AL): Results of a Phase 1 Study in 54th ASH Annual Meeting and Exposition. 2012. Atlanta, Georgia.

10. Kumar, S. et al. A Phase 1/2 Study of Weekly MLN9708, an Investigational Oral Proteasome Inhibitor, in Combination with lenalidomide and Dexamethasone in Patients with Previously Untreated Multiple Myeloma (MM) in 54th ASH Annual Meeting and Exposition. 2012. Atlanta, Georgia.

11. Richardson, P.G., et al. MLN9708, an investigational proteasome inhibitor, in combination with Lenalidomide and dexamethasone in previously untreated multiple myeloma patients (pts):Evaluation of weekly and twice-weekly dosing in 17th EHA Annual Congress. 2012. Amsterdam, the Netherlands.

12. San Miguel, J., et al. Oral MLN9708, an an investigational proteasome inhibitor, in combination with melphalan and prednisone in patients with previously untreated multiple myeloma: a phase 1 study in 17th EHA Annual Congress. 2012. Amsterdam, the Netherlands.

13. Richardson P, Baz R, Wang L, Jakubowiak A, Berg D, Liu G, et al. Investigational Agent MLN9708, An Oral Proteasome Inhibitor, in Patients (Pts) with Relapsed and/or Refractory Multiple Myeloma (MM): Results From the Expansion Cohorts of a Phase 1 Dose-Escalation Study In: 53rd ASH Annual Meeting and Exposition; 2011 10-13 Dec; San Diego, CA; p. abstr 301.

14. Lonial S, Baz R, Wang M, Talpaz M, Liu G, Berg D, et al. Phase I study of twice weekly dosing of the investigational oral proteasome inhibitor MLN9708 in patients (pts) with relapsed and/or refractory multiple myeloma (MM). J Clin Oncol (ASCO Meeting Abstracts) 2012;30(15 suppl):abstr 8017.

15. Kumar S, Bensinger W, Reeder C, Zimmerman T, Berenson J, Berg D, et al. Weekly Dosing of the Investigational Oral Proteasome Inhibitor MLN9708 in Patients with Relapsed and/or Refractory Multiple Myeloma: Results From a Phase 1 Dose- Escalation Study In: 53rd ASH Annual Meeting and Exposition;

16. McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. N Engl J Med 2012;366:1770-1781

# 14. APPENDICES

## 14.1 Eastern Cooperative Oncology Group (ECOG) Scale for Performance Status

| Grade | Description |
|---|---|
| 0 | Normal activity. Fully active, able to carry on all pre-disease performance without restriction |
| 1 | Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work) |
| 2 | In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. |
| 3 | In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. |
| 4 | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair |
| 5 | Dead |

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6):649-55.

### 14.2 Cockcroft-Gault Equation

For males:

$$\text{Creatinine Clearance} = \frac{(140 - \text{age[years]} \times \text{weight [kg]})}{72 \times (\text{serum creatinine[mg/dL]})} \quad \text{OR} \quad \frac{(140 - \text{age[years]} \times \text{weight [kg]})}{0.81 \times (\text{serum creatinine[}\mu\text{mol/L]})}$$

For females:

$$\text{Creatinine Clearance} = \frac{0.85\,(140 - \text{age[years]} \times \text{weight [kg]})}{72 \times (\text{serum creatinine[mg/dL]})} \quad \text{OR} \quad \frac{0.85\,(140 - \text{age[years]} \times \text{weight [kg]})}{0.81 \times (\text{serum creatinine[}\mu\text{mol/L]})}$$

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.

## 14.3 Response Criteria for Multiple Myeloma

IMWG Criteria

| *Response* | *IMWG criteria*[1,2] |
|---|---|
| sCR<br><br>Stringent Complete Response | CR as defined below plus:<br>• normal FLC ratio and<br>• absence of clonal cells in bone marrow by immunohistochemistry or 2 – 4 color flow cytometry |
| CR<br><br>Complete Response | • Negative immunofixation on the serum and urine and<br>• disappearance of any soft tissue plasmacytomas and<br>• < 5% plasma cells in bone marrow.<br>• In patients with only FLC disease, a normal FLC ratio of 0.26–1.65 is required. |
| VGPR<br><br>Very Good Partial Response | • Serum and urine M-protein detectable by immunofixation but not on electrophoresis or<br>• ≥ 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 h.<br>• In patients with only FLC disease, >90% decrease in the difference between involved and uninvolved FLC levels is required. |
| PR<br><br>Partial Response | • 50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by ≥90% or to < 200 mg/24 h<br>• If the serum and urine M-protein are unmeasurable,[3] a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria<br>• If serum and urine M-protein are not measurable, and serum free light assay is also not measureable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30%<br>• In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required |
| Stable Disease | • Not meeting criteria for CR, VGPR, PR or progressive disease |

