Chemotherapy plus lenalidomide versus autologous transplantation, followed by lenalidomide plus prednisone versus lenalidomide maintenance, in patients with multiple myeloma: A randomised, multicentre, phase 3 trial

UNIVERSITÀ DEGLI STUDI DI TORINO

Chemotherapy plus lenalidomide versus autologous transplantation, followed by lenalidomide-prednisone versus lenalidomide maintenance in multiple myeloma: a phase III trial

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ABSTRACT (max 300 words): 299

Background. High-dose melphalan plus autologous stem-cell transplantation (MEL200-ASCT) is the standard approach in newly diagnosed, transplant-eligible myeloma patients. We compared consolidation with MEL200- ASCT versus cyclophosphamide–lenalidomide-dexamethasone (CRD), and maintenance with lenalidomide-prednisone versus lenalidomide alone.

Methods. This is an open-label, randomized, phase 3 study. We enrolled newly diagnosed, transplant-eligible myeloma patients aged ≤65 years. Using a 2-by-2 partial factorial design, we randomized patients to consolidation with 6 cycles of CRD (cyclophosphamide 300 mg/m^2 days 1, 8, 15; dexamethasone 40 mg days 1, 8, 15, 22; lenalidomide 25 mg days 1–21) or 2 courses of melphalan 200 mg/m^2 (MEL200-ASCT); and to maintenance with lenalidomide-prednisone (lenalidomide 10 mg days 1–21; prednisone 50 mg every other day) or lenalidomide alone. The primary endpoint was progression-free survival (PFS). This study is registered at ClinicalTrials.gov, number NCT01091831.

Findings. 389 patients were enrolled between July 6, 2009 and May 6, 2011, with 256 randomized to consolidation and 223 randomized to maintenance therapy. Median follow-up was 52·0 months. PFS (median: 28·6 versus 43·3 months; HR 2·51, P<0·001) and overall survival (OS; 4-year: 73% versus 86%; HR 2·40, P=0·004) were significantly inferior with CRD compared with MEL200-ASCT. Median PFS was 37·5 months with lenalidomide-prednisone versus 28·5 months with lenalidomide alone (HR 0·84, P=0·336); 3-year OS was 83% with lenalidomide-prednisone versus 88% with lenalidomide maintenance (HR 1·53, P=0·210). Grade 3-4 hematologic toxicities (26%versus 84%, P<0·001), gastrointestinal toxicities (5%versus 20%, P<0·001) and infections (6%versus 19%, P=0·002) were lower with CRD than with MEL200-ASCT. No significant difference in toxicities between lenalidomide-prednisone and lenalidomide was noticed.

Interpretation. PFS and OS were significantly inferior with CRD compared with MEL200-ASCT. Lenalidomide-prednisone maintenance did not significantly improve PFS and OS compared with lenalidomide alone.

Funding. Celgene.

Text word count (max 3000): 2999

Introduction

High-dose therapy with autologous stem-cell transplantation (ASCT) prolongs progression-free survival (PFS) and overall survival (OS) compared with conventional chemotherapy in newly diagnosed multiple myeloma (NDMM) patients and is currently the standard of care for fit patients ≤65 years.[1-3] Immunomodulatory drugs (IMiDs; thalidomide and lenalidomide) and proteasome inhibitors (PIs; bortezomib) significantly improved survival in transplant-eligible and -ineligible patients.[4-15] Given the survival rate in transplant-ineligible patients and the substantial toxicity of high-dose melphalan (melphalan 200 mg/m^2 [MEL200]), the role of ASCT has become an area of debate, and the comparison with less toxic, oral novel agents-based treatments a high research priority. Cyclophosphamide-lenalidomide-dexamethasone (CRD) showed a partial response rate of 85% and a good safety profile.[16] To date, one study compared MEL200-ASCT versus melphalan–prednisone–lenalidomide (MPR), showing an improvement in PFS and OS with MEL200-ASCT.[17] Two other ongoing trials are comparing high-dose chemotherapy plus ASCT with bortezomib-melphalan-prednisone and with bortezomib-lenalidomide-dexamethasone (Clinicaltrials.gov NCT01208766, NCT01191060). IMiDs and PIs have been used as part of maintenance strategies to extend PFS and OS.[18] In four randomized studies, lenalidomide maintenance significantly reduced the risk of progression (hazard ratio [HR] 0·34-0·50) in comparison with no maintenance, but the survival advantage was inconsistent.[13-15,17] A randomized trial showed a significant PFS benefit in patients receiving maintenance with pharmacologic (50 mg every other day) vs physiologic doses of prednisone.[19] Maintenance with thalidomide-prednisone prolonged PFS, with conflicting OS results.[20,21]

This study aims to compare the efficacy and safety of consolidation with CRD versus MEL200-ASCT, followed by maintenance with lenalidomide-prednisone versus lenalidomide alone, in NDMM patients eligible for transplantation.

METHODS

Patients

Patients aged ≤65 years with symptomatic, measurable, NDMM were eligible for study inclusion. Other inclusion criteria were: Karnofsky performance status ≥60%; life expectancy >6 months; absolute neutrophil count ≥1,500/ml^3; platelet count ≥75,000/ml^3; normal cardiac/pulmonary function; creatinine clearance ≥20 ml/min. Exclusion criteria included other malignancies within the past 3 years, and peripheral neuropathy of grade $\geq$2. The study was approved by the institutional review boards of each participating center, and was conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent.

Study design, randomization and masking

This was a 2-by-2 partial factorial, randomized, open-label, phase 3 trial. Patients were recruited from July, 2009 to May, 2011 at 59 centers in Australia, Czech Republic and Italy. A simple randomization sequence, stratified according to International Staging System (ISS) stage[22] (I/II versus III) and age (≤60 versus 61–65 years), was generated by a computer program and implemented into a web-based procedure. All patients were randomized at enrollment into one of the four groups, with a 1:1:1:1 ratio, but the results of the random assignment were concealed until patients reached the end of the induction period and confirmed their eligibility for consolidation and maintenance. Patients and physicians did not know the random assignment until that time, (Supplement).

Procedures

All patients received induction with four 28-day cycles of lenalidomide (25 mg daily on days 1–21) plus dexamethasone (40 mg daily on days 1, 8, 15, and 22) (Rd). Cyclophosphamide and granulocyte colony-stimulating factor were used to mobilize stem cells. The consolidation regimen comprised six 28-day cycles of cyclophosphamide (300 mg/m^2 on days 1, 8, 15), dexamethasone (40 mg on days 1, 8, 15, 22) and lenalidomide (25 mg on

days 1–21) or two cycles of MEL200- ASCT. Maintenance started within 3 months following completion of consolidation and consisted of lenalidomide (10 mg on days 1–21 of each 28-day cycle) plus prednisone (50 mg every other day) or lenalidomide alone (10 mg on days 1–21 of each 28-day cycle) administered until progression or the development of unacceptable adverse events (AEs). Dose modification guidelines are provided in the Supplement.

Role of the funding source

Celgene provided an unrestricted grant to conduct the study but had no role in study design, data collection, analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Outcomes

The primary study endpoint was PFS. Secondary endpoints included OS, overall response rate, and safety. PFS was calculated until the date of progression, death from any cause during treatment, or data censoring at the last date on which the patient was known to be progression-free. OS was calculated until the date of either death from any cause or data censoring at the last date at which the patient was known to be alive. Response was assessed using the International Uniform Response Criteria for Multiple Myeloma.[23] AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3·0).[24]

Statistical analysis

The primary comparison was between CRD and MEL200-ASCT. A design of non-inferiority was chosen. With an alpha error of 0·05 (1-sided), 390 patients (195 per arm) would need to be enrolled to have a statistical power of 80% to detect a HR of 1·43 in favor of CRD versus MEL200-ASCT (corresponding to a 2-year PFS of 0·65 in both arms), assuming 3 years of

accrual, a minimum follow-up of 2 year, and a drop-out rate of 5%; 390 patients were expected to yield the necessary number of events (N=195) for the primary analysis, calculated with the formula of Schoenfeld.[25] The secondary comparison was between lenalidomide-prednisone and lenalidomide maintenance. We expected that approximately 230 patients (115 per arm) would be eligible for maintenance. With an alpha error of 0·05 (2-sided), this sample size had a statistical power of 80% to detect an improvement from 0·70 to 0·82 in 2-year PFS in favor of lenalidomide-prednisone (corresponding to a HR of 0·55).

To estimate the effect of the complete treatment strategy (induction, consolidation, maintenance), PFS and OS since the date of study enrollment were estimated for the four groups on all enrolled patients. All comparative analyses were performed with an intention-to-treat approach, on the two randomized populations: a) the consolidation-phase population, including all patients eligible for CRD or MEL200-ASCT (starting time of analyses: date of random disclosure); and b) the maintenance-phase population, including all patients eligible for lenalidomide-prednisone or lenalidomide maintenance (starting time of analyses: date of clinical evaluation after consolidation), (Supplement). One interim analysis, according to the O'Brien and Fleming design, was specified by the protocol for the MEL200-ASCT versus CRD comparison when 78 progression events (40%) had occurred.

The safety analysis population included all patients who received at least one dose of the study drugs. Response and safety data were compared by means of the chi-square or the Fisher's exact test, when required. Time-to-event data were analyzed using the Kaplan–Meier method; treatment groups were compared with the log-rank test. Cox proportional hazards models were used to estimate HRs and 95% confidence intervals (CIs) for the main comparisons, and Grambsch and Therneau test for testing the proportional hazard assumption.[26]Cox models, adjusted for age and ISS stage, were used to explore any effect modification of consolidation or maintenance between different subgroups (including the prespecified subgroups by age and ISS stage), using interaction terms. Since Grambsch and Therneau test suggested a violation of proportional hazard assumption about the

comparison CRD versus MEL200-ASCT, the time-varying effect of treatment was evaluated in the Cox model according to two periods of post-randomization follow-up: the first 24 months after randomization, and from 24 months after randomization to the end of follow-up. Between-group differences in patient characteristics were evaluated using the Mann–Whitney U test and the Chi-squared or Fisher's exact test, as appropriate, for continuous and categorical variables, respectively. Statistical analyses were performed using SAS software (Version 8·2) and R (Version 3·1·1). The data cut-off point was March 30, 2015.

RESULTS

Three hundred and eighty-nine patients were enrolled; 387 entered the induction/mobilization phase, and 256 remained eligible for consolidation with CRD or MEL200-ASCT; the main reason for discontinuation during induction/mobilization was progression. At the end of consolidation, 223 patients were eligible for maintenance (Figure 1). Baseline demographics and disease characteristics were well balanced across treatment arms (Table 1). At the data cut-off, 236 (39%) patients had progressed or died, 42 patients (36%) were receiving lenalidomide-prednisone, and 36 patients (34%) were on lenalidomide alone. The median durations of follow-ups are reported in Table 1.

