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Carfilzomib with cyclophosphamide and dexamethasone or lenalidomide and dexamethasone plus autologous transplantation or carfilzomib plus lenalidomide and dexamethasone, followed by maintenance with carfilzomib plus lenalidomide or lenalidomide alone for patients with newly

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Carfilzomib combined with cyclophosphamide and dexamethasone or lenalidomide and dexamethasone plus autologous transplantation or carfilzomib plus lenalidomide and dexamethasone, followed by maintenance with carfilzomib-lenalidomide or single-agent lenalidomide for patients with newly diagnosed multiple myeloma (FORTE): a randomised, phase 2 trial

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Original article (randomised controlled trial)

SUMMARY

Background. Bortezomib-based induction followed by high-dose melphalan and autologous stem-cell transplantation (MEL200-ASCT) and maintenance with lenalidomide alone (R) is the current standard approach for fit patients with newly diagnosed multiple myeloma (NDMM). We aimed to evaluate efficacy and safety of different carfilzomib-based induction/consolidation approaches with or without transplant and of carfilzomib-lenalidomide vs. lenalidomide maintenance in NDMM.

Methods. We conducted an open-label, randomised, multicentre, phase II study in 42 Italian centres. We enrolled transplant-eligible NDMM patients aged ≤ 65 years and Karnofsky Performance Status $\geq 60\%$. Patients were stratified according to International Staging System (ISS) stage (I vs. II/III) and age (< 60 vs. 60–65 years) and randomised (1:1:1) to KRd-ASCT: four 28-day induction cycles with carfilzomib-lenalidomide-dexamethasone (KRd), melphalan at 200 mg/m² and autologous stem-cell transplantation (MEL200-ASCT), four 28-day KRd consolidation cycles; KRd12: twelve 28-day KRd cycles; or KCd-ASCT: four 28-day carfilzomib-cyclophosphamide-dexamethasone (KCd) induction cycles, MEL200-ASCT, 4 28-day KCd consolidation cycles. Carfilzomib was administered intravenously at 36 mg/m² on days 1, 2, 8, 9, 15, and 16; lenalidomide orally at 25 mg on days 1–21; cyclophosphamide orally at 300 mg/m² on days 1, 8, 15; and dexamethasone orally at 40 mg on days 1, 8, 15, and 22. Thereafter, patients stratified according to induction/consolidation treatment and randomised (1:1) to maintenance treatment with carfilzomib-lenalidomide (KR) vs. lenalidomide (R). Carfilzomib was administered intravenously at 36 mg/m² on days 1–2, 15–16 every 28 days for up to 2 years; lenalidomide orally at 10 mg on days 1–21 every 28 days until progression/intolerance in both arms.

The primary endpoints were the rate of at least very good partial response (\geq VGPR) after induction with KRd vs. KCd and progression-free survival (PFS) with KR vs. R maintenance, both assessed in the intention-to-treat population. This trial is registered with ClinicalTrials.gov (NCT02203643). Study recruitment is complete, and all patients are in the follow-up/maintenance phases.

Findings. Between February 23, 2015, and April 05, 2017, 474 patients were randomised (158 KRd-ASCT; 157 KRd12; 159 KCd-ASCT). The \geq VGPR rate after induction was 70% with KRd vs. 53% with KCd (OR 2.14, 95% CI 1.44–3.19, $p=0.0002$); the rates of stringent complete response (sCR) after consolidation were 46%, 44%, and 32% with KRd-ASCT, KRd12 and KCd-ASCT, respectively (KRd-ASCT vs. KCd-ASCT: OR 1.77, 95% CI 1.12–2.81, $p=0.014$; KRd12 vs. KCd-ASCT: OR 1.66, 95% CI 1.05–2.63, $p=0.030$). The 4-year PFS was 69%, 56% and 51% with KRd-ASCT, KRd12, and KCd-ASCT (KRd-ASCT vs. KCd-ASCT: HR 0.54, 95% CI 0.38–0.78, $p=0.0008$; KRd12 vs. KCd-ASCT HR 0.88, 95% CI 0.64–1.22, $p=0.45$). 356 patients were randomised to maintenance treatment (178 in each arm). The 3-year PFS was 75% with KR vs. 65% with R (HR 0.64, 95% CI 0.44–0.94, $p=0.023$).

During induction/consolidation, the most common grade 3–4 adverse events (AEs) were neutropenia (21 [13%] of 158 patients in the KRd-ASCT group vs. 15 [10%] of 156 patients in the KRd12 group vs. 18 [11%] of 159 patients in the KCd-ASCT group); dermatological toxicity (9 [6%] vs 12 [8%] vs 1 [1%]); and hepatic toxicity (13 [8%] vs. 12 [8%] vs. 0 [0%]). Treatment-related serious AEs (SAEs) were reported in 18 (11%) of 158, 29 (19%) of 156, and 17 (11%) of 159 patients in the KRd-ASCT, KRd12, and KCd-ASCT arms, respectively. The most common SAE was pneumonia (in 7 [4%] of 158, 4 [3%] of 156, and 5 (3%) of 159 patients, respectively). Treatment-emergent deaths were reported in 2 (1%) of 158, 2 (1%) of 156, and 3 (2%) of 159 patients in the KRd-ASCT, KRd12, and KCd-ASCT arms, respectively.

During maintenance, the most common grade 3–4 AEs were neutropenia (35 [20%] of 173 patients in the KR group vs 41 [23%] of 177 patients in the R group), infections (8 [5%] vs. 13 [7%]); and vascular events (12 [7%] vs. 1 [1%]). Treatment-related SAEs were reported in 24 (14%) of 173 vs. 15 (8%) of 177 patients in the KR vs. R arms, respectively. The most common SAE was pneumonia (in 6 [3%] of 173 vs. 5 [3%] of 177 patients, respectively); 1 patient died of treatment-emergent death in the KR arm.

Interpretation. Our data showed the superiority of KRd-ASCT over the other two arms and support the prospective randomised evaluation of KRd-ASCT vs. standards of care such as daratumumab-bortezomib-thalidomide-dexamethasone-ASCT in the transplant-eligible population. KR maintenance was superior to the standard-of-care R alone.

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Keywords. Newly diagnosed multiple myeloma; carfilzomib; lenalidomide; cyclophosphamide; dexamethasone; autologous stem-cell transplantation; maintenance treatment

RESEARCH IN CONTEXT

Evidence before this study

The combination of the second-generation proteasome inhibitor (PI) carfilzomib with lenalidomide and dexamethasone (KRd) showed efficacy in relapsed/refractory patients with multiple myeloma (MM) and was considered an emerging option for first-line therapy. Based on the good efficacy–safety profile of the bortezomib-cyclophosphamide-dexamethasone combination upfront, carfilzomib in combination with cyclophosphamide and dexamethasone (KCd) was also considered as a potential alternative.

On August 11, 2021, we searched the database PubMed.gov, using the search terms “myeloma”, “newly diagnosed”, “carfilzomib”, “lenalidomide” or “cyclophosphamide”, and “maintenance” in the “title/abstract” field and we added the search filter “clinical trial”. We identified 8 full-text articles reporting data from clinical trials: 3 phase I/II trials using KCd, and 3 phase II trials and 1 phase III trial evaluating KRd.

So far, upfront autologous stem-cell transplantation (ASCT) showed a consistent advantage in terms of progression-free survival (PFS) over all tested combinations containing novel agents. Nevertheless, no trials have previously evaluated a carfilzomib-based first-line therapy with or without ASCT intensification in a randomised fashion.

PIs such as bortezomib and ixazomib have also been tested in the maintenance setting. In an attempt to improve the efficacy of the standard-of-care lenalidomide alone, in our study the PI carfilzomib was added to lenalidomide alone in maintenance treatment, with a reduced intensity in the schedule of administration and for a fixed duration of 2 years.

Added value of this study

To our knowledge, the FORTE study is the first multicentre randomised trial enrolling transplant-eligible, newly diagnosed (ND)MM patients and comparing different carfilzomib-based therapies in the context of upfront or delayed transplantation. Moreover, so far, no trial has compared the efficacy and toxicity profiles of carfilzomib-lenalidomide (KR) vs. lenalidomide alone (R) as maintenance treatments. Our data confirmed the superiority of combinations between PIs and immunomodulatory (IMiD) agents over PI plus chemotherapy. Furthermore, our exploratory analysis comparing KRd-ASCT vs. KRd for 12 cycles confirmed the important additive role of transplantation in prolonging PFS even in the context of a very effective approach based on KRd.

KR maintenance was superior to the standard-of-care R alone in terms of PFS and rate of conversion to MRD negativity. Despite, as expected, a higher rate of non-haematological AEs with a doublet vs. a single agent (mainly vascular and cardiac events in the KR arm), no increase in treatment discontinuation due to toxicity was observed in the KR vs. the R arm.

The subgroup analyses showed a consistent benefit of KRd-ASCT and KR maintenance in all prognostic subgroups, with similar hazard ratios in the high-risk and standard-risk populations.

Implication of all the available evidence

Our results confirm that a triplet based on carfilzomib and lenalidomide (KRd) plus high-dose chemotherapy and ASCT lead to deep and durable responses, without a high burden of toxicity. A carfilzomib-based therapy is also particularly effective in high-risk patients, which currently represent an unmet clinical need. These data compare favourably with standards of care such as bortezomib-lenalidomide-dexamethasone-ASCT and daratumumab-bortezomib-thalidomide-dexamethasone in patients eligible for ASCT (including high-risk patients) and support the further evaluation of KRd-ASCT alone or in combination with anti-CD38 monoclonal antibodies.

Maintenance treatment with KR, even if associated with slightly higher toxicity, showed a high level of efficacy, which supports its potential role as a new standard of care, especially with the use of strategies to minimize the risk of toxicity and improve compliance (e.g., weekly carfilzomib administration).

Future steps, regarding both the induction/consolidation and the maintenance phases, may include a more tailored approach to treatment, which may be based on patient eligibility to specific therapies, risk-adapted therapy and response-adapted therapy, in order to avoid unnecessary toxicity and maximize treatment efficacy.

INTRODUCTION

The survival of patients with newly diagnosed multiple myeloma (NDMM) dramatically improved in the last 20 years, due to shift from chemotherapy-based regimes to new drugs that are now considered the cornerstones of MM therapy, namely proteasome inhibitors (PIs) and immunomodulatory (IMiD) agents. In particular, in the transplant-eligible (TE) setting, about 60% of patients are alive at 8 years after diagnosis with a sequential approach including bortezomib-lenalidomide-dexamethasone (VRD) induction, high-dose chemotherapy (melphalan at 200 mg/m²) followed by autologous stem-cell transplantation (MEL200-ASCT), VRD consolidation, and lenalidomide maintenance.¹ As part of the induction/consolidation treatment, PIs have also been evaluated in combination with chemotherapy, especially with cyclophosphamide (VCD), which was widely used until few years ago due to its manageable safety profile.²⁻⁴ More recently, the introduction of the anti-CD38 monoclonal antibody (mAb) daratumumab^{5,6} as a fourth drug in the induction/consolidation therapy containing bortezomib-thalidomide-dexamethasone (Dara-VTD) has become a new standard of care.⁷ One of the limitations of the bortezomib-based treatment is the burden of neurotoxic adverse events (AEs) that can lead to discontinuation or dose reduction. The second-generation PI carfilzomib demonstrated superiority over bortezomib in the relapse setting, with neglectable neurological toxicity.^{8,9} The main AEs related to carfilzomib are cardiovascular, although less frequent in young fit patients.¹⁰ This provided the rationale to evaluate carfilzomib in the context of upfront PI-based induction/consolidation in TE patients. In this evolving scenario, impressively effective PI-IMiD combinations were also tested as alternatives to the standard MEL200-ASCT combination, which, despite having been a standard procedure with a very low mortality rate in the recent years, is associated with a significant toxicity burden. Indeed, the last update from the IFM2009 trial confirmed a higher progression-free survival (PFS; median, 47 vs. 35 months) with MEL200-ASCT vs. VRD alone, but no overall survival (OS) advantage.¹ The role of MEL200-ASCT in comparison with potentially more active regimens (quadruplets including mAbs or carfilzomib-based triplets) is currently unknown.

For NDMM TE patients, the actual standard of care after induction and MEL200-ASCT ±consolidation, is continuous lenalidomide maintenance until progressive disease (PD) or intolerance.¹¹⁻¹³ In the maintenance setting, other drugs are under evaluation as single agents or in combination with lenalidomide, aiming at improving outcome without adding an important toxicity burden.

We conducted a phase II randomised multicentre trial to evaluate the role of carfilzomib in the upfront treatment of TE NDMM patients. We aimed to evaluate two different carfilzomib-based induction therapies (carfilzomib-lenalidomide-dexamethasone [KRd] vs. carfilzomib-cyclophosphamide-dexamethasone [KCd]) and three different upfront treatment approaches (KRd-ASCT, KRd for 12 cycles [KRd12] without ASCT, and KCd-ASCT). We also aimed to evaluate the role of carfilzomib-lenalidomide (KR) maintenance compared to the standard-of-care lenalidomide alone (R).

MATERIALS AND METHODS

Study design and participants

This was a randomised, open-label, phase II trial including patients enrolled in 42 Italian centres (appendix pp 8-9). Transplant-eligible NDMM patients aged ≤65 years with symptomatic, measurable disease defined according to standard criteria¹⁴ were eligible. Other inclusion criteria were: Karnofsky performance status ≥60%; life expectancy >6 months; absolute neutrophil count ≥1×10⁹/L; platelet count ≥70×10⁹/L; left ventricular ejection fraction ≥40%; creatinine clearance ≥30 ml/min. Exclusion criteria included: other malignancies within the past 3 years; peripheral neuropathy of grade >2 or grade 2 with pain; unstable angina or myocardial infarction within 4 months prior to randomisation; New York Heart Association functional class III/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 the patient had a pacemaker; and any significant clinical condition that placed the patient at a significant risk if he/she participated in the study. This trial, its protocol, and its amendments (appendix pp 5, 7, 10, and 27) were 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.

Randomisation and masking

At enrolment, a computer system randomly assigned patients to treatment into one of the three induction/consolidation arms (1:1:1 ratio). A block randomisation (block size 12), stratified according to International Staging System (ISS)¹⁵ stage (I vs. II/ III) and age (<60 vs. 60–65 years), was generated at enrolment by a computer program and implemented into a web-based procedure. Patients were eligible for maintenance treatment if they did not experience unacceptable toxicity or progression during the induction/intensification/consolidation phases. Maintenance randomisation was balanced using permuted block (block size 8) and was stratified according to induction/consolidation treatment (1:1 ratio).

Procedures

At enrolment, patients were randomised (first randomisation [Random1]) into one of the three induction/intensification/consolidation arms (appendix p 15).

Patients in the KRd-ASCT arm received 4 28-day induction cycles with KRd (carfilzomib 20 mg/m² intravenous (IV) on days 1-2 of cycle 1, followed by 36 mg/m² IV on days 8-9, 15-16 of cycle 1, then for all subsequent doses 36 mg/m² IV on days 1-2, 8-9, 15-16; lenalidomide 25 mg orally (PO) on days 1-21; dexamethasone 20 mg PO/IV on days 1-2, 8-9, 15-16, 22-23), followed by stem-cell mobilisation and collection (cyclophosphamide at 2000 mg/m² IV on day 1 plus granulocyte colony-stimulating factor [G-CSF] 10 µg/kg subcutaneous from day 5 until stem-cell collection was completed). Thereafter, patients received intensification with MEL200-ASCT and, between day 90 and 120, started consolidation with 4 KRd cycles (same dose and schedule used during the induction phase).

Patients in the KRd12 arm received 4 28-day induction cycles with KRd, followed by stem-cell mobilisation and collection as in the other arms, but they did not proceed with MEL200-ASCT; instead, they received 8 KRd cycles (same dose and schedule used during the induction phase).

Patients in the KCd-ASCT arm received 4 28-day induction cycles with KCd (carfilzomib 20 mg/m² IV on days 1-2 of cycle 1, followed by 36 mg/m² IV on days 8-9, 15-16 of cycle 1, then for all subsequent doses 36 mg/m² IV on days 1-2, 8-9, 15-16; cyclophosphamide 300 mg/m² PO on days 1, 8, 15; dexamethasone 20 mg PO/IV on days 1-2, 8-9, 15-16, 22-23), followed by stem-cell mobilisation and collection and MEL200-ASCT as in the KRd-ASCT arm. Between day 90 and 120, patients started consolidation with 4 KCd cycles (same dose and schedule used during the induction phase).

After the end of consolidation, eligible patients were randomised (second randomisation [Random2]) to maintenance with either lenalidomide (R; 10 mg daily on days 1-21 every 28 days until progression/intolerance) plus carfilzomib (K; 36 mg/m² IV once daily on days 1-2, 15-16 every 28 days; the study was subsequently amended, changing the carfilzomib dose and schedule to 70 mg/m² IV once daily on days 1, 15 for up to 2 years) or lenalidomide alone until progression/intolerance (R).

Carfilzomib dose reductions, delays, or interruptions were permitted after occurrence of haematological adverse events (grade 4 thrombocytopenia with active bleeding and grade 4 lymphopenia > 14 days) and grade 3-4 non hematological adverse events related to carfilzomib (allergic reaction, tumor lysis syndrome, infection, herpes zoster, neuropathy, renal dysfunction with creatinine clearance < 30 ml/min, heart failures). Subsequent treatment with carfilzomib could be resumed reducing the dose by 1 level, according to protocol (appendix pp 9,10). If toxicity continued or re-occurred after 2 dose reductions, the carfilzomib administration was interrupted. Lenalidomide dose adjustments were based on clinical and laboratory findings (appendix pp 10,11). Patients enrolled with creatinine clearance (CrCl) <50 mL/min started with a reduced dose of lenalidomide according to the Dose Adjustment Guideline for Renal Dysfunction (appendix pp 10). In case of grade 4 haematological and grade 3-4 non-haematological toxicities related to cyclophosphamide, the drug was held up to 4 weeks, until the AE was resolved. Dexamethasone dose modifications due to common dexamethasone-related toxicities are listed in appendix. Details on dose reductions/interruptions and other study procedures are included in the appendix (pp 3, 6-7, and 9-12).

Magnetic resonance imaging (MRI), positron emission tomography/computed tomography (PET/CT) or RX skeletal survey were performed within 8 weeks before the first dose of study drug. RX skeletal survey was performed during the screening period and then once a year. MRI, (low dose) CT, or PET/CT were performed at screening and, in case of bone lesions or bone-soft tissue plasmacytoma, were performed after 4 cycles of

the induction phase or after the mobilization phase and at the end of the consolidation phase (before maintenance treatment), in order to evaluate response to treatment, and, thereafter, when clinically indicated. Laboratory tests for haematology clinical chemistry were performed prior to carfilzomib before every infusion during first induction cycle and, from cycle 2, they were repeated only once weekly at physician's discretion and based on patient's condition. Disease assessments, comprising serum protein electrophoresis, 24-h urine protein electrophoresis were done every cycle at day 1. Serum Free Light Chain (FLC) analysis was 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

The response rate was defined according to the International Uniform Response Criteria.¹⁶ A centralised MRD evaluation was performed before maintenance and, thereafter, every 6 months during maintenance by multiparameter flow cytometry (MFC; sensitivity of 10^{-5})¹⁷ in all patients achieving \geq VGPR and by next-generation sequencing (NGS, sensitivity of 10^{-5})¹⁸ in a subset of patients achieving \geq CR (pre-planned sub-study). AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTC version 4.0)¹⁹ and summarised by the worst NCI-CTC grade. More details on response definition are provided in appendix p 4.)

Outcomes

The primary study endpoints were the rate of at least very good partial response (\geq VGPR) with KRd vs. KCd induction and PFS from maintenance randomisation with KR vs. R. Key secondary endpoints were the rate of stringent complete response (sCR) and PFS with KRd-ASCT and KRd12 vs. KCd-ASCT. Other secondary endpoints included OS, overall response rate, minimal residual disease (MRD) negativity, safety, exploratory comparative analyses between subgroups of patients, defined according to known prognostic factors (a detailed list is provided in the appendix, p 4).

Statistical analysis

The calculation of the sample size for the first primary endpoint (rate of \geq VGPR after induction with KRd vs. KCd) was based on the following assumptions, considering the ITT population: 2-sided alpha =0.05 and power =90%; \geq VGPR rate with KCd =62%; and \geq VGPR rate with KRd =80%. The KRd-ASCT and KRd12 arms were pooled (2:1) for the analysis of \geq VGPR, since the treatment population was the same until that point. Using the two-group continuity-corrected chi-square test, the sample size for each arm was 143, for a total of 429 patients. Considering a 10% of patients lost to follow-up, the total sample size was 477 patients. The calculation of the sample size for the second primary endpoint (PFS from Random2 with KR vs. R) was based on the following assumption, considering the ITT population: 4-year PFS 40% with R and 60% with KR (HR=0.558) with a 2-sided alpha=0.05 and beta=0.2. Using an unstratified log-rank test, the sample size required was 196 patients and the number of events required 92.

Efficacy analyses were based on the intention-to-treat (ITT) principle. All patients eligible to treatment and randomised were included. A hierarchical testing procedure was used for the first primary (H1: \geq VGPR rate with KRd vs. KCd induction) and key secondary endpoints (H2: sCR rate; H3: PFS from Random1 in the three induction/intensification/consolidation arms) to achieve control of the overall familywise Type I error rate at a two-sided significance level =0.05. Details regarding the statistical analysis of key secondary endpoints are reported in the appendix (p 5).

A post-hoc analysis was conducted to compare the KRd-ASCT and KRd12 arms and to analyse the different MRD conversion rates (from positive to negative) from pre-maintenance phase and during maintenance, in the different maintenance arms.

The MFC MRD negativity rate was analysed according to the ITT principle, and patients missing MRD evaluation or not achieving a partial response or better ($<$ PR) were considered MRD positive. The NGS MRD negativity rate was instead calculated in patients who achieved a CR and were included in the substudy. For the analysis of the rate of 1-year sustained MFC MRD negativity, patients were considered sustained MRD negative if they were negative before maintenance treatment and maintained MRD negativity for at least 1 year. 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 non-sustained MRD. We used Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the main comparisons. We performed the Grambsch and Therneau test for the proportional hazards

assumption.²⁰ All analyses were adjusted according to stratification factors. Details regarding the analysed outcomes are reported in the appendix (p 4).

Data from all subjects who received any study drug were included in the safety analyses. AEs leading to death or to treatment discontinuation, grade 3–4 events, study-drug-related events, and serious AEs (SAEs) were summarised separately. An independent data monitoring committee reviewed the safety data. Between-group differences in responses/AEs were evaluated using the Mann–Whitney U-test and the chi-squared or Fisher's exact tests, as appropriate, for continuous and categorical variables, respectively. Statistical analyses were performed using R (Version 4.0.2). The data cut-off point was January 7, 2021.

This trial is registered with ClinicalTrials.gov (NCT02203643).

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RESULTS

Four-hundred and seventy-seven patients were enrolled between February 23, 2015 and April 05, 2017; 474 were randomised to one of the induction/intensification/consolidation arms (KRd-ASCT, n=158; KRd12, n=157; KCd-ASCT, n=159), 3 patients were not included due to screening failure. A similar proportion of patients in the three arms entered the intensification and consolidation phases. At the end of consolidation, 356 patients were eligible for maintenance and randomised to KR (n=178) or R (n=178; Figure 1). Baseline demographics and disease characteristics were well balanced across arms (Table 1). At the data cut-off, 198 (42%) of 474 patients progressed or died, 106 (60%) of 178 patients were receiving therapy with KR (all of them completed 2 years of carfilzomib and were receiving lenalidomide alone), and 98 (55%) of 178 with R alone. The median duration of the follow-up was 50.9 months (IQR 45.7–55.3) from Random1 and 37.3 months (IQR 32.9–41.9) from Random2.

With regard to the primary endpoint related to Random1, the rate of \geq VGPR after induction by ITT analysis was significantly higher with KRd (222 [70%] of 315 patients) vs. KCd (84 [53%] of 159 patients; OR 2.14, 95% CI 1.44–3.19, $p=0.0002$; appendix p 12). Responses increased during intensification (appendix p 12) and consolidation, thus leading, to significantly different rates of \geq VGPR, \geq CR, and sCR in the three arms (Table 2). In particular, the sCR rates by ITT (first key secondary endpoint) were 72 (46%) of 158, 69 (44%) of 157, and 51 (32%) of 159 patients in the KRd-ASCT, KRd12, and KCd-ASCT arms, respectively (KRd-ASCT vs. KCd-ASCT: OR 1.77, 95% CI 1.12–2.81, $p=0.014$; KRd12 vs. KCd-ASCT: OR 1.66, 95% CI 1.05–2.63, $p=0.030$). The rate of pre-maintenance MFC MRD negativity (10^{-5}) by ITT was significantly higher with KRd-ASCT (98 [62%] of 158 patients) and KRd12 (88 [56%] of 157 patients) than with KCd-ASCT (69 [43%] of 159 patients; KRd-ASCT vs. KCd-ASCT: OR 2.14, 95% CI 1.36–3.35, $p=0.0010$; KRd12 vs. KCd-ASCT: OR 1.66, 95% CI 1.07–2.60, $p=0.025$). The rate of 1-year sustained MRD negativity (MFC, 10^{-5} cut-off) by ITT was higher with KRd-ASCT (74 [47%] of 158 patients) vs. KRd12 (54 [35%] of 157 patients) vs. KCd-ASCT (39 [25%] of 159 patients; KRd-ASCT vs. KCd-ASCT: OR 2.72, 95% CI 1.69–4.44, $p<0.0001$; KRd-ASCT vs. KRd12: OR 1.69, 95% CI 1.07–2.66, $p=0.024$).

