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Continuous Therapy in Standard- and High-Risk Newly-Diagnosed Multiple Myeloma: a Pooled Analysis of 2 Phase III Trials

Running title: Continuous therapy in NDMM according to patient prognosis

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Authorship

MD, MB and FG designed the study; MD collected and assembled the data; all authors provided patients and/or materials in the source trials; MD, SS, MB, FG analyzed and interpreted the data; MD wrote the first draft of the manuscript; all authors had access to the final data, critically revised the draft manuscript, and approved the final version before submission.

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Conflicts of interest disclosure

LDP has served on the advisory boards for Celgene, Amgen, Janssen, Gilead, Abbvie. MO has received honoraria from Celgene. MTP has served on the advisory boards for and received honoraria from Celgene, Janssen-Cilag, BMS, Takeda, and Amgen. GDS has served on the advisory board for Celgene. FP has received speaker's fees and travel grants from MSD, Jazz, Medac and Neovii. AP is currently a Takeda employee. VM has served on the advisory boards for and received lecture fees from Celgene and Janssen. MB has received honoraria from Sanofi, Celgene, Amgen, Janssen, Novartis, Abbvie, BMS, and research funding from Celgene, Janssen, Amgen, BMS, Mundipharma, Novartis, and Sanofi. FG has served on the advisory boards for Takeda, Seattle Genetics, Roche, Mundipharma, Janssen and has received honoraria from Takeda, Amgen, Celgene, Janssen, and BMS. The other authors declare no competing financial interests.

Continuous Therapy in Standard- and High-Risk Newly-Diagnosed Multiple Myeloma: a Pooled Analysis of 2 Phase III Trials

Running title: Continuous therapy in NDMM according to patient prognosis

Abstract

Background. Risk-adapted therapy is a common strategy in curable hematologic malignancies: standard-risk patients receive less intensive treatment, whereas high-risk patients require a more intensive approach. This model cannot be applied in multiple myeloma (MM), which is still incurable.
Continuous treatment (CT) is a key strategy for MM treatment, since it improves duration of remission. However, the role of CT according to standard- or high-risk baseline prognosis remains an open question.
Patients and methods. We performed a pooled analysis of 2 phase III trials (GIMEMA-MM-03-05 and RV-MM-PI-209) that randomized patients to CT vs fixed-duration-therapy (FDT).
Results. In the overall patient population (n=550), CT improved progression-free survival1 (PFS1) (HR 0.54), PFS2 (HR 0.61) and overall survival (OS) (HR 0.71) vs FDT. CT improved PFS1 both in R-ISS I (HR 0.49) and R-ISS II/III patients (HR 0.55). Four-year PFS1 was 38% in R-ISS II/III patients receiving CT and 25% in R-ISS I patients receiving FDT, with similar trends for PFS2 and OS. High-risk patients benefited more from proteasome-inhibitor plus immunomodulatory-based CT than immunomodulatory alone.
Conclusion. Good prognosis patients receiving FDT lose their prognostic advantage over high-risk patients receiving CT and high-risk patients may benefit from more intensive maintenance including proteasome inhibitors and immunomodulators.

Keywords: multiple myeloma; newly diagnosed; continuous therapy; high risk; novel agents

Figures: 3
References: 25
Supplementary appendix: uploaded as separate file

Introduction

Multiple myeloma (MM) is a clonal plasma cell disorder representing 1% of all cancers and 13% of all hematologic tumors (Howlader et al., 2013). The introduction of novel agents (thalidomide, bortezomib and lenalidomide) into clinical practice greatly improved the outcome of MM patients in the last decades (Kumar et al., 2008). Currently, treatment of newly-diagnosed MM (NDMM) patients is differentiated according to transplant-eligibility. One of the standards of care in transplant-ineligible patients is continuous therapy (CT) with lenalidomide plus low-dose dexamethasone (Rd) until progression (Facon et al., 2017). More recently, the addition of bortezomib to Rd proved to be superior to Rd alone as induction treatment in patients without an immediate intent to transplant (Durie et al., 2017). Of note, in this trial, both bortezomib-Rd and Rd induction arms were followed by Rd CT. Another standard of care is bortezomib-melphalan-prednisone (VMP) for 9 cycles.

CT with bortezomib has been also evaluated. In transplant ineligible patients, bortezomib-melphalan-prednisone-thalidomide followed by bortezomib-thalidomide (VMPT-VT) maintenance showed a progression-free survival (PFS) and overall survival (OS) advantage over VMP with no maintenance (Palumbo et al., 2014a, 2010).

Again in transplant-ineligible NDMM patients, a Spanish phase III trial showed a remarkable median PFS of 35 months and a 5-year OS of 58% with bortezomib-prednisone or bortezomib-thalidomide maintenance after bortezomib-based induction (Mateos et al., 2012).

In transplant-eligible patients, an induction treatment with proteasome inhibitors plus immunomodulatory agents (IMiDs)/chemotherapy followed by high-dose melphalan and autologous stem-cell transplantation (ASCT) is the standard (Palumbo and Cavallo, 2012). Post-transplantation lenalidomide approximately doubled PFS in all randomized clinical trials performed so far, and a recent meta-analysis showed an advantage in OS as well (Attal et al., 2016, 2012; Jackson et al., 2016; McCarthy et al., 2012; Palumbo et al., 2014b). Post-transplantation maintenance with bortezomib has also been evaluated. In the phase III Hovon-65/GMMG-HD4 trial, bortezomib-based treatment before and after ASCT showed a PFS advantage compared with classical cytotoxic induction therapy followed by post-ASCT thalidomide maintenance (Goldschmidt et al., 2017). Of note, the negative prognostic effects on PFS and OS of deletion 17p13 and

baseline renal impairment were abrogated in patients receiving bortezomib-based CT. In another phase III trial, post-ASCT maintenance with thalidomide-bortezomib showed a PFS advantage over interferon-alpha2b and thalidomide maintenance (Rosiñol et al., 2017).

The rationale of implementing CT in patient's care is to enhance the results of upfront induction/consolidation therapy, preventing or delaying tumor progression and eventually death. Although efficacy data about CT strongly support its use, there are still some unanswered key questions. In curable hematologic malignancies, risk-adapted therapy is commonly applied: standard-risk patients may be cured with less intensive and shorter duration of treatment, which can minimize the risk of drug-related adverse events; whereas high-risk patients require more intensive regimens. In MM, this model may not be applicable, since the disease is still incurable. The goal of this study was to dissect the role of CT in standard- and high-risk NDMM patients, to specifically evaluate if CT could be avoided in standard-risk patients.

Methods

Patients and treatment

We performed an individual patient data pooled analysis of two phase III clinical trials (GIMEMA-MM-03-05 and RV-MM-PI-209) coordinated by the same principal investigator, in which NDMM patients were randomly assigned to CT or FDT with novel-agents (*Table S1*). The two studies were approved by the institutional review boards of each participating center and are registered at ClinicalTrials.gov. All patients provided written informed consent before entering the source trials. The work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Patient prognosis was defined according to the revised International Staging System (R-ISS), which combines the International Staging System (ISS), baseline cytogenetics and LDH (Palumbo et al., 2015a). FDT was defined as an upfront treatment (induction/consolidation) for up to 1 year, CT was defined as an upfront treatment (induction/consolidation) followed by maintenance lasting at least for 2 years. Both definitions are based upon an intention-to-treat (ITT) population. Details of the inclusion/exclusion criteria of the source studies have been previously published (Palumbo et al., 2014a,

2014b, 2010). A detailed description of the treatment is given in the *Supplementary Appendix*. Briefly, the GIMEMA-MM-03-05 trial included NDMM elderly ASCT-ineligible patients, who were randomized to receive 9 cycles of VMPT followed by 2 years of VT maintenance versus 9 cycles of VMP with no maintenance (Palumbo et al., 2014a, 2010). The RV-MM-PI-209 trial included NDMM ASCT-eligible patients, who received induction therapy with 4 cycles of Rd and then were randomized to consolidation with two courses of melphalan 200 mg/m^2 followed by ASCT (MEL200-ASCT) or six 28-day cycles of oral chemotherapy plus lenalidomide. In this trial patients were also randomized to maintenance with lenalidomide versus no maintenance after consolidation (Palumbo et al., 2014b).