In the total enrolled population, the median PFS from enrollment was 24·2 months with CRD+lenalidomide-prednisone, 27·6 months with CRD+lenalidomide, 37·6 months with MEL200-ASCT+lenalidomide-prednisone, and 31·5 months with MEL200-ASCT+lenalidomide (Figure 2A). The 4-year OS was 68% with CRD+lenalidomide-prednisone, 76% with CRD+lenalidomide, 77% with MEL200-ASCT+lenalidomide-prednisone, and 75% with MEL200-ASCT+lenalidomide (Figure 2B).

After the induction/mobilization phase, the random assignment to CRD or MEL200-ASCT was disclosed for the 256 patients eligible for consolidation. The median PFS was significantly shorter with CRD (28·6 months) than with MEL200-ASCT (43·3 months; HR for the first 24 months 2·51, 95% CI 1·60–3·94, P<0·001; Figure 2C). The inferiority of CRD was less evident after 24 months. The 4-year OS rate was significantly lower with CRD compared

with MEL200-ASCT (73% versus 86%; HR 2·40, 95% CI 1·32–4·38, P=0·004; Figure 2D). The 3-year OS from consolidation was 87% with MEL200-ASCT and 84% with CRD. Subgroup analysis of PFS confirmed the inferiority of CRD versus MEL200-ASCT in most of the subgroups analyzed, including the lenalidomide-prednisone and lenalidomide populations (P value for interaction=0.58), (Figure S1). Subgroup analysis of OS confirmed the inferiority of CRD compared with MEL200-ASCT in the lenalidomide-prednisone and lenalidomide populations (P value for interaction=0.21), (Figure S2). Figure S3 showed PFS and OS in CRD and MEL200-ASCT arms according to cytogenetic data.

In the 223 patients eligible for maintenance, the median PFS was longer with lenalidomide-prednisone (37·5 months) than with R (28·5 months) but the difference was not statistically significant (HR 0·84, 95% CI 0·59–1·20, P=0·336; Figure 2E). No significant difference in the 3-year OS rate was noticed between lenalidomide-prednisone and lenalidomide (83% versus 88%; HR 1·53, 95% CI 0·79–2·98, P=0·210; Figure 2F).

The 4-year PFS2 from diagnosis was 47% with CRD+lenalidomide-prednisone, 51% with CRD+lenalidomide, 66% with MEL200-ASCT+lenalidomide-prednisone, and 57% with MEL200-ASCT+lenalidomide (Figure S4). Analyses of treatment and outcome after relapse is reported in the Supplement.

Response rate improved during consolidation and maintenance (Table S6). At data cut-off, the complete response (CR) rate was 23% with CRD+lenalidomide-prednisone, 27% with CRD+lenalidomide, 37% with MEL200-ASCT+lenalidomide-prednisone, and 33% with MEL200-ASCT+lenalidomide (Table S7).

During induction, the most frequent grade ≥3 AEs were neutropenia (10%), anemia (8%), infections (8%), systemic toxicities (6%) and thrombotic events (5%). Three toxic deaths occurred (septic shock, n=2; cardiac failure, n=1) and 16 patients (4%) discontinued treatment for AEs.

During consolidation, hematologic grade 3-4 AEs occurred less frequently with CRD than with MEL200-ASCT (26% versus 84%, P<0·001). They were mainly neutropenia (24%

versus 80%, P<0·001) and thrombocytopenia (5% versus 82%, P<0·001). Grade 3-4 non-hematologic AEs were less common with CRD than with MEL200-ASCT (23% vs 39%, P=0·01). The most frequent were gastrointestinal events (5% versus 20%, P<0·001) and infections (6% versus 19%, P=0·002). Although MEL200-ASCT induced a higher rate of grade 3-4 AEs, no increase in serious AEs or toxic deaths was noticed (1 toxic death due to septic shock was reported with CRD). Four patients (3%) in the CRD arm and 1 patient (1%) in the MEL200-ASCT arm discontinued therapy for toxicity.

The toxicity profile of the lenalidomide-prednisone and lenalidomide maintenance was similar. The most frequent grade 3-4 hematologic AEs were neutropenia (8% with lenalidomide-prednisone versus 13% with lenalidomide; P=0·193), infections (8% with lenalidomide-prednisone versus 5% with lenalidomide; P=0·417), systemic AEs (6% vs 2%; P=0·174) and vascular AEs (4% with lenalidomide-prednisone versus 2% with lenalidomide; P=0·449) (Table 2). In the lenalidomide-prednisone arm, lenalidomide dose-reduction for AEs was required in 11 patients (9%); prednisone dose-reduction was required in 42 patients (36%) (median time to prednisone dose-reduction: 4 months); 6 patients (5%) discontinued treatment for toxicity and 3 patients stopped treatment after developing a second primary malignancy (SPM) (melanoma, n=1; gastrointestinal, n=1; bladder, n=1). In the lenalidomide arm, lenalidomide dose-reduction was required in 23 patients (22%); 8 patients (8%) discontinued lenalidomide for toxicity and 2 patients stopped treatment after developing a SPM (glioblastoma, n=1; breast cancer, n=1), The median duration of maintenance was comparable in the 2 groups (Table 3). Compliance with lenalidomide in the 2 arms was not affected by previous therapy with CRD or MEL200-ASCT (Supplement).

Eighteen patients (5%) developed SPMs. During the screening, one patient developed renal cancer. During the induction/mobilization, one patient developed breast cancer, one gastrointestinal cancer and one squamous cell carcinoma. During maintenance, seven patients developed squamous cell carcinoma (CRD+lenalidomide-prednisone n=1; MEL200-ASCT+lenalidomide-prednisone, n=3; MEL200-ASCT+lenalidomide, n=3), one a

glioblastoma (CRD+lenalidomide), one a renal cancer (CRD+lenalidomide), one had a breast cancer relapse (CRD+lenalidomide), one developed a colorectal cancer (CRD+lenalidomide-prednisone), one a melanoma (MEL200-ASCT+lenalidomide-prednisone), one a prostate cancer (MEL200-ASCT+lenalidomide-prednisone), and one a bladder cancer (MEL200-ASCT+lenalidomide-prednisone).

DISCUSSION

In this randomized study with NDMM patients, CRD significantly increased the risk of progression or death (HR 2·51) and shortened OS (HR 2·40) compared with MEL200-ASCT. With the present follow-up, maintenance with lenalidomide-prednisone did not significantly improve PFS or OS compared with lenalidomide alone. These results confirm a net clinical benefit of MEL200-ASCT consolidation in comparison with chemotherapy plus oral alkylating agents, as demonstrated in a previous trial.[17]

The benefit on PFS and OS for MEL200-ASCT was independent of the maintenance treatment. An increase in hematologic and non-hematologic AEs was noticed with MEL200-ASCT, but toxicities were manageable and did not increase the rate of early death or treatment discontinuation. Although stem cells were collected from all patients before consolidation, ASCT was performed in only 43% of CRD patients at relapse, predominantly due to a worsening of clinical condition; this was true in particular for patients >60 years. Thus, delaying ASCT until relapse is not always feasible and this option should be considered with caution. Furthermore, CRD was associated with a significantly shorter PFS2 compared with MEL200-ASCT: salvage therapy did not cancel the advantage of upfront ASCT.

Response rate after consolidation was comparable between CRD and MEL200-ASCT. Depth of response improved during maintenance in both groups. Higher rates of CR and very good partial responses were noticed during maintenance in patients who previously

received MEL200-ASCT. This could be related to a delayed response to MEL200-ASCT, as suggested by a study showing that time to best response occurs 9 months post-ASCT.[27] Results about CRD versus MEL200-ASCT were comparable to those of the RV-MM-209 trial comparing consolidation with melphalan-prednisone-lenalidomide versus MEL200-ASCT. Survival rates in the MEL200-ASCT arms of the two trials, and in the chemotherapy-lenalidomide arms (MPR/CRD) were similar. Yet, CRD showed a lower rate of neutropenia compared with MPR.[17]

Despite a trend towards a better median PFS with lenalidomide-prednisone (37·5 vs 28·5 months) the difference was not significant; furthermore, 3-year OS was 83% with lenalidomide-prednisone vs 88% with lenalidomide (P=0·210). In previous reports, lenalidomide maintenance increased remission duration in comparison with no maintenance, with inconsistent OS advantage.[13-15] Nevertheless, these studies were not powered to determine an OS benefit. The role of prednisone plus IMiDs (thalidomide) has been evaluated in two studies, in comparison with prednisone alone/no maintenance, showing an improved PFS but an inconsistent OS advantage.[20,21] None of the trials published compared prednisone plus IMiD with IMiD alone. The advantage of adding steroids to IMiDs during maintenance is unclear. The therapeutic efficacy of IMiDs probably originate at least in part from the activation of cytotoxic NK-cells. Steroids synergize with lenalidomide to inhibit tumor growth but they also inhibit NK-cell activity, even when administered in combination with IMiDs.[28]

The toxicities with lenalidomide-prednisone and lenalidomide maintenance were comparable. Nine percent of patients required lenalidomide dose-reduction in the lenalidomide-prednisone arm versus 22% in the lenalidomide arm (p=0.004). The increase in dose-reduction was related mainly to the occurrence of mild cutaneous toxicity and neutropenia, less frequent with prednisone administration; the rate of lenalidomide dose-reduction in both arms was not affected by previous treatment with CRD or MEL200-ASCT. Prednisone dose-reductions were required in 36% of patients and the median time to

prednisone dose-reduction was short: this may in part explain the absence of a clear long-term advantage with lenalidomide-prednisone.

The rate of SPMs was low; no between-group differences were noted, except for an increase in non-invasive skin cancers during maintenance in the MEL200-ASCT arm. The rate of non-invasive skin cancers was comparable to the one reported in the RV-MM-209 study.[17] No hematologic SPMs were observed, similarly to the RV-MM-209 study[17] (only one hematologic SPM occurred). This incidence is low if compared with the one in the CALGB100104 and the IFM0502 studies.[13,14] The use of a specific alkylating-free induction in the present and the RV-MM-209[17] trials may in part explain this difference.
A limitation of this study was that randomization was performed at enrolment and both random were disclosed before consolidation. Only 65% of the enrolled patients were eligible for consolidation; our drop-out rate is similar to the rate reported in the phase 3 US Intergroup Trial S9321.[29] The main reasons for discontinuation during induction were PD and the choice of alternative therapies in patients with a suboptimal response. Outcome of patients who discontinued during induction was particularly poor (Figure S5). Of note, rate of grade 3-4 AEs and toxic deaths were low during induction, confirming the safety profile of Rd, as reported in the ECOG E4A03 trial.[30] We investigated only lenalidomide, and did not include bortezomib in the induction and consolidation. Building on Rd with the association of a PI improved response rates with manageable toxicity; this can get more patients into transplant. Bortezomib-based combinations with alkylating agents or IMiDs induce a high-quality response and improve outcomes in transplant-eligible and transplant-ineligible patients.[5,9] Results of two ongoing studies will shed further light on this issue. The two trials are comparing effective drug combinations that include bortezomib plus lenalidomide or plus melphalan versus ASCT (CT.gov NCT01208766; CT.gov NCT01191060; NCT01208662).

