Update #09

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

PROTOCOL UPDATE TO ALLIANCE A061202

A PHASE I/II STUDY OF POMALIDOMIDE, DEXAMETHASONE AND IXAZOMIB VS. POMALIDOMIDE AND DEXAMETHASONE FOR PATIENTS WITH MULTIPLE MYELOMA RELAPSING ON LENALIDOMIDE AS PART OF FIRST LINE THERAPY

Pomalidomide (NSC #767909, IND #120020) is supplied by Celgene Corporation and distributed by McKesson Specialty Pharmacy.
Ixazomib (NSC #767907, IND #120020) is supplied by Millennium Pharmaceuticals and distributed by McKesson Specialty Pharmacy.
Dexamethasone is commercially available.

[X] **Update:**	[ ] **Status Change:**
[ ] Eligibility changes	[ ] Activation
[ ] Therapy / Dose Modifications / Study Calendar changes	[ ] Closure
[X] Informed Consent changes	[ ] Suspension / temporary closure
[ ] Scientific / Statistical Considerations changes	[ ] Reactivation
[ ] Data Submission / Forms changes	
[ ] Editorial / Administrative changes	
[X] Other: Pomalidomide CAEPR update	

The changes included in this update to A061202 have been made in response to the NCI Action Letter from [redacted] This Action Letter is posted on the A061202 study page on the Alliance and CTSU websites. A revised CAEPR for pomalidomide with new risks has been added to the protocol. Therefore, the model consent form has been revised to incorporate these new risks, consistent with the NCI Model Consent Template instructions. There are no changes to the risk/benefit ratio.

The proposed changes in this amendment are minor and do not affect the overall risk/benefit ratio. IRB approval (or disapproval) is required within 90 days. Expedited review is allowed. Please follow your local IRB guidelines.

Re-consent is not required by the Alliance. Please follow the policy of your IRB of record regarding notifying patients of new information contained in this update.

UPDATES TO THE PROTOCOL:

Section 9.3 (Comprehensive Adverse Events and Potential Risks List (CAEPR) for Pomalidomide (CC-4047, NSC 767909))

This section has been revised to include the updated pomalidomide CAEPR (Version 2.4, May 22, 2022) provided by CTEP. Changes from Version 2.3 to Version 2.4 include the following:

- Added New Risk:
  - Rare but Serious: Nervous system disorders - Other (Progressive multifocal leukoencephalopathy)
  - Also Reported on Pomalidomide Trials But With Insufficient Evidence for Attribution: Atrial fibrillation; CD4 lymphocytes decreased; CPK increased; Chest wall pain; Colonic perforation; Death NOS; Disease progression; Dysphasia; Erythema multiforme; Eye disorders - Other (eyelid swelling); Hematuria; Hyperuricemia; Ischemia cerebrovascular; Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (multiple myeloma, myelofibrosis, progression of MM); Seizure; Tumor pain; Vascular disorders - Other (hyperviscosity syndrome)

- Increase in Risk Attribution:
  - Changed to Likely from Less Likely: Anemia

- Decrease in Risk Attribution:
  - Changed to Rare but Serious from Less Likely: Anorexia; Bone pain; Cough; Dizziness; Dyspnea; Nausea; Rash maculo-papular; Thromboembolic event
  - Changed to Also Reported on Pomalidomide Trials But With Insufficient Evidence for Attribution from Less Likely: Creatinine increased; Headache; Hypercalcemia; Muscle cramp; Pruritus; Tremor; Vomiting; White blood cell decreased
  - Changed to Also Reported on Pomalidomide Trials But With Insufficient Evidence for Attribution from Rare but Serious: Blood and lymphatic system disorders - Other (sickle cell anemia with crisis); Febrile neutropenia; Sinus tachycardia

- Deleted Risk:
  - Less Likely: Alkaline phosphatase increased; Aspartate aminotransferase increased; Non-cardiac chest pain
  - Also Reported on Pomalidomide Trials But With Insufficient Evidence for Attribution: Abdominal distension; Atrioventricular block complete; Hypertension; Hyperthyroidism; Hypomagnesemia; Hypophosphatemia; Memory impairment; Pain; Peripheral motor neuropathy; Urticaria

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UPDATES TO THE PHASE I MODEL CONSENT:

What possible risks can I expect from taking part in this study?

Based on the updated CAEPR described above, the following changes have been made to the NCI condensed risk profile for pomalidomide (found under "Possible Side Effects of Pomalidomide"):

- Added New Risk:
    - Rare: Abnormal unpleasant sensation; Damage to the brain which may cause changes in thinking and may be life-threatening; Feeling of "pins and needles" in arms and legs

- Increase in Risk Attribution
    - Changed to Common from Occasional: Anemia which may require blood transfusion

- Decrease in Risk Attribution:
    - Changed to Occasional from Common: Tiredness
    - Changed to Rare from Occasional: Blood clot which may cause swelling, pain, shortness of breath; Cough, shortness of breath; Nausea; Headache; Rash
    - Changed to Also Reported on Pomalidomide Trials But With Insufficient Evidence for Attribution from Occasional (i.e., removed from the Risk Profile): Vomiting; Abnormal body movement; Itching
    - Changed to Also Reported on Pomalidomide Trials But With Insufficient Evidence for Attribution from Rare (i.e., removed from the Risk Profile): Abnormal heartbeat; Sickle cell anemia with crisis

- Provided Further Clarification:
    - Infection, especially when while blood cell count is low (under Occasional) is now reported as Infection (under Occasional).

UPDATES TO THE PHASE II MODEL CONSENT:

What possible risks can I expect from taking part in this study?

Based on the updated CAEPR described above, the following changes have been made to the NCI condensed risk profile for pomalidomide (found under "Possible Side Effects of Pomalidomide"):

- Added New Risk:
    - Rare: Abnormal unpleasant sensation; Damage to the brain which may cause changes in thinking and may be life-threatening; Feeling of "pins and needles" in arms and legs

- Increase in Risk Attribution
    - Changed to Common from Occasional: Anemia which may require blood transfusion

- Decrease in Risk Attribution:
    - Changed to Occasional from Common: Tiredness
    - Changed to Rare from Occasional: Blood clot which may cause swelling, pain, shortness of breath; Cough, shortness of breath; Nausea; Headache; Rash
    - Changed to Also Reported on Pomalidomide Trials But With Insufficient Evidence for Attribution from Occasional (i.e., removed from the Risk Profile): Vomiting; Abnormal body movement; Itching
    - Changed to Also Reported on Pomalidomide Trials But With Insufficient Evidence for Attribution from Rare (i.e., removed from the Risk Profile): Abnormal heartbeat; Sickle cell anemia with crisis

- Provided Further Clarification:
    - Infection, especially when while blood cell count is low (under Occasional) is now reported as Infection (under Occasional).

Replacement protocol and model consent documents have been issued.
This study remains closed to new patient accrual.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALLIANCE A061202

A PHASE I/II STUDY OF POMALIDOMIDE, DEXAMETHASONE AND IXAZOMIB VS. POMALIDOMIDE AND DEXAMETHASONE FOR PATIENTS WITH MULTIPLE MYELOMA RELAPSING ON LENALIDOMIDE AS PART OF FIRST LINE THERAPY

Clinicaltrials.gov identifier: NCT02004275

*The Phase I portion will be a **limited access study**, available to the following institutions (the Phase II portion is open to all Alliance member institutions)*
*Limited Access Participating Institutions (ALL ARE ALLIANCE Institutions): **NC007**/UNC Lineberger*

[redacted]

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Ixazomib (NSC #767907, Alliance IND #120020) is supplied by Millennium Pharmaceuticals and distributed by McKesson Specialty Pharmacy.
Dexamethasone is commercially available.

Study Chair

[redacted]

Myeloma Committee Chair

[redacted]

Myeloma Committee Co-Chair

[redacted]

Community Oncology Co-chair

[redacted]

Correlative Committee Chair

[redacted]

Correlative Study Co-Chair

[redacted]

ECOG Champion

[redacted]

Primary Statistician

[redacted]

Secondary Statistician

[redacted]

Protocol Coordinator

[redacted]

Data Manager

[redacted]

Participating Organizations: **ALLIANCE**/Alliance for Clinical Trials in Oncology, **ECOG-ACRIN**/ECOG-ACRIN Cancer Research Group, **SWOG**/SWOG

Study Resources:

Expedited Adverse Event Reporting

[redacted]

Medidata Rave® iMedidata portal

[redacted]

OPEN (Oncology Patient Enrollment Network)

[redacted]

Biospecimen Management System

[redacted]

Protocol Contacts:

A061202 Nursing Contact

[redacted]

A061202 Pharmacy Contact

[redacted]

Alliance Biorepository at Ohio State University (OSU)

T[redacted]

Alliance Hematologic Malignancy Biorepository

[redacted]

Protocol-related questions may be directed as follows:	
Questions	**Contact (via email)**
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, Protocol Coordinator, or (where applicable) Data Manager
Questions related to data submission, RAVE or patient follow-up:	Data Manager
Questions regarding the protocol document:	Protocol Coordinator
Questions related to IRB issues and model consent revisions:	Regulatory Affairs Manager: [redacted]
Questions regarding CTEP-AERS reporting:	Pharmacovigilance Inbox [redacted]
Questions regarding specimens/specimen submissions:	Alliance Biorepository at Ohio State University or The Alliance Hematologic Malignancy Biorepository

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at [redacted] and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at [redacted] to receive further instruction and support. Contact the CTSU Regulatory Help Desk at [redacted] for regulatory assistance.	Please refer to the patient enrollment section for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at [redacted] Contact the CTSU Help Desk with any OPEN-related questions at [redacted]	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.

The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page of the CTSU Member website located at [redacted] Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

For clinical questions (i.e. patient eligibility or treatment-related) see the Protocol Contacts, Page 2.

For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail:
CTSU General Information Line – [redacted] All calls and correspondence will be triaged to the appropriate CTSU representative.

The CTSU website is located at [redacted]

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Eligibility Criteria (see Section 3.0)

- Histologically confirmed diagnosis of relapsed symptomatic multiple myeloma.
- Measureable or non-measurable disease (see section 3.2.2)
- Prior Treatment(s) (see section 3.2.3)
  - Progression on lenalidomide
  - Pomalidomide naïve
  - Proteasome inhibitor naïve or sensitive
  - 1 prior line of therapy
- Not pregnant and not nursing (see section 3.2.4)
- ≥18 years of age
- ECOG Performance Status 0-2 (see Appendix I)
- ≤ Grade 2 Peripheral Neuropathy
- Adequate cardiac function (see section 3.2.10)
- Not on strong inducers or potent inhibitors of CYP3A4 or CYP1A2 (see section 3.2.11)
- Patients with HIV infection are eligible, provided they meet guidelines listed in section 3.2.12

Required Initial Laboratory Values

Absolute Neutrophil Count (ANC)	≥ 1.0 x 10^9/L
Platelet Count	≥ 50 x 10^9/L
Calculated Creatinine Clearance*	≥ 30 mL/min
Total Bilirubin	< 1.5 x upper limit of normal
AST, ALT	< 2.5 x upper limit of normal

* May be assessed via the Cockcroft-Gault formula or 24-hour urine testing (See Appendix II).

A PHASE I/II STUDY OF POMALIDOMIDE, DEXAMETHASONE AND IXAZOMIB VS. POMALIDOMIDE AND DEXAMETHASONE FOR PATIENTS WITH MULTIPLE MYELOMA RELAPSING ON LENALIDOMIDE AS PART OF FIRST LINE THERAPY

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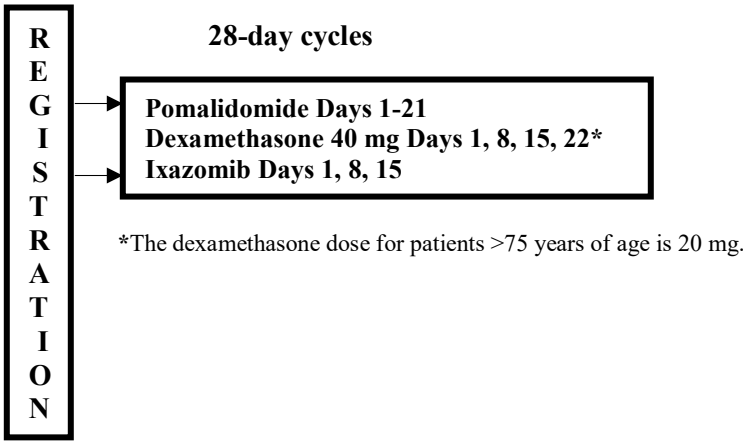
PHASE I (CLOSED AS OF FEBRUARY 4, 2016)



*The dexamethasone dose for patients >75 years of age is 20 mg.

Dose Escalation Schema

Cohort	Pomalidomide (mg)	Ixazomib (mg)
0	2	2.3
1	**2**	**3**
2	3	3
3	4	3
4	4	4

Phase I

If cohort 2 is the maximum tolerated dose, a dose level 2A will be pursued evaluating a 2 mg dose of pomalidomide and 4 mg dose of ixazomib. If cohort 3 is the maximum tolerated dose, a dose level 3A will be pursued evaluating a 3 mg dose of pomalidomide and 4 mg dose of ixazomib.

Pomalidomide/Dexamethasone/Ixazomib

Cycle length: 28 days

Pomalidomide: Orally once daily on days 1-21 out of 28 days.

Dexamethasone: 40 mg orally once weekly on days 1, 8, 15, and 22. The dose of dexamethasone for patients >75 years of age is 20 mg utilizing the same schedule.

Ixazomib: Orally once weekly on days 1, 8, and 15.

Dose escalation will follow a standard 3+3 design (see Section 13.0). Dosing will begin with cohort 1. Patients may remain on treatment until disease progression, unacceptable toxicity, or withdrawal of consent.

Please Note: For the phase I portion of this study, patient enrollment will be facilitated using the Slot-Reservation System in conjunction with the Registration system on Oncology Patient Enrollment Network (OPEN). Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System to insure that a slot on the protocol is available to the patient. Once a slot reservation confirmation is obtained, site staff may then proceed to enroll patients to this study.

A PHASE I/II STUDY OF POMALIDOMIDE, DEXAMETHASONE AND IXAZOMIB VS. POMALIDOMIDE AND DEXAMETHASONE FOR PATIENTS WITH MULTIPLE MYELOMA RELAPSING ON LENALIDOMIDE AS PART OF FIRST LINE THERAPY

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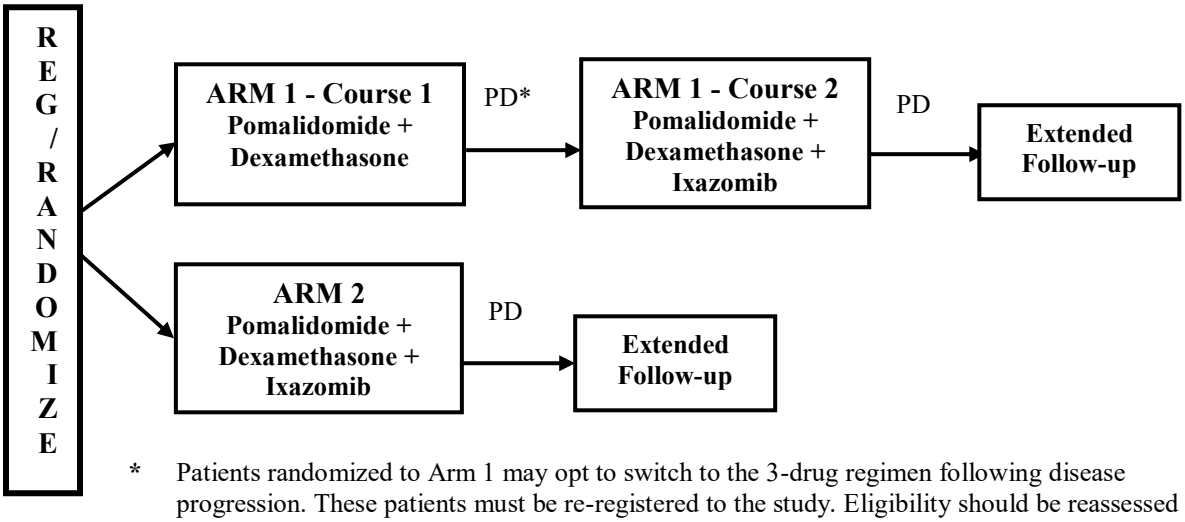
PHASE II



* Patients randomized to Arm 1 may opt to switch to the 3-drug regimen following disease progression. These patients must be re-registered to the study. Eligibility should be reassessed per Section 3.3 prior to re-registration.

Patients may remain on treatment until disease progression, unacceptable toxicity, or withdrawal of consent.

Phase II Treatment

Arm 1 (Course 1): Pomalidomide + Dexamethasone. 28-day cycles.

Pomalidomide: 4 mg orally once daily on days 1-21.

Dexamethasone: 40 mg orally once weekly on days 1, 8, 15 and 22. The dose of dexamethasone for patients > 75 years or age will be 20 mg, utilizing the same schedule.

See Section 7.2 for the Course 2 treatment plan for patients randomized to Arm 1 who opt to receive the 3-drug regimen following progression.

Arm 2: Pomalidomide + Dexamethasone + Ixazomib. 28-day cycles.

Pomalidomide: 4 mg orally once daily on days 1-21.

Dexamethasone: 40 mg once weekly on days 1, 8, 15 and 22. The dose of dexamethasone for patients > 75 years of age will be 20 mg, utilizing the same schedule.

Ixazomib: 4 mg orally once weekly on days 1, 8 and 15.

PLEASE REFER TO THE FULL PROTOCOL TEXT FOR A COMPLETE DESCRIPTION OF THE ELIGIBILITY CRITERIA AND TREATMENT PLAN.

Table of Contents

1.0 BACKGROUND

1.1 Immunomodulatory drug/proteasome inhibitor combination therapy for multiple myeloma

Multiple myeloma is the second most common hematologic malignancy in adults and associated with significant mortality and morbidity [1]. Fortunately, the advent of the immunomodulatory drugs (IMiDs), thalidomide, lenalidomide, and pomalidomide, and the proteasome inhibitors bortezomib and carfilzomib have significantly improved survival of patients with multiple myeloma [2-13]. Unfortunately, the majority of patients will experience repeated relapses and ultimately succumb to refractory disease. With the rapidly changing therapeutic landscape in multiple myeloma, it is imperative that we not only develop novel agents to improve patient outcomes, but understand how to better utilize these agents in combination and best sequence them in the continuum of myeloma therapy.

Notable advances have been made in the understanding of optimal combination therapies of patients with multiple myeloma. In particular, the clinical activity of IMiD/proteasome inhibitor plus dexamethasone triplet combinations has been particularly promising [14-25]. In patients with newly-diagnosed multiple myeloma, the combination of bortezomib, thalidomide and dexamethasone (VDT) as induction therapy led to an increased overall response rate (ORR) and higher rate of deep responses (very good partial responses [VGPRs] or better) compared to either the thalidomide-dexamethasone or bortezomib-dexamethasone doublet [18, 24]. Importantly, the higher rate of VGPRs and better seen with VDT persisted after high-dose melphalan supported by autologous stem cell transplantation (ASCT). In the Cavo study, VDT induction and post-ASCT consolidation led to an improvement in progression-free survival (PFS) compared with thalidomide and dexamethasone, thus establishing VTD as a standard of care for newly-diagnosed, transplant-eligible multiple myeloma patients [18]. VTD has performed well in patients with relapsed multiple myeloma, as well. A phase III study comparing VDT to thalidomide and dexamethasone was conducted in patients with a first relapse of their multiple myeloma after prior ASCT [25]. As such, this was a second line therapy study. Importantly, not only was there an improvement in the ORR and rate of VGPRs or better, the median time to progression (TTP) was improved with VTD (19.5 vs 13.8 months, hazard ratio [HR] 0.59; $P = 0.001$), thus establishing VTD as a standard of care in relapsed multiple myeloma, as well.

The incorporation of the proteasome inhibitors bortezomib and carfilzomib into the lenalidomide-dexamethasone backbone has also led to notable gains in clinical outcomes for patients with multiple myeloma. The combination of lenalidomide, bortezomib and dexamethasone (RVD) outperformed the lenalidomide-dexamethasone doublet in patients with newly-diagnosed multiple myeloma not undergoing ASCT as part of their first line therapy [20]. Specifically, the ORR and rate of VGPRs were higher with RVD. This improvement in response rate not only translated into an improvement in progression-free survival (PFS, 43 vs 30 months, HR 0.712, $P = 0.0018$)) but in overall survival, as well (75 vs 64 months, HR 0.709, $P = 0.025$). Thus, RVD has become an important standard of care for patients with newly-diagnosed multiple myeloma. The RVD regimen has not been studied in relapsed/refractory multiple myeloma in the phase III setting. However, for patients with relapsed multiple myeloma who had received 1 – 3 prior lines of therapy, the combination of carfilzomib, lenalidomide and dexamethasone (CRD) led to an improvement in ORR (87.1% vs 66.7%, $P < 0.001$), rate of VGPRs or better (69.9% vs 40.4%, $P < 0.001$) and median PFS (26.3 vs 17.6 months, HR 0.69, $P = 0.0001$) compared with lenalidomide and dexamethasone [21]. It should be noted that patients with disease refractory to bortezomib or lenalidomide as part of last line therapy were not eligible to participate in this study. Thus, the CRD regimen represents a newer standard of care regimen for patients with relapsed multiple myeloma who have received 1 – 3 prior lines

of therapy and have bortezomib and lenalidomide naïve or sensitive disease. CRD has performed well in phase I/II studies of newly-diagnosed multiple myeloma patients [22]. A phase III study comparing RVD and CRD in newly-diagnosed multiple myeloma patients not receiving ASCT as part of first line therapy is ongoing and will help clarify the relative efficacy and safety of the two IMiD / proteasome inhibitor/dexamethasone triplets (NCT01863550).

1.2 The rationale for the incorporation of the proteasome inhibitor ixazomib into IMiD-dexamethasone-based multiple myeloma therapy

Ixazomib, or MLN9708, is a citrate ester that in aqueous solution and plasma is hydrolyzed to the biologically active dipeptide boronic acid proteasome inhibitor, MLN2238. Importantly, ixazomib has been formulated for oral administration, making it one of the first orally bioavailable proteasome inhibitors in clinical development. Like bortezomib, ixazomib is a reversible inhibitor of the β5 subunit of the proteasome. However, ixazomib has a proteasome dissociation half-life that is approximately 6-fold faster than bortezomib. This faster dissociation half-life is hypothesized to play a role in the ability of ixazomib to distribute to tumors more efficiently than bortezomib, owing to the fact that high levels of whole blood proteasome activity sequester bortezomib from sites of disease. Indeed, studies have shown an increased blood volume of distribution at steady state, increased tumoral proteasome inhibition, and increased efficacy of ixazomib compared to bortezomib in pre-clinical models of multiple myeloma [26-28]. Importantly, synergistic activity with lenalidomide was also seen. Please see the ixazomib Investigator's Brochure for further preclinical information.

Results from two phase I studies of single agent ixazomib administered on a weekly or twice weekly schedule for patients with relapsed and relapsed/refractory multiple myeloma have been published. In the twice-weekly dosing study, escalating doses of ixazomib were administered on days 1, 4, 8 and 11 of a 21-day cycle. Sixty patients had enrolled on the study and 26 to the dose escalation cohorts. The median time from diagnosis was 4.8 years and patients had received a median of 4 prior lines of therapy (range 1 – 28). The MTD was 2.0 mg/m^2. Of 55 patients evaluable for response, 6 had achieved ≥ PRs, 1 had achieved an MR, and 33 patients achieved stable disease (SD), thus yielding a disease control rate (DCR, or ≥ SD rate) of 76%. Eighteen percent of the patients remained on therapy for ≥ 12 cycles [29]. More common side effects with twice weekly dosing included fatigue (40% total, 7% grade 3), thrombocytopenia (42% total, 37% ≥grade 3), nausea (42%), vomiting (25%), rash (40% total, 8% grade 3) and diarrhea (23%). Seventeen percent of patients had peripheral neuropathy, none of which was ≥ grade 3 in severity. In the weekly dosing study, escalating doses of single agent ixazomib were administered on days 1, 8 and 15 of a 28-day cycle. The MTD on this schedule was 2.97 mg/m^2. Common AEs included thrombocytopenia (43%, ≥ grade 3 33%), neutropenia (22%, ≥ grade 3 18%), diarrhea (38%, ≥ grade 3 17%), nausea (38%, ≥ grade 3 7%), vomiting (35%, ≥ grade 3 5%), decreased appetite (25%, ≥ grade 3 7%) and fatigue (37%, ≥ grade 3 8%). The rate of peripheral neuropathy was 20%, almost all of which was grade 1 or 2 in severity (1 episode of grade 3 and no episodes of grade 4 or 5 neuropathy were seen). Rash was seen in 22% of patients, but only 3% experienced ≥ grade 3 rash. For those patients treated at the MTD, the ORR was 26%, a respectable result for a patient population that had received a median of 4 prior lines of therapy, 72% of whom were refractory to their last treatment regimen [30].

