original reports

High Levels of Circulating Tumor Plasma Cells as a Key Hallmark of Aggressive Disease in Transplant-Eligible Patients With Newly Diagnosed Multiple Myeloma

Luca Bertamini, MD[1]; Stefania Oliva, MD, PhD[1]; Delia Rota-Scalabrini, MD[2]; Laura Paris, MD[3]; Sonia Morè, MD[4]; Paolo Corradini, MD[5]; Antonio Ledda, MD[6]; Massimo Gentile, MD[7]; Giovanni De Sabbata, MD[8]; Giuseppe Pietrantuono, MD[9]; Anna Pascarella, MD[10]; Patrizia Tosi, MD[11]; Paola Curci, MD[12]; Milena Gilestro, BSc[1]; Andrea Capra, MScEng[1]; Piero Galieni, MD[13]; Francesco Pisani, MD[14]; Ombretta Annibali, MD, PhD[15]; Federico Monaco, MD[16]; Anna Marina Liberati, MD[17]; Salvatore Palmieri, MD[18]; Mario Luppi, MD, PhD[19]; Renato Zambello, MD[20]; Francesca Fazio, MD[21]; Angelo Belotti, MD[22]; Paola Tacchetti, MD, PhD[23]; Pellegrino Musto, MD[12,24]; Mario Boccadoro, MD[1]; and Francesca Gay, MD, PhD[1]

abstract

PURPOSE High levels of circulating tumor plasma cells (CTC-high) in patients with multiple myeloma are a marker of aggressive disease. We aimed to confirm the prognostic impact and identify a possible cutoff value of CTC-high for the prediction of progression-free survival (PFS) and overall survival (OS), in the context of concomitant risk features and minimal residual disease (MRD) achievement.

METHODS CTC were analyzed at diagnosis with two-tube single-platform flow cytometry (sensitivity 4×10^{-5}) in patients enrolled in the multicenter randomized FORTE clinical trial (ClinicalTrials.gov identifier: NCT02203643). MRD was assessed by second-generation multiparameter flow cytometry (sensitivity 10^{-5}). We tested different cutoff values in series of multivariate (MV) Cox proportional hazards regression analyses on PFS outcome and selected the value that maximized the Harrell's C-statistic. We analyzed the impact of CTC on PFS and OS in a MV analysis including baseline features and MRD negativity.

RESULTS CTC analysis was performed in 401 patients; the median follow-up was 50 months (interquartile range, 45-54 months). There was a modest correlation between the percentage of CTC and bone marrow plasma cells ($r = 0.38$). We identified an optimal CTC cutoff of 0.07% (approximately 5 cells/μL, C-index 0.64). In MV analysis, CTC-high versus CTC-low patients had significantly shorter PFS (hazard ratio, 2.61; 95% CI, 1.49 to 2.97, $P < .001$; 4-year PFS 38% *v* 69%) and OS (hazard ratio, 2.61; 95% CI, 1.49 to 4.56; $P < .001$; 4-year OS 68% *v* 92%). The CTC levels, but not the bone marrow plasma cell levels, affected the outcome. The only factor that reduced the negative impact of CTC-high was the achievement of MRD negativity (interaction $P = .039$).

CONCLUSION In multiple myeloma, increasing levels of CTC above an optimal cutoff represent an easy-to-assess, robust, and independent high-risk factor. The achievement of MRD negativity is the most important factor that modulates their negative prognostic impact.

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Data Supplement
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INTRODUCTION

Despite the recent advances in the treatment of multiple myeloma (MM), high-risk patients still experience early relapse and short survival.[1-4] Many high-risk features, such as abnormal albumin and β2-microglobulin, elevated lactate dehydrogenase (LDH),[5] and cytogenetic abnormalities (CA),[6-8] have been associated with adverse outcome in MM and combined to develop risk assessment tools at diagnosis.[9,10] Bone marrow plasma cell (BMPC) infiltration is an important marker of disease burden in monoclonal gammopathies, helping to discriminate among monoclonal gammopathy of undetermined significance, smoldering MM, and symptomatic MM. Indeed, BMPC ≥ 60% was recently included in the criteria for starting MM treatment, even in the absence of traditional end-organ damage.[11] Nevertheless, the prognostic role of BMPC in patients with MM is modest, likely because of patchy bone disease.[12]

Circulating tumor plasma cells (CTC) can be detected by blood count and blood smear in the peripheral blood and are a distinctive diagnostic feature of plasma cell leukemia, a very aggressive plasma cell dyscrasia[13,14] that is defined by an amount of plasma cells (PC) ≥ 20% of white blood cells (or > 2,000/μL), although evidence supported the reduction of this threshold to 5%.[15] Moreover, lower CTC levels detected with more

CONTEXT

Key Objective

Despite the improvement of multiple myeloma (MM) risk assessment, some patients still show dismal outcomes. Retrospective and real-world studies confirmed that the detection of circulating tumor plasma cells (CTC) is a biomarker of adverse outcome. We prospectively evaluated the presence of CTC by flow cytometry [FC] at diagnosis in patients with MM treated with novel agents and transplant in the FORTE trial. We aimed to identify a prognostic cutoff in the context of concomitant risk features and minimal residual disease (MRD).

Knowledge Generated

Elevated CTC, with an optimal 0.07% cutoff, were associated with shorter progression-free survival and overall survival (OS), independently of other established risk features (International Staging System [ISS] stage, cytogenetics, and lactate dehydrogenase levels). MRD negativity is the most important factor that modulates the adverse prognosis of CTC.

Relevance

The incorporation of CTC detected at diagnosis by FC into the standard-risk assessment improves the identification of high-risk patients to better define treatment intensity.

sensitive techniques (ie, flow cytometry [FC]; and even without evidence at blood smear) were associated with shorter progression-free survival (PFS) and overall survival (OS).[16-23]

Most of the published studies on the prognostic role of CTC in MM are retrospective or prospective but observational. No data from clinical trials and large series of patients receiving novel highly effective regimens are available, and no cutoff has been universally recommended in clinical practice.

Our aim was to identify an optimal CTC cutoff by multiparameter FC (MFC; sensitivity of 10^{-4}) in the context of other concomitant prognostic factors, including static baseline features and dynamic prognostic factors (minimal residual disease [MRD] negativity), to predict PFS in patients with newly diagnosed MM (NDMM) treated with novel agents.

METHODS

Study Population

We prospectively evaluated the presence of CTC at diagnosis in patients with NDMM age $<$ 65 years and eligible for autologous stem-cell transplantation (ASCT) enrolled in the phase II multicenter randomized FORTE clinical trial.[24] Patients were randomly assigned at diagnosis (R1) into three arms: carfilzomib-lenalidomide-dexamethasone (KRd)-ASCT (four KRd induction cycles, melphalan at 200 mg/m^2 [MEL200] and ASCT, and four KRd consolidation cycles); KRd12 (12 KRd cycles); or carfilzomib-cyclophosphamide-dexamethasone (KCd)-ASCT (four KCd induction cycles, MEL200-ASCT, and four KCd consolidation cycles). Patients were subsequently randomly assigned (R2) into two maintenance arms: carfilzomib-lenalidomide or lenalidomide until progression or intolerance (Fig 1 and Data Supplement [Supplementary Methods], online only). This analysis was conducted in accordance with the protocol of the UNITO-MM-01/FORTE trial (see the Redacted Protocol, online only), which was approved by the institutional review boards at each of the participating centers and registered at ClinicalTrials.gov (NCT02203643). All patients provided written informed consent before entering the study, which was performed in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines.

