Comparison of isatuximab-pomalidomide-dexamethasone *versus* elotuzumab-pomalidomide-dexamethasone in relapsed/refractory multiple myeloma patients: a target trial emulation using real-world data

Advances in multiple myeloma (MM) treatment have significantly improved survival, yet most patients ultimately relapse and develop refractory disease. For those patients with relapsed/refractory MM after at least two prior therapies, two approved triplet regimens are available: isatuximab, pomalidomide and dexamethasone (IsaPd) and elotuzumab, pomalidomide and dexamethasone (EloPd).[1] IsaPd and EloPd were evaluated in the ICARIA-MM[2,3] and ELOQUENT-3[4,5] randomized controlled trials, both demonstrating efficacy and safety. Real-world studies confirmed these findings,[6-8] but the optimal choice remains unclear because of the lack of direct comparisons. To address this gap, we applied target trial emulation (TTE),[9,10] to compare the safety and efficacy of IsaPd and EloPd in two previously described real-world cohorts of patients with relapsed/refractory MM.[6-8] The study was approved by institutional ethics committees and conducted following the principles of the Declaration of Helsinki.

The cohorts were merged into a meta-database to emulate a target trial. TTE is a methodology designed to reduce biases in observational research, approximating randomized conditions.[9,10] Inverse probability of treatment weighting (IPTW) was used to balance baseline characteristics, creating a pseudo-randomized cohort.[6-8] Mann-Whitney and χ^2 tests were applied to compare groups, while standardized mean differences (SMD) (>|0.1|) identified confounders for multivariable logistic regression and propensity score (PS) calculations. IPTW weights were “1/PS” for IsaPd and “[1/(1-PS)]” for EloPd. Weighted logistic regression was used to assess response, neutropenia, and infections, while Cox models were used to evaluate progression-free survival (PFS) and overall survival (OS). Effect modification by daratumumab refractoriness was tested. Results are reported as odds ratios (OR) or hazard ratios (HR) with 95% confidence intervals (95% CI). Statistical analyses were performed using R (Survival version 4.2.3), SPSS (version 29), and STATA (version 16).

Of 596 eligible patients (*Online Supplementary Table S1*), 319 were excluded because of missing fluorescence *in situ* hybridization (FISH) data, leaving 277 for analysis. The median age was 69.9 years (interquartile range, 63.4-75.7), and 54.9% were male (Table 1A). The EloPd group (N=130, 46.9%) and IsaPd group (N=147, 53.1%) were generally comparable, although EloPd patients were older, more of them were refractory to daratumumab, and more had high-risk FISH profiles. SMD exceeded |0.1| for all except prior treatment lines and disease status. IPTW generated a balanced pseudo-population of 280 cases (130 treated with EloPd, 150 treated with IsaPd; all SMD <0.07) (Table 1B). The overall response rate was 66.8%, with IsaPd-treated patients showing a higher probability of response (76.9% *vs*. 55.4%, OR=2.68; *P*<0.001) (*Online Supplementary Table S2*). However, the difference in overall response rate was not statistically significant after IPTW (OR=1.51; *P*=0.093), nor in the fully adjusted model (OR=1.45; *P*=0.262). Factors independently associated with response included International Staging System (ISS) stage III disease (OR=0.41; *P*=0.027), daratumumab refractoriness (OR=2.30; *P*=0.013), and high-risk FISH (OR=0.57; *P*=0.048).

Although in an unadjusted evaluation for treatment response, IsaPd was associated with a significantly higher rate of responders compared to EloPd, after adjusting for confounders through TTE, the difference in overall response rate between patients treated with IsaPd or EloPd no longer reached statistical significance. In the multivariable logistic regression analysis, ISS stage III, daratumumab refractoriness, and high-risk cytogenetic abnormalities independently affected the overall response rate. These findings underscore the importance of patient- and disease-specific characteristics in predicting treatment response, suggesting that therapeutic decisions should consider individual baseline risk factors rather than solely focusing on the treatment regimen.

