3332

Adjusted Comparison of Daratumumab Monotherapy Versus Real-world Historical Control Data From the Czech Republic in Heavily Pretreated and Highly Refractory Multiple Myeloma Patients

Roman Hájek[1], Tomáš Jelínek[2,*], Vladimír Maisnar[3], Luděk Pour[4], Ivan Špička[5], Jiří Minařík[6], Evžen Gregora[7], Petr Kessler[8], Michal Sýkora[9], Hana Fraňková[10], Dagmar Adamová[11], Marek Wróbel[12], Peter Mikula[13], Jiří Jarkovský[14], Joris Diels[15], Xenia Gatopoulou[16], Sarka Vesela[17], Hervé Besson[15], Lucie Brožová[14], Tetsuro Ito[18]

[1]Department of Hemato-Oncology, University Hospital Ostrava Faculty of Medicine, Ostrava, Czech Republic; [2]Department of Hemato-Oncology, University Hospital Ostrava and Faculty of Medicine, University of Ostrava, Ostrava, Czech Republic; [3]4th Department of Internal Medicine–Hematology, Charles University Faculty Hospital and Faculty of Medicine, Hradec Králové, Czech Republic; [4]Department of Internal Medicine, Hematology and Oncology, University Hospital Brno and Faculty of Medicine Masaryk University, Brno, Czech Republic; [5]Charles University in Prague First Faculty of Medicine and General Teaching Hospital, Prague, Czech Republic; [6]Department of Hemato-Oncology, University Hospital Olomouc and Faculty of Medicine and Dentistry, Palacky University Olomouc, Olomouc, Czech Republic; [7]Department of Internal Medicine and Hematology, University Hospital Kralovske Vinohrady, Prague, Czech Republic; [8]Department of Hematology and Transfusion Medicine, Pelhrimov Hospital, Pelhrimov, Czech Republic; [9]Department of Clinical Hematology, Hospital Ceske Budejovice, Ceske Budejovice, Czech Republic; [10]Department of Hematology, General Hospital Liberec, Liberec, Czech Republic; [11]Department of Clinical Hematology, Silesian Hospital Opava, Opava, Czech Republic; [12]Department of Hematology, Hospital Novy Jicin , Novy Jicin, Czech Republic; [13]Department of Clinical Hematology, General Hospital Havirov, Havirov, Czech Republic; [14]Institute of Biostatistics and Analyses, Faculty of Medicine and Faculty of Science, Masaryk University, Brno, Czech Republic; [15]Janssen Health Economics & Market Access EMEA Statistics & Modelling, Beerse, Belgium; [16]Janssen Health Economics & Market Access EMEA, Athens, Greece; [17]Janssen-Cilag s.r.o, Prague, Czech Republic; [18]Janssen Health Economics & Market Access EMEA, High Wycombe, UK.

*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]
  - An International Myeloma Working Group study determined that the median overall survival (OS) for patients refractory to both a PI and an IMiD was 13 months[1]
  - A retrospective analysis of the IMS LifeLink and OPTUM databases for the years 2000-2014 found that the median OS was 7.9 months for patients who were refractory to both a PI and an IMiD or who received ≥3 prior lines of therapy (LOTs), including a PI and an IMiD, and showed disease progression within 60 days of the most recent regimen[2]
- Daratumumab (DARA) is a human monoclonal antibody targeting CD38 that has been shown to provide superior clinical benefit to other established regimens for the treatment of MM in patients with ≥1 prior LOT[2-5]
- A combined analysis of 2 studies (GEN501 and SIRIUS) of DARA 16 mg/kg monotherapy in patients with heavily pre-treated/highly refractory MM yielded an overall response rate of 31% and a median OS of 20.1 months[3]
- DARA 16 mg/kg monotherapy is approved by the US Food and Drug Administration (FDA) for patients with MM who have received ≥3 prior treatments, including a PI and an IMiD, or who are double refractory to a PI and an IMiD[6,7]
  - More recently, DARA received approval by the FDA for use in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with MM who have received at least 1 prior therapy[6]
- DARA 16 mg/kg was also recently approved by the European Medicines Agency as monotherapy for adult patients with relapsed and refractory MM whose prior therapy included a PI and an IMiD and who have demonstrated disease progression on the last therapy[8]
- The use of 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 this patient population
- In the absence of head-to-head clinical trial results, adjusted treatment comparisons may provide useful insights for clinicians and other health care decision makers on the relative efficacies and potential benefits of novel MM therapies such as DARA

