Lenalidomide maintenance after bortezomib, thalidomide and dexamethasone (VTD) induction and autologous stem cell transplantation: an Italian real-life study of 602 patients

The established treatment of newly diagnosed, transplant-eligible multiple myeloma (MM) patients is an induction phase followed by single or tandem autologous stem cell transplantation (ASCT) and lenalidomide maintenance.[1] Before the approval of the daratumumab plus bortezomib-thalidomide-dexamethasone (D-VTD) regimen,[2] in Italy newly diagnosed, fit MM patients received VTD induction;[3] however, in the meta-analysis by McCarthy *et al.*,[4] focused on lenalidomide maintenance, only a minority of patients received VTD induction and a single ASCT was performed in most of them. Therefore, there is no single prospective trial evaluating the past standard of care for the treatment of transplant-eligible MM patients.

The present retrospective study aimed at evaluating the efficacy and safety of lenalidomide maintenance after VTD induction and single or tandem ASCT in fit, newly diagnosed MM patients.

Between May 2018 and January 2023, 602 MM patients followed in 21 Italian Centers received lenalidomide maintenance after VTD induction and ASCT (single or tandem, according to local clinical practice). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments. The study was approved by the ethical committee of Ospedale dell'Angelo Venezia-Mestre (protocol number VE-MM-01). All participants provided informed consent.

The study cohort's demographics and clinical and biological characteristics at diagnosis are reported in *Online Supplementary Table S1*.

Maintenance was started with lenalidomide 10 mg in almost the entire cohort (96.2%), with a 21/28-day schedule in 56.8% of patients and a 28/28-day schedule in 41.7% (Table 1). With a median number of 22 cycles (range, 1-60) administered, 87.8% of the patients achieved a high-quality response (very good partial response or better). The rate of complete responses plus stringent complete responses before starting lenalidomide was 47.6% and increased with maintenance to 58.3% (*Online Supplementary Table S1* and Table 1, respectively). Most importantly, the 2-year complete and stringent complete response rates in evaluable patients were superimposable (40.5% and 16.5%, respectively, and 57% overall). Considering the different treatment schedules, the complete plus stringent complete response rates before maintenance were 50% in the 21/28-day group and 44% in the 28/28-day group and increased with lenalidomide to 61% and 55.1%, respectively. Regarding hematologic toxicities, neutropenia was the most frequent adverse event, being reported in 51.3% of patients, with grade 3-4 events in 18.8% of cases. Thrombocytope-

Table 1. Maintenance therapy.

Characteristic	Cohort, N=602
Dose of lenalidomide, N/total N (%) 5 mg 10 mg 15 mg 25 mg	 20/602 (3.3) 579/602 (96.2) 2/602 (0.3) 1/602 (0.2)
Schedule, N/total N (%) 21 days 28 days Other	 342/602 (56.8) 251/602 (41.7) 9/602 (1.5)
N of cycles, median [Q1;Q3] (range)	22 [10;34] (1-60)
Best response, N/total N (%) Progressive disease Stable disease Partial response Very good partial response Complete response Stringent complete response	 3/597 (0.5) 26/597(4.4) 44/597 (7.4) 176/597 (29.5) 240/597 (40.2) 108/597 (18.1)
Time to best response, months, median [Q1;Q3] (range)	3 [1;7] (0-56)
2-year response rate, N/total N (%) Progressive disease Stable disease Minor response Partial response Very good partial response Complete response Stringent complete response	 42/370 (11.4) 6/370 (1.6) 1/370 (0.3) 24/370 (6.5) 86/370 (23.2) 150/370 (40.5) 61/370 (16.5)
Patients on treatment, N/total N (%)	405/602 (67.3)
Patients with dose reductions, N/total N (%) Reduced dose Reduced schedule Reduced dose and schedule	199/602 (33.1) 104/199 (52.3) 74/199 (37.2) 21/199 (10.6)
Treatment discontinuation, N/total N (%)	197/602 (32.7)
Discontinuation due to disease progression, N/total N (%)	143/602 (23.8)

Percentages might not add up to 100 because of rounding. The denominator might not be equal to 602 due to missing data; Q: quartile.