After a median follow-up of 21.7 months (95% CI: 19.7-23.5), 168 patients progressed or died. The median PFS was 12.5 months (95% CI: 9.53-16.7). Unadjusted analysis favored treatment with IsaPd (median 17.5 *vs*. 7.9 months, HR=0.55 [95% CI: 0.41-0.75]; *P*=0.001) (Table 2, Figure 1A), but after IPTW, the difference was not statistically significant (IsaPd 10.1 *vs*. EloPd 8.9 months, HR=0.92 [95% CI: 0.68-1.24]; *P*=0.59) (Table 2, Figure 1B). Multivariable analysis confirmed no treatment effect on PFS (HR=0.92 [95% CI: 0.61-1.38]; *P*=0.694). Independent PFS predictors were ISS stage II disease (HR=1.44; *P*=0.047), ISS stage III disease (HR=3.24; *P*<0.001), daratumumab refractoriness (HR=0.51; *P*=0.001), prior autologous stem cell transplantation (HR=0.68; *P*=0.045), and high-risk FISH profiles (HR=1.75; *P*=0.001) (Table 2).

The median OS was not reached for patients treated with IsaPd and was 22.9 months for those treated with EloPd.

Table 1A. Baseline characteristics of the original cohorts according to treatment arm.

Characteristics	EloPd N=130	IsaPd N=147	All N=277	*P*	SMD
Age in years Mean (SD) Median (IQR)	 70.2 (8.6) 71.8 (64.1-76.9)	 67.7 (9.2) 68.7 (62.7-74.9)	 68.9 (9.0) 69.9 (63.4-75.7)	0.02	0.29
Gender, N (%) Male Female	 75 (57.7) 55 (42.3)	 77 (52.4) 70 (47.6)	 152 (54.9) 125 (45.1)	0.38	0.107
Creatinine clearance, mL/min, Mean (SD) Median (IQR)	 69.2 (22.5) 70 (58.0-80.0)	 71.8 (24.6) 70 (54.7-90.0)	 70.6 (23.6) 70 (56.0-87.0)	0.36	0.111
International Staging System, N (%) I II II	 50 (38.5) 51 (39.2) 29 (22.3)	 70 (47.6) 57 (38.8) 20 (13.6)	 120 (43.3) 108 (39.0) 49 (17.7)	0.12	0.25
Previous lines of treatment Mean (SD) Median (IQR)	 2.5 (1.0) 2 (2.0-3.0)	 2.5 (0.9) 2 (2.0-3.0)	 2.5 (0.9) 2 (2.0-3.0)	0.52	0.041
LDH concentration, N (%) Normal Elevated°	 95 (73.1) 35 (26.9)	 119 (81.0) 28 (19.0)	 214 (77.3) 63 (22.7)	0.12	0.188
Refractory to daratumumab, N (%) Yes No	 99 (76.2) 31 (23.8)	 28 (19.0) 119 (81.0)	 127 (45.8) 150 (54.2)	<0.001	1.394
Previous ASCT, N (%) Yes No	 65 (50.0) 65 (50.0)	 85 (57.8) 62 (42.2)	 150 (54.2) 127 (45.8)	0.19	0.157
Disease status, N (%) Biochemical relapse Symtomatic relapse Refractory disease	 26 (20.0) 56 (43.1) 48 (36.9)	 30 (20.4) 68 (46.3) 49 (33.3)	 56 (20.2) 124 (44.8) 97 (35.0)	0.81	0.078
Cytogenetics, N (%) Low risk High risk*	 75 (57.7) 55 (42.3)	 104 (70.7) 43 (29.3)	 179 (64.6) 98 (35.4)	0.023	0.275

Table 1B. Baseline characteristics of the weighted cohort according to treatment arm.

