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ORIGINAL ARTICLE

Is re-challenge still an option as salvage therapy in multiple myeloma? The case of REal-life BOrtezomib re-Use as secoND treatment for relapsed patients exposed frontline to bortezomib-based therapies (the REBOUND Study)

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Abstract

Therapeutic re-challenge is currently a debated issue in the field of multiple myeloma (MM), given the recent availability of several new drugs and combinations. However, very few specific evidences are available about bortezomib re-use at first relapse. This multicenter, observational, retrospective study enrolled 134 MM patients with significant response after bortezomib-based frontline regimens and who had received a first salvage treatment containing bortezomib at relapse. The overall response rate was 71%, including 40% partial responses, 24% very good partial responses, and 7% complete responses. Re-treatment was well-tolerated, with no significant new or unexpected toxicities observed. The median duration of second progression-free survival (PFS) was 15 months, while median PFS2 was 55 months. With a median follow-up of 56 months, overall survival was 94 months for the entire series, without significant differences between patients undergoing or not undergoing transplant procedures. This real-life survey indicates that re-treatment including bortezomib as a first salvage therapy could be still considered in MM patients achieving durable response after initial exposure to bortezomib.

Keywords Myeloma · Bortezomib · Re-treatment · Salvage therapy · First relapse

Introduction

Despite the improved responses and outcomes, thanks to the introduction of several novel effective drugs and combinations, multiple myeloma (MM) remains incurable, mainly due to subsequent relapses that, ultimately, causes the death of patients [1, 2].

Given the availability of regulatory agencies approval in the early 2000, bortezomib-based regimens are extensively used worldwide in clinical practice as the backbone of first-line therapy in younger, in transplant-eligible, and in older MM patients [3–5]. The treatment choice at relapse should consider the definition of patient characteristics, the efficacy of the previous treatment and its duration, and the toxicity observed,

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along with the availability of alternative therapies [6–8]. Generally, a progression occurring during therapy or early after its discontinuation lays for a resistant disease, and a change in drug class is necessary. By contrast, for late relapses, although several alternative options are available today, a re-challenge with the prior regimen might be still suitable.

Retrospective studies [9–13] and prospective trials [14–16] have suggested that bortezomib re-challenge is well-tolerated and effective, resulting in substantial clinical response rates with no additional or cumulative toxicity. However, very few data are available on the efficacy of bortezomib re-treatment at first relapse [13, 15]. Thus, the present study aimed to investigate this specific setting of MM patients.

Patients and methods

This retrospective, real-life, observational study included MM patients who had been treated initially (both in daily practice and clinical trials) and at first relapse with a regimen containing bortezomib. After Local Ethic Committee approval, charts of 134 MM eligible patients treated in 12 Italian centers from January 2002 to May 2015 were reviewed. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Due to the restrospective, observational nature of the study and according to current Italian law, obligatory informed consent was not necessary from all patients for being included in the study.

Bortezomib-based treatments were performed according to current clinical practice at local institutions. Response rates were assessed by using updated IMWG criteria [17]. Adverse events were graded according to NCI CTCAE, v4.

Patients were considered eligible for the analysis if (i) at least partial response (PR) was documented after first-line bortezomib-containing therapies; (ii) ≥ 2 cycles of bortezomib-based re-treatment were administered. The overall response rate (ORR) at relapse included only patients with at least PR. The per-protocol population was evaluated for efficacy and safety; response rates and descriptive statistics were calculated. Continuous variables were reported as means and standard deviations or medians and interquartile range, according to variable distribution. Categorical variables were reported as count and percentage. Time-to-event variables were represented with Kaplan–Meier plots and the log rank test was used for comparison. Progression-free survival after first-line therapy (PFS1), PFS after second-line therapy (second PFS), and PFS2 (defined as the time from the date of starting first-line treatment to the date of disease progression or death from any cause after second-line therapy), and overall survival (OS) were evaluated. Statistical significance was defined as $p < 0.05$. Analyses were performed using package R version 3.2.3 (The R Project for Statistical Computing).