In conclusion, our results confirm that consolidation with MEL200-ASCT remains the preferred therapeutic option in transplant-eligible patients with NDMM. This regimen improves PFS and OS at a cost of increased but manageable toxicity. Long-term steroid

therapy is not well tolerated in about one-third of patients and, with the present follow-up, the addition of prednisone to lenalidomide maintenance did not significantly affect survival.

Contributors: FG, RH, ASpencer, MB, and AP designed the study, and supervised its conduct and the data analysis. FG, SO, RH, MTP, LC, PC, ASiniscalchi, VM, LP, AC, AM, AMC, NP, PO, PC, ANL, MO, RR, SP, FP, CC, ASpencer, MB, AP recruited patients in the source studies and/or provided relevant data. FG collected and assembled the data. AE and SS performed the statistical analysis. FG and AP analyzed and interpreted the data. FG and AP drafted the initial manuscript. All authors critically reviewed the manuscript drafts and approved the final version.

Conflicts of interest: FG has received honoraria from and served on the advisory committee for Celgene; RH has received honoraria from Amgen and consultancy fees from Celgene and Janssen; MTP has received honoraria from Celgene, Janssen-Cilag, Mundipharma, Sanofi, Amgen, Bristol-Myers Squibb; MO has received honoraria from Celgene; FP has served on the advisory boardof Celgene Janssen, MSD, Mundipharma, Bristol; ASpencer has received honoraria from Celgene; MB has received research support, consultancy fees from and served on the advisory board of Celgene; AP has received honoraria and consultancy fees from Celgene.

Acknowledgments: The study was funded by Celgene. We thank all the patients who participated in the study, the nurses Simona Bera and Daniela Boetto, the data managers Marta Santoro and Giulia Lupparelli, Dr. Chiara Cerrato and the editorial assistant Giorgio Schirripa

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Research in Context

Evidence before this study

When this trial was developed, the survival of MM patients had considerably improved over the preceding 10 years thanks to the introduction of novel agents (thalidomide, bortezomib and lenalidomide). Before the introduction of new drugs, high-dose therapy with ASCT proved to be superior to conventional chemotherapy in terms of both PFS and OS in patients with newly diagnosed MM, but at a cost of increased toxicity. The survival rate achieved in transplant-ineligible patients with novel agents-based, well tolerated therapy, questioned the role of ASCT in younger patients. In particular, the comparison of high-dose chemotherapy and ASCT with less toxic, orally administered novel agents-based treatments has become a high research priority. We searched PubMed using the terms “multiple myeloma”, “clinical trials”, “transplantation”, “proteasome inhibitors”, and “immunomodulatory drugs” for articles published in English up to June 2015. Search results showed that only one trial has so far addressed this issue, namely the phase 3 RV-MM-PI-209 trial that compared high-dose chemotherapy and ASCT with the triplet oral combination MPR. Results of that trial were not available when the present trial (CRD versus MEL200-ASCT) was planned. Data from a phase 1-2 trial indicated a high response rate with MPR treatment, but a high-rate of haematological toxicity. Cyclophosphamide, another alkylating agent efficacious in MM patients was considered a good alternative to oral melphalan in combination with lenalidomide, given the better safety-efficacy profile (PR rate was 85% and with manageable AEs and a reduction in haematological toxicities in comparison with MPR).

When our trial was designed, thalidomide alone or in association with prednisone had been used in other trials as part of maintenance strategy to extend remission, showing a prolonged PFS, but conflicting results in terms of OS. Thalidomide use was limited by a significant long-term toxicity (neuropathy). Lenalidomide, a more potent second generation IMiD with a different safety profile (with rarely reported neuropathy), was considered an optimal drug to be used as continuous treatment to prolong remission duration. Steroids

were also evaluated as maintenance therapy: pharmacologic doses (50 mg every other day) of prednisone during maintenance significantly improved PFS in comparison with physiologic doses. The combination of lenalidomide plus prednisone, given the synergistic antitumor activity of steroids, was deemed a valuable alternative option to lenalidomide alone. In addition, our PubMed search found that no other trial has so far compared the efficacy and toxicity of prednisone plus lenalidomide with lenalidomide alone.

Added value of this study

This study showed the inferiority of CRD vs MEL200-ASCT. MEL200-ASCT significantly improved PFS and OS in NDMM. An increase in AEs was noticed with MEL200-ASCT, but toxicities were manageable and did not increase the rate of early death or treatment discontinuation. Our results confirmed the role of MEL200-ASCT in the novel agent era, in comparison with oral chemotherapy plus lenalidomide, strengthening the results of the phase 3 RV-MM-PI-209 trial published in 2014. Furthermore, our results showed that transplant at relapse is no more a feasible option in around 50% of the patients. In addition, this is the first trial comparing the efficacy and toxicity of prednisone plus lenalidomide with lenalidomide alone. The high survival rate achieved with continuous treatment is comparable with the results of other trials evaluating lenalidomide maintenance. Despite an early benefit with the association of steroids plus lenalidomide, the long-term use of steroids is not well tolerated, and does not provide a significant survival advantage in comparison with lenalidomide alone.

Implication of all the available evidence

Our results suggest that high-dose chemotherapy and transplant should still be considered a standard treatment, even in the era of novel agents, if compared with oral chemotherapy plus lenalidomide. Around 50% of patients considered eligible for high-dose chemotherapy and ASCT at diagnosis may no longer be eligible for ASCT at relapse; clinicians should keep

into account this possibility, together with the high efficacy of upfront ASCT, when selecting the treatment strategy. Maintenance with lenalidomide alone is a well-tolerated treatment, and the addition of long-term steroids does not induce any significant advantage. Two ongoing trials are comparing combinations that include a proteasome inhibitor plus lenalidomide or plus melphalan versus ASCT; those studies aim to evaluate the benefit of early versus late transplant, and the effects of different durations of maintenance therapy. The results of these trials, and future meta-analyses on these data, should shed further light on these issues.

Tables

Table 1 Demographic and Baseline Characteristics of the Enrolled Population and the Randomized Treatment Groups.

	ALL N=389		CRD N=129		MEL200-ASCT N=127		Lenalidomide-prednisone N=117		Lenalidomide N=106	
	N	%	N	%	N	%	N	%	N	%
Age-year										
Median (range)	57 (18-65)		56 (36-65)		57 (32-65)		57(33-64)		56(37-65)	
IQR	53-61		51-61		53-62		53-61		51-61	
Gender										
Male	196	50	59	46	61	48	58	50	50	47
ISS Stage										
I	170	44	58	45	64	50	60	51	51	48
II	148	38	48	37	45	35	43	37	39	37
III	71	18	23	18	18	14	14	12	17	16
Karnofsky PS										
70-100%	334	86	115	89	106	83	105	90	88	83
60-70%	55	14	14	11	21	17	12	10	18	17
Creatinine (mg/dL)										
Median (range)	0·9 (0·38-3·2)		0·9 (0·5-2·2)		0·9(0·48-3·2)		0·9(0·48-1·6)		0·9(0·58-3·2)	
IQR	0·8-1·1		0·8-1·1		0·7-1·1		0·7-1·1		0·7-1·1	
Missing data	21	5	5	4	3	2	8	7	5	5
LDH (U/L)										
Median (range)	243 (6-1143)		233 (64-1104)		259 (6-649)		258(61-649)		243(6-1104)	
IQR	170-326		166-322		187-330		17-334		164-322	
Missing data	54	14	20	16	10	8	17	15	17	16
Hemoglobin g/L										
Median (range)	11·3 (5·1-17·1)		11·4 (6·3-17·1)		11·6(6·04-17)		11·9(7·8-17)		11·2(6·3-15·1)	
IQR	9·6-12·7		9·7-13·1		9·9-13·0		10·2-13·4		9·6-12·7	
Missing data	18	5	6	5	9	7	2	2	5	5
Platelet (x10^3/L)										
Median (range)	232(75-723)		236 (76-679)		247 (94-723)		247(94-679)		241(75-723)	
IQR	188-297		189-297		196-307		199-297		194-316	

Missing data	0	0	0	0	0	0	0	0	0	0
Cytogenetic features										
Deletion 17p	29	8	10	8	6	5	4	3	8	8
Translocation (4;14)	41	11	17	13	11	9	15	13	5	5
Translocation (14;16)	19	5	6	5	6	5	5	4	7	7
High-risk	80	21	30	23	23	18	22	19	19	18
Missing data	106	27	31	24	30	24	23	20	27	26
R-ISS Stage										
R-ISS 1	66	17	23	18	30	24	29	25	20	19
R-ISS 2	193	50	93	72	91	72	59	50	51	48
R-ISS 3	18	5	6	5	4	3	3	3	3	3
Not evaluable	110	28	7	5	2	1	26	22	32	30
Median time from enrollment (months)	-		6·0		5·9		12·9		13·1	
Median duration of follow-up from enrollment (months)	52·0		-		-		-		-	
Median duration of follow-up from consolidation (months)	-		46·9		47·9		-		-	
Median duration of follow-up from maintenance (months)	-		-		-		41·0		42·3	

IQR, interquartile range; ISS, International Staging System; R-ISS: revised International Staging System; MEL200-ASCT,melphalan 200 mg/m^2 plus autologous stem cell transplantation; CRD, cyclophosphamide-lenalidomide-dexamethasone, PS, Performance Status. Percentages may not total 100 because of rounding.

Table 2 Most frequent grade ≥3 adverse events according to treatment phase

GRADE 3-4 TOXICITY	INDUCTION		CONSOLIDATION				MAINTENANCE			
	RD N=387		CRD N=129		MEL200-ASCT N=127		Lenalidomide-prednisone N=117		Lenalidomide N=106	
	N	%	N	%	N	%	N	%	N	%
At least 1 hematologic AE	63	16	34	26	107	84	11	9	15	14
anemia	29	8	3	2	18	14	1	1	0	0
neutropenia	40	10	31	24	102	80	9	8	14	13
thrombocytopenia	8	2	6	5	104	82	1	1	0	0
At least 1 hematologic SAE	3	1	2	2	0	0	0	0	0	0
At least 1 non-hematologic AE	104	27	30	23	49	39	33	28	20	19
infection	31	8	8	6	24	19	9	8	5	5
gastrointestinal	17	4	6	5	25	20	4	3	0	0
cardiac	10	3	2	2	2	2	0	0	2	2
vascular	19	5	1	1	0	0	5	4	2	2
systemic	22	6	6	5	6	5	7	6	2	2
dermatologic	13	3	4	3	0	0	1	1	3	3
At least 1 non-hematologic SAE	54	14	13	10	9	7	13	11	10	9
Discontinuation due to AEs	16	4	4	3	1	1	6*	5	8^	8

AE, adverse event; SAE, serious adverse event; MEL200-ASCT,melphalan 200 mg/m^2 plus autologous stem cell transplantation; CRD, cyclophosphamide-lenalidomide-dexamethasone. Percentages may not total 100 because of rounding. ^3 patients who previously received CRD and 5 patients who previously received MEL200-ASCT; *3 patients who previously received CRD and 3 patients who previously received MEL200-ASCT.

