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Randomized, Open-label, Phase 3 Study of Subcutaneous Daratumumab (DARA SC) Versus Active Monitoring in Patients With High-risk Smoldering Multiple Myeloma (SMM): AQUILA

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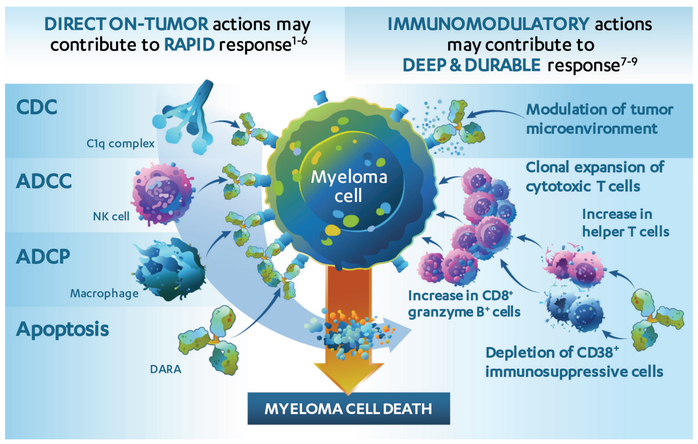
INTRODUCTION

- Smoldering multiple myeloma (SMM) is a pre-malignant asymptomatic precursor state to multiple myeloma (MM)[1]
- Patients with high-risk SMM have an approximately 50% risk of progression to MM within the first 2 years[1]
- Current guidelines for SMM recommend active monitoring for progression to symptomatic MM before initiating treatment as standard of care[1]
- However, earlier treatment may benefit patients with SMM at risk of progression
  - In the QuiRedex study of lenalidomide and dexamethasone (Rd) versus observation in patients with high-risk SMM, treatment with Rd significantly delayed progression to symptomatic MM[2]
  - However, several limitations of the QuiRedex study leave an unmet need for a less toxic treatment for this asymptomatic patient population
- Daratumumab (DARA) is a human IgGκ anti-CD38 monoclonal antibody with direct on-tumor–mediated mechanisms of action that include complement-dependent cytotoxicity,[3] antibody-dependent cellular cytotoxicity,[3] antibody-dependent cellular phagocytosis,[4] apoptosis,[5] and direct enzymatic inhibition[6] (**Figure 1**)
- DARA also demonstrates an immunomodulatory mechanism of action and can induce lysis of myeloid-derived suppressor cells, regulatory B cells, and a subpopulation of regulatory T cells ($CD4^+CD25^+CD127^{dim}$) to promote T-cell activity[7] (**Figure 1**)
- DARA (16 mg/kg intravenously) is approved[8]:
  - As monotherapy in heavily pre-treated MM patients who received ≥3 prior lines of therapy, including a proteasome inhibitor and an immunomodulatory drug, or who are double refractory to these agents
  - In combination with lenalidomide and dexamethasone or bortezomib and dexamethasone for MM patients who received ≥1 prior therapy
  - In combination with pomalidomide and dexamethasone for MM patients who received ≥2 prior therapies, including lenalidomide and a proteasome inhibitor
  - In combination with bortezomib, melphalan, and prednisone for the treatment of patients with newly diagnosed MM who are ineligible for autologous stem cell transplant



DARA, daratumumab; CDC, complement-dependent cytotoxicity; ADCC, antibody-dependent cellular cytotoxicity; NK, natural killer; ADCP, antibody-dependent cellular phagocytosis.

1. DARZALEX® (daratumumab) injection, for intravenous use [package insert]. Horsham, PA: Janssen Biotech, Inc.; 2018. 2. Liszewski MK, et al. *Adv Immunol*. 1996;61:201-283. 3. Debets JM, et al. *J Immunol*. 1988;141(4):1197-1201. 4. Overdijk MB, et al. *MAbs*. 2015;7(2):311-321. 5. Lokhorst HM, et al. *N Engl J Med*. 2015;373(13):1207-1219. 6. Plesner T, et al. Presented at: ASH; December 8-11, 2012; Atlanta, GA. Abstract 73. 7. Krejcik J, et al. *Blood*. 2016;128(3):384-394. 8. Adams H, et al. Presented at: ASH; December 3-6, 2016; San Diego, CA. Abstract 4521. 9. Chiu C, et al. Presented at: ASH; December 3-6, 2016; San Diego, CA. Abstract 4531.

Figure 1. DARA mechanism of action.

