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(Article begins on next page)

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Article (original research)

Carfilzomib Induction, Consolidation, and Maintenance With or Without Autologous Stem-Cell Transplantation in Patients With Newly Diagnosed Multiple Myeloma: Pre-planned Cytogenetic Subgroup Analysis of the randomized, phase 2 FORTE Trial

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SUMMARY

Background. Patients with newly diagnosed multiple myeloma (NDMM) and high-risk cytogenetic abnormalities (HRCA) represent an unmet medical need. In the FORTE trial, KRd induction resulted in a higher proportion of patients with at least a very good partial response as compared to KCd, and KR maintenance prolonged progression-free survival (PFS) as compared with R maintenance. In this analysis we described the outcomes of patients enrolled in the FORTE trial according to their cytogenetic risk.

Methods. UNITO-MM-01/FORTE was a randomized, open-label, phase 2 trial that enrolled transplant-eligible patients with newly diagnosed multiple myeloma aged 65 years or younger. At enrollment, patients were were stratified according to International Staging System stage (I *vs* II/III) and age (<60 years *vs* 60–65 years) and randomised (1:1:1) to KRd plus ASCT (four 28-day induction cycles with carfilzomib plus lenalidomide plus dexamethasone [KRd], melphalan at 200 mg/m2 and autologous stem-cell transplantation [MEL200-ASCT], followed by four 28-day KRd consolidation cycles), KRd12 (12 28-day KRd cycles), or KCd plus ASCT (four 28-day induction cycles with carfilzomib plus cyclophosphamide plus dexamethasone [KCd], MEL200-ASCT, and four 28-day KCd consolidation cycles). Carfilzomib 36 mg/m2 was administered intravenously on days 1, 2, 8, 9, 15, and 16; lenalidomide 25 mg administered orally on days 1–21; cyclophosphamide 300 mg/m2 administered orally on days 1, 8, and 15; and dexamethasone 20 mg administered orally or intravenously on days 1, 2, 8, 9, 15, 16, 22, and 23. After the consolidation phase, patients were stratified according to induction–consolidation treatment and randomly assigned (1:1) to maintenance treatment with carfilzomib plus lenalidomide or lenalidomide alone. Carfilzomib 36 mg/m2 was administered intravenously on days 1–2 and 15–16 every 28 days for up to 2 years; lenalidomide 10 mg was administered orally on days 1–21 every 28 days until progression or intolerance in both groups. The primary endpoints were the proportion of patients with at least a very good partial response after induction with KRd versus KCd and PFS with carfilzomib plus lenalidomide versus lenalidomide alone as maintenance treatment. In this pre-planned analysis, we included patients enrolled in the FORTE trial with complete cytogenetic data on del(17p), t(4;14), t(14;16), del(1p), and gain(1q) (3 copies)/amp(1q) (≥4 copies) assessed by fluorescence *in situ* hybridisation (FISH) analysis on CD138+ sorted cells. We evaluated PFS, overall survival and minimal residual disease negativity (MRD) rates according to the presence of 0, 1 and 2+ HRCA across treatment groups. The FORTE trial is currently ongoing, and registered with ClinicalTrials.gov, NCT02203643.

Findings.

Between February 23, 2015, and April 5, 2017, 477 patients (female, 176; male, 220) were enrolled, of whom 396 (83%) had complete cytogenetic data and were analysed. The median follow-up from first randomisation was 50·9 months (IQR 45·7–55·3). The 4-year PFS was 71% (95% CI 64%–78%), 60% (95% CI 52%-69%) and 39% (95% CI 30%-50%) in patients with 0, 1 and 2+ HRCA, respectively. As compared to patients with 0 HRCA, the risk of progression or death was similar in patients with 1 HRCA (HR 1·33 [95% CI 0·90–1·97] p=0·15) and higher in patients with 2+ HRCA (HR 2·56 (95% CI 1·74–3·75) p<0·0001) across the induction/intensification/consolidation groups.

The rates of 1-year sustained MRD negativity were comparable in the 0 and 1 HRCA groups (35% [53 of 153] and 41% [57 of 138]) and were lower in the 2+ HRCA group (24% [25 of 105]). The median duration of follow-up from second randomization was 37 months (IQR 33–42). The 3-year PFS from the second randomisation was 80% (95% CI 74%–88%), 68% (95% CI 59%–78%), and 53% (95% CI 42%–67%) in patients with 0, 1, and 2+ HRCA, respectively

A higher risk of progression or death was observed in patients with 1 (HR=1·68 [95% CI 1·01–2·8], p=0·048) and 2+ HRCA (HR=2·74 [95% CI 1·6–4·69], p=0·0003) as compared to patients with 0 HRCA.
Interpretation. This pre-planned analysis of the FORTE trial showed that carfilzomib-based induction/intensification/consolidation regimens are effective strategies in patients with standard risk (0 HRCA) and high-risk (1 HRCA) myeloma, resulting in similar PFS and 1-year sustained MRD negativity rates. Despite promising PFS rates, ultra-high risk patients (2+ HRCA) still have a higher risk of progression and death and therefore represent a currently unmet medical need.
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Keywords. Newly diagnosed multiple myeloma; cytogenetic abnormalities; high risk; carfilzomib; autologous stem-cell transplantation; induction and consolidation treatment; maintenance treatment

RESEARCH IN CONTEXT

Evidence before this study

The current standard approach to transplant-eligible patients with newly-diagnosed multiple myeloma (MM) consists of an induction and consolidation regimen including a proteasome inhibitor, bortezomib, and an immunomodulatory drug, with or without an anti-CD38 monoclonal antibody, autologous stem-cell transplantation (ASCT), and lenalidomide maintenance.

In the FORTE trial, carfilzomib-lenalidomide-dexamethasone (KRd) induction demonstrated to be superior to carfilzomib-cyclophosphamide-dexamethasone (KCd), the incorporation of upfront autologous stem-cell transplantation (KRd plus ASCT) led to prolonged progression-free survival (PFS) compared with a non-transplant approach (12 KRd cycles [KRd12]), and KR maintenance reduced the risk of progression compared with standard lenalidomide (R).

On September 19, 2022, we searched PubMed using the search terms “myeloma”, “cytogenetic” or “high risk”, “maintenance”, and “transplant” or “transplantation” in the “title/abstract” field. Previous studies reported that not only the presence, but also the number of genetic lesions impact the survival of MM patients, as patients with 2 or more HRCA (2+) display shorter PFS and overall survival (OS) than those of patients with no (0) or a single (1) HRCA. In several randomised studies, upfront ASCT reduced the risk of progression or death in both standard-risk and high-risk patients, as compared with a non-transplant regimen. However, patients with HRCA consistently displayed a shorter PFS, as compared with standard-risk patients. HRCA patients also benefited less from the addition of daratumumab to bortezomib-lenalidomide-dexamethasone (VRd) induction/consolidation, while the addition of elotuzumab to VRd did not improve survival outcomes, as compared with VRd only. In a meta-analysis of four randomized studies, no difference in terms of PFS was associated with lenalidomide maintenance over no maintenance in patients with HRCA. In the Myeloma XI study, despite a PFS benefit in favour of lenalidomide over no maintenance also in HRCA patients, these patients showed a significantly shorter PFS, as compared with standard-risk patients. Altogether, these data confirmed that MM patients with HRCA represent an unmet medical need.

Added value of this study

We demonstrated that a carfilzomib-based induction and consolidation regimen, with or without ASCT, resulted in similar PFS rates between patients with 0 or 1 HRCA. KRd plus ASCT and the use of a 2-drug KR maintenance led to high rates of minimal residual disease (MRD)

negativity and prolonged PFS not only in 0 HRCA but also in 1 HRCA and 2+ HRCA patients, as compared with KCd plus ASCT and KRd12 induction/consolidation and R maintenance. We also demonstrated that sustained MRD negativity modulated the risk associated with the presence of HRCA. Eventually, the inferior results observed in patients with at least 2 (2+) HRCA as compared to those with 0 HRCA prompt the investigation of alternative treatment strategies for this ultra-high-risk population.

Implications of all the available evidence

Carfilzomib-based regimens are highly effective treatment options in patients with and without HRCA. Our results support the use of upfront ASCT and 2-drug maintenance treatment not only in patients with high-risk MM, but also in patients with standard-risk disease. The excellent PFS and high sustained MRD negativity rates in patients with HRCA support the ongoing investigation of KRd, in combination with anti-CD38 monoclonal antibodies, as initial treatment for transplant-eligible NDMM patients.

BACKGROUND

The prognosis of multiple myeloma patients (MM) is greatly influenced by the presence of high-risk cytogenetic abnormalities (HRCA).[1,2] Despite the introduction of proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs) and monoclonal antibodies (mAbs), as well as the use of high-dose chemotherapy and autologous stem-cell transplantation (ASCT), progression-free (PFS) and overall survival (OS) in patients with high-risk MM are shorter than those in standard-risk patients.[3–7]
In the upfront setting, bortezomib-based induction before ASCT prolonged median PFS in high-risk patients, as compared with non-bortezomib-based regimens (32 *vs* 22 months; $P<0{\cdot}001$);[8] in the relapse setting, the addition of carfilzomib (KRd *vs* Rd: hazard ratio [HR]=0·7) or ixazomib (IRd *vs* Rd: HR, 0·54) to lenalidomide and dexamethasone (Rd) reduced the risk of progression or death in high-risk patients, as compared with Rd alone.[9–11]
Gay et al. reported that the randomised phase II FORTE trial (NCT02203643), conducted in NDMM patients, met its primary endpoints, based on a higher rate of at least very good partial response (≥VGPR) with KRd *vs* carfilzomib-cyclophosphamide-dexamethasone (KCd) induction (70% *vs* 53%, odds ratio [OR] 2.14; power 90%) and a reduced risk of progression in favour of carfilzomib-lenalidomide (KR) *vs* R maintenance (HR=0·64; power 80%).[12]
Here we report a pre-planned analysis to assess the impact of HRCA on the outcomes of patients treated in the FORTE trial and to compare the efficacy of the induction/intensification/consolidation as well as maintenance strategies tested in the FORTE trial according to cytogenetic risk status.

METHODS

Study design and participants

The UNITO-MM-01/FORTE was a randomised, open-label, phase 2 trial conducted at 42 Italian centers that enrolled transplant-eligible patients with newly diagnosed multiple myeloma aged 65 years or younger with symptomatic, measurable disease defined according to standard criteria.[13] Other inclusion criteria were a Karnofsky performance status of 60% or higher, adequate bone marrow function (platelet count of at least 70 × 109 per L and absolute neutrophil count of at least 1 × 109 cells per L), creatinine clearance of 30 mL/min or greater and left ventricular ejection fraction of 40% or greater. Exclusion criteria included peripheral neuropathy worse than grade 2 or grade 2 with pain; unstable angina or myocardial infarction within 4 months before randomisation; uncontrolled angina or history of severe coronary artery disease; New York Heart Association functional class III or IV heart failure; grade 3 conduction system abnormalities unless the patient had a pacemaker; malignancies within the past 3 years; and life expectancy greater than 6 months. The protocol is included in the online Appendix (p. 20). The FORTE trial was approved by the ethics or institutional review boards at each of the participating centres. All patients gave written informed consent before entering the study, which was performed in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. Patients with complete baseline cytogenetic data were included in this analysis and were stratified into three main subgroups according to the presence of 0, 1 or at least 2 (2+) HRCA.

Randomisation and masking

At enrolment, patients were randomly assigned (1:1:1) to one of the three induction–intensification–consolidation groups. A block randomisation (block size 12), stratified according to International Staging System (ISS) stage (I *vs* II/III) and age (<60 years *vs* 60–65

years), was generated at enrolment by a computer program and implemented into a web-based procedure by the investigator or designated research staff. Patients who did not experience unacceptable toxicity or progression during the induction, intensification, and consolidation phases were eligible for maintenance treatment. Maintenance randomisation was balanced with a permuted block (block size 8) and was stratified according to induction–intensification–consolidation treatment in a 1:1 ratio.

Procedures

At enrolment patients were randomised into one of the three induction-intensification-consolidation arms. Patients in the KRd plus ASCT arm received four 28-day induction cycles with KRd, ASCT conditioned with melphalan at 200 mg/m^2 (MEL200-ASCT), and four KRd consolidation cycles. Patients in the KRd12 arm received four 28-day induction cycles with KRd, stem-cell mobilisation and collection, and eight KRd consolidation cycles without upfront MEL200-ASCT. Patients in the KCd plus ASCT arm received four 28-day induction cycles with KCd, MEL200-ASCT, and four KCd consolidation cycles. After the consolidation phase, eligible patients underwent a second randomisation (1:1) and were assigned to receive maintenance with lenalidomide (R) until progression or lenalidomide until progression plus carfilzomib for up to 2 years. Specifications of the treatment schedule have been reported previously (Appendix p.5 for full details on study treatment).[12]

Protocol-defined dose modifications (delay, reduction, omissions) were allowed for haematological and non-hematological toxicities if deemed clinically necessary (Appendix p.65). Details of dose reductions and interruptions and other study procedures are included in the Appendix and have been previously described.[12]

Cytogenetic risk was centrally assessed by FISH analysis on CD138+ sorted cells (200 nuclei analysed) from bone marrow samples collected during the screening phase according to the European Myeloma Network (EMN) guidelines.[14] HRCA included t(4;14), t(14;16), 17p deletion [(del(17p)], del(1p), 1q gain [gain(1q)] (3 copies) or 1q amplification [amp(1q)] (≥4 copies).[15] The cut-off for HRCA positivity was 15% for translocations and 10% for deletions and gain(1q), based on the mean plus 3 standard deviations of abnormal cells in bone marrow plasma cells from 15 healthy donors, and 20% for amp(1q).[14,16]

In all patients, radiological assessment was performed with MRI, PET/CT, or x-ray skeletal survey done during the screening phase or within 8 weeks before the first dose of the study drug, and repeated as clinically indicated, except for the x-ray skeletal survey, which was performed once a year.

Laboratory tests for haematology clinical chemistry were performed before every carfilzomib infusion during the first induction cycle and then at least weekly; disease assessment was performed at every cycle on day 1, as previously described.[12]

A centralised evaluation of minimal residual disease (MRD) by multiparameter flow cytometry (MFC; sensitivity threshold of 10^{-5})[12] was performed before maintenance and thereafter every 6 months during maintenance in all patients achieving ≥VGPR.

Outcomes

The primary endpoints of the FORTE study were the proportion of patients with at least a very good partial response with KRd versus KCd as induction therapy and PFS from maintenance randomisation with KR versus R. Key secondary endpoints included the proportion of patients with a stringent complete response and PFS with KRd plus ASCT and KRd12 versus KCd plus ASCT, overall response rate, minimal residual disease negativity and 1-year sustained minimal

residual disease negativity rates, duration of response, time to progression, time to next treatment, PFS 2, OS and safety. The response rate was defined according to the International Uniform Response Criteria.[17] PFS was calculated from the date of first randomisation for the comparison KRd plus ASCT *vs* KRd12 *vs* KCd plus ASCT, and from the date of second randomisation for the comparison KR *vs* R, to the date of first observation of progressive disease (PD) or death from any cause as an event. OS was calculated from the date of the first randomisation to the date of death from any cause. Patients who did not progress, died, were lost to follow-up, or withdrew from the trial were censored at the time of the last disease assessment. According to the intention-to-treat (ITT) principle, patients with a negative pre-maintenance MRD test result were considered MRD negative; patients with a positive MRD test result or who had not undergone MRD testing (either because they missed evaluation or did not achieve a VGPR) were considered MRD positive. 1-year sustained MRD negativity was defined as 2 consecutive MRD-negative test results, the first at the pre-maintenance time point and the second at least 12 months apart. Patients who tested negative at the pre-maintenance time point and had a subsequent positive MRD result or relapsed within 12 months were considered unsustained MRD negative. According to the ITT principle, patients who were positive before maintenance treatment, or missed the follow-up MRD evaluation, or had a positive MRD evaluation at 1 year were considered MRD positive.
In this pre-planned analysis, we evaluated the impact of HRCA (0, 1, 2+) on PFS and OS in the overall patient population, in the three induction-intensification-consolidation groups and the two maintenance groups; we compared KRd plus ASCT *vs* KRd12 *vs* KCd plus ASCT, and KR *vs* R maintenance, in terms of PFS, OS and MRD negativity and sustained MRD negativity rates across the cytogenetic risk groups. In addition, we evaluated the PFS of patients stratified according to the IMWG [13] and R2-ISS risk[36] stratification models.

Statistical analysis

Sample size calculations for the main FORTE trial have been reported previously.[12] For this pre-planned subgroup analysis, no formal power calculations were included in the protocol. Therefore, for a more accurate interpretation of the results, a power analysis reporting the power curves for different numbers of events and allocation ratios, with a significance level of the test set at the conventional value of 0·05 (two-side; Appendix p.17).
The efficacy analysis included patients in the ITT population who met the biomarker criteria for risk assessment, while patients with incomplete cytogenetic data were excluded from this analysis. Patients with complete cytogenetic data were stratified into one of the three risk groups according to presence of 0, 1 or 2+ HRCA Time-to-event data were analysed using the Kaplan-Meier method. The Cox proportional hazards model was used to estimate the HR values and the 95% confidence intervals (CIs). Cox and logistic models were adjusted for International Staging System (ISS) stage (ISS I *vs* II/III) and levels of lactate dehydrogenase (LDH; >upper limit of normal [ULN] *vs* ≤ULN) for the KRd plus ASCT *vs* KRd12 *vs* KCd plus ASCT comparison and adjusted for ISS stage (ISS I *vs* II/III), LDH levels (>ULN *vs* ≤ULN), and induction/intensification/consolidation (KRD PLUS ASCT *vs* KRd12 *vs* KCd plus ASCT) for the KR *vs* R comparison. The significance level was set at $p<0·05$ (Wald test). The proportional hazards assumption was checked by use of Grambsch and Therneau test for PFS and OS and was not found to be violated (Appendix p.4).
To determine whether the effect of cytogenetic risk was modified by the treatments received, models containing treatment groups, HRCA groups and the interaction between them were fitted. The presence of significant interaction would indicate effect modification. In the absence of significant interaction, simple additive models were fitted.
A sensitivity analysis adopting a different cut-off (≥55% of nuclei) for the positivity to del(17p) was performed.

The statistical analyses were performed using R (v4.0·2). The data cut-off point was January 7, 2021. This trial is registered with ClinicalTrials.gov, NCT02203643.

Role of the funding source
The UNITO-MM-01/FORTE trial was sponsored by the Università degli Studi di Torino (Italy), Department of Molecular Biotechnology and Health Sciences. Amgen and Celgene/Bristol-Myers Squibb provided an unrestricted grant to conduct the trial, but had no role in study design, data collection, analysis, interpretation, writing of the report, or the decision to submit this manuscript for publication.

RESULTS

Patients and treatments

A total of 477 NDMM patients were enrolled in the FORTE trial between February 23, 2015, and April 5, 2017; 396 of 477 (83%) had complete cytogenetic data and were analysed: 132 received KRd plus ASCT, 126 KRd12, and 138 KCd plus ASCT (Figure 1). Overall, 153 (39%) of 396 patients had 0 HRCA, 138 (35%) of 396 had 1 HRCA, and 105 (27%) of 396 had 2+ HRCA. Patient demographic and disease characteristics are reported in Table 1.

At the data cutoff (January 7, 2021), 166 (42%) of 396 patients had progressed or died: 47 (31%) of 153 in the 0 HRCA group, 56 (41%) of 138 in the 1 HRCA group and 63 (60%) of 105 in the 2+ HRCA group.

The median duration of follow-up from first randomisation was 51 months (interquartile range [IQR] 46-56). There was no significant interaction between HRCA and treatment groups for the PFS (p-interaction=0·75) and OS (p-interaction=0·65) from first randomization, and for the PFS from second randomization (p-interaction=0·93

Overall, the 4-year PFS from the first randomisation were 71% (95% CI 64%–78%; median not reached [NR; 95% CI NE–NE]) in patients with 0 HRCA, 60% (95% CI 52%-69%; median NR [95% CI 54–NE]) in patients with 1 HRCA, and 39% (95% CI 30%-50%; median 34 [95% CI 26–44]) in patients with 2+ HRCA, respectively (Figure 2a and Table 2). The PFS from first randomisation was not significant different in patients with 1 and 0 HRCA across the three induction/intensification/consolidation groups (HR 1·33 [95% CI 0·90–1·97] p=0·15). By contrast, patients with 2+ HRCA had a higher risk of progression or death, as compared with patients with 0 HRCA (HR 2·56 (95% CI 1·74–3·75) p<0·0001; Figure 3a-c and Table 2). Subgroup analysis for PFS from first randomization of KRd plus ASCT vs KRd12 and vs KCd plus ASCT across all cytogenetic risk groups are shown in Figure S2.

At the last data cutoff, death was reported in 73 (18%) of 396 patients: 10 (6%) of 153 in the 0 HRCA group, 24 (17%) of 138 in the 1 HRCA group and 39 (37%) of 105 in the 2+ HRCA group. The 4-year OS rates from the first randomisation were 94% (95% CI 91%-98%; median NR [95% CI NE–NE]) in patients with 0 HRCA, 83% (95% CI 76%-90%; median NR [95% CI NE–NE]) in patients with 1 HRCA, and 63% (95% CI 54%-74%; median 59 [95% CI 58–NE]) in patients with 2+ HRCA, respectively (Figure 2b and Table 2). A significantly higher risk of death as compared to patients with 0 HRCA was observed in patients with 1 (HR 2·55 (95% CI 1·22–5·36) p=0·013) and 2+ HRCA (HR 6·53 (95% CI 3·24–13·18) p<0·0001).

At a sensitivity threshold of 10^{-5}, the pre-maintenance rates of MRD negativity in patients with 0, 1, and 2+ HRCA were 52% (80 of 153), 64% (88 of 138), and 44% (46 of 105), respectively (Table 3). The rates of 1-year sustained MRD negativity were comparable in patients with 0 and 1 HRCA (35% [53 of 153] and 41% [57 of 138]) and were lower in patients with 2+ HRCA (24% [25 of 105]). The majority of high-risk patients with 1-year sustained MRD negativity not only

had only 1 HRCA (70%), but also a baseline ISS stage of I (49%) or II (39%) and a low frequency of amp(1q) (14%). Patients with 2+ HRCA had a higher risk of losing the MRD-negative status or of progression, as compared with patients with 0 HRCA (HR=2·22, 95% CI 1·33–3·71).
KRd plus ASCT was associated with higher rates of 1-year sustained MRD negativity, as compared with KRd12 and KCd plus ASCT across the 0, 1, and 2+ HRCA subgroups (Table 3). Patients with 1-year sustained MRD negativity displayed a similar PFS regardless of their cytogenetic status, with respectively 89% (95% CI 80%-98%), 92% (95% CI 86%-100%), and 80% (95% CI 66%-97%) of 0, 1, and 2+ HRCA patients who were alive and free from progression at 4 years from the first randomisation (Appendix pp.7-10).
After the consolidation phase, among 292 patients with complete cytogenetic data, 140 were randomised to KR and 152 to R maintenance; 120 (41%) of 292, 109 (37%) of 292, and 63 (22%) of 292 had 0, 1, and 2+ HRCA, respectively (Table 1).
From the second randomisation, the median duration of follow-up was 37 months (IQR 33–42). The 3-year PFS from the second randomisation was 80% (95% CI 74%–88%; median NR [95% CI NE–NE]), 68% (95% CI 59%–78%; median NR [95% CI 42–NE]), and 53% (95% CI 42%–67%; median 40 [NR; 95% CI 23–NE]) in patients with 0, 1, and 2+ HRCA, respectively (Figure 4a and Table 2).
A higher risk of progression or death was reported in both patients with 1 (HR=1·68 [95% CI 1·01–2·8], p=0·048) and 2+ HRCA (HR=2·74 [95% CI 1·6–4·69], p=0·0003), as compared with patients with 0 HRCA. PFS was significantly inferior for patients with 2+ vs 0 HRCA in both KR and R patient groups (Figures 4b, 4c and Table 2). Subgroup analysis for PFS from second randomization of KR vs R across all cytogenetic risk groups are shown in Appendix p.11. PFS according to IMWG high risk classification and R2-ISS is reported Appendix pp.12-16.
When analysing the outcomes of patients stratified according to the Second Revision of the ISS (R2-ISS), we observed, across all treatment arms, that patients with intermediate-low risk (R2-ISS stage II) had a similar PFS as compared to low risk patients (R2-ISS stage I), while patients with intermediate-high (R2-ISS III) and high risk (R2-ISS IV) still had an inferior PFS (Appendix pp.14-16).

DISCUSSION

Several important points emerge from this pre-planned analysis of the FORTE trial. First, a carfilzomib-based triplet with or without ASCT as upfront treatment for NDMM patients resulted in similar 4-year PFS (71% *vs* 60%) and sustained MRD negativity rates (35% *vs* 41%) in patients with 0 or 1 HRCA, thus abrogating the higher risk of progression associated with the presence of a single HRCA. In this context, KRd plus ASCT consistently led to higher 4-year PFS and 1-year sustained MRD negativity rates across all cytogenetic risk subgroups, as compared with KRd12 and KCd plus ASCT. Importantly, although patients with 2+ HRCA showed a higher risk of progression or death as compared with patients with 0 or 1 HRCA across all treatment arms, thus representing a currently unmet medical need, KRd plus ASCT was associated with promising results in this ultra-high-risk population in terms of 4-year PFS (55%) and 1-year sustained MRD negativity (38%). As the 4-year PFS in patients with 2+ HRCA who achieved 1-year sustained MRD negativity (80%) was similar to that in patients with 0 (89%) or 1 HRCA (92%), our results highlighted the importance of sustained MRD negativity as a key endpoint to modulate the baseline risk associated with the presence of unfavourable HRCA.
A second important point is that, consistently with the findings from the IFM 2009 and DETERMINATION trials comparing VRd with or without ASCT, in our study upfront ASCT

confirmed its PFS benefit also in standard-risk (0 HRCA) patients, as compared with KRd12 without transplant (HR=0·41).[18,19]
Another important point is that KR maintenance reduced the risk of progression or death *vs* R alone not only in patients with high-risk myeloma (2+ HRCA: HR=0·53), but also in patients with standard-risk disease (0 HRCA: HR=0·41). These data highlight the potential importance of treatment intensification also in standard-risk patients, although a longer follow-up and a risk-benefit evaluation are needed.
Finally, the inclusion of chromosome 1 abnormalities in the definition of "HRCA" and a stratification that takes into account not only the presence but also the number of CA allowed a better risk classification, identifying a subgroup of patients with an excellent prognosis (0 HRCA) and two subgroups of patients with a worse, yet distinct, OS (HRCA 1 and 2+).
In a cohort of 1000 NDMM patients treated with VRd induction plus ASCT (75% of patients upfront), despite the use of a risk-adapted, 3-drug (including PIs and IMiDs) maintenance, high-risk patients displayed a significantly shorter PFS (median, 40 *vs* 77 months) as compared with standard-risk patients.[5] Similar results (median PFS of 36 months) were reported in high-risk patients treated with VRd-ASCT in the control arm of the GRIFFIN trial.[20] Although cross-trial comparisons should be approached with caution, when analysing the outcome of high-risk patients based on the presence of del(17p), t(4;14), or t(14;16), the results observed in the KRd plus ASCT arm compared favourably with those reported by the Emory group (40-month PFS: 65% *vs* 50%), the GRIFFIN trial (36-month PFS: 69% *vs* 50%), and the EMN02 trial (37-month PFS: 69% *vs* 50%).[5,20,21] Of note, the median PFS in high-risk patients who did not receive upfront ASCT was 17 months with VRd in the DETERMINATION trial and 29 months with KRd in the FORTE trial.[18]
Furthermore, the 3-year PFS of patients harbouring del(17p) was 75% with KRd plus ASCT in the FORTE trial, as compared to 50% with VRd-ASCT in the Emory cohort.[5]
Altogether, these results support the investigation of KRd as a backbone for multi-drug regimens including anti-CD38 mAbs in patients carrying HRCA, as currently ongoing in clinical trials.[22,23]
Lenalidomide maintenance after transplant is a worldwide standard of care, although data in high-risk MM patients are conflicting: in a meta-analysis including four randomised, phase III studies, patients with HRCA did not show a significant PFS benefit from lenalidomide maintenance over no maintenance.[24] In the Myeloma XI study, instead, lenalidomide maintenance also reduced the risk of progression or death in patients with 1 (HR, 0·45) or 2+ HRCA (HR, 0·42) over no maintenance. Despite the benefit observed with lenalidomide maintenance, the median PFS in patients carrying 1 HRCA (54 months), and particularly that in patients carrying 2+ HRCA (<24 months), was still shorter than that in patients without HRCA (NR).[25]
In the HOVON65/GMMG-HD4 trial, bortezomib-based induction and maintenance abrogated the poor prognosis associated with del(17p) in terms of PFS and OS.[26] In the TOURMALINE-MM3 trial, a comparable decrease in the risk of progression or death in patients receiving ixazomib, as compared with placebo, was observed in standard-risk (HR 0·65) and high-risk patients (HR, 0·62).[27] While, in our analysis, the addition of carfilzomib to lenalidomide maintenance prolonged PFS across all cytogenetic subgroups, in the GEM2014MAIN trial no PFS benefit was observed with the addition of ixazomib to Rd (IRd) maintenance after ASCT.[28]
These differences are likely due to the different potency among PIs, as already reported by the SWOG S0777 trial, in which a survival benefit from the addition of bortezomib to Rd was observed, whereas no PFS difference was observed in the TOURMALINE-MM2 trial with ixazomib combined with Rd *vs* Rd alone.[9,29]
Despite the only partially overlapping definition of "high-risk" MM and the clear limitations of cross-trial comparisons, the 3-year PFS from the start of maintenance reported with KR in our

trial also compared favourably with that reported with single-agent lenalidomide in patients with 2+ HRCA treated in the Myeloma XI study (67% *vs* 30%),[25] thus supporting the use of maintenance treatment with a PI+IMiD doublet in patients with HRCA.

Carfilzomib-based induction/intensification/consolidation regimens were able to induce and maintain MRD negativity in a similar proportion of patients with 0 and 1 HRCA, while patients with 2+ HRCA had a higher risk of losing their MRD-negative status and of progression, as also reported by Costa et al. in the MASTER trial.[22] These data are of great importance, since several studies reported that sustained MRD negativity can mitigate or even abrogate the poor prognosis conferred by the presence of HRCA at diagnosis.[30–32] This was also confirmed in our analysis, where the 4-year PFS from enrolment was similar in patients with 1-year sustained MRD negativity, regardless of their cytogenetic risk (HRCA: 0, 89%, 1 92%, and 2+ 80%), thus supporting sustained MRD negativity as a key treatment goal (particularly for high-risk patients) and providing the rationale to explore MRD-driven strategies. Of note, despite similar pre-maintenance MRD negativity rates, KRd plus ASCT consistently increased the rates of sustained 1-year MRD negativity in all cytogenetic subgroups, as compared with KRd12.

The poor prognosis conferred by the presence of copy-number alterations involving chromosome 1, detected in up to 30%–40% of MM patients, is well known.[1] Therefore, consistently with the definition of "high risk" adopted in other studies,[23,25,33] in our definition of HRCA we included gain/amp(1q) and del(1p) along with t(4;14), t(14;16), and del(17p). Not surprisingly, this led to an enriched high-risk group of MM patients whose proportion, however, was consistent with that reported in the Myeloma XI trial, which also included patients with gain/amp(1q).[25] Nonetheless, even adopting the risk classification by the International Myeloma Working Group (IMWG) including only del(17p), t(4;14), and t(14;16),[13] the PFS benefits observed with KRd plus ASCT and KR maintenance were confirmed (Appendix pp.12-13).

The most appropriate cut-off value of the cancer clonal fraction to evaluate del(17p) positivity is currently a matter of debate, ranging from 1 to ≥55 positive cells.[34,35] In a sensitivity analysis adopting a cut-off ≥55% for del(17p) positivity, the results of our analysis were confirmed (Appendix p.4).

Indeed, the lack of a consistent and updated definition of "high-risk" MM is a limitation for the interpretation of the results observed in this subset of patients. In this analysis, we focused on the impact of HRCA; however, other MM-related risk factors have been shown to impact the prognosis of MM patients.[36] Consistently with the results in the three HRCA subgroups, we observed, across all treatment arms, a similar PFS between patients with low (R2-ISS stage I) and low-intermediate risk (R2-ISS II), while patients with intermediate-high (R2-ISS III) and high risk (R2-ISS IV) still showed an inferior PFS. Indeed, efforts should be made to reach a consensus on an updated definition of high-risk MM – considering new baseline risk factors (e.g., chromosome 1 alterations, tumour circulating plasma cells, extra-medullary disease, and gene expression profile) as well as dynamic factors (MRD status) – that allows investigators to test new strategies and to compare results from studies conducted in a homogenous population.

A limitation of this analysis is represented by the small sample sizes for each individual HRCA that reduce the power of the analysis and do not allow us to draw definitive conclusions on the efficacy of the tested regimens in subgroups of patients with specific HRCA (Appendix p.17).

In conclusion, this analysis of the FORTE trial showed that carfilzomib-based induction/intensification/consolidation regimens produce similar PFS and 1-year sustained MRD negativity rates in patients with 0 and 1 HRCA. In this context, KRd plus ASCT was more effective than KRd12 and KCd plus ASCT in terms of PFS and 1-year sustained MRD negativity across all cytogenetic subgroups. Importantly, the addition of a PI (carfilzomib) to R maintenance (KR) confirmed its PFS advantage over R alone across all cytogenetic risk groups.

Despite the promising results observed with KRd plus ASCT and KR maintenance, patients harbouring 2+ HRCA still showed an inferior PFS, thus prompting the investigation of additional or alternative strategies and compounds for the treatment of this ultra-high risk population.

Contributors

All authors contributed equally to the acquisition, analysis, or interpretation of data for this work. All authors critically reviewed the work for important intellectual content, approved the final version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors had access to and verified the underlying data. RM, AC, LB, PM, MB, and FG contributed to conceptualisation, formal analysis, methodology, and writing of the original draft. RM, LB, and AC contributed to software and visualisation. PM, MB, and FG contributed to supervision. All authors contributed equally to data curation, investigation, resources, validation, and writing of the manuscript in terms of review and editing. All authors had access to all the data reported in the study and had final responsibility for the decision to submit this manuscript for publication.

Data sharing

After the publication of this article, data collected for this analysis and related documents will be made available to others upon reasonably justified request, which needs to be written and addressed to the attention of the corresponding author Dr. FG at the following e-mail address: francesca.gay[at]unito.it. The sponsor of the trial, the University of Torino (Italy), via the corresponding author Dr. FG is responsible to evaluate and eventually accept or refuse every request to disclose data and their related documents, in compliance with the ethical approval conditions, in compliance with applicable laws and regulations, and in conformance with the agreements in place with the involved subjects, the participating institutions, and all the other parties directly or indirectly involved in the participation, conduct, development, management and evaluation of this analysis.

Declaration of interests

RM has received honoraria from Janssen, Celgene, Takeda, and Amgen; has served on the advisory boards for Janssen, Celgene, Takeda, Bristol Myers Squibb, and Amgen; has received consultancy fees from Janssen, Takeda, and Sanofi.

PM has received honoraria from Celgene, Janssen, Takeda, Bristol Myers Squibb, Amgen, Novartis, Gilead, Jazz, Sanofi, AbbVie, and GlaxoSmithKline, and has served on scientific advisory boards for Celgene, Janssen, Takeda, Bristol Myers Squibb, Amgen, Jazz, Sanofi, AbbVie, and GlaxoSmithKline.

LP has received honoraria from Celgene, Takeda, Amgen, Bristol Myers Squibb, and Janssen; has served on the advisory boards for Celgene, Bristol Myers Squibb, Amgen, and Janssen; has received consultancy fees from Janssen.

BG has received honoraria from Amgen, Bristol Myers Squibb, Janssen, and Takeda; has served on the advisory boards for Amgen, Bristol Myers Squibb, GlaxoSmithKline, Janssen, Sanofi, and Takeda.

AP has served on the advisory boards for Amgen; has received support for meeting fees, travel, and lodging expenses from Amgen, Celgene, and Janssen; has received non-financial support from Celgene, Janssen, Roche, Takeda, and Amgen.

NG has received research grants from Celgene and Janssen Pharmaceutical; has received sponsorship for clinical studies from Janssen Pharmaceutical and Millennium Pharmaceutical; has served on the advisory boards for Celgene, Takeda, and Janssen Pharmaceutical; has received support for attending meetings from Janssen Pharmaceutical, Celgene, and Bristol Myers Squibb.

AG has received honoraria from Celgene, Takeda, Amgen, and Janssen; has served on the advisory boards for Takeda and Janssen.

MC has received advisory fees from Celgene, Janssen, and Takeda; has received research funding from Celgene.

SB has received honoraria from Sanofi, Celgene, Takeda, and Janssen.

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AB has served on the advisory boards for Amgen, Janssen, Celgene, GlaxoSmithKline, and Takeda.

MB has received honoraria from Sanofi, Celgene, Amgen, Janssen, Novartis, Bristol Myers Squibb, and AbbVie; has served on the advisory boards for Janssen and GlaxoSmithKline; has received research funding from Sanofi, Celgene, Amgen, Janssen, Novartis, Bristol Myers Squibb, and Mundipharma.

FG has received honoraria from Amgen, Celgene, Janssen, Takeda, Bristol Myers Squibb, AbbVie, and GlaxoSmithKline; has served on the advisory boards for Amgen, Celgene, Janssen, Takeda, Bristol Myers Squibb, AbbVie, GlaxoSmithKline, Roche, Adaptive Biotechnologies, Oncopeptides, bluebird bio, and Pfizer.

The other authors declare no competing financial interests.

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Table and figures: titles and legends

Table 1. Patient characteristics

Data are n (%) or median (IQR).
**1 HRCA was defined as the presence of 1 of the following high-risk cytogenetic abnormalities: del(17p), t(4;14), t(14;16), del(1p), gain(1q), or amp(1q). 2+ HRCA was defined as the presence of at least 2 high-risk cytogenetic abnormalities.*
Abbreviations. IQR, interquartile range; ISS, International Staging System stage; LDH, lactate dehydrogenase; ULN, upper limit of normal; t, translocation; del, deletion; amp, amplification; FISH, fluorescence *in situ* hybridisation; HRCA, high-risk cytogenetic abnormalities; R-ISS, Revised ISS stage; KRd, carfilzomib-lenalidomide-dexamethasone; ASCT, autologous stem-cell transplantation; KCd, carfilzomib-cyclophosphamide-dexamethasone; MEL200, melphalan at 200 mg/m^2; KRd plus ASCT, 4 KRd induction cycles, MEL200-ASCT, 4 KRd consolidation cycles; KRd12, 12 KRd cycles; KCd plus ASCT, 4 KCd induction cycles, MEL200-ASCT, 4 KCd consolidation cycles; KR, maintenance treatment with carfilzomib-lenalidomide; R, maintenance treatment with lenalidomide alone.