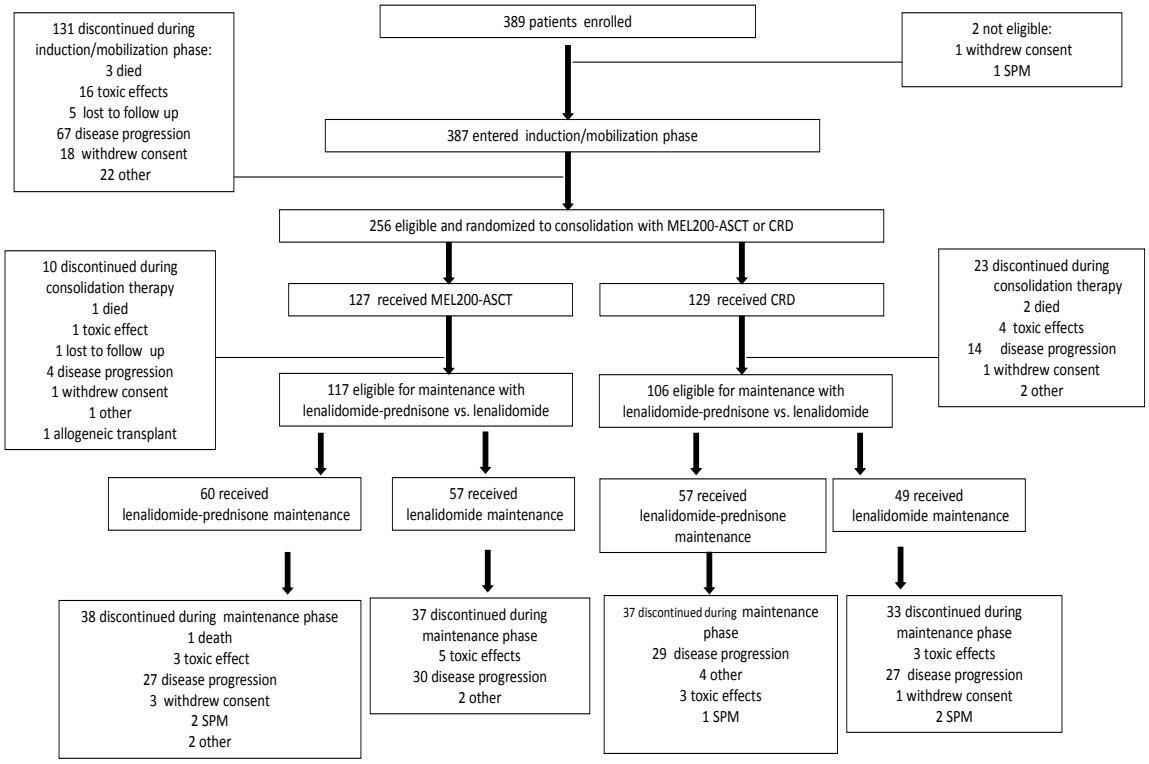
Table 3 Lenalidomide and prednisone dose-reduction and duration of maintenance

Dose-reduction	Lenalidomide-prednisone N=117		Lenalidomide N=106	
	N	%	N	%
Lenalidomide dose				
Full dose 10 mg	106	91	83	78
Reduced dose	11*	9	23*	22
7·5 mg	3	3	7	7
5 mg	8	7	16	15
Median duration of treatment (months)	28·9		25·3	
Reasons for dose reduction				
Hematological AEs	1	1	8	8
Dermatologic AEs	1	1	5	5
Infections	0	0	4	4
Gastrointestinal AEs	5	4	3	3
Peripheral neuropathy	2	2	1	1
Other reasons	2	2	2	2
Prednisone dose				
Full dose 50 mg	75	64		
Reduced dose	42	36		
25 mg	27	23		
12·5 mg	15	13		
Median duration of treatment (months)	26·1			
Reasons for dose reduction				
Psychiatric disorders	10	9		
Endocrinopathy	6	5		
Hyperglycemia	4	3		
Cardiovascular AEs	5	4		
Gastrointestinal AEs	3	3		
Musculoskeletal AEs	2	2		
Weight gain	2	2		
Other reasons	10	9		

AEs: Adverse Events. Percentages may not total 100 because of rounding. *P=0.004

Figure Legends

Figure 1. Consort Diagram: Randomization, Treatment Phases, and Follow-up of Patients

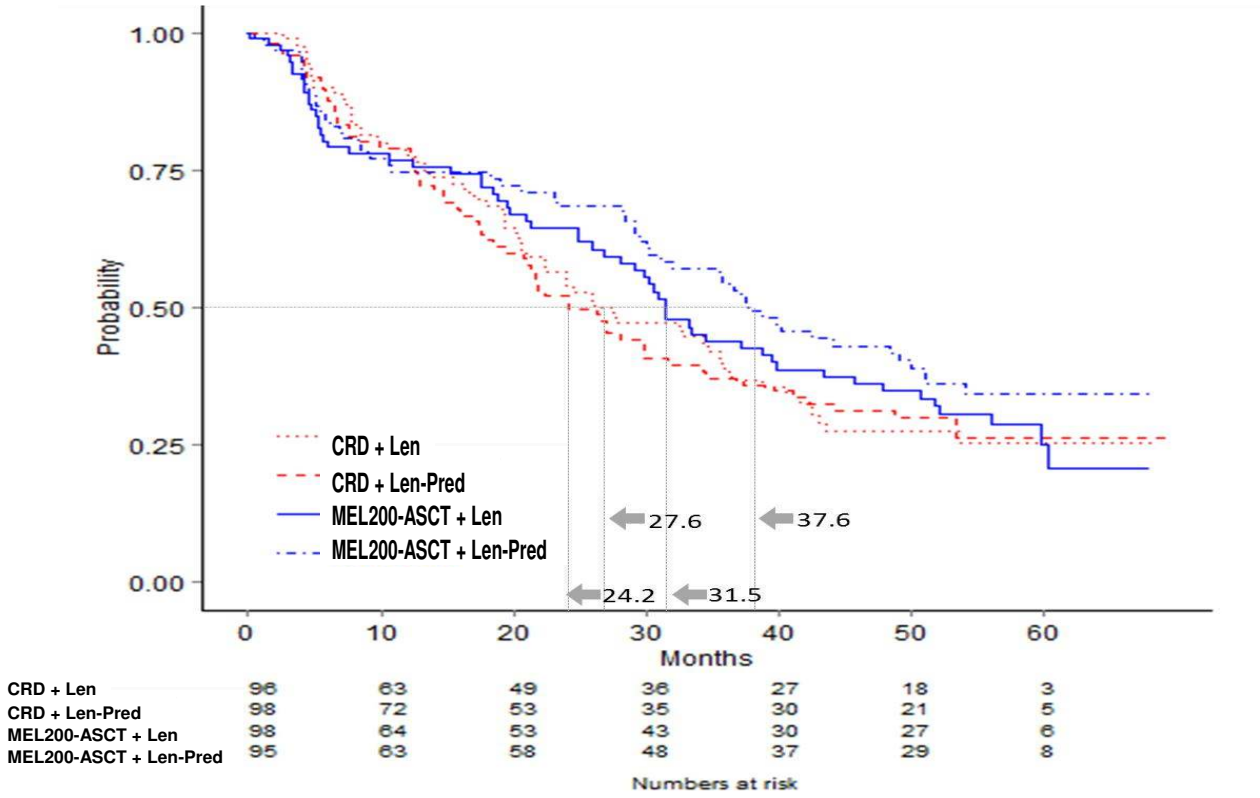


MEL200-ASCT, 2 courses of melphalan 200 mg/m^2 plus autologous stem cell transplantation; 6 cycles of CRD, cyclophosphamide-lenalidomide-dexamethasone; SPM, second primary malignancy.

Figure 2. Kaplan-Meier Estimates of Progression-Free Survival and Overall Survival for the Population Eligible and Randomized to CRD or MEL200-ASCT, and to lenalidomide-prednisone vs lenalidomide maintenance

Panel A shows progression-free survival from diagnosis with CRD followed by lenalidomide-prednisone maintenance, CRD followed by lenalidomide maintenance, MEL200-ASCT followed by lenalidomide-prednisone maintenance, and MEL200-ASCT followed by lenalidomide maintenance. Panel B shows overall survival with CRD followed by lenalidomide-prednisone maintenance, CRD followed by lenalidomide maintenance, MEL200-ASCT followed by lenalidomide-prednisone maintenance, and MEL200-ASCT followed by lenalidomide maintenance. Panel C shows progression-free survival from the start of CRD or MEL200-ASCT. Panel D shows overall survival from the start of CRD or MEL200-ASCT. Panel E shows progression-free survival from the start of lenalidomide-prednisone maintenance or lenalidomide maintenance. Panel F shows overall survival from the start of lenalidomide-prednisone maintenance or start of lenalidomide maintenance. MEL200-ASCT: melphalan 200 mg/m^2 plus autologous stem cell transplantation; CRD cyclophosphamide–prednisone–lenalidomide; len-pred: lenalidomide-prednisone; len: lenalidomide.