OBJECTIVE

- To perform an adjusted comparison of progression-free survival (PFS) and OS for DARA monotherapy versus physician's choice, as observed in a real-world historical control cohort from the Czech Republic, using patient-level data

METHODS

Real-world Historical Controls

- Patient-level data were pooled from the Czech Registry of Monoclonal Gammopathies (RMG)
  - Pooled data represent real-world treatment observations among patients with MM from 12 centers
- Patients previously received ≥2 prior LOTs, including a PI and an IMiD
- Longitudinal follow-up of subsequent treatment lines was available for patients receiving their third (n = 206), fourth (n = 256), fifth (n = 203), and sixth or more (n = 307) LOT
- The unit of observation for the RMG cohort was treatment line within each patient. Individual patients could contribute information to the analysis for multiple LOTs, with baseline defined as the date of initiation of the actual treatment line
  - Baseline values of covariates for each patient were specific to the treatment line
  - The clustering of observations at treatment-line level within patients was controlled by using the robust sandwich estimate for the covariance matrix

Patients Treated With DARA

- Data from patients treated with DARA 16 mg/kg monotherapy in GEN501 (ClinicalTrials.gov Identifier: NCT00574288) and SIRIUS (NCT01985126) clinical studies were pooled

Inclusion Criteria

- Key inclusion criteria
  - In both studies: age ≥18 years and an Eastern Cooperative Oncology Group performance status ≤2[9,10]
  - In GEN501: relapsed from or refractory to ≥2 prior LOTs that included a PI and/or an IMiD[9]
  - In SIRIUS: relapsed from or refractory to ≥3 prior LOTs that included a PI and an IMiD OR double refractory to a PI and an IMiD[10]

Study Design

- GEN501 was an open-label, phase 1/2, dose-escalation and dose-expansion study[9]
- SIRIUS was an open-label, multicenter, phase 2 study[10]

Endpoints

- For patients identified in the RMG cohort, OS was defined as the number of days from the initiation of treatment to death; patients were censored at the last known date that the patient was alive
  - For the definition of PFS, missing data for the date of disease progression for patients in the RMG who initiated subsequent therapy were replaced by the conservative proxy of the date of initiation of the next treatment
- For patients in the GEN501 and SIRIUS studies, OS was defined as the number of days from the first dose of DARA to death; patients alive at the time of the data cut were censored
  - PFS was defined as the time between the date of the first dose of DARA and either disease progression or death, whichever occurred first

Adjusted Treatment Comparison

- The relative treatment effect of DARA versus physician's choice was estimated using patient-level data from real-world historical controls (RMG database) and clinical studies (pooled analysis of patients who received DARA 16 mg/kg in GEN501 Part 2 and SIRIUS)
- Statistical adjustments for differences in baseline characteristics were made using patient-level data
- Multivariate proportional hazards regression modeling included the following baseline covariates:
  - Age, gender, albumin, thrombocytopenia, beta-2 microglobulin, prior pomalidomide/carfilzomib exposure, LOTs, and refractory status

