CORRESPONDENCE

# Impact of daratumumab on collection and engraftment in multiple myeloma patients undergoing hematopoietic stem cell mobilization with G-CSF plus on-demand plerixafor



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## INTRODUCTION

Despite the high efficacy of quadruplets incorporating anti-CD38 monoclonal antibodies, as showed in the phase III CASSIOPEIA [1] and PERSEUS [2] studies, high-dose melphalan (HDM) followed by autologous stem-cell transplant (ASCT) remains a standard of care in young and fit newly diagnosed (ND) multiple myeloma (MM) patients [3]. Therefore, an ideal induction regimen should not only achieve rapid and deep disease control but also allow an optimal hematopoietic stem-cell (HSC) collection.

HSC mobilization strategies include a steady-state mobilization with granulocyte colony-stimulating factor (G-CSF) only or a combination of conventional chemotherapy (e.g., cyclophosphamide at different dose of 2–4 g/m$^2$) and G-CSF, with additional plerixafor that has significantly reduced the number of mobilization failure patients [4].

Here we report the results of a retrospective, observational study conducted in two Italian centers, "Città della Salute e della Scienza di Torino" and "Istituto di Ricovero e Cura a Carattere Scientifico (IRCSS) Istituto Clinico Humanitas" evaluating the impact of daratumumab on HSC collection, as well as post-transplant engraftment, in MM patients treated with VTd or VTd plus daratumumab (DVTd) induction who underwent chemotherapy-free mobilization with G-CSF with "on-demand" plerixafor.

## MATERIALS AND METHODS

Consecutive, transplant eligible, NDMM patients, who received induction therapy with DVTd or VTd and underwent HSC mobilization only with G-CSF (10 mcg/Kg per day) plus "on-demand" plerixafor, were analysed.

According to its label, "on-demand Plerixafor" was administered in patients with <20 CD34$^+$ cells/L after at least four consecutive days of G-CSF or in patients unable to collect at least $1 \times 10^6$ mg/kg after the first day of apheresis. The primary endpoint of the study was the rate of poor mobilizers, defined as the rate of patients who collected $<2 \times 10^6$ CD34$^+$ cells/Kg ("mobilization failure") [4] or who required plerixafor to complete HSC collection.

Collection failure, suboptimal collection and optimal collection were defined as <2, 2–4 and $\geq 4 \times 10^6$ CD34$^+$/Kg cells collected, respectively. Neutrophil and platelet recovery were defined as the first day with an absolute neutrophil count ≥500/mL post-ASCT nadir and as the first day with a count ≥20,000/mL without platelet transfusion for 3 days, respectively. Patients' charts were reviewed to collect data on baseline patient and disease characteristics (online Supplementary Appendix).

Statical methods, ethics approval, and informed patient statement were described in online Supplementary Appendix.

## RESULTS

A total of 217 NDMM patients undergoing HSC mobilization between May 2015 and October 2023 were included in the analysis, 83 (38%) treated with DVTd and 134 (62%) with VTd. Baseline characteristics were well balanced within the two groups and are summarized in Table 1.