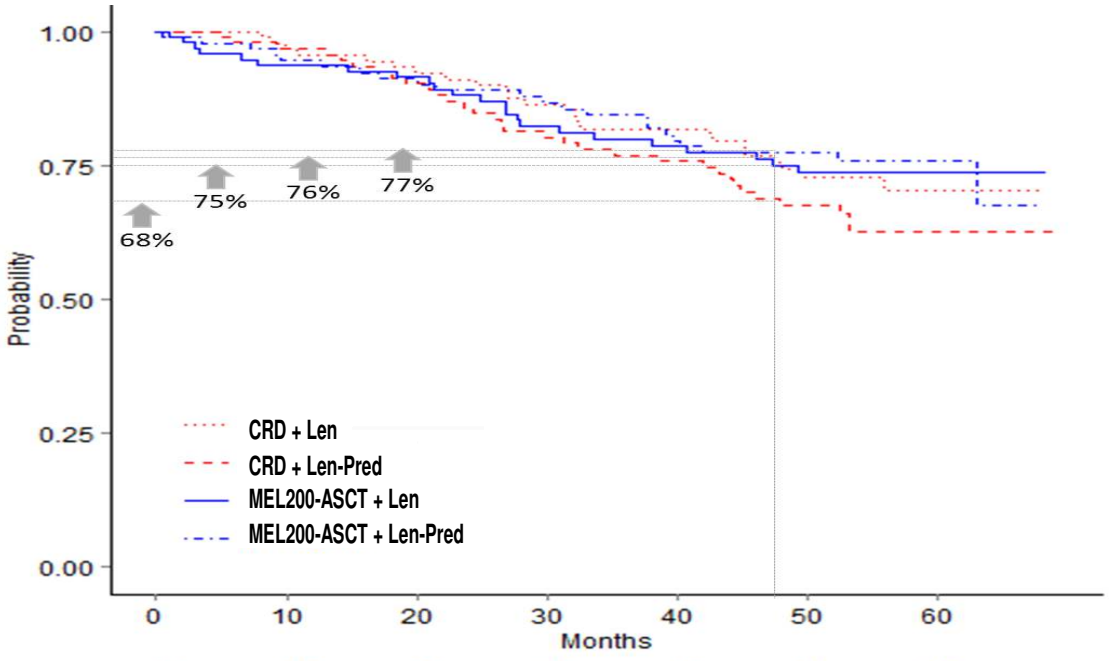
2A



CRD + Len	96	63	49	36	27	18	3
CRD + Len-Pred	98	72	53	35	30	21	5
MEL200-ASCT + Len	98	64	53	43	30	27	6
MEL200-ASCT + Len-Pred	95	63	58	48	37	29	8

Numbers at risk

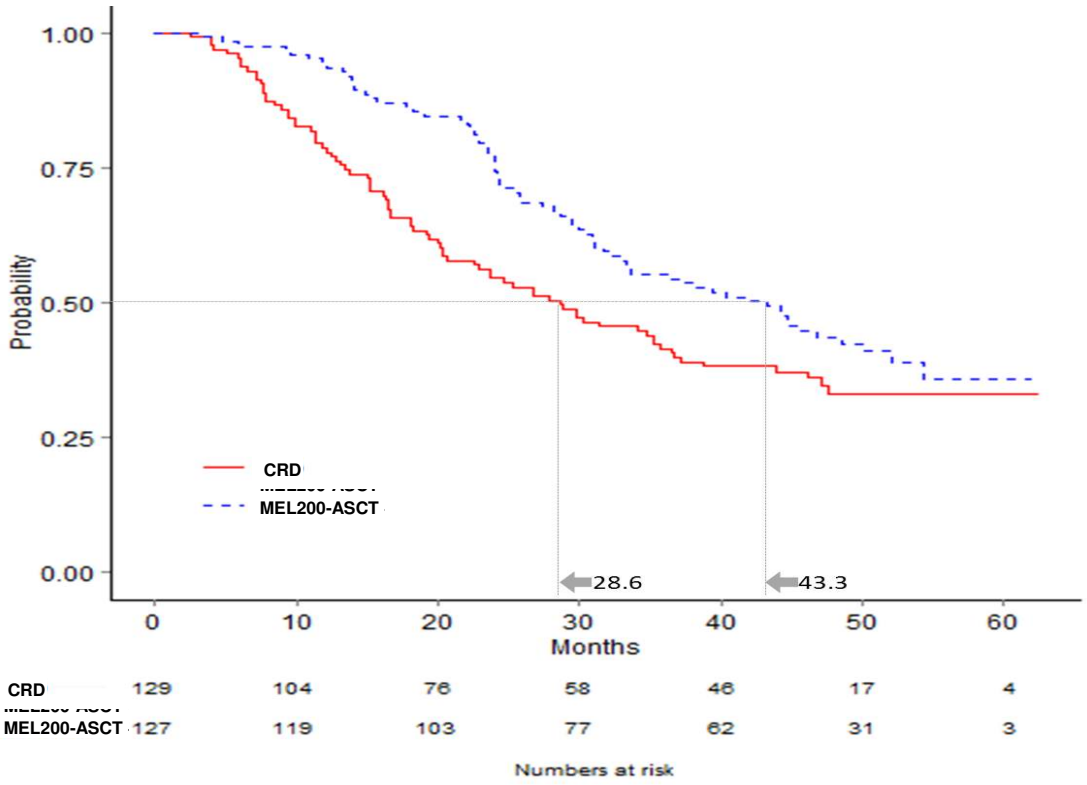
2B



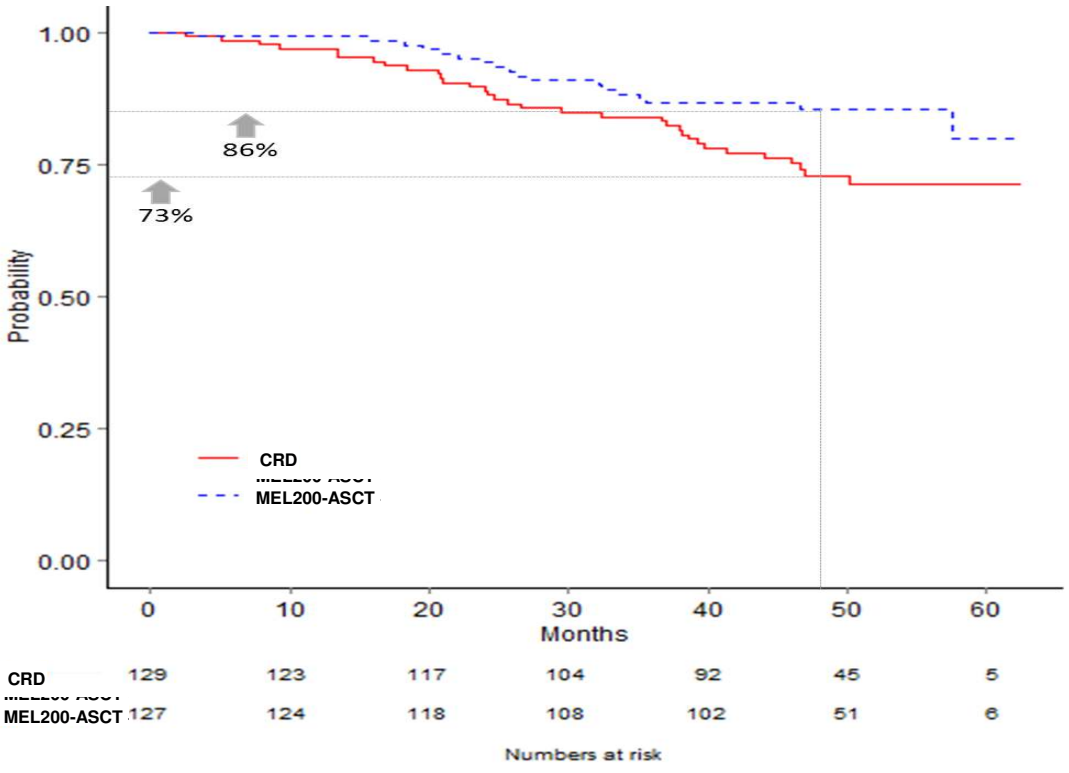
CRD + Len	96	88	81	75	69	53	11
CRD + Len-Pred	98	90	82	71	67	51	10
MEL200-ASCT + Len	98	86	81	69	65	56	14
MEL200-ASCT + Len-Pred	95	85	81	75	68	59	16

Numbers at risk

2C


1.00
0.75
0.50
0.25
0.00
Probability
CRD
MEL200-ASCT
28.6
43.3
0
10
20
30
40
50
60
Months
CRD 129 104 76 58 46 17 4
MEL200-ASCT 127 119 103 77 62 31 3
Numbers at risk

2D


1.00
0.75
0.50
0.25
0.00
Probability
86%
73%
CRD
MEL200-ASCT
0
10
20
30
40
50
60
Months
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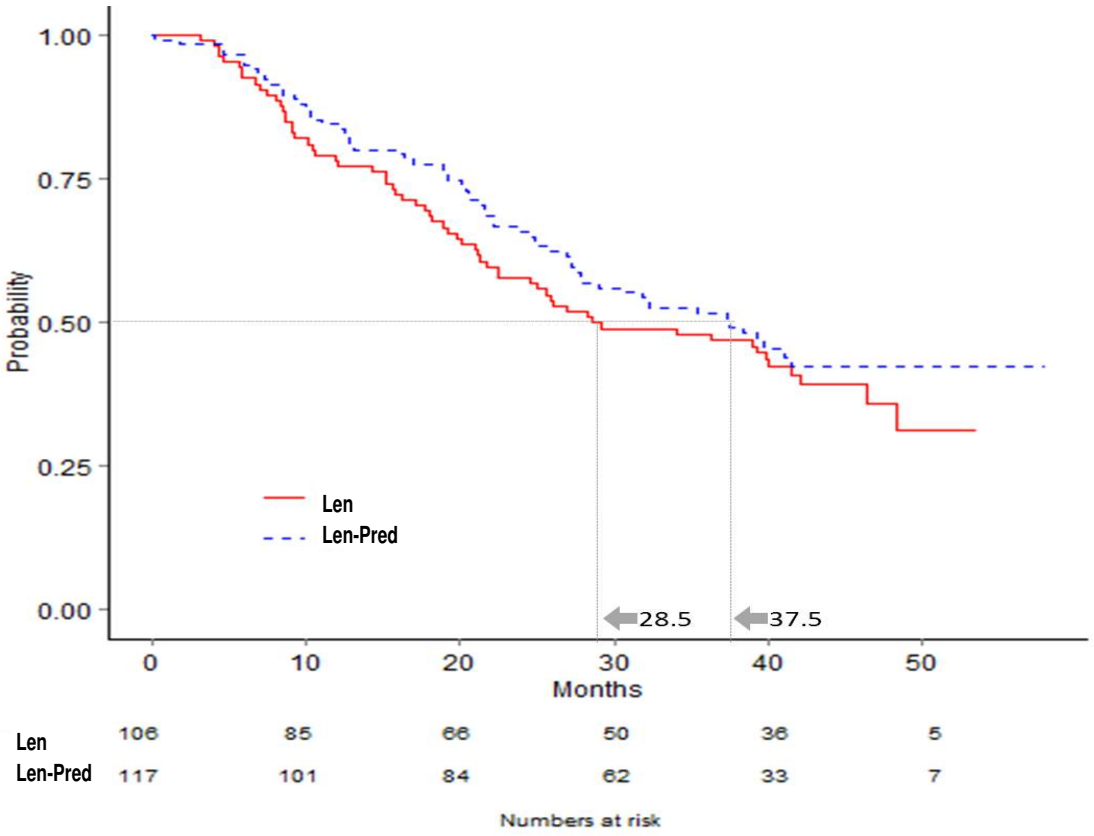
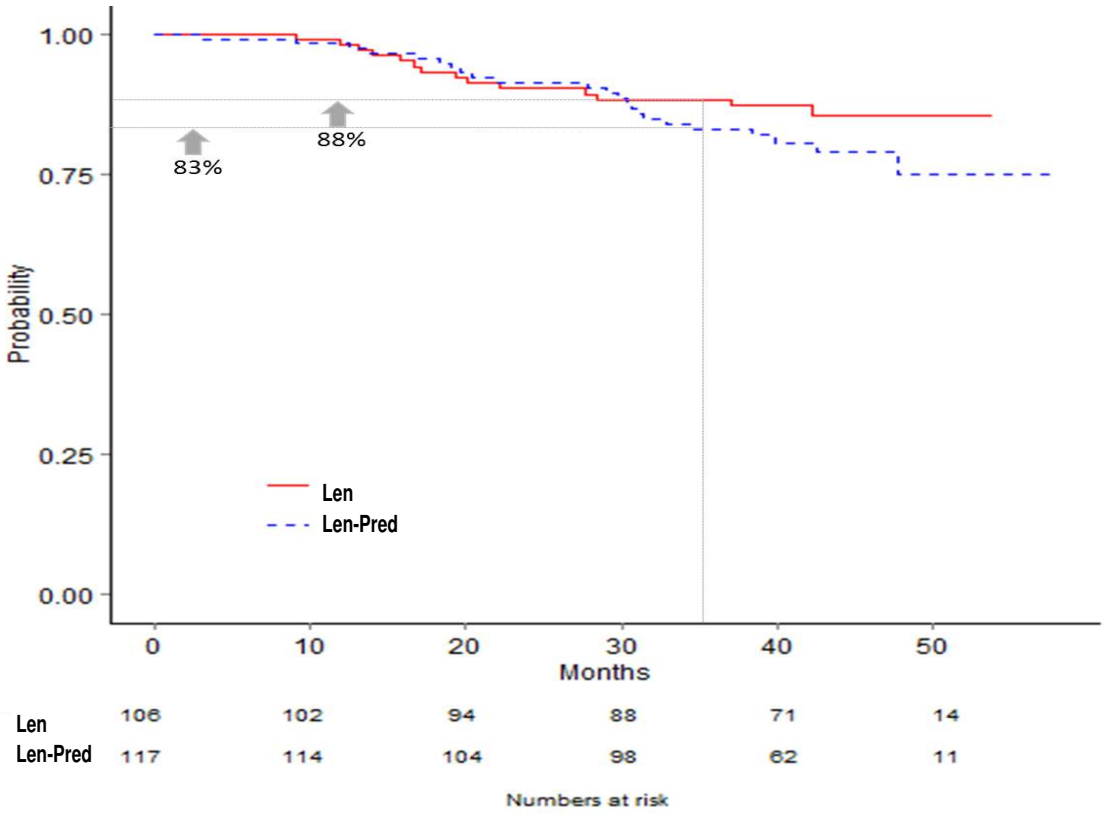
MEL200-ASCT 127 124 118 108 102 51 6
Numbers at risk

