Impact of performance status on overall survival in patients with relapsed and/or refractory multiple myeloma: Real-life outcomes of daratumumab treatment

Garbriel Afram | Charlotte Gran | Johanna Borg Bruchfeld | Arnika Kathleen Wagner | Alamdar Hussain | Evren Alici | Hareth Nahi

Karolinska Institutet Department of Medicine Huddinge, Stockholm, Sweden

Correspondence
Gabriel Afram, Karolinska Institutet, Department of Medicine, Huddinge (MedH), H7, Research, Unit for Haematology M 54, Karolinska Universitetssjukhuset Huddinge, 141 86 Stockholm, Sweden.
Email: gabriel.afram@sll.se

Abstract
Background: Little is reported on the real-life impact of daratumumab in relapsed and/or refractory multiple myeloma patients (RRMM). We analyzed a cohort of 156 patients who received daratumumab as a single agent concerning ECOG status, eGFR, cytogenetics, lines of prior treatment, and their impact on survival.

Results: Eighty-two (53%) patients were triple refractory, 54 (35%) patients were single or double refractory, and 20 (12%) patients were non-refractory. Following daratumumab treatment, the progression-free survival (PFS) in these groups was 7.2%, 11.4%, and 53% (P < .001), and overall survival (OS) was 34%, 73%, and 58% (P < .001) at 36 months, respectively. Poor ECOG, three lines of prior treatment, and triple refractoriness were all associated with inferior PFS and OS in a multivariate analysis including ECOG, high-risk chromosomal aberrations, refractoriness, number of treatment lines, and eGFR.

Conclusion: Daratumumab remains an attractive treatment option, especially in patients with poor performance and increased frailty. Furthermore, our observations suggest that patients with ECOG 2 and 3 status require additional supportive and/or palliative therapies to compensate for a potentially effective but encompassing late-line therapy. In conclusion, further prospective studies are needed to elucidate the impact of ECOG 2 and 3 status in patients with RRMM.

KEYWORDS
multiple myeloma, quality of life, supportive care
The human anti-CD38 antibody daratumumab is one such treatment that has had a significant impact on patients with RRMM. Daratumumab has in this setting demonstrated single-agent efficacy and tolerability.\(^1\)\(^3\) Although antibody therapies seem to provide new possibilities with unprecedented response and survival rates in the RRMM group of patients, there is still a lack of long-term outcome data with regard to patients’ performance status.\(^4\)\(^-\)\(^7\)

**Novelty Statement**
- The impact of performance status on outcome
- The clarification of daratumumab in such patients
- Daratumumab is a highly attractive treatment option for our most frail patients.