nia (any grade, 23.8%; grade 3-4, 2.2%) and anemia (any grade 16.6%; grade 3-4, 1.7%) were less frequent. Among non-hematologic adverse events, infections were the most common (any grade, 42.2%; grade 3-4, 4.3%), followed by gastrointestinal disorders (any grade, 33.6%; grade 3-4, 3.3%) and peripheral neuropathy (any grade, 14.0%; grade 3-4, 1.2%). Most infectious events were respiratory tract infections (23.1%) and were mostly grade <3. Finally, 11 cases (1.8%) developed a secondary primary malignancy. With a median follow-up of 30 months, the median progression-free survival (PFS) and overall survival (OS) were not reached. The 30-month PFS and OS rates from starting maintenance were 75.2% and 95.2%, respectively (*Online Supplementary Figure S1A, B*).

Table 2 reports univariable Cox proportional hazards regression analysis to assess the characteristics significantly associated with PFS. Analyzed according to Revised International Staging System (R-ISS) group, patients with R-ISS I showed improved PFS as compared to patients with R-ISS II (P=0.0348) and R-ISS III (P=0.0009) (*Online Supplementary Figure S2B*). Using the second revision of the prognostication system (R2-ISS), low-risk disease (R2-ISS I) was confirmed to be associated with a better outcome as compared to R2-ISS II (P=0.0525), R2-ISS III (P=0.0556), and especially to R2-ISS IV (P<0.0001) (*Online Supplementary Figure S2C*). Considering cytogenetic risk status, standard-risk patients displayed a significantly prolonged PFS compared to high-risk patients, including those with t(4;14), t(14,16) and del17p (P<0.0001). At the same time, no significant difference was observed in patients harboring isolated +1q (P=0.145) (Figure 1A). Accumulation of high-risk cytogenetic abnormalities was associated with a worse outcome, with a significantly lower PFS in patients with at least two high-risk abnormalities than in patients with one or no high-risk aberrations (P=0.02 and P<0.0001, respectively) (Figure 1B). Regarding other clinical and biological high-risk disease features, baseline high lactate dehydrogenase levels were associated with an inferior outcome (P=0.0011) (*Online Supplementary Figure S2D*). We then analyzed the impact of previous single *versus* tandem ASCT on the outcome following lenalidomide maintenance and found no significant differences in the overall population (P=0.44) (Figure 1C). Considering the schedule, patients receiving 21/28-day lenalidomide showed better PFS compared to those given the drug with the 28/28-day schedule (P=0.057) (Figure 1D).

Finally, we evaluated the impact of the depth of response on the patients' outcomes. Patients obtaining a complete response or better before starting maintenance had a better PFS compared to those with inferior responses (P=0.0005) (*Online Supplementary Figure S2E*). Of note, we performed a 2-year landmark analysis confirming that the patients in complete remission or better at 2 years after starting maintenance displayed a significantly better outcome (P<0.0001) (*Online Supplementary Figure S2F*).

We then performed a multivariable Cox regression analysis including all the variables that had been significant in univariate analysis to identify factors that retain an independently significant impact on outcome. According to this analysis, R2-ISS IV and high-risk cytogenetic status were confirmed to be independently associated with a dismal PFS, while a compete response or better status before starting maintenance was the best predictor of improved PFS in our cohort of patients.

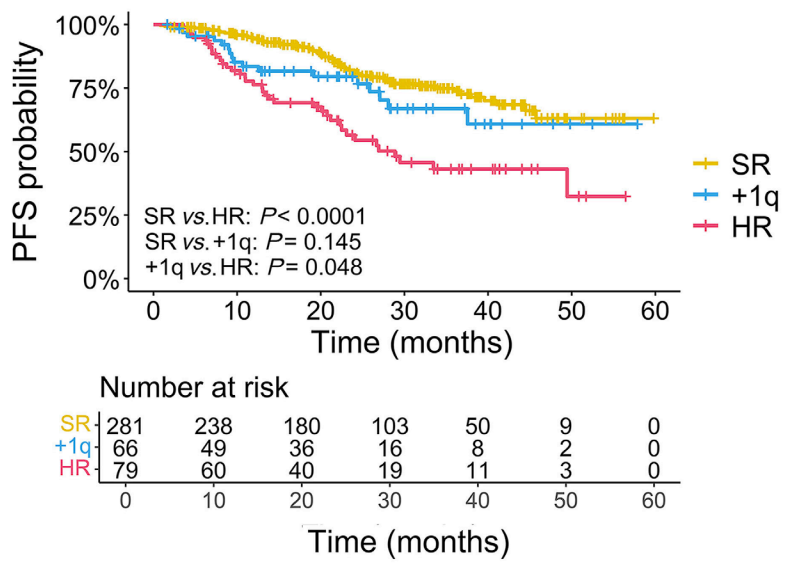
Considering OS, overall high-risk cases did not show a significant survival reduction (Figure 1E), while accumu-