The rate of poor mobilizers was higher in patients receiving DVTd as compared to those who received VTd induction (64% vs. 30%; $p = 0.002$), mainly due to a higher use of plerixafor in the DVTd as compared to the VTd group (57% vs. 26%; $p = 0.006$), while no significant difference in the rate of patients who were unable to collect $\geq 2 \times 10^6$ CD34+ cells/kg was observed (7% vs. 4%; $p = 0.6$). Overall, 93% in the DVTd and 96% in VTd collected at least $2 \times 10^6$/Kg CD34$^+$ cells ($p = 0.58$) with the first mobilization attempt. A similar proportion of patients in the DVTd and VTd group achieved an optimal (88% vs 91%; $p = 0.4$) or a suboptimal collection (5% vs 6%; $p = 0.7$), respectively. The median number of CD34$^+$ x $10^6$/Kg collected was similar in the two groups (DVTd, 7.04; VTd, 7.84; $p = 0.08$). Despite a lower median number of CD34$^+$/L on the first day of count in the DVTd group (18, IQR 7–27) as compared to the VTd group (24, IQR 14–42; $p = 0.002$), a similar increase in the median number of CD34$^+$/L after the first dose of plerixafor was observed in the DVTd (45, IQR 30–62) and VTd (55, IQR 38–70) group, respectively ($p = 0.4$). The median number of apheresis was 2 (IQR 1-2) in the DVTd and 1 (IQR 1-2) in the VTd group ($p = 0.58$). Eleven patients (DVTd, $n = 6$; VTd, $n = 5$; total 5%) failed to collect at least $2 \times 10^6$ CD34+ cells/kg; of these, 6/10 and 4/10were respectively rescued with cyclophosphamide plus G-CSF and plerixafor "on demand" ($n = 4$, all in the DVTd group). Overall, 100 and 99% of patients in the two arms collected $\geq 2 \times 10^6$ CD34$^+$ cells/kg and were able to proceed to ASCT. Mobilization and harvest data are summarized in Table 1, Figs. S1–S3.

Engraftment outcomes were analysed in 108 patients (DVTd, 51/83; VTd, 57/134) who received post-transplant G-CSF starting between day +3 and +5 after ASCT. The median number of CD34$^+$cells/kg transplanted was 3.60 (IQR 2.96–3.69) and 3.28 (IQR 3.20–3.90) in the DVTd and VTd groups, respectively ($p = 0.39$). Hematopoietic recovery was obtained in 100% of patients. Median time to neutrophil recovery was 12 (IQR 12–13) and 13 days (IQR 12–15) in the DVTd and VTd groups, respectively, ($p = 0.02$) and a median time to platelet recovery was of 13 (IQR 12–15) and 15

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**Table 1.** Baseline characteristics and study results.

