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

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Continuous vs fixed duration of therapy in newly diagnosed multiple myeloma patients

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Running head: CT vs FDT for newly diagnosed MM patients

Abstract:

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

Methods: We included patients enrolled in 3 phase III trials that randomized patients to novel agent-based CT vs FDT. Primary analyses were restricted to the intention-to-treat population eligible for CT (ITT-CT) (patients progression-free and alive at 1-year from randomization). Primary endpoints were PFS1, PFS2 and OS. All hazard ratios and 95%CI were adjusted for several potential confounders using Cox's models.

Results: In the pooled analysis of the 3 trials, 604 patients were randomized to CT and 614 to FDT. Median follow-up was 52 months. In the ITT-CT population, CT (n=417) significantly improved PFS1 (median 32 vs 16 months, HR 0.47; 95% CI 0.40-0.56, P<0.001), PFS2 (median 55 vs 40 months, HR 0.61, 95% CI 0.50-0.75, p<0.001) and OS (4-year OS 69% vs 60%, HR 0.69, 95% CI 0.54-0.88, P=0.003) in comparison with FDT (n=410).

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 endpoint to estimate long-term clinical benefit and should be included in future trials.

Introduction

Multiple myeloma (MM) is a plasma cells disorder that accounts for ~13% of all hematologic cancers.[1] In Europe, melphalan-prednisone (MP) plus thalidomide (MPT) or bortezomib (MPV) are the standards of care for transplant-ineligible patients with newly diagnosed MM (NDMM).[2-4] In transplant-eligible patients, a novel agent-based induction followed by high-dose therapy and autologous transplantation (ASCT) is the standard approach.[5] Several studies evaluated the impact of continuous treatment (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 (MPR-R) significantly increased progression-free survival (PFS) in comparison with MPR and MP, but no differences in OS were reported.[7] Bortezomib-melphalan-prednisone-thalidomide followed by bortezomib-thalidomide maintenance (VMPT-VT) significantly prolonged PFS and overall survival (OS) in comparison with VMP.[8,9] Continuous lenalidomide and low-dose dexamethasone (Rd) significantly increased PFS and OS in comparison with MPT.[10] In patients who received ASCT, post-transplant lenalidomide maintenance improved PFS by at least 50%, with conflicting results in terms of OS.[11-14]

Despite the recent encouraging results, most of MM patients eventually relapse. Initial therapy may affect the tumor drug-resistance profile: there is some concern that patients progressing 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, simple to measure, 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 (EMA) recommended to include PFS2 endpoint to evaluate the impact of CT on outcome.[15] PFS1 defines the time from randomization until the first progression (PD1) or death, whereas PFS2 defines the time from randomization until the second 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 vs fixed duration of therapy (FDT) on time-to-event endpoints, particularly on PFS2 and OS, in NDMM patients treated with novel agents.

Methods

Patients and treatment

For this pooled analysis, we selected three phase III trials (GIMEMA-MM-03-05, GIMEMA-RV-MM-209, MM-015) coordinated by the same principal investigator.[7-9,14] In the three studies, NDMM patients were randomized to CT or FDT with novel agents (thalidomide, lenalidomide, 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 (Table 1S). FDT was defined as an upfront treatment (induction/consolidation) for up to 1 year. CT was defined as an upfront therapy (induction/consolidation) followed by maintenance lasting at least 2 years. Both definitions were based on the intention-to-treat population.
For completeness, in Table 2S we described the other phase III trials comparing CT vs FDT that were excluded from our analysis, highlighting the differences with the three trials included.

Clinical endpoints

The primary study endpoints were PFS1, PFS2 and OS in the intention-to-treat population eligible for CT vs FDT (ITT-CT), according to the randomization. Because patients were randomized 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 randomization, which corresponds to the average duration of induction/consolidation in the 3 trials

(landmark analysis). For the primary analyses, based on the ITT-CT population, all time-to-event endpoints were calculated from the time of inclusion in the landmark analysis. For descriptive purposes, and to account for failures occurred during the induction/consolidation, we provided also survival probability estimates since patients' randomization.

PFS1 was calculated until the date of first progression (PD1) or death. PFS2 was calculated until the date of second progression (PD2) or 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 cut-off date (following 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 endpoints definitions are described in the supplementary appendix.

Statistical analysis

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

The Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) and the 95% confidence intervals (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 therapy if they differed within the trial), gender, age, International Staging System (ISS) stage, cytogenetic profile and Karnofsky performance status. Subgroup analyses were performed to determine the consistency of treatment effects of CT vs FDT between different subgroups (detailed in the Supplementary Appendix) using interaction terms between treatment and each of the covariate included in the Cox model. We did a sensitivity analysis excluding one trial at a time. All hazard ratios were estimated with their 95% confidence intervals (95%CI) and two sided p-values.

Data were analyzed as of May, 2014 using STATA 11.2 (StataCorpLP, College Station, TX, USA).

Results

Patients

The three trials randomly assigned 1372 patients with NDMM to treatment; the GIMEMA-MM-0305 and MM-015 studies enrolled patients ineligible for ASCT; the GIMEMA-RV-MM-209 study randomized patients eligible for ASCT. One-hundred and fifty-four patients in the MM-015 study randomized to MP were excluded from our analysis. The remaining 1218 patients were included in the descriptive analysis to estimate the survival probability since diagnosis for PFS1, PFS2, OS; 604 patients in the three studies were randomly allocated to CT and 614 to FDT. A total of 417 CT patients and 410 FDT patients were included in the ITT-CT population for comparative analyses (Figure 1). Patients demographics and disease characteristics in the two groups were well balanced at enrolment and in the ITT-CT population (Table 1). At data cut-off, 145 patients in the CT arm vs 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% AEs were reported.

PFS1, PFS2 and OS analyses

The median follow-up for survivors was 52 months (minimum 51 months in the GIMEMA-MM-RV-209 trial, maximum 62 in the MM-015 trial). In the overall population of patients included in the descriptive analysis (n=1218), the 4-year PFS1 from randomization was 38% (95% CI 34-43%) in CT patients and 16% (95% CI 12-19%) in FDT patients; the 4-year PFS2 from randomization was 55% (95% CI 51-59%) in CT patients vs 43% (95% CI 39%-48%) in FDT patients; the 4-year OS from randomization was 69% (95% CI 65-73%) in CT patients vs 61% (95% CI 57-65%) in FDT patients (Table 3S, Figure 1S, Panel A,B,C).
In the ITT-CT population (n=827), the median PFS1 from landmark-point was 32 months with CT vs 16 months with FDT. CT significantly reduced the risk of PD1/death in comparison with FDT (HR 0.47; 95%

CI 0.40-0.56, P<0.001; Figure 2A).The advantage of CT vs 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 0.20-0.44, P=0.055 for interaction) (Figure 3A).

The median PFS2 from landmark-point was 55 months with CT vs 40 months with FDT; CT significantly reduced the risk of PD2/death in comparison with FDT (HR 0.61, 95% CI 0.50-0.75, P<0.001, Figure 2B). The benefit of CT vs FDT was evident in all the subgroups according to trial and induction/consolidation treatment (P=0.861 for interaction) and in most of the analyzed subgroups according to baseline features, with a possible weaker effect on females (Figure 3B).

The 4-year OS from landmark-point was 69% with CT vs 60% with FDT; CT significantly reduced the risk of death in comparison with FDT (HR 0.69, 95% CI 0.54-0.88, P=0.003, Figure 2C). The statistical power of the subgroup analysis of OS was limited by the low number of events, but the benefit of CT vs FDT was confirmed in all the subgroups according to trial and induction/consolidation treatment (P=0.703 for interaction); regarding baseline features, a weaker effect was estimated for females (P=0.054 for interaction) and in patients with a Karnofsky performance status 90-100% (P=0.059 for interaction) (Figure 3C).