**TABLE 1** Patient Characteristics

|                      | All patients (N = 156) | Relapsed and refractory | P-value |            |
|----------------------|------------------------|-------------------------|---------|------------|
|                      |                        | Single/double (N = 54)  | Triple (N = 82) | Non (N = 20) | Single/double vs Triple | Non vs Triple |
| Median (IQR)         |                        |                        |         |            |
| Age at start of daratumumab, years median (IQR) | 71 (62-75) | 71 (65-75) | 72 (63-74) | 63 (60-71) | .60 | .40 |
| Hemoglobin, g/dL     | 111 (100-125)          | 112 (102-123)          | 106 (96-125) | 116 (109-127) | .07 | .06 |
| eGFR, mL/min/1.73 m\(^2\) | 63 (39-74)          | 68 (47-74)          | 60 (33-74) | 69 (53-82) | .14 | .04 |
| Calcium, mmol/L      | 2.3 (2.2-2.4)          | 2.3 (2.2-2.4)          | 2.3 (2.1-2.4) | 2.3 (2.3-2.4) | .64 | .84 |
| Albumin, g/L         | 33 (30-37)             | 33 (31-37)             | 33 (28-37) | 35 (33-38) | .51 | .14 |
| Prior lines of treatment | 2.9 (1-5)             | 2.8 (1.5)             | 3.4 (1-8) | 1.8 (1-4) | <.001 | <.001 |
| No. patients (%)     |                        |                        |         |            |
| ECOG                 |                        |                        |         |            |
| 0                    | 12 (7)                 | 8 (15)                 | 1 (1)    | 3 (15)    | .069 | .63 |
| 1                    | 105 (61)               | 37 (69)               | 57 (68)  | 12 (60)   |            |
| 2                    | 34 (20)                | 8 (15)                | 21 (26)  | 5 (25)    |            |
| 3                    | 5 (3)                  | 1 (2)                 | 4 (5)    | 0         |            |
| Type of heavy chain  |                        |                        |         |            |
| IgG                  | (67)                   | (72)                   | (65)    |            | .37 | .61 |
| IgA                  | (15)                   | (16)                   | (12)    |            |            |
| Bence Jones          |                        |                        |         |            |
| Other Ig             |                        |                        |         |            |
| Type of light chain  |                        |                        |         |            |
| Kappa                | 100 (67)               | 29 (58)               | 57 (71)  | 14 (70)   | .12 | .91 |
| Lambda               | 50 (33)                | 21 (42)               | 23 (29)  | 6 (30)    |            |
| Cytogenetic risk     |                        |                        |         |            |
| Standard             | 26 (48)                | 12 (63)                | 12 (39)  | 2 (50)    | .10 | .68 |
| High                 | 28 (52)                | 7 (37)                | 19 (61)  | 2 (50)    |            |
| Relapsed and refractory |                    |                        |         |            |
| PI                   | 112 (73)               | 31 (57)               | 82 (100) |            |            |
| IMiD                 | 125 (81)               | 36 (67)               | 82 (100) |            |            |
| AA                   | 0 (0)                  | 0 (0)                 | 82 (100) |            |            |
| PI + IMiD            | 99 (64)                | 14 (26)               | 82 (100) |            |            |
| PI + AA              | 90 (58)                | 8 (15)                | 82 (100) |            |            |
| IMiD + AA            | 86 (56)                | 4 (7)                 | 82 (100) |            |            |

Statistically significant values are in bold.
Thus, the purpose of the current retrospective, non-interventional, single-center study is to assess real-life data in daratumumab-treated RRMM patients with emphasis on patient performance using Eastern Cooperative Oncology Group status (ECOG) [8].

### MATERIAL AND METHODS

#### 2.1 Study population and data collection

The study has received approval from the Ethics Committee in Stockholm (EPN 2014/526-31/3 and 2015/973-32). It was performed at the Department of Hematology Karolinska University Hospital in accordance with the Helsinki declaration.

One hundred and fifty-six (n = 156) patients with at least one prior line of treatment to receiving daratumumab were included in this retrospective single-center study. All patients meeting the criteria of at least one prior line of treatment and subsequently starting daratumumab treatment between 2014 and April of 2019 were included in this study. Accordingly, no patients were excluded. Diagnosis and staging was defined according to the international myeloma working group (IMWG) criteria [9]. Relapse was defined as biochemical M-protein progression of at least 25% from baseline and/or myeloma defining events. Refractory patients were defined as progressing within 100 days after treatment cessation or during ongoing treatment. Fluorescence in situ hybridization reports conducted at diagnosis were collected. Clinical data including age, gender, myeloma subtype, and ECOG performance score were obtained from the electronic medical records at the start of daratumumab treatment. Baseline laboratory values of serum M-protein, urine M-protein, serum-free light chains (sFLC), calcium, hemoglobin (Hb), albumin, and creatinine were obtained at the same time point from the same electronic medical records.

### RESULTS

Patient characteristics are summarized in Table 1. Of the 156 RRMM patients included, 20 patients (13%) were neither refractory nor resistant (RR) to earlier lines of treatment, 54 patients (35%) were single- or double RR to PI, and/or IMiD. Eighty-two patients (52%) were triple RR to PI, IMiD, and alkylating agents. The median time from diagnosis to the start of daratumumab treatment was 4.7 years (0.5-12).

