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Adjusted Comparisons Suggest Daratumumab is Associated with Prolonged Survival Compared with Standard of Care Therapies in Patients with Heavily Pre-treated and Highly Refractory Multiple Myeloma

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INTRODUCTION

- Daratumumab (DARA) is a monoclonal antibody that targets CD38-expressing multiple myeloma (MM) cells.
- Two key single-arm studies supported the regulatory approval of DARA 16 mg/kg monotherapy in the United States and Europe for patients with heavily pre-treated and highly refractory MM: the phase I/II GEN501 study[1], and the phase II SIRIUS study[2].
  - GEN501 was an open-label, phase I/II study initiated in March 2008 in the US, Denmark, the Netherlands, and Sweden. This study recruited MM patients who relapsed from or were refractory to ≥2 prior lines of therapy, including a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD)[1].
  - SIRIUS was an open-label, phase II study initiated in September 2013 in the US, Canada, and Spain. This study enrolled MM patients who had received ≥3 prior lines of therapy, including a PI and an IMiD, or who were double refractory to a PI and an IMiD[2].
- A pooled analysis of the GEN501 part 2 and SIRIUS studies has shown that DARA 16 mg/kg monotherapy demonstrates clinical benefit in terms of progression-free survival (PFS) and overall survival (OS) in patients with heavily pre-treated and highly refractory MM[3].
- A retrospective International Myeloma Foundation (IMF) chart review was performed to evaluate OS and to document current patterns of real-world standard of care (SOC) therapies among patients with heavily pre-treated and highly refractory MM[4].
  - The IMF chart review was conducted at global sites including North America, Europe, and Asia-Pacific, and included patients diagnosed with MM on or after January 1, 2006. Eligible patients were double refractory to both a PI and an IMiD, had received ≥3 prior lines of therapy, and had been exposed to an alkylating agent.
- To fully contextualize the benefit of novel agents such as DARA monotherapy for the treatment of patients with heavily pre-treated and highly refractory MM, it is critical to understand the real-world outcomes of this patient population on current SOC therapies.

OBJECTIVE

- To determine the comparative effectiveness of DARA monotherapy versus real-world SOC therapies among patients with heavily pre-treated and highly refractory MM using two adjusted comparison methodologies: propensity score matching (PSM) and multivariate Cox regression analyses.

METHODS

- Data for patients treated with DARA 16 mg/kg monotherapy were available from clinical trials SIRIUS (n=106) and GEN501 part 2 (n=42), while patients treated with SOC therapies were derived from the IMF chart review (n=543)[4].
  - The pooled DARA studies demonstrated a median OS of 20.1 months versus 13.0 months for SOC[3,4].
- For the IMF chart review, baseline, denoted as time zero (T_0) was defined as the date when patients fulfilled the chart review inclusion criteria.
- The relative treatment effect of DARA 16 mg/kg versus SOC was estimated using PSM and multivariate Cox regression analyses, using individual patient data (IPD) for both methodologies.

Propensity Score Matching

- PSM methods were used to form well balanced DARA and SOC cohorts by adjusting for cross-study differences in baseline characteristics.
- Modeled covariates were age, gender, prior lines of therapy, albumin, and refractory status to bortezomib (BOR), carfilzomib (CAR), lenalidomide (LEN), and pomalidomide (POM).
- Due to a discrepancy in the percentage of POM refractory patients at baseline in the DARA cohort (55%) versus the SOC cohort (5.5%), a secondary analysis of the IMF chart review using T_0 shifting was conducted to increase the proportion of POM refractory patients in the SOC cohort to enable PSM.
  - After T_0 shifting and excluding patients who were missing covariate data, 380 SOC patients were available for PSM with DARA patients.
- The base case PSM analysis was performed using caliper matching with a caliper width 25% of the standard deviation (SD) of the logit-transformed propensity score (LTPS), using sampling without replacement.
- Three sensitivity analyses were performed to assess the robustness of findings from the base case analysis: (1) repetition of base case analysis using sampling with replacement; (2) reduction of the caliper width to 20% of the SD of the LTPS (sampling without replacement); and (3) using a global optimal matching algorithm (all DARA patients match to SOC patients).