Laboratory Analysis

CTC were assessed as a clinical trial-correlative study at diagnosis by two-tube single-platform FC. The first tube allowed to select and quantify the absolute count of PC and identify those with abnormal phenotype (likely monoclonal) by using the antibody combination CD38PC7/CD138FITC/CD45KO/CD56PE/CD19PB (Navios FC acquisition). To reduce the acquisition of cellular debris and lysed red cell, a live gate acquisition was performed. Live gate strategy consisted in excluding all CD38-negative and CD45-negative events (debris and red cells). Thereafter, PC were identified by CD38/CD138 gate (CD38+/CD138+), and pathologic PC by CD19/CD56 gate (CD19-/CD56+). Similarly, a second tube with intracellular antibody combination cy-kappa-FITC/cy-lambda-PE/CD38PE-CY7/CD138PC5.5/CD45KO/CD56APC/CD19PB was performed to assess and confirm the CTC clonality (Data Supplement Fig S1). The threshold for CTC detection was defined as 20 PC events out of 500,000 events analyzed after debris exclusion. The sensitivity in terms of limit of detection was 10^{-4} (4×10^{-5}). The minimum number of cells analyzed was 500,000.

MRD was assessed by MFC on bone marrow (BM) samples according to EuroFlow-based methods (eight colors, two tubes) for sample processing and cell acquisition.[25] Data were acquired using a Navios flow cytometer and analyzed with Kaluza software (Beckman Coulter, Brea, CA). We aimed to acquire $\geq$ 3.5 million cells. The antibody combination in the first tube was CD81FITC / CD27PE /

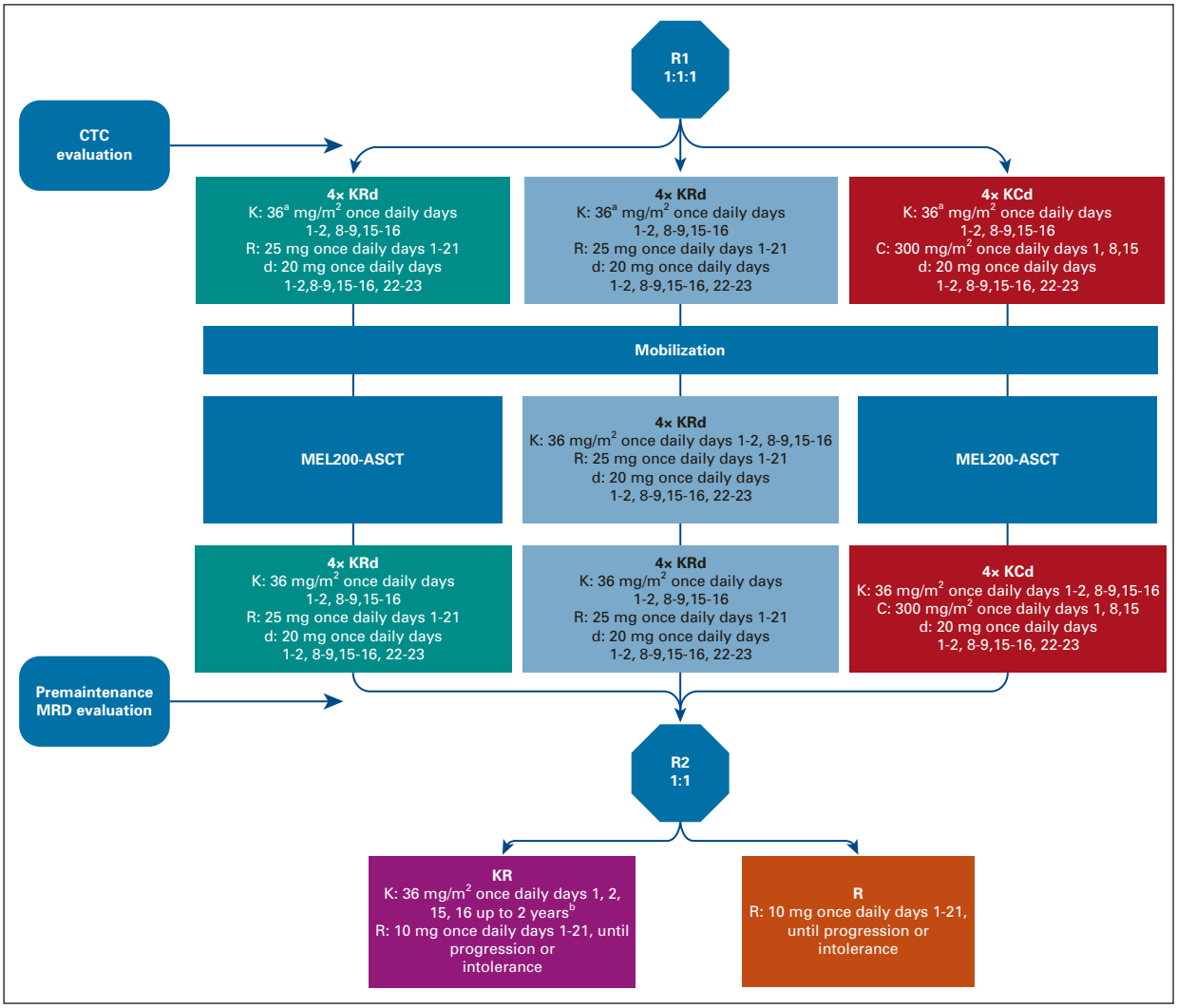

FIG 1. Design of the FORTE clinical trial. [a]20 mg/m^2 once daily days 1-2, cycle 1 only. [b]Carfilzomib 70 mg/m^2 once daily days 1, 15 every 28 days up to 2 years for patients who started maintenance treatment from 6 months before the approval of Amendment 5.0 onward. ASCT, autologous stem-cell transplantation; C, cyclophosphamide; CTC, circulating tumor plasma cells; d, dexamethasone; K, carfilzomib; MEL200, melphalan at 200 mg/m^2; MRD, minimal residual disease; R, lenalidomide; R1, first random assignment (induction/intensification/consolidation treatment); R2, second random assignment (maintenance treatment).

CD138PC5.5 / CD38PC7 / CD56APC / CD20APC-Alexa750 / CD19PB / CD45KO, and the combination used in the second tube to confirm clonality included cy-kappa-FITC / cy-lambda-PE / CD138PC5.5 / CD38PC7 / CD56APC / CD117APC-Alexa750 / CD19PB / CD45KO. The sensitivity was 10^{-5}.

The CA detected by fluorescence in situ hybridization were 17p deletion [del(17p)], t(4;14), t(11;14), and t(14;16) translocations, and 1q amplification [amp(1q)]. Details on the monoclonal antibodies used for FC and CA are reported in the Data Supplement (Supplementary Methods and Table S1).

