A PHASE I/II STUDY OF POMALIDOMIDE, DEXAMETHASONE AND IXAZOMIB VS. POMALIDOMIDE AND DEXAMETHASONE FOR PATIENTS WITH MULTIPLE MYELOMA REFRACTORY TO LENALIDOMIDE AND PROTEASOME INHIBITOR-BASED THERAPY

Schema page 1 of 3

Eligibility Criteria (see Section 3.0)

- Histologically confirmed diagnosis of relapsed symptomatic multiple myeloma.
- Measureable disease (see section 3.2.2)
- Prior Treatment(s) (see section 3.2.3)
- ≥2 prior lines of prior therapy (see section 3.2.3)
- Not on strong inducers or potent inhibitors of CYP3A4 or CYP1A2 (see section 3.2.4h)
- Refractory to lenalidomide- AND proteasome inhibitor-based therapy** (see section 3.2.3)
- Non-pregnant and non-nursing (see section 3.2.4a)
- ≥18 years of age
- ECOG Performance Status of 0-2 (see Appendix I)
- Intercurrent or Recent Illness (see section 3.2.4e)
- ≤ Grade 2 Peripheral Neuropathy
- Adequate cardiac function (see section 3.2.4g)
- Patients with HIV infection are eligible, provided they meet guidelines listed in section 3.2.4i

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

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

** Refractory to any proteasome inhibitor-based regimen (see Appendix VII).

A PHASE I/II STUDY OF POMALIDOMIDE, DEXAMETHASONE AND IXAZOMIB VS. POMALIDOMIDE AND DEXAMETHASONE FOR PATIENTS WITH MULTIPLE MYELOMA REFRACTORY TO LENALIDOMIDE AND PROTEASOME INHIBITOR-BASED THERAPY

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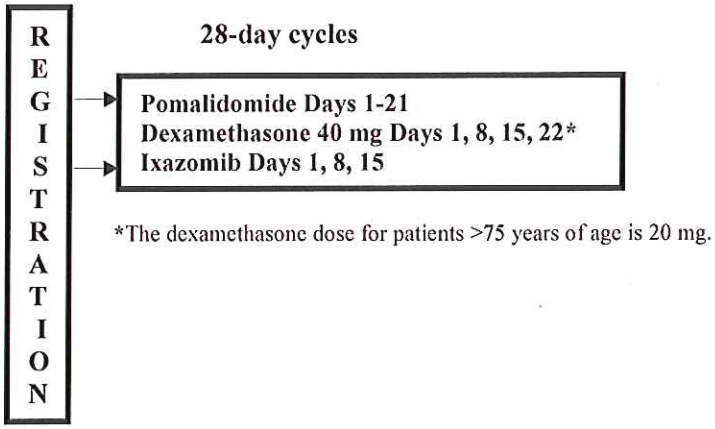
PHASE I



*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.