In the ITT population, the 4-year PFS from Random1 was 69% with KRd-ASCT (95% CI 62–77%; median not reached [NR]), 56% with KRd12 (95% CI 48–64%; median 55.3 months), and 51% with KCd-ASCT (95% CI 44–60%; median 53 months; Figure 2A). Patients in the KRd-ASCT arm had a significant reduction in the risk of progression/death, as compared with patients treated with KCd-ASCT (HR 0.54, 95% CI 0.38–0.78, $p=0.0008$); no significant differences were reported between the KRd12 and KCd-ASCT arms (HR 0.88, 95% CI 0.64–1.22, $p=0.45$). Subgroup analyses of the KRd-ASCT vs. KCd-ASCT arms are reported in the appendix (p 16). In a post-hoc analysis, we also observed a significant advantage of KRd-ASCT vs. KRd12 (HR 0.61, 95% CI 0.43–0.88, $p=0.0084$) that was consistent in all subgroups (appendix p 17). The advantage with KRd-ASCT (4-year PFS 83%, 95% CI 75–91%) vs. KCd-ASCT (4-year PFS 63%, 95% CI 53–76%; HR

0.44, 95% CI 0.24-0.80, $p=0.0077$) and vs. KRd12 (4-year PFS 69%, 95% CI 75-91%; HR 0.51, 95% CI 0.28-0.92, $p=0.026$) was also retained in patients who were MFC MRD negative before maintenance. By contrast, a similar 4-year PFS was reported in the three arms in patients who achieved a 1-year sustained MRD negativity: 4-year PFS of 87% with KRd-ASCT (95% CI 80-95%), of 92% with KRd12 (95% CI 85-100%), and of 84% with KCd-ASCT (95% CI 74-97%; appendix p 18). The 4-year OS was 86% with KRd-ASCT (95% CI 81-92%), 85% with KRd12 (95% CI 80-91%), and 76% with KCd-ASCT (95% CI 70-84%), with no significant differences at the current follow-up (appendix p 19).

During maintenance, the depth of response increased in both arms (Table 2). To clarify the role of maintenance in improving response, in a post-hoc analysis, we evaluated the rate of MRD conversion from positivity to negativity with KR vs. R in patients who were MRD-positive before maintenance and who had a second sample available within 2 years of maintenance. Twenty-nine (46%) of 63 patients turned MRD-negative by MFC with KR vs. 18 (30%) of 60 with R ($p=0.046$, adjusted for first randomisation); 14 (56%) of 25 patients turned MRD-negative by NGS with KR vs. 7 (30%) of 23 with R ($p=0.046$, adjusted for first randomisation). With regard to the primary endpoint related to the maintenance comparison, the 3-year PFS from Random2 in the ITT population was 75% with KR (95% CI 68-82%, median NR) vs. 65% with R (95% CI 58-72%, median NR; HR 0.64, 95% CI 0.44-0.94, $p=0.023$; Figure 2B). A subgroup analysis of KR vs. R is shown in appendix (p 20). The significant advantage of KR vs. R was also maintained in MRD-negative patients: 3-year PFS of 82% with KR (95% CI 75-89%) vs. 72% with R (95% CI 65-80%; HR 0.59, 95% CI 0.36-0.95, $p=0.030$). The 3-year OS was 94% with KR (95% CI 90-98%) vs. 90% with R (95% CI 85-95%), with no significant differences at the current follow-up (appendix p 21).

The most common grade 1-2, grade 3 and 4 AEs related to study drugs (carfilzomib, lenalidomide, dexamethasone, and cyclophosphamide) are summarised in Table 3. Toxicities occurred during the standard-of-care treatment with mobilisation and MEL200-ASCT are not reported, except when they caused protocol discontinuation.

During induction/consolidation, the most common grade 3-4 adverse events (AEs) were neutropenia (21 [13%] of 158 patients in the KRd-ASCT group vs. 15 [10%] of 156 patients in the KRd12 group vs. 18 [11%] of 159 patients in the KCd-ASCT group); dermatological toxicity (9 [6%] vs. 12 [8%] vs. 1 [1%]); and hepatic toxicity (13 [8%] vs 12 [8%] vs 0 [0%]). In the pre-maintenance phase, treatment-related SAEs were reported in 18 (11%) of 158, 29 (19%) of 156, and 17 (11%) of 159 in the KRd-ASCT, KRd12, and KCd-ASCT arms, respectively. The most common treatment-related SAEs were pneumonia (7 [4%] of 158, 4 [3%] of 156, and 5 (3%) of 159 patients in the KRd-ASCT, KRd12, and KCd-ASCT arms, respectively) and renal failure (2 [1%] of 158, 3 [2%] of 156, and 2 [1%] of 159 patients in the KRd-ASCT, KRd12, and KCd-ASCT arms, respectively). The rates of treatment discontinuation due to AE were similar in the three arms: 11 (7%) of 158, 12 (8%) of 156, and 12 (8%) of 159 patients in the KRd-ASCT, KRd12, and KCd-ASCT arms, respectively. In the appendix (pp 13-14), we summarise the main causes of treatment discontinuation due to toxicity in each arm according to each treatment phase (induction/mobilisation/intensification/consolidation) and details on cardiac, pulmonary and renal adverse events (appendix pp 5,13).

Four patients discontinued due to mobilisation failure after induction treatment with KRd vs. 1 patient with KCd. The median number of CD34+ stem cells collected was $6.7 \times 10^6/\text{kg}$ (IQR 4.7×10^6 to 9×10^6) with KRd vs. $8.9 \times 10^6/\text{kg}$ (IQR 7×10^6 to 11.2×10^6) with KCd ($p<0.0001$). Overall, 76 (26%) of 288 patients required plerixafor after induction with KRd vs. 8 (6%) of 141 with KCd ($p<0.0001$). The median number of CD34+ transplanted cells was $3.9 \times 10^6/\text{kg}$ (IQR $3.4\text{-}4.6 \times 10^6$) in the KRd-ASCT arm and $4.4 \times 10^6/\text{kg}$ (IQR $3.5\text{-}5.38 \times 10^6$) in the KCd-ASCT arm ($p=0.0001$).

Five patients died during induction, 1 due to PD (in the KCd-ASCT arm), 4 due to AE (KRd-ASCT, $n=1$ heart failure; KRd12, $n=1$ cardiac arrest; KCd-ASCT, $n=1$ pneumonia and $n=1$ cardiac arrest). Two patients died during intensification due to AE (KCd-ASCT, $n=1$ heart failure; KRd12, $n=1$ cardiac arrest). One patient died during consolidation in the KRd-ASCT arm due to cardiac arrest.

Regarding maintenance, the most common grade 3-4 AEs were neutropenia (35 [20%] of 173 patients in the KR group vs 41 [23%] of 177 patients in the R group), infections (8 [5%] vs. 13 [7%]); and vascular events (12 [7%] vs. 1 [1%]). During maintenance treatment, study-related SAEs were reported in 24 (14%) of 173 patients in the KR arm vs. 15 (8%) of 177 in the R arm. The most common treatment-related SAEs were pneumonia (KR 6 [3%] of 173 vs. R 5 [3%] of 177), thrombotic microangiopathy (KR 5 [3%] of 173 vs. R 0 [0%] of 177), renal failure (KR 2 [1%] of 173 vs. R 1 [1%] of 177), and coronary artery disease (KR 2 [1%]

of 173 vs. R 0 [0%] of 177). The rates of treatment discontinuation due to AE were similar in the two maintenance arms: 20 [12%] of 173 patients in the KR arm vs. 22 [12%] of 177 in the R arm (appendix pp 6,7). During maintenance treatment, 1 patient died in the KR arm due to AE (acute renal failure). Fourteen (3%) of 474 patients developed second primary malignancies (SPMs). During mobilisation, 1 patient was diagnosed with melanoma (in the KRd-ASCT arm) and 1 with metastatic breast cancer (KCd-ASCT). During intensification, 1 patient was diagnosed with melanoma (KCd-ASCT). During consolidation, 1 patient developed non-melanoma skin cancer (KRd12). During maintenance, SPMs were detected in 6 patients in the KR arm (n=1 colon carcinoma, n=1 non-melanoma skin cancer, n=1 myelodysplastic syndrome, n=1 thyroid cancer, n=1 duodenal cancer, and n=1 breast cancer) vs. 4 patients in the R arm (n=3 non-melanoma skin cancer and n=1 endometrial cancer).

DISCUSSION

To our knowledge, this was the first randomised trial investigating carfilzomib-based treatment in TE NDMM patients. A significantly larger proportion of patients treated with KRd vs. KCd induction achieved \geq VGPR, thus confirming the superiority of a PI plus IMiD-based therapy over PI plus chemotherapy also with the more effective second-generation PI carfilzomib. Non-haematological AEs were higher with KRd, but the rate of discontinuation for toxicity after induction was comparable (4% vs. 3% with KCd). Similarly, treatment in both arms allowed the collection of an adequate number of stem cells to proceed with MEL200-ASCT, even if the use of plerixafor was necessary in a higher proportion of KRd vs. KCd patients. In line with the superiority of the PI+IMiD combination,² KRd-ASCT was superior to KCd-ASCT in terms of pre-maintenance sCR and MRD negativity, with a highly significant PFS difference. Indeed, we reached the preplanned statistically significant difference in terms of sCR ($p<0.025$) only in the KRd-ASCT vs. KCd-ASCT comparison. Of note, the difference in the MRD rate between the two arms was even more significant. MRD is currently considered to have a stronger prognostic impact than CR/sCR and to be a candidate surrogate endpoint for PFS and OS.^{21,22} We failed to find a significant difference between KRd12 and KCd-ASCT in terms of sCR, at the prespecified statistical cut-off ($p>0.025$). Due to the potential limitation related to the sCR endpoint and the high difference in terms of MRD negativity (included as secondary endpoint in the trial), we decided to proceed anyway with the PFS analysis, despite the original hierarchical design. The PFS analysis corroborated our findings, showing a superimposable PFS between the two arms. In the exploratory analysis of the role of KRd with/without ASCT, the benefit of MEL200-ASCT was confirmed, supporting its established impact on PFS also in this context. Of note, the benefit of KRd-ASCT vs. KCd-ASCT and KRd12 was also confirmed in pre-maintenance MRD-negative patients and was probably related to the higher rate of 1-year sustained MRD negativity reported with KRd-ASCT.

In line with previously published smaller phase I/II trials,²³⁻²⁷ our results showed a high rate of 10^{-5} pre-maintenance MRD negativity (62% in the ITT analysis) in the KRd-ASCT arm and a 4-year PFS of 69% with a median NR after 4 years of follow-up. Cross-trial comparisons should be interpreted with caution, since they are limited by differences in trial design, methodology, and inclusion criteria. Nevertheless, our data showed that KRd-ASCT compared favourably with VRD-ASCT (median PFS 47 months).¹ At present, no randomised comparison of these two regimens in the context of transplant has been reported. The ENDURANCE trial randomly compared VRD vs. KRd, but in a population of older patients without an immediate intent to transplant (median age of 64-65 years, 31-32% of patients aged ≥ 70 years; only 28-27% of patients who received ASCT) and without high-risk features (standard- and intermediate-risk patients included). It should be noted, however, that the trial did include 26-29% of patients with ISS stage III disease. In that population, no differences in terms of PFS were observed between the two treatment arms (median PFS for VRD and KRd: 34.4 and 34.6 months, respectively).²⁸ Despite the limitations of cross-trial comparisons, the rate of grade ≥ 3 non-haematological AEs reported with KRd was higher than in our study (48% in the ENDURANCE and 27-33% in the FORTE trials, respectively), and this may be related to the different trial population. In the KRd arm of the ENDURANCE trial, the total rate of cardiac-pulmonary-renal grade 3-5 AEs was 16.1% vs. 3-4% in the FORTE trial (appendix p 14), again suggesting a better tolerance in the latter patient population. Our data support the prospective randomised evaluation of KRd induction/consolidation vs. VRD induction/consolidation in a TE population, in which potentially more effective regimens can be

better tolerated, while in a different population they may lead to higher toxicity, and, eventually, lower efficacy.

New options, including the anti-CD38 mAb daratumumab plus the standards of care VRD or VTD, showed MRD negativity rates after consolidation between 47% and 64% and a 24 month PFS around 93-94%.^{5,7} More recently, data from the CASSIOPEIA trial were updated, showing, after a median follow-up of 44 months, a median PFS not yet reached with the Dara-VTD combination.^{29,30} Again, despite the limitations of cross-trial comparisons, our data with a three-drug regimen compared favourably also with these quadruplets. Dara-VTD has recently been approved as a new standard of care for TE NDMM patients, and a large phase III trial is currently comparing Dara-VRD vs. VRD in the TE setting.³¹ Results of this trial may support the introduction of Dara-VRD as a new standard of care, with high efficacy and, likely, a better safety profile than Dara-VTD, due to the replacement of thalidomide with lenalidomide, which rarely causes neuropathy. The possible use of KRd upfront needs to be evaluated in the context of these new regimens including mAbs. All treatments proved to be manageable in the TE setting, with a low rate of treatment discontinuation for toxicity and adequate stem-cell mobilisation. The subgroup analyses in the Dara-VTD and Dara-VRD studies showed the benefit of adding a mAb in the majority of patients, although this was less evident in high-risk vs. standard-risk patients. Interestingly, in our study, the advantage of KRd-ASCT vs. KCd-ASCT was observed in all groups, with similar HRs in high-risk and standard-risk patients. This, in line with other data,²⁴ may support the choice of KRd-ASCT in this setting. A further step forward could be combining KRd with anti-CD38 mAbs, and phase I/II studies are currently evaluating Dara-KRd³² and isatuximab-KRd³³ upfront, with preliminary high rates of response and MRD negativity in both standard-risk and high-risk subgroups.

An open issue remains: the role of transplant in the context of anti-CD38 mAb-based therapies upfront. So far, all published studies that did not include CD38 mAbs upfront proved the superiority of ASCT vs. no ASCT in terms of PFS. Data on anti-CD38 mAb-based treatment in the non-transplant setting are definitely promising. For instance, a 60-month PFS of 52% has recently been reported with the Dara-Rd combination in elderly patients.³⁴ Although it is not possible to perform cross-trial comparisons, this high efficacy – which is potentially higher in the context of quadruplet regimens including mAbs, PIs, and IMiD agents and in a fit population – may again question the role of upfront ASCT also in transplant-eligible patients. This questioning should be properly addressed in a randomised study, also considering (1) the well-known higher toxicity related to the transplant procedure (mainly haematological and gastrointestinal AEs and infections) that was always reported in studies comparing ASCT vs. no ASCT and (2) the likely better quality of life (QoL) in patients receiving an outpatient, well tolerable regimen, as compared with ASCT (which can also require prolonged hospitalisation). A limitation of our study is that we did not collect ASCT-related toxicities (since this regimen was considered a standard of care) and we do not have available QoL data. Nevertheless, our data showed no significant excess in treatment discontinuation or toxic deaths.

Maintenance treatment with KR significantly improved PFS, as compared with R alone, with a reduction of about 34% in the risk of progression/death. Most patients, given the high efficacy of the upfront induction/intensification/consolidation therapy, were already MRD-negative at the start of maintenance treatment. The proportion of MRD-negative patients in both the maintenance arms was consequently high (and not so different between KR and R). Nevertheless, a higher rate of patients who were MRD-positive at the start of maintenance turned MRD-negative within 2 years of maintenance, thus suggesting that, in responsive patients, continuous carfilzomib therapy may progressively improve the depth of response, which is an established, and extremely strong, prognostic factor.³⁵ Again, the advantage of adding carfilzomib to lenalidomide was consistently detected in all groups of patients, with similar HRs for the high-risk and standard-risk subsets. This finding confirmed the efficacy of this drug also in the high-risk setting, in line with the efficacy of maintenance treatment with PIs in this specific population.³⁶ An open issue is the different impact of KR vs. R maintenance in patients previously randomised to KRd-ASCT or KRd12 vs KCd-ASCT. The second randomisation was stratified according to induction treatment, and the multivariate logistic regression analysis was adjusted according to the same factor. A longer follow-up is needed to evaluate the impact of KR vs. R according to induction/intensification/consolidation arm.

Although treatment was manageable, with comparable rates of discontinuation due to AE in the two arms, the rate of non-haematological toxicities was higher with KR, with main differences related to a higher frequency of vascular events (hypertension and thrombotic microangiopathy) and cardiac events that, nevertheless, were both reported as grade 3-4 in less than 5% of patients. This, together with the intravenous infusion, may be

the main limitations to the use of carfilzomib in this setting. A more feasible approach could include its weekly administration, which – despite the low number of patients treated in our study – did not increase toxicity and was more acceptable in terms of treatment compliance. No increase in SPMs was noticed adding carfilzomib to lenalidomide. A limitation of our study is the lack of QoL data during maintenance treatment. For sure, this is an important factor to consider, together with the balance in terms of efficacy/toxicity during the evaluation of a new therapeutic approach.

In conclusion, in patients with NDMM eligible for ASCT, KRd-ASCT provided a significant and clinically meaningful benefit, as compared with KCd-ASCT and KRd12. This supports the further evaluation of this regimen alone or as backbone in association with anti-CD38 mAbs, in comparison with current standards of care. In a TE patient population, maintenance treatment with KR proved to be effective, safe, and superior to standard R alone.

Contributors

All authors equally contributed to the acquisition, analysis, or interpretation of data for the work. All authors critically reviewed the work for important intellectual content, finally approved the 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. FG, PM, LB, AC, and MB contributed to conceptualisation, formal analysis, methodology, and writing – original draft. LB and AC contributed to software and visualisation. FG, PM, and MB contributed to supervision. All authors equally contributed to data curation, investigation, resources, validation, and writing – review & editing.

Declaration of interests

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

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

AB has served on the advisory boards for Janssen, Celgene, Amgen, and GSK; has received consultancy fees from Takeda.

MGa has received, in the last two years, honoraria from BMS/Celgene, Janssen, and Takeda.

MO has received honoraria from and/or served on the scientific advisory boards for Amgen, Bristol-Myers Squibb, Celgene, GlaxoSmithKline, Janssen, Sanofi, and Takeda.

EZ has received honoraria from and has served on the advisory boards for Janssen, BMS, Takeda, Sanofi, Amgen, GSK, and Oncopeptides.

SB has received honoraria from and/or served on the scientific advisory boards for Celgene, Janssen, Takeda, Bristol-Myers Squibb, Amgen, and Novartis.

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

FP has served on the advisory boards for Celgene, Janssen, and GSK.

MD has received honoraria for lectures from Sanofi and GSK; has served on the advisory boards for GSK.

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.

AP has received support for meetings fees and travel and lodging expenses from Amgen, Celgene, and Janssen; has received non-financial support from Celgene, Janssen, Roche, Takeda, and Amgen.

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

RZ has served on the advisory boards for Celgene, Janssen, GSK, Amgen, and Takeda.

MTP has received honoraria from and has served on the advisory boards for Celgene, Janssen-Cilag, BMS, Takeda, Amgen, Sanofi, and Karyopharm.

PC has received honoraria from AbbVie, ADC Therapeutics, Amgen, Celgene, Daiichi Sankyo, Gilead/Kite, GSK, Incyte, Janssen, Kyowa Kirin, Nerviano Medical Science, Novartis, Roche, Sanofi, and Takeda; has received support for attending meetings and/or travel from Novartis, Janssen, Celgene, BMS, Takeda, Gilead/Kite, Amgen, and AbbVie; has participated on a data safety monitoring board or advisory board for ADC Therapeutics.

MC has received honoraria from Janssen, Celgene, Bristol-Myers Squibb, GSK, Amgen, Takeda, AbbVie, Sanofi, and Roche; has served on the advisory boards for Janssen, Celgene, Bristol-Myers Squibb, GSK, Amgen, Takeda, AbbVie, Sanofi, Roche, and Adaptive Biotechnologies.

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

The remaining authors declare no competing financial interests.

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. Francesca Gay 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. Francesca Gay, 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.

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REFERENCES

- 1 Perrot A, Lauwers-Cances V, Cazaubiel T, *et al.* Early Versus Late Autologous Stem Cell Transplant in Newly Diagnosed Multiple Myeloma: Long-Term Follow-up Analysis of the IFM 2009 Trial. *Blood* 2020; **136**: 39 [Abstract #143, ASH 2020 62nd Meeting].
- 2 Moreau P, Hulin C, Macro M, *et al.* VTD is superior to VCD prior to intensive therapy in multiple myeloma: Results of the prospective IFM2013-04 trial. *Blood* 2016; **127**: 2569–74.
- 3 Moreau P, San Miguel J, Sonneveld P, *et al.* Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2017; **28**: iv52–61.
- 4 Cavo M, Gay F, Beksac M, *et al.* Autologous haematopoietic stem-cell transplantation versus bortezomib–melphalan–prednisone, with or without bortezomib–lenalidomide–dexamethasone consolidation therapy, and lenalidomide maintenance for newly diagnosed multiple myeloma (EMN02/HO95): a mult. *Lancet Haematol* 2020; **7**: e456–68.
- 5 Voorhees PM, Kaufman JL, Laubach J, *et al.* Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial. *Blood* 2020; **136**: 936–45.
- 6 Yimer H, Melear J, Faber E, *et al.* Daratumumab, bortezomib, cyclophosphamide and dexamethasone in newly diagnosed and relapsed multiple myeloma: LYRA study. *Br J Haematol* 2019; **185**: 492–502.
- 7 Moreau P, Attal M, Hulin C, *et al.* Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study. *Lancet* 2019; **394**: 29–38.
- 8 Dimopoulos MA, Moreau P, Palumbo A, *et al.* Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): And randomised, phase 3, open-label, multicentre study. *Lancet Oncol* 2016; **17**: 27–38.
- 9 Stewart AK, Rajkumar SV, Dimopoulos MA, *et al.* Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. *N Engl J Med* 2015; **372**: 142–52.
- 10 Waxman AJ, Clasen S, Hwang W-T, *et al.* Carfilzomib-Associated Cardiovascular Adverse Events: A Systematic Review and Meta-analysis. *JAMA Oncol* 2018; **4**: e174519–e174519.
- 11 McCarthy PL, Owzar K, Hofmeister CC, *et al.* Lenalidomide after Stem-Cell Transplantation for Multiple Myeloma. *N Engl J Med* 2012; **366**: 1770–81.
- 12 McCarthy PL, Holstein SA, Petrucci MT, *et al.* Lenalidomide Maintenance After Autologous Stem-Cell Transplantation in Newly Diagnosed Multiple Myeloma: A Meta-Analysis. *J Clin Oncol* 2017; **35**: 3279–89.
- 13 Gay F, Jackson G, Rosiñol L, *et al.* Maintenance Treatment and Survival in Patients With Myeloma. A Systematic Review and Network Meta-analysis. *JAMA Oncol* 2018; **4**: 1389–97.
- 14 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.
- 15 Greipp PR, San Miguel J, Durie BGM, *et al.* International staging system for multiple myeloma. *J Clin Oncol* 2005; **23**: 3412–20.
- 16 Kumar S, Paiva B, Anderson KC, *et al.* International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol* 2016; **17**: e328–46.
- 17 Flores-Montero J, de Tute R, Paiva B, *et al.* Immunophenotype of normal vs. myeloma plasma cells: Toward antibody panel specifications for MRD detection in multiple myeloma. *Cytometry B Clin Cytom* 2016; **90**: 61–72.
- 18 Monter A, Nomdedéu JF. ClonoSEQ assay for the detection of lymphoid malignancies. *Expert Rev Mol Diagn* 2019; **19**: 571–8.
- 19 US Dept of Health and Human Services - National Institutes of Health - National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). Version 4.0. 2009. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf (accessed April 28, 2021).
- 20 Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals.

Biometrika 1994; **81**: 515–26.