The point estimates of the HRs in favor of CT vs FDT for PFS1, PFS2 and OS were confirmed in the sensitivity analysis after exclusion of each single trial (Table 4S).

Outcomes after first relapse

Overall, 280 (46%) CT patients and 407 (66%) FDT patients experienced PD1. Ninety percent of relapsing patients in the CT group and 88% 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 since a higher number of patients relapsed in the FDT. Overall, types of second-line therapy were well balanced between CT and FDT patients (around 40% of patients in each group received bortezomib or IMIDs-based treatment), but differed between the treatment arms in the three trials (Figure 2S).

Discussion

Several trials have shown a remarkable risk reduction in progression/death with CT in young and elderly NDMM patients, but this clinically relevant benefit did not always translate into an OS improvement (Table 5S).[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 EMA has recently suggested to include the PFS2 endpoint 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 endpoint than PFS1.

In our pooled analysis of IPD from 3 randomized trials, CT significantly prolonged the median PFS1 and PFS2 by ~1 year, and improved OS by ~10%. Our findings suggest that most of the PFS1 advantage associated with CT upfront is maintained after first relapse and that CT does not induce a significant chemo-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 transplant-ineligible NDMM patients receiving continuous Rd in comparison with MPT.[10] In the CALGB-100104 trial, lenalidomide maintenance improved PFS1 and OS in patients who received transplantation, but PFS2 was not assessed.[11] In the IFM-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 a PFS1 improvement, with conflicting OS results. However, most of the trials compared thalidomide CT vs FDT without novel agents and no data on PFS2 were available (Table 2S, 4S).[19-25,27,28] Meta-analyses of published data indicates a survival advantage for CT with thalidomide/lenalidomide.[29,30]

In all studies PFS1 improvement correlated with PFS2 improvement, although inconsistently with OS. Treatment choice at relapse is determined by several factors, i.e. 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 ineligible for transplant.[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. Yet, 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 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 relapsed patients in both groups received a second-line therapy, suggesting that CT did not induce a significant long-term toxicity.

Including PFS2 as one of the primary endpoints in randomized clinical trials has many advantages. PFS2 assesses the impact of two lines of therapy over a longer time-period, while PFS1 evaluates first-line therapy only. The PFS2 analysis produces more conservative results: patients who have not progressed after first-line are censored, as well as patients who have progressed after their first-line therapy but not yet after second-line. Similarly to PFS1 and OS, PFS2 includes all randomized patients. In contrast, outcomes like second PFS or OS from relapse are intrinsically biased since they are based on the subset of patients who experienced first relapse (~60% in our analysis). These patients are generally considered at poor prognosis,

because usually early progression is associated with a more aggressive disease. Nevertheless, the analysis of second PFS or OS from relapse (Additional Methods in the Supplementary Appendix) excludes patients who never relapsed (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 if 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 endpoint closer to OS than PFS1. Therefore PFS2 could be a preferable primary endpoint 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 transplant. Data on cytogenetic were lacking in ~30% of patients. Maintenance was continued until progression in the GIMEMA-RV-MM-209 and the MM-015 trials, but up to two years in the GIMEMA-MM-03-05 study. In the GIMEMA-MM-03-05, part of the advantage of CT could be related to the association of thalidomide with VMP. Post-relapse therapies depend on several factors: start and type of treatment at relapse were not pre-specified in all the study protocols, but left to the investigator's discretion, and the availability of active trials could have influenced the treatment choice. The PFS2 endpoint was not pre-specified in the original study protocols. When the date of progression after second-line 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, 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 both in the CT and FDT arms, ~15% of patients were not strictly eligible for CT (for toxicity, refusal, 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 ~1 year, and an OS improvement of ~10% in NDMM patients. The improvement in PFS2 suggests that most of the benefit observed during the first remission is not affected by a very short second remission.

This was true in the three trials where lenalidomide, thalidomide and bortezomib were evaluated. Future studies evaluating other new, effective anti-myeloma 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 endpoint to estimate long-term clinical benefit and should be included in future trials to evaluate the impact of chemo-resistance. Future IPD analyses on larger populations are needed to formally validate the role of PFS1 and PFS2 as surrogate endpoints for OS in MM.

Conflicts of interest

AP has received honoraria and consultancy fees from Celgene and Janssen-Cilag. FG has received honoraria from Celgene and Janssen-Cilag, and served on the advisory committee for Celgene. FC has received honoraria from Celgene, Janssen-Cilag, Onyx, and served on the advisory committee for Celgene. FDR has received honoraria from Bristol-Myers Squibb, Celgene, Novartis, Janssen-Cilag. AL has received Honoraria from Celgene and Janssen-Cilag. AN is a Novartis scientific advisory board member, has received honoraria, research grants and/or consultancy fees from Biolinerx, Curetech, Medison, Neopharm Israel, Novartis, and Sigma Tau, and is a principal investigator at the Chaim Sheba site for clinical studies funded by Celgene, Curetech, Johnson & Johnson, Merck, Millennium, Novartis, Onyx, and Sigma-Tau. MTP has received honoraria from Janssen, Celgene, Sanofi, and Bristol-Myers Squibb. RH has received consultancy fees from Merck and Celgene, and honoraria from Merck, Celgene, Janssen. MD has received honoraria from and served on the advisory board for Celgene. FP has received honoraria from Celgene and Janssen-Cilag and served advisory board for Janssen-Cilag. CN has received honoraria from Celgene and Janssen-Cilag. ZY owns Celgene stocks. TC has received research funding from Celgene and honoraria from J&J. GB has received honoraria from Janssen-Cilag and Sanofi. TG has received research funding from Celgene. CJ owns Celgene stocks. MAD has received honoraria from Celgene, Ortho-Biotech and Onyx. PM has received honoraria from Celgene, Janssen-Cilag, and Novartis and served on the scientific advisory board for Janssen Cilag, Sandoz and Sanofi. MB has received consultancy from and served on the scientific advisory board for Celgene, Janssen Cilag, Onyx and Sanofi. PC has received honoraria and speaker bureau from Roche,

Celgene, Janssen-Cilag, Sanofi Novartis, Gentium Gilead. MC has received consultancy fees from Janssen, Celgene, Millennium Pharmaceuticals, Bristol-Myers Squibb, Sanofi, Novartis and Onyx Pharmaceuticals, and honoraria from Janssen and Celgene.

Contributors

AP, FG, GC, MB, designed the study, and supervised its conduct and the data analysis. FG, FC, FDR, AL, IH, AN, MTP, RH, SP, MD, FP, FD, CC, CN, ZY, TC, GB, TG, DV, CJ, MAD, PM, PC, MC recruited patients in the source studies and provided relevant data. FG collected and assembled the data. LB and GC performed the statistical analysis. AP and FG analysed and interpreted the data. AP and FG drafted the initial manuscript. All authors were given unrestricted access to the data, critically reviewed the manuscript drafts, approved the final version, and made the decision to submit it for publication.

