Original Study

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Early Access Program Results From Turkey and a Literature Review on Daratumumab Monotherapy Among Heavily Pretreated Patients With Relapsed/Refractory Myeloma

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Abstract

The present study investigated the efficacy and safety profile of daratumumab monotherapy in 42 patients with relapsed refractory multiple myeloma through a Turkish early access program. The current findings have confirmed the efficacy of daratumumab monotherapy in heavily pretreated patients with refractory multiple myeloma because of the deep and durable responses and favorable safety and tolerability profile.

Background: In countries where frontline drug approval is limited to first-generation proteasome inhibitors or immunomodulatory drugs, relapses have been both more frequent and less durable. We investigated real world data on the efficacy and safety of daratumumab monotherapy among patients with relapsed refractory multiple myeloma (RRMM) from Turkey using a prospective early access program. **Patients and Methods:** A total of 42 patients with RRMM after a minimum of 3 previous lines of proteasome inhibitor/immunomodulatory drug-based treatments were included from 25 centers across Turkey. Daratumumab monotherapy was administered intravenously at a dose of 16 mg/kg weekly (cycles 1-2), on alternate weeks (cycles 3-6), and monthly thereafter. **Results:** The median daratumumab monotherapy duration was 5.5 months (range, 0.2-28.7 months). The overall response rate was 45.2%, including 14 (33.3%) partial responses, 4 (9.5%) very good partial responses, and 1 (2.4%) complete response. The

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median duration of response was 4.9 months. The median progression-free survival (PFS) was 5.5 (95% confidence interval, 2.6-8.4 months) with 12- and 18-month PFS rates of 35.7% and 31.0%, respectively. The median overall survival was not reached; the 12- and 18-month overall survival rates were 64.3% and 59.5%, respectively. The depth of response had a significant effect on PFS (log-rank test, $P = .026$). Overall, of the 76 adverse events reported, 33 (43.4%) were grade $\geq$ 3; only 4 (9.52%) were grade 3 infusion-related reactions. No infusion-related reactions or adverse events led to treatment discontinuation. **Conclusion:** The present findings from our daratumumab early access program have confirmed the efficacy and safety profile of daratumumab monotherapy in heavily pretreated Turkish patients with RRMM.

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Introduction

Multiple myeloma, a neoplasm characterized by clonal expansion of malignant plasma cells in the bone marrow, represents the second most common hematologic malignancy.[1] Although the 5- and 10-year survival rates have improved with use of modern therapeutic agents, such as proteasome inhibitors (PIs) and immunomodulatory drugs (IMiDs),[2] the prognosis of patients with relapsed multiple myeloma and those with disease refractory to PIs and IMiDs has remained very poor.[1,3,4]

Given its high and uniform expression on malignant plasma cells, CD38 has been considered a promising therapeutic target in the treatment of multiple myeloma with anti-CD38 monoclonal antibodies.[1,5,6] Daratumumab is a human anti-CD38 monoclonal antibody that displays specific targeting ability to abnormal white blood cells overexpressing CD38 and provides efficacious therapy for multiple myeloma.[6,7]

With data from the GEN501[8] and Sirius[9] studies indicating the efficacy of daratumumab monotherapy, daratumumab was approved for single-agent use in 2015 by the US Food and Drug Administration and in 2016 by the European Medicines Agency for relapsed or refractory multiple myeloma (RRMM).[3] A pooled analysis of these monotherapy studies showed an overall response rate (ORR) of 31.1%, median progression-free survival (PFS) of 4.0 months, median overall survival (OS) of 20.1 months, and a manageable toxicity profile for patients treated with daratumumab at 16 mg/kg.[10] The efficacy and favorable tolerability of daratumumab monotherapy has been consistently reported from recent real-world studies performed in countries such as the United States, Korea, Poland, Spain, Italy, Russia, the United Kingdom, Hungary, and Japan, with the ORR ranging from 23% to 56.3%[11-17] (Table 1).

The present prospective study was designed to provide real-world data from the daratumumab early access program (EAP) in Turkey regarding the efficacy and safety of daratumumab monotherapy in heavily pretreated patients with RRMM. Used as monotherapy, our results will enable better recognition of the response kinetics of daratumumab.

Patients and Methods

Study Population

A total of 42 patients with RRMM who had received $\geq$ 3 previous lines of therapy (that had included a PI and an IMiD) and had initiated daratumumab monotherapy in accordance with the daratumumab EAP were included in the present open-label, multicenter, real-world study conducted from June 2016 to October 2018 at 25 centers across Turkey. The inclusion and exclusion criteria are listed in Table 2. Each patient had provided written informed consent for EAP enrollment. The present study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and approved by the institutional ethics committee (approval date, April 5, 2017; reference no. 46004091-302.14.06; protocol no. E23167).

Data Collection

The baseline data included patient demographics, disease characteristics, laboratory findings, and treatment characteristics. The treatment response (ORR), OS, PFS, adverse events (AEs), and infusion-related reactions (IRRs) were analyzed using an anonymized data set. The treatment response was determined locally as the ORR, which included the sum of the patients who had had a partial response (PR), very good partial response (VGPR), complete response (CR), stable disease (SD), or progressive disease (PD). OS and PFS were analyzed according to response status and the number of previous lines of therapy.

Daratumumab Treatment

Daratumumab monotherapy was administered at a 16-mg/kg dose, using 28-day cycles, with a frequency of once weekly for the first and second cycle, biweekly for the third to sixth cycles, and monthly thereafter. All patients received acetaminophen and antihistaminic agents before each daratumumab infusion to limit the risk of IRRs. Daratumumab monotherapy was continued until PD.

Statistical Analysis

Statistical analysis was performed using SPSS Statistics for Windows, version 22.0 (IBM Corp, Armonk, NY). Descriptive statistics were used to summarize the baseline characteristics. Survival was evaluated using Kaplan-Meier analysis, and comparisons were performed using the log-rank test. Correlates of survival were determined using Cox regression analysis. Data are reported as the (median and range), 95% confidence intervals (CIs), and percentages, as appropriate.