Characteristics	EloPd, N=130	IsaPd, N=150	SMD
Age in years, mean (SD)	68.27 (9.3)	-	0.07
Female, N (%)	60.40 (46.5)	68.9 (46.1)	0.008
Creatinine clearance, mL/min, mean (SD)	69.86 (25.2)	69.10 (27.9)	0.029
International Staging System, N (%) I II III	 57.0 (43.9) 50.7 (39.0) 22.3 (17.2)	 67.1 (44.9) 55.1 (36.8) 27.4 (18.3)	0.047
Elevated LDH°, N (%)	31.5 (24.2)	39.8 (26.6)	0.055
Not refractory to daratumumab, N (%)	70.3 (54.1)	79.4 (53.1)	0.02
No previous ASCT, N (%)	61.0 (46.9)	75.1 (50.2)	0.066
High-risk* cytogenetics, N (%)	45.5 (35.0)	50.5 (33.8)	0.026

°Elevated: higher-than-normal lactate dehydrogenase levels. *High risk: patients with t(4;14), t(14;16) or del(17p). EloPd: elotuzumab, pomalidomide, dexamethasone; IsaPd: isatuximab, pomalidomide, dexamethasone; SMD: standardized mean differences; SD: standard deviation; IQR: interquartile range; LDH: lactate dehydrogenase; ASCT: autologous stem cell transplantation.

Unadjusted OS favored IsaPd treatment (HR=0.57 [95% CI: 0.38-0.85]; *P*=0.007) (Table 2, Figure 1C), but after IPTW, the difference was not statistically significant (IsaPd 25.6 *vs*. EloPd 22.9 months, HR=0.84 [95% CI: 0.57-1.22]; *P*=0.35) (Table 2, Figure 1D). Multivariable analysis confirmed no OS difference (HR=0.85 [95% CI: 0.51-1.42]; P=0.54). Independent predictors of shorter OS were ISS stage II disease (HR=2.12; *P*=0.005), ISS stage III disease (HR=3.82; *P*<0.001), and elevated lactate dehydrogenase (HR=1.79; *P*=0.009) (Table 2). A trend was observed for daratumumab refractoriness (HR=0.61; *P*=0.055) and high-risk FISH profiles (HR=1.49; *P*=0.069).

This is the first hematology study to apply TTE to compare outcomes and safety in two large, real-world cohorts[6-8] of relapsed/refractory MM patients treated with EloPd and IsaPd. By emulating the design of randomized controlled trials, TTE mitigates observational biases, balances baseline characteristics, controls for confounders, and strengthens causal inference in real-world settings.[9,10] Indeed, applying TTE to real-world data offers a valuable approach for addressing clinical questions unresolved by randomized controlled trials, particularly in underrepresented populations and specific subgroups. In our IsaPd-treated cohort,[8] 29.3% had high-risk cytogenetics, a substantially higher proportion than in the ICARIA-MM trial,[4,5] and ~20% were refractory to daratumumab,[11] a group excluded from ICARIA-MM.[4,5] Likewise, the real-world EloPd cohort had a higher prevalence of older patients (>75 years), severe renal impairment, advanced ISS stage, and high-risk cytogenetics compared to the patients in ELOQUENT-3.[2,3,6,7] Moreover, our cohort included daratumumab-refractory cases,[12] a population absent in ELOQUENT-3.[2,3] These findings underscore the critical role of real-world data in evaluating treatment efficacy and safety across diverse populations often un-

Table 2. Univariate and multivariate Cox regression analyses of progression-free survival and overall survival.

