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Autologous transplant vs oral chemotherapy and lenalidomide in newly diagnosed young myeloma

patients: a pooled analysis

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Running head: MEL200-ASCT vs CC+R for newly diagnosed young MM patients

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Abstract:

In newly diagnosed myeloma patients, upfront autologous transplant (ASCT) prolongs progression-free survival-1 (PFS1) compared with chemotherapy plus lenalidomide (CC+R). Salvage ASCT at first relapse may still effectively rescue patients who did not receive upfront ASCT. To evaluate the long-term benefit of upfront ASCT vs CC+R and the impact of salvage ASCT in patients who received upfront CC+R, we conducted a pooled analysis of 2 phase III trials (RV-MM-209 and EMN-441). Primary endpoints were PFS1, progression-free survival-2 (PFS2), overall survival (OS). A total of 268 patients were randomized to 2 courses of melphalan 200 mg/m² and ASCT (MEL200-ASCT) and 261 to CC+R. Median follow-up was 46 months. MEL200-ASCT significantly improved PFS1 (median: 42 vs 24 months, HR 0.53; P<0.001), PFS2 (4-year: 71% vs 54%, HR 0.53, p<0.001) and OS (4-year: 84% vs 70%, HR 0.51, P<0.001) compared with CC+R. The advantage was noticed in good and bad prognosis patients. Only 53% of patients relapsing from CC+R received ASCT at first relapse. Upfront ASCT significantly reduced the risk of death (HR 0.51; P=0.007) in comparison with salvage ASCT. In conclusion, these data confirm the role of upfront ASCT as the standard approach for all young myeloma patients.

Introduction

Multiple myeloma (MM) is a hematological malignancy that represents 1% of all cancers and 13% of all hematologic tumors. Median age at diagnosis is 70 years but in 35% of cases MM develops in patients younger than 65 years.¹

Survival of MM patients has considerably improved over the last 10 years thanks to novel agents (thalidomide, bortezomib and lenalidomide).² The standard of care for fit patients \leq 65 years is a novel agent-based induction and subsequent consolidation with high-dose chemotherapy followed by autologous stem cell transplant (HDT-ASCT).^{3,4} In elderly/unfit patients, the standard of care is conventional chemotherapy (CC) or steroids plus novel agents.⁵⁻⁷

Before the introduction of new drugs, HDT-ASCT significantly prolonged progression-free survival (PFS) in comparison with CC in patients with newly diagnosed MM (NDMM). Yet, HDT-ASCT induced more toxicity, with conflicting results in terms of overall survival (OS) (Table 1S, 2S). Recently, novel agent-based therapies that can be administered in the outpatient setting have questioned the role of ASCT, and the comparison of HDT-ASCT with less toxic, novel agent-based treatments has become a high research priority.

Two published studies showed the superiority of HDT-ASCT versus CC plus lenalidomide (CC+R) (Table 3S) in terms of both PFS and OS in patients ≤ 65 years.^{8,9} Other ongoing trials (NCT01208766, NCT01191060/ NCT01208662), evaluating the role of HDT-ASCT in comparison with bortezomib-based regimens (Table 4S) showed a significant advantage in terms of PFS for HDT-ASCT.^{10,11} Nevertheless, some relevant unanswered questions about HDT remain: is the benefit of HDT-ASCT equal in all patients? Or is there a subset of patients, perhaps those with low-risk disease, that could be effectively treated with outpatient, less toxic regimens?

The optimal timing of transplantation is another open issue. Based on the impressive efficacy and safety of CC plus novel agents upfront^{6,7,12,13}, delaying ASCT until first relapse seems an attractive option. There are no recent data from randomized prospective trials that evaluate the efficacy of salvage ASCT in patients

receiving CC plus novel agents upfront, only data from single center or retrospective analyses are available.^{14,15} Before the introduction of novel agents, an inconsistent OS advantage for HDT-ASCT in comparison with standard-dose therapy was reported.¹⁶

The primary endpoint of this pooled analysis of two randomized trials was to evaluate the impact on outcome of HDT-ASCT versus CC+R in NDMM patients, focusing in particular on long-term endpoints, progression-free survival 2 (PFS2), overall survival (OS) and on the benefit in specific subsets of patients with different prognostic features. Efficacy of rescue ASCT in patients receiving upfront CC +R was the secondary endpoint.