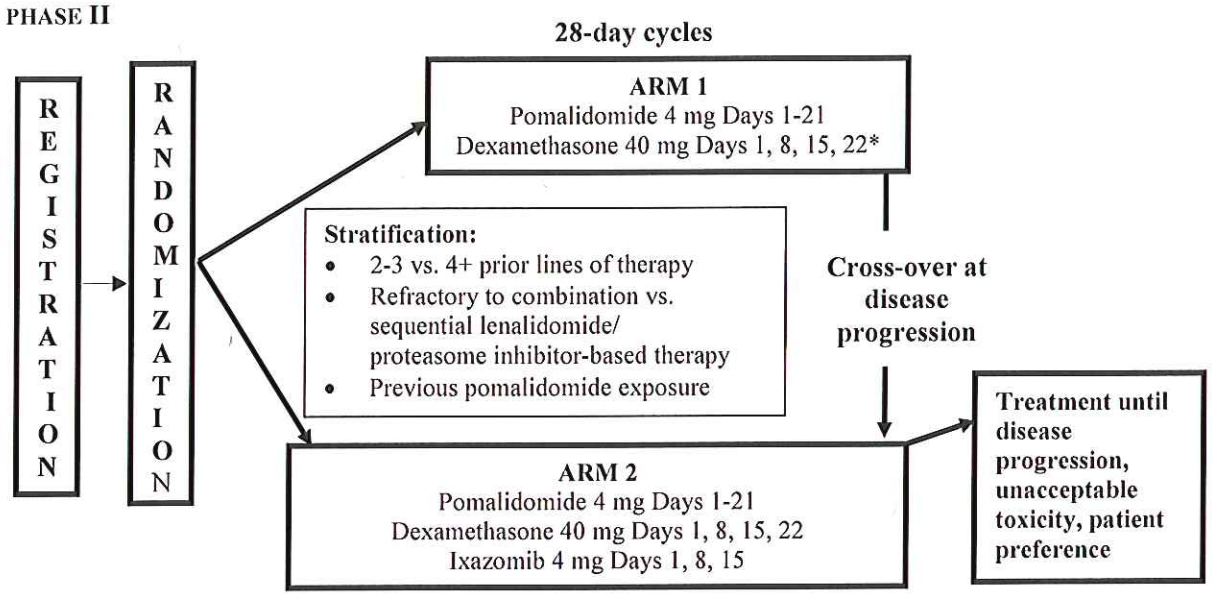
Dose escalation will follow a standard 3+3 design (see section 13.0). Dosing will begin with cohort 1. Patients may remain on treatment until disease progression, unacceptable toxicity, or withdrawal of consent.

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.

NOTE: Phase I closed to accrual as of February 04, 2016.

A PHASE I/II STUDY OF POMALIDOMIDE, DEXAMETHASONE AND IXAZOMIB VS. POMALIDOMIDE AND DEXAMETHASONE FOR PATIENTS WITH MULTIPLE MYELOMA REFRACTORY TO LENALIDOMIDE AND PROTEASOME INHIBITOR-BASED THERAPY

Schema page 3 of 3



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

Phase II

Arm 1: Pomalidomide + Dexamethasone. 28-day cycle.

Pomalidomide: 4 mg 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 or age will be 20 mg, utilizing the same schedule.

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

Pomalidomide: 4 mg orally once daily on days 1-21 out of 28 days.

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.

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

Patients who progress on arm 1 will have the option of crossing over to treatment arm 2 and receiving the 3-drug combination. Please note, patients who opt to cross over must be re-registered to the study. In addition, please make sure to reassess eligibility (section 3.2) at re-registration.

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

and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

In addition:

- 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 3.2.4a.

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 as defined in Section 11.0.**

Measurable disease

___ Serum M-protein ≥1.0 g/dL (≥0.5 g/dL for IgA myeloma) 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 and/or

___ Baseline marrow burden of myeloma of at least 30%

Please Note: For patients participating in the phase II portion of the study who elect to cross-over from Treatment Arm 1 to Treatment Arm 2 at the time of disease progression, the serum M protein should be 0.5 g/dL or more if that is the parameter being followed to measure response.

___ **3.2.3 Prior Treatment**

___ Previously treated symptomatic multiple myeloma.

___ Lenalidomide AND proteasome inhibitor-refractory multiple myeloma (dual refractory disease). Please refer to Appendix VII for a list of proteasome inhibitors.

Please Note: Lenalidomide and proteasome inhibitor-refractory disease is defined as disease progression on or progression within 60 days of the last dose of a lenalidomide- AND proteasome inhibitor-based treatment [42,43]. Patients should have received at least 2 cycles of a lenalidomide- or proteasome inhibitor-based

regimen at standard doses to be evaluable for refractoriness. Patients can be refractory to any proteasome inhibitor – they do NOT need to be refractory to all available proteasome inhibitors (see Appendix VII). In addition, patients can be refractory to lenalidomide and proteasome inhibitors given sequentially as part of different lines of therapy OR therapy that includes a combination of lenalidomide and a proteasome inhibitor. Please see section 11.4 for the International Myeloma Working Group (IMWG) response criteria for progressive disease (PD).