Variable	Unadjusted model		IPTW model		Fully adjusted model	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Progression-free survival						
Therapy IsaPd *vs*. EloPd	0.55 (0.41-0.75)	0.001	0.92 (0.68-1.24)	0.593	0.92 (0.61-1.38)	0.694
Age	-	-	-	-	1.01 (0.99-1.04)	0.210
Gender: female *vs*. male	-	-	-	-	1.21 (0.88-1.68)	0.242
Creatinine clearance	-	-	-	-	1.00 (0.99-1.01)	0.703
International Staging System I	-	-	-	-	1	-
International Staging System II	-	-	-	-	1.44 (1.00-2.06)	0.047
International Staging System III	-	-	-	-	3.24 (1.98-5.29)	0.000
LDH: elevated° *vs*. normal	-	-	-	-	1.33 (0.94-1.90)	0.109
Daratumumab refractory: no *vs*. yes	-	-	-	-	0.51 (0.34-0.77)	0.001
Previous ASCT: no *vs*. yes	-	-	-	-	0.68 (0.47-0.99)	0.045
Cytogenetics: high* *vs*. low risk	-	-	-	-	1.75 (1.27-2.43)	0.001
Overall survival						
Therapy IsaPd *vs*. EloPd	0.57 (0.38-0.85)	0.007	0.84 (0.57-1.22)	0.35	0.85 (0.51-1.42)	0.544
Age	-	-	-	-	1.01 (0.98-1.04)	0.533
Gender: female *vs*. male	-	-	-	-	1.18 (0.76-1.81)	0.465
Creatinine clearance	-	-	-	-	0.99 (0.98-1.00)	0.230
International Staging System I	-	-	-	-	1	-
International Staging System II	-	-	-	-	2.12 (1.25-3.58)	0.005
International Staging System III	-	-	-	-	3.82 (2.00-7.30)	0.000
LDH: elevated° *vs*. normal	-	-	-	-	1.79 (1.16-2.78)	0.009
Daratumumab refractory: no *vs*. yes	-	-	-	-	0.61 (0.36-1.01)	0.055
Previous ASCT: no *vs*. yes	-	-	-	-	0.73 (0.44-1.22)	0.228
Cytogenetics: high* *vs*. low risk	-	-	-	-	1.49 (0.97-2.30)	0.069

°Elevated: higher-than-normal lactate dehydrogenase levels. *High risk: patients with t(4;14), t(14;16) or del(17p). IPWT: inverse probability of treatment weighting; HR: hazard ratio; 95% CI: 95% confidence interval; EloPd: elotuzumab, pomalidomide, dexamethasone; IsaPd: isatuximab, pomalidomide, dexamethasone; LDH: lactate dehydrogenase; ASCT: autologous stem cell transplantation.

derrepresented in randomized controlled trials. By bridging the gap between data from randomized controlled trials and real-world clinical scenarios, TTE generates clinically relevant evidence to guide treatment decisions in these challenging settings.[9,10]

In the original population, IsaPd was associated with a 45% lower risk of progression or death than EloPd, but this difference lost significance after IPTW adjustment, highlighting baseline imbalances. Independent predictors of worse PFS included ISS stage II/III disease, daratumumab refractoriness, high-risk cytogenetics, and prior autologous stem cell transplantation. OS predictors were similar, with elevated lactate dehydrogenase concentration as an additional risk factor, while prior autologous stem cell transplantation did not have a negative impact in the fully adjusted model.

TTE performed in our study provides reasonable explanations of the differences in PFS and OS that emerged from our previous analysis of real-world evidence. Indeed, PFS and OS in the IsaPd real-world study[8] were 17.5 months and not reached, respectively, while the corresponding values in the EloPd real-world study were 7.9 and 22.9 months, respectively.[6,7] One possible reason behind this discrepancy may be that these two real-world studies effectively intercepted different populations in terms of patients and disease characteristics, with qualitatively more favorable cases being enrolled in the IsaPd real-world analysis.

The findings of this study confirm prior observations from analysis of the IsaPd real-world trial in which ISS stage II/III disease, elevated lactate dehydrogenase, and daratumumab refractoriness were identified as independent prognostic factors for both PFS and OS.[8,11] These predictors also held significance in patients treated with EloPd, consistent with previous findings.[6,7] The impact of prior anti-CD38 monoclonal antibody therapy, such as daratumumab, aligns with evidence of pronounced $CD38^{+}$ NK-cell depletion, potentially reducing elotuzumab's efficacy, which relies on NK-cell-mediated-dependent cellular cytotoxicity.[13]

Daratumumab refractoriness did not significantly modify the effect of IsaPd *versus* EloPd on overall response rate (P=0.10), PFS (P=0.71), or OS (P=0.16), indicating consistent treatment effects regardless of prior exposure (P>0.10), confirming that the effectiveness of IsaPd versus EloPd was unaffected by daratumumab refractoriness. This finding is clinically relevant, as it challenges the theoretical concern that shared molecular targeting between isatuximab and daratumumab might compromise therapeutic outcomes in daratumumab-exposed or potentially refractory patients. On the other hand, the results also imply that elotuzumab, which operates via a distinct mechanism of action, does not confer a measurable advantage in this subset of patients, despite its independence from CD38-targeted pathways.