Table 2. Kaplan-Meier estimates of progression-free survival and overall survival according to cytogenetic risk

**1 HRCA was defined as the presence of 1 of the following high-risk cytogenetic abnormalities: del(17p), t(4;14), t(14;16), del(1p), gain(1q), or amp(1q). 2+ HRCA was defined as the presence of at least 2 high-risk cytogenetic abnormalities.*
Abbreviations. PFS, progression-free survival; HRCA, high-risk cytogenetic abnormalities; KRd, carfilzomib-lenalidomide-dexamethasone; ASCT, autologous stem-cell transplantation; KCd, carfilzomib-cyclophosphamide-dexamethasone; MEL200, melphalan at 200 mg/m^2; KRd plus ASCT, 4 KRd induction cycles, MEL200-ASCT, 4 KRd consolidation cycles; KRd12, 12 KRd cycles; KCd plus ASCT, 4 KCd induction cycles, MEL200-ASCT, 4 KCd consolidation cycles; KR, maintenance treatment with carfilzomib-lenalidomide; R, maintenance treatment with lenalidomide alone; CI, confidence interval; p, p-value; del, deletion; t, translocation; amp, amplification.

Table 3. Rates of pre-maintenance and sustained minimal residual disease negativity

**1 HRCA was defined as the presence of 1 of the following high-risk cytogenetic abnormalities: del(17p), t(4;14), t(14;16), del(1p), gain(1q), or amp(1q). 2+ HRCA was defined as the presence of at least 2 high-risk cytogenetic abnormalities.*
Abbreviations. HRCA, high-risk cytogenetic abnormalities; MRD, minimal residual disease; KRd, carfilzomib-lenalidomide-dexamethasone; ASCT, autologous stem-cell transplantation; KCd, carfilzomib-cyclophosphamide-dexamethasone; MEL200, melphalan at 200 mg/m2; KRd plus ASCT, 4 KRd induction cycles, MEL200-ASCT, 4 KRd consolidation cycles; KRd12, 12 KRd cycles; KCd plus ASCT, 4 KCd induction cycles, MEL200-ASCT, 4 KCd consolidation cycles; del, deletion; t, translocation; amp, amplification.

Figure 1. Trial profile

**Two patients proceeded from intensification to maintenance without consolidation:*
- One in KRd-ASCT for prolonged thrombocytopenia Grade 2
- One in KCd-ASCT arm for prolonged thrombocytopenia Grade 3
Abbreviations. KRd, carfilzomib-lenalidomide-dexamethasone; ASCT, autologous stem-cell transplantation; KRd12, 12 KRd cycles; KCd, carfilzomib-cyclophosphamide-dexamethasone.

Figure 2. Kaplan-Meier estimates of progression-free survival and overall survival from first randomisation according to cytogenetic risk in the overall population

1 HRCA was defined as the presence of 1 of the following high-risk cytogenetic abnormalities: del(17p), t(4;14), t(14;16), del(1p), gain(1q), or amp(1q). 2+ HRCA was defined as the presence of at least 2 high-risk cytogenetic abnormalities.
***The Cox model was adjusted for LDH levels, ISS stage II/III vs I, and first randomisation (induction/intensification/consolidation treatment).*
Abbreviations. PFS, progression-free survival; OS, overall survival; HRCA, high-risk cytogenetic abnormalities; HR, hazard ratio; CI, confidence interval; p, p-value; del, deletion; t, translocation; amp, amplification; LDH, lactate dehydrogenase; ISS, International Staging System.

Figure 3. Kaplan-Meier estimates of progression-free survival from first randomisation according to cytogenetic risk and induction, intensification, and consolidation arm

1 HRCA was defined as the presence of 1 of the following high-risk cytogenetic abnormalities: del(17p), t(4;14), t(14;16), del(1p), gain(1q), or amp(1q). 2+ HRCA was defined as the presence of at least 2 high-risk cytogenetic abnormalities.
***The Cox model was adjusted for LDH levels and ISS stage II/III vs I.*

Abbreviations. PFS, progression-free survival; OS, overall survival; HRCA, high-risk cytogenetic abnormalities; HR, hazard ratio; CI, confidence interval; p, p-value; KRd, carfilzomib-lenalidomide-dexamethasone; ASCT, autologous stem-cell transplantation; KCd, carfilzomib-cyclophosphamide-dexamethasone; MEL200, melphalan at 200 mg/m^2; KRd plus ASCT, 4 KRd induction cycles, MEL200-ASCT, 4 KRd consolidation cycles; KRd12, 12 KRd cycles; KCd plus ASCT, 4 KCd induction cycles, MEL200-ASCT, 4 KCd consolidation cycles; del, deletion; t, translocation; amp, amplification; LDH, lactate dehydrogenase; ISS, International Staging System.

Figure 4. Kaplan-Meier estimates of progression-free survival from second randomisation according to cytogenetic risk and maintenance arm

1 HRCA was defined as the presence of 1 of the following high-risk cytogenetic abnormalities: del(17p), t(4;14), t(14;16), del(1p), gain(1q), or amp(1q). 2+ HRCA was defined as the presence of at least 2 high-risk cytogenetic abnormalities.
**The Cox model was adjusted for LDH levels, ISS stage II/III vs I, and first randomisation (induction/intensification/consolidation treatment).*
Abbreviations. PFS, progression-free survival; HRCA, high-risk cytogenetic abnormalities; HR, hazard ratio; CI, confidence interval; p, p-value; KR, maintenance treatment with carfilzomib-lenalidomide; R, maintenance treatment with lenalidomide alone; HRCA, high-risk cytogenetic abnormalities; del, deletion; t, translocation, amp, amplification; LDH, lactate dehydrogenase; ISS, International Staging System.

Table 1. Patient characteristics

		First randomization				Second randomization		
		All	**KRd plus ASCT**	**KRd12**	**KCd plus ASCT**	**All**	**KR**	**R**
		N=396	**n=132**	**n=126**	**n=138**	**N=292**	**n=140**	**n=152**
Age	Median (IQR)	57 (51-62)	57 (51-62)	57 (51.25-62)	57 (51-62)	57 (52-61)	57 (52-61)	57 (51-61)
	<60	242 (61)	82 (62)	76 (60)	84 (61)	188 (64)	91 (65)	97 (64)
	≥60	154 (39)	50 (38)	50 (40)	54 (39)	104 (36)	49 (35)	55 (36)
Sex	Female	176 (44)	59 (45)	54 (43)	63 (46)	134 (46)	58 (41)	76 (50)
	Male	220 (56)	73 (55)	72 (57)	75 (54)	158 (54)	82 (59)	76 (50)
ISS	I	191 (48)	65 (49)	61 (48)	65 (47)	149 (51)	70 (50)	79 (52)
	II	135 (34)	47 (36)	41 (33)	47 (34)	101 (35)	44 (31)	57 (38)
	III	70 (18)	20 (15)	24 (19)	26 (19)	42 (14)	26 (19)	16 (11)
LDH	≤ULN	327 (86)	110 (85)	105 (87)	112 (85)	248 (89)	118 (89)	130 (88)
	>ULN	54 (14)	19 (15)	16 (13)	19 (15)	32 (11)	14 (11)	18 (12)
	Missing	15	3	5	7	12	8	4
t(4;14)	No	331 (84)	112 (85)	104 (83)	115 (83)	256 (88)	123 (88)	133 (88)
	Yes	65 (16)	20 (15)	22 (17)	23 (17)	36 (12)	17 (12)	19 (12)
t(14;16)	No	376 (95)	121 (92)	124 (98)	131 (95)	276 (95)	130 (93)	146 (96)
	Yes	20 (5)	11 (8)	2 (2)	7 (5)	16 (5)	10 (7)	6 (4)
del(17p)	No	336 (85)	110 (83)	111 (88)	115 (83)	257 (88)	126 (90)	131 (86)
	Yes	60 (15)	22 (17)	15 (12)	23 (17)	35 (12)	14 (10)	21 (14)
gain(1q)	No	270 (68)	92 (70)	85 (67)	93 (67)	195 (67)	95 (68)	100 (66)
	Yes	126 (32)	40 (30)	41 (33)	45 (33)	97 (33)	45 (32)	52 (34)
amp(1q)	No	347 (88)	117 (89)	111 (88)	119 (86)	266 (91)	125 (89)	141 (93)
	Yes	49 (12)	15 (11)	15 (12)	19 (14)	26 (9)	15 (11)	11 (7)
del(1p)	No	352 (89)	121 (92)	114 (90)	117 (85)	262 (90)	124 (89)	138 (91)
	Yes	44 (11)	11 (8)	12 (10)	21 (15)	30 (10)	16 (11)	14 (9)
FISH risk*	0 HRCA	153 (39)	52 (39)	55 (44)	46 (33)	120 (41)	52 (37)	68 (45)
	1 HRCA	138 (35)	48 (36)	39 (31)	51 (37)	109 (37)	60 (43)	49 (32)

	2+ HRCA	105 (27)	32 (24)	32 (25)	41 (30)	63 (22)	28 (20)	35 (23)
R-ISS	I	124 (32)	37 (27)	40 (32)	47 (36)	105 (37)	48 (35)	57 (38)
	II	227 (58)	86 (64)	73 (59)	68 (52)	157 (55)	73 (54)	84 (56)
	III	38 (10)	12 (9)	11 (9)	15 (12)	24 (8)	15 (11)	9 (6)
	Missing	7	3	2	2	6	4	2

Data are n (%) or median (IQR).
**1 HRCA was defined as the presence of 1 of the following high-risk cytogenetic abnormalities: del(17p), t(4;14), t(14;16), del(1p), gain(1q), or amp(1q). 2+ HRCA was defined as the presence of at least 2 high-risk cytogenetic abnormalities.*
Abbreviations. IQR, interquartile range; ISS, International Staging System stage; LDH, lactate dehydrogenase; ULN, upper limit of normal; t, translocation; del, deletion; amp, amplification; FISH, fluorescence *in situ* hybridisation; HRCA, high-risk cytogenetic abnormalities; R-ISS, Revised ISS stage; KRd, carfilzomib-lenalidomide-dexamethasone; ASCT, autologous stem-cell transplantation; KCd, carfilzomib-cyclophosphamide-dexamethasone; MEL200, melphalan at 200 mg/m^2; KRd plus ASCT, 4 KRd induction cycles, MEL200-ASCT, 4 KRd consolidation cycles; KRd12, 12 KRd cycles; KCd plus ASCT, 4 KCd induction cycles, MEL200-ASCT, 4 KCd consolidation cycles; KR, maintenance treatment with carfilzomib-lenalidomide; R, maintenance treatment with lenalidomide alone.

Table 2. Progression-free survival and overall survival according to cytogenetic risk and treatment arm

Treatment arm(s)	0 HRCA (n=153)	1 HRCA* (n=138)	2+ HRCA* (n=105)	1 *vs* 0 HRCA*	2+ *vs* 0 HRCA*	2+ *vs* 1 HRCA*
4-year PFS from first randomisation§						
All	71% (64%–78%)	60% (52%–69%)	39% (30%–50%)	HR 1·33 (95% CI 0·90–1·97) p=0·15	HR 2·56 (95% CI 1·74–3·75) p<0·0001	HR 1·92 (95% CI 1·34–2·76) p=0·0004
KRd plus ASCT	82% (72%–93%)	67% (55%–82%)	55% (40%–76%)	HR 1·89 (95% CI 0·86–4·13) p=0·11	HR 2·70 (95% CI 1·17–6·24) p=0·020	HR 1·43 (95% CI 0·69–2·99) p=0·34
KRd12	67% (55%–81%)	57% (44%–76%)	31% (18%–53%)	HR 1·11 (95% CI 0·57–2·15) p=0·76	HR 2·35 (95% CI 1·26–4·37) p=0·0070	HR 2·12 (95% CI 1·11–4·04) p=0·022
KCd plus ASCT	62% (49%–78%)	55% (43%–71%)	33% (21%–52%)	HR 1·13 (95% CI 0·60–2·14) p=0·70	HR 2·45 (95% CI 1·33–4·53) p=0·0040	HR 2·16 (95% CI 1·22–3·83) p=0·0082
3-year PFS from second randomisation¥						
All	80% (74%–88%)	68% (59%–78%)	53% (42%–67%)	HR 1·68 (95% CI 1·01–2·8) p=0·048	HR 2·74 (95% CI 1·6–4·69) p=0·0003	HR 1·63 (95% CI 1·00–2·66) p=0·051
KR	90% (82%–99%)	69% (58%–83%)	67% (52%–87%)	HR 2·59 (95% CI 1·02–6·60) p=0·046	HR 3·26 (95% CI 1·15–9·23) p=0·026	HR 1·26 (95% CI 0·58–2·75) p=0·56
R	73% (64%–85%)	67% (55%–82%)	42% (29%–63%)	HR 1·52 (95% CI 0·79–2·92) p=0·21	HR 2·69 (95% CI 1·42–5·10) p=0·0024	HR 1·78 (95% CI 0·92–3·41) p=0·085
4-year OS from first randomisation°						
All	94% (91%–98%)	83% (76%–90%)	63% (54%–74%)	HR 2·55 (95% CI 1·22–5·36) p=0·013	HR 6·53 (95% CI 3·24–13·18) p<0·0001	HR 2·56 (95% CI 1·53–4·28) p=0·0004
KRd plus ASCT	93% (87%–100%)	87% (77%–97%)	74% (61%–91%)	HR 1·91 (95% CI 0·56–6·59) p=0·30	HR 3·96 (95% CI 1·21–13·0) p=0·023	HR 2·07 (95% CI 0·75–5·69) p=0·16
KRd12	96% (91%–100%)	84% (73%–97%)	62% (46%–83%)	HR 2·09 (95% CI 0·52–8·44) p=0·30	HR 9·62 (95% CI 2·68–34·51) p=0·0005	HR 4·61 (95% CI 1·66–12·8) p=0·0034
KCd plus ASCT	93% (86%–100%)	78% (67%–91%)	55% (41%–74%)	HR 2·69 (95% CI 0·74–9·82) p=0·13	HR 6·92 (95% CI 2·01–23·79) p=0·0022	HR 2·57 (95% CI 1·16–5·69) p=0·020

**1 HRCA was defined as the presence of 1 of the following high-risk cytogenetic abnormalities: del(17p), t(4;14), t(14;16), del(1p), gain(1q), or amp(1q). 2+ HRCA was defined as the presence of at least 2 high-risk cytogenetic abnormalities.*
p-interaction=0·75; ¥p-interaction=0·65; °p-interaction=0·93.

Abbreviations. PFS, progression-free survival; HRCA, high-risk cytogenetic abnormalities; KRd, carfilzomib-lenalidomide-dexamethasone; ASCT, autologous stem-cell transplantation; KCd, carfilzomib-cyclophosphamide-dexamethasone; MEL200, melphalan at 200 mg/m^2; KRd-ASCT, 4 KRd induction cycles, MEL200-ASCT, 4 KRd consolidation cycles; KRd12, 12 KRd cycles; KCd-ASCT, 4 KCd induction cycles, MEL200-ASCT, 4 KCd consolidation cycles; KR, maintenance treatment with carfilzomib-lenalidomide; R, maintenance treatment with lenalidomide alone; CI, confidence interval; p, p-value; del, deletion; t, translocation; amp, amplification.

Table 3. Rates of pre-maintenance and sustained minimal residual disease negativity

Treatment arm(s)	0 HRCA (n=153)	1 HRCA* (n=138)	2+ HRCA* (n=105)
Pre-maintenance MRD negativity			
All	80 of 153 (52%)	88 of 138 (64%)	46 of 105 (44%)
KRd plus ASCT	33 of 52 (63%)	33 of 48 (69%)	14 of 32 (44%)
KRd12	28 of 55 (51%)	28 of 39 (72%)	16 of 32 (50%)
KCd plus ASCT	19 of 46 (41%)	27 of 51 (53%)	16 of 41(39%)
Sustained MRD negativity			
All	53 of 153 (35%)	57 of 138 (41%)	25 of 105 (24%)
KRd plus ASCT	24 of 52 (46%)	24 of 48 (50%)	12 of 32 (38%)
KRd12	17 of 55 (31%)	16 of 39 (41%)	8 of 32 (25%)
KCd plus ASCT	12 of 46 (26%)	17 of 51 (33%)	5 of 41 (12%)

**1 HRCA was defined as the presence of 1 of the following high-risk cytogenetic abnormalities: del(17p), t(4;14), t(14;16), del(1p), gain(1q), or amp(1q). 2+ HRCA was defined as the presence of at least 2 high-risk cytogenetic abnormalities.*

Abbreviations. HRCA, high-risk cytogenetic abnormalities; MRD, minimal residual disease; KRd, carfilzomib-lenalidomide-dexamethasone; ASCT, autologous stem-cell transplantation; KCd, carfilzomib-cyclophosphamide-dexamethasone; MEL200, melphalan at 200 mg/m^2; KRd plus ASCT, 4 KRd induction cycles, MEL200-ASCT, 4 KRd consolidation cycles; KRd12, 12 KRd cycles; KCd plus ASCT, 4 KCd induction cycles, MEL200-ASCT, 4 KCd consolidation cycles; del, deletion; t, translocation; amp, amplification.

Figure 1

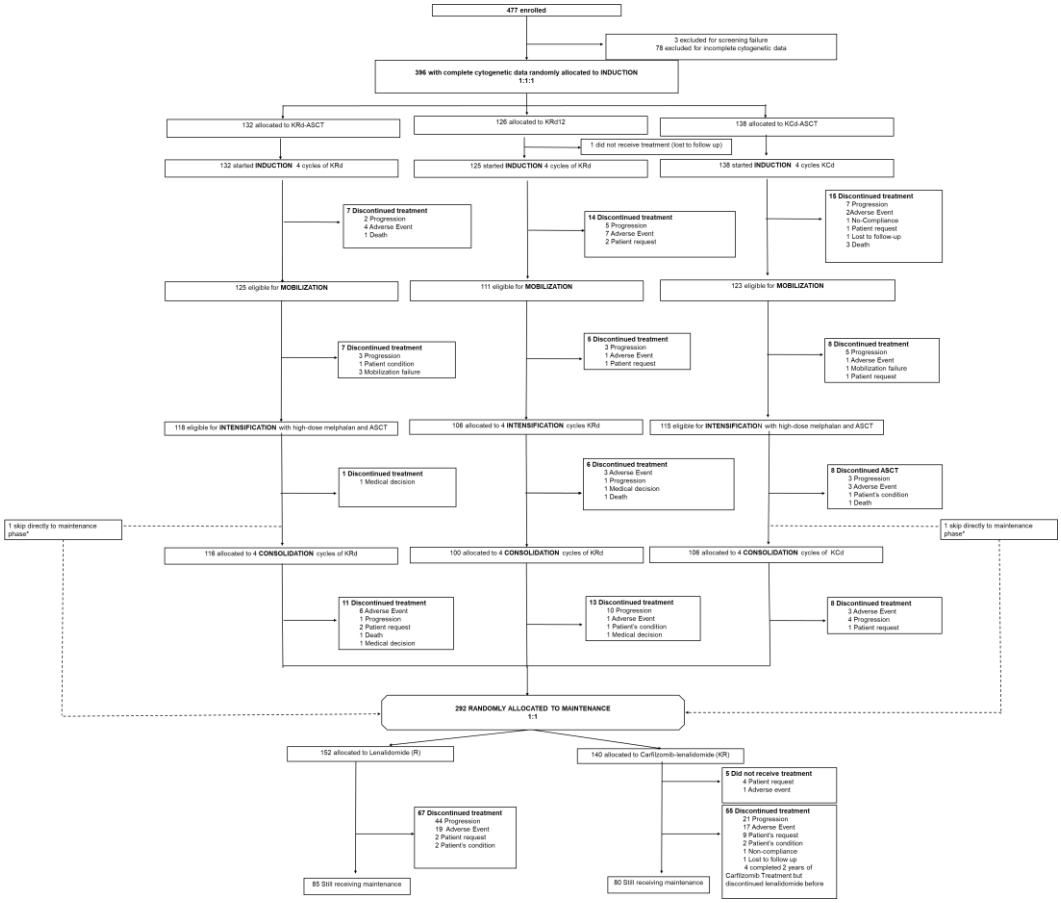
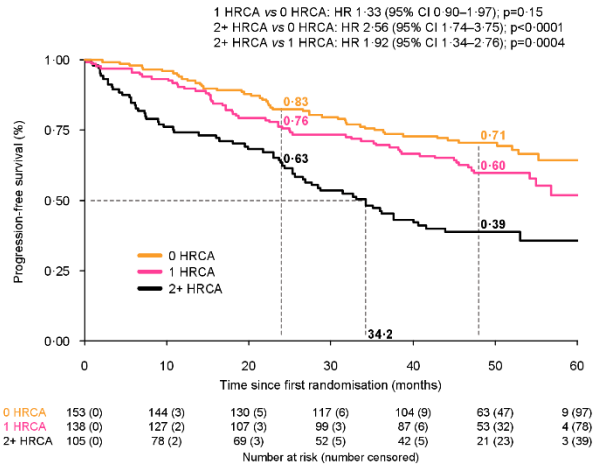

477 enrolled
3 excluded for screening failure
78 excluded for incomplete cytogenetic data
396 with complete cytogenetic data randomly allocated to INDUCTION
1:1:1
132 allocated to KRd-ASCT
126 allocated to KRd12
138 allocated to KCd-ASCT
1 did not receive treatment (lost to follow up)
132 started INDUCTION 4 cycles of KRd
125 started INDUCTION 4 cycles of KRd
138 started INDUCTION 4 cycles KCd
7 Discontinued treatment
2 Progression
4 Adverse Event
1 Death
14 Discontinued treatment
5 Progression
7 Adverse Event
2 Patient request
15 Discontinued treatment
7 Progression
2Adverse Event
1 No-Compliance
1 Patient request
1 Lost to follow-up
3 Death
125 eligible for MOBILIZATION
111 eligible for MOBILIZATION
123 eligible for MOBILIZATION
7 Discontinued treatment
3 Progression
1 Patient condition
3 Mobilization failure
5 Discontinued treatment
3 Progression
1 Adverse Event
1 Patient request
8 Discontinued treatment
5 Progression
1 Adverse Event
1 Mobilization failure
1 Patient request
118 eligible for INTENSIFICATION with high-dose melphalan and ASCT
106 allocated to 4 INTENSIFICATION cycles KRd
115 eligible for INTENSIFICATION with high-dose melphalan and ASCT
1 Discontinued treatment
1 Medical decision
6 Discontinued treatment
3 Adverse Event
1 Progression
1 Medical decision
1 Death
8 Discontinued ASCT
3 Progression
3 Adverse Event
1 Patient's condition
1 Death
1 skip directly to maintenance phase*
1 skip directly to maintenance phase*
116 allocated to 4 CONSOLIDATION cycles of KRd
100 allocated to 4 CONSOLIDATION cycles of KRd
106 allocated to 4 CONSOLIDATION cycles of KCd
11 Discontinued treatment
6 Adverse Event
1 Progression
2 Patient request
1 Death
1 Medical decision
13 Discontinued treatment
10 Progression
1 Adverse Event
1 Patient's condition
1 Medical decision
8 Discontinued treatment
3 Adverse Event
4 Progression
1 Patient request
292 RANDOMLY ALLOCATED TO MAINTENANCE
1:1
152 allocated to Lenalidomide (R)
140 allocated to Carfilzomib-lenalidomide (KR)
5 Did not receive treatment
4 Patient request
1 Adverse event
67 Discontinued treatment
44 Progression
19 Adverse Event
2 Patient request
2 Patient's condition
55 Discontinued treatment
21 Progression
17 Adverse Event
9 Patient's request
2 Patient's condition
1 Non-compliance
1 Lost to follow up
4 completed 2 years of Carfilzomib Treatment but discontinued lenalidomide before
85 Still receiving maintenance
80 Still receiving maintenance

Figure 2

1a. PFS according to cytogenetic risk: overall population*



1b. OS according to cytogenetic risk: overall population*

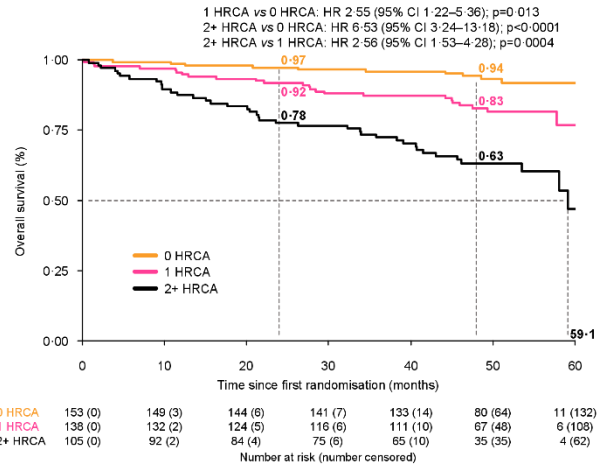
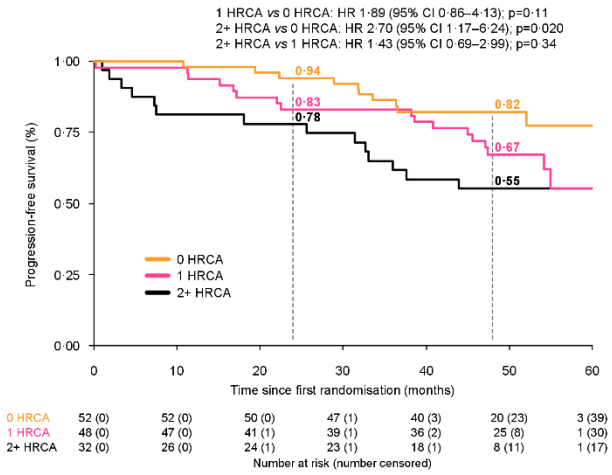
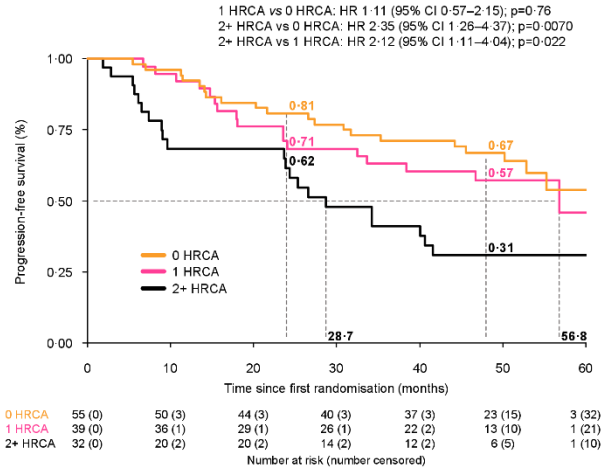


Figure 3

2a. PFS according to cytogenetic risk: KRd plus ASCT arm*



2b. PFS according to cytogenetic risk: KRd12 arm*



2c. PFS according to cytogenetic risk: KCd plus ASCT arm*

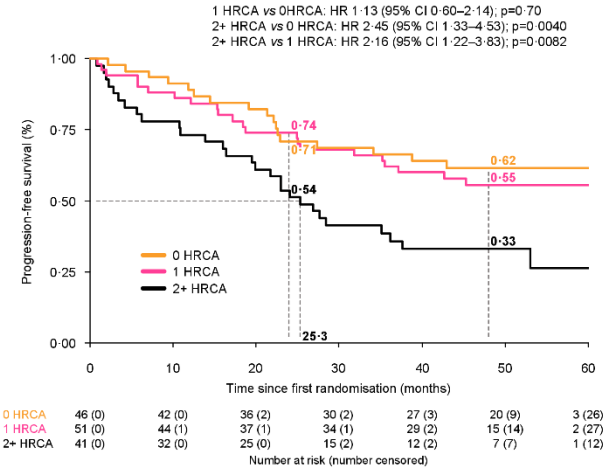
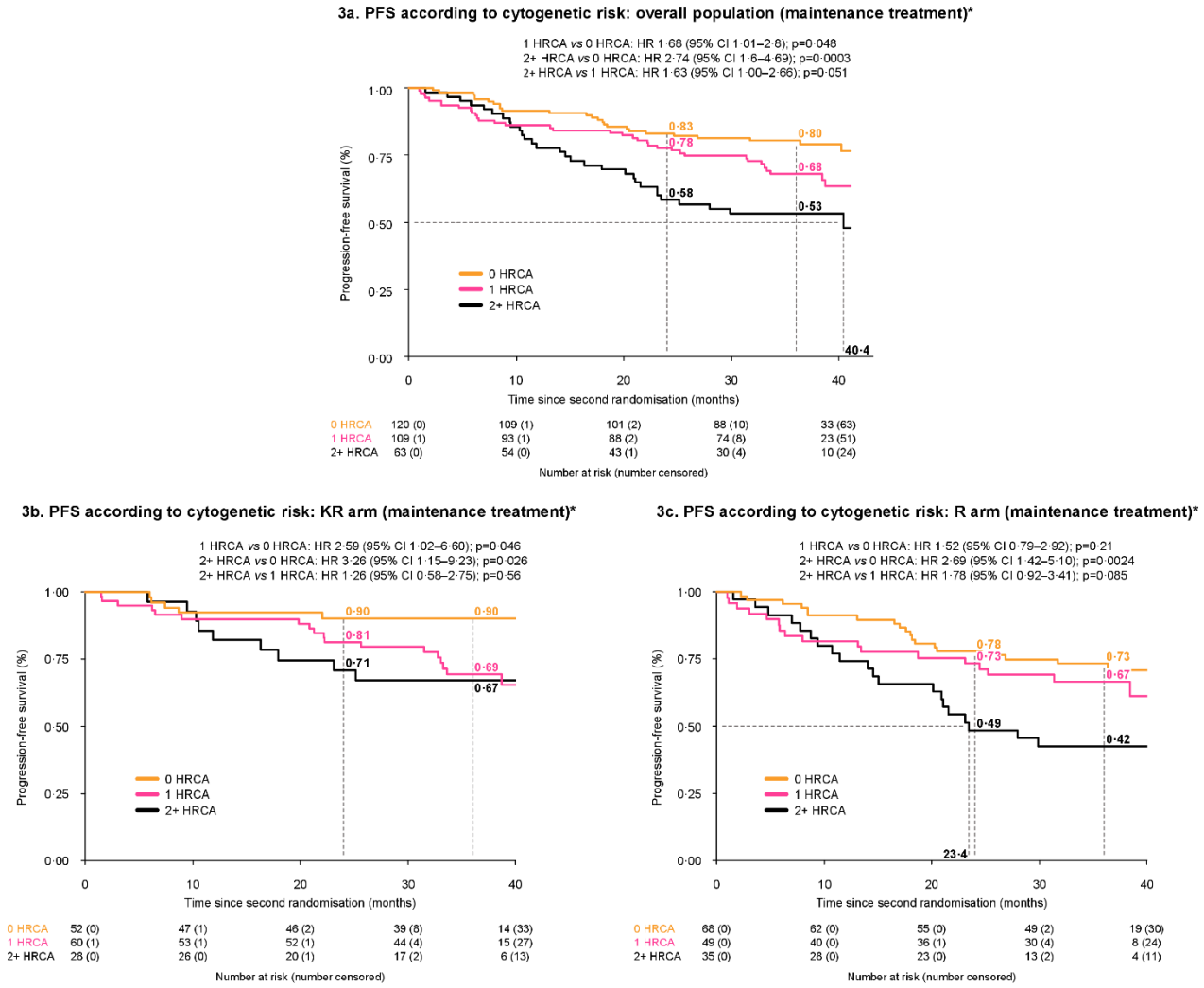


Figure 4


3a. PFS according to cytogenetic risk: overall population (maintenance treatment)*
1 HRCA vs 0 HRCA: HR 1·68 (95% CI 1·01–2·8); p=0·048
2+ HRCA vs 0 HRCA: HR 2·74 (95% CI 1·6–4·69); p=0·0003
2+ HRCA vs 1 HRCA: HR 1·63 (95% CI 1·00–2·66); p=0·051
Progression-free survival (%)
Time since second randomisation (months)
0 HRCA
1 HRCA
2+ HRCA
0·83
0·78
0·80
0·68
0·58
0·53
40·4
0 HRCA 120 (0) 109 (1) 101 (2) 88 (10) 33 (63)
1 HRCA 109 (1) 93 (1) 88 (2) 74 (8) 23 (51)
2+ HRCA 63 (0) 54 (0) 43 (1) 30 (4) 10 (24)
Number at risk (number censored)
3b. PFS according to cytogenetic risk: KR arm (maintenance treatment)*
1 HRCA vs 0 HRCA: HR 2·59 (95% CI 1·02–6·60); p=0·046
2+ HRCA vs 0 HRCA: HR 3·26 (95% CI 1·15–9·23); p=0·026
2+ HRCA vs 1 HRCA: HR 1·26 (95% CI 0·58–2·75); p=0·56
0·90
0·90
0·81
0·71
0·69
0·67
0 HRCA 52 (0) 47 (1) 46 (2) 39 (8) 14 (33)
1 HRCA 60 (1) 53 (1) 52 (1) 44 (4) 15 (27)
2+ HRCA 28 (0) 26 (0) 20 (1) 17 (2) 6 (13)
3c. PFS according to cytogenetic risk: R arm (maintenance treatment)*
1 HRCA vs 0 HRCA: HR 1·52 (95% CI 0·79–2·92); p=0·21
2+ HRCA vs 0 HRCA: HR 2·69 (95% CI 1·42–5·10); p=0·0024
2+ HRCA vs 1 HRCA: HR 1·78 (95% CI 0·92–3·41); p=0·085
0·78
0·73
0·73
0·67
0·49
0·42
23·4
0 HRCA 68 (0) 62 (0) 55 (0) 49 (2) 19 (30)
1 HRCA 49 (0) 40 (0) 36 (1) 30 (4) 8 (24)
2+ HRCA 35 (0) 28 (0) 23 (0) 13 (2) 4 (11)

SUPPLEMENTARY APPENDIX

Supplementary methods **3**
Sensitivity analysis: 17p deletion 3
Progression-free survival according to the IMWG and R2-ISS risk stratification models 3
Supplementary results **4**
Supplementary tables **4**
Table S1. Sensitivity analysis for progression-free survival with cut-offs of 10% and 55% for del(17p) positivity 4
Supplementary figures **5**
Figure S1. Design of the FORTE clinical trial 5
Figure S2. Subgroup analysis of progression-free survival from first randomisation according to specific cytogenetic abnormalities 6
S2a. PFS: KRd plus ASCT vs KRd12 ..... *6*
S2b. PFS: KRd plus ASCT vs KC plus ASCT *6*
Figure S3. Kaplan-Meier estimates of progression-free survival according to minimal residual disease status 7
*S3a. PFS in 0 HRCA patients with sustained MRD negativity by ITT** *7*
*S3b. PFS in 0 HRCA patients with unsustained MRD negativity by ITT** *7*
*S3c. PFS in 0 HRCA patients with MRD positivity by ITT** *7*
*S3d. PFS in 1 HRCA patients with sustained MRD negativity by ITT** *8*
*S3e. PFS in 1 HRCA patients with unsustained MRD negativity by ITT** *8*
*S3f. PFS in 1 HRCA patients with MRD positivity by ITT** *8*
*S3g. PFS in 2+ HRCA patients with sustained MRD negativity by ITT** *9*
*S3h. PFS in 2+ HRCA patients with unsustained MRD negativity by ITT** *9*
*S3i. PFS in 2+ HRCA patients with MRD positivity by ITT** *9*
Figure S4. Subgroup analysis of progression-free survival from second randomisation according to specific cytogenetic abnormalities 11
Figure S5. Kaplan-Meier estimates of progression-free survival according to cytogenetic risk, as defined by the IMWG 12
*S5a. PFS from first randomisation in patients with standard-risk cytogenetics according to the IMWG [absence of t(4;14), t(14;16), and del(17p)]** *12*
*S5b. PFS from first randomisation in patients with high-risk cytogenetics according to the IMWG [presence of t(4;14) and/or t(14;16) and/or del(17p)]** *12*
*S5c. PFS from second randomisation in patients with standard-risk cytogenetics according to the IMWG [absence of t(4;14), t(14;16), and del(17p)]*** *13*
*S5d. PFS from second randomisation in patients with high-risk cytogenetics according to the IMWG [presence of t(4;14) and/or t(14;16) and/or del(17p)]*** *13*
Figure S6. Kaplan-Meier estimates of progression-free survival from first and second randomisation according to R2-ISS 14
S6a. PFS according to R2-ISS: KRd plus ASCT *14*
S6b. PFS according to R2-ISS: KCd plus ASCT *14*
S6c. PFS according to R2-ISS: KRd12 ..... *15*
Figure S7. Kaplan-Meier estimates of progression-free survival from second randomisation according to R2-ISS 16
S7a. PFS according to R2-ISS: KR maintenance treatment *16*

S7b. PFS according to R2-ISS: R maintenance treatment *16*
Figure S8. Power analysis 17
Participating sites list **18**
References **19**
Redacted trial protocol **20**

This supplementary material was provided by the authors to give readers additional information about their work.

Supplementary methods

Sensitivity analysis: 17p deletion

A sensitivity analysis adopting a different cut-off (≥55% of nuclei) for the positivity to del(17p) was used to evaluate the prognostic impact of cytogenetic risk (0 HRCA *vs* 1 HRCA *vs* 2+ HRCA).

Progression-free survival according to the IMWG and R2-ISS risk stratification models

The PFS analysis included all patients in the ITT population with complete cytogenetic data. PFS was calculated from the date of first randomisation for the comparison KRd plus ASCT *vs* KRd12 *vs* KCd plus ASCT, and from the date of second randomisation for the comparison KR *vs* R, to the date of first observation of progressive disease (PD) or death from any cause as an event.
For the analysis presented in Figure S5a–d, patients were stratified into standard risk or high-risk groups respectively in the absence or presence of t(4;14), t(14;16), and/or del(17p), as defined by the IMWG.[1]
For the analysis presented in Figures S6a–c and S7a-b, patients were stratified into stage I, II, III, and IV according to the R2-ISS score.[2]

Abbreviations. del, deletion; HRCA, high-risk cytogenetic abnormalities; IMWG, International Myeloma Working Group; R2-ISS, Second Revision of the International Staging System; PFS, progression-free survival; KRd, carfilzomib-lenalidomide-dexamethasone; ASCT, autologous stem-cell transplantation; KCd, carfilzomib-cyclophosphamide-dexamethasone; MEL200, melphalan at 200 mg/m^2; KRd plus ASCT, 4 KRd induction cycles, MEL200-ASCT, 4 KRd consolidation cycles; KRd12, 12 KRd cycles; KCd plus ASCT, 4 KCd induction cycles, MEL200-ASCT, 4 KCd consolidation cycles; KR, maintenance treatment with carfilzomib-lenalidomide; R, maintenance treatment with lenalidomide alone; t, translocation.

Supplementary results

We performed the Grambsch and Therneau test on PFS from first randomization, PFS from second randomization and on OS, which confirmed that the proportional hazards assumption was not violated for HRs related to HRCA (p=0·50 for first randomization, p=0·71 for second randomization, p=0·86 for OS).