Methods

Patients and treatment

We pooled together data from 2 phase III trials (GIMEMA-RV-MM-209 and EMN-441) (Table 3S). In the two studies, NDMM patients received induction with lenalidomide plus low dose dexamethasone. Cyclophosphamide and granulocyte colony-stimulating factor were used to mobilize stem cells. Using a 2-by-2 partial factorial design, patients were randomized to consolidation with two courses of melphalan 200 mg/m2 followed by ASCT (MEL200-ASCT) or six 28-day cycles of oral chemotherapy plus lenalidomide (CC+R). In both trials patients were also randomized to 2 different maintenance treatments (supplement).^{8,9} In each trial, a simple randomization sequence, stratified according to International Staging System (ISS)¹⁸ (I/II versus III) stage and age (\leq 60 versus 61–65 years) was generated by a computer program and implemented into a web-based procedure. Treatment at relapse was not pre-specified in the MEL200-ASCT arm. In patients relapsing from the CC+R arms of the 2 trials, ASCT was the recommended treatment at first relapse, but the choice of therapy was made at physician discretion according to the patient's clinical conditions. The 2 trials included in this analysis are the only trials published so far comparing MEL200-ASCT vs CC+R in young NDMM patients. Table 1S reports other phase III trials comparing ASCT vs chemotherapy plus

thalidomide in elderly patients. Table 4S describes the ongoing trials comparing MEL200-ASCT vs bortezomib-lenalidomide-dexamethasone and vs bortezomib-melphalan-prednisone.

Clinical endpoints

The primary endpoints were PFS1, PFS2^{19,20} and OS in the population eligible for MEL200-ASCT vs CC+R, for whom the randomization was disclosed. Detailed definitions are in the supplementary appendix.

Statistical analysis

Data of the two trials were pooled together and analysed. Patients enrolled but not eligible for MEL200-ASCT vs CC+R were excluded. All the other patients were included. Time-to-event data were analyzed using the Kaplan–Meier method; treatment groups were compared with the log-rank test. 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 MEL200-ASCT vs CC+R were adjusted for the trial effect, age, ISS stage, cytogenetic profile and Easter Oncology Cooperative Group performance status (ECOG-PS). Subgroup analyses were performed to determine the consistency of treatment effects of MEL200-ASCT vs CC+R between different subgroups using interaction terms between treatment and each of the covariate included in the Cox model plus the specific maintenance therapy. All HRs were estimated with their 95% confidence intervals (95%CI) and two sided p-values (supplement). We initially assessed the risk of death (OS) with upfront MEL200-ASCT (regardless of second-line therapy) vs CC+R followed by salvage ASCT using a Cox model adjusted for age, sex, ISS stage, cytogenetic profile, ECOG-PS and trial as stratification factor. In this analysis we excluded patients who received CC+R upfront and no salvage ASCT at first relapse. Subsequently, we also estimated survival value of relapsed patients who received CC+R at first line and no ASCT at relapse as if they had actually received salvage ASCT. We used multiple imputation method²¹ considering upfront CC+R patients who actually received salvage ASCT as reference group , and we took into account the most important baseline prognostic features (age, sex, ISS stage, cytogenetic profile, LDH, ECOG-PS) and time

from randomization until first progression. Results of multiple imputation analysis were then combined in order to have one single HR for the comparison. Data were analyzed as of December, 2015 using SAS software (Version 8.2) and R (Version 3.1.1).

Results

Patients

The two trials randomly assigned 791 patients with NDMM to treatment; 262 patients were not eligible for MEL200-ASCT vs CC+R and were excluded. The main reason for exclusion was progressive disease (113 patients).^{8,9} The remaining 529 patients were included in the analysis (Figure 1). Patients demographics, disease characteristics, response at the time of random disclosures in the two groups were well balanced (Table 5S). At data cut-off, 91/268 (34%) patients in the MEL200-ASCT arm vs 56/261 (21%) patients in the CC+R arm were on study, either on maintenance after consolidation or progression-free after treatment-discontinuation for reasons other than progression.

MEL200-ASCT vs CC+R in the overall population

The median follow-up was 52 months from enrollment and 46 months from random disclosure. In the population of patients eligible for consolidation (n=529) MEL200-ASCT significantly improved PFS1 (median: 42 vs 24 months, HR 0.53, 95% CI 0.42-0.66, P<0.001) in comparison with CC+R (Figure 2A). The advantage with MEL200-ASCT vs CC+R was consistent across all patient subgroups defined according to baseline features, protocol and post-consolidation maintenance, with a possible weaker effect in patients enrolled in the EMN-441 trial (P=0.01 for interaction) (Figure 3A).

Overall, 134 (50%) MEL200-ASCT patients and 176 (67%) CC+R patients experienced PD1; 125 patients in the MEL200-ASCT group and 175 in the CC+R group received second-line therapy. Of note, the number of patients is unbalanced because a higher number of patients relapsed in the CC+R group.

