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ORIGINAL REPORT

Continuous Therapy Versus Fixed Duration of Therapy in Patients With Newly Diagnosed Multiple Myeloma

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ABSTRACT

Purpose
Continuous therapy (CT) prolongs progression-free survival 1 (PFS1; time from random assignment until the first progression or death), but chemotherapy-resistant relapse may negatively impact overall survival (OS). Progression-free survival 2 (PFS2; time from random assignment until the second progression or death) may represent an additional tool to estimate outcome. This study evaluates the benefit of novel agent–based CT versus fixed duration of therapy (FDT) in patients with newly diagnosed myeloma.

Methods
We included patients enrolled onto three phase III trials that randomly assigned patients to novel agent–based CT versus FDT. Primary analyses were restricted to the intent-to-treat population eligible for CT (patients progression free and alive at 1 year after random assignment). Primary end points were PFS1, PFS2, and OS. All hazard ratios (HRs) and 95% CIs were adjusted for several potential confounders using Cox models.

Results
In the pooled analysis of the three trials, 604 patients were randomly assigned to CT and 614 were assigned to FDT. Median follow-up was 52 months. In the intent-to-treat CT population, CT (n = 417), compared with FDT (n = 410), significantly improved PFS1 (median, 32 *v* 16 months, respectively; HR, 0.47; 95% CI, 0.40 to 0.56; $P < .001$), PFS2 (median, 55 *v* 40 months, respectively; HR, 0.61; 95% CI, 0.50 to 0.75; $P < .001$), and OS (4-year OS, 69% *v* 60%, respectively; HR, 0.69; 95% CI, 0.54 to 0.88; $P = .003$).

Conclusion
In this pooled analysis, CT significantly improved PFS1, PFS2, and OS. The improvement in PFS2 suggests that the benefit reported during first remission is not cancelled by a shorter second remission. PFS2 is a valuable end point to estimate long-term clinical benefit and should be included in future trials.

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INTRODUCTION

Multiple myeloma (MM) is a plasma cells disorder that accounts for approximately 13% of all hematologic cancers.[1] In Europe, melphalan-prednisone (MP) plus thalidomide (MPT) or bortezomib is the standard of care for transplantation-ineligible patients with newly diagnosed MM (NDMM).[2-4] In transplantation-eligible patients, a novel agent–based induction followed by high-dose therapy and autologous stem-cell transplantation (ASCT) is the standard approach.[5] Several studies evaluated the impact of continuous therapy (CT) in MM. CT aims to maintain the results of first-line therapy by keeping the patient symptom free and preventing or delaying tumor progression and, ultimately, death.[6] In patients ineligible for high-dose therapy, MP plus lenalidomide followed by lenalidomide maintenance significantly increased progression-free survival (PFS) compared with MP plus lenalidomide and MP, but no differences in overall survival (OS) were reported.[7] Bortezomib-melphalan-prednisone-thalidomide followed by bortezomib-thalidomide maintenance significantly prolonged PFS and OS compared with bortezomib-melphalan-prednisone.[8,9] Continuous lenalidomide and

low-dose dexamethasone significantly increased PFS and OS compared with MPT.[10] In patients who received ASCT, post-transplantation lenalidomide maintenance improved PFS by at least 50%, with conflicting results in terms of OS.[11-14]

Despite the recent encouraging results, most patients with MM eventually experience relapse. Initial therapy may affect the tumor drug-resistance profile; there is some concern that patients who experience progression while on CT may become resistant to at least that therapy. In MM, similarly to other cancers, the occurrence of resistant relapse may reduce the duration of subsequent remissions, with negative impact on OS. OS is a clinically relevant outcome that is simple to measure and easy to interpret and includes the impact of subsequent therapies. However, the evaluation of OS often requires an extended follow-up. In 2012, the European Medicines Agency recommended to include a PFS2 end point to evaluate the impact of CT on outcome.[15] PFS1 is defined as the time from random assignment until the first disease progression (PD1) or death, whereas PFS2 is defined as the time from random assignment until the second disease progression (PD2) or death, estimating the impact of both first- and second-line therapies on outcome. Because PFS2 is able to capture possible negative effects on next-line therapy, the evaluation of PFS2 instead of PFS1 in studies assessing the net long-term benefit of CT can be a valuable option.

This pooled analysis including individual patient data (IPD) of three randomized trials aims to evaluate the impact of CT versus fixed duration of therapy (FDT) on time-to-event end points, particularly on PFS2 and OS, in patients with NDMM treated with novel agents.

METHODS

Patients and Treatment

For this pooled analysis, we selected three phase III trials (Italian Group for Hematologic Diseases in Adults [GIMEMA] -MM-03-05, RV-MM-PI-209, and CC-5013-MM-015) coordinated by the same principal investigator.[7-9,14] In the three studies, patients with NDMM were randomly assigned to CT or FDT with novel agents (thalidomide, lenalidomide, or bortezomib), patients received novel agents from diagnosis, PFS2 data were available, and the follow-up time was adequate for our analysis (median time, > 4 years). Details of the inclusion criteria and treatment regimens of the source studies have been previously published (Appendix Table A1, online only). FDT was defined as an up-front treatment (induction/consolidation) for up to 1 year. CT was defined as an up-front therapy (induction/consolidation) followed by maintenance lasting at least 2 years. Both definitions were based on the intent-to-treat (ITT) population. For completeness, in Appendix Table A2 (online only), we describe the other phase III trials comparing CT versus FDT that were excluded from our analysis, highlighting the differences with the three trials included.

Clinical End Points

The primary study end points were PFS1, PFS2, and OS in the ITT population eligible for CT versus FDT (ITT-CT), according to the random assignment. Because patients were randomly assigned at study entry, to approximate the ITT-CT population and to assess more specifically the effect of CT, in the primary comparative analyses, we included all patients alive and progression free after 12 months from random assignment, which corresponds to the average duration of induction/consolidation in the three trials (landmark analysis). For the primary analyses, on the basis of the ITT-CT population, all time-to-event end points were calculated from the time of inclusion in the landmark analysis. For descriptive purposes and to account for failures that occurred during the induction/consolidation, we also provided survival probability estimates since the patients' random assignment.

PFS1 was calculated from random assignment until the date of PD1 or death. PFS2 was calculated from random assignment until the date of PD2, start of third-line therapy if date of PD2 was not available, or death.[15] Disease progression was defined according to standard criteria.[16,17] Patients who did not experience progression/death at the cutoff date (after their first- or second-line therapy) were censored at the last date they were known to be in remission or alive (if response assessment on second-line therapy was not available). OS was calculated until the date of death or censored at the date the patient was last known to be alive. Detailed definitions of end points are provided in the Appendix (online only).

Statistical Analysis

Data of the three trials were pooled together and analyzed. Patients randomly assigned to the MP arm in the CC-5013-MM-015 trial were excluded because they did not receive novel agents up front.[13] All other patients enrolled onto the three trials were included in the descriptive analyses, but only those alive and progression free after 12 months from random assignment were included in the ITT-CT population. Survival curves were estimated according to the Kaplan-Meier method.

Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) and the 95% CIs in the ITT-CT population. To account for potential confounders, the comparisons between CT and FDT were adjusted for the trial effect (and for specific induction/consolidation therapies if they differed within the trial), sex, age, International Staging System stage, cytogenetic profile, and Karnofsky performance status. Subgroup analyses were performed to determine the consistency of treatment effects of CT versus FDT between different subgroups (detailed in the Appendix) using interaction terms between treatment and each of the covariates included in the Cox model. We did a sensitivity analysis excluding one trial at a time. All HRs were estimated with their 95% CIs and two-sided *P* values. Data were analyzed as of May 2014 using STATA 11.2 (StataCorp, College Station, TX).

RESULTS

Patients

The three trials randomly assigned 1,372 patients with NDMM to treatment. The GIMEMA-MM-03-05 and CC-5013-MM-015 studies enrolled patients ineligible for ASCT; the RV-MM-PI-209 study randomly assigned patients eligible for ASCT. One hundred fifty-four patients in the CC-5013-MM-015 study randomly assigned to MP were excluded from our analysis. The remaining 1,218 patients were included in the descriptive analysis to estimate the survival probability since diagnosis for PFS1, PFS2, and OS; 604 patients in the three studies were randomly allocated to CT, and 614 were assigned to FDT. A total of 417 CT patients and 410 FDT patients were included in the ITT-CT population for comparative analyses (Fig 1). Patient demographics and disease characteristics in the two groups were well balanced at enrollment and in the ITT-CT population (Table 1). At data cutoff, 145 patients in the CT arm versus 90 patients in the FDT arm were on study, either on maintenance or progression free after treatment discontinuation. The median estimated duration of maintenance was 22 months. The main reasons for maintenance discontinuation in the CT group were progression (42%) and adverse events (AEs) (12%). In the FDT group, during the observation after induction/consolidation, 70% of patients experienced progression and 2% experienced AEs.

PFS1, PFS2, and OS Analyses

The median follow-up time for survivors was 52 months (minimum, 51 months in the MM-RV-PI-209 trial; maximum, 62 months in the CC-5013-MM-015 trial). In the overall population of patients

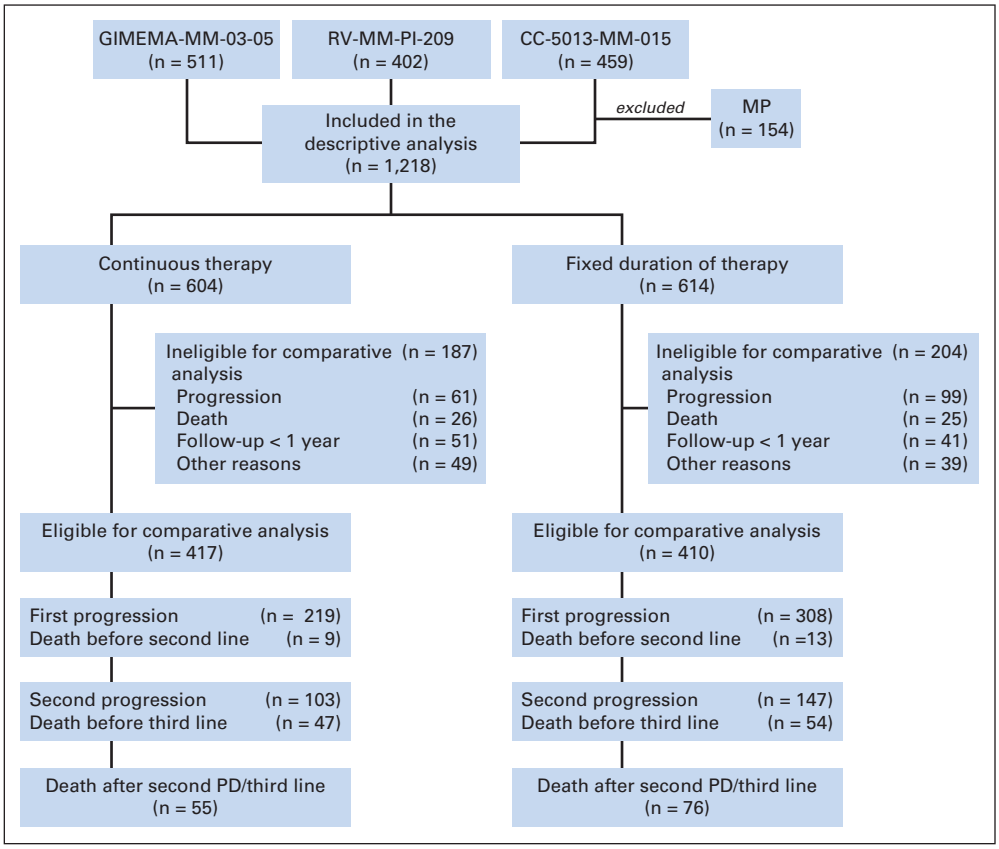

Fig 1. Study flow. Other reasons for ineligibility include stopping treatment for toxicity, consent withdrawn, medical decision, loss to follow-up, and no available data on remission status at 1 year from enrollment. GIMEMA, Italian Group for Hematologic Diseases in Adults; MP, melphalan and prednisone; PD, disease progression.

included in the descriptive analysis (n = 1,218), the 4-year PFS1 from random assignment was 38% (95% CI, 34% to 43%) in CT patients and 16% (95% CI, 12% to 19%) in FDT patients; the 4-year PFS2 from random assignment was 55% (95% CI, 51% to 59%) in CT patients and 43% (95% CI, 39% to 48%) in FDT patients; and the 4-year OS from random assignment was 69% (95% CI, 65% to 73%) in CT patients and 61% (95% CI, 57% to 65%) in FDT patients (Appendix Table A3 and Fig A1, online only).

In the ITT-CT population (n = 827), the median PFS1 from landmark point was 32 months with CT versus 16 months with FDT. CT significantly reduced the risk of PD1 or death compared with FDT (HR, 0.47; 95% CI, 0.40 to 0.56; $P < .001$; Fig 2A). The advantage of CT versus FDT was consistent across all patient subgroups, including trial and induction/consolidation treatment, even if a stronger effect is suggested for the MM-015 trial (HR, 0.29; 95% CI, 0.20 to 0.44; $P = .055$ for interaction; Fig 3A).

The median PFS2 from landmark point was 55 months with CT versus 40 months with FDT; CT significantly reduced the risk of PD2 or death compared with FDT (HR, 0.61; 95% CI, 0.50 to 0.75; $P < .001$; Fig 2B). The benefit of CT versus FDT was evident in all of the subgroups according to trial and induction/consolidation treatment ($P = .861$ for interaction) and in most of the analyzed subgroups according to baseline features, with a possible weaker effect on women (Fig 3B).