In both trials, the median follow-up time was > 4 years.

Statistical analysis

The primary endpoints were PFS1, PFS2 and OS in the ITT population eligible for CT vs FDT (detailed endpoints definition in the *Supplementary*) according to patients' baseline prognosis (R-ISS I-standard risk vs R-ISS II/III-high risk) (Palumbo et al., 2015a).

Data of the two trials were pooled together and analysed. Patients enrolled but not eligible for CT vs FDT were excluded. Because patients were randomly assigned at study enrolment, to specifically assess the effect of CT we included all patients alive and progression-free after 10 months from random assignment – which corresponds to the average duration of induction/consolidation in the two trials (landmark analysis). Baseline R-ISS Stage assessment was based on the International Myeloma Working Group guidelines.(Palumbo et al., 2015a)

Time-to-event endpoints were calculated from the time of inclusion in the landmark analysis and were analyzed using the Kaplan–Meier method. Treatment groups were compared with the log-rank test. Stratified log-rank test was used for comparisons within groups. The Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) and the 95% confidence intervals (CIs) for the main comparisons, and Grambsch and Therneau test for testing the proportional hazard assumption. To account for potential confounders, the Cox models for the comparison CT vs FDT were adjusted for the trial effect, best response pre-maintenance, R-ISS stage and Easter Oncology Cooperative Group performance status (ECOG-PS).

Subgroup analyses were performed using interaction terms between treatment and each of the covariates included in the Cox model. All HRs were estimated with their 95% confidence intervals (95% CI) and two-sided p-values.

Data were analyzed using SAS software (Version 8.2) and R (Version 3.1.1).

Results

Patients

The two trials enrolled 913 NDMM patients (511 ASCT-ineligible patients in the GIMEMA-MM-03-05 trial and 402 ASCT-eligible patients in the RV-MM-PI-209 trial). A total of 363 patients were not eligible for CT vs FDT comparison and were excluded. The main reasons for exclusion were progressive disease (119 patients) or unacceptable adverse events (122 patients) during the induction/consolidation phase (Palumbo et al., 2014a, 2014b, 2010). The remaining 550 patients were included in the analysis (*Figure S1*), 275 randomly allocated to CT, 275 to FDT. Patients demographics and disease characteristics in the two groups were well balanced (*Table S2*). The median follow-up was 57 months from enrollment and 47 months from landmark point. At the last follow-up, 105/275 (38.2%) patients in the CT arm vs 48/275 (17.5%) patients in the FDT arm were on study, either on maintenance or progression-free after treatment discontinuation for reasons other than progression. In the CT arm, the rate of discontinuation due to disease progression was 37.8%, while only 9.1% of patients discontinued treatment for adverse events. The median duration of maintenance was 23.4 months.

Progression-free survival 1

CT significantly improved PFS1 (4-year 38% vs 18% HR 0.54, 95% CI 0.44-0.66, p<0.001) compared to FDT in the overall patient population (*Figure 1A*). The advantage of CT over FDT was confirmed across all patient subgroups; specifically, CT significantly prolonged PFS1 in R-ISS I patients (HR 0.49, 95% CI 0.29-0.81), as well as in R-ISS II/III patients (HR 0.55, 95% CI 0.42-0.73) (*Figure 1B*). The 4-year PFS1 was 46% in R-ISS I patients receiving CT, 38% in R-ISS II/III patients receiving CT, 25% in R-ISS I patients receiving FDT, 18% in R-ISS II/III patients receiving FDT (R-ISS stratified Log-rank p<0.001) (*Figure 1C*).

Of note, standard-risk patients receiving FDT showed a worse 4-year PFS1 rate compared to high-risk patients receiving CT.

Progression-free survival 2

CT patients performed better than FDT patients also in terms of PFS2 (4-year 65% vs 44% HR 0.61, 95% CI 0.47-0.79, p<0.001) (*Figure 2A*). This advantage was again confirmed across all patient subgroups, with no significant differences within each subgroup; again, there was a reduction in the risk of second progression/death with CT compared to FDT for both R-ISS I patients (HR 0.58, 95% CI 0.28-1.17) and R-ISS II/III patients (HR 0.60, 95% CI 0.43-0.84) (*Figure 2B*). The 4-year PFS2 was 69% in R-ISS I patients receiving CT, 62% in R-ISS II/III patients receiving CT, 61% in R-ISS I patients receiving FDT, 41% in R-ISS II/III patients receiving FDT (R-ISS stratified Log-rank p<0.001) (*Figure 2C*). Standard-risk patients receiving FDT and high-risk patients receiving CT showed a superimposable 4-year PFS2 rate.

Overall survival

The advantage of CT over FDT in PFS1 and PFS2 also led to an advantage in OS (CT vs FDT 4-year OS 74% vs 67%, HR 0.71, 95% CI 0.52-0.98, p=0.04) (*Figure 3A*). Results of the subgroup analysis might be limited by the low number of events, in particular in good prognosis patients, however a trend towards a better OS for both R-ISS I patients (HR 0.70, 95% CI 0.29-1.68) and R-ISS II/III patients (HR 0.66, 95% CI 0.43-0.99) was shown (*Figure 3B*).

The 4-year OS was 76% in R-ISS I patients receiving CT, 73% in R-ISS II/III patients receiving CT, 77% in R-ISS I patients receiving FDT, 63% in R-ISS II/III patients receiving FDT (R-ISS stratified Log-rank p=0.015) (*Figure 3C*).

Subgroup analysis in bortezomib/thalidomide- and lenalidomide-based CT

In our study, 149 patients received bortezomib/thalidomide (VT) based CT and 126 lenalidomide (R) based CT.

CT discontinuation due to adverse events was more frequent with VT than with R (13% vs 5%, respectively). On the contrary, discontinuation due to disease progression was slightly lower with VT than with R (36% vs 40%, respectively), but this was likely due to the different duration of maintenance (2 years with VT, until PD with R). Nevertheless, the median duration of maintenance was 23.4 months and was comparable between the two trials.

In the VT-based group, both R-ISS I and R-ISS II/III patients reported similar PFS1 (*Figure S2A,* HR 0.94, 95% CI 0.50-1.79, p=0.87), while in the R-based CT group, R-ISS I patients showed a trend toward better PFS1 than R-ISS II/III patients (*Figure S2B*, HR 0.61, 95% CI 0.33-1.14, p=0.12).

The different effect of VT and R-based CT was also evident in PFS2 and OS (*Figure S3*). In the VT-based CT group, R-ISS I and R-ISS II/III patients had similar PFS2 (Figure S2A, HR 0.89, 95% CI 0.43-1.95, p=0.77) and OS (Figure S3C, HR 1.00, 95% CI 0.40-2.52, p=0.99). Whereas, in the R-based CT group, R-ISS I patients showed a significantly better PFS2 (Figure S3B, HR 0.34, 95% CI 0.13-0.91, p=0.03) and OS (Figure S3D, HR 0.27, 95% CI 0.08-0.94, p=0.04) compared to R-ISS II/III patients.