2E


1.00
0.75
0.50
0.25
0.00
Probability
Len
Len-Pred
28.5
37.5
0
10
20
30
40
50
Months
Len 106 85 66 50 36 5
Len-Pred 117 101 84 62 33 7
Numbers at risk

2F


1.00
0.75
0.50
0.25
0.00
Probability
83%
88%
Len
Len-Pred
0
10
20
30
40
50
Months
Len 106 102 94 88 71 14
Len-Pred 117 114 104 98 62 11
Numbers at risk

Supplementary Appendix

Methods

Study design, randomization and masking

An informatics system randomly assigned patients to treatment at enrolment, but disclosed the treatment allocation only when the patient was eligible for consolidation. Patients were eligible for consolidation if they did not experience unacceptable toxicity and did not experience progression 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.

Procedures: dose modification guidelines

The dose of lenalidomide, cyclophosphamide, prednisone or dexamethasone were reduced in case of pre-specified hematological or non-hematological drug related toxicities (mainly grade 3-4 toxicities). Steroids related toxicities were managed according to specific guidelines (the drug could be reduced for specific grade $\geq$2 toxicities). Dose reductions were required also for delay between 2 to 4 weeks from planned cycle date. Table 1S, 2S, 3S and 4S show dose reductions steps of lenalidomide, cyclophosphamide, dexamethasone and prendnisone.

Procedures: treatment after relapse

Patients experiencing progressive disease (PD) during treatment were treated according to local standards and maintained in the trial for later outcome evaluations. Treatment with ASCT at relapse was suggested for patients who were randomized to CRD, but not mandatory. The decision on second-line therapy was left to the treating physician. Data on second-line therapy (type, date of start of second-line therapy, progression after second-line) were prospectively collected for all patients enrolled in the trial.

Statistical Analyses

The comparative analyses of CRD vs MEL200-ASCT included only patients for whom randomization was disclosed and the starting time of analyses was the date of disclosure of randomization. The comparative analyses of maintenance with lenalidomide-prednisone vs

lenalidomide alone included all patients eligible for lenalidomide-prednisone or lenalidomide maintenance. Patients were considered eligible for maintenance if they did not experience unacceptable toxicity and did not experience progression during consolidation phase; the starting time of analyses was the date of clinical evaluation after the consolidation phase.
In a post-hoc analysis not prespecified in the protocol, we evaluated progression-free survival-2 (PFS2). PFS2 endpoint included all patients randomized in the first line of therapy to the 4 treatment arms. It is the time from randomization in the first line of therapy 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 therapy 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.
In a subsequent post-hoc analysis not prespecified in the protocol, we evaluated OS from relapse. OS from relapse was calculated from the date of first relapse until the date of either death from any cause or data censoring at the last date at which the patient was known to be alive.

Results

Lenalidomide and prednisone dose-reduction according to previous treatment with CRD or MEL200-ASCT

In the RP arm, 11 patients required lenalidomide dose reductions: 5 patients received previous consolidation with CRD and 6 patients received previous consolidation with MEL200. In the same arm, 42 patients required prednisone dose-reduction: 16 patients

received previous consolidation with CRD and 26 patients received previous consolidation with MEL200.

In the R arm, 23 patients required lenalidomide dose reductions: 10 patients received previous consolidation with CRD and 13 patients received previous consolidation with MEL200.

Post-hoc analysis of outcome of patients ineligible at consolidation

One-hundred and thirty-one patients went off-protocol before consolidation. Of the 67 patients who progressed before consolidation, 26 (39%) received ASCT, 33 (49%) received bortezomib-based regimen, 8 (12%) other therapies. Of the 66 patients who went off-protocol before consolidation for reasons other than progression, 19 (29%) received ASCT, 18 (27%) received bortezomib-based regimen, 8 (12%) other therapies; 21 (32%) patients did not received any other therapy (these include patients who went off protocol for unacceptable adverse events, consent withdrawal, lost to follow-up, death).

Outcome of patients who went off protocol before consolidation was particularly poor. Figures 5S shows OS in patients eligible for consolidation and in patients who were not (that were those patients who went off-protocol before consolidation). The 4-year OS was 82% in patients who proceeded with consolidation and 55% in patients who discontinued before consolidation (Figure S5).

Outcome after relapse

Table S5 shows treatment at relapse in the 4 treatment arms. In the CRD arm, only 43% of patients received ASCT at relapse; 60% of them were older than 60 years of age.

The 3-year OS from relapse in the 4 treatment arms was 44% with CRD+lenalidomide-prednisone, 67% with CRD+lenalidomide, 50% with MEL200-ASCT+lenalidomide-prednisone, and 62% with MEL200-ASCT+lenalidomide. No significant differences were noticed.

We analysed OS from relapse in patients who relapsed from CRD according to treatment administered at relapse, to see if transplant at relapse, when applicable, could improve

outcome. The 3-year OS from relapse in patients who received ASCT at relapse was 60%; 3-year OS from relapse in patients who received no transplant was 46%.

Supplementary Tables

Table S1. Lenalidomide dose reduction steps*

Starting dose	Lenalidomide 25 mg daily for 21 days every 28 days
Dose Level-1	Lenalidomide 15 mg daily for 21 days every 28 days
Dose Level-2	Lenalidomide 10 mg daily for 21 days every 28 days
Dose Level-3	Lenalidomide 7.5 mg daily for 21 days every 28 days
Dose Level-4	Lenalidomide 5 mg daily for 21 days every 28 days
Dose Level-5	Lenalidomide 2.5 mg daily for 21 days every 28 days

*Lenalidomide dose reduction during maintenance follows the steps resumed in the table, considering a starting dose of 10 mg.

Table S2 Cyclophosphamide dose reduction steps

Starting dose	Cyclophosphamide 300 mg/m^2 days 1,8,15
Dose Level-1	Cyclophosphamide 200 mg/m^2 days 1,8,15
Dose Level-2	Cyclophosphamide 100 mg/m^2 days 1,8,15

Table S3 Dexamethasone dose reduction steps

Starting dose	Dexamethasone 40 mg daily (d 1,8, 15 and 22) every 28 days
Dose Level-1	Dexamethasone 30 mg daily (d 1, 8, 15 and 22) every 28 days
Dose Level-2	Dexamethasone 20 mg daily (d 1, 8, 15 and 22) every 28 days

Table S4 Prednisone dose reduction steps

Starting dose	Prednisone 50 mg every other day
Dose Level-1	Prednisone 25 mg every other day
Dose Level-2	Prednisone 12,5 mg every other day

Table S5 Treatment at relapse in the four treatment arms

	CRD+lenalidomide-prednisone N=61		CRD+lenalidomide N=63		MEL200-ASCT+lenalidomide-prednisone N=54		MEL200-ASCT+lenalidomide-prednisone N=63	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
ASCT	**30**	**50**	**23**	**37**	**13**	**24**	**12**	**19**
bortezomib based	15	25	15	24	8	15	7	11
IMiD based	0	0	0	0	0	0	2	3
Other	15	25	8	13	5	9	3	5
No ASCT	**31**	**50**	**40**	**63**	**41**	**76**	**51**	**81**
bortezomib based	27	44	31	49	34	63	36	57
IMiD based	2	3	5	8	3	6	12	19
Other	2	3	4	6	4	7	3	5

ASCT, autologous stem cell transplantation; IMiD, immunomodulatory drug; MEL200-ASCT, melphalan 200 mg/m^2 plus autologous stem cell transplantation; CRD, cyclophosphamide-lenalidomide-dexamethasone. Percentages may not total 100 because of rounding.