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Tables

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

	Overall population of patients included in the descriptive analyses				Overall population of patients included in the ITT-CT population			
	CONTINUOUS THERAPY (N=604)		FIXED DURATION OF THERAPY (N=614)		CONTINUOUS THERAPY (N=417)		FIXED DURATION OF THERAPY (N=410)	
	N	%	N	%	N	%	N	%
Age, years								
median	68		69		68		68	
IQR	62-73		62-74		61-73		61-73	
Gender, Male	307	51	317	52	218	52	215	52
Karnofsky PS								
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*								
del13	212	50	206	48	139	47	136	47
del17	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
del17 or 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

GIMEMA-RV-MM-209 (14)	198	33	204	33	137	33	142	35
MM-015 (7)	152	25	153	25	80	19	77	19

*percentage calculated on number of patients whose data were available

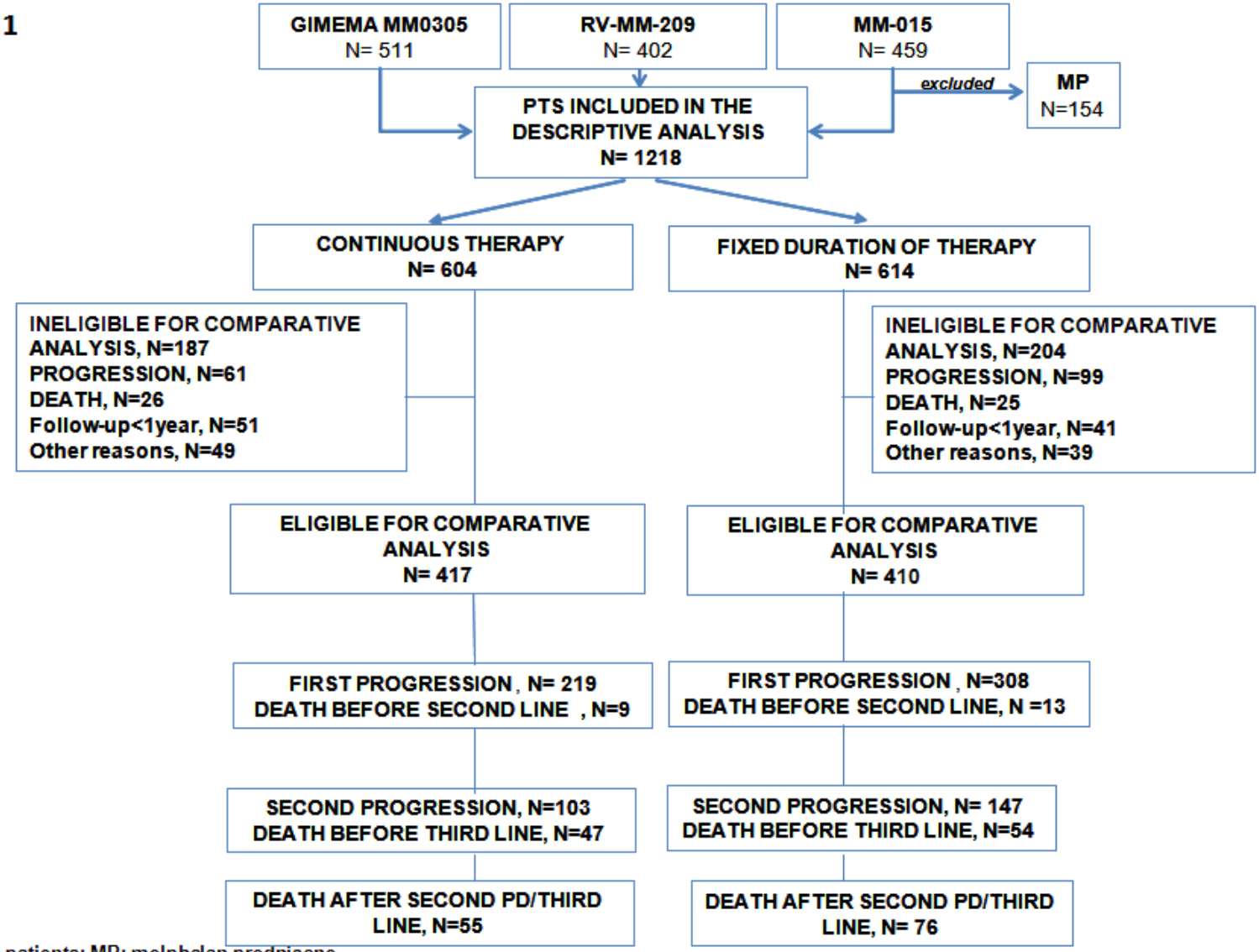
Figures

Figure 1. Study flow.

Figure 2. PFS1 (Panel A), PFS2 (Panel B) and OS (Panel C) in the ITT-CT population of patients randomized to receive continuous therapy vs patients randomized to fixed duration of therapy. HR= adjusted hazard ratios

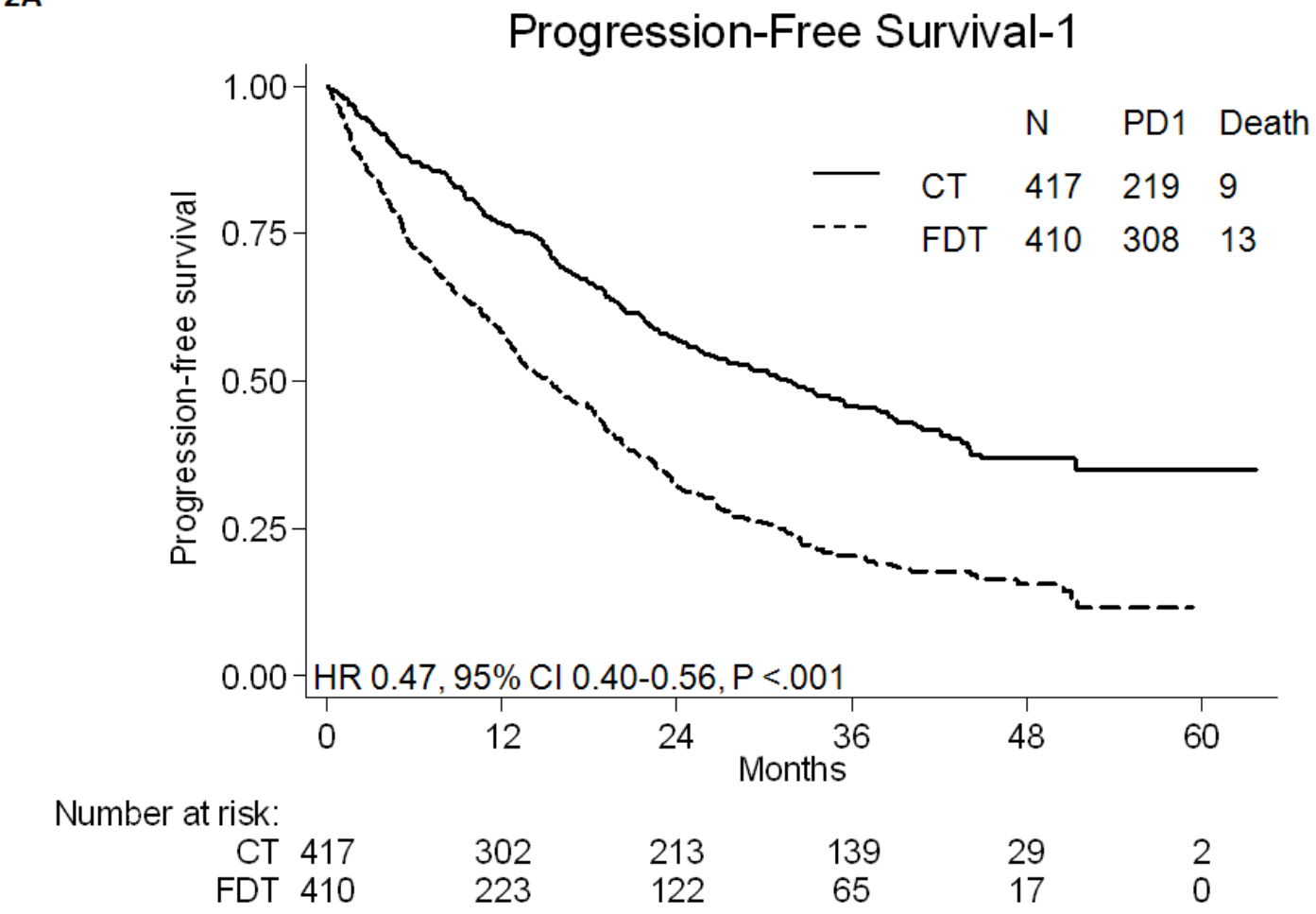
Figure 3 Subgroup analysis of PFS1 (panel A), PFS2 (panel B) and OS (panel C) in the ITT-CT population. HR= adjusted hazard ratios