To evaluate the impact of both first- and second-line therapies, we assessed PFS2. PFS2 was significantly superior with MEL200-ASCT vs CC+R (4-year: 71% vs 54%, HR 0.53, 95% CI 0.40-0.71, P<0.001; Figure 2B). The benefit of MEL200-ASCT vs CC+R was again evident in all the analyzed subgroups (Figure 3B).

The advantage in PFS1 and PFS2 translated into a significant advantage in OS with MEL200-ASCT vs CC+R (4-year OS: 84% vs 70%; HR 0.51, 95% CI 0.35-0.76, P<0.001) (Figure 2C). The statistical power of the subgroup analysis of OS was limited by the low number of events, but the benefit of MEL200-ASCT vs CC+R was confirmed in all the subgroups, with a possible weaker effect in patients younger than 60 years (P=0.03 for interaction) (Figure 3C); this lower difference could be related to the low number of events with the current follow-up in the younger patient population.

MEL200-ASCT vs CC+R in risk-defined subgroups

MEL200-ASCT improved PFS1, PFS2 and OS both in good and in bad prognosis patients as compared with CC+R (Figure 3A, B, C). To estimate the impact on survival of treatment and baseline prognostic features, we analyzed PFS1, PFS2, OS in the MEL200-ASCT vs CC+R populations according to baseline R-ISS Stage, the new staging system that incorporates ISS Stage, cytogenetic profile and LDH.

The median PFS1 was 50 months in patients with R-ISS Stage I randomized to MEL200-ASCT, 33 months in patients with R-ISS Stage I randomized to CC+R, 32 months in those with R-ISS Stage II/III randomized to MEL200-ASCT and 20 months in those with R-ISS Stage II/III randomized to CC+R (Figure 4A).

The 4-year PFS2 was 83% in patients with R-ISS Stage I assigned to MEL200-ASCT, 71% in patients with R-ISS Stage I assigned to CC+R, 60% in those with R-ISS Stage II/III assigned to MEL200-ASCT and 43% in those with R-ISS Stage II/III assigned to CC+R (Figure 4B).

The 4-year OS was 95% in patients with R-ISS Stage I randomized to MEL200-ASCT, 88% in patients with R-ISS Stage I randomized to CC+R, 75% in those with R-ISS Stage II/III randomized to MEL200-ASCT and 61% in those with R-ISS Stage II/III randomized to CC+R (Figure 4C).

Impact of upfront and salvage treatment on long-term endpoints

At data cut-off, in the MEL200-ASCT group, only 11/125 patients (9%) received ASCT at first relapse; 114 (91%) did not receive ASCT at relapse but bortezomib-based regimens (68%), immunomodulatory drugs (IMIDs; 16%) or other therapies (7%). In the CC+R group, ASCT was recommended but not mandatory at relapse, and the choice of therapy was based on patient's will and physician discretion according to the

patient's condition (eligibility to ASCT): 93/175 patients (53%) received ASCT at first relapse of whom 78 (84%) received re-induction with bortezomib; 82 (47%) did not receive ASCT at relapse but bortezomibbased regimens (38%), IMIDs (6%) or other therapies (3%).

In the CC+R group, ASCT at relapse (n=93) prolonged OS from randomization in comparison with no ASCT at relapse (n=82) (4-year OS: 69% vs 52% respectively, HR 0.60; 95% CI 0.35-1.04; P=0.07). To evaluate the impact of upfront vs rescue transplant, we first compared upfront MEL200-ASCT (n=268) vs upfront CC+R followed by salvage ASCT (n=93): upfront MEL200ASCT significantly reduced the risk of death (HR 0.51, 95% CI 0.31-0.83. P=0.007) (Figure 1S). Similarly, by comparing upfront MEL200-ASCT (n=268) vs upfront CC+R and estimating that all CC+R relapsed patients had received salvage ASCT (n=261) with multiple imputation analysis, we found a survival advantage in favor of upfront MEL200-ASCT (HR 0.65, 95% CI 0.42-1.03. P=0.064) (Figure 2S).