Table 2. Univariable and multivariable Cox proportional hazards regression analysis.

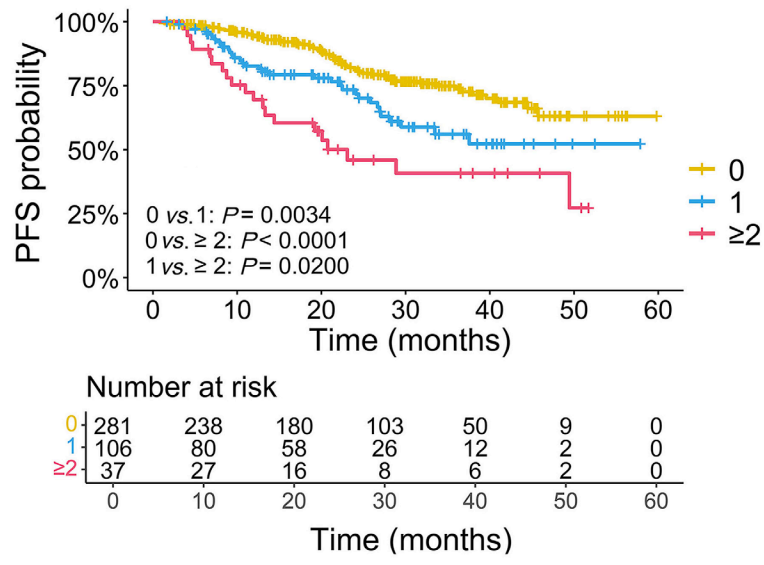
Characteristic	Univariable analysis			Multivariable analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
ISS III	1.21	0.82-1.80	0.3	-	-	-
R-ISS III	1.87	1.13-3.10	0.015	-	-	-
R2-ISS IV	3.55	2.11-5.97	<0.001	2.30	1.24-4.29	0.009
High-risk cytogenetics	2.57	1.73-3.81	<0.001	2.11	1.26-3.52	0.004
Cytogenetic abnormalities ≥2	2.82	1.74-4.59	<0.001	-	-	-
Isolated t(4;14)	2.77	1.45-5.29	0.002	-	-	-
Isolated t(14;16)	2.55	0.35-18.5	0.4	-	-	-
Isolated del(17p)	2.33	0.93-5.82	0.070	-	-	-
Extramedullary disease	1.03	0.60-1.76	>0.9	-	-	-
High lactate dehydrogenase	2.02	1.32-3.12	0.001	-	-	-
28/28 schedule	1.38	0.99-1.93	0.057	-	-	-
≥CR before starting maintenance	0.55	0.39-0.77	<0.001	0.52	0.34-0.80	0.003

HR: hazard ratio; 95% CI: 95% confidence interval; ISS: International Staging System; R-ISS: Revised ISS; R2-ISS: second revision of the ISS; ≥CR: complete response or stringent complete response.