The 4-year OS rate from landmark point was 69% with CT versus 60% with FDT; CT significantly reduced the risk of death compared with FDT (HR, 0.69; 95% CI, 0.54 to 0.88; $P = .003$; Fig 2C). The statistical power of the subgroup analysis of OS was limited by the low number of events, but the benefit of CT versus FDT was confirmed in all of the subgroups according to trial and induction/consolidation treatment ($P = .703$ for interaction); regarding baseline features, a weaker effect was estimated for women ($P = .054$ for interaction) and in patients with a Karnofsky performance status of 90% to 100% ($P = .059$ for interaction; Fig 3C). The point estimates of the HRs in favor of CT versus FDT for PFS1, PFS2, and OS were confirmed in the sensitivity analysis after exclusion of each single trial (Appendix Table A4, online only).

Outcomes After First Relapse

Overall, 280 CT patients (46%) and 407 FDT patients (66%) experienced PD1. Ninety percent of patients who experienced relapse in the CT group and 88% of patients who experienced relapse in the FDT group received second-line therapy. In the ITT-CT group, 219 CT patients and 308 FDT patients experience PD1. Of note, the patients included in this analysis are unbalanced in numbers because a higher number of patients experienced relapse in the FDT. Overall, types of second-line therapy were well balanced between CT and FDT patients (approximately 40% of patients in each group received bortezomib or immunomodulatory drug–based treatment) but differed between the treatment arms in the three trials (Appendix Fig A2, online only).

DISCUSSION

Several trials have shown a remarkable risk reduction in progression and death with CT in young and elderly patients with NDMM, but this

Table 1. Baseline Patient Characteristics in the Population of Patients Included in the Descriptive Analyses and in the ITT-CT Population of Patients Included in the Primary Analyses

Characteristic	Overall Population of Patients Included in the Descriptive Analyses				Overall Population of Patients Included in the ITT-CT Population			
	CT (n = 604)		FDT (n = 614)		CT (n = 417)		FDT (n = 410)	
	No.	%	No.	%	No.	%	No.	%
Age, years								
Median	68		69		68		68	
Interquartile range	62-73		62-74		61-73		61-73	
Male sex	307	51	317	52	218	52	215	52
Karnofsky performance status								
60%-70%	168	28	141	23	112	27	86	21
80%	137	23	173	28	82	20	111	27
90%-100%	299	50	300	49	223	53	213	52
International Staging System stage*								
I	185	33	182	33	140	37	143	39
II	203	37	197	35	148	39	130	35
III	168	30	179	32	93	24	98	26
Missing values	48		56		36		39	
Cytogenetic abnormalities*								
del 13	212	50	206	48	139	47	136	47
del 17	53	12	56	13	28	9	35	12
t(11;14)	68	16	58	14	47	16	40	14
t(4;14)	61	14	48	11	44	15	34	12
t(14;16)	16	4	14	3	13	4	8	3
del 17, t(4;14), or t(14;16)	106	25	105	25	68	23	69	24
Missing values	172		188		122		119	
Protocol								
GIMEMA-MM-03-05[8,9]	254	42	257	42	200	48	191	47
RV-MM-PI-209[14]	198	33	204	33	137	33	142	35
CC-5013-MM-015[7]	152	25	153	25	80	19	77	19

Abbreviations: CT, continuous therapy; FDT, fixed duration of therapy; GIMEMA, Italian Group for Hematologic Diseases in Adults; ITT, intent-to-treat.
*Percentage calculated using number of patients whose data were available.

clinically relevant benefit did not always translate into an OS improvement (Appendix Table A5, online only).[7-14,18-25] Some concerns have emerged about drug resistance with CT, which may negatively impact on the efficacy of next-line therapy and OS. This potential concern and the balance between efficacy and toxicity have to be carefully assessed before recommending CT as standard approach. The European Medicines Agency has recently suggested including the PFS2 end point in trials exploring the role of CT.[15] PFS2, which incorporates the treatment effects of first- and second-line therapy, can be informative on drug resistance and should be evaluated as a longer term efficacy end point than PFS1.

In our pooled analysis of IPD from three randomized trials, CT significantly prolonged the median PFS1 and PFS2 by approximately 1 year and improved OS by approximately 10%. Our findings suggest that most of the PFS1 advantage associated with CT up front is maintained after first relapse and that CT does not induce a significant chemotherapy resistance. The concept of a long-term operational cure demonstrated with continuous imatinib treatment in chronic myeloid leukemia might be applicable in MM.[26] Published studies on CT in MM have different study designs and patient populations; thus, it is difficult to make cross-trial comparisons. Preliminary results of the MM-020 trial showed an improvement in PFS1, PFS2, and OS for transplantation-ineligible patients with NDMM receiving continuous lenalidomide and low-dose dexamethasone compared with MPT.[10] In the Cancer and Leukemia Group B 100104 trial, lenalidomide maintenance improved PFS1 and OS in patients who received transplantation, but PFS2 was not assessed.[11] In the Intergroupe Francophone du Myelome 2005-02 trial, lenalidomide maintenance improved PFS1, but not OS; a trend toward a better PFS2 for patients receiving maintenance was noticed.[13] Previous studies exploring the role of thalidomide CT showed an improvement in PFS1, with conflicting OS results. However, most of the trials compared thalidomide CT versus FDT without novel agents, and no data on PFS2 were available (Appendix Tables A2 and A5).[19-25,27,28] Meta-analyses of published data indicate a survival advantage for CT with thalidomide/lenalidomide.[29,30]

In all studies, PFS1 improvement correlated with PFS2 improvement, although it inconsistently correlated with OS. Treatment choice at relapse is determined by several factors (eg, performance status; type, response, and toxicity of previous therapy; physician's choice; availability of clinical trials). Accordingly, second-line treatments differed in the three trials. Similarly, treatments administered after second-line therapy may be extremely variable. Multiple effective salvage therapies are available, including regimens that have shown remarkable OS benefit, and this may explain the inconsistent OS improvement reported in the source trials.

The three trials included in this pooled analysis evaluated different types of CT and different patient populations, eligible and