Results

Table 1 summarizes patient characteristics at diagnosis and details regarding first-line therapy. The mean age was 60.9 ± 11.1 years. The median number of cycles during first-line therapy was 4 (IQR 3–9): 4 (IQR 3–4), for patients who underwent autologous stem cell transplantation (AuSCT) and 8.5 (IQR 4–9), for those who did not. First-line therapy consisted of VD (bortezomib + dexamethasone) 28%; VTD

Table 1 Clinical characteristics and treatments employed at diagnosis

Age (years)	
Mean ± SD	60.9 ± 11.1
Sex, *n* (%)	
Male	80 (59.7)
Female	54 (40.3)
ISS, *n* (%)	
Stage I	40 (29.9)
Stage II	41 (30.6)
Stage III	53 (39.5)
r-ISS, *n* (%) (in 45 cases)	
Stage I	11 (24.4)
Stage II	20 (44.4)
Stage III	14 (31.1)
First-line induction regimens, *n* (%)	
VD	36 (26.9)
VTD	34 (25.4)
VMP	28 (20.9)
PAD	13 (9.7)
VCD	10 (7.1)
VMP + VCD	9 (7)
VMPT	4 (3)
Bortezomib schedule/route, *n* (%)	
Twice a week	110 (82.1)
Once a week	24 (17.9)
i.v.	96 (71.6)
s.c.	38 (28.4)
AuSCT, *n* (%) (in 75 patients, 56%)	
Single	54 (72)
Double	21 (28)
Response, *n* (%)	
ORR	100
PR	87 (64.9)
VGPR	20 (14.9)
CR	27 (20.2)

i.v., intravenous; *s.c.*, subcutaneous; *ISS*, International Staging System; *r-ISS*, revised ISS; *VD*, bortezomib/dexamethasone; *VTD*, bortezomib/thalidomide/dexamethasone; *VMP*, bortezomib/melphalan/prednisone; *PAD*, bortezomib/doxorubicin/dexamethasone; *VCD*, bortezomib/cyclophosphamide/dexamethasone; *VMPT*, bortezomib/melphalan prednisone/thalidomide; *ORR*, overall response rate; *PR*, partial response; *VGPR*, very good partial response; *CR*, complete response

(bortezomib + thalidomide + dexamethasone) 26%; VMP (bortezomib + melphalan + prednisone) 21%; PAD (bortezomib + doxorubicin + dexamethasone) 10%; VCD (bortezomib + cyclophosphamide + dexamethasone) 6%; VMP + VCD 6%; and VMPT (bortezomib + melphalan + prednisone + thalidomide) 3%.

Most patients received twice-weekly bortezomib (82%) with intravenous administrations (72%). A significant proportion of patients were addressed to AuSCT after bortezomib-based induction (56%); in particular, 72% of these patients received a single-transplant procedure, 28% a tandem transplant.

Per inclusion criteria, all patients enrolled had to gain at least a PR after first-line bortezomib-based therapy and no patient progressed during or was resistant to such a treatment; in this series, 35% of patients registered at least a very good PR (VGPR) according to IMWG criteria, including 20% of patients who reached a complete response (CR). The Median PFS1 was 31 months (95% CI 27–36 months) (Fig. 1a). No significant difference in terms of PFS1 comparing patients undergoing or not undergoing AuSCT was found (35 months vs 27 months, respectively; log rank test, $p = 0.3$).

Table 2 summarizes main characteristics of patients at first relapse. Of note, most patients (66%) showed an overt clinical progression, according to IMWG criteria; the remaining 34% had asymptomatic laboratory relapse. The median number of bortezomib cycles during second-line therapy was 6 (IQR 2–11). Second-line salvage regimens consisted of VD 43%; PAD 14%; VCD 11%; VTD 7%; BVD (bendamustine + bortezomib + dexamethasone) 7%; VMP 6%; VRD (bortezomib + lenalidomide + dexamethasone) 4%; VRCD (bortezomib + lenalidomide + cyclophosphamide + dexamethasone) 2%; 6% of patients were addressed to other bortezomib combinations, including vorinostat, panobinostat, elotuzumab, and masitinib.

Different from first line, most patients received once-weekly bortezomib (73%) with subcutaneous administrations (64%). Twenty-six patients (20%) received AuSCT as part of their salvage therapy, 4 patients (3%) underwent allogeneic SCT (AlloSCT), and 5 (4%) received a tandem sequence of AuSCT followed by AlloSCT.