Discussion

Before the introduction of novel agents, ASCT was associated with a remarkable improvement in PFS1 compared with CC in young NDMM patients, although OS results were conflicting (Table 4S).¹⁶ In most of the trials, salvage ASCT after CC was not a preplanned option. Only one randomized trial compared upfront vs rescue ASCT showing a significant advantage with upfront ASCT in event-free survival and longer intervals free of symptoms, treatment and treatment-related toxicity, despite comparable OS.¹⁷ Based on these data, HDT-ASCT is considered a standard option for NDMM. The impressive survival improvement with novel agents (thalidomide, bortezomib and lenalidomide) plus CC in the non-transplant setting has led clinicians to hypothesize that MM could be managed without HDT or that HDT could be a valid salvage approach.^{6,7,12} The IFM9906 trial was the first to address this issue: melphalan-prednisone-thalidomide was superior to reduced-intensity ASCT in terms of both PFS and OS in patients aged 65-75 years.²² Nevertheless, patients randomized to ASCT received a reduced-intensity conditioning regimen, novel agents were not administered as induction in the transplant-arm, and salvage transplant was not a preplanned option in the melphalan-prednisone-thalidomide arm.

This pooled analysis of the RV-MM-209 and EMN-441 trials showed that MEL200-ASCT significantly prolonged median PFS1 by 18 months in comparison with CC+R, despite the similar CR rate reported with MEL200-ASCT and CC+R arms in the 2 trials.^{8,9} The advantage was consistent across all subgroups of patients with different prognostic features and across patients receiving different maintenance approaches. Because different types of CC+R were used in the source studies, in the present analysis results were carefully adjusted to consider the trial effect and the impact of maintenance. A lower difference was seen in the EMN441 trial, possibly related to the use of post-consolidation maintenance in all patients (in the RV-MM-209 trial 50% of patients received no maintenance).^{8,9} CC plus novel agents was considered an appealing option for the lower toxicity in comparison with MEL200-ASCT and for the outpatient administration. Indeed, the rate of hematologic and non-hematologic adverse events was higher with MEL200-ASCT. Nevertheless, in both source trials, there was no increase in deaths due to toxicity nor in SPM with MEL200-ASCT.^{8,9} In this pooled analysis, the difference in PFS1 between the two arms was related to an increased rate of PD with CC+R (175 vs 134), while the number of deaths was comparable (7 with CC+R vs 5 with MEL200-ASCT). In the context of the significant PFS1 gain associated with MEL200-ASCT, the risk/benefit profile of MEL200-ASCT remained positive.

We prospectively collected data about treatment after relapse in the two source studies. In the MEL200-ASCT arm, only 9% of patients received ASCT also at relapse and most of the patients were treated with bortezomib-based regimens: this is reasonable because, with the present follow-up, we are capturing mainly early relapses in the ASCT arm. In the CC+R group, ASCT at relapse was recommended but not mandatory. Only 53% of patients received ASCT (mostly preceded by bortezomib re-induction) and 28% bortezomib-based regimens. Indeed, despite being eligible for high-dose therapy and ASCT at diagnosis, patients may no longer be eligible for that treatment at relapse, thus losing the opportunity to receive an efficacious treatment. It is hard to compare these data with results of studies published before the introduction of novel agents: the rate of ASCT at relapse varies from 6% to 77%.^{17,22-29} Of note, the availability of novel agents and of different treatment options including clinical trials could have also affected treatment choice in the present study.

To evaluate the treatment effects of both first- and second-line therapies, we analyzed PFS2: MEL200-ASCT significantly increased the 4-year PFS2 by approximately 20%. The advantage for MEL200-ASCT was consistent across all subgroups of patients defined by prognostic features and the post-consolidation maintenance approaches.

The PFS1 and PFS2 advantage in patients randomized to MEL200-ASCT also translated into a marked OS benefit, with a significant increase in 4-year OS of approximately 15%. In the subgroup analysis of OS, all estimates of the HRs were again in favor of MEL200-ASCT. A significant interaction between treatment groups and age was found for OS, suggesting a lower difference in OS between MEL200-ASCT and CC+R in patients \leq 60 years of age. Yet, the value of the subgroup analysis of OS in patients \leq 60 years of age was limited by the low number of events.

We assessed OS with upfront MEL200-ASCT (regardless of second-line therapy) vs CC+R followed by salvage ASCT in order to evaluate the specific impact of rescue ASCT. Even in this subset, upfront ASCT significantly reduced the risk of death (HR 0.51, P=0.007). For this analysis, in the CC+R arm, we focused only on relapsing patients receiving ASCT (53%) and not on all randomized patients, and this can be a limitation; nevertheless, within relapsing patients, those receiving rescue ASCT had probably a better performance status if compared with patients who did not receive transplant at relapse. To try to overcome the selection bias limitation, we used the multiple imputation method to assess OS with upfront MEL200-ASCT vs upfront CC+R, assuming that all patients relapsing from CC+R had received rescue ASCT. This is quite an optimistic scenario, since in no previous trial 100% of relapsing patients were able to receive ASCT at relapse. Yet, results were again in favor of upfront ASCT (HR 0.65, P=0.064).