Statistical Analysis

All patients with available CTC data were included in this analysis. The patient distribution according to CTC and the Pearson's correlation coefficient (*r*) between CTC and BMPC as continuous variables were evaluated.

The prognostic role of CTC in terms of risk of progression or death (PFS event) was evaluated by comparing the discrimination ability (Harrell's C-statistic) of Cox proportional hazards regression of different models: a model with well-known prognostic factors (International Staging System [ISS] stage, CA, LDH, or Revised ISS [R-ISS] stage; null model), a model with the same risk factors plus CTC, and a model with CTC alone. CTC were modeled as linear predictor, with spline function, as log-transformed, or with different possible cutoff values. To compare different models, the likelihood ratio test was used for nested models, whereas the Akaike's information criterion was used for non-nested models.

After testing models with different possible CTC cutoffs, we selected the value (C) that maximized the Harrell's C-statistic. The bootstrap method was used to reduce overfitting and, consequently, to achieve a more realistic model performance (Data Supplement [Supplementary Methods]) and identify the CI and standard error of the optimal cutoff. The *P* value for the comparison of CTC above versus below the cutoff was adjusted using the Bonferroni method.

We compared baseline features (age, ISS, LDH, CA, R-ISS, plasmacytoma, and BMPC) and response (MRD negativity) in patients with CTC above versus below the optimal selected cutoff (CTC-high *v* CTC-low; Data Supplement [Supplementary Methods]).

A multivariate (MV) Cox proportional hazards regression analysis adjusted for treatment (R1) and prognostic factors (ISS-LDH-CA or R-ISS, plasmacytoma, and amp(1q)) was performed to compare the impact of CTC and BMPC and to assess the impact of CTC-high versus CTC-low on PFS and OS and the occurrence of early relapse at 18 months.

Subgroup analyses were performed to determine the role of CTC, using interaction terms between baseline prognostic factors (ISS-LDH-CA) and response (MRD negativity included as time-dependent covariate). The null hypothesis examined with the interaction test was that the hazard ratio (HR) of CTC-high versus CTC-low was the same in each subgroup.

Cox proportional hazards regression models were used to estimate HRs and 95% CIs for the main comparisons. Landmark analyses of PFS and OS were performed with a landmark point at 12 months from diagnosis, excluding patients who progressed/died before that time point. The statistical analysis was performed using R (v.4.1.0). The data cutoff was January 7, 2021.

RESULTS

CTC Detection

We analyzed 401 patients with available baseline CTC data, out of 474 patients enrolled in the FORTE trial. We did not include 73 patients enrolled in the main study before the start of this correlative study. The included study population had baseline clinical features comparable with those of the overall FORTE trial population and of the excluded patients (Data Supplement Table S2). The median follow-up of this study population was 50 months (interquartile range [IQR], 45.3-54.0 months).

CTC were detected by MFC in 269/401 (67%) patients at diagnosis. The median CTC percentage was 0.02% (IQR 0%-0.14%), corresponding to a median absolute number of 1.24 cells/μL (IQR 0-7.79 cells/μL). The CTC distribution in the population is shown in the Data Supplement (Figs S2a and S2b).

A moderate correlation between CTC and BMPC was observed ($r = 0.382$, $P < .01$; Data Supplement Fig S3). Increasing levels of CTC as a continuous value were associated with worse PFS (Data Supplement Figs S4 and S5). The inclusion of CTC as a continuous variable in different models incorporating traditional risk factors (ISS-LDH-CA or R-ISS) increased their prognostic impact on PFS (Data Supplement Tables S3a and S3b).

Optimal CTC Cutoff

We performed a Cox proportional hazards regression analysis for PFS adjusted for established risk factors (ISS, LDH, and CA) and identified an optimal prognostic CTC cutoff with the highest C-index (0.64) corresponding to 0.07% (approximately five cells/μL; 95% CI, 0.02% to 0.33%, standard error 0.20%; Data Supplement Fig S6 and Table S4). For the internal validation, the bootstrap method was used (Data Supplement [Supplementary Methods]). The cutoff (0.01%) selected in the companion study by the GEM/PETHEMA cooperative study group[26] (Data Supplement [Supplementary Results]) had a similar prognostic power when included in our data set (C-index 0.62). Two populations were identified using our cutoff: patients with CTC > 0.07% (CTC-high, n = 130, 32%) and ≤ 0.07% (CTC-low, n = 271, 68%). Of note, half of CTC-low patients (n = 132, 33% of the overall population) had undetectable CTC with the sensitivity of 4×10^{-5}. The inclusion of CTC with the selected cutoff (either 0.07% or 0.01%), rather than as a continuous variable, confirmed the increased prognostic impact of the model incorporating CTC (Data Supplement Tables S3a and S3b).

Adverse prognostic factors were significantly more frequent in CTC-high patients (Table 1). Nevertheless, approximately 27% of patients who were considered to be at standard risk had CTC-high (27% of patients with standard-risk cytogenetics, 27% with low LDH, and 27% with ISS I/II; Table 1). Patients who were CTC-high versus CTC-low had lower rates of MRD negativity by intention-to-treat at premaintenance (42% *v* 59%, $P = .001$) and had lower rates of at least a complete response at premaintenance (43% *v* 54%; $P = .055$; Table 1).

In univariate analysis, CTC-high versus CTC-low patients had significantly shorter PFS (4-year PFS 38% [95% CI, 31% to 48%] *v* 69% [95% CI, 64% to 75%], HR, 2.66, 95% CI, 1.95 to 3.61, $P < .001$) and OS (4-year OS 68% [95% CI, 60% to 77%] *v* 92% [95% CI, 88% to 95%], HR, 4.43, 95% CI, 2.67 to 7.35, $P < .001$; Figs 2A and 2B). No significant differences in terms of PFS and OS were observed in patients with undetectable versus detectable CTC-low (Data Supplement Fig S7). The performance of the cutoff value selected in the companion study (0.01%)[26] was confirmed in our data set (PFS: HR, 1.76, 95% CI, 1.26 to 2.47, $P < .001$; OS: HR, 2.3, 95% CI, 1.29 to 4.09, $P < .005$; Data Supplement Fig S8).