Response rates at the end of second-line therapy were as follows: ≥PR in 71% of patients, ≥VGPR 24%, CR (including stringent and near-CR) 7%. Of note, improvement of renal failure in 14 patients with abnormal serum creatinine levels (median values 2.2 mg/dl, IQR 1.9–3.2) was complete in 4 and partial in 6 patients, respectively. Bone disease improvement was registered in 23/74 (31%) of patients with progression of osteolytic lesions at time of bortezomib re-treatment.

The median second PFS was 15 months (95% CI 11–22) (Fig. 1b). The median PFS2 was 55 months (95% CI 48–60) (Fig. 1c); it was 60 months (95% CI 48–70) for patients who underwent AuSCT and 49 months (95% CI 42–58) for those who did not (p 0.6). Median bortezomib-free interval (BFI) between first and second treatments was 29.8 months (95% CI 25.8–34.7) in the whole population, 27 months (95% CI 12.2–33.7) in non-responders, and 30.7 months (95% CI 25.8–38.1) in responders. Response rates after first salvage therapy were not influenced by type or sequence of treatment (grouping combinations of bortezomib with dexamethasone alone, alkilators, IMIDs, or doxorubicin), number of received cycles, and length of BFI after frontline treatment (supplementary file).

The median OS was 94 months (95% CI 77–107) for the entire series (Fig. 1d), 94 months (95% CI 76–107) for patients undergoing AuSCT, and 86 months (95% CI 68–98) for those who did not receive AuSCT (p 0.9). After a median follow-up of 56 months, 85 patients (63.4%) were still alive, with 54 of them maintaining sustained response after second-line, bortezomib-based therapies. No new or cumulative toxicities were observed when bortezomib was employed as first salvage treatment (Table 2). Grade 3–4 hematological toxicities occurred in 17% of patients and were mainly attributable to myelotoxicity due to bortezomib partners (particularly melphalan, bendamustine, lenalidomide, and doxorubicin). These toxicities were easily managed and dose reductions were needed in only 11% of patients. Infections (mainly pneumonia and herpes zoster) represented the large majority of non-hematological grade 3–4 toxicities (7%). No patient reported grade 3/4 neuropathy, while a second primary malignancy occurred.

Discussion

Given the growing availability of new drugs and combinations, re-treatment has become a controversial issue in MM, though it is still considered a possible therapeutic option for selected groups of patients. For example, in a retrospective recent analysis of 476 patients at first relapse, changing therapy strategy did not result in significant clinical benefit in patients who had not received maintenance therapy and in those where PFS1 was longer than 27 months [7]. In particular, according to recent real-life data describing practice patterns across European countries, it has been estimated that 47% of MM patients treated upfront with bortezomib-based therapies still received regimens containing the same drug at first relapse [18].

Data coming from different studies on relapsed/refractory patients previously exposed to bortezomib treatment have shown efficacy and good tolerance of bortezomib re-treatment [9–16]. A recent meta-analysis of 1051 patients enrolled in 23 studies in which bortezomib re-treatment was used as a single agent or in different combinations showed a pooled, weighted average ORR of 39.1%, with a weighted average median PFS and OS of 7.5 and 16.6 months, respectively [19]. Notably, better results for relapsed but not