1



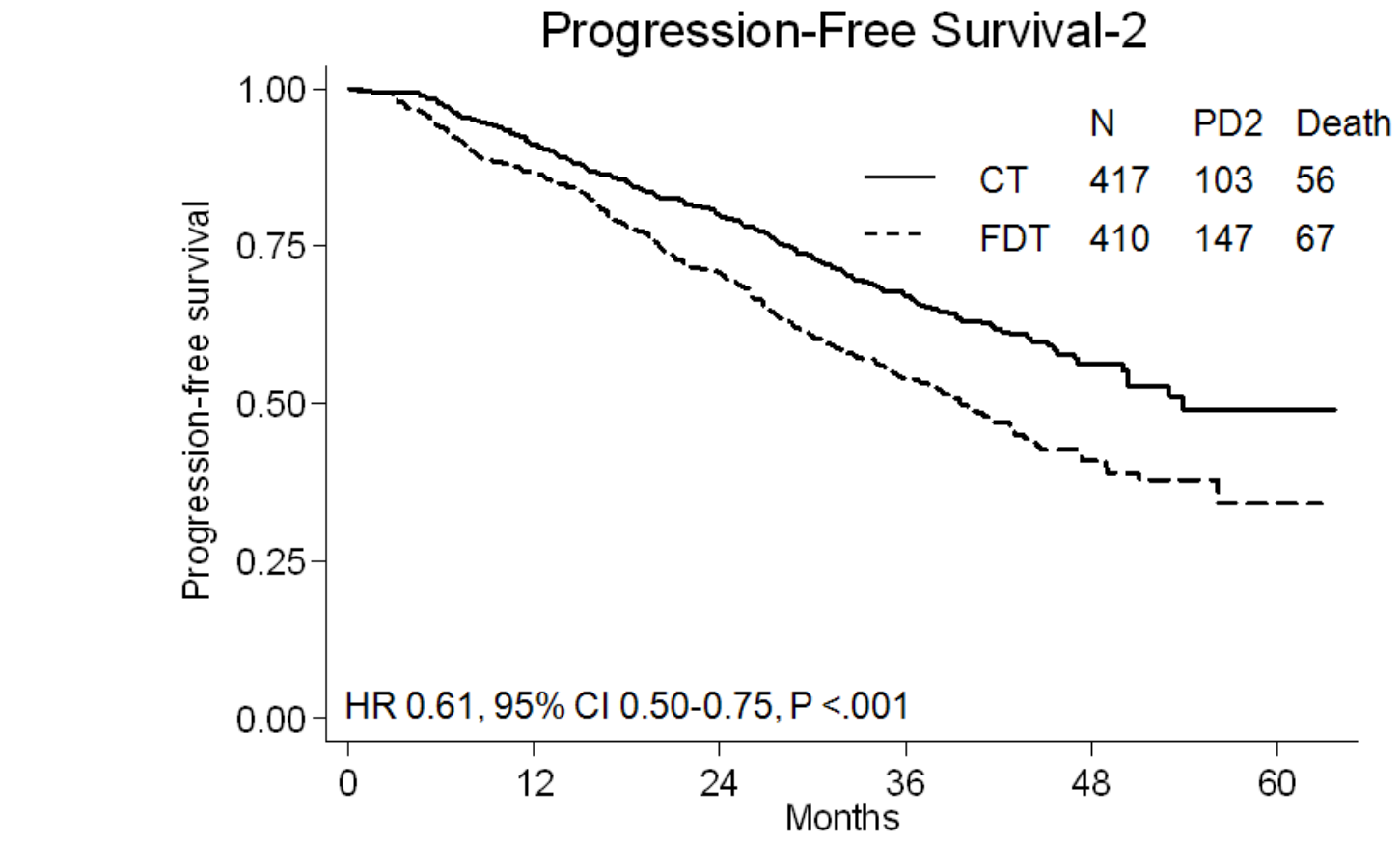
Pts: patients; MP: melphalan-prednisone.
Other reasons: include patients who stopped treatment for toxicity, consent withdrawn, medical decision, lost to follow-up and with no available data on remission status at 1 year from enrollment.

2A



CT: continuous therapy; FDT: fixed duration of therapy, PD: progression

2B

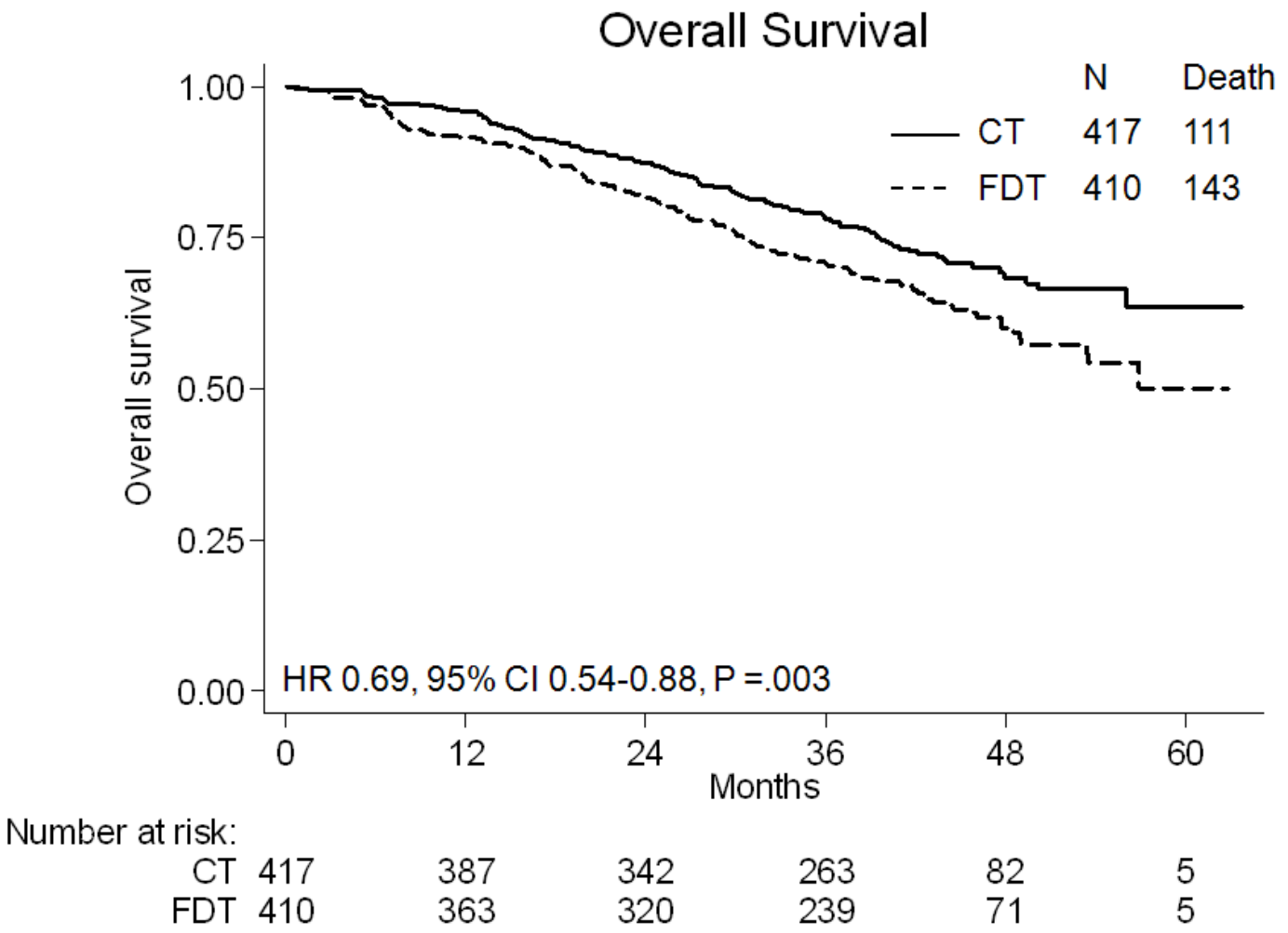


Number at risk:

