TPS8058

Randomized, Open-label, Non-inferiority, Phase 3 Study of Subcutaneous (SC) Versus Intravenous (IV) Daratumumab (DARA) Administration in Patients With Relapsed or Refractory Multiple Myeloma (RRMM): COLUMBA

Saad Z. Usmani,[1,*] Maria-Victoria Mateos,[2] Nizar Bahlis,[3] Sebastian Grosicki,[4] Andrew Spencer,[5] Rajesh Bandekar,[6] Tara Masterson,[6] Pamela L. Clemens,[6] Christoph Heuck,[7] Ming Qi,[6] Hareth Nahi[8]

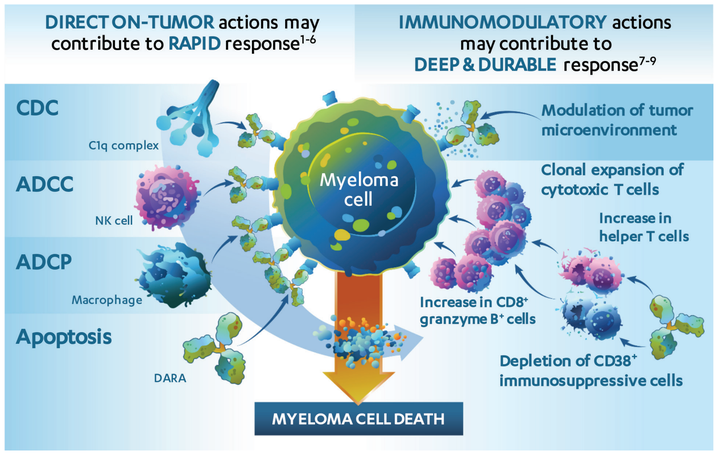
[1]Levine Cancer Institute/Atrium Health, Charlotte, NC, USA; [2]University Hospital of Salamanca/IBSAL, Salamanca, Spain; [3]Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA; [4]Department of Cancer Prevention, School of Public Health,Silesian Medical University in Katowice, Katowice, Poland; [5]Malignant Haematology and Stem Cell Transplantation Service, Alfred Health–Monash University, Melbourne, Australia; [6]Janssen Research & Development, LLC, Spring House, PA, USA; [7]Janssen Research & Development, LLC, Raritan, NJ, USA; [8]Karolinska Institute, Department of Medicine, Division of Hematology, Karolinska University Hospital at Huddinge, Stockholm, Sweden.

Email: Saad.Usmani@carolinashealthcare.org

*Presenting author.

INTRODUCTION

- Patients with multiple myeloma (MM) who have relapsed disease or are refractory to both a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD) have a poor prognosis, with a median overall survival (OS) of about 8 months[1,2]
- 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, 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; 8-11 December 2012; Atlanta, GA. Abstract 73. 7. Krejcik J, et al. *Blood*. 2016;128(3):384-394. 8. Adams H, et al. Presented at: ASH; 3-6 December 2016; San Diego, CA. Abstract 4521. 9. Chiu C, et al. Presented at: ASH; 3-6 December 2016; San Diego, CA. Abstract 4531.

Figure 1. DARA mechanism of action.

- DARA (16 mg/kg intravenously [IV]) induces deep and durable responses in patients with relapsed or refractory MM (RRMM) and is approved as monotherapy and in combination with standard of care regimens for the treatment of patients with RRMM or newly diagnosed MM[8-14]
- To shorten the infusion time and decrease the risk of infusion-related reactions (IRRs) with DARA, a subcutaneous co-formulation of DARA (DARA SC) with recombinant human hyaluronidase PH20 (rHuPH20; ENHANZE® drug delivery technology, Halozyme, Inc.) has been developed
- In a phase 1b study in patients with RRMM,[15,16] DARA SC was found to be well tolerated, with low IRR rates and response rates that were similar to those observed historically with DARA IV[10,11]
- The results of that study provide a rationale for further investigation of DARA SC in patients with RRMM

OBJECTIVE

- To compare the efficacy, pharmacokinetics, and IRRs of DARA SC versus DARA IV in patients with RRMM