Supplementary tables

Table S1. Sensitivity analysis for progression-free survival with cut-offs of 10% and 55% for del(17p) positivity

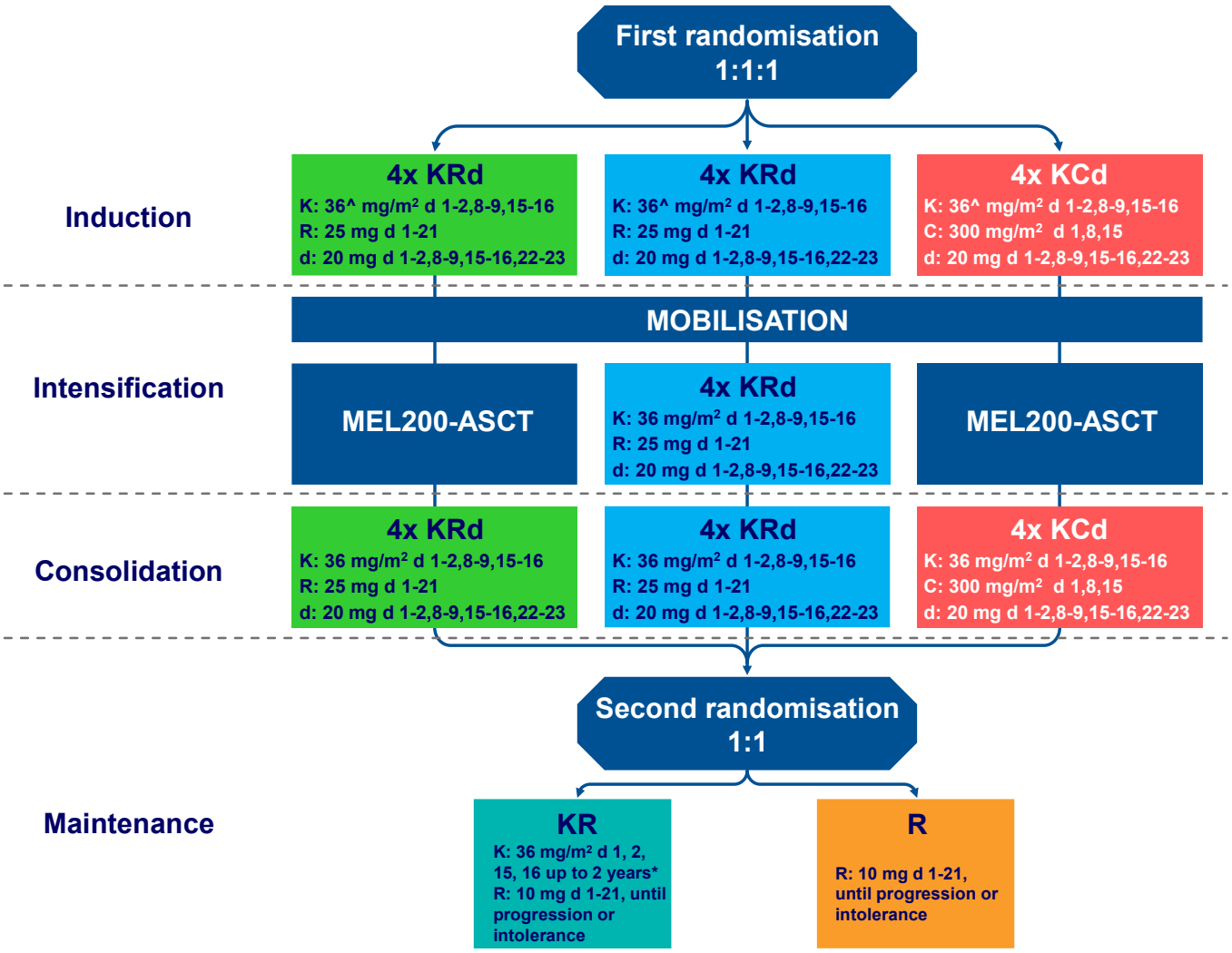
	1 *vs* 0 HRCA*		**2+ *vs* 0 HRCA***		**2+ *vs* 1 HRCA***	
	del(17p) ≥10%	**del(17p) ≥55%**	**del(17p) ≥10%**	**del(17p) ≥55%**	**del(17p) ≥10%**	**del(17p) ≥55%**
All patients	60% *vs* 71% HR 1.33	59% *vs* 72% HR 1.48	39% *vs* 71% HR 2.56	37% *vs* 72% HR 2.96	39% *vs* 60% HR 1.92	37% *vs* 59% HR 2.00

**1 HRCA was defined as the presence of 1 of the following high-risk cytogenetic abnormalities: del(17p), t(4;14), t(14;16), del(1p), gain(1q), or amp(1q). 2+ HRCA was defined as the presence of at least 2 high-risk cytogenetic abnormalities.*
Adjusted for LDH levels, ISS stage II/III vs I, and first randomisation (induction/intensification/consolidation treatment).

Abbreviations. HRCA, high-risk cytogenetic abnormalities; del, deletion; HR, hazard ratio; p, p-value; t, translocation; amp, amplification; LDH, lactate dehydrogenase; ISS, International Staging System.

Supplementary figures

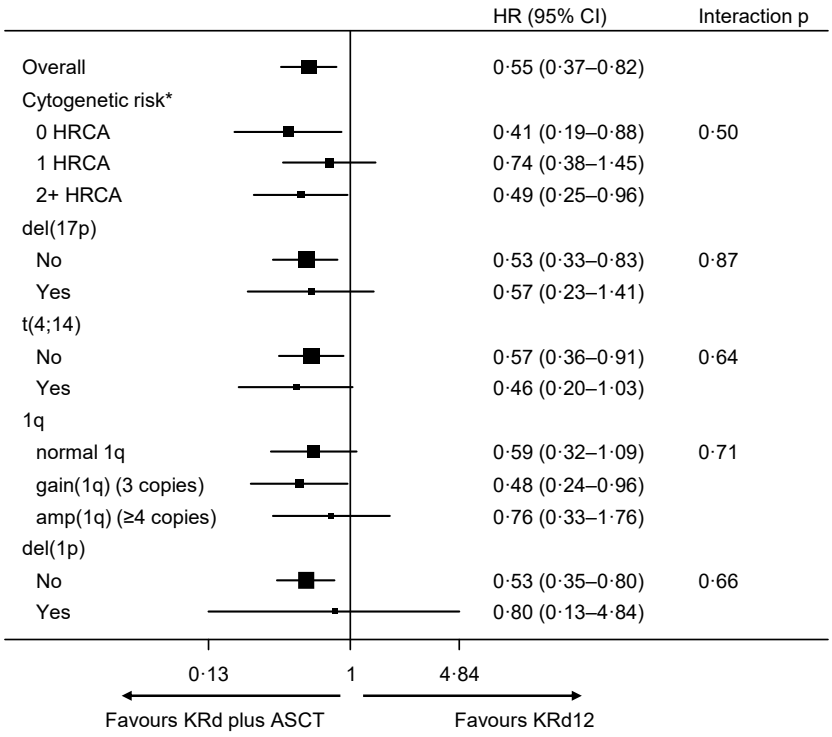
Figure S1. Design of the FORTE clinical trial



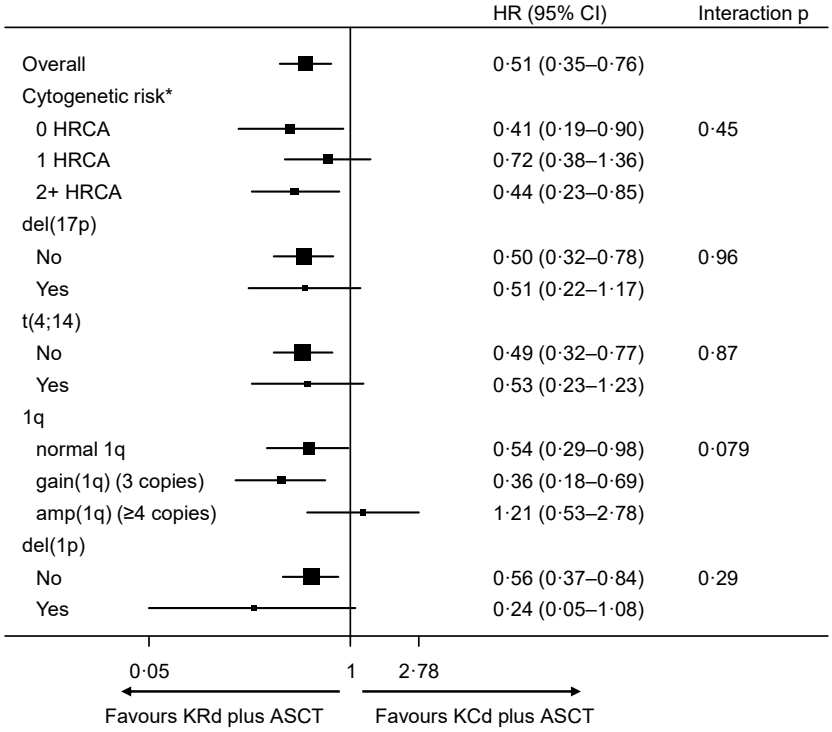
^20 mg/m² on days 1-2, cycle 1 only.
**Carfilzomib 70 mg/m² days 1, 15 every 28 days up to 2 years for patients that have started the maintenance treatment from 6 months before the approval of Amendment 5.0 onwards.*
Abbreviations. K, carfilzomib; C, cyclophosphamide; R, lenalidomide; -d, dexamethasone; d, days; MEL200, melphalan at 200 mg/m²; ASCT, autologous stem-cell transplantation.

Figure S2. Subgroup analysis of progression-free survival from first randomisation according to specific cytogenetic abnormalities

S2a. PFS: KRd plus ASCT vs KRd12



S2b. PFS: KRd plus ASCT vs KC plus ASCT

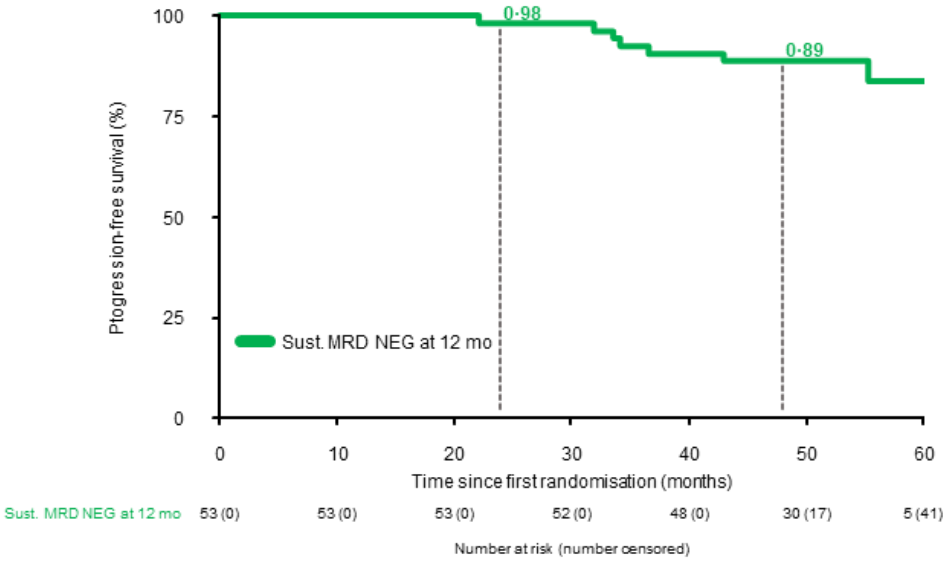


**1 HRCA was defined as the presence of 1 of the following high-risk cytogenetic abnormalities: del(17p), t(4;14), t(14;16), del(1p), gain(1q), or amp(1q). 2+ HRCA was defined as the presence of at least 2 high-risk cytogenetic abnormalities.*

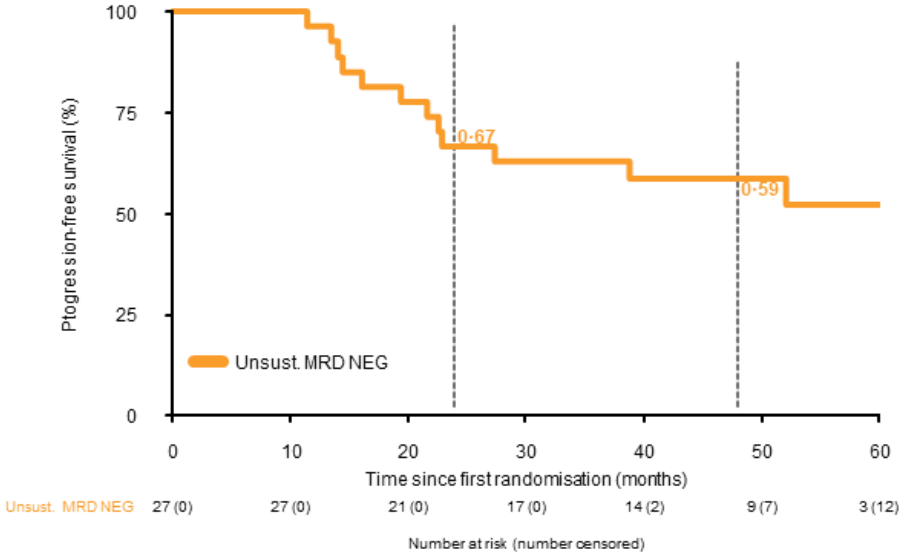
Abbreviations. PFS, progression-free survival; KRd, carfilzomib-lenalidomide-dexamethasone; ASCT, autologous stem-cell transplantation; KCd, carfilzomib-cyclophosphamide-dexamethasone; MEL200, melphalan at 200 mg/m^2; KRd plus ASCT, 4 KRd induction cycles, MEL200-ASCT, 4 KRd consolidation cycles; KRd12, 12 KRd cycles; KCd plus ASCT, 4 KCd induction cycles, MEL200-ASCT, 4 KCd consolidation cycles; HR, hazard ratio; CI, confidence interval; p, p-value; HRCA, high-risk cytogenetic abnormalities; del, deletion, t, translocation; amp, amplification.

Figure S3. Kaplan-Meier estimates of progression-free survival according to minimal residual disease status

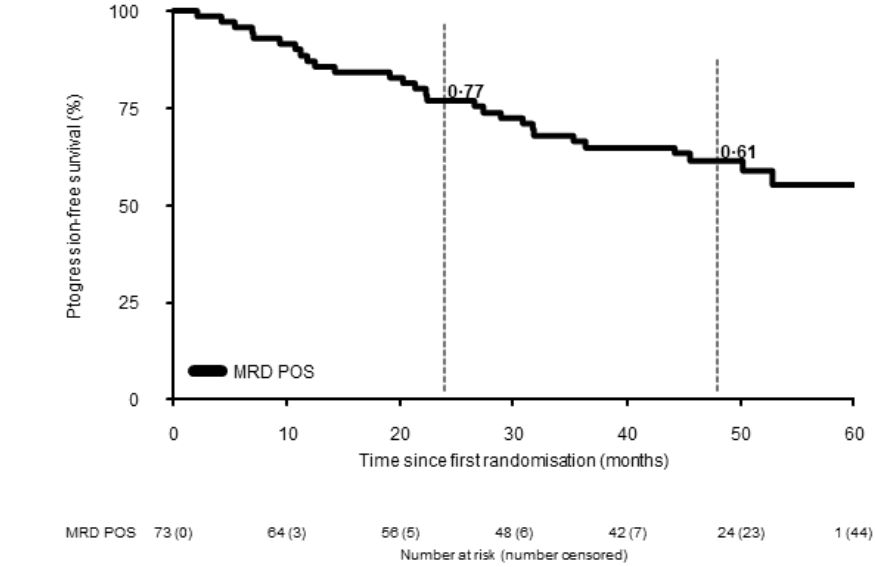
*S3a. PFS in 0 HRCA patients with sustained MRD negativity by ITT**



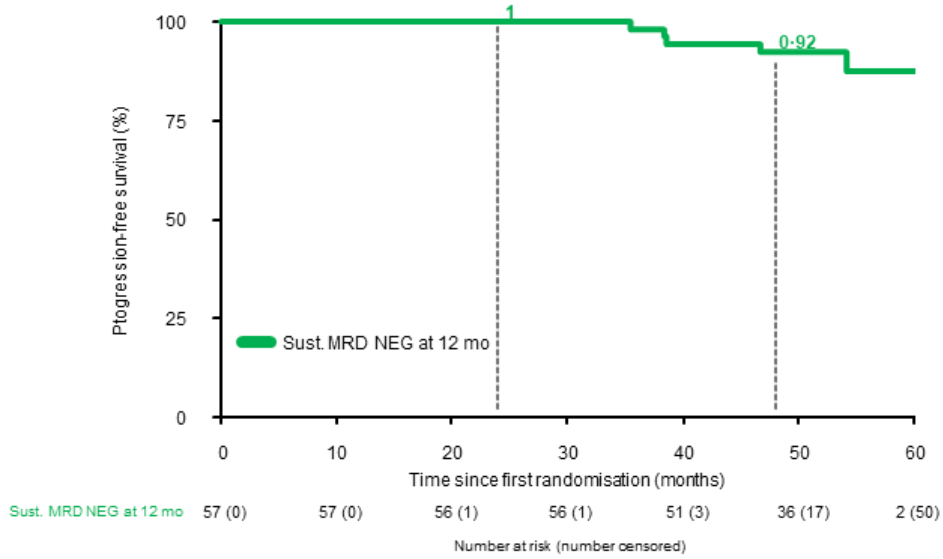
*S3b. PFS in 0 HRCA patients with unsustained MRD negativity by ITT**



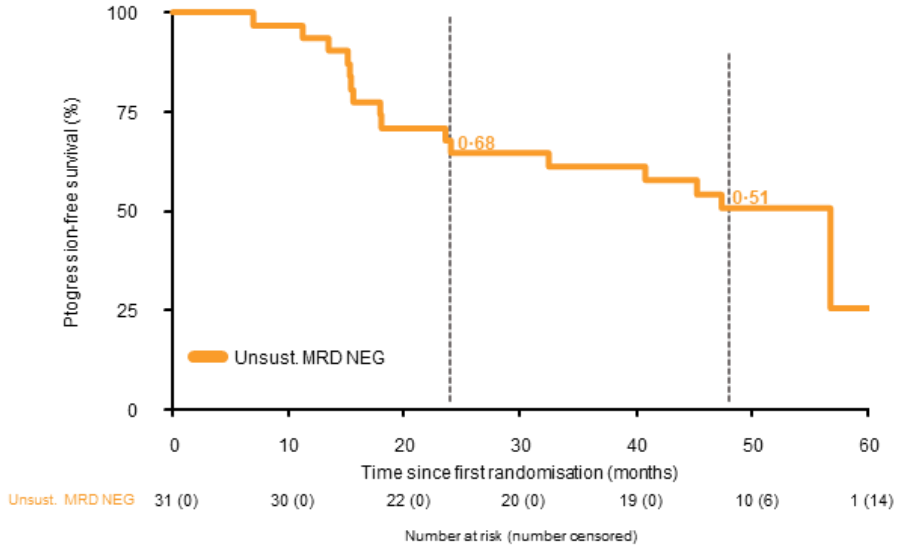
*S3c. PFS in 0 HRCA patients with MRD positivity by ITT**



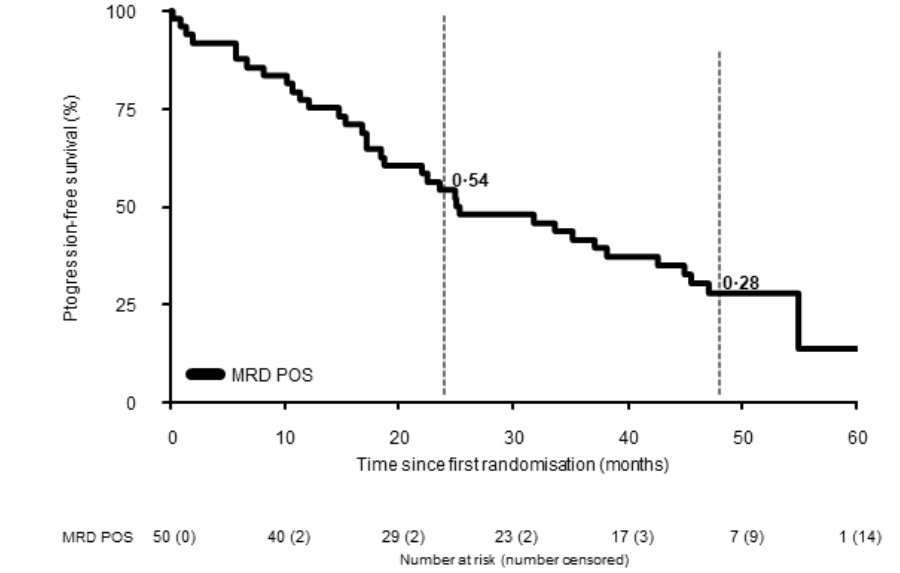
*S3d. PFS in 1 HRCA patients with sustained MRD negativity by ITT**



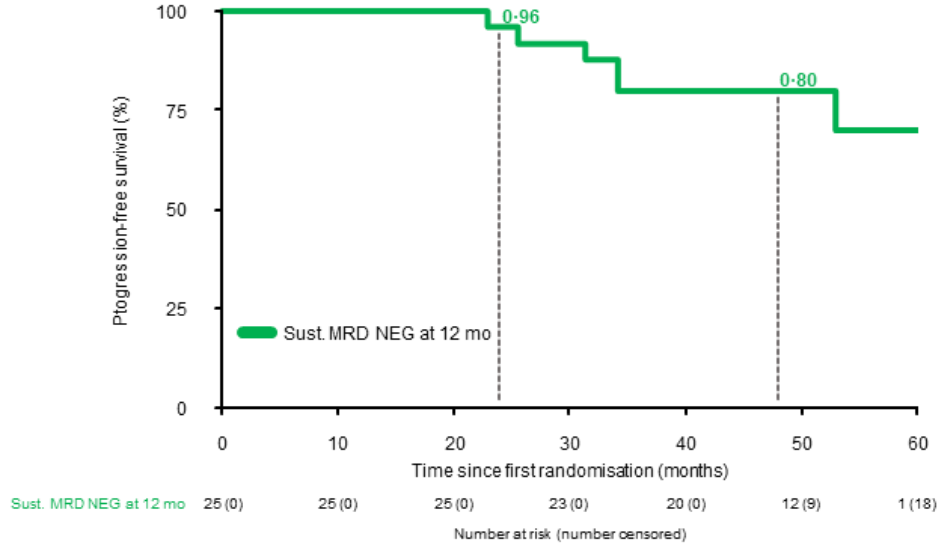
*S3e. PFS in 1 HRCA patients with unsustained MRD negativity by ITT**



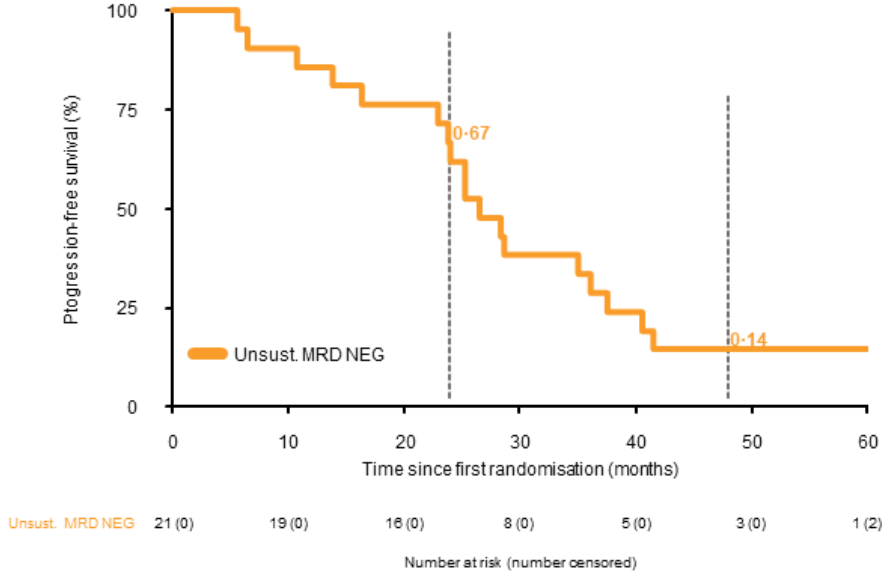
*S3f. PFS in 1 HRCA patients with MRD positivity by ITT**



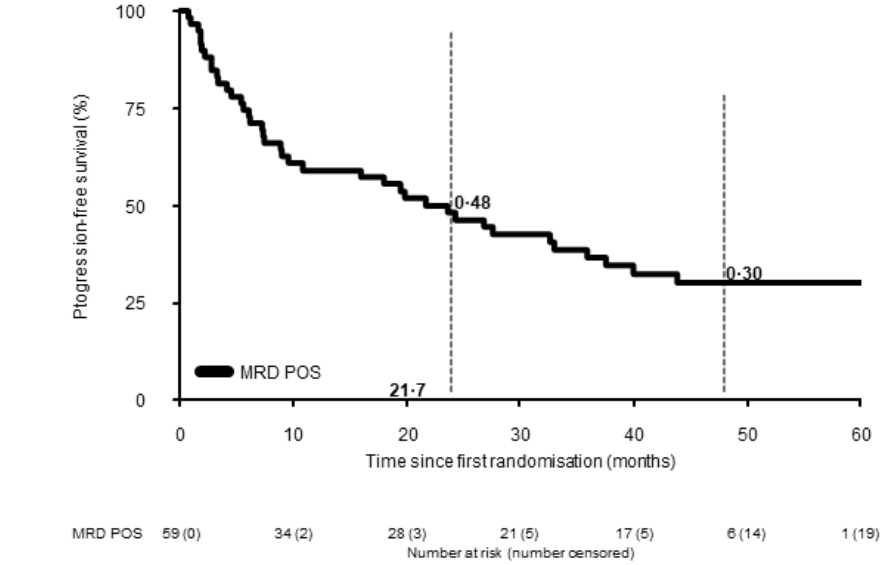
*S3g. PFS in 2+ HRCA patients with sustained MRD negativity by ITT**



*S3h. PFS in 2+ HRCA patients with unsustained MRD negativity by ITT**



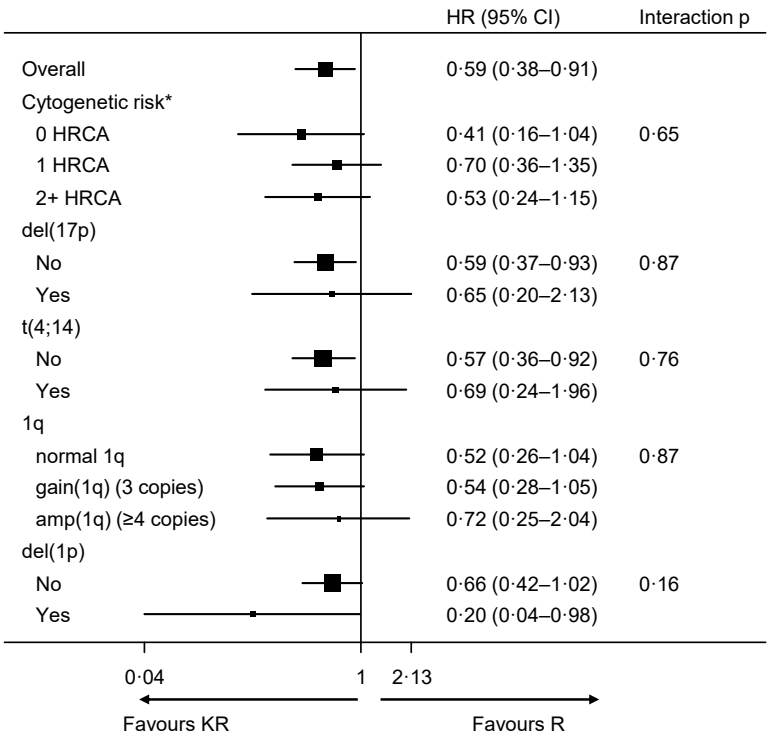
*S3i. PFS in 2+ HRCA patients with MRD positivity by ITT**



1 HRCA was defined as the presence of either del(17p), t(4;14), t(14;16), del(1p), gain(1q), or amp(1q); 2+ HRCA was defined as the presence of at least 2 high-risk cytogenetic abnormalities.

**Adjusted for LDH levels, ISS stage II/III vs I, and first randomisation (induction/intensification/consolidation treatment).*
Abbreviations. PFS, progression-free survival; HRCA, high-risk cytogenetic abnormalities; MRD, minimal residual disease; ITT, intention to treat; unsust., unsustained; NEG, negativity; POS, positivity; sust., sustained; mo, months; HR, hazard ratio; CI, confidence interval; p, p-value; del, deletion; t, translocation; amp, amplification.

Figure S4. Subgroup analysis of progression-free survival from second randomisation according to specific cytogenetic abnormalities

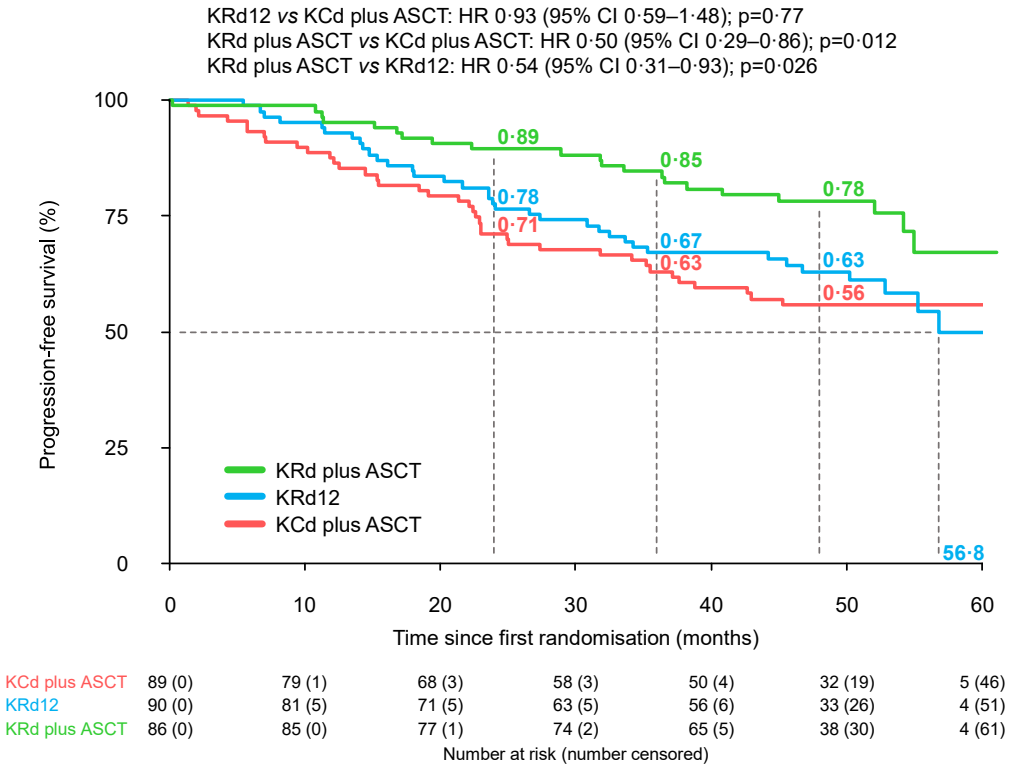


**1 HRCA was defined as the presence of 1 of the following high-risk cytogenetic abnormalities: del(17p), t(4;14), t(14;16), del(1p), gain(1q), or amp(1q). 2+ HRCA was defined as the presence of at least 2 high-risk cytogenetic abnormalities.*

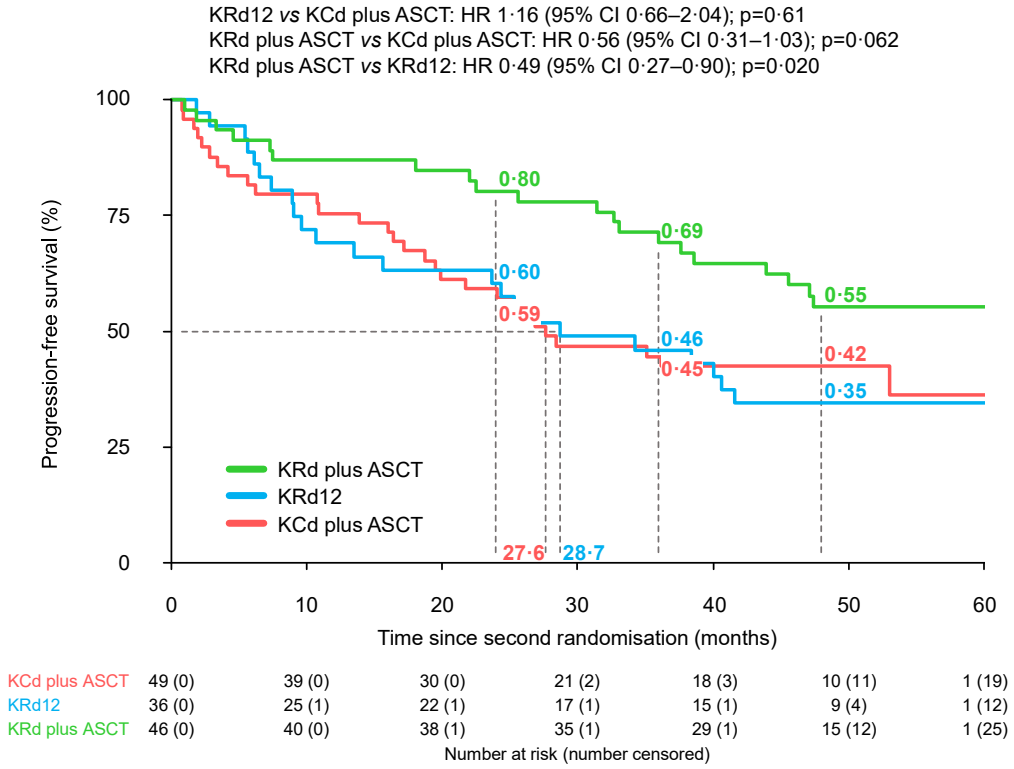
Abbreviations. KR, maintenance treatment with carfilzomib-lenalidomide; R, maintenance treatment with lenalidomide alone; HR, hazard ratio; CI, confidence interval; p, p-value; HRCA, high-risk cytogenetic abnormalities; del, deletion, t, translocation; amp, amplification.

Figure S5. Kaplan-Meier estimates of progression-free survival according to cytogenetic risk, as defined by the IMWG

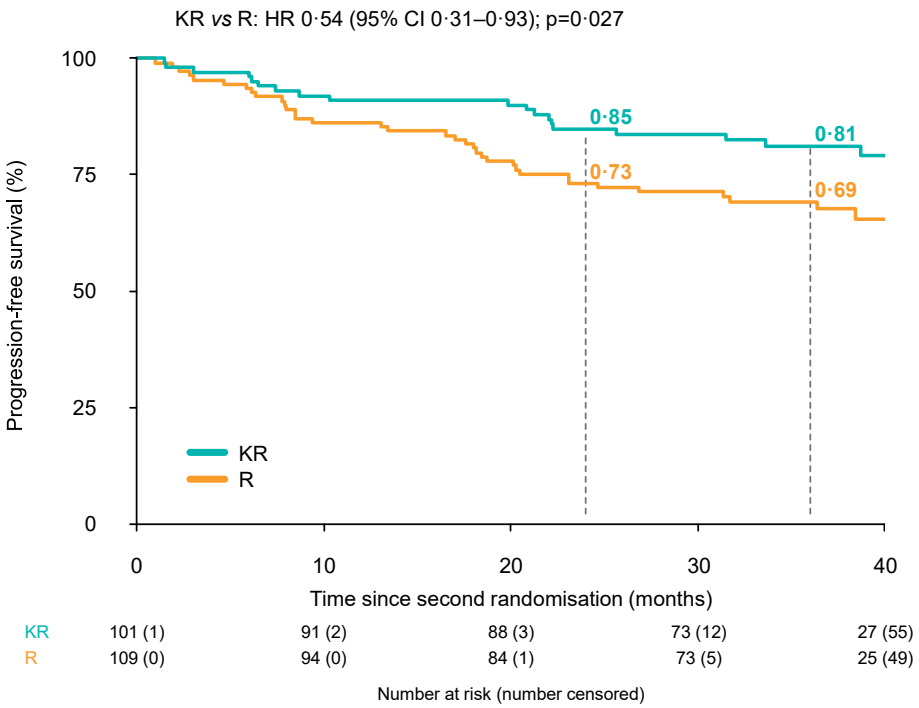
*S5a. PFS from first randomisation in patients with standard-risk cytogenetics according to the IMWG [absence of t(4;14), t(14;16), and del(17p)]**



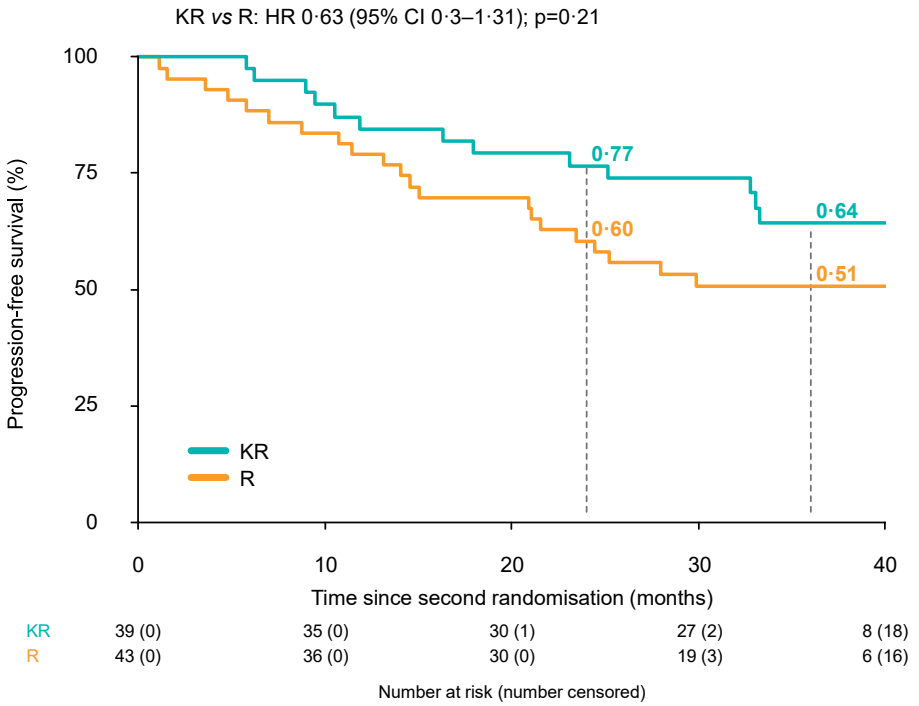
*S5b. PFS from first randomisation in patients with high-risk cytogenetics according to the IMWG [presence of t(4;14) and/or t(14;16) and/or del(17p)]**



*S5c. PFS from second randomisation in patients with standard-risk cytogenetics according to the IMWG [absence of t(4;14), t(14;16), and del(17p)]***



*S5d. PFS from second randomisation in patients with high-risk cytogenetics according to the IMWG [presence of t(4;14) and/or t(14;16) and/or del(17p)]***



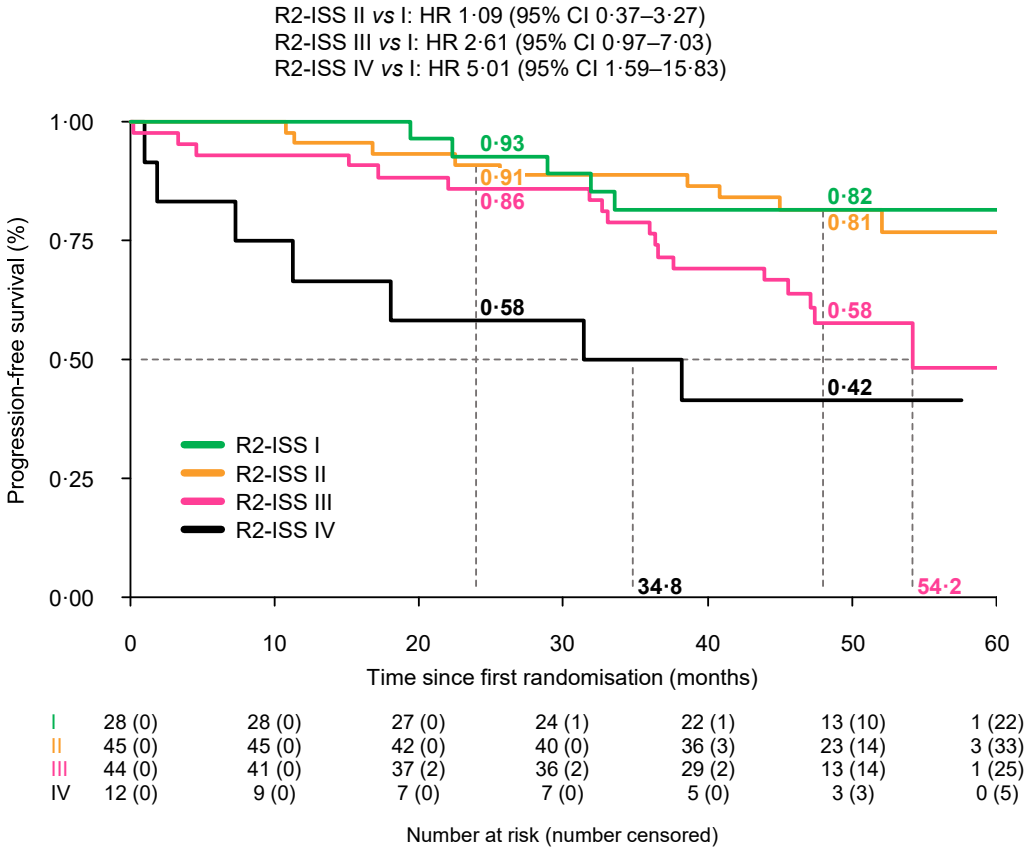
**Adjusted for LDH levels and ISS II/III vs I. **Adjusted for LDH levels, ISS II/III vs I, and first randomisation* (induction/intensification/consolidation treatment).