- In a phase 1b relapsed or refractory MM (RRMM) study, a subcutaneous co-formulation of DARA (DARA SC) with recombinant human hyaluronidase PH20 (rHuPH20; ENHANZE® drug delivery technology, Halozyme, Inc.) showed low infusion reaction rates and similar response rates to those seen with the intravenous (IV) formulation of DARA in RRMM[9]
- Single-agent DARA IV demonstrated encouraging efficacy and tolerability in a phase 2 study of intermediate- or high-risk SMM[10]
  - Based on the long dosing schedule:
    - Overall response rate was 56%, with 29% ≥very good partial responses and 2% ≥complete response
    - 12-month progression-free survival (PFS) rate based on SLiM-CRAB criteria[11] was 95%
    - 12-month PFS rate based on biochemical or diagnostic (SLiM-CRAB) progression was 93%
- We hypothesized that DARA SC may delay progression of high-risk SMM to MM compared with active monitoring

OBJECTIVE

- To evaluate the efficacy, safety, pharmacokinetics, and biomarkers of DARA SC versus active monitoring in patients with high-risk SMM

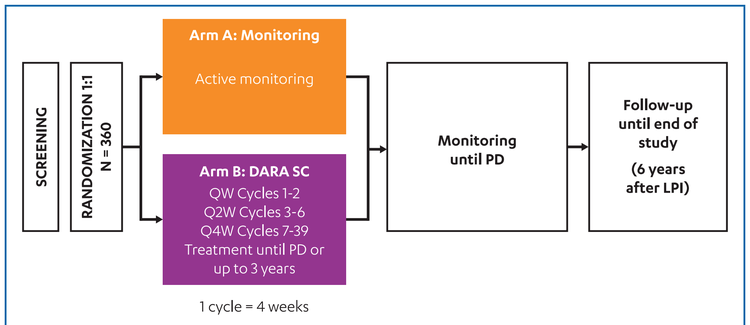
METHODS

Key Eligibility Criteria

- ≥18 years of age
- Confirmed diagnosis of SMM (per International Myeloma Working Group [IMWG] criteria[11]) for ≤5 years with measurable disease, defined as:
  - Serum M-protein ≥10 g/L, or
  - Urine M-protein ≥200 mg/24 hours, or
  - Involved serum free light chain (FLC) ≥100 mg/L and abnormal serum FLC ratio
- Factors indicating a high risk of progression, including clonal bone marrow plasma cells (BMPCs) ≥10% and ≥1 of the following:
  - Serum M-protein ≥30 g/L
  - Immunoglobulin A (IgA) SMM
  - Immunoparesis with reduction of 2 uninvolved Ig isotypes
  - Serum involved:uninvolved FLC ratio ≥8 to <100
  - Clonal BMPCs >50% to <60% with measurable disease
- Eastern Cooperative Oncology Group performance status of ≤1
- Pre-treatment clinical laboratory values meeting the following criteria during the screening phase:
  - Absolute neutrophil count ≥1.0 × 10^9/L
  - Platelet count ≥50 × 10^9/L
  - Aspartate aminotransferase ≤2.5 × upper limit of normal (ULN)
  - Alanine aminotransferase ≤2.5 × ULN
  - Total bilirubin ≤2.0 × ULN
- No MM per SLiM-CRAB criteria or primary systemic light chain amyloidosis
- No prior exposure to approved or investigational treatments for SMM or MM

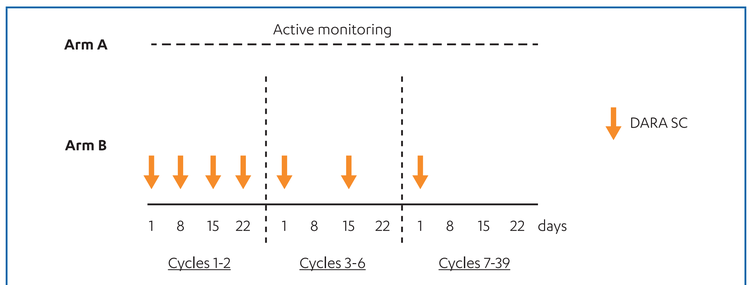
Study Design

- AQUILA is an ongoing, phase 3, randomized, open-label, multicenter study in patients with high-risk SMM
- Approximately 360 patients will be stratified and randomized in a 1:1 ratio to receive active monitoring (no study medication; Arm A) or DARA SC (Arm B) for up to 39 cycles or up to 36 months or until confirmed disease progression (**Figure 2**)
- Randomization will be stratified based on the number of factors associated with progression to MM (<3 vs ≥3); factors include the following:
  - Involved:uninvolved FLC ratio ≥8 (yes vs no)
  - Serum M-protein ≥30 g/L (yes vs no)
  - IgA SMM (yes vs no)
  - Immunoparesis (reduction of 2 uninvolved Ig isotypes vs other)
  - BMPCs (>50% to <60% vs ≤50%)
- The dosing schedule is summarized in **Figure 3** (28-day cycles)
  - Arm A (active monitoring)
    - No study medication
  - Arm B (DARA SC; 1,800 mg DARA + rHuPH20 [2,000 U/mL])
    - DARA SC weekly for Cycles 1 and 2, every 2 weeks for Cycles 3 through 6, and every 4 weeks thereafter
    - Administered by manual injection (15 mL) over approximately 5 minutes at alternating abdominal locations
- The study will include approximately 170 sites that span 25 countries (**Figure 4**)