To estimate the impact of treatment and baseline prognostic features on survival, we analyzed PFS1, PFS2, OS in the MEL200-ASCT vs CC+R populations according to baseline R-ISS Stage, the new staging system that incorporates both ISS Stage, cytogenetic abnormalities and LDH levels. As expected, the highest PFS1 was noticed in good prognosis patients randomized to MEL200-ASCT (53% at 4 year); lower and comparable 4-year survival times were reported in patients with ISS Stage I randomized to CC+R (36%) and patients with ISS Stage II/III randomized to MEL200-ASCT (35%); only 19% of patients with ISS Stage II/III disease randomized to CC+R were progression-free at 4 years. Similar features were noticed in terms of

PFS2 and OS. These data first suggest that patients with good prognosis and chemo-sensitive disease benefit from HDT and upfront ASCT; and second, better treatment options are still needed in patients with high-risk disease. Several reports showed higher efficacy of proteasome inhibitors in patients with high-risk disease.^{30-³² In the two source trials, the main reasons for the high early discontinuation were PD and the patient's decision to choose an alternative therapy due to suboptimal response after induction. Of note, in the source trials, suboptimal induction treatments were adopted in the non-transplant arms. In fact, the standard induction now consists of bortezomib-based or bortezomib-IMIDs-based combinations. Such combinations also induced higher response rates if compared with CRD and MPR as consolidation.^{33,34} Nevertheless, preliminary results from ongoing trials still showed a significant PFS1 advantage with MEL200-ASCT vs bortezomib-lenalidomide-dexamethasone and bortezomib-melphalan-prednisone. Longer follow-up will establish whether, even in the context of proteasome inhibitor based-treatments, HDT and ASCT will be the best option regardless of patients prognosis, and if there will be any difference in OS.^{10,11} Preliminary data suggest high efficacy of monoclonal antibodies in combination with bortezomib and lenalidomide in the relapsed setting,^{35,36} and future studies will clarify their role also in newly diagnosed, transplant-eligible patients.}

This study has other limitations. The lack of cytogenetic data in ~30% of patients might have affected the subgroup analyses according to prognostic features. Different maintenance approaches were used, including no maintenance in the GIMEMA-RV-MM-209. Although data on second-line therapies were collected prospectively, the PFS2 endpoint was not pre-specified in the original study protocols. Post-relapse therapies depend on several factors: treatments at relapse were based on the investigator's discretion and the availability of active trials.

In conclusion, MEL200-ASCT improved the median PFS1 by approximately 1.5 years and PFS2 and OS by ~20% and 15% respectively in NDMM patients. The improvement in PFS2 suggests that most of the benefit observed during the first remission is maintained after relapse. In some cases, ASCT may no longer be a feasible option at relapse, and even when administered at first relapse, may not induce a survival benefit comparable to upfront ASCT. Intensified treatment in good prognosis patients significantly prolongs survival. In good prognosis patients, lenalidomide induction followed by MEL200-ASCT provided a 4-year

OS of 95%, significantly superior to CC+R. The advantage for MEL200-ASCT was evident also in bad prognosis patients, but with inferior outcome; ongoing trials exploring the use of bortezomib plus lenalidomide or melphalan and future trials with monoclonal antibodies could help draw definitive conclusions on the role and timing of ASCT.

Authorship

FG, AP and MB designed the study; FG and AP collected and assembled the data; FG, AE, SS, MS, AP, MB analysed and interpreted the data; FG wrote the first draft of the manuscript; all authors had access to the final data and approved the final manuscript.

Conflicts of interest: FG has received honoraria from Amgen, BMS, Celgene and Takeda, and served on the advisory committee for Janssen, Mundipharma, and Takeda. SO has received honoraria from Takeda and Celgene. MTP has received honoraria from Celgene, Janssen-Cilag, Bristol-Myers Squibb, Amgen, Takeda, Mundipharma, Sanofi. PM has received honoraria from Celgene, Janssen, Novartis, Sanofi, Bristol-Myers Squibb, Takeda, Amgen. MO has received honoraria from Celgene. TC has received honoraria from Celgene, Janssen, Novartis, Sanofi, Bristol-Myers Squibb, Takeda, Amgen, Bristol-Myers Squibb, and consultancy fees from Takeda. FP has received honoraria from MSD Italia, Celgene, and served on the advisory board of Janssen, Mundipharma, Amgen, Bristol-Meyers Squibb. AS has received honoraria from Celgene. RH has received consultancy fees from Celgene, Janssen, and honoraria from Amgen. AP has received consultancy fees, honoraria and research funding from Celgene, and is a Takeda employee. MB has received consultancy fees from Janssen, Sanofi, Onyx, Amgen, Celgene. The other authors have no potential conflicts of interest.