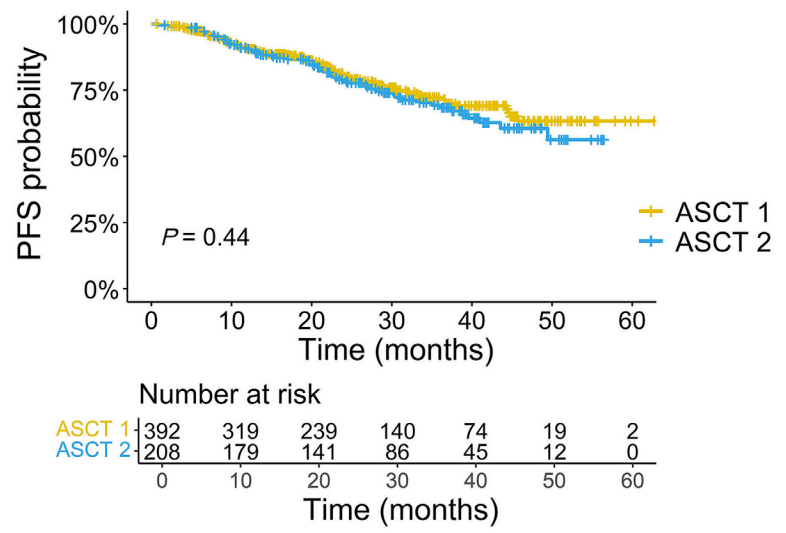
A



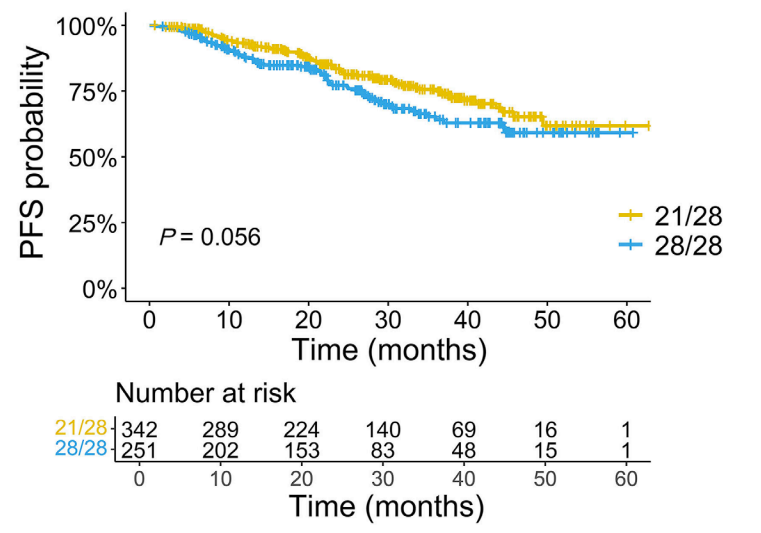
B



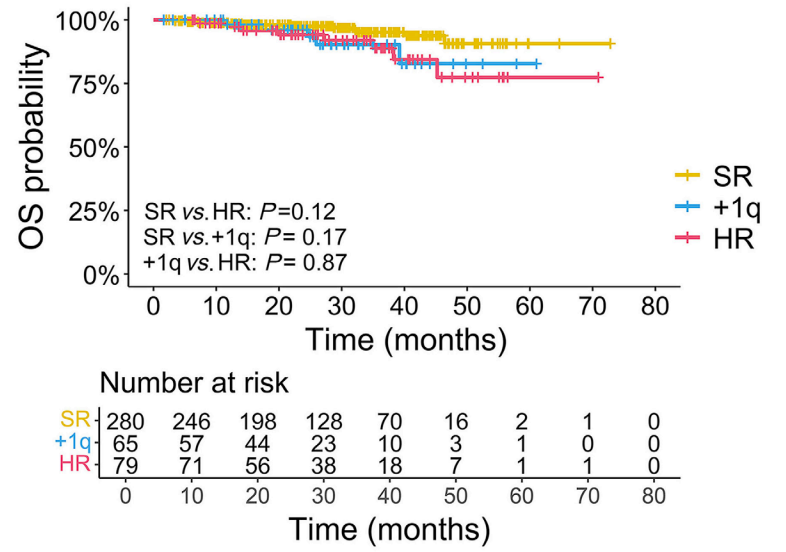
C