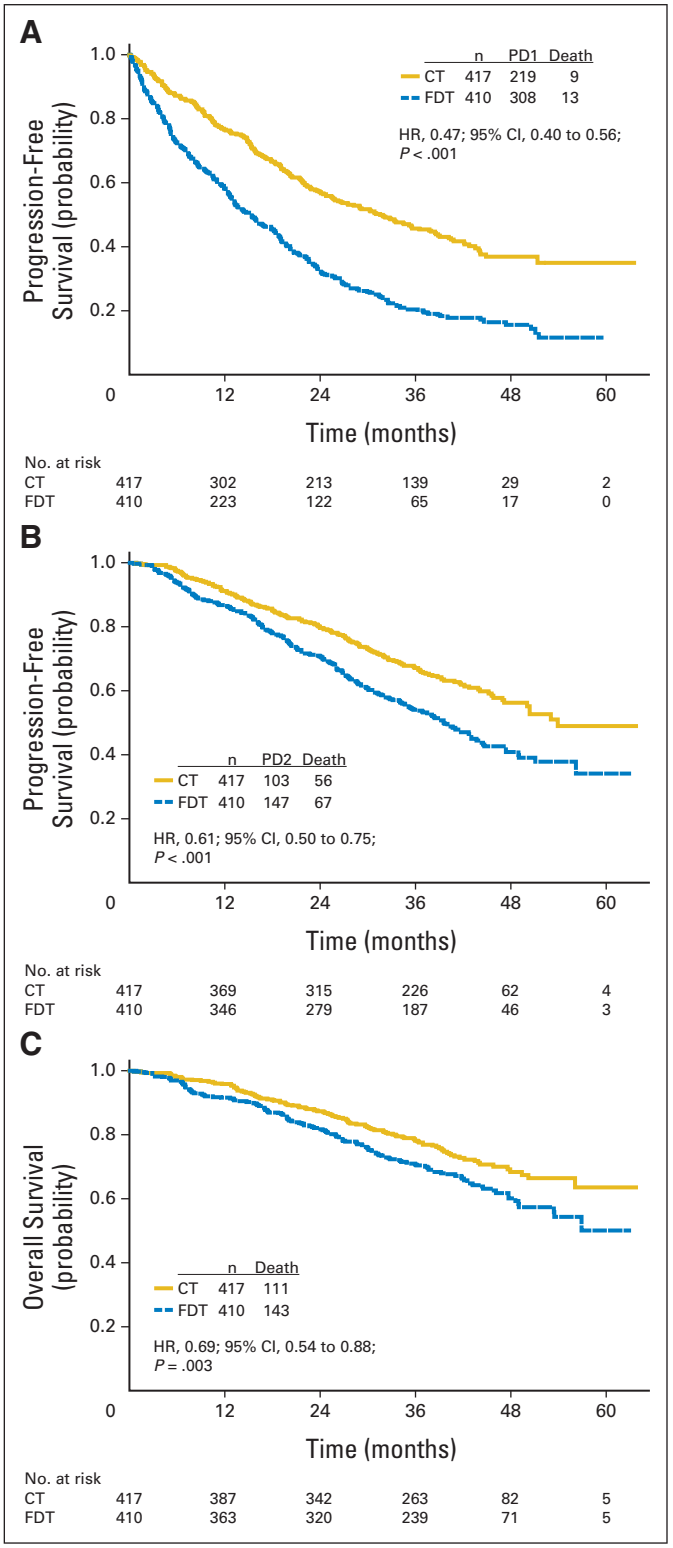

Fig 2. (A) Progression-free survival (PFS) 1, (B) PFS2, and (C) overall survival in the intent-to-treat population eligible for continuous therapy (CT) randomly assigned to receive CT versus fixed duration of therapy (FDT). HR, adjusted hazard ratio; PD1, first disease progression; PD2, second disease progression.

ineligible for transplantation.[7-9,14] This variability was managed through a careful adjustment, including the trial effect and the induction treatment, and with a sensitivity analysis by removing one trial at a time. The analyses confirmed the benefit of CT on PFS1 and PFS2, without meaningful differences for most of the comparisons. In the subgroup analysis of OS, all estimates of the HRs were in favor of CT. However, the subgroup analysis of OS is limited by the low number of events and, therefore, has a limited statistical power to detect small or medium heterogeneity between strata.

The safety profile was different according to the patient population analyzed and the treatment administered. In the context of the significant PFS1 gain associated with CT, the risk/benefit profile of CT remained positive in all of the source studies.[7-9,14] In the pooled analysis, discontinuation for AEs during induction/consolidation was similar in the two groups (data not shown). After induction/consolidation, the discontinuation rate for AEs was 12% in CT patients (maintenance treatment) and 2% in FDT patients (no treatment administered). This difference did not negatively affect efficacy, confirming the overall benefit of CT. Concerns arose about the possible long-term toxicity of CT, which could prevent patients from receiving treatment at relapse. In our study, 90% of patients who experienced relapse in both groups received a second-line therapy, suggesting that CT did not induce significant long-term toxicity.

Including PFS2 as one of the primary end points in randomized clinical trials has many advantages. PFS2 assesses the impact of two lines of therapy over a longer time period, whereas PFS1 evaluates first-line therapy only. The PFS2 analysis produces more conservative results; patients who have not experienced progression after first-line therapy are censored, as are patients who have experienced progression after their first-line therapy but not yet after second-line therapy. Similarly to PFS1 and OS, PFS2 includes all randomly assigned patients. In contrast, outcomes like second PFS or OS from relapse are intrinsically biased because they are based on the subset of patients who experienced first relapse (approximately 60% in our analysis). These patients are generally considered as having a poor prognosis, because usually early progression is associated with a more aggressive disease. Nevertheless, the analysis of second PFS or OS from relapse (see Appendix) excludes patients who never experienced relapse (underestimating the positive impact on outcome of first-line therapy, in particular in good-prognosis patients) as well as those who died before second-line therapy (underestimating the effects of toxicity and aggressive progressive disease that may lead to death).

In our study, in the PFS1 analysis, only 4% of the events were deaths. In the PFS2 analysis, this percentage was considerably higher (29%). Determining whether PFS1 or PFS2 could be valid surrogates for OS was not an objective of our analysis; however, the longer follow-up and the higher proportion of deaths included as events in the PFS2 analysis suggests that PFS2 is an end point closer to OS than PFS1. Therefore, PFS2 could be a preferable primary end point to PFS1, particularly in effectiveness trials and when there is a concern that the advantage of a first-line treatment could be lost after the first relapse.

Our study has some limitations. The analysis included patients eligible and ineligible for transplantation. Data on cytogenetics were lacking in approximately 30% of patients. Maintenance was continued until progression in the RV-MM-PI-209 and the CC-5013-MM-015 trials but continued up to 2 years in the GIMEMA-MM-03-05 study. In the GIMEMA-MM-03-05 trial, part of the advantage of CT