CT	417	369	315	226	62	4
FDT	410	346	279	187	46	3

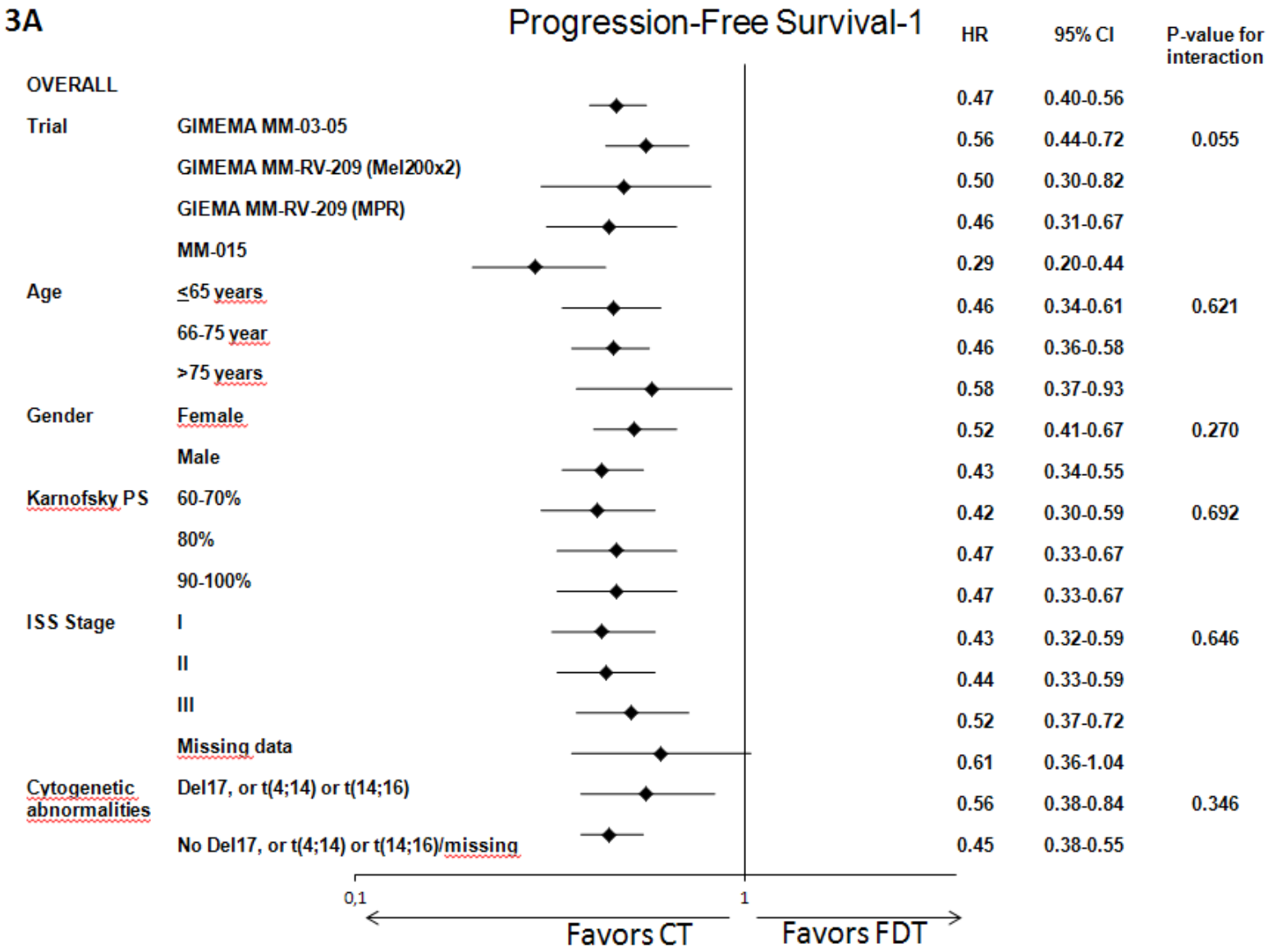
CT: continuous therapy; FDT: fixed duration of therapy, PD: progression

2C



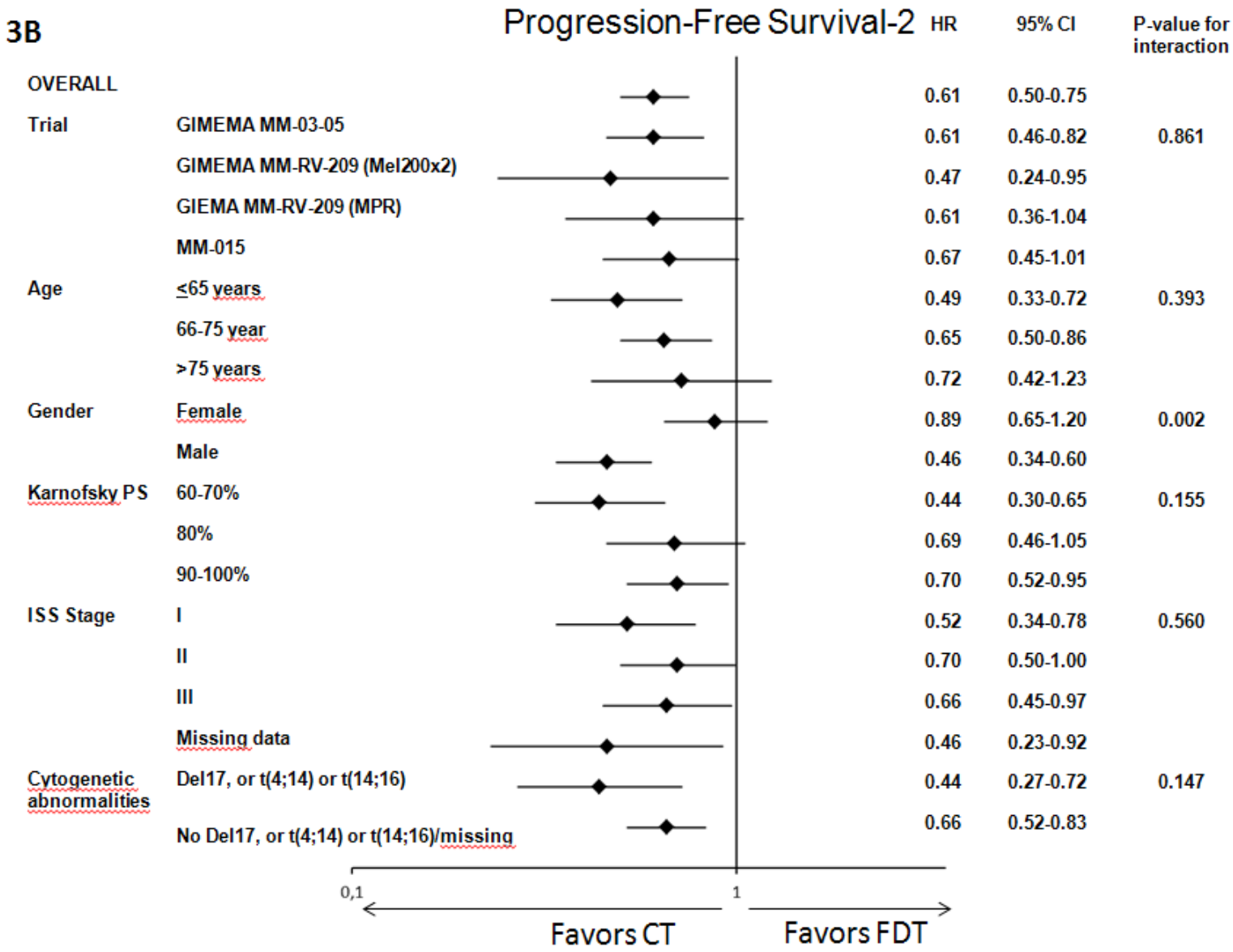
CT: continuous therapy; FDT: fixed duration of therapy, PD: progression