A phase I/II study was conducted evaluating the combination of ixazomib, lenalidomide and dexamethasone in newly-diagnosed multiple myeloma [31]. Given a terminal half-life of ~7 days, a once weekly dosing strategy of ixazomib was chosen for combination therapy (28-day cycle: lenalidomide 25 mg days 1-21; dexamethasone 40 mg days 1, 8, 15, 22; and ixazomib days 1, 8, 15). The recommended phase II dose (RP2D) of ixazomib was determined to be 2.23 mg/m^2 when combined with lenalidomide and dexamethasone. Population-based pharmacokinetic studies of several ixazomib studies demonstrated that the plasma

concentration-time profile of ixazomib can be described by a three-compartment model with first order elimination process. Body size did not significantly impact AUC or C_{max}, supporting utilization of flat dosing in future studies. Thus, the recommended phase II dose (RP2D) of ixazomib in combination with lenalidomide and dexamethasone was found to be 4.0 mg. For the 64 evaluable patients, the ORR was 88% with 58% of patients achieving ≥VGPRs and 27% CRs. The most common Grade 3/4 AEs included rash (17%), neutropenia (12%), vomiting (6%), back pain (7%), thrombocytopenia (8%), anemia (3%), fatigue (9%), diarrhea (6%) and nausea (5%), dehydration (3%), hypokalemia (6%), and hypophosphatemia (5%). Peripheral neuropathy was seen in 32% of patients (N=21, 4 of which were grade 3 in severity). Importantly, there was no PK interaction between ixazomib and lenalidomide.

The results of a phase III study comparing lenalidomide and dexamethasone to lenalidomide, ixazomib and dexamethasone for patients with relapsed and/or refractory multiple myeloma who had received 1 – 3 prior lines of therapy were published [32]. It should be noted that patients with lenalidomide-refractory disease were not eligible for the study. At the first interim analysis, the median PFS for those receiving the 3-drug combination was superior to lenalidomide and dexamethasone alone (median PFS 20.6 months versus 14.7 months, respectively, HR 0.742, *P*=0.01). Patients with high risk cytogenetics derived an even greater magnitude of benefit (median PFS 21.4 vs 9.7 months, HR 0.54, *P* = 0.02). Importantly, the addition of ixazomib to lenalidomide and dexamethasone was well tolerated, but there was a higher incidence of thrombocytopenia, nausea, vomiting, diarrhea, constipation, rash and edema. Peripheral neuropathy was seen in 27% of patients receiving the triplet compared with 22% for those patients on lenalidomide and dexamethasone. The incidence of grade 3 peripheral neuropathy was only 2% in each arm and no grade 4 peripheral neuropathy was seen. Furthermore, the incidence of congestive heart failure, acute renal failure, hypertension, interstitial lung disease and myocardial infarction was not different between the two arms. Based on these data, the FDA approved the lenalidomide, ixazomib and dexamethasone regimen for myeloma patients who have received at least one prior therapy in 11/2015. A phase III study evaluating lenalidomide, ixazomib and dexamethasone versus lenalidomide and dexamethasone in patients with newly-diagnosed multiple myeloma is ongoing and will help define the role of this triplet in the frontline setting (NCT01850524).

The table below includes adverse events reported by Millennium from studies with ixazomib in combination with other agents. Attribution to a specific agent is not assigned.

Summary of Most Common (At Least 10% of Total) Treatment- Emergent Adverse Events (Oral MLN9708 Combination Agent [C16005/6/8] Safety Population)

Primary System Organ Class	**Preferred Term and Incidence N= 96 n (%)**
Subjects with at Least One Adverse Event 135 (92)	
Gastrointestinal disorders 70 (73)	Nausea 32 (33); Constipation 29 (30); Vomiting 25 (26); Diarrhoea 22 (23)
General disorders and administration site conditions 64 (67)	Fatigue 37 (39); Oedema peripheral 20 (21); Pyrexia 19 (20)
Skin and subcutaneous tissue disorders 57 (59)	Rash 13 (14)
Nervous system disorders 46 (48)	Neuropathy peripheral 13 (14); Dysgeusia 12 (13) Dizziness 11 (11)
Musculoskeletal and connective tissue disorders 45 (47)	Back pain 18 (19); Muscle spasms 10 (10)

Blood and lymphatic system disorders 42 (44)	Thrombocytopenia 28 (29); Anaemia 22 (23); Neutropenia 19 (20)
Infections and infestations 40 (42)	Upper respiratory tract infection 17 (18);
Metabolism and nutrition disorders 38 (40)	Decreased appetite 11 (11)
Respiratory, thoracic and mediastinal disorders 34 (35)	Dyspnoea 13 (14); Cough 11 (11)
Psychiatric disorders 23 (24)	Insomnia 15 (16)

Source: MLN9708 Investigator's Brochure Edition 6.

Treatment emergent is defined as any AE that occurs after administration of the first dose of any study drug through 30 days after the last dose of any 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 by the investigator to be drug-related.

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

1.3 The evolving armamentarium of combination therapies for patients with relapsed or relapsed and refractory multiple myeloma who have received at least 1 prior line of therapy

1.3.1 Lenalidomide-dexamethasone-based triplets for relapsed multiple myeloma

Numerous regimens have recently received approval for patients with relapsed or relapsed and refractory multiple myeloma who have received 1 or more prior lines of therapy. Four triplets have been approved utilizing the lenalidomide-dexamethasone backbone; specifically lenalidomide and dexamethasone in combination with ixazomib, carfilzomib, elotuzumab and daratumumab [21, 32-34]. The triplets combining lenalidomide and dexamethasone with carfilzomib and ixazomib have been outlined above *see sections 1.1 and 1.2, respectively). Elotuzumab and daratumumab are monoclonal antibodies targeting SLAMF7 and CD38 on plasma cells, respectively. In a phase III study of patients with relapsed and/or refractory multiple myeloma who had received 1 – 3 prior lines of therapy, the addition of elotuzumab to lenalidomide and dexamethasone led to improved ORRs (79% vs 66%, P <0.001) and median PFS (19.4 vs 14.9 months, HR 0.70, P <0.001) [33]. The triplet was well tolerated, although an increased rate of grade 3 or higher lymphopenia was seen, as well as grade 1 and 2 fatigue, pyrexia, edema, nasopharyngitis, diarrhea, constipation and cough. The combination of daratumumab with lenalidomide and dexamethasone was also shown to be superior to lenalidomide-dexamethasone in a phase III study of patients with relapsed and relapsed/refractory multiple myeloma who had received at least 1 prior line of therapy, with improved ORRs (92.9 vs 76.4%, P <0.001), high quality response rates (≥VGPRs 75.8% vs 44.2%, P <0.001) and median PFS (not reached vs 18.4 months, HR 0.37, P <0.001) [34]. As with elotuzumab, the addition of daratumumab to lenalidomide and dexamethasone was well tolerated, although there was a higher rate of neutropenia, nausea, vomiting, diarrhea, fatigue, pyrexia, cough, dyspnea, upper respiratory tract infections, nasopharyngitis and muscle spasms, most of which was grade 1 and 2 in severity. As such, lenalidomide and dexamethasone in combination with elotuzumab and daratumumab have become important standards of care in patients with relapsed multiple myeloma.

1.3.2 The challenge of lenalidomide-dexamethasone-based triplet therapy for relapsed multiple myeloma in evolving treatment paradigms

In the above described phase III studies that led to FDA approval of 4 different lenalidomide-dexamethasone-based combinations for relapsed multiple myeloma, patients were required to have lenalidomide-sensitive or -naïve disease. As such, these data are not applicable to those patients with lenalidomide-refractory disease. This is important, because an increasing proportion of patients in the United States with newly-diagnosed multiple myeloma are treated with lenalidomide until disease progression, rendering their disease lenalidomide-refractory at the time of first disease progression. This pattern of practice has largely been driven by two phase III studies. The first study was a phase III trial in transplant-ineligible patients comparing lenalidomide and dexamethasone for a total duration of 18 months to indefinite lenalidomide and dexamethasone therapy until disease progression [35]. The median PFS was superior for those who received treatment until disease progression (20.7 months versus 25.5 months), and the hazard ratio (HR) for PFS was 0.70 (P<0.001) [35]. It should also be noted that the phase III study that demonstrated an improvement in median PFS and OS with RVD compared to lenalidomide and dexamethasone utilized lenalidomide and dexamethasone until disease progression after receipt of an initial 8 cycles of RVD [20]. The second study evaluated the role of lenalidomide as a maintenance therapy after recovery from high dose melphalan and autologous stem cell transplantation. Patients were treated with placebo or lenalidomide until disease progression. Notably, the median time to progression was 46 months in the lenalidomide arm compared with 27 months for those taking placebo [7]. Additionally, a more recent analysis has revealed an overall survival advantage with the use of lenalidomide maintenance after transplant (HR 0.60, P=0.001). Additional studies evaluating lenalidomide as a maintenance therapy after autologous stem cell transplantation have also demonstrated improvements in median PFS of a similar magnitude [36]. Thus, the majority of patients in the United States will have lenalidomide resistance at first or second progression. Clearly, a better understanding of optimal therapy for relapsed myeloma in the changing paradigm of myeloma therapy and lenalidomide resistance after 1 prior line of therapy is critical.

1.3.3 Non-lenalidomide-based therapy for relapsed multiple myeloma

Several non-lenalidomide-based regimens have recently been FDA approved for patients with relapsed and relapsed/refractory multiple myeloma who have received 1 or more prior lines of therapy. Carfilzomib and dexamethasone was compared to bortezomib and dexamethasone in the context of a phase III study for patients with relapsed multiple myeloma who had received 1 – 3 prior lines of therapy [37]. Notably, carfilzomib and dexamethasone was superior with regards to ORR (77% vs 63%, P <0.0001), VGPR or better (54% vs 29%) and median PFS (18.7 vs 9.4 months, HR 0.53, P <0.0001). However, it should be noted that only 38% of patients on this study had received prior lenalidomide (20.3 – 22% of those who had previously been treated with just 1 prior line of therapy). Furthermore, the median PFS for carfilzomib and dexamethasone was only 8.6 months for those who were refractory to lenalidomide compared with not evaluable for those with lenalidomide-sensitive disease (P <0.0001) [38]. Furthermore, for patients with high risk cytogenetics treated with carfilzomib and dexamethasone, the median PFS was only 8.8 months as opposed to 6.0 months for those patients treated with bortezomib and dexamethasone [39]. These data would suggest that while the carfilzomib-dexamethasone doublet is active and represents an important standard of care for patients with relapsed multiple myeloma, there is clear room for improvement for patients with high risk cytogenetic or disease that is refractory to lenalidomide. Furthermore, carfilzomib and

dexamethasone was associated with a higher rate of hypertension, acute renal failure, pulmonary hypertension, congestive heart failure and ischemic heart disease compared with bortezomib and dexamethasone. For patients who are 75 years of age and older, the risk of grade 3 or higher congestive heart failure was 10.4% with carfilzomib and dexamethasone, as opposed to 3.1% with bortezomib-dexamethasone [40]. As such, the regimen must be used cautiously, especially for those with underlying cardiovascular comorbidity.

The addition of daratumumab to bortezomib and dexamethasone has been shown to be superior to the bortezomib-dexamethasone doublet in the context of a phase III study [41]. Specifically, the daratumumab-bortezomib-dexamethasone combination was superior with regards to ORR (82.9% vs 63.2%, P <0.001), rate of high quality responses (VGPRs or better 59.2% vs 29.1%, P <0.001)), and median PFS (not reached vs 7.2 months, HR 0.39, P <001). However, only 32.9% of patients had disease refractory to IMiDs, and many of these IMiD-refractory patients were likely thalidomide and not lenalidomide-refractory given the large contribution of patient enrollment to this study outside of the United States. Furthermore, daratumumab is currently being evaluated in several randomized studies for patients with newly-diagnosed multiple myeloma. As such, barring unexpected toxicity in newly-diagnosed patients, it is expected that daratumumab will become an important component of frontline therapy. Its role in the relapsed setting after use in the frontline setting remains an important area for future investigation. Lastly, the combination of the histone deactylase inhibitor, panobinostat, with bortezomib-dexamethasone was superior to bortezomib and dexamethasone in the phase III setting [42]. The addition of panobinostat to bortezomib-dexamethasone led to improved median PFS (11.99 months vs 8.08 months, HR 0.63, P <0.0001). However, due to notable constitutional, gastrointestinal and hematologic toxicity and no signal of an OS advantage, the combination was given conditional approval by the FDA for patients with relapsed multiple myeloma who have received 2 or more prior therapies for their myeloma, including bortezomib and an IMiD. In this group of patients, the median PFS was 12.5 months with the triplet compared to 4.7 months for those receiving bortezomib and dexamethasone alone [43]. Ongoing studies are seeking to clarify the optimal dose and schedule of panobinostat with bortezomib and dexamethasone, as well as its best partner myeloma regimen.

Thus, to summarize, while notable gains have been made for patients with relapsed multiple myeloma who have received at least 1 prior therapy, data in patients treated with frontline lenalidomide-based therapy until disease progression are lacking. Furthermore, for patients with relapsed multiple myeloma and lenalidomide-refractory disease, there is room for improvement upon carfilzomib-dexamethasone and bortezomib-dexamethasone-panobinostat, and, while the daratumumab-bortezomib-dexamethasone regimen is a reasonable option in this situation, daratumumab will likely make its way into frontline therapy in the not-too-distant future. As such, there is a compelling need to develop non-daratumumab-based regimens in this space.

1.4 Pomalidomide and dexamethasone

The IMiDs, thalidomide and lenalidomide, are currently Food and Drug Administration (FDA) approved for the treatment of newly-diagnosed and/or relapsed multiple myeloma and have played a central role in the improved survival of myeloma patients over the last decade. However, of a panel of amino-substituted thalidomide analogs (including lenalidomide), CC-4047, or pomalidomide, was the most potent inhibitor of lipopolysaccharide-mediated tumor necrosis factor-α production in vitro [44]. In fact, pomalidomide was ~15,000 times more potent than thalidomide in this regard. Subsequent studies have demonstrated promising activity of pomalidomide in pre-clinical models of multiple myeloma, including cell lines resistant to

conventional multiple myeloma therapy and patient multiple myeloma samples, thus providing the basis for further clinical development [45, 46].

Pomalidomide has demonstrated striking clinical activity in patients with relapsed multiple myeloma, including patients with lenalidomide- and dual lenalidomide/bortezomib-refractory disease [47-54]. An initial phase I study of single agent pomalidomide therapy was conducted in 24 patients with relapsed or refractory multiple myeloma. The median age of participants was 66, and patients had received a median of 3 prior lines of therapy. Only 29% of patients had previously received thalidomide. Patients received 1 to 10 mg of pomalidomide daily. The maximum tolerated dose (MTD) was 2 mg. Hematologic toxicity was most prominent, with 6 patients developing grade 4 neutropenia. Deep vein thrombosis was seen in 4 patients, one of whom had metastatic melanoma. No other grade 3 or higher non-hematologic toxicity was noted. Peripheral neuropathy was only seen in 3 patients and was of grade 1 severity in all cases. Four patients achieved a complete response (CR), 3 a very good partial response (VGPR), 6 a PR and 4 patients an MR. Thus, the ORR was an impressive 54% and CBR 71%. Median PFS was 39 weeks and OS 90 weeks [50]. A subsequent single arm, phase II study was conducted evaluating the combination of pomalidomide and dexamethasone in patients with relapsed or refractory multiple myeloma. Pomalidomide was administered at 2 mg on days 1-28 of a 28-day cycle and dexamethasone at 40 mg weekly. Sixty patients participated. The median age was 66 and median time from diagnosis 44 months. Thirty-seven percent and 35% of patients had received 2 and 3 prior multiple myeloma regimens, respectively. With appropriate thromboprophylaxis (either aspirin, low molecular weight heparin or warfarin), only 1 patient suffered a venous thromboembolic event. Grade 3 or 4 fatigue and pneumonia were seen in 17% and 8% of patients, respectively. Grade 3 or 4 neutropenia and thrombocytopenia were seen in 32% and 3% of patients. The ORR was 63%, with a CR rate of 5%, VGPR rate of 28% and PR rate of 30%. Forty percent of patients with lenalidomide-resistant disease responded to therapy and, of 5 patients with dual lenalidomide- and bortezomib-refractory disease, 2 had PRs and 1 a VGPR. The median PFS was 11.6 months [48].

Given the rapidly changing landscape of multiple myeloma therapy, the nature of relapsed and refractory disease has evolved over time. Nonetheless, pomalidomide-based therapy has continued to perform well in more recent studies, including in patients with lenalidomide and/or bortezomib-refractory disease. Thirty-four patients with relapsed, lenalidomide-refractory multiple myeloma were treated with pomalidomide and dexamethasone in the context of a phase II study. Pomalidomide was administered at 2 mg daily and dexamethasone 40 mg weekly. The median time from diagnosis to study participation was 62 months, and the median number of prior therapies was 4. Notably, the ORR was 32%, CBR 47%, median PFS 4.8 months and median OS 13.9 months [49]. A follow-up study from the same group compared a 2 mg vs. 4 mg dose of pomalidomide in combination with once weekly dexamethasone for patients with multiple myeloma that was refractory to both lenalidomide and bortezomib. The median number of prior regimens for both dose cohorts was 6 and the median time from diagnosis to study participation was 57 and 72 months, respectively. The ORR was 25% and 29%, CBR 49% and 43%, and median PFS 6.5 and 3.2 months, respectively [47].

More recently, a phase I followed by randomized phase II study comparing single-agent pomalidomide to pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma previously treated with both lenalidomide- and bortezomib-based therapy was conducted [51-53]. In the phase I portion of the study, the MTD of the combination was found to be pomalidomide administered at 4 mg on days 1-21 of a 28-day cycle and dexamethasone administered at 40 mg once weekly. Dosing at 5 mg was associated with an increased rate of dose limiting toxicity (DLT), especially neutropenia, and the need for dose reductions in all patients. A trend towards improved response rates was seen at the 4 mg dose compared with the 2 mg dose [51]. Patients enrolled in the phase II portion of the study had

previously received a median of 5 prior therapies and 62% were refractory to both lenalidomide and bortezomib. The ORR was 18% and 33%, CBR 31% and 45%, median PFS 2.6 months and 4.6 months, and median OS 13.6 months and 16.5 months for patients receiving single-agent pomalidomide or the combination of pomalidomide and dexamethasone, respectively. Of those patients with lenalidomide and bortezomib-refractory disease treated with pomalidomide and dexamethasone, the median PFS and OS were 3.9 and 13.7 months, respectively. Toxicity with the combination was largely manageable, but grade 3/4 neutropenia, thrombocytopenia, anemia, pneumonia, fatigue, and dyspnea were seen in 41%, 19%, 22%, 22%, 14% and 13% of patients, respectively. Importantly, no cases of grade 3 or 4 peripheral neuropathy were seen, only 2% of patients suffered thromboembolic events, 3% of patients developed grade 3/4 febrile neutropenia, and only 2% of patients discontinued therapy due to treatment toxicity [52, 53]. A similarly designed phase II randomized study conducted by the IFM compared two different dosing schedules of pomalidomide in combination with dexamethasone (pomalidomide 4 mg on days 1 – 21 of a 28-day cycle vs. 4 mg on days 1 – 28) [50]. No significant differences were seen in efficacy between the 2 arms. Grade 3 and 4 adverse events (AEs) included neutropenia 62%, anemia 36%, thrombocytopenia 27%, pneumonia 13%, bone pain 11%, renal failure 11% and dyspnea 12%. Notably, the ORR was 31% and median PFS 3.8 months and OS 13.8 months in patients with lenalidomide- and bortezomib-refractory multiple myeloma [54]. Based on the results from these studies, the pomalidomide and dexamethasone regimen was approved by the FDA in February of 2013 for patients with relapsed and refractory multiple myeloma who have received ≥2 prior lines of therapy that have included lenalidomide- and bortezomib-based therapy. Clearly, pomalidomide and dexamethasone represents a highly promising treatment strategy for patients with multiple myeloma. However, for patients with lenalidomide and lenalidomide/bortezomib refractory disease, there remains considerable room for improvement.

As lenalidomide is being used increasingly as part of frontline therapy and lenalidomide is often continued until disease progression, rendering patients refractory to lenalidomide at first relapse, there is a clear need to gain further experience with pomalidomide/proteasome inhibitor combinations for this group of patients. Pomalidomide has been combined with carfilzomib in phase I and II studies [55]. However, there are no ongoing or planned randomized studies evaluating the impact of the addition of carfilzomib to the pomalidomide and dexamethasone backbone. Furthermore, the onerous schedule of carfilzomib administration makes long term treatment with this agent challenging. Lastly, for patients with significant cardiovascular comorbidities, carfilzomib may be associated with increased risk for cardiac events. The addition of bortezomib to pomalidomide and dexamethasone has been studied in the context of phase I/II studies [56, 57]. There is an ongoing phase III study evaluating the combination of pomalidomide, bortezomib and dexamethasone versus bortezomib and dexamethasone (NCT01734928). However, there are several important differences between the ongoing phase III study and our phase II proposal. First, patients in the phase III study are allowed to have received 1 – 3 prior lines of therapy and may have lenalidomide-sensitive, -naive or –refractory disease, thus yielding a highly heterogeneous patient population. Secondly, the ongoing phase III study is utilizing the bortezomib-dexamethasone doublet as the comparator arm, and we now know that the carfilzomib-dexamethasone doublet or the addition of daratumumab or panobinostat to bortezomib-dexamethasone are superior to bortezomib-dexamethasone alone in relapsed multiple myeloma.

To conclude, given the well documented clinical activity of pomalidomide and dexamethasone in patients with lenalidomide-refractory disease; improved PK and PD characteristics of ixazomib compared with bortezomib; superior pre-clinical anti-tumor efficacy of ixazomib compared to bortezomib; and promising clinical activity of ixazomib as a single agent and in combination therapy with lenalidomide and dexamethasone, we hypothesize that the addition of ixazomib to pomalidomide and dexamethasone therapy will further improve outcomes for

patients with multiple myeloma whose disease is progressing on lenalidomide as part of first line therapy. Our study will provide the initial signal of efficacy of the pomalidomide-ixazomib-dexamethasone regimen as compared to pomalidomide-dexamethasone in an emerging, important and understudied patient population, thus supporting the development and informing the study design of a future phase III study.

1.5 Registration Quality of Life (QOL) Measurements

QOL measurements of fatigue and overall perception of QOL are routinely included in Alliance studies and will be assessed upon registration in this study. Evidence has arisen indicating that baseline single-item assessments of fatigue and overall QOL are strong prognostic indicators for survival in cancer patients, independent of performance status. This evidence was derived from two separate meta-analyses presented at ASCO, the first involving 23 NCCTG and Mayo Clinic Cancer Center oncology clinical trials, the second involving 43 clinical trials [58, 59]. Routine inclusion of these measures should be considered similar to that of including performance status, either as stratification or prognostic covariates.

1.6 Establishment of the Maximum Tolerated Dose (MTD) of Pomalidomide, Ixazomib, and Dexamethasone in Phase I

A total of 26 patients consented to participate in the phase I portion of the study. Two patients were not treated on protocol; one patient had a platelet count that had dropped below 50 prior to the start of therapy and was no longer eligible; a second patient was discovered to have MDS on the screening marrow. Three patients were treated at dose level 1, all 3 of whom were evaluable for DLTs. No DLTs were encountered in these first 3 patients. Five patients were enrolled on dose level 2, 3 of whom were evaluable for DLTs. One patient was inevaluable for DLTs as they inadvertently received the dose of pomalidomide utilized in dose level 1 during their first cycle of therapy. A second patient was inevaluable for DLTs, as they were not treated on study as a result of the presence of MDS on the screening marrow evaluation. Of the 3 evaluable patients, none experienced DLTs. Seven patients were enrolled at dose level 3, 6 of whom were evaluable for DLTs. One patient did not receive protocol therapy as a result of rapid disease progression and clinical deterioration in the lead up to treatment. Of the 6 evaluable patients, 1 experienced a DLT of grade 3 febrile neutropenia resulting from sinusitis. Eleven patients were enrolled on dose level 4, 6 of whom were evaluable for DLTs. One patient experienced a DLT of grade 3 febrile neutropenia. Five patients were not evaluable for DLTs: 1 due to treatment disruption during cycle 1 as a result of grade 2 sinus bradycardia; 1 due to treatment disruption during cycle 1 as a result of TIAs that were present prior to the start of protocol therapy and deemed not treatment related; 1 patient had therapy disrupted during cycle 1 for neutropenia that was felt to be disease related; 1 due to treatment disruption during cycle 1 for grade 4 thrombocytopenia that was felt to be related to disease progression; and 1 due to treatment disruption over cycle 1 for fatigue, rash and diarrhea that did not rise to the level of DLTs. The DLT data were reviewed by the Principal Investigators at the 4 participating sites and the Alliance Myeloma Committee Chair. Dose level 4 was deemed the MTD of the regimen by unanimous decision and the recommended phase II dose moving forward. It should be noted that the MTD and recommended phase II dose was established in lenalidomide and proteasome inhibitor dual refractory patients. However, we feel that the patient population in the phase II portion of the study, specifically patients with lenalidomide but not proteasome inhibitor refractory disease who have only received 1 prior line of therapy, will tolerate the combination better than the more heavily pretreated cohort in phase I.

2.0 OBJECTIVES

2.1 Primary Phase I Objectives

To establish the MTD for combination therapy Pomalidomide / Dexamethasone / Ixazomib

Note: The MTD will be determined by DLTs seen in cycle 1 of therapy. Please reference section 13.1 for the definition of DLT. The RP2D will be based on MTD; signals of cumulative toxicities seen during the course of treatment; and patient adherence.