These data suggest that different drugs used as maintenance during first-line treatment may play a different role in standard- and high-risk patients. Moreover, this effect is evident also in PFS2 and OS, despite the difference between-second line therapies used in VT-based and R-based CT groups (*Figure S4*). At relapse, the majority of patients (65%) treated with VT-based CT in first line received an IMiD-based second-line therapy; whereas, the majority of patients (88%) treated with R-based CT in first line received a proteasome inhibitor-based second-line therapy.

Discussion

CT with novel agents in NDMM patients was associated with a remarkable improvement in patients' outcome in several large randomized clinical trials, thus it is becoming a new standard of care (Palumbo et al., 2015b).

In curable hematologic malignancies, such as Hodgkin's lymphoma, it is reasonable to tailor therapy according to baseline disease risk and avoiding overtreatment and toxicity is a key point. In MM, whether

standard-risk patients require intensification and/or prolonged treatment is currently a matter of debate (Remer and Johnson, 2015).

Our analysis showed the advantage of CT over FDT both in high- and standard-risk patients, thus further supporting the use of CT as a standard approach in all NDMM patients.

Furthermore, disease progression was the main reason leading to CT discontinuation and determined MM patients' long-term outcome. CT discontinuation due to drug-related adverse events was less than 10%, a particularly relevant aspect to assess the efficacy/safety balance of this approach. Indeed, an effective CT treatment should be associated with low toxicity and discontinuation rate, while delivering a high percentage of the planned dose of maintenance drugs. The phase III trials included in this analysis did meet such requirements, and CT successfully translated into a significant clinical benefit (Palumbo et al., 2014a, 2014b).

In our study, a shorter therapeutic strategy (i.e. FDT) in standard-risk patients led to an unacceptable worsening of clinical outcome, which becomes similar to the one of high-risk patients. This is also consistent with the MRC XI trial in the upfront setting (Jackson et al., 2016). Therefore, CT should certainly be the preferred option in both standard and high-risk disease. This is in line with recently risk-adapted proposed approaches.

In our analysis, patients with high-risk disease did benefit from CT. However, the outcome of high-risk patients is still poor and inferior to the one of standard-risk patients, prompting the need for other therapeutic strategies to mitigate – and possibly cancel – this prognostic difference. Most of the studies exploring the role of CT with initial thalidomide and subsequent lenalidomide found that IMiDs alone may be suboptimal in high-risk patients (Attal et al., 2016; Benboubker et al., 2014) Conversely, there is evidence supporting the use of prolonged bortezomib in patients with high-risk cytogenetics (Cavo et al., 2012; Dispenzieri, 2016; Neben et al., 2012; Sonneveld et al., 2015; Straka et al., 2015) To shed light on this aspect, we also analyzed the different impact of maintenance with IMiD alone or proteasome inhibitor (PI) + IMiDs. Interestingly, we found that IMiDs + PI-based CT mitigated the harmful effect of baseline R-ISS II/III as compared to IMiDs alone-based CT. This is again in line with recent recommendations on the management of high-risk patients (Mikhael et al., 2013).

Nevertheless, in our patient population, the R-based CT group showed a better outcome than the VT-based CT group. This may be due to fact that patients treated with VT-based CT were transplant-ineligible, while those treated with R-based CT were younger and eligible for MEL200-ASCT.

Our study has some limitations. The analysis included both patients eligible and ineligible for transplantation; still, the number of patients undergoing ASCT was well balanced between CT and FDT groups. Baseline R-ISS was not available in 27% of patients. In the GIMEMA-MM-03-05 trial, the advantage of CT could partly be related at least to the association of thalidomide with bortezomib, melphalan, and prednisone during induction phase. Subsequent therapeutic lines were not prespecified in the study protocols and were left to investigators' discretion. PFS2 end-point was not included in the original study protocols. The inclusion of R-ISS II and R-ISS III patients in the same baseline risk group, due to the low numbers of R-ISS III patients, may lead to a possible overestimation of the outcome of very high-risk patients.

In conclusion, CT improved the median PFS1 by approximately 18 months in NDMM patients. The PFS1 advantage of CT over FDT translated into an advantage in PFS2 and OS. Our analysis adds another piece of evidence to the adoption of CT as the preferred treatment modality in all NDMM patients, regardless of baseline risk assessment. Data suggest that good-prognosis patients receiving FDT lose their prognostic advantage over high-risk patients receiving CT and that high-risk patients may benefit from more intensive maintenance including PI and IMiDs.

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Main Figures: titles and legends

Figure 1. PFS1 analysis in patients receiving CT vs FDT: (A) Overall population; (B) subgroup analysis; (C) Outcome according to R-ISS stage.
HR, adjusted hazard ratio; MPR: Melphalan-Prednisone-Lenalidomide; MEL200-ASCT, melphalan at 200 mg/m^2 followed by autologous stem cell transplantation.

Figure 2. PFS2 analysis in patients receiving CT vs FDT: (A) Overall population; (B) Subgroup analysis; C) Outcome according to R-ISS stage.
HR, adjusted hazard ratio; MPR, melphalan-prednisone-lenalidomide; MEL200-ASCT, melphalan at 200 mg/m^2 followed by autologous stem cell transplantation.

Figure 3. OS analysis in patients receiving CT vs FDT: (A) Overall population; (B) Subgroup analysis; C) Outcome according to R-ISS stage.
HR, adjusted hazard ratio; MPR, melphalan-prednisone-lenalidomide. MEL200-ASCT, melphalan at 200 mg/m^2 followed by autologous stem cell transplantation.

Supplementary tables and figures: titles and legends [Supplementary Appendix file]

Table S1. Characteristics of the two source trials comparing CT vs FDT
CT: Continuous therapy; FDT: Fixed-duration therapy; NDMM: newly diagnosed multiple myeloma; PBSC: peripheral blood stem cell; G-CSF: granulocyte colony stimulating factor; Cy: cyclophosphamide; Mel200: melphalan at 200 mg/m^2; ASCT: autologous stem cell transplantation; MPR: melphalan, prednisone, lenalidomide; Rd: lenalidomide, low-dose dexamethasone; R: lenalidomide; VMPT: bortezomib, melphalan, prednisone, thalidomide; VT: bortezomib, thalidomide; VMP: bortezomib, melphalan, prednisone.

Table S2. Baseline patient characteristics
ISS: International Staging System; ECOG: Eastern Cooperative Oncology Group; R-ISS: Revised International Staging System; CT, continuous therapy; FDT, fixed duration of therapy; ASCT, autologous stem cell transplantation; Mel200: melphalan at 200 mg/m^2; High cytogenetic risk defined as FISH positivity for at least one of the following: t(4;14)-t(14;16)-del17p; IQR, interquartile range.

Figure S1. Study flow
PD, progressive disease; CT, continuous therapy (upfront treatment + maintenance lasting at least 2 years); FDT, fixed-duration therapy (<1 year of upfront treatment).

Figure S2. PFS1 in the population of patients receiving CT according to baseline R-ISS
Panel A: patients enrolled in the GIMEMA-MM-03-05 trial receiving a Bortezomib/Thalidomide-based CT.
Panel B: patients enrolled in the RV-MM-PI-209 trial receiving a Lenalidomide-based CT.

R-ISS: Revised International Staging System; CT, continuous therapy (upfront treatment + maintenance lasting at least 2 years); HR, hazard ration; CI, confidence interval, P, P value.