TABLE 1. Baseline Features and Response to Therapy in Patients With CTC-Low Versus CTC-High

Feature/Response	CTC-Low (≤ 0.07%), No. (%)	CTC-High (> 0.07%), No. (%)	*P*
Total	271 (68)	130 (32)	
ISS			
I	165 (61)	38 (29)	< .001
II	72 (27)	52 (40)	
III	34 (13)	40 (31)	
CA[a]			
Standard risk	164 (74)	65 (53)	< .001
High risk[b]	57 (26)	58 (47)	
Missing	50	7	
del(17p)	25 (11)	26 (21)	.017
Missing	50	7	
t(4;14)	30 (14)	28 (23)	.035
Missing	49	7	
t(14;16)	6 (3)	13 (11)	.005
Missing	49	8	
amp(1q)	90 (41)	71 (59)	.002
Missing	52	9	
t(11;14)	43 (20)	33 (27)	.10
Missing	51	9	
LDH high[a]	20 (8)	31 (25)	< .001
Missing	6	5	
R-ISS[a]			
I	89 (40)	15 (12)	< .001
II	124 (55)	85 (69)	
III	12 (5)	24 (19)	
Missing	46	6	
BMPC (> 60%)	70 (26)	67 (52)	< .001
Plasmacytoma[c]	49 (18)	15 (12)	.109
Premaintenance ≥ VGPR	234 (86)	103 (79)	.080
Premaintenance ≥ CR	145 (54)	56 (43)	.055
Premaintenance ITT MRD negativity	160 (59)	54 (42)	.001

Abbreviations: amp, amplification; BMPC, bone marrow plasma cells; CA, cytogenetic abnormalities; CR, complete response; CT, computed tomography; CTC, circulating tumor plasma cells; CTC-high, CTC > 0.07%; CTC-low, CTC ≤ 0.07%; del, deletion; ISS, International Staging System; ITT, intention-to-treat; LDH, lactate dehydrogenase; MRD, minimal residual disease; MRI, magnetic resonance imaging; R-ISS, Revised ISS; t, translocation; VGPR, very good partial response.

[a]CA, high LDH levels, and R-ISS stage show the percentage of evaluable patients.

[b]High-risk CA: high risk was defined as the presence of either del(17p), t(4;14), or t(14;16).

[c]Evaluated by clinical assessment, CT scan, or MRI in patients with clinically suspected extramedullary disease.

Comprehensive Risk Assessment: CTC, Baseline Risk Features, Depth of Response, and Treatment

In the MV analysis including CTC and BMPC as continuous variables, only the former were predictive of both PFS and OS (Data Supplement Table S5).

In the MV analysis including baseline features and therapy (Table 2), CTC-high was one of the most significant features associated with shorter PFS (HR, 2.11, 95% CI, 1.49 to 2.97, $P < .001$), together with high LDH (HR, 2.22, 95% CI, 1.48 to 3.33, $P < .001$) and amp(1q) (HR, 2.03, 95% CI, 1.42 to 2.91, $P < .001$). CTC-high was one of the strongest factors independently associated with lower OS (HR, 2.61, 95% CI, 1.49 to 4.56, $P < .001$), along with high LDH (HR, 4.77, 95% CI, 2.77 to 8.19, $P < .001$), amp(1q) (HR, 1.94, 95% CI, 1.06 to 3.54, $P = .030$), and high-risk CA (HR, 2.53, 95% CI, 1.43 to 4.48, $P = .001$). Similarly, the cutoff value of 0.01% proposed by the companion study[26] confirmed that CTC-high was an independent prognostic factor (Data Supplement Table S6). Additionally, CTC showed a prognostic impact on the identification of patients at high risk for early relapse (Data Supplement Tables S7 and S8).

The achievement of MRD negativity before maintenance significantly reduced the risk of both progression/death and death, regardless of the treatment received at R1 (Table 2).

CTC-high maintained its prognostic impact on PFS and OS in all baseline risk subgroups (Figs 3A and 3B). Indeed, patients with CTC-high plus another baseline high-risk feature (high-risk CA, elevated LDH, or amp(1q)) had an even worse survival (Data Supplement Figs S9a-f). To consider the importance of each risk factor, we developed a prognostic nomogram including CTC value and established risk features to estimate PFS. For the sake of accuracy, a calibration plot with graphical comparisons between expected and observed PFS rates was also included (Data Supplement Figs S10 and S11).

The combined evaluation of CTC and R-ISS stage improved the prognostic assessment, especially in the large, but conceivably heterogeneous, R-ISS II group: patients with R-ISS II and CTC-high had PFS and OS rates similar to those in R-ISS III patients (Data Supplement Fig S12).

The only factor interfering with the prognostic impact of CTC levels on PFS was the achievement of MRD negativity (PFS: interaction $P = .039$). In the OS analysis, MRD-negative versus MRD-positive patients showed a better HR (1.63 [95% CI, 0.63 to 4.19] *v* 2.89 [95% CI, 1.50 to 5.57]), but the *P* value for interaction was not significant ($P = .311$; Figs 3A and 3B), potentially because of the low number of events in the OS analysis or because of an impact of outcome after relapse.

The combined evaluation of baseline CTC and pre-maintenance MRD status in a landmark analysis at 12 months from diagnosis showed that CTC-low MRD-negative patients