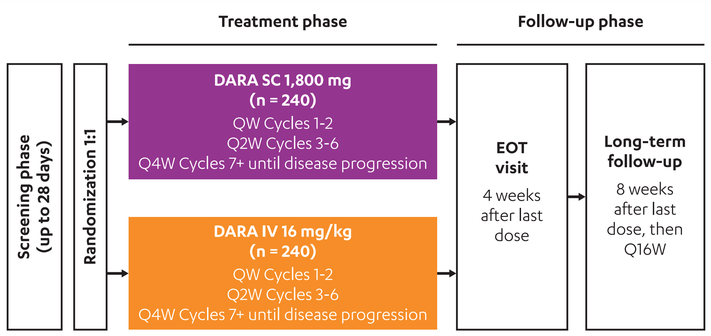
METHODS

Key Eligibility Criteria

- ≥18 years of age
- Documented MM, as defined by the following:
  - MM diagnosis according to International Myeloma Working Group (IMWG) diagnostic criteria[17]
  - Measurable disease at screening, as defined by the following:
    - Serum M-protein level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours, or
    - Light chain MM without measurable disease in the serum or the urine: serum immunoglobulin free light chain (FLC) ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda FLC ratio
- Evidence of response (partial response [PR] or better based on investigator's determination of response by IMWG criteria) to ≥1 prior treatment regimen
- Relapsed or refractory disease
  - Relapsed disease: initial response to previous treatment, followed by confirmed progressive disease (PD) by IMWG criteria >60 days after cessation of treatment
  - Refractory disease: <25% reduction in M-protein or confirmed PD by IMWG criteria during previous treatment or ≤60 days after cessation of treatment
- Treatment history that includes the following:
  - ≥3 prior lines of therapy, including a PI and an IMiD in any order during the course of treatment, or
  - Shown to be refractory to both a PI and an IMiD
- Eastern Cooperative Oncology Group performance status of ≤2
- Pre-treatment clinical laboratory values meeting the following criteria during the screening phase:
  - Hemoglobin ≥7.5 g/dL (≥5 mmol/L)
  - 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
  - Estimated creatinine clearance >20 mL/min per 1.73 m^2
- No prior treatment with DARA or other anti-CD38 therapies
- No known chronic obstructive pulmonary disease with a forced expiratory volume in 1 second <50% of predicted normal
- No known moderate or severe persistent asthma, or history of asthma within the last 2 years, or current uncontrolled asthma of any classification
- No clinically significant cardiac disease

Study Design

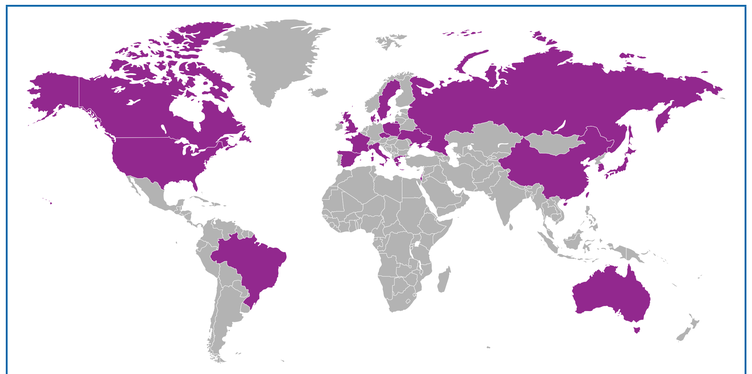
- COLUMBA is an ongoing phase 3, randomized, open-label, multicenter, non-inferiority study of DARA SC versus DARA IV
- Patients are randomly assigned to treatment in a 1:1 ratio (**Figure 2**) and receive
  - DARA SC (1,800 mg DARA in combination with rHuPH20 [2,000 U/mL] administered by manual push [15 mL] over 3-5 minutes at alternating left/right abdominal sites), or
  - DARA IV (16 mg/kg IV infusion)
- Both DARA SC and DARA IV are administered weekly for Cycles 1 and 2, every 2 weeks for Cycles 3 to 6, and every 4 weeks thereafter until disease progression or unacceptable toxicity
  - Cycles are 28 days



DARA, daratumumab; SC, subcutaneous; QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks; IV, intravenously; EOT, end-of-treatment; Q16W, every 16 weeks.

Figure 2. COLUMBA study design.

- Randomization will be stratified by the following:
  - Body weight at baseline (≤65 kg, 66 kg to 85 kg, >85 kg)
  - Number of prior lines of therapy (≤4 vs >4)
  - Type of myeloma (Immunoglobulin G [IgG] vs non-IgG)
- Patients in both groups receive DARA pre- and post-infusion medications
  - Pre-infusion medication
    - Acetaminophen 650-1,000 mg IV or orally (PO)
    - Diphenhydramine 25-50 mg IV or PO (or equivalent)
    - Methylprednisolone 100 mg IV or PO (or equivalent) for the first 2 doses and 60 mg for all subsequent doses
    - Leukotriene inhibitor (montelukast 10 mg PO [or equivalent]) is optional on Cycle 1 Day 1
  - Post-infusion medication
    - Methylprednisolone 20 mg PO (or equivalent) on the 2 days following each DARA administration
    - Patients with higher risk of respiratory complications were recommended diphenhydramine, short-acting ß2 adrenergic receptor agonist, and control medications for lung disease
- A total of 480 patients are expected to enroll in 157 sites that span 19 countries (**Figure 3**)



Study sites are in Australia, Brazil, Canada, China, Czechia, France, Greece, Israel, Italy, Japan, Republic of Korea, Poland, Russian Federation, Spain, Sweden, Taiwan, Ukraine, the United Kingdom, and the United States (shaded in purple).