- 21 Munshi NC, Avet-Loiseau H, Anderson KC, *et al.* A large meta-analysis establishes the role of MRD negativity in long-term survival outcomes in patients with multiple myeloma. *Blood Adv* 2020; **4**: 5988–99.
- 22 Costa LJ, Derman BA, Bal S, *et al.* International harmonization in performing and reporting minimal residual disease assessment in multiple myeloma trials. *Leukemia*. 2021; **35**: 18–30.
- 23 Jakubowiak AJ, Dytfield D, Griffith KA, *et al.* A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma. *Blood* 2012; **120**: 1801–9.
- 24 Jasielec JK, Kubicki T, Raje N, *et al.* Carfilzomib, lenalidomide, and dexamethasone plus transplant in newly diagnosed multiple myeloma. *Blood* 2020; **136**: 2513–23.
- 25 Roussel M, Lauwers-Cances V, Willeme S, *et al.* Upfront Carfilzomib, Lenalidomide, Dexamethasone with Transplant in Multiple Myeloma Patients, the IFM KRd final results. *Blood* 2021; published online April 7. DOI:10.1182/blood.2021010744.
- 26 Brinchen S, Petrucci MT, Larocca A, *et al.* Carfilzomib, cyclophosphamide, and dexamethasone in patients with newly diagnosed multiple myeloma: A multicenter, phase 2 study. *Blood* 2014; **124**: 63–9.
- 27 Yong K, Popat R, Wilson W, *et al.* Efficacy and Safety of Carfilzomib at 56mg/m² with Cyclophosphamide and Dexamethasone (K56Cd) in Newly Diagnosed Multiple Myeloma Patients Followed By ASCT or K56Cd Consolidation: Initial Results of the Phase 2 Cardamon Study. *Blood* 2019; **134**: Abstract #861 [ASH 2019 61st Meeting].
- 28 Kumar SK, Jacobus SJ, Cohen AD, *et al.* Carfilzomib or bortezomib in combination with lenalidomide and dexamethasone for patients with newly diagnosed multiple myeloma without intention for immediate autologous stem-cell transplantation (ENDURANCE): a multicentre, open-label, phase 3, randomised, controlled trial. *Lancet Oncol* 2020; **21**: 1317–30.
- 29 Moreau P, Sonneveld P, Investigators for the CS. Daratumumab (DARA) maintenance or observation (OBS) after treatment with bortezomib, thalidomide and dexamethasone (VTd) with or without DARA and autologous stem cell transplant (ASCT) in patients (pts) with newly diagnosed multiple myeloma (NDMM): CASSIOPEIA Part 2. https://doi.org/10.1200/JCO20213915_suppl8004 2021; **39**: Abstract #8004 [ASCO 2021 Annual Meeting].
- 30 Moreau P, Hulin C, Perrot A, *et al.* DARATUMUMAB MAINTENANCE VS OBSERVATION IN PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA TREATED WITH BORTEZOMIB, THALIDOMIDE, AND DEXAMETHASONE ± DARATUMUMAB AND ASCT: CASSIOPEIA PART 2 RESULTS. *HemaSphere* 2021; **5**: 45-46 [Abstract #S180, EHA 2021 26th Congress].
- 31 Sonneveld P, Broijl A, Gay F, *et al.* Bortezomib, lenalidomide, and dexamethasone (VRd) ± daratumumab (DARA) in patients (pts) with transplant-eligible (TE) newly diagnosed multiple myeloma (NDMM): A multicenter, randomized, phase III study (PERSEUS). *J Clin Oncol* 2019; **37**: Abstract #TPS8055 (ASCO 2019 Annual Meeting).
- 32 Costa LJ, Chhabra S, Godby KN, *et al.* Daratumumab, Carfilzomib, Lenalidomide and Dexamethasone (Dara-KRd) Induction, Autologous Transplantation and Post-Transplant, Response-Adapted, Measurable Residual Disease (MRD)-Based Dara-Krd Consolidation in Patients with Newly Diagnosed Multiple Myeloma (NDMM). *Blood* 2019; **134**: 860–860.
- 33 Weisel K, Asemisen AM, Besemer B, *et al.* Depth of response to isatuximab, carfilzomib, lenalidomide, and dexamethasone (Isa-KRd) in front-line treatment of high-risk multiple myeloma: Interim analysis of the GMMG-CONCEPT trial. *J Clin Oncol* 2020; **38**: Abstract #8508 [ASCO 2020 Annual Meeting].
- 34 Facon T, Kumar SK, Plesner T, *et al.* OVERALL SURVIVAL RESULTS WITH DARATUMUMAB, LENALIDOMIDE, AND DEXAMETHASONE VERSUS LENALIDOMIDE AND DEXAMETHASONE IN TRANSPLANT-INELIGIBLE NEWLY DIAGNOSED MULTIPLE MYELOMA: PHASE 3 MAIA STUDY. In: EHA 2021 26th Congress - <https://library.ehaweb.org/eha/2021/eha2021-virtual-congress/330171/thierry.facon.overall.survival.results.with.daratumumab.lenalidomide.and.html?f=m>

enu%3D6%2Abrowseby%3D8%2Asortby%3D2%2Amedia%3D3%2Ace_id%3D2035%2Amarker%3D1284%2A. 2021: EHA Library, Abstract #LB1901.

- 35 Hofste op Bruinink D, Oliva S, Rihova L, *et al.* Standardization of Flow Cytometric Minimal Residual Disease Assessment in 2 International Clinical Trials – a Feasibility Study from the European Myeloma Network. *Haematologica* 2021; **106**: 1496–9.
- 36 Dimopoulos MA, Gay F, Schjesvold F, *et al.* Oral ixazomib maintenance following autologous stem cell transplantation (TOURMALINE-MM3): a double-blind, randomised, placebo-controlled phase 3 trial. *Lancet* 2019; **393**: 253–64.

Tables: titles and legends

Table 1. Patient characteristics in the three induction/consolidation arms and in the two maintenance arms

* Percentage calculated on subjects with available data.

LDH>ULN was defined according to the upper limit of normal determined by laboratories in different participating centres; percentage may not total 100 because of rounding.

Abbreviations. KRd, carfilzomib-lenalidomide-dexamethasone; ASCT, autologous stem-cell transplantation; KCd, carfilzomib-cyclophosphamide-dexamethasone; MEL200, melphalan at 200 mg/m²; 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; ISS, International Staging System stage; del, deletion; t, translocation; amp, amplification; R-ISS, Revised ISS stage; IQR, interquartile range; LDH, lactate dehydrogenase; ULN, upper limit of normal.

Table 2. Best response in the three induction-intensification-consolidation arms (achieved before maintenance) and best response in the two maintenance arms (achieved during maintenance)

*P-value for the overall comparison =0.027; §p-value for the overall comparison =0.016; ^p-value for the overall comparison =0.0070; #p-value for the overall comparison =0.0032.

° on CR-evaluable patients.

Abbreviations. KRd, carfilzomib-lenalidomide-dexamethasone; ASCT, autologous stem-cell transplantation; KCd, carfilzomib-cyclophosphamide-dexamethasone; MEL200, melphalan at 200 mg/m²; 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; ITT, intention-to-treat; sCR stringent complete response; CR complete response; ≥, at least; VGPR, very good partial response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; MRD, minimal residual disease; MFC, multiparameter flow cytometry; NGS, next-generation sequencing

Table 3. Treatment-emergent adverse events related to study drugs*

*Only treatment-emergent AEs related to study drugs are reported. All G1-2 AE occurring in at least 10% of patients are included. All G 3-4 are reported and all G1-2 of the same event class (even when they did not occur in ≥10% of patients) are included. AEs that occurred during the intensification phase with ASCT and are considered as part of the standard-of-care treatment are not reported. Grade 5 AEs during the pre-maintenance phase: 2 heart failure (KRd-ASCT, n=1, KCd-ASCT, n=1), 4 cardiac arrest (KRd-ASCT, n=1; KRd12, n=2; KCd-ASCT, n=1), and 1 pneumonia (KCd-ASCT). During maintenance treatment, 1 patient had G5 acute renal failure in the KR arm. ^At least 1 haematological AE; §at least 1 non-haematological AE; *other renal AEs include: urinary retention, dysuria, haematuria, and stranguria; ‡only 1 case of grade 4 pulmonary embolism in a patient treated in the KRd arm during induction.

Abbreviations. AE, adverse event; KRd, carfilzomib-lenalidomide-dexamethasone; ASCT, autologous stem-cell transplantation; KCd, carfilzomib-cyclophosphamide-dexamethasone; MEL200, melphalan at 200 mg/m²; 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; G, grade; SAE, serious adverse event; FUO, fever of unknown origin.

Figures: titles and legends

Figure 1. Trial profile

**After intensification, 2 patients proceeded directly to maintenance treatment: 1 patient from the KRd-ASCT arm due to grade 2, prolonged thrombocytopenia and 1 patient from the KCd-ASCT arm due to grade 3 prolonged thrombocytopenia.*

Abbreviations. KRd, carfilzomib-lenalidomide-dexamethasone; ASCT, autologous stem-cell transplantation; KCd, carfilzomib-cyclophosphamide-dexamethasone; MEL200, melphalan at 200 mg/m²; 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.

Figure 2. Survival outcomes according to first- and second (maintenance)-randomisation

2A. Kaplan–Meier estimates of progression-free survival from first randomisation

2.B. Kaplan–Meier estimates of progression-free survival from second randomisation

Abbreviations. KRd, carfilzomib-lenalidomide-dexamethasone; ASCT, autologous stem-cell transplantation; KCd, carfilzomib-cyclophosphamide-dexamethasone; MEL200, melphalan at 200 mg/m²; 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; HR, hazard ratio; CI, confidence interval; p, p-value.

Table 1. Patient characteristics in the three induction/consolidation arms and in the two maintenance arms

	KRd-ASCT (N= 158)	KRd12 (N=157)	KCd-ASCT (N=159)	KR (N=178)	R (N=178)
Age, years median (IQR)	57 (52-62)	57 (51-62)	57 (52-62)	56 (52-62)	57 (51-62)
≥60 years	62 (39%)	60 (38%)	62 (39%)	62 (35%)	66 (37%)
Gender	71 (45%)	69 (44%)	72 (45%)	76 (43%)	88 (49%)
Female					
ISS					
I	80 (51%)	80 (51%)	80 (50%)	96 (54%)	98 (55%)
II	55 (35%)	46 (29%)	51 (32%)	52 (29%)	61 (34%)
III	23(15%)	31 (20%)	28 (18%)	30 (17%)	19 (11%)
Chromosomal abnormalities*					
High risk					
[del(17p), t(4;14), t(14;16)]	46 (34%)	38 (29%)	49 (35%)	39 (27%)	44 (28%)
missing	22	27	17	33	23
[del(17p), t(4;14), t(14;16), amp(1q)]	80 (59%)	68 (52%)	86 (61%)	80 (56%)	82 (53%)
missing	23	27	19	36	23
LDH >ULN	22 (14%)	18 (12%)	22 (15%)	17 (10%)	18 (10%)
missing	3	5	8	9	4
R-ISS					
I	49 (35%)	40 (30%)	38 (27%)	50 (34%)	58 (37%)
II	76 (54%)	80 (60%)	91 (65%)	82 (55%)	89 (57%)
III	16 (11%)	14 (10%)	12 (9%)	16 (11%)	9 (6%)
NE	17	23	18	30	22

* Percentage calculated on subjects with available data.

LDH>ULN was defined according to the upper limit of normal determined by laboratories in different participating centres; percentage may not total 100 because of rounding.

Abbreviations. KRd, carfilzomib-lenalidomide-dexamethasone; ASCT, autologous stem-cell transplantation; KCd, carfilzomib-cyclophosphamide-dexamethasone; MEL200, melphalan at 200 mg/m²; 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; ISS, International Staging System stage; del, deletion; t, translocation; amp, amplification; R-ISS, Revised ISS stage; IQR, interquartile range; LDH, lactate dehydrogenase; ULN, upper limit of normal.

Table 2. Best response in the three induction-intensification-consolidation arms (achieved before maintenance) and best response in the two maintenance arms (achieved during maintenance)

	KRd-ASCT	KRd12	KCd-ASCT	KR	R
ITT analysis	N= 158	N=157	N=159	N=178	N=178
sCR*	72 (46%)*	69 (44%)*	51 (32%)*	121 (68%)	115 (65%)
CR	13 (8%)	20 (13%)	15 (9%)	17 (10%)	18 (10%)
≥CR [§]	85 (54%) [§]	89 (57%) [§]	66 (42%) [§]	138 (78%)	133 (75%)
VGPR	55 (35%)	47 (30%)	55 (35%)	38 (21%)	38 (21%)
≥VGPR [^]	140 (89%) [^]	136 (87%) [^]	121 (76%) [^]	176 (99%)	171 (96%)
PR	13 (8%)	12 (8%)	23 (14%)	2 (1%)	7 (4%)
SD	2 (1%)	1 (1%)	6 (4%)	-	-
PD	1 (1%)	-	5 (3%)	-	-
NE	2 (1%)	8 (5%)	4 (3%)	-	-
MRD MFC 10 ⁻⁵ [#]	98 (62%) [#]	88 (56%) [#]	69 (43%) [#]	145 (81%)	140 (79%)
CR: evaluable population	N= 56	N=58	N=41	N=100	N=99
MRD NGS 10 ⁻⁵ [°]	45 (80%)	40 (69%)	30 (73%)	88 (88%)	82 (83%)

*P-value for the overall comparison =0.027; [§]p-value for the overall comparison =0.016; [^]p-value for the overall comparison =0.0070; [#]p-value for the overall comparison =0.0032.

[°] on CR-evaluable patients.

Abbreviations. KRd, carfilzomib-lenalidomide-dexamethasone; ASCT, autologous stem-cell transplantation; KCd, carfilzomib-cyclophosphamide-dexamethasone; MEL200, melphalan at 200 mg/m²; 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; ITT, intention-to-treat; sCR stringent complete response; CR complete response; ≥, at least; VGPR, very good partial response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; MRD, minimal residual disease; MFC, multiparameter flow cytometry; NGS, next-generation sequencing.

Table 3. Treatment-emergent adverse events related to study drugs*

AE	KRd-ASCT N=158			KRd12 N=156			KCd-ASCT N=159			KR N=173			R N=177		
	G1-2 N (%)	G 3 N (%)	G 4 N (%)	G1-2 N (%)	G 3 N (%)	G 4 N (%)	G1-2 N (%)	G 3 N (%)	G 4 N (%)	G1-2 N (%)	G 3 N (%)	G 4 N (%)	G1-2 N (%)	G 3 N (%)	G 4 N (%)
OVERALL	105 (66)	56 (35)	12 (8)	107 (69)	50 (32)	13 (8)	76 (48)	33 (21)	10 (6)	109 (63)	64 (37)	20 (12)	85 (48)	56 (32)	12 (7)
HAEMATOLOGICAL[^]	38 (24)	27 (17)	8 (5)	30 (19)	19 (12)	5 (3)	27 (17)	21(13)	5 (3)	17 (10)	29 (17)	15 (9)	18 (10)	35 (20)	11 (6)
Anaemia	26 (16)	3 (2)	-	15 (10)	3 (2)	-	20 (13)	5 (3)	-	4 (2)	4 (2)	1 (1)	4 (2)	1 (1)	-
Neutropenia	6 (4)	16 (10)	5 (3)	9 (6)	13 (8)	2 (1)	3 (2)	13 (8)	5 (3)	10 (6)	26 (15)	9 (5)	7 (4)	32 (18)	9 (5)
Thrombocytopenia	19 (12)	12 (8)	3 (2)	13 (8)	8 (5)	3 (2)	9 (6)	5 (3)	1 (1)	6 (3)	2 (1)	5 (3)	9 (5)	2 (1)	3 (2)
NON-HAEMATOLOGICAL[§]	98 (62)	36 (23)	4 (3)	101 (65)	41 (26)	9 (6)	67 (42)	19 (12)	5 (3)	108 (62)	42 (24)	6 (3)	78 (44)	24 (14)	1 (1)
Cardiac	3 (2)	2 (1)	-	6 (4)	1 (1)	1 (1)	5 (3)	2 (1)	-	3 (2)	5 (3)	-	1 (1)	-	1 (1)
Coronary heart disease	-	1 (1)	-	-	-	1 (1)	-	-	-	-	2 (1)	-	-	-	1 (1)
Heart failure	2 (1)	-	-	-	-	-	2 (1)	1 (1)	-	-	3 (2)	-	-	-	-
Tachyarrhythmia	1 (1)	1 (1)	-	4 (3)	1 (1)	-	3 (2)	-	-	1 (1)	3 (2)	-	-	-	-
Dermatological	27 (17)	9 (6)	-	28 (18)	11 (7)	1 (1)	5 (3)	1 (1)	-	14 (8)	2 (1)	-	12 (7)	3 (2)	-
Rash	23 (15)	9 (6)	-	21 (13)	11 (7)	1 (1)	3 (2)	1 (1)	-	9 (5)	2 (1)	-	8 (5)	3 (2)	-
Gastroenterological	28 (18)	3 (2)	-	36 (23)	2 (1)	-	13 (8)	1 (1)	-	55 (32)	9 (5)	-	38 (21)	4 (2)	-
Diarrhoea	15 (9)	3 (2)	-	16 (10)	1 (1)	-	5 (3)	1 (1)	-	28 (16)	7 (4)	-	35 (20)	2 (1)	-
Nausea and Vomiting	9 (6)	1 (1)	-	7 (4)	1 (1)	-	7 (4)	-	-	37 (21)	2 (1)	-	1 (1)	-	-
Hepatic	7 (4)	11 (7)	2 (1)	13 (8)	10 (6)	2 (1)	5 (3)	-	-	3 (2)	2 (1)	-	4 (2)	-	-
Cholestasis	2 (1)	2 (1)	-	1 (1)	3 (2)	-	-	-	-	1 (1)	-	-	-	-	-
Hepatic failure	-	2 (1)	-	1 (1)	-	-	-	-	-	-	1 (1)	-	-	-	-
Transaminases increase	5 (3)	7 (4)	2 (1)	9 (6)	6 (4)	2 (1)	4 (3)	-	-	2 (1)	1 (1)	-	4 (2)	-	-
Infection	24 (15)	9 (6)	-	25 (16)	9 (6)	(1)	14 (9)	6 (4)	1 (1)	28 (16)	8 (5)	-	30 (17)	13 (7)	-
Febrile neutropenia	-	-	-	-	1 (1)	-	-	-	-	-	-	-	-	2 (1)	-
Sepsis	1 (1)	1 (1)	-	-	-	1 (1)	-	-	1 (1)	-	-	-	-	-	-
Pneumonia	2 (1)	5 (3)	-	3 (2)	5 (3)	-	4 (3)	6 (4)	-	3 (2)	5 (3)	-	6 (3)	4 (2)	-
Lower respiratory tract	9 (6)	1 (1)	-	4 (3)	1 (1)	-	1 (1)	-	-	10 (6)	1 (1)	-	10 (6)	2 (1)	-
Upper respiratory tract	8 (5)	1 (1)	-	9 (6)	1 (1)	-	8 (5)	-	-	10 (6)	1 (1)	-	17 (10)	-	-

Gastroenteritis	-	1 (1)	-	-	-	-	-	-	1 (1)	-	-	1 (1)	-	-
Genito-urinary tract	1 (1)	-	-	7 (4)	-	-	1 (1)	-	3 (2)	-	-	3 (2)	1 (1)	-
Neurological	19 (12)	2 (1)	-	27 (17)	1 (1)	-	11 (7)	-	14 (8)	2 (1)	1 (1)	11 (6)	1 (1)	-
Cerebrovascular disease	-	-	-	-	-	-	-	-	-	-	-	1 (1)	1 (1)	-
Renal^{&}	3 (2)	-	2 (1)	10 (6)	2 (1)	1 (1)	4 (3)	2 (1)	3 (2)	-	2 (1)	3 (2)	1 (1)	-
Creatinine increase	2 (1)	-	-	3 (2)	-	-	3 (2)	(1)	-	-	-	1 (1)	-	-
Renal failure	-	-	2 (1)	-	2 (1)	1 (1)	1 (1)	2 (1)	-	1 (1)	-	2 (1)	1 (1)	-
Respiratory	13 (8)	-	-	14 (9)	-	-	10 (6)	1 (1)	1 (1)	12 (7)	2 (1)	-	2 (1)	-
Respiratory failure	-	-	-	-	-	-	-	-	1 (1)	1 (1)	-	-	-	-
Vascular	27 (17)	4 (3)	-	21 (13)	11 (7)	3 (2)	14 (9)	5 (3)	-	28 (16)	8 (5)	4 (2)	3 (2)	-
Hypertension	4 (3)	3 (2)	-	8 (5)	10 (6)	-	10 (6)	4 (3)	-	18 (10)	6 (3)	-	-	-
Venous thromboembolism[‡]	9 (6)	-	-	5 (3)	-	1 (1)	-	1 (1)	-	-	1 (1)	-	1 (1)	-
Other thrombosis	11 (7)	-	-	10 (6)	-	-	3 (2)	1 (1)	-	4 (2)	-	-	1 (1)	-
Thrombotic microangiopathy	-	-	-	-	-	2 (1)	-	-	-	-	1 (1)	4 (2)	-	-
Other	45 (28)	7 (4)	-	48 (31)	6 (4)	-	28 (18)	3 (2)	-	63 (36)	2 (1)	-	21 (12)	5 (3)
Fatigue	17 (11)	1 (1)	-	16 (10)	3 (2)	-	5 (3)	-	-	13 (8)	1 (1)	-	6 (3)	5 (3)
FUO	18 (11)	2 (1)	-	26 (17)	2 (1)	-	16 (10)	2 (1)	-	36 (21)	1 (1)	-	7 (4)	-

**Only treatment-emergent AEs related to study drugs are reported. All G1-2 AE occurring in at least 10% of patients are included. All G 3-4 are reported and all G1-2 of the same event class (even when they did not occur in $\geq 10\%$ of patients) are included. AEs that occurred during the intensification phase with ASCT and are considered as part of the standard-of-care treatment are not reported. Grade 5 AEs during the pre-maintenance phase: 2 heart failure (KRd-ASCT, n=1, KCd-ASCT, n=1), 4 cardiac arrest (KRd-ASCT, n=1; KRd12, n=2; KCd-ASCT, n=1), and 1 pneumonia (KCd-ASCT). During maintenance treatment, 1 patient had G5 acute renal failure in the KR arm. ^At least 1 haematological AE; §at least 1 non-haematological AE; *other renal AEs include: urinary retention, dysuria, haematuria, and stranguria; ‡only 1 case of grade 4 pulmonary embolism in a patient treated in the KRd arm during induction.*

Abbreviations. AE, adverse event; KRd, carfilzomib-lenalidomide-dexamethasone; ASCT, autologous stem-cell transplantation; KCd, carfilzomib-cyclophosphamide-dexamethasone; MEL200, melphalan at 200 mg/m²; 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; G, grade; SAE, serious adverse event; FUO, fever of unknown origin.