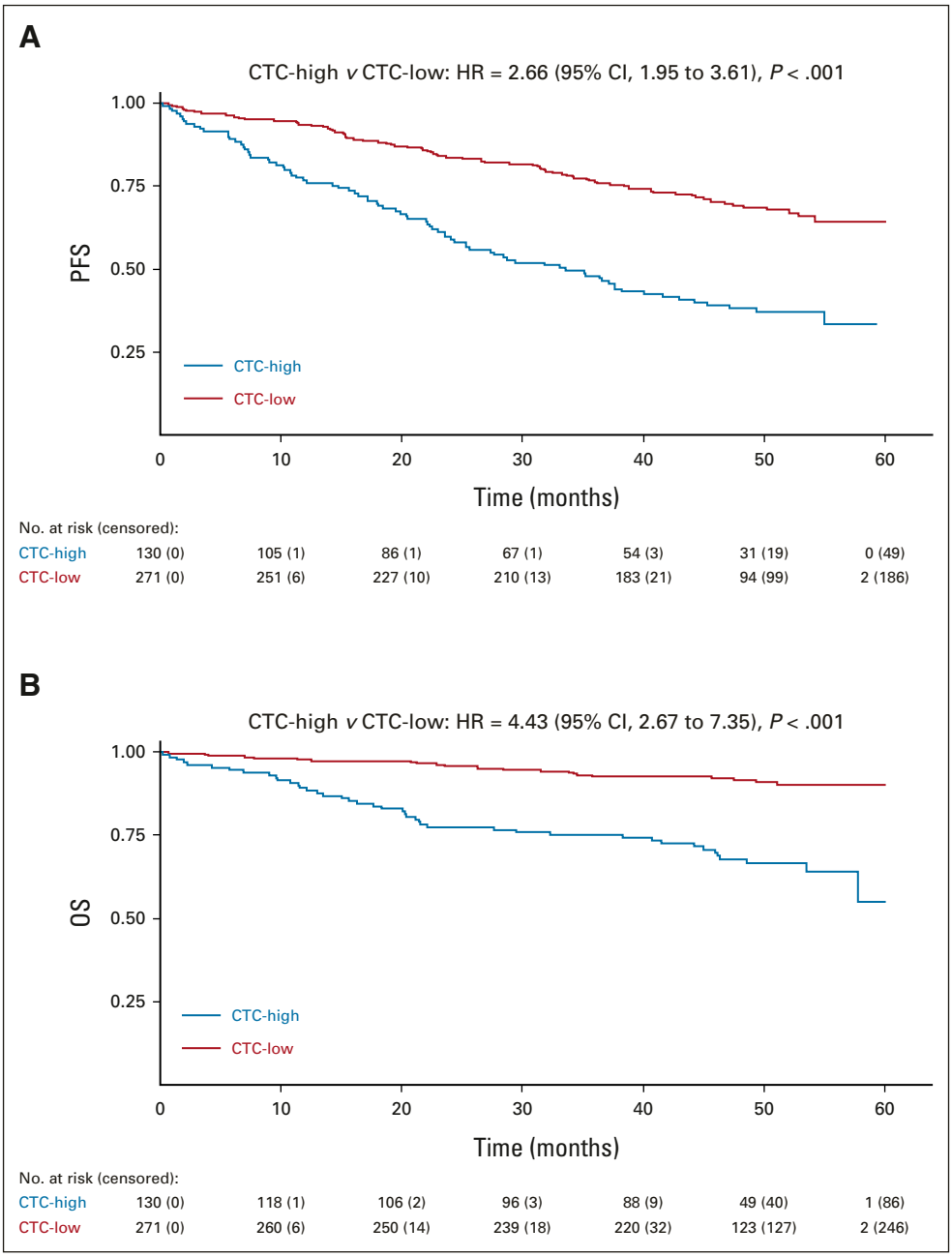

FIG 2. Kaplan-Meier estimates of (A) PFS and (B) OS according to CTC cutoff discriminating CTC-high and CTC-low patients (> 0.07% *v* ≤ 0.07%). CTC, circulating tumor plasma cells; CTC-high, CTC > 0.07%; CTC-low, CTC ≤ 0.07%; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

had the best prognosis (4-year PFS from diagnosis 78%, 95% CI, 71% to 85%; 4-year OS from diagnosis 96%, 95% CI, 93% to 99%), whereas CTC-high MRD-positive patients had a dismal outcome (4-year PFS 37%, 95% CI, 25% to 54%; 4-year OS 66%, 95% CI, 55% to 79%). Interestingly, CTC-high MRD-negative patients (4-year PFS 62%, 95% CI, 50% to 77%; 4-year OS 88%, 95% CI, 79% to 98%) and CTC-low MRD-positive patients (4-year PFS 67%, 95% CI, 58% to 79%; 4-year OS 89%, 95% CI, 83% to 96%) showed similar survival rates (Figs 4A and 4B).

We then investigated whether the more intensive therapeutic approach could improve survival in CTC-high patients. Despite the overall adverse outcome observed in CTC-high patients, treatment with KRd-ASCT led to an increase in PFS, compared with KRd12 and KCd-ASCT (4-year PFS: 58% with KRd-ASCT *v* 29% with KCd-ASCT *v* 34% with KRd12; Data Supplement Fig S13).

TABLE 2. Multivariable Cox Proportional Hazards Regression Analysis for PFS and OS

	PFS		OS	
Covariate	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
CTC cutoff				
CTC-high *v* CTC-low	2.11 (1.49 to 2.97)	< .001	2.61 (1.49 to 4.56)	< .001
ISS				
II/III *v* I	1.04 (0.74 to 1.46)	.812	1.08 (0.62 to 1.87)	.792
LDH				
High *v* low	2.22 (1.48 to 3.33)	< .001	4.77 (2.77 to 8.19)	< .001
CA				
High risk[a] *v* standard risk	1.33 (0.93 to 1.90)	.123	2.53 (1.43 to 4.48)	.001
amp(1q)				
Yes *v* no	2.03 (1.42 to 2.91)	< .001	1.94 (1.06 to 3.54)	.030
Depth of response				
MRD NEG *v* POS[b]	0.53 (0.37 to 0.75)	< .001	0.41 (0.23 to 0.73)	.002

Abbreviations: amp, amplification; CA, cytogenetic abnormalities; CTC, circulating tumor plasma cells; CTC-high, CTC > 0.07%; CTC-low, CTC ≤ 0.07%; del, deletion; HR, hazard ratio; ISS, International Staging System; ITT, intention-to-treat; LDH, lactate dehydrogenase; MFC, multiparameter flow cytometry; MRD, minimal residual disease; NEG, negativity; OS, overall survival; PFS, progression-free survival; POS, positivity; t, translocation.

[a]High-risk CA: high risk was defined as the presence of either del(17p), t(4;14), or t(14;16).

[b]Premaintenance ITT MRD by MFC (sensitivity of 10^{-5}).

DISCUSSION

In the past years, disease risk assessment in MM has greatly improved, because of the introduction of the R-ISS (including ISS, LDH, and high-risk CA),[5,9,10] the discovery of other specific CA[8] and, more recently, the development of complex genomic and gene expression analyses.[27-29] Nevertheless, some patients show dismal outcomes even without these high-risk features.[30] In this study, we demonstrated that the presence of high levels of MM cells in the peripheral blood (ie, CTC) is a strong and independent prognostic factor, in accordance with previously reported findings.[16-22]

The biological function of MM cells in the bloodstream has been actively investigated, although it remains a matter of debate. CTC showed the ability to give rise to other BM lesions, similarly to metastatic cancer cells, displaying a more proliferative potential when cocultured with BM stromal cells, compared with BMPC.[31] Besides, CTC, as well as cell-free DNA, display a genomic landscape similar to that of BMPC,[32-36] thus paving the way to a liquid biopsy approach to track the clonal evolution of the disease.[32,35]

Some open issues hinder the inclusion of CTC detection and quantification in the routine risk assessment at baseline: the absence of standardized methods and cutoff and the presence of evidence coming mainly from retrospective studies, without clean data from clinical trials including more attractive therapies.

In our analysis, we prospectively evaluated CTC by MFC (sensitivity of 4×10^{-5}) in the context of established static baseline and dynamic prognostic factors (namely MRD) in patients enrolled in the FORTE trial. We first confirmed the prognostic impact of CTC as a continuous variable, showing how their inclusion in a prognostic model with classic risk factors (ISS, cytogenetics, and LDH) led to a slight, but statistically significant, increase in predictive power. To create a simple prognostic tool, we proposed an optimal CTC cutoff (0.07%) to be used in clinical practice (similar to the 0.01% cutoff in the companion study),[26] which identified a CTC-high population with poor outcome (HR for progression/death 2.11 and HR for death 2.61). Of note, the use of CTC as a cutoff value did not reduce its prognostic impact, compared with its use as a continuous variable. To our knowledge, our contribution and its companion article[26] are the first studies in the field using MV analysis with internal validation for the cutoff identification.

Furthermore, CTC evaluation supported the correct classification of those patients who would otherwise have been misclassified as standard-risk patients: one of four (27%) presented with elevated CTC. Moreover, survival curves confirmed that CTC levels affected the outcome in patients with both standard-risk and high-risk features (Data Supplement Fig S9a). Additionally, elevated CTC seemed to be a strong predictor of early relapse, a hallmark of dismal outcome.