2.2 Primary Phase II Objectives

To assess whether the combination of pomalidomide/dexamethasone/ixazomib improves PFS relative to pomalidomide/dexamethasone.

2.3 Secondary Phase I Objectives

2.3.1 To determine DLTs

2.3.2 To analyze type and grade of all Serious Adverse Events (SAEs)

2.3.3 To analyze type and grade of all Adverse Events (AEs)

2.3.4 To analyze the reason for and incidence of dose modifications/omissions/delays

2.3.5 To assess preliminary evidence of clinical efficacy

2.4 Secondary Phase II Objectives

2.4.1 To assess whether the Overall Response Rate (ORR), Partial Response (PR), Very Good Partial Response (VGPR), Complete Response (CR) or stringent CR (sCR) rate differ with respect to treatment regimen.

2.4.2 To assess the Clinical Benefit Rate (CBR: Minimal Response (MR) + ORR) for Pomalidomide/Dexamethasone/Ixazomib compared to Pomalidomide/Dexamethasone.

2.4.3 To assess the Disease Control Rate (DCR: Stable Disease (SD) + CBR) for Pomalidomide/Dexamethasone/Ixazomib compared to Pomalidomide/Dexamethasone.

2.4.4 For those patients achieving a PR or better, we will assess whether the combination of Pomalidomide/Dexamethasone/Ixazomib increases the Duration of Response (DOR) compared to Pomalidomide/Dexamethasone.

2.4.5 To assess whether the combination of Pomalidomide/Dexamethasone/Ixazomib improves Overall Survival (OS) compared to those taking Pomalidomide/Dexamethasone alone.

2.4.6 To assess Time to Next Treatment (TNT) for patients taking Pomalidomide/Dexamethasone/Ixazomib compared to those on Pomalidomide/Dexamethasone.

2.4.7 To evaluate the safety of Pomalidomide/Dexamethasone/Ixazomib compared with Pomalidomide/Dexamethasone.

2.4.8 For patients on the Pomalidomide/Dexamethasone arm who opt to cross-over to the Pomalidomide/Dexamethasone/Ixazomib arm, assessment of response rate (ORR, CBR, DCR) DOR, TNT, PFS, and OS will be evaluated from date of cross-over.

2.4.9 To determine if baseline level of perceived fatigue and overall QOL is associated with OS.

2.5 Correlative Science Objectives for Phase II

As of Update #04, no new patients will be registered to the A061202-ST1 substudy which was designed to address these objectives.

2.5.1 Primary Objective

To determine the extent to which cereblon expression (via quantitative PCR and IHC) is associated with therapeutic response.

2.5.2 Secondary Objectives

2.5.2.1 To examine whether PFS or OS differs with respect to cereblon expression levels.

2.5.2.2 To examine whether therapeutic response, PFS, and OS differs with respect to either the percentage of IRF-4 or c-Myc positivity in plasma cells or IHC staining intensity in plasma cells at baseline.

2.5.2.3 To examine whether resistance mutations in the IMiD binding domain of cereblon emerge in patients with an initial response to therapy (MR or better) who then progress.

2.5.2.4 To examine the percent agreement between cereblon expression levels at baseline and progression as well as the percentage of patients with expression gain or loss.

2.5.2.5 To examine whether reduced expression of Ikaros (*IKZF1*) and/or Aiolos (*IKZF3*) transcription factors is associated with inferior clinical efficacy (ORR, PFS, OS).

2.5.2.6 To determine whether resistance mutations in Ikaros and Aiolos develop in patients with an initial response to therapy (MR or better) who then progress.

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Contact Information page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.1 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Physicians should consider whether any of the following may render the patient inappropriate for this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection, uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients who cannot swallow oral formulations of the agent(s).
- Patients cannot have other prior or concomitant malignancies with the exception of:
    - Non-melanoma skin cancer
    - In-situ malignancy
    - Low-risk prostate cancer after curative therapy
    - Other cancer for which the patient has been disease free for ≥ 3 years.

In addition:

- Women and men of reproductive potential, please refer to section 3.2.4.

3.2 Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

___ 3.2.1 Documentation of Relapsed Symptomatic Multiple Myeloma:

Histologically confirmed diagnosis of symptomatic multiple myeloma. Relapsed disease is myeloma that has previously responded to prior therapy (MR or better) and subsequently progressed.

___ 3.2.2 Measurable disease or non-measurable disease as defined in Section 11.0.

Patient must have measurable disease or non-measurable disease, defined as one or more of the following holding true:

Measurable disease:

- Serum M-protein ≥0.5 g/dL ***and/or***
- Urine M-protein ≥200 mg/24 hours ***and/or***
- Involved serum free light chain level ≥10 mg/dL AND an abnormal serum free light chain ratio

For non-measurable disease:

- Baseline marrow burden of myeloma of at least 30%

3.2.3 Prior Treatment

___ Progression on lenalidomide as part of first line therapy (lenalidomide-refractory disease)

Lenalidomide-refractory disease is defined as disease progression on or progression within 60 days of the last dose of a lenalidomide-based treatment. [60, 61]. Patients should have received at least 2 cycles of a lenalidomide-based regimen to be evaluable for refractoriness. Examples: 1) progression on lenalidomide maintenance therapy after initial induction ± consolidation; 2) initial response followed by progression on continuous lenalidomide-dexamethasone ± elotuzumab or daratumumab.

___ Pomalidomide naïve disease

___ Proteasome inhibitor naïve or sensitive disease. Proteasome inhibitor sensitive disease is defined as a PR or better to prior proteasome inhibitor-based therapy that is maintained for ≥ 60 days from the last dose of the proteasome inhibitor. Please refer to Appendix VII for a list of proteasome inhibitors.

A patient who receives induction therapy with lenalidomide, bortezomib and dexamethasone and achieves a PR or better but subsequently progresses on continued lenalidomide or lenalidomide-dexamethasone would be eligible provided the progression occurs 60 days or more after discontinuation of the bortezomib. Similarly, ixazomib exposure is allowed provided they meet the definition of proteasome inhibitor sensitive disease.

___ 1 prior line of systemic therapy for multiple myeloma, where a line of therapy for myeloma is defined as 1 or more planned cycles of single agent or combination therapy, as well as a planned series of treatment regimens administered in a sequential manner (e.g. lenalidomide, bortezomib and dexamethasone induction therapy for 4 cycles followed by autologous stem cell transplantation and then lenalidomide maintenance therapy would be considered 1 line of prior therapy). A new line of therapy begins when a planned therapy is modified to

include other treatment agents (alone or in combination) as a result of disease progression or relapse (e.g. a patient is progressing in the face of lenalidomide maintenance therapy and has bortezomib and dexamethasone added into their regimen). A new line of therapy also begins when a planned treatment-free interval is interrupted by the need to start treatment due to disease relapse/progression (e.g. a patient with relapsed myeloma achieves a partial response after a planned 8 cycles of cyclophosphamide, bortezomib and dexamethasone, enjoys an 8-month period off therapy but then experiences disease progression requiring re-initiation of therapy).

___ Allogeneic stem cell transplantation is allowed provided the patient is ≥ 1 year from transplant at time of registration, is not on immunosuppressive therapy to treat/prevent graft-versus-host disease, has no evidence of active graft versus host disease, and no evidence of active infection.

___ No chemotherapy or radiation therapy within 14 days prior to registration.

___ No investigational therapy within 14 days prior to registration.

___ No major surgery within 28 days prior to registration.

___ No G-CSF (Filgrastim) or GM-CSF (Sargramostim) within 7 days of registration or Pegfilgrastim within 14 days of registration to meet eligibility criteria.

___ No platelet transfusions within 7 days of registration to meet eligibility criteria. **Note:** Red blood cell transfusions are allowed at any time.

___ 3.2.4 Not pregnant and not nursing

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

Women of childbearing potential:

- must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/ml no more than 14 days prior to registration and must agree to repeat this test within 24 hours of starting pomalidomide.
- must either commit to complete abstinence from heterosexual contact or begin TWO acceptable methods of birth control, one highly effective method and one additional effective (barrier) method, AT THE SAME TIME, before starting pomalidomide.
- must agree to ongoing pregnancy testing.
- must agree to not become pregnant or breast feed a child during treatment on this protocol.

Men must practice complete abstinence or agree to use a condom during sexual contact with a female of childbearing potential, even if they have had a successful vasectomy.

Note: All participants must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure. Please reference section 5.0 for details on pregnancy monitoring during the duration of the trial.

___ 3.2.5 ≥18 years of age

___ 3.2.6 ECOG Performance status 0-2 (see Appendix I)

___ 3.2.7 Required Initial Laboratory Values:

Absolute Neutrophil Count (ANC)	≥ 1.0 x 10^9/L
Platelet Count	≥ 50 x 10^9/L

Calc. Creatinine Clearance*	≥ 30 mL/min
Total Bilirubin	< 1.5 x upper limits of normal (ULN)
AST and ALT	< 2.5 x upper limits of normal (ULN)

* *Calculated utilizing the Cockcroft-Gault formula or 24-hour urine collection (see Appendix II)*

Note: G-CSF and platelet transfusions cannot be used to increase counts to meet eligibility criteria. Please refer to section 3.2.3.

3.2.8 Intercurrent or Recent Illness

Patients cannot have any of the following:

___ Central nerve system involvement

___ Primary refractory multiple myeloma, where primary refractory multiple myeloma is defined as disease that is nonresponsive – patients who have never achieved an MR or better – with any therapy over the course of their disease. It includes patients who never achieve MR or better in whom there is no significant change in M-protein and no evidence of clinical progression as well as patients who meet criteria for true progressive disease (PD).

___ Primary or secondary plasma cell leukemia

___ AL amyloidosis or POEMS syndrome

___ Known active hepatitis C based on:

+HCV antibody (confirmed)

+HCV RNA

Liver disease with history of positive serology

Note: patients with a prior history of hepatitis C that has been successfully eradicated with antiviral therapy are eligible.

___ Known hepatitis B surface antigen positivity

___ Previous hypersensitivity to any of the components of the study treatment

___ Prior history of erythema multiforme with thalidomide or lenalidomide treatment

___ **3.2.9 ≤ Grade 2 Peripheral Neuropathy**

___ **3.2.10 Adequate cardiac function, defined as:**

___ No EKG evidence of acute ischemia

___ No EKG evidence of active, clinically significant conduction system abnormalities

___ No EKG evidence of >Grade 2 (>480 ms) QTc prolongation

___ Prior to study entry, any EKG abnormality at screening not felt to put the patient at risk has to be documented by the investigator as not medically significant

___ No uncontrolled angina or severe ventricular arrhythmias

___ No clinically significant pericardial disease

___ No history of myocardial infarction within 6 months prior to registration

___ No Class 3 or higher New York Heart Association Congestive Heart Failure (see Appendix IV)

3.2.11 Concomitant Treatment

___ No strong inducers of cytochrome P450 (CYP) 3A4 or CYP1A2 or strong inhibitors of CYP3A4 or CYP1A2 within 14 days prior to registration.

Note: Ixazomib is a substrate of CYP3A4 and CYP1A2. See sections 8.1.12 and 10.1.3 for additional information about potential drug-drug and drug-food interactions with ixazomib.

Refer to Appendix V for a list of strong inhibitors of CYP3A4 and CYP1A2.

3.2.12 HIV Infection

___ Patients with HIV infection are eligible, provided they meet all of the following criteria:

- No history of AIDS-defining conditions or other HIV related illness
- CD4+ cells nadirs >350/mm^3 within 28 days prior to registration
- Treatment sensitive HIV and, if on anti-HIV therapy, HIV viral load < 50 copies/mm^3 within 28 days prior to registration

Note: HIV+ patients who enroll on this study and are assigned to treatment with ixazomib may need to modify their anti-retroviral therapy prior to receiving protocol therapy if they are on strong inducers or potent inhibitors of cytochrome P450 3A4 (see section 3.2.11).

3.3 Re-Registration Eligibility Criteria (Step 2)

Patients randomized to Arm 1 may opt to switch to the 3-drug regimen following disease progression. These patients must be re-registered to the study and meet the eligibility criteria below.

___ 3.3.1 Measurable disease or non-measurable disease as defined in Section 11.0.

Patient must have measurable disease or non-measurable disease **after progression on Pomalidomide + Dexamethasone**, defined as one or more of the following holding true:

Measurable disease:

- Serum M-protein ≥0.5 g/dL ***and/or***
- Urine M-protein ≥200 mg/24 hours ***and/or***
- Involved serum free light chain level ≥10 mg/dL AND an abnormal serum free light chain ratio

For non-measurable disease:

- Marrow burden of myeloma of at least 30%

___ 3.3.2 Not pregnant and not nursing

Women of childbearing potential:

- must have a negative serum or urine pregnancy test within 72 hours prior to re-registration.
- must either commit to complete abstinence from heterosexual contact or begin TWO acceptable methods of birth control, one highly effective method and one additional effective (barrier) method, AT THE SAME TIME, before starting pomalidomide.
- must agree to ongoing pregnancy testing.
- must agree to not become pregnant or breast feed a child during treatment on this protocol.

Men must practice complete abstinence or agree to use a condom during sexual contact with a female of childbearing potential, even if they have had a successful vasectomy.

Note: All participants must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure. Please reference Section 5.0 for details on pregnancy monitoring during the duration of the trial.

___ **3.3.3 ECOG Performance Status 0-2 (see Appendix I)**

___ **3.3.4 Required Laboratory Values***

Absolute Neutrophil Count (ANC)	$\geq 1.0 \times 10^9$/L
Platelet Count	$\geq 50 \times 10^9$/L
Calc. Creatinine Clearance*	≥ 30 mL/min
Total Bilirubin	< 1.5 x upper limits of normal (ULN)
AST and ALT	< 2.5 x upper limits of normal (ULN)

* *Calculated utilizing the Cockcroft-Gault formula or 24-hour urine collection (see Appendix II)*

Note: G-CSF and platelet transfusions cannot be used to increase counts to meet eligibility criteria.

___ **3.3.5 ≤ Grade 2 Peripheral Neuropathy**

3.3.6 Concomitant Treatment

___ No strong inducers of cytochrome P450 (CYP) 3A4 or CYP1A2 or strong inhibitors of CYP3A4 or CYP1A2

Note: Ixazomib is a substrate of CYP3A4 and CYP1A2. See section 8.1.12 and 10.1.3 for additional information about potential drug-drug and drug-food interactions with ixazomib.

4.0 PATIENT REGISTRATION

4.1 Phase I Registration Requirements

PHASE I CLOSED TO ACCRUAL AS OF FEBRUARY 04, 2016.

- **Informed consent:** the patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.
- **Limited access information:** Enrollment into the phase I portion of the study will be restricted to the following Alliance sites: 1) The University of North Carolina/Lineberger Comprehensive Cancer Center; 2) The Dana Farber Cancer Institute; 3) The Memorial Sloan-Kettering Cancer Center, and 4) The Ohio State University Comprehensive Cancer Center.
- For the phase I portion of the study, patient enrollment will be facilitated using the Slot-Reservation System in conjunction with the Registration system on Oncology Patient Enrollment Network (OPEN). Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System to insure that a slot on the protocol is available to the patient. Once a slot reservation confirmation is obtained, site staff may then proceed to enroll patients to this study.
- Alliance sub-study A061202-ST1 will not be activated during the phase I portion of the study but will be available for the phase II portion.

4.2 Phase II Registration Requirements

- **Informed consent:** the patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.
- As part of the enrollment/informed consent procedures, the patient should be counseled on the risk of interactions of study medications with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.
- During the consenting process and at a minimum of every 28 days, all patients must be counseled about pregnancy precautions and risks of fetal exposure.
- Enrollment into the phase II portion of the study will be available to all Alliance sites.
- For the Phase II portion of the study, patients will be randomized to one of two intervention arms: Arm 1 or Arm 2.

4.3 Patient Registration/Randomization

4.3.1 CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account [redacted] In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e.,

clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) [redacted] Documentation requirements per registration type are outlined in the table below.

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

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

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

Additional information can be found on the CTEP website at < [redacted] >. For questions, please contact the RCR ***Help Desk*** by email at < [redacted] >.

4.3.2 CTSU Registration Procedures

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

IRB Approval:

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

Downloading Site Registration Documents:

Site registration forms may be downloaded from the A061202 protocol page located on the CTSU members' website.

- Go to [redacted] and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the Alliance link to expand, then select trial protocol A061202
- Click on LPO Documents, select the Site Registration Documents link, and download and complete the forms provided.

Requirements for A061202 Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal:
[redacted] (members' area) → Regulatory Tab → Regulatory Submission

When applicable, original documents should be mailed to:

[redacted]

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately [redacted] in order to receive further instructions and support.

Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website.

- Go to [redacted] and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3.3 OPEN Access Requirements and Procedures

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < [redacted] >) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at [redacted] or from the OPEN tab on the CTSU members' side of the website at [redacted] To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval.

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

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

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

To receive site reimbursement for patient participation in A061202-ST1, completion dates must be entered in the OPEN Funding screen post registration. Please refer to the protocol specific funding page on the CTSU members' website for additional information. Timely entry of completion dates is recommended as this will trigger site reimbursement.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at [redacted] For any additional questions contact the CTSU Help Desk at [redacted]

Phase I patient enrollment: For the phase I portion of the study, patient enrollment will be facilitated using the Slot-Reservation System in conjunction with the Registration system in OPEN. Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System to insure that a slot on the protocol is available to the patient.

Once a site logs into the OPEN system during the phase I portion of the study, the number of slots available in the phase I dose assignment will be listed. If the current dose assignment is on hold, the OPEN system will indicate that registration is on hold until the next dose assignment is available.

4.4 Stratification Factors (Phase II)

At the time of registration, patients will be randomized to treatment independently of each other using a dynamic allocation scheme with the following stratification factors:

1) ISS 1 and 2 disease vs. ISS 3 (current ISS stage based off screening beta 2 microglobulin and albumin)
2) Standard risk vs. high risk cytogenetics

   High risk cytogenetics: del(1p), gain of 1q, t(4;14), t(14;16), t(14; 20), del(17p)
3) *Proteasome inhibitor naïve vs. exposed*

4.5 Registration to Correlative and Companion Studies

4.5.1 Registration to Substudy described in Section 14.0

As of Update #04, no new patients will be registered to the A061202-ST1 substudy.

There is the A061202-ST1 substudy within Alliance A061202. This correlative science study **must be offered to all patients** enrolled on the phase II portion of Alliance A061202 (although patients may opt to not participate). This substudy does not require separate IRB approval. The substudy included within Alliance A061202 is:

- "Evalution of the cereblon/IRF-4/c-Myc pathway in resistance to Pomalidomide-based therapy", Alliance A061202-ST1 (Section 14.1)

If a patient answers "yes" to "Optional Sample Collections for Laboratory Studies," Question #1 in the model consent for Phase II portion of the study "My coded samples and related coded information may be used in the research described above to learn about, prevent, find, or treat cancer. This may also include research on inherited traits (genes passed on in families)," they have consented to participate in the substudy described in Section 14.1. The patient should be registered to Alliance A061202-ST1 at the same time they are registered to the treatment trial (A061202). Samples should be submitted per Section 6.2.

4.6 Re-registration at the time of progression (Arm 1 patients only)

Upon confirmation of progression on Course 1 treatment (pomalidomide and dexamethasone), patients may elect to cross-over to Course 2 treatment (3-drug combination). Patients who opt to cross over must be re-registered within 14 days of confirmation of progression. **Please make sure to reassess eligibility (section 3.3) at re-registration.** Women of child-bearing potential must have a negative pregnancy test within 72 hours prior to re-registration.

Re-registration procedures:

OPEN may be accessed at [redacted] from the OPEN tab on the CTSU website at [redacted] or from the OPEN Registration tab on the Alliance website.

To enroll a patient within OPEN, institution staff must have:

1. A valid and active CTEP-IAM account. This is the same user ID and password used for CTSU's website (for more information see [redacted]

2. Enrollment of patients on Alliance coordinated protocols requires a "Registrar" role in the Alliance roster. Assignment of the "Registrar" role is managed through the Alliance Central Office via submission of a roster update form signed by the Principal Investigator of the member network.

The OPEN system will provide the registering site with a printable confirmation of re-registration. Please print the confirmation for your records. Further instructional information is provided on the CTSU members' website OPEN tab, or within the OPEN URL. For any additional questions, contact the CTSU Help Desk at [redacted]

5.0 STUDY CALENDAR

Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this study will be cared for by physicians experienced in the treatment and supportive care of patients similar to those on this trial.

Pre-Study Testing Intervals

- To be completed ≤ 14 DAYS before registration: All laboratory studies, history and physical, EKG
- To be completed ≤ 28 DAYS before registration: Bone marrow aspirate and biopsy and baseline scans for those with known or clinically suspected extramedullary plasmacytomas.
- To be completed ≤ 42 DAYS before registration: Skeletal survey.

5.1 Main Study Calendar

All patients in the phase I portion, patients randomized to Arm 2 in phase II, and patients randomized to Arm 1 in phase II who have not continued to Course 2 treatment (3 drug regimen) will be followed per the study calendar below. **Arm 1 patients who opt to receive the 3 drug regimen following disease progression must be re-registered to the study and will be followed per the study calendar in Section 5.2.**

	Prior to Registration*	Every 28-day Cycle (±3 days)			End of Treatment **	Clinical Follow Up ***
		D1	D15	D22		
Tests & Observations						
History and physical, weight, PS	X	X	X (1)		X	X
Height	X					
Pulse, Blood Pressure, Temperature, Respiratory Rate.	X	X	X (1)		X	X
EKG	X			X (2)		
Adverse Event Assessment		X	X (1)		X	X
Patient Medication Diary		X (3)			X	
Registration Fatigue/Uniscale Assessment	X (4)					
Laboratory Studies						
Complete Blood Count, Differential, Platelets	X	X	X (5)		X	X
Serum Sodium, Potassium, Chloride, Carbon dioxide, Blood Urea Nitrogen, Creatinine Glucose, Calcium, Magnesium, Phosphorus, Albumin	X	X	X (5)		X	X
LDH and CRP	X					
β2-microglobulin	X					
AST, ALT, Alkaline Phosphatase, Total Bilirubin	X	X	X (1)		X	X
Serum or Urine HCG	X (6)	X (6)			X (6)	
Staging						
Tumor (M-protein) Assessment	X (7)	X (7)			X (7)	X (7)
Bone Marrow Aspirate and Biopsy with Cytogenetic Evaluation	X (8)	X (8)			X (8)	X (8)
Radiologic Tumor Measurement	X (9)	X (9)			X (9)	X (9)
Skeletal Survey	X (10)			X (10)		

* Labs (including those completed prior to registration) may be used for day 1 of a cycle if obtained ≤ 3 days prior to treatment.

Otherwise, they will need to be repeated. Lab values obtained on cycle 1, day 1 must remain within the parameters set in the eligibility criteria before starting treatment.

** An end-of-treatment evaluation should be performed as soon as possible after the last dose of therapy and no later than 4 weeks after the end of treatment, regardless of the reason for discontinuation.

*** After discontinuation of treatment, clinical follow-up visits will occur every 4 weeks until disease progression, death, withdrawal of informed consent, or start of new treatment; thereafter, survival information, late adverse events, and data regarding start of new treatment (if applicable) are required every 3 months for a maximum of 3 years from registration. See also Section 12.0. **Note:** Arm 1 patients who discontinue Course 1 treatment due to progression and who continue onto Course 2 treatment should be followed according to the study calendar in Section 5.2.