| Variables | | Overall (n = 217) | DVTd (n = 83) | VTd (n = 134) | p-value |
|---|---|---|---|---|---|
| Age (years) | Median (IQR) | 63 (56–68) | 63 (56–68) | 63 (55–68) | 0.63 |
| | ≤60, n (%) | 89 (41) | 34 (41) | 55 (41) | 1 |
| | >60, n (%) | 128 (59) | 49 (59) | 79 (59) | |
| Sex | Female, n (%) | 94 (43) | 36 (43) | 58 (43) | 1 |
| | Male, n (%) | 123 (57) | 47 (57) | 76 (57) | |
| Isotype | IgG, n (%) | 115 (53) | 45 (54) | 70 (52) | 0.9 |
| | IgA, n (%) | 39 (18) | 13 (16) | 26 (19) | |
| | BJ, n (%) | 47 (22) | 19 (23) | 28 (21) | |
| | NS, n (%) | 8 (4) | 2 (2) | 6 (5) | |
| | Other, n (%) | 7 (3) | 3 (4) | 4 (3) | |
| | Missing, n (%) | 1 (<1) | 1 (<1) | 0 | |
| LDH > UNL | No, n (%) | 155 (71) | 64 (77) | 91 (68) | 0.71 |
| | Yes, n (%) | 26 (12) | 9 (11) | 17 (13) | |
| | Missing, n (%) | 36 (17) | 10 (12) | 26 (19) | |
| FISH[a] | Yes, n (%) | 162 (75) | 64 (77) | 98 (73) | 0.75 |
| | Standard risk, n (%) | 114 (70) | 43 (67) | 71 (72) | |
| | High risk, n (%) | 48 (30) | 21 (33) | 27 (28) | |
| | Missing, n (%) | 55 (25) | 19 (23) | 36 (27) | |
| ISS | I, n (%) | 87 (40) | 32 (39) | 55 (41) | 0.72 |
| | II, n (%) | 46 (21) | 18 (22) | 28 (21) | |
| | III, n (%) | 53 (25) | 25 (30) | 28 (21) | |
| | Missing | 31 (14) | 8 (9) | 23 (17) | |
| R-ISS | I, n (%) | 57 (26) | 18 (22) | 39 (29) | 0.30 |
| | II, n (%) | 63 (29) | 33 (40) | 30 (22) | |
| | III, n (%) | 20 (9) | 7 (8) | 13 (10) | |
| | Missing, n (%) | 77 (36) | 25 (30) | 52 (39) | |
| Number of induction cycles | Median (IQR) | 4 (4-4) | 4 (4-4) | 4 (4-4) | 0.06 |
| | ≥4, n (%) | 183 (84) | 79 (92) | 107 (80) | 0.14 |
| | <4, n (%) | 34 (16) | 7 (8) | 27 (20) | |
| Best response | SD, n (%) | 5 (2) | 2 (2) | 3 (2) | 0.13 |
| | PR, n (%) | 60 (28) | 16 (19) | 44 (33) | |
| | VGPR, n (%) | 97 (45) | 49 (59) | 48 (36) | |
| | ≥CR, n (%) | 54 (25) | 15 (18) | 39 (29) | |
| | Missing, n (%) | 1 ( < 1) | 1 ( < 1) | 0 | |
| Radiotherapy | No, n (%) | 174 (80) | 70 (84) | 194 (78) | 0.52 |
| | Yes, n (%) | 43 (20) | 13 (16) | 30 (22) | |
| Hematologic toxicity during induction[b] | No, n (%) | 208 (96) | 79 (95) | 129 (96) | 0.73 |
| | Yes, n (%) | 8 (4) | 4 (6) | 4 (3) | |
| | Missing, n (%) | 1 ( < 1) | 0 | 1 ( < 1) | |
| Time from end of induction therapy and stem cell mobilization | Median (IQR) | 28 (15–37) | 31 (23–37) | 24 (12.5–36) | 0.65 |
| | ≤30, n (%) | 119 (55) | 39 (47) | 80 (60) | 0.25 |
| | >30, n (%) | 93 (43) | 42 (51) | 51 (38) | |
| | Missing, n (%) | 5 (2) | 2 (2) | 3 (2) | |
| $CD34^+$/L at day 4 of count | Median (IQR) | 21 (11–33) | 18 (7–26.5) | 24 (14–42) | **0.002** |
| | <20, n (%) | 90 (42) | 46 (55) | 44 (33) | 0.4 |
| | ≥20, n (%) | 107 (49) | 34 (41) | 73 (54) | |
| | Missing, n (%) | 20 (9) | 3 (4) | 17 (13) | |
| CD34 + /L increase after first PLX administration | Median (IQR) | 50.5 (33.8–66.3) | 45 (29.5–62) | 55 (38–70) | 0.48 |
| Plerixafor administration | No, n (%) | 135 (62) | 36 (43) | 99 (74) | **0.006** |
| | Yes, n (%) | 82 (38) | 47 (57) | 35 (26) | |

**Table 1.** continued

| Variables | | Overall (n = 217) | DVTd (n = 83) | VTd (n = 134) | p-value |
|---|---|---|---|---|---|
| Reason for Plerixafor administration[c] | <1 × 10^6 CD34+/Kg after first apheresis, n (%) | 6 (7) | 3 (6) | 3 (8) | 1 |
| | <20 CD34+/L, n (%) | 74 (90) | 43 (92) | 31 (89) | |
| | Missing, n (%) | 2 (3) | 1 (2) | 1 (3) | |
| CD34+ x10^6 cells/Kg | Median (IQR) | 7.52 (6.10–9.37) | 7.04 (5.76–8.85) | 7.84 (6.30–10.1) | 0.08 |
| | Suboptimal, n (%) | 11 (6) | 4 (5) | 7 (6) | 0.7 |
| | Optimal, n (%) | 195 (90) | 73 (88) | 122 (91) | 0.4 |
| Successful mobilization | No, n (%) | 11 (5) | 6 (7) | 5 (4) | 0.58 |
| | Yes, n (%) | 206 (95) | 77 (93) | 129 (96) | |
| Poor mobilization patients | No, n (%) | 124 (57) | 30 (36) | 94 (70) | **0.002** |
| | Yes, n (%) | 93 (43) | 53 (64) | 40 (30) | |
| Apheresis days | 1, n (%) | 101 (46) | 32 (38.6) | 69 (51.5) | 0.58 |