High risk was defined by the International Myeloma Working Group (IMWG) as the presence of at least 1 of the following cytogenetic abnormalities: t(4;14) and/or t(14;16) and/or del(17p).[1]

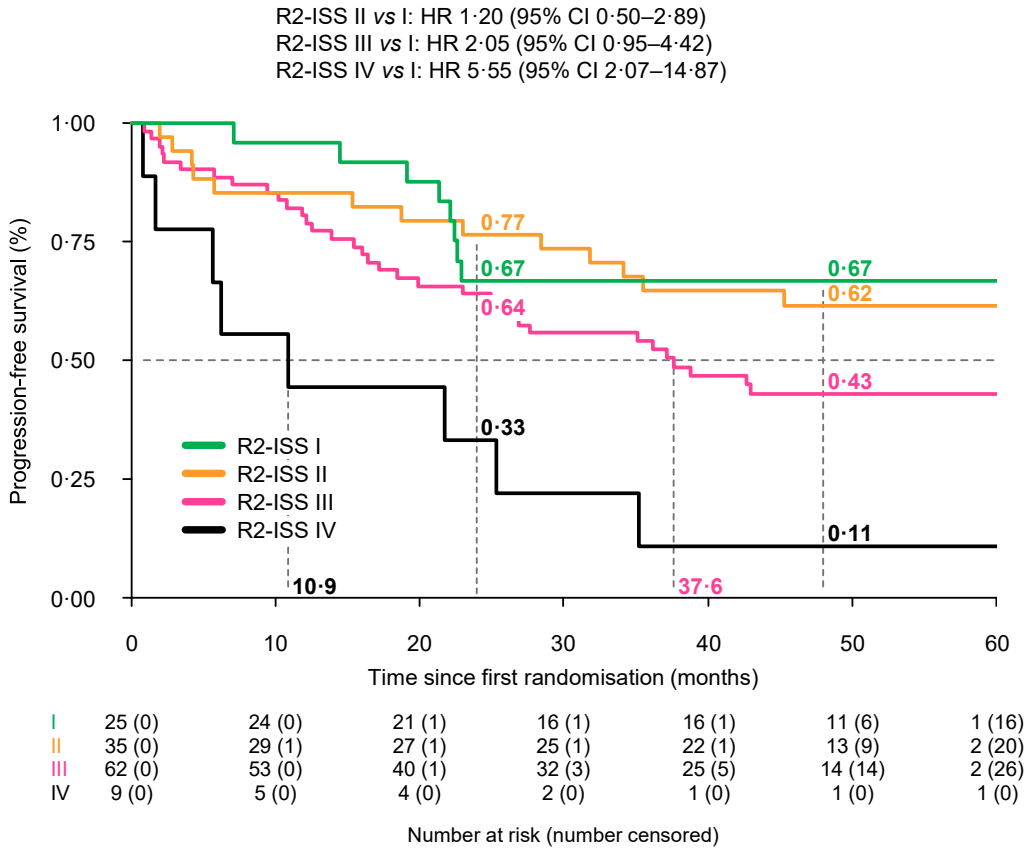
Abbreviations. IMWG, International Myeloma Working Group; PFS, progression-free survival; HRCA, high-risk cytogenetic abnormalities; del, deletion; t, translocation; KRd, carfilzomib-lenalidomide-dexamethasone; ASCT, autologous stem-cell transplantation; KCd, carfilzomib-cyclophosphamide-dexamethasone; MEL200, melphalan at 200 mg/m^2; KRd plus ASCT, 4 KRd induction cycles, MEL200-ASCT, 4 KRd consolidation cycles; KRd12, 12 KRd cycles; KCd plus ASCT, 4 KCd induction cycles, MEL200-ASCT, 4 KCd consolidation cycles; HR, hazard ratio; CI, confidence interval; p, p-value; KR, maintenance treatment with carfilzomib-lenalidomide; R, maintenance treatment with lenalidomide alone; LDH, lactate dehydrogenase; ISS, International Staging System stage.

Figure S6. Kaplan-Meier estimates of progression-free survival from first and second randomisation according to R2-ISS

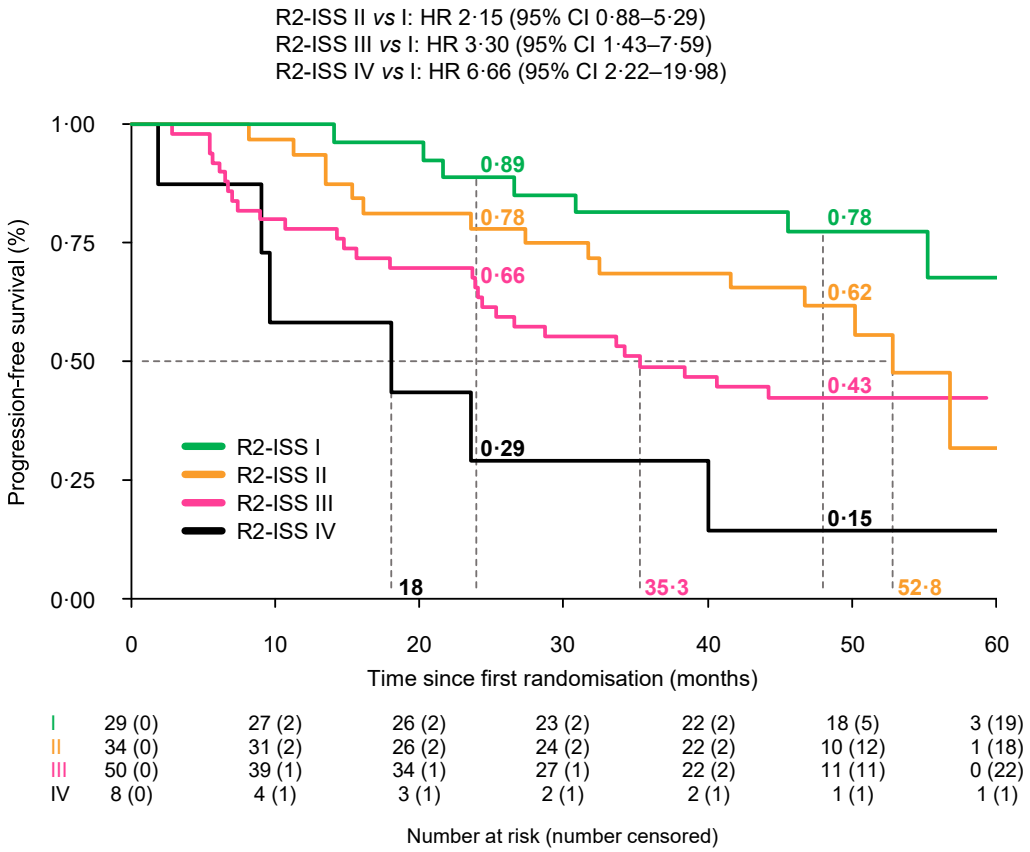
S6a. PFS according to R2-ISS: KRd plus ASCT



S6b. PFS according to R2-ISS: KCd plus ASCT



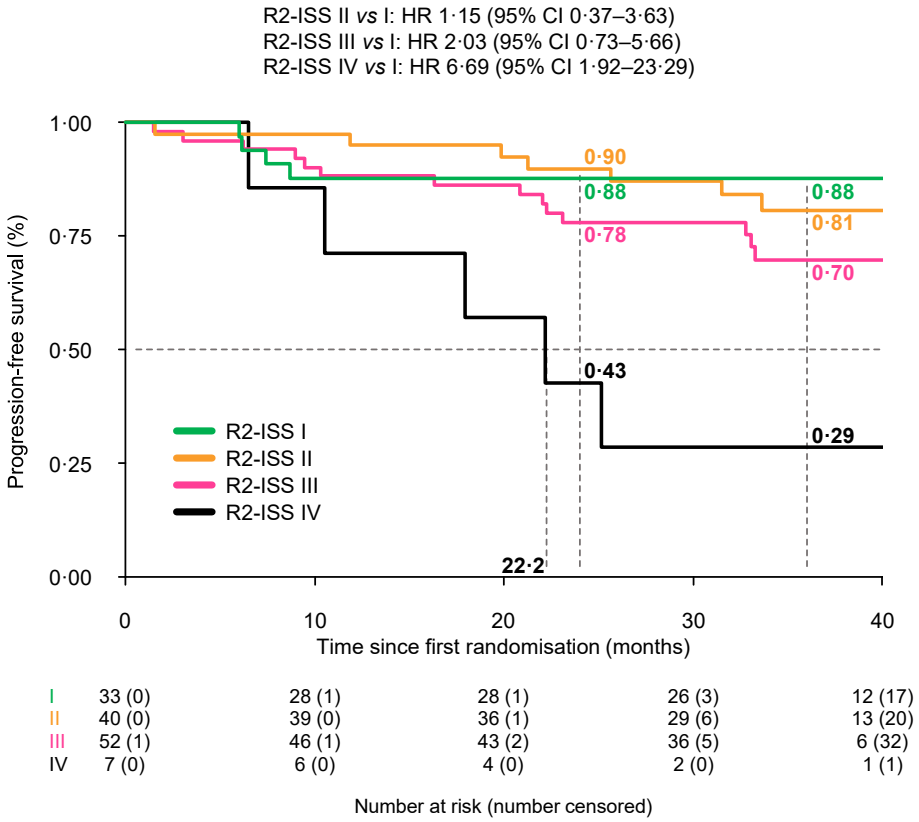
S6c. PFS according to R2-ISS: KRd12



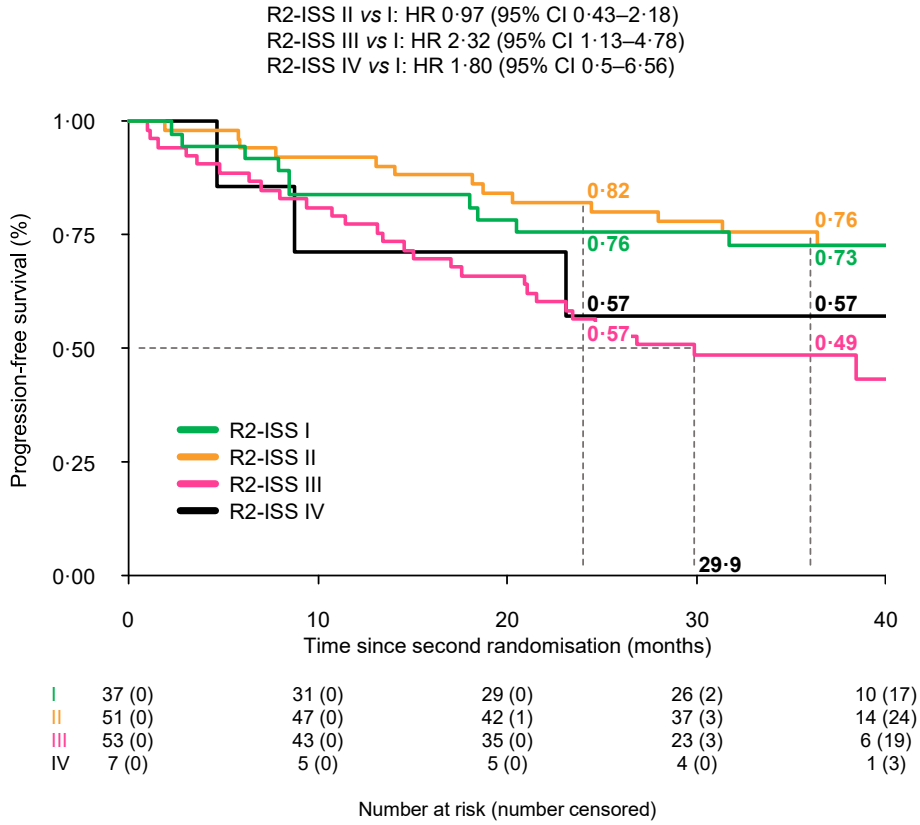
Abbreviations. R2-ISS, Second Revision of the International Staging System[2] (stage); KRd, carfilzomib-lenalidomide-dexamethasone; ASCT, autologous stem-cell transplantation; KCd, carfilzomib-cyclophosphamide-dexamethasone; MEL200, melphalan at 200 mg/m^2; KRd plus ASCT, 4 KRd induction cycles, MEL200-ASCT, 4 KRd consolidation cycles; KRd12, 12 KRd cycles; KCd plus ASCT, 4 KCd induction cycles, MEL200-ASCT, 4 KCd consolidation cycles; HR, hazard ratio; CI, confidence interval; p, p-value.

Figure S7. Kaplan-Meier estimates of progression-free survival from second randomisation according to R2-ISS

S7a. PFS according to R2-ISS: KR maintenance treatment



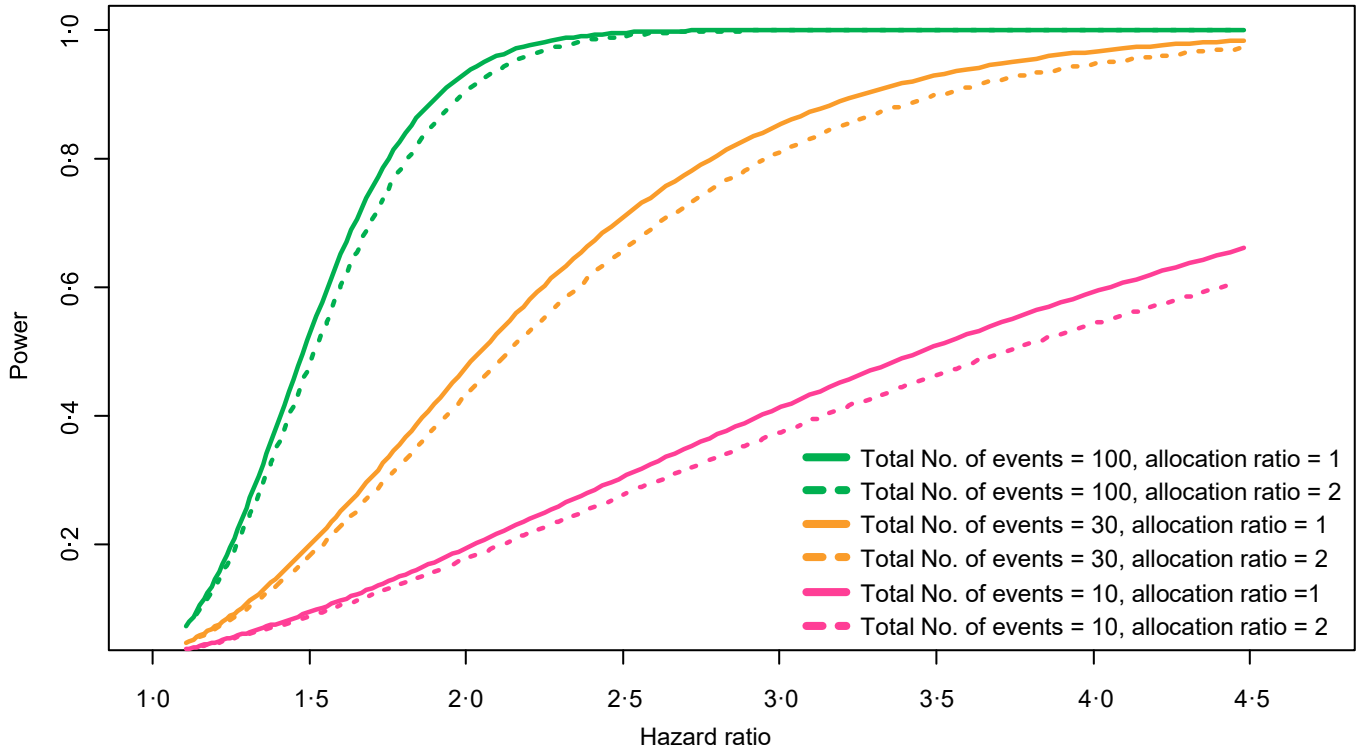
S7b. PFS according to R2-ISS: R maintenance treatment



Abbreviations. R2-ISS, Second Revision of the International Staging System[2] (stage); KR, maintenance treatment with carfilzomib-lenalidomide; R, maintenance treatment with lenalidomide alone; HR, hazard ratio; CI, confidence interval; p, p-value.

Figure S8. Power analysis

The plot shows the power curves for different numbers of events (10, 30, 100) and allocation ratios (1, 2). The power as a function of hazard ratio is reported for each curve. The significance level of the test is set at the conventional value of 0·05 (two-side).



Participating sites list

Site	PI name	Enrolled patients
IT-Candiolo-ISTITUTO PER LA RICERCA E LA CURA DEL CANCRO DI CANDIOLO IRCC FPO-Clinical Oncologia Medica	Dr Aglietta	40
IT-Brescia-Spedali Civili	Dr Rossi	33
IT-Bergamo-Ospedali Riuniti-Divisione di Ematologia	Dr Rambaldi	31
IT-Bologna-Instituto di Ematologia e Oncologia Medica	Dr Cavo	27
IT-Ancona-AOU Umberto I-Clinica di Ematologia	Dr Offidani	24
IT-Roma-Ospedale Umberto I	Dr Martelli	20
IT-Milano INT-Istituto Nazionale per lo Studio e la Cura dei Tumori-UO Ematologia e Trapianto di Midollo Osseo Allogenico	Dr Corradini	17
IT-Padova-Azienda Ospedaliera di Padova-Divisione di Ematologia e Immunologia Clinica Universitaria	Dr Zambello	16
IT-Cagliari-Presidio Ospedaliero R. Binaghi	Dr Ledda	15
IT-Reggio Emilia-Azienda Ospedaliera S. Maria Nuova-Servizio di Ematologia	Dr Gamberi	13
IT-Cuneo-Ospedale Civico S. Croce e Carle -Divisione di Ematologia	Dr Grasso	12
IT-Nuoro-Presidio Ospedaliero San Francesco	Dr Palmas	12
IT-Perugia-Azienda Ospedaliera S. Maria della Misericordia-Ematologia e Immunologia Clinica	Dr Ballanti	12
IT-Genova-Azienda Ospedaliera Universitaria S. Martino_Ematologia 1	Dr Angelucci	11
IT-Pescara-Presidio Ospedaliero dello Spirito Santo	Dr Fioritonri	11
IT-Roma-Ospedale S.Eugenio-Divisione di Ematologia	Dr De Fabritiis	11
IT-Genova-Azienda Ospedaliera Universitaria S. Martino_Clinica Ematologica	Dr Cea	10
IT-Parma-Azienda Ospedaliero-Universitaria di Parma	Dr Crugnola	10
IT-Udine-A.O.U. “S. Maria della Misericordia”-Clinica Ematologica	Dr Patriarca	10
IT-Cosenza-Azienda Ospedaliera di Cosenza-Presidio Ospedaliero dell'Annunziata	Dr Gentile	9
IT-Modena- Policlinico-Servizio di Ematologia	Dr Luppi	9
IT-Trieste-AOU Ospedali Riuniti-Medicina II Ematologia	Dr De Sabbata	9
IT-Napoli-Ospedale Cardarelli-Ematologia e Trapianto di Midollo Osseo	Dr Palmieri	8
IT-Rionero in Vulture-IRCCS-CROB	Dr Pietrantuono	8
IT-Terni-St. Maria-Oncoematologia	Dr Liberati	8
IT-Mestre-Ospedale dell'Angelo- U.O. di Ematologia - Az. Uls 12 veneziana	Dr Bassan	8
IT-Alessandria-Az. Osp. "SS. Antonio e Biagio-Dipartimento di Ematologia e Medicina Trasfusionale	Dr Monaco	7
IT-Rimini-Ospedale Infermi	Dr Tosi	7
IT-Roma-Istituto Regina Elena-SC Ematologia IFO	Dr Pisani	7
IT-Roma-Università Campus Biomedico-Divisione di Ematologia	Dr Avvisati	7
IT-Ascoli Piceno-Ospedale C. e G. Mazzoni-Ascoli Piceno	Dr Galieni	6
IT-Bari-Policlinico di Bari -U.O. di Ematologia con Trapianto	Dr Musto	6
IT-Bolzano-Ospedale Generale Regionale-Divisione di Ematologia e Centro Trapianto Midollo Osseo	Dr Pescosta	6
IT-Tricase (Lecce)-AO Cardinale G. Panico	Dr Pavone	6
IT-Roma-Ospedale San Camillo Forlanini	Dr De Rosa	6
IT-Siena-AOU Senese Policlinico S. Maria alle Scotte-UOC di ematologia e trapianti	Dr Gozzetti	5
IT-Meldola-IRST	Dr Ronconi	4
IT-Ravenna-Ospedale Santa Maria delle Croci-Sezione di Ematologia	Dr Cellini	4
IT-Reggio Calabria-Ospedale Riuniti	Dr Vincelli	4
IT-Messina-Policlinico Gaetano Martino	Dr Musolino	3
IT-Milano-Ospedale Niguarda Cà Granda	Dr Cafro	3
IT-Catanzaro-A.O.Pugliese Ciaccio -U.O. di Oncologia Medica	Dr Molica	2

References

1 Rajkumar SV, Dimopoulos MA, Palumbo A, *et al.* International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014; **15**: e538–48.

2 D'agostino M, Cairns DA, Lahuerta JJ, *et al.* Second Revision of the International Staging System (R2-ISS) for Overall Survival in Multiple Myeloma: A European Myeloma Network (EMN) Report Within the HARMONY Project. *Journal of Clinical Oncology* 2022; **364**: 10.1200/JCO.21.02614. Epub ahead of print.

Redacted trial protocol

A MULTICENTER, RANDOMIZED, OPEN LABEL PHASE II STUDY OF CARFILZOMIB, CYCLOPHOSPHAMIDE AND DEXAMETHASONE (CCyd) as pre transplant INDUCTION and post transplant consolidation or CARFILZOMIB, LENALIDOMIDE AND DEXAMETHASONE (CRd) as pre transplant INDUCTION and post transplant consolidation or continuous treatment with CARFILZOMIB, LENALIDOMIDE AND DEXAMETHASONE (12 cycles) without transplant, all followed by MAINTENANCE with LENALIDOMIDE (R) versus LENALIDOMIDE AND CARFILZOMIB (CR) IN NEWLY DIAGNOSED MULTIPLE MYELOMA (MM) PATIENTS ELEGIBLE FOR AUTOLOGOUS TRANSPLANT

STUDY DRUG:	Carfilzomib and Lenalidomide
PROTOCOL NUMBER:	UNITO-MM-01/FORTE
ORIGINAL VERSION: 1.0	30 June 2014
FINAL VERSION: 1.1	9 December 2014 11
LAST VERSION: 6.0	June 2020
	01 February 2016
AMENDMENT: version 2.0	
AMENDMENT: version 3.0	20 Oct 2017
AMENDMENT: version 4.0	09 March 2018
AMENDMENT: version 5.0	11 Feb 2019
AMENDMENT: version 6.0	11 June 2020

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PROTOCOL INFORMATION

Study Title: A MULTICENTER, RANDOMIZED, OPEN LABEL PHASE II STUDY OF CARFILZOMIB, CYCLOPHOSPHAMIDE AND DEXAMETHASONE (CCyd) as pre transplant INDUCTION and post transplant consolidation or CARFILZOMIB, LENALIDOMIDE AND DEXAMETHASONE (CRd) as pre transplant INDUCTION and post transplant consolidation or continuous treatment with CARFILZOMIB, LENALIDOMIDE AND DEXAMETHASONE (12 cycles) without transplant, all followed by MAINTENANCE with LENALIDOMIDE (R) versus LENALIDOMIDE AND CARFILZOMIB (CR) IN NEWLY DIAGNOSED MULTIPLE MYELOMA (MM) PATIENTS ELEGIBLE FOR AUTOLOGOUS TRANSPLANT

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

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Date

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Printed Name of Principal Investigator: [redacted]

Institution Name: [redacted]

By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from Sponsor representatives, the Declaration of Helsinki, ICH Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.

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Signature of Sponsor Representative Date

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Printed Name of Representative

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PROTOCOL SYNOPSIS

TITLE: A MULTICENTER, RANDOMIZED, OPEN LABEL PHASE II STUDY OF CARFILZOMIB, CYCLOPHOSPHAMIDE AND DEXAMETHASONE (CCyd) as pre transplant INDUCTION and post transplant consolidation or CARFILZOMIB, LENALIDOMIDE AND DEXAMETHASONE (CRd) as pre transplant INDUCTION and post transplant consolidation or continuous treatment with CARFILZOMIB, LENALIDOMIDE AND DEXAMETHASONE (12 cycles) without transplant, all followed by MAINTENANCE with LENALIDOMIDE (R) versus LENALIDOMIDE AND CARFILZOMIB (CR) IN NEWLY DIAGNOSED MULTIPLE MYELOMA (MM) PATIENTS ELEGIBLE FOR AUTOLOGOUS TRANSPLANT

OBJECTIVES: Primary Objective: To determine the efficacy, in term of at least very good partial response (VGPR), of the combination of Carfilzomib and dexamethasone with cyclophosphamide or lenalidomide after 4 cycles of induction treatment in newly diagnosed MM patients eligible for autologous transplantation (ASCT).

To determine the progression-free survival in the 2 maintenance arms.

Secondary Objectives:
Key secondary objectives:

To determine the stringent complete response (sCR) rate in the 3 arms after complete induction/consolidation therapy (induction, ASCT and consolidation for the transplant arms and after 12 cycles in the long treatment arm)

To determine the progression-free survival in in the 3 induction/consolidation arms

Other secondary objectives:

To determine Minimal Residual Disease (MRD) negativity rate in the 3 arms after complete primary therapy (induction, ASCT and consolidation for the transplant arms and after 12 cycles in the long treatment arm).
To determine the Sustained MRD

To determine the response in the 3 arms after complete primary therapy (induction, ASCT and consolidation for the transplant arms and after 12 cycles in the long treatment arm).

To determine the safety in the 3 induction/consolidation arms (including ASCT) and in the 2 maintenance arms.

To determine the time to next therapy in the 3 induction/consolidation arms and in the 2 maintenance arms.
To determine the time to progression in the 3 induction/consolidation arms and in the 2 maintenance arms.
To determine the progression-free survival 2 in the 3 induction/consolidation arms and in the 2 maintenance arms.
To determine overall survival in the 3 induction/consolidation arms and in the 2 maintenance arms.
To determine the duration of response (DOR) in the 3 induction/consolidation arms and in the 2 maintenance arms.

Determine the success of stem cell harvest according to baseline characteristics and therapy

Determine whether tumor response and outcome may change in subgroups with different prognosis according to current prognostic factors

To perform explorative comparative analyses between subgroups of patients, defined according to known prognostic factors

STUDY DESIGN: This protocol is a phase II randomized, multicenter study designed to assess the safety and the efficacy of different carfilzomib combinations in newly diagnosed MM patients eligible for autologous transplantation (ASCT).

STUDY POPULATION: 477 newly diagnosed MM patients eligible for ASCT

INCLUSION CRITERIA:

Age ≥ 18 years
Newly diagnosed MM based on standard CRAB criteria (see appendix B).

Patient ≤ 65 years* eligible for ASCT.

Patient has given voluntary written informed consent.

Patient agrees to use acceptable methods for contraception. Patient has a Karnofsky performance status ≥ 60% (see appendix G).

Pretreatment clinical laboratory values within 30 days of enrollment:

- Platelet count ≥75 x 10^9/L (≥50 x 10^9 /L if myeloma involvement in the bone marrow is > 50%)
- Absolute neutrophil count (ANC) ≥ 1 x 10^9/L without the use of growth factors
- Corrected serum calcium ≤14 mg/dL (3.5 mmol/L)
- Alanine transaminase (ALT): ≤ 3 x the ULN
- Aspartate transaminase (AST): ≤ 3 x the ULN
- Total bilirubin: ≤ 2 x the ULN Calculated or measured creatinine clearance: ≥ 30 mL/minute. LVEF ≥ 40%. 2-D transthoracic echocardiogram (ECHO) is the preferred method of evaluation. Multigated Acquisition Scan (MUGA) is acceptable if ECHO is not available

*until the day before the 66th birthday

Life expectancy ≥ 3 months

EXCLUSION CRITERIA:

Previous treatment with anti-myeloma therapy (does not include radiotherapy, bisphosphonates, or a single short course of steroid ≤ to the equivalent of dexamethasone 40 mg/day for 4 days)

Patients with non-secretory MM unless serum free-light chains are

Patient has measurable disease according to IMWG criteria.

present and the ratio is abnormal or a plasmocytoma with minimum largest diameters of > 2 cm

Patients ineligible for autologous transplantation

Pregnant or lactating females Presence of:

- Clinical active infectious hepatitis type A, B, C or HIV
- Acute active infection requiring antibiotics or infiltrative pulmonary disease
- Myocardial infarction or unstable angina ≤ 4 months or other clinically significant heart disease
- Peripheral neuropathy or neuropathic pain grade 2 or higher, as defined by National Cancer Institute Common Toxicity Criteria (NCI CTC) 4.0 (Appendix A)

Known history of allergy to Captisol ® (a cyclodextrin derivative used to solubilize carfilzomib)

Contraindication to any of the required drugs or supportive treatments

Invasive malignancy within the past 3 years

Serious medical condition, laboratory abnormality or psychiatric illness that prevented the subject from the enrollment or place the subject at unacceptable risk.

PROCEDURES:

Patients will be randomized to receive 4 cycles of CCyd followed by ASCT and subsequent consolidation with 4 cycles of CCyd vs 4 cycles of CRd followed by ASCT and subsequent consolidation with 4 cycles of CRd vs 12 cycles of continuous CRd. At the end of consolidation/12 cycles of CRd treatment patients will be randomized to receive R vs CR as maintenance treatment.

STUDY TREATMENT:

Treatment schedule for induction/consolidation:
All patients will be randomized to receive:

ARM A: CCyd

1. Carfilzomib = 20 mg/m^2 IV on days 1-2 cycle 1 only, followed by 36 mg/m^2 IV once daily on days 8-9, 15-16 cycle 1 then for all subsequent doses 36 mg/m^2 IV once daily on days 1-2, 8-9, 15-16.
2. Cyclophosphamide = 300 mg/m^2 orally on days 1, 8, 15.
3. Dexamethasone = 20 mg orally or IV on days 1, 2, 8, 9, 15, 16, 22, 23.

Repeat for 4 28-day cycles

All patients will be given Cyclophosphamide at the dose of 2 g/m^2, followed by G-CSF for stem cell collection. Cyclophosphamide will start 4-6 weeks after day 21 of cycle 4.

Stem cell collection will be performed as soon as CD34+ cells are present in peripheral blood, which is usually between 9-14 days after first day of Cyclophosphamide. Stem cells will be harvested at a minimum of 4 x 10^6 CD34+ cells/kg and cryopreserved. In case insufficient stem cells are collected the procedure may be repeated or alternatively bone marrow stem cell collection may be performed or Plerixafor may be used.
4-6 weeks after chemotherapy patients will be treated with High Dose Melphalan followed by autologous stem cell reinfusion according to the schedule below.

Agent	Dose/day	Route
Melphalan	200 mg/ m^2 day -2	i.v. rapid infusion
Stem cell infusion	Minimum of 2 x 10^{6}CD34+cells/kg day 0	

90-120 days after Melphalan treatment:

1. Carfilzomib = 36 mg/m^2 IV once daily on days 1-2, 8-9, 15-16.
2. Cyclophosphamide = 300 mg/m^2 orally on days 1, 8, 15.
3. Dexamethasone = 20 mg orally or IV on days 1, 2, 8, 9, 15, 16, 22, 23.

Repeat for 4 28-day cycles

In case patients do not have the criteria to start the consolidation treatment (ANC ≥1.0x10^9/L and platelets ≥75 x10^9/L and no grade >1 extra-hematologic toxicity) within 120 days from Melphalan infusion, they will go on with the maintenance treatment.

ARM B: CRd

1. Carfilzomib = 20 mg/m^2 IV on days 1-2 cycle 1 only, followed by 36 mg/m^2 IV once daily on days 8-9, 15-16 cycle 1 then for all subsequent doses 36 mg/m^2 IV once daily on days 1-2, 8-9, 15-16.
2. Lenalidomide= 25 mg PO daily on days 1-21.
3. Dexamethasone = 20 mg orally or IV on days 1, 2, 8, 9, 15, 16, 22, 23.

Repeat for 4 28-day cycles

All patients will be given Cyclophosphamide at the dose of 2 g/m^2, followed by G-CSF for stem cell collection. Cyclophosphamide will start 4-6 weeks after day 21 of cycle 4.
Stem cell collection will be performed as soon as CD34+ cells are present in peripheral blood, which is usually between 9-14 days after first day of Cyclophosphamide. Stem cells will be harvested at a minimum of 4 x 10^6 CD34+ cells/kg and cryopreserved. In case insufficient stem cells are collected the procedure may be repeated or alternatively bone marrow stem cell collection may be performed or Plerixafor may be used.
4-6 weeks after chemotherapy patients will be treated with High Dose Melphalan followed by autologous stem cell reinfusion according to the schedule below.

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Melphalan	200 mg/ m^2 day -2	i.v. rapid infusion
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90-120 days after Melphalan treatment:

1. Carfilzomib = 36 mg/m^2 IV once daily on days 1-2, 8-9, 15-16.
2. Lenalidomide= 25 mg PO daily on days 1-21.
3. Dexamethasone = 20 mg orally or IV on days 1, 2, 8, 9, 15, 16, 22, 23.

Repeat for 4 28-day cycles

In case patients do not have the criteria to start the consolidation treatment (ANC ≥1.0x10^9/L and platelets ≥75 x10^9/L and no grade >1 extra-hematologic toxicity) within 120 days from Melphalan infusion, they will go on with the maintenance treatment.

ARM C: CRd long treatment

1. Carfilzomib = 20 mg/m^2 IV on days 1-2 cycle 1 only, followed by 36 mg/m^2 IV once daily on days 8-9, 15-16 cycle 1 then for all subsequent doses 36 mg/m^2 IV once daily on days 1-2, 8-9, 15-16.
2. Lenalidomide= 25 mg PO daily on days 1-21.
3. Dexamethasone = 20 mg orally or IV on days 1, 2, 8, 9, 15, 16, 22, 23.

Repeat for 4 28-days cycles

All patients will be given Cyclophosphamide at the dose of 2 g/m^2, followed by G-CSF. Cyclophosphamide will start 4-6 weeks after day 21 of cycle 4.

Stem cell collection will be performed as soon as CD34+ cells are present in peripheral blood, which is usually between 9-14 days after first day of Cyclophosphamide. Stem cells will be harvested at a minimum of 4 x 10^6 CD34+ cells/kg and cryopreserved. In case insufficient stem cells are collected the procedure may be repeated or alternatively bone marrow stem cell collection may be performed or Plerixafor may be used.

30-60 days after Cyclophosphamide

1. Carfilzomib = 36 mg/m^2 IV once daily on days 1-2, 8-9, 15-16.
2. Lenalidomide= 25 mg PO daily on days 1-21.
3. Dexamethasone = 20 mg orally or IV on days 1, 2, 8, 9, 15, 16, 22, 23.

Repeat for 8 28-days cycles

Treatment schedule for maintenance:

After the end of consolidation all patients will be randomized to receive:

1. Lenalidomide 10 mg PO daily on days 1-21 every 28 days.
2. Lenalidomide 10 mg PO daily on days 1-21 *AND* Carfilzomib* 70 mg/m^2 IV once daily on days 1, 15 every 28 days for patients that have started maintenance within 6 months from amendment 5.0 approval.

OR

2. Lenalidomide 10 mg PO daily on days 1-21 *AND* Carfilzomib* 36 mg/m^2 IV once daily on days 1, 2, 15, 16 every 28 days for patients that have started maintenance more than 6 months before the amendment 5.0 approval.

Patients will receive carfilzomib maintenance for a maximum of 2 years and lenalidomide maintenance until any sign of progression or intolerance. Patients that decreased carfilzomib and/or lenalidomide dose in the induction/consolidation treatment will continue with a reduced drug dose during the maintenance period.

Maintenance can only start if ANC ≥ 0.75 x 10^9/l and platelets > 50 x 10^9/l. Moreover all extra-hematological toxicities should be resolved to ≤ grade 1.
* Patients will receive 8 mg of dexamethasone as pre-medication before carfilzomib administration during the first cycle of maintenance and for subsequent cycles according to physician opinion

PRIMARY ENDPOINT

All patients will be included in the Intent-to-Treat (ITT) analysis.
Efficacy will be assessed by considering VGPR or better (VGPR, sCR and CR) at cycle 4 in the 3 arms.
Assessment of VGPR rate will be performed according to the criteria of the International Myeloma Working Group (Appendix D).

To determine the progression-free survival in the 2 maintenance arms.