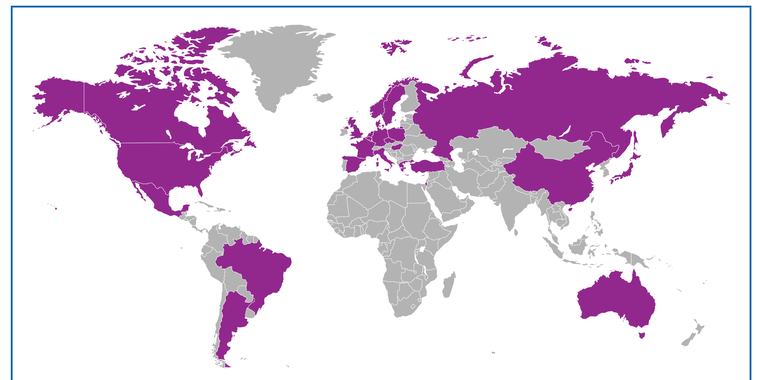
DARA, daratumumab; SC, subcutaneous; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; PD, progressive disease; LPI, last patient in.

Figure 2. AQUILA study design.



DARA, daratumumab; SC, subcutaneous; IV, intravenously; PO, orally; IRR, injection-related reaction.
Arrows indicate when DARA is administered. DARA is administered on Days 1, 8, 15, and 22 for Cycles 1 and 2, on Days 1 and 15 for Cycles 3 through 6, and on Day 1 for each cycle thereafter. DARA will be administered until discontinuation criteria are met. Patients in Arm B will receive the following pre-medications 1 to 3 hours prior to each DARA administration: acetaminophen 650 to 1,000 mg IV or PO, diphenhydramine 25 to 50 mg (or equivalent) IV or PO, and methylprednisolone 100 mg (or equivalent) IV or PO for the first 2 doses and 60 mg for all subsequent doses (in the absence of IRRs). Pre-dose administration of montelukast 10 mg (or equivalent) PO is also recommended on Cycle 1 Day 1. Patients will also receive methylprednisolone 20 mg (or equivalent) PO on the 2 days following each DARA administration; in the absence of IRR after the first 3 doses of DARA, post-dose corticosteroids should be administered per investigator discretion. Each cycle is 28 days.

Figure 3. AQUILA dosing schedule.



Study sites are in Argentina, Australia, Belgium, Brazil, Canada, China, Czechia, Denmark, France, Germany, Greece, Hungary, Israel, Italy, Japan, Mexico, The Netherlands, Norway, Poland, Russia, Spain, Sweden, Turkey, United Kingdom, and United States (shaded in purple).

Figure 4. AQUILA clinical sites.

Study Endpoints and Evaluations

- Primary
  - PFS, as assessed by an independent review committee according to IMWG diagnostic criteria[11]
- Secondary
  - Time to biochemical or diagnostic (SLiM-CRAB) progression
  - Overall response rate
  - Complete response rate
  - Time to first-line treatment for MM
  - Progression-free survival on first-line treatment for MM (PFS2)
  - Overall survival
  - Incidence of MM with adverse prognostic features
  - Pharmacokinetics and immunogenicity
  - Health-related quality of life
  - Duration of and time to response

Statistical Analyses

- The primary analysis population will be the intent-to-treat population
- Randomization of approximately 360 patients is estimated to provide ≥85% power to detect a 37.5% improvement in PFS with a 1-sided alpha of 0.025
- An interim analysis of efficacy and safety will occur when approximately 60% of the PFS events (99) have occurred, which is expected to occur approximately 8 months after the last patient has been randomized
- The primary efficacy analysis will occur when approximately 165 PFS events have been observed, which is expected to occur approximately 2 years after the last patient has been randomized

CONCLUSIONS

- **AQUILA is a phase 3, randomized, open-label, multicenter trial of active monitoring versus DARA SC in patients with high-risk SMM**
- **This study is currently enrolling patients**
  - **The first patient was randomized on December 10, 2017**

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DISCLOSURES

SVR has no conflicts of interest to report. PMV consulted for Celgene, Janssen, Bristol-Myers Squibb, Novartis, Oncopeptides, and TeneoBio; and served on speakers bureaus for Amgen, Celgene, and Janssen. HG received honoraria from Celgene, Janssen, Novartis, Chugai, Bristol-Myers Squibb, and ArtTempi; consulted for Adaptive Biotechnologies, Amgen, Bristol-Myers Squibb, Celgene, Janssen, Sanofi, and Takeda; received research funding from Amgen, Bristol-Myers Squibb, Celgene, Chugai, Janssen, Sanofi, Mundipharma, Takeda, and Novartis; and received travel expenses from Amgen, Bristol-Myers Squibb, Celgene, Janssen, Sanofi, and Takeda. RIB received honoraria from Bayer, Shire, Pfizer, Daiichi Sankyo, CSL Behring, Roche, Amgen, Celgene, Rigel Pharmaceuticals, AbbVie, Sanofi, MorphoSys AG, Acerta Pharma, and Janssen; served on a speakers bureau for Roche; received research funding from Shire, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Portola, and Technoclone; and received travel expenses from Shire, Roche, CSL Behring, Bayer, and Bristol-Myers Squibb. RB, SK, TN, and MQ are employees of Janssen. MAD received honoraria from and consulted for Celgene, Janssen, Takeda, and Amgen.

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