___ At least 2 or more prior lines of systemic therapy for multiple myeloma.

Please note: 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, disease relapse or treatment-related toxicity (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 $\geq$ 1 year from transplant, is not on immunosuppressive therapy to treat/prevent graft-versus-host disease, has no evidence of active graft versus host disease, no evidence of active infection and meets all other criteria for participation.

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

___ No investigational agent within 21 days prior to registration.

___ Pomalidomide naïve and pomalidomide sensitive disease are allowed during phase I and phase II.

Please note: Sensitivity to pomalidomide is defined as an MR or better to prior pomalidomide-based therapy that is maintained for $\geq$60 days from the last dose of therapy.

___ No concurrent investigational therapy.

___ No major surgery within 28 days prior to registration.

___ Patients cannot have received G-CSF (Filgrastim) or GM-CSF (Sargramostim) within 1 week of screening or Pegfilgrastim within 2 weeks of screening to meet eligibility criteria.

___ Patients cannot have received a platelet transfusion within 7 days of screening to meet eligibility criteria. Red blood cell transfusions are allowed at any time.

___ **3.2.4a Non-pregnant and non-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). Please note the information below

is strictly for eligibility purposes, please reference section 5.0 for details on pregnancy monitoring during the duration of the trial.

Therefore, 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 therapy and repeated again within 24 hours of starting pomalidomide and 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. Females of childbearing potential must also agree to ongoing pregnancy testing. 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. All participants must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure. Participating women cannot be pregnant or nursing.

___ **3.2.4b ≥18 years of age**

___ **3.2.4c ECOG Performance status 0-2 (see Appendix I)**

___ **3.2.4d Required Initial Laboratory Values:**

Absolute Neutrophil Count (ANC)	$\geq 1.0 \times 10^9$/L
Platelet Count	$\geq 50 \times 10^9$/L
Calc. Creatinine Clearance*	≥ 50 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)

___ **3.2.4e Intercurrent or Recent Illness**

Patients cannot have:

___ Central nerve system involvement

___ Primary refractory multiple myeloma

Note: 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

Patients cannot have:

___ Known active hepatitis C based on:

+HCV antibody (confirmed)

+HCV RNA

Liver disease with history of positive serology

___ Known hepatitis B surface antigen positivity

___ Patients cannot have had previous hypersensitivity to any of the components of the study treatment

___ Patients cannot have had a prior history of erythema multiforme with thalidomide or lenalidomide treatment

___ **3.2.4f Peripheral Neuropathy**

≤ Grade 2 Peripheral Neuropathy

___ **3.2.4g 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 the last 6 months

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

___ **3.2.4h Concomitant Treatment**

Patients cannot be on 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.

Chronic concomitant treatment with strong CYP3A4 inducers is not allowed (*e.g.* phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St. John's Wort). Please note that drugs that strongly induce or inhibit CYP3A4 are not allowed. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently updated list such as **http://medicine.iupui.edu/clinpharm/ddis/**; medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions 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.

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

___ **3.2.4i HIV Infection**

Patients with HIV infection are eligible, provided they meet the following:

___ No history of AIDS-defining conditions or other HIV related illness

___ CD4+ cells nadirs >350/mm^3

___ Treatment sensitive HIV and, if on anti-HIV therapy, HIV viral load < 50 copies/mm^3

Please 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 3.2.4h).

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.
- 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.
- Participation in Alliance sub-study A061202-ST1 ("Evaluation of the cereblon/IRF-4/c-Myc pathway in resistance to Pomalidomide-based therapy") will be activated for the phase II portion of the study. This sub-study must be offered to all patients enrolled in the phase II portion of A061202 (although patients may opt to not participate). See section 6.2.2 and section 14.0 for further details.