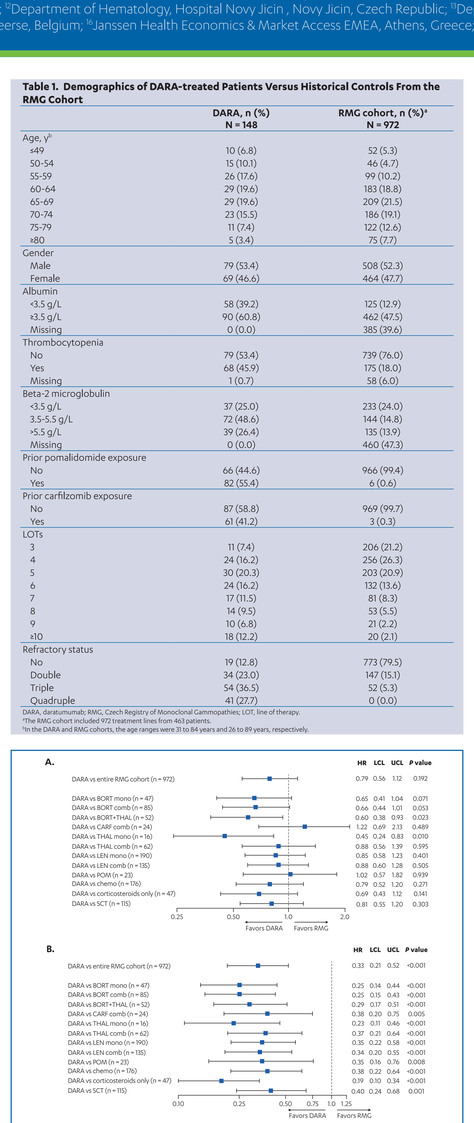
RESULTS

- In the RMG cohort, 972 treatment lines were available from 463 patients
  - Median PFS was 5.8 months (95% confidence interval [CI]: 5.5-6.3)
    - For 147 (15%) of the treatment lines in the RMG cohort, the missing disease progression date was replaced by the start date of the next therapy
  - Median OS was 11.9 months (95% CI: 11.2-13.1)
- Patient demographics from GEN501 (n = 42) and SIRIUS (n = 106) were pooled (N = 148)
  - Median PFS was 4.0 months (95% CI: 2.8-5.6)[3]
  - Median OS was 20.1 months (95% CI: 16.6 months-not estimable)[3]
- Demographics for the pooled DARA-treated and RMG cohorts are shown in **Table 1**
  - Patients in the DARA cohort were younger (median age 64 vs 67 years) and had more prior therapy lines (median 5 vs 4)
  - DARA-treated patients were more likely than historical controls to have received carfilzomib (41.2% vs 0.3%) or pomalidomide (55.4% vs 0.6%), or to be triple or quadruple refractory (64.2% vs 5.3%), respectively
- The unadjusted hazard ratio (HR) for DARA-treated patients compared with historical controls was
  - 1.14 (95% CI: 0.94-1.39) for PFS
  - 0.61 (95% CI: 0.48-0.78) for OS
- The adjusted HR, based on the multivariate Cox proportional hazards regression model, was 0.79 (95% CI: 0.56-1.12; *P* = 0.192) for PFS (**Figure 1A**) and 0.33 (95% CI: 0.21-0.52; *P* <0.001) for OS (**Figure 1B**)
- The adjusted HR for PFS in DARA-treated patients versus individual treatment regimens from the RMG cohort ranged from 0.45 (95% CI: 0.24-0.83) for thalidomide only to 1.22 (95% CI: 0.69-2.13) for carfilzomib-containing combination therapy (**Figure 1A**)
- The adjusted HR for OS in DARA-treated patients versus individual treatment regimens from the RMG cohort ranged from 0.19 (95% CI: 0.10-0.34) for corticosteroid treatment only to 0.40 (95% CI: 0.24-0.68) for stem cell transplantation. All HRs were significantly lower than 1 (**Figure 1B**)
- The adjusted HR for OS in DARA-treated patients versus RMG-cohort patients treated with pomalidomide was 0.35 (95% CI: 0.16-0.76); *P* = 0.008 (**Figure 1B**)
- **Figure 2** illustrates the impact for each of the included baseline characteristics, which was adjusted for in the multivariate model
  - High beta-2 microglobulin levels, 5 prior LOTs, double-refractory status, and triple-refractory status were statistically significant independent risk factors for worse outcome in terms of PFS (**Figure 2A**)
  - Older age, high beta-2 microglobulin levels, thrombocytopenia, and refractory status were statistically significant independent risk factors for worse outcome in terms of OS (**Figure 2B**)
  - Later LOTs were numerically associated with poorer OS

Table 1. Demographics of DARA-treated Patients Versus Historical Controls From the RMG Cohort

