Département d'oncologie
Plateformes du DO
Bâtiment Maternité PAV1
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Indication	Patients atteints d'un myélome multiple nouvellement diagnostiqué et non-éligibles pour une greffe
Title	**A Randomized, Open-label Phase 3 Study of Carfilzomib, Melphalan, and Prednisone versus Bortezomib, Melphalan, and Prednisone in Transplant-ineligible Patients with Newly Diagnosed Multiple Myeloma**
Protocol ID	**Clarion 2010-005**
Phase	**Phase III**
Sponsor	Onyx Therapeutics, INC.
Local Principal Investigator	Dr. A. Cairoli
Primary Objective	The primary objective is to compare the PFS of transplant-ineligible subjects newly diagnosed with multiple myeloma who are treated with carfilzomib, melphalan and prednisone versus those treated with bortezomib (Velcade), melphalan and prednisone.
Inclusion/exclusion criteria	**Inclusion Criteria** 1. Newly diagnosed symptomatic multiple myeloma 2. Transplant-ineligibility 3. Measurable disease, as defined by one or more of the following (assessed within 21 days prior to randomization): • Serum M-protein ≥ 0.5 g/dL, or • Urine M-protein ≥ 200 mg/24 hours, or • In subjects without detectable serum or urine M-protein, serum-free light chain (SFLC) > 100 mg/L (involved light chain) and an abnormal κ/λ ratio 4. No prior treatment for multiple myeloma 5. Males and females ≥ 18 years of age 6. Eastern Cooperative Oncology Group (ECOG) performance status 0–2 7. Adequate hepatic function within 21 days prior to randomization, with bilirubin < 1.5 times the upper limit of normal (ULN), and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 3 times the ULN 8. Absolute neutrophil count (ANC) ≥ 1.0×10^9/L 9. Hemoglobin (Hgb) ≥ 8.0 g/dL within 21 days prior to randomization. Use of erythropoietic stimulating factors and red blood cell (RBC) transfusions per institutional guidelines is allowed. 10. Platelet count ≥ 50×10^9/L 11. Calculated or measured creatinine clearance (CrCl) of ≥ 15 mL/min within 21 days prior to randomization based on the Cockcroft and Gault formula. 12. Left ventricular ejection fraction (LVEF) ≥ 40%; 2-d transthoracic echocardiogram (ECHO) is the preferred method of evaluation; multiple gated

acquisition scan (MUGA) is acceptable if ECHO is not available.

13. Females of child-bearing potential (FCBP) must have a confirmed negative serum pregnancy test within 21 days prior to randomization (performed at central laboratory) and agree to use an effective method of contraception during and for 6 months following the last dose of all study drugs (more frequent pregnancy tests may be conducted if required by local regulations). This protocol defines a FCBP as a sexually mature woman who:

1) has not undergone a hysterectomy or bilateral oophorectomy, or

2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

14. Male subjects must use an effective barrier method of contraception during study and for 6 months following the last dose of all study drugs if sexually active with a female of child-bearing potential

15. Written informed consent in accordance with federal, local, and institutional guidelines

Exclusion Criteria

1. Multiple Myeloma of IgM subtype

2. Glucocorticoid therapy within 14 days prior to randomization that equals or exceeds a cumulative dose of 160 mg of dexamethasone

3. POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)

4. Plasma cell leukemia (> 2.0×10^9/L circulating plasma cells by standard differential)

5. Waldenström macroglobulinemia (WM)

6. Known amyloidosis

7. Focal radiation therapy within 7 days prior to randomization

8. Any immunotherapy within 21 days prior to randomization.

9. Major surgery within 21 days prior to randomization

10. Active congestive heart failure (New York Heart Association [NYHA] Class III to IV), symptomatic ischemia, conduction abnormalities uncontrolled by conventional intervention, acute diffuse infiltrative pulmonary disease, pericardial disease, or myocardial infarction within 6 months prior to randomization.

11. Active infection within 14 days prior to randomization

12. Known human immunodeficiency virus (HIV) seropositive, hepatitis C infection, and/or hepatitis B (subjects with hepatitis B surface antigen [SAg] or core antibody receiving and responding to antiviral therapy directed at hepatitis B are allowed)

13. Known cirrhosis

14. Second malignancy within the past 5 years except:

- Adequately treated basal cell or squamous cell skin cancer,
- Carcinoma in situ of the cervix, or

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	• Prostate cancer < Gleason score 6 with undetectable prostate-specific antigen (PSA) over 12 months, or • Ductal breast carcinoma in situ with full surgical resection (i.e., negative margins), or • Treated medullary or papillary thyroid cancer, or • Similar condition with an expectation of > 95 % 5-year disease free survival 15. Myelodysplastic syndrome 16. Significant neuropathy (Grades ≥ 2) within 14 days prior to randomization 17. Female subjects who are pregnant or lactating 18. Known history of allergy to Captisol (a cyclodextrin derivative used to solubilize carfilzomib) 19. Hypersensitivity to boron, or mannitol (associated with parenteral bortezomib administration) 20. Hypersensitivity to melphalan or to any of the excipients of Alkeran 21. Contraindication to prednisone or dexamethasone 22. Contraindication to any of the required concomitant drugs or supportive treatments, including hypersensitivity to antiviral drugs, or intolerance to hydration due to preexisting pulmonary or cardiac impairment 23. Pleural effusions requiring thoracentesis 24. Ascites requiring paracentesis 25. Uncontrolled hypertension or uncontrolled diabetes 26. Any other clinically significant medical disease or condition that, in the investigator's opinion, may interfere with protocol adherence or a subject's ability to give informed consent