Table 1 Daratumumab, 16 mg/kg, RRMM Monotherapy Real-World Studies

Characteristic	Chari et al[11]	Park et al[12]	Salomon-Perzyński et al[13]	Cejalvo et al[14]	Cook et al[15]	Lovas et al[16]	Iida et al[17]	Present Study (Turkish Cohort)
Study type	EAP	EAP	EAP	Open label (dialysis patients)	EAP	Real-world data	Phase I, dose-escalation study	EAP
Median follow-up duration, mo	2.8	12	7.2	12	6.3	18.6	9.9	14.8
Patients, n	348	16	30	12	293	99		42
Median age, y	65	69	62.4	62	64			56.5
Median interval since diagnosis, y	NR	6.95	4.1	2.2	NR			5.1
Median previous therapy lines, n	>3	4	4	3	≥3	3	≥2	5.5
Median duration of daratumumab therapy, mo	1.9	10.0	5.6	1.5	4.2			6
Median PFS, mo	NR	2.7	9.5	NR	4.63	17.0	9.5	5.5
Median OS, mo	NR	9.8-10.7	13.8	NR	NR	NR		19.3 (mean)
ORR (PR or better), %	23	56.3	42.8	50	33.1	63.6	44.0	45.2
CR or better, %	1	25	18.5	0	2.7	13.6		9.5

Abbreviations: CR = complete response; EAP = early access program; NR = not reported; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; RRMM = relapsed or refractory multiple myeloma.

Table 2 Inclusion and Exclusion Study Criteria

Criteria
Inclusion
Age, ≥ 18 y
Diagnosis of multiple myeloma and disease progression in accordance with criteria defined by International Multiple Myeloma Working Group
≥3 Steps of previous treatment, including a PI and an IMiD or refractoriness to both PI and IMiD, and ECOG PS of 0-2
Exclusion
Previous participation in, or current candidacy for, another daratumumab clinical trial
Previous exposure to an anti-CD38 monoclonal antibody
Concomitant antimyeloma therapy with other agents (chemotherapy, anticancer immunotherapy, systemic steroids for > 10 days equivalent to ≥ 20 mg of prednisone therapy or experimental therapy)
FEV_1 values of >50%, moderate to severe persistent asthma within previous 2 years, or current diagnosis of uncontrolled asthma
Comorbidities likely to jeopardize participation in program (ie, active systemic infection)
Laboratory findings, including absolute neutrophil count of ≤0.5 × 10^9/L, hemoglobin level of ≤7 g/dL, thrombocyte count of <50 × 10^9/L, alanine aminotransferase level of ≥2.5 times ULN, total bilirubin level of ≥2 times ULN, direct bilirubin level of 2 times ULN (except for Gilbert syndrome), creatinine clearance of ≤20 mL/min/1.73 m^2, potassium level of <3.0 mEq/L, and/or corrected serum calcium level of >14.0 mg/dL

Abbreviations: ECOG = Eastern Cooperative Oncology Group; FEV_1 = forced expiratory volume in 1 second; IMiD = immunomodulatory drug; PI = proteasome inhibitor; PS = performance status; ULN = upper limit of normal.

Results

Baseline Demographic and Clinical Characteristics

The median patient age was 56.5 years (range, 41-81 years), and 69.0% of the study population were men (Table 1). The median interval from diagnosis was 5.1 years (range, 0.2-13.1 years). Neuropathy (28.6%) and chronic kidney disease (17.5%) were the 2 most common comorbidities. The Eastern Cooperative Oncology Group performance status was 0 to 1 for 63.1% of the patients. At diagnosis, extramedullary plasmacytoma was detected in 26.2% of the patients and bone involvement was found in 50.0% of the patients. International Staging System (ISS) grade III was noted in 51.4% of patients at diagnosis and 47.2% of patients at the beginning of daratumumab therapy. At baseline (before daratumumab initiation), plasma cells in bone marrow were > 30% in 19.0% of patients, and creatinine clearance was ≥ 30 to ≤ 60 mL/min/1.73 m^2 in 14.3% of the patients (Table 3).

Previous Lines of Therapy and Characteristics of Daratumumab Therapy

Overall, the median number of previous therapy lines was 5.5 (range, 3.0-8.0; ≥ 5 in 50.0% of patients) at the onset of daratumumab therapy (Table 4). Bortezomib (95.2%) and lenalidomide (81.0%) were the most commonly prescribed PI and IMiD agents, respectively, and 78.6% of patients had a history of stem cell transplantation.

Treatment Response and Survival Data

The median interval from diagnosis to inclusion in the present study was 66.8 months (range, 9.5-170.2 months). The median follow-up duration was 14.8 months (range, 4.8-16.5 months). The median duration of daratumumab treatment was 5.5 months (range, 0.2-28.7 months). The best ORR was 45.2%, which included 14 PRs (33.3%), 4 VGPRs (9.5%), and 1 CR (2.4%). The PD and SD rates were 21.4% and 26.2%, respectively. The median interval to the best response was 3.2 months (range, 0.3-10.8 months). The median duration of response was 4.9 months. The median PFS was 5.5 months (95% CI, 2.6-8.4 months), with a 12- and 18-month PFS rate of 35.7% and 31.0%, respectively. The median OS was not reached; however, the 12- and 18-month OS rates were 64.3% and 59.5%, respectively (Table 5 and Figure 1).

Considering the change in the depth of response to treatment over time, the proportion of patients with a CR had increased from 2.9% at month 1% to 5.3% at month 3% and 7.1% at month 6 of daratumumab therapy. A deeper response to therapy was noted in particular at month 4 in terms of the VGPR (10.5%), CR (5.3%), SD (52.6%), and PD (10.5%) rates. At month 6 of therapy, the PR, VGPR, and CR rates were 28.6%, 7.1%, and 7.1%, respectively, and the SD and PD rates were 35.7% and 21.4%, respectively (Figure 2).

Case-based data on survival and treatment response in the overall study population are shown in Figure 3. At the last follow-up examination, 8 of the 42 patients in the EAP were continuing to receive daratumumab monotherapy and 6 of these 8 patients had completed 2 years of monotherapy.

OS and PFS According to Treatment Response

When stratified according to the treatment response, the 12- and 18-month PFS rates were 54.4% and 24.2% with a PR and 40.0% and 30.0% with SD, respectively. The 12- and 18-month OS rates were 91.7% and 55.6% with a PR, 70.0% and 70.0% with SD, and 42.3% and 22.6% with PD, respectively. A significant difference was noted in PFS (log-rank test, $P = .026$; Figure 4) according to the depth of response to treatment.