KEY SECONDARY ENDPOINTS:

To determine the stringent complete response (sCR) rate in the 3 arms after complete induction/consolidation therapy (induction, ASCT and consolidation for the transplant arms and after 12 cycles in the long treatment arm)

To determine the progression-free survival in in the 3 induction/consolidation arms

OTHER SECONDARY ENDPOINTS:

- Determine the MRD negativity rate in the 3 arms after complete primary therapy (induction, ASCT, consolidation)
- To determine the Sustained MRD
- To determine the response in the 3 arms after complete primary therapy (induction, ASCT and consolidation for the transplant arms and after 12 cycles in the long treatment arm).
- Determine the rate of adverse events in the 3 induction/consolidation arms (including ASCT) and in the 2 maintenance arms.
- Determine the time to next therapy in the 3 induction/consolidation arms and in the 2 maintenance arms.
- Determine the time to progression in the 3 induction/consolidation arms and in the 2 maintenance arms.
- Determine the overall survival (OS) in the 3 induction/consolidation arms and in the 2 maintenance arms
- Determine the duration of response (DOR) in the 3 induction/consolidation arms and in the 2 maintenance arms.
- Determine the Progression Free Survival-2 (PFS2) defined as the time from initial randomization (to first line therapy) until to second objective disease progression on next line treatment, or death from

any cause in the 3 induction/consolidation arms and in the 2 maintenance arms

- Determine the safety and the PFS, PFS2 and OS of twice weekly administration of carfilzomib + lenalidomide maintenance vs once weekly administration of carfilzomib + lenalidomide maintenance (after amendment 5).
- Determine the success of stem cell harvest according to baseline characteristics
- Determine whether tumor response and outcome may change in subgroups with different prognosis according to current prognostic factors
- To perform explorative comparative analyses between subgroups of patients, defined according to known prognostic factors

STATISTICAL METHODS:

Assumptions:

- 2-sided alpha level equal to 0.05 and a power of 90%:
- VGPR rate for CCyd arm: 62%
- VGPR rate for CRd with transplantation = CRd without transplantation: 80%

The study will be powered to compare *CCyd* arm (Carfilzomib, Cyclophosphamide, Dexamethasone) and *CRd* arms (Carfilzomib, Lenalidomide, Dexamethasone plus transplant combined with Carfilzomib, Lenalidomide Dexamethasone long treatment).
The randomization would be 1:1:1, but the 2 CRd groups would be pooled (2:1) for the analysis of VGPR, since the patient population and treatment is the same until that point (end of 4 cycles of induction).
Comparison between CCyd arm and CRd no ASCT will be done only in an explorative manner and will be part of the secondary endpoints.
This is an efficient solution for having a 96% power for the main comparison and not decreasing the alpha, as it would be required in multiple comparisons.

Using the “Two group continuity corrected Chi square test” the sample size for each arm is 143, for a total of 429 patients. Considering a 10% of patients lost to follow-up, the total sample size is about 477 patients.

A hierarchical testing procedure will be used for the key secondary endpoints to achieve control of the overall familywise Type I error rate at a two-sided significance level of 0.05. The details of the testing procedure will be prespecified in multiplicity section.

The power of 90% (β= 0.10) for first key endpoint (sCR rate after induction/consolidation) was done with the following assumptions by the X2 test with Yates’ continuity correction, consider ITT population:

alpha 0.025, 2-sided for each comparison

- sCR rate for CCyd arm = 20%
- sCR rate for CRd long treatment = 40%
- sCR rate for CRd = 60%
- Lost to Follow-up = 10%

Alpha was split according to Bonferroni adjustment to perform comparison between CRd long treatment vs CCyd and CRd vs CCyd.

The power of 80% (β= 0.20) for second key endpoint (PFS) was done with the following assumptions by Schoenfeld formula, consider ITT population:

- alpha 0.025, 2-sided for each comparison
- 3-years PFS for CCyd arm = 55%
- 3-years PFS for CRd long treatment = 70% (HR=0.60)
- 3-years PFS for CRd = 80% (HR = 0.37)
- Accrual time: 36 months
- Follow-up time: 36 months
- Lost to follow-up: 5%

Alpha was split according to Bonferroni adjustment to perform comparison between CRd long treatment vs CCyd and CRd vs CCyd. To achieve 80% power, 146 and 39 PFS events are needed for the comparison CRd long treatment vs CCyd and CRd vs CCyd respectively.

Randomizations should be done separately, the first at induction and the second one at the end of induction and consolidation period.
In this way it avoids an unbalance in the maintenance arms.
Responding patients will be randomized before maintenance and the two arms will be balanced, permitting a better comparison on PFS for the two groups. The randomization into two different maintenance regimens will be stratified by the three induction/consolidation arms.

The first interim analysis aims to evaluate safety of the induction (all adverse events including the occurrence of posterior reversible encephalopathy syndrome (PRES) and failure of mobilization of PBSC). It is planned after 90 patients have completed the induction phase. Since this is not the principal aim of the study, no statistical correction of the sample size or of the alpha error have been done. In case of mobilization failure in more than 15% of the patients or DMC recommendation, after the analysis of safety data, the study will be interrupt.
Considering 4-years PFS improvement from 40% to 60% (HR=0.558) with a 2-sided alpha of 0.05 and beta=0.2, using an unstratified log-rank test, the sample size required is equal to 196 patients and the number of events is equal to 92. For this reason, the 477 patients calculated for the induction part of the study are considered adequate.

Considering the change in the schedule of carfilzomib applied with amendment 5.0, a safety analysis will be performed after the first 18

patients will complete the first 4 cycles of weekly carfilzomib maintenance. The safety data of carfilzomib 70 mg/m^2 on day 1, 15 will be compared with the data of the last 18 patients randomized to maintenance with carfilzomib 36 mg/m2 on day 1, 2, 15, 16. DMC will evaluate the incidence of all adverse events including PRES and at DMC discretion, a possible interruption will be considered.

SCHEME

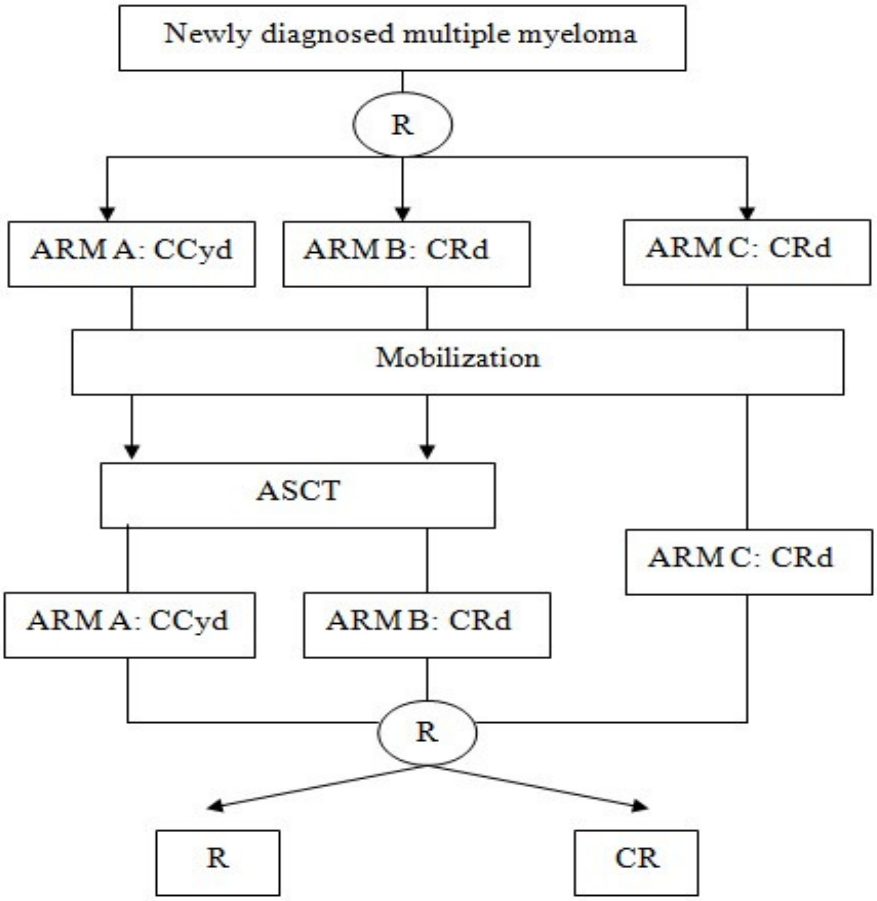

Table of Contents

INTRODUCTION 23

DISEASE SPECIFIC BACKGROUND 23
PROTEASOME BACKGROUND 23
CARFILZOMIB BACKGROUND 23
Carfilzomib Preclinical Antitumor Activity 24
IMMUNOMODULATORY DRUGS (IMIDS): LENALIDOMIDE 24
Experience with Carfilzomib in Combination with LenAlidomide and Dexamethasone *25*
Experience with Carfilzomib in Combination with CYCLOPHOSPHAMIDE and Dexamethasone *26*

CONSOLIDATION AND MAINTENANCE 28

DOSE RATIONALE 29
STUDY RATIONAL 32

OBJECTIVES 34

PRIMARY OBJECTIVE 34
SECONDARY OBJECTIVES 34
Key secondary objectives 34
Other secondary objectives 34

EXPERIMENTAL PLAN 36

STUDY DESIGN 36
NUMBER OF CENTERS 36
NUMBER OF SUBJECTS 37
ESTIMATED STUDY DURATION 37
TREATMENT SCHEME 37

SUBJECT SELECTION 41

INCLUSION CRITERIA 41
EXCLUSION CRITERIA 42

SUBJECT ENROLLMENT AND RANDOMIZATION 44
TREATMENT PROCEDURES 45

CARFILZOMIB: DRUG PREPARATION AND ADMINISTRATION 45
LENALIDOMIDE: ADMINISTRATION 46
DOSE REDUCTIONS/ADJUSTMENTS 46
CARFILZOMIB Dose Reductions for Hematologic Toxicities: 46
CARFILZOMIB Dose Reductions for Non-Hematologic Toxicities 47
LENALIDOMIDE DOSE REDUCTION STEP 50
CYCLOPHOSPHAMIDE DOSE REDUCTION STEP 52
DEXAMETHASONE dose modification..... 52
DEXAMETHASONE DOSE REDUCTION STEP 54
Increased Creatinine or Decreased CrCl 54
SAFETY CONSIDERATIONS 55
INDUCTION TREATMENT 55
CONSOLIDATION TREATMENT 56
INFECTIONS 57
CONDITIONS NOT REQUIRING DOSE REDUCTION 57
Missed Doses..... 57
Changes in BSA 58

Dosing Modifications *58*
CONCOMITANT MEDICATIONS 60
Required Concomitant Medications *61*
Optional and Allowed Concomitant Medications *62*
Excluded Concomitant Medications *63*
Guidelines for Monitoring, Prophylaxis, and Treatment of Tumor Lysis Syndrome (TLS) *63*

STUDY TESTS AND OBSERVATIONS 65

MINIMAL RESIDUAL DISEASE (MRD) MEASUREMENT 67
CIRCULATING PLASMA CELLS 68

STUDY DISCONTINUATION 70
SALVAGE THERAPY .....
71 STATISTICAL ANALYSIS.....
79

STUDY DESIGN 79
PRIMARY Endpoints *79*
KEY SECONDARY Endpoints *79*
OTHER SECONDARY Endpoints *80*
SAMPLE SIZE CONSIDERATIONS 82
PLANNED METHODS OF ANALYSIS 85
MULTIPLICITY 85
SAFETY ANALYSIS 85
STATISTICAL ANALYSIS PLAN 86

INVESTIGATIONAL PRODUCT 87

CARFILZOMIB 87
Description *87*
Formulation *87*
Storage *88*
Accountability *88*
LENALIDOMIDE 88
DESCRIPTION *88*
FORMULATION *89*
STORAGE CONDITIONS *89*
ACCOUNTABILITY *89*
Unused study drug supplies *89*

OTHER STUDY DRUGS 90

DEXAMETHASONE 90
DESCRIPTION *90*
FORMULATION *90*

STORAGE CONDITIONS *90*
ACCOUNTABILITY *90*
CYCLOPHOSPHAMIDE 90
DESCRIPTION *90*
FORMULATION *90*
STORAGE CONDITIONS *90*
ACCOUNTABILITY *91*
CORRELATIVE STUDIES 92
IDENTIFICATION OF MOLECULAR PROFILES IN YOUNG MULTIPLE MYELOMA PATIENTS 92
MOLECULAR MRD ANALYSIS BY DEEP SEQUENCING METHOD 93
PROGNOSTIC ROLE OF 18F-FDG PET/CT IN YOUNG MM PATIENTS RECEIVING UP-FRONT NOVEL AGENTS 95
OUTCOME AFTER RELAPSE 97
ANALYSIS OF INTRA-CLONAL HETEROGENEITY IN MM PATIENTS 97
LOW-LEVEL DETECTION AND QUANTIFICATION OF MONOCLONAL PROTEIN BY MASS SPECTROMETRY AS A MEANS OF ASSESSING FOR RESPONSE AND MINIMAL RESIDUAL DISEASE 98
ANALYSIS OF THE ROLE OF CLONAL HEMATOPOIESIS OF INDETERMINATE POTENTIAL IN MULTIPLE MYELOMA PATIENTS TREATED WITH CARFILZOMIB ... 100
STUDY COMMITTEE 101
REGULATORY OBLIGATIONS 102
INFORMED CONSENT 102
COMPLIANCE WITH LAWS AND REGULATIONS 102
PRE-STUDY DOCUMENTATION REQUIREMENTS 103
Subject Confidentiality *103*
ADMINISTRATIVE AND LEGAL OBLIGATIONS 104
GOOD CLINICAL PRACTICE 104
ETHICAL CONSIDERATIONS 104
PATIENT INFORMATION AND INFORMED CONSENT 104
PATIENT CONFIDENTIALITY 104
INVESTIGATOR COMPLIANCE 105
ON-SITE AUDITS 105
INVESTIGATOR AND SITE RESPONSIBILITY FOR DRUG ACCOUNTABILITY 105
PRODUCT COMPLAINTS 105
CLOSURE OF THE STUDY 106
RECORD RETENTION 106

REFERENCES 108
APPENDIX A: NCI-CTCAE VERSION 5.0 113
APPENDIX B: MULTIPLE MYELOMA DIAGNOSTIC CRITERIA 114
APPENIDX C: STAGING 115
APPENDIX D: CRITERIA FOR RESPONSE 117
APPENDIX E: CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE 120
APPENDIX F:KARNOFSKY PERFORMANCE STATUS SCALE 122
APPENDIX G: SKELETAL SURVEY FILMS 123
APPENDIX H: PREGNANCY TESTING GUIDELINES AND ACCEPTABLE BIRTH CONTROL METHODS 124
APPENDIX I: SAMPLES COLLECTION AND SHIPMENT TIMETABLE FOR ALL PATIENTS ENTERED THE STUDY 126
***REGARDLESS OF THE TREATMENT PHASE OR MONTH FROM THE BEGINNING OF TREATMENTAPPENDIX J: NEUROLOGICAL ASSESSMENT..... 128**
APPENDIX K: PROCEDURES FOR AE AND SAE REPORTING 130
APPENDIX L: EORTC QLQ-C30 QUALITY OF LIFE QUESTIONNAIRE EORTC QLQC30 (VERSION 3) ..... 132 APPENDIX M: EORTC QLQ-MY20 QUALITY OF LIFE QUESTIONNAIRE EORTC QLQ-MY20 136

LIST OF TABLES

Table 1: Thrombocytopenia Carfilzomib ……..49
Table 2: Neutropenia Carfilzomib……..50
Table 3: Non hematological toxicities Carfilzomib……51
Table 4a: Carfilzomib dose reduction step…….……52
Table 4b: Carfilzomib dose reduction step during maintenance treatment (after amendment 5)…….……...……52
Table 5 : Management of patients with lenalidomide-related toxicities…….…….53
Table 6: Lenalidomide dose reduction step…….……...54
Table 7: Cyclophosphamide dose reduction step……...5
Table 8: Management of patients with dexamethasone-related toxicities…….…..55-6
Table 9: Dexamethasone dose reduction step…….……57
Table 10: Dose Adjustment Guideline for Renal Dysfunction…….....58

LIST OF ABBREVIATIONS

Abbreviation	Definition
□C	degrees Centigrade
□F	degrees Fahrenheit
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time (also PTT)
ASaT	All Subjects as Treated
AST	aspartate aminotransferase
bid	Twice daily
BSA	Body surface area
BUN	Blood urea nitrogen
CBC	complete blood count
CCyd	carfilzomib-cyclophosphamide-dexamethasone
Cd	carfilzomib-dexamethasone
CFR	Code of Federal Regulations
CHF CRd	congestive heart failure carfilzomib-lenalidomide-dexamethasone
CR	complete response
CrCl	Creatinine Clearance
CRF	case report form(s)

CRO	clinical research organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	curriculum vitae
dL	Deciliter
DLT	dose-limiting toxicity
DOR	duration of response
DVT	deep venous thrombosis
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FAS	Full Analysis Set
FCBP	Females of childbearing potential
FDA	Food and Drug Administration
FISH	fluorescent in situ hybridization
FLC	free light chain
G-CSF	granulocyte colony stimulating factor
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GM-CSF	granulocyte macrophage colony stimulating factor
h	hour(s)
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug (Application)
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous
kg	kilogram(s)
LDH	lactate dehydrogenase
mg	milligram(s)
min	minute(s)
mIU	Milli International Units
mL	milliliter(s)

MM	multiple myeloma
mm^2	millimeter(s) squared
mm^3	millimeter cubed
MR	minimal response
MTD	maximum tolerated dose
NCI	National Cancer Institute
NHL	non-Hodgkin's lymphoma
ORR	overall response rate
PBMC	peripheral blood mononuclear cells
PD	progressive disease
PFS	progression-free survival
PK	Pharmacokinetics
PO	per os (oral)
PR	partial response
PSA	prostate-specific antigen
PT	prothrombin time
PTT	partial thromboplastin time
QDx5	Daily dosing for five days
QIU	Qualified Investigator Undertaking Form
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
sCR	stringent complete response
SD	stable disease
SEER	Surveillance, Epidemiology, and End Results
SPEP	serum protein electrophoresis
STD_{10}	severely toxic dose in 10% of animals
TLS	Tumor lysis syndrome
TTP	time to tumor progression
ULN	upper limit of the normal range
UPEP	Urine protein electrophoresis
VGPR	very good partial response
WBC	White blood count

INTRODUCTION

DISEASE SPECIFIC BACKGROUND

Multiple myeloma (MM) is the second most common hematologic malignancy, characterized by the malignant proliferation of clonal plasma cells in the bone marrow microenviroment, monoclonal protein in blood or urine, and associated organ dysfunction. The annual incidence rates in Western countries is of 5.6 cases per 100.000 people[1]. The median age at diagnosis is 70 years[2]. Symptomatic disease is characterized by organ damage caused by plasma cell proliferation and is defined by the presence of the CRAB features (C:hypercalcemia, R:renal failure, A:anemia and B:bone disease). Treatment should be started immediately for patients with symptomatic disease, while asymptomatic MM only requires clinical observation[3].

PROTEASOME BACKGROUND

The proteasome is a multicatalytic proteinase complex that is responsible for degradation of a wide variety of protein substrates within normal and transformed cells. Intracellular proteins targeted for degradation by the proteasome are first ubiquitinated via the ubiquitin conjugation system. Ubiquitinated proteins are cleaved within the proteasome by one or more of three separate threonine protease activities: a chymotrypsin-like activity, a trypsin-like activity, and a caspase-like activity.

CARFILZOMIB BACKGROUND

Carfilzomib (PR-171) is a tetrapeptide ketoepoxide-based inhibitor specific for the chymotrypsinlike active site of the 20S proteasome. Carfilzomib is structurally and mechanistically distinct from the dipeptide boronic acid proteasome inhibitor bortezomib (Velcade®). In addition, when measured against a broad panel of proteases including metallo, aspartyl, and serine proteases, carfilzomib demonstrated less reactivity against non-proteasomal proteases when compared to bortezomib[4,5].

CARFILZOMIB PRECLINICAL ANTITUMOR ACTIVITY

Based upon the results of *in vitro* and *in vivo* studies, it is anticipated that the more intense and longer duration of proteasome inhibition that can be achieved with carfilzomib will result in enhanced anti-tumor activity compared to bortezomib. Continuous (72 hr) exposure to carfilzomib is associated with potent cytotoxic and pro-apoptotic activity across a broad panel of tumor-derived cell lines in culture[1,6]. Incubation of hematologic tumor cell lines with carfilzomib leads to rapid inhibition of proteasome activity followed by accumulation of polyubiquitinated proteins and induction of apoptotic cell death. Carfilzomib has also been demonstrated to be cytotoxic in bortezomib-resistant tumor cell lines[4,9].

The anti-tumor efficacy of carfilzomib has been tested in immunocompromised mice implanted with a variety of tumor cell lines. In a human colorectal adenocarcinoma model HT-29, administration of carfilzomib on a twice-weekly Day 1, Day 2 schedule resulted in significant reduction in tumor size and was superior to a twice-weekly Day 1, Day 4 schedule using the same dose of carfilzomib, and a once-weekly dosing schedule using twice the dose level. Moreover, this xenograft model was no sensitive to bortezomib, using its maximum tolerated dose (MTD) at the standard Day 1, Day 4 schedule.

IMMUNOMODULATORY DRUGS (IMIDs): LENALIDOMIDE

Thalidomide was the first IMID discovered and its encouraging activity prompted the search for more potent and less toxic thalidomide derivates. Novel agents with increased anti-inflammatory activities and a more favourable toxicity profile were created by chemical modification of the structural backbone of thalidomide.

Lenalidomide is an oral glutamic acid derivative with direct anti-proliferative and pro-apoptotic effects. The similar activity of thalidomide is increased in vitro of 50-2000 times, in reducing cytokines production by lipopolysaccharide (LPS)-stimulated peripheral blood mononuclear cells (PBMC).

Two randomized Phase 3 studies established that lenalidomide (25 mg/day on Days 1–21 of a 28day cycle) in combination with high-dose dexamethasone (40 mg/day on Days 1–4, 9–12, and 17– 20 of a 28-day cycle) produced a significant improvement in response rate and time to progression (TTP) compared with high-dose dexamethasone alone (11.2 months vs 4.7 months) in relapsed multiple myeloma subjects with up to 3 prior therapies[10, 11].

EXPERIENCE WITH CARFILZOMIB IN COMBINATION WITH LENALIDOMIDE AND DEXAMETHASONE

The combination of a proteasome inhibitor and an IMID agent is attractive, as the expected overlapping toxicities would be manageable.

Preclinical studies show that lenalidomide sensitizes MM to the proteasome inhibitor bortezomib, suggesting that combination therapy may enhance clinical activity.

Carfilzomib appears to have clinically meaningful single-agent activity and is well tolerated in subjects' refractory to bortezomib with lower rates of peripheral neuropathy than have been reported with bortezomib. Taken together, these properties make carfilzomib a promising proteasome inhibitor to combine with lenalidomide in this setting.

Actually, PX-171-006 is an ongoing Phase 1b study in patients with relapsed multiple myeloma in which carfilzomib is administered in combination with lenalidomide (Revlimid®) and dexamethasone. "Low-dose" dexamethasone 40 mg/day is given on Days 1, 8, 15, and 22 in all cases. Carfilzomib is administered IV on Days 1, 2, 7, 8, 15, and 16; lenalidomide is administered PO on Days 1 through 21. Enrollment has closed in this study, and no MTD was reached. The maximum per protocol doses of carfilzomib (27 mg/m^2) with lenalidomide 25 mg and low dose dexamethasone are being used[12]. After 8 patients tolerated these doses well, an additional 44 patients were enrolled in an "expansion" cohort at this level, and this regimen is being taken into Phase III in study PX-171-009.

The overall response rate (ORR) and Clinical Benefit Rate (CBR) for the 29 evaluable patients are 59% and 72%, respectively. Response data are shown in the table below. Initial responses improved

with continued therapy, (up to 18 cycles). Median duration of response (DOR) has not been reached (median follow-up 5.2 months). No dose-limiting toxicities or deaths attributed to study treatment have been observed. Several patients have completed the study (in the lower dose cohorts) after 18 cycles and are continuing in an extension study. Updated efficacy data are presented in the following table:

	CRd: Cohorts 1–5 (CFZ: 15 to 20 mg/m2; LEN: 10 to 25 mg)		
Response	**Relapsed (n=16)**	**Refractory (n=13)**	**Overall (n=29)**
≥ CR/nCR	5 (31)	1 (8)	6 (21)
≥ VGPR	7 (44)	4 (31)	11 (38)
≥ PR	9 (56)	8 (62)	17 (59)
≥ MR	11 (67)	10 (77)	21 (72)

Together, these results suggest that carfilzomib, lenalidomide, and low-dose dexamethasone (CRd) in combination are active and well tolerated and that there are no significant overlapping toxicities (in the dose ranges tested). Importantly, lenalidomide-associated neutropenia and thrombocytopenia do not appear to be exacerbated by concurrent treatment with carfilzomib, even up to 27 mg/m^2, suggesting that carfilzomib will combine well with other anti-cancer agents.

A phase Ib/II study assessed the combination of carfilzomib with lenalidomide and low-dose dexamethasone as a frontline treatment for MM. After 4 cycle transplant-eligible candidates underwent stem cell collection (SCC). The CRd treatment did not have an adverse impact on SCC and responses were rapid, improved with continued treatment, and durable. In the overall population 62% of patients achieved at least a near complete response (nCR) and 98% at least a partial response (PR) after a median of 12 cycles. The progression free survival (PFS) rate was 97% at 12 months and 92% at 24 months. The most common toxicities of any grade were hyperglycemia (72%), thrombocytopenia (68%), anaemia (60%), oedema (47%), hypophosphatemia (45%), and fatigue (38%). Extended treatment in the CRd maintenance phase was also generally well tolerated. The most common toxicities (all grades) during maintenance were lymphopenia (30%), leukopenia (26%), and fatigue (25%)[13].

EXPERIENCE WITH CARFILZOMIB IN COMBINATION WITH CYCLOPHOSPHAMIDE AND DEXAMETHASONE

A phase II study is studying the association of carfilzomib-cyclophosphamide-dexamethasone in thirty-four patients. The trial consists of the administration of carfilzomib (20 mg/m^2 on days 1, 2, and 36 mg/m^2 on days 8, 9, 15, 16, cycle 1; 36 mg/m^2 on days 1, 2, 8, 9, 15, 16, cycles 2–9), cyclophosphamide (300 mg/m^2 on days 1, 8, 15) and dexamethasone (40 mg on days 1, 8, 15, 22) for 9 cycles, followed by carfilzomib maintenance (36 mg/m^2 on days 1, 2, 15, 16) every 28 days until progression or intolerance. The median age of this group of patients was 70 years. All patients achieved at least PR, 74% at least very good partial response (VGPR), 42% at least CR/n-CR, including 10% stringent-CR (sCR). After a median follow-up of 7.5 months no patient has progressed or died. At least one G3-4 non-hematologic event was reported in 4 patients (21%). No patient discontinued treatment and 4 patients (21%) required carfilzomib dose reductions due to adverse events[14].

CONSOLIDATION AND MAINTENANCE

High dose therapy with autologous stem cell transplantation (ASCT) is the standard of care for eligible newly diagnosed MM patients. Consolidation therapy after induction and transplantation is one strategy that improves outcomes in MM patients.

In a study bortezomib, thalidomide, dexamethasone (VTD) was administered as consolidation treatment in 39 multiple myeloma patients. This treatment increased the quality of clinical response in almost half patients. Consolidation therapy after transplantation could provide further cytoreduction and therefore improve PFS and overall survival (OS) in MM patients. The rate of patients tolerating 200 mg/d of thalidomide in the VTD regimen was inferior to that reported when using thalidomide alone or in combination with steroids in the post-transplantation setting, probably due to the overlapping neurotoxicity of bortezomib and thalidomide and potentially to the dosage of bortezomib used in this trial. This suggests an alternative approach with lenalidomide[15].

In a study the combination of thalidomide-dexamethasone was compared with the combination of bortezomib-thalidomide-dexamethasone as induction-consolidation treatment. Consolidation with VTD improves the CR/nCR rate. The probability of upgrading from less than CR before consolidation therapy to CR after consolidation was significantly higher in patients receiving VTD than in those receiving TD[16].

The IMID drug thalidomide has been studied with 7 randomized trials evaluating post-ASCT thalidomide maintenance. Thalidomide maintenance showed consistently associated with longer PFS but variable OS benefit. Despite its demonstrated efficacy, thalidomide maintenance therapy has limited by the neurotoxicity (up to 75% of discontinuation)[17,21].

Lenalidomide maintenance was studied in 2 randomized trial. Both of these trials reported excellent TTP and PFS with a survival benefit. Short-term toxicities in these trials are acceptable[22, 23].

In the study of McCarty et al, lenalidomide was compared with placebo as maintenance postASCT. Lenalidomide maintenance therapy appeared to increase TTP in patients who did not achieve

complete remission at day 100 after transplantation, thus generating outcome similar to those patients with complete remission[24].

In the study of Attal et al, lenalidomide consolidation and maintenance treatment improved the rate of VGPR and CR in patients with newly diagnosed multiple myeloma. Lenalidomide maintenance therapy is feasible and toxic effects are moderate and manageable; this type of therapy significantly improves progression-free and event-free survival but without improvement in OS[25].

Promising results for consolidation and maintenance therapies have been observed, even if these results have to be confirmed in terms of OS.

DOSE RATIONALE

Preliminary data suggest that carfilzomib as a single agent can produce substantial response rates in myeloma subjects across a variety of dosing cohorts. Responses were seen over a wide therapeutic window, from 15 to 27 mg/m^2. Maximum proteasome inhibition was seen at doses 11 mg/m^2 and higher in whole blood samples taken 1 hour after the first dose. The final analysis of the human pharmacokinetic (PK) data is ongoing but appears to be rapid and similar to the results from the animal studies. Carfilzomib is rapidly cleared from plasma with an elimination half-life of < 60 minutes at the 20 mg/m^2 dose. Large, single arm studies of the 27 mg/m^2 dose are ongoing and suggest that this dose is very well tolerated with patients being treated for >10 cycles without cumulative toxicities.

By the end of 2009, 269 patients with relapsed and refractory multiple myeloma have been enrolled in the PX-171-003-A1 study. The goal of dose escalating to 27 mg/m^2 beginning with Cycle 2 is to improve ORR, DOR, and TTP.

In multiple preclinical studies, the tolerability of carfilzomib in rats has been shown to be significantly higher when administered as a 30 min infusion as compared to a rapid IV bolus. Toxicities observed with IV bolus injection of carfilzomib *above the MTD* at a dose of 48 mg/m^2 include evidence of

prerenal azotemia (transient increases in BUN > creatinine) as well as lethargy, piloerection, dyspnea, and gastrointestinal bleeding. Notably, death occurred in ~50% of animals at 48 mg/m^2 when carfilzomib was given as a bolus. Administration of the same dose (48 mg/m^2) as a 30 min continuous infusion was well tolerated, with no changes in BUN and creatinine and substantially reduced signs of lethargy, piloerection, or dyspnea. Moreover, all animals in the infusion treatment groups survived. The only toxicity observed following infusion of carfilzomib for 30 min was gastrointestinal bleeding. The reduced toxicity seen with dosing by infusion may reflect the reduced C_{max} of carfilzomib vs that with bolus dosing. Inhibition of the pharmacological target of carfilzomib (the chymotrypsin-like activity of the proteasome) was equivalent in the bolus and infusion treatment groups.

A phase 1 dose escalation study (PX-171-007) of single agent carfilzomib administered is ongoing and as of 10 July 2009, over 65 patients with solid tumors had started treatment in the initial Phase 2 portion of the study at 36 mg/m^2 (bolus administration over 2-10'). A review of the tolerability of 36 mg/m^2 carfilzomib in these patients indicates that this regimen was very well tolerated with only one dose limiting toxicity (DLT) (fatigue) and an overall adverse event profile similar to that seen with the 27 mg/m^2 carfilzomib experience with bolus dosing (see IB for details). Three patients completed > 12 cycles of therapy at 36 mg/m^2 with no evidence of cumulative toxicity. There were no significant DLTs observed; the majority of discontinuations on the study were due to progressive disease. Because of the long-term tolerability carfilzomib, the Phase 1b portion of this study was reopened, and a separate arm for multiple myeloma was added.

In the PX-171-007 trial, more recently patients have been treated with carfilzomib given as a 30minute infusion in order to potentially minimize C_{max}-related infusion events. The protocol was amended and dose of 20/36 (20 mg/m^2 given on Days 1 and 2 of cycle 1 only; followed by 36 mg/m^2 for all subsequent doses), 20/45, 20/56 mg/m^2 and so forth are being investigated. Doses of 20/56 mg/m^2 are currently being given in two separate cohorts of patients with advanced MM and advanced solid tumors; the lower doses were well tolerated. Preliminary tolerability information at this dose

level (20/56 mg/m^2) indicated that it is reasonably well tolerated, with minimal infusion reactions. In some cases at 20/56 mg/m^2, dexamethasone was increased from 4 mg/dose to 8 mg with the 56 mg/m^2 doses in order to reduce fevers and hypotension. As of March 20, 2010, seven patients have received 20/56 mg/m^2 and are tolerating it. Patients with advanced, refractory MM being treated at 36 mg/m^2 and 45 mg/m^2 have shown very good tolerability (>6 months in some cases) with documented minimal and partial responses in these heavily pretreated patients. These data indicate that carfilzomib 30-minute infusion can be given at very high levels, with >95% inhibition of blood proteasome levels achievable and with (at least) acute tolerability. All protocols using ≥ 36 mg/m^2 carfilzomib are now administering the drug as a 30-minute infusion.

In addition to the above observations, a phase I study of carfilzomib in patients with relapsed and refractory multiple myeloma (RRMM) was reported in abstract form at the 2009 American Society of Hematology meeting which demonstrated that carfilzomib can be safely administered to patients with substantial renal impairment (CrCl < 30, including patients on dialysis) without dose adjustment[12]. These data indicate that carfilzomib does not exacerbate underlying renal dysfunction, and confirm the "pre-renal" etiology of the BUN/creatinine elevations observed with IV bolus carfilzomib.

Data showed that Carfilzomib maintenance at the dose of 36 mg/m^2 was well tolerated in elderly patients and responses obtained during induction treatment improved with maintenance treatment [39]. The phase II dose-expansion and a phase I/II studies showed good tolerability and efficacy in relapsed or progressive MM [12, 13] and as frontline treatment of Carfilzomib-lenalidomide and dexamethasone in prolonged treatment.

Moreover, in the phase 1/2 study CHAMPION-1, once-weekly carfilzomib at the dose of 20/70 mg/m^2 with dexamethasone showed acceptable safety and efficacy with an ORR of 77% and median PFS of 12.6 months among patients with RRMM[49]. The pharmacokinetics and pharmacodynamic results from this study are supportive of a once-weekly, 70 mg/m^2 regimen as an effective dose and

schedule for carfilzomib. The current study showed that this regimen delivered higher weekly AUC exposure compared with that provided by the current approved dose regimen[50].

The same dose and schedule of carfilzomib has been studied in different combinations with novel agents. Carfilzomib weekly at the dose of 70 mg/m^2 combined with daratumumab showed an ORR of 84% and the 12-month PFS rate was 74% proving a safety profile consistent with that of the individual therapies[51]. In a phase Ib study carfilzomib has been evaluated at dose of 56 mg/m^2 and 70 mg/m^2 in combination with lenalidomide and dexamethasone. Two dosages have been showed a promising efficacy and safety and an expansion cohort at the dose of 70 mg/m^2 in NDMM and RRMM is ongoing[52].

STUDY RATIONAL

This is a phase II study to assess the efficacy and feasibility of carfilzomib combined with cyclophosphamide and dexamethasone (CCyd) or lenalidomide and dexamethasone (CRd) as pretransplant induction. As secondary endpoints this study will evaluate the efficacy and feasibility of CCyd or CRd followed by ASCT and subsequent consolidation with CCyd or CRd or 12 cycles of carfilzomib combined with dexamethasone and lenalidomide; best maintenance treatment between lenalidomide and lenalidomide combined with carfilzomib will be also evaluated.

The rational for including carfilzomib in CCyd induction chemotherapy is based on different mechanisms of actions and synergism of carfilzomib with cyclophosphamide and/or dexamethasone. A phase II study demonstrated an encouraging activity in patients with newly diagnosed MM and a good tolerability with a frequency of at least one grade 3-4 non-hematologic adverse events of 21%[14].

A phase Ib/II study assessed the combination of carfilzomib with lenalidomide and low-dose dexamethasone as a frontline treatment for MM followed by transplantation. The CRd treatment did not appear to have an adverse impact on stem cell collection (SCC) and the extension treatment in the CRd maintenance phase was also generally well tolerated.

Although a cure for MM is still not possible in most patients, achievement of a prolonged progression-free interval with minimal toxicity is an important goal in the management of this disease. The role of lenalidomide maintenance is analyzed in different studies in patients who underwent stem-cell transplantation or not. Although preliminary data showed that lenalidomide as consolidation/maintenance therapy after ASCT improved responses and give benefit to patients, further studies are needed to determine the best lenalidomide-combination and duration of treatment. Some studies (MAG90, CIAM) directly evaluating “early” (upfront) high-dose therapy followed by autologous stem cell transplantation (HDT) versus “delayed” HDT (no upfront transplantation, with provision for rescue HDT) independently concluded that there was no OS benefit to upfront HDT. Within a median follow-up time of approximately 10 years, this study confirmed a benefit of HDT in terms of EFS but did not provide evidence for superiority of HDT compared with conventional chemotherapy (CCT) in OS of patients aged 55 to 65 years with symptomatic newly diagnosed MM[26].

In a meta-analysis of different randomized controlled clinical trials, the totality of the randomized data indicates PFS benefit but not OS benefit for HDT with single autologous transplantation performed in the first line treatment of MM patients. Sensitivity and subgroup analyses supported the findings and indicated that PFS benefit with upfront HDT is not restricted to chemoresponsive MM. However, the overall risk of developing treatment-related mortality with HDT was increased significantly. Evaluating alternative therapeutic options upfront may also be reasonable[27].

Future studies should be aimed at identifying patients who may benefit from maintenance and the optimal maintenance treatment that prolong PFS with acceptable toxicity, and not compromise treatment at the time of relapse, and, furthermore, prolong OS.

OBJECTIVES

PRIMARY OBJECTIVE

To determine the efficacy, in term of at least VGPR, of the combination of carfilzomib, dexamethasone with cyclophosphamide or lenalidomide after 4 cycles of induction treatment in newly diagnosed MM patients eligible for ASCT.

To determine the progression-free survival in the 2 maintenance arms.

SECONDARY OBJECTIVES

KEY SECONDARY OBJECTIVES

To determine the sCR in the 3 arms after complete primary therapy (induction, ASCT and consolidation for the transplant arms and after 12 cycles in the long treatment arm).