Bold values indicate statistical significance $p < 0.05$.
Suboptimal collection was defined as 2 to $4 \times 10^6$ CD34 + /Kg cells collected. Optimal collection was defined as ≥ 4 × 10^6 CD34 + /Kg cells collected. Successful mobilization was defined as ≥ 2 × 10^6 CD34 + /Kg cells collected. Poor mobilization was defined as failure to collect ≥ 2 × 10^6 CD34 + /Kg or requiring plerixafor for complete collection after the first mobilization attempt.
*BJ* Bence-Jones protein, *LDH* lactate dehydrogenase, *ULN* upper limit normal, *FISH* fluorescent in situ hybridization, *HR* high-risk, *ISS* International Staging System, *R-ISS* Revised International Staging System, *SD* stable disease, *PR* partial response, *VGPR* very good partial response, *CR* complete response, *PLX* plerixafor.
[a]Percentage of standard risk and high-risk patients calculated among patients with available FISH (n = 162).
[b]Hematologic toxicity, including anemia, thrombocytopenia, or neutropenia, grade ≥ 3 was defined according in CTCAE v5.0.
[c]Percentage calculated in patients who need plerixafor.

(IQR 13–17) days in the DVTd and VTd groups, respectively (p = 0.1).

## DISCUSSION

In this real-word study, we showed that HSC collection with G-CSF and on-demand plerixafor was effective irrespective of the prior use of daratumumab, although a higher use of plerixafor (57% vs. 26%; p = 0.006) was observed in patients treated with a daratumumab-based induction. Results from our study are in line with prior observations concerning the impact of daratumumab on HSC mobilization. In the CASSIOPEIA and PERSEUS studies, in which the majority of patients underwent HSC mobilization with cyclophosphamide plus G-CSF, a greater use plerixafor (40% vs. 23% and 22% vs. 8%, respectively) and a lower HSC yield (6.7 vs $10 \times 10^6$ CD34+/Kg and 5.5 vs $7.4 \times 10^6$/kg) was reported among patients treated with upfront daratumumab [1, 2, 5], a phenomenon that could be at least partially explained by the expression of CD38 on CD34+ mobilized cells [6]. Our data are also in line with other retrospective real-world studies that, regardless of the mobilization strategy adopted, demonstrated a higher use of plerixafor patients exposed to daratumumab during induction (37–51%) [7–9].

In our study, a broad use of "on-demand" plerixafor, along with G-CSF, resulted in a similar median number of CD34+ × $10^6$/kg cells collected in the DVTd (7.04) and VTd groups (7.84; p = 0.08). Of note, despite adoption of a steady-state mobilizing strategy without chemotherapy, the median HSC yield obtained in our study with in daratumumab-treated patients is comparable to those reported in the CASSIOPEIA and PERSEUS studies (median $7.04 \times 10^6$/kg vs. mean 6.7 and median $5.5 \times 10^6$/kg), although this came at the cost of a higher plerixafor use (57% vs 22% and 40%, respectively) [1, 5], thus supporting a chemotherapy-sparing mobilization strategy also in daratumumab-exposed patients.

Data regarding the time to engraftment in patients receiving daratumumab are conflicting [2, 5, 9–11]; however, in our study hematological recovery was achieved in all patients and no difference in terms of both neutrophil and platelet recovery in patients who received daratumumab as compared to those of who did not was observed.