Figure 1

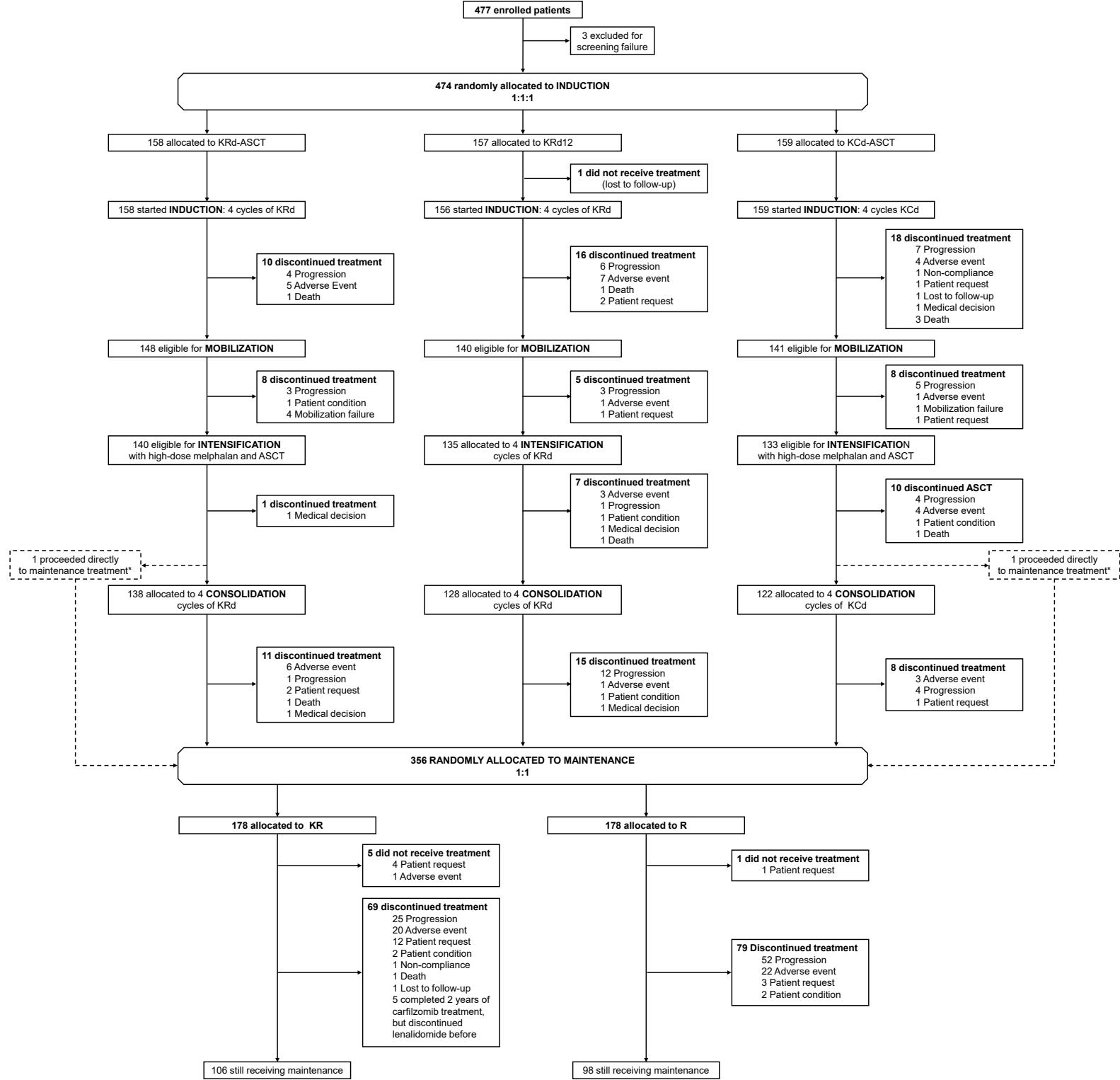
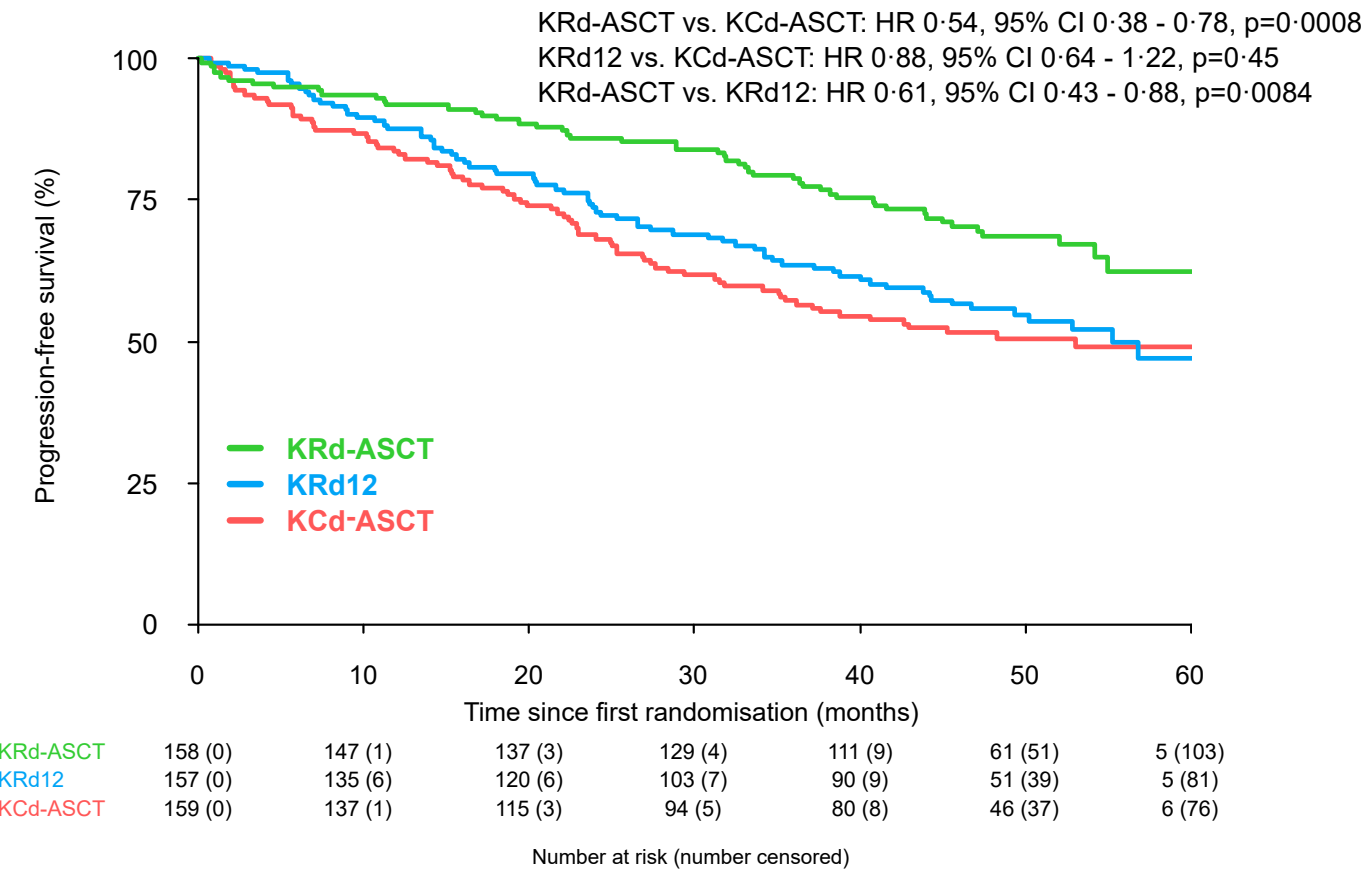
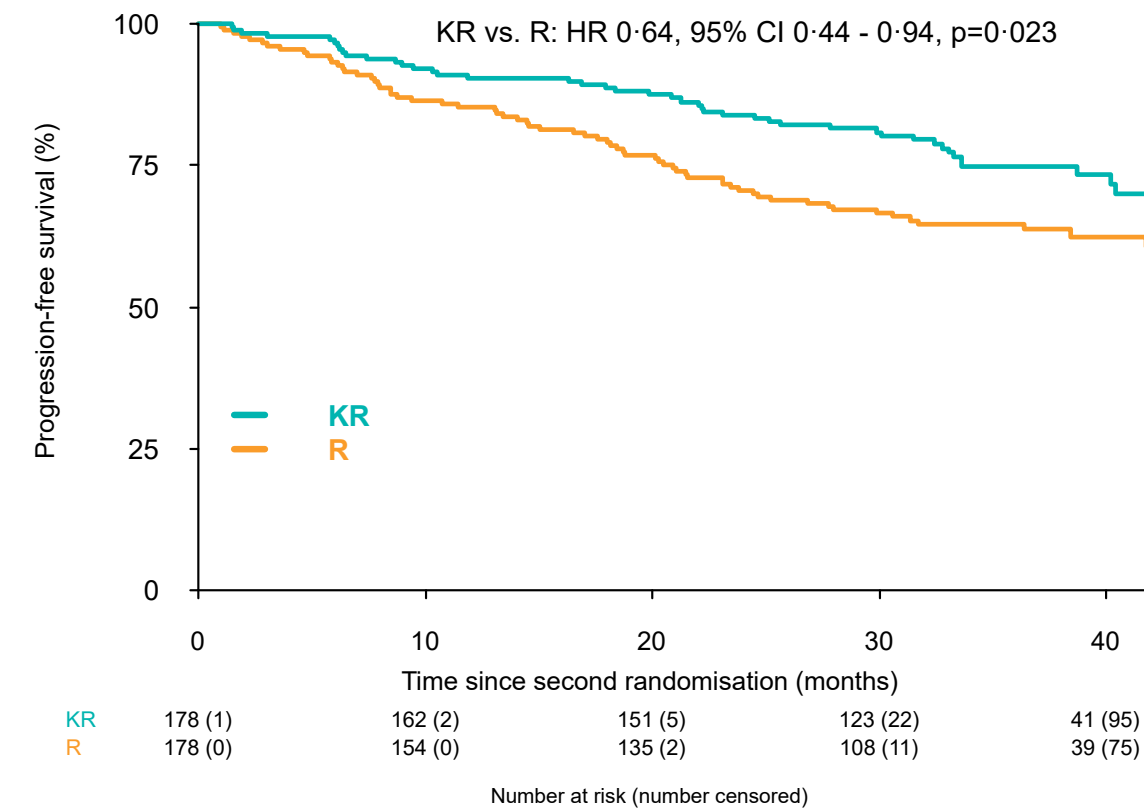


Figure 2

2A



2B



Carfilzomib combined with cyclophosphamide and dexamethasone or lenalidomide and dexamethasone plus autologous transplantation or carfilzomib plus lenalidomide and dexamethasone, followed by maintenance with carfilzomib-lenalidomide or single-agent lenalidomide for patients with newly diagnosed multiple myeloma (FORTE): a randomised, phase 2 trial

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Supplementary methods

Procedures

Carfilzomib dose reductions and interruption

Carfilzomib dose reductions due to haematological toxicities are reported in Table S2 (in this Appendix).

Carfilzomib dose reductions due to non-haematological toxicities are reported in Table S3. After the resolution of the adverse event (AE) to $G \leq 1$ or to baseline levels, if the AE was not treatment-related, subsequent treatment with carfilzomib could resume at full dose. If the AE was treatment-related, subsequent treatment with carfilzomib could resume reducing the dose by 1 level, according to Tables S4 and S5 (i.e., to 20 mg/m² in patients previously receiving 27 mg/m² and to 27 mg/m² in patients previously receiving 36 mg/m²). If toxicity continued or recurred, a second carfilzomib dose reduction was allowed at the discretion of the investigator. No more than 2 dose reductions were allowed in enrolled patients. If toxicity continued or recurred after 2 dose reductions, the carfilzomib administration was interrupted. If the reduced dose was tolerated for 2 cycles, the dose could be restored to the level used before the reduction. If a carfilzomib-related AE persisted after 4 weeks of treatment suspension, treatment was interrupted.

Patients who required a dose reduction during the induction/consolidation phases started maintenance treatment at the dose tolerated during the induction/consolidation phases:

- patients who tolerated 36 mg/m² twice weekly received 70 mg/m² on days 1 and 15 during maintenance treatment;
- patients who reduced the dose to 27 mg/m² twice weekly during the induction/consolidation phases received 56 mg/m² on days 1 and 15 during maintenance treatment;
- patients who reduced the dose to 20 mg/m² twice weekly during the induction/consolidation phases received 36 mg/m² on days 1 and 15 during maintenance treatment.

The levels of carfilzomib dose reduction are reported in Tables S4 and 5.

Lenalidomide dose reduction and interruption

Dose adjustments were based on clinical and laboratory findings (see Table S6- S7).

Granulocyte colony-stimulating factor (G-CSF) was administered if the absolute neutrophil count (ANC) was $<1 \times 10^9/L$. If G-CSF overcame neutropenia, its administration continued as needed to maintain the ANC $>1 \times 10^9/L$. Lenalidomide was administered only if the ANC was $>1 \times 10^9/L$. Moreover, if platelet levels decreased to $<50 \times 10^9/L$, lenalidomide administration was delayed until platelet levels were restored to levels $>50 \times 10^9/L$. If platelet levels decreased again to $<50 \times 10^9/L$, lenalidomide administration restarted at the next lower dose level when toxicity decreased to $G \leq 2$.

The levels of lenalidomide dose reduction are reported in Table S8.

Cyclophosphamide dose reduction and interruption

Tables S9 shows dose reduction levels for cyclophosphamide.

Dexamethasone dose modification

Tables S10 and S11 provide the guidelines that were observed for dose modification due to common dexamethasone-related toxicities. For steroid-related toxicities that are not specifically listed in Tables S10 and S11, the general guideline was to continue dexamethasone administration for up to 2 weeks until the AE decreased to $G \leq 2$, and the dose decreased to 50% for $G \geq 3$ non-haematological AEs. In this case, the required support therapy was administered.

Adverse event monitoring

AEs were recorded by the investigators from the time the patient signed the 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 was longer. Serious adverse events (SAEs) were reported within 24 hours after the investigator's knowledge of the event.

Outcomes

Detailed list of all secondary endpoints and exploratory analyses

- To determine the rate of minimal residual disease (MRD) negativity after complete pre-maintenance phase in the three arms, which are KRd-ASCT (four 28-day induction cycles with carfilzomib-lenalidomide-dexamethasone [KRd], melphalan at 200 mg/m² and autologous stem-cell transplantation [MEL200-ASCT], and four 28-day KRd consolidation cycles); KRd12 (twelve 28-day KRd cycles; KCd-ASCT: four 28-day carfilzomib-cyclophosphamide-dexamethasone [KCd] induction cycles, MEL200-ASCT, and four 28-day KCd consolidation cycles).
- To determine the rate of 1-year sustained MRD negativity.
- To determine the response in the three arms after complete pre-maintenance therapy.
- To determine the rate of AEs in the three pre-maintenance arms and in the two maintenance treatment arms (carfilzomib-lenalidomide [KR] and lenalidomide alone [R]).
- To determine the time to next treatment (TTNT) in the three induction/consolidation arms and in the two maintenance arms.
- To determine the time to progression (TTP) in the three induction/consolidation arms and in the two maintenance arms.
- To determine the overall survival (OS) in the three induction/consolidation arms and in the two maintenance arms.
- To determine the duration of response (DOR) in the three induction/consolidation arms and in the two maintenance arms.
- To determine the progression-free survival-2 (PFS2) in the three induction/consolidation arms and in the two maintenance arms.
- To determine safety, PFS, PFS2, and OS of the twice-weekly administration of carfilzomib plus lenalidomide maintenance treatment vs. the once-weekly administration of carfilzomib plus lenalidomide maintenance treatment.
- To determine the success of stem-cell harvest according to baseline characteristics.
- To determine whether tumour response and outcome changed in subgroups with different prognosis, according to current prognostic factors.
- To perform exploratory, comparative analyses between different subgroups of patients defined according to known prognostic factors.

Details regarding the analysis of outcomes

The Kaplan–Meier product limit method was used to estimate the survival functions for PFS and OS endpoints. PFS was calculated from the date of randomisation (first randomisation to the three induction/consolidation arms [Random1] or second randomisation to the two maintenance arms [Random2], according to the endpoint) until the date of progression, the date of death from any cause during treatment, or the last date of data censoring on which the patient was known to be progression-free. OS was calculated from the date of randomisation (Random1 or Random2, according to the endpoint) until the date of either death from any cause or the last date of data censoring on which the patient was known to be alive. PFS-2 was defined as the time from date of randomisation (first randomisation to the three induction/consolidation arms [Random1] or second randomisation to the two maintenance arms [Random2], according to the endpoint) until the second objective disease progression during the following line of treatment or death from any cause. The DOR is measured from the time measurement criteria are met for complete response (CR)/partial response (PR) (whichever status is recorded first) until the first date that recurrent or progressive disease is objectively documented (taking the smallest measurements recorded since treatment start as reference for progressive disease).

Responses are defined according IMWG response criteria.¹ Very good partial response (VGPR) was defined as serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M protein level < 100 mg per 24 h; if the serum and urine M-protein are unmeasurable, a > 90% decrease in the difference between involved and uninvolved Free Light Chain (FLC) levels is required in place of the M-protein criteria. Stringent Complete response (sCR) was defined as negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow and normal FLC ratio and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence.

Statistical analysis

Key secondary endpoints

The power of 90% ($\beta=0.10$) for the first key secondary endpoint (stringent complete response [sCR]) was calculated with the following assumptions by the X2 test with Yates' continuity correction, considering the intention-to-treat (ITT) population: $\alpha=0.025$, 2-sided for each comparison; sCR rate 20%, 40%, and 60% for KCd-ASCT, KRd12, and KRd-ASCT, respectively; lost to follow-up =10%. The power of 80% ($\beta=0.20$) for the second key endpoint (PFS) was based on the following assumptions by Schoenfeld formula, considering the ITT population: $\alpha=0.025$, 2-sided for each comparison; 3-year PFS: KCd-ASCT 55%, KRd12 70% (HR=0.60), KRd-ASCT 80% (HR 0.37); accrual time =36 months; follow-up time =36 month; lost to follow-up =5%. To achieve a power of 80%, 39 and 146 PFS events were needed for the comparisons KRd-ASCT vs. KCd-ASCT and KRd12 vs. KCd-ASCT-KCd, respectively. Alpha was split according to the Bonferroni adjustment.

Interim analyses

Two safety interim analyses were planned. The first one was planned after the first 90 patients completed the induction phase. Since this was not the major aim of our study, no statistical corrections of the sample size or of the alpha error have been done.² In case of mobilisation failure in more than 15% of patients and recommendation by the Data Monitoring Committee, the study had to be interrupted after the analysis of safety data. Considering the change in the schedule of carfilzomib applied with the protocol Amendment 5.0, a second safety analysis was performed after the first 20 patients completed the first 4 cycles of weekly carfilzomib during the maintenance treatment. The safety data of carfilzomib at 70 mg/m² were compared with the data from the last 20 patients randomised to carfilzomib at 36 mg/m² during maintenance treatment.

Supplementary results

Outcomes

TTP, TTNT and DOR are reported in Figures S6, S7, S8, and S9.

PFS-2 data are immature and are not reported in this contribution, due to the very low number of PFS-2 events.

PFS, PFS2 and OS for the comparison of once-weekly and twice-weekly administrations of carfilzomib in the maintenance phase are not reported because of the low number of patients who received the once-weekly administration (n=19). This was due to the late approval of amendment 5, which allowed using the once-weekly schedule.

We performed the Grambsch and Therneau test on PFS and PFS from maintenance outcomes,³ which confirmed that the proportional hazards assumption was not violated for HRs related to therapies ($p=0.13$ for first randomization and $p=0.19$ for second randomization).

Cardiac toxicities during treatment

Overall, treatment-emergent cardiac AEs of all grades were reported in 22 (5%) of 473 patients during the induction/intensification/consolidation phases and in 12 (3%) of 350 patients during the maintenance phase. G3-4 AEs or SAEs were reported in 3 (2%) of 158 patients in the KRd-ASCT arm; in 2 (1%) of 159 patients in the KCd-ASCT arm; in 3 (2%) of 156 patients in the KRd12 arm; in 7 (4%) of 173 patients in the KR maintenance arm; and in 1 (1%) of 177 patients in the R maintenance arm.

Coronary artery disease (CAD) events were all G \geq 3/SAEs and were reported in 1 (1%) of 158 patients in the KRd-ASCT arm, in 1 (1%) of 156 patients in the KRd12 arm, in 2 (1%) of 173 patients in the KR maintenance arm, and in 1 (1%) of 177 patients in the R maintenance arm. Only 1 patient had previous medical history of glucose intolerance and hypertension; the other patients had no previous medical history of cardiovascular risk factors.

Heart failure was reported during the induction/intensification/maintenance phases in 3 (2%) of 158 patients in the KRd-ASCT arm (1 G \geq 3/SAE), in 4 (3%) of 159 patients in the KCd-ASCT arm (1 G \geq 3/SAE), and was not reported in any patients in the KRd12 arm; 3 events occurred during the induction phase (KRd, n=1; KCd, n=2), 2 during mobilisation (KRd, n=1, KCd, n=1), and 2 during consolidation (KRd-ASCT, n=1; KCd-ASCT, n=1). During the maintenance phase, heart failure occurred in 3 (2%) of 173 patients in the KR arm (all G3) and in 0 (0%) of 177 patients in the R arm. One patient with heart failure had a cardiovascular risk factor (obesity) and 1 patient had previous hypertension.

Tachyarrhythmias were reported during the induction/intensification/consolidation phases in 2 (1%) of 158 patients in the KRd-ASCT arm (1 G \geq 3/SAE), in 3 (2%) of 159 patients in the KCd-ASCT arm (all G1-2), and in 5 (3%) of 156 patients in the KRd12 arm (2 G \geq 3/SAE); 10 AEs occurred during the induction phase (KRd, n=7; KCd, n=3) and 1 during consolidation (KRd-ASCT). During the maintenance phase, tachyarrhythmias were reported in 4 (2%) of 173 patients in the KR arm (3 G \geq 3/SAE). Regarding comorbidities, 1 patient had prior history of heart failure, 4 of hypertension, 1 of tachyarrhythmia, 2 of diabetes mellitus/glucose intolerance, and 1 of hypercholesterolemia.

Dose reductions and drug discontinuations in different treatment arms and treatment phases

Induction/intensification/consolidation phases

A carfilzomib dose reduction was required by 18 (11%) of 158, 15 (10%) of 156, and 7 (4%) of 159 patients in the KRd-ASCT, KRd12, and KCd-ASCT arms, respectively ($p=0.054$). More specifically, during the induction phase, carfilzomib was reduced in 11 (7%) of 158, 7 (4%) of 156, and 3 (2%) of 159 patients in the KRd-ASCT, KRd12, and KCd-ASCT arms, respectively. During the consolidation phase, carfilzomib was reduced in 7 (5%) of 138, 8 (6%) of 135, and 4 (3%) of 122 patients in the KRd-ASCT, KRd12, and KCd-ASCT arms, respectively. In patients who received a reduced dose of carfilzomib, 27 mg/m² was the last administered dose in 12 (8%) of 158 patients in the KRd-ASCT arm, in 10 (6%) of 156 in the KRd12 arm, and in 4 (3%) of 159 in the KCd-ASCT arm; 20 mg/m² was the last dose administered in 1 (1%) of 158 patient in the KRd-ASCT arm, in 3 (2%) of 156 in the KRd12 arm, and in 2 (1%) of 159 in the KCd-ASCT arm. The main reasons for carfilzomib dose reduction during the pre-maintenance phases were liver toxicity (n=11), haematological toxicity (n=8), and cardiac toxicity (n=4). Three (2%) of 156 patients discontinued carfilzomib in the KRd12 arm (heart failure, n=1; febrile neutropenia, n=1; and medical decision, n=1).

Lenalidomide dose reductions were reported in 40 (25%) of 158 patients in KRd-ASCT and 33 (21%) of 156 in KRd12. More specifically, during the induction phase, lenalidomide was reduced in 20 (13%) of 158 patients in the KRd-ASCT arm and in 20 (13%) of 156 patients in the KRd12 arm. During the consolidation phase, 22 (16%) of 138 and 17 (13%) of 135 patients in the KRd-ASCT and KRd12 arms respectively reduced lenalidomide. In patients who received a reduced dose of lenalidomide, 15 mg was the last administered dose in 27 (17%) of 158 patients in the KRd-ASCT arm and in 18 (12%) of 156 patients in the KRd12 arm; 10 mg was the last administered dose in 4 (3%) of 158 patients in the KRd-ASCT arm and in 11 patients (7%) of 156 in the KRd12 arm; 7.5 mg was the last administered dose in 1 patient (1%) of 158 in the KRd-ASCT arm; 5 mg was the last administered dose in 2 (1%) of 158 patients in the KRd-ASCT arm and in 2 patients (1%) of 156 in the KRd12 arm. The main reasons for lenalidomide dose reduction were dermatological toxicity (n=23), haematological toxicity (n=22), liver toxicity (n=11), peripheral neuropathy (n=5), and renal toxicity (n=4). Two (1%) of 158 patients required lenalidomide discontinuation in the KRd-ASCT arm (dermatological toxicity, n=2).

Cyclophosphamide dose reductions were reported in 10 (6%) of 159 patients in the KCd-ASCT arm. Cyclophosphamide was reduced in 2 (1%) of 159 patients during the induction phase and in 8 (7%) of 122 patients during the consolidation phase. The last administered dose of cyclophosphamide was 200 mg/m² in 9 (6%) of 159 and 100 mg/m² in 1 (1%) of 159 patients. The main reasons for cyclophosphamide dose reduction during the pre-maintenance phases were haematological (n=7). No patient had to discontinue the drug.

Dexamethasone dose reductions were comparable in the three arms (KRd-ASCT 12 (8%) of 158, KRd12 14 (9%) of 156, and KCd-ASCT 11 (7%) of 159), with no discontinuation reported. During the induction phase, dexamethasone was reduced in 7 (4%) of 158, 4 (3%) of 156, and 6 (4%) of 159 patients in the KRd-ASCT, KRd12, and KCd-ASCT arms, respectively. During the consolidation phase, dexamethasone was reduced in 7 (5%) of 138, 11 (8%) of 135, and 6 (5%) of 122 patients in the KRd-ASCT, KRd12, and KCd-ASCT arms, respectively. Among patients who received a reduced dose of dexamethasone, 15 mg was the last administered dose in 3 (2%) of 158, 2 (1%) of 156, and 1 (1%) of 159 patients in the KRd-ASCT, KRd12, and KCd-ASCT arms, respectively; 10 mg was the last administered dose in 6 (4%) of 158, 12 (8%) of 156, and 9 (6%) of 159 patients in the KRd-ASCT, KRd12, and KCd-ASCT arms, respectively; 4 mg was the last administered dose in 1 patient (1%) of 158 in the KRd-ASCT arm. The main reasons for dexamethasone dose reduction during the pre-maintenance phases were hyperglycaemia (n=7), liver toxicity (n=5), constitutional symptoms (n=5), gastric toxicity (n=4), and infections (n=4).

Maintenance treatment

During the maintenance treatment, in the KR arm, 11 patients (6%) of 173 started carfilzomib with a reduced dose due to a previous reduction during the induction/intensification/consolidation phases. One (1%) of 173 patients did not receive carfilzomib because of a drug-related AE in the induction/intensification/consolidation phases (pulmonary hypertension). Thirty-four (20%) of 173 patients received a carfilzomib dose reduction, and the main reasons were: haematological (n=9), gastroenterological (n=9), hypertension (n=4), and cardiac (n=3).