#### 3.1 Response to treatment

The response distribution in the whole population is reported in Table 2. One hundred and five patients (n = 105) relapsed while on daratumumab treatment, 8 patients (8%) were not RR, 34 patients (32%) were single- or double RR, and 63 patients (60%) were triple RR before the start of daratumumab.

### 2.2 Outcome measures

Overall survival (OS) and progression-free survival (PFS) were the primary endpoints. OS was defined as the time from the start of daratumumab treatment until death or the date of the last follow-up. PFS was defined as the time from the beginning of daratumumab treatment until progression or death. Response and progression in MM patients were defined as per IMWG response criteria [9]. Complete response (CR), very good partial response (VGPR), and partial response (PR) were pooled together as ≥PR. Progressive disease (PD), minimal response (MR), and non-response (NR) were combined as <PR.
3.2 | Progression-free and overall survival

We have compared the PFS and OS of patients stratified by ECOG status (Figure 1A-B, Table 3). In this cohort, we observed an extremely short PFS in those with higher ECOG status and this finding reflected on the OS.

PFS was shorter for triple RR compared to single/double RR with a median PFS of 7 vs 11.5 months ($P = .006$), respectively (Figure 2B). There was no difference in PFS when comparing non-RR and single/double RR ($P = .14$). Furthermore, lower eGFR and increasing lines of treatment before daratumumab were also associated with shorter PFS (Table 3).

OS was shorter in the triple-RR group compared to single/double RR (Figure 2A). OS was also significantly impacted by lower eGFR and increasing lines of treatment prior to daratumumab (Table 3). OS analysis in the triple, single/double and the non-RR patients who progressed on daratumumab showed a 12-month survival of 50.1%, 76.2%, and 100%, respectively.

In the multivariate analysis, poor ECOG performance status was confirmed to be associated with shorter PFS and OS. Furthermore,
the same association was found when analyzing the non-RR, single/double RR, and triple-RR sub-groups (Table 4).

4 | DISCUSSION

The prognostic implication of patient performance status has recently been shown to impact OS in RRMM. However, there is a lack of prospective information on how these patients are managed in real life and how outcomes relate to subsequent treatments. As daratumumab is becoming more commonly used due to its efficiency and tolerability in a broad range of patients, we aim to assess real-life outcomes in patients who have received daratumumab after at least one prior treatment regimen.

Our study focuses on daratumumab treatment for RRMM where we show outcomes with a median PFS of 7.2 months and median OS of 20 months. Our findings suggest that daratumumab treatment may be more efficient in RRMM compared to other treatment options. In a recent report, a cohort of 462 MM patients receiving additional treatment after being found resistant to both a PI and an IMiD as well as already being exposed to an alkylating agent were reported to have a median PFS of 5 months and a median OS of 15 months. The contrast to our study can be attributed to temporal and treatment regimen differences in the study cohort.

Daratumumab treatment has shown high efficacy and safety in MM patients. In our study, 56% of the patients achieved ≥PR according to the IMWG response criteria, regardless of refractoriness. 69% of patients in our cohort relapsed while on daratumumab at the time of this study. We found a correlation of higher relapse rates with increasing refractoriness. In a previously reported study, the observed treatment response rates after progression on PI, IMiD, and anti-CD38 were dismal. Specifically, the average response rate was 31%, with a median PFS of 3.4 months and median OS of 9.3 months.

We also demonstrate a lower OS and PFS for patients who are triple refractory vs non-/single/double refractory prior to daratumumab treatment. Although we did not categorize our patients as being penta-refractory since we utilize daratumumab before carfilzomib at our center, we show a higher median OS for our most refractory patients as compared to the abovementioned study (7 vs 5.6 months). However, in this population, comparisons are very difficult except within a randomized trial due to many apparent and subtle variations between studies. Such a difference is clearly in the same range and cannot be basis for any statement of a significant difference.