OS and PFS According to Previous Lines of Therapy

When analyzed according to the number of previous lines of therapy, the 12- and 18-month PFS rates were 60.0% and 40.0% for patients with < 5.5 previous lines of therapy and 40.0% and 10.0% for patients with ≥ 5.5 previous lines of therapy. The corresponding 12- and 18-month OS rates were 75.0% and 72.6% and 54.7% and 69.1%, with no significant differences in OS (log-rank test, $P = .378$; Figure 5) and PFS (log-rank test, $P = .112$; Figure 5).

Safety Data

Overall, 76 AEs were reported, with 33 (43.4%) grade ≥ 3 AEs. Although overall, 10 IRRs were reported (dyspnea in 5 patients), only 4 (9.52%) were grade 3 IRRs. No IRRs or AEs led to treatment discontinuation. The main toxicities, including IRRs, are summarized in Table 6.

Discussion

The present daratumumab EAP findings in Turkish patients revealed a favorable efficacy and safety profile for daratumumab monotherapy in patients with heavily pretreated RRMM. The best ORR was 45.2%, including a (PR in 14 patients (33.3%), VGPR in 4 patients (9.5%), and CR in 1 patient (2.4%). The median

Table 3 Baseline Demographic and Clinical Characteristics

Variable	Value
Age, y	
Mean ± SD	58.6 ± 10.1
Median	56.5
Range	41.0-81.0
Gender, n (%)	
Female	13 (31.0)
Male	29 (69.0)
Interval since diagnosis, y	
Median	5.1
Range	0.2-13.1
Comorbidities, n (%)	
Neuropathy	12 (28.6)
Chronic kidney disease	7 (17.5)
Diabetes mellitus	5 (12.5)
Cardiac disease	5 (12.5)
Hypertension	4 (10.0)
Obesity	4 (10.0)
DVT history	3 (7.1)
Thyroid disorder	2 (5.0)
ECOG PS (n = 38), n (%)	
0	17 (44.7)
1	7 (18.4)
2	9 (23.7)
3	4 (10.5)
4	1 (2.6)
ISS score at diagnosis (n = 37), n (%)	
1	5 (13.5)
2	13 (35.1)
3	19 (51.4)
ISS score at daratumumab therapy (n = 36), n (%)	
1	6 (16.7)
2	13 (36.1)
3	17 (47.2)
Revised ISS score at diagnosis (n = 22), n (%)	
1	5 (22.7)
2	8 (36.4)
3	9 (40.9)
Cytogenetic profile, n (%)	
t(4,14)	3 (7.1)
del17p	2 (4.8)
del13q	3 (7.1)
amp1q21	2 (4.8)
M protein type (serum), n (%)[a]	
IgG kappa	19 (45.2)
IgA kappa	7 (16.7)
IgG lambda	5 (11.9)
Light chain lambda	3 (7.1)
IgD lambda	1 (2.4)
IgG	1 (2.4)
M protein type (urine), n (%)	
Kappa	9 (21.4)
Lambda	7 (16.7)
Extramedullary plasmacytoma, n (%)[b]	11 (26.2)
Bone involvement at diagnosis, n (%)[c]	21 (50.0)
Bone marrow percentage of plasma cells at baseline, n (%)[d]	
≤30	18 (42.9)
>30 to ≤60	3 (7.1)
>60	5 (11.9)
Creatinine clearance at baseline (mL/min), n (%)[e]	
<30	3 (7.1)
≥30 to ≤60	6 (14.3)
>60	25 (59.5)
Elevated LDH, n (%)	8 (19.0)

Abbreviations: DVT = deep vein thrombosis; ECOG = Eastern Cooperative Oncology Group; ISS = International Staging System; PS = performance status.
[a]Data missing for 6 patients.
[b]Data missing for 5 patients.
[c]Data missing for 9 patients.
[d]Data missing for 16 patients.
[e]Data missing for 8 patients.

duration of response was 4.9 months. The best response was achieved after 3.2 months (range, 0.3-10.8 months) of monotherapy. The median PFS was 5.5 months (95% CI, 2.6-8.4 months), with 12- and 18-month PFS rates of 35.7% and 31.0%, respectively. The median OS was not reached; however, the 12- and 18-month OS rates were 64.3% and 59.5%, respectively. The depth of response to treatment had a significant effect on PFS, but the number of previous lines of therapy had no effect on PFS or OS.

The studies that led to daratumumab approval were phase II daratumumab monotherapy (16 mg/kg) trials (GEN501[8] and Sirius[9] studies). These studies had included patients who had received ≥ 2[8] and ≥ 3[9] previous lines of therapy. They reported an ORR of 36% (PR or better in 15 patients, CR in 2 patients, VGPR in 2 patients)[8] and an ORR of 29% (stringent CR in 3 patients [2.8%] patients, VGPR in 10 patients [9.4%], and PR in 18 patients [17.0%]),[9] respectively. In the GEN501 trial,[8] the median PFS was 5.6 months (95% CI, 4.2-8.1 months), and the 12-month PFS was 65% (95% CI, 28%-86%). In the Sirius trial,[9] the median PFS was 3.7 months (95% CI, 2.8-4.6 months), the median OS was 17.5 months (18.6 months according to the final data cut, with a median follow-up of 36.7 months), and the 12-month OS rate was 64.8% (95% CI, 51.2%-75.5%).[9,18]

A pooled analysis of these 2 monotherapy studies (median number of previous lines of therapy, 5) revealed an ORR of 31.1% (CR in 4.7%), a median duration of response of 7.6 months, a median PFS of 4.0 months, and a median OS of 20.1 months.[10] Our findings have indicated a similar durable response and

Table 4 Previous Lines of Therapy and Characteristics of Daratumumab Therapy

Variable	Value
Previous therapy lines, n	
Median	5.5
Range	3.0-8.0
Patients with ≥ 5 previous lines of therapy, n (%)	21 (50.0)
Previous PI, n (%)	42 (100)
Bortezomib	40 (95.2)
Carfilzomib	16 (38.1)
Previous IMiD, n (%)	42 (100)
Lenalidomide	34 (81.0)
Pomalidomide	18 (42.9)
Thalidomide	18 (42.9)
Other treatment before daratumumab, n (%)	
Stem cell transplantation	33 (78.6)
Radiotherapy	9 (21.4)
Line of therapy at daratumumab initiation, n (%)	
4	12 (28.6)
5	9 (21.4)
6	8 (19.0)
7	7 (16.7)
8	2 (4.8)
9	4 (9.5)

Abbreviations: IMiD = immunomodulatory drug; PI = proteasome inhibitor.

clinical benefit with daratumumab monotherapy in heavily pretreated patients with ≥ 3 previous therapy lines (range 3.0-8.0).