Figure S3. PFS2 (Panels A-B) and OS (Panels C-D) in the population of patients receiving CT according to baseline R-ISS
Panels A and C: patients enrolled in the GIMEMA-MM-03-05 trial receiving a Bortezomib/Thalidomide-based CT.
Panels B and D: patients enrolled in the RV-MM-PI-209 trial receiving a Lenalidomide-based CT.

R-ISS: Revised International Staging System; CT, continuous therapy (upfront treatment + maintenance lasting at least 2 years); HR, hazard ration; CI, confidence interval, P, P value.

Figure S4. Types and frequency of second-line therapies
CT, continuous therapy; FDT, fixed duration of therapy; IMiDs, immunomodulatory drugs; PIs, proteasome inhibitors

Figure 1A

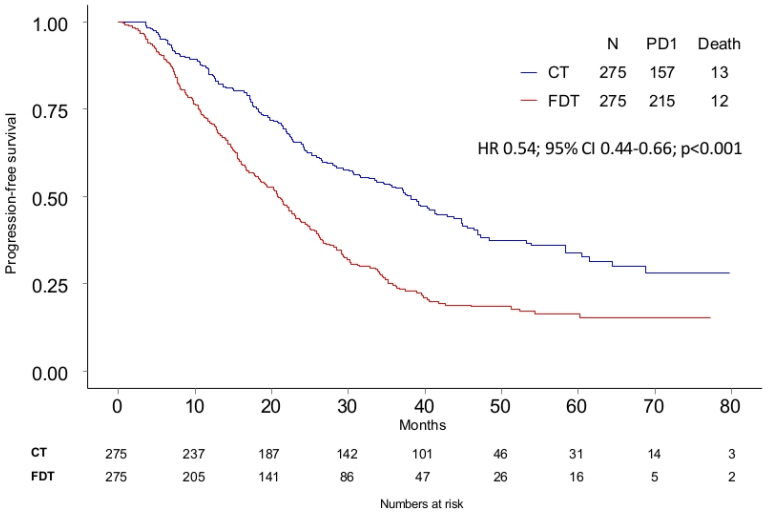


Figure 1B

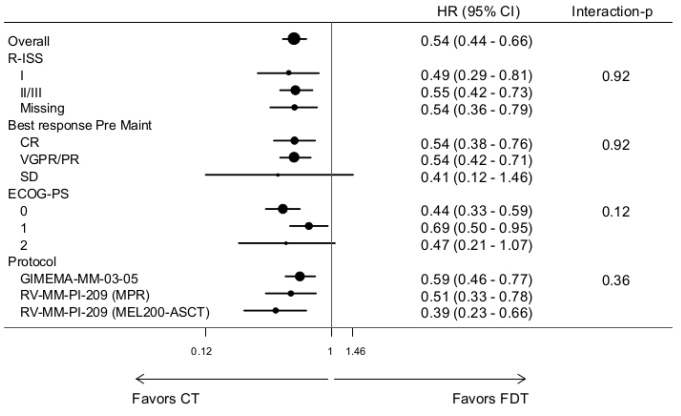


Figure 1C

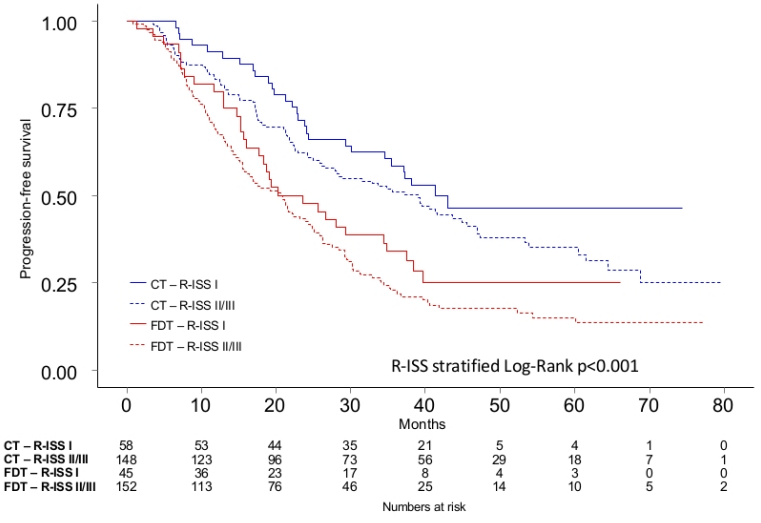
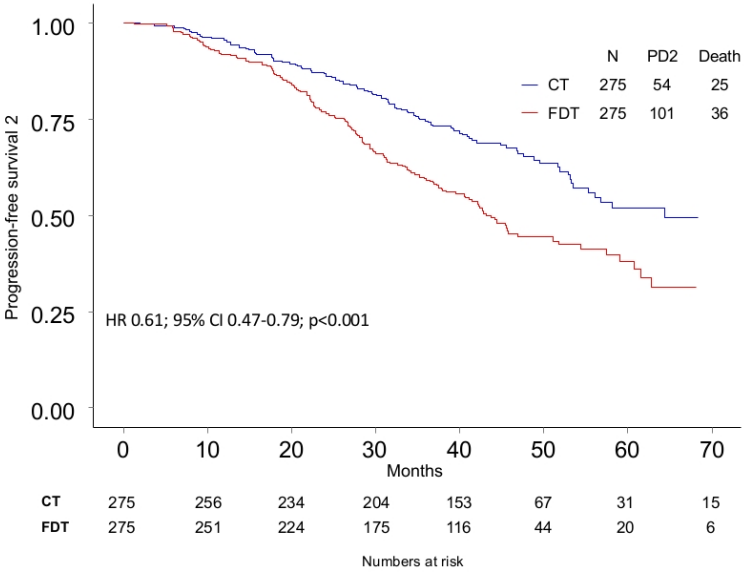


Figure 2A



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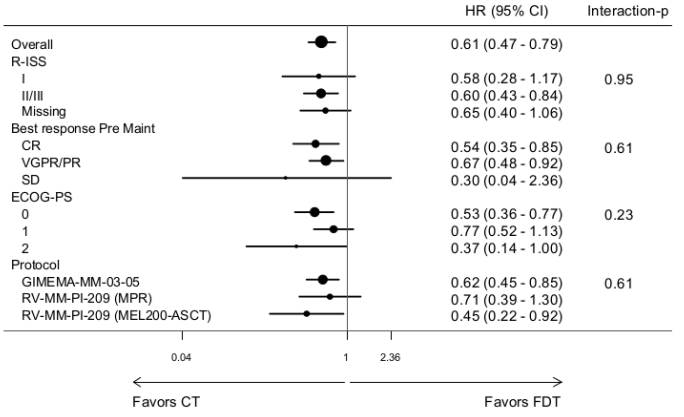

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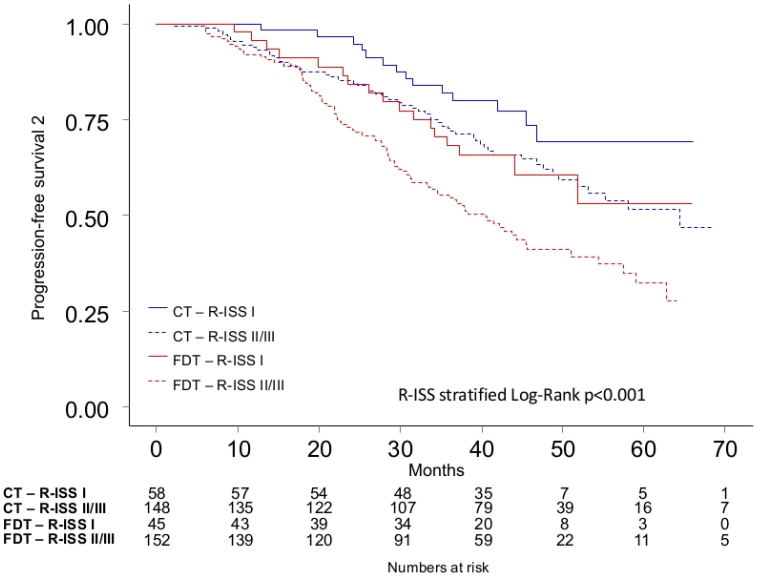