Multivariate Cox Regression Analysis

- Patients from the SOC cohort who received multiple treatment lines after T_0 contributed information to the analysis for multiple lines of therapy, with baseline defined as the date of initiation of the actual treatment line.
  - Patients receiving experimental treatments or treatments not available in daily clinical practice were excluded.
  - Therefore, 510 patients from the SOC cohort were included in the primary analysis and contributed to a total of 903 treatment lines.
- Covariates included in the regression model were age, gender, prior lines of therapy, albumin, beta-2 microglobulin, prior exposure to POM and CAR, and PI/IMiD refractory status.
- Clustering of observations at the treatment-line level within patients was controlled for using robust sandwich estimate for the covariance matrix.
- All statistical analyses for both methodologies were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina, USA). Statistical significance testing was performed using a two-tailed p-value of <0.05, and all comparisons between treatment groups were reported with hazard ratios (HRs) and 95% CIs.

RESULTS

Propensity Score Matching

- Out of the 148 DARA patients, 126 (85.1%) were successfully matched to SOC patients in the base case analysis.
- Prior to PSM, imbalances between the DARA and SOC groups were significant for prior lines of therapy and proportions of patients refractory to POM, CAR, BOR, and LEN. After PSM, the DARA and SOC groups were well balanced for all covariates included in propensity score calculations (**Table 1**).

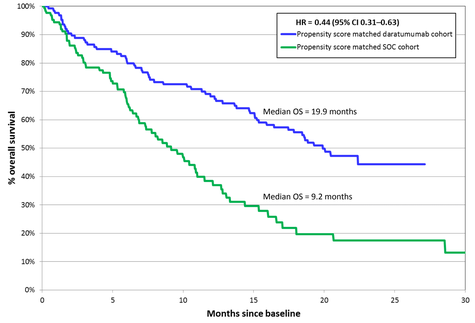
Table 1. Summary of characteristics for the treatment groups before and after the base case PSM analysis

Covariate	Prior to PSM (All Patients)				After PSM (Matched Groups)			
	DARA	SOC	Standardized Difference Pre-Match	P-Value for Difference between Groups	DARA	SOC	Standardized Difference Post-Match	P-Value for Difference between Groups
Patients, N	***148***	***380***	NA	NA	***126***	***126***	NA	NA
Mean Age (yrs)	63.2	62.5	0.7	0.48	63.2	62.2	**0.11**	0.36
% Male	53.4	61.6	**-0.17**	0.09	52.4	54.8	-0.05	0.71
Albumin (g/L)	35.8	34.6	**0.18**	0.07	35.5	35.5	-0.002	0.81
Mean Prior Lines of Therapy	5.4	4.9	**0.21**	**0.04**	5.4	5.4	0.01	0.99
% POM Refractory	55.4	37.6	**0.36**	**<0.01**	57.1	56.4	0.02	0.90
% CAR Refractory	39.2	15.3	**0.56**	**<0.01**	40.5	41.3	-0.02	0.90
% BOR Refractory	84.5	94.2	**-0.32**	**<0.01**	88.1	84.1	**0.11**	0.36
% LEN Refractory	83.8	98.4	**-0.53**	**<0.01**	95.2	95.2	0	1

Standardized differences >0.1 suggest potentially important imbalances. P-values from t-tests comparing mean values between groups are shown; values <0.05 denote statistical significance.
PSM, propensity score matching; DARA, daratumumab; SOC, standard of care; NA, not available; POM, pomalidomide; CAR, carfilzomib; BOR, bortezomib; LEN, lenalidomide.

- The unadjusted hazard ratio for OS was 0.51 [95% CI 0.39–0.67]. After PSM, comparisons found significant improvement in favor of DARA relative to SOC for OS (HR=0.44 [95% CI 0.31–0.63]). Median OS was 19.9 months in the DARA group and 9.2 months in the SOC group (**Figure 1**).

Figure 1. Kaplan–Meier overall survival curves in daratumumab and SOC cohorts that were formed using propensity score matching



- Findings were robust across sensitivity analyses, and were consistent with pre-PSM unadjusted comparison analysis (**Figure 3A**).