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Figures

Figure 1. Study flow.



MEL200-ASCT, Melphalan 200 mg/m² followed by autologous stem cell transplantation; CC+R, chemotherapy plus lenalidomide

Figure 2. PFS1 (Panel A), PFS2 (Panel B) and OS (Panel C) in the population of patients randomized to MEL200-ASCT vs patients randomized to CC+R. HR= adjusted hazard ratio.











Figure 3 Subgroup analysis of PFS1 (panel A), PFS2 (panel B) and OS (panel C) in the population of patients randomized to MEL200-ASCT vs patients randomized to CC+R. HR= adjusted hazard ratio.

Panel A



Panel B







Figure 4. PFS1 (Panel A), PFS2 (Panel B) and OS (Panel C) in the population of patients randomized to MEL200-ASCT vs patients randomized to CC+R according to baseline R-ISS Stage (I vs II/III).

1.00 Progression-free survival-1 0.75 0.50 MEL200-ASCT - RISS I MEL200-ASCT - RISS II/III 0.25 CC+R - RISS I CC+R - RISS II/III 0.00 Months 52 127 72 19 0 2 2 MEL200-ASCT - RISS I MEL200-ASCT - RISS II/III CC+R - RISS I CC+R - RISS II/III Numbers at risk

Panel A

Panel B



27

Panel C



Supplementary Appendix

Supplementary Methods

Treatment

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

Consolidation with MEL200-ASCT: in both trials 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..

Consolidation with CC+R: In the GIMEMA-RV-MM-209 trial 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); in the EMN-441 trial, treatment consisted of cyclophosphamide (300 mg/m2 days 1, 8, 15), dexamethasone (40 mg days 1, 8, 15, 22) lenalidomide (25 mg days 1–21) (CRD).

Maintenance therapy: in the GIMEMA-RV-MM-209 trial, lenalidomide (R) alone (10 mg on days 1–21 every 28 days until progressive disease (PD) or until tolerated, or no maintenance; in the EMN-441 trial, R alone (10 mg on days 1–21 every 28 days) or plus prednisone (50 mg every other day) (RP), until PD or until tolerated.

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 confirmed their eligibility for consolidation. Patients were eligible for consolidation if they did not experience unacceptable toxicity or progressive disease (PD) during the induction/mobilization phase and if they collected an adequate amount of stem cells for a double ASCT. Both the patient and the treating physician did not know the consolidation and maintenance arm until that time.

Endpoints definition

Endpoints included in the analysis:

All time-to-event endpoints were calculated from the time of randomization disclosure. Disease progression was defined according to standard criteria. **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 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.

Subgroup analysis:

Subgroups were defined according to: baseline patient characteristics (age [\leq 60, >60]; ECOG-PS [0, 1, 2]; ISS stage [stage I, II, III]; 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); missing data]; Revised ISS (R-ISS) stage [stage I, II, III]; protocol (RV-MM-209; EMN441); maintenance (none, R, RP).

Supplementaly Tables

Table 1S. Characteristic of published trials comparing high-dose chemotherapy followed by autologous stem cell transplant vs conventional chemotherapy.