TABLE 3 Univariate analysis, factors associated with progression-free survival and overall survival

| Overall survival | Progression-free survival |
|------------------|---------------------------|
|                   | Median (months) | 36 mo (%) | P value | Median (months) | P value |
| **ECOG**          |                |           |         |                |         |
| 0                 | NR             | 100       | <.001   | 18.5           | <.001   |
| 1                 | NR             | 53        |         | 10.2           |         |
| 2                 | 13             | 26        |         | 3.7            |         |
| 3                 | 2              | 0         |         | 1.3            |         |
| **Relapsed and refractory** | | | | | |
| Non               | NR             | 58        | <.001   | NR (53%*)      | <.001   |
| Single/double     | NR             | 73        |         | 11.4           |         |
| Triple            | 20             | 34        |         | 7.2            |         |
| **Prior lines of treatment** | | | | | |
| One               | NR             | 92        | <.001   | 18.5           | <.001   |
| Two               | NR             | 72        |         | 12             |         |
| Three             | NR             | 64        |         | 7.8            |         |
| Four or more      | 18             | 19        |         | 5.8            |         |
| **eGRF**          |                |           |         |                |         |
| <30               | 13             | 40        | .003    | 8.8            | .375    |
| 30-60             | NR             | 51        |         | 10             |         |
| >60               | NR             | 57        |         | 8.8            |         |
| **Cytogenetic risk** | | | | | |
| High              | 28             | 43        | .322    | 9              | .112    |
| Standard          | NR             | 57        |         | 15             |         |

Note: NR denoted not reached, ECOG Eastern Cooperative Oncology Group performance status * Median PFS not reached, presented in % PFS at 36 mo. Log-rank test for P-values.
Statistically significant values are in bold.
In the current study, we show that performance status significantly affects PFS and OS. One of the reasons for utilizing daratumumab is its beneficial safety profile in this patient population. We demonstrate that outcomes are, in fact, severely impacted by ECOG status regardless of refractoriness or cytogenetic risk. The median OS and PFS were significantly lower in ECOG ≥ 2 compared to the ECOG ≤ 1 patients. This difference was further enhanced in the triple-refractory population. Nevertheless, the proportion of patients with ECOG ≥ 2 were higher in this cohort compared to the previously reported studies with targeted immunotherapies including CAR-T cells. When choosing a treatment for patients with poor performance status in the RRMM group, our results show that daratumumab remains a viable option. Usually, such patient groups with poor performance are lacking in clinical trials. We are able to highlight results indicating a viable treatment option and such results could not be deduced from previous clinical trials.

In conclusion, the current real-life results confirm the benefits of daratumumab on PFS and OS. More importantly, our data suggest that performance status has more impact on outcome than
previously reported. In the future, this could potentially be salvaged with novel, potentially cellular, immunotherapies. Until then, we suggest considering performance status of RRMM patients in choosing the optimal treatment regime.

ORCID
Garbriel Afram https://orcid.org/0000-0002-7376-535X
Charlotte Gran https://orcid.org/0000-0002-6069-6615
Johanna Borg Bruchfeld https://orcid.org/0000-0001-7006-311X
Arnika Kathleen Wagner https://orcid.org/0000-0002-0339-8259