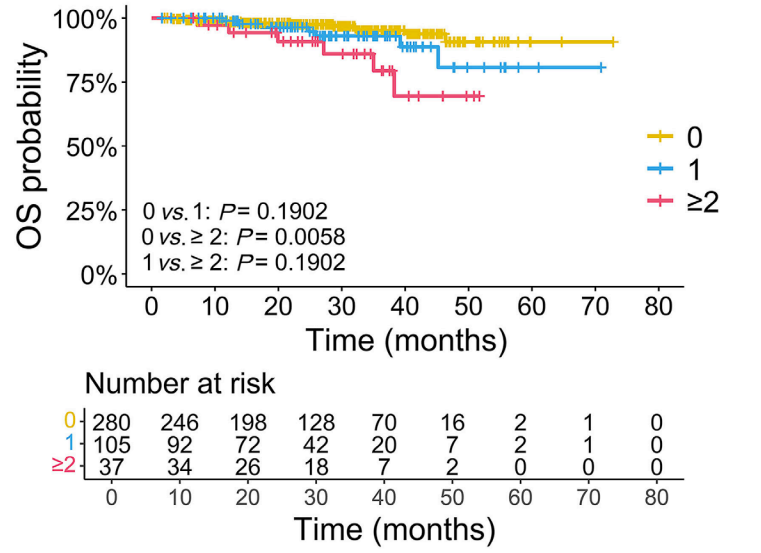
D



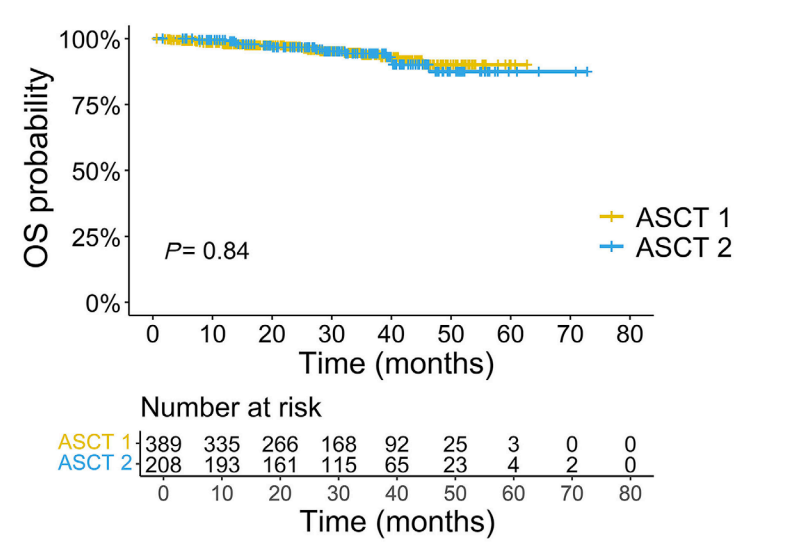
E



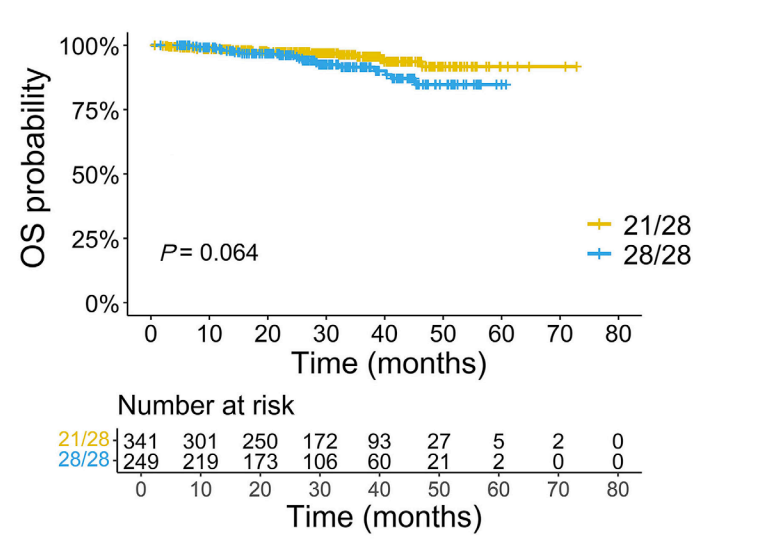
F



G



H



Continued on following page.