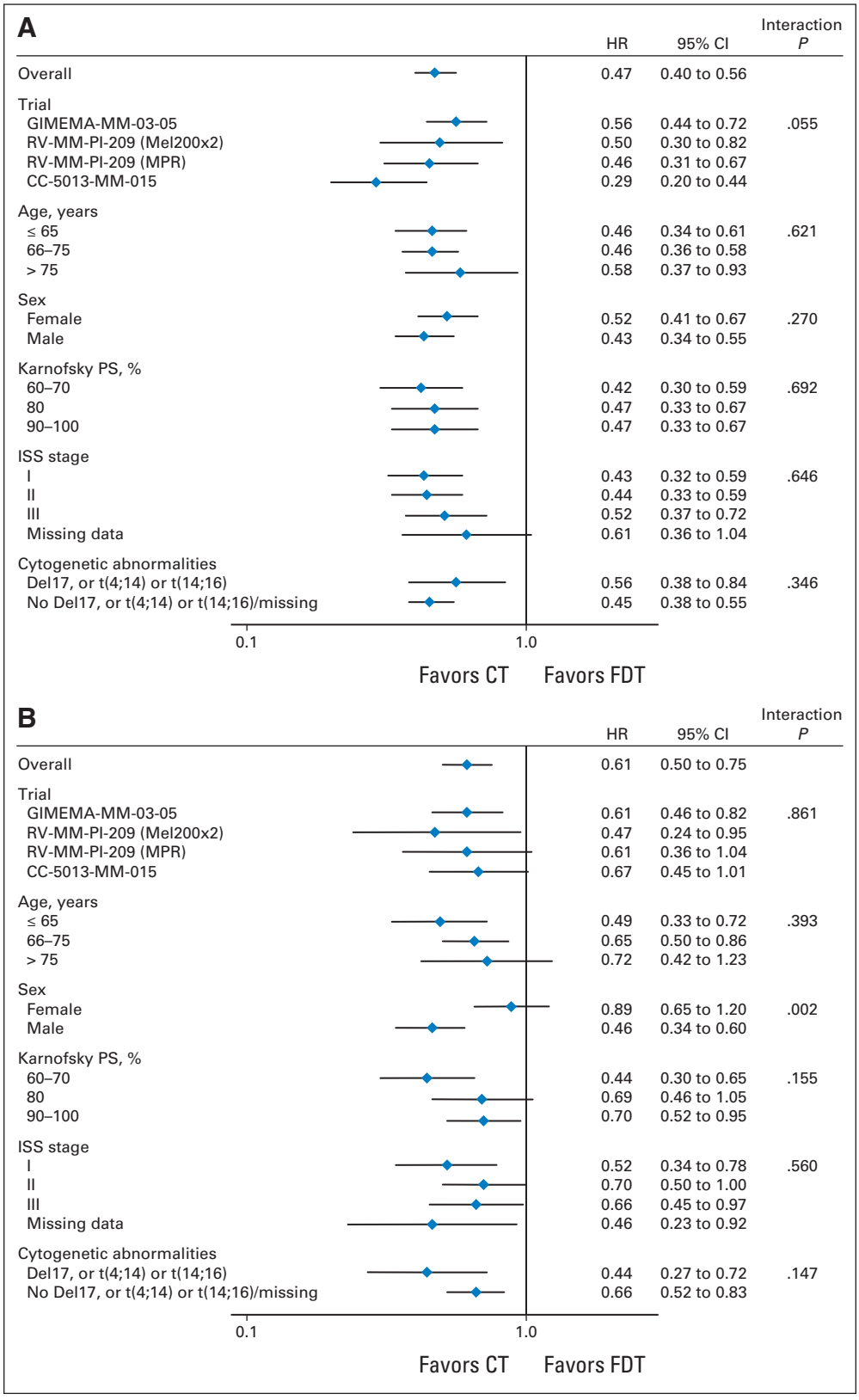

Fig 3. Subgroup analysis of (A) progression-free survival (PFS) 1, (B) PFS2, and (C) overall survival in the intent-to-treat population eligible for continuous therapy (CT). FDT, fixed duration of therapy; GIMEMA, Italian Group for Hematologic Diseases in Adults; HR, adjusted hazard ratios; ISS, International Staging System; PS, performance status.

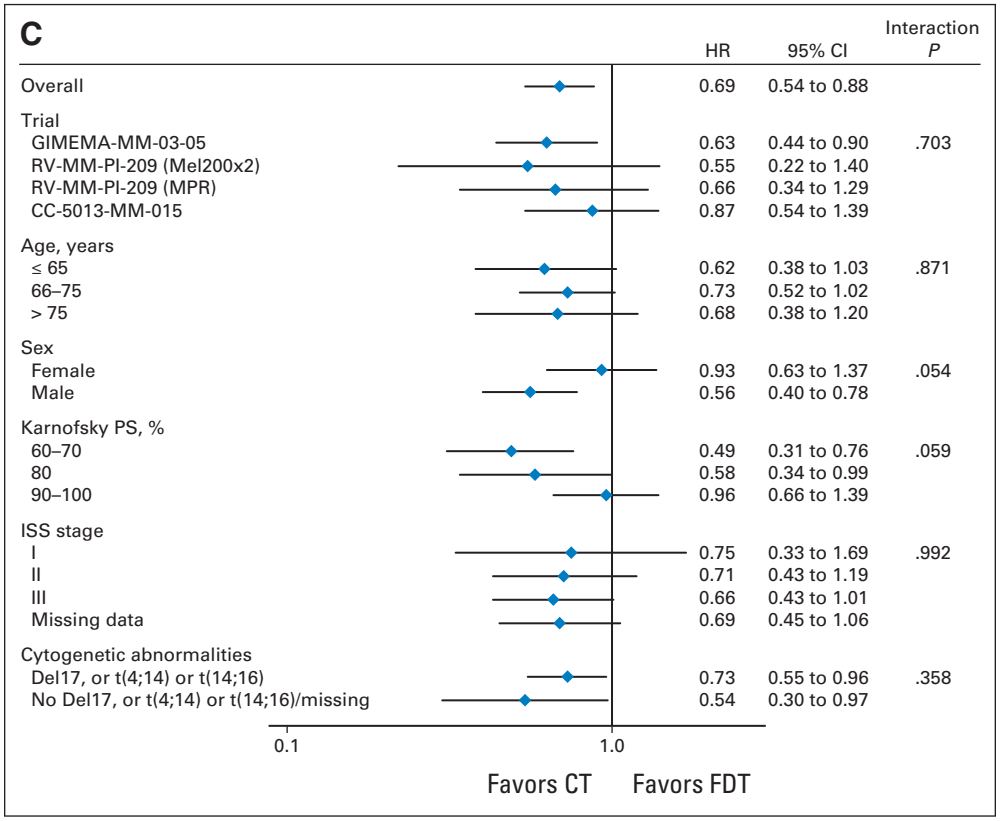

Fig 3. (Continued).

could be related to the association of thalidomide with bortezomib, melphalan, and prednisone. Postrelapse therapies depend on several factors; start and type of treatment at relapse were not prespecified in all of the study protocols, but were left to the investigators' discretion, and the availability of active trials could have influenced the treatment choice. The PFS2 end point was not prespecified in the original study protocols. When the date of progression after second-line therapy was not available, the start date of third-line therapy was used to estimate PFS2. PFS2 analysis did not account for the impact of therapies administered after second-line therapy, which may have impacted on OS. The landmark analysis, based on the ITT-CT population, included all patients alive and progression free at 1 year, but in both the CT and FDT arms, approximately 15% of patients were not strictly eligible for CT (as a result of toxicity, refusal, or other reasons), and their inclusion in the analysis may have caused a bias with an underestimation of the effect of CT.