Hence, our findings indicate that daratumumab monotherapy is an effective and tolerable treatment option for RRMM in Turkish patients, similar to that consistently reported in recent real-world studies from other countries.[11-17]

The findings from the US cohort of a multicenter, open-label, daratumumab EAP study of patients with RRMM and ≥ 3 previous therapy lines revealed an ORR of 23% (PR in 18%, VGPR in 5%, stringent CR in 0.6%). Data were limited to the response rate and duration without any PFS or OS data included.[11] Also, the median treatment duration was very short (1.9 months).

In a multicenter retrospective study of 16 Korean patients after 4 lines of therapy, daratumumab monotherapy was reported to be associated with a higher ORR of 56.3% (PR in 31.3%, VGPR in 0%, CR in 25.0%).[12] The median PFS was 2.7 months (28.9% at 6 months).[12] However, after a median of 10 months of treatment, the PFS was considerably short (2.7months).

Data from the daratumumab compassionate use program in Poland of 30 patients with RRMM after a median of 4 previous lines of therapy revealed an ORR of 40.7% (CR in 5 patients [18.5%], VGPR in 2 patients [7.4%], SD in 12 patients [44.4%]), and 3 deaths from PD.[13] However, data on the median PFS and OS were reported.[13]

The preliminary findings from a retrospective, multicenter, open-label study of patients with end-stage renal failure and RRMM from Spain revealed an ORR and clinical benefit rate (SD or better) of 50% (2 VGPR, 2 PR, and 2 SD) after a median follow-up of 12 months.[14] The investigators considered daratumumab monotherapy to be an efficacious and safe therapeutic option for patients presenting with end-stage renal failure requiring dialysis.[14] The AE profile was similar to that reported for patients with normal or moderately impaired renal function.[14]

The results from a pooled analysis of 293 heavily pretreated patients with RRMM enrolled in the MMY3010 EAP of daratumumab monotherapy from Spain, Italy, Russia, and the United Kingdom revealed a similar ORR of 33.1% (VGPR in 12.3%, CR or better in 2.7%) after a median follow-up of 6.3 months.[15] In addition, the median PFS was 4.63 months, and the estimated 6-month PFS rate was 42.9%.[15] The investigators emphasized that the pooled analysis had confirmed the safety profile and efficacy of DARA monotherapy in patients with heavily pretreated RRMM, without identification of new safety concerns and with maintenance of health-related quality of life during a median of 4.2 months of daratumumab treatment.[15]

In another real-world retrospective analysis of 99 patients with RRMM with a median of 3 previous therapy lines from Hungarian centers, the ORR was assessable for 88 patients (CR, 13.6%; VGPR, 11.4%; PR, 38.6%).[16] In the Hungarian cohort, 48 of 99 patients had received monotherapy with dexamethasone only; for the others, either bortezomib or lenalidomide was combined.[16] The investigators reported a median PFS of 17.0 months after a median follow-up of 18.6 months.[16] The ISS and number of previous lines of therapy were reported to have significantly affected PFS.[16]

Daratumumab monotherapy (16 mg/kg) among Japanese patients with RRMM with ≥ 2 previous therapies was reported to be associated with an ORR of 44% (PR in 3 patients) and a median PFS of 9.5 months at a median follow-up duration of 9.9 months.[17]

The present daratumumab EAP cohort from Turkey included 47.4% patients with ISS grade III, 23.8% with high-risk cytogenetics, 78.6% with previous stem cell transplantation, and a median number of previous lines of therapy of 5.5. In our study, responses were obtained within a median of 4.9 months (range, 4.4-7.8 months) of therapy. However, earlier studies lacked response kinetics data. Our findings revealed a significant effect on PFS from the depth of response but not from the number of previous lines of therapy. Our findings have indicated the best OS and PFS with daratumumab monotherapy compared with all EAP data reported to date.

Overall, 76 AEs reported, with 33 (43.4%) grade ≥ 3 and only 4 (9.52%) grade 3 IRRs. No IRRs or AEs led to treatment discontinuation. These are similar to previously reported findings,[8,9,11-15,17] supporting the favorable tolerability and safety profile of daratumumab monotherapy in patients with RRMM. The likelihood of grade ≥ 3 AEs (mostly pneumonia, thrombocytopenia, and anemia) and serious AEs (mostly infection related) was low, with a manageable toxicity profile in terms of IRRs (mostly related to respiratory symptoms, including cough, dyspnea, throat irritation, and nasal congestion).[10-12,15,16]

Overall, the current daratumumab EAP findings are consistent with previously reported findings from trials and real-world studies and have confirmed the efficacy and safety profile of daratumumab in heavily pretreated Turkish patients with RRMM. Also, indirect

Table 5 Treatment Response and Survival Data

Variable	Total	Line of Therapy at Initiation			
		4	5	6	≥7
Treatment response, n (%)					
ORR (PR or CR)	19 (45.2)	11 (57.9)	3 (15.8)	2(10.5)	3 (15.8)
CR	1 (2.4)	1 (100)	0 (0.0)	0 (0.0)	0 (0.0)
VGPR	4 (9.5)	2 (50.0)	0 (0.0)	1 (25.0)	1 (25.0)
PR	14 (33.3)	8 (57.2)	3 (21.4)	1 (7.1)	2 (14.2)
MR/SD	11 (26.2)				
PD	9 (21.4)				
Duration of follow-up, mo					
Median	14.8				
Range	4.8-16.5				
Duration of treatment, mo					
Median	5.5				
Range	0.2-28.7				
Duration of treatment response, mo					
Median	4.9				
95% CI	4.4-7.8				
OS rate, %					
12-mo	64.3				
18-mo	59.5				
OS, mo					
Mean ± SE	19.3 ± 1.8				
95% CI	15.7-22.9				
PFS rate, %					
12-mo	35.7				
18-mo	31.0				
PFS, mo					
Mean ± SE (95% CI)	11.4 ± 1.8 (7.9-14.9)				
Median ± SE (95% CI)	5.5 ± 1.5 (2.6-8.4)				