Figure 1. Progression-free survival and overall survival of patients receiving lenalidomide maintenance treatment. (A-D) Kaplan-Meier curves showing the progression-free survival of patients who received lenalidomide maintenance according to cytogenetic status (A), the number of high-risk cytogenetic abnormalities (B), the number of autologous stem cell transplants (C) and the lenalidomide schedule (D). (E-H) Kaplan-Meier curves showing the overall survival of patients who received lenalidomide maintenance according to cytogenetic status (E), the number of high-risk cytogenetic abnormalities (F), the number of autologous stem cell transplants (G) and the lenalidomide schedule (H). PFS: progression-free survival; SR: standard risk; HR: high risk; OS: overall survival; ASCT: autologous stem cell transplant.

lation of high-risk cytogenetic abnormalities was associated with reduced survival, especially compared to that of standard-risk patients (≥2 *vs*. 0, *P*=0.0058; ≥2 *vs*. 1, *P*=0.1902) (Figure 1F). Finally, no significant differences in OS were found according to single *versus* tandem ASCT or the 21/28-day *versus* the 28/28-day schedule (Figure 1G, H, respectively).

To our knowledge, this is the first study evaluating the safety and efficacy of lenalidomide maintenance after VTD induction followed by single or tandem ASCT. Our results prove that patients with clinical and biological low-risk disease, specifically those with R-ISS or R2-ISS I, and those without high-risk cytogenetic abnormalities, and patients achieving a complete response before starting maintenance showed improved outcomes with lenalidomide maintenance.

One of the major issues regarding maintenance is the duration of treatment. In all the randomized studies included in the meta-analysis by McCarthy *et al*.,[4] as well as in the EMN02 trial,[5] maintenance was given until progression or unacceptable toxicities. Conversely, in the IFM 2009 study, lenalidomide was administered with a fixed duration schedule of 1 year.[6] In our study, a median number of 22 cycles was administered with an approximately 32% discontinuation rate, mostly due to progressive disease. It is the subject of debate whether, in specific subsets of patients, maintenance can be reasonably stopped. The results presented herein demonstrate that low-risk patients had prolonged PFS. Data from the Myeloma XI trial showed that after 4 or 5 years of maintenance, there is no further improvement in PFS, especially in patients without minimal residual disease (MRD), in whom the benefit decreased after 3 years of maintenance.[7] The results suggest the possibility of stopping lenalidomide safely in this subgroup of patients. In the coming years, MRD assessment will be more widely and routinely used in clinical practice to help clinicians tailor treatment.

Despite the clear benefit of lenalidomide maintenance in transplant-eligible patients, confirmed in our study, the outcome of high-risk and very high-risk patients is still dismal. This is particularly evident in our cohort for patients with high-risk disease according to the R-ISS and R2-ISS classifications and high-risk cytogenetic profile. One possible strategy to improve the outcome of these patients is to use two drugs for maintenance treatment. In the FORTE trial, two-drug maintenance with carfilzomib and lenalidomide translated into better PFS and lower risk of unsustained MRD negativity as compared to after lenalidomide alone.[8, 9] Of note, the probability of unsustained MRD negativity was superimposable between the two groups when patients interrupted carfilzomib and continued with lenalidomide alone.[9] Daratumumab and lenalidomide maintenance, as investigated in the Perseus trial, also represents an interesting possibility.[10]

Another alternative strategy is to use tandem ASCT in high-risk patients. Based on the data of the EMN02 trial, the 2021 ESMO guidelines recommend a tandem ASCT in genetically high-risk patients or in patients who received VCD induction.[1,5] Our results in a cohort of patients treated with VTD induction showed a benefit, although non-statistically significant, of tandem ASCT in genetically high-risk patients. Unfortunately, in both the Cassiopeia[2] and Perseus[10] trials all patients received a single ASCT, and so it is difficult to understand whether tandem ASCT for high-risk patients still retains a role in the era of daratumumab-based quadruplet therapy.

Our study has several inherent limitations, including its retrospective nature, missing data and lack of MRD assessment. In addition, daratumumab is going to be added to VTD or VRD (bortezomib-lenalidomide-dexamethasone) as first line therapy in transplant-eligible MM, thus modifying the near-future landscape of induction therapy. Nevertheless, our real-life study confirms the benefit of lenalidomide maintenance in a cohort of patients who received VTD as induction treatment, especially in those with low-risk disease, and demonstrated its favorable safety profile. Clinical and biological high-risk patients, particularly ultra-high risk ones, still have an inferior outcome that can be partly mitigated by tandem ASCT, and this subset of patients could benefit from a more intensive maintenance approach.

