E1263

Indirect Comparison of Daratumumab Monotherapy Versus Real-world Historical Control Data in Patients With Multiple Myeloma Who Are Heavily Pretreated and Highly Refractory

Joris Diels,[1,*] Annette Lam,[2] Tetsuro Ito,[3] Yvette Ng,[2] Maneesha Mehra,[2] Imran Khan[4]

[1]Janssen Health Economics & Market Access EMEA Statistics & Modeling, Beerse, Belgium; [2]Janssen Global Services, Raritan, NJ, USA; [3]Janssen Health Economics & Market Access EMEA, High Wycombe, UK; [4]Janssen Research & Development, LLC, Raritan, NJ, USA.

*Presenting author.

INTRODUCTION

- Despite the introduction of immunomodulatory drugs (IMiDs), such as thalidomide and lenalidomide, and the proteasome inhibitor (PI) bortezomib, outcomes remain poor in patients with relapsed and refractory multiple myeloma (MM)[1]
  - In 2012, an International Myeloma Working Group study determined that the median overall survival (OS) for patients refractory to bortezomib and ≥1 IMiD was 9 months[1]
- Daratumumab (DARA) is a human IgG1 monoclonal antibody that binds CD38, which is highly and ubiquitously expressed on myeloma cells[2,3]
- Combined analysis of 2 studies of DARA 16 mg/kg monotherapy in patients with heavily pretreated/highly refractory MM yielded an overall response rate of 31% and a median OS of 20.1 months[4]
- Using current, real-world experience to understand the outcomes in patients with MM who are heavily pretreated/refractory is important to fully evaluate the potential benefit of DARA in the treatment of this patient population

OBJECTIVE

- To establish the comparative efficacy of DARA versus real-world historical controls (physician's choice) through adjusted treatment comparison using patient-level data

METHODS

Real-world Historical Controls

- Medical records from the following 2 independent databases, composed of US patients, were evaluated:
  - The IMS LifeLink database, with an indexing period of 2007 to 2014
  - The OPTUM database, with an indexing period of 2007 to 2014
- Key inclusion criteria
  - Diagnosis of MM from 2000 to 2011 in the IMS LifeLink database or from 2007 to 2014 in the OPTUM database
    - ICD-9 codes for MM were 203X, 203.0X, 203.00X, 203.01X, and 203.02X in both databases
  - No other cancer diagnosis prior to the diagnosis of MM, with the exception of benign and in situ neoplasms, basal cell carcinoma, and squamous cell carcinoma
  - At least 3 prior lines of therapy (LOTs) that include a PI and an IMiD and progression of disease within 60 days of completion of the most recent regimen OR refractory to both a PI and an IMiD, as defined in **Table 1**

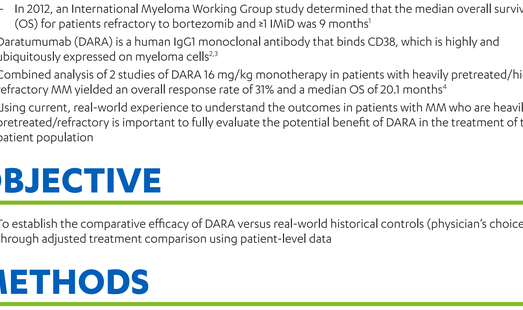
Table 1. Definitions of Refractory Status

Definition 1	Duration of therapy of current regimen ≤60 days AND none of the current drugs in next regimen
Definition 2	Time to next regimen ≤60 days AND none of the current drugs in next regimen
Definition 3	Both baseline and follow-up M-protein values available but no >25% decline

Patients Treated With DARA

Inclusion Criteria

- Pooled analysis of outcomes in patients from 2 open-label studies of DARA 16 mg/kg (GEN501 [ClinicalTrials.gov Identifier: NCT00574288] and SIRIUS [NCT01985126]) as monotherapy (**Figure 1**)



QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks; DARA, daratumumab.

Figure 1. Study design for GEN501 and SIRIUS.