Figure 3A

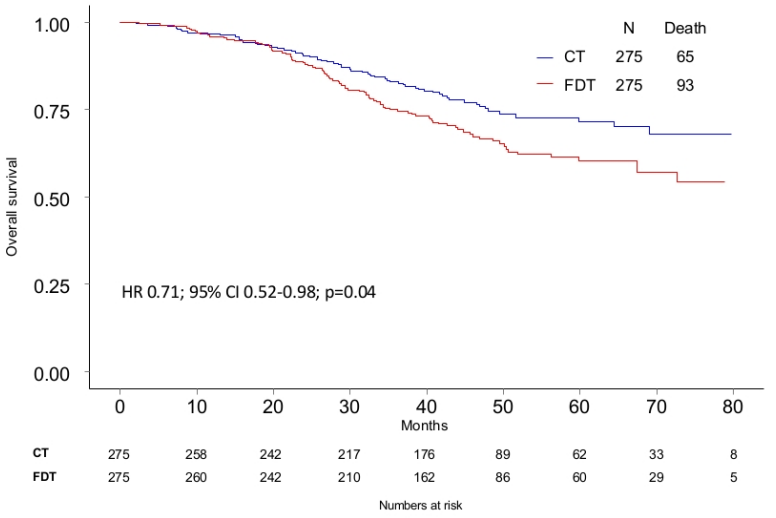
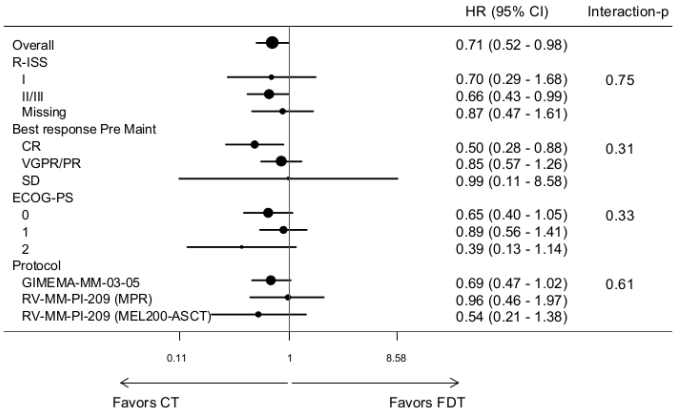


Figure 3B



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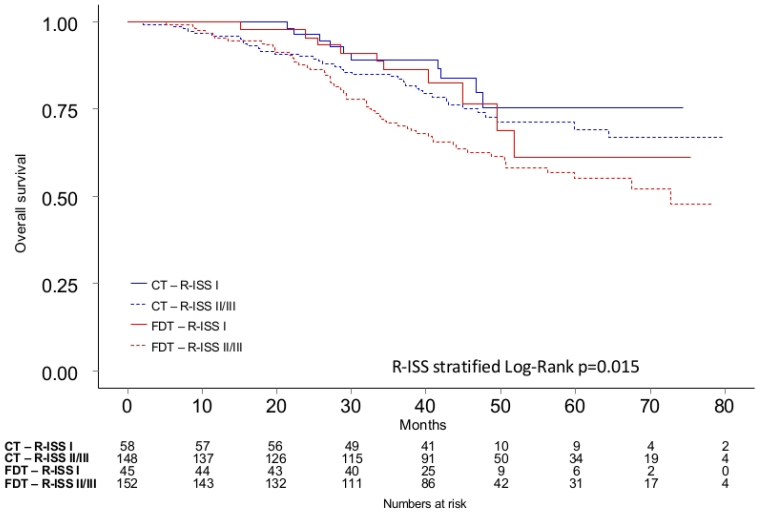

Continuous Therapy in Standard- and High-Risk Newly-Diagnosed Multiple Myeloma: a Pooled Analysis of 2 Phase III Trials

Supplementary Appendix

Supplementary Methods

Treatment

RV-MM-PI-209

Induction: four 28-day cycles of lenalidomide (25 mg days 1-21) and dexamethasone (40 mg days 1,8,15,22).

Consolidation (randomization, MEL200-ASCT vs conventional chemotherapy): MEL200-ASCT melphalan 200 mg/sqm (day -2) followed by stem cell support (day 0). Two cycles were planned, one cycle only was allowed for patients achieving at least a VGPR after the first one. Conventional chemotherapy: patients received melphalan (0.18 mg/kg on days 1–4), prednisone (2 mg/kg on days 1–4) and lenalidomide (10 mg on days 1–21) (MPR).

Maintenance (Randomization, lenalidomide vs no maintenance): lenalidomide 10 mg on days 1–21 every 28 days until progressive disease (PD) or until tolerated, or no maintenance.

Randomization: an informatics system randomly assigned patients to treatment at enrolment, but disclosed the treatment allocation only when the patient reached the end of the induction and their eligibility for the consolidation and maintenance regimens was confirmed. Patients were eligible for maintenance if they did not experience unacceptable toxicity or progressive disease (PD) during the induction/consolidation phase. Both the patient and the treating physician did not know the consolidation and maintenance arm until the end of induction phase.

GIMEMA-MM-03-05

This phase III study represents a prospective randomized open label randomized (1:1) trial.

Experimental therapy (Arm A) consisted of induction with nine 6-week cycles of oral melphalan 9 mg/m^2 on days 1 to 4; oral prednisone 60 mg/m^2 on days 1 to 4; intravenous bortezomib 1.3 mg/m^2 on days 1, 4, 8, 11,

22, 25, 29, and 32 during cycles 1 to 4 and on days 1, 8, 22, and 29 during cycles 5 to 9; and thalidomide 50 mg per day continuously. After the last VMPT course, patients received maintenance therapy with bortezomib 1.3 mg/m^2 every 14 days and thalidomide 50 mg per day for 2 years or until progression or relapse.

Standard therapy (Arm B) consisted of induction therapy with nine 6-week cycles of VMP at the same doses as previously described, without maintenance.

After a safety interim analysis, the protocol was amended to reduce the incidence of peripheral neuropathy. After the inclusion of the first 139 patients, both VMPT-VT and VMP induction schedules were changed to nine 5-week cycles and bortezomib dose was modified to 1.3 mg/m^2 on days 1, 8, 15, and 22 during cycles 1 to 9.

Treatment was withheld on withdrawal of the patient's consent, disease progression, or the occurrence of any grade 4 hematologic adverse events or grade 3 to 4 nonhematologic toxic effects.

Endpoint definition

Endpoints included in the analysis:

Because patients were randomly assigned at study entry, to approximate the Continuous Therapy (CT) population and to assess more specifically the effect of CT, we included all patients alive and progression free after 10 months from random assignment, which corresponds to the average duration of induction/consolidation in the two trials (landmark analysis). For the analyses, on the basis of the CT population, all time-to-event endpoints were calculated from the time of inclusion in the landmark analysis.

PFS1 is the time from the inclusion in the landmark analysis 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.(European Medicines Agency, 2012)

PFS2 is the time from the inclusion in the landmark analysis 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 is the time from the inclusion in the landmark analysis 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.