In conclusion, our results indicate that CT provides a clinically relevant improvement in median PFS1 and PFS2 of approximately 1 year and an OS improvement of approximately 10% in patients with NDMM. The improvement in PFS2 suggests that most of the benefit observed during the first remission is not affected by a short second remission. This was true in the three trials where lenalidomide, thalidomide, and bortezomib were evaluated. Future studies evaluating other new, effective antimyeloma agents with a different mechanisms of action (such as new-generation proteasome inhibitors and immunomodulatory agents or monoclonal antibodies) will shed further light on the role of CT. PFS2 is a strong candidate end point to estimate long-term clinical benefit and should be included in future trials to evaluate the impact of chemotherapy resistance. Future IPD analyses on larger populations are needed to formally validate the role of PFS1 and PFS2 as surrogate end points for OS in MM.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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Final approval of manuscript: All authors

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Continuous Therapy Versus Fixed Duration of Therapy in Patients With Newly Diagnosed Multiple Myeloma

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Appendix

Original Trials

In the Italian Group for Hematologic Diseases in Adults (GIMEMA) MM-03-05 trial (ClnicalTrials.gov identifier: NCT01063179), patients were allocated to bortezomib-melphalan-prednisone-thalidomide followed by bortezomib-thalidomide maintenance or to bortezomib-melphalan-prednisone and no maintenance; random assignment was performed at diagnosis. In the GIMEMA-RV-MM-209 trial (ClinicalTrials.gov identifier: NCT00551928), patients received lenalidomide and low-dose dexamethasone (Rd) induction and, in a 2 × 2 design, autologous stem-cell transplantation versus melphalan-prednisone (MP) plus lenalidomide (MPR) consolidation, and lenalidomide maintenance versus no maintenance; random assignment was performed at diagnosis. In the MM-015 trial (ClinicalTrials.gov identifier: NCT00405756), patients were randomly assigned to MPR followed by lenalidomide maintenance, MPR and no maintenance, or MP and no maintenance; random assignment was performed at diagnosis (Appendix Table A1).[5,6,7,13] All trials recruited patients between January 2005 and December 2009. Trial protocols were approved by the ethics committee at each participating institution. All patients gave written informed consent before enrollment. The studies were conducted in compliance with the independent ethics committee procedures, the Declaration of Helsinki, the International Conference on Harmonization, Good Clinical Practice guidelines, and local regulations governing the conduct of clinical studies. Coordinating groups coded data to render them anonymous in a standardized fashion for inclusion in a database.

Individual Patient Data Extraction

We selected the following baseline data for each patient: age, sex, creatinine levels or creatinine clearance, lactate dehydrogenase and hemoglobin levels, International Staging System stage, presence of chromosomal abnormalities detected by fluorescent in situ hybridization, date of diagnosis, date of random assignment, date of first disease progression, second-line therapy, date of second disease progression (or start date of third-line therapy if the date of second progression was not available), date of death or last contact, and reason for treatment discontinuation. Cutoff dates were November 2012 for GIMEMA-MM-03-05, April 2013 for GIMEMA-RV-MM-209, and April 2013 for MM-015, representing a longer follow-up as compared with the original publication.

Definition of End Points Included in the Analysis

Progression-free survival (PFS) 1. All patients randomly assigned in the first line of therapy are included. PFS1 is the time from random assignment to progression or death after first-line therapy. Patients in remission after or during the first line of therapy are censored at the last date they are known to be in remission. Patients experiencing progression or dying after or during the first-line therapy are considered as having treatment failure at the date of progression or death, whichever comes first.

PFS2. All patients randomly assigned in the first line of therapy are included. PFS2 is the time from random assignment to first-line therapy to progression or death after second-line therapy. Patients who experienced progression after first-line therapy, received a second-line therapy, and experienced progression or died after second-line therapy are considered as having treatment failure at the date of progression or death after second-line therapy, whichever came first. Patients who died after the first-line therapy without experiencing progression or receiving a second-line therapy are considered as having treatment failure at the date of death. Patients who experienced progression after first-line therapy, received second-line therapy, and did not experience progression or die after second-line therapy are censored at the last date they are known to be in remission or alive. Patients in remission after or during first-line therapy are censored at the last date they are known to be in remission.

Overall survival (OS). All patients randomly assigned in the first line of therapy are included. OS is the time from random assignment to first-line therapy to death. Patients who died are considered as having treatment failure at the date of death. Patients who did not die are censored at the last date they are known to be alive.

Definition of End Points Excluded From the Analysis and Reported for Completeness

Second PFS. Only patients who experienced first progression are included. Second PFS is the time from first relapse to second relapse or death. Patients experiencing progression or dying after or during the second line of therapy are considered as having treatment failure at the date of progression or death, whichever comes first. Patients in remission after or during the second line of therapy are censored at the last date they are known to be in remission.

OS from first relapse. Only patients who experienced first progression are included. OS from first relapse is the time from first relapse to death. Patients who died are considered as having treatment failure at the date of death. Patients who did not die are censored at the last date they are known to be alive

Subgroups Analysis

Subgroups were defined according to protocol (GIMEMA-MM-03-05, RV-MM-PI-209, or CC-5013-MM-015); because in the RV-MM-PI-209 trial patients randomly assigned to continuous therapy versus fixed duration of therapy received two different inductions (Rd-MPR or Rd-melphalan 200 mg/m^2), two subgroups were evaluated for this protocol.

Baseline patient characteristics included age (≤ 65, 66-75, or > 75 years), sex, Karnofsky performance status (60% to 70%, 80%, or 90% to 100%), International Staging System stage (stage I, II, or III, or missing data), and cytogenetic profile defined by fluorescent in situ hybridization analysis [high risk: presence of del 17 or t(4;14) or t(14;16); standard risk: absence of del 17, t(4;14), and t(14;16)]. Most of the missing cytogenetic data came from one single study. Therefore, the category of missing cytogenetic data was mainly represented by data of one of the three trials. This could have resulted in a substantial bias. To avoid this bias, missing data where included in the standard-risk group.

Table A1. Characteristics of the Trials Included in the Pooled Analysis

Characteristic	GIMEMA-MM-03-05[8,9]		RV-MM-PI-209[14]		CC-5013-MM-015[7]	
	CT	FDT	CT	FDT	CT	FDT
Enrollment period	2006-2009		2007-2009		2007-2009	
No. of patients randomly assigned	511		402		459	
Time of random assignment	At diagnosis		At diagnosis		At diagnosis	
Eligibility criteria						
NDMM setting	TNE		TE		TNE	
Age, years	≥ 65		≤ 65		≥ 65	
Treatment						
Induction	VMPT	VMP	Rd	Rd	MPR	MPR or MP
Consolidation			MPR, MEL200-ASCT	MPR, MEL200-ASCT		
Maintenance	VT		R		R	
Duration of treatment, months						
Induction	~12	~12	~9-12	~9-12	9	9
Maintenance	24		Until PD		Until PD	
Median follow-up time from random assignment, months	54		51		62	

Abbreviations: CT, continuous therapy; FDT, fixed duration of therapy; GIMEMA, Italian Group for Hematologic Diseases in Adults; MEL200-ASCT, melphalan 200 mg/m^2 followed by autologous stem-cell transplantation; MP, melphalan and prednisone; MPR, melphalan, prednisone, and lenalidomide; NDMM, newly diagnosed multiple myeloma; PD, progressive disease; R, lenalidomide; Rd, lenalidomide and low-dose dexamethasone; TE, transplantation eligible; TNE, transplantation not eligible; VMP, bortezomib, melphalan, and prednisone; VMPT, bortezomib, melphalan, prednisone, and thalidomide; VT, bortezomib and thalidomide.