Figure 3. COLUMBA clinical sites.

Study Endpoints and Sample Size Determination

- Co-primary endpoints
  - Overall response rate
  - Maximum C_{trough} (serum pre-dose DARA concentration on Cycle 3 Day 1)
- Secondary endpoints
  - IRR rate
  - Progression-free survival
  - Rate of very good partial response or better and complete response or better
  - Time to next therapy
  - OS
  - Patient-reported satisfaction with therapy (mean of responses to 7 of 9 questions in the modified Cancer Therapy Satisfaction Questionnaire)
  - Duration of and time to response
- Sample size determination
  - Non-inferiority of DARA SC to DARA IV in the current study is defined using a 60% retention of the lower bound (20.8%) of the 95% confidence interval from the SIRIUS study[11]
  - With a planned 1:1 randomization, 480 patients (n = 240 in each group) will be needed to demonstrate non-inferiority with a power of 80% and a 1-sided alpha = 0.025, assuming that the true overall response rate is the same for both groups
  - To establish non-inferiority of maximum C_{trough} between groups based on the planned 1:1 randomization of 480 patients and a 1-sided alpha = 0.05, the power will be >95%. This assumes a true ratio of the maximum C_{trough} of 1, a non-inferiority margin of ≥80% of the geometric mean ratio, and a coefficient of variation of 0.6

CONCLUSIONS

- **COLUMBA is a phase 3, randomized, open-label, multicenter, non-inferiority study comparing the efficacy, pharmacokinetics, and IRRs of DARA SC versus DARA IV in patients with RRMM**
- **This study is currently enrolling patients**
  - **The first patient was dosed on November 14, 2017**

REFERENCES

1. Kumar SK, et al. *Leukemia*. 2012;26(1):149-157.
2. Usmani S, et al. *Oncologist*. 2016;21(11):1355-1361.
3. de Weers M, et al. *J Immunol*. 2011;186(3):1840-1848.
4. Overdijk MB, et al. *MAbs*. 2015;7(2):311-321.
5. Overdijk MB, et al. *J Immunol*. 2016;197(3):807-813.
6. Lammerts van Bueren J, et al. *Blood*. 2014;124(21):3474.
7. Krejcik J, et al. *Blood*. 2016;128(3):384-394.
8. DARZALEX® (daratumumab) injection, for intravenous use [package insert]. Horsham, PA: Janssen Biotech, Inc; 2018.
9. European Medicines Agency. Summary of opinion (post authorisation). Darzalex (daratumumab). 2017.
10. Lokhorst HM, et al. *N Engl J Med*. 2015;373(13):1207-1219.
11. Lonial S, et al. *Lancet*. 2016;387(10027):1551-1560.
12. Palumbo A, et al. *N Engl J Med*. 2016;375(8):754-766.
13. Dimopoulos MA, et al. *N Engl J Med*. 2016;375(14):1319-1331.
14. Mateos MV, et al. *N Engl J Med*. 2018;378(6):518-528.
15. Chari A, et al. Presented at: Annual Meeting of the American Society of Hematology (ASH); December 9-12, 2017; Atlanta, GA. Abstract 838.
16. Usmani SZ, et al. Presented at: Annual Meeting of the American Society of Hematology (ASH); December 3-6, 2016; San Diego, CA. Abstract 1149.
17. Rajkumar SV, et al. *Lancet Oncol*. 2014;15:e538-e548.

ACKNOWLEDGMENTS

The authors would like to acknowledge the patients participating in this study and their families, as well as the global network of investigators, research nurses, study coordinators, and operations staff. This study (ClinicalTrials.gov Identifier: NCT03277105) is sponsored by Janssen Research & Development, LLC. Editorial and medical writing support were provided by Jason Jung, PhD, of MedErgy, and were funded by Janssen Global Services, LLC.

DISCLOSURES

SZU consulted for Celgene, Amgen, Takeda, Sanofi, Skyline, Onyx, Millennium, and Janssen; received research funding from Onyx, Sanofi, Array BioPharma, Pharmacyclics, Takeda, Celgene, and Bristol-Myers Squibb; served on a speakers bureau for Celgene, Amgen, and Takeda; provided expert testimony to Janssen and Celgene; and received travel expenses from Janssen, Celgene, Amgen, and Takeda. M-VM received honoraria from and consulted for Celgene, Janssen, Takeda, and Amgen. NB received honoraria from and consulted for Celgene, Janssen, Takeda, and Amgen; served on a speakers bureau for Janssen, Celgene, and Amgen; and received research funding from Janssen and Celgene. AS received research funding and honoraria from Janssen. RB, TM, PLC, CH, and MQ are employees of Janssen. SG and HN have no conflicts of interest to report.

POSTER PRESENTED AT THE ANNUAL MEETING OF THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO); JUNE 1-5, 2018; CHICAGO, ILLINOIS.