Cancer Research Consortium of West Michigan
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FAST FACTS

S2209: "A Phase III Randomized Trial For Newly Diagnosed Multiple Myeloma (NDMM) Patients Considered Frail Or In A Subset of "Intermediate Fit" Comparing Upfront Three-Drug Induction Regimens Followed by Double- or Single-Agent Maintenance."

ELIGIBILITY CRITERIA

5.1 Disease Related Criteria

a. Participants must have documented multiple myeloma satisfying standard International Myeloma Working Group (IMWG) see section 4.1. diagnostic criteria within 28 days prior to registration for participants with no prior therapy, or within 28 days prior to initiation of first induction course for participants who had prior therapy.

b. Participants must have measurable disease within 28 days prior to registration (or prior to initiation of first induction course for participants who had prior therapy) as defined by any of the following:

1. immunoglobulin (Ig) G myeloma (serum monoclonal paraprotein [Mprotein] level ≥0.5 gram/deciliter [g/dL] or urine M-protein level ≥200 milligram[mg]/24 hours[hrs]; OR

2. IgA, IgM, IgD, or IgE multiple myeloma (serum M-protein level ≥0.2 g/dL or urine M-protein level ≥200 mg/24 hrs); OR

3. light chain multiple myeloma (serum immunoglobulin free light chain ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio).

All disease must be assessed and documented on the baseline/Pre-Registration Tumor Assessment Form.

5.2 Prior/Concurrent Therapy Criteria

a. Participants must not have received any prior systemic therapy for multiple myeloma with the exception of any one or more of the following:

1. An emergency use of a short course of corticosteroids (equivalent of dexamethasone 160 mg) any time before registration, or

2. Up to one complete cycle of a non-daratumumab and hyaluronidase-fihj containing anti-myeloma regimen (1 cycle = 21 or 28 days depending on the regimen being used), or

3. Localized palliative radiation therapy for multiple myeloma, as long as the radiation therapy is completed at least 3 days prior to starting the systemic treatment as per the study protocol.

5.3 Clinical/Laboratory Criteria

a. Participants must have a calculated myeloma frailty index (Myeloma Frailty Score Calculator; http://www.myelomafrailtyscorecalculator.net/) categorized as frail or intermediate fit (regardless of age) within 28 days prior to registration.

1. For Participants Meeting "Frail" Status:
    i. Participants with any degree of kidney dysfunction not requiring dialysis are allowed.

    ii. Participants must have adequate bone marrow function as evidenced by all of the following:

        a. Hemoglobin ≥7 g/dL
        b. Platelets ≥50x109/L
        c. ANC ≥0.75 x109/L.

    (Note: growth factor and transfusion utilization are allowed if cytopenias are considered secondary to bone marrow involvement from MM)

Note: All labs must be performed within 28 days prior to registration.

2. For Participants Meeting "Intermediate Fit" Status, at least one of the following five criteria must be present (NOTE: As long as participants meet any of the below criteria for intermediate fit, the remaining criteria are not mandatory):

    i. Kidney dysfunction showing calculated CrCl <30 ml/min (participants on dialysis are not eligible). Calculated as:

    Calculated Creatinine Clearance =

$$\frac{(140 - \text{age}) \times (\text{weight in kg})\ \dagger}{72 \times \text{serum creatinine}\ *}$$

    Multiply this number by 0.85 if the participant is a female.

    † The kilogram weight is the participant weight with an upper limit of 140% of the IBW.

    *Actual lab serum creatinine value with a minimum of 0.7 mg/dL.

    ii. Hemoglobin $\geq$ 7 and < 8 g/dL, OR
    iii. Platelets $\geq$ 50 and < 75 x109/L, OR
    iv. ANC $\geq$ 0.75 and < 1 x109/L.

    (Note: growth factor and transfusion utilization are allowed as long as cytopenias are considered secondary to bone marrow involvement from MM)

v. R-ISS stage III disease.

b. Participants must have a complete medical history and physical exam within 28 days prior to registration.

c. Participants must have whole body imaging within 60 days prior to registration.

The recommended method of imaging is a PET/CT; a low-dose whole body CT scan or whole-body MRI or skeletal survey should be done only if a PET/CT scan cannot be done or is non-feasible. This must be documented in the comments section of the Onstudy form.

Scan must be completed prior to initiation of any treatment for multiple myeloma with the exception of localized palliative radiation therapy.

d. Participants must have adequate organ function as defined below within 28 days prior to registration:

1. total bilirubin ≤ 2 times institutional upper limit of normal (ULN) unless history of Gilbert's disease. Participants with history of Gilbert's disease must have total bilirubin ≤ 5 x institutional ULN.

2. AST/ALT ≤ 3 × institutional ULN

e. Participants must have adequate cardiac function, as assessed by the treating physician within 14 days prior to registration. Participants with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, must have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification (see Section 18.3), and must not be assessed as Class 3 or 4.

f. Participants with known diabetes must show evidence of controlled disease within 14 days prior to registration. Uncontrolled diabetes is defined as: An HgA1C > 9%.
Participants on dialysis are ineligible.

g. Participants must have an ECOG/Zubrod performance status score of 0-2 (See Section 10.8). (Note: Participants with ECOG/Zubrod PS 3, especially where the deterioration of PS is considered secondary to the MM diagnosis, will be allowed.)

h. Participants with known human immunodeficiency virus (HIV)-infection must be receiving anti-retroviral therapy and have an undetectable viral load test on the most recent test result obtained, within 6 months prior to registration.

i. All participants with evidence of chronic hepatitis B virus (HBV) infection must have undetectable HBV viral load on suppressive therapy within 28 days prior to registration. Participants with known history of HBV must be screened using realtime polymerase

chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. EXCEPTION: Subjects with serologic findings suggestive of HBV
vaccination (anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by PCR.

j. Participants with a history of hepatitis C virus (HCV) infection must have been treated and cured. For participants with HCV infection who are currently on treatment, participant must have an undetectable HCV viral load within 28 days prior to registration.

k. Participants must not have evidence of greater than or equal to grade 3 peripheral neuropathy prior to study registration.

l. Participants must not have uncontrolled blood pressure within 14 days prior to registration, to be determined by the treating physician.

m. Participants must not have known allergies to any of the study drugs.

n. Participants must not have had a major surgery within 14 days prior to registration and be fully recovered from any prior surgery prior to registration.