Forty-one (24%) of 173 patients discontinued carfilzomib due to AE: thrombotic microangiopathy, n=5, neutropenia, n=4; anaemia, n=1; thrombocytopenia, n=1; acute renal failure, n=3; second primary malignancy, n=3; heart failure, n=1; reduced cardiac function, n=1; coronary artery disease, n=1; diarrhoea, n=3; gastritis, n=1; fever of unknown origin, n=3; hepatitis B virus (HBV) reactivation, n=1; haematuria, n=1; hypertension, n=3; infusion reaction, n=1; mandibular osteonecrosis, n=1; atrial fibrillation, n=1; pneumonia and pleuritis, n=5; and pulmonary hypertension, n=1.

During the maintenance treatment, lenalidomide was reduced in 40 (23%) of 173 patients in the KR arm and in 52 (29%) of 177 patients in the R arm.

The last administered dose of lenalidomide was 10 mg in 128 (75%) of 173 patients in the KR arm and in 125 (71%) of 177 in the R arm. Among patients who received a reduced dose of lenalidomide, the last administered dose was 7.5 mg

in 3 (2%) of 173 patients in the KR arm and in 1 (1%) of 177 in the R arm; 5 mg in 31 (18%) of 173 patients in the KR arm and in 47 (27%) of 177 in the R arm; and 2.5 mg in 8 (5%) of 173 patients in the KR arm and in 4 (2%) of 177 in the R arm. Overall, the main reasons for lenalidomide dose reduction were similar in the two arms: haematological (KR, n= 19; R, n= 22), diarrhoea (KR, n= 8; R, n= 6), dermatological (KR, n=4; R, n= 6), infection (KR, n= 0; R, n= 4). In the KR arm, lenalidomide was discontinued due to AE in 33 (19%) of 173 patients: thrombotic microangiopathy, n=3; neutropenia, n=6; thrombocytopenia, n=2; dermatological toxicity, n=1; acute renal failure, n=4; diarrhoea, n=2; nausea and vomiting, n=1; fever of unknown origin, n=3; second primary malignancy, n=4; HBV reactivation, n=1; haematuria, n=1; reduced cardiac function, n=1; infection, n=1; mandibular osteonecrosis, n=1; asthma, n=1; and pleuritis, n=1. Discontinuation of lenalidomide due to AE in the R arm is reported in the main text (since it coincided with treatment discontinuation).

The rates of treatment discontinuation due to AE were similar in the two maintenance arms: 20 (12%) of 173 patients in the KR arm (second primary malignancies [SPMs], n=4; thrombotic microangiopathy, n=3; pneumonia, n=2; acute renal failure, n=2; neutropenia, n=1; thrombocytopenia, n=1; anaemia, n=1; diarrhoea, n=2; gastritis, n=1; fever of unknown origin, n=1; hepatitis B virus (HBV) reactivation, n=1; infusion reaction, n=1) vs. 22 (12%) of 177 patients in the R arm (neutropenia, n=3; pancytopenia, n=3; thrombocytopenia, n=2; dermatological toxicity, n=2; liver toxicity, n=2; cerebrovascular disease, n=2; coronary heart disease, n=1; reduced cardiac function, n=1; diarrhoea, n=1; dyspnoea, n=1; Guillain–Barré syndrome, n=1; pneumonia, n=1; upper respiratory tract infection, n=1; herpes zoster reactivation, n=1).

Preplanned safety analysis during maintenance treatment

A safety interim analysis after 4 cycles of maintenance treatment in the first 19 patients who received 70 mg/m² of carfilzomib once every other week, according to the Amendment 5.0, was planned to describe AEs observed during maintenance treatment with KR. The safety data of carfilzomib at 70 mg/m² were compared with the data of the last 19 patients randomised to maintenance treatment with carfilzomib at 36 mg/m² at the time of analysis.

Unfortunately, by the time the Amendment 5.0 was approved, only 19 patients randomised to the KR arm were included in the twice-weekly schedule, and the majority of patients had already been randomised, had received more than 6 cycles of maintenance treatment, and were therefore not eligible to start weekly therapy, according to the Amendment 5.0. For this reason, the interim analysis was focused only on the first 19 patients in each group. At the time of the interim analysis, no increased toxicity was observed with the use of carfilzomib at 70 mg/m² once every other week, as compared to 36 mg/m² twice weekly every other week (Table S16).

Supplementary tables

Table S1. List of study sites with ≥ 1 patient recruited (descending by total)

Participating site	Principal investigator	Total number of enrolled patients (N=477)*
Multidisciplinary Oncology Outpatient Clinic, Candiolo Cancer Institute, FPO - IRCCS, Torino, Italy, Candiolo (TO), Italy	Massimo Aglietta	41
Department of Hematology, ASST Spedali Civili di Brescia, Brescia, Italy	Giuseppe Rossi	33
UO Ematologia, ASST Papa Giovanni XXIII, Bergamo, Italy	Alessandro Rambaldi	31
IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Bologna, Italy	Michele Cavo	27
Clinica di Ematologia, AOU Ospedali Riuniti di Ancona, Ancona, Italy	Massimo Offidani	24
Hematology, Azienda Ospedaliera Policlinico Umberto I, Roma, Italy	Maurizio Martelli	20
Hematology and Bone Marrow Transplant Unit, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milano; Italy	Paolo Corradini	17
Hematology and Clinical Immunology Section, Department of Medicine (DIMED), Padova University School of Medicine, Azienda Ospedale-Università Padova, Padova, Italy	Renato Zambello	16
Ematologia/CTMO, Ospedale "A. Businco", Cagliari, Italy	Ledda Antonio	15
Azienda USL - IRCCS di Reggio Emilia, Reggio Emilia, Italy	Barbara Gamberi	13
S.C. Ematologia, Azienda Ospedaliera Santa Croce - Carle, Cuneo, Italy	Mariella Grasso	12
Ematologia, Ospedale S. Francesco Nuoro, ATS Sardegna, Nuoro, Italy	Angelo Palmas	12
Divisione di Ematologia con Trapianto, Azienda ospedaliera Santa Maria della Misericordia di Perugia, Perugia, Italy	Stelvio Ballanti	12
Ematologia e Centro Trapianti, IRCCS Ospedale Policlinico San Martino, Genova, Italy	Emanuele Angelucci	11
Unità Operativa Complessa Ematologia Clinica, Azienda Sanitaria Locale di Pescara, Pescara, Italy	Francesca Fioritoni	11
Hematology, St. Eugenio Hospital, ASL Roma 2, Roma, Italy	Paolo de Fabritiis	11
Clinic of Hematology, IRCCS Ospedale Policlinico San Martino, Genova, Italy	Michele Cea	10
UO di Ematologia e CTMO, Azienda Ospedaliero-Universitaria di Parma, Parma, Italy	Monica Crugnola	10
Clinica Ematologica e Unità di Terapie Cellulari, Azienda Sanitaria Universitaria Friuli Centrale (ASUFC), Udine, Italy	Francesca Patriarca	10
Hematology Unit, Azienda Ospedaliera di Cosenza, Cosenza, Italy	Massimo Gentile	9
UOC Ematologia, Azienda Ospedaliero-Universitaria di Modena, Modena, Italy	Franco Narni	9
Ematologia, Azienda Sanitaria Universitaria Giuliano Isontina, Trieste, Italy	Giovanni De Sabbata	9
UOC Ematologia, Ospedale dell'Angelo, Venezia Mestre, Italy	Renato Bassan	8
Division of Hematology, Cardarelli Hospital, Napoli, Italy	Salvatore Palmieri	8
Oncoematologia, Azienda Ospedaliera Santa Maria Terni, Terni, Italy	Anna Marina Liberati	8
SC Ematologia, Azienda Ospedaliera SS. Antonio e Biagio e Cesare Arrigo, Alessandria, Italy	Anna Baraldi	7
Hematology Unit, "Infermi" Hospital, Rimini, Italy	Patrizia Tosi	7
Hematology and Stem Cell Transplantation Unit, IRCCS Centro di Riferimento Oncologico della Basilicata (CROB), Rionero in Vulture, Italy	Giuseppe Pietrantonio	7
Hematology and Stem Cell Transplant Unit, IRCCS Istituto Regina Elena National Cancer Institute, Roma, Italy	Francesco Pisani	7
Unit of Hematology, Stem Cell Transplantation, University Campus Bio-Medico, Roma, Italy	Giuseppe Avvisati	7
UOC Ematologia e Terapia cellulare, Ospedale C. e G. Mazzoni, Ascoli Piceno, Italy	Piero Galieni	6
Unit of Hematology and Stem Cell Transplantation, AOUC Policlinico, Bari, Italy	Pellegrino Musto	6
Reparto di Ematologia e Centro TMO, Ospedale Centrale, Bolzano, Italy	Norbert Pescosta	6
Hematology and Stem Cell Transplantation Unit, Azienda Ospedaliera San Camillo Forlanini, Roma, Italy	Luca De Rosa	6
UOC Ematologia e trapianto, AO Cardinale G. Panico, Tricase (Lecce), Italy	Vincenzo Pavone	6
UOC Ematologia, AOU Senese, Ospedale Santa Maria alle Scotte, Siena, Italy	Alessandro Gozzetti	5
Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy	Sonia Ronconi	4
U.O.C. Ematologia, Ospedale "Santa Maria delle Croci" di Ravenna, Ravenna, Italy	Claudia Cellini	4
Divisione di Ematologia, Grande Ospedale Metropolitano Bianchi-Melacrino-Morelli, Reggio Calabria, Italy	Iolanda Donatella Vincelli	4
Azienda Ospedaliera Universitaria Gaetano Martino, Messina, Italy	Caterina Musolino	3

Ematologia, ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy	Anna Maria Cafro	3
Ematologia, Azienda Ospedaliera "Pugliese Ciaccio", Catanzaro, Italy	Stefano Molica	2

**All patients were enrolled between February 23, 2015 and April 05, 2017.*

Table S2. Carfilzomib dose reduction or interruption due to haematological toxicity

Event	Recommended Action
When Platelets	Carfilzomib
Fall to $<30 \times 10^9/L$	Interrupt carfilzomib, follow CBC weekly
Return to $\geq 30 \times 10^9/L$	Resume at full dose
Subsequently drop to $<30 \times 10^9/L$	Interrupt carfilzomib, follow CBC weekly
Return to $\geq 30 \times 10^9/L$	Resume at 1 dose decrement
When ANC	Carfilzomib
Falls to $<0.5 \times 10^9/L$	Interrupt carfilzomib add G-CSF if G3 with fever or G4, follow CBC weekly
Returns to $>1.0 \times 10^9/L$ (if neutropenia was the only toxicity noted)	Resume at full dose
Returns to $>1.0 \times 10^9/L$ (if other toxicity noted)	Resume at 1 dose decrement
Subsequently drops to $<0.5 \times 10^9/L$	Interrupt carfilzomib
Returns to $>1.0 \times 10^9/L$	Resume at full dose

Abbreviations. CBC, complete blood count; ANC, absolute neutrophil count; G-CSF, granulocyte colony-stimulating factor; G, grade.

Table S3. Carfilzomib dose reduction or interruption due to non-haematological toxicity

Symptom	Recommended action for carfilzomib administration
Allergic reaction/hypersensitivity	
G2-3	Hold carfilzomib until $\leq G1$; restore at full dose.
G4	Discontinue carfilzomib.
Tumour lysis syndrome (≥ 3 of the following: $\geq 50\%$ increase in creatinine, uric acid, or phosphate; $\geq 30\%$ increase in potassium; $\geq 20\%$ decrease in calcium; or ≥ 2 -fold increase in LDH)	Hold carfilzomib until all abnormalities in serum chemistry have resolved. Restore at full doses.
$G \geq 3$ infection	Hold carfilzomib until systemic treatment for infection is complete. If no neutropenic, restart at full dose. If neutropenic, follow instructions for neutropenia.
Herpes zoster or simplex of any G	Hold carfilzomib until lesions are dry. Restore at full dose
G2 treatment-emergent neuropathy with pain or G3 neuropathy	Continue reducing carfilzomib by 1 dose level. If neuropathy persists for more than 2 weeks, hold carfilzomib until neuropathy decreases to $\leq G2$ without pain; then restart reducing carfilzomib by 1 dose level.
G4 neuropathy	Discontinue carfilzomib.
Renal dysfunction	
$CrCl \leq 30$ mL/min	Hold carfilzomib until $CrCl > 30$ mL/minute; restart reducing by 1 dose level.
Congestive heart failure	Any patient with symptoms of congestive heart failure, whether drug related, must have the carfilzomib dose held until resolution or return to baseline levels, after which treatment may continue at a reduced dose, or the patient may be withdrawn from the study. If there is no resolution after 4 weeks, the patient is withdrawn from the study.
Other non-haematological toxicity assessed as $G \geq 3$ carfilzomib-related	Hold carfilzomib dose until toxicity decreases to $\leq G1$ or baseline levels. Restart reducing carfilzomib by 1 dose level.

Abbreviations. G, grade, LDH, lactate dehydrogenase; CrCl, creatinine clearance.

Table S4. Carfilzomib: levels of dose reduction during induction treatment

STARTING DOSE	Carfilzomib 36 mg/m ²
Dose level -1	Carfilzomib 27 mg/m ²
Dose level -2	Carfilzomib 20 mg/m ²

Table S5. Carfilzomib: levels of dose reduction during maintenance treatment (after Amendment 5.0)

STARTING DOSE	Carfilzomib 70 mg/m ²
Dose level -1	Carfilzomib 56 mg/m ²
Dose level -2	Carfilzomib 45 mg/m ²
Dose level -3	Carfilzomib 36 mg/m ²
Dose level -4	Carfilzomib 27 mg/m ²
Dose level -5	Carfilzomib 20 mg/m ²

Table S6. Management of patients with lenalidomide-related toxicities

Adverse events	Action on study drug	Further consideration
G3-4 toxicities considered to be related to lenalidomide	Hold lenalidomide treatment and restart at the next lower dose level when toxicity has been resolved to G \leq 1.	
G \geq 2 thrombosis/embolism	Hold lenalidomide treatment and start anticoagulation therapy as per standard guidelines; restart at investigator's discretion after adequate anticoagulation; maintain dose level.	
G3 skin rash	Hold lenalidomide treatment, add antihistaminic therapy, and decrease lenalidomide by 1 dose level when dosing restarts at the subsequent cycle (rash must decrease to G \leq 1).	
G4 exfoliative or bullous rash, or suspected Stevens-Johnson Syndrome (SJS), or suspected Toxic Epidermal Necrolysis (TEN)	Permanently discontinue lenalidomide.	
Any angioedema	Permanently discontinue lenalidomide.	
Tumour lysis syndrome	Reduce lenalidomide dose.	Monitor closely and take appropriate medical precautions.

Abbreviations. G, grade.

Table S7. 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 is based on the treatment tolerance of each patient.
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 is based on the treatment tolerance of each patient.
CrCl <30 mL/min (with dialysis)	Hold carfilzomib until CrCl \geq 15 mL/min; restart decreasing the dose by 1 level*	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 the treatment tolerance of each patient.

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

Abbreviations. CrCl, creatinine clearance.

Table S8. Lenalidomide: levels of dose reduction

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

Table S9. Cyclophosphamide: levels of dose reduction

STARTING DOSE	Cyclophosphamide 300 mg/m ² , days 1, 8, 15
Dose level -1	Cyclophosphamide 200 mg/m ² , days 1, 8, 15
Dose level -2	Cyclophosphamide 100 mg/m ² , days 1, 8, 15

Table S10. Management of patients with dexamethasone-related toxicities

CATEGORY	TOXICITY	GRADE	DOSE CHANGE
Gastrointestinal Disorders	Dyspepsia, gastric or duodenal ulcer, or gastritis	G1-2 (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%.
		G≥ 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 the above measures, permanently discontinue dexamethasone.
	Acute pancreatitis	G≥3	Permanently discontinue dexamethasone.
Vascular disorders	Oedema	G≥3 (limiting function and unresponsive to therapy or anasarca)	Administer diuretics, as needed, and decrease the dexamethasone dose by 25%. If oedema persists despite the above measures, decrease the dexamethasone dose to 50% of the initial dose. If symptoms persist despite a 50% dose reduction, then permanently discontinue dexamethasone.
Neurological disorders	Confusion or mood alteration	G≥ 2 (interfering with function and/or 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 despite the above measures, then permanently discontinue dexamethasone.
Musculoskeletal, connective tissue, and bone disorders	Muscle weakness	G≥2 (symptomatic and interfering with function and/or interfering with ADLs)	Decrease the dexamethasone dose by 25%. If symptoms persist despite the above measures, decrease the dexamethasone dose to 50% of the initial dose. If symptoms persist despite a 50% dose reduction, then permanently discontinue dexamethasone.
Metabolism and nutrition disorders	Hyperglycaemia	G≥3	Administer insulin or oral hypoglycaemics, as needed. If hyperglycaemia is not controlled despite treatment, decrease the dexamethasone dose by 25%, until adequate glucose levels are achieved.

Abbreviations. G, grade; ADL, Activities of Daily Living.

Table S11. Dexamethasone: levels of dose reduction

STARTING DOSE	Dexamethasone 20 mg daily, days 1-2, 8-9, 15-16, 22-23
Dose level -1	Dexamethasone 30 mg daily, days 1, 8, 15, 22; or 15 mg daily, days 1-2, 8-9, 15-16, 22-23
Dose level -2	Dexamethasone 20 mg daily, days 1, 8, 15, 22; or 10 mg daily, days 1-2, 8-9, 15-16, 22-23

Table S12. Best response rates after carfilzomib-lenalidomide-dexamethasone (KRd) vs. carfilzomib-cyclophosphamide-dexamethasone (KCd) induction by intention-to-treat analysis

	KRd (N=315)	KCd (N=159)
ITT analysis		
sCR	19 (6%)	6 (4%)
CR	5 (2%)	3 (2%)
≥CR	24 (8%)	9 (6%)
VGPR	198 (62%)	75 (47%)
≥VGPR	222 (70%)	84 (53%)
PR	71 (23%)	51 (32%)
SD	5 (2%)	12 (8%)
PD	2 (1%)	3 (2%)
NE	15 (5%)	9 (6%)

Abbreviations. KRd, carfilzomib-lenalidomide-dexamethasone; KCd, carfilzomib-cyclophosphamide-dexamethasone; ITT, intention-to-treat; sCR stringent complete response; CR complete response; ≥, at least; VGPR, very good partial response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable.

Table S13. Response rates after intensification in the KRd-ASCT, KRd12, and KCd-ASCT arms by intention-to-treat analysis*

	KRd-ASCT (N= 158)	KRd12 (N=157)	KCd-ASCT (N=159)	P-VALUE for the overall comparison
ITT analysis				
sCR	39 (25%)	45 (29%)	22 (14%)	0.004
CR	10 (6%)	11 (7%)	12 (8%)	-
≥CR	49 (31%)	57 (36%)	34 (21%)	0.016
VGPR	80 (51%)	77 (49%)	71 (45%)	-
≥VGPR	129 (82%)	133 (85%)	105 (66%)	<0.001
PR	24 (15%)	15 (10%)	34 (21%)	-
SD	1 (1%)	2 (1%)	11 (7%)	-
PD	2 (1%)	-	3 (2%)	-
NE	2 (1%)	7 (4%)	6 (4%)	-

*Responses were evaluated after ASCT in the KRd-ASCT and KCd-ASCT arms and after 8 KRd cycles in the KRd12 arm.

Abbreviations. KRd, carfilzomib-lenalidomide-dexamethasone; ASCT, autologous stem-cell transplantation; KCd, carfilzomib-cyclophosphamide-dexamethasone; MEL200, melphalan at 200 mg/m²; 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; ITT, intention-to-treat; sCR stringent complete response; CR complete response; ≥, at least; VGPR, very good partial response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable.

Table S14. Grade 3-4 adverse events according to treatment phase (induction, intensification, and consolidation)

	KRd-ASCT		KRd12			KCd-ASCT	
	<i>Induction</i>	<i>Consolidation</i>	<i>Induction</i>	<i>Intensification</i>	<i>Consolidation</i>	<i>Induction</i>	<i>Consolidation</i>
	N=158	N=138	N=156	N=135	N=128	N=159	N=122
Haematological	15 (9)	22 (16)	9 (6)	10 (7)	8 (6)	8 (5)	17 (14)
Anaemia	3 (2)		1 (1)	1 (1)	1 (1)	3 (2)	2 (2)
Neutropenia	12 (8)	12 (9)	7 (4)	8 (6)	5 (4)	7 (4)	11 (9)
Thrombocytopenia	4 (3)	11 (8)	5 (3)	3 (2)	5 (4)	2 (1)	4 (3)
Non-haematological	33 (21)	8 (6)	31 (20)	15 (11)	12 (9)	16 (10)	10 (8)
Cardiac	2 (1)	-	2 (1)	-	-	2 (1)	-
Dermatological	8 (5)	1 (1)	10 (6)	2 (1)	-	1 (1)	-
Gastroenterological	1 (1)	2 (1)	-	1 (1)	1 (1)	-	1 (1)
Hepatic	12 (8)	2 (1)	8 (5)	4 (3)	4 (3)	-	-
Infection	7 (4)	2 (1)	5 (3)	2 (1)	3 (2)	4 (3)	3 (2)
Vascular	4 (3)	-	5 (3)	5 (4)	3 (2)	3 (2)	4 (3)

Abbreviations. KRd, carfilzomib-lenalidomide-dexamethasone; ASCT, autologous stem-cell transplantation; KCd, carfilzomib-cyclophosphamide-dexamethasone; MEL200, melphalan at 200 mg/m²; 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.

Table S15. Causes of discontinuation due to adverse events according to first trial randomisation and treatment phase

	KRd-ASCT				KRd12				KCd-ASCT			
	<i>Induction</i>	<i>Mobilisation</i>	<i>Intensification</i>	<i>Consolidation</i>	<i>Induction</i>	<i>Mobilisation</i>	<i>Intensification</i>	<i>Consolidation</i>	<i>Induction</i>	<i>Mobilisation</i>	<i>Intensification</i>	<i>Consolidation</i>
	N=158	N=148	N=140	N=138	N=156	N=140	N=135	N=128	N=159	N=141	N=133	N=122
Haematological												
Pancytopenia	1	-	-	2	-	1	-	-	-	-	-	-
Thrombocytopenia	-	-	-	-	-	-	1	1	-	-	3	1
Non-haematological												
Acute renal failure	1	-	-	-	1	-	-	-	1	-	-	-
Thrombotic microangiopathy	-	-	-	-	-	-	2	-	-	-	-	-
Heart failure	1	-	-	1	-	-	-	-	1	-	1	-
Coronary Heart disease	-	-	-	-	1	-	-	-	-	-	-	-
Tachyarrhythmia	1	-	-	-	-	-	-	-	-	-	-	-
Liver toxicity	-	-	-	-	-	-	-	-	1	-	-	-
Pneumonia	-	-	-	3	1	-	-	-	1	-	-	2
Sepsis	-	-	-	-	1	-	-	-	-	-	-	-
Infusion reaction	1	-	-	-	1	-	-	-	-	-	-	-
Dermatological toxicity	-	-	-	-	2	-	-	-	-	-	-	-
Second primary Malignancy	-	-	-	-	-	-	-	-	-	1	-	-
Overall	5	-	-	6	7	1	3	1	4	1	4	3

Abbreviations. KRd, carfilzomib-lenalidomide-dexamethasone; ASCT, autologous stem-cell transplantation; KCd, carfilzomib-cyclophosphamide-dexamethasone; MEL200, melphalan at 200 mg/m²; 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.

Table S16. Interim analysis of maintenance treatment in the carfilzomib-lenalidomide (KR) arm: comparison of treatment-related adverse events in the weekly and twice-weekly carfilzomib administrations

AE category	Weekly 70 mg/m ² N=19		Twice weekly 36 mg/m ² N=19	
	All N (%)	G 3-4/SAE N (%)	All N (%)	G 3-4/SAE N (%)
Haematological	1 (5)	1 (5)	1 (5)	1 (5)
Neutropenia	1 (5)	1 (5)	1 (5)	1 (5)
Non-haematological	8 (42)	3 (16)	6 (32)	3 (16)
Gastroenterological	5 (26)	1 (5)	3 (16)	-
Infection	-	-	1 (5)	-
Vascular	2 (11)	2 (11)	1 (5)	1 (5)
<i>Hypertension</i>	1 (5)	1 (5)	-	-
<i>Thrombotic microangiopathy*</i>	1 (5)	1 (5)	1 (5)	1 (5)

**In both groups, the thrombotic microangiopathy adverse event led to study discontinuation.*

Abbreviations. KR, maintenance treatment with carfilzomib-lenalidomide; AE, adverse event; G, grade; SAE, serious adverse event.