Trial	IFM	90 ²²	MAG	G90 ¹⁷	MAG	91 ²³	MRC	VII ²⁴	S9321	25	PETH	IEMA ²⁶	ноу	ON ²⁷	M97(2 ²⁸	IFM99	906 ²¹
Enrollment period	Oct 90 –	May 93	Jan 90 –	June 95	Nov 91 –	Sep 98	Oct 1993 200	3 – Oct)0	Not avai	lable	May 94	– Oct 99	Nov 95 0	5 – Apr 0	Oct 97 – I	Dec 00	May 2000 200) – Aug)5
Number enrolled patients	20)	20	02	190)	40	7	899		2	16	20	61	194		44	7
Time of random assignment	Diagn	osis	After colle	PBSC	Diagn	osis	Diagn	nosis	After VAD i	nduction	After V VBAD	BMCP / induction	After indu	VAD ction	Diagno	osis	Diagn	osis
Eligibility criteria	NDMM Age≤0	I, TE, 55 yrs	NDMI Age <	M, TE, 56 yrs	NDMM Age 55-0	, TE, 65 yrs	NDMM Age≤0	1, TE, 65 yrs	NDMM Age ≤ 70	, TE, 0 yrs	ND Age ≤	MM, ≤65 yrs	NDMI Age≤	M, TE, 65 yrs	NDMM Age 50-7	, TE, 70 yrs	MM, Age 65-	TE 75 yrs
Treatment	HDT	СС	HDT	CC	HDT	CC	HDT	CC	HDT	СС	HDT	CC	HDT	CC	HDT	CC	HDT	CC
Induction	4-6 VMCP/ BVAP	18 VMC	3-4 VAMP	VMCP until	3-4 VAMP	VMCP until	3 VAMPC	4-12 ABCM	4 VA	D	4 VB VE	MCP / BAD	4 V	AD	2 VAD	6 MP	2 VAD	12 MP or
Consolidation	Mel140 / TBIAS CT	P/ BVA P	LVP CyMel1 40-TBI- ASCT	respons e plateau (median 8 cycles)	Bu/Mel140 or Mel200- ASCT	respons e plateau (median 12 cycles)	Mel200 or Mel140 / TBI- ASCT		Mel140/TBI- -ASCT	VBMCP for 1 year	Mel200 or Mel140 / TBI ASCT	8 VBMCP / VBAD	2 Mel70 Cy 60x2 x 2 days / TBI ASCT	2 Mel70	2 Mel100- ASCT		2 Mel100- ASCT	12 MPT
Maintenance	IFI	٧	IF	FN	IFN	1	IFI	N	IFN vs 1	none	IFN	l + D	IF	FN	IFN +	D	Noi	ne

Median	HDT	СС	HDT	CC	HDT	CC												
follow-up,																		
months	41	37	58	3	120		42	!	76		56	5	33	3	41	39	52	

ASCT indicates autologous stem cell transplantation; CC: conventional chemotherapy; HDT: "high-dose" myeloablative therapy with autologous stem cell transplantation; NDMM: newly diagnosed multiple myeloma; PBSC: peripheral blood stem cell; PR: partial response; TE: transplant eligible. ABCM indicates doxorubicin, carmustine, cyclophosphamide, melphalan; Bu/Mel: busulphan, melphalan; BVAP: carmustine, vincristine, doxorubicin, prednisone; Cy 60: cyclophosphamide at 60 mg/kg; Mel70, 100, 140, 200: melphalan at 70, 100, 140, 200 mg/m²; MP: melphalan, prednisone; MPT: melphalan, prednisone, thalidomide; T-regimen: thalidomide based regimens; TBI: total body irradiation; VAD: vincristine, doxorubicin, dexamethasone; VAMP: vincristine, doxorubicin, methylprednisolone, cyclophosphamide; VBAD: vincristine, doxorubicin, dexamethasone; VBMCP: vincristine, melphalan, cyclophosphamide, prednisone; VMCP: vincristine, melphalan, cyclophosphamide, prednisone; VMCP: vincristine, melphalan, cyclophosphamide, prednisone; LVP Cy: lomustine, VP16, Cyclophoaphamide.

Table 2S. Results of published trials comparing trasplant vs conventional chemotherapy.

	IFM90 ²²	MAG90 17	MAG91 ²³	MRC VII ²⁴	S9321 ²⁵	PETHEMA ²⁶	HOVON ²⁷	M97G ²⁸	IFM9906 ²¹
MEDIAN PFS, months									
HDT	27*§	39 [§]	25 [§]	32*	17% at 7 years	42	21 [§]	28*§	19*
CC	18* [§]	13 [§]	19 [§]	20*	14% at 7 years	33	22 [§]	16*§	18 (MP) -28 (MPT)*
MEDIAN OS, months									
HDT	52% at 5 years*	65	48	54*	37% at 7 years	61	47	Not reached*	38*
CC	12% at 5 years*	64	48	42*	42% at 7 years	66	50	42*	33 (MP) – 52 (MPT)*

HDT: "high-dose" myeloablative therapy with autologous stem cell transplantation; OS: overall survival; PFS: progression-free survival; CC: conventional chemotherapy; *the difference between HDT and CC was statistically significant; [§]event-free survival;

	GIMEMA-RV-	MM-209 ⁸	EMN	-441 ⁹		
	ASCT	CC+R	ASCT	CC+R		
Enrollment period	2007-20	09	2009-	2011		
Number of patients enrolled	402		38	9		
Time of random disclosure	After PBSC co	ollection	After PBSC	collection		
N° pt eligible for consolidation with ASCT vs CC+R	273		25	6		
Eligibility criteria						
NDMM setting	Transplant e	ligible	Transplant eligible			
Age, years	≤65		≤ 65			
Treatment						
Induction	4 Rd, then Cy 4g/n PBSC colle	n ² , G-CSF & ection	4 Rd then Cy 3 gr/m collec	^{2,} G-CSF & PBSC tion		
Consolidation	2 Mel200- ASCT	6 MPR	2 Mel200- ASCT	6 CRD		
Maintenance	R vs nor	ne	RP vs R			
Median follow-up time from enrollment, months	54		52	2		
Median follow-up time from random disclosure, months	43	44	48	47		

Table 3S Results of the two source trials comparing trasplant vs conventional chemotherapy.