Subgroup analysis

Subgroups were defined according to: Revised ISS (R-ISS) stage [stage I, II/III, Missing]; Best Response before maintenance therapy [CR, VGPR/PR, other]; ECOG-PS [0, 1, 2]; Protocol (GIMEMA-MM-03-05, RV-MM-PI-209 MPR, RV-MM-PI-209 Mel200-ASCT).

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Table S1. Characteristics of the two source trials comparing CT vs FDT

	RV-MM-PI-209		GIMEMA-MM-03-051	
	CT	***FDT***	***CT***	***FDT***
Enrollment period	2007-2009		2006-2009	
Number of patients enrolled	402		511	
N° pts eligible for maintenance	251		299	
Eligibility criteria				
NDMM setting	Transplant eligible		Transplant ineligible	
Age, years	≤ 65		≥ 65 or any age with coexisting comorbidities	
Treatment				
Induction	4 Rd; Cy 4g/m^2+ G-CSF & PBSC collection		9 VMPT	9 VMP
Consolidation	2 Mel200-ASCT vs 6 MPR		no	No
Maintenance	R	no	VT	No

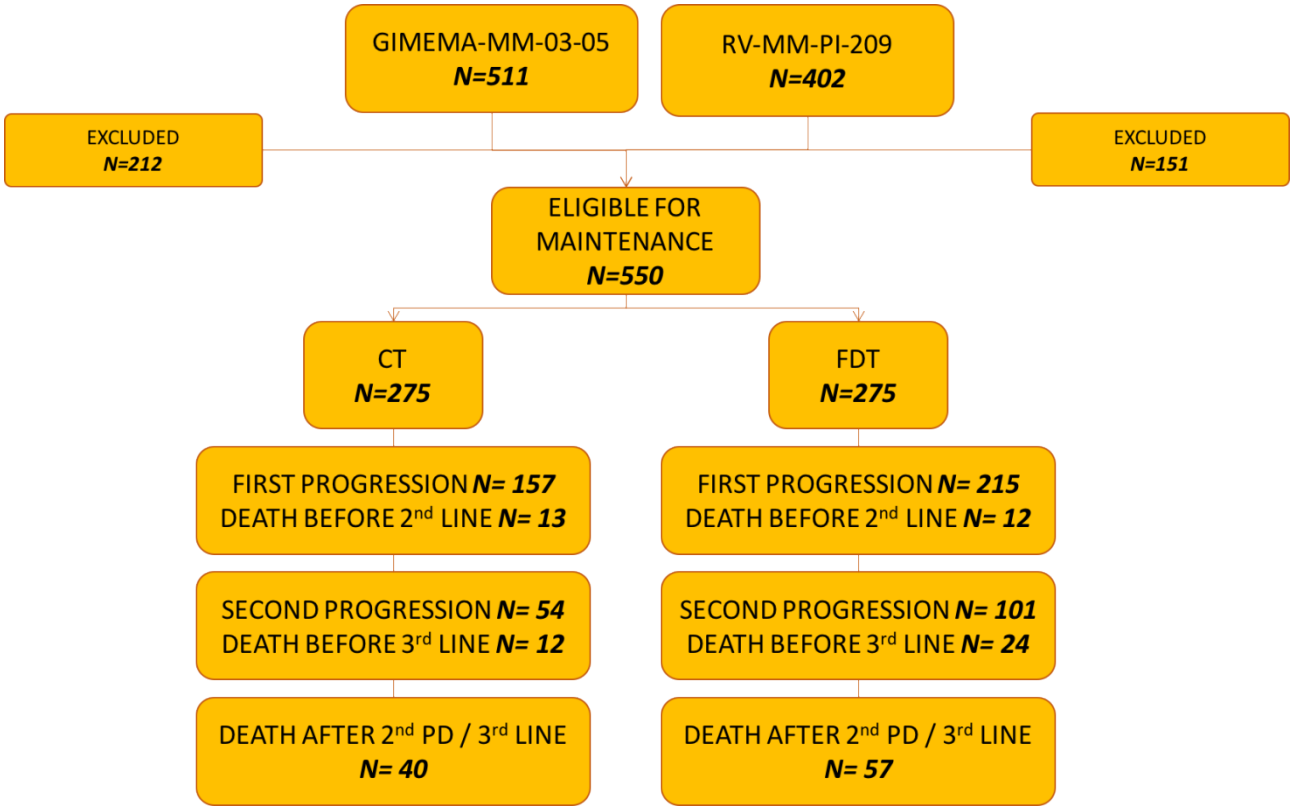
CT: Continuous therapy; FDT: Fixed-duration therapy; NDMM: newly diagnosed multiple myeloma; PBSC: peripheral blood stem cell; G-CSF: granulocyte colony stimulating factor; Cy: cyclophosphamide; Mel200: melphalan at 200 mg/m^2; ASCT: autologous stem cell transplantation; MPR: melphalan, prednisone, lenalidomide; Rd: lenalidomide, low-dose dexamethasone; R: lenalidomide; VMPT: bortezomib, melphalan, prednisone, thalidomide; VT: bortezomib, thalidomide; VMP: bortezomib, melphalan, prednisone.

Table S2. Baseline patient characteristics

	All patients N=550	%	CT N=275	%	FDT N=275	%
Age						
≤ 65 years	252	46	130	47	122	44
> 65 years	298	54	145	53	153	56
ISS Stage						
I	214	39	109	40	105	38
II	181	33	92	33	89	32
III	100	18	50	18	50	18
Missing	55	10	24	9	31	11
Cytogenetic profile						
Standard-risk	288	52	146	53	142	52
High-risk	101	18	53	19	48	17
Missing	161	29	76	28	85	31
LDH						
Median	278		275.5		275.5	
Missing	45	8	28	10	17	6
ECOG Performance status						
0	301	55	153	56	148	54
1	221	40	108	39	113	41
2	28	5	14	5	14	5
R-ISS						
I	103	19	58	21	45	16
II	273	50	133	48	140	51
III	27	5	15	5	12	4
Missing	147	27	69	25	78	28
Protocol						
GIMEMA-MM-03-05	299	54	149	55	150	54
RV-MM-PI 209 (MPR)	116	21	59	21	57	21
RV-MM-PI 209 (Mel200-ASCT)	135	25	67	24	68	25

ISS: International Staging System; ECOG: Eastern Cooperative Oncology Group; R-ISS: Revised International Staging System; CT, continuous therapy; FDT, fixed duration of therapy; ASCT, autologous stem cell transplantation; Mel200: melphalan at 200 mg/m^2; High cytogenetic risk defined as FISH positivity for at least one of the following: t(4;14)-t(14;16)-del17p; IQR, interquartile range.