3A



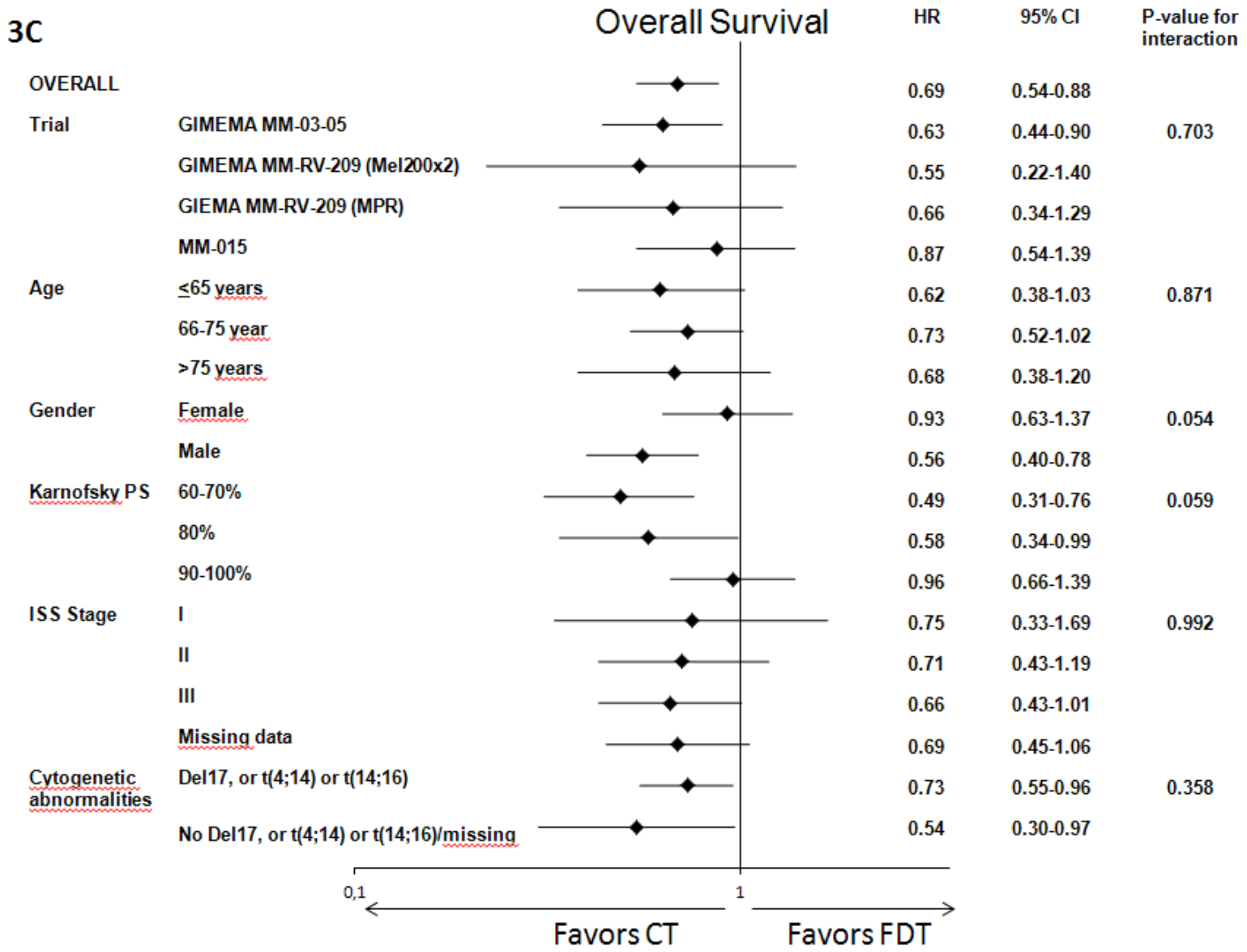
CT: continuous therapy; FDT: fixed duration of therapy, PS: performance status; ISS: International Staging System.

3B



CT: continuous therapy; FDT: fixed duration of therapy, PS: performance status; ISS: International Staging System.

3C



CT: continuous therapy; FDT: fixed duration of therapy, PS: performance status; ISS: International Staging System.

SUPPLEMENTARY APPENDIX

Additional Methods

Original trials

In the GIMEMA-MM-03-05 trial (ClnicalTrials.gov NCT01063179) patients were allocated to VMPT-VT maintenance or to VMP-no maintenance; randomization was performed at diagnosis. In the GIMEMA-RV-MM-209 trial (ClinicalTrials.gov NCT00551928) patients received Rd induction, and in a 2 x 2 design, ASCT vs MPR consolidation, and lenalidomide maintenance vs no maintenance; randomization was performed at diagnosis. In the MM-015 trial (ClinicalTrials.gov NCT00405756) patients were randomly assigned to MPR-R maintenance or MPR-no maintenance or MP-no maintenance; randomization was performed at diagnosis (Table 1S).[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 enrolment. 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, gender, creatinine levels or creatinine clearence, LDH and Hb levels, international staging system (ISS) stage, presence of chromosomal abnormalities detected by FISH, date of diagnosis, date of randomization, date of PD1, second-line therapy, date of PD2 (or start date of third-line therapy if the date of second progression was not available), date of death or last contact, reason of treatment discontinuation. Cut-off dates were November 2012 for the GIMEMA-MM-03-05, April 2013 for the GIMEMA-RV-MM-209, and April 2013 for the MM-015 trials, representing a longer follow up as compared to the original publication.

Endpoints definition

Endpoints included in the analysis:

PFS1: All patients randomized in the first line of therapy are included. It is the time from randomization in the first line to progression/death after first line. 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 progressing or dying after or during the first line of therapy are considered as failures at the date of progression/death whichever comes first.

PFS2: All patients randomized in the first line of therapy are included. It is the time from randomization in the first line to progression/death after second line. Patients who progressed after the first line of therapy, received a second-line therapy and progressed/died after second line are considered as failures at the date of progression/death after second line whichever comes first. Patients who died after the first line of therapy without progressing or receiving a second–line therapy are considered as failures at the date of death. Patients who progressed after the first line of therapy, received a second-line therapy and did not progress/die after second line are censored at the date they are known to be in remission/alive. Patients in remission after or during the first line of therapy are censored at the last date they are known to be in remission.

OS: All patients randomized in the first line of therapy are included. It is the time from randomization in the first line to death. Patients who died are considered as failures at the date of death. Patients who did not die are censored at the date they are known to be alive.

Endpoints excluded from the analysis and reported for completeness:

Second PFS : only patients who experienced first progression are included. It is the time from first relapse to second relapse/death. Patients progressing or dying after or during the second line of therapy are considered as failures at the date of progression/death whichever comes first. Patients in remission after or during the first 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. It is the time from first relapse to death. Patients who died are considered as failures at the date of death. Patients who did not die are censored at the date they are known to be alive

Subgroups Analysis

Subgroups were defined according to:

- protocol: GIMEMA-MM-03-05 , GIMEMA-RV-MM-209, MM-015; since in the GIMEMA-MM-RV-209 trial patients randomized to CT vs FDT received 2 different inductions (Rd-MPR or Rd-Mel200), 2 subgroups were evaluated for this protocol.