- Key inclusion criteria
  - In both studies, age ≥18 years and Eastern Cooperative Oncology Group (ECOG) performance status ≤2
  - In GEN501, relapsed from or refractory to ≥2 prior LOTs that include a PI and an IMiD
  - In SIRIUS, relapsed from or refractory to ≥3 prior LOTs that include a PI or an IMiD OR double refractory to a PI and an IMiD

Study Designs

- GEN501 was an open-label, phase 1/2, dose-escalation and dose-expansion study[5]
- SIRIUS was an open-label, multicenter, phase 2 study[6]

Endpoints

- For patients identified in IMS LifeLink or OPTUM databases, OS from the start of the last LOT was defined based on death or loss to follow-up >30 days prior to the study end date
- For patients in the GEN501 and SIRIUS studies, OS was defined as the number of days from the first dose of DARA to death

Adjusted Treatment Comparison

- The relative treatment effect of DARA was estimated using patient-level data from real-world historical controls (US claims databases) and clinical studies (pooled analysis of patients receiving DARA 16 mg/kg in GEN501 Part 2 and SIRIUS)
- Statistical adjustments were made using patient-level data, assuming no unobserved confounders
  - Multivariate proportional hazards regression modeling was used
    - Covariates included age, gender, exposure to prior therapies, LOT, albumin and hemoglobin levels, and refractory status

RESULTS

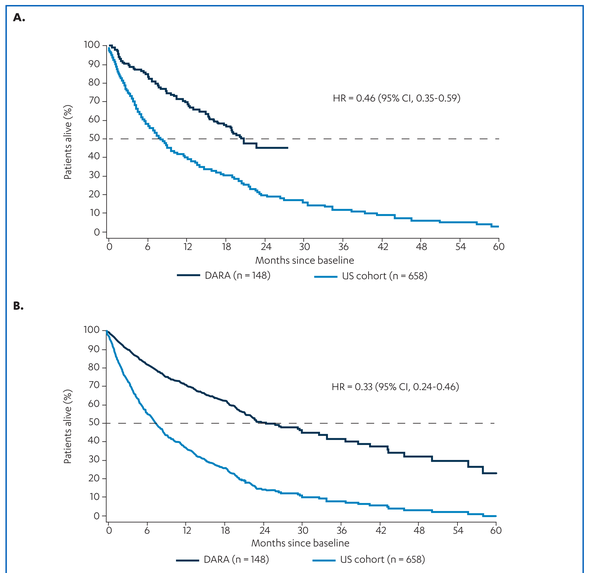
- Demographics from the US databases were consistent, so the data were pooled (N = 658)
  - Median OS was 7.9 months
- Similarly, demographics from GEN501 and SIRIUS were comparable and were pooled (N = 148)
  - Median OS was 20.1 months
- Demographics for the pooled DARA-treated and US claims datasets are shown in **Table 2**
  - Median age (64 years vs 69 years) and median number of prior LOTs (5 vs 4) were similar between DARA-treated patients and historical controls, respectively
  - DARA-treated patients were more likely than historical controls to have received carfilzomib (41% vs 28%) or pomalidomide (55% vs 15%), or to be triple/quadruple refractory (64% vs 14%), respectively

Table 2. Demographics of DARA-treated Patients Versus Historical Controls From US Claims Databases

	DARA (N = 148)	US claims (N = 658)
Median (range) age, y	64 (31-84)	69 (31-83)
Gender, %		
Male	53	53
Female	47	47
Median (range) number of prior LOTs, %	5 (2-14)	4 (1-28)
Hemoglobin, %		
<80 g/L	5	10
80-100 g/L	42	20
>100 g/L	53	52
Data missing	0	19
Beta 2 microglobulin, %		
<3.5 mg/L	39	30
≥3.5 mg/L	61	47
Data missing	0	22
Prior exposure to, %		
Carfilzomib	41	28
Pomalidomide	55	15
Refractory status, %		
Not double refractory	13	33
Double refractory	23	53
Triple/quadruple refractory	64	14

DARA, daratumumab; LOT, line of therapy.

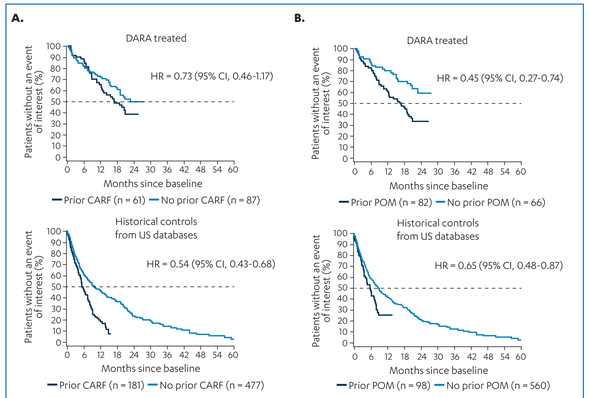
- The unadjusted hazard ratio (HR) for DARA-treated patients was 0.46 (95% confidence interval [CI], 0.35-0.59; *P* <0.001; **Figure 2A**) compared with historical controls
- **Figure 2B** represents the predicted survival for the US cohort as treated versus under DARA treatment, based on the multivariate Cox proportional hazards regression model (HR = 0.33 [95% CI, 0.24-0.46]; *P* <0.001)
- Refractory status and prior pomalidomide/carfilzomib exposure had the greatest impact on adjustment



OS, overall survival; DARA, daratumumab; HR, hazard ratio; CI, confidence interval.