1. To be obtained during the first two cycles of phase I only. May be obtained in the phase II portion of the study as clinically indicated
2. A repeat EKG is required if a new medication that has the potential to prolong the QTcF interval is started and as clinically indicated.
3. The diary must begin the day the patient starts taking the medication and must be completed per protocol and returned to the treating institution OR compliance must be documented in the medical record by any member of the care team. See Appendix VI.
4. To be completed after registration and ≤ 7 days prior to treatment, see Section 1.4 and Appendix III.
5. For patients on the phase II portion of the study and for those on the phase I portion of the study who have completed two cycles of therapy, a Day 15 CBC can be performed at a local laboratory not participating in the study provided the results are made available to the treating study health care provider within 24 hours. Day 15 chemistries for patients who have completed 2 cycles of therapy in phase I and phase II will be performed as clinically indicated and can also be performed at a local laboratory as described above. A day 15 CBC for patients who have completed 4 cycles of therapy in phase I and phase II will be performed as clinically indicated.
6. For women of childbearing potential (see Section 3.2.4). Must be done within 10 – 14 days prior to registration and again within 24 hours prior to initiation of pomalidomide. FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days and then every 28 days while on study treatment (including breaks in treatment); at discontinuation of pomalidomide and at day 28 post the last dose of pomalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on study treatment (including breaks in treatment), at discontinuation of pomalidomide and at Day 14 and Day 28 post the last dose of pomalidomide). A new cycle of pomalidomide cannot be dispensed until a negative pregnancy test is confirmed
7. M protein assessment is every 4 weeks (with each cycle of treatment). In addition, please note the assessment for the previous cycle should occur before treatment is given on day 1 of the subsequent cycle. Assessment includes: Serum protein electrophoresis (SPEP), serum immunofixation, serum free kappa and lambda light chain levels, quantitative serum IgG, IgA and IgM, 24-hour urine protein electrophoresis (UPEP) and immunofixation. In order to obtain an accurate determination of response and time of progression, a uniform approach to response assessment must be applied, and all measures of M-protein should be performed for all patients on the study. For patients with unmeasurable disease on 24-hour UPEP, 24-hour urine testing can be done once every other cycle. **Repeat testing is required to confirm a response (MR or better) or disease progression and should occur-no later than 28 days after first documentation of response or progression.**
8. A baseline bone marrow aspirate and biopsy should be obtained ≤28 days prior to registration. Although central review will not be required, the following information will be captured in the eCRFs: 1) marrow burden of myeloma. Note: flow cytometry should NOT be used to assess marrow burden of disease. Marrow burden should be determined by aspirate differential and CD138 immunohistochemistry. 2) Fluorescent in situ hybridization testing for the following high-risk cytogenetic abnormalities: t(4;14), t(14;20), t(14;16), del(17p), del(1p), and gain of 1q21. **Plasma cell purification prior to FISH testing is strongly recommended.** A repeat bone marrow aspirate and biopsy should be performed within 14 days after CR or sCR is documented. For patients with non-secretory disease who are being followed for response by serial bone marrow examinations (must have ≥30% involvement of the marrow space prior to treatment), a repeat bone marrow aspirate and biopsy should be performed once every 2 cycles until the end of treatment and every 12 weeks thereafter until disease progression, death or withdrawal of consent. In these cases, the same method to assess marrow burden of disease should be used throughout treatment.
9. Baseline scans can include either: 1) a CT or MRI, or 2) a whole body FDG-PET scan and diagnostic CT performed with both IV and oral contrast, and the CT acquired with 5 mm or less slice thickness. Baseline scans are NOT required for those patients who do not have documented or suspected measurable extramedullary plasmacytomas at the time of enrollment. Baseline scans are required ≤28 days prior to registration for those with known or clinically suspected measurable extramedullary disease. Measurable extramedullary disease will require monitoring every other cycle (every 8 weeks) while on treatment (i.e. cycle 3, day 1, cycle 5, day 1, etc.). An end of treatment scan is required if one has not been performed within the last 8 weeks (unless treatment was stopped due to disease progression). Scans will need to be followed once every 12 weeks after treatment has ended until withdrawal of consent, disease progression or death, whichever occurs first. The same imaging modality initially used to measure disease at baseline should be used over the course of the study to document response/progression
10. A baseline skeletal survey should be completed ≤42 days prior to registration. Otherwise, the skeletal survey should be repeated only as clinically indicated.

5.2 Arm 1 Course 2 Study Calendar

Patients randomized to Arm 1 in phase II who opt to receive the 3 drug regimen following disease progression must be re-registered to the study and will be followed per the study calendar below.

	Every 28-day Cycle (±3 days)			End of Treatment**	Clinical Follow Up***
	D1*	D15	D22		
Tests & Observations					
History and physical, weight, PS	X	X (1)		X	X
Height					
Pulse, Blood Pressure, Temperature, Respiratory Rate.	X	X (1)		X	X
EKG			X (2)		
Adverse Event Assessment	X	X (1)		X	X
Patient Medication Diary	X (3)			X	
Laboratory Studies					
Complete Blood Count, Differential, Platelets	X	X (4)		X	X
Serum Sodium, Potassium, Chloride, Carbon dioxide, Blood Urea Nitrogen, Creatinine Glucose, Calcium, Magnesium, and Phosphorus, Albumin	X	X (4)		X	X
AST, ALT, Alkaline Phosphatase, Total Bilirubin,	X	X (1)		X	X
Serum or Urine HCG	X (5)			X (5)	
Staging					
Tumor (M-protein) Assessment	X (6)			X (6)	X (6)
Bone Marrow Aspirate and Biopsy with Cytogenetic Evaluation				X (7)	X (7)
Radiologic Tumor Measurement				X (8)	X (8)
Skeletal Survey			X (9)		

* Labs may be used for day 1 of a cycle (including those completed prior to re-registration) if obtained ≤ 3 days prior to treatment. Otherwise, they will need to be repeated.

** An end-of-treatment evaluation should be performed as soon as possible after the last dose of therapy and no later than 4 weeks after the end of treatment, regardless of the reason for discontinuation.

*** After discontinuation of treatment, clinical follow-up visits will occur every 4 weeks until disease progression, death, withdrawal of informed consent or the start of new treatment. Thereafter, survival information is required every 3 months for a maximum of 3 years from re-registration. See also Section 12.0.

1. May be obtained in the phase II portion of the study as clinically indicated
2. A repeat EKG is required if a new medication that has the potential to prolong the QTcF interval is started and as clinically indicated.
3. The diary must begin the day the patient starts taking the medication and must be completed per protocol and returned to the treating institution OR compliance must be documented in the medical record by any member of the care team. See Appendix VI.
4. Day 15 CBC can be performed at a local laboratory not participating in the study provided the results are made available to the treating study health care provider within 24 hours. Day 15 chemistries for patients who have completed 2 cycles of therapy will be performed as clinically indicated and can also be performed at a local laboratory as described above. A day 15 CBC for patients who have completed 4 cycles of therapy will be performed as clinically indicated.
5. For women of childbearing potential. Must be done within 72 hours prior to re-registration and again within 24 hours prior to initiation of pomalidomide. FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days and

then every 28 days while on study treatment (including breaks in treatment); at discontinuation of pomalidomide and at day 28 post the last dose of pomalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on study treatment (including breaks in treatment), at discontinuation of pomalidomide and at Day 14 and Day 28 post the last dose of pomalidomide). A new cycle of pomalidomide cannot be dispensed until a negative pregnancy test is confirmed

6. M protein assessment is every 4 weeks (with each cycle of treatment). In addition, please note the assessment for the previous cycle should occur before treatment is given on day 1 of the subsequent cycle. Assessment includes: Serum protein electrophoresis (SPEP), serum immunofixation, serum free kappa and lambda light chain levels, quantitative serum IgG, IgA and IgM, 24-hour urine protein electrophoresis (UPEP) and immunofixation. In order to obtain an accurate determination of response and time of progression, a uniform approach to response assessment must be applied, and all measures of M-protein should be performed for all patients on the study. For patients with unmeasurable disease on 24-hour UPEP, 24-hour urine testing can be done once every other cycle. **Repeat testing is required to confirm a response (MR or better) or disease progression and should occur-no later than 28 days after first documentation of response or progression.**
7. A repeat bone marrow aspirate and biopsy should be performed within 14 days after CR or sCR is documented. For patients with non-secretory disease who are being followed for response by serial bone marrow examinations (must have ≥30% involvement of the marrow space prior to treatment), a repeat bone marrow aspirate and biopsy should be performed once every 2 cycles until the end of treatment and every 12 weeks thereafter until disease progression, death or withdrawal of consent. In these cases, the same method to assess marrow burden of disease should be used throughout treatment.
8. The same imaging modality initially used to measure disease at baseline should be used over the course of the study to document response/progression
9. A skeletal survey should be completed prior to start of Course 2 treatment. Otherwise, the skeletal survey should be repeated only as clinically indicated.

6.0 DATA AND SPECIMEN SUBMISSION

6.1 Data collection and submission

Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at < [redacted]>) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login [redacted] using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at [redacted] or by contacting the CTSU Help Desk at [redacted]

6.2 Specimen collection and submission

Central histopathology review is not required on this study. However, a baseline bone marrow aspirate and biopsy should be obtained ≤28 days prior to registration. The following information from the baseline bone marrow will be captured in the eCRFs:

1. Marrow burden of myeloma. Note: flow cytometry should NOT be used to assess marrow burden of disease. Marrow burden should be determined by aspirate differential and CD138 immunohistochemistry.
2. Fluorescent in situ hybridization testing for the following high-risk cytogenetic abnormalities: t(4;14), t(14;20), t(14;16), del(17p), del(1p) and gain of 1q21. **Plasma cell purification prior to FISH testing is strongly recommended.**

Submission of source documentation detailing the above results will be required.

To minimize the number of bone marrow core biopsies performed, the bone marrow block from the initial staging evaluation (obtained in all patients) will be used for the pre-treatment immunohistochemical correlative studies for those patients that agree to participate in Alliance sub-study A061202-ST1.

6.2.1 Alliance Substudy A061202-ST1

As of Update #04, no new patients will be registered to the A061202-ST1 substudy.

For patients registered to substudy A061202-ST1: All participating institutions must ask patients for their consent to participate in the correlative substudies planned for Alliance A061202-ST1, although patient participation is optional. Biomarker studies will be performed. Rationale and methods for the scientific components of these studies are described in Section 14.0. For patients who consent to participate, formalin fixed paraffin embedded (FFPE) bone marrow biopsy tissue and, fresh liquid bone marrow aspirate sample will be collected at baseline (at the time of the staging bone marrow aspirate and biopsy) and at disease progression for those who achieve a ≥MR with initial therapy.

	Prior to initiation of therapy	Attainment of complete remission	At first disease Progression*	Submit to:
For patients registered to A061202-ST1[1], submit the following:				
Formalin fixed paraffin embedded block of bone marrow OR Bone Marrow Biopsy Slides (See section 6.2.4)	X**		X**	ABOSU
Fresh, liquid bone marrow aspirate	5 mL in 1 or 2 EDTA/lavender top tubes***		5 mL in 1 or 2 EDTA/lavender top tubes***	Alliance Hematologic Malignancy Biorepository

* Samples are expected from Arm 1 patients after progression on Pomalidomide + Dexamethasone and from Arm 2 patients after progression on Pomalidomide + Dexamethasone + Ixazomib. Progression samples may be collected and submitted up to 1 month after progression but must be obtained prior to the start of a new treatment regimen.

** Bone marrow blocks/cores to be used for biomarker/TMA analyses described in Section 14.1.3

*** Bone marrow aspirates to be used for biomarker analyses described in Section 14.1.3

1. Collect and submit only from patients who consent to model consent questions #1, 2 and 3. **Also please note: A061202-ST1 is only for patients on the phase II study.**

6.2.2 Specimen submission using the Alliance Biospecimen Management System (For A061202-ST1)

USE OF THE ALLIANCE BIOSPECIMEN MANAGEMENT SYSTEM (BioMS) IS MANDATORY AND ALL SPECIMENS MUST BE LOGGED AND SHIPPED VIA THIS SYSTEM.

BioMS is a web-based system for logging and tracking all biospecimens collected on Alliance trials. Authorized individuals may access BioMS at the following URL: [redacted] using most standard web browsers (Safari, Firefox, Internet Explorer). For information on using the BioMS system, please refer to the 'Help' links on the BioMS web page to access the on-line user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors, please contact: [redacted] For assistance in using the application or questions or problems related to specific specimen logging, please contact: [redacted]

After logging collected specimens in BioMS, the system will create a shipping manifest. This shipping manifest must be printed and placed in the shipment container with the specimens.

All submitted specimens must be labeled with the protocol number (A061202), Alliance patient number, patient's initials and date and type of specimen collected (e.g., serum, whole blood).

A copy of the Shipment Packing Slip produced by BioMS must be printed and placed in the shipment with the specimens.

Instructions for the collection of samples are included below. Please be sure to use a method of shipping that is secure and traceable. Extreme heat precautions should be taken when necessary.

6.2.3 Bone Marrow Aspirate Submission (Alliance A061202-ST1)

From all patients, collect 5 mL of bone marrow aspirate prior to initiation of therapy and at disease progression (for those with ≥MR), in an EDTA tube. If a patient has a dry tap, please submit the requested biopsy without the bone marrow aspirate.

Specimens for patients registered on this study must be logged and shipped using the online Alliance BioMS, as described above.

The specimens should be labeled with the study number (A061202), Alliance patient ID, patient's initials, institution, and date and time of specimen procurement, and sample type. A copy of the Shipment Packing Slip produced by the BioMS must be printed and placed in the shipment with the specimens. **Specimens should be sent at ambient temperature on the same day as collection to the Alliance Hematologic Malignancy Biorepository:**

Alliance Hematologic Malignancy Biorepository
[redacted]

Ship specimens by overnight courier to the Alliance Hematologic Malignancy Biorepository the same day they are collected. Shipment on Monday through Thursday by overnight service to assure receipt is encouraged. Do not ship specimens on Fridays or Saturdays. Please be sure to use a method of shipping that is secure and traceable.

For the baseline bone marrow aspirate submission: Because sites may be awaiting local lab results to confirm eligibility on the day of specimen collection, patients may not yet be registered in order to obtain a patient ID number for logging these specimens in BioMS. In this case, please use the ***"BioMS Specimen Log and Shipping Manifest Form"*** for submission of the prior to initiation of therapy bone marrow aspirate. The form is posted on the "Supplemental Materials" page of the A061202 study page on the Alliance website. Please follow all instructions on the form. A copy of this form must accompany specimens with the shipment. The CRA responsible for the specimens MUST contact the biorepository to inform them of patient registration IDs AND screen failures once an eligibility determination has been made locally. Once patients are registered to the trial, their specimens should be backlogged in BioMS, and the packing slip created must be forwarded to the biorepository.

6.2.4 Paraffin-Embedded Block of Bone Marrow (A061202-ST1)

For patients who consent to participate in A061202-ST1, bone marrow blocks will be used for the analyses described in Section 14.1.2. The bone marrow block obtained at the time of the baseline staging bone marrow aspirate and biopsy will be used as the baseline biopsy for those participating in A061202-ST1.

Paraffin blocks of formalin fixed bone marrow tissue obtained prior to initiation of therapy and at disease progression should be sent to the Alliance Biorepository at Ohio State University (ABOSU).

The Alliance has instituted special considerations for the small percentage of hospitals whose policy prohibits long-term storage of blocks, and the smaller percentage of hospitals whose policies prohibit release of any block. Those institutions unable to send the formalin fixed paraffin embedded bone marrow biopsy tissue block may instead send 12 unstained bone marrow biopsy tissue sections, 3-4 microns thick on charged glass slides appropriate for immunohistochemical staining. These should be sent to the Alliance Biorepository at Ohio State University (ABOSU) at the address below. If there are questions about this policy, please call the ABOSU at [redacted]

The goal of the ABOSU is to provide investigators with quality histology sections for their research while maintaining the integrity of the tissue. All paraffin blocks that are to be stored at the ABOSU will be vacuum packed to prevent oxidation and will be stored at 4º C to minimize degradation of cellular antigens. For these reasons it is preferred that the ABOSU bank the block until the study investigator requests thin sections. Please contact the ABOSU if additional assurances with your hospital pathology department are required.

The specimens should be labeled with the study number (A061202), Alliance patient ID, patient's initials, institution, and date and time of specimen procurement, and sample type. A copy of the Shipment Packing Slip produced by the BioMS must be printed and placed in the shipment with the specimens. Specimens should be sent at ambient temperature to the Alliance Biorepository at Ohio State University (ABOSU):

Innovation Centre
[redacted]

Ship specimens by overnight courier to the Alliance ABOSU Monday through Thursday by overnight service to assure receipt is encouraged. Do not ship specimens on Fridays or Saturdays. Please be sure to use a method of shipping that is secure and traceable. Ship specimens to the Alliance ABOSU.

7.0 TREATMENT PLAN/INTERVENTION

Protocol treatment is to begin ≤ 7 days of registration.

Pomalidomide, dexamethasone and ixazomib are administered as flat doses and not based on weight or body surface area. Pomalidomide should be administered at approximately the same time each day. Please refer to Section 8.1 for ancillary/supportive therapy, Section 8.2 for instructions regarding dose modifications and Section 10.0 for drug formulation, availability and preparation.

It is acceptable for individual chemotherapy doses to be delivered ≤ a 24-hour (business day) window before and after the protocol-defined date for Day 1 of a new cycle. For example, if the treatment due date is a Friday, the window for treatment includes the preceding Thursday through the following Monday. If a patient forgets to take their dexamethasone or ixazomib on the scheduled day, they can

take it up to 72 hours late. If >72 hours have elapsed, the dose should be omitted and not made up. Subsequent doses of dexamethasone and ixazomib will be administered on the original schedule. Missed pomalidomide doses will not be made up. In addition, patients are permitted to have a new cycle of chemotherapy delayed up to 7 days for major life events (e.g., serious illness in a family member, major holiday, vacation that cannot be rescheduled) without this being considered a protocol violation. Documentation to justify this delay should be provided. **Treatment will continue until disease progression, unacceptable toxicity despite appropriate supportive care and dose modifications, or withdrawal of informed consent.**

7.1 Phase I (Description/Treatment Plan)/ Definition of DLT

All patients on the phase I portion of the study will receive the combination of pomalidomide, dexamethasone and ixazomib. The dose of pomalidomide and ixazomib will be dictated by the dose cohort to which a patient is assigned. All patients will receive either a 40 mg (≤75 years old) or 20 mg (>75 years old) dose of dexamethasone. Patients will be assigned to a new dose cohort only after it has been determined that the MTD has not been exceeded in the previous dose cohort (see Section 13.0 for details).

Protocol therapy will consist of pomalidomide, dexamethasone and ixazomib administered over a 28-day cycle. Pomalidomide will be administered orally on days 1 through 21. It is recommended that pomalidomide be taken at night. Ixazomib will be given orally on days 1, 8 and 15. Patients ≤ 75 years of age will receive a 40 mg dose of dexamethasone and those over the age of 75 will receive a 20 mg dose of dexamethasone orally on days 1, 8, 15 and 22 (weekly). Dexamethasone should be taken with food, preferably in the morning when possible. A patient medication diary will be used to assess adherence to therapy.

Please refer to Section 5.0 for details regarding required evaluations (history and physicals, vital signs and performance status assessment, laboratory testing, myeloma assessments, etc).

Given the increased risk of venous thromboembolic events with the use of pomalidomide and dexamethasone, thromboprophylaxis is required while patients are on protocol therapy and should consist of either aspirin (81 mg or 325 mg daily), a prophylactic dose of low molecular weight heparin (e.g. enoxaparin 40 mg SC daily), warfarin targeting an INR of 2 – 3, or other equivalent. Thromboprophylaxis should be held in the presence of ≥grade 3 thrombocytopenia (see section 8.2 for details). For patients with poor oral intake and frequent ≥grade 3 thrombocytopenia, low molecular weight heparin is preferred over warfarin.

Proteasome inhibitor-based therapy is associated with an increased risk of herpes zoster reactivation. As such, patients on treatment with ixazomib are required to receive herpes zoster reactivation prophylaxis (e.g. valacyclovir 500 mg orally once to twice daily or its equivalent).

For the phase I portion of the protocol, filgrastim, sargramostim and pegfilgrastim cannot be used during cycle 1 of therapy but can be used in subsequent cycles as clinically indicated (see sections 8.1 and 8.2 for details).

Given the high rates of pneumonia seen in this patient population, anti-bacterial prophylaxis is recommended for patients with ≥grade 3 neutropenia (e.g. levofloxacin or its equivalent) and/or significant immunoparesis (low immunoglobulin levels).

Please see section 8.1 for additional information regarding ancillary therapy.

A new cycle of therapy cannot begin until the ANC has recovered to 1.0 x 10^9/L, the platelet count to 50 x 10^9/L and all other criteria for resumption of therapy have been met (please refer to section 8.2 for details).

7.1.1 Phase I- Determination of Maximum Tolerated Dose (MTD)

Dose Levels

All patients on the phase I portion of the study will receive the combination of pomalidomide, dexamethasone and ixazomib. The dose of pomalidomide and ixazomib will be dictated by the dose cohort to which a patient is assigned. All patients will receive either a 40 mg (≤75 years old) or 20 mg (>75 years old) dose of dexamethasone. Patients will be assigned to a new dose cohort only after it has been determined that the MTD has not been exceeded in the previous dose cohort (see section 13.0 for details).

Table 7.1.1- Phase I Dose Finding Plan

Dose level	Pomalidomide (mg) Days 1 – 21	Dexamethasone (mg) Days 1, 8, 15, 22	Ixazomib (mg) Days 1, 8, 15
0	2	40 (20 for > 75 years)	2.3
***1**	**2**	40 (20 for > 75 years)	**3**
2	3	40 (20 for > 75 years)	3
3	4	40 (20 for > 75 years)	3
4	4	40 (20 for > 75 years)	4

* **Starting dose level**

- If cohort 2 is the maximum tolerated dose, a dose level 2A will be pursued evaluating a 2 mg dose of pomalidomide and 4 mg dose of ixazomib. If cohort 3 is the maximum tolerated dose, a dose level 3A will be pursued evaluating a 3 mg dose of pomalidomide and 4 mg dose of ixazomib.
- Three to 6 patients will be treated at each dose level and observed for a minimum of 28 days to assess adverse events in cycle 1 before new patients are treated. Intra-patient escalation of dosing is allowed if it has been determined that the MTD has not been exceeded for the next dose level, and the patient has not required any dose modifications or delays as a result of adverse events related to protocol therapy. Patients who have had their dexamethasone dose reduced as a result of AEs will be eligible for dose escalation of the pomalidomide and ixazomib if they otherwise meet criteria to do so. The MTD will be determined by DLTs seen in cycle 1 of therapy (please refer to section 13.1 for details regarding definition of the MTD and criteria for dose level escalation and de-escalation).
- Phase I conference calls will be held every other week and are mandatory for all sites with a patient registered on the phase I portion of the study. These calls will be used to review adverse events, assess study enrollment and address any questions that arise over the course of the study. These calls can be attended by the Principal Investigator, a Co-Investigator or Study Coordinator at that site. In addition, a Dose Escalation conference call will be held immediately after a dose cohort has completed accrual and all patients have been treated for 28 days (1 cycle). All phase I Principal Investigators should participate in these calls.

7.1.2 Definitions of DLT

DLTs will be determined during cycle 1 of therapy. Adverse events will be graded per CTCAE, version 4.0.

For this protocol, DLT will be defined by the following adverse events at least possibly related to study therapy:

Grade 3 or higher non-hematologic adverse events, with the following exceptions:

- Alopecia is not expected but is not considered a DLT

- Nausea, vomiting and diarrhea will only be considered DLTs if they cannot be adequately managed with optimal supportive care (see section 8.1 and 8.2)
- Grade 3 or 4 hypergylcemia due to dexamethasone will only be considered a DLT if it cannot be controlled with appropriate therapy.

Grade 4 hematologic adverse events, with the following exceptions:

- Grade 4 lymphopenia is expected with this regimen and will not be construed as a DLT
- Grade 4 neutropenia will only be considered a DLT if it lasts longer than 7 days
- Grade 4 thrombocytopenia will only be considered a DLT if it lasts longer than 7 days or is associated with a ≥grade 3 bleeding event.

The maximum tolerated dose is the dose level where at most 1 out of 6 patients treated at that dose level report a DLT and the next higher dose level is such that 2 or more patients treated at that dose level reported a DLT. If the planned dose levels are exhausted without observing a dose level where 2 or more patients treated at that dose level reported a DLT then the recommended phase II dose will be dose level #4 (the highest dose level tested).

7.2 Phase II Description/Treatment Plan

Patients on the phase II portion of the study will be randomly assigned to the combination of pomalidomide and dexamethasone (Treatment Arm 1) or the combination of pomalidomide, dexamethasone and ixazomib (Treatment Arm 2). The dose of pomalidomide and dexamethasone in Treatment Arm 1 will be the same as the FDA approved dosing for the combination (see below). In Treatment Arm 2, the dose of pomalidomide will be 4 mg and the dose of ixazomib will be 4 mg. All patients will receive either a 40 mg (≤75 years old) or 20 mg (>75 years old) dose of dexamethasone.

Treatment Arm 1: Pomalidomide and dexamethasone

Protocol therapy will consist of pomalidomide and dexamethasone administered over a 28-day cycle. Pomalidomide will be administered at 4 mg orally daily for days 1 through 21. It is recommended that pomalidomide be taken at night. Patients ≤ 75 years of age will receive a 40 mg dose of dexamethasone and those over the age of 75 will receive a 20 mg dose of dexamethasone orally on days 1, 8, 15 and 22 (weekly). Dexamethasone should be taken with food, preferably in the morning when possible. A patient medication diary will be used to assess adherence to therapy.

At the time of progression: If a patient experiences disease progression on pomalidomide and dexamethasone alone (as defined in section 11.0), they will be allowed to continue on to Course 2 treatment, where they will receive the combination of pomalidomide, dexamethasone and ixazomib. Patients should remain on the dose of pomalidomide and dexamethasone they tolerated in Course 1. The ixazomib dose should be 4 mg. **Note:** Patients who opt to continue to Course 2 treatment must be re-registered to the study within 14 days of confirmation of progression per section 4.6. Treatment should begin ≤ 3 days following re-registration.

Treatment Arm 2: Pomalidomide, dexamethasone and ixazomib

Protocol therapy will consist of pomalidomide, dexamethasone and ixazomib administered over a 28-day cycle. Pomalidomide will be administered at 4 mg orally daily for days 1 through 21. It is recommended that pomalidomide be taken at night. Patients ≤ 75 years of age will receive a 40 mg dose of dexamethasone and those over the age of 75 will receive a 20 mg dose of dexamethasone orally on days 1, 8, 15 and 22 (weekly). Dexamethasone should be taken with food, preferably in the morning when possible. Ixazomib will be administered at 4 mg orally on days 1, 8 and 15. A patient medication diary will be used to assess adherence to therapy.

Ancillary Therapy for Patients on Treatment Arms 1 and 2

Please refer to section 5.0 for details regarding required evaluations (history and physicals, vital signs and performance status assessment, laboratory testing, myeloma assessments, etc).