Currently, the R-ISS is widely accepted as a risk stratification system, but it is limited by the vast and heterogeneous population classified as R-ISS stage II. Two studies showed how the integration of CTC into the R-ISS could better define the prognosis of this subset of patients,[37,38] and this was confirmed in our analysis. In an attempt to improve the current scoring systems and better predict

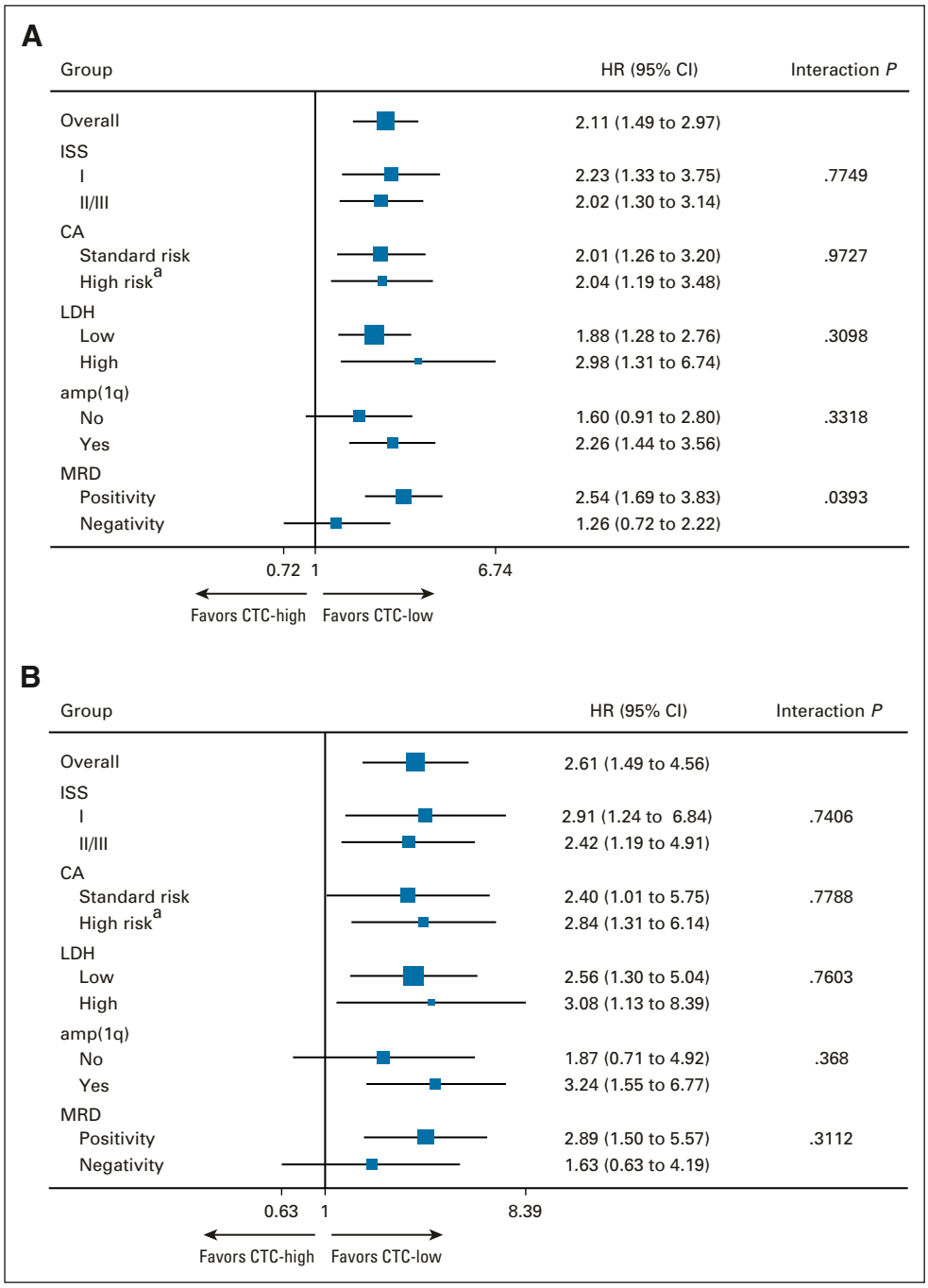

FIG 3. Subgroup analysis of (A) PFS according to CTC-high versus CTC-low (> 0.07 $v \leq 0.07\%$) and (B) OS according to CTC-high versus CTC-low (> 0.07 $v \leq 0.07\%$). [a]High-risk CA: high risk was defined as the presence of either del(17p), t(4;14), or t(14;16). amp, amplification; CA, cytogenetic abnormalities; CTC, circulating tumor plasma cells; CTC-high, CTC > 0.07%; CTC-low, CTC ≤ 0.07%; del, deletion; HR, hazard ratio; ISS, International Staging System; LDH, lactate dehydrogenase; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival; t, translocation.

PFS, we also developed a nomogram including the actual value of CTC and traditional features for risk assessment.

In our study, the achievement of BM MRD negativity was the only factor that modulated and partially abrogated the bad prognosis associated with CTC-high. This may be explained by several hypotheses, such as focal extramedullary residual disease not detected by BM MRD or low BM MRD sensitivity (10^{-5}). Our study has some limitations: a routine assessment of extramedullary disease was not performed at diagnosis;