- baseline patient characteristics: age (≤65, 66-75, >75); gender, Karnofsky performance status (60-70%, 80%, 90-100%) ISS stage (stage I, stage II, stage III, missing data); cytogenetic profile defined by FISH 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 "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 1S Characteristics of the trials included in the pooled analysis

	GIMEMA MM-03-05 (8,9)		GIMEMA RV-MM-209(14)		MM-015(7)		
Recruitment							
Enrollment period	2006-09		2007-09		2007-09		
N° pts Randomized	511		402		459		
Time of randomization	at diagnosis		at diagnosis		at diagnosis		
Eligibility criteria							
NDMM setting	TNE		TE		TNE		
Age	≥65		≤65		≥65		
Treatment schema	**CT**	**FDT**	**CT**	**FDT**	**CT**	**FDT**	**FDT**
Induction	VMPT	VMP	Rd	Rd	MPR	MPR	MP
Consolidation			MPR MEL200-ASCT	MPR MEL200-ASCT			
Maintenance	VT	-	R		R	-	-
Duration of treatment							
Induction, months	~12	~12	~9-12	~9-12	9	9	9
Maintenance, months	24	-	Until PD	-	Until PD	-	-
Follow-up from random							
Median , months	54		51		62		

CT: continuous therapy; FDT: fixed duration of therapy; pts: patients; NDMM: newly diagnosed multiple myeloma; VMP: bortezomib-melphalan-prednisone; PS: performance status; VMPT: Bortezomib-melphalan-prednisone-thalidomide; VT: Bortezomib-thalidomide; Rd: Lenalidomide-low dose Dexamethasone; MPR: Melphalan-prednisone-lenalidomide; MEL200-ASCT: Melphalan 200 mg/m^2 followed by autologous stem cell transplantation; R: Lenalidomide; MP: Melphalan-prednisone; PD: progressive disease, TE: transplant-eligible, TNE: transplant not eligible.

Table 2S: Characteristics of the trial excluded from the pooled analysis

	IFM-2005-02 (12,13)		NCT-0114101 (11)		MM-020-IFM-07-01 (10)			IFM-99 (24)			MRC Myeloma IX (21,27)							
Recruitment																		
Enrollment period	2006-08		2005-09		2008-2013			2000-2003			2003-2007							
N° pts Randomized	614		460		1623			597			1970 / 820							
Time of Randomization	after ASCT		after ASCT		at diagnosis			at maintenance			at diagnosis / at maintenance							
Eligibility criteria																		
NDMM setting	TE		TE		TNE			TE			TE and NTE							
Age	≤65		≤71		≥65			<65			≥18							
Treatment schema	**CT**	**FDT**	**CT**	**FDT**	**CT**	**FDT**	**FDT**	**CT**	**FDT**	**FDT**	**CT**				**FDT**			
											Intensive		Non intensive		Intensive		Non intensive	
Induction	Any	Any	Any	Any				VAD	VAD	VAD	CTD	CVAD	MP	CTDa	CTD	CVAD	MP	CTDa
Consolidation	ASCT + R	ASCT	ASCT	ASCT	Rd	Rd	MPT	ASCT	ASCT	ASCT	ASCT	ASCT			ASCT	ASCT		
Maintenance	R	-	R	-	Rd	-	-	Pam+T	Pam	-	T	T	T	T	-	-	-	-
Duration of treatment																		
Induction, months	NA	NA	NA	NA	Until PD	18	18	~9	~9	~9	~9		~9		~9		~9	
Maintenance, months	Until PD	-	Until PD	-	-	-	-	Until PD	Until PD	-	Until PD		Until PD		-		-	
Follow-up from random																		
Median , months	67		34		37			29	29	30	38							
Difference from the included trials	Induction treatment not specified (not restricted to		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							

	novel agent- based therapy)

	HOVON-49 (20)		NMSG-12 (28)		GISMM-2001 (19)		MY.10 (25)	
Recruitment								
Enrollment period	2002-07		2002-07		2002-05		2002-09	
N° pts Randomized	344		363		331		332	
Time of Randomization	at diagnosis		at diagnosis		at diagnosis		after ASCT	
Eligibility criteria								
NDMM setting	TNE		TNE		TNE		TE	
Age	≥65		-		≥65		≥65	
Treatment schema	**CT**	**FDT**	**CT**	**FDT**	**CT**	**FDT**	**CT**	**FDT**
Induction	MPT	MP	MPT	MP	MPT	MP	NA	NA
Consolidation							ASCT	ASCT
Maintenance	T	-	T	-	T	-	TP	-
Duration of treatment								
Induction, months	~8	~8	Until plateau phase	Until plateau phase	~6	~6	NA	NA
Maintenance, months	Until PD	-	Until PD	-	Until PD	-	48 or Until PD	-
Follow-up from random								
Median, months	39		42		~38		49	
Differences compared with the included trials	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)	

CT: continuous therapy; FDT: fixed duration of therapy; pts: patients; NDMM: newly diagnosed multiple myeloma; ASCT: autologous stem cell transplantation ; R: Lenalidomide ; Rd: Lenalidomide-low dose Dexamethasone; MPT: Melphalan-prednisone-thalidomide; VAD: vincristine-adriamycin-dexamethasone; Pam: pamidronate; T: thalidomide; TP: thalidomide-prednisone; CVAD: cyclophosphamide-vincristine-adriamycin-dexamethasone; CTD cyclophosphamide- thalidomide- dexamethasone; CTDa, attenuated CTD; MP: melphalan-prednisone; PD: progressive disease, TE: transplant-eligible, TNE: transplant not eligible; NA: not available.

Table 3S. Survival estimates (PFS1, PFS2 and OS from randomization) including all 1218 patients randomized at enrolment.

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

Table 4S. PFS1, PFS2 and OS in patients enrolled in the trials: sensitivity analysis.

	HR	95% CI	P value
PFS1			
All trials	0.47	0.40-0.56	<0.001
Excluding GIMEMA MM-03-05	0.41	0.32-0.52	<0.001
Excluding GIMEMA MM-RV-209	0.48	0.39- 0.59	<0.001
Excluding MM-015	0.51	0.42- 0.62	<0.001
PFS2			
All trials	0.61	0.50-0.75	<0.001
Excluding GIMEMA MM-03-05	0.64	0.47-0.86	0.003
Excluding GIMEMA MM-RV-209	0.64	0.50-0.81	<0.001
Excluding MM-015	0.58	0.46-0.74	<0.001
OS			
All trials	0.69	0.54-0.88	0.003
Excluding GIMEMA MM-03-05	0.79	0.55-1.13	0.193
Excluding GIMEMA MM-RV-209	0.72	0.54-0.95	0.022
Excluding MM-015	0.62	0.46-0.84	0.002

Table 5S. PFS1, PFS2 and OS in patients enrolled in the trials excluded from this pooled analysis