Given the increased risk of venous thromboembolic events with the use of pomalidomide and dexamethasone, thromboprophylaxis is required while patients are on protocol therapy and should consist of either aspirin (81 mg or 325 mg), a prophylactic dose of low molecular weight heparin (e.g. enoxaparin 40 mg SC daily) or warfarin targeting an INR of 2 – 3, or other equivalent. Thromboprophylaxis should be held in the presence of ≥grade 3 thrombocytopenia (see section 8.2 for details). For patients with poor oral intake and frequent ≥grade 3 thrombocytopenia, low molecular weight heparin is preferred over warfarin.

Proteasome inhibitor-based therapy is associated with an increased risk of herpes zoster reactivation. As such, patients on treatment with ixazomib are required to receive herpes zoster reactivation prophylaxis (e.g. valacyclovir 500 mg orally once to twice daily or its equivalent).

Filgrastim, sargramostim and pegfilgrastim can be used at any time during the study as clinically indicated (see sections 8.1 and 8.2 for details).

Given the high rates of pneumonia seen in this patient population, anti-bacterial prophylaxis is recommended for patients with ≥grade 3 neutropenia (e.g. levofloxacin or its equivalent) and/or significant immunoparesis (low immunoglobulin levels).

Please see section 8.1 for additional information regarding ancillary therapy.

A new cycle of therapy cannot begin until the ANC has recovered to 1.0 x 10^9/L, the platelet count to 50 x 10^9/L and all other criteria for resumption of therapy have been met (please refer to section 8.1 and 8.2 for details).

Table 7.2a: Phase II Dosing – Treatment Arm 1

Agent	Dose	Route	Days
Course 1			
Pomalidomide	4 mg	Orally	Days 1 – 21
Dexamethasone	40 mg (20 mg for those > 75 years of age)	Orally	Days 1, 8, 15 and 22
Course 2*			
Pomalidomide	Dose tolerated in Course 1	Orally	Days 1 – 21
Dexamethasone	Dose tolerated in Course 1	Orally	Days 1, 8, 15, and 22
Ixazomib	4 mg	Orally	Days 1, 8, and 15

* *Following progression on Course 1 treatment, patients in Arm 1 may opt to receive Course 2 treatment. These patients must be re-registered to the study prior to starting Course 2.*

Table 7.2b: Phase II Dosing – Treatment Arm 2

Agent	Dose	Route	Days
Pomalidomide	4 mg	Orally	Days 1 – 21
Dexamethasone	40 mg (20 mg for those > 75 years of age)	Orally	Days 1, 8, 15 and 22
Ixazomib	4 mg	Orally	Days 1, 8 and 15

8.0 DOSE AND TREATMENT MODIFICATIONS

8.1 Ancillary therapy, concomitant medications, and supportive care

- Suspend thromboprophylaxis in presence of platelet count < 50,000. Resume prophylaxis as soon as platelet count ≥ 50,000. If bleeding requiring medical intervention occurs while on thromboprophylaxis, treating physician should weigh risks and benefits of continuing thromboprophylaxis.
- For dyspepsia due to dexamethasone, institute H2 blocker or proton pump inhibitor
- For edema due to dexamethasone, institute diuretic as clinically appropriate

8.1.1 Patients should not receive any other agent which would be considered treatment for the primary neoplasm or impact the primary endpoint.

8.1.2 Patients should receive full supportive care while on this study. This includes blood product support (e.g. packed red blood cells and platelets), antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antibiotics, antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until the end of treatment visit will be recorded in the medical records.

8.1.3 Treatment with hormones or other chemotherapeutic agents may not be administered except for steroids given for adrenal failure or hormones administered for non-disease-related conditions (e.g., insulin for diabetes). Use of dexamethasone and other steroidal antiemetics is prohibited in this protocol. Patients who need a therapeutic course of a corticosteroid for a non-myeloma related condition (e.g. bronchospasm related to a respiratory tract infection) should be discussed with the Study Chair. For more urgent corticosteroid indications, treatment may proceed and discussed with the Study Chair thereafter. Any corticosteroid administration should be documented, along with reason for treatment and doses.

8.1.4 Antiemetics may be used at the discretion of the treating physician and are strongly encouraged given the fact that nausea and vomiting are expected side effects of this treatment regimen.

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

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

If grade 3 or 4 diarrhea is associated with fever or neutropenia (grade 3 or 4), broad-spectrum antibiotics should be prescribed. Patients with grade 3 or 4 diarrhea or any diarrhea associated with nausea and vomiting **should be evaluated for need of intravenous fluids, correction of electrolyte imbalances, and consideration for whether hospitalization is necessary.**

8.1.6 Radiation Therapy. Palliative radiation therapy while on study treatment may not be administered with the exception of radiation therapy to a pathological fracture site to enhance bone healing or to treat post-fracture pain that is refractory to narcotic analgesics. Symptomatic lesions, or ones that may produce disability (e.g., unstable femur) should be irradiated prior to study initiation, provided other measurable disease is present. Please hold

dexamethasone, pomalidomide and ixazomib if radiation therapy is performed, treatment can resume as soon as radiation therapy is complete.

Patients who require radiation therapy during protocol treatment for reasons other than the exceptions outlined above will be removed from protocol therapy due to disease progression.

8.1.7 Alliance Policy Concerning the Use of Growth Factors

Blood products and growth factors should be utilized as outlined in the protocol (see section 8.2) and as clinically warranted following institutional policies and recommendations.

Epoetin (EPO): Please note that there is an increased risk of thrombosis related to EPO. As such, given the additional risk of thrombosis with pomalidomide-based therapy, caution must be exercised when using it in this patient population and its routine use discouraged.

Filgrastim (G-CSF) and sargramostim (GM-CSF)

1. Utilization of filgrastim (G-CSF)/pegfilgrastim and sargramostim (GM-CSF) for management of neutropenia encountered on this study should follow guidelines outlined in the dose modifications section (see section 8.2). **GCSF/GMCSF is not permitted in patients during cycle 1 of treatment in the phase I study.**
2. The use of white blood cell growth factors not otherwise specified in the protocol should follow published guidelines of the American Society of Clinical Oncology 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based, Clinical Practice Guideline. J Clin Oncol 24(19): 3187-3205, 2006.
3. Filgrastim/pegfilgrastim and sargramostim may not be used:
   a. To avoid dose reductions, delays or to allow for dose escalations specified in the protocol.
   b. For the treatment of febrile neutropenia the use of CSFs should not be routinely instituted as an adjunct to appropriate antibiotic therapy. However, the use of CSFs may be indicated in patients who have prognostic factors that are predictive of clinical deterioration such as pneumonia, hypotension, multi-organ dysfunction (sepsis syndrome) or fungal infection, as per the ASCO guidelines. Investigators should therefore use their own discretion in using the CSFs in this setting. The use of CSF (filgrastim/pegfilgrastim or sargramostim) must be documented and reported.
   c. If filgrastim/pegfilgrastim or sargramostim are used, they must be obtained from commercial sources.

8.1.8 Bisphosphonates (e.g. zoledronic acid, pamidronic acid) may be used at the discretion of the treating physician.

8.1.9 Thromboprophylaxis. The combination of pomalidomide and dexamethasone increases the risk of venous thromboembolic events. As such, thromboprophylaxis is required for all patients on this study. Thromboprophylaxis may consist of either aspirin (81 or 325 mg daily), a prophylactic dose of low molecular weight heparin (e.g. enoxaparin 40 mg SC daily), warfarin, targeting an INR of 2 – 3 or an equivalent strategy. However, thromboprophylaxis should be held for those patients who experience ≥grade 3 thrombocytopenia. For patients with poor oral intake and frequent ≥grade 3 thrombocytopenia, low molecular weight heparin is preferred over warfarin.

Smoking cessation, avoiding dehydration, and avoiding extended periods of inactivity should be encouraged to decrease risk of thrombosis.

8.1.10 Herpes zoster reactivation prophylaxis. Patients on proteasome inhibitor-based regimens are at increased risk of herpes zoster reactivation. Therefore, all patients who receive ixazomib should receive appropriate prophylaxis (e.g. valacyclovir 500 mg orally once to twice daily or its equivalent). Patients receiving only pomalidomide and dexamethasone on Treatment Arm 1 of the phase II portion of the study do not need to receive herpes zoster reactivation prophylaxis unless they cross-over to receive ixazomib.

8.1.11 Bacterial infection prophylaxis. Prophylaxis against bacterial infection is not mandated. However, it must be recognized that participants on this study represent a patient population at high risk of bacterial infections due to the presence of immunoparesis and frequent neutropenia. Additionally, ≥grade 3 pneumonia was a common adverse event encountered in pomalidomide studies. Therefore, anti-bacterial prophylaxis is strongly recommended for patients with ≥grade 3 neutropenia and/or significant immunoparesis (low immunoglobulin levels) (e.g. a fluoroquinolone or its equivalent). In addition, use of prophylactic IVIG therapy is allowed if clinically indicated.

8.1.12 Strong CYP3A4 and CYP1A2 inducers and inhibitors: Use of strong CYP3A4 and CYP1A2 inducers or inhibitors is not allowed while patients are treated on this study. Patients should be educated on potential drug interactions. A wallet-size card providing information for patients regarding potential drug interactions has been made available at the study-specific page of the CTSU. Please refer to Appendix V for a list of strong inhibitors and inducers of CYP3A4 and CYP1A2.

8.1.13 Patients with impaired renal function, high tumor burdens, and diabetes and obesity may be at increased risk for tumor lysis syndrome (TLS) with pomalidomide-based therapy. As such, consider increased monitoring for TLS during cycle 1 in these patients.

8.1.14 Patients should be encouraged to receive pneumococcal and influenza vaccinations if appropriate.

8.2 Dose Modifications General Principles:

- **GCSF/GMCSF are not permitted in patients during cycle 1 of treatment in the phase I study unless a DLT has already occurred and their use is indicated.**
- If the start of a new cycle of therapy is delayed for >21 days beyond the originally planned start date as a result of adverse events at least possibly attributable to study treatment, protocol therapy will be discontinued.
- Omitted doses of therapy should not be made up. If more than 7 days of treatment in any individual cycle are missed, the remainder of the cycle should be omitted and dosing resumed with the next cycle of therapy.
- If multiple adverse events are seen, administer dose based on the greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior evaluation.
- Pomalidomide, dexamethasone and ixazomib will not be re-escalated once dose reduced.
- A new cycle of therapy cannot begin until the ANC has recovered to 1.0 x 10^9/L, the platelet count to 50 x 10^9/L, and all other protocol therapy related and unrelated adverse events have improved to grade 1 or baseline. If grade 2 toxicities persist but the treating physician feels it is in the best interested of the patient to continue therapy (e.g. fatigue), contact the Study Chair to help determine the best course of action.
- If an adverse event can be attributed to a specific agent or agents, the non-implicated agent(s) may be continued without modification of the dose or schedule if appropriate.

- Dose delays may occur as a result of adverse events that are related or unrelated to protocol therapy. However, dose modifications and drug discontinuations will only be applied to adverse events that are at least possibly related to protocol therapy.

8.2.1 Pomalidomide Dose Levels

Please note that the pomalidomide starting dose in the phase I portion of the protocol will be dictated by the dose level to which the patient is assigned.

Table 8.2.1-Pomalidomide Dose Levels

Dose Level	Pomalidomide (Days 1 – 21 of a 28-day cycle)	Pomalidomide (Days 1 – 21 of a 28-day cycle)	Pomalidomide (Days 1 – 21 of a 28-day cycle)
0*	4 mg	3 mg	2 mg
-1	3 mg	2 mg	1 mg
-2	2 mg	1 mg	Not applicable
-3	1 mg	Not applicable	Not applicable

*Dose level 0 refers to the starting dose.

8.2.2 Ixazomib Dose Levels

Please note that the ixazomib starting dose in the phase I portion of the protocol will be dictated by the dose level to which the patient is assigned.

Table 8.2.2- Ixazomib Dose Levels

Dose Level	Ixazomib (Days 1, 8 and 15 of a 28-day cycle)	Ixazomib (Days 1, 8 and 15 of a 28-day cycle)	Ixazomib (Days 1, 8 and 15 of a 28-day cycle)
0*	4 mg	3 mg	2.3 mg
-1	3 mg	2.3 mg	Not applicable
-2	2.3 mg	Not applicable	Not applicable

*Dose level 0 refers to the starting dose.

8.2.3 Dexamethasone Dose Levels

The starting dose for dexamethasone is 40 mg for patients ≤ 75 years of age, 20 mg for patients >75 years of age.

Table 8.2.3- Dexamethasone Dose Levels

Dose Level	Dexamethasone (Days 1, 8, 15, 22 of a 28-day cycle)	Dexamethasone (Days 1, 8, 15, 22 of a 28-day cycle)
0*	40 mg	20 mg
-1	20 mg	12 mg
-2	12 mg	8 mg

Dose Level	Dexamethasone (Days 1, 8, 15, 22 of a 28-day cycle)	Dexamethasone (Days 1, 8, 15, 22 of a 28-day cycle)
-3	8 mg	Not applicable

*Dose level 0 refers to the starting dose.

8.3 Dose Modification Guidelines for Pomalidomide and Ixazomib:

- A new cycle of therapy cannot begin until the ANC has recovered to 1.0 x 10^9/L, the platelet count to 50 x 10^9/L, and all other protocol therapy-related and -unrelated adverse events have improved to grade 1 or baseline. If grade 2 toxicities persist but the treating physician feels it is in the best interest of the patient to continue therapy (e.g. fatigue), contact the Study Chair to help determine the best course of action.
- If an adverse event can be attributed to a specific agent or agents, the non-implicated agent(s) may be continued without modification of the dose or schedule if appropriate.
- Dose delays may occur as a result of adverse events that are related or unrelated to protocol therapy. **However, dose modifications and drug discontinuations will only be applied to adverse events that are at least possibly related to protocol therapy.**

8.3.1 Hematologic Toxicity:

During CYCLE 1 ONLY (for patients on the phase I portion of the study. Dose modifications apply to any day of the treatment cycle):

- For grade 4 neutrophil count decrease OR for any grade febrile neutropenia**, delay pomalidomide and ixazomib** until recovery to grade 2 neutrophil count (ANC ≥ 1000). Restart at **SAME** dose level for both **pomalidomide and ixazomib**.
    - **NOTE:** G-CSF or GM-CSF may **NOT** be used **during the phase I portion of the trial cycle 1 but should be considered for cycle 2 and beyond if deemed clinically appropriate.** Patients on the phase II portion of the study may receive G-CSF during any cycle as clinically indicated**.**
    - If a patient on the phase I portion of the protocol has already met criteria for a DLT in cycle 1 and would benefit from continue participation in the study as determined by the treating investigator, G-CSF may be used as clinically indicated for the remainder of cycle 1.
- For grade 4 platelet count decrease, **delay pomalidomide and ixazomib** until recovery to grade 2 platelet count (platelet ≥ 50,000). Restart at **SAME** dose level for both **pomalidomide and ixazomib**

During CYCLE 2 and BEYOND for those on the phase I portion of the study, CYCLE 1 and BEYOND for those on the phase II portion. (Dose modifications apply to any day of the treatment cycle):

- For grade 4 neutrophil count decrease OR for any grade febrile neutropenia**, delay pomalidomide and ixazomib** until recovery to grade 2 neutrophil count (ANC ≥ 1000). Restart at same dose **IF** toxicity occurred without the use of G-CSF or GM-CSF and G-CSF or GM-CSF are going to be used with subsequent protocol therapy. Restart at 1 dose level decreased for **pomalidomide** if toxicity occurred with the use of G-CSF or GM-CSF, or if G-CSF or GM-CSF will not be used upon re-initiation of protocol therapy. If grade 4 neutrophil count decrease recurs despite a lowering of the pomalidomide to 2 mg, restart at 1 dose level decreased for **ixazomib**.

- For grade 4 platelet count decrease, **delay pomalidomide and ixazomib** until recovery to grade 2 platelet count (platelet ≥ 50,000). Restart at 1 dose level decreased for both **pomalidomide and ixazomib.**
- The phase I experience with this regimen revealed more significant neutropenia and thrombocytopenia for those patients with a large burden of disease at baseline. If a large disease burden is felt to be a significant contributor to grade 4 neutrophil and/or platelet count decrease, clearance to resume therapy without a dose reduction of the pomalidomide and/or ixazomib must be approved by the Study Chair. In such a case, if grade 4 neutrophil and/or platelet count decrease recurs despite a reduction in disease burden, the dose modifications above should be implemented.

8.3.2 Skin Toxicity:

- For grade 2 or higher skin ulceration, discontinue **pomalidomide and ixazomib**
- For grade 3 erythema multiforme, discontinue **pomalidomide and ixazomib**
- For grade 3 acneiform rash, delay **pomalidomide and ixazomib** until grade 1, then restart at 1 dose level decreased for **pomalidomide and ixazomib**
- For grade 3 maculo-papular rash, delay **pomalidomide and ixazomib** until grade 1, then restart at 1 dose level decreased for **pomalidomide and ixazomib**
- For grade 4 rash any type, discontinue **pomalidomide and ixazomib**
- For Stevens-Johnson syndrome, discontinue **pomalidomide and ixazomib**
- For toxic epidermal necrolysis, discontinue **pomalidomide and ixazomib**

8.3.3 Allergic Reaction:

- For grade 2 allergic reaction, delay the offending agent **(pomalidomide OR ixazomib)** until recovery to grade 1 then restart at 1 dose level decreased for the offending agent **(pomalidomide OR ixazomib)**
- For grade 3 allergic reaction, discontinue the offending agent **(pomalidomide OR ixazomib)**
- For any grade anaphylaxis, discontinue the offending agent **(pomalidomide OR ixazomib)**

8.3.4 GI Toxicity:

- For grade 3 or 4 diarrhea that persists despite optimal supportive care, delay **pomalidomide and ixazomib** until recovery to grade 1, then restart at 1 dose level decreased for **pomalidomide and ixazomib.**
- For grade 3 or 4 nausea or vomiting that persists despite optimal supportive care, delay **pomalidomide and ixazomib** until recovery to grade 1, then restart at 1 dose level decreased for **pomalidomide and ixazomib.**

8.3.5 Neurotoxicity:

- For grade 2 sensory and or motor neuropathy in patients with baseline grade 0 or 1 neuropathy, delay **pomalidomide and ixazomib** until at patient's baseline neuropathy then resume at 1 dose level decreased for **pomalidomide and ixazomib**
- For new onset neuropathic pain regardless of grade, delay **pomalidomide and ixazomib** until pain is resolved/controlled, then restart at 1 dose level decreased for **pomalidomide and ixazomib**

- For grade 3 sensory and or motor neuropathy, delay **pomalidomide and ixazomib** until recovery to grade 1 OR to patient's baseline neuropathy, then restart at 1 dose level decreased for **pomalidomide and discontinue ixazomib.**
- For grade 4 sensory or motor neuropathy, discontinue **pomalidomide and ixazomib.**

8.3.6 Nephrotoxicity:

- For grade 2 creatinine increased, delay **pomalidomide and ixazomib** until recovery to grade 1, then restart **pomalidomide and ixazomib** at same dose.
- For grade 3 creatinine increased, discontinue **pomalidomide.** For grade 3 creatinine increased, delay **ixazomib** until recovery to grade 1, then restart at same dose
- For grade 4 creatinine increased, discontinue **ixazomib and pomalidomide**
- For grade 3 hyponatremia, delay **ixazomib** until recovery to grade 2, then restart at 1 dose level decreased for **ixazomib**
- For grade 4 hyponatremia, discontinue **ixazomib**
- For grade 3 hypophosphatemia (despite oral replacement therapy), delay **ixazomib** until recovery to grade 2, then restart at 1 dose level decreased for **ixazomib**
- For grade 4 hypophosphatemia (despite oral replacement therapy), discontinue **ixazomib**
- For grade 3 hypokalemia (despite oral replacement therapy), delay **ixazomib** until recovery to grade 2, then restart at 1 dose level decreased for **ixazomib**
- For grade 4 hypokalemia (despite oral replacement therapy), discontinue **ixazomib**

8.3.7 Vascular:

- For grade 1 thromboembolic event that occurs while not on thromboprophylaxis or therapeutic anticoagulation, delay **pomalidomide** until thromboprophylaxis is initiated and then restart **pomalidomide** at the same dose.
- For grade 2 or higher thromboembolic event that occurs while not on thromboprophylaxis or therapeutic anticoagulation, delay **pomalidomide** until anticoagulation is initiated and at stable dose, and then restart **pomalidomide** at same dose
- For grade 1 thromboembolic event that occurs while on thromboprophylaxis, delay **pomalidomide** until it is ensured that therapeutic anticoagulation is at stable dose, and then restart **pomalidomide** at same dose.
- For grade 2 or 3 thromboembolic event that occurs while on thromboprophylaxis, delay **pomalidomide** until therapeutic anticoagulation is initiated and at stable dose, and then restart **pomalidomide** at 1 dose level decreased
- For grade 4 thromboembolic event that occurs while on thromboprophylaxis, discontinue **pomalidomide**
- For grade 1 thromboembolic event that occurs while on therapeutic anticoagulation, delay **pomalidomide** until it is ensured that anticoagulation is at stable dose, and then restart **pomalidomide** at 1 dose level decreased
- For grade 2,3,4 thromboembolic event that occurs while on therapeutic anticoagulation, discontinue **pomalidomide**

8.3.8 Respiratory:

- For grade 3 dyspnea, delay **pomalidomide** until recovery to grade 1 then restart **pomalidomide** at 1 dose level decreased.
- For grade 4 dyspnea, discontinue **pomalidomide.**

8.3.9 Other:

- For grade 3 non-hematologic toxicity not specified above, delay offending agent **(pomalidomide or ixazomib)** until recovery to grade1, then restart at 1 dose level decreased.
- For grade 4 non-hematologic toxicity not specified above, discontinue **pomalidomide or ixazomib.**

8.4 Dose Modification Guidelines for Dexamethasone:

8.4.1 GI Toxicity:

For grade 3 or 4 dyspepsia, despite optimal supportive care, delay dexamethasone until recovery to grade 1, then restart at 1 dose level decreased

8.4.2 Edema:

For grade 3 or 4 edema, despite optimal supportive care, delay dexamethasone until recovery to grade 1, then restart at 1 dose level decreased

8.4.3 Psychiatric:

- For grade 2 agitation, anxiety, delirium, depression, hallucinations, mania, personality change, psychosis, or confusion, delay dexamethasone until resolution to grade 1, then restart at 1 dose level decreased
- For grade 3 or 4 agitation, anxiety, delirium, depression, hallucinations, mania, personality change, psychosis, or confusion, discontinue dexamethasone

8.4.4 Metabolism:

For grade 3 or 4 hyperglycemia, despite optimal supportive care, delay dexamethasone until grade 1, then restart at 1 dose level decreased

8.4.5 Musculoskeletal:

For grade 3 or 4 generalized muscle weakness, delay dexamethasone until grade 1, then restart at 1 dose level decreased

8.4.6 Other:

- For grade 3 non-hematologic toxicity not specified above, delay offending agent **(dexamethasone)** until recovery to grade 1, then restart at 1 dose level decreased.
- For grade 4 non-hematologic toxicity not specified above, discontinue **dexamethasone**

8.5 Dose Modifications for Obese Patients

Dose modifications for obese patients are not applicable to this study. Pomalidomide, ixazomib and dexamethasone dosing is not based on body weight or body surface area.

9.0 ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. However, CTCAE version 5.0 must be used for serious AE reporting through CTEP-AERS as of April 1, 2018. The CTCAE is available at [redacted] Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms, using the codes provided.

9.1 Routine adverse event reporting

Adverse event data collection and reporting, which are required as part of every clinical trial are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times according to the study calendar in Section 5.0. For this trial, please use the forms for routine AE reporting in Rave.

Solicited Adverse Events: The following adverse events are considered "expected" and their presence/absence should be solicited, and severity graded, at baseline and for each cycle of treatment.

CTCAE v4.0 Term	CTCAE v4.0 System Organ Class (SOC)
Neutrophil count decreased	Investigations
Platelet count decreased	Investigations
Lymphocyte count decreased	Investigations
Anemia	Blood and lymphatic system disorders
Rash maculo-papular	Skin and subcutaneous tissue disorders
Thromboembolic event	Vascular disorders
Hemorrhage/Bleeding events	Distributed throughout multiple SOCs
Peripheral sensory neuropathy	Nervous system disorders
Diarrhea	Gastrointestinal disorders
Nausea	Gastrointestinal disorders
Vomiting	Gastrointestinal disorders
Fatigue	General disorders and administration site conditions
Febrile neutropenia	Blood and lymphatic system disorders

9.2 Expedited Adverse event reporting (CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined below. Alliance investigators are required to notify, the Alliance Central Office, the Study Chair, and their Institutional Review Board if a patient has an adverse event requiring expedited reporting. All such events must be reported in an expedited manner using the NCI Adverse Event Expedited Reporting System (CTEP-AERS). The Alliance requires investigators to route all

expedited adverse event reports through the Alliance Central Protocol Operations Program Office for Alliance-coordinated studies. Be sure to read this entire protocol section, as requirements are described in both the table and the bullet points following the table. The additional instructions or exclusions are protocol specific, and in the case of a conflict, the additional instructions or exclusions supersede the table. The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for reporting beginning April 1, 2018. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site [redacted] All reactions determined to be "reportable" in an expedited manner must be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS), accessed via the CTEP website, [redacted]

9.2.1 Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a CTEP or non-CTEP IND within 30 Days of Treatment[1]

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

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

Death

A life-threatening adverse event

An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours

A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

A congenital anomaly/birth defect.

Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

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

Expedited AE reporting timelines are defined as:

"24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.

"10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:
All Grade 3, 4, and Grade 5 AEs
Expedited 10 calendar day reports for:
Grade 2 AEs resulting in hospitalization or prolongation of hospitalization
Effective Date: May 5, 2011

Additional Instructions or Exclusions to CTEP-AERS:

- All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB, according to local IRB policies.
- Alliance A061202 uses two drugs under an Alliance IND. These reporting requirements should be followed for all agents (any arm) in this trial.
- Grade 1-3 nausea or vomiting and hospitalization resulting from such do not require CTEP-AERS reporting, but should be reported via routine AE reporting.
- Grade 1-3 fatigue and hospitalization resulting from such do not require CTEP-AERS reporting, but should be reported via routine AE reporting.
- Grade 1-3 hyperglycemia with hospitalization resulting from such do not require CTEP-AERS reporting, but should be reported via routine AE reporting
- Grade 3 hyperglycemia does not require CTEP-AERS reporting, but should be reported via routine AE reporting
- Grade 1-3 insomnia, psychosis, depression with hospitalization resulting from such do not require CTEP-AERS reporting, but should be reported via routine AE reporting
- Grade 3 insomnia, psychosis, depression do not require CTEP-AERS reporting, but should be reported via routine AE reporting.
- Grade 1-3 fluid retention and edema, hypertension with hospitalization resulting from such do not require CTEP-AERS reporting, but should be reported via routine AE reporting
- Grade 3 fluid retention and edema, hypertension do not require CTEP-AERS reporting, but should be reported via routine AE reporting
- Grade 1-3 hematosuppression (leukopenia, neutropenia, lymphopenia, anemia, and thrombocytopenia) with hospitalization resulting from such do not require CTEP-AERS reporting, but should be reported via routine AE reporting
- Grade 3 hematosuppression (leukopenia, neutropenia, lymphopenia, anemia, and thrombocytopenia) does not require CTEP-AERS reporting, but should be reported via routine AE reporting
- Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (*e.g.,* radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.
- All new malignancies must be reported through CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e. solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome (MDS)/acute myelogenous leukemia (AML), and in situ tumors.

Secondary Malignancy:

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

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

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

Second Malignancy:

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

- Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history or prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.
- All pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) occurring in female patients during therapy or within 28 days after completion of treatment on A061202 must be reported via CTEP-AERS. In CTCAE version 5.0, use the event term, *"pregnancy, puerperium, and perinatal condition-other, pregnancy (grade 3)"*. Include the potential risk of exposure of the fetus to the agent(s) in the CTEP-AERS "Description of Events".
    - CTEP-AERS reports should be amended upon completion of the pregnancy to report pregnancy outcome (e.g. normal, spontaneous abortion, therapeutic abortion, fetal death, congenital abnormalities).
    - In CTCAE version 5.0, pregnancy loss is defined as "Death in utero," and any pregnancy loss should be reported expeditiously as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC. A pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC as currently CTEP-AERS recognizes this event as a patient death.
    - The CTEP-AERS report should be amended for any neonatal deaths or complications occurring within 28 days of birth independent of attribution. Infant deaths occurring after 28 days considered to be related to in utero exposure to the agents used in this trial should be reported via CTEP-AERS.
    - A neonatal death should be reported expeditiously as Grade 4, "Death neonatal" under the General disorders and administration SOC.
    - Congenital abnormalities should be reported as "congenital familial and genetic disorders-other, specify".

- If a female partner of a male patient becomes pregnant, the male patient should notify the investigator, and the pregnant female partner should be advised to call their healthcare provider. CTEP-AERS reporting is not required

- The reporting of adverse events described in the table above is in addition to and does not supplant the reporting of adverse events as part of the report of the results of the clinical trial, e.g. cooperative group data reporting.

9.3 Comprehensive Adverse Events and Potential Risks List (CAEPR) for Pomalidomide (CC-4047, NSC 767909)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' [redacted] for further clarification. *Frequency is provided based on 2133 patients.* Below is the CAEPR for Pomalidomide (CC-4047).

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

Version 2.4, May 22, 2022[1]

Adverse Events with Possible Relationship to Pomalidomide (CC-4047)[2] (CTCAE 5.0 Term) [n= 2133]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia[3]			***Anemia[3] (Gr 2)***
CARDIAC DISORDERS			
		Myocardial infarction[4]	
GASTROINTESTINAL DISORDERS			
	Constipation		***Constipation (Gr 2)***
	Diarrhea		***Diarrhea (Gr 2)***
		Nausea	***Nausea (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		***Edema limbs (Gr 2)***
	Fatigue		***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
		Sudden death NOS	
HEPATOBILIARY DISORDERS			
		Hepatic failure	
IMMUNE SYSTEM DISORDERS			
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
	Infection[5]		***Infection[5] (Gr 2)***
\INVESTIGATIONS			

Adverse Events with Possible Relationship to Pomalidomide (CC-4047)[2] (CTCAE 5.0 Term) [n= 2133]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Alanine aminotransferase increased		
	Blood bilirubin increased		
	Lymphocyte count decreased		
Neutrophil count decreased			***Neutrophil count decreased (Gr 2)***
	Platelet count decreased		***Platelet count decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
		Anorexia	***Anorexia (Gr 2)***
	Hyperkalemia		
	Hyponatremia		
		Tumor lysis syndrome	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Back pain		
		Bone pain	***Bone pain (Gr 2)***
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (second primary malignancies) [2]	
		Treatment related secondary malignancy[2]	
NERVOUS SYSTEM DISORDERS			
	Depressed level of consciousness		
		Dizziness	***Dizziness (Gr 2)***
		Dysesthesia	
		Paresthesia	
	Peripheral sensory neuropathy		
		Nervous system disorders - Other (progressive multifocal leukoencephalopathy)	
		Stroke[4]	
PSYCHIATRIC DISORDERS			
	Confusion		
		Hallucinations	
RENAL AND URINARY DISORDERS			
	Acute kidney injury		
	Urinary retention		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
		Cough	***Cough (Gr 2)***
		Dyspnea	***Dyspnea (Gr 2)***
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Rash maculo-papular	***Rash maculo-papular (Gr 2)***
		Skin and subcutaneous tissue disorders - Other (DRESS syndrome)	

Adverse Events with Possible Relationship to Pomalidomide (CC-4047)[2] (CTCAE 5.0 Term) [n= 2133]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Stevens-Johnson syndrome[2]	
		Toxic epidermal necrolysis	
VASCULAR DISORDERS			
		Thromboembolic event[4]	

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

[2]While not observed in human trials of pomalidomide, teratogenic effects (birth defects), thromboembolic events increases in secondary malignancy, tumor lysis syndrome, Stevens-Johnson syndrome, and thyroiditis/hypothyroidism are known events for this class of agents that include thalidomide and lenalidomide.

[3]Sickle cell crises in patients with SCD is a rare but serious event.

[4]Venous thromboembolic events (e.g., deep vein thrombosis and pulmonary embolism) and arterial thromboembolic events (e.g., myocardial infarction and stroke) have been observed to occur more frequently in multiple myeloma patients treated with pomalidomide and dexamethasone.

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

Adverse events reported on Pomalidomide (CC-4047) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Pomalidomide (CC-4047) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (sickle cell anemia with crisis)[3]; Febrile neutropenia
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Heart failure; Sinus tachycardia
EAR AND LABYRINTH DISORDERS - Vertigo
EYE DISORDERS - Blurred vision; Eye disorders - Other (eyelid swelling)
GASTROINTESTINAL DISORDERS - Abdominal pain; Colonic perforation; Dry mouth; Dyspepsia; Enterocolitis; Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Death NOS; Disease progression; Malaise
IMMUNE SYSTEM DISORDERS - Allergic reaction
INVESTIGATIONS - CD4 lymphocytes decreased; CPK increased; Creatinine increased; Weight gain; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia; Hyperuricemia; Hypocalcemia; Hypokalemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Chest wall pain; Generalized muscle weakness; Muscle cramp; Myalgia; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (multiple myeloma, myelofibrosis, progression of MM); Tumor pain
NERVOUS SYSTEM DISORDERS - Dysphasia; Headache; Intracranial hemorrhage; Ischemia cerebrovascular; Seizure; Syncope; Tremor
PSYCHIATRIC DISORDERS - Anxiety; Depression; Insomnia
RENAL AND URINARY DISORDERS - Hematuria
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Pelvic pain

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Epistaxis; Nasal congestion; Oropharyngeal pain; Postnasal drip; Productive cough; Pulmonary hypertension; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (sputum discolored)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Erythema multiforme; Hyperhidrosis; Pruritus
VASCULAR DISORDERS - Vascular disorders - Other (hyperviscosity syndrome)

Note: Pomalidomide (CC-4047) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

9.4 Comprehensive Adverse Events and Potential Risks List (CAEPR) for Ixazomib (MLN9708, NSC 767907)

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

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

Version 2.1, March 26, 2022[1]

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

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

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

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

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia
CARDIAC DISORDERS - Myocardial infarction
EYE DISORDERS - Blurred vision; Retinal detachment
GASTROINTESTINAL DISORDERS - Enterocolitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Disease progression; Flu like symptoms; Malaise
HEPATOBILIARY DISORDERS - Bile duct stenosis
INFECTIONS AND INFESTATIONS - Bronchial infection; Fungemia; Infections and infestations - Other (Parainfluenza Infection); Lung infection; Pharyngitis; Sepsis; Shingles; Sinusitis

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall; Injury, poisoning and procedural complications - Other (femoral neck fracture); Spinal fracture
INVESTIGATIONS - Aspartate aminotransferase increased; Lymphocyte count decreased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypokalemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Muscle weakness lower limb; Myalgia; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (non-Hodgkin's lymphoma); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (plasma cell myeloma); Tumor pain
NERVOUS SYSTEM DISORDERS - Dizziness; Dysgeusia
PSYCHIATRIC DISORDERS - Insomnia
RENAL AND URINARY DISORDERS - Acute kidney injury
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchial obstruction
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Erythema multiforme; Pruritus
VASCULAR DISORDERS - Hypotension

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

10.0 DRUG INFORMATION

10.1 General Considerations:

- Pomalidomide, ixazomib and dexamethasone will be administered at flat doses. Therefore, dosing will not be based on body weight or body surface area.
- Qualified personnel who are familiar with procedures that minimize undue exposure to themselves, others and the environment should undertake the handling and disposal of the agents used in this study.
- Institutions should follow their own policies for handling and disposal of the agents used in this study.

10.1.1 Dexamethasone (Decadron) (NSC # 34521)

Procurement

Dexamethasone is commercially available and therefore is to be purchased by a third party. This drug will not be supplied by the NCI.

Formulation

Dexamethasone is available in seven potencies (0.5 mg, 0.75 mg, 1mg, 1.5 mg, 2 mg, 4 mg, and 6 mg) in tablet form.

Storage and Stability

Store tablets at room temperature between 15ºC and 30ºC (59ºF and 86ºF).

Preparation

Refer to package insert for complete dispensing instructions.

Administration

In this study dexamethasone is administered orally.

Drug Interactions

Antacids may decrease the bioavailability of dexamethasone. Separate doses by two or more hours.

Pharmacokinetics

Metabolism: Hepatic; Subtrate of CYP3A4 (Major)

Half-life elimination: Normal renal function: 1.8-3.5 hours; Biological half-life: 36-54 hours

Time to peak, serum: Oral: 1-2 hours;

Excretion: Urine and feces

Adverse Events

Possible adverse events associated with the use of dexamethasone are:

Gastrointestinal: Nausea, vomiting, anorexia, increased appetite, weight gain; aggravation of peptic ulcers.

Dermatologic: Rash, skin atrophy, facial hair growth, acne, facial erythema, ecchymoses.

Genitourinary: Menstrual changes (amenorrhea, menstrual irregularities).

Neurologic: Insomnia, euphoria, headache, vertigo, psychosis, depression, seizures, muscle weakness.

Cardiovascular: Fluid retention and edema, hypertension; rarely, thrombophlebitis.

Ocular: Cataracts, increased intraocular pressure, exophthalmos.

Metabolic: Hyperglycemia, decreased glucose tolerance, aggravation or precipitation of diabetes mellitus, adrenal suppression (with Cushingoid features), hypokalemia.

Hematologic: Leukocytosis.

Other: Osteoporosis (and resulting back pain), appearance of serious infections including herpes zoster, varicella zoster, fungal infections, Pneumocystis carinii, tuberculosis; muscle wasting; delayed wound healing; suppression of reactions to skin tests.

Nursing Guidelines

Monitor regularly for hypertension, CHF and other evidence of fluid retention.

Advise patient of possible mood or behavioral changes, i.e., depression, euphoria, insomnia, even psychosis. Instruct patient to report any suspected changes to healthcare team.

Assess for symptoms of gastric ulcer, heartburn, or gastritis. Instruct patient to report symptoms to healthcare team if unable to control.

Evaluate signs of infection, particularly local candidal infections and treat appropriately.

Monitor blood glucose frequently.

Instruct patient to report frequent, unrelenting headaches or visual changes to healthcare team.

Advise patient that easy bruising is a side effect.

When administered orally, give with food or milk.

Observe for signs of hyperglycemia.

Observe for subtle signs of infection (fever, pain).

10.1.2 Pomalidomide (Pomalyst, CC-4047) (NSC# 767909, Alliance IND# 120020)

Procurement

Pomalidomide will be provided by Celgene and distributed by McKesson Specialty Pharmacy in accordance with Celgene Corporation's Pomalyst REMS™ requirements, all physicians who prescribe pomalidomide for study patients in this trial, and all patients enrolled in this trial, must be registered and must comply with all requirements of the Pomalyst REMS™ program. The order form is found on the study website. McKesson Specialty Pharmacy will ship patient-specific supplies to the institution. Only enough pomalidomide for one cycle of therapy will be supplied for each patient for each cycle.

Storage and Stability

Store drug at controlled room temperature, between 68-77 ºF (20-25ºC) or as indicated on the manufacturer's label. The expiration date is indicated on the label.

Only enough study drug for one cycle of therapy may be dispensed with each cycle of therapy.

Preparation

Pomalidomide (CC-4047) capsules can be 0.5-mg gelatin capsules (size 4 reddish brown), 1-mg gelatin capsules (size 4 reddish brown), 2-mg (size 2 reddish-brown), 3-mg and 4-mg gelatin capsules (size 2 reddish-brown), and 5-mg gelatin capsules (size 1 reddish-brown), containing CC-4047, mannitol, pregelatinized starch, and sodium stearyl fumarate.

Pomalidomide (CC-4047) capsules are supplied in high density polyethylene (HDPE) containers fitted with induction seals and child-resistant plastic closures or PVC/PCTFE blister with push-through foil.

Administration

Pomalidomide is administered by mouth at approximately the same time each day. Capsules should be swallowed whole, and should not be broken, chewed or opened. If a dose of pomalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up. Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to the study doctor at the end of treatment. Patients who take more than the prescribed dose of pomalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

Drug Interactions

Based on in vitro metabolism data, pomalidomide did not inhibit or induce CYPP450 isoenzymes or inhibit several studied transporters (P-glycoprotein, BCRP, OAT1, OAT3, OATP1B1, OATP1B3 and OCT2). Therefore, pomalidomide is not likely to precipitate drug-drug interactions due to inhibition or induction when co-administered with cytochrome P-450 substrates or with substrates of these transporters.

Since pomalidomide is eliminated in humans via multiple pathways, it is not anticipated that co-administration of an inhibitor or inducer of cytochrome P450 isoenzymes will have a significant impact on pomalidomide pharmacokinetics. The potential for clinically relevant drug-drug interactions when pomalidomide is co-administered with inhibitors of P-glycoprotein has not been evaluated.

Pharmacokinetics

a) Absorption – oral absorption has been moderately rapid with first dose Cmax occurring in 1.5 to 4 hrs. More than 70% of the pomalidomide dose is absorbed in humans. A high fat meal decreased the rate of absorption but had minimal effect on overall extent of absorption.

b) Distribution – Apparent volume of distribution in healthy subjects ranged from 74-138 L across a dose range of 1 to 10 mg daily. Pomalidomide protein binding in human plasma is low to moderate (15.8% for R-enantiomer, 42.2% for S-enantiomer) and the binding is concentration independent in the concentration range of 30 and 1000 ng/mL. Drug distributes into semen.

c) Metabolism – Eight metabolites were detected in plasma, each at exposures < 10% of the plasma pomalidomide. CYP-dependent metabolites accounted for approximately 43% of the excreted radioactivity, while non-CYP dependent hydrolytic metabolites accounted for 25%, and excretion of unchanged pomalidomide accounted for 10%.

d) Excretion – In healthy patients, 72.8% of the dose was recovered in urine and 15.5% was recovered in feces. Less than 3% of the dose is excreted as unchanged pomalidomide in the urine. The geometric mean terminal elimination half-life (t1/2) of pomalidomide was approximately 7.5 hours.

Adverse Events

Common known potential toxicities, > 10% [L SEP]

Blood and lymphatic system disorders: Anemia, leukopenia, neutropenia, thrombocytopenia, lymphopenia

Gastrointestinal disorders: Constipation, diarrhea, nausea, vomiting[L SEP]General disorders: Asthenia, chills, fatigue, pyrexia, pain, peripheral edema

Infections and infestations: Bronchitis, pneumonia, upper respiratory tract infection, urinary tract infection, nasopharyngitis

Metabolism and nutrition disorders: Decreased appetite, hyperglycemia, hyponatremia, hypercalcaemia, hypocalcaemia, hypokalemia

Musculoskeletal and connective tissue disorders: Musculoskeletal chest pain, back pain, muscle spasm, arthralgia, musculoskeletal pain, pain in extremity, muscular weakness, bone pain

Nervous system disorders: Dizziness, tremor

Psychiatric disorders: Insomnia, confusional state

Renal and urinary tract disorders: Renal failure

Respiratory, thoracic and mediastinal disorders: Dyspnea, cough, dyspnea exertional, epistaxis

Skin and subcutaneous tissue disorders: Rash, hyperhidrosis, night sweats, dry skin

Less common known potential toxicities, 1% - 10%:

Blood and lymphatic system disorders: Febrile neutropenia

Cardiac disorders: Atrial fibrillation, cardiac failure congestive, tachycardia

Eye disorders: Blurred vision

Gastrointestinal disorders: Abdominal pain, dry mouth, upper abdominal pain

General disorders: Chest pain

Infections and infestations: Candidiasis, oral candidiasis, sinusitis, bronchopneumonia

Metabolism and nutrition disorders: Hyperkalemia, dehydration, hypophosphatemia, hypoalbuminemia, hypomagnesemia

Nervous system disorders: Headache, dysgeusia, peripheral neuropathy, somnolence, syncope, lethargy

Psychiatric disorders: Anxiety, altered mood, depression

Renal and urinary tract disorders: Acute renal failure

Respiratory, thoracic and mediastinal disorders: Pulmonary embolism, oropharyngeal pain, productive cough, dysphonia, nasal congestion

Skin and subcutaneous tissue disorders: Pruritus

Vascular disorders: Deep vein thrombosis, hypotension, hypertension

Rare known potential toxicities, <1% (Limited to important or life-threatening): Secondary cancer, interstitial lung disease, respiratory distress, hyperbilirubinemia.

Pomalidomide (CC-4047) was found to be teratogenic in a developmental study in rabbits. Pomalidomide therefore is considered as having the potential to cause teratogenic effects in humans. Celgene therefore mandates the fetal exposure risk management described below. Patients will be counseled in accordance with the Celgene Pregnancy Prevention Counseling Program (CPPCP) by a trained counselor. A minimum of two counselors must be identified at each site for this purpose.

- All subjects (male and females with or without childbearing potential) must agree to abstain from donating tissue (including blood or blood products and semen or sperm) while taking study drug and for 28 days after the last dose of study drug.
- Pomalidomide (CC-4047) must not be administered to pregnant or lactating females.
- Females of Child-Bearing Potential (FCBP) must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting study drug. The first pregnancy test must be performed within 10-14 days prior to the start of study drug and the second

pregnancy test must be performed within 24 hours prior to the start of study drug. The patient may not receive study drug until the study doctor has verified that the results of these pregnancy tests are negative.

- Sexually active FCBP must agree to use protocol-specified contraceptive methods at least 28 days before, during participation in the clinical studies and for at least 28 days after discontinuation from the study.
- Sexually active males (including those who have had a vasectomy) must agree to use protocol-specified contraceptive methods during participation in the clinical studies and for at least 28 days after discontinuation from the study (additional precaution due to lack of data on effect on male sexual organs and sperm).
- Pomalidomide (CC-4047) should not be handled by non-patient FCBP or non-patient partners of PCBP unless gloves are worn.

Caution should be exercised when enrolling subjects known to be at risk of developing torsade de pointes. To date, clinical data reveal variable QTc values and modest, infrequent and inconsistent changes that do not reveal any clear trend or pattern of QTc prolongation, and do not appear to have significantly translated into symptomatic or clinically meaningful events.

Neutropenia was the most frequently reported grade 3/4 AE in subjects with relapsed/refractory MM. The majority of these occurred without associated infection and neutropenia was the dose limiting toxicity.

Routine hematologic monitoring and dose modification as specified in the protocol are recommended to manage hematologic toxicities, especially neutropenia.

Subjects receiving pomalidomide (CC-4047) have developed venous thromboembolic events (DVTs and PEs) reported as SAEs. Anticoagulant prophylaxis is recommended as a precaution per protocol.

Nursing Guidelines

Agent is known to be teratogenic in rabbits. Therefore all women who are pregnant or who could become pregnant should not handle the agent outside of the original packaging. Chemotherapy gloves should be worn if contact is necessary.

Because of the similarity of this agent to thalidomide certain precautions MUST be employed by all subjects on protocol and for 4 weeks after discontinuation of agent. Instruct patients the following must be adhered to: No donation of tissue/blood/semen/sperm; sexually active males/ females must use protocol-specific contraception (regardless of fertility status-i.e. history of vasectomy).

Cytopenias are common (neutropenia most common). Monitor CBC closely and instruct patient to report any signs/symptoms of infection or unusual bruising or bleeding to the study team.

Thrombotic events have been reported. Anticoagulation prophylaxis may be recommended. Instruct patients to report any problems with bleeding, extremity pain or swelling, or shortness of breath to the study team immediately.

Patients may experience cough, URI, pneumonia, or sinusitis. Instruct patients to report respiratory symptoms to the study team.

Gastrointestinal side effects consisting of diarrhea, constipation, stomatitis, nausea, decreased appetite, and abdominal pain have been seen. Treat symptomatically and monitor for effectiveness.

10.1.3 Ixazomib (MLN9708) (Supplied) (NSC# 767907 Alliance IND# 120020)

Procurement

Ixazomib will be provided by Millennium Pharmaceuticals: A Takeda Oncology Company and distributed by McKesson Specialty Pharmacy. The order form is found on the study website. At the end of the study, any unused supplies should be destroyed on site according to institutional procedures.

Product complaints are verbal, written or electronic expression of dissatisfaction with the identity, strength, purity, quality or stability of a drug. **Product complaints are not the same as adverse events**. Any such product complaints about ixazomib should be reported to the Alliance Central Protocol Operations Program Office.

Storage and Stability

Ixazomib capsules, individually packaged in foil-foil blisters of three capsules with child resistant paper backing, should be stored unopened. Do not store above 30°C (86°F). Do not freeze.

Ixazomib that is dispensed to the patient for take-home dosing should remain in the blister packaging until the point of use. Only a one-month supply (3 capsule; 1 blister card) may be dispensed at a time. Patients should be instructed to store the blister card in the refrigerator. Patients will be instructed to store the blister card in the refrigerator.

Preparation

The ixazomib capsule drug product formulation consists of drug substance, microcrystalline cellulose, talc, and magnesium stearate. Three different capsule strengths are manufactured: 2.3, 3.0, and 4.0 mg; each capsule strength has a unique color. Dosage strength is stated as the active boronic acid. Ixazomib capsules are individually packaged in blisters with a paper backing for child resistance.

Ixazomib drug product is a cytotoxic anticancer drug. As with other potentially toxic compounds, caution should be exercised when handling ixazomib.

Administration

Ixazomib capsules must be administered by mouth as intact capsules and are not intended to be opened or manipulated in any way. **Capsules should be taken on an empty stomach (no food for 2 hours before and 1 hour after)** with approximately 8 oz (1 cup) of water. Missed doses can be taken as soon as the patient remembers if the next schedule dose is 72 hours or more away. In case of vomiting, the dose should not be repeated

Pharmacokinetics and Drug Interactions

Data is available from two weekly dosing studies, one in multiple myeloma (C16004, escalating BSA dosing) and one in amyloidosis patients (C16007, dose levels 4 and 5.5 mg). PK data in these two patient populations appear to be similar.