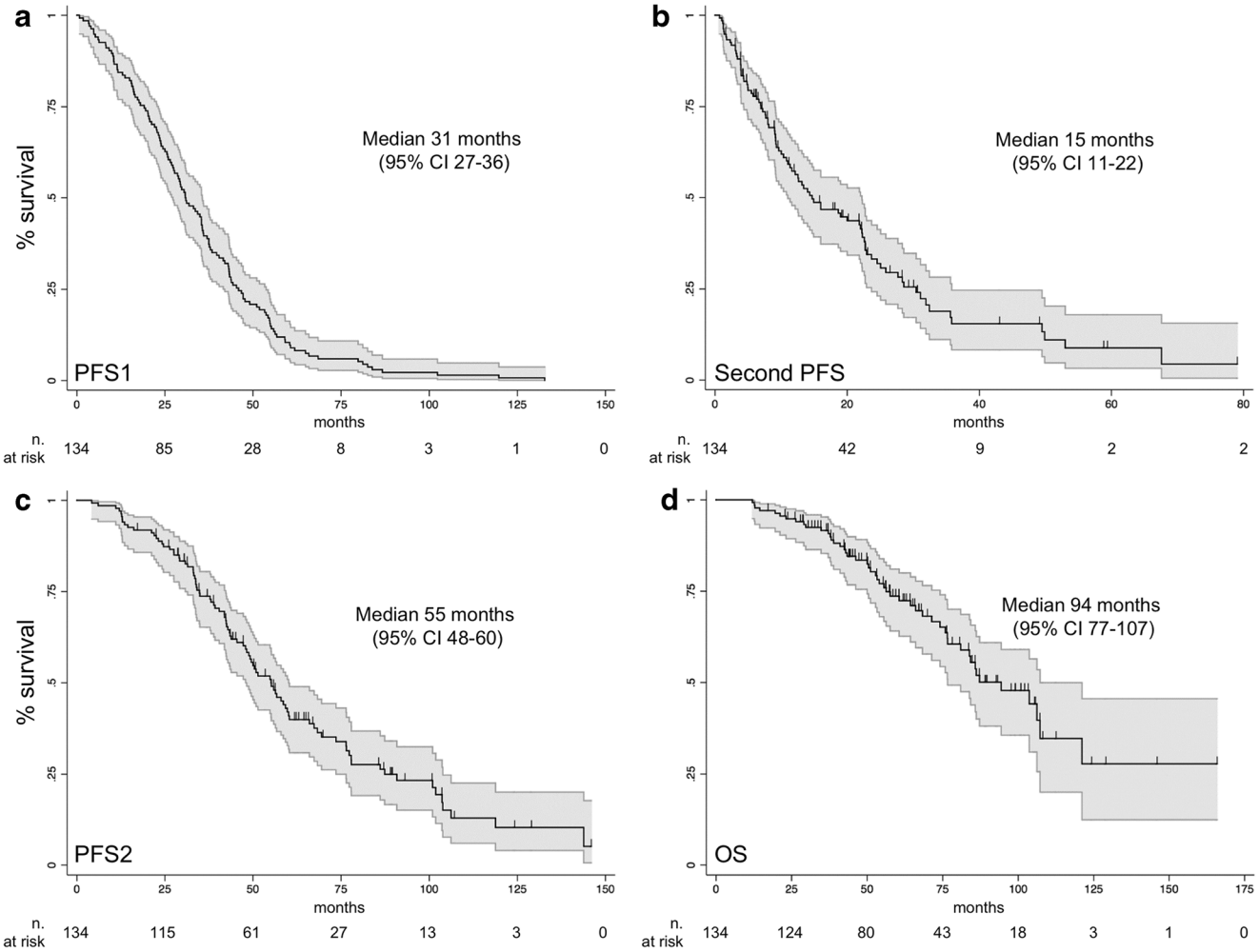

Fig. 1 Survival curves of 134 multiple myeloma patients exposed frontline to bortezomib and re-treated with bortezomib-based regimens at first relapse. **a** First progression-free survival. **b** Second progression-free survival. **c** Progression-free survival 2. **d** Overall survival

refractory patients are addressed to bortezomib re-challenge after fewer therapy lines, supporting the idea of best benefit of early re-treatment during disease history for those patients with a good response to previous exposure [16, 19]. As a matter of fact, a recent report on a small group of 35 bortezomib-treated patients who received again bortezomib at first relapse confirmed the remarkable efficacy of this approach (ORR 80%, median second PFS 15 months) [13].

Our experience allowed an extensive evaluation of early bortezomib re-treatment, including a significantly higher number of patients. Given the known impact of duration, as well as of depth of first response in decision making process at relapse, re-challenge seems to be a possible effective choice, particularly for those patients achieving good and durable disease control after first-line bortezomib-based therapies [7]. Patients entering our study met these peculiar characteristics, with a significant proportion of them reaching at least a VGPR at the end of first-line bortezomib (35%) and a median PFS1 of 33 months. In particular, in our series, bortezomib induction followed by single or double AuSCT represented a very common first-line therapy with 56% of patients enrolled receiving upfront such a transplant procedure. However, we were not able to identify any specific type or sequence of treatment, among those employed, related to response after bortezomib re-challenge.