Table S6 Best Response according to treatment phase

	Rd N=387		CRD N=129		MEL200-ASCT N=127		Lenalidomide-prednisone N=117		Lenalidomide N=106	
	N	%	N	%	N	%	N	%	N	%
CR	8	2	15	12	17	13	35	30	32	30
VGPR	48	12	50	39	52	41	39	33	41	39
≥VGPR	56	14	65	50	69	54	74	63	73	69
PR	220	57	50	39	46	36	30	26	24	23
≥PR	276	71	115	89	115	91	104	89	97	92
SD	98	25	11	9	7	6	5	4	4	4
PD	2	1	0	0	0	0	1	1	1	1
NA	11	3	3	2	5	4	7	6	4	4

CR, complete response; VGPR, very good partial response, PR, partial response; SD, stable disease; PD, progressive disease; NA, not available; Rd, lenalidomide-dexamethasone; MEL200-ASCT, melphalan 200 mg/m^2 plus autologous stem cell transplantation; CRD, cyclophosphamide-lenalidomide-dexamethasone. Percentages may not total 100 because of rounding.

Table S7 Best Response at data cut-off in the four treatment arms.

Overall best response	CRD+ lenalidomide-prednisone N=57		CRD+ lenalidomide N=49		MEL200-ASCT+ lenalidomide-prednisone N=60		MEL200-ASCT+ lenalidomide N=57	
	N	%	N	%	N	%	N	%
CR	13	23	13	27	22	37	19	33
VGPR	14	25	15	31	25	42	26	46
≥VGPR	27	47	28	57	47	78	45	79
PR	20	35	15	31	10	17	9	16
≥PR	47	82	43	88	57	95	54	95
SD	3	5	4	8	2	3	0	0
PD	1	2	0	0	0	0	1	2
NA	6	11	2	4	1	2	2	4

CR, complete response; VGPR, very good partial response, PR, partial response; SD, stable disease; PD, progressive disease; NA, not available; Rd, lenalidomide-dexamethasone; MEL200-ASCT, melphalan 200 mg/m^2 plus autologous stem cell transplantation; CRD, cyclophosphamide-lenalidomide-dexamethasone. Percentages may not total 100 because of rounding.

Figure S1

Subgroup analysis of PFS: CRD vs MEL200-ASCT comparison. MEL200-ASCT, melphalan 200 mg/m^2 plus autologous stem cell transplantation; CRD, cyclophosphamide-lenalidomide-dexamethasone; ISS: International Staging System

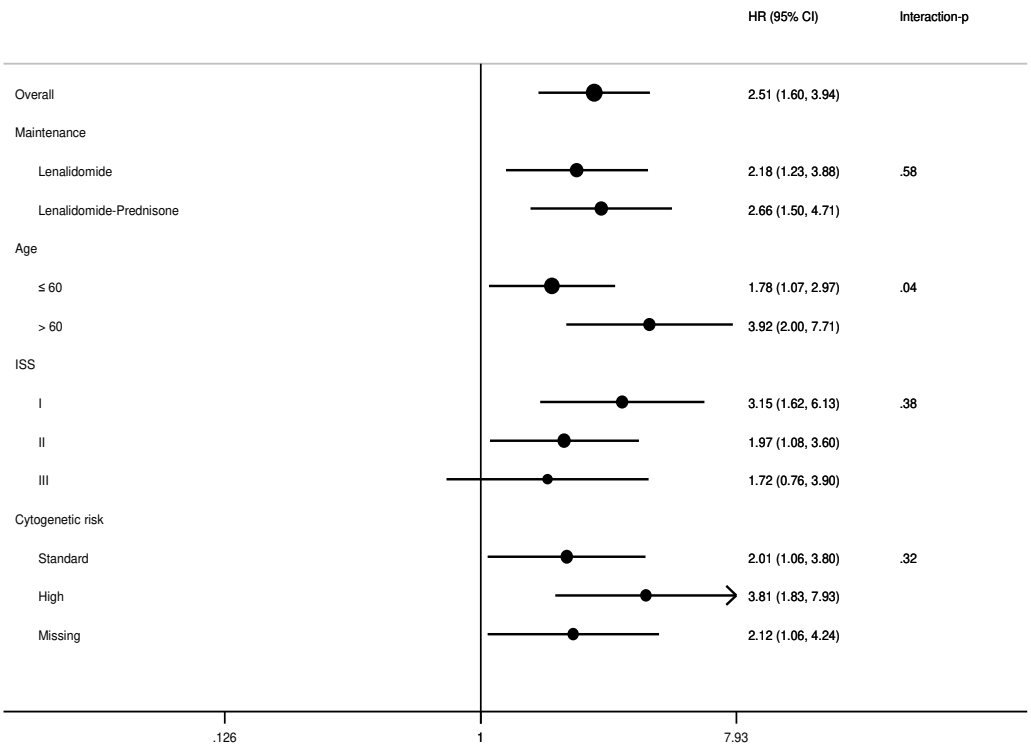


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Figure S2

Subgroup analysis of OS: CRD vs MEL200-ASCT comparison. MEL200-ASCT, melphalan 200 mg/m^2 plus autologous stem cell transplantation; CRD, cyclophosphamide-lenalidomide-dexamethasone. ISS: International Staging System

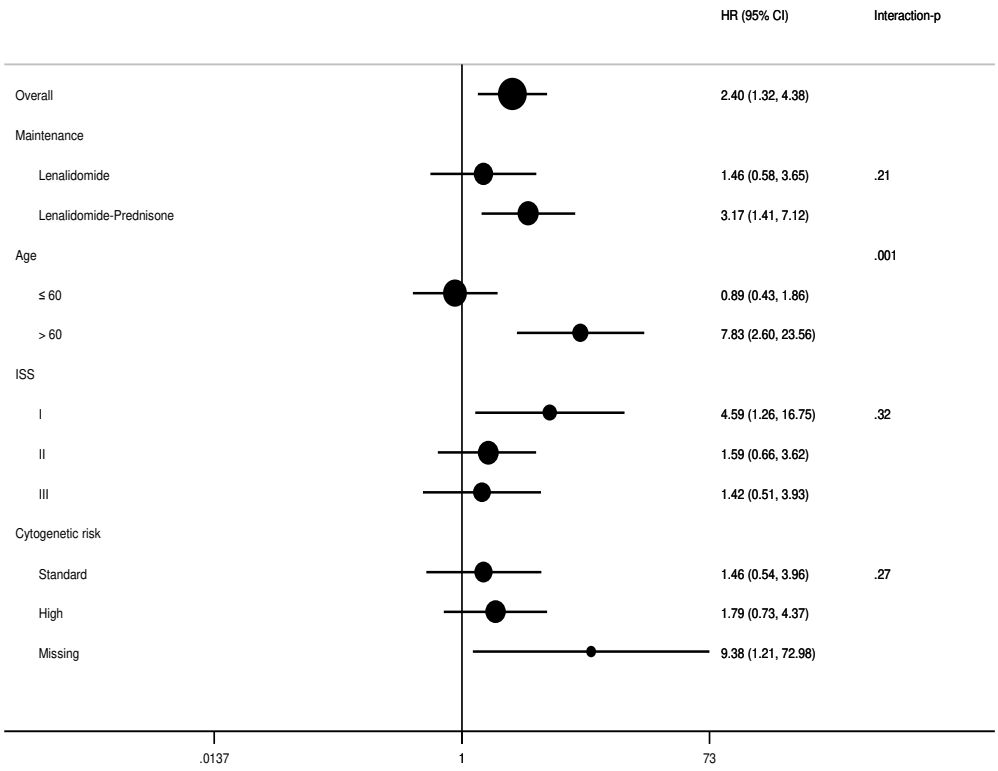
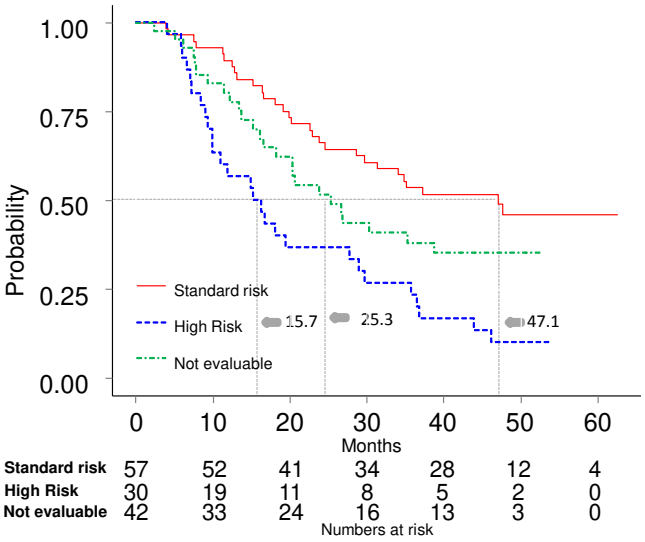
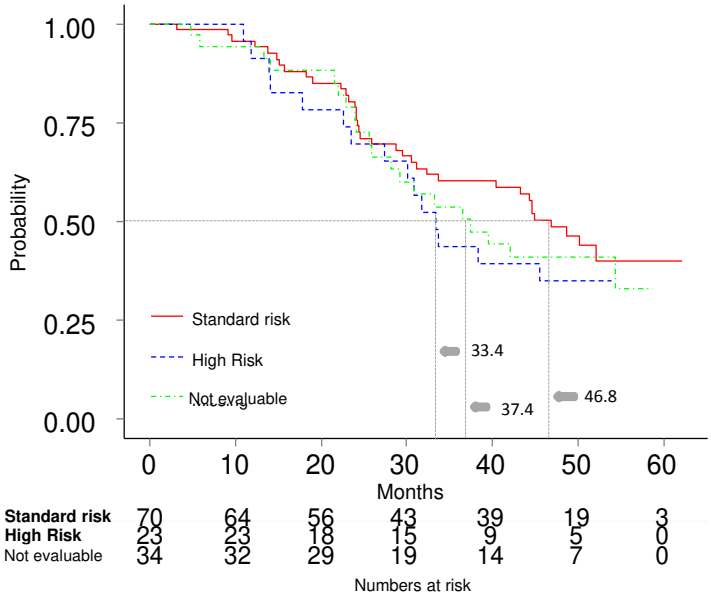


Figure S3 Panel A shows PFS in the CRD arm according to cytogenetic data. Panel B shows PFS in the MEL200-ASCT arm according to cytogenetic data. Panel C shows OS in the CRD arm according to cytogenetic data. Panel D shows OS in the MEL200-ASCT arm according to cytogenetic data. MEL200-ASCT, melphalan 200 mg/m^2 plus autologous stem cell transplantation; CRD, cyclophosphamide-lenalidomide-dexamethasone High-risk: del17 or t(4;14) or t(14;16); Standard-risk: no del17, t(4;14), t(14;16)