Oral Ixazomib is absorbed rapidly with a Tmax of approximately 0.5 to 2 hours, absolute bioavailability is reported to be 67%. The terminal half-life following multiple dosing is 5-7 days. Results of a population PK analysis (N = 137) show that there is no relationship between body surface area or body weight and clearance. Based on these data, a recommendation was made for fixed dosing clinical trials. Ixzaomib is eliminated primarily by hepatic metabolism, with <3% of a dose excreted in the urine. In vitro studies demonstrate metabolism by CYP3A4 (34.2%), 1A2 (30.7%), 2D6 (14.7%), 2C9 (12.1%), 2C19 (4%). Based on these in vitro studies, the potential exists for increased exposure when Ixazomib is administrated concomitantly with strong inhibitors of CYP3A4 or 1A2. Ixazomib is not an inhibitor of CYP isoenzymes.

Ixazomib AUC in combination with lenalidomide and dexamethasone appear similar to single-agent ixazomib. This suggests that there is no readily apparent effect of co-administration of lenalidomide and dexamethasone on the clinical PK of ixazomib.

Adverse Events

See the current version of the Investigator's Brochure for more complete information including potential risks, as well as recommendations for clinical monitoring and medical management of toxicity.

Adverse events reported with single agent oral ixazomib to date include (all severity grades):

Blood and lymphatic system disorders- Anemia (21%)

Investigations: thrombocytopenia (41%), neutropenia (16%), leukopenia (10%)

Gastrointestinal disorders – diarrhea (38%), nausea (47%), vomiting (35%), abdominal pain (14%), constipation (14%)

General disorders and administration site conditions – fatigue (49%), fever (21%), peripheral edema (10%)

Skin and subcutaneous tissue disorders – rash, maculo-papular (12%)

Respiratory, thoracic and mediastinal disorders- cough (15%), dyspnea (14%)

Nervous system disorders- headache (14%), dizziness (12%)

Metabolism and nutrition disorders- anorexia (27%), dehydration (14%)

Musculoskeletal and connective tissue disorders- arthralgia (14%), back pain (12%)

Infections and infestations- upper respiratory infection (14%)

Nursing Guidelines

Capsules must be administered intact and should not be opened or manipulated in any way. Additionally, capsules should remain in the blister packs until they are ready to be taken.

Capsules should be taken on an empty stomach with 8 oz of water.

Thrombocytopenia has been observed with this agent. Monitor platelet count and instruct patients to report any unusual bruising or bleeding to the study team.

GI side effects have been seen (nausea, diarrhea, vomiting), treat symptomatically and monitor for effectiveness of intervention.

Rash has been seen. Instruct patients to report any rash to study team.

Assess patient's concomitant medications, including over the counter and supplements. Ixazomib is metabolized through both CYP and non-CYP enzymes, and drug to drug interactions exist. Instruct patients not to start any new medications or supplements without checking with the study team first.

11.0 MEASUREMENT OF EFFECT

Response and progression will be evaluated in this study using the International Myeloma Working Group uniform response criteria. The International Myeloma Working Group has also endorsed the inclusion of minimal response (MR) for relapsed/refractory myeloma as adapted from the European Group for Blood and Marrow Transplantation (EBMT). Therefore, MRs will be evaluated as part of this study, as well [61, 62].

11.1 Schedule of Evaluations

For the purposes of this study, patients should be reevaluated for biochemical response on day 1 of each treatment cycle, the end of treatment visit (if appropriate) and every 4 weeks thereafter

until disease progression, death, the start of a new treatment or withdrawal of consent. The start of a new treatment cycle does NOT need to be delayed awaiting the results of the disease assessment.

A response (≥MR) or progression of disease should be followed up with a confirmatory evaluation as soon as possible but no later than 28 days after the initial documentation of response or progression. For time-to-event analyses, the date of the first documented progression or response should be used. Determination of a complete response (CR) or stringent complete response (sCR) requires a confirmatory bone marrow examination. A second bone marrow examination is not needed for additional confirmation of CR or sCR.

For patients with non-secretory disease who are being followed for response by serial bone marrow examinations (must have ≥30% involvement of the marrow space prior to treatment), a repeat bone marrow aspirate and biopsy should be performed once every 2 cycles (prior to registration, cycle 3, day 1, cycle 5, day 1, etc), at the end of treatment (if not performed within the previous 8 weeks) and every 12 weeks thereafter until disease progression, death or withdrawal of consent. In these cases, the same method to assess marrow burden of disease should be used throughout treatment. A repeat bone marrow is not required for confirmation of response under these circumstances.

For patients with measurable extramedullary plasmacytomas, patients should be reevaluated once every 2 cycles (8 weeks) while on protocol treatment, the end of treatment visit (if not performed within the previous 8 weeks) and once every 12 weeks thereafter until disease progression, death, withdrawal of consent or the start of new treatment, utilizing the same imaging modality used at initial screening (CT, MRI or PET/CT). A repeat scan is not required for confirmation of radiographic response or progression.

11.2 Definitions of Measurable and Non-Measurable Disease

11.2.1 Measureable Disease

Disease assessments by serial monitoring of the monoclonal protein are to be performed if the patient meets at least 1 of the following criteria:

1. Serum M protein ≥0.5 g/dL and/or
2. Urine M protein ≥200 mg/24 hours and/or
3. Involved serum free light chain≥10 mg/dL AND an abnormal serum free light chain ratio

11.2.2 Non-Measureable Disease

Patients who do not meet criteria outlined in section 11.2.1 will be considered to have non-measureable (non-secretory) disease. However, if a patient does not have measurable disease by one of the 3 above criteria, they can still be followed with serial bone marrow examinations for response, provided the marrow burden of myeloma is at least 30% at registration or at re-registration for Arm 1 patients who go on to Course 2 treatment.

11.3 Guidelines for Evaluation of Measurable Disease

11.3.1 Measurement Methods:

- Determination of biochemical response requires a serum protein electrophoresis and immunofixation, 24-hour urine protein electrophoresis and immunofixation and serum free light chain test at each scheduled evaluation of response for all patients. All measurements must be performed in all patients at the times indicated in Section 5.0. Quantitative serum immunoglobulins and 24-hour urine light chain quantitation via

nephelometry should not be used as a substitute for determining response. Additionally, measurement of an entire region of the serum protein electrophoresis cannot be used as a substitute for measurement of the M protein. For example, an IgA kappa M protein that falls within the beta region of the serum protein electrophoresis should not be monitored solely by assessment of the quantitative IgA level or measurement of the protein concentration in the entire beta region of the serum protein electrophoresis.

- Any serologic and/or urine testing that indicates a response (≥MR) or disease progression (PD) should be confirmed as soon as possible after the initial assessment of response/progression but no later than 28 days.
- For patients with measurable extramedullary plasmacytomas, the same method of assessment and the same technique must be used to characterize each identified and reported lesion at registration and during treatment.
- For patients with non-secretory disease who are being followed for response by serial bone marrow examinations, the same method to assess marrow burden of disease should be used throughout treatment. A repeat bone marrow is not required for confirmation of response under these circumstances.

11.3.2 Acceptable Modalities for Measurable Extramedullary Disease:

- **Conventional CT and MRI:** This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

  As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.
- **PET-CT:** If the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.
- **Physical Examination:** For superficial non-nodal lesions, physical examination is acceptable, but imaging is preferable, if both can be done. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

11.4 THE IMWG Uniform Response Criteria

International Myeloma Working Group (IMWG) Uniform Response Criteria + Definition of Minimal Response (MR) as Adopted from the EBMT Criteria

The IMWG uniform response criteria will be used for determining response to therapy and progression of disease. Minimal response, as adapted from the EBMT, will also be assessed [61, 62]. Source documentation for all biochemical and radiographic evaluations of disease will be collected for confirmation of response and disease progression.

Table 11.4- THE IMWG Uniform Response Criteria

Response Category	Response Criteria	Response Criteria for Disease Measurable by Serum FLC Testing Only
Complete Response (CR)	Negative serum immunofixation and 24-hour urine immunofixation, disappearance of all extramedullary plasmacytomas (if present at baseline) and <5% plasma cells on repeat bone marrow examination.	All other criteria for CR met + normal serum free light chain ratio.
Stringent Complete Response (sCR)	All criteria for CR must be met + normal serum free light chain ratio + absence of clonal plasma cells on bone marrow examination by immunohistochemistry or 2- to 4-color flow cytometry.	All other criteria for sCR met + normal serum free light chain ratio.
Very Good Partial Response (VGPR)	Serum and urine M-protein detectable on immunofixation testing but not on electrophoresis OR ≥90% reduction in serum M-protein plus urine M-protein <100 mg/24 hours.	≥90% reduction in the difference between the involved and uninvolved serum free light chain level.
Partial Response (PR)	≥50% decrease in the serum M-protein + ≥90% reduction in the urine M-protein OR to <200 mg/24 hours + ≥50% reduction in the size of extramedullary plasmacytomas (if present at baseline).*	≥50% reduction in the difference between the involved and uninvolved serum free light chain level.
Minimal Response (MR)	25% - 49% decrease in the serum M-protein + 50 – 89% reduction in the urine M-protein + 25% – 49% reduction in the size of extramedullary plasmacytomas (if present at baseline) + no increase in size or number of lytic bone lesions (development of compression fracture does not exclude response).*	
Stable Disease (SD)	Not meeting criteria for CR, sCR, VGPR, PR, MR or progressive disease (PD)	
Progressive Disease (PD)	Increase of ≥25% from lowest response value (nadir)** in any of the following: 1) Serum M-protein (absolute increase must be ≥0.5 g/dL) AND/OR: 2) Urine M-protein (absolute increase must be ≥200 mg/24 hours) AND/OR: 3) For patients without a measurable serum or urine M-protein but measurable disease by serum free light chain testing: Difference between the involved and uninvolved serum free light chain level (absolute increase must be ≥10 mg/dL) AND/OR: 4) For patients without a measurable serum or urine M-component or serum free light chain level: % marrow involvement with myeloma (absolute increase must be ≥10%). Definite development of new bone lesions or extramedullary plasmacytomas or definite increase in the size of existing bone lesions or extramedullary plasmacytomas. Hypercalcemia (corrected serum calcium > 11.5 mg/dL) attributable to myeloma (e.g not due to omitted doses of biophosphonate).	

* For patients who do not have measurable disease by M-protein measurement or serum free light chain levels but ≥30% involvement of the marrow at baseline, a ≥50% reduction of bone marrow involvement is required to meet criteria for a PR.

** The lowest response value (nadir) does not have to be a value that has been confirmed by repeat measurement.

12.0 END OF TREATMENT/INTERVENTION

12.1 Duration of Treatment

12.1.1 Phase I cohort and patients randomized to Arm 2 in Phase II:

- Patients who have not progressed and have not experienced unacceptable toxicity will continue on therapy at their current dose level until disease progression, unacceptable toxicity, withdrawal of consent, start of non-protocol anti-cancer treatment, or death.
- Those patients who have not progressed and who have experienced an unacceptable adverse event may be eligible for re-treatment at a lower dose. (See section 8.0.)

12.1.2 Patients randomized to Arm 1 in Phase II

- Patients who have not progressed and have not experienced unacceptable toxicity will continue on Course 1 therapy at their current dose level until disease progression, unacceptable toxicity, withdrawal of consent, start of non-protocol anti-cancer treatment, or death.
- Those patients who have not progressed and who have experienced an unacceptable adverse event may be eligible for re-treatment at a lower dose of Course 1 treatment (see section 8.0).
- Patients who discontinue Course 1 treatment *due to disease progression* may choose to receive Course 2 treatment. These patients must be re-registered to the study and will be followed per the study calendar in section 5.2. Patients may remain on Course 2 treatment until disease progression, initiation of non-protocol treatment, refusal, unacceptable toxicity, or death.

12.2 Discontinuation of Protocol Therapy

12.2.1 Criteria for discontinuation of protocol therapy include:

- Request by the patient to withdraw from protocol treatment
- Disease progression
- Unacceptable toxicity
- Inter-current illness
- Administration of alternative treatment
- Pregnancy

12.2.2 Follow-up after treatment discontinuation

Phase I cohort and patients randomized to Arm 2 in Phase II:

- Patients who discontinue treatment for reasons other than progression or start of non-protocol treatment will enter the clinical follow-up period, where they will be followed per the study calendar in section 5.1 for a maximum of 3 years from registration.
- Patients who begin non-protocol treatment or who experience disease progression during treatment or clinical follow-up will enter the extended follow-up phase, where they will be followed for survival and late adverse events every 3 months for a maximum of 3 years from registration.

Patients randomized to Arm 1 in Phase II:

- Patients who discontinue Course 1 treatment for reasons other than disease progression or start of non-protocol treatment will enter the clinical follow-up period, where they will

be followed per the study calendar in section 5.1 for a maximum of 3 years from registration.

- Patients who discontinue Course 1 treatment due to disease progression and choose not to receive Course 2 treatment will enter the extended follow-up phase, where they will be followed for survival and late adverse events every 3 months for a maximum of 3 years from registration.
- Patients who discontinue Course 2 treatment for reasons other than disease progression or start of non-protocol treatment will enter the clinical follow-up period, where they will be followed per the study calendar in section 5.2 for a maximum of 3 years from re-registration.
- Patients who discontinue Course 2 treatment due to disease progression will enter the extended follow-up phase, where they will be followed for survival and late adverse events every 3 months for a maximum of 3 years from re-registration.
- Patients in clinical follow-up who have disease progression or begin non-protocol treatment will enter the extended follow-up phase, where they will be followed for survival and late adverse events every 3 months for a maximum of 3 years from registration or re-registration.

12.3 Follow-up for patients found to be ineligible on case review or cancel participation prior to receiving any protocol treatment

12.3.1 Patients who cancel participation prior to receiving any protocol treatment

Study participants who are registered to the trial but who never receive study intervention (regardless of eligibility) will go off study. On study forms, baseline measurement forms, baseline laboratory forms, baseline patient status forms, and baseline supporting forms are to be submitted. No research specimens are to be submitted. Any further treatment is at the discretion of the patient's medical team.

12.3.2 Patients found to be ineligible prior to the start of any protocol treatment

A study participant who is registered to the trial but does not meet all of the eligibility criteria will be deemed ineligible upon case review. Patients found to be ineligible prior to the start of any protocol treatment will go off study. On study forms, baseline measurement forms, baseline laboratory forms, baseline patient status forms, and baseline supporting forms are to be submitted. No research specimens are to be submitted. Any further treatment is at the discretion of the patient's medical team.

12.3.3 Patients found to be ineligible after starting any protocol treatment

- Patients who are deemed ineligible after registering may continue protocol treatment, provided the treating physician, study chair, and executive officer agree there are no safety concerns if the patient continues protocol treatment. All scans, tests, and data submission are to continue as if the patient were eligible. Notification of the local IRB may be necessary per local IRB policies.
- Patients who are deemed ineligible after registering and do not continue protocol treatment should complete all case report forms required prior to treatment discontinuation as well as the end of treatment form. No further follow-up is required.

13.0 STATISTICAL CONSIDERATIONS

This study began with a phase I tolerability/toxicity assessment followed by a phase II component in adult patients with lenalidomide and proteasome inhibitor refractory multiple myeloma.

The phase II portion opened on 7/15/2016 and then temporarily closed to enrollment on June 1, 2017 having enrolled 12 patients (6 patients per arm) due to the regulatory approvals of daratumumab alone or in combination with pomalidomide and dexamethasone for the treatment of relapsed multiple myeloma patients with double (lenalidomide and proteasome inhibitor) refractory disease. The phase II portion of the trial was redesigned to assess the impact on PFS of the addition of ixazomib to the combination of pomalidomide and dexamethasone in patients with lenalidomide-refractory multiple myeloma who received 1 prior line of therapy.

The treatment course, adverse events, and clinical outcomes (response, duration of response, progression-free survival times, and overall survival times) of the patients with double (lenalidomide and proteasome inhibitor) refractory disease who met eligibility criteria and began treatment will be summarized descriptively. No formal comparisons of the two treatment arms will be undertaken.

13.1 Phase I Study Design

The phase I portion of this trial is designed to assess tolerability and toxicity profiles for the combination therapy of Pomalidomide, Dexamethasone and Ixazomib. As such, it will follow a standard "3 +3" dose escalation design: Starting with the first cohort, 3 to 6 patients will be treated at this and each subsequent dose level.

All eligible patients who have begun treatment will be included in the determination of the maximum tolerated dose. Descriptive statistics will be used to summarize the frequency and severity of adverse events and the incidence of dose reductions and delays.

13.1.1 MTD Definition and Determination

The maximum tolerated dose (MTD) is defined as the highest dose level where at most 1 patient (of the 6 treated) develops a DLT, and 2 or more of the 3 to 6 patients developed a DLT at the next higher dose level unless the MTD is identified as dose level 4.

MTD Determination:

- The first cohort of three patients will be treated at the starting dose level 1.
- Three patients will be treated at a given dose level combination and observed for at least 28 days (1 cycle) from start of treatment to assess toxicity.
- If DLT is not seen in any of the 3 patients, 3 new patients will be accrued and treated at the next higher dose level. If DLT is seen in 2 or 3 of 3 patients treated at a given dose level, then the next 3 patients will be treated at the next lower dose level, if only 3 patients were enrolled and treated at this lower dose level.
- If DLT is seen in 1 of 3 patients treated at a given dose level, up to 3 additional patients will be enrolled and treated at the same dose level. If DLT is seen in at least one of these additional three patients (≥2 of 6), the MTD will have been exceeded, and further accrual will cease to this cohort. If dose-limiting toxicity (DLT) is not seen in any of the three additional patients, 3 new patients will be accrued and treated at the next higher dose level.
- After enrolling 6 patients on a specific dose level, if DLT is observed in at least 2 of 6 patients, then the MTD will have been exceeded and defined as the previous dose unless only 3 patients were treated at the lower dose level. In that case, 3 additional patients will be treated at this lower dose level such that a total of 6 patients are treated at the MTD to more fully assess the toxicities associated with the MTD.

13.1.2 Definition of DLT

For this protocol, dose-limiting toxicity (DLT) will be defined by the following adverse events at least possibly related to study therapy:

Grade 3 or higher non-hematologic toxicity, with the following exceptions:

- Alopecia is not expected but would not be considered a DLT
- Nausea, vomiting and diarrhea will only be considered a DLT if it cannot be adequately managed with optimal supportive care
- Grade 3 or 4 hyperglycemia due to dexamethasone will only be considered a DLT if it cannot be controlled with appropriate therapy

Grade 4 hematologic toxicity, with the following exceptions:

- Grade 4 lymphopenia is expected with this regimen and will not be construed as a DLT
- Grade 4 neutropenia will only be considered a DLT if it lasts longer than 7 days despite appropriate supportive care
- Grade 4 thrombocytopenia will only be considered a DLT if it lasts longer than 7 days or is associated with a ≥grade 3 bleeding event

13.2 Phase I Sample Size and Study Duration

The phase I component of this study will open at a limited number of sites using a slot reservation system, thus we anticipate an accrual rate of 2 eligible patients per month. Based on this low accrual rate, the minimum sample size is 4 patients (2 experiencing DLTs at dose level 1 prior to a third accrual and 2 at dose level 0), for a minimum duration of < 4 months (1 month accrual + < 1 month follow up per cohort). The maximum phase I sample size is 24 patients, 6 patients per dose level evaluation 1, 2, 3, and 4, which would take 20 months to complete (2.5 months [1.5 accrual + 1 follow up] per each 3 patient cohort).

13.3 Phase II Study Design for patients on first line therapy with disease progression on lenalidomide

A randomized phase II clinical trial will be conducted to assess the impact on PFS of the addition of ixazomib to the combination of pomalidomide and dexamethasone in patients with multiple myeloma relapsing on lenalidomide as part of first line therapy.

The primary endpoint is progression-free survival (PFS), defined as the time from randomization to the date the International Myeloma Working Group (IMWG) criteria for disease progression is met [60, 61]. If a patient initiates another anti-cancer treatment prior to disease progression, they will be censored at the date of initiation of this treatment.

Patients will be randomized to treatment using the Pocock-Simon algorithm balancing the distribution of the following stratification factors between the two treatment arms:

1) ISS 1-2 disease vs. ISS 3 disease (current ISS stage based off screening beta 2 microglobulin and albumin)
2) High risk cytogenetics features: yes vs. no

   High risk cytogenetics features include: del(1p), gain of 1q, t(4;14), t(14;16), t(14; 20), del(17p)
3) Prior treatment with a proteasome inhibitor: yes vs. no

Analysis Cohort: All patients meeting the eligibility criteria who have signed a consent form, have been randomized, and have begun treatment will be evaluable for assessment of all clinical endpoints. Patients will be included in the treatment group they were randomized to, regardless

of their actual treatment or duration of treatment. Summary statistics for patient and tumor characteristics, eligibility rates, length of follow-up, and treatment acceptance rates will be determined by assigned treatment arm.

13.4 Phase II Sample Size and Study Duration

13.4.1 Determination of Sample Size

- It is anticipated the median time to progression with the combination of pomalidomide and dexamethasone is 6 months in patients refractory to lenalidomide based therapy but proteasome inhibitor naïve or sensitive to a proteasome inhibitor. We would consider the addition of ixazomib to pomalidomide and dexamethasone significant if the median PFS time was increased to at least 12 months in this patient population.
- It is anticipated that the accrual rate will be 5 patients per month based on accrual history of a randomized phase 2 clinical trial in refractory multiple myeloma comparing pomalidomide to pomalidomide plus dexamethasone.
- It is assumed that the PFS times for each treatment regimen follow an exponential distribution and the hazard of disease progression with pomalidomide and dexamethasone is proportional (and constant across time) to the hazard of disease progression with pomalidomide and dexamethasone plus ixazomib.

With a sample size of 70 patients (35 patients per Arm) enrolled over a 15 month period and followed for a minimum of 15 months after the close of enrollment and 57 disease progressions observed during this 30 month period, a one sided alpha=0.10 log rank test will have a 90% chance of detecting an increase in median PFS time from 6 months to 12 months with the addition of Ixazomib to pomalidomide and dexamethasone. That is, under these conditions, there will be adequate power to detect a hazard ratio of 2.0 or greater.

An additional 3 patients may be enrolled to replace patients who have signed a consent form but withdraw consent before any protocol treatment is administered or is found to be ineligible before any protocol treatment is administered.

13.4.2 Accrual Time and Study Duration

We anticipate the accrual period will be 15 months and the follow-up after the close of enrollment will be 15 months. With an additional 6 months for data preparation and analysis, it is anticipated that the primary efficacy findings of the phase II portion of this trial will be available to the study team approximately 36 months after activation.

13.5 Phase II Analysis Plans

13.5.1 Arm 1 Course 1 and Arm 2

- **Progression-free survival (PFS):** defined as the time from randomization to the date the International Myeloma Working Group (IMWG) criteria for disease progression is met [60, 61]. If a patient initiates another anti-cancer treatment prior to disease progression, they will be censored at the date of initiation of this treatment.

  The distribution of PFS for each treatment arm will be estimated using the Kaplan-Meier method. Cox modeling will be used to obtain a point and interval estimate of the hazard of disease progression among those randomized to the 3 drug regimen relative to disease progression among those randomized to the 2 drug regimen adjusted for patient and disease characteristics.
- **Overall Response Rate (ORR), Complete Response (CR), and Clinical Benefit Rate (CBR):** The proportion of patients meeting the criteria for the response of interest

will be calculated as the number of patients with the response of interest documented during treatment (Arm 1: Course 1 treatment and Arm 2 treatment) divided by the total number of patients randomized and who have begun treatment on that treatment arm.

For each treatment arm, a point and interval estimate of ORR, CR, and CBR will be obtained using the properties of the binomial distribution.

- **Duration of Response:** Duration of response is defined as the time from when a PR or better is first documented during treatment (Arm 1: Course 1 treatment and Arm 2 treatment) to date of progression or death. If a patient has not progressed or died, the patient will be censored at the date of last clinical follow-up for this disease if no alternative treatment was initiated. Otherwise, the patient will be censored on the date alternative treatment was begun.

  The distribution of response durations for each treatment arm will be estimated using the Kaplan-Meier method.

- **Overall Survival (OS):** defined as the time from randomization to death due to any cause.

  The distribution of OS for each treatment arm will be estimated using the Kaplan-Meier method. As this study was not designed to test whether OS differs with respect to treatment, hypothesis testing will not be carried out to assess whether OS differs with respect to treatment at the time of the primary efficacy analysis of this trial. Instead, stratified Cox modeling will be used to obtain a point and interval estimate of the hazard of death among those randomized to the 3 drug regimen relative to death among those randomized to the 2 drug regimen, adjusting for patient and disease characteristics.

- **Adverse Events:** adverse events will be assigned a grade of severity and attribution using the CTCAE criteria. The frequency and severity of adverse events documented during treatment prior to progression or the initiation of another treatment be tabled.

13.5.2 Arm 1 Course 2

- **Progression-free survival (PFS):** Progression free survival in this setting is defined as the time from the start of Course 2 (3 drug regimen) to the date the International Myeloma Working Group (IMWG) criteria for disease progression is met [60, 61]. If a patient initiates another anti-cancer treatment prior to disease progression, they will be censored at the date of initiation of this treatment.

  The distribution of PFS times will be estimated using the Kaplan-Meier method.

- **Overall Response Rate (ORR), Complete Response (CR), and Clinical Benefit Rate (CBR):** The proportion of patients meeting the criteria for the response of interest will be calculated as the number of patients with the response of interest documented during Course 2 treatment divided by the total number of patients who have begun Course 2 treatment.