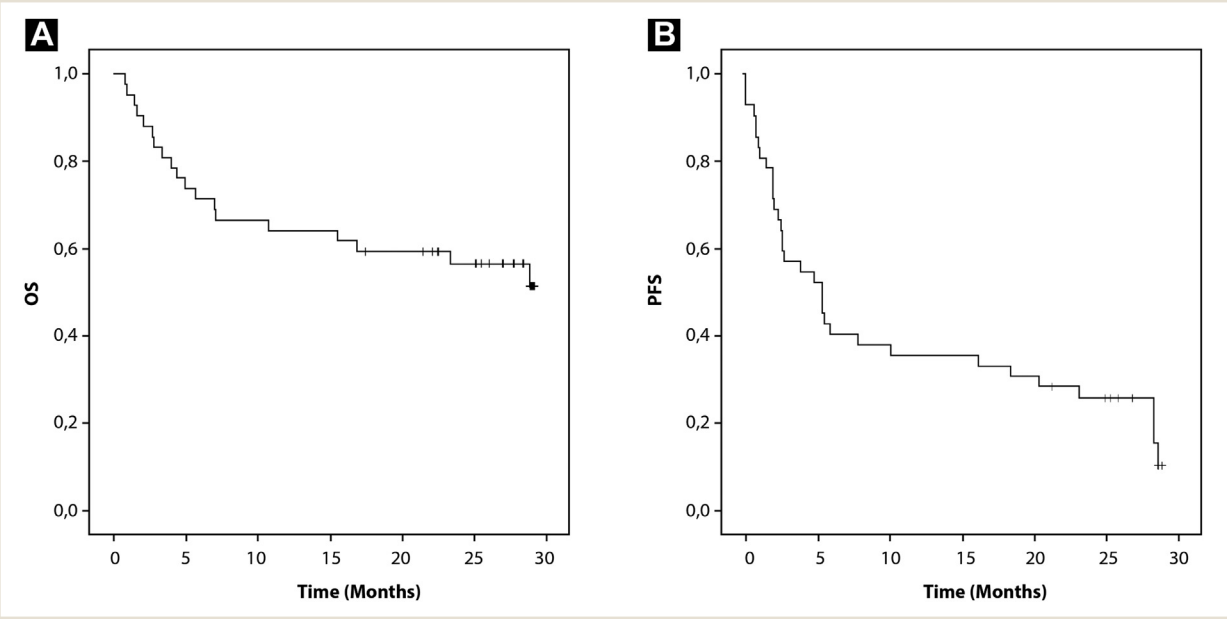
Abbreviations: CI = confidence interval; CR = complete response; MR = minimal response; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease; SE = standard error; VGPR = very good partial response.

treatment comparison studies of daratumumab monotherapy (pooled from the GEN501 and SIRIUS studies) and comparator therapies (different retrospective cohort studies) have indicated a consistent OS benefit for daratumumab monotherapy.[4,19-24] Adjusted comparisons of patient-level data pooled from daratumumab monotherapy clinical studies (patients treated with 16 mg/kg in the SIRIUS/GEN501 studies) with standard care real-world data from the Czech Republic,[21] United States,[22] International Myeloma Foundation,[23] and International Myeloma Working Group[24] historical control cohorts of patients with RRMM revealed improved OS for daratumumab compared with the real-world historical control data (adjusted hazard ratio for OS, 0.35, 0.30, 0.41, and 0.44, respectively) in heavily pretreated patients with RRMM.

Data from the Czech registry revealed that the control cohort differed in median age (64 vs. 62 years), median number of previous therapy lines (5 vs. 4), previous exposure to carfilzomib (41.2% vs. 0.3%) and pomalidomide (55.4% vs. 0.6%), triple or more refractory status (64.2% vs. 5.3%), and OS (11.9 vs. 20.1 months) from daratumumab trial patients.[21] Data from a US database revealed that the US cohort differed in median age (64 vs. 69 years), median previous number of therapy lines (5 vs. 4), previous exposure to carfilzomib (41% vs. 28%) and pomalidomide (55% vs. 15%), triple/quadruple refractory status (64% vs. 14%) and OS (19.9 vs. 7.9 months) from the daratumumab trial patients.[22]

Data from the International Myeloma Foundation historic control group, focusing on patients treated with European Union—approved therapy regimens revealed that patients in daratumumab monotherapy trials compared with controls had better OS (18.6 vs. 10.8 months), a lower rate of treatment discontinuation and adverse events (5 [4.7%] vs. 34 [13.2%]; adjusted HR, 0.23 in favor of daratumumab monotherapy), and identification of no interaction for the region subgroup in the analysis of the United States versus European Union versus other.[23] Given the consistency of their findings throughout several different sensitivity analyses, the investigators suggested improved efficacy and safety for

Figure 1 Kaplan-Meier Analysis for (A) Overall Survival (OS) and (B) Progression-free Survival (PFS)



daratumumab monotherapy compared with approved therapy regimens used in clinical practice.[23]

Data from the International Myeloma Working Group registry also revealed significantly prolonged OS (19.9 vs. 9.2 months) and PFS (3.9 vs. 1.6 months) for patients in daratumumab monotherapy trials compared with patients receiving standard care.[24]

The daratumumab monotherapy regimen has included the concomitant use of steroids, such as methylprednisolone for premedication (100 mg at maximum one time) and postmedication (20 mg at maximum once daily for 2 days after daratumumab administration), in line with the GEN501 and SIRIUS study protocols. However, a recent phase II study of an investigational anti-CD38 antibody, isatuximab, assessed the safety and efficacy of isatuximab as a single agent (20 mg/kg every week for cycle 1 and then every 2 weeks) and isatuximab and dexamethasone combined (same dosage for isatuximab as a single agent plus dexamethasone 40 mg once each week or 20 mg once each week for those aged $\geq$ 75

Figure 2 Treatment Response From Month 3 to Month 27 of Treatment, Including Partial Response (PR), Very Good Partial Response (VGPR), Complete Response (CR), Stable Disease (SD), and Progressive Disease (PD)

