Cancer Research Consortium of West Michigan
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FAST FACTS

A061202: A Phase II Study of Pomalidomide, Dexamethasone and Ixazomib VS. Pomalidomide and Dexamethasone for Patients with Multiple Myeloma Refractory to Lenalidomide and Proteasome Inhibitor-Based Therapy

Eligibility Criteria

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.

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. 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, 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 ≥ 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.

4. Non-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.

5. ≥18 years of age

6. ECOG Performance status 0-2 (see Appendix I)

7. Required Initial Laboratory Values:
   - Absolute Neutrophil Count (ANC) ≥ 1.0 x 109/L
   - Platelet Count ≥ 50 x 109/L
   - Calc. Creatinine ≥ 30 mL/min

Clearance*

- 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.

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

9. ≤ Grade 2 Peripheral Neuropathy

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 (Appendix IV)

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

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/mm3 within 28 days prior to registration

    • Treatment sensitive HIV and, if on anti-HIV therapy, HIV viral load < 50 copies/mm3 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).