ASCT indicates autologous stem cell transplantation; CC+R: oral chemotherapy plus lenalidomide; NDMM: newly diagnosed multiple myeloma; PBSC: peripheral blood stem cell; G-CSF: granulocyte colony stimulating factor. TE: transplant eligible. CRD: cyclophosphamide, lenalidomide, dexamethasone; Cy indicates cyclophosphamide; Mel200: melphalan at 200 mg/m2; MPR: melphalan, prednisone, lenalidomide; Rd: lenalidomide, low-dose dexamethasone; R: lenalidomide; RP: lenalidomide, prednisone.

	EMN	EMN02 ^{11§} IFM/DFCI2009 ^{10#}					
Enrollment period	Feb 2011 –	- Aug 2014	Sep 10 – Recruiting				
Number of patients	15	03	1360				
Time of random assignment	After 4 VCD, Cy colled	/ 2g/m ² & PBSC ction	At diagnosis				
Eligibility criteria	MM, TE, A	$ge \le 65 yrs$	NDMM, TE, Age \leq 65 yrs				
Treatment	HDT	CC	HDT	CC			
Induction	4 V	CD	3 VRD				
Consolidation	1 or 2 Mel200-	4 VMP	Mel200-ASCT	5 VRD			
	2 VRD vs none	2 VRD vs none	2 VRD				
Maintenance	R unt	il PD	R until PD or for up to 1 year*				

Table 4S. Characteristic of ongoing trials comparing trasplant vs chemotherapy plus novel agents.

ASCT indicates autologous stem cell transplantation; CC: conventional chemotherapy; HDT: "high-dose" myeloablative therapy with autologous stem cell transplantation; NDMM: newly diagnosed multiple myeloma; PBSC: peripheral blood stem cell collection; TE: transplant eligible. Cy indicates cyclophosphamide; Mel100, 200: melphalan at 100, 200 mg/m²; RD: lenalidomide, dexamethasone; VCD: bortezomib, cyclophosphamide, dexamethasone; VRD: bortezomib, lenalidomide, dexamethasone; R: lenalidomide; PD: progressive disease. *the study enrolled patients in France, where maintenance with lenalidomide was administered for up to 1 year, and in the USA, where maintenance is planned until PD. [§]trial registered as NCT01208766; [#]trial registered as NCT01191060/ NCT01208662

Table 5S. Baseline patient characteristics.

	All patients	%	MEL200- ASCT	%	CC+R N=261	%
	N=529		N=268			
Age						
<u><</u> 60 years	391	74	198	74	193	74
> 60 years	138	26	70	26	68	26
ISS Stage						
Ι	264	50	140	52	124	48
II	176	33	89	33	87	33
III	89	17	39	15	50	19
Cytogentic profile						
Standard-risk	267	50	136	51	131	50
High-risk	103	20	50	19	53	20
Missing	159	30	82	30	77	30
ECOG Performance status						
0	332	63	168	63	164	63
1	176	33	89	33	87	33
2	21	4	11	4	10	4
R-ISS						
I	126	24	66	25	60	23
II	270	51	134	50	136	52
III	23	4	10	4	13	5
Missing	110	21	58	21	52	20
Maintenance						
None	138	26	71	26	67	26
R	258	49	133	50	125	48
RP	133	25	64	24	69	26
Protocol						
GIMEMA-RV-MM-209	273	52	141	53	132	51
EMN-441	256	48	127	47	129	49
Response at random						
disclosure						
≥VGPR	150	29	69	26	81	31
PR	256	48	129	48	127	49
SD	113	21	64	24	49	19

ISS: International Staging System; ECOG: Eastern Cooperative Oncology Group; R-ISS: Revised International Staging System; MEL200-ASCT: melphalan 200 mg/m²followed by Autologous stem cell transplant. CC+R: conventional chemotherapy plus lenalidomide.





Figure 2S OS with upfront MEL200-ASCT vs upfront CC+R estimating that all CC+R relapsed patients had received salvage ASCT: best model obtained with the multiple imputation method.