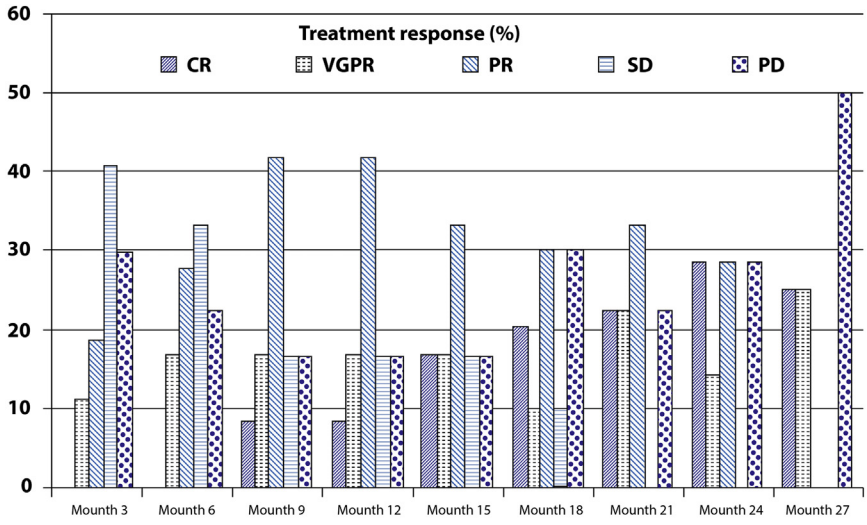
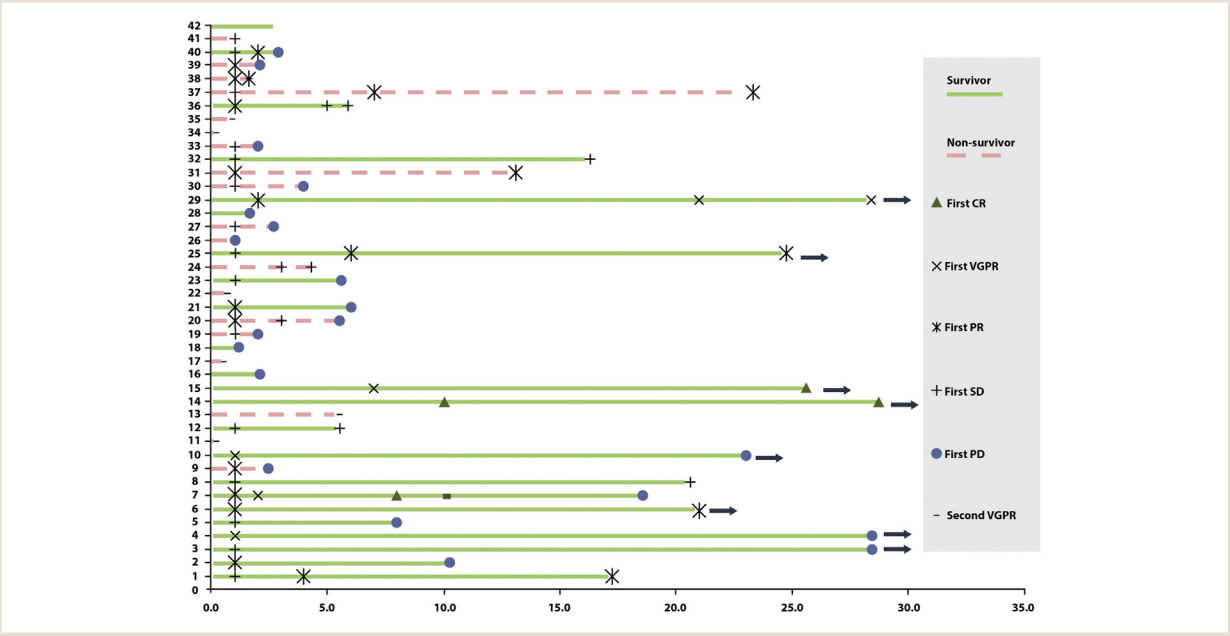


Figure 3 Case-based Data on Survival and Treatment Response



Abbriviations: CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease; VGPR = very good partial response.

years).[24] The addition of dexamethasone treatment to isatuximab improved the ORR from 26% for isatuximab alone to 44% for isatuximab plus dexamethasone. A similar improvement in median PFS was also observed (4.9 months for isatuximab alone vs. 9.3 months for isatuximab plus dexamethasone). However, steroid-related toxicities (psychiatric, eye, gastrointestinal disorders) increased with the addition of dexamethasone.[25] In another study of a human IgG1 CD38 monoclonal antibody MOR202 administered in heavily pretreated patients with RRMM, the investigators reported a favorable safety profile, promising efficacy, and long-lasting

Figure 4 Kaplan-Meier Analysis for (A) Overall Survival (OS) and (B) Progression-free Survival (PFS) According to Response Status, Including Partial Response (PR), Very Good Partial Response (VGPR), Complete Response (CR), Stable Disease (SD), and Progressive Disease (PD)