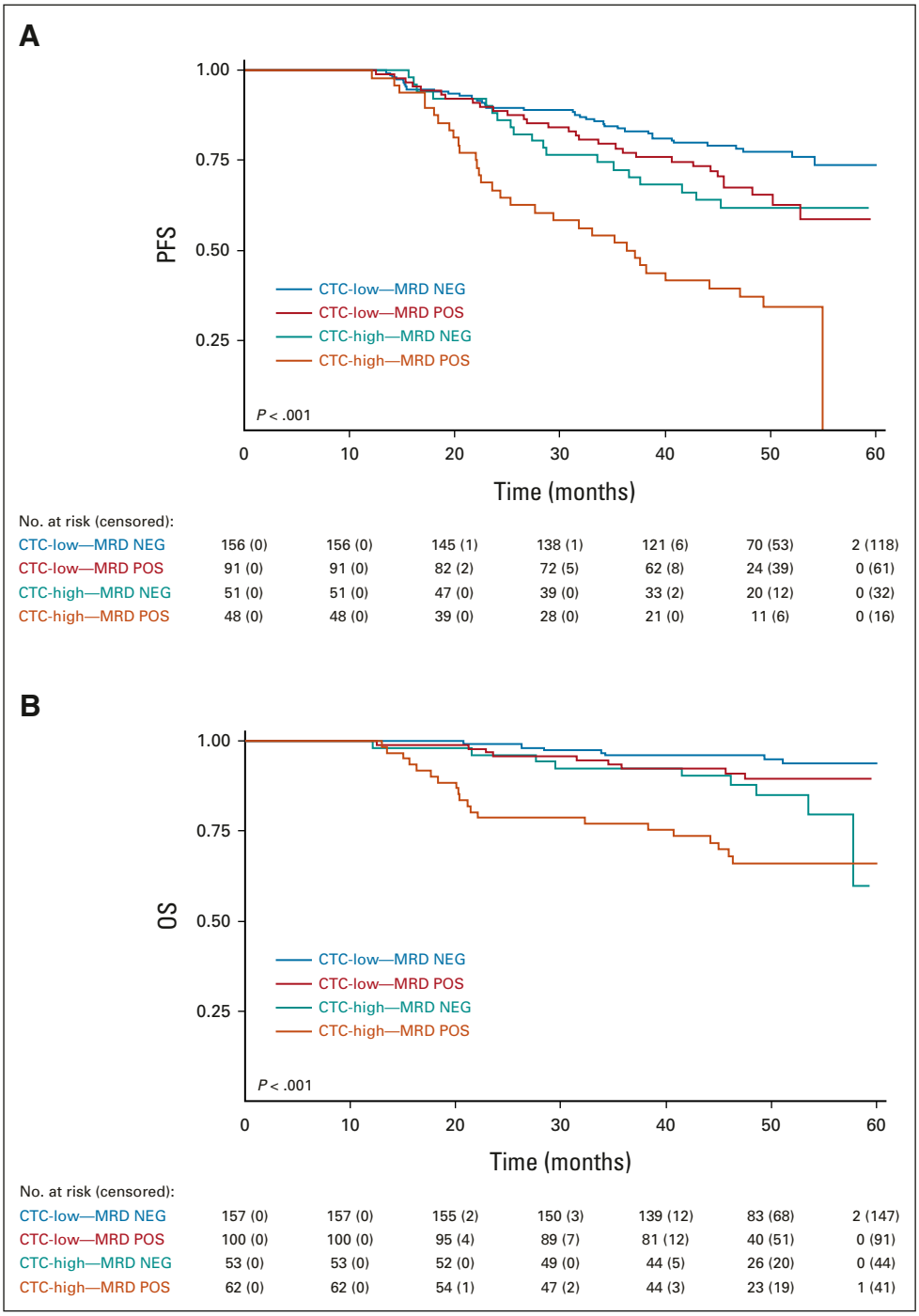

FIG 4. Kaplan-Meier estimates of (A) PFS and (B) OS according to CTC status at baseline and the achievement of premaintenance MRD negativity. CTC, circulating tumor plasma cells; CTC-high, CTC > 0.07%; CTC-low, CTC ≤ 0.07%; MRD, minimal residual disease; NEG, negativity; OS, overall survival; PFS, progression-free survival; POS, positivity.

imaging MRD by positron emission tomography-computed tomography was performed only in a subgroup of patients and was not included in this analysis[39]; and, finally, a serial longitudinal detection of CTC after therapy was not performed, whereas it could have been complementary to BM MRD detection.[40,41]

Along with the introduction of more effective therapies, the identification of high-risk patients becomes essential to correctly determine therapeutic intensity. Indeed, a recent meta-analysis showed that the inclusion of daratumumab in the first-line setting improved outcome in standard-risk, but not in high-risk, patients.[42] Thus, more intensive regimens are strongly

needed to treat high-risk patients; in this setting, preliminary results from the GMMG-CONCEPT trial (exploring isatuximab-KRd plus ASCT) and OPTIMUM/MUKnine trial (daratumumab-cyclophosphamide-bortezomib-lenalidomide-dexamethasone plus ASCT) reported amazing response rates and encouraging PFS rates.[43,44] In this light, we showed that a more intensive regimen with KRd-ASCT, compared with KRd12 and KCd-ASCT, led to better PFS rates in CTC-high patients. This was similarly reported for other established high-risk features.[45]

Recently, the International Myeloma Working Group updated and reduced from 20% to 5% the cutoff for the diagnosis of plasma cell leukemia.[46] Our study and its companion[26] showed that a lower threshold for the definition of high CTC levels by FC (0.01%-0.07%, ie, 100 times lower than 5%) was associated with a poor prognosis. Moreover, the two research groups reproduced each other's findings in the context of two important prospective trials including highly effective modern drug combinations (ie, proteasome inhibitors, immunomodulatory drugs, ASCT, and maintenance), and the slight difference between the two cutoffs was likely because of differences in patient treatment (carfilzomib-based *v* bortezomib-based), in the FC sensitivity, and, probably, in the number of patients with high CTC levels. Indeed, the proportion of patients with undetectable CTC was higher in our data set than in the companion data set (33% *v* 8%), likely because of the lower sensitivity (4×10^{-5}) compared with next-generation flow (2×10^{-6}). Nonetheless, a second-generation flow method, as in our analysis, may be widely implemented, while next-generation flow (which will become the preferred technique in the future) is not currently performed in routine clinical practice because of its high cost and time-consuming technology.

In conclusion, the presence of high CTC levels assessed by a simple and widely available FC is one of the most prognostic baseline features and is partially modulated by the achievement of MRD negativity following highly effective anti-MM treatment.

We believe that these data can open the way to the incorporation of CTC into a wider clinical use for the routine diagnosis of patients with MM. Future analyses of larger cohorts (including transplant-ineligible patients, patients treated with anti-CD38 monoclonal antibodies, and real-life patients) will help overcome the differences between our study and its companion study, to identify a definitive cutoff. This will be the next step for the implementation of CTC in comprehensive staging systems and risk-adapted therapeutic approaches.

AFFILIATIONS

[1]SSD Clinical Trial in Oncoematologia e Mieloma Multiplo, Division of Hematology, University of Torino, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Torino, Italy
[2]Multidisciplinary Oncology Outpatient Clinic, Candiolo Cancer Institute, FPO – IRCCS, Torino, Italy
[3]Division of Hematology, ASST Papa Giovanni XXIII, Bergamo, Italy
[4]Clinica di Ematologia, AOU Ospedali Riuniti di Ancona, Ancona, Italy
[5]Hematology and Bone Marrow Transplant Unit, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, University of Milan, Milan, Italy
[6]Ematologia/CTMO, Ospedale "A. Businco," Cagliari, Italy
[7]Hematology Unit, AO of Cosenza, Cosenza, Italy
[8]Ematologia, Azienda Sanitaria Universitaria Giuliano Isontina, Trieste, Italy
[9]Hematology and Stem Cell Transplantation Unit, IRCCS Centro di Riferimento Oncologico della Basilicata, Rionero in Vulture, Italy
[10]UOC Ematologia, Ospedale dell'Angelo, Venezia Mestre, Italy
[11]Hematology Unit, Infermi Hospital, Rimini, Italy
[12]Unit of Hematology and Stem Cell Transplantation, AOUC Policlinico, Bari, Italy
[13]UOC Ematologia e Terapia cellulare, Ospedale C. e G. Mazzoni, Ascoli Piceno, Italy
[14]Hematology and Stem Cell Transplant Unit, IRCCS Regina Elena National Cancer Institute, Rome, Italy
[15]Unit of Hematology, Stem Cell Transplantation, University Campus Bio-Medico, Rome, Italy
[16]SC Ematologia, Azienda Ospedaliera SS. Antonio e Biagio e Cesare Arrigo, Alessandria, Italy
[17]Università degli Studi di Perugia, Azienda Ospedaliera Santa Maria, Terni, Italy
[18]Division of Hematology, Cardarelli Hospital, Napoli, Italy
[19]Dipartimento di Scienze Mediche e Chirurgiche Materno Infantili e dell'Adulto, UNIMORE, UOC Ematologia, Azienda Ospedaliero-Universitaria di Modena, Modena, Italy
[20]Department of Medicine (DIMED), Hematology and Clinical Immunology Section, Padova University School of Medicine, Padova, Italy
[21]Hematology, Department of Translational and Precision Medicine, Azienda Ospedaliera Policlinico Umberto I, Sapienza University of Rome, Rome, Italy
[22]Department of Hematology, ASST Spedali Civili di Brescia, Brescia, Italy
[23]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli," Bologna, Italy
[24]Department of Emergency and Organ Transplantation, "Aldo Moro" University School of Medicine, Bari, Italy