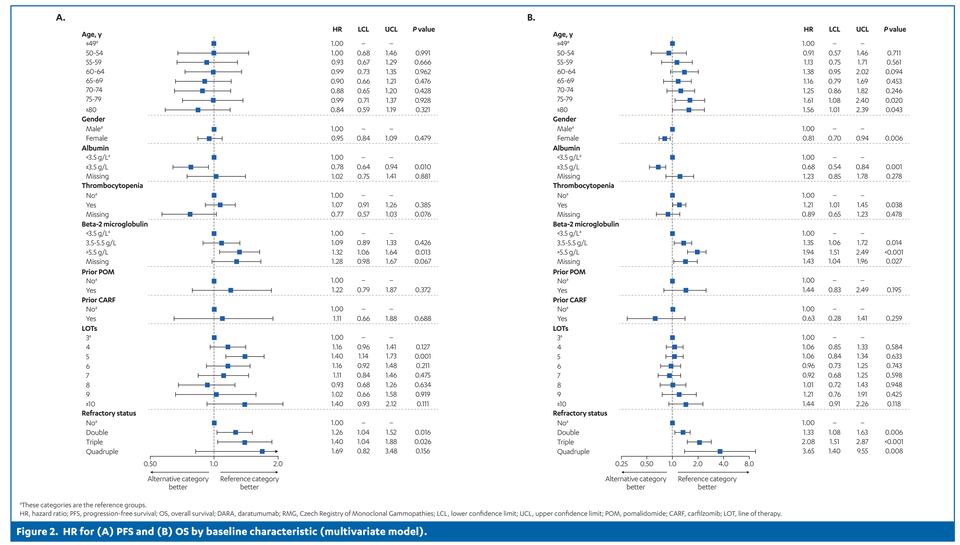
	DARA, n (%) N = 148	RMG cohort, n (%)[a] N = 972
Age, y[b]		
≤49	10 (6.8)	52 (5.3)
50-54	15 (10.1)	46 (4.7)
55-59	26 (17.6)	99 (10.2)
60-64	29 (19.6)	183 (18.8)
65-69	29 (19.6)	209 (21.5)
70-74	23 (15.5)	186 (19.1)
75-79	11 (7.4)	122 (12.6)
≥80	5 (3.4)	75 (7.7)
Gender		
Male	79 (53.4)	508 (52.3)
Female	69 (46.6)	464 (47.7)
Albumin		
<3.5 g/L	58 (39.2)	125 (12.9)
≥3.5 g/L	90 (60.8)	462 (47.5)
Missing	0 (0.0)	385 (39.6)
Thrombocytopenia		
No	79 (53.4)	739 (76.0)
Yes	68 (45.9)	175 (18.0)
Missing	1 (0.7)	58 (6.0)
Beta-2 microglobulin		
<3.5 g/L	37 (25.0)	233 (24.0)
3.5-5.5 g/L	72 (48.6)	144 (14.8)
>5.5 g/L	39 (26.4)	135 (13.9)
Missing	0 (0.0)	460 (47.3)
Prior pomalidomide exposure		
No	66 (44.6)	966 (99.4)
Yes	82 (55.4)	6 (0.6)
Prior carfilzomib exposure		
No	87 (58.8)	969 (99.7)
Yes	61 (41.2)	3 (0.3)
LOTs		
3	11 (7.4)	206 (21.2)
4	24 (16.2)	256 (26.3)
5	30 (20.3)	203 (20.9)
6	24 (16.2)	132 (13.6)
7	17 (11.5)	81 (8.3)
8	14 (9.5)	53 (5.5)
9	10 (6.8)	21 (2.2)
≥10	18 (12.2)	20 (2.1)
Refractory status		
No	19 (12.8)	773 (79.5)
Double	34 (23.0)	147 (15.1)
Triple	54 (36.5)	52 (5.3)
Quadruple	41 (27.7)	0 (0.0)

DARA, daratumumab; RMG, Czech Registry of Monoclonal Gammopathies; LOT, line of therapy.
[a]The RMG cohort included 972 treatment lines from 463 patients.
[b]In the DARA and RMG cohorts, the age ranges were 31 to 84 years and 26 to 89 years, respectively.



HR, hazard ratio; PFS, progression-free survival; OS, overall survival; DARA, daratumumab; RMG, Czech Registry of Monoclonal Gammopathies; LCL, lower confidence limit; UCL, upper confidence limit; BORT, bortezomib; mono, monotherapy; comb, combination; THAL, thalidomide; CARF, carfilzomib; LEN, lenalidomide; POM, pomalidomide; chemo, chemotherapy; SCT, stem cell transplantation.

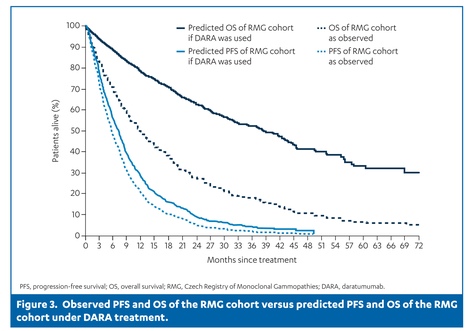
Figure 1. Adjusted HR for (A) PFS and (B) OS: DARA-treated versus RMG-cohort patients.



[a]These categories are the reference groups.
HR, hazard ratio; PFS, progression-free survival; OS, overall survival; DARA, daratumumab; RMG, Czech Registry of Monoclonal Gammopathies; LCL, lower confidence limit; UCL, upper confidence limit; POM, pomalidomide; CARF, carfilzomib; LOT, line of therapy.

