### Treatment Plan:

1 cycle = 21 days; repeat until disease progression or unacceptable toxicity

**Arms A, B, C (Phase I):**
- Daratumumab 16 mg/kg IV days 1, 8, 15, cycles 1-3; 16 mg/kg IV day 1, cycles 4+
- Bortezomib 1.3 mg/m² SC days 1, 8, 15, cycles 1-8
- Dexamethasone 40 mg PO days 1, 8, 15 cycles 1-8
- Venetoclax every cycle:
  - Arm A 400 mg PO days 1-21
  - Arm B 600 mg PO days 1-21
  - Arm C 800 mg PO days 1-21

**Arm D (Phase II):**
- Venetoclax recommended phase 2 dose PO days 1-21, every cycle
- Daratumumab 16 mg/kg IV days 1, 8, 15, cycles 1-3; 16 mg/kg IV day 1, cycles 4+
- Bortezomib 1.3 mg/m² SC days 1, 8, 15, cycles 1-8
- Dexamethasone 40 mg PO days 1, 8, 15 cycles 1-8

**Arm E (Phase II):**
- Daratumumab 16 mg/kg IV days 1, 8, 15, cycles 1-3; 16 mg/kg IV day 1, cycles 4+
- Bortezomib 1.3 mg/m² SC days 1, 8, 15, cycles 1-8
- Dexamethasone 40 mg PO days 1, 8, 15 cycles 1-8

**Notes:**
- **Dosing is based on actual body weight; dexamethasone dose is permitted to be reduced for certain criteria per protocol**
- **See the protocol for recommended concomitant medications for Daratumumab**

### Patient Population:

**See Protocol Section 3.0 for Complete Eligibility Details**

**Phase I (Arms A, B, C) - Step 1 And Phase II (Arms D, E) - Step 1:**
- Age ≥ 18 years, ECOG PS 0-2, and adequate lab values
- Must have been diagnosed with symptomatic relapsed/refractory multiple myeloma (defined per protocol)
- t(11;14) status must be determined
- Must not have bortezomib refractory disease; prior lenalidomide refractory patients are allowed
- Must have been treated with 1 or more lines of therapy (defined per protocol)
  - Auto stem transplant is allowed provided the patient is 100 days out from stem cell infusion
  - No prior venetoclax
  - Allogeneic SCT patients are excluded
- Must have measurable disease (defined per protocol)
- Women must not be pregnant or breastfeeding
- Must not have > grade 2 neuropathy and/or POEMS
- Must not have NYHA Class III/IV heart failure or myocardial infarction within 6 months prior to registration
- Must avoid concomitant use of venetoclax with moderate/strong CYP3A inhibitors/inducers, P-gp inhibitors, or narrow therapeutic index P-gp substrates
- Must not be seropositive for hepatitis B (PCR positive patients are not eligible) or C; see protocol for details

**Notes:**
- Dosing is based on actual body weight; dexamethasone dose is permitted to be reduced for certain criteria per protocol
- See the protocol for recommended concomitant medications for Daratumumab

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**Patient Enrollment**

All Sites: Oncology Patient Enrollment Network (OPEN) [https://open.ctsu.org](https://open.ctsu.org)

**Protocol Information**

ECOG-ACRIN Operations-Boston: 857-504-2900, [http://ecog-acrin.org](http://ecog-acrin.org) (Member Login)

Please Enroll Your Eligible Patients!
**Phase I Schema**

**Arm A:**
- Venetoclax: 400 mg PO days 1-21 every cycle
- Daratumumab: 16 mg/kg IV days 1, 8, 15 cycles 1-3, day 1 cycles 4 and on
- Bortezomib: 1.3 mg/m² SC days 1, 8, 15 cycles 1-8
- Dexamethasone: 40 mg PO days 1, 8, 15 cycles 1-8

Continue treatment until disease progression or unacceptable toxicity

**Arm B:**
- Venetoclax: 600 mg PO days 1-21 every cycle
- Daratumumab: 16 mg/kg IV days 1, 8, 15 cycles 1-3, day 1 cycles 4 and on
- Bortezomib: 1.3 mg/m² SC days 1, 8, 15 cycles 1-8
- Dexamethasone: 40 mg PO days 1, 8, 15 cycles 1-8

Continue treatment until disease progression or unacceptable toxicity

**Arm C:**
- Venetoclax: 800 mg PO days 1-21 every cycle
- Daratumumab: 16 mg/kg IV days 1, 8, 15 cycles 1-3, day 1 cycles 4 and on
- Bortezomib: 1.3 mg/m² SC days 1, 8, 15 cycles 1-8
- Dexamethasone: 40 mg PO days 1, 8, 15 cycles 1-8

Continue treatment until disease progression or unacceptable toxicity

Cycle = 3 weeks (21 days)
Phase I Accrual Goal: 3-18 patients

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**Phase II Schema**

**Arm D:** Dvd + Venetoclax
- Venetoclax: RP2D PO days 1-21 every cycle
- Daratumumab: 16 mg/kg IV days 1, 8, 15 cycles 1-3, day 1 cycles 4 and on
- Bortezomib: 1.3 mg/m² SC days 1, 8, 15 cycles 1-8
- Dexamethasone: 40 mg PO days 1, 8, 15 cycles 1-8

Continue treatment until disease progression or unacceptable toxicity

**Arm E:** Dvd
- Daratumumab: 16 mg/kg IV days 1, 8, 15 cycles 1-3, day 1 cycles 4 and on
- Bortezomib: 1.3 mg/m² SC days 1, 8, 15 cycles 1-8
- Dexamethasone: 40 mg PO days 1, 8, 15 cycles 1-8

Continue treatment until disease progression or unacceptable toxicity

Cycle = 3 weeks (21 days)
Phase II Accrual Goal: 254 patients

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1. All patients will be classified by t(11;14) status at baseline prior to randomization