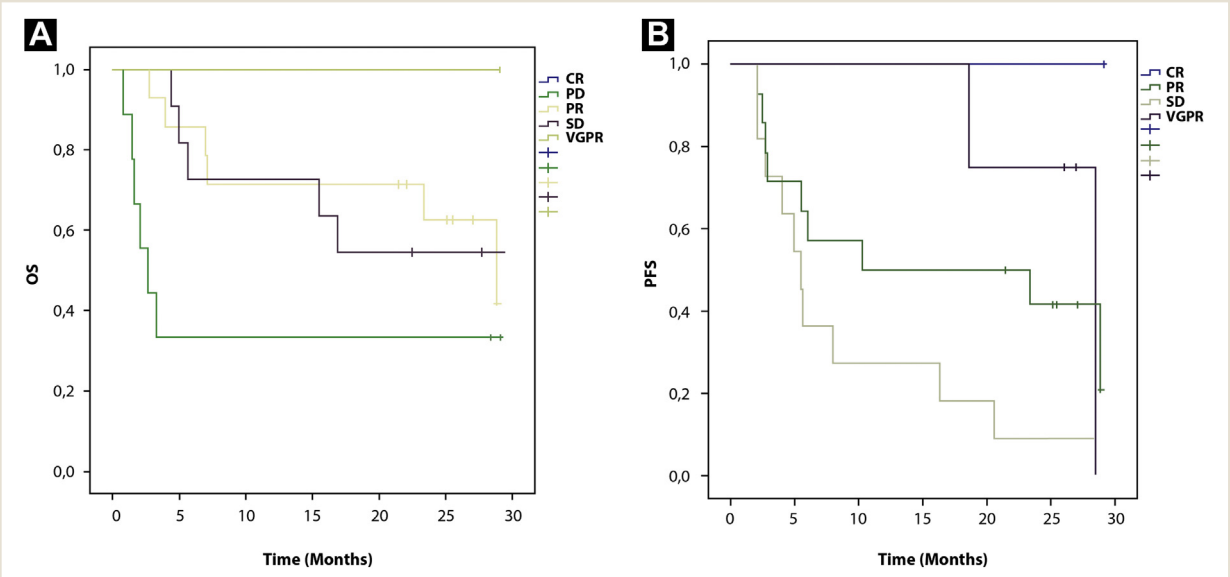
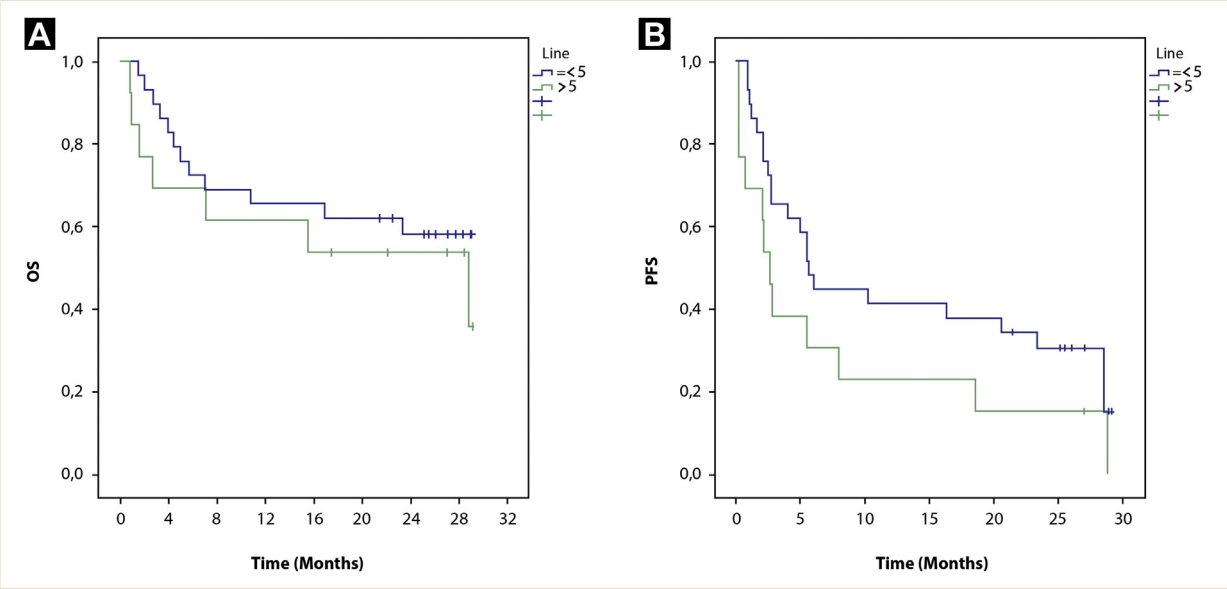


Figure 5 Kaplan-Meier Analysis for (A) Overall Survival (OS) and (B) Progression-free Survival (PFS) According to Previous Lines of Therapy



tumor control.[26] These results suggest increased antimyeloma efficacy of short duration with anti-CD38 regimens. Ongoing clinical trials and real-world studies have proved the efficacy of anti-CD38 antibodies with IMiDs and PIs. The data from the present study enable the analysis of the response kinetics with daratumumab.

The daratumumab approvals worldwide have been extremely heterogeneous. In economically advanced countries, reimbursements have been very liberal. However, in less advanced countries, daratumumab might be limited to single-agent use. Thus, our current data could provide guidance for such situations. Furthermore, the very successful results from clinical trials regarding the role of daratumumab among patients with newly diagnosed myeloma, which were completed during the present study, led to the approval of daratumumab combined with bortezomib-melphalan and prednisolone (ALCYONE study)[27] or lenalidomide (MAIA study).[28] The activity of daratumumab in the frontline is such that the response rates, duration, and, moreover, survival have improved dramatically. This is an expected finding because, as also observed in our study, daratumumab can provide clinical benefit even as a single agent among patients with heavily pretreated RRMM.

Conclusion

The present findings from our daratumumab EAP have confirmed the efficacy and safety profile of daratumumab for Turkish patients with heavily pretreated RRMM. Based on the deep depth of response, which occurred considerably quickly, and lasted $\leq$ 7.8 months, and the favorable safety and tolerability profile, our findings emphasize the likelihood of daratumumab monotherapy as an effective and suitable option even after 3 to 8 lines of treatment. The present study has provided real-word data on daratumumab within the context of an EAP and, thus, is no substitute for data from a phase study. Furthermore, our findings emphasize the effect of the depth of response, regardless of the number of previous lines of therapy, to daratumumab monotherapy on the prolongation of OS.

Clinical Practice Points

- Daratumumab was approved as a single agent in 2015 by the US Food and Drug Administration and in 2016 by the European Medicines Agency for RRMM.

Table 6 Adverse Events and Infusion-related Reactions

Variable	Any Grade, n	Grade ≥3, n
Adverse events		
Total	76	33
Thrombocytopenia	13	6
Anemia	12	4
Neutropenia	8	3
Neuropathy	3	2
Fatigue	11	5
Upper respiratory tract infection	3	1
Lower respiratory tract infection	8	4
Other infection	8	4
Infusion-related reactions		
Total	10	4
Dyspnea	5	1
Nausea	2	1
Fever	2	2
Rash	1	0

- In countries where frontline drug approval has been limited to first-generation PIs or IMIDs, relapses have been both more frequent and less durable.
- Our Turkish EAP has provided real-word data on the efficacy and safety profile of daratumumab monotherapy in 42 patients with RRMM in Turkey.
- The present findings have confirmed the efficacy of daratumumab monotherapy owing to the deep and durable responses that lasted $\leq$ 2 years, favorable safety and tolerability.
- The present study has provided real-word data on daratumumab within the context of an EAP and, thus, is no substitute for data from a phase study.
- Our findings have also emphasized the effect of the depth and kinetics of response, regardless of the number of previous lines of therapy, on OS.

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Disclosure

The authors have stated that they have no conflicts of interest.