There are a considerable number of evidences that combination regimens based on bortezomib + dexamethasone backbone are effective in relapsed setting [6, 8]. Bortezomib triplet combinations were given in most of our patients at time of re-treatment (57% of patients), possibly explaining for the average good response achieved. In detail, activity of bortezomib was registered in most patients, with a final rate of at least PR of 71% and 23% of patients obtaining at least VGPR (7% CR). Disease control after re-challenge was confirmed by a not negligible median second PFS of 15 months (Fig. 1b). These findings were further consolidated by the assessment of PFS2, which in our series was 55 months (Fig. 1c). Interestingly, such results are not so different from those achieved, for example, in the same setting of first-relapsed patients with the combination of lenalidomide and

Table 2 Second-line treatments (efficacy and toxicity)

Second-line regimens, *n* (%)	
VD	58 (43.3)
PAD	18 (13. 4)
VCD	14 (10.4)
VTD	10 (7.4)
BVD	9 (6.7)
VMP	7 (5.5)
VRD	6 (4.5)
VRCD	3 (2.2)
Others	9 (6.7)
Bortezomib schedule/route, *n* (%)	
Twice a week	36 (26.9)
Once a week	98 (73.1)
i.v.	48 (35.8)
s.c.	86 (64.2)
Grade 3–4 toxicity, *n* (%)	
Hematological*	23 (17.2)
Anemia	7 (5.2)
Neutropenia	12 (8.9)
Thrombocytopenia	7 (5.2)
Non-hematological	9 (6.7)
Gastro-intestinal	2 (1.5)
Infections	5 (3.7)
Other	2 (1.5)
Response, *n* (%)	
ORR	95 (71)
PR	53 (39.6)
VGPR	32 (23.9)
CR	10 (7.5)

i.v., intravenous; *s.c.*, subcutaneous; *VD*, bortezomib/dexamethasone; *PAD*, bortezomib/doxorubicin/dexamethasone; *VCD*, bortezomib/cyclophosphamide/dexamethasone; *VTD*, bortezomib/thalidomide/dexamethasone; *BVD*, bendamustine/bortezomib/dexamethasone; *VMP*, bortezomib/melphalan/prednisone; *VRD*, bortezomib/lenalidomide/dexamethasone; *VRCD*, bortezomib/lenalidomide/cyclophosphamide/dexamethasone; *ORR*, overall response rate; *PR*, partial response; *VGPR*, very good partial response; *CR*, complete response

*Three patients had two events at the same time

dexamethasone [20] or with triplets including next-generation drugs, such as elotuzumab [21] or ixazomib [22], combined with an IMID backbone. Other combinations, based on carfilzomib [23–25] or daratumumab [26, 27], have demonstrated a significant superiority; however, they may be also burdened by a higher toxicity, as well as by a not negligible economic impact, which would make them not affordable for all patients and difficult to use in developing countries.

Of note, at the time of re-challenge, in our study, there was a progressive switch from intravenous to the better tolerated subcutaneous administration; once-weekly bortezomib was also more commonly used with respect to first line. Subcutaneous [28], as well as once-weekly [29] administrations, may help to improve bortezomib tolerance; this may account for the limited toxicity due to bortezomib registered in our study, with only a small fraction of patients needing dose reduction. In particular, when focusing on peripheral neuropathy, none of patients enrolled experienced grades 3–4 neurotoxicity.

In conclusion, at the best of our knowledge, this is the largest experience so far on MM patients treated at first relapse with bortezomib-based regimens as re-challenge. Our study has, naturally, all the limits related to its retrospective nature and to the heterogeneity of regimens applied, where the contribution of other effective drugs remains, in particular, difficult to evaluate. Notwithstanding, we show here that, despite the progressive availability in the routine clinical practice of novel drugs that are rapidly changing the current armamentarium for MM, bortezomib re-treatment could still represent an effective, well-tolerated, and cost-saving choice for MM patients showing sustained response after first-line, bortezomib-based therapies.

Author contributions PM designed the study and is the responsible for the concept of this manuscript; VS analyzed database and performed statistical analysis; NC, AF, MTP, LC, FDR, CC, RR, LC, DS, LM, AG, OV, GP, GD, GM, SB, MG, NDR, GR, AG, TC, and MB recruited patients and provided relevant data; DS and GM collected, assembled, and managed database; PM, SM, and AC coordinated the various authors and wrote the paper. All authors critically reviewed the manuscript drafts, approved the final version, and made the decision to submit the manuscript for publication.

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Compliance with ethical standards

After Local Ethic Committee approval, charts of 134 MM eligible patients treated in 12 Italian centers from January 2002 to May 2015 were reviewed. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Due to the restrospective, observational nature of the study and according to current Italian law, obligatory informed consent was not necessary from all patients for being included in the study. Bortezomib-based treatments were performed according to current clinical practice at local institutions.