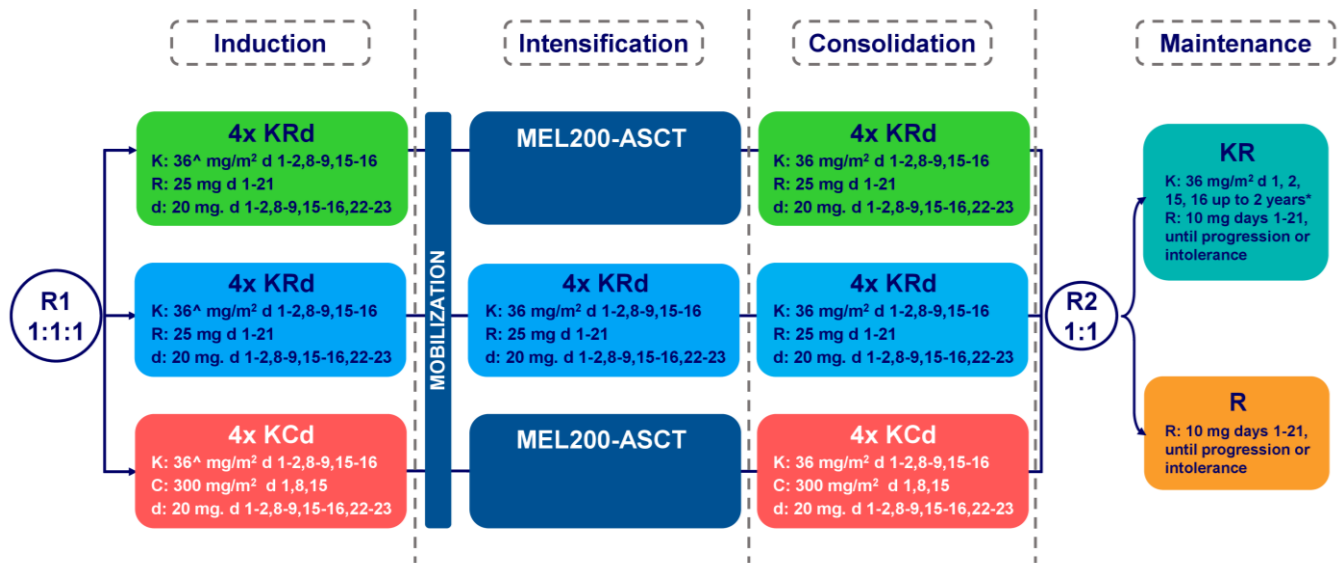
Table S17. Grade 3-5 cardiac, pulmonary, and renal toxicities and serious adverse events (SAEs) in the pre-maintenance phases

	KRd-ASCT	KRd12	KCd-ASCT	All
	N= 158	N=157	N=159	N=473
Cardiac	3 (2)	4 (3)	2 (1)	9 (2)
Cardiac arrest	1 (1)	1 (1)	-	2 (0)
Coronary heart disease	-	1 (1)	1 (1)	2 (0)
Heart failure	1 (1)	-	-	1 (0)
Tachyarrhythmia	-	2 (1)	1 (1)	3 (1)
Pulmonary	2 (1)	-	1 (1)	3 (1)
Respiratory failure	1 (1)	-	-	1 (1)
Renal	2 (1)	3(2)	2 (1)	7 (1)
Renal failure	2 (1)	3(2)	2 (1)	7 (1)
All	7 (4)	6 (4)	5 (3)	18 (4)

Abbreviations. KRd, carfilzomib-lenalidomide-dexamethasone; ASCT, autologous stem-cell transplantation; KCd, carfilzomib-cyclophosphamide-dexamethasone; MEL200, melphalan at 200 mg/m²; 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; G, grade; SAE, serious adverse event.

Supplementary figures

Figure S1. FORTE clinical trial design

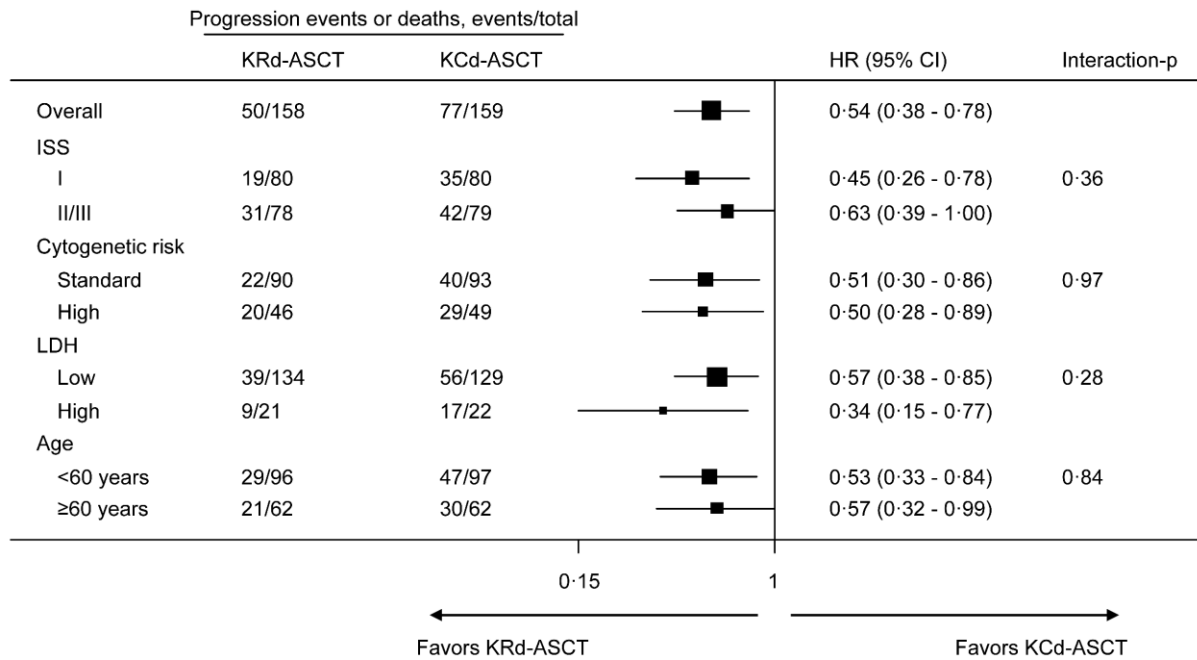


[^]20 mg/m² on days 1-2, cycle 1 only.

*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.

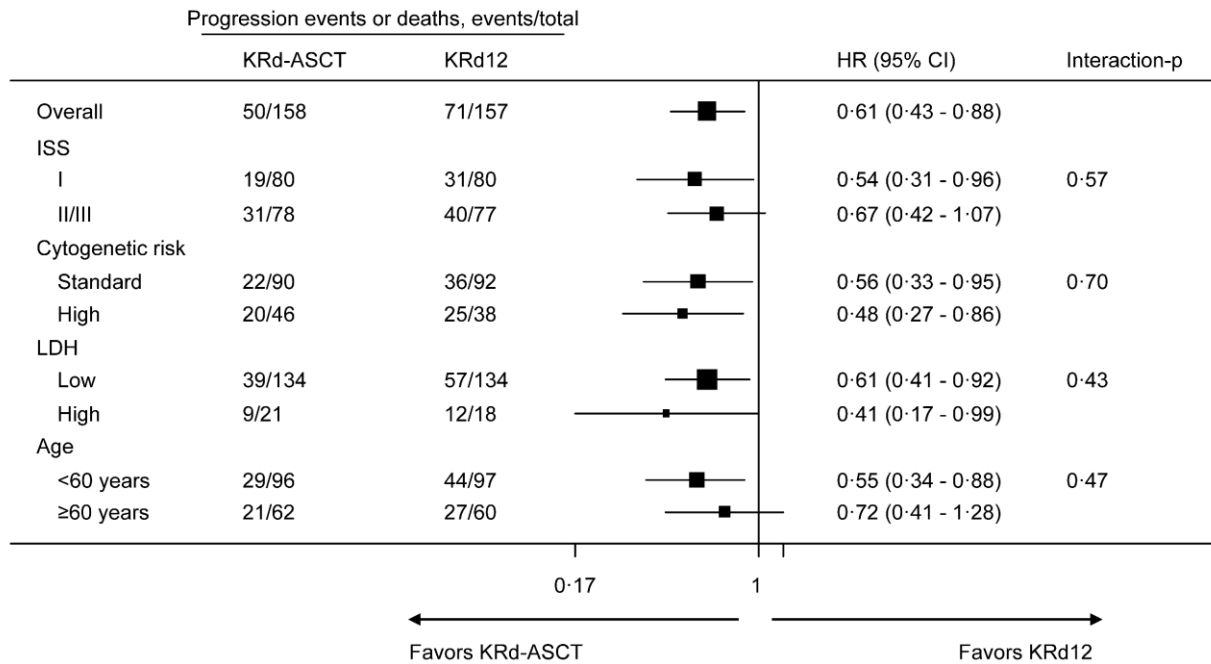
Abbreviations. R1, first randomisation (induction/consolidation treatment); R2, second randomisation (maintenance treatment); K, carfilzomib; C, cyclophosphamide; R, lenalidomide; -d, dexamethasone; d, days; MEL200, melphalan at 200 mg/m²; ASCT, autologous stem-cell transplantation.

Figure S2. Subgroup analysis of progression-free survival (PFS) with KRd-ASCT vs. KCd-ASCT



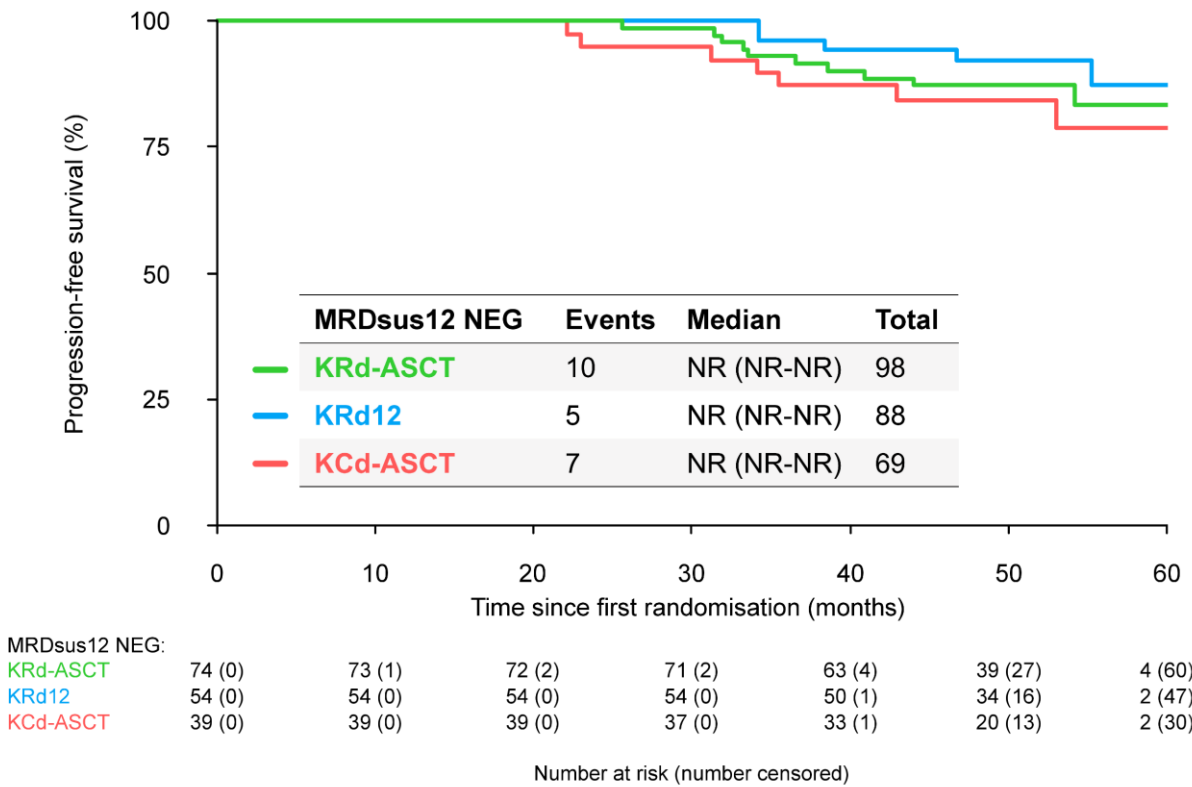
Abbreviations. KRd, carfilzomib-lenalidomide-dexamethasone; ASCT, autologous stem-cell transplantation; KCd, carfilzomib-cyclophosphamide-dexamethasone; MEL200, melphalan at 200 mg/m²; KRd-ASCT, 4 KRd induction cycles, MEL200-ASCT, 4 KRd consolidation cycles; KRd12, 12 KRd cycles; KCd-ASCT, 4 KCd induction cycles, MEL200-ASCT, 4 KCd consolidation cycles; HR, hazard ratio; CI, confidence interval; p, p-value; ISS, International Staging System stage; LDH, lactate dehydrogenase.

Figure S3 Subgroup analysis of progression-free survival (PFS) with KRd-ASCT vs. KRd12



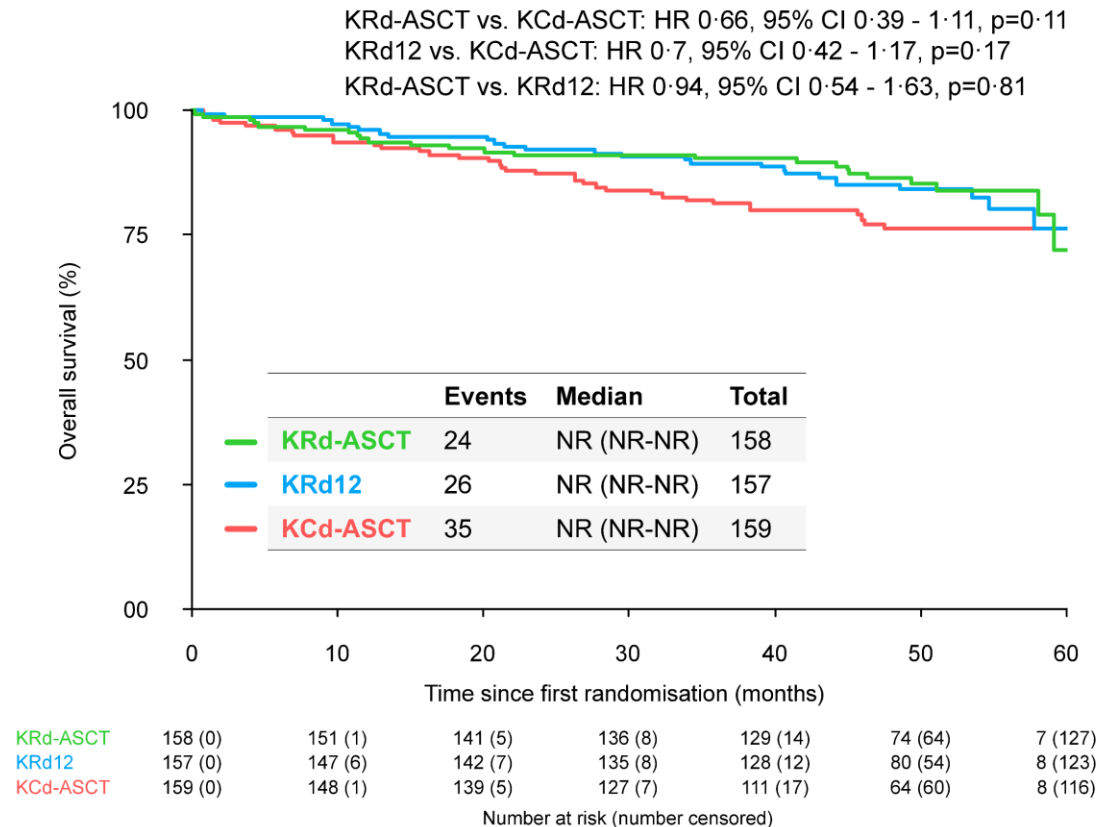
Abbreviations. KRd, carfilzomib-lenalidomide-dexamethasone; ASCT, autologous stem-cell transplantation; KCd, carfilzomib-cyclophosphamide-dexamethasone; MEL200, melphalan at 200 mg/m²; KRd-ASCT, 4 KRd induction cycles, MEL200-ASCT, 4 KRd consolidation cycles; KRd12, 12 KRd cycles; KCd-ASCT, 4 KCd induction cycles, MEL200-ASCT, 4 KCd consolidation cycles; HR, hazard ratio; CI, confidence interval; p, p-value; ISS, International Staging System stage; LDH, lactate dehydrogenase.

Figure S4. Kaplan–Meier estimates of progression-free survival (PFS) from first randomisation in patients with 1-year sustained MRD negativity



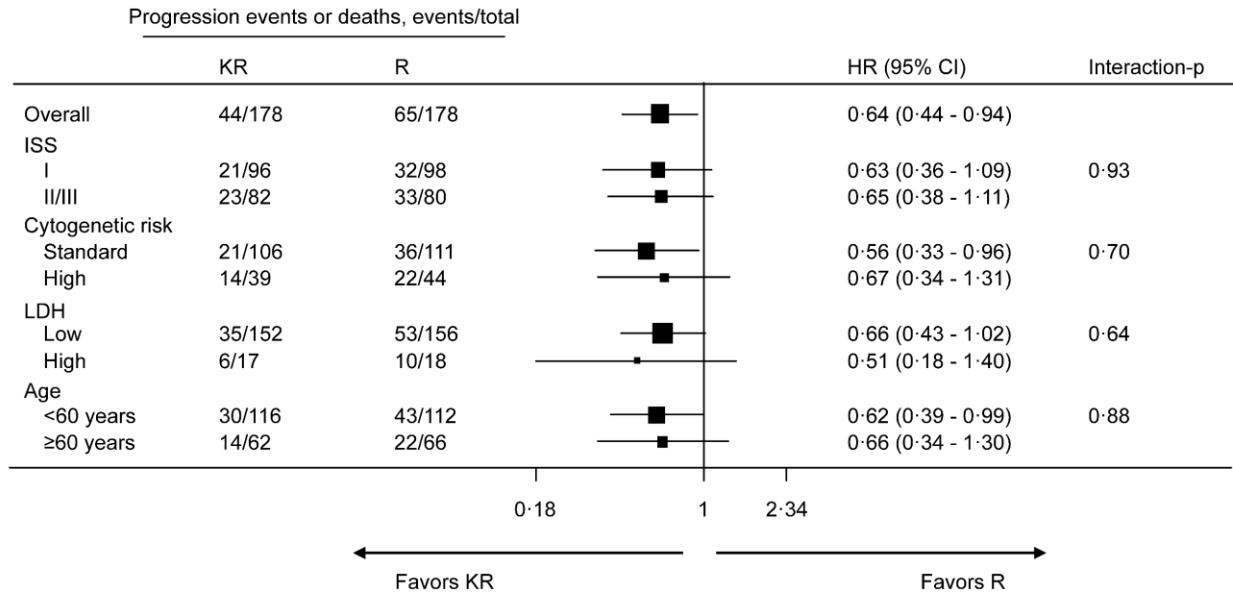
Abbreviations. KRd, carfilzomib-lenalidomide-dexamethasone; ASCT, autologous stem-cell transplantation; KCd, carfilzomib-cyclophosphamide-dexamethasone; MEL200, melphalan at 200 mg/m²; KRd-ASCT, 4 KRd induction cycles, MEL200-ASCT, 4 KRd consolidation cycles; KRd12, 12 KRd cycles; KCd-ASCT, 4 KCd induction cycles, MEL200-ASCT, 4 KCd consolidation cycles; MRDsus12 NEG, 1-year sustained minimal residual disease negativity; HR, hazard ratio; CI, confidence interval; p, p-value.

Figure S5. Kaplan–Meier estimates of overall survival (OS) according to the first trial randomisation



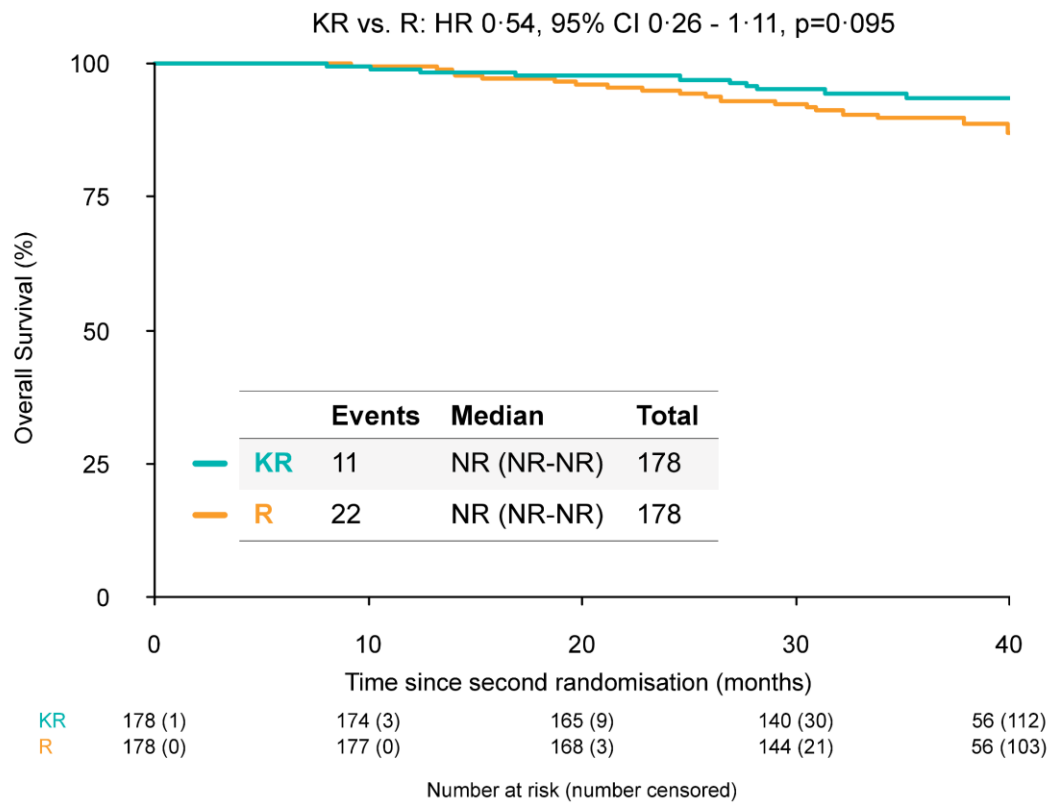
Abbreviations. KRd, carfilzomib-lenalidomide-dexamethasone; ASCT, autologous stem-cell transplantation; KCd, carfilzomib-cyclophosphamide-dexamethasone; MEL200, melphalan at 200 mg/m²; KRd-ASCT, 4 KRd induction cycles, MEL200-ASCT, 4 KRd consolidation cycles; KRd12, 12 KRd cycles; KCd-ASCT, 4 KCd induction cycles, MEL200-ASCT, 4 KCd consolidation cycles; HR, hazard ratio; CI, confidence interval; p, p-value.

Figure S6. Subgroup analysis of progression-free survival (PFS) with KR vs. R



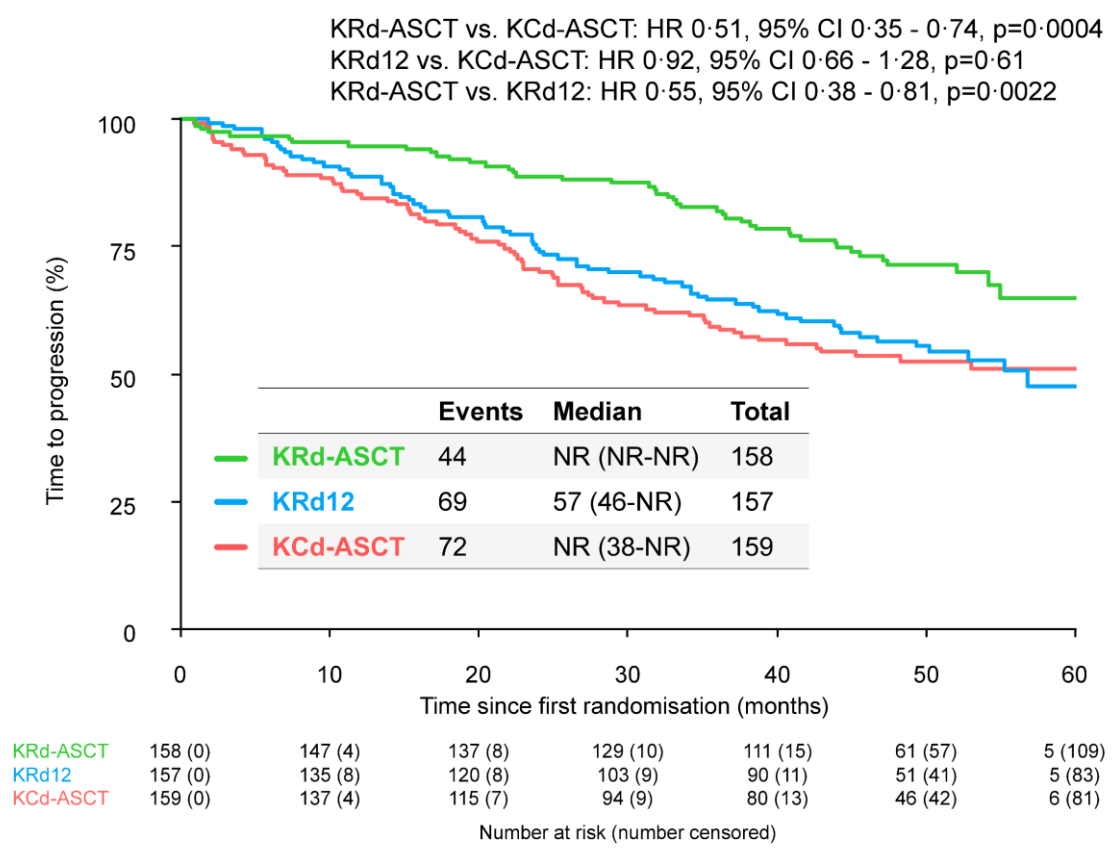
Abbreviations. KR, maintenance treatment with carfilzomib-lenalidomide; R, maintenance treatment with lenalidomide alone; HR, hazard ratio; CI, confidence interval; p, p-value; ISS, International Staging System stage; LDH, lactate dehydrogenase.