To determine the progression-free survival in in the 3 induction/consolidation arms

OTHER SECONDARY OBJECTIVES

To determine the MRD negativity rate in the 3 arms after complete primary therapy (induction, ASCT and consolidation for the transplant arms and after 12 cycles in the long treatment arm) i.

To determine the Sustained MRD

To determine the response in the 3 arms after complete primary therapy (induction, ASCT and consolidation for the transplant arms and after 12 cycles in the long treatment arm).

To determine the safety in the 3 induction/consolidation arms (including ASCT) and in the 2 maintenance arms.

To determine the time to next therapy in the 3 induction/consolidation arms and in the 2 maintenance arms.

To determine the time to progression in the 3 induction/consolidation arms and in the 2 maintenance arms.

To determine the progression-free survival 2 in the 3 induction/consolidation arms and in the 2 maintenance arms.

To determine the overall survival in the 3 induction/consolidation arms and in the 2 maintenance arms.

Determine the success of stem cell harvest according to baseline characteristics

Determine whether tumor response and outcome may change in subgroups with different prognosis according to current prognostic factors

To perform explorative comparative analyses between subgroups of patients, defined according to known prognostic factors

EXPERIMENTAL PLAN

STUDY DESIGN

This protocol is a phase II multicenter, international, randomized, open label study designed to jointly assess the safety and the efficacy of different pathway of treatment providing carfilzomib combinations in newly diagnosed MM patients.
Patients will be evaluated at scheduled visits in up to 4 study periods: pre-treatment, treatment, maintenance and long-term follow-up (LTFU).

The pre-treatment period includes screening visits, performed at study entry. After providing written informed consent to participate in the study, patients will be evaluated for study eligibility.
The screening period includes the availability of inclusion criteria described above.

The treatment period for arms A and B includes administration of 4 28-day cycles of induction treatment; then patients will undergo to transplant and finally they will receive 4 28-day cycles of consolidation treatment. The treatment period for arms C includes administration of 12 28-day cycles of induction treatment. The response will be assessed after each 28-day cycle.

The maintenance period includes two types of treatment: lenalidomide alone or lenalidomide combined with carfilzomib. It will be initiated at the end of the 12th induction cycle in patients who did not received ASCT/4th cycle of consolidation treatment in patients who received ASCT and will be stopped at progression or intolerance.

The LTFU period will start after development of confirmed progressive disease (PD), all patients are to be followed for survival during the LTFU period every 3 months via telephone or office visit.

NUMBER OF CENTERS

Approximately 50 centers will participate into the protocol.

NUMBER OF SUBJECTS

Up to 477 patients will be enrolled from different centers.

ESTIMATED STUDY DURATION

The duration of the induction, transplantation and consolidation treatment is approximately 12-15 months. This length of time is required to complete 4 cycles of induction, transplant and 4 cycles of consolidation after transplantation in arm A and B or 12 cycles of induction in arm C. The maintenance period in all arms will start at the end of the 12th induction cycle in patients who did not receive ASCT/4th cycle of consolidation in patient who received ASCT and will be stopped at progression or intolerance. The median expected duration of the maintenance treatment is approximately 2 years. The duration of the study is estimated as 9 years from the enrolment of the last patient.

TREATMENT SCHEME

Patients will start the induction treatment, as soon as the screening visits of the pretreatment period have been terminated.

Treatment schedule for induction/consolidation:
All patients will be randomized to receive:
ARM A: CCyd

1. Carfilzomib = 20 mg/m^2 IV on days 1-2 cycle 1 only, followed by 36 mg/m^2 IV once daily on days 8-9, 15-16 cycle 1 then for all subsequent doses 36 mg/m^2 IV once daily on days 1-2, 8-9, 15-16.
2. Cyclophosphamide = 300 mg/m^2 orally on days 1, 8, 15.
3. Dexamethasone = 20 mg orally or IV on days 1, 2, 8, 9, 15, 16, 22, 23. Repeat for 4 28-day cycles

Stem cell mobilization and collection after 4 cycles of Ccyd:
Cyclophosphamide will start 4-6 weeks after day 21 of cycle 4.

Agent	Dose/day	Route	Days
Cyclophosphamide	2000 mg/m²	i.v.	1
G-CSF (filgastrim)	10 µg/kg (divided in 2 gifts daily, according to local rules)	s.c.	5

Stem cell collection will be performed as soon as CD34+ cells are present in peripheral blood, which is usually between 9-14 days after first day of Cyclophosphamide. Stem cells will be harvested at a minimum of 4 x 10^6 CD34+ cells/kg and cryopreserved. In case insufficient stem cells are collected the procedure may be repeated or alternatively bone marrow stem cell collection may be performed or Plerixafor may be used.

Intensification
All patients randomized to intensification with High Dose Melphalan will start intensification with HDM between 4 and 6 weeks after chemotherapy.
Patients will be treated with High Dose Melphalan followed by autologous stem cell reinfusion according to the schedule below.

Agent	Dose/day	Route
Melphalan	200 mg/ m² day -2	i.v. rapid infusion
Stem cell infusion	Minimum of 2 x 10^{6}CD34+cells/kg day 0	

Consolidation (90-120 days from Melphalan and ASCT):
1. Carfilzomib = 36 mg/m^2 IV once daily on days 1-2, 8-9, 15-16.
2. Cyclophosphamide = 300 mg/m^2 orally on days 1, 8, 15.
3. Dexamethasone = 20 mg orally or IV on days 1, 2, 8, 9, 15, 16, 22, 23. Repeat for 4 28-day cycles

ARM B: CRd

1. Carfilzomib = 20 mg/m^2 IV on days 1-2 cycle 1 only, followed by 36 mg/m^2 IV once daily on days 8-9, 15-16 cycle 1 then for all subsequent doses 36 mg/m^2 IV once daily on days 1-2, 8-9, 15-16.
2. Lenalidomide = 25 mg PO daily on days 1-21.
3. Dexamethasone = 20 mg orally or IV on days 1, 2, 8, 9, 15, 16, 22, 23. Repeat for 4 28-day cycles

Stem cell mobilization and collection after 4 cycles of CRd:
Cyclophosphamide will start 4-6 weeks after day 21 of cycle 4.

Agent	Dose/day	Route	Days
Cyclophosphamide	2000 mg/m²	i.v.	1
G-CSF (filgastrim)	10 µg/kg (divided in 2 gifts daily, according to local rules)	s.c.	5

Stem cell collection will be performed as soon as CD34+ cells are present in peripheral blood, which is usually between 9-14 days after first day of Cyclophosphamide. Stem cells will be harvested at a minimum of 4 x 10^6 CD34+ cells/kg and cryopreserved. In case insufficient stem cells are collected the procedure may be repeated or alternatively bone marrow stem cell collection may be performed or Plerixafor may be used.

Intensification
All patients randomized to intensification with High Dose Melphalan will start intensification with HDM between 4 and 6 weeks after chemotherapy.
Patients will be treated with High Dose Melphalan followed by autologous stem cell reinfusion according to the schedule below.

Agent	Dose/day	Route
Melphalan	200 mg/ m² day -2	i.v. rapid infusion
Stem cell infusion	Minimum of 2 x 10^{6}CD34+cells/kg day 0	

Consolidation (90-120 days from Melphalan and ASCT):
1. Carfilzomib = 36 mg/m^2 IV once daily on days 1-2, 8-9, 15-16.
2. Lenalidomide= 25 mg PO daily on days 1-21.

3. Dexamethasone = 20 mg orally or IV on days 1, 2, 8, 9, 15, 16, 22, 23. Repeat for 4 28-day cycles

Patients who will be enrolled with CrCl < 50 mL/min should start with a reduced dose of lenalidomide according to the Dose Adjustment Guideline for Renal Dysfunction

ARM C: CRd long treatment

1. Carfilzomib = 20 mg/m^2 IV on days 1-2 cycle 1 only, followed by 36 mg/m^2 IV once daily on days 8-9, 15-16 cycle 1 then for all subsequent doses 36 mg/m^2 IV once daily on days 1-2, 8-9, 15-16.
2. Lenalidomide= 25 mg PO daily on days 1-21.
3. Dexamethasone = 20 mg orally or IV on days 1, 2, 8, 9, 15, 16, 22, 23. Repeat for 4 28-days cycles

All patients will be given Cyclophosphamide at the dose of 2 g/m^2, followed by G-CSF for stem cell collection after 4 cycles of CRd
Cyclophosphamide will start 4-6 weeks after day 21 of cycle 4.

Agent	Dose/day	Route	Days
Cyclophosphamide	2000 mg/m²	i.v.	1
G-CSF (filgastrim)	10 µg/kg (divided in 2 gifts daily, according to local rules)	s.c.	5

Stem cell collection will be performed as soon as CD34+ cells are present in peripheral blood, which is usually between 9-14 days after first day of Cyclophosphamide. Stem cells will be harvested at a minimum of 4 x 10^6 CD34+ cells/kg and cryopreserved. In case insufficient stem cells are collected the procedure may be repeated or alternatively bone marrow stem cell collection may be performed or Plerixafor may be used.
After at least 30-60 days from cyclophosphamide:

1. Carfilzomib =36 mg/m^2 IV once daily on days 1-2, 8-9, 15-16.
2. Lenalidomide= 25 mg PO daily on days 1-21.
3. Dexamethasone = 20 mg orally or IV on days 1, 2, 8, 9, 15, 16, 22, 23. Repeat for 8 28-days cycles

Patients who will be enrolled with CrCl < 50 mL/min should start with a reduced dose of lenalidomide according to the Dose Adjustment Guideline for Renal Dysfunction

Treatment schedule for maintenance:

After the end of consolidation all patients will be randomized to receive:

1. Lenalidomide 10 mg daily on days 1-21.
2. Lenalidomide 10 mg daily on days 1-21 *AND* Carfilzomib* 70 mg/m^2 IV once daily on days 1, 15 for patients that have started maintenance within 6 months from amendment 5.0 approval.
   OR

2. Lenalidomide 10 mg PO daily on days 1-21 AND Carfilzomib* 36 mg/m2 IV once daily on days 1, 2, 15, 16 every 28 days for patients that have started maintenance more than 6 months before the amendment 5.0 approval.

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Patients will receive carfilzomib maintenance for a maximum of 2 years and lenalidomide maintenance until any sign of progression or intolerance. Patients that decreased carfilzomib and/or lenalidomide dose in the induction/consolidation treatment will continue with a reduced drug dose during the maintenance period.

Maintenance can only start if ANC $\geq 0.75 \times 10^9$/l and platelets $> 50 \times 10^9$/l. Moreover, all extrahematological toxicities should be resolved to grade ≤ 1.

*Patients will receive 8 mg of dexamethasone as pre-medication before carfilzomib administration during the first cycle of maintenance and for subsequent cycles according to physician opinion.

SUBJECT SELECTION

INCLUSION CRITERIA

Subjects must meet all of the following inclusion criteria to be eligible to enroll in this study.

Disease-related:

1. Patient is a newly diagnosed symptomatic MM patient (see Appendix B)
2. Patient is $\leq$ 65 years old* and is eligible for autologous stem cell transplantation
3. Patient has measurable disease, defined as follows: any quantifiable serum monoclonal protein value (generally, but not necessarily, $\geq$ 0.5 g/dL of M-protein) and/or urine lightchain excretion > 200 mg/24 hours. For patients with oligo or non-secretory MM, it is required that they have measurable plasmacytoma > 2 cm as determined by clinical examination or applicable radiographs (i.e. MRI, CT-Scan) or an abnormal free light chain ratio (n.v.: 0.26-1.65) and involved FLC level $\geq$10 mg/dl. We anticipate that less than 10% of patients admitted to this study will be oligo- or non-secretory MM with free light chains only in order to maximize interpretation of benefit results.

* until the day before the 66th birthday

Demographic:

4. Age $\geq$ 18 years

5. Life expectancy ≥ 3 months
6. Karnofsky performance status ≥ 60% (see Appendix F)

Laboratory

7. Adequate hepatic function, with serum (alanine aminotransferase) ALT ≤ 3 times the upper limit of normal (ULN), AST (aspartate transaminase) ≤ 3 x the ULN
8. Serum direct bilirubin ≤ 2 mg/dL (34 µmol/L) within 14 days prior to randomization
9. Absolute neutrophil count (ANC) ≥ 1.0×10^9/L within 14 days prior to randomization
10. Platelet count ≥ 75×10^9/L (≥ 50×10^9/L if myeloma involvement in the bone marrow is > 50%) within 14 days prior to randomization
11. Creatinine clearance (CrCl) ≥ 30 mL/minute within 7 days prior to randomization, either measured or calculated using a standard formula (eg, Cockcroft and Gault)
12. Corrected serum calcium ≤ 14 mg/dL (3.5 mmol/L)
13. LVEF ≥ 40%. 2-D transthoracic echocardiogram (ECHO) is the preferred method of evaluation. Multigated Acquisition Scan (MUGA) is acceptable if ECHO is not available.

Ethical/Other

14. Written informed consent in accordance with federal, local, and institutional guidelines.
15. Females of childbearing potential (FCBP) must agree to ongoing pregnancy testing and to practice contraception.
16. Male subjects must agree to practice contraception.

EXCLUSION CRITERIA

Disease-related

1. Previous treatment with anti-myeloma therapy (does not include radiotherapy, bisphosphonates, or a single short course of steroid ≤ to the equivalent of dexamethasone 40 mg/day for 4 days).
2. Patients with non-secretory MM unless serum free light chains are present and the ratio is abnormal or a plasmacytoma with minimum largest diameters of > 2 cm. *Concurrent Conditions*
3. Patient ineligible for autologous transplantation
4. Pregnant or lactating females
5. Acute active infection requiring treatment (systemic antibiotics, antivirals, or antifungals) within 14 days prior to randomization

6. Known human immunodeficiency virus infection (HIV)
7. Active hepatitis A, B or C infection
8. Unstable angina or myocardial infarction within 4 months prior to randomization, NYHA Class III or IV heart failure, uncontrolled angina, history of severe coronary artery disease, severe uncontrolled ventricular arrhythmias, sick sinus syndrome, or electrocardiographic evidence of acute ischemia or Grade 3 conduction system abnormalities unless subject has a pacemaker
9. Non-hematologic malignancy within the past 3 years with the exception of a) adequately treated basal cell carcinoma, squamous cell skin cancer, or thyroid cancer; b) carcinoma in situ of the cervix or breast; c) prostate cancer of Gleason Grade 6 or less with stable prostate-specific antigen levels; or d) cancer considered cured by surgical resection or unlikely to impact survival during the duration of the study, such as localized transitional cell carcinoma of the bladder or benign tumors of the adrenal or pancreas
10. Significant neuropathy (Grades 3–4, or Grade 2 with pain) within 14 days prior to randomization as defined by National Cancer Institute Common Toxicity Criteria (NCI CTC) 4.0 (Appendix A)
11. Known history of allergy to Captisol® (a cyclodextrin derivative used to solubilize carfilzomib)
12. Contraindication to any of the required concomitant drugs or supportive treatments, including hypersensitivity to all anticoagulation and antiplatelet options, antiviral drugs, or intolerance to hydration due to preexisting pulmonary or cardiac impairment
13. Any other clinically significant medical disease or condition that, in the Investigator's opinion, may interfere with protocol adherence or a subject's ability to give informed consent

SUBJECT ENROLLMENT AND RANDOMIZATION

The first step is the screening period where patients are evaluated with different tests. Then patients begin the therapy and after 4 cycles of consolidation (arms A-B) or 12 cycles of induction (arm C), will receive maintenance. All the tests needed to evaluate patients are reported in *Study test and observation* Section.

Up to 477 patients will be enrolled from different centres and all patients have to sign the informed consent prior to any study related procedures.

The subject will be randomized to receive combination of Carfilzomib-dexamethasone with cyclophosphamide or lenalidomide as induction and consolidation treatment or 12 cycles of Carfilzomib-dexamethasone-lenalidomide. Randomization will be stratified based on:

- International Staging System (ISS): I vs II/III
- Age: ≥ 60 years old vs < 60 years old

The first randomization will be provided at the enrolment of the subject, the second randomization will be provided before the beginning of the maintenance.

All patients eligible for randomization can be randomized by web and the following information will be required:

- Protocol number
- Patient's study number
- Eligibility criteria

The result of randomization will be given immediately.

A unique subject study number will be assigned at the time of the first randomization that will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

TREATMENT PROCEDURES

CARFILZOMIB: DRUG PREPARATION AND ADMINISTRATION

Carfilzomib for Injection is supplied as a lyophilized parenteral product in single-use vials. The lyophilized product is reconstituted with Water for Injection to a final carfilzomib concentration of 2.0 mg/mL prior to administration. The dose will be calculated using the subject's actual body surface area (BSA) at baseline. Subjects with a BSA > 2.2 m^2 will receive a dose based upon a 2.2 m^2 BSA.

IV hydration will be given immediately prior to carfilzomib during Cycle 1. This will consist of 250 mL normal saline or other appropriate IV fluid. If lactate dehydrogenase (LDH) or uric acid is elevated (and/or in subjects considered still at risk for TLS) at Cycle 2 Day 1, then the recommended IV hydration should be given additionally before each dose in Cycle 2. The goal of the hydration program is to maintain robust urine output (eg, ≥ 2 L/day). Subjects should be monitored periodically during this period for evidence of fluid overload (see Section Study test and observation).

If the subject has a dedicated line for carfilzomib administration, the line must be flushed with a minimum of 20 mL of normal saline prior to and after drug administration.

Carfilzomib will be given as an IV infusion over approximately 30 minutes. The dose will be administered at a facility capable of managing hypersensitivity reactions. Subjects will remain at the clinic under observation for at least 1 hour following each dose of carfilzomib in Cycle 1 and following the dose on Cycle 2 Day 1. During these observation times, **post dose IV hydration** (250 mL of normal saline or other appropriate IV fluid formulation) will be given during cycle 1, as needed, and at the investigator's discretion in Cycle 2 and higher. Subjects should be monitored periodically during this period for evidence of fluid overload.

After amendment 5, patients will receive 8 mg of dexamethasone as pre-medication before carfilzomib administration during the first cycle of maintenance and for subsequent cycles according to physician opinion.

LENALIDOMIDE: ADMINISTRATION

Lenalidomide will be given as a single, daily oral dose for a total of 21 days out of a 28 day cycle. Lenalidomide is administered with water and may be taken on a full or empty stomach.

Subjects should not break, chew or open capsules. Lenalidomide may be self-administered at home by the subject and should be taken at approximately the same time each day. Missed doses of lenalidomide will not be made up. Patients who take more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

DOSE REDUCTIONS/ADJUSTMENTS

CARFILZOMIB DOSE REDUCTIONS FOR HEMATOLOGIC TOXICITIES:

Study drug will be withheld from subjects with:

- Grade 4 lymphopenia persisting for > 14 days, if lymphopenia was not pre-existing
- Grade 4 thrombocytopenia with active bleeding

Grade 4 anemia and thrombocytopenia (without active bleeding) do not require the carfilzomib dose to be withheld. However, subjects should receive supportive measures in accordance with institutional guidelines. *For patients with Grade 4 thrombocytopenia without evidence of bleeding, study drug dose modification may occur at the discretion of the investigator.*

The following table outlines the dose reduction guidelines for carfilzomib for thrombocyctopenia and neutropenia:

Table 1-Thrombocytopenia Carfilzomib

When Platelets:	Recommended Action Carfilzomib
Fall to < 30×10^9/L	Interrupt carfilzomib, follow CBC weekly
Return to ≥ 30×10^9/L	Resume at full dose
Subsequently drop to < 30×10^9/L	Interrupt carfilzomib, follow CBC weekly
Return to ≥ 30×10^9/L	Resume at 1 dose decrement

Table 2-Neutropenia Carfilzomib

Recommended Action	
When ANC	**Carfilzomib**
Falls to < 0.5×10^9/L	Interrupt carfilzomib add G-CSF if G 3 with fever or G 4, follow CBC weekly
Returns to > 1.0×10^9/L (if neutropenia was the only toxicity noted)	Resume at full dose
Returns to > 1.0×10^9/L (if other toxicity noted)	Resume at 1 dose decrement
Subsequently drops to < 0.5×10^9/L	Interrupt carfilzomib
Returns to > 1.0×10^9/L	Resume at full dose

CARFILZOMIB DOSE REDUCTIONS FOR NON-HEMATOLOGIC TOXICITIES

Study drug should be held /reduced according to table below (table 3).

After resolution of the event to ≤ Grade 1 or return to baseline, if the adverse event was not treatment-related, subsequent treatment with carfilzomib may resume at full dose. If the event was treatment-related, subsequent treatment with carfilzomib will resume at one level dose reduction according to Table 3, i.e., to 20 mg/m^2 for subjects previously receiving 27 mg/m^2 and to 27 mg/m^2 for subjects previously receiving 36 mg/m^2. If toxicity continues or recurs, a 2nd carfilzomib dose reduction may be permitted at the discretion of the investigator. No more than two dose reductions will be permitted in an individual subject on study. If toxicity continues or recurs after two dose reductions, the subject should stop carfilzomib administration.

If the subject tolerates the reduced dose for two cycles, subject may be dose escalated to the dose prior to reduction

If there is no resolution of toxicity carfilzomib-related after 4 weeks of withholding treatment, the subject should stop treatment.

Dose adjustment guidelines for non-hematologic toxicities are summarized as follows:

Table 3- Non hematological toxicities Carfilzomib

Symptom	**Recommended Action Carfilzomib**
Allergic reaction/hypersensitivity G 2 – 3 G 4	 Hold until ≤ Grade 1, reinstitute at full dose. Discontinue
Tumor lysis syndrome (≥ 3 of following: ≥ 50% increase in creatinine, uric acid, or phosphate; ≥ 30% increase in potassium; ≥ 20% decrease in calcium; or ≥ 2-fold increase in LDH)	Hold carfilzomib until all abnormalities in serum chemistries have resolved. Reinstitute at full doses.
Infection G ≥ 3	Hold carfilzomib until systemic treatment for infection complete. If no neutropenia, restart at full dose. If neutropenic, follow neutropenic instructions.
Herpes zoster or simplex of any grade	Hold carfilzomib until lesions are dry. Reinstitute at full dose
G 2 treatment emergent neuropathy with pain or G 3 neuropathy Grade 4 neuropathy	Continue to dose. If neuropathy persists for more than two weeks hold carfilzomib until resolved to ≤ Gr 2 without pain. Then restart at 1 dose decrement Discontinue

Renal Dysfunction	
CrCl ≤ 30 mL/min	Hold until CrCl > 30 mL/minute; restart at 1 dose decrement

Congestive heart failure	Any subject with symptoms of congestive heart failure, whether or not drug related, must have the dose held until resolution or return to baseline, after which treatment may continue at a reduced dose, or the subject may be withdrawn from the study. If no resolution after 4 weeks, the subject will be withdrawn from the study.
Other non-hematologic toxicity assessed as carfilzomib-related G ≥ 3	Hold dose until toxicity resolves to ≤ Grade 1 or baseline. Restart at 1 dose decrement.

Table 4a: Carfilzomib dose reduction step during induction treatment:

STARTING DOSE	Carfilzomib 36 mg/m²
Dose Level -1	Carfilzomib 27 mg/m²
Dose Level -2	Carfilzomib 20 mg/m²

Table 4b: Carfilzomib dose reduction step during maintenance treatment (after amendment 5):

STARTING DOSE	Carfilzomib 70 mg/m²
Dose Level -1	Carfilzomib 56 mg/m²
Dose Level -2	Carfilzomib 45 mg/m²
Dose Level -3	Carfilzomib 36 mg/m²
Dose Level -4	Carfilzomib 27 mg/m²

Dose Level -5	Carfilzomib 20 mg/m²

Patients who required dose reduction during induction/consolidation will start maintenance at the dose tolerated during induction/consolidation:

-Patients who tolerated 36 mg/m^2 twice a week will receive 70 mg/m^2 day 1 and 15 during maintenance;

-Patients who reduced to 27 mg/m^2 twice a week during induction/consolidation will receive 56 mg/m^2 day 1 and 15 during maintenance;

-Patients who reduced to 20 mg/m^2 twice a week during induction/consolidation will receive 36 mg/m^2 day 1 and 15 during maintenance.

LENALIDOMIDE DOSE REDUCTION STEP

Dose adjustments are allowed based on clinical and laboratory findings.

Patients who will be enrolled in this trial with CrCl < 50 mL/min should start with a reduced dose of lenalidomide according to the Dose Adjustment Guideline for Renal Dysfunction.

Table 5 : Management of patients with lenalidomide-related toxicities

Adverse events	**Action on study drug**	**Further consideration**
Grade 3-4 toxicities judged to be related to lenalidomide	Hold lenalidomide treatment and restart at the next lower dose level when toxicity has been resolved to Grade ≤ 1	

Grade ≥ 2 thrombosis/embolism	Hold lenalidomide and start anticoagulation therapy as per standard guidelines; restart at investigator's discretion after adequate anticoagulation; maintain dose level	
Grade 3 skin rash	Hold lenalidomide, add antihistaminic therapy and decrease by one dose level when dosing restarted at next cycle (rash must resolve to Grade ≤ 1)	
Grade 4 exfoliative or bullous rash or if Stevens-Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN) suspected	Permanently discontinue lenalidomide	
Any grade angioedema	Permanently discontinue lenalidomide	
Tumor lysis yndrome	Reduce dose	Monitor closely and take appropriate medical precautions

In case ANC < 1 x 10^9/L, G-CSF must be administered. If neutropenia is overcomed by G-CSF, continue G-CSF as needed to maintain ANC > 1 x 10^9/L. Patients can receive lenalidomide only if ANC > 1 x 10^9/L. Moreover, if platelets fall to < 50 × 10^9/L, lenalidomide administration should be delayed until platelets return to > 50 × 10^9/L. If platelets fall again to < 50 × 10^9/L, lenalidomide should be restarted at the next lower dose level when toxicity will be recovered to Grade ≤ 2

Table 6: Lenalidomide dose reduction step:

STARTING DOSE	Lenalidomide 25 mg once daily

Dose Level – 1	Lenalidomide 15 mg once daily
Dose Level –2	Lenalidomide 10 mg once daily
Dose Level – 3	Lenalidomide 7.5 mg once daily
Dose Level – 4	Lenalidomide 5 mg once daily
Dose Level – 5	Lenalidomide 5 mg every other day

CYCLOPHOSPHAMIDE DOSE REDUCTION STEP

For Grade 4 hematological and Grade 3-4 non-hematological "drug-related" toxicities specifically related to cyclophosphamide, the drug should be held for up to 4 weeks until the toxicity resolves to Grade 2 and dose decreased as outlined in table:

Table 7: Cyclophosphamide dose reduction step

STARTING DOSE	**Cyclophosphamide 300 mg/m² days 1,8,15**
Dose Level-1	Cyclophosphamide 200 mg/m² days 1,8,15
Dose Level-2	Cyclophosphamide 100 mg/m² days 1,8,15

DEXAMETHASONE DOSE MODIFICATION

To minimize patient discomfort, dietary salt restriction, antacids, histamine type 2 (H2)- blockers, potassium supplements and other comparable medications (i.e. proton pump inhibitors) may be used as needed.

Precautions should be taken when patients are withdrawing from high dose corticosteroid therapy. Drug-induced secondary adrenocortical insufficiency may result from too rapid withdrawal of corticosteroids. Table 8 provides dose modification guidelines for the management of common dexamethasone-related toxicities. For steroid-related toxicities that occur but are not specifically listed in the table, the general guideline is that dexamethasone should be held for up to 2 weeks until the toxicity resolves to Grade ≤ 2 and the dose decreased 50% for Grade 3 or greater nonhematological toxicity. The patient should be given all support therapy necessary in these instances.

Table 8: Management of patients with dexamethasone-related toxicities:

CATEGORY	TOXICITY	GRADE	DOSE CHANGE
Gastrointestinal Disorders	Dyspepsia, gastric or duodenal ulcer, or gastritis	Grade 1-2 (requiring Medical Management)	Treat with H_2 blockers, sucralfate, omeprazole, or other comparable medications (i.e. proton pump inhibitors). If symptoms persist despite treatment, permanently decrease the dexamethasone dose by 50%.
		Grade ≥ 3 (requiring hospitalisation or surgery)	Interrupt dexamethasone for up to 2 weeks until symptoms are adequately controlled. Thereafter, resume dexamethasone at a dose reduced by 50% with concomitant H_2 blockers, sucralfate, omeprazole, or other comparable medications (i.e. proton pump inhibitors). If symptoms persist despite above measures, permanently discontinue dexamethasone
	Acute pancreatitis	Grade ≥ 3	Permanently discontinue dexamethasone
Vascular disorders	Edema	Grade ≥ 3 (limiting function and unresponsive to therapy or anasarca)	Administer diuretics, as needed, and decrease dexamethasone dose by 25%. If edema persists despite above measures, decrease dexamethasone dose to 50% of initial dose. If symptoms persist despite a 50% dose reduction, then permanently discontinue dexamethasone.

Neurology	Confusion or mood alteration	Grade ≥ 2 (interfering with function +/- interfering with ADLs)	Interrupt dexamethasone for up to 2 weeks until symptoms resolve. If symptoms resolve, restart dexamethasone at a dose reduced by 50%. If symptoms persist above measures, then permanently discontinue dexamethasone.
Musculoskeletal, connective tissue, and bone disorders	Muscle weakness	Grade ≥ 2 (symptomatic and interfering with function +/- interfering with ADLs)	Decrease dexamethasone dose by 25%. If symptoms persist despite above measures, decrease dexamethasone dose to 50% of initial dose. If symptoms persist despite a 50% dose reduction, then permanently discontinue dexamethasone.
Metabolism and nutrition disorders	Hyperglycemia	Grade ≥ 3	Administer insulin or oral hypoglycemics as needed. If hyperglycemia is not controlled despite treatment, decrease the dexamethasone dose in 25% increments until satisfactory glucose levels are achieved.

DEXAMETHASONE DOSE REDUCTION STEP

Table 9: Dexamethasone dose reduction step:

STARTING DOSE	Dexamethasone 20 mg daily (d 1-2, 8-9, 15-16, 22-23)
Dose level -1	Dexamethasone 30 mg daily (d 1, 8, 15 and 22) or 15 mg daily (d 1-2, 8-9, 15-16, 22-23)
Dose level -2	Dexamethasone 20 mg daily (d 1, 8, 15 and 22) or 10 mg daily (d 1-2, 8-9, 15-16, 22-23)

Increased Creatinine or Decreased CrCl

A phase I study of Carfilzomib in patients with relapsed and refractory multiple myeloma and varying degrees of renal insufficiency has been initiated and preliminary results were reported at the 2009 American Society of Hematology meeting. At the time of this preliminary analysis, 22 patients had

been treated on the trial. Ten patients had creatinine clearance ≥ 80 mL/min; 9 had creatinine clearance 50-79 mL/min; 9 patients had creatinine clearance 30-49 mL/min; 9 patients had creatinine clearance < 30 mL/min and 2 patients were on chronic dialysis. Adverse events in these patient groups were similar regardless of degree of renal dysfunction and included anemia, fatigue, and diarrhea as the most common adverse events observed.

Table 10: Dose Adjustment Guideline for Renal Dysfunction

Renal Dysfunction	Recommended Action for Carfilzomib	Recommended Action for Lenalidomide
CrCl 30-50 mL/min	Full dose	10 mg once daily. After 2 cycles the dose can be increased to 15 mg once daily, if patients have positive effects and tolerate the drug. Further dose modification will be based on individual subject treatment tolerance
CrCl < 30 mL/min (without dialysis)	Full dose	15 mg every other day. If patients tolerate the drug, the dose can be increased to 10 mg once daily. Further dose modification will be based on individual subject treatment tolerance
CrCl < 30 mL/min (with dialysis)	Hold carfilzomib until CrCl ≥ 15 mL/min; restart at one level dose reduction	5 mg once daily. In the dialysis day, the administration of the drug must be done after dialysis. Further dose modification will be based on individual subject treatment tolerance

Carfilzomib should be always held in case of CrCl< 15 mL/min

SAFETY CONSIDERATIONS

in case of toxicity that could be related to either carfilzomib/lenalidomide/cyclophosphamide or dexametasone, the patient can start with one of the drug only (after resolution of the previous toxicity and with dose reductions if needed), and then add the second and third one sequentially, to better understand the correlation, at investigator discrection.

INDUCTION TREATMENT

Subjects with the following laboratory values can start each induction cycle:

- Platelet count ≥75 x 10^9/L
- Absolute neutrophil count (ANC) ≥ 1 x 10^9/L without the use of growth factors
- Extra-hematologic toxicities ≤1

CONSOLIDATION TREATMENT

Subjects with the following laboratory values can be admitted to the consolidation treatment:

- Platelet count ≥75 x 10^9/L
- Absolute neutrophil count (ANC) ≥ 1 x 10^9/L without the use of growth factors
- Extra-hematologic toxicities grade ≤ 1

The same values are required to start each cycle.

In case patients do not satisfy the requirement, the start of consolidation treatment should be postponed until the achievement of laboratory values. The maximum delay admitted for the start of consolidation treatment is 4 weeks, otherwise patients will not receive consolidation, and will start the maintenance treatment.

If a subject requires interruption of treatment for more than 4 consecutive weeks due to unresolved toxicity, during induction or consolidation, the subject should be permanently discontinued from study treatment.

MAINTENANCE TREATMENT

Randomization for maintenance can be performed only if ANC ≥ 0.75 x 10^9/l and platelets > 50 x 10^9/l. If patients have ANC < 1 x 10^9/l , they will receive G-CSF until ANC ≥ 1 x 10^9/l. Patients can start maintenance treatment only when ANC ≥ 1 x 10^9/l

Moreover all extra-hematological toxicities should be resolved to grade ≤ 1.

Patients that decreased carfilzomib and/or lenalidomide dose in the induction/consolidation treatment will continue with a reduced drug dose during the maintenance period.

If a subject requires interruption of treatment for more than 4 consecutive weeks due to unresolved toxicity, the subject should be permanently discontinued from study treatment.

POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME (PRES) MONITORING

Posterior reversible encephalopathy syndrome (PRES) is a rare condition that causes swelling of the brain. A person with PRES may experience headaches, confusion, loss or decreased level of consciousness, blurred vision or blindness, seizures, and possibly death. If caught early and treated, PRES may be reversed. Considering the correlation of this syndrome with study drugs, PRES incidence will be evaluated by the DMC at the first interim analysis and it will be monitored during the study to evaluate the effect of study drugs in MM patients, also at long term treatment during maintenance. Each event of PRES will be notified to the Competent Authority.

INFECTIONS

Subjects with active or suspected grade 3-4 infections should have treatment withheld until infection has resolved and anti-infective treatment has been completed. After the infection has resolved and anti-infective treatment has been completed, treatment may continue at the original dose. If there is no resolution of toxicity after 4 weeks, the subject will be withdrawn from the study.

CONDITIONS NOT REQUIRING DOSE REDUCTION

The following conditions are exceptions to the above guidelines. Study drugs do not need to be held in the following cases:

- Grade 3 nausea, vomiting or diarrhea (unless persisting > 3 days with adequate treatment of antiemetics or anti-diarrheals)
- Grade 3 fatigue (unless persisting for >14 days)
- Alopecia
- ≥ Grade 3 hyperglycemia attributed to dexamethasone

MISSED DOSES

For dosing cycles where Day 1 is delayed, the entire cycle should shift to accommodate. Carfilzomib will be administered within ± 2 days of the scheduled study day of each carfilzomib administration. Every effort should be made to maintain the dosing scheduled and if this is not possible due to extenuating circumstances then priority should be made to maintain consecutive dosing days. If a mid-cycle dose is missed, that dosing day should be skipped and not made up.

Missed doses will not be replaced during a cycle.

CHANGES IN BSA

Dose adjustments do not need to be made for weight gains/losses of ≤ 20%. Subjects with a BSA of greater than 2.2 m^2 will receive a capped dose of 44 mg of carfilzomib (at the 20 mg/m^2 dose level) or 660 mg of cyclophosphamide.

DOSING MODIFICATIONS

Dose modifications and delays different from those stated in the protocol, for management of toxicities, will be permitted at the discretion of the Investigator.

CARFILZOMIB CONSIDERATIONS:

Based upon the experience in the Phase 1 and 2 clinical studies with carfilzomib, the following observations are noted:

- A "first dose effect" has been seen, which is notable for fever, chills, rigors, and/or dyspnea occurring during the evening following the first day of infusion and an increase in creatinine on Day 2, which may be the clinical sequelae of rapid tumor lysis and/or cytokine release.
- Should a "first dose" effect occur at any point during Cycle 1 or 2, treatment with high dose glucocorticoids (e.g. methylprednisolone 50–100 mg) is recommended. In addition, intravenous fluids, vasopressors, oxygen, bronchodilators, and acetaminophen should be available for immediate use and instituted, as medically indicated.

- Dexamethasone 4 mg PO/IV will be administered prior to all carfilzomib doses during the 1st cycle and prior to all carfilzomib doses during the first dose-escalation (36 mg/m^2) cycle. If treatment-related fever, rigors, chills, and/or dyspnea are observed post any dose of carfilzomib after dexamethasone has been discontinued, dexamethasone (4 mg PO/IV) should be re-started and administered prior to subsequent doses.
- Patients will receive 8 mg of dexamethasone as pre-medication before carfilzomib administration during the first cycle of maintenance (at the dose of 70 mg/m^2) and for subsequent cycles during maintenance according to physician opinion.
- Acyclovir or similar should be given to all subjects, per institutional prophylaxis guidelines, unless contraindicated.
- CrCl changes are mostly transient, reversible, and non-cumulative. All subjects should be well hydrated. Clinically significant electrolyte abnormalities should be corrected prior to dosing with carfilzomib. Renal function must be monitored closely during treatment with carfilzomib. Serum chemistry values, including creatinine, must be obtained and reviewed prior to each dose of carfilzomib during Cycles 1 and 2. Carfilzomib must be held for subjects with a CrCl < 15 mL/min at any time during study participation as outlined in Table 10.
- Subjects with symptoms of CHF or any other suspected acute cardiac event, whether or not drug related, must have the dose held until resolution. After the event has resolved or returned to baseline, treatment may continue at a reduced dose, with the approval of the Principal Investigator or the subject may be withdrawn from the study. If there is no resolution of CHF after 4 weeks, the subject will be withdrawn from the study.
- Thrombocytopenia has been transient and typically resolves during the week between treatments. For platelet counts ≤ 30,000/mm^3, carfilzomib dosing must be held. If platelet counts do not recover, the dose of carfilzomib may be reduced or held according to the Dose Reductions/Adjustments rules as outlined in the section *Carfilzomib dose reductions for hematologic toxicities*.
- Subjects should have anemia corrected in accordance with the Institutional guidelines.