Multivariate Cox Regression Analysis

- The DARA cohort included more highly (triple/quadruple) refractory patients, or patients with prior exposure to POM and CAR, and with more prior lines of treatment. Patients with missing data for albumin or beta-2 microglobulin were categorized separately and were included in the regression analysis (**Table 2**).

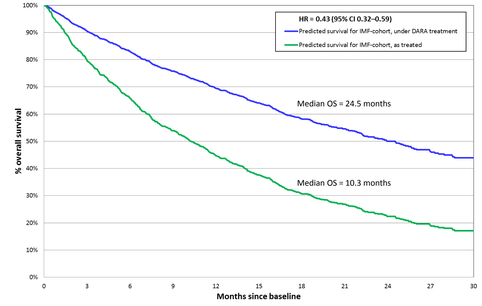
Table 2. Patient characteristics at treatment initiation in the pooled GEN501/SIRIUS daratumumab studies and the SOC cohort

Characteristic	IMF Chart Review: SOC Patients (N = 903)	GEN501/SIRIUS: DARA Patients (N = 148)
Age, median	62	63
Males, %	60.1%	60.3%
Albumin		
<3.5 g/L	31.2%	39.2%
≥3.5 g/L	29.5%	60.8%
Missing	39.3%	0.0%
Beta-2 microglobulin		
<3.5 g/L	13.7%	25.0%
3.5-5.5 g/L	7.1%	20.3%
≥5.5 g/L	13.2%	26.4%
Missing	66.0%	28.4%
Prior pomalidomide exposure	18.3%	55.4%
Prior carfilzomib exposure	15.8%	41.2%
Line of therapy		
3	3.0%	7.4%
4	18.7%	16.2%
5	28.8%	20.3%
6	24.5%	16.2%
7	18.1%	11.5%
8	10.6%	9.5%
9	7.2%	6.8%
10+	11.2%	12.2%
Refractory status		
<Double	0.0%	12.8%
Double	72.6%	23.0%
Triple	23.7%	36.5%
Quadruple	3.7%	27.7%
Region		
European Union	57.4%	25.0%
United States	54.6%	60.1%
Other	10.1%	14.9%

IMF, International Myeloma Foundation; SOC, standard of care; DARA, daratumumab.

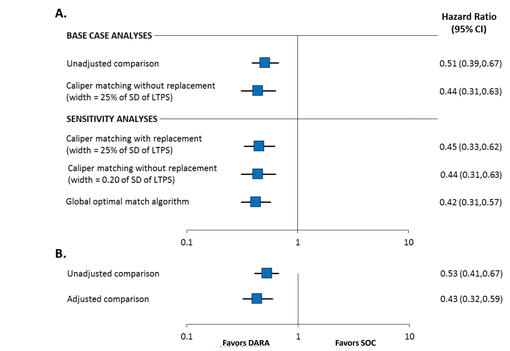
- Male gender, low albumin and high beta-2 microglobulin levels and high refractory status were independent significant predictors for worse overall survival. Prior POM exposure and later treatment lines were numerically associated with worse survival.
- The unadjusted hazard ratio for OS was 0.53 [95% CI 0.41–0.67]. After adjustment for differences in all covariates included in the Cox regression between the DARA and SOC groups, results showed significant improvement in favor of DARA compared with SOC for OS (HR=0.43 [95% CI 0.32–0.59]) (**Figure 3B**).
- Median predicted OS was 24.5 months in the DARA group and 10.3 months in the SOC group (**Figure 2**).

Figure 2. Predicted overall survival for IMF cohort based on multivariate Cox proportional hazards regression model



- Findings from the PSM (including sensitivity analyses) and regression analyses were consistent and favored DARA vs. SOC (**Figure 3A & 3B**).

Figure 3. Forest plot summary of overall survival in unadjusted and adjusted comparisons via (A) propensity score matching, and (B) multivariate Cox regression analysis



CI, confidence interval; SD, standard deviation; LTPS, logit transformed propensity score.

CONCLUSION

- **Findings from both PSM and regression analyses were consistent and suggest that DARA is associated with significant gains in OS compared with current real-world SOC therapies for patients with heavily pre-treated and highly refractory MM.**

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