Table A2. Characteristics of the Trials Excluded From the Pooled Analysis

Characteristic	IFM-2005-02[12,13]	NCT-0114101[11]	MM-020-IFM-07-01[10]	IFM-99[24]	MRC Myeloma IX[21,27]	HOVON-49[20]	NMSG-12[28]	GISMM-2001[19]	MY.10[25]
Enrollment period	2006-2008	2005-2009	2008-2013	2000-2003	2003-2007	2002-2007	2002-2007	2002-2005	2002-2009
No. of patients randomly assigned	614	460	1,623	597	1,970/820	344	363	331	332
Time of random assignment	After ASCT	After ASCT	At diagnosis	At maintenance	At diagnosis/at maintenance	At diagnosis	At diagnosis	At diagnosis	After ASCT
Eligibility criteria									
NDMM setting	TE	TE	TNE	TE	TE and TNE	TNE	TNE	TNE	TE
Age	≤ 65	≤ 71	≥ 65	< 65	≥ 18	≥ 65	—	≥ 65	≥ 65
Treatment schema	CT / FDT	CT / FDT	CT / FDT / FDT	CT / FDT / FDT	CT / FDT	CT / FDT	CT / FDT	CT / FDT	CT / FDT
Intensity					Intensive / Non-intensive / Intensive / Non-intensive				
Induction	Any ASCT + R	Any ASCT R	Rd	VAD ASCT Pam+T	CTD ASCT T / CVAD ASCT T / MP T / CTDa T	MPT	MPT	MPT	NA
Consolidation			Rd	VAD ASCT Pam	CTD ASCT — / CVAD ASCT — / MP — / CTDa —	MP	MP	MP	ASCT
Maintenance	R	R	Rd	VAD ASCT —	—	T	T	T	TP
	—	—	—	—	—	—	—	—	—
Duration of treatment, months									
Induction	NA	NA	Until PD / 18 / 18	~9 / ~9 / ~9	~9 / ~9 / ~9	~8 / ~8	Until plateau phase	Until plateau phase	~6 / ~6
Maintenance	Until PD	Until PD	— / — / —	Until PD / Until PD / —	Until PD / Until PD / — / —	Until PD / —	Until PD / —	Until PD / —	NA / 48 or until PD
Median follow-up time from random assignment, months	67	34	37	29 / 29 / 30	38	39	42	~38	49
Difference from the included trials	Induction treatment not specified (not restricted to novel agent-based therapy)	Induction treatment not specified (not restricted to novel agent-based therapy)	Enrollment period until 2013, shorter follow up	Induction treatment not specified (not restricted to novel agent- based therapy)	Not all patients randomized to maintenance with thalidomide received novel agents from diagnosis	No novel agents in the control arm	No novel agents in the control arm	No novel agents in the control arm	Induction treatment not specified (not restricted to novel agent-based therapy)

Abbreviations: ASCT, autologous stem-cell transplantation; CT, continuous therapy; CTD, cyclophosphamide, thalidomide, and dexamethasone; CTDa, attenuated CTD; CVAD, cyclophosphamide, vincristine, doxorubicin, and dexamethasone; FDT, fixed duration of therapy; MP, melphalan and prednisone; MPT, melphalan, prednisone, and thalidomide; NA, not available; Pam, pamidronate; PD, progressive disease; R, lenalidomide; Rd, lenalidomide and low-dose dexamethasone; T, thalidomide; TE, transplantation eligible; TNE, transplantation not eligible; TP, thalidomide and prednisone; VAD, vincristine, doxorubicin, and dexamethasone.

Table A3. Survival Estimates (PFS1, PFS2, and OS from random assignment) Including All 1,218 Patients Randomly Assigned at Enrollment

	Estimate (%; 95% CI)					
	PFS1		PFS2		OS	
Time (months)	CT	FDT	CT	FDT	CT	FDT
12	84 (81 to 87)	78 (74 to 81)	90 (87 to 92)	88 (86 to 91)	92 (90 to 94)	92 (89 to 94)
24	64 (60 to 68)	45 (41 to 50)	80 (77 to 83)	71 (67 to 75)	86 (83 to 89)	78 (76 to 83)
36	48 (43 to 52)	25 (21 to 29)	66 (62 to 70)	57 (53 to 61)	78 (74 to 82)	70 (66 to 74)
48	38 (34 to 43)	16 (12 to 19)	55 (51 to 59)	43 (39 to 48)	69 (65 to 73)	61 (57 to 65)
60	31 (26 to 36)	12 (9 to 16)	45 (40 to 50)	33 (28 to 37)	60 (55 to 65)	51 (46 to 55)

Abbreviations: CT, continuous therapy; FDT, fixed duration of therapy; OS, overall survival; PFS1, progression-free survival 1; PFS2, progression-free survival 2.

Table A4. PFS1, PFS2, and OS in Patients Enrolled Onto the Trials: Sensitivity Analysis

Outcome	HR	95% CI	*P*
PFS1			
All trials	0.47	0.40 to 0.56	< .001
Excluding GIMEMA-MM-03-05	0.41	0.32 to 0.52	< .001
Excluding RV-MM-PI-209	0.48	0.39 to 0.59	< .001
Excluding CC-5013-MM-015	0.51	0.42 to 0.62	< .001
PFS2			
All trials	0.61	0.50 to 0.75	< .001
Excluding GIMEMA-MM-03-05	0.64	0.47 to 0.86	.003
Excluding RV-MM-PI-209	0.64	0.50 to 0.81	< .001
Excluding CC-5013-MM-015	0.58	0.46 to 0.74	< .001
OS			
All trials	0.69	0.54 to 0.88	.003
Excluding GIMEMA-MM-03-05	0.79	0.55 to 1.13	.193
Excluding RV-MM-PI-209	0.72	0.54 to 0.95	.022
Excluding CC-5013-MM-015	0.62	0.46 to 0.84	.002

Abbreviations: GIMEMA, Italian Group for Hematologic Diseases in Adults; HR, hazard ratio; OS, overall survival; PFS1, progression-free survival 1; PFS2, progression-free survival 2.