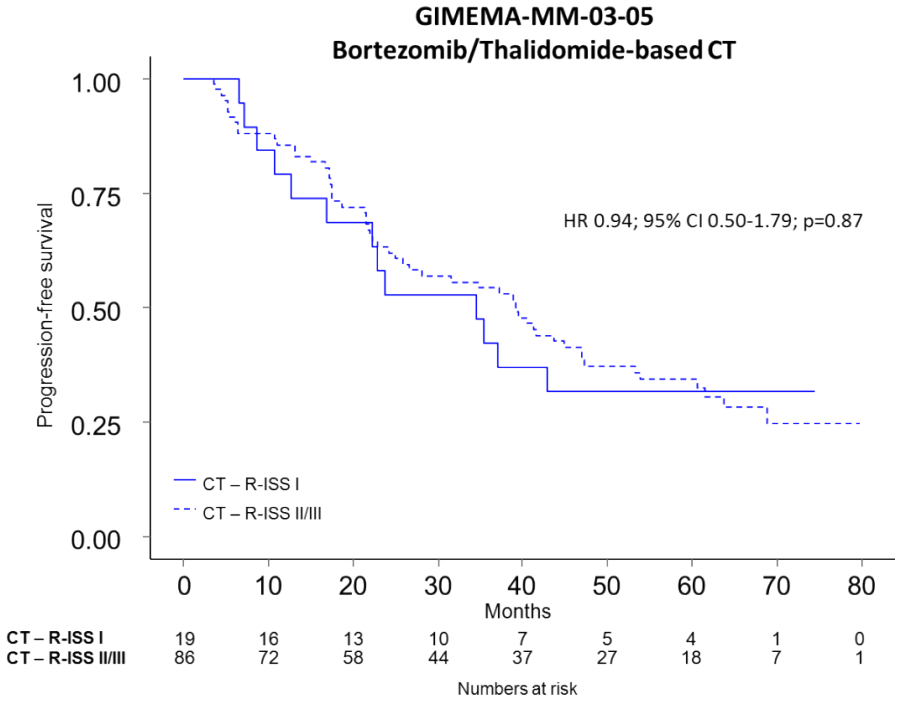
Figure S1. Study flow



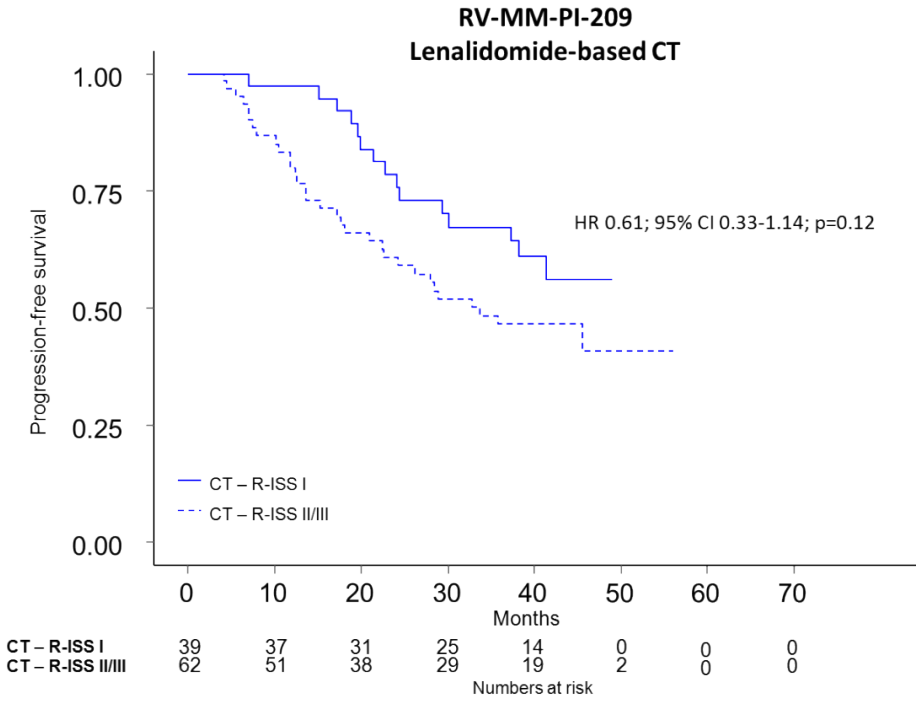
PD, progressive disease; CT, continuous therapy (upfront treatment + maintenance lasting at least 2 years); FDT, fixed-duration therapy (<1 year of upfront treatment).

Figure S2. PFS1 in the population of patients receiving CT according to baseline R-ISS
Panel A: patients enrolled in the GIMEMA-MM-03-05 trial receiving a Bortezomib/Thalidomide-based CT.
Panel B: patients enrolled in the RV-MM-PI-209 trial receiving a Lenalidomide-based CT.

Panel A



Panel B

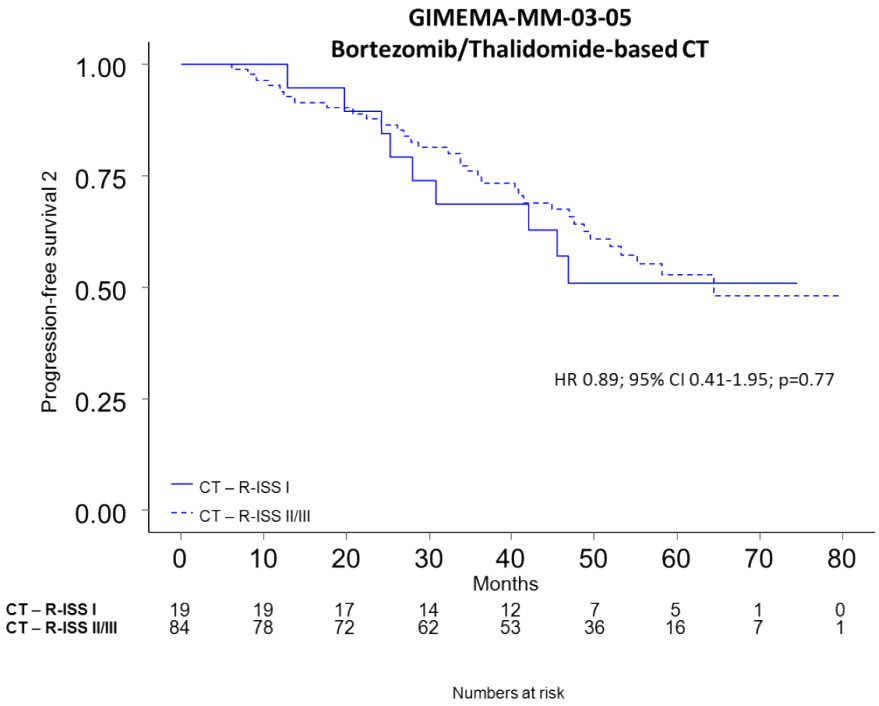


R-ISS: Revised International Staging System; CT, continuous therapy (upfront treatment + maintenance lasting at least 2 years); HR, hazard ration; CI, confidence interval, P, P value.

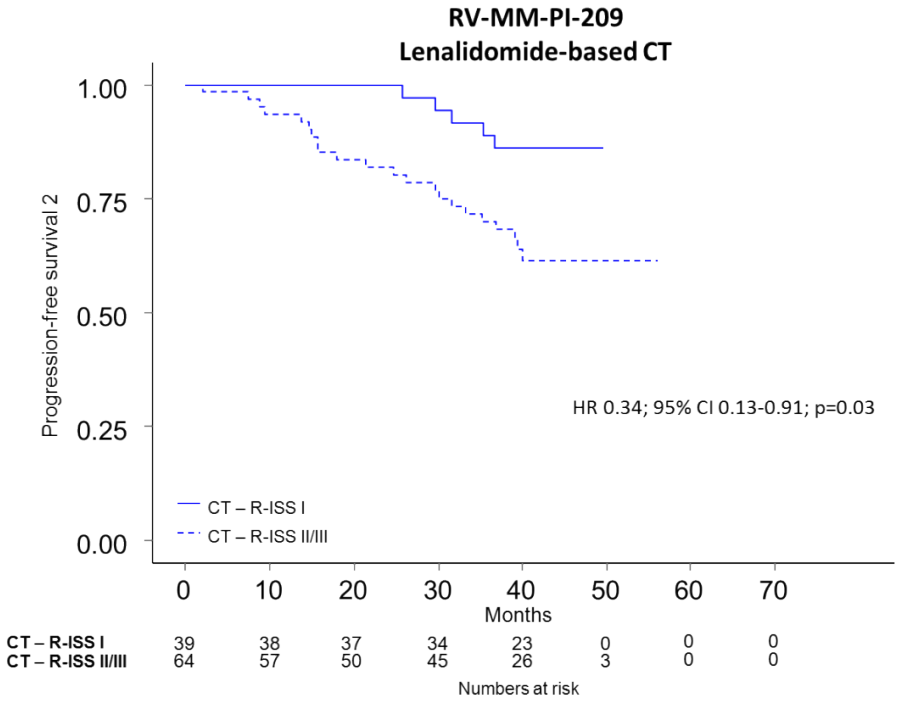
Figure S3. PFS2 (Panels A-B) and OS (Panels C-D) in the population of patients receiving CT according to baseline R-ISS

Panels A and C: patients enrolled in the GIMEMA-MM-03-05 trial receiving a Bortezomib/Thalidomide-based CT.
Panels B and D: patients enrolled in the RV-MM-PI-209 trial receiving a Lenalidomide-based CT.