  A point and interval estimate of ORR, CR, and CBR will be obtained using the properties of the binomial distribution. Cross tables of the best response during Course 1 treatment with best response during Course 2 treatment will be constructed.

- **Duration of Response:** Duration of response is defined as the time from when a PR or better is first documented during Course 2 treatment to date of progression or death. If a patient has not progressed or died, the patient will be censored at the date of last clinical follow-up for this disease if no alternative treatment was initiated. Otherwise, the patient will be censored on the date alternative treatment was begun.

The distribution of response durations will be estimated using the Kaplan-Meier method.

- **Overall Survival (OS):** defined as the time from start of Course 2 treatment to death due to any cause.

  The distribution of OS times will be estimated using the Kaplan-Meier method.

- **Adverse Events:** adverse events will be assigned a grade of severity and attribution using the CTCAE criteria. The frequency and severity of adverse events documented during Course 2 treatment prior to progression or the initiation of another treatment be tabled.

13.5.3 Interim Analysis Design for Primary Endpoint

During the course of the study, we will monitor accrual assumptions and recommend changes to the DSMB if assumptions do not appear appropriate.

One interim analysis is planned after 75% of the required events have been observed to evaluate whether the addition of ixazomib to pomalidomide plus dexamethasone increased PFS survival time relative to pomalidomide plus dexamethasone alone. To preserve the Type I error rate, the Lan-DeMets error spending rate function with the O'Brien-Fleming boundaries will be applied. Findings will be presented to the DSMB for their recommended course of action.

Information fraction	Alpha spent	Boundary to reject H_0
0.75	0.058	-1.576
1.0	0.100	-1.380

The interim futility stopping rule proposed by Weiand, Schroeder, and O'Fallon will be applied as soon as 50% of the expected number of events associated with the sample size have occurred [63]. If the rate of patients experiencing progression on the ixazomib + pomalidomide/dexamethasone treatment arm is greater than the rate of patients progressing on the pomalidomide/dexamethasone arm, it will be assumed that the addition of ixazomib does not significantly improve PFS, and the study team will discuss termination of trial enrollment with the DSMB.

13.6 Study Monitoring (reports, summaries)

As a randomized phase II trial, this study will be monitored by the Alliance Data and Safety Monitoring Board (DSMB). The DSMB follows the Alliance Policies and Procedures for all randomized phase II trials. The DSMB will review accrual, toxicity, and interim analyses results. All summary findings of the DSMB will be communicated to study investigators by the Alliance. In addition the Alliance Statistical Data Center will submit quarterly reports to CTEP by electronic means using the Clinical Data Update System.

We will hold at least once monthly teleconferences to be attended by the study investigators or their representatives, the principal investigator, data management, and the statistical data center to review adverse events, accrual and other issues that arise over the course of the study. This teleconference is only required for those sites with patients on study.

13.7 Primary Endpoint Completion Time Estimation

Based on aforementioned accrual rates and a phase II start date of 07/15/2016, we would estimate a Primary Completion Date of 12/31/2018.

13.8 Inclusion of Women and Minorities

All studies must address the issue of inclusion of women and minorities in clinical research and whether gender or race/ethnicity differences in the intervention effect are to be expected.

PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	1	1	0	0	2
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	4	5	0	0	9
White	22	38	1	1	62
More Than One Race	0	0	0	0	0
Total	27	44	1	1	73

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

Not Hispanic or Latino

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

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

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

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

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

14.0 CORRELATIVE AND COMPANION STUDIES

As of Update #04, no new patients will be registered to A061202-ST1.

14.1 Correlative Science Substudy Alliance A061202-ST1

Evaluation of the cereblon/IRF-4/c-Myc pathway in resistance to Pomalidomide-based therapy.

14.1.1 Background

Cereblon, IRF-4 and c-Myc in IMiD Resistance

Recently, significant progress has been made in better understanding the mechanistic basis of IMiD activity in multiple myeloma. In 2010, investigators determined that the teratogenicity of the IMiDs is mediated by their binding to the protein cereblon [64]. Cereblon forms part of an E3 ubiquitin ligase complex with damaged DNA binding protein 1 (DDB1) and Cul4A. The IMiDs bind cereblon and modify the substrate specificity of this E3 ubiquitin ligase complex. By extension, more recent pre-clinical studies have demonstrated that the cytotoxicity of the IMiDs in myeloma cells also requires expression of and IMiD binding to cereblon [65, 66]. Notably, multiple myeloma cell lines with innate resistance to the IMiDs, a multiple myeloma cell line with acquired resistance to the IMiDs after prolonged incubation with increasing concentrations of lenalidomide, and multiple myeloma samples from patients with IMiD-resistant disease frequently had reduced expression of cereblon. Additionally, shRNA knockdown of cereblon conferred resistance in IMiD-sensitive multiple myeloma cell lines. More recently, cereblon expression was retrospectively evaluated using gene expression profiles from 53 patients treated on a series of pomalidomide studies at the Mayo Clinic. Notably, the partial response rate or better was 0% for those with a cereblon expression level of <0.81, 19% for those with a cereblon expression level of 0.81 – 0.90 and 33% for those with an expression level of >0.90 [67].

Interestingly, both shRNA-mediated silencing of cereblon expression and treatment of myeloma cells with IMiDs led to down-regulation of IRF-4 and c-Myc expression. Moreover, although IRF-4 expression was down-regulated in lenalidomide-sensitive cell lines, its expression was unchanged in resistant myeloma cells treated with lenalidomide. Given the critical role of the transcription factors IRF-4 and c-Myc in myeloma cell survival [68, 69], it is hypothesized that down-regulation of these factors is critical for IMiD-mediated cytotoxicity. However, it must be recognized that pomalidomide retains activity in a sizable proportion of patients with lenalidomide refractory disease, suggesting that there must be additional pathways to IMiD resistance beyond decreased expression of cereblon.

Based on previous studies, high cereblon expression appears positively correlated with response to IMiDs. However, we anticipate identifying patients who initially respond but then progress on pomalidomide despite high expression of cereblon. We may find that over- or under-expression of particular cereblon isoforms, such as those lacking the IMiD binding domain, correlate with resistance [70]. Alternatively, resistance could potentially be explained by the emergence of point mutations in cereblon that prevent IMiD binding but allow cereblon to retain its native function. This situation would be analogous to mutations in the BCR-ABL kinase domain of CML patients that impart resistance to tyrosine kinase inhibitors. Although these types of mutations have not yet been thoroughly evaluated in MM patients, we believe that this study is particularly well suited for investigating this potentially important pathway of IMiD resistance. In support of this possible mechanism of resistance, a cereblon mutation was recently identified in a patient with extramedullary multiple myeloma [71].

Most recently, several groups have determined a critical role for the transcription factors Ikaros (*IKZF1*) and Aiolos *(IKZF3*) in IMID-mediated cytotoxicity [72-74]. Specifically,

upon binding of IMIDs to cereblon in multiple myeloma cells, the E3 ubiquitin ligase complex substrate specificity changes, preferentially binding and ubiquitinating Ikaros and Aiolos, thus targeting them for degradation through the proteasome [72, 73]. Importantly, Ikaros and Aiolos are important in plasma cell development, highly expressed in multiple myeloma, and drive transcription of IRF4. Additionally, their down regulation is required for IMID-mediated cytotoxicity [72, 73]. Early retrospective data from gene expression profiling would suggest that patients with the lowest quartile of *IKZF1* expression are less likely to respond to pomalidomide and dexamethasone and have an inferior overall survival. In contrast, responses to bortezomib were no different between those with low or high *IKZF1* expression, thus demonstrating a potentially drug class specific effect on outcome [74].

14.1.2 Objectives

Primary Objective:

- To determine the extent of which cereblon expression (via quantitative PCR and IHC) is associated with therapeutic response.

Secondary Objectives:

- To examine whether PFS differs with respect to cereblon expression levels from baseline aspirates.
- To examine whether therapeutic response or PFS differs with respect to either the percentage of IRF-4 or c-Myc positivity in plasma cells or IHC staining intensity in plasma cells in samples obtained prior to start of protocol treatment.
- To examine whether resistance mutations in the IMiD binding domain of cereblon emerge in patients with response to therapy and then progress.
- To examine the concordance between cereblon expression levels prior to the start of protocol treatment and progression as well as the percentage of patients with expression gain or loss.
- To examine whether reduced expression of Ikaros (*IKZF1*) and Aiolos (*IKZF3*) transcription factors is associated with inferior clinical efficacy (ORR, PFS, OS).
- To determine whether resistance mutations in Ikaros and Aiolos develop in patients with an initial response to therapy (MR or better) who then progress.

Our correlative aims should help validate cereblon mRNA expression level as a marker of response to pomalidomide therapy and establish appropriate cut points for expression level utilizing quantitative PCR for validation in future studies. Additionally, it is not known whether IRF-4, c-Myc, Ikaros or Aiolos are affected in cases of IMiD resistance where cereblon expression is intact. We will therefore look at expression of these factors to get preliminary information as to whether or not they are down-regulated in cases of IMiD resistance, irrespective of cereblon expression.

In addition, plasma cell RNA leftover from the planned analyses performed as part of A061202-ST1 will be stored for future correlative studies as new insights into the basis of IMiD and proteasome inhibitor resistance emerge. Similarly, unstained bone marrow biopsy recuts will be also stored for potential use in future correlative studies. Plasma cell depleted bone marrow will be stored as a frozen cell pellet for use in potential future studies requiring DNA and/or RNA.

14.1.3 Methods

Sample collection

Bone marrow aspirates and biopsies will be obtained at baseline (with the mandatory staging marrow aspirate and biopsy), and for those with an initial MR or better, a bone marrow aspirate and biopsy will be obtained at disease progression, both to be used in correlative analyses. Samples will be tested for cereblon mRNA expression by RT-PCR and for immunohistochemical markers such as cereblon, IRF-4, c-Myc, Ikaros and Aiolos. Other immunohistochemical markers including BLIMP-1, which has been shown to be important for the maintenance of plasma cells [75], may be performed as well and correlated with outcome. Cereblon expression will also be assessed via RT-PCR and immunohistochemistry at the time of disease progression for those with an initial response (MR or better) to therapy. Samples from patients with an initial response to therapy (MR or better) followed by disease progression will also be evaluated for the emergence of putative resistance mutations in the IMiD binding domain of cereblon.

Sample processing and facilities

Correlative studies will be performed in the laboratory of Todd W. Kelley, M.D., Associate Professor, Department of Pathology, University of Utah and Medical Director of Molecular Hematopathology at ARUP Laboratories (Salt Lake City UT, an enterprise of the University of Utah Department of Pathology). The necessary equipment, including real-time PCR instruments, DNA sequencers, automated immunostainers and microscopic slide scanners, are available for this project at ARUP Laboratories. Bone marrow aspirates will be routed through the Alliance Hematologic Malignancy Biorepository located at Ohio State University. The Alliance Hematologic Malignancy Biorepository will perform CD138-based isolation of plasma cells from the aspirates. Isolated plasma cells will be pelleted, frozen at -70C, then be sent to Todd Kelley's laboratory in Utah for RNA extraction and analysis. FFPE bone marrow biopsy tissue blocks will be routed through the Alliance Biorepository, also located at Ohio State. The bone marrow cells remaining after plasma cell shave been removed will be pelleted and stored frozen at the Alliance Hematologic Malignancy Biorepository for use in potential future studies. This will provide an opportunity for studying other hematopoietic components that may be important in the disease process, particularly the myeloid fraction.

Scientists at Celgene have developed and validated a monoclonal antibody (CRBN65) for accurate immunohistochemical evaluation of cereblon protein expression in FFPE tissue [76]. This antibody has been made available for use in this study but only through a reference laboratory (Quest) contracted by Celgene. This laboratory has also validated Ikaros and Aiolos immunohistochemical stains and these will be performed as well. Therefore, unstained tissue recuts from the bone marrow biopsies will be sent to Quest for staining for these markers.

Cereblon expression and sequencing

Bone marrow aspirates will be available at baseline and at the time of progression. Viable CD138-positive cells will be isolated from the bone marrow aspirate samples using a bead-based positive selection kit (Stem Cell Technologies). Total RNA will then be extracted from myeloma cells using a commercially available RNA extraction kit (Qiagen). Importantly, this RNA will be used for the subsequently described studies but will also be archived and available for potential future studies including gene expression profiling.

Cereblon mRNA expression will be evaluated by converting 100 ng of total RNA into random-primed cDNA using the Superscript III First Strand cDNA Synthesis Kit (Invitrogen). The cDNAs will then be assayed in duplicate with primer and hydrolysis probe

(TaqMan probe) mixes specific for the different isoforms of cereblon that have been identified [70] and the reference genes GAPDH (ABI Cat. # Hs03929097) and TBP (ABI Cat. # Hs00427621) using TaqMan Universal PCR Master Mix (Life Technologies). Samples will then be assayed on a Roche Lightcycler (LC480) real time PCR instrument and analyzed with the absolute quant/second derivative max option. In this manner, expression of the various isoforms will be separately normalized across all samples to expression of the housekeeping genes GAPDH and TBP. Normalized cereblon mRNA expression for the measured isoforms in myeloma cells will be correlated with therapeutic response and other clinical efficacy measures.

We will also sequence the IMiD binding domain of cereblon in patients who initially respond to pomlidomide-based therapy (MR or better) but then progress. If mutations are identified, we will go back to the baseline samples of these specific cases and evaluate for the presence of cereblon mutations at study entry to determine whether the mutations were present at baseline or acquired over the course of treatment. In addition, if mutations are identified in acquired pomalidomide resistance, we will screen baseline samples in all patients to determine if mutations present at baseline predict for lack of response to pomalidomide-based treatment (pending additional funding). The IMiD binding region of cereblon has been mapped to the C-terminal 104 amino acids, particularly residues Y384 and W386.40 Briefly, RNA from myeloma cells will be converted to cDNA, as above, and subjected to PCR amplification using primers flanking the IMiD binding domain of cereblon. The resulting amplicons will then be subjected to DNA sequencing using an ABI 3700 DNA sequencer (Life Technologies). Sequences will be analyzed using Mutation Surveyer software (Softgenetics).

Immunohistochemical analysis

Formalin fixed paraffin embedded (FFPE) bone marrow biopsy tissue will be available from patients at baseline and at progression (for those who achieve an initial MR or better). These samples will be subjected to immunohistochemical (IHC) staining in order to evaluate plasma cells for expression of cereblon, IRF-4 and c-Myc protein. Briefly, tissue sections will be cut onto slides then subjected to double IHC staining with antibodies to CD138 (expressed in a membrane pattern) to identify plasma cells, and either IRF-4 or c-Myc. Thus, the double staining combinations will be CD138/IRF-4 and CD138/c-Myc. Double immunostaining with a combination of membrane and nuclear antigens is a simple but effective method to limit quantification of staining to a particular cell population of interest. IHC staining will be performed on a Ventana automated immunostaining system (Roche). IRF-4 and c-Myc expression will be digitally quantified in CD138-positive plasma cells using an automated microscopic slide scanner (Aperio) and image analysis software. The relative percentage of IRF-4 and c-Myc positivity in plasma cells and the relative staining intensity in plasma cells will be derived using image analysis. These findings will then be correlated with therapeutic response. Additional immunohistochemical markers, particularly BLIMP-1, may also be analyzed in this fashion and also correlated with outcome. Cereblon/CD138, Ikaros and Aiolos/CD138 double immunohistochemical staining will be performed at Quest Laboroatories as outlined above. The resulting immunostains will be analyzed and interpreted by Quest pathologists using an algorithm validated by Celgene (unpublished communication). Cereblon, Ikaros and Aiolos immunohistochemical protein expression data derived from these analyses will be correlated with outcome as outlined below.

14.1.4 Analysis Plans

Based on previous experience, we can expect between 65 and 72 samples obtained prior to start of treatment from consenting patients based on a 50%-80% consent rate.

The ability to detect differences in clinical outcome with respect to biomarker profile is primarily dependent on the consent rate, access to viable samples, and the prevalence of the biomarker poor risk group.

At present, there is no historical data by which to determine risk categories for the biomarkers of interest. As such, we will examine in each treatment arm separately the following cut points as a potential means to define risk groups: 25th percentile, median, and 75th percentile of the biomarker distribution in that treatment arm. For each dichotomization of the biomarker, the parameters from fitting a univariate logistic regression model will be used to obtain a point and interval estimate of the odds of response in the biomarker high cohort relative to the biomarker low cohort in that treatment arm. This will lead to insights into which if any of cut points should be used for further testing of the biomarker.

The candidate dichotomization from the analysis of the response data will be used to examine whether PFS differs with respect to these risk groups. For each biomarker the parameters from fitting a univariate Cox regression model will be used to obtain a point and interval estimate of the hazard of progression in the biomarker high cohort relative to the biomarker low cohort in a given treatment arm.

The correlative studies in this protocol will give us preliminary data as to the proportion of pomalidomide resistance that is associated with reduced expression of cereblon and its downstream targets. The data derived from this study will be used to appropriately power future prospective studies of lenalidomide- or pomalidomide-based therapy.

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APPENDIX I: ECOG PERFORMANCE STATUS

ECOG Performance Status Scale	
Grade	**Descriptions**
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.

APPENDIX II: COCKCROFT-GAULT FORMULA

$$\text{Creatinine Clearance} = \frac{(140 - \text{age}) \times \text{weight (kg)} \times 0.85 \text{ (for females)}}{72 \times \text{Serum Creatinine (mg/dL)}}$$

APPENDIX III: REGISTRATION FATIGUE/UNISCALE ASSESSMENTS

Registration Fatigue/Uniscale Assessments

At patient registration, this form is to be administered by a nurse/CRA, completed by the patient, and recorded on the Registration Fatigue/Uniscale Assessments Form (see Forms Packet).

If needed, this appendix can be adapted to use as a source document. A booklet containing this assessment does not exist – please do not order this booklet.

How would you describe:

your level of fatigue, on the average in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
No Fatigue										Fatigue as bad as it can be

your overall quality of life in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

APPENDIX IV: CONGESTIVE HEART FAILURE CLASSIFICATION SYSTEM

New York Heart Association Congestive Heart Failure Classification System		
Class	**Functional Capacity**	**Objective Assessment**
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

APPENDIX V: CYTOCHROME P450 1A2 INHIBITORS AND CYTOCHROME P450 3A4 INHIBITORS AND INDUCERS

Strong CYP1A2 inhibitors	Moderate CYP1A2 inhibitors
Fluvoxamine	Cimetidine
Ciprofloxacin	
This database of CYP inhibitors was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table. Strong inhibitors are predicted to increase CYP3A4 substrates >5-fold, and moderate inhibitors are predicted to increase CYP3A4 substrates ≥2-fold but <5-fold. Please note that this is not an all-inclusive list. Any new medications prescribed or complementary therapies should be assessed for their potential to inhibit or induce CYP1A2. For the latest publically available updates please visit the Indiana University School of Medicine Drug Interaction Database at: [redacted]	

Cytochrome P450 3A4 Inhibitors and Inducers:

Strong CYP3A4 inhibitors	Moderate CYP3A4 inhibitors	CYP3A4 inducers
Clarithromycin	Aprepitant	Avasimibe
Conivaptan	Atazanavir	Barbiturates
Grapefruit juice	Cimetidine	Bosentan
Indinavir	Ciprofloxacin	Carbamazepine
Itraconazole	Darunavir	Efavirenz
Ketoconazole	Diltiazem	Etravirine
Lopinavir	Erythromycin	Systemic glucocorticoids*
Mibefradil	Fluconazole	Modafenil
Nefazodone	Tofisopam	Nafcillin
Nelfinavir	Verapamil	Nevirapine
Posaconazole	Amprenavir	Oxcarbazepine
Ritonavir	Fosamprenavir	Phenobarbital
Saquinavir	Imatinib	Phenytoin
Telithromycin	Elvitegravir	Pioglitazone
Troleandomycin	Tipranavir	Rifabutin, rifapentine
Voriconazole		Rifampin
		St. John's wort
		Talviraline
		Tipranavir
		Topiramate
		Troglitazone
This database of CYP inhibitors was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table and from the University of Washington's Drug Interaction Database based on *in vitro* studies. Strong inhibitors are predicted		

Strong CYP3A4 inhibitors	Moderate CYP3A4 inhibitors	CYP3A4 inducers

to increase CYP3A4 substrates >5-fold, and moderate inhibitors are predicted to increase CYP3A4 substrates ≥2-fold but <5-fold.

This database of CYP inducers was compiled from the FDA's "Guidance for Industry, Drug Interaction Studies" from the Indiana University School of Medicine's "Clinically Relevant" Table; and from Pursche et al. Curr Clin Pharm.2008;3:198-203.

*Although dexamethasone is an inducer of CYP3A4, ixazomib pharmacokinetics do not appear to be affected by dexamethasone.

Herbal therapies with potential CYP3A4 interactions: St. John's Wort and gingko biloba.

Foods with potential CYP3A4 interactions: Grapefruit or grapefruit juice, grapefruit hybrids, Seville oranges, pummelos and exotic citrus fruits (e.g. starfruit).

Please note that this is not an all-inclusive list. Any new medications prescribed or complementary therapies should be assessed for their potential to inhibit or induce CYP3A4.

For the latest publically available updates please visit the Indiana University School of Medicine Drug Interaction Database at: [redacted]

APPENDIX VI: PATIENT MEDICATION LOGS

POMALIDOMIDE MEDICATION LOG

Pill Diary for Alliance Protocol A061202: A Phase I/II Study of Pomalidomide, Dexamethasone and Ixazomib VS Pomalidomide and Dexamethasone for Patients with Multiple Myeloma Relapsing on Lenalidomide as Part of First Line Therapy

Number of Capsules Given:_____ Capsule Bottle(s) returned: Circle Yes or No
Total Daily Dose:_____ Number of Capsules returned:_____
(To be Completed by RN)

PLEASE FILL OUT AND BRING THIS SHEET TO ALL VISITS.

CYCLE #:_____ # of WEEKS_____

DAY	Medication	DATE	TIME		# of XX mg Capsules taken	Comments
Example	Pomalidomide	*07/01/12*	*9:00*	*AM*	*1 XX mg capsules taken + 2 XX mg capsules taken*	
1	Pomalidomide					
2	Pomalidomide					
3	Pomalidomide					
4	Pomalidomide					
5	Pomalidomide					
6	Pomalidomide					
7	Pomalidomide					
8	Pomalidomide					
9	Pomalidomide					
10	Pomalidomide					
11	Pomalidomide					
12	Pomalidomide					
13	Pomalidomide					
14	Pomalidomide					
15	Pomalidomide					
16	Pomalidomide					
17	Pomalidomide					
18	Pomalidomide					
19	Pomalidomide					
20	Pomalidomide					
21	Pomalidomide					

Patient Signature: _____Date:_____

Consenting Professional/Research RN Signature: _____Date:_____

Comments:_____

DEXAMETHASONE MEDICATION LOG

Pill Diary for Alliance Protocol A061202: A Phase I/II Study of Pomalidomide, Dexamethasone and Ixazomib VS Pomalidomide and Dexamethasone for Patients with Multiple Myeloma Relapsing on Lenalidomide as Part of First Line Therapy

Number of Tablets Given:_____ Tablet Bottle(s) returned: Circle Yes or No
Total Daily Dose:_____ Number of Tablets returned:_____
(To be Completed by RN)

PLEASE FILL OUT AND BRING THIS SHEET TO ALL VISITS.
CYCLE #:_____ # of WEEKS_____

DAY	Medication	DATE	TIME		# of XX mg tablets taken	Comments
Example	Dexamethasone	*07/01/12*	*9:00*	*AM*	*1 XX mg tablets taken + 2 XX mg tablets taken*	
1	Dexamethasone					
2						
3						
4						
5						
6						
7						
8	Dexamethasone					
9						
10						
11						
12						
13						
14						
15	Dexamethasone					
16						
17						
18						
19						
20						
21						
22	Dexamethasone					

Patient Signature: _____Date:_____

Consenting Professional/Research RN Signature: _____Date:_____

Comments:_____

IXAZOMIB MEDICATION LOG

Pill Diary for Alliance Protocol A061202: A Phase I/II Study of Pomalidomide, Dexamethasone and Ixazomib VS Pomalidomide and Dexamethasone for Patients with Multiple Myeloma Relapsing on Lenalidomide as Part of First Line Therapy

Number of Capsules Given:_____ Blister Pack returned: Circle Yes or No
Total Daily Dose:_____ Number of Capsules returned:_____
(To be Completed by RN)

PLEASE FILL OUT AND BRING THIS SHEET TO ALL VISITS.
CYCLE #:_____ # of WEEKS_____

DAY	Medication	DATE	TIME		# of XX mg Capsules taken	Comments
Example	Ixazomib	*07/01/12*	*9:00*	*AM*	*1 XX mg capsules taken + 2 XX mg capsules taken*	
1	Ixazomib					
2						
3						
4						
5						
6						
7						
8	Ixazomib					
9						
10						
11						
12						
13						
14						
15	Ixazomib					

Patient Signature: _____Date:_____

Consenting Professional/Research RN Signature: _____Date:_____

Comments:_____

APPENDIX VII PROTEASOME INHIBITORS

Drug	Commercial Name	Investigational Name
Bortezomib	Velcade	PS-341
Carfilzomib	Kyprolis	PR-171
Ixazomib	Ninlaro	MLN9708
Oprozomib		ONX-0912
Marizomib		NPI-0052