Figure 2. Unadjusted (A) and adjusted (B) OS in DARA-treated patients versus historical controls from US claims databases.

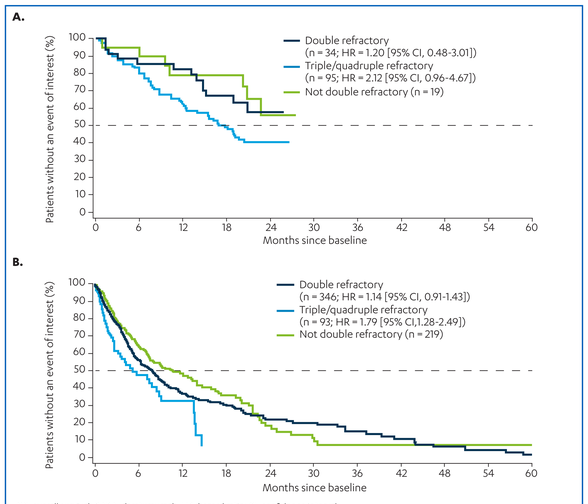
- In both DARA-treated patients and patients from US claims databases, hazard ratios were lower in patients without prior exposure to carfilzomib than in patients with prior exposure (0.73 [95% CI, 0.46-1.17] and 0.54 [95% CI, 0.43-0.68], respectively; **Figure 3A**)
- Similarly, in both DARA-treated patients and patients from US claims databases, HRs were lower in patients without prior exposure to pomalidomide than in patients with prior exposure (0.45 [95% CI, 0.27-0.74] and 0.65 [95% CI, 0.48-0.87], respectively; **Figure 3B**)



OS, overall survival; DARA, daratumumab; HR, hazard ratio; CI, confidence interval; CARF, carfilzomib; POM, pomalidomide.

Figure 3. OS of DARA-treated patients and historical controls from US claims databases by prior exposure to carfilzomib (A) or pomalidomide (B).

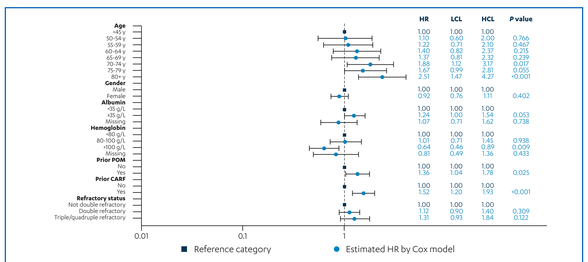
- DARA treatment improved OS in patients who were double refractory, triple/quadruple refractory, or not double refractory to treatment compared with the historical controls (**Figure 4**)



OS, overall survival; DARA, daratumumab; HR, hazard ratio; CI, confidence interval.

Figure 4. OS of DARA-treated patients (A) and historical controls from US claims databases (B) by refractory status.

- Cox proportional HRs were calculated for patient subgroups according to age, gender, albumin level, hemoglobin level, prior exposure to pomalidomide and carfilzomib, and refractory status (**Figure 5**)



HR, hazard ratio; OS, overall survival; LCL, lower confidence level; HCL, higher confidence level; POM, pomalidomide; CARF, carfilzomib.

Figure 5. HRs for OS by baseline covariate: multivariate proportional hazards regression.

CONCLUSIONS

- **Real-world data indicate that, despite the use of newer PIs and IMiDs such as carfilzomib and pomalidomide, outcomes remain poor in patients with heavily pretreated/refractory MM**
  - **Median OS was approximately 8 months among patients with >3 prior LOTs or those who were double refractory to a PI and an IMiD**
- **These data highlight the need for new MM treatments and provide a benchmark against which novel agents can be evaluated**
- **This adjusted treatment comparison suggests that DARA provides a substantial benefit to OS, compared with real-world historical controls, in patients with heavily pretreated/refractory MM**
- **In the absence of head-to-head trials, comparative analyses adjusting for differences in patient characteristics using patient-level data can provide useful insights to clinicians and reimbursement decision makers on the relative efficacy of DARA versus a wider range of treatments**

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