- Carfilzomib treatment can cause nausea, vomiting, diarrhea, or constipation sometimes requiring the use of antiemetics or antidiarrheals. Fluid and electrolyte replacement should be administered to prevent dehydration.
- Patients should be monitored periodically during the infusion period for evidence of fluid overload, that can cause side effect to heart, lungs, and kidneys

LENALIDOMIDE CONSIDERATIONS:

- While on lenalidomide, patients should be on routine thromboprophylaxis. During the first 4 cycles of induction treatment the prophylaxis with low molecular weight heparin (LMWH) is recommended for all patients, regardless of prior history of thrombosis. After induction, prophylaxis therapy with aspirin (81 - 325 mg PO once daily) or low LMWH (equivalent to enoxaparin 40 mg subcutaneous [sc] per day) per published standard or institutional standard of care is required for all patients to prevent thromboembolic complications that may occur with lenalidomide-based regimens in combination with dexamethasone. Thromboprophylaxis according to the American Society of Clinical Oncology (ASCO) guidelines or institutional standard of care is recommended. In subjects with a prior history of deep vein thrombosis, low-molecular-weight heparin or therapeutic doses of warfarin (for a target international normalized ratio of 2-3) are required. In case of intolerance to other antiplatelet or anticoagulation medications, Aspirin (enteric-coated) PO QD at the standard prophylactic dose, continuing for the duration of treatment with lenalidomide should be started at least 24 hours prior to Cycle 1 Day 1 (subjects with known high thrombotic risk, eg, prior thrombosis, deep vein thrombosis, etc, should receive full anticoagulation at the

  Investigator's discretion).
- According to lenalidomide information, in case PMN < $1x10^9$/L, G-CSF must be administered and lenalidomide treatment should be held until PMN > $1x10^9$/L.

- Lansoprazole (or other proton pump inhibitor) while taking dexamethasone, and a prophylactic antibiotic (eg, either ciprofloxacin, amoxicillin, trimethoprim sulfa, or other) are required as concomitant medications.

CONCOMITANT MEDICATIONS

Concomitant medication is defined as any prescription or over-the-counter preparation including vitamins and supplements. Concomitant medications should be recorded from 14 days before Day 1 through the end of the subject's study participation. Any change in concomitant medications must be recorded.

REQUIRED CONCOMITANT MEDICATIONS

Female subjects of child-bearing potential must agree to use dual methods of contraception for the duration of the study. Male subjects must agree to use a barrier method of contraception for the duration of the study if sexually active with a female of child-bearing potential. In addition, subjects should receive acyclovir or similar (famiciclovir, valacyclovir) anti-varicella (anti-herpes) agent prophylaxis.

Lansoprazole (or other proton pump inhibitor) while taking dexamethasone, and a prophylactic antibiotic (eg, either ciprofloxacin, amoxicillin, trimethoprim sulfa, or other) are required as concomitant medications.

While on lenalidomide, patients should be on routine thromboprophylaxis. During the first 4 cycles of induction treatment the prophylaxis with low molecular weight heparin (LMWH) is recommended for all patients, regardless of prior history of thrombosis. After induction, prophylaxis therapy with aspirin (81 - 325 mg PO once daily) or low LMWH (equivalent to enoxaparin 40 mg subcutaneous [sc] per day) per published standard or institutional standard of care is required for all patients to prevent thromboembolic complications that may occur with lenalidomide-based regimens in combination with dexamethasone.

In subjects with a prior history of deep vein thrombosis, low-molecular-weight heparin or therapeutic doses of warfarin (for a target international normalized ratio of 2-3) are required.

In subjects with PMN < $0.5x10^9$/L G-CSF is recommended.

All subjects must receive prophylaxis with hydration (see *Carfilzomib consideration* Section).

Patients with previous HBV infection should be strictly monitored to identify signs of virus reactivation for the entire duration of treatment with lenalidomide.
Patients will receive 8 mg of dexamethasone as pre-medication before carfilzomib administration during the first cycle of maintenance. In subsequent cycles, dexamethasone pre-medication can be administered according to physician opinion.

OPTIONAL AND ALLOWED CONCOMITANT MEDICATIONS

Allopurinol (in subjects at risk for TLS due to high tumor burden) is optional and will be prescribed at the Investigator's discretion. These subjects may receive allopurinol 300 mg PO BID (Cycle 1 Day -2, Day -1), continuing for 2 days after Cycle 1 Day 1 (total of 4 days), then reduce dose to 300 mg PO QD, continuing through Day 17 of Cycle 1. Allopurinol dose should be adjusted according to the package insert. Subjects who do not tolerate allopurinol should be discussed with the Lead Principal Investigator.

Approved bisphosphonates and erythropoietic agents and transfusions are allowed. Subjects may receive antiemetics and antidiarrheals as necessary, but these should not be administered unless indicated. Colony-stimulating factors may be used if neutropenia occurs.

Vitamins and supplements should be recorded on the concomitant medication page. All transfusions and/or blood product related procedures must be recorded on the appropriate form.

When digoxin was co-administered with lenalidomide, the digoxin AUC was not significantly different; however, the digoxin Cmax was increased by 14%. Periodic monitoring of digoxin plasma

levels in accordance with clinical judgment and based on standard clinical practice in patients receiving this medication is recommended during administration of lenalidomide.

Mycostatin or oral fluconazole to prevent oral thrush is optional and may be given at the Investigator's discretion.

Subjects who require repeated platelet transfusion support should be discussed. Palliative radiation for pain management is permitted with the written approval of the Principal Investigator.

EXCLUDED CONCOMITANT MEDICATIONS

Concurrent therapy with an approved or investigative anticancer therapeutic with activity against multiple myeloma is not allowed.

Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided with impaired renal function given reported NSAID-induced renal failure in patients with decreased renal function

Other investigative agents should not be used during the study.

GUIDELINES FOR MONITORING, PROPHYLAXIS, AND TREATMENT OF TUMOR LYSIS SYNDROME (TLS)

TLS, which may be associated with multiorgan failure, has been observed in treatment Cycles 1 and 2 in some patients with MM who have been treated with carfilzomib.

The following safety measures are mandatory for all subjects. In addition, MM subjects with high tumor burden (e.g., Durie-Salmon or ISS Stage II/III) or rapidly increasing M-protein or light chains or compromised renal function (CrCl < 50 mL/min) should be considered to be at particularly high risk.

Hydration and Fluid Monitoring

Intravenous Fluids

250 mL of IV normal saline (or other appropriate IV fluid formulation) must be given before *and* after each carfilzomib dose during cycle 1, after cycle 1 at investigator's discretion. The goal of the hydration program is to maintain robust urine output, (e.g., ≥ 2 L/day). Subjects should be monitored periodically during this period for evidence of fluid overload.

Patients in whom this program of oral and IV fluid hydration is contraindicated, e.g., due to preexisting pulmonary, cardiac, or renal impairment, will not be eligible to participate in the clinical trial.

Laboratory Monitoring

Appropriate chemistries, including creatinine, and complete blood counts (CBC) with platelet count should be obtained and reviewed prior to carfilzomib dosing. Results of laboratory studies must be reviewed and deemed acceptable prior to administering the carfilzomib dose. Subjects with laboratory abnormalities consistent with lysis of tumor cells (e.g., serum creatinine ≥ 50% increase, LDH ≥ 2-fold increase, uric acid ≥ 50% increase, phosphate ≥ 50% increase, potassium ≥ 30% increase, calcium ≥ 20% decrease) prior to dosing should not receive the scheduled dose. Subjects with such abnormalities should be re-evaluated again within the next 24 hours (or sooner, if clinically indicated) and then periodically as clinically indicated. **Clinical Monitoring**

Inform subjects of signs and symptoms that may be indicative of TLS, such as fevers, chills/rigors, dyspnea, nausea, vomiting, muscle tetany, weakness, or cramping, seizures, and decreased urine output. Advise subjects to report such symptoms immediately and seek medical attention. **Management of Tumor Lysis Syndrome (TLS)**

If TLS occurs, cardiac rhythm, fluid, and serial laboratory monitoring should be instituted. Correct electrolyte abnormalities, monitor renal function and fluid balance, and administer therapeutic and supportive care, including dialysis, as clinically indicated.

All cases of TLS must be reported to the Sponsor as a Serious Adverse Event (SAE) through the normal process within 24 hours of the clinical site becoming aware of the event.

STUDY TESTS AND OBSERVATIONS

Procedure	Screening ≤ 28 days from Baseline	Induction and consolidation phase Cycles 1-12			Mobilization and intensification phase[15]	Maintenance phase (Arm 1: lenlidomide Arm 2: lenalidomide + carfilzomib) At the end of 12th induction (Arm C)/4th consolidation cycle (Arm A and B),		Follow up every 3 Months
		Day 1-2	Day 8-9	Day 15-16		Day 1 (Arm 1 and 2)	Day 15 (only for Arm 2)	
Informed consent	X							
Eligibility criteria	X							
Medical history	X							
Physical examination[1], vital signs[14], weight	X	X	X	X		X	X	X
Pregnancy test[2, 14]	X	X				X		
Symptoms-directed physical examination[14]	X	X	X	X		X	X	X
Neurotoxicity assessment	X[12]	X[12]	X[12]	X[12]		X[12]		X
12-lead ECG and ECHO[3]	X							X
Chest x-ray[3, 14]	X							
Skeletal Survey,PET/CT, CT, MRI[4]	X					X		
Hematology[6, 14]	X	X	X	X		X	X[10]	X
Serum chemistry[6, 14]	X	X	X	X		X	X[10]	X
Urinalysis[14]	X							
Myeloma protein in serum* and urine	X	X[13]			X	X[13]		X
Serum FLC[7]*	X	X				X		X
Bone marrow biopsy/ aspiration[5]	X[5]					X[9]		X[9]
Coagulation[14]	X							

Qol assessment[8]	X	X				X		
Research samples[11,9, 14] (peripheral blood	X	X				X		

and bone marrow samples)								
Record adverse events	X	X	X	X	X	X	X	X
Record concomitant therapies/procedure	X	X	X	X	X	X	X	X
Study drug (dispensing)		X	X	X	X	X	X	
Perform drug accountability		X				X		
Follow-up anticancer treatments								X
Follow-up survival information								X

1. *Vital signs include: blood pressure, heart rate, temperature, oxygen saturation and respiratory rate and will be conducted during the screening period and at the end of treatment. Weight is to be measured on day 1 of each cycle.*
2. *Pregnancy test has to be performed to Baseline and also pregnancy test is needed if the patient misses her period or has unusual menstrual bleeding. It should be repeated during the treatment before start each cycle.*
3. *To be repeated before transplant to confirm eligibility. Pulmonary function test should be included in the pretransplant evaluation.*
4. *MRI, PET/CT or RX may be performed within 8 weeks before the first dose of study drug. XR during the screening period and then once a year. MRI, (low dose) CT or PET/CT to be performed at screening and, if positive for bone lesions or bone-soft tissue plasmacytoma, after 4 cycles of induction or post mobilization and at the end of consolidation (before maintenance) to evaluate response to treatment, and thereafter when clinically indicated.*
5. *Bone marrow aspiration and/or biopsy for morphology, immunophenotype and FISH assessment, to be performed at screening (centralized analyses- Appendix 1).*
6. *To Baseline and prior to carfilzomib (Platelet count, absolute neutrophil count, Hemoglobin levels, corrected serum calcium, alanine transaminase (ALT), aspartate transaminase (AST), acid uric, potassium, magnesium, glucose, potassium, sodium, bilirubin, creatinine clearance, LDH, β2-micoglobulin, albumin, phosphate). At cycle 1 on days 1, 2, 8, 9, 15, 16. From cycle 2, hematology and serum chemistry analyses can be repeated only on days 1, 8, 15 at physician discretion and basing on patient condition.*
7. *They will be performed at screening, to evaluate response for patients with oligosecretory or non-secretory MM and to confirm sCR for patients with baseline serum FLC levels >10 mg/dl.*
8. *At the day 1 of each cycle during induction and consolidation and every 3 months during maintenance.*
9. *Bone marrow (BM) aspiration for monitoring of minimal residual disease (MRD) and for Correlative studies will be performed in all patients at diagnosis and after around 6 months (that is after 4 cycles of induction and CTX followed by PBSC mobilization), at first and at second progression. In patients achieving at least a VGPR BM aspiration will be performed also after around 12 months of therapy (that is after consolidation and before maintenance), after 6 months of maintenance therapy and then every 6 months until first clinical progression.*
10. *If clinically indicated.*
11. *A sample of peripheral blood for correlative studies will be collected for all patients at diagnosis, after approximately 3 months (after 3 cycles of induction), 6 months (that is after 4 cycles of induction and CTX followed by PBSC mobilization), 9 months (after transplant/8 cycles of CRD in the no transplant arm) after starting treatment, at first clinical progression and at the second clinical progression. Patients, who achieve a VGPR after*

induction/consolidation need to undergo PB collection approximately at 12 months from the start of therapy (that is after consolidation and before maintenance); then need to undergo PB collection every 3 months since the maintenance period has been started until first clinical relapse.

12. Neurological physical exam includes PN Grade using CTCAE v 4.03, assessment muscle weakness, peripheral sensory neuropathy, and neuralgia. The neurological physical exam and the questionnaire should occur each visit day

(see appendix J) 13.

Only on day 1.

14. Tests will not be collected in e-crf every visit, but test should be performed to evaluate disease status and safety; any abnormal results should be reported as adverse events

15. Date of drugs administration and collection will be collected. Also the use of plerixafor will be registered.

** Eventually, if not performed at study sites, serum myeloma protein and serum FLC could be performed by Laboratorio di Biochimica Clinica Baldi e Riberi in Torino.*

MINIMAL RESIDUAL DISEASE (MRD) MEASUREMENT

In most hematologic malignancies, response to frontline therapies is a good predictor of prognosis, with the longest survival reported in patients achieving complete response (CR), defined by absence of monoclonal (M) protein in the serum and urine by immunofixation (IF), along with 5% bone marrow (BM) plasma cells. Incorporation of novel agents into ASCT for MM has affected unprecedented rates of CR. As a result, interest in the evaluation of the depth of response has progressively grown. Highly sensitive techniques, such as multiparametric flow cytometry (MFC) and polymerase chain reaction (PCR), can carefully detect the presence or absence of minimal residual disease (MRD) at the bone marrow level, thus allowing identifying subgroups of patients with conventionally defined CR who are at different risk of progression or death. MFC, although less sensitive than PCR methods, seems to be applicable to a greater proportion of patients and is potentially more suited to routine practice.

In this trial, the importance of flow cytometric Minimal Residual Disease (MRD) negativity will be investigated.

All patients need to undergo BM aspiration at diagnosis, at CR confirmation and after around 6 months (that is after 4 cycles of induction and cyclophosphamide followed by PBSC mobilization). Patients, who achieve a VGPR after induction/consolidation, need to undergo BM aspiration (approximately at 12-15 months from the start of therapy, that is after consolidation and before

maintenance); then patients need to undergo BM aspirates every six months since the maintenance period has been started, and at clinical relapse. BM samples collected will be processed and stored in the Hematological Laboratory of Turin.
For all these samples, detailed clinical records at diagnosis and during follow-up are available on informatics database updated every six months.

Flow cytometric analysis will be performed in the Hematological Laboratory of the University of Turin according to the principles outlined by the European Myeloma Network. MRD analyses by flow cytometry are typically performed regionally with a NAVIOS (Beckam Coulter, United States). MRD determination will be performed on erythrocyte-lysed whole bone marrow using a 8color direct immunofluorescence technique. At diagnosis, to identify patients-specific phenotypic characteristics of plasma cells to be used for assessment of MRD after therapy, the monoclonal antibody that will be used following European Myeloma Network guidelines are: CD38, CD138, CD19, CD20, CD45, CD56, CD117, cyKappa, cyLambda. A minimum of $5x10^6$ BM cells will be acquired per each patient. Similar flow cytometry investigation to detect malignant plasma cells will be performed.

Moreover, in a subset of patients, a next generation flow (NGF)-MRD approach developed by International Myeloma Foundation (IMF) will be used following the EuroFlow Consortium guidelines. This is an ultrasensitive technique which allows to reach a sensitivity between 10^{-5} to 10^{-6} using a 10-color antibody panel. A comparison with standard flow cytometry MRD and NGS will also be performed in this cohort of patients.

CIRCULATING PLASMA CELLS

The clinical outcome of multiple myeloma (MM) is heterogeneous and new tools can be useful to detect patients with more aggressive disease. The presence of Circulating Plasma Cells (CPC) in Multiple Myeloma patients has been demonstrated by some Authors, but their clinical and prognostic

significance is still matter of debate. Moreover, to date CPC have been evaluated with different and low sensitive methods.

Aims

Our aim is to perform a single flow cytometric platform absolute count of CPC in order to study the correlation with the most relevant prognostic factors at diagnosis and to define CPC relevance in prognostic stratification of MM patients at diagnosis enrolled in the FORTE trial.

Material and methods

For the single platform tube the antibody combination

CD38PC7/CD138PC5.5/CD45KO/CD56PE/CD184APC/CD19PB will be used, mixed with 100 L of EDTA peripheral blood dispensed with reverse pipetting, added with 500 L of lysing solution and, after 15 min, 100 L of flow counts will be dispensed with reverse pipetting and cells acquired with Navios flow cytometer. The clonality of plasma cells will be confirmed by intracytoplasmic evaluation of kappa and lambda chains.

STUDY DISCONTINUATION

Subjects may withdraw from treatment at any time. The Investigator may discontinue study treatment for any of the following reasons:

• Subject desires discontinuation of treatment (ie, withdraws consent for treatment);

• Disease progression;

• Unacceptable toxicity or treatment delay for more than 4 weeks for unresolved toxicity;

• Noncompliance with study procedures, including administration of non-protocol therapies;

• Requirement for alternative therapy;

• Intercurrent illness or worsening of a chronic condition.

Patients that discontinue study treatment for reasons other than PD (except for consent withdrawal) will be followed until PD for response and MRD assessment, as patients who are still on therapy.

The reason for withdrawal from treatment will be documented in the CRF. Post-treatment followup for disease status and survival will continue until death unless any of the criteria for early study withdrawal are met.

If the reason for withdrawal is AE, the subject will be followed by the Investigator until such events resolve, stabilize, and, according to the Investigator's judgment, there is no need for further followup. Subjects may discontinue one or more drugs in their assigned regimen and still be considered on treatment as long as they are still receiving one protocol-specified drug.

Salvage therapy

For patients in the arm C or who did not receive ASCT, physicians are recommended to choose as best salvage therapy ASCT, unless not clinically indicated. For patients who receive ASCT the best salvage therapy recommended is the standard of care.

ADVERSE EVENTS Monitoring, Recording and Reporting of Adverse Events

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria below), regardless of etiology. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a preexisting condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the e-CRF rather than the individual signs or symptoms of the diagnosis or syndrome.

If special reporting conditions are applicable (e.g., disease progression is not to be reported as an adverse event), it should be clearly explained here and also cross-referenced to the section defining efficacy endpoints in the protocol.

An overdose, accidental or intentional, whether or not it is associated with an AE, or abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. If an overdose is associated with an AE, the overdose and adverse event should be reported as separate terms.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or other appropriate tests and procedures.

All AEs will be recorded by the Investigator from the time the subject signs informed consent until 30 days after the last dose of study drug or until the start of subsequent antineoplastic therapy or until the last study visit, whichever period is longer. The Investigator will instruct the patient how to communicate any AEs occurred in the study period.

AEs and serious adverse events (SAEs) will be recorded on the AE page of the e-CRF and in the subject's source documents. All SAEs must be reported to the Sponsor within 24 hours of the Investigator's knowledge of the event by fax or email, using the SAE Report Form. When filling in SAE form, the Investigator may provide a Initial information (she/he will subsequently give a Follow-up/Final information) or even the final information in case all data, including outcome, are immediately available. In accordance with IEC requirements, the Investigator must also notify IEC of any SAEs according the guidelines of the IEC. All protocol modifications (substantial and not substantial), must be communicated to Amgen and Celgene and approved by them prior to submit them to EC; informed consent documents must be reviewed by Amgen and Celgene prior to IEC submission; all SAEs and all other information must be communicated to Celgene and Amgen.

Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

Seriousness

A serious adverse event (SAE) is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (i.e., in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life activities);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event.

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Second primary malignancies will be monitored as events of interest and must be reported as serious adverse events regardless of the treatment arm the subject is in. This includes any second primary malignancy, regardless of causal relationship to the study drug, occurring at any time for the duration of the study, from the time of signing the ICD up to 3 years (follow up period of the study). Events of second primary malignancy are to be reported using the SAE report form and must be considered an "Important Medical Event" even if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the e-CRF and subject's source documents. Documentation on the diagnosis of the second primary malignancy must be provided at the time of reporting as a serious adverse event (e.g., any confirmatory histology or cytology results, X-rays, CT scans, etc.).

Events **not considered** to be SAEs are hospitalizations for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.

- The administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (i.e., planned prior to starting of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of a pre-existing condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.
- Expected progression of disease should not be considered an AE (or SAE). However, if determined by the investigator to be more likely related to the study treatment than the underlying disease, the clinical signs or symptoms of progression and the possibility that the study treatment is enhancing disease progression, should be reported per the usual reporting requirements.

If an AE is considered serious, both the AE page/screen of the CRF and the SAE Report Form must be completed.

For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to IP, action taken regarding IP, and outcome.

Severity / Intensity

For both AEs and SAEs, the Investigator must assess the severity / intensity of the event. The severity / intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0);
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

AEs that are not defined in the NCI CTCAE should be evaluated for severity / intensity according to the following scale:

- *Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required*

- *Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required*
- *Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible*
- *Grade 4 = Life threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable* • *Grade 5 = Death the event results in death*

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as "serious" which is based on subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

Causality

The Investigator must determine the relationship between the administration of IP and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected:	The temporal relationship of the adverse event to IP administration makes **a causal relationship unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	The temporal relationship of the adverse event to IP administration makes **a causal relationship possible**, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

Action Taken

The Investigator will report the action taken with IP as a result of an AE or SAE, as applicable (e.g., discontinuation or reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

Outcome

The investigator will report the outcome of the event for both AEs and SAEs.

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered, recovered with sequelae, not recovered (death due to another cause) or death (due to the SAE).

Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE.

Pregnancy

Females of Childbearing Potential

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on study drug, or within 28 days of the subject's last dose of study drug, are considered immediately reportable events. Study drug is to be discontinued immediately and the subject instructed to return any unused portion of the study drug to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the Sponsor pharmacovigilance contact who will inform the companies immediately using the Pregnancy Reporting Form. The exposure of any pregnant female (e.g., caregiver or pharmacist) to lenalidomide is also an immediately reportable event.

The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.
The Investigator will follow the female subject until completion of the pregnancy, and must notify to pharmacovigilance contact immediately about the outcome of the pregnancy (either normal or abnormal outcome).

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of

the serious criteria, it must be reported as an SAE within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in uterus exposure to the IP should also be reported within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

Male Subjects

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking study drug should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

If a pregnancy related event is reported in a female partner of a male subject, the investigator should ask if the female partner is willing to share information with Celgene Drug Safety and allow the pregnancy related event to be followed up to completion.
The Sponsor will inform Celgene and Amgen immediately, using the Pregnancy Reporting Form, of any information related to pregnancies or suspected pregnancies (including a positive pregnancy test regardless of age or disease state) occurring in partner of Patients while the Patients are still treated with the Investigational Product or within 28 days of the Patients' last dose of Investigational Product.

Expedited Reporting of Adverse Events

Reporting to Regulatory Authorities and the Ethics Committee

The Sponsor will inform relevant Regulatory Authorities and Ethics Committees

- of all relevant information about serious unexpected adverse events suspected to be related to the IP that are fatal or life-threatening as soon as possible, and in any case no later than seven days after knowledge of such a case. Relevant follow-up information for these cases will be subsequently be submitted within additional eight days
- of all other serious unexpected events suspected to be related to the IP as soon as possible, but within a maximum of fifteen days of first knowledge by the investigator.

Immediate reporting by Investigator to Sponsor and Sponsor to Celgene and Amgen

The investigator will inform the Sponsor of all SAEs within 24 hours in order that the sponsor can fulfill their regulatory reporting obligations within the required timeframes.

The Sponsor will supply companies with a copy of all SAEs which involve *exposure* to a company product within 24 hours of being made aware of the event regardless of whether or not the event is listed in the reference document (e.g. IB, SmPC).

The Sponsor will provide companies with a copy of Development Safety Update Report (DSUR) at the time of submission to the Regulatory Authority and Ethics Committee.

Contact details for Sponsor Pharmacovigilance

[redacted]

STATISTICAL ANALYSIS

STUDY DESIGN

This protocol is a phase II multicenter, randomized, open label study designed to jointly assess the safety and the efficacy of different Carfilzomib combinations and treatment approaches in newly diagnosed MM patients.

PRIMARY ENDPOINTS

All patients will be included in the Intent-to-Treat (ITT) analysis. Efficacy will be assessed by considering VGPR or better (VGPR, sCR, CR) at cycle 4 in the 3 arms. Assessment of VGPR rate will be performed according to the criteria of the International Myeloma Working Group (Appendix D). Patients will be classified as not achieved at least a VGPR if they have only not evaluable assessment or drop out before the end of first cycle.

Progression-free survival in the 2 maintenance arms from R2: PFS of maintenance will be measured from the date of second randomization to the date of first observation of disease progression or death to any cause as an event. Subjects who withdraw from the study will be considered censored at the time of the last complete disease assessment (cut-off date). Subjects who have not progressed, and are still alive at the cut-off date of final analysis will be censored at the cut-off date. All subjects who were lost to follow-up , and are still alive and no progressed will also be censored at the time of last contact

KEY SECONDARY ENDPOINTS

The ITT sCR rate is determined as the proportion of patients who achieved sCR according to IMWG criteria, using ITT principle. Patients will be classified as not achieved a sCR if they have only not evaluable assessment or drop out before the end of first cycle.

PFS at in the 3 induction/consolidation arms: PFS will be measured from the date of first randomization to the date of first observation of disease progression or death to any cause as an event. Subjects who withdraw from the study will be censored at the time of the last complete disease assessment (cut-off date). Subjects not progressed, and are still alive at the cut-off date of final analysis will be censored at the cut-off date. All subjects who were lost to follow-up prior , and are still alive and no progressed will also be censored at the time of last contact

OTHER SECONDARY ENDPOINTS

Determine the rate of MRD in the 3 arms after complete primary therapy (induction, ASCT and consolidation for the transplant arms and after 12 cycles in the long treatment arm) in an explorative manner.

The ITT MRD Negativity rate by MFC is determined as the proportion of patients with MRD negativity (at different cut off levels, 10^{-4} and $\geq 10^{-5}$ sensitivity level) at different timepoints using ITT principle. For patients who withdraw from the study or are lost to follow up before specific timepoints, the best MRD assessment will be considered. Patients will be classified as MRD positive if they have only MRD positive test results or do not undergo MRD assessment.
ITT MRD Negativity rate by MFC will be measured in different timepoint: after 4 cycle of induction/mobilization, after intensification, before and after maintenance.

ITT Persisitent MRD-negative is determined as MFC MRD negativity in the marrow as defined by patitents with MRD negative result confirmed for a minImun of 1 year. Data might also be presented as persistent MRD neagtivity at 2-years, 3 years and so on, according to the duration of remission. Data on persistent MRD negativity might be presented also as per protocol analyses (i.e: referring only to those patients who can be evaluable for persistent MRD at the different timepoint) To determine the response in the 3 arms after complete primary therapy (induction, ASCT and consolidation for the transplant arms and after 12 cycles in the long treatment arm): ORR will include at least PR will include stringent Complete Response (sCR), CR, VGPR, PR. If, during the course of the study, other relevant categories are identified in the literature, then these categories may be added. Responders are defined as subjects with at least a PR.
Determine the rate of adverse events in the 3 induction/consolidation arms (including ASCT) and in the 2 maintenance arms.
OS: OS is defined as the time between the date of randomization and death. Subject who die, regardless the cause of death, will be uncensored as an event. Alive subjects who withdraw consent for study will be censored at the time of withdrawal. Subjects who are still alive at the cut-off date

of final analysis will be censored at the cut-off date. All subjects who were lost to follow-up prior to the end of the study will also be censored at the time of last contact.

Time to next treatment: TNT will be measured from the date of randomization to the date of next anti-myeloma therapy. Death due to disease progression before starting therapy or death of any causes, will be considered as an event. Subjects who withdraw from the study will be considered censored at the time of the last complete disease assessment. Subject who have no progressed, and are still alive at the cut-off date of final analysis will be censored at the cut-off date. All subjects who were lost to follow-up will also be censored at the time of last contact.

Time to progression (TTP): TTP will be measured from the date of randomization to the date of first observation of PD, or deaths due to PD. Subjects who withdraw from the study or die from causes other than PD will be censored at the time of the last complete disease assessment. Subjects who have not progressed, and are still alive at the cut-off date of final analysis will be censored at the cut-off date. Subjects lost to FU will also be censored at the time of last contact.

Progression-free survival 2 (PFS2) will be measured from the date of randomization to the date of observation of second disease progression (i.e. progression after the second line of therapy) or death to any cause as an event. In case of date of second progression is not available, date of start of third line treatment can be used. Subjects who have no progressed, and are still alive at the cut-off date of final analysis will be censored at last complete disease assessment. All subjects who were lost to follow-up will also be censored at the time of last contact.

Determine the safety and the PFS, TNT, PFS2 and OS of maintenance with carfilzomib 36 mg/m^2 on day 1, 2, 15, 16 + lenalidomide vs carfilzomib 70 mg/m^2 day 1, 15 + lenalidomide maintenance (after amendment 5) in an explorative manner.

Determine the success of stem cell harvest according to baseline characteristics and treatment

Determine whether tumor response and outcome may change in subgroups with different prognosis according to current prognostic factors

Perform explorative comparative analyses between subgroups of patients, defined according to known prognostic factors

OTHER ANALYSES

For the comparisons of PFS from randomization 1, will be a sensitivity analysis regarding the comparison between CCyd vs CRd long treatment vs CRd. In this analysis CRd arm will be censored at time of second randomization for patients randomized to maintenance with carfilzomib.

SAMPLE SIZE CONSIDERATIONS

The calculation of the sample size for primary endpoint was done with the following assumptions, consider ITT population:

- 2-sided alpha level equal to 0.05 and a power of 90%:
- VGPR rate for CCyd arm= 62% o VGPR rate for CRd with transplantation arm = CRd without transplantation arm = 80% The study will be powered to compare *CCyd* arm (Carfilzomib, Cyclophosphamide, Dexamethasone) and *CRd ASCT* arm (Carfilzomib, Lenalidomide, Dexamethasone plus transplant).

The randomization would be 1:1:1, but the 2 CRd groups would be pooled (2:1) for the analysis of VGPR, since the patient population and treatment is the same until that point (end of 4 cycles of induction).

Using the “Two group continuity corrected Chi square test” the sample size for each arm is 143, for a total of 429 patients. Considering a 10% of patients lost to follow-up, the total sample size is about 477 patients.

A hierarchical testing procedure will be used for the key secondary endpoints to achieve control of the overall familywise Type I error rate at a two-sided significance level of 0.05. The details of the testing procedure will be prespecified in multiplicity section.

The power of 90% (β= 0.10) for first key endpoint (sCR rate after induction/consolidation) was done with the following assumptions by the X2 test with Yates' continuity correction, consider ITT population:

- alpha 0.025, 2-sided for each comparison
- sCR rate for CCyd arm = 20%
- sCR rate for CRd long treatment = 40%
- sCR rate for CRd = 60%
- Lost to Follow-up = 10%

Alpha was split according to Bonferroni adjustment to perform comparison between CRd long treatment vs CCyd and CRd vs CCyd.

The power of 80% (β= 0.20) for second key endpoint (PFS) was done with the following assumptions by Schoenfeld formula, consider ITT population:

- alpha 0.025, 2-sided for each comparison
- 3-years PFS for CCyd arm = 55%
- 3-years PFS for CRd long treatment = 70% (HR=0.60)
- 3-years PFS for CRd = 80% (HR = 0.37)
- Accrual time: 36 months
- Follow-up time: 36 months
- Lost to follow-up: 5%

Alpha was split according to Bonferroni adjustment to perform comparison between CRd long treatment vs CCyd and CRd vs CCyd.

To achieve 80% power, 146 and 39 PFS events are needed for the comparison CRd long treatment vs CCyd and CRd vs CCyd respectively.

Randomizations should be done separately, the first at induction and the second one at the end of induction and consolidation period.

In this way it avoids an unbalance in the maintenance arms.

Responding patients will be randomized before maintenance and the two arms will be balanced, permitting a better comparison on PFS for the two groups. The randomization into two different maintenance regimens will be stratified by the three induction arms. Considering 4-years PFS improvement from 40% to 60% (HR=0.558) with a 2-sided alpha of 0.05 and beta=0.2, using an unstratified log-rank test, the sample size required is equal to 196 patients and the number of events is equal to 92. For this reason the 477 patients calculated for the induction part of the study are considered adequate.

PLANNED METHODS OF ANALYSIS

The analysis consists in evaluating the efficacy and safety (see below). Primary efficacy analyses will be based on the intent-to-treat principle. Response rate will be defined according to the International Uniform Response Criteria[35]. Categories of response will include sCR, CR, VGPR, PR and PD (Appendix D). If, during the course of the study, other relevant categories are identified in the literature, then these categories may be added. Responders are defined as subjects with at least a PR. The Kaplan-Meier product limit method will be used to estimate the survivorship functions for PFS endpoints. The Cox proportional hazards regression model will be used to assess the effect of demographic and prognostic variables on relative treatment differences. Summary statistics (standard deviation, median, minimum and maximum) will be provided for relevant variables.

MULTIPLICITY

A hierarchical testing procedure will be used for primary (H1 as VGPR rate) and key secondary endpoints (H2 as sCR and H3 as PFS) to achieve control of the overall familywise Type I error rate at a two-sided significance level of 0.05.

H1 will be tested at 0.05 alpha level; if H1 fails no other test will be performed. If H1 will be significant, H2 will be tested at 0.05 alpha level; if H2 fails no other test will be performed. If H2 will be significant, H3 will be tested at 0.05 alpha level. H3 cannot be tested if one of H1 or H2 fails.

SAFETY ANALYSIS

Data from all subjects who receive any study drug will be included in the safety analyses. The severity of the toxicities will be graded according to the NCI CTC whenever possible. In the bysubject analysis, a subject having at least one event will be counted only once. Adverse events will be summarized by worst NCI CTC grade. Adverse events leading to death or to discontinuation from treatment, events classified as NCI CTC Grade 3 or Grade 4, study-drug-related events, and serious adverse events will be summarized separately. Laboratory data will be graded according to NCI CTC severity grade.

The first interim analysis aims to evaluate safety (all adverse events including the PRES incidence, and failure of mobilzation of PBSC). It is planned after 90 patients have completed the induction phase. Since this is not the principal aim of the study, no statistical correction of the sample size or of the alpha error have been done. In case of mobilization failure in more than 15% of the patients and recommendation by DMC, after analysis of safety data, the study will be interrupt. DMC will evaluate the incidence of all adverse events including PRES and at DMC discretion, a possible interruption will be considered.

Considering the change in the schedule of carfilzomib applied with amendment 5.0, a safety analysis will be performed after the first 18 patients will complete the first 4 cycles of weekly carfilzomib maintenance. The safety data of carfilzomib 70 mg/m^2 will be compared with the data of the last 18 patients randomized to carfilzomib 36 mg/m^{2}maintenance. DMC will evaluate the incidence of all adverse events including PRES and at DMC discretion, a possible interruption will be considered.

STATISTICAL ANALYSIS PLAN

A Statistical Analysis Plan (SAP) will be prepared by the trial statistician and approved by the principal investigator. It will describe in detail the analyses to be performed.

INVESTIGATIONAL PRODUCT

All IMPs (Carfilzomib and Lenalidomide), are manufactured, packaged, labelled, tested and certified for clinical use according to the principle of GMP and Local Legislation.

Complete details and requirements for study drug packaging, labelling, storage, preparation, administration and accountability are written in a separate document, that will be available in Italian. Labelling details will be provided to the Ethical Committee for evaluation, as required by the Local Legislation.

The Pharmacy of the Clinic Centres involved in the Study and the Investigator will be responsible for receipt and proper storage of the Study medication, which will be kept in a secure location, for the whole Study duration and maintained at temperature 2-8 °C for Carfilzomib, as indicated in the Investigator's Brochure, at not more than 25°C for Lenalidomide, as indicated in the Summary of Product Characteristics (RCP), and according to instructions for use provided by the Sponsor

CARFILZOMIB

DESCRIPTION

Carfilzomib is a synthetic small molecule peptide bearing the chemical name (2S)-N-((S)-1-((S)-4methyl-1-((R)-2-methyloxiran-2-yl)-1-oxopentan-2-ylcarbamoyl)-2-phenylethyl)-2-((S)-2-(2morpholinoacetamido)-4-phenylbutanamido)-4-methylpentanamide. The molecular formula is $C_{40}H_{57}N_5O_7$ and the molecular weight is 719.92. It specifically functions as an inhibitor of the chymotrypsin-like activity of the 20S proteasome which leads to the accumulation of protein substrates within the cell and induction of apoptosis.

FORMULATION

Carfilzomib for Injection will be provided as a lyophilized powder which, when reconstituted, contains 2 mg/mL isotonic solution of carfilzomib Free Base in 10 mM sodium citrate buffer (pH 3.5) containing 10% (w/v) sulfobutylether-□-cyclodextrin (SBE-□-CD, Captisol®).

STORAGE

Lyophilized Carfilzomib for Injection must be stored at 2–8ºC under the conditions outlined in the separate “Instructions for storage and use of lyophilized Carfilzomib for injection” in a securely locked area to which access is limited to appropriate study personnel.

ACCOUNTABILITY

Amgen, Inc. and the Investigator will maintain records of each shipment of investigational product to the study Sites. The records will document shipment dates, method of shipment, batch numbers, and quantity of vials contained in the shipment. Upon receipt of the investigational product, the designated recipient at the study site will inspect the shipment, verify the number and condition of the vials, and prepare an inventory or drug accountability record.

Drug accountability records must be readily available for inspection by representatives of the Sponsor and by regulatory authorities.

Empty and partially used vials should be accounted for and destroyed at the study site in accordance with the internal standard operating procedures. Drug destruction records must be readily available for inspection by representatives of the Sponsor and/or its designee and by regulatory authorities.

Only sites that cannot destroy unused drug on-site will be required to return their unused supply of investigational product.

LENALIDOMIDE

DESCRIPTION

Lenalidomide, a thalidomide analogue, is an immunomodulatory agent with anti-angiogenic and antineoplastic properties. The chemical name is
3-(4'-amino-1,3-dihydro-1-oxo-2H-isoindol-2-yl)-2,6-piperidinedione The empirical formula for lenalidomide is C13H13N3O3, and the gram molecular weight is 259.3. Lenalidomide is off-white to pale-yellow solid powder.

FORMULATION

REVLIMID® (lenalidomide) is commercially available in 2.5 mg, 5 mg, 10 mg, 15 mg or 25 mg capsules for PO administration only. For the study lenalidomide will be supplied as capsules of 2.5mg, 5 mg, 10 mg and 25 mg. The capsules also contain the following inactive ingredients: lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The capsule shells contain gelatin and titanium dioxide. Complete information on REVLIMID® may be found in the Package Insert (RCP).

STORAGE CONDITIONS

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F).

ACCOUNTABILITY

The site Pharmacy will supply the study site with lenalidomide capsules. Supplies of lenalidomide capsules will contain a sufficient number of capsules for 1 cycle of dosing. Remaining supplies should be returned to the pharmacy at the end of the cycle.