IsaPd was associated with higher rates of grade 3-4 he-

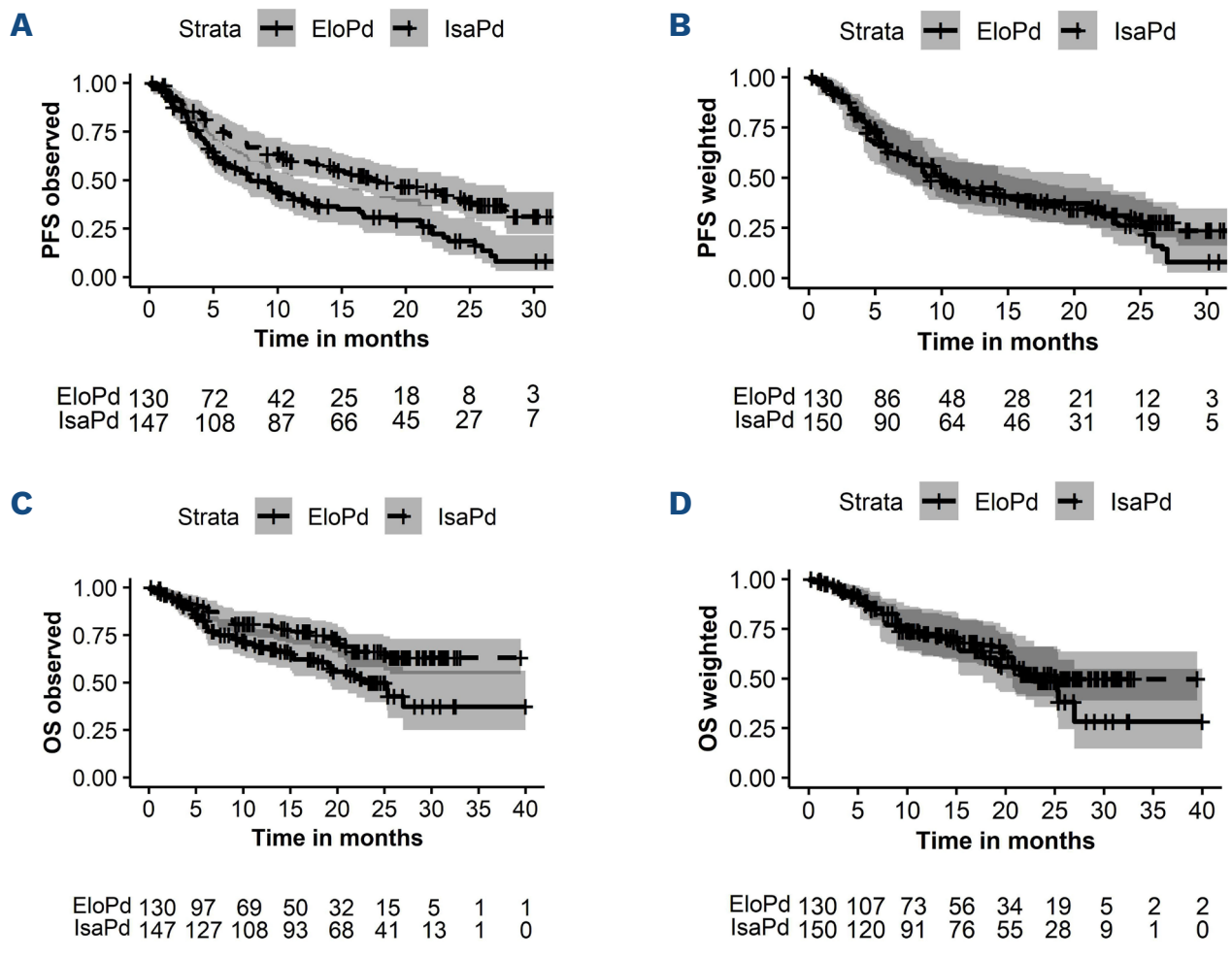

Figure 1. Kaplan-Meier survival curves for all 596 patients with relapsed/refractory multiple myeloma treated with isatuximab-pomalidomide-dexamethasone or elotuzumab-pomalidomide-dexamethasone. (A, B) Kaplan-Meier curves of progression-free survival according to treatment arm in the original cohort (A) and in the weighted cohort (B). (C, D) Kaplan Meier curves of overall survival according to treatment arm in the original cohort (C) and in the weighted cohort (D). EloPd: elotuzumab, pomalidomide, dexamethasone; IsaPd: isatuximab, pomalidomide, dexamethasone; PFS: progression-free survival; OS: overall survival.

matologic (neutropenia: 59.2% *vs*. 31.5%; *P*<0.001) and non-hematologic (infections: 55.1% *vs*. 34.6%; *P*<0.001) toxicities, while gastrointestinal and fatigue rates were similar (*Online Supplementary Table S3A*). Discontinuation due to adverse events was rare and comparable between the two treatment groups (IsaPd 2.0% *vs*. EloPd 4.6%; *P*=0.228). Logistic regression confirmed a higher risk of neutropenia with IsaPd treatment (unadjusted OR=3.15; *P*<0.001; IPTW OR=2.09; *P*=0.024; fully adjusted OR=2.45; *P*=0.005) (*Online Supplementary Table S3B*). Daratumumab refractoriness (OR=2.21; *P*=0.012) and older age (OR=1.04; *P*=0.031) increased the risk of neutropenia, while prior autologous stem cell transplantation was marginally protective (OR=0.55; *P*=0.053). IsaPd treatment increased