Table A5. PFS1, PFS2, and OS in Patients Enrolled Onto the Trials Excluded From This Pooled Analysis

	IFM-2005-02[12,13]				NCT-0114101[11]				MM-020[10]*				IFM-99[24]†				MRC Myeloma IX[21,27]			
Outcome	CT (median, months)	FDT (median, months)	HR (95% CI)	*P*	CT (median, months)	FDT (median, months)	HR (95% CI)	*P*	CT (median, months)	FDT (median, months)	HR (95% CI)	*P*	CT (median, months)	FDT (median, months)	HR (95% CI)	*P*	CT (median, months)	FDT (median, months)	HR (95% CI)	*P*
PFS1	46	24	NA	< .001	46‡	27‡	0.48 (0.36 to 0.63)	< .001	25	21	0.72 (0.61 to 0.85)	< .001	NA	NA	NA	.002	23	15	1.45 (1.22 to 1.73)	< .001
PFS2	NA	NA	NA	NA	NA	NA	NA	NA	43	36	0.78‖	.005	NA	NA	NA	NA	NA	NA	NA	NA
OS	82	81	NA	.80	NR	NR	0.62 (0.40 to 0.95)	.03	NA	NA	0.78 (0.64 to 0.96)	.02	NR	NR	NA	.04	NA	NA	0.91 (0.72 to 1.17)	.4

	HOVON-49[20]				NMSG-12[28]				GISMM-2001[19]				MY.10[25]			
Outcome	CT (median, months)	FDT (median, months)	HR (95% CI)	*P*	CT (median, months)	FDT (median, months)	HR (95% CI)	*P*	CT (median, months)	FDT (median, months)	HR (95% CI)	*P*	CT (median, months)	FDT (median, months)	HR (95% CI)	*P*
PFS1	13§	9§	NA	< .001	15	14	NA	NA	21.8	14.4	0.63 (0.48 to 0.81)	< .001	NA	NA	NA	< .001
PFS2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
OS	40	31	NA	.05	29	32	NA	.16	45	47.6	1.04 (0.76 to 1.44)	.79	NR	NR	NA	.18

Abbreviations: CT, continuous therapy; FDT, fixed duration of therapy; HR, hazard ratio; NA, not available; NR, not reported; OS, overall survival; PFS1, progression-free survival 1; PFS2, progression-free survival 2.

*In MM-020, data refer to the comparison of lenalidomide and low-dose dexamethasone until progressive disease (CT) versus melphalan, prednisone, and thalidomide (FDT), because this was the main comparison of the trial.

†In IFM-99, data refer to the comparison of pamidronate and thalidomide maintenance (CT arm) versus no maintenance or pamidronate alone.

‡Time to progression.

§Event-free-survival.

‖Data for 95% CI are not available.

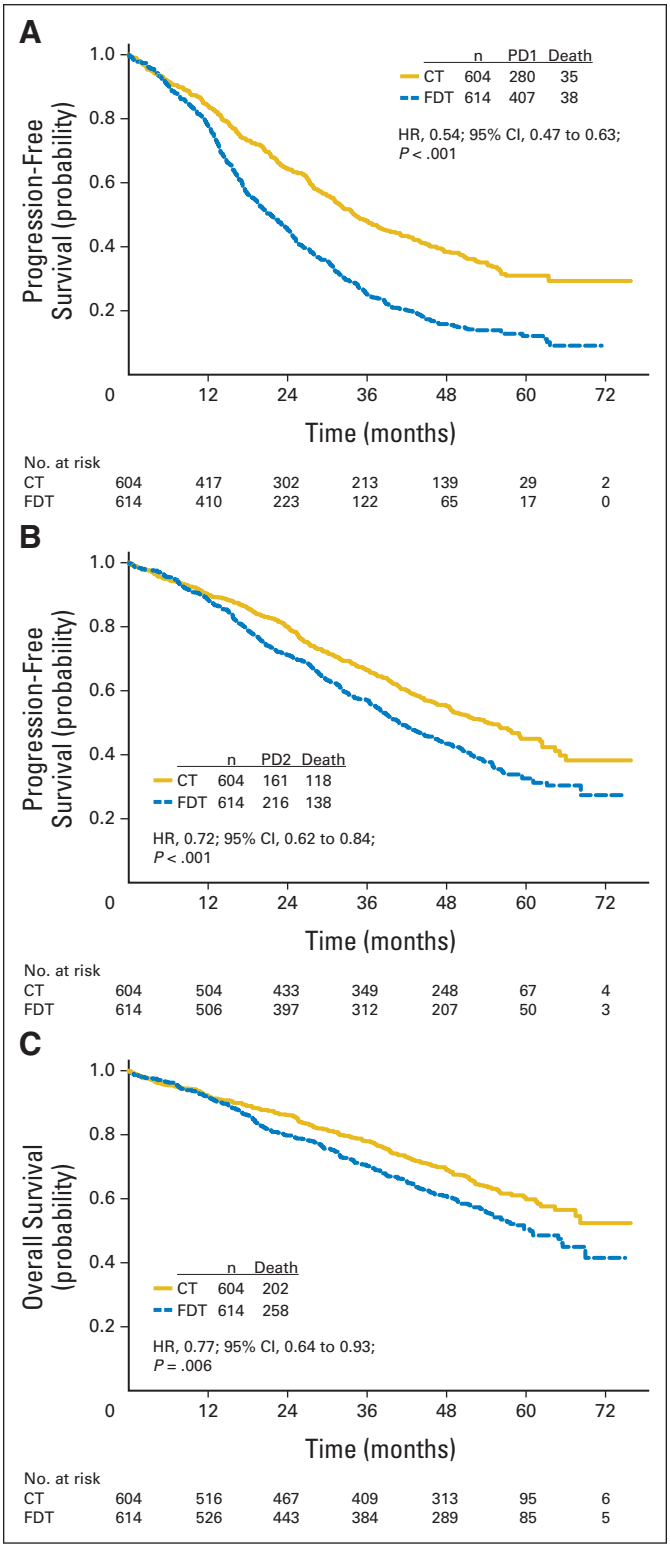

Fig A1. (A) Progression-free survival (PFS) 1 from enrollment. (B) PFS2 from enrollment. (C) Overall survival from enrollment. CT, continuous therapy; FDT, fixed duration of therapy; HR, hazard ratio; PD1, first disease progression; PD2, second disease progression.

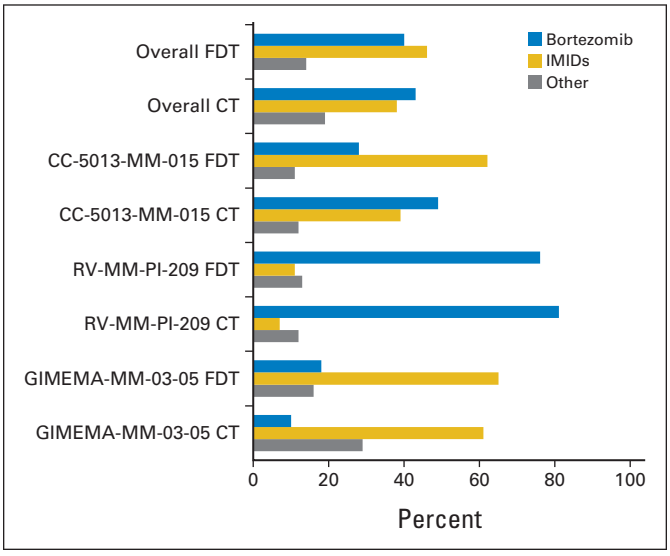

Fig A2. Types and frequency of second-line therapies. CT, continuous therapy; FDT, fixed duration of therapy; GIMEMA, Italian Group for Hematologic Diseases in Adults; IMIDs, immunomodulatory drugs.