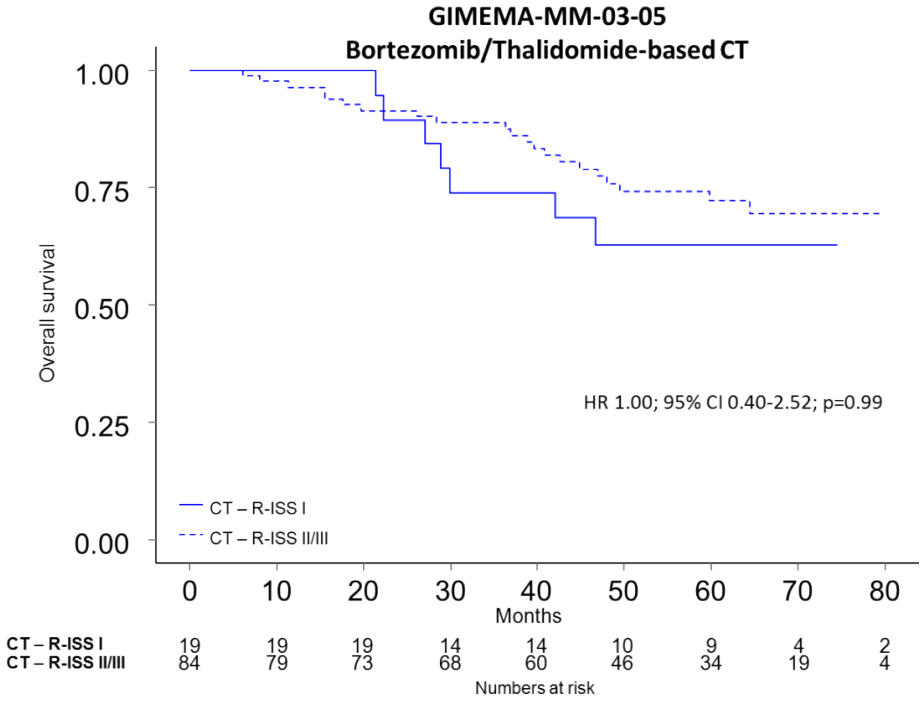
Panel A



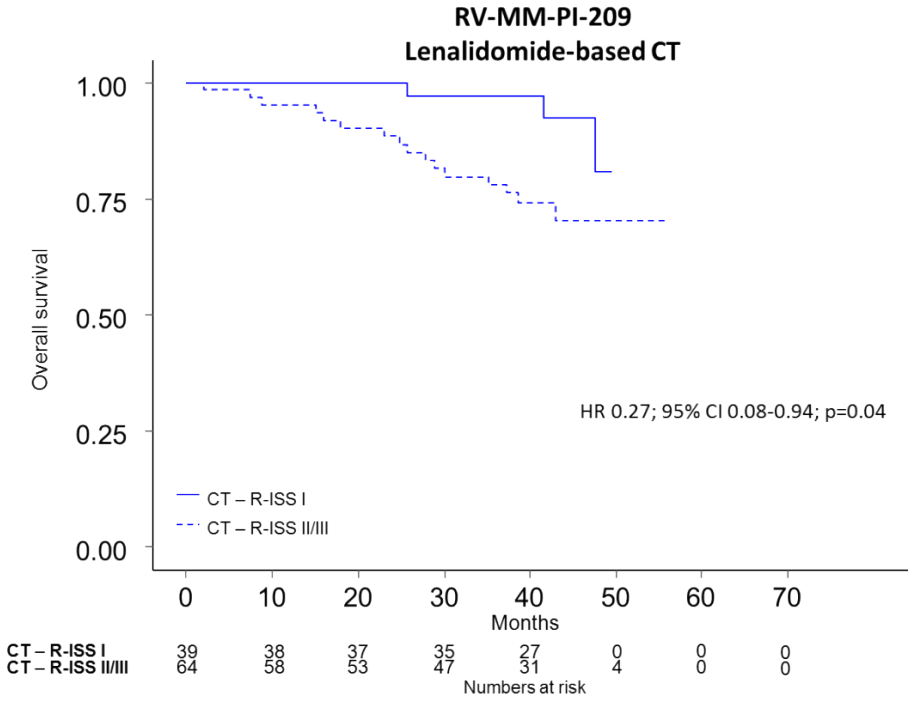
Panel B



Panel C

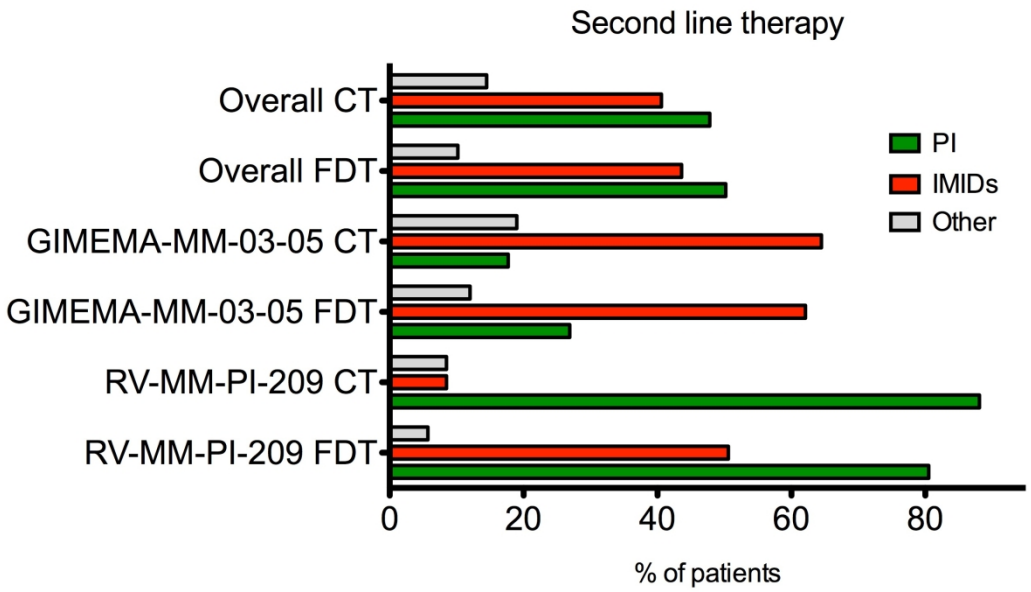


Panel D



R-ISS: Revised International Staging System; CT, continuous therapy (upfront treatment + maintenance lasting at least 2 years); HR, hazard ration; CI, confidence interval, P, P value.

Figure S4. Types and frequency of second-line therapies



CT, continuous therapy; FDT, fixed duration of therapy; IMiDs, immunomodulatory drugs; PIs, proteasome inhibitors