Conflict of interest Regarding possible COI with the present paper, PM has participated to Advisory Boards of and has received honoraria from Celgene, Janssen-Cilag, BMS, Amgen, and Takeda; MTP is a member of the Advisory Board and has received honoraria from Celgene, Janssen-Cilag, BMS, Amgen, and Takeda; RR is a member of the Advisory Board of Janssen-Cilag, Consultant for CSL Behring and Speakers bureau for Janssen-Cilag, Celgene, Italfarmaco, BMS, Amgen, and CSL Behring; TC is a member of the Advisory board of Janssen-Cilag, Celgene, BMS, Amgen, and Takeda and received research funds from Celgene; SB is a member of the Advisory Board of Janssen-Cilag, Amgen, and Takeda and received honoraria from Janssen and Cilag, Celgene, Amgen, and BMS; MB is a member of the Advisory Board and has received honoraria from Celgene, Janssen-Cilag, BMS, Amgen, and Takeda. Other authors did not declare any COI.

References

1. Kumar SK, Dispenzieri A, Lacy MQ, Gertz MA, Buadi FK, Pandey S, Kapoor P, Dingli D, Hayman SR, Leung N, Lust J, McCurdy A, Russell SJ, Zeldenrust SR, Kyle RA, Rajkumar SV (2014) Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. Leukemia 28: 1122–1128. https://doi.org/10.1038/leu.2013.313
2. Blimark CH, Turesson I, Genell A, Ahlberg L, Björkstrand B, Carlson K, Forsberg K, Juliusson G, Linder O, Mellqvist UH, Nahi H, Kristinsson SY, for the Swedish Myeloma Registry (2018) Outcome and survival of myeloma patients diagnosed 2008-2015. Real-world data on 4904 patients from the Swedish Myeloma Registry. Haematologica 103:506–513. https://doi.org/10.3324/haematol.2017.178103
3. Cavo M, Terpos E, Bargay J, Einsele H, Cavet J, Greil R, de Wit E (2018) The multiple myeloma treatment landscape: international guideline recommendations and clinical practice in Europe. Expert Rev Hematol 11:1–19. https://doi.org/10.1080/17474086.2018.1437345
4. Kumar SK, Rajkumar V, Kyle RA, van Duin M, Sonneveld P, Mateos MV, Gay F, Anderson KC (2017) Multiple myeloma. Nat Rev Dis Prim 3:17046. https://doi.org/10.1038/nrdp.2017.46
5. Gay F, Engelhardt M, Terpos E, Wäsch R, Giaccone L, Auner HW, Caers J, Gramatzki M, van de Donk N, Oliva S, Zamagni E, Garderet L, Straka C, Hajek R, Ludwig H, Einsele H, Dimopoulos M, Boccadoro M, Kröger N, Cavo M, Goldschmidt H, Bruno B, Sonneveld P (2018) From transplant to novel cellular therapies in multiple myeloma: European Myeloma Network guidelines and future perspectives. Haematologica 103:197–211. https://doi.org/10.3324/haematol.2017.174573
6. Sonneveld P (2017) Management of multiple myeloma in the relapsed/refractory patient. Hematol Am Soc Hematol Educ Progr 2017:508–517. https://doi.org/10.1182/asheducation-2017.1.508
7. Offidani M, Corvatta L, Bringhen S, Gentili S, Troia R, Maracci L, Larocca A, Gay F, Leoni P, Boccadoro M (2017) Salvage therapy in first relapse: a retrospective study in a large patient population with multiple myeloma. Eur J Haematol 98:289–295. https://doi.org/10.1111/ejh.12834
8. Chim CS, Kumar SK, Orlowski RZ, Cook G, Richardson PG, Gertz MA, Giralt S, Mateos MV, Leleu X, Anderson KC (2018) Management of relapsed and refractory multiple myeloma: novel agents, antibodies, immunotherapies and beyond. Leukemia 32: 252–262. https://doi.org/10.1038/leu.2017.329
9. Conner TM, Doan QD, Walters IB et al (2008) An observational, retrospective analysis of retreatment with bortezomib for multiple myeloma. Clin Lymphoma Myeloma 8:140–145. https://doi.org/10.3816/CLM.2008.n.016
10. Hrusovsky I, Emmerich B, von Rohr A, Voegeli J, Taverna C, Olie RA, Pliskat H, Frohn C, Hess G (2010) Bortezomib retreatment in relapsed multiple myeloma - results from a retrospective multicentre survey in Germany and Switzerland. Oncology 79: 247–254. https://doi.org/10.1159/000322866
11. Taverna C, Voegeli J, Trojan A et al (2012) Effective response with bortezomib retreatment in relapsed multiple myeloma – a multicentre retrospective survey in Switzerland. Swiss Med Wkly 142:w13562. https://doi.org/10.4414/smw.2012.13562