the risk of grade 3-4 infection (unadjusted OR=2.32; *P*<0.001), but the statistical significance of this difference was lost after adjustment (IPTW OR=1.50; *P*=0.2; fully adjusted OR=1.47; *P*=0.204) (*Online Supplementary Table S3C*). Daratumumab refractoriness increased the risk of infection (OR=1.92; *P*=0.035).

EloPd and IsaPd exhibit distinct safety profiles, particularly with regard to hematologic toxicity. IsaPd treatment was associated with a significantly higher rate of grade 3-4 neutropenia (59.2% *vs*. 31.5%; *P*<0.001), an effect which remained in adjusted analyses (logistic regression OR=2.09; multivariable analysis OR=2.45). This suggests that patients treated with IsaPd require closer monitoring and proactive management, such as growth factor support or dose adjustments.

By comparing IsaPd and EloPd treatment in real-world settings, our findings may influence clinical practice. As third-line treatments often yield transient responses, these regimens could serve as bridges to therapy with chimeric antigen receptor T cells[14] or bispecific antibodies, such as teclistamab,[15] available from the fourth line. Both triplets (IsaPd and EloPd) produce comparable survival outcomes, with distinct toxicity profiles. EloPd potentially offers a lower risk of infections, which may be relevant for patient selection in cases in which infection risk is a major concern. Nevertheless, daratumumab refractoriness remains a dominant predictor of outcomes, representing an unmet clinical need.