In conclusion, our study shows that daratumumab exposure during induction does not impair HSC collection nor post-transplant hematopoietic recovery in NDMM patients undergoing steady-state mobilization and that G-CSF plus "on demand plerixafor" is an effective mobilization strategy also in daratumumab-exposed patients. These results, along with those reported by the GRIFFIN and the MASTER studies [12], further support the use of a chemotherapy-free mobilization strategy in the era of quadruplet induction regimens.

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## DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## REFERENCES

1. Moreau P, Attal M, Hulin C, Arnulf B, Belhadj K, Benboubker L, et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study. Lancet. 2019;394:29–38. https://doi.org/10.1016/S0140-6736(19)31240-1.
2. Sonneveld P, Dimopoulos MA, Boccadoro M, Quach H, Ho J, Beksac M, et al. Daratumumab, bortezomib, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med. 2024;390:301–13. https://doi.org/10.1056/nejmoa2312054.
3. Dimopoulos MA, Moreau P, Terpos E, Mateos MV, Zweegman S, Cook G, et al. Multiple myeloma: EHA-ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2021;32:309–22. https://doi.org/10.1016/j.annonc.2020.11.014.
4. Mohty M, Hübel K, Kröger N, Aljurf M, Apperley J, Basak GW, et al. Autologous haematopoietic stem cell mobilisation in multiple myeloma and lymphoma patients: a position statement from the European Group for blood and marrow transplantation. Bone Marrow Transplant. 2014;49:865–72. https://doi.org/10.1038/bmt.2014.39.
5. Hulin C, Offner F, Moreau P, Roussel M, Belhadj K, Benboubker L, et al. Stem cell yield and transplantation in transplant-eligible newly diagnosed multiple myeloma patients receiving daratumumab plus bortezomib/thalidomide/dexamethasone in the phase III CASSIOPEIA study. Haematologica. 2021;106:2257–60. https://doi.org/10.3324/haematol.2020.261842.
6. Zappaterra A, Civettini I, Cafro AM, Pezzetti L, Pierini S, Anghilieri M, et al. Anti-CD38 monoclonal antibody impairs CD34+ mobilization and affects clonogenic potential in multiple myeloma patients. Blood Transfus. 2024;22:328–37. https://doi.org/10.2450/BloodTransfus.667.
7. Lemonakis K, Tätting L, Lisak M, Carlson K, Crafoord J, Blimark C, et al. Impact of daratumumab-based induction on stem cell collection parameters in Swedish myeloma patients. Haematologica. 2023;108:610–4. https://doi.org/10.3324/haematol.2022.281610.
8. Thurlapati A, Roubal K, Davis JA, Shah SZ, Smith D, McGann M, et al. Stem cell mobilization for multiple myeloma patients receiving daratumumab-based induction therapy: a real- world experience. Transplant Cell Ther. 2023;29:340.e1–340.e4. https://doi.org/10.1016/j.jtct.2023.02.013.
9. Eleutherakis Papaiakovou E, Terpos E, Kanellias N, Magdalini M, Gavriatopoulou M, Ntanasis-Stathopoulos I, et al. Impact of daratumumab on stem cell mobilization and collection, engraftment and early post-transplant complications among multiple myeloma patients undergoing autologous stem cell transplantation. Leuk Lymphoma. 2023;64:2140–7. https://doi.org/10.1080/10428194.2023.2253479.
10. Manjappa S, Fox R, Reese J, Firoozamand A, Schmikla H, Nall S, et al. Impact of daratumumab on stem cell collection, graft composition and engraftment among multiple myeloma patients undergoing autologous stem cell transplant. Blood. 2020;136:35–37. https://doi.org/10.1182/blood-2020-142115.
11. Al Saleh AS, Sidiqi MH, Gertz MA, Muchtar E, Lacy MQ, Warsame RM, et al. Delayed neutrophil engraftment in patients receiving daratumumab as part of their first induction regimen for multiple myeloma. Blood. 2019;134:4505–4505. https://doi.org/10.1182/blood-2019-131380.
12. Chhabra S, Callander NS, Costa LJ, Kaufman JL, Laubach JP, Sborov DW, et al. Stem cell collection with daratumumab (DARA)-based regimens in transplant-eligible newly diagnosed multiple myeloma (NDMM) patients (pts) in the Griffin and Master Studies. Blood. 2021;138:2852. https://doi.org/10.1182/blood-2021-149028.