12. Wolf J, Richardson PG, Schuster M, LeBlanc A, Walters IB, Battleman DS (2008) Utility of bortezomib retreatment in relapsed or refractory multiple myeloma patients: a multicenter case series. Clin Adv Hematol Oncol 6:755–760
13. Oriol A, Giraldo P, Kotsianidis I, Couturier C, Olie R, Angermund R, Corso A (2015) Efficacy and safety of bortezomib-based retreatment at the first relapse in multiple myeloma patients: a retrospective study. Hematology 20:405–409. https://doi.org/10.1179/1607845414Y.0000000218
14. Petrucci MT, Giraldo P, Corradini P, Teixeira A, Dimopoulos MA, Blau IW, Drach J, Angermund R, Allietta N, Broer E, Mitchell V, Bladé J (2013) A prospective, international phase 2 study of bortezomib retreatment in patients with relapsed multiple myeloma. Br J Haematol 160:649–659. https://doi.org/10.1111/bjh.12198
15. Sood R, Carloss H, Kerr R, Lopez J, Lee M, Druck M, Walters IB, Noga SJ (2009) Retreatment with bortezomib alone or in combination for patients with multiple myeloma following an initial response to bortezomib. Am J Hematol 84:657–660. https://doi.org/10.1002/ajh.21517
16. Terpos E, Gobbi M, Potamianou A, Lahaye M, Couturier C, Cavo M (2018) Retreatment and prolonged therapy with subcutaneous bortezomib in patients with relapsed multiple myeloma: a randomized, controlled, phase III study. Eur J Haematol 100:10–19. https://doi.org/10.1111/ejh.12937
17. Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, Munshi N, Lonial S, Bladé J, Mateos MV, Dimopoulos M, Kastritis E, Boccadoro M, Orlowski R, Goldschmidt H, Spencer A, Hou J, Chng WJ, Usmani SZ, Zamagni E, Shimizu K, Jagannath S, Johnsen HE, Terpos E, Reiman A, Kyle RA, Sonneveld P, Richardson PG, McCarthy P, Ludwig H, Chen W, Cavo M, Harousseau JL, Lentzsch S, Hillengass J, Palumbo A, Orfao A, Rajkumar SV, Miguel JS, Avet-Loiseau H (2016) International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol 17:e328–e346. https://doi.org/10.1016/S1470-2045(16)30206-6
18. Raab MS, Cavo M, Delforge M, Driessen C, Fink L, Flinois A, Gonzalez-McQuire S, Safaei R, Karlin L, Mateos MV, Schoen P, Yong K (2016) Multiple myeloma: practice patterns across Europe. Br J Haematol 175:66–76. https://doi.org/10.1111/bjh.14193
19. Knopf KB, Duh MS, Lafeuille M-H, Gravel J, Lefebvre P, Niculescu L, Ba-Mancini A, Ma E, Shi H, Comenzo RL (2014) Meta-analysis of the efficacy and safety of bortezomib re-treatment in patients with multiple myeloma. Clin Lymphoma Myeloma Leuk 14:380–388. https://doi.org/10.1016/j.clml.2014.03.005
20. Stadtmauer EA, Weber DM, Niesvizky R, Belch A, Prince MH, San Miguel JF, Facon T, Olesnyckyj M, Yu Z, Zeldis JB, Knight RD, Dimopoulos MA (2009) Lenalidomide in combination with dexamethasone at first relapse in comparison with its use as later salvage therapy in relapsed or refractory multiple myeloma. Eur J Haematol 82:426–432. https://doi.org/10.1111/j.1600-0609.2009.01257.x
21. Dimopoulos MA, Lonial S, White D, Moreau P, Palumbo A, San-Miguel J, Shpilberg O, Anderson K, Grosicki S, Spicka I, Walter-Croneck A, Magen H, Mateos MV, Belch A, Reece D, Beksac M, Bleickardt E, Poulart V, Sheng J, Sy O, Katz J, Singhal A, Richardson P (2017) Elotuzumab plus lenalidomide/dexamethasone for relapsed or refractory multiple myeloma: ELOQUENT-2 follow-up and post-hoc analyses on progression-free survival and tumour growth. Br J Haematol 178:896–905. https://doi.org/10.1111/bjh.14787
22. Mateos MV, Masszi T, Grzasko N, Hansson M, Sandhu I, Pour L, Viterbo L, Jackson SR, Stoppa AM, Gimsing P, Hamadani M, Borsaru G, Berg D, Lin J, di Bacco A, van de Velde H, Richardson PG, Moreau P (2017) Impact of prior therapy on the efficacy and safety of oral ixazomib-lenalidomide-dexamethasone vs. placebo-lenalidomide-dexamethasone in patients with relapsed/refractory multiple myeloma in TOURMALINE-MM1. Haematologica 102:1767–1775. https://doi.org/10.3324/haematol.2017.170118
23. Dimopoulos MA, Stewart AK, Masszi T, Špička I, Oriol A, Hájek R, Rosiñol L, Siegel D, Mihaylov GG, Goranova-Marinova V, Rajnics P, Suvorov A, Niesvizky R, Jakubowiak A, San-Miguel J,