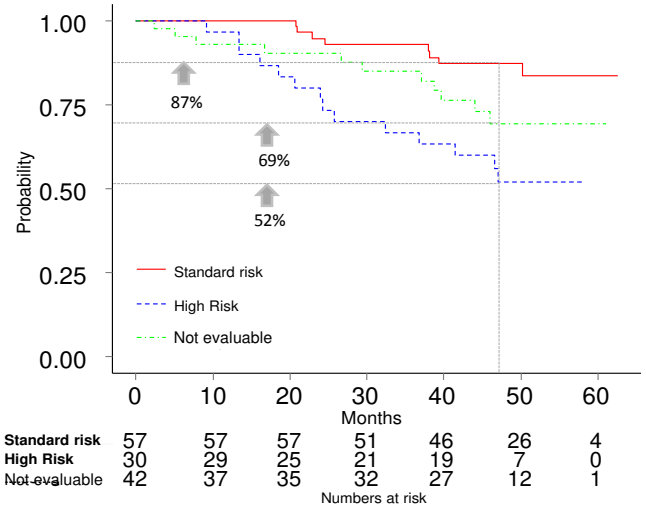
A


1.00
0.75
0.50
0.25
0.00
Probability
Standard risk
High Risk
Not evaluable
15.7
25.3
47.1
0
10
20
30
40
50
60
Months
Standard risk 57 52 41 34 28 12 4
High Risk 30 19 11 8 5 2 0
Not evaluable 42 33 24 16 13 3 0
Numbers at risk

B


1.00
0.75
0.50
0.25
0.00
Probability
Standard risk
High Risk
Not evaluable
33.4
37.4
46.8
0
10
20
30
40
50
60
Months
Standard risk 70 64 56 43 39 19 3
High Risk 23 23 18 15 9 5 0
Not evaluable 34 32 29 19 14 7 0
Numbers at risk

C


1.00
0.75
0.50
0.25
0.00
Probability
87%
69%
52%
Standard risk
High Risk
Not evaluable
0
10
20
30
40
50
60
Months
Standard risk 57 57 57 51 46 26 4
High Risk 30 29 25 21 19 7 0
Not evaluable 42 37 35 32 27 12 1
Numbers at risk

D

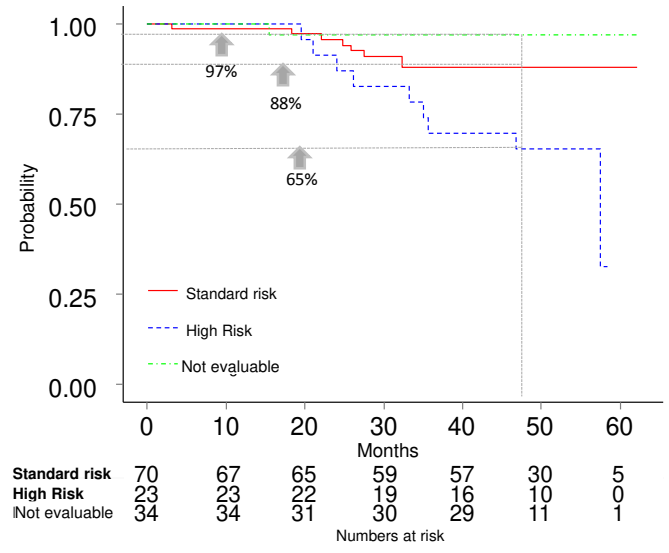

1.00
0.75
0.50
0.25
0.00
Probability
97%
88%
65%
Standard risk
High Risk
Not evaluable
0
10
20
30
40
50
60
Months
Standard risk 70 67 65 59 57 30 5
High Risk 23 23 22 19 16 10 0
Not evaluable 34 34 31 30 29 11 1
Numbers at risk

Figure S4 Kaplan-Meier Estimates of PFS-2 for the Population of in the MEL200-ASCT or CRD, and to lenalidomide-prednisone vs lenalidomide maintenance. MEL200-ASCT melphalan 200mg/m^2 plus autologous stem cell transplantation; CRD cyclophosphamide–prednisone–lenalidomide; len-pred: lenalidomide-prednisone; len: lenalidomide.

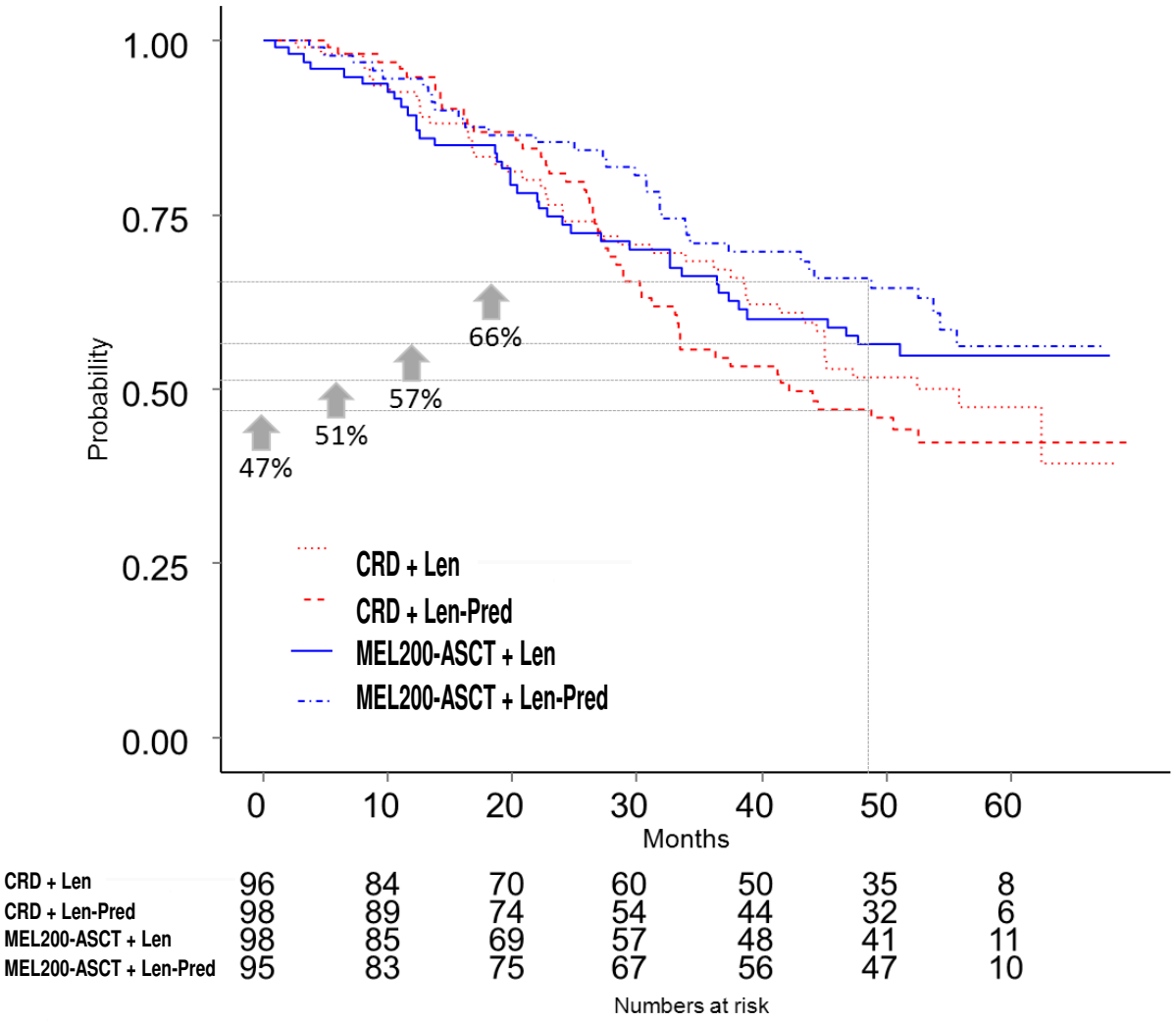
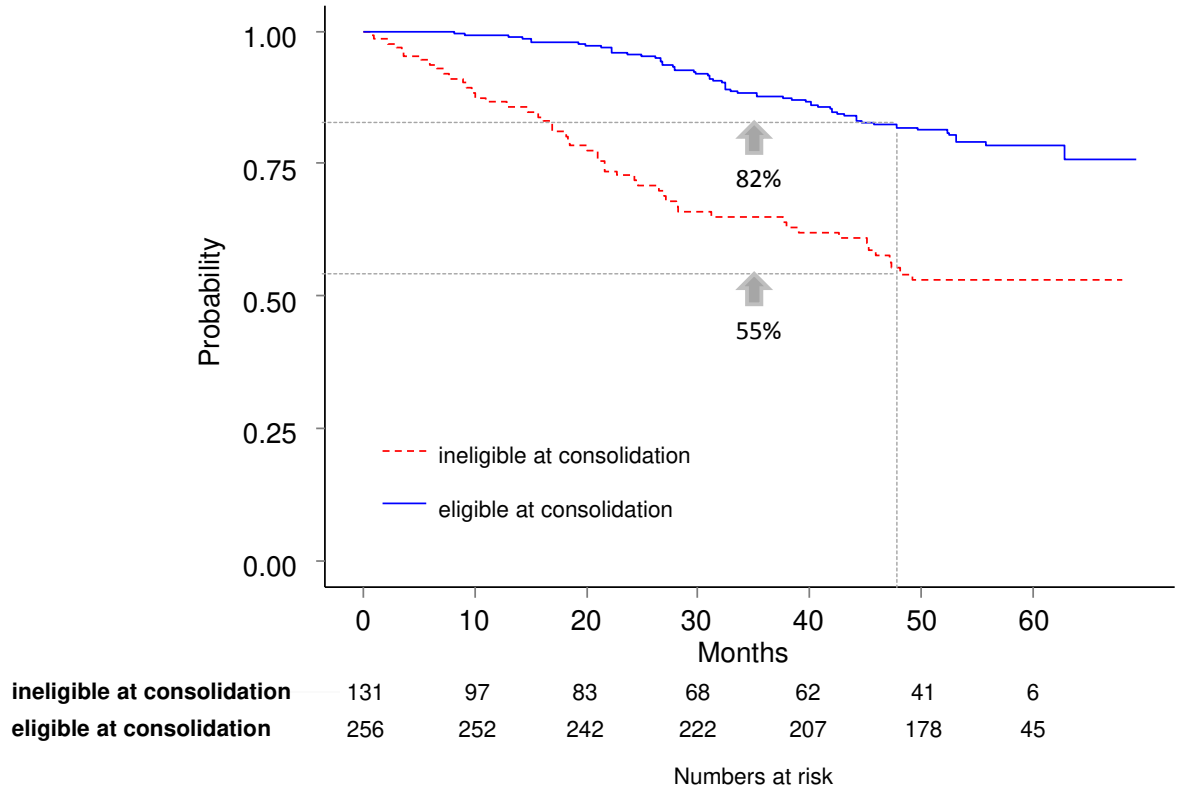


Figure S5 OS of patients eligible at consolidation and those ineligible at consolidation



ineligible at consolidation	131	97	83	68	62	41	6
eligible at consolidation	256	252	242	222	207	178	45

Numbers at risk