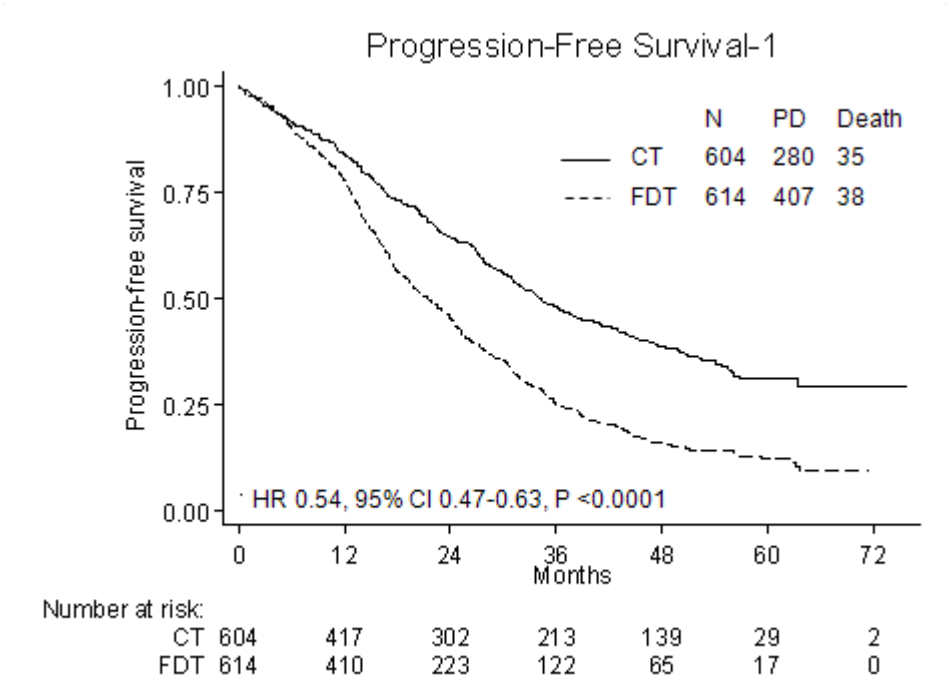
	IFM-2005-02 (12,13)				NCT-0114101(11)				MM-020 (10)°				IFM-99 (24)§				MRC Myeloma IX (21,27)			
	CT (median, months)	FDT (median, months)	HR (IC 95%)	P	CT (median, months)	FDT (median, months)	HR (IC 95%)	P	CT (median, months)	FDT(median, months)	HR (IC 95%)	P	CT (median, months)	FDT (median, months)	HR (IC 95%)	P	CT (median, months)	FDT (median, months)	HR (IC 95%)	P
PFS1	46	24	NA	<0.001	46*	27*	0.48 (0.36-0.63)	<0.001	25	21	0.72 (0.61-0.85)	<0.001	NA	NA	NA	0.002	23	15	1.45 (1.22-1.73)	<0.001
PFS2	NA	NA	NA	NA	NA	NA	NA	NA	43	36	0.78^	0.005	NA	NA	NA	NA	NA	NA	NA	NA
OS	82	81	NA	0.80	NR	NR	0.62 (0.40-0.95)	0.03	NA	NA	0.78 (0.64-0.96)	0.02	NR	NR	NA	0.04	NA	NA	0.91 (0.72-1.17)	0.4

	HOVON-49 (20)				NMSG-12 (28)				GISMM-2001 (19)				MY.10(25)			
	CT (median, months)	FDT (median, months)	HR (IC 95%)	P	CT (median, months)	FDT (median, months)	HR (IC 95%)	P	CT (median, months)	FDT (median, months)	HR (IC 95%)	P	CT (median, months)	FDT (median, months)	HR (IC 95%)	P
PFS1	13**	9**	NA	<0.001	15	14	NA	NA	21.8	14.4	0.63(0.48-0.81)	<0.001	NA	NA	NA	<0.0001
PFS2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
OS	40	31	NA	0.05	29	32	NA	0.16	45	47.6	1.04(0.76-1.44)	0.79	NR	NR	NA	0.18

CT: continuous therapy; FDT: fixed duration of therapy; PFS1: progression-free survival1; PFS2: progression-free survival2; OS: overall survival; NA not available; y:year. ^95% CI not available; *Time to progression.° MM-020: data refers to the comparison Rd until PD (CT) vs MPT (FDT), since this was the main comparison of the trial. §IFM-99: data refer to the comparison Pamidronate-thalidomide maintenance (CT arm) vs no maintenance or pamidronate alone.**Event-free-survival.

Figure 1S. A) Progression-free survival-1 from enrollment; B) Progression-free survival-2 from enrollment; C) Overall survival from enrollment. CT, continuous therapy; FDT, fixed duration of therapy, PD, progressive disease.

A



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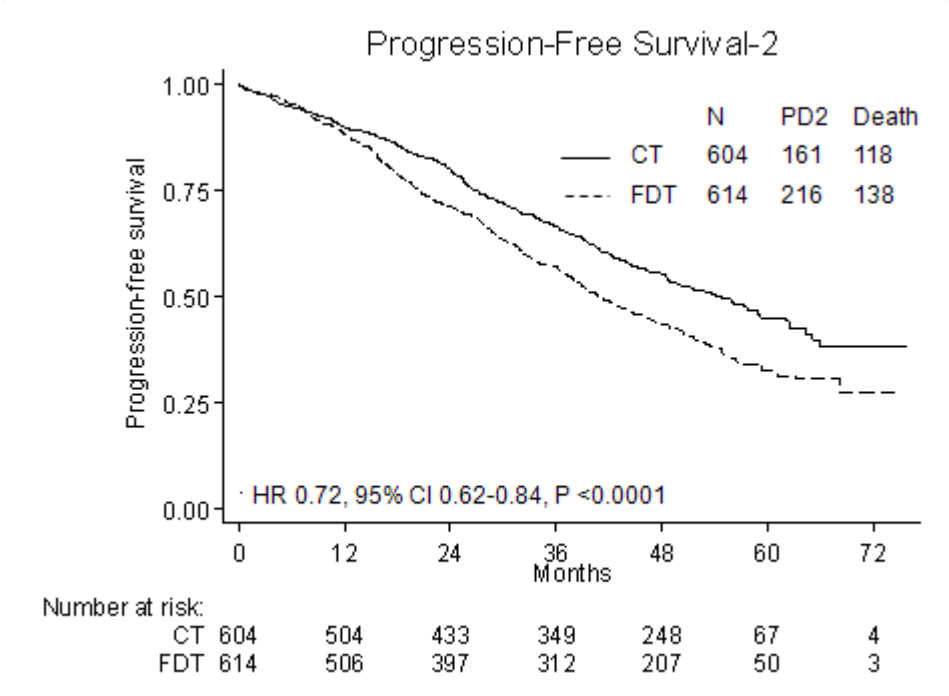

C

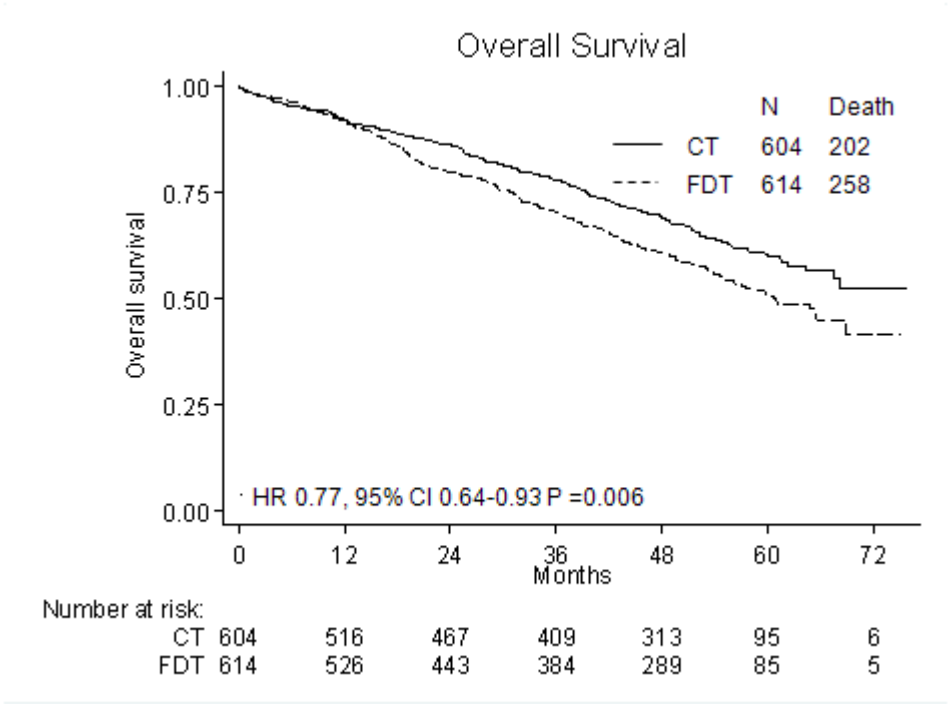
Overall Survival
1.00
0.75
0.50
0.25
0.00
Overall survival
N Death
CT 604 202
FDT 614 258
HR 0.77, 95% CI 0.64-0.93 P =0.006
0 12 24 36 48 60 72
Months
Number at risk:
CT 604 516 467 409 313 95 6
FDT 614 526 443 384 289 85 5

Figure 2S. Types and frequency of second-line therapies