Ludwig H, Ro S, Aggarwal S, Moreau P, Palumbo A (2017) Carfilzomib-lenalidomide-dexamethasone vs lenalidomide-dexamethasone in relapsed multiple myeloma by previous treatment. Blood Cancer J 7:e554. https://doi.org/10.1038/bcj.2017.31

24. Siegel DS, Dimopoulos MA, Ludwig H, Facon T, Goldschmidt H, Jakubowiak A, San-Miguel J, Obreja M, Blaedel J, Stewart AK (2018) Improvement in overall survival with carfilzomib, lenalidomide, and dexamethasone in patients with relapsed or refractory multiple myeloma. J Clin Oncol 36(8):728–734. https://doi.org/10.1200/JCO.2017.76.5032
25. Dimopoulos MA, Goldschmidt H, Niesvizky R, Joshua D, Chng WJ, Oriol A, Orlowski RZ, Ludwig H, Facon T, Hajek R, Weisel K, Hungria V, Minuk L, Feng S, Zahlten-Kumeli A, Kimball AS, Moreau P (2017) Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomised, phase 3 trial. Lancet Oncol 18(10):1327–1337. https://doi.org/10.1016/S1470-2045(17)30578-8
26. Spencer A, Hungria VTM, Mateos M-V et al (2017) Daratumumab, bortezomib, and dexamethasone (DVd) versus bortezomib and dexamethasone (Vd) in relapsed or refractory multiple myeloma (RRMM): updated efficacy and safety analysis of castor. Blood 130:3145 http://www.bloodjournal.org/content/130/Suppl_1/3145
27. Moreau P, Oriol A, Kaufman JL et al (2017) Daratumumab, lenalidomide, and dexamethasone (DRd) versus lenalidomide and dexamethasone (Rd) in relapsed or refractory multiple myeloma (RRMM) based on prior treatment history, renal function, and cytogenetic risk: subgroup analyses of pollux. Blood 130:1883 http://www.bloodjournal.org/content/130/Suppl_1/1883
28. Moreau P, Pylypenko H, Grosicki S, Karamanesht I, Leleu X, Grishunina M, Rekhtman G, Masliak Z, Robak T, Shubina A, Arnulf B, Kropff M, Cavet J, Esseltine DL, Feng H, Girgis S, van de Velde H, Deraedt W, Harousseau JL (2011) Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study. Lancet Oncol 12:431–440. https://doi.org/10.1016/S1470-2045(11)70081-X
29. Bringhen S, Larocca A, Rossi D, Cavalli M, Genuardi M, Ria R, Gentili S, Patriarca F, Nozzoli C, Levi A, Guglielmelli T, Benevolo G, Callea V, Rizzo V, Cangialosi C, Musto P, de Rosa L, Liberati AM, Grasso M, Falcone AP, Evangelista A, Cavo M, Gaidano G, Boccadoro M, Palumbo A (2010) Efficacy and safety of once-weekly bortezomib in multiple myeloma patients. Blood 116:4745–4753. https://doi.org/10.1182/blood-2010-07-294983

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