REFERENCES
1. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood. 2008;111(5):2516-2520.
2. Pozzi S, Marcheselli L, Bari A, et al. Survival of multiple myeloma patients in the era of novel therapies confirms the improvement in patients younger than 75 years: a population-based analysis. Br J Haematol. 2013;163(1):40-46.
3. Lokhorst HM, Plesner T, Laubach JP, et al. Targeting CD38 with Daratumumab Monotherapy in Multiple Myeloma. N Engl J Med. 2015;373(13):1207-1219.
4. Zhao WH, Liu J, Wang BY, et al. A phase 1b, open-label study of LCAR-B38M, a chimeric antigen receptor T cell therapy directed against B cell maturation antigen, in patients with Relapsed/Refractory Multiple Myeloma (RRMM). 61st American Society of Hematology annual meeting and exposition. 2019;Oral Abstract 579.
5. Madduri D. Results from CARTITUDE-a: A Phase 1b/2 Study of JNJ-4528, a CAR-T Cell Therapy Directed Against B-Cell Maturation Antigen (BCMA), in Patients with Relapse and/or Refractory Multiple Myeloma (R/R MM). 61st American Society of Hematology annual meeting and exposition. 2019;Oral Abstract 577.
6. Wang BY. Long-Term Follow-up of a Phase 1, First-in-Human Open-Label Study of LCAR-B38: A Structurally Differentiated Chimeric Antigen Receptor T (CAR-T) Cell Therapy Targeting B-Cell Maturation Antigen (BCMA), in Patients with Relapsed/Refractory Multiple Myeloma (RRMM). 61st American Society of Hematology annual meeting and exposition. 2019;Oral Abstract 579.
7. Raje N, Berdeja J, Lin Y, et al. Anti-BCMA CAR T-cell therapy bb2121 in relapsed or refractory multiple myeloma. N Engl J Med. 2019;380(18):1726-1737.
8. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the eastern-cooperative-oncology-group. Am J Clin Oncol-Canc. 1982;5(6):649-655.
9. Kyle RA, Rajkumar SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. Leukemia. 2009;23(1):3-9.
10. Stege CAM, van der Holt B, Dinmohamed AG, et al. Validation of the FIRST simplified frailty scale using the ECOG performance status instead of patient-reported activities. Leukemia. 2020. [Epub ahead of print].
11. Mateos MV, Spencer A, Nooka AK, et al. Daratumumab-based regimens are highly effective and well tolerated in relapsed or refractory multiple myeloma regardless of patient age: subgroup analysis of the phase 3 CASTOR and POLLUX studies. Haematologica. 2019;105(2):468-477.
12. Kumar SK, Dimopoulos MA, Kastritis E, et al. Natural history of relapsed myeloma, refractory to immunomodulatory drugs and proteasome inhibitors: a multicenter IMWG study. Leukemia. 2017;31(11):2443-2448.
13. Gandhi UH, Cornell RF, Lakshman A, et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. Leukemia. 2019;33(9):2266-2275.
14. Byun JM, Yoon SS, Koh Y, et al. Daratumumab monotherapy in heavily pretreated asian patients with relapsed and refractory multiple myeloma: a real-world experience. Anticancer Res. 2019;39(9):5165-5170.

How to cite this article: Afram G, Gran C, Borg Bruchfeld J, et al. Impact of performance status on overall survival in patients with relapsed and/or refractory multiple myeloma: Real-life outcomes of daratumumab treatment. Eur J Haematol. 2020;105:196–202. https://doi.org/10.1111/ejh.13426

|                        | Progression-free survival | Overall survival |
|------------------------|----------------------------|-----------------|
|                        | HR (95% CI) P value        | HR (95% CI) P value |
| Age at start of daratumumab | 1.01 (0.99-1.03) .36  | 1.02 (0.99-1.05) .26 |
| Hb                     | 1.30 (0.94-1.80) .11      | 0.64 (0.41-1.01) .054 |
| ECOG performance status|                           |                 |
| 0-1                    | 1.00 (0.99-1.05) .005     | 1.00 (0.99-1.05) .004 |
| 2-3                    | 2.12 (1.26-3.57) .23     | 2.71 (1.37-5.36) .16 |
| Cytogenetics at MM diagnose |                       |                 |
| Standard               | 1.00 (0.99-1.05) .36  | 1.00 (0.99-1.05) .36 |
| High risk              | 1.26 (1.03-1.53) .23   | 1.21 (0.93-1.59) .16 |
| Response to daratumumab|                           |                 |
| ≤PR                    | 1.00 (0.99-1.05) .36  | 1.00 (0.99-1.05) .36 |
| ≥VGPR                  | 0.27 (0.16-0.44) .001  | 0.43 (0.22-0.83) .011 |

Statistically significant values are in bold.