## AUTHOR CONTRIBUTIONS

GB, BG, AC, RM and SB designed the study. GB, BG and AC collected data. SM performed data analyses. GB, GB, AC, RM and SB wrote the manuscript. GB edited all the figures. All authors identified eligible patients included in the study. All authors reviewed the manuscript. RM and SB supervised the study.

## COMPETING INTERESTS

RM has received honoraria from Sanofi, Pfizer, Amgen, Takeda, Celgene, Janssen; has served on the advisory boards for Bristol Myers Squibb, Amgen, Takeda, Celgene, Janssen; has received consultancy fees from Sanofi, Takeda. FG has received honoraria from AbbVie, Roche, Takeda, Pfizer, Sanofi, Celgene/Bristol Myers Squibb, Janssen, GlaxoSmithKline; has served on advisory board for Abbvie, Roche, Takeda, Pfizer, Sanofi, Celgene/Bristol Myers Squibb, Oncopeptides, Janssen¸ GlaxoSmithKline. MD has received honoraria from GlaxoSmithKline, Sanofi, and Janssen; has served on the advisory boards for GlaxoSmithKline, Sanofi, Adaptive Biotechnologies, and Bristol Myers Squibb. SO has received honoraria from Abbvie, Takeda, Celgene/Bristol Myers Squibb, Amgen; has received consultancy fees from Janssen, Amgen, Adaptive Biotechnologies. AL has received honoraria from Janssen, GlaxoSmithKline, Menarini, Pfizer, Sanofi; has served on the advisory board for Janssen, GlaxoSmithKline, Menarini, Pfizer, Sanofi. GB has received honoraria from Bristol Myers Squibb, Janssen, Novartis, Jansen; has received consultancy fees from Bristol Myers Squibb, Janssen, Novartis. BB has received honoraria from Amgen, Janssen, Novartis, BeiGene, Bristol Myers Squibb, GlaxoSmithKline, Jazz Pharmaceuticals, AstraZeneca, Incyte; has served on advisory boards for Amgen, Jazz Pharmaceuticals. AS has received honoraria from Eisai, Pfizer, Gilead, Servier, Celgene/Bristol Myers Squibb, Bayer, Merck MSD, Roche, Abbvie, Amgen; AstraZeneca; Eli Lilly; Sandoz; Novartis; has served on the advisory board for Eisa, Pfizer, Gilead, Servier, Bristol Myers Squibb, Bayer, Merck MSD; has received consultancy fees from Incyte, Sanofi. SB has received honoraria from Celgene, Amgen, Janssen, Bristol Myers Squibb; has served on the board of directors or advisory committees for Celgene, Amgen, Janssen, GlaxoSmithKline, Sanofi, Pfizer; has received consultancy fees from Janssen, Takeda, Celgene, Bristol Myers Squibb. The other authors have nothing to declare.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was conducted in accordance with the Declaration of Helsinki and received approval from the Ethics Committee or institutional review boards at each of the participating centers (Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino and IRCCS Humanitas Research Hospital). All participants were provided with comprehensive information about the study. Written informed consent was obtained from all participants prior to their inclusion in the study. Personal data were collected and stored in a secure and anonymized manner to ensure participants' confidentiality and privacy.

## ADDITIONAL INFORMATION

**Supplementary information** The online version contains supplementary material available at https://doi.org/10.1038/s41409-024-02432-x.

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