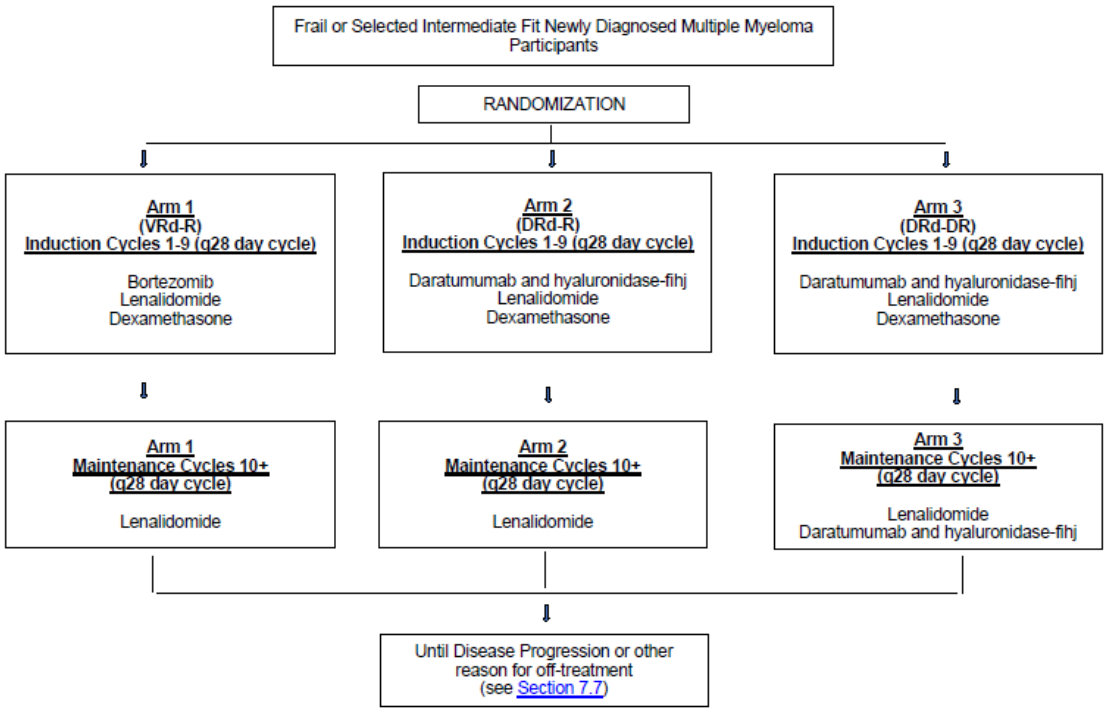
o. Participants must not have a known or uncontrolled chronic obstructive pulmonary disease with prior testing resulting in a forced expiratory volume in 1 second (FEV1) <50% of predicted normal.

p. Participants must not have received vaccination with live attenuated vaccines within 28 days prior to Registration.

q. Participants must not have a prior or concurrent malignancy whose natural history or treatment (in the opinion of the treating physician) has the potential to interfere with the safety or efficacy assessment of the investigational regimen.

r. Participants of childbearing potential must have a negative pregnancy test 14 days prior to registration and again within 24 hours prior to starting treatment on Cycle 1, Day 1 (See section 7.2 and 9.0 for additional details). Participants must not be pregnant or nursing. Individuals who are of reproductive potential must have agreed to use an effective contraceptive method with details provided as a part of the consent process. A person who has had menses at any time in the preceding 24 consecutive months or who has semen likely to contain sperm is considered to be of "reproductive potential." In addition to routine contraceptive methods, "effective contraception" also includes refraining from sexual activity that might result in pregnancy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) including hysterectomy, bilateral oophorectomy, bilateral tubal ligation/occlusion, and vasectomy with testing showing no sperm in the semen.

SCHEMA


Frail or Selected Intermediate Fit Newly Diagnosed Multiple Myeloma Participants
RANDOMIZATION
Arm 1
(VRd-R)
Induction Cycles 1-9 (q28 day cycle)
Bortezomib
Lenalidomide
Dexamethasone
Arm 2
(DRd-R)
Induction Cycles 1-9 (q28 day cycle)
Daratumumab and hyaluronidase-fihj
Lenalidomide
Dexamethasone
Arm 3
(DRd-DR)
Induction Cycles 1-9 (q28 day cycle)
Daratumumab and hyaluronidase-fihj
Lenalidomide
Dexamethasone
Arm 1
Maintenance Cycles 10+
(q28 day cycle)
Lenalidomide
Arm 2
Maintenance Cycles 10+
(q28 day cycle)
Lenalidomide
Arm 3
Maintenance Cycles 10+
(q28 day cycle)
Lenalidomide
Daratumumab and hyaluronidase-fihj
Until Disease Progression or other reason for off-treatment
(see Section 7.7)