Figure 2. HR for (A) PFS and (B) OS by baseline characteristic (multivariate model).

- **Figure 3** represents the predicted PFS and OS for the RMG cohort as treated versus under DARA treatment, based on the multivariate Cox proportional hazards regression model; the difference between both survival curves reflects the adjusted HR



PFS, progression-free survival; OS, overall survival; RMG, Czech Registry of Monoclonal Gammopathies; DARA, daratumumab.

Figure 3. Observed PFS and OS of the RMG cohort versus predicted PFS and OS of the RMG cohort under DARA treatment.

CONCLUSIONS

- **This adjusted treatment comparison suggests improved OS for DARA-treated patients compared to real-world historical control data from patients with heavily pretreated or refractory MM in the Czech Republic**
  - **For PFS, only a numerical trend in favor of DARA was observed**
- **Limitations include the following:**
  - **Although a wide range of clinically relevant prognostic factors were adjusted for, residual confounding bias cannot be completely excluded, as is the case in any observational study**
  - **PFS benefit of DARA versus standard of care may be underestimated due to the fact that PFS for patients in the RMG cohort was a mix of actual PFS and time to the next treatment (for patients with a missing progression date)**
  - **Some of the baseline characteristics were missing in the RMG cohort (eg, beta-2 microglobulin)**
- **In the absence of head-to-head comparative studies for DARA monotherapy, the results from this adjusted comparison can provide useful insights to clinicians and reimbursement decision makers on relative treatment efficacies**

REFERENCES

1. Kumar S, et al. Presented at: 58th ASH Annual Meeting & Exposition; December 3-6, 2016; San Diego, CA. Abstract 4414.
2. Usmani SZ, et al. *Oncologist*. 2016;21(11):1355-1361.
3. Usmani SZ, et al. *Blood*. 2016;128(1):37-44.
4. Palumbo A, et al. *N Engl J Med*. 2016;375(8):754-766.
5. Dimopoulos MA, et al. *N Engl J Med*. 2016;375(14):1319-1331.
6. DARZALEX™ (daratumumab) injection, for intravenous use [package insert]. Horsham, PA: Janssen Biotech, Inc.; 2016.
7. McKeage K. *Drugs*. 2016;76(2):275-281.
8. European Medicines Agency. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004077/WC500207296.pdf. Accessed September 22, 2016.
9. Lokhorst HM, et al. *N Engl J Med*. 2015;373(13):1207-1219.
10. Lonial S, et al. *Lancet*. 2016;387(10027):1551-1560.

ACKNOWLEDGMENTS

This study was sponsored by Janssen Global Services, LLC. Medical writing and editorial support were provided by Jason Jung, PhD, of MedErgy, and were funded by Janssen Global Services, LLC.

DISCLOSURES

RH consulted for Takeda Pharmaceutical, Novartis, Onyx, and Bristol-Myers Squibb; received grant support from Takeda Pharmaceutical, Novartis, Amgen, and Celgene; received honoraria from Takeda Pharmaceutical, Novartis, Onyx, Bristol-Myers Squibb, and Amgen; and served on advisory boards for Takeda Pharmaceutical, Novartis, Onyx, and Bristol-Myers Squibb. VM consulted for Amgen, Bristol-Myers Squibb, Celgene, Janssen-Cilag, and Takeda; received grant support from The Binding Site; received honoraria from Amgen, Bristol-Myers Squibb, Celgene, and Janssen-Cilag; and served on advisory boards for Amgen, Bristol-Myers Squibb, Celgene, Janssen-Cilag, and Takeda. JS consulted for Bristol-Myers Squibb, Celgene, Janssen-Cilag, and Amgen; received honoraria from Bristol-Myers Squibb, Celgene, Janssen-Cilag, Amgen, and Millennium; and has been involved in advisory boards for Bristol-Myers Squibb, Celgene, and Janssen-Cilag. JD, XG, SV, HB, and TI are employees of Janssen, and JD and TI hold stock in Johnson & Johnson. All remaining authors have no disclosures to report.

An electronic version of the poster can be viewed by scanning the QR code. The QR code is intended to provide scientific information for individual reference. The PDF should not be altered or reproduced in any way.
http://jjd_ash.scientificpresentations.org/Hajek_JJD0200.pdf

POSTER PRESENTED AT THE 58TH AMERICAN SOCIETY OF HEMATOLOGY (ASH) ANNUAL MEETING & EXPOSITION; DECEMBER 3-6, 2016; SAN DIEGO, CALIFORNIA.