Authors

Enrica Antonia Martino,[1*] Annalisa Pitino,[2*] Massimo Offidani,[3] Roberta Della Pepa,[4] Alessandro Gozzetti,[5] Velia Bongarzoni,[6] Antonio Maroccia,[7] Valeria Amico,[8] Paola Stefanoni,[9] Elena Zamagni,[10] Sofia Terlizzi,[11] Daniele Derudas,[12] Salvatore Palmieri,[13] Rosario Bianco,[14] Concetta Conticello,[15] Marino Brunori,[16] Angela Rago,[17] Flavia Lotti,[18] Raffaele Fontana,[19] Nicola Sgherza,[20] Elena Rossi,[21] Anna Maria Cafro,[22] Massimiliano Arangio Febbo,[23] Angela Maria Quinto,[24] Claudio Cerchione,[25] Gloria Margiotta Casaluci,[26] Annalisa Citro,[27] Catello Califano,[28] Renato Zambello,[29] Silvia Mangiacavalli,[30] Carmine Liberatore,[31,32] Gabriele Buda,[33] Claudio De Magistris,[34] Angela Amendola,[35] Ernesto Vigna,[1] Antonella Bruzzese,[1] Emiliano Barbieri,[36,37] Micol Quaresima,[36] Daniela Roccotelli,[38] Francesca Farina,[39] Jacopo Micozzi,[40] Iolanda Donatella Vincelli,[41] Giuseppe Tarantini,[42] Elisabetta Antonioli,[43] Sara Aquino,[44] Alessandro Maggi,[45] Alessandra Lombardo,[46] Giuseppe Bertuglia,[47] Anna Furlan,[48] Anna Mele,[49] Ombretta Annibali,[50] Emilia Cotzia,[51] Pietro Benvenuti,[52] Lorenzo De Paoli,[53] Gregorio Barilà,[54] Sonia Morè,[3] Valerio De Stefano,[21] Francesco Di Raimondo,[15] Maria Teresa Petrucci,[40] Niccolò Bolli,[34] Pellegrino Musto,[55] Antonino Neri,[56] Fortunato Morabito,[57] Giovanni Tripepi[58] and Massimo Gentile[1,59]

[1]Department of Onco-Hematology, Hematology Unit, Azienda Ospedaliera Annunziata, Cosenza; [2]Institute of Clinical Physiology (IFC-CNR), Rome; [3]Hematology Unit, AOU delle Marche, Ancona; [4]Department of Clinical Medicine and Surgery, University Federico II, Naples; [5]Department of Medicine, Surgery and Neurosciences, University of Siena Policlinico S Maria alle Scotte, Siena; [6]UOC of Hematology San Giovanni-Addolorata Hospital, Rome; [7]Hematology Unit - Ospedale dell'Angelo Azienda ULSS n.3 Serenissima, Venezia Mestre; [8]UOSD Ematologia, AORN San Pio, Benevento; [9]Hematology and Bone Marrow Transplant Unit, ASST Papa Giovanni XXIII, Bergamo; [10]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Bologna; Dipartimento di Scienze Mediche e Chirurgiche, Università di Bologna, Bologna; [11]Department of Hematology ASST Spedali Civili di Brescia, Brescia; [12]Department of Hematology, Businco Hospital, Cagliari; [13]Hematology Unit, Ospedale Cardarelli, Naples; [14]Hematology, Hospital "Sant'Anna e San Sebastiano", Caserta; [15]Division of Hematology, Azienda Policlinico-S. Marco, University of Catania, Catania; [16]Internal Medicine, Ospedale Santa Croce, Fano; [17]UOSD Ematologia ASL Roma 1, Rome; [18]Institute of Hematology, TMO Azienda Universitaria-Ospedaliera Santa Maria della Misericordia di Perugia, Perugia; [19]Hematology and Transplant Center, University Hospital "San Giovanni di Dio e Ruggi d'Aragona", Salerno; [20]Unit of Hematology and Stem Cell Transplantation, AOUC Policlinico, Bari; [21]Section of Hematology, Catholic University, Fondazione Policlinico Gemelli IRCCS, Rome; [22]Department of Hematology, GOM Niguarda Hospital, Milan; [23]Onco Hematology Unit, Veneto Institute of Oncology IOV-IRCCS, Padua; [24]Haematology and Transplant Unit, IRCCS - Istituto Tumori "Giovanni Paolo II", Bari; [25]Department of Hematology, IRCCS Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST), Meldola, Forlì-Cesena; [26]Division of Hematology, Department of Translational Medicine, University of Eastern Piedmont, Novara; [27]Hematology Unit, Legnano General Hospital, Legnano; [28]Onco-Hematology Unit, "A. Tortora" Hospital, Pagani; [29]Department of Medicine (DIMED), Hematology and Clinical Immunology, Padua University School of Medicine, Padua; [30]Division of Hematology, IRCCS Fondazione Policlinico San Matteo, Pavia; [31]Hematology Unit, Department of Oncology and Hematology, Ospedale Santo Spirito, Pescara; [32]Department of Medicine and Aging Sciences, University of Chieti-Pescara, Chieti; [33]Department of Clinical and Experimental Medicine, Hematology, University of Pisa, Pisa; [34]Hematology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan; [35]Hematology Unit, Azienda Ospedaliera Regionale "San Carlo", Potenza; [36]Hematology Unit, Azienda USL-