| | |
|---|---|
| Progressive disease | Increase of ≥ 25% from lowest response value in any one of the following:<br>• Serum M-component (the absolute increase must be ≥ 0.5 g/dL)[4] and/or<br>• Urine M-component (the absolute increase must be ≥ 200 mg/24 h)and/or<br>• Only in patients without measurable serum and urine M-protein, the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL<br>• Only in patients without measurable serum and urine M-protein and without measurable disease by FLC levels, bone marrow plasma cell percentage (absolute % must be ≥ 10%)<br>• Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas<br>• Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder |

All relapse categories (CR, sCR, VGPR, and PD) require two consecutive assessments made at any time before the institution of any new therapy; complete response and PR and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable in serum, urine both or either. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For progressive disease, serum M-component increases of ≥ I gm/dl are sufficient to define response if starting M-component is ≥ 5 g/dl.

IMWG clarification for coding PD:

- Clarified that bone marrow criteria for PD are to be used only in patients without measurable disease by M protein and by FLC levels.
- Clarified that 25% increase refers to M protein, FLC, and bone marrow results and does not refer to bone lesions, soft tissue plasmacytomas or hypercalcemia. Note the lowest response value does not need to be a confirmed value.

**Additional response criteria for specific disease states[1,2,3,4]**

| | |
|---|---|
| Minor response in patients with relapsed and refractory myeloma adapted from the EMBT criteria3 | ≥ 25% but < 49% reduction of serum M protein and reduction in 24 hour urine M protein by 50 – 89%, which still exceeds 200 mg/24hrs.<br><br>In addition to above; if present at baseline, 25-49% reduction in the size of soft tissue plasmacytomas is also required<br><br>No increase in size or number of lytic bone lesions (development of compression fractures does not exclude response) |
| Near Complete Response nCR | The absence of myeloma protein on |

| | |
|---|---|
| | electrophoresis, with positive immunofixation, stable bone disease, and a normal serum calcium concentration |
| Immunophenotypic CR | Stringent CR plus<br>Absence of phenotypic aberrant PC (clonal) in bone marrow with a minimum of one million of total BM cells analyzed by multiparametric flow cytometry (with ≥4 colors) |
| Molecular CR | Stringent CR plus negative ASO-PCR (sensitivity $10^{-5}$) |

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4. Richardson et al. Bortezomib or High-Dose Dexamethasone for Relapsed Multiple Myeloma. N Eng J Med. 352:2487-98, 2005

### 14.4 FACT/GOG-Neurotoxicity Questionnaire, Version 4.0

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

| ADDITIONAL CONCERNS | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|
| I have numbness or tingling in my hands…… | 0 | 1 | 2 | 3 | 4 |
| I have numbness or tingling in my feet…… | 0 | 1 | 2 | 3 | 4 |
| I feel discomfort in my hands……. | 0 | 1 | 2 | 3 | 4 |
| I feel discomfort in my feet…… | 0 | 1 | 2 | 3 | 4 |
| I have joint pain or muscle cramps…… | 0 | 1 | 2 | 3 | 4 |
| I feel weak all over…… | 0 | 1 | 2 | 3 | 4 |
| I have trouble hearing…… | 0 | 1 | 2 | 3 | 4 |
| I get a ringing or buzzing in my ears…… | 0 | 1 | 2 | 3 | 4 |
| I have trouble buttoning buttons…… | 0 | 1 | 2 | 3 | 4 |
| I have trouble feeling the shape of small objects when they are in my hand…… | 0 | 1 | 2 | 3 | 4 |
| I have trouble walking…… | 0 | 1 | 2 | 3 | 4 |

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Sources: Cella DF, Tulsky DS, Gray G, Sarafian B, Lloyd S, Linn E, et al. The functional assessment of cancer therapy (FACT) scale: development and validation of the general measure. *J ClinOncol* 1993; 11(3):570-79.

### 14.5 Quality of Life Assessment Tool

EORTC QLQ – C30 (version 3.0)

EORTC QLQ – MY20

### 14.6 Lenalidomide Risk Evaluation and Mitigation Strategy (REMS)™ Program

http://www.revlimidrems.com/pdf/REV_Prescriber_Guide.pdf

### 14.7 Lenalidomide Prescribing Information 2013

http://dailymed.nlm.nih.gov/dailymed/getFile.cfm?setid=5fa97bf5-28a2-48f1-8955-f56012d296be&type=pdf&name=5fa97bf5-28a2-48f1-8955-f56012d296be