Figure S7. Kaplan–Meier estimates of overall survival (OS) according to the second trial randomisation to maintenance treatment



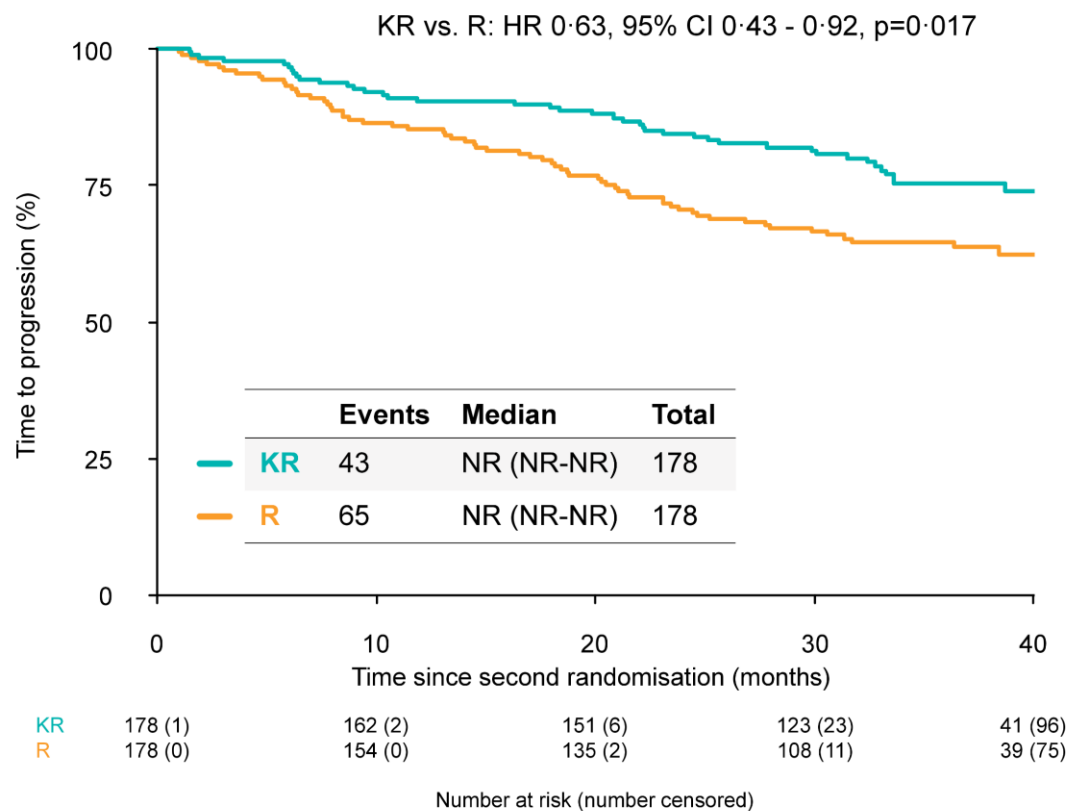
Abbreviations. KR, maintenance treatment with carfilzomib-lenalidomide; R, maintenance treatment with lenalidomide alone; HR, hazard ratio; CI, confidence interval; p, p-value.

Figure S8. Kaplan–Meier estimates of time to progression (TTP) according to the first trial randomisation



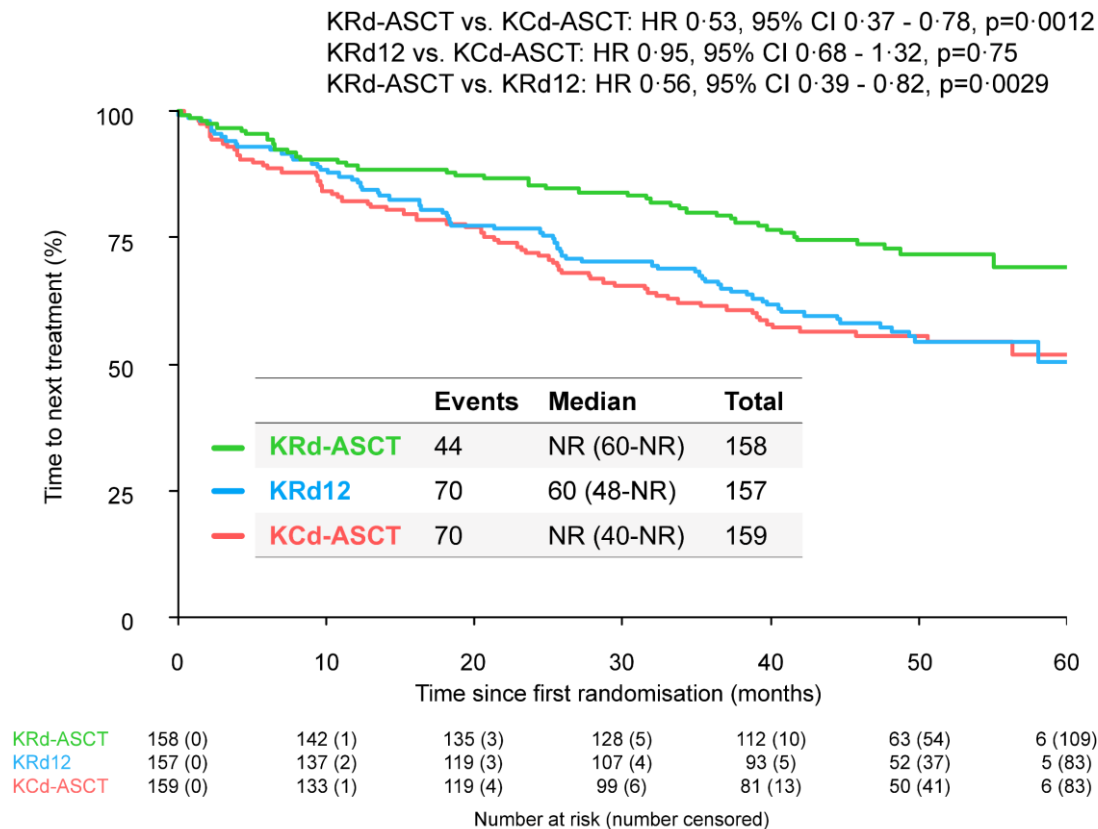
Abbreviations. KRd, carfilzomib-lenalidomide-dexamethasone; ASCT, autologous stem-cell transplantation; KCd, carfilzomib-cyclophosphamide-dexamethasone; MEL200, melphalan at 200 mg/m²; KRd-ASCT, 4 KRd induction cycles, MEL200-ASCT, 4 KRd consolidation cycles; KRd12, 12 KRd cycles; KCd-ASCT, 4 KCd induction cycles, MEL200-ASCT, 4 KCd consolidation cycles; HR, hazard ratio; CI, confidence interval; p, p-value.

Figure S9. Kaplan–Meier estimates of time to progression (TTP) according to the second trial randomisation



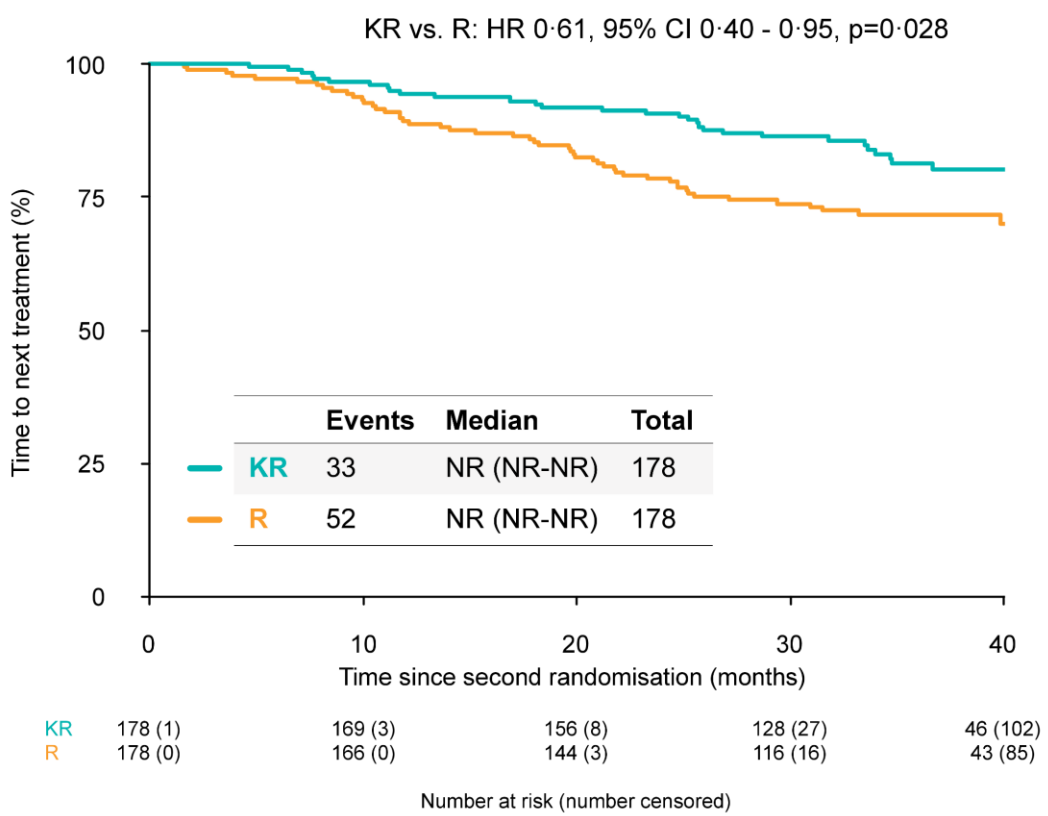
Abbreviations. KR, maintenance treatment with carfilzomib-lenalidomide; R, maintenance treatment with lenalidomide alone; HR, hazard ratio; CI, confidence interval; p, p-value.

Figure S10. Kaplan–Meier estimates of time to next treatment (TTNT) according to the first trial randomisation



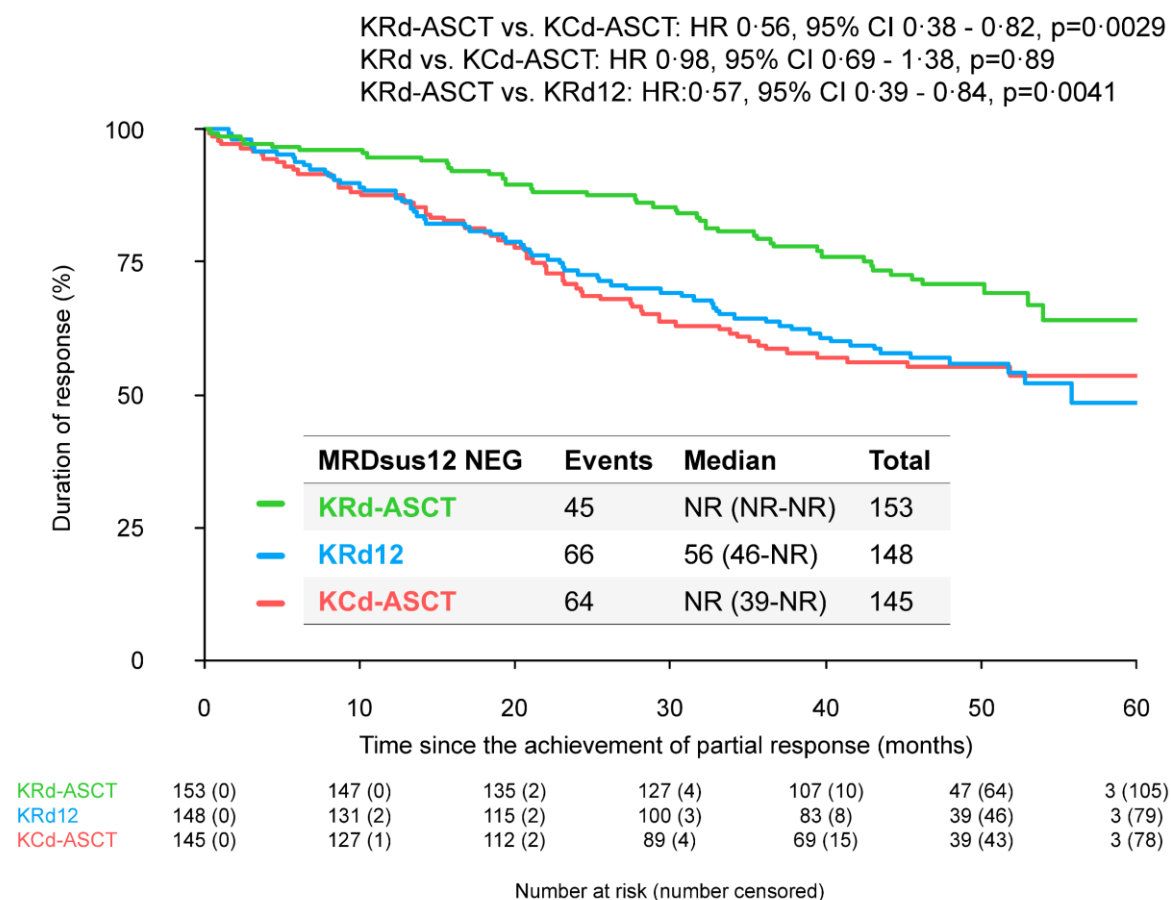
Abbreviations. KRd, carfilzomib-lenalidomide-dexamethasone; ASCT, autologous stem-cell transplantation; KCd, carfilzomib-cyclophosphamide-dexamethasone; MEL200, melphalan at 200 mg/m²; KRd-ASCT, 4 KRd induction cycles, MEL200-ASCT, 4 KRd consolidation cycles; KRd12, 12 KRd cycles; KCd-ASCT, 4 KCd induction cycles, MEL200-ASCT, 4 KCd consolidation cycles; HR, hazard ratio; CI, confidence interval; p, p-value.

Figure S11. Kaplan–Meier estimates of time to next treatment (TTNT) according to the second trial randomisation



Abbreviations. KR, maintenance treatment with carfilzomib-lenalidomide; R, maintenance treatment with lenalidomide alone; HR, hazard ratio; CI, confidence interval; p, p-value.

Figure S12. Kaplan–Meier estimates of duration of response according to the first trial randomisation



Abbreviations. KRd, carfilzomib-lenalidomide-dexamethasone; ASCT, autologous stem-cell transplantation; KCd, carfilzomib-cyclophosphamide-dexamethasone; MEL200, melphalan at 200 mg/m²; 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; HR, hazard ratio; CI, confidence interval; p, p-value.

References

1 Kumar S, Paiva B, Anderson KC, *et al.* International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol* 2016; **17**: e328–46.

2 Gay FM, Scalabrini DR, Belotti A, *et al.* Carfilzomib-lenalidomide-dexamethasone (KRd) vs carfilzomib-cyclophosphamide-dexamethasone (KCd) induction: Planned interim analysis of the randomized FORTE trial in newly diagnosed multiple myeloma (NDMM). *J Clin Oncol* 2017; **35**: Abstract #8003 [ASCO 2017 Annual Meeting].

3 Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika* 1994; **81**: 515–26.

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

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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 UNITO-MM-01/FORTE

Final Version 6.0 – 11.06.2020

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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

Signature of Principal Investigator

[Redacted Signature]

Date

[Redacted Date]

Printed Name of Principal Investigator:

[Redacted Name]

Institution Name:

[Redacted Institution Name]

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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SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Site Principal Investigator



Printed Name of Site Principal Investigator:



Institution Name:



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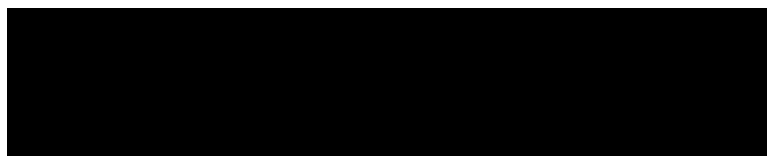
SPONSOR SIGNATURE PAGE

Promoter



Signature of Sponsor Representative

Date



Printed Name of Representative

By my signature, I agree to supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/EC procedures, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and local regulations governing the conduct of clinical studies.

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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.

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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: INCLUSION CRITERIA:

477 newly diagnosed MM patients eligible for ASCT

Age \geq 18 years

Newly diagnosed MM based on standard CRAB criteria (see appendix B).

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EXCLUSION CRITERIA:

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 $\geq 60\%$ (see appendix G).

Pretreatment clinical laboratory values within 30 days of enrollment:

Platelet count $\geq 75 \times 10^9/L$ ($\geq 50 \times 10^9/L$ if myeloma involvement in the bone marrow is $> 50\%$)

Absolute neutrophil count (ANC) $\geq 1 \times 10^9/L$ without the use of growth factors

Corrected serum calcium ≤ 14 mg/dL (3.5 mmol/L)

Alanine transaminase (ALT): $\leq 3 \times$ the ULN

Aspartate transaminase (AST): $\leq 3 \times$ the ULN

Total bilirubin: $\leq 2 \times$ the ULN Calculated or measured creatinine clearance: ≥ 30 mL/minute. LVEF $\geq 40\%$. 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

Previous treatment with anti-myeloma therapy (does not include radiotherapy, bisphosphonates, or a single short course of steroid \leq 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.

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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/m² IV on days 1-2 cycle 1 only, followed by 36 mg/m² IV once daily on days 8-9, 15-16 cycle 1 then for all subsequent doses 36 mg/m² IV once daily on days 1-2, 8-9, 15-16.
2. Cyclophosphamide = 300 mg/m² 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/m², 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 10⁶ 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/m² IV once daily on days 1-2, 8-9, 15-16.
2. Cyclophosphamide = 300 mg/m² 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

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In case patients do not have the criteria to start the consolidation treatment (ANC $\geq 1.0 \times 10^9/L$ and platelets $\geq 75 \times 10^9/L$ 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/m² IV on days 1-2 cycle 1 only, followed by 36 mg/m² IV once daily on days 8-9, 15-16 cycle 1 then for all subsequent doses 36 mg/m² 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/m², 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 4×10^6 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 2×10^6 CD34+cells/kg day 0	

90-120 days after Melphalan treatment:

1. Carfilzomib = 36 mg/m² 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 $\geq 1.0 \times 10^9/L$ and platelets $\geq 75 \times 10^9/L$ and no grade >1 extra-hematologic toxicity) within 120 days from Melphalan infusion, they will go on with the maintenance treatment.

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ARM C: CRd long treatment

1. Carfilzomib = 20 mg/m² IV on days 1-2 cycle 1 only, followed by 36 mg/m² IV once daily on days 8-9, 15-16 cycle 1 then for all subsequent doses 36 mg/m² 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/m², 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 10⁶ 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/m² 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/m² 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/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.

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.

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Maintenance can only start if ANC $\geq 0.75 \times 10^9/l$ and platelets $> 50 \times 10^9/l$. Moreover all extra-hematological toxicities should be resolved to \leq 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 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

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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% ($\beta = 0.10$) 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:

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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% ($\beta = 0.20$) 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

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patients will complete the first 4 cycles of weekly carfilzomib maintenance. The safety data of carfilzomib 70 mg/m² 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

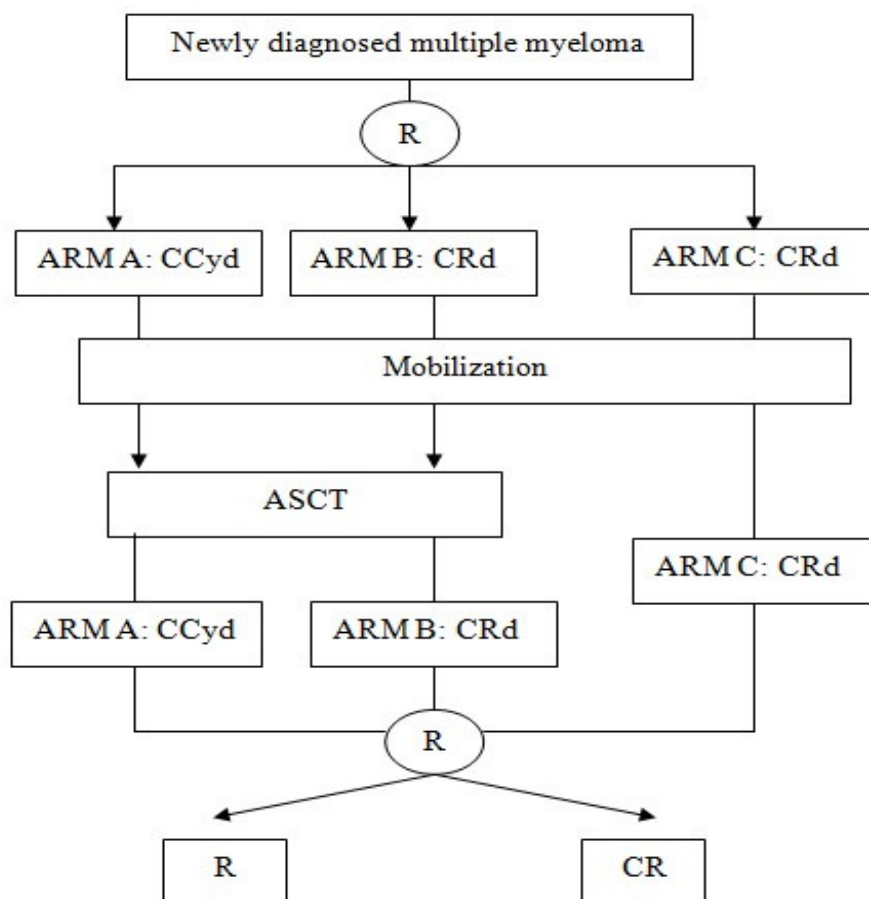


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LIST OF ABBREVIATIONS

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)

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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)

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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

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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 microenvironment, 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 people¹. The median age at diagnosis is 70 years². 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 observation³.

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 derivatives. 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/m²) with lenalidomide 25 mg and low dose dexamethasone are being used¹². 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/m², 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/m² on days 1, 2, and 36 mg/m² on days 8, 9, 15, 16, cycle 1; 36 mg/m² on days 1, 2, 8, 9, 15, 16, cycles 2–9), cyclophosphamide (300 mg/m² on days 1, 8, 15) and dexamethasone (40 mg on days 1, 8, 15, 22) for 9 cycles, followed by carfilzomib maintenance (36 mg/m² 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 events¹⁴.

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 lenalidomide¹⁵.

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 TD¹⁶.

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 remission²⁴.

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 OS²⁵.

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/m². Maximum proteasome inhibition was seen at doses 11 mg/m² 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/m² dose. Large, single arm studies of the 27 mg/m² 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/m² 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/m² 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/m² when carfilzomib was given as a bolus. Administration of the same dose (48 mg/m²) 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/m² (bolus administration over 2-10'). A review of the tolerability of 36 mg/m² 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/m² carfilzomib experience with bolus dosing (see IB for details). Three patients completed > 12 cycles of therapy at 36 mg/m² 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/m² given on Days 1 and 2 of cycle 1 only; followed by 36 mg/m² for all subsequent doses), 20/45, 20/56 mg/m² and so forth are being investigated. Doses of 20/56 mg/m² 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/m²) indicated that it is reasonably well tolerated, with minimal infusion reactions. In some cases at 20/56 mg/m², dexamethasone was increased from 4 mg/dose to 8 mg with the 56 mg/m² doses in order to reduce fevers and hypotension. As of March 20, 2010, seven patients have received 20/56 mg/m² and are tolerating it. Patients with advanced, refractory MM being treated at 36 mg/m² and 45 mg/m² 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/m² 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 adjustment¹². 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/m² was well tolerated in elderly patients and responses obtained during induction treatment improved with maintenance treatment³⁹. 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/m² with dexamethasone showed acceptable safety and efficacy with an ORR of 77% and median PFS of 12.6 months among patients with RRMM⁴⁹. The pharmacokinetics and pharmacodynamic results from this study are supportive of a once-weekly, 70 mg/m² 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 regimen⁵⁰.

The same dose and schedule of carfilzomib has been studied in different combinations with novel agents. Carfilzomib weekly at the dose of 70 mg/m² 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 therapies⁵¹. In a phase Ib study carfilzomib has been evaluated at dose of 56 mg/m² and 70 mg/m² 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/m² in NDMM and RRMM is ongoing⁵².

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 MM²⁶.

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 reasonable²⁷.