CORRESPONDING AUTHOR

Francesca Gay, MD, PhD, SSD Clinical Trial in Oncoematologia e Mieloma Multiplo, Division of Hematology, University of Torino, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, via Genova 3, 10126 Torino, Italy; e-mail: francesca.gay@unito.it.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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DATA SHARING STATEMENT

After the publication of this article, data collected for this analysis and related documents will be made available to others upon reasonably justified request, which needs to be written and addressed to the attention of the corresponding author Dr Francesca Gay at the following e-mail address: francesca.gay@unito.it. The sponsor of the trial, the University of Torino (Italy), via the corresponding author Dr Francesca Gay, is responsible to evaluate and eventually accept or refuse every request to disclose data and their related documents, in compliance with the ethical approval conditions, in compliance with applicable laws and regulations, and in conformance with the agreements in place with the involved subjects, the participating institutions, and all the other parties directly or indirectly involved in the participation, conduct, development, management, and evaluation of this analysis.

AUTHOR CONTRIBUTIONS

Conception and design: Luca Bertamini, Stefania Oliva, Mario Boccadoro, Francesca Gay

Provision of study materials or patients: Delia Rota-Scalabrini, Laura Paris, Paolo Corradini, Giovanni De Sabbata, Giuseppe Pietrantuono, Anna Pascarella, Patrizia Tosi, Paola Curci, Milena Gilestro, Federico Monaco, Anna Marina Liberati, Salvatore Palmieri, Mario Luppi, Renato Zambello, Pellegrino Musto

Collection and assembly of data: Luca Bertamini, Stefania Oliva, Delia Rota-Scalabrini, Sonia Morè, Paolo Corradini, Antonio Ledda, Massimo Gentile, Giovanni De Sabbata, Giuseppe Pietrantuono, Anna Pascarella, Paola Curci, Milena Gilestro, Piero Galieni, Francesco Pisani, Ombretta Annibali, Federico Monaco, Anna Marina Liberati, Salvatore Palmieri, Mario Luppi, Renato Zambello, Francesca Fazio, Angelo Belotti, Paola Tacchetti, Pellegrino Musto, Francesca Gay

Data analysis and interpretation: Luca Bertamini, Stefania Oliva, Laura Paris, Patrizia Tosi, Milena Gilestro, Andrea Capra, Anna Marina Liberati, Mario Luppi, Renato Zambello, Francesca Fazio, Francesca Gay

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

High Levels of Circulating Tumor PC as a Key Hallmark of Aggressive Disease in Transplant-Eligible Patients With NDMM

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Stefania Oliva
Honoraria: Amgen, Celgene/Bristol Myers Squibb, Janssen
Consulting or Advisory Role: Adaptive Biotechnologies, Janssen, Amgen, Takeda

Laura Paris
Honoraria: Celgene/Bristol Myers Squibb, Takeda, Amgen, Janssen Oncology
Consulting or Advisory Role: Celgene/Bristol Myers Squibb, Amgen, Janssen Oncology
Travel, Accommodations, Expenses: Celgene/Bristol Myers Squibb, Janssen Oncology, Takeda

Paolo Corradini
Honoraria: AbbVie, Amgen, Celgene, Daiichi Sankyo, Gilead Sciences, Kite, a Gilead company, Janssen, KiowaKirin, Novartis, Roche, Sanofi, Takeda
Consulting or Advisory Role: AbbVie, Amgen, Celgene, Daiichi Sankyo, Gilead Sciences, Incyte, Janssen, Jazz Pharmaceuticals, Kite/Gilead, KiowaKirin, Novartis, Roche, Sanofi, Takeda, Nerviano Medical Sciences
Travel, Accommodations, Expenses: AbbVie, Celgene, Gilead Sciences, Janssen, Kite, a Gilead company, Novartis, Takeda

Federico Monaco
Honoraria: Takeda, Amgen
Consulting or Advisory Role: Takeda, Amgen, GlaxoSmithKline

Anna Marina Liberati
Consulting or Advisory Role: Servier
Research Funding: Novartis (Inst), Janssen-Cilag (Inst), AbbVie (Inst), Roche (Inst), Amgen (Inst), Sanofi (Inst), Celgene (Inst), Bristol Myers Squibb (Inst), Takeda (Inst), Incyte (Inst), Beigene (Inst), Oncopeptides (Inst), Verastem (Inst), Karyopharm Therapeutics (Inst), Archigen Biotech (Inst), Debiopharm Group (Inst), MorphoSys (Inst), FibroGen (Inst), Onconova Therapeutics (Inst)
Travel, Accommodations, Expenses: Bristol Myers Squibb, Sanofi, Takeda, Roche, Celgene, Novartis, AbbVie, IQVIA, Verastem

Salvatore Palmieri
Honoraria: Amgen, Celgene/Bristol Myers Squibb, Janssen, Sanofi, Takeda
Consulting or Advisory Role: Celgene/Bristol Myers Squibb, Amgen

Mario Luppi
Honoraria: Gilead Sciences, Daiichi Sankyo/Lilly, AbbVie, MSD, Novartis, Jazz Pharmaceuticals, Sanofi
Travel, Accommodations, Expenses: Gilead Sciences

Renato Zambello
Consulting or Advisory Role: Celgene, Janssen, GlaxoSmithKline, Takeda, Amgen

Francesca Fazio
Honoraria: Janssen Oncology

Angelo Belotti
Consulting or Advisory Role: Amgen, Celgene, GlaxoSmithKline, Janssen Oncology, Takeda

Paola Tacchetti
Honoraria: Janssen-Cilag, Amgen, Takeda, Oncopeptides, AbbVie, GlaxoSmithKline, Sanofi, Bristol Myers Squibb/Celgene
Consulting or Advisory Role: Amgen, Takeda, Janssen-Cilag, Bristol Myers Squibb/Celgene, Sanofi
Travel, Accommodations, Expenses: Janssen-Cilag, Celgene, Amgen, Sanofi

Pellegrino Musto
Honoraria: Celgene/Bristol Myers Squibb, Janssen, Amgen, Sanofi, Takeda, GlaxoSmithKline

Mario Boccadoro
Honoraria: Sanofi, Celgene, Amgen, Janssen, Novartis, Bristol Myers Squibb, AbbVie
Consulting or Advisory Role: Janssen, GlaxoSmithKline
Research Funding: Sanofi (Inst), Celgene (Inst), Amgen (Inst), Janssen (Inst), Novartis (Inst), Bristol Myers Squibb (Inst), Mundipharma (Inst)

Francesca Gay
Honoraria: Amgen, Celgene, Janssen, Takeda, Bristol Myers Squibb, AbbVie, GlaxoSmithKline
Consulting or Advisory Role: Amgen, Celgene, Janssen, Takeda, Bristol Myers Squibb, AbbVie, GlaxoSmithKline, Roche, Adaptive Biotechnologies, Oncopeptides, bluebird bio, Pfizer

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