Authors

Gregorio Barilà,[1] Angela Grassi,[2] Concetta Conticello,[3] Roberto Mina,[4] Chiara Marcon,[5°] Francesca Fazio,[6] Claudio Salvatore Cartia,[7] Martina Tinelli,[8] Maria Livia Del Giudice,[9] Sofia Pilerci,[10°°] Angelo Belotti,[11] Anna Pascarella,[12] Mariantonietta Tafuri,[13] Serena Rocchi,[14,15] Katia Mancuso,[14,15] Nicola Sgherza,[16] Giuseppe Mele,[17] Edoardo Scomazzon,[1] Massimo Gentile,[18,19] Marika Porrazzo,[20] Norbert Pescosta,[21] Anna Furlan,[22] Massimiliano Arangio Febbo,[23] Cristina Clissa,[8] Andrea Casson,[4] Rossella Ribolla,[11] Antonio Maroccia,[12] Chiara Lisi,[6] Enrica Antonia Martino,[18] Ombretta Annibali,[13] Gabriele Buda,[9] Elisabetta Antonioli,[10]

Silvia Mangiacavalli,[7] Alberto Tosetto,[1] Pellegrino Musto,[24] Francesca Gay,[4,25] Elena Zamagni,[14,15] Maria Teresa Petrucci,[6] Francesco Di Raimondo,[3] Francesca Patriarca[5] and Renato Zambello[26]

[1]Hematology Unit, San Bortolo Hospital, Vicenza; [2]Clinical Research Unit, Veneto Institute of Oncology, IOV-IRCCS, Padova; [3]Division of Hematology, Azienda Policlinico-S. Marco, University of Catania, Catania; [4]Division of Hematology, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Turin; [5]Hematology and Transplant Center Unit, Udine University Hospital, DAME, University of Udine, Udine; [6]Division of Hematology, Department of Translational and Precision Medicine, Azienda Ospedaliera Universitaria Policlinico Umberto I, Sapienza University of Rome, Rome; [7]Division of Hematology, Fondazione IRCCS Policlinico San Matteo, Pavia; [8]Department of Medicine, Section of Hematology, University of Verona, Verona; [9]Department of Clinical and Experimental Medicine, Hematology, University of Pisa, Pisa; [10]Hematology Unit, Careggi Hospital, Florence; [11]Department of Hematology, ASST Spedali Civili di Brescia, Brescia; [12]Hematology Unit, Azienda ULSS3 Serenissima, Ospedale dell'Angelo, Venezia-Mestre; [13]Hematology and Stem Cell Transplantation Unit, Campus Bio-Medico University, Rome; [14]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia Seràgnoli, Bologna; [15]Dipartimento di Scienze Mediche e Chirurgiche, Università di Bologna, Bologna; [16]Hematology and Stem Cell Transplantation Unit, AOU Consorziale Policlinico, Bari; [17]Hematology and Stem Cell Transplant Unit, Ospedale Antonio Perrino, Brindisi; [18]Hematology Unit, Department of Onco-hematology, A.O. of Cosenza, Cosenza; [19]Department of Pharmacy, Health and Nutritional Science, University of Calabria, Rende; [20]Hematology Unit, Azienda Sanitaria Universitaria Giuliano Isontina, Trieste; [21]Ematologia e Centro TMO, Ospedale Centrale Bolzano, Bozen; [22]Hematology Unit, Ospedale Santa Maria di Ca' Foncello, Treviso; [23]Onco-hematology, Department of Oncology, Veneto Institute of Oncology IOV - IRCCS, Padua; [24]Department of Precision and Regenerative Medicine and Ionian Area, "Aldo Moro" University School of Medicine and Hematology and Stem Cell Transplantation Unit, AOU Consorziale Policlinico, Bari; [25]Department of Molecular Biotechnology and Health Science, Turin and [26]Department of Medicine (DIMED), Hematology and Clinical Immunology Section, Padua University School of Medicine, Padua, Italy.

°Current address: Centro Immunotrasfusionale, Ospedale Santa Maria della Misericordia, ASUFC, Udine, Italy.