IRCCS di Reggio Emilia, Reggio Emilia; [37]Clinical and Experimental Medicine PhD Program, University of Modena and Reggio Emilia, Modena; [38]Department of Hematology and Bone Marrow Transplant, IRCSS Casa Sollievo Della Sofferenza, San Giovanni Rotondo; [39]Hematology and BMT Unit, IRCCS Ospedale San Raffaele, Milan; [40]Department of Translational and Precision Medicine, Hematology Azienda Policlinico Umberto I Sapienza University of Rome, Rome; [41]Department of Hemato-Oncology and Radiotherapy, Hematology Unit, Great Metropolitan Hospital "Bianchi-Melacrino-Morelli", Reggio Calabria; [42]Hematology Unit, "Dimiccoli" Hospital, Barletta; [43]Hematology Unit, Careggi University Hospital, Florence, Italy; [44]Hematology and Hematopoietic Stem Cell Transplantation Unit, IRCCS Ospedale Policlinico San Martino, Genoa; [45]Hematology, Ospedale G. Moscati, Taranto; [46]Onco-Hematology Unit Azienda Ospedaliera Santa Maria of Terni, Terni; [47]Division of Hematology, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, University of Turin, Turin; [48]Division of Hematology Ospedale Ca' Foncello di Treviso, Treviso; [49]Hematology, Ospedale Cardinale Panico, Tricase, Italy; [50]Hematology, Stem Cell Transplantation, Fondazione Policlinico Universitario Campus Biomedico di Roma, Rome; [51]Section of Hematology- Ospedale E. Muscatello-Augusta, Siracusa; [52]Department of Medicine and Surgery, University of Insubria and Department of Oncology, Ospedale di Circolo, Varese; [53]Division of Hematology, Ospedale Sant'Andrea, Vercelli; [54]Hematology Unit, Ospedale San Bortolo, Vicenza; [55]Department of Precision and Regenerative Medicine and Ionian Area, "Aldo Moro" University School of Medicine, Bari; [56]Scientific Directorate, Azienda USL-IRCCS of Reggio Emilia, Reggio Emilia; [57]Gruppo Amici Dell'Ematologia Foundation-GrADE, Reggio Emilia; [58]Institute of Clinical Physiology (IFC-CNR), Clinical Epidemiology and Physiopathology of Renal Diseases and Hypertension of Reggio Calabria, Reggio Calabria and [59]Department of Pharmacy, Health and Nutritional Science, University of Calabria, Rende, Italy.

**EAM and AP contributed equally as first authors.*

Correspondence:
M. GENTILE - massim.gentile@tiscali.it
A. NERI - antonino.neri@ausl.re.it

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No conflicts of interest to disclose.

Contributions

EAM, AP, MG, FDR, VDS, NB, GT, AN, FM, MTP, and PM designed the study. GT, AP, MG and FM performed statistical analyses. DD, ER, PS, SM, EZ, MO, AMQ, RDP, GB, EB, CC, CDM, VB, AMC, AM, NS, GMC, OA, AR, RF, EV, AB, AA, ACi, AG, VB, VA, PS, ST, SP, RB, MB, FL, MAF, CCe, CCa, RZ, CL, DR, FF, JM, IDV, GT, EA, SA, AM, AL, GBe, AF, AM, PB, LDP, GBa and SMo acquired, analyzed and interpreted data. EAM, AP, GT, MG, and FM wrote the manuscript. All authors revised the manuscript and gave final approval. All authors agreed to be accountable for all aspects of the manuscript in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Data-sharing statement

Data are available upon reasonable request and submission of a research project proposal to the corresponding authors.

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