References

1. Morandi F, Horenstein AL, Costa F, Giuliani N, Pistoia V, Malavasi F. CD38: a target for immunotherapeutic approaches in multiple myeloma. *Front Immunol* 2018; 9:2722.
2. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood* 2008; 111:2516-20.
3. van de Donk NWCJ, Richardson PG, Malavasi F. CD38 antibodies in multiple myeloma: back to the future. *Blood* 2018; 131:13-29.
4. Usmani SZ, Diels J, Ito T, Mehra M, Khan I, Lam A. Daratumumab monotherapy compared with historical control data in heavily pretreated and highly refractory patients with multiple myeloma: an adjusted treatment comparison. *Am J Hematol* 2017; 92:E146-52.
5. Funaro A, Spagnoli GC, Ausiello CM, et al. Involvement of the multilineage CD38 molecule in a unique pathway of cell activation and proliferation. *J Immunol* 1990; 145:2390-6.
6. Jelínek T, Mihályová J, Hájek R. CD38 targeted treatment for multiple myeloma. *Vnitr Lek* 2018; 64:939-48.
7. Zhang X, Zhang C, Yang X, et al. Design, synthesis and evaluation of anti-CD38 antibody drug conjugate based on daratumumab and maytansinoid. *Bioorg Med Chem* 2019; 27:479-82.
8. Lokhorst HM, Plesner T, Laubach JP, et al. Targeting CD38 with daratumumab monotherapy in multiple myeloma. *N Engl J Med* 2015; 373:1207-19.
9. Lonial S, Weiss BM, Usmani SZ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. *Lancet* 2016; 387:1551-60.
10. Usmani SZ, Weiss BM, Plesner T, et al. Clinical efficacy of daratumumab monotherapy in patients with heavily pretreated relapsed or refractory multiple myeloma. *Blood* 2016; 128:37-44.
11. Chari A, Lonial S, Mark TM, et al. Results of an early access treatment protocol of daratumumab in United States patients with relapsed or refractory multiple myeloma. *Cancer* 2018; 124:4342-9.
12. Park SS, Eom HS, Kim JS, et al; Korean Multiple Myeloma Working Party. Brief report: clinical experiences after emergency use of daratumumab monotherapy for relapsed or refractory multiple myeloma in real practice. *Jpn J Clin Oncol* 2019; 49:92-5.
13. Salomon-Perzyński A, Walter-Croneck A, Usnarska-Zubkiewicz L, et al. Efficacy of daratumumab monotherapy in real-world heavily pretreated patients with relapsed or refractory multiple myeloma. *Adv Med Sci* 2019; 64:349-55.
14. Cejalvo M, Legarda M, Abella E, et al. Single-agent daratumumab in patients with relapsed and refractory multiple myeloma requiring dialysis: results of a Spanish retrospective, multicentre study [e-pub ahead of print]. *Br J Haemato*. https://doi.org/10.1111/bjh.16286. accessed December 2, 2019.
15. Cook G, Corso A, Streetly M, et al. Results of the daratumumab monotherapy early access treatment protocol (EAP) in patients from Europe and Russia with relapsed or refractory multiple myeloma. *HemaSphere* 2019; 3:656, Poster session II: myeloma and other monoclonal gammopathies—Clinica PS1425.
16. Lovas S, Varga G2, Farkas P, et al. Real-world data on the efficacy and safety of daratumumab treatment in Hungarian relapsed/refractory multiple myeloma patients. *Int J Hematol* 2019; 110:559-65.
17. Iida S, Suzuki K, Kusumoto S, et al. Safety and efficacy of daratumumab in Japanese patients with relapsed or refractory multiple myeloma: a multicenter, phase 1, dose-escalation study. *Int J Hematol* 2017; 106:541-51.
18. Janssen Research & Development, LLC. October 2017; Final Clinical Study Report. Available at: https://clinicaltrials.gov/ct2/show/NCT01985126. Accessed: February 18, 2019
19. Usmani S, Ahmadi T, Ng Y, et al. Analysis of real-world data on overall survival in multiple myeloma patients with $\geq$3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD), or double refractory to a PI and an IMiD. *Oncologist* 2016; 21:1355-61.
20. Van Sanden S, Ito T, Diels J, Vogel M, Belch A, Oriol A. Comparative efficacy of daratumumab monotherapy and pomalidomide plus low-dose dexamethasone in the treatment of multiple myeloma: a matching adjusted indirect comparison. *Oncologist* 2018; 23:279-87.
21. Jelínek T, Maisnar V, Pour L, et al. Adjusted comparison of daratumumab monotherapy versus real-world historical control data from the Czech Republic in heavily pretreated and highly refractory multiple myeloma patients. *Curr Med Res Opin* 2018; 34:775-83.
22. Diels J, Lam A, Ito T, Ng Y, Mehra M, Khan I. Indirect comparison of daratumumab monotherapy versus real-world historical control data in patients with multiple myeloma who are heavily pre-treated and highly refractory. *Value Health* 2016; 19:A140.
23. Demmer I, Huschens S, Potthoff D, et al. Indirect comparison using individual patient level data comparing efficacy and safety of a daratumumab monotherapy vs. EU approved comparator therapies in patients with multiple myeloma. ASH 2018 Annual Meeting. *Blood* 2018; 132(suppl 1):P3541.
24. Kumar S, Durie B, Nahi H, et al. Propensity score matching analysis to evaluate the comparative effectiveness of daratumumab versus real-world standard of care therapies for patients with heavily pretreated and refractory multiple myeloma. *Leuk Lymphoma* 2019; 60:163-71.
25. Dimopoulos M, Bringhen S, Anttila P, et al. Results from a phase II study of isatuximab as a single agent and in combination with dexamethasone in patients with relapsed/refractory multiple myeloma. ASH 2018 Annual Meeting. *Blood* 2018; 132(suppl 1):P155.
26. Raab MS, Goldschmidt H, Agis H, et al. Phase I/IIa study of the human anti-CD38 antibody MOR202 (MOR03087) in relapsed or refractory multiple myeloma (rrMM). *J Clin Onco* 2015; 33(suppl 15), abstract 8574.
27. Mateos MV, Cavo M, Blade J, et al. Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial. *Lancet* 2020; 395:132-41.
28. Facon T, Kumar S, Plesner T, et al. Daratumumab plus lenalidomide and dexamethasone for untreated myeloma. *N Engl J Med* 2019; 380:2104-15.