UNUSED STUDY DRUG SUPPLIES

Patients will be instructed to return empty blister or unused capsules. Unused or returned study drug will be destroyed locally in compliance with local pharmacy destruction procedures and drug disposition must be appropriately documented in the study file. The local pharmacy is responsible for the drug destruction. If any study drug is lost or damaged, its disposition should be documented in the source documents (i.e.: drug accountability records).

OTHER STUDY DRUGS

DEXAMETHASONE

DESCRIPTION

Dexamethasone, a synthetic adrenocortical steroid, is a white-to-practically-white, odorless, crystalline powder.

FORMULATION

Dexamethasone is a commercially available drug, supplied both as drops for PO administration and as various sterile formulations for parenteral administration.

STORAGE CONDITIONS

Dexamethasone is to be stored at controlled room temperature 20 to 25ºC (68 to 77ºF). Consult the package insert of the respective product for additional storage and usage instructions.

ACCOUNTABILITY

Sites will be required to record and document subject compliance regarding dexamethasone dosing.

CYCLOPHOSPHAMIDE

DESCRIPTION

Cyclophosphamide, a nitrogen mustard alkylating agent, is a crystalline powder with a molecular weight of 279.1.

FORMULATION

Cyclophosphamide 50 mg tablets for oral administration is available as blister containing 50 tablets.

STORAGE CONDITIONS

Cyclophosphamide tablets may be stored at controlled room temp (<25°C), in a dry place, protected from light. Consult the package insert of the respective product for additional storage and usage instructions.

ACCOUNTABILITY

Sites will be required to record and document subject compliance regarding cyclophosphamide dosing.

CORRELATIVE STUDIES

IDENTIFICATION OF MOLECULAR PROFILES IN YOUNG MULTIPLE MYELOMA PATIENTS

Rationale:

Understanding the molecular basis of cancer is a critical step toward devising the most effective treatment to a single patient and moving from a one-fits-all therapeutic approach to a more personalized medicine. In MM, molecular targeted therapies and personalized approach is still limited, despite extensive basic research as well as clinical advances. What is well understood is that myeloma is a heterogeneous disease with great genetic and epigenetic complexity[28,29]. However, the translation of this huge amount of data into clinical arena is still lacking and understanding myeloma patient biology in the context of current patient care is still an unmet medical need[30].

Objectives:

The primary objective of this substudy is to identify the molecular profiles and clinical characteristics that define subsets of MM patients at diagnosis and at relapse of disease.

The secondary objectives are:

- To study utility of molecular profiles and clinical characteristics as predictors of clinical benefit (response rates, PFS, and OS).
- To evaluate the utility of potential biomarkers from blood and bone marrow samples to assess response and relapse.
- To identify potential targets for novel MM therapeutics.
- To characterize bone disease and response to bone directed therapies in genomically defined subsets of MM.

Biological samples required and time points

Bone marrow and peripheral blood samples are required at baseline, whenever a CR is reached and at first and second clinical relapse, therefore no additional samples are collected. All samples should be sent to the central laboratory located in Turin that will be responsible for management, analyses and storage of these samples. Further investigations could potentially be done if included in written collaboration between the Hematological Department of the University of Turin and Italian or International public and private Institutions. All samples will be centralized in Laboratory of Cytofluorimetry – University of Torino and they will be sent to TGen in Phoenix (Arizona) and VARI in Bostwick (Michigan) and Spectrum Health in Grand Rapids (Michigan) for lab analyses.

MOLECULAR MRD ANALYSIS BY DEEP SEQUENCING METHOD

Background

Novel drugs have been recently introduced in the treatment of MM determining improvement in quality of response and prolonged OS. There is increasing evidence that the depth of the response (CR) using traditional tools has low sensitivity, since residual tumor cells are always present despite the achievement of CR. More sensitive techniques are now showing better correlation between a deep response level and improved outcome, thus they may be used to identify and monitor patients achieving an optimal serological response. Assessing MRD using multiparameter flow cytometry (MFC) and RT-PCR has a prognostic significance in different cohorts of leukemia, lymphoma and MM patients[31-34] . However the sensitivity of these techniques has generally limited their use to the assessment of BM samples, are time-consuming or not sensitive enough. Recently, a new molecular approach, based on next-generation sequencing, displayed promising results on MRD analyses for acute lymphoblastic leukemia[35,36] and chronic lymphocytic leukemia[37]. Preliminary data on MM are also available, showing that there is a high correlation with MFC results and that MRD negativity by sequencing may be a better prognostic indicator than CR by traditional response criteria, with a sensitivity level of 10^{-5} or higher[38]. The increased sensitivity of this technique could lead to proper settings for MRD analyses also on PB and/or serum samples of MM patients. In this way, in a future

perspective, BM aspirates could be avoided at every timepoint, during follow-up, and patients could take advantage of that.

Aim

The project aims to develop a new approach using a novel technique to monitor response to treatment in patients with MM, thus to evaluate the role of molecular MRD as marker of prognosis and early relapse in MM. The main goals we plan to achieve are as following:

- to evaluate the percentage of patients with molecular marker, using this technique;

- to investigate the rate of molecular remission and tumor load reduction in MM patients receiving aggressive therapy and comparison with MFC results;

- to evaluate the prognostic impact of single MRD technique in predicting clinical outcome;

- to investigate plasma cells intraclonal heterogeneity and comparison between diagnosis and relapse.

Patients and Methods

MRD monitoring will be assessed on patients that will reach at least a VGPR before starting maintenance, in the main study. A novel deep sequencing based technique (Sequenta clonoSIGHT) will be used to monitor molecular MRD. All samples will be collected in Laboratory of Cytofluorimetry – University of Torino following standard operation procedures. Flow cytometry analyses will also be assessed. Molecular MRD analyses will be performed in the Sequenta Facility.

Timing of analyses

- at diagnosis (baseline): BM + PB + serum samples

- after about 3, 6, 9 months after starting treatment: PB + serum
- after induction: BM + PB + serum samples

- just before beginning of maintenance: BM + PB + serum samples
- every 3 months during maintenance: PB + serum samples
- every 6 months during maintenance: BM
- First relapse: BM + PB + serum samples for clonal evolution analysis
- Second relapse: BM + PB + serum samples for clonal evolution analysis

PROGNOSTIC ROLE OF 18F-FDG PET/CT IN YOUNG MM PATIENTS RECEIVING UP-FRONT NOVEL AGENTS

Rationale

Incorporation of novel agents into ASCT for MM has affected unprecedented rates of CR. As a result, interest in the evaluation of the depth of response has progressively grown. Assessing MRD allow to identify subgroups of patients with conventionally defined CR who are at different risk of progression or death, but fail to identify the possible persistence of bone focal lesions (FLs) potentially harbouring non secretory MM cells or of sites of active disease outside of the medullary cavity of the bone.

FDG-PET/CT detects with high sensitivity and specificity the presence of myeloma bone lesions and/or bone marrow involvement at the onset of the disease. In particular, PET/CT involvement in terms of number of FLs at diagnosis was shown to be closely associated with different outcomes; highlighting the extremely poor prognosis of patients with extramedullary disease (EMD) at diagnosis. In addition, PET/CT appeared also as a reliable tool for predicting the outcomes (PFS and OS) after both induction and high-dose therapy. In particular, PET-CT negativity after ASCT identified patients with better outcomes in comparison with that of patients with PET-CT positivity.

Objectives

Primary end-points

-To confirm the impact of PET/CT involvement at baseline on clinical outcomes of young MM patients treated up-front with novel agents, particularly on CR duration, TTP, PFS, TFI, TTNT and OS

- To evaluate whether PET/CT involvement at baseline correlates with other prognostic factors, in particular cytogenetic and molecular abnormalities

-To assess the impact of PET/CT negativity after induction therapy and ASCT(s) or consolidation/induction therapy on TTP, PFS, TFI, TTNT and OS

Secondary end-points

-To evaluate the correlation between PET-CT changes and response after induction, ASCT(s) or consolidation therapy according to conventional criteria

-To evaluate the prognostic role of PET/CT changes after treatment in the sub-group of patients with immunophenotypic CR

Design of the sub-study

All patients will be studied at baseline with whole body X Ray (WBXR) or CT or MRI and 18FFDG PET-CT. PET/CT will be repeated after induction (after 4 cycles of treatment) and before the start of lenalidomide maintenance.

Eligibility criteria

Newly diagnosed MM patients enrolled in the CFZ IST trial for whom PET-CT study can be planned and who provide written informed consent to receive PET scans at appropriate timelines.

PET/CT Imaging protocol

Whole-body (including skull, superior limbs and femurs) PET/CT will be carried out using standard procedures in each participating centre. In order to avoid heterogeneity in the interpretation of the

results, PET/CT images will be centralized and revised from an imaging commission, already created. Criteria used to define PET/CT positivity and PET/CT response will be those previously established by the imaging commission.

OUTCOME AFTER RELAPSE

Background:

When using PFS as primary endpoint for confirmatory studies there is the risk that the tumor's drug resistance profile is affected by therapy. The risk has mainly been emphasized in the setting of "continuous treatment", such as maintenance. In such situations, OS rather than PFS is the preferable endpoints.

Objective:

To evaluate the impact of continuous treatment on outcome in MM patients.

To evaluate outcome after relapse. (PFS2 defined as time from randomization to relapse after 2° line therapy), PFS on second line therapy, OS from first relapse, OS from diagnosis in the different treatments arms).

Methods:

We will collect baseline patient characteristics at diagnosis and at the beginning of 2° line therapy (age, ISS, FISH), type and date of 1° line and 2° line therapy, date of progression/death/last followup after 1° line and 2° line of therapy.

ANALYSIS OF INTRA-CLONAL HETEROGENEITY IN MM PATIENTS

Rationale and aim

Multiple Myeloma (MM) is characterized by genomic heterogeneity, with multiple and different clones coexisting and evolving according to a branching evolution model. Therapy of MM has been

improved by the introduction of new non-genotoxic drugs, which have contributed to doubling the average life expectancy of the patients.
In order to improve the understanding of the dynamics of MM clonal diversification and selection, this sub-study is aimed at the evaluation of the impact of the different treatment strategies proposed by the clinical trial (either CCyd, or CRd, or R or CR) on MM clonal evolution.

Methods and samples

We are planning to assess the fluctuation of specific genomic lesions under the therapeutic selective pressure, in order to compare the genomic clonal architecture of sequential disease phases with the different treatments (e.g. triplet, doublet, single agent) actually received. FISH analysis, SNPs array analysis and ultra-deep amplicon sequencing will be used to evaluate the genomic lesions, in order to analyze the presence of both major and putative minor(s) clone(s).

To perform this study, paired samples, taken before starting up-front therapy and at the time of first and subsequent relapse(s) are requested. Approximately 50 patients for each treatment arm should be included in this sub-study.

An aliquot (approximately $1x10^6$ cells) of the CD138+ bone marrow plasma cells fraction, obtained from the patients at the time points specified above should be send to the Molecular Biology lab of the Institute of Haematology "L.A.Seràgnoli", located in Bologna, which will perform the analysis. The CD138- cell fraction should be sent as well.

MONITORING OF RESPONSE AND MINIMAL RESIDUAL DISEASE BY MASS SPECTROMETRY DETECTION OF MONOCLONAL PROTEIN IN NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS TREATED WITH NOVEL AGENTS

Background Multiple myeloma's (MM) novel therapeutic strategies have led to unprecedent rates of response and survival outcomes. Traditionally response to therapy in was assessed by detection and quantitative measurement of serum and urine monoclonal protein (M-protein) through protein electrophoresis (PEP), immunofixation (IFE), and serum free light chain analysis (FLC).

In addition, minimal residual disease (MRD) assessed by multiparameter flow cytometry (MFC) or high-throughput immunoglobulin gene sequencing (NGS) of the bone marrow (BM) cells identifies a deeper level of response, associate to favorable long-term outcome [53, 54].

Though high sensitivity, BM MRD evaluation by NGS or MFC, do not allow to detect extramedullary disease. This can partially be overcome by PET-CT imaging-MRD detection. Some problematic issues in the use of these methods are the costs, inter-laboratory variability, the invasiveness (i.e. BM biopsy) required to assess MRD and the lack of correlation BM and peripheral blood MRD status [55].

Mass spectrometry (MS) is an innovative and highly sensitive method to identify and measure Mprotein. MS is non-invasive and can be used as systemic marker of MRD.

In a retrospective study of patients who had undergone autologous stem cell transplantation (ASCT) 81% of patients who had achieved stringent Complete Response (sCR) after transplant still had detectable M-protein by LC-ESI-TOF-based monoclonal Ig rapid accurate mass measurements (miRAMM) [4]. Moreover, both persistent miRAMM negativity and declining M-protein levels by miRAMM during the first post-transplant year were strongly associated with PFS (51.6 months versus 17.9 months in patients with rising levels by miRAMM $P<0.0017$) [56].

MS to detect MRD and the comparison with Next Generation Flow (NGF) has been performed by Puig et al in the GEM-CESAR trial exploring KRd and ASCT in smoldering MM. Their preliminary results shows how MS by QIP-MS have similar rate of MRD detection as NGF, with low level of discordance [57].

Currently no data are available regarding MS evaluation and their potential significance in the context NDMM examining both transplant and non-transplant approaches.

Aim

- Determine the rate of MS positivity in patients in ≥VGPR/ sCR pre-maintenance in the FORTE trial (NCT02203643)
- Determine the correlation and differences of MRD detection by MS, MFC (10-5 sensitivity) and NGS (10-5/10-6 sensitivity) in the same population
- Determine association between MS negativity/kinetics and PFS/OS

Methods

- MS will be evaluated immediately prior to maintenance in all patients who have achieved ≥VGPR, and at the time of first IFE-positivity during the maintenance phase in patients who had previously achieved sCR.
- Samples from patients who had achieved sCR at the start of maintenance will be analyzed with MS over the course of maintenance at six-month intervals until progression.
- Peripheral blood samples matched to marrow samples at the time of MRD assessment will also undergo MS analysis.

ANALYSIS OF THE ROLE OF CLONAL HEMATOPOIESIS OF INDETERMINATE POTENTIAL IN MULTIPLE MYELOMA PATIENTS TREATED WITH CARFILZOMIB

Background

Clonal hematopoiesis of indeterminate potential (CHIP) is mainly defined as the presence of somatic mutations that leads to an expansion of a hematopoietic stem cell clone, which is correlated to aging of hematopoietic system. CHIP is associated with higher incidence of hematological neoplasia and an increase of all-cause mortality, in particular due to an increased risk of cardiovascular disease[58,59,60,61]. CHIP has been detected in multiple myeloma (MM) with an overall incidence of about 11% (n = 18/161), 13.4% (n= 7/52) and 32% (n=204/629) in subjects undergoing autologous stem cell transplantation (ASCT)[62,63,64].

Secondary primary malignancies (SPM) are reported in patients with MM which underwent therapy with alkylating agents and immunomodulatory drugs (IMiDs), in particular lenalidomide[65,66,67,68]. Treatment with Carfilzomib is associated with increased risk of cardiovascular adverse events. Still it is not clear if CHIP could play a role in the myeloma disease phenotype, risk of therapy-related malignancies, cardiovascular complications, likely all-cause mortality. Therefore, it is critical to understand the role of CHIP in MM patients who are treated with carfilzomib and lenalidomide.

Aims and methods

Bone marrow whole blood, peripheral blood and serum sample of MM patients will be analyzed with high throughput sequencing technologies.

Presence of CHIP mutations will be correlated with clinical data regarding therapy, survival outcomes, occurrence of secondary malignancies and toxicities.

STUDY COMMITTEE

A steering committee that includes a subset of investigators in this study will be formed to provide advice on the conduct of the study and publications. This policy may be changed with the agreement of the investigators will routinely monitor the safety in this study including at prespecified interim analyses. At pre-specified interim analyses, renal, infective, cardiologic and all drug-related AEs will be presented to the DMC. Moreover, DMC will evaluate the rate of failed mobilizations. In case more than 15% of patients will fail the mobilization, or DMC recommendation after the analysis of safety data, the study will be interrupt.

REGULATORY OBLIGATIONS

INFORMED CONSENT

The Investigator must obtain informed consent of a subject or his/her designee prior to any study related procedures as per GCPs as set forth in the CFR and ICH guidelines. Documentation that informed consent occurred prior to the subject's entry into the study and the informed consent process should be recorded in the subject's source documents. The original consent form, signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study, must be maintained in the Investigator's study files.

COMPLIANCE WITH LAWS AND REGULATIONS

The study will be conducted in accordance with the Ethical Principles arising from the Helsinki Declaration (see link http://www.wma.net/en/30publications/10policies/b3/), Guidelines of the Good Clinical Practice (GCP) and applicable regulatory requirements. This study must have the approval of a properly constituted IRB or Ethics Committee. Before the investigational drug is shipped to the Investigator, the Investigator or designee will provide the Sponsor with a copy of the IRB or Ethics Committee approval letter stating that the study protocol and any subsequent amendments and informed consent form have been reviewed and approved.

The Investigator is responsible for notifying their IRB or Ethics Committee of any significant adverse events that are serious and/or unexpected.

Amgen and Celgene will provide the Sponsor and the Sponsor will provide the study sites with any expedited safety reports generated from any ongoing studies with Carfilzomib and Lenalidomide, changes to the Investigator's Brochure, and any other safety information which changes the risk/benefit profile of Carfilzomib and Lenalidomide during the conduct of the study, to allow

him/her to fulfill his/her obligation for timely reporting to the IRB/ECs and other Investigators participating in the study.

Upon completion of the trial, the Investigator must provide the IRB or Ethics Committee with a summary of the trial's outcome.

PRE-STUDY DOCUMENTATION REQUIREMENTS

SUBJECT CONFIDENTIALITY

Subject medical information obtained as part of this study is confidential, and must not be disclosed to third parties, except as noted below. The subject may request in writing that medical information be given to his/her personal physician.

The Investigator/Institution will permit direct access to source data and documents by the Sponsor and/or its designee and/or other applicable regulatory authorities The access may consist of trialrelated monitoring, audits, IRB or Ethics Committee reviews, and any other National or foreign regulatory agency.

Release of research results should preserve the privacy of medical information and must be carried out in accordance with the Legislative Decree n.196 of 30 june 2003 "Personal Data Protection Code".

ADMINISTRATIVE AND LEGAL OBLIGATIONS

GOOD CLINICAL PRACTICE

The study will be conducted in accordance with the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at

the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

ETHICAL CONSIDERATIONS

The study will be conducted in accordance with applicable regulatory requirement(s) and will adhere to GCP standards. The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will be conducted only at sites where IRB/IEC approval has been obtained.

PATIENT INFORMATION AND INFORMED CONSENT

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

PATIENT CONFIDENTIALITY

In order to maintain patient privacy, all data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient study number. If requested, the investigator will grant monitor(s) and auditor(s) from the Sponsor or its designees and regulatory authority(ies) access to the patient's original medical records for verification of data gathered on the data capture records and to audit the data collection process.

The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

INVESTIGATOR COMPLIANCE

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Any departures from the protocol must be fully documented in the source documents.

ON-SITE AUDITS

Regulatory authorities, the IEC/IRB and/or Sponsor may request access to all source documents, data capture records, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

INVESTIGATOR AND SITE RESPONSIBILITY FOR DRUG ACCOUNTABILITY

Accountability for the study drug at all study sites is the responsibility of the principal investigator. The investigator will ensure that the drug is used only in accordance with this protocol. Drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each patient, will be maintained by the clinical site. Accountability records will include dates, quantities, lot numbers, expiration dates (if applicable), and patient numbers; accountability records should be send to the sponsor if requested.

PRODUCT COMPLAINTS

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact the Sponsor and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Quality representative. Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to the Sponsor.

CLOSURE OF THE STUDY

This study may be prematurely terminated, if in the opinion of the investigator or the Sponsor there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided by the Sponsor, to the Sponsor by the Site Investigator, to the IEC and regulatory authorities

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient, incomplete and/or unevaluable data
- Determination of efficacy based on interim analysis
- Plans to modify, suspend or discontinue the development of the drug

RECORD RETENTION

The investigator will maintain all study records according to the ICH-GCP and applicable regulatory requirement(s).

USE OF INFORMATION

All information regarding Carfilzomib and Lenalidomide supplied by the Sponsor to the investigator is privileged and confidential information. The investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. The Sponsor will use the information obtained from this clinical study toward the development of Carfilzomib and lenalidomide and may be disclosed to regulatory authority(ies), other investigators, corporate partners, or consultants as required. Upon completion of the clinical study, the Sponsor, the study Sites (investigators) may publish or disclose the clinical trial results pursuant to the applicable regulations, in particular in compliance with art. 5 par 3 lett. c) of the Ministerial Decree of 12 may 2006.

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Appendix A: NCI-CTCAE Version 5.0

Common Terminology Criteria for Adverse Events (CTCAE) of the
National Cancer Institute (NCI) v5.0

Publish Date: November 27, 2017

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_8.5x11.pdf

APPENDIX B: MULTIPLE MYELOMA DIAGNOSTIC CRITERIA

THE INTERNATIONAL MYELOMA WORKING GROUP DIAGNOSTIC CRITERIA:

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma defining events:

- Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
- Hypercalcaemia: serum calcium >0,25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2,75 mmol/L (>11 mg/dL)
- Renal insufficiency: creatinine clearance <40 mL per min† or serum creatinine >177 µmol/L (>2 mg/dL)
- Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L
- Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT‡
- Any one or more of the following biomarkers of malignancy:
- Clonal bone marrow plasma cell percentage* ≥60%
- Involved:uninvolved serum free light chain ratio§ ≥100
- >1 focal lesions on MRI studies

*Clonality should be established by showing κ/λ-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used.

†Measured or estimated by validated equations.

‡If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.

§These values are based on the serum Freelite assay. The involved free light chain must be ≥100 mg/L.

¶Each focal lesion must be 5 mm or more in size.

APPENIDX C: STAGING

DURIE AND SALMON Staging System Stage I

All of the following:

Haemoglobin>10 g/dl

Normal serum calcium <12 mg/dl Skeletal

survey normal bone structure Low M

component production rates:

•IgG < 5 g/dL

•IgA < 3 g/dL

•Urine light chain M component on electrophoresis < 4 g/24h

Stage II

Overall data not as minimally abnormal as shown for stage I and no single value abnormal as defined for stage III

Stage III

One or more of the following:

Hemoglobin < 8.5 g/dL

Serum calcium value > 12 mg/dL Advanced

lytic bone lesions, three or more High M

component rates:

•IgG > 7 g/dL

•IgA > 5 g/dL

•Urine light chain M component on electrophoresis > 12 g/24h

Subclassification

A = relatively normal renal function (serum creatinine value < 2 mg/dL)

B = abnormal renal function (serum creatinine > 2 mg/dL)

INTERNATIONAL MYELOMA WORKING GROUP STAGING SYSTEM

•Stage I	Serum β_2-microglobulin < 3.5 mg/L; Serum Albumin ≥ 3.5 g/dL
•Stage II	Neither Stage I or Stage III
•Stage III	Serum β_2-microglobulin >5.5 mg/L

APPENDIX D: CRITERIA FOR RESPONSE

RESPONSE	CRITERIA FOR RESPONSE[a] [49]
Stringent Complete Response (sCR)	CR as defined below plus Normal Free Light Chain (FLC) ratio and Absence of clonal cells in bone marrow[b] by immunohistochemistry or immunofluorescence[c]

Complete response (CR)	Negative immunofixation on the serum and urine and Disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow[b]
Very Good Partial Response (VGPR)	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine Mprotein level < 100 mg per 24 h If the serum and urine M-protein are unmeasurable[d] a ≥ 90% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria
Partial Response (PR)	≥ 50% reduction of serum M-protein and reduction in 24-h urinary Mprotein by ≥ 90% or < 200mg per 24 h If the serum and urine M-protein are unmeasurable[d] a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30%

	In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
Stable Disease (SD) (not recommended for use as an indicator of response; stability of disease is best described by providing the time to progression estimates)	Not meeting criteria for CR, VGPR, PR or progressive disease
Progressive disease[a] To be used for calculation of time to progression and progression-free survival end points for all patients including those in CR (includes primary progressive disease and disease progression on or off therapy)	Progressive disease: required one or more of the following: Increase of ≥ 25% from nadir in Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dl)[e] Urine M-component and/or (the absolute increase must be ≥ 200 mg/24 h Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels. The absolute increase must be >10 mg/dl. Bone marrow plasma cell percentage: the absolute % must be ≥ 10%[f] Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas. Development of hypercalcemia (corrected serum calcium ≥ 11.5 mg/dl or 2.65 mmol/l) that can be attributed solely to the plasma cell proliferative disorder

Clinical Relapse[a]	Clinical relapse requires one or more of: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features)[e]. It is not used in calculation of time to progression or progression-free survival but is listed here as something that can be reported optionally or for use in clinical practice
	1. Development of new soft tissue plasmacytomas or bone lesions 2. Definite increase in the size of existing plasmacytomas or bonelesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the crossdiameters of the measurable lesion 3. Hypercalcemia (411.5 mg/dl) [2.65 mmol/l] 4. Decrease in hemoglobin of ≥ 2 g/dl [1.25 mmol/l] 5. Rise in serum creatinine by 2 mg/dl or more [177 mmol/l or more]

[a] All response and relapse categories require two consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. [b] Confirmation with repeat bone marrow biopsy not needed.

[c] Presence/absence of clonal cells is based upon the k/l ratio. An abnormal k/l ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is k/l of > 4:1 or < 1:2. [d] Measurable disease is defined by at least one of the following three measurements:

4. Serum M-protein > 1 g/dl (> 10 gm/l)[10 g/l]
5. Urine M-protein > 200 mg/24 h
6. Serum FLC assay: Involved FLC level > 10 mg/dl (>100 mg/l) provided serum FLC ratio is abnormal

[e] For progressive disease, serum M-component increases of >1 gm/dl are sufficient to define relapse if starting M-component is > 5 g/dl.

[f] Relapse from CR has the 5% cutoff versus 10% for other categories of relapse.

[g] For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease.

APPENDIX E: CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE

The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

•Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR/PR (whichever status is recorded first) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

• Progression-Free survival

Progression Free Survival will be measured as the time from randomizations to the time the patient is first recorded as having disease progression, or the date of death if the patient dies due to causes other than disease progression.

• Time To Progression

Time to Progression will be measured as the time from randomizations to the time the patient is first recorded as having disease progression

• Time to next therapy

Time to the next anti-myeloma therapy calculated as the time from randomizations to the time when the next anti-myeloma therapy is administered (either after discontinuation from the treatment phase or during the treatment phase) or the date of death. Time to the next anti-myeloma therapy will be censored at the last assessment date or visit date for subjects who have not been administered another anti-myeloma therapy by the time of analysis.

- **Progression-Free survival 2**

Progression-free survival 2 (PFS2) will be measured from the date of randomizations to the date of observation of second disease progression (i.e. progression after the second line of therapy) or death to any cause as an event. In case of date of second progression is not available, date of start of third line treatment can be used. Subjects who withdraw from the study will be considered at the time of the last complete disease assessment. Subjects who have no progressed, and are still alive at the cut-off date of final analysis will be censored at the cut-off date. All subjects who were lost to follow-up prior to the end of the study, have no progressed, and are still alive will also be censored at the time of last contact.

- **Overall Survival**

Overall Survival will be measured as the time from randomizations to the date of death or the last date the patient was known to be alive.

APPENDIX F:KARNOFSKY PERFORMANCE STATUS SCALE

POINTS	DESCRIPTION
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or to do active work
60	Requires occasional assistance but is able to care for most of his/her needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization indicated. Death not imminent
20	Very sick; hospitalization necessary; active support treatment necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

APPENDIX G: SKELETAL SURVEY FILMS

The following are the minimum plain radiologic films required for skeletal (bone) survey:

•Lateral skull

•AP and lateral cervical spine

•AP and lateral thoracic spine

•AP and lateral lumbar spine

•PA chest

•PA pelvis

•AP upper extremities, shoulder to elbow

•AP lower extremities, hip to knee

Other radiologic film may be necessary to view symptomatic areas or known pre-existing lesions in skeletal regions not included in the films above.

APPENDIX H: PREGNANCY TESTING GUIDELINES AND ACCEPTABLE BIRTH CONTROL METHODS

Women of Child Bearing Potential:

Only 2 criteria are allowed for the status of not of childbearing potential, hysterectomy or menopausal for 24 consecutive months. Women of childbearing potential must confirm to the best of their knowledge that they are not pregnant nor intend to become pregnant during the study. They must be informed and understand the risk of birth defects, and agree not to become pregnant while taking study drugs.

Pregnancy Testing Requirements:

Women of childbearing potential must have two negative pregnancy tests (sensitivity of at least 50 mIU/mL). The first should be performed within 10 – 14 days and the second within 24 hours before the start of study drugs therapy. If the subject is pregnant, she cannot take the study drugs. The subject must have a pregnancy test done by the doctor every week during the first 4 weeks of treatment. She will then have a pregnancy test every 4 weeks if her menstrual cycles are regular or every 2 weeks if her cycles are irregular. The subject may also need to have a pregnancy test if she misses her period or has unusual menstrual bleeding.

Birth Control Methods

If there is ANY chance that the subject can get pregnant, she must either commit to continued abstinence from heterosexual intercourse or begin TWO methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 4 weeks before she starts taking study drugs. Barrier methods alone (i.e. condoms) are not sufficient. These birth control methods must be used for at least 4 weeks before starting therapy, all during treatment and for at least 4 weeks after treatment has stopped. The subject must be given information about the following acceptable birth control methods:

Highly Effective Methods	Additional Effective Methods
Intrauterine device (IUD)	Latex condom
Hormonal (birth control pills, injections, implants)	Diaphragm
Tubal ligation	Cervical Cap
Partner's vasectomy	

Remember: The subject must use at least one highly effective method and one additional effective method AT THE SAME TIME. However, the doctor may recommend that the subject use two barrier methods for medical reasons. The subject must talk to the doctor before changing any birth control methods she has already agreed to use.

If the subject has sex without birth control or if for any reason she thinks she may be pregnant, she must IMMEDIATELY stop taking study drugs and IMMEDIATELY tell the doctor. If the subject gets pregnant, she must IMMEDIATELY contact the doctor to discuss the pregnancy.
The subject must not breast-feed a baby while she is being treated with study drugs. The subject must NEVER donate blood or ova while she is being treated with study drugs. Study drugs do not induce abortion of the fetus and should never be used for contraception.

Men:
The subject must be informed and understand the risk of birth defects, and agrees to use latex condoms every time he has sex with a woman while he is taking study drugs and for 4 weeks after he stops taking the drugs even if he has had a successful vasectomy.
The subject must tell the doctor if he has sex with a woman without using a latex condom, or if he thinks for any reason that his partner may be pregnant.

The subject must NOT be a sperm or blood donor while he is being treated with carflilzomib.

APPENDIX I: SAMPLES COLLECTION AND SHIPMENT TIMETABLE FOR ALL PATIENTS ENTERED THE STUDY

At screening
20 ml bone marrow aspirate in Na citrate
10 ml peripheral blood in Na citrate
5 ml peripheral blood in EDTA
7 ml peripheral blood in red top (serum)

3 months after starting treatment
10 ml peripheral blood in Na citrate
7 ml peripheral blood in red top (serum)

6 months after starting treatment
20 ml bone marrow aspirate in Na citrate
10 ml peripheral blood in Na citrate
5 ml peripheral blood in EDTA
7 ml peripheral blood in red top (serum)

9 months after starting treatment
10 ml peripheral blood in Na citrate
7 ml peripheral blood in red top (serum)

At CR confirmation (regardless of the treatment phase or month from the beginning of treatment)
20 ml bone marrow aspirate in Na citrate
10 ml peripheral blood in Na citrate
5 ml peripheral blood in EDTA
7 ml peripheral blood in red top (serum)

ONLY FOR PATIENTS ACHIEVING AT LEAST A VGPR

After consolidation and before starting maintenance (about 12 months after starting treatment)
20 ml bone marrow aspirate in Na citrate
10 ml peripheral blood in Na citrate
5 ml peripheral blood in EDTA
7 ml peripheral blood in red top (serum)

During maintenance (every 3 months until clinical progression)
10 ml peripheral blood in Na citrate
7 ml peripheral blood in red top (serum)

During maintenance (every 6 months until clinical progression)
20 ml bone marrow aspirate in Na citrate
10 ml peripheral blood in Na citrate
5 ml peripheral blood in EDTA
7 ml peripheral blood in red top (serum)

At first and second clinical relapse
20 ml bone marrow aspirate in Na citrate
10 ml peripheral blood in Na citrate
5 ml peripheral blood in EDTA
7 ml peripheral blood in red top (serum)

TIMEPOINTS	**SAMPLES**			
	BM in Na citrate (20 ml)	PB in EDTA (5 ml)	PB in Na citrate (10 ml)	PB in red top (serum) (7 ml)
All patients				
Screening	X	X	X	X
3 months after staring treatment			X	X
6 months after staring treatment	X	X	X	X
9 months after staring treatment			X	X
At CR confirmation*	X	X	X	X
At first and second clinical relapse	X	X	X	X
Only patients achieving at least a VGPR				
After consolidation and before starting maintenance (about 12	X	X	X	X

months after starting treatment)				
During maintenance (every 3 months until clinical progression)			X	X
During maintenance (every 6 months until clinical progression)	X	X	X	X

*Regardless of the treatment phase or month from the beginning of treatmentAPPENDIX J: Neurological assessment

Subject number_____ Initials_____ Date of visit_____

For any abnormal finding during exam, Grade should be assigned according to the CTCAE version 5.0 criteria

Motor

		Normal	Abnormal	Not Done	If abnormal, describe		
					CTCAE Grade	Primary relationship	Description
Muscle weakness	Upper extremities						
	Lower extremities						

Muscle weakness grades:
1=Symptomatic, perceived by patient but not evident on physical exam;
2=Symptomatic, evident on physical exam, limiting instrumental activities of daily living (ADL);
3=Limiting self care, ADL, disabling

Sensory

Deep tendon reflexes grades:

1=Asymptomatic or mild symptoms, clinical or diagnostic observations only, intervention not indicated;
2=Moderate; minimal, local or nonivasive intervention indicated; limiting age-appropriate instrumental ADL;
3=Severe or medically significant but not immediately life-threatening, hospitalization or prolongation of existing hospitalization indicated, disabling, limiting self care ADL 4=Life-threatening consequences; urgent intervention indicated;
5=Death

Paresthesia grades: 1=Mild symptoms;
2=Moderate symptoms, limiting instrumental ADL; 3=Severe symptoms, limiting self care ADL.

Pain grades:
1=Mild pain;
2=Moderate pain, limiting instrumental ADL; 3=Severe symptoms, limiting self care ADL.

Principal or Sub-Investigator Signature: _____
Date_____

Print Name of Principal or Sub-Investigator:
_____

APPENDIX K: Procedures for AE and SAE reporting

The SPONSOR will submit to the Company's representative identified using forms provided, all Serious Adverse Event and pregnancy reports in clinical trials involving Study Drug regardless of whether causality with the administration of Study Drug is suspected by the investigator. The SPONSOR will transmit the SAE report to the Company's representative within 24 hours of becoming aware of the event(s). Follow-up information will be transmitted within a further 2 working days. Any serious adverse event will be to reportable to Ethics Committees and to Health Authority. In addition, the SPONSOR will send copies of any relevant correspondence with regulatory authorities regarding any and all serious adverse event, irrespective of association of the study drug (s) in the course of the clinical trial, within 24 hours of such report or correspondence being sent to applicable regulatory authorities. Copies should be sent via fax or via email directly to the Companies representative. The Company's representative will create and provide the SPONSOR, the Principal Investigator, the promoter and the sites with a quarterly frequency of reconciliation of the serious adverse event reports of the study trial. Once at year, the SPONSOR will create and provide the Companies, the Ethics Committes and the Principal Investigator of the trial and all the principal Investigators of all sites of an Development Safety Update Report (DSUR) of the events happened in the study.

The SPONSOR will evaluate if the SAE qualifies as a suspected unexpected serious adverse reaction (SUSAR); for any serious unexpected suspected adverse reaction (SUSAR) from any sites participating in the trial which are considered to be reportable, will have responsibility for reporting such events to Principal Investigator, Health Authorities, Ethics Committees, Companies representative within 7 calendar days for fatal or life-threatening reports and within 15 calendar days for all the other cases.

SPONSOR will notify the SUSAR, after the SAE's evaluation, into the Eudravigilance (EVWEB) All the SUSAR forms will be sent as soon as possible but at latest within 7 calendar days after SPONSOR received the report for fatal life-threatening SUSARS and within 15 calendar days for the other SUSARS.

APPENDIX L: EORTC QLQ-C30 Quality of Life Questionnaire EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: __ __ __ __

Your birthdate (Day, Month, Year): __ __ __ __ __ __ __ __

Today's date (Day, Month, Year): __ __ __ __ __ __ __ __

	at Not All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4

4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	**A Little**	**Quite a Bit**	**Very Much**
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4

15. Have you vomited?	1	2	3	4

During the past week:

	Not at All	**A Little**	**Quite a Bit**	**Very Much**
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4

24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7

Very poor Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor Excellent

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APPENDIX M: EORTC QLQ-MY20 Quality of Life Questionnaire

EORTC QLQ-MY20

Patients sometimes report that they have the following symptoms. Please indicate the extent to which you have experienced these symptoms during the past weeks. Please answer by circling the answer that best applies to you.

During the past week:

	Not at All	**A Little**	**Quite a Bit**	**Very Much**
31. Have you had bone aches or pain?	1	2	3	4
32. Have you had bone pain in your back?	1	2	3	4
33. Have you had pain in your hip?	1	2	3	4
34. Have you had pain in your arm or shoulder?	1	2	3	4
35. Have you had pain in your chest?	1	2	3	4
36. If you had pain did it increase with activity?	1	2	3	4
37. Did you feel drowsy?	1	2	3	4
38. Did you feel thirsty?	1	2	3	4
39. Have you felt ill?	1	2	3	4

40. Have you had a dry mouth?	1	2	3	4
41. Have you lost any hair?	1	2	3	4
42. Answer this question only if you lost any hair: were you upset by the loss of your hair?	1	2	3	4
43. Did you have tingling hands or feet?	1	2	3	4
44. Did you feel restless or agitated?	1	2	3	4
45. Have you had acid indigestion or heartburn?	1	2	3	4
46. Have you had burning or sore eyes?	1	2	3	4

During the past week:

	Not at All	**A Little**	**Quite a Bit**	**Very Much**
51. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
52. Have you been thinking about your illness?	1	2	3	4
53. Have you been worried about dying?	1	2	3	4

54. Have you worried about your health in the future?	1	2	3	4

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APPPENDIX N: MOBILIZATION QUESTIONNAIRE

ID PATIENT:

1) Was mobilization performed at the first attempt?

YES

NO

2) Was plerixafor used to reach the target of cells for mobilization?

YES Date of plerixafor administration_____ NO

3) In case the first mobilization failed, was a second mobilization performed?

YES

NO

4) If a second mobilization has been performed, which technique has been performed?

Cyclophosphamide + G-CSF

Date of cyclophosphamide administration:_____

Dose of cyclophosphamide:_____

Date of G-CSF administration:_____

G-CSF

Date of G-CSF administration:_____

Other:_____

5) Was plerixafor used also during the second mobilization?

YES

NO