°°Current address: Hematology Unit, Versilia Hospital, Lido di Camaiore, Italy.

Correspondence:
R. ZAMBELLO - r.zambello@unipd.it

https://doi.org/10.3324/haematol.2024.286825

Received: December 11, 2024.
Accepted: April 23, 2025.
Early view: April 30, 2025.

Disclosures

GBa has received honoraria from Amgen, GlaxoSmithKline, Bristol-Myers Squibb and Johnson & Johnson, has served on advisory boards for Johnson & Johnson, Pfizer and Menarini-Stemline and has received consultancy fees from Johnson & Johnson, Sanofi and Amgen. AB has served on advisory boards for Johnson &Johnson, Pfizer, Menarini-Stemline, GlaxoSmithKline and Amgen. SR has received honoraria from Amgen, Pfizer, GlaxoSmithKline, Bristol-Myers Squibb and Sanofi. KM has received honoraria from Celgene, Takeda, Amgen, Sanofi and Johnson & Johnson. RZ has served on advisory boards for Amgen, Takeda, Bristol-Myers Squibb, Johnson & Johnson, Sanofi and Pfizer. The other authors have no conflicts of interest to disclose.

Contributions

GBa designed the research, analyzed data, and wrote the manuscript. AG analyzed data, performed the statistical analysis and wrote the manuscript. CCo, RM, CM, FF, CSC, MT, MLDG, SP, MT, SR, KM, ES, MP, NP, AF, MAF, CCl, AC, RR, AM, CL and EAM provided patients' data. AB, GM, MG, OA, GBu, EA, SM, AT, PM, FG, MTP, FDR and FP participated in the analysis of data and critically reviewed and edited the manuscript. RZ designed the study, analyzed data, wrote the manuscript, and supervised the study. All the authors approved the final version of this manuscript.

Data-sharing statement

Original data are available in anonymous form on reasonable request to the corresponding author.

References

1. Dimopoulos MA, Moreau P, Terpos E, et al. Multiple myeloma: EHA-ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Hemasphere. 2021;5(2):e528.
2. Moreau P, Attal M, Hulin C, 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(10192):29-38.
3. Cavo M, Tacchetti P, Patriarca F, et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. Lancet. 2010;376(9758):2075-2085.
4. McCarthy PL, Holstein SA, Petrucci MT, et al. Lenalidomide maintenance after autologous stem-cell transplantation in

newly diagnosed multiple myeloma: a meta-analysis. J Clin Oncol. 2017;35(29):3279-3289.
5. Cavo M, Gay F, Beksac M, et al. Autologous haematopoietic stem-cell transplantation versus bortezomib-melphalan-prednisone, with or without bortezomib-lenalidomide-dexamethasone consolidation therapy, and lenalidomide maintenance for newly diagnosed multiple myeloma (EMN02/HO95): a multicentre, randomised, open-label, phase 3 study. Lancet Haematol. 2020;7(6):e456-e468.
6. Attal M, Lauwers-Cances V, Hulin C, et al. Lenalidomide, bortezomib, and dexamethasone with transplantation for myeloma. N Engl J Med. 2017;376(14):1311-1320.
7. Pawlyn C, Menzies T, Davies FE, et al. Defining the optimal duration of lenalidomide maintenance after autologous stem cell transplant - data from the Myeloma XI trial. Blood. 2022;140(Supplement 1):1371-1372.
8. Gay F, Musto P, Rota-Scalabrini D, et al. Carfilzomib with cyclophosphamide and dexamethasone or lenalidomide and dexamethasone plus autologous transplantation or carfilzomib plus lenalidomide and dexamethasone, followed by maintenance with carfilzomib plus lenalidomide or lenalidomide alone for patients with newly diagnosed multiple myeloma (FORTE): a randomised, open-label, phase 2 trial. Lancet Oncol. 2021;22(12):1705-1720.
9. D'Agostino M, Bertuglia G, Rota-Scalabrini D, et al. Predictors of unsustained measurable residual disease negativity in patients with multiple myeloma. Blood. 2024;143(7):592-596.
10. Sonneveld P, Dimopoulos MA, Boccadoro M, et al. Daratumumab, bortezomib, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med. 2024;390(4):301-313.