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.

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

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.

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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.

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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/m² IV on days 1-2 cycle 1 only, followed by 36 mg/m² IV once daily on days 8-9, 15-16 cycle 1 then for all subsequent doses 36 mg/m² IV once daily on days 1-2, 8-9, 15-16.
2. Cyclophosphamide = 300 mg/m² 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/m ²	i.v.	1
G-CSF (filgrastim)	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 10⁶ 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/ m ² day -2	i.v. rapid infusion
Stem cell infusion	Minimum of 2 x 10 ⁶ CD34+cells/kg day 0	

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Consolidation (90-120 days from Melphalan and ASCT):

1. Carfilzomib = 36 mg/m² IV once daily on days 1-2, 8-9, 15-16.
2. Cyclophosphamide = 300 mg/m² 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/m² IV on days 1-2 cycle 1 only, followed by 36 mg/m² IV once daily on days 8-9, 15-16 cycle 1 then for all subsequent doses 36 mg/m² 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/m ²	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 10⁶ 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/ m ² 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/m² IV once daily on days 1-2, 8-9, 15-16.
2. Lenalidomide= 25 mg PO daily on days 1-21.

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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/m² IV on days 1-2 cycle 1 only, followed by 36 mg/m² IV once daily on days 8-9, 15-16 cycle 1 then for all subsequent doses 36 mg/m² 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/m², 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/m ²	i.v.	1
G-CSF (filgrastim)	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 10⁶ 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/m² 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/m² IV once daily on days 1, 15 for patients that have started maintenance within 6 months from amendment 5.0 approval.
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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.

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 ≤ 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, ≥ 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 ≥ 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 ≥ 18 years

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

Laboratory

7. Adequate hepatic function, with serum (alanine aminotransferase) ALT ≤ 3 times the upper limit of normal (ULN), AST (aspartate transaminase) $\leq 3 \times$ the ULN
8. Serum direct bilirubin ≤ 2 mg/dL (34 μ mol/L) within 14 days prior to randomization
9. Absolute neutrophil count (ANC) $\geq 1.0 \times 10^9$ /L within 14 days prior to randomization
10. Platelet count $\geq 75 \times 10^9$ /L ($\geq 50 \times 10^9$ /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 $\geq 40\%$. 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 \leq 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 m² will receive a dose based upon a 2.2 m² 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 thrombocytopenia and neutropenia:

Table 1-Thrombocytopenia Carfilzomib	
When Platelets:	Recommended Action Carfilzomib
Fall to $< 30 \times 10^9/L$	Interrupt carfilzomib, follow CBC weekly
Return to $\geq 30 \times 10^9/L$	Resume at full dose
Subsequently drop to $< 30 \times 10^9/L$	Interrupt carfilzomib, follow CBC weekly
Return to $\geq 30 \times 10^9/L$	Resume at 1 dose decrement

Table 2-Neutropenia Carfilzomib

Recommended Action	
When ANC	Carfilzomib
Falls to $< 0.5 \times 10^9/L$	Interrupt carfilzomib add G-CSF if G 3 with fever or G 4, follow CBC weekly Resume at full dose
Returns to $> 1.0 \times 10^9/L$ (if neutropenia was the only toxicity noted)	
Returns to $> 1.0 \times 10^9/L$ (if other toxicity noted)	Resume at 1 dose decrement
Subsequently drops to $< 0.5 \times 10^9/L$ Returns to $> 1.0 \times 10^9/L$	Interrupt carfilzomib 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 \leq 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	Hold until \leq Grade 1, reinstitute at full dose.
G 4	Discontinue
Tumor lysis syndrome (≥ 3 of following: $\geq 50\%$ increase in creatinine, uric acid, or phosphate; $\geq 30\%$ increase in potassium; $\geq 20\%$ 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	Continue to dose. If neuropathy persists for more than two weeks hold carfilzomib until resolved to \leq Gr 2 without pain. Then restart at 1 dose decrement
Grade 4 neuropathy	Discontinue

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Renal Dysfunction

$\text{CrCl} \leq 30 \text{ mL/min}$

Hold until $\text{CrCl} > 30 \text{ mL/minute}$;
restart at 1 dose decrement

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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 $G \geq 3$	Hold dose until toxicity resolves to \leq Grade 1 or baseline. Restart at 1 dose decrement.

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

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

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

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

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Dose Level -5	Carfilzomib 20 mg/m ²
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Patients who required dose reduction during induction/consolidation will start maintenance at the dose tolerated during induction/consolidation:

-Patients who tolerated 36 mg/m² twice a week will receive 70 mg/m² day 1 and 15 during maintenance;

-Patients who reduced to 27 mg/m² twice a week during induction/consolidation will receive 56 mg/m² day 1 and 15 during maintenance;

-Patients who reduced to 20 mg/m² twice a week during induction/consolidation will receive 36 mg/m² 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	

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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 syndrome	Reduce dose	Monitor closely and take appropriate medical precautions

In case ANC $< 1 \times 10^9/L$, G-CSF must be administered. If neutropenia is overcome by G-CSF, continue G-CSF as needed to maintain ANC $> 1 \times 10^9/L$. Patients can receive lenalidomide only if ANC $> 1 \times 10^9/L$. Moreover, if platelets fall to $< 50 \times 10^9/L$, lenalidomide administration should be delayed until platelets return to $> 50 \times 10^9/L$. If platelets fall again to $< 50 \times 10^9/L$, 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

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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/m ² days 1,8,15
Dose Level-2	Cyclophosphamide 100 mg/m ² 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.

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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.

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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

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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.

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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 \geq 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 discretion.

INDUCTION TREATMENT

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

- Platelet count $\geq 75 \times 10^9/L$
- Absolute neutrophil count (ANC) $\geq 1 \times 10^9/L$ 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 $\geq 75 \times 10^9/L$
- Absolute neutrophil count (ANC) $\geq 1 \times 10^9/L$ 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 $\geq 0.75 \times 10^9/l$ and platelets $> 50 \times 10^9/l$. If patients have ANC $< 1 \times 10^9/l$, they will receive G-CSF until ANC $\geq 1 \times 10^9/l$. Patients can start maintenance treatment only when ANC $\geq 1 \times 10^9/l$

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
- \geq 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 $\leq 20\%$. 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/m²) 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/m²) 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 $\leq 30,000/\text{mm}^3$, 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 $PMN < 1 \times 10^9/L$, G-CSF must be administered and lenalidomide treatment should be held until $PMN > 1 \times 10^9/L$.

- 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 (famciclovir, 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.

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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 < 0.5x10⁹/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 C_{max} was increased by 14%. Periodic monitoring of digoxin plasma

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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 ($\text{CrCl} < 50 \text{ mL/min}$) 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 $\geq 50\%$ increase, LDH ≥ 2 -fold increase, uric acid $\geq 50\%$ increase, phosphate $\geq 50\%$ increase, potassium $\geq 30\%$ increase, calcium $\geq 20\%$ 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.

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STUDY TESTS AND OBSERVATIONS

Procedure	Screening ≤ 28 days from Baseline	Induction and consolidation phase			Mobilization and intensification phases ¹⁵	Maintenance phase (Arm 1: lenlidomide Arm 2: lenalidomide + carfilzomib)		Follow up every 3 Months
		Cycles 1-12				At the end of 12 th induction (Arm C)/4 th consolidation cycle (Arm A and B),		
		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							

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QoI assessment⁸	X	X				X		
Research samples^{11,9, 14} (peripheral blood	X	X				X		

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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, sodium, bilirubin, creatinine clearance, LDH, β_2 -microglobulin, 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

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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

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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 5×10^6 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 µL of EDTA peripheral blood dispensed with reverse pipetting, added with 500 µL of lysing solution and, after 15 min, 100 µL 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*

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- *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

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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 utero 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

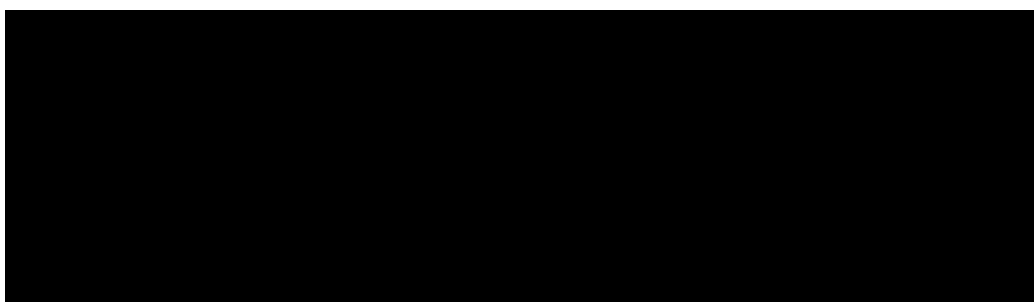
The investigator will inform the Sponsor of all SAEs within 24 hours in order that the sponsor can fulfill their regulatory reporting obligations within the required timeframes.

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

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



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.

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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 Persistent MRD-negative is determined as MFC MRD negativity in the marrow as defined by patients with MRD negative result confirmed for a minimum of 1 year. Data might also be presented as persistent MRD negativity 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/m² on day 1, 2, 15, 16 + lenalidomide vs carfilzomib 70 mg/m² 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% ○ 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% ($\beta = 0.10$) 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% ($\beta = 0.20$) 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 Criteria³⁵. 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 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 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/m² will be compared with the data of the last 18 patients randomized to carfilzomib 36 mg/m² 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- β -cyclodextrin (SBE- β -CD, Captisol®).

STORAGE

Lyophilized Carfilzomib for Injection must be stored at 2–8°C 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.

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

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.

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

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 25°C (68 to 77°F). 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.

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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 need³⁰.

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.

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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 patients³¹⁻³⁴. 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 leukemia³⁷. 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 higher³⁸. 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

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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 intracлонаl 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

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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

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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 1×10^6 cells) of the CD138+ bone marrow plasma cells fraction, obtained from the patients at the time points specified above should be sent 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 unprecedented 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 status⁵⁵.

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 discordance⁵⁷.

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 \geq 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 \geq 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.

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

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.

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 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 trial-related 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 sent 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.

REFERENCES

1. Altekruse SF, Kosary CL, Krapcho M, Neyman N, Aminou R, Waldron W, et al. (eds). SEER Cancer Statistics Review, 1975-2007, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2007/, based on November 2009 SEER data submission, posted to the SEER website 2010.
2. Palumbo A, Anderson K, Multiple Myeloma, *N Engl J Med*, 2011; 364:1046-60.
3. Palumbo A, Magarotto V, Novel treatment paradigm for elderly patients with multiple Myeloma, *Am J Blood Res* 2011; 1(2):190-203.
4. Demo SD, Kirk CJ, Aujay MA, et al. Anti-tumor activity of PR-171, a novel irreversible inhibitor of the proteasome. *Cancer Res*. 2007; 67(13):6383-91.
5. Arastu-Kapur S, Shenk K, Parlati F and Bennett M. Non-Proteasomal Targets of Proteasome Inhibitors Bortezomib and Carfilzomib. *Blood (ASH Annual Meeting Abstracts)*, Nov 2008; 112: 2657.
6. Kirk CJ, Jiang J, Muchamuel T, Dajee M, Swinarski D, Aujay M, Bennett MK, Yang J, Lewis E, Laidig G and Molineaux CJ. The Selective Proteasome Inhibitor Carfilzomib Is Well Tolerated in Experimental Animals with Dose Intensive Administration. *Blood (ASH Annual Meeting Abstracts)*, Nov 2008; 112: 2765.
7. Bortezomib Summary Basis of Approval (www.fda.gov/cder/foi/nda/2003/21602_Velcade.htm)
8. Bross PF, Kane R, Farrell AT, Abraham S, Benson K, Brower ME, Bradley S, Gobburu JV, Goheer A, Lee SL, Leighton J, Liang CY, Lostritto RT, McGuinn WD, Morse DE, Rahman A, Rosario LA, Verbois SL, Williams G, Wang YC, Pazdur R Approval summary for bortezomib for injection in the treatment of multiple myeloma. *Clin Cancer Res*. 2004 10(12 Pt 1):3954-64.
9. Kuhn DJ, Chen Q, Voorhees PM, Strader JS, Shenk KD, Sun CM, Demo SD, Bennett SD, van Leeuwen, F, Chanan-Khan, A and Orlowski, RZ. Potent activity of carfilzomib, a novel, irreversible inhibitor of the ubiquitin-proteasome pathway, against preclinical models of multiple myeloma. *Blood*. 2007 Nov 1;110(9):3281-90.
10. DM Weber, C Chen, R Niesvizky, M Wang, A Belch, EA Stadtmauer, D Siegel, I Borrello, SV Rajkumar, AA Chanan-Khan, S Lonial, Z Yu, J Patin, M Olesnyckyj, JB Zeldis, and RD Knight. Lenalidomide plus Dexamethasone for Relapsed Multiple Myeloma in North America. *N Engl J Med* 2007; 357:2133-2142
11. M Dimopoulos, A Spencer, M Attal, HM Prince, JL Harousseau, A Dmoszynska, J San Miguel, A Hellmann, T Facon, R Foà, A Corso, Z Masliak, M Olesnyckyj, Z Yu, J Patin, JB Zeldis, and RD Knight. Lenalidomide plus Dexamethasone for Relapsed or Refractory Multiple Myeloma. *N Engl J Med* 2007; 357:2123-2132
12. Niesvizky R, Wang L, Orlowski RZ, Bensinger W, Alsina M, Gabrail N, Gutierrez A, Lori Kunkel, Michael Kauffman, and The Multiple Myeloma Research Consortium (MMRC) Phase Ib Multicenter Dose Escalation Study of Carfilzomib Plus Lenalidomide and Low Dose Dexamethasone (CRd) in Relapsed and Refractory Multiple Myeloma (MM). *Blood (ASH Annual Meeting Abstracts)*, Nov 2009; 114: 304.
13. AJ Jakubowiak, D Dytfeld, S Jagannath, DH Vesole, TB Anderson1, BK Nordgren, K Detweiler-Short, D Lebovic, KE Stockerl-Goldstein, KA Griffith, TL Jobkar, DE Durecki, SM Wear, RF Ott, A Al-Zoubi, MA Mietzel, M Hussein, D Couriel, JA Leveque, and R Vij, Final Results of a Frontline Phase 1/2 Study of Carfilzomib, Lenalidomide, and Low-Dose Dexamethasone (CRd) in Multiple Myeloma (MM). Abstract ASH 631 2011
14. Antonio Palumbo, Sara Bringhen, Oreste Villani, Agostina Siniscalchi, Eleonora Russo, Giuseppina Uccello, Chiara Cerrato, Milena Gilestro, Davide Rossi and Mario Boccadoro. Carfilzomib, Cyclophosphamide and Dexamethasone (CCd) for Newly Diagnosed Multiple Myeloma (MM) Patients. *Blood (ASH Annual Meeting Abstracts)* 2012 120: Abstract 730.
15. Marco Ladetto, Gloria Pagliano, Simone Ferrero, Federica Cavallo, Daniela Drandi, Loredana Santo, Claudia Crippa, Luca De Rosa, Patrizia Pregno, Mariella Grasso, Anna Marina Liberati, Tommaso Caravita, Francesco Pisani, Tommasina Guglielmelli, Vincenzo Callea, Pellegrino Musto, Clotilde Cangialosi, Roberto Passera, Mario Boccadoro and Antonio Palumbo. Major Tumor Shrinking and Persistent Molecular Remissions After Consolidation With Bortezomib, Thalidomide, and Dexamethasone in Patients With Autografted Myeloma. *JCO* April 20, 2010 vol. 28 no. 12 2077-2084
16. Prof Michele Cavo, Paola Tacchetti, Francesca Patriarca, Maria Teresa Petrucci, Lucia Pantani, Monica Galli, Prof Francesco Di Raimondo, Claudia Crippa, Elena Zamagni, Antonio Palumbo, Massimo Offidani, Prof Paolo

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- Corradini, Franco Narni, Antonio Spadano, Norbert Pescosta, Prof Giorgio Lambertenghi Delilieri, Antonio Ledda, Claudia Cellini, Tommaso Caravita, Patrizia Tosi, Prof Michele Baccarani. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. *The Lancet*, Volume 376, Issue 9758, Pages 2075 - 2085, 18 December 2010
17. Michel Attal, Jean-Luc Harousseau, Serge Leyvraz, Chantal Doyen, Cyrille Hulin, Lofti Benboubker Ibrahim Yakoub Agha, Jean-Henri Bourhis, Laurent Garderet, Brigitte Pegourie, Charles Dumontet, Marc Renaud, Laurent Voillat, Christian Berthou, Gerald Marit, Mathieu Monconduit, Denis Caillot, Bernard Grobois, Herve Avet-Loiseau, Philippe Moreau and Thierry Facon. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. *Blood*, 2006 108: 3289-3294
 18. Andrew Spencer, H. Miles Prince, Andrew W. Roberts, Ian W. Prosser, Kenneth F. Bradstock, Luke Coyle, Devinder S. Gill, Noemi Horvath, John Reynolds, and Nola Kennedy. Consolidation Therapy With Low-Dose Thalidomide and Prednisolone Prolongs the Survival of Multiple Myeloma Patients Undergoing a Single Autologous Stem-Cell Transplantation Procedure. *J Clin Oncol* 2009; 27:1788-1793
 19. Bart Barlogie., Guido Tricot, Elias Anaissie, John Shaughnessy, Erik Rasmussen, Frits van Rhee, Athanasios Fassas, Maurizio Zangari, Klaus Hollmig, Mauricio Pineda-Roman, Choon Lee, Giampaolo Talamo, Raymond Thertulien, Elias Kiwan, Somashekar Krishna, Michele Fox, and John Crowley. Thalidomide and Hematopoietic-Cell Transplantation for Multiple Myeloma. *N Engl J Med* 2006;354:1021-30.
 20. Gareth J. Morgan, Walter M. Gregory, Faith E. Davies, Sue E. Bell, Alexander J. Szubert, Julia M. Brown, Nuria N. Coy, Gordon Cook, Nigel H. Russell, Claudius Rudin, Huw Roddie, Mark T. Drayson, Roger G. Owen, Fiona M. Ross, Graham H. Jackson, J. Anthony Child. The role of maintenance thalidomide therapy in multiple myeloma: MRC Myeloma IX results and meta-analysis. *Blood* 2012 119: 7-15
 21. Henk M. Lokhorst, Bronno van der Holt, Sonja Zweegman, Edo Vellenga, Sandra Croockewit, Marinus H. van Oers, Peter von dem Borne, Pierre Wijermans, Ron Schaafsma, Okke de Weerd, Shulamiet Wittebol, Michel Delforge, Henriëtte Berenschot, Gerard M. Bos, Kon-Siong G. Jie, Harm Sinnige, Marinus van Marwijk-Kooy, Peter Joosten, Monique C. Minnema, Rianne van Ammerlaan and Pieter Sonneveld. A randomized phase 3 study on the effect of thalidomide combined with adriamycin, dexamethasone, and highdose melphalan, followed by thalidomide maintenance in patients with multiple myeloma. *Blood* 2010 115: 1113-1120
 22. Michel Attal, Valerie cances Lauwers, Gerald Marit, Service, d'hématologie, clinique, et, de, thérapie, cellulaire, Denis Caillot, Thierry Facon, Cyrille Hulin, Philippe Moreau, Claire Mathiot, Murielle Roussel, Catherine Payen, H. Avet-Loiseau and Jean Luc Harousseau. Maintenance Treatment with Lenalidomide After Transplantation for MYELOMA: Final Analysis of the IFM 2005-02. *Blood (ASH Annual Meeting Abstracts)* 2010 116: Abstract 310
 23. Philip L. McCarthy, Kouros Owzar, Kenneth C. Anderson, Craig C. Hofmeister, David Duane Hurd, Hani Hassoun, Sergio Giralt, Edward A. Stadtmauer, Paul G Richardson, Daniel J. Weisdorf, Ravi Vij, Jan S Moreb, Natalie Scott Callander, Koen Van Besien, Teresa Gentile, Luis Isola, Richard T Maziarz, Don A. Gabriel, Asad Bashey, Heather Landau, Thomas Martin, Muzaffar H. Qazilbash, Denise Levitan, Brian McClune, Vera Hars, John Postiglione, Chen Jiang, Elizabeth Bennett, Susan S Barry, Linda Bressler, Michael Kelly, Michele Sexton, Cara Rosenbaum, Hari Parameswaran, Marcelo C Pasquini, Mary M. Horowitz, Thomas C. Shea, Steven M Devine, and Charles Linker. Phase III Intergroup Study of Lenalidomide Versus Placebo Maintenance Therapy Following Single Autologous Hematopoietic Stem Cell Transplantation (AHSCT) for Multiple Myeloma: CALGB 100104. *Blood (ASH Annual Meeting Abstracts)* 2010 116: Abstract 37
 24. Philip L. McCarthy, Kouros Owzar, Craig C. Hofmeister, David D. Hurd, Hani Hassoun, Paul G. Richardson, Sergio Giralt, Edward A. Stadtmauer, Daniel J. Weisdorf, Ravi Vij, Jan S. Moreb, Natalie Scott Callander, Koen Van Besien, Teresa Gentile, Luis Isola, Richard T. Maziarz, Don A. Gabriel, Asad Bashey, Heather Landau, Thomas Martin, Muzaffar H. Qazilbash, Denise Levitan, Brian McClune, Robert Schlossman, Vera Hars, John Postiglione, Chen Jiang, Elizabeth Bennett, Susan Barry, Linda Bressler, Pharm.D., Michael Kelly, Michele Seiler, Cara Rosenbaum, Parameswaran Hari, Marcelo C. Pasquini, Mary M. Horowitz, Thomas C. Shea, Steven M. Devine, Kenneth C. Anderson, and Charles Linker. Lenalidomide after Stem-Cell Transplantation for Multiple Myeloma. *N Engl J Med* 2012;366:1770-81

Confidential

Protocol UNITO-MM-01/FORTE

Version 6.0, 12.05.2019

25. Michel Attal, Valerie Lauwers-Cances, Gerald Marit, enis Caillot, Philippe Moreau, Thierry Facon, Anne Marie Stoppa, Cyrille Hulin, Lofti Benboubker, Laurent Garderet, Olivier Decaux, Serge Leyvraz, MarieChristiane Vekemans, Laurent Voillat, Mauricette Michallet, Brigitte Pegourie, Charles Dumontet, Murielle Roussel, Xavier Leleu, Claire Mathiot, Catherine Payen, Hervé Avet-Loiseau, and Jean-Luc Harousseau. Lenalidomide Maintenance after Stem-Cell Transplantation for Multiple Myeloma. *N Engl J Med* 2012;366:1782-91.
26. Jean-Paul Fermand, Sandrine Katsahian, Marine Divine, Veronique Leblond, Francois Dreyfus, Margaret Macro, Bertrand Arnulf, Bruno Royer, Xavier Mariette, Edouard Pertuiset, Coralie Belanger, Maud Janvier, Sylvie Chevret, Jean Claude Brouet, and Philippe Ravaud. High-Dose Therapy and Autologous Blood StemCell Transplantation Compared With Conventional Treatment in Myeloma Patients Aged 55 to 65 Years: Long-Term Results of a Randomized Control Trial From the Group Myelome-Autogreffe. 2005 *J Clin Oncol* 23:9227-9233.
27. John Koreth,¹ Corey S. Cutler,¹ Benjamin Djulbegovic,³ Rajesh Behl,¹ Robert L. Schlossman, Nikhil C. Munshi,² Paul G. Richardson,² Kenneth C. Anderson,² Robert J. Soiffer,¹ Edwin P. Alyea. High-dose Therapy with Single Autologous Transplantation versus Chemotherapy for Newly Diagnosed Multiple Myeloma: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *Biology of Blood and Marrow Transplantation* 13:183-196 (2007)
28. Sawyer, J.R. (2011). The prognostic significance of cytogenetics and molecular profiling in multiple myeloma. *Cancer Genetics*. 204:3–12.
29. Zhou, Y., Barlogie, B., Shaughnessy, J.D., Jr. (2009). The molecular characterization and clinical management of multiple myeloma in the post-genome era. *Leukemia*. 23:1941–56.
30. Lonial, S. (2010). Presentation and risk stratification – improving prognosis for patients with multiple myeloma. *Cancer Treatment Reviews*. 36S2: S12–7.
31. Ludwig H, Avet-Loiseau H, Bladé J, Boccadoro M, Cavenagh J, Cavo M, Davies F, de la Rubia J, Delimpasi S, Dimopoulos M, Drach J, Einsele H, Facon T, Goldschmidt H, Hess U, Mellqvist UH, Moreau P, San-Miguel J, Sondergeld P, Sonneveld P, Udvardy M, Palumbo A. European perspective on multiple myeloma treatment strategies: update following recent congresses. *Oncologist*. 2012;17(5):592-606. doi: 10.1634/theoncologist.2011-0391. Epub 2012 May 9. Review. Erratum in: *Oncologist*. 2012;17(7):1005.
32. Paiva B, Vidriales MB, Cerveró J, Mateo G, Pérez JJ, Montalbán MA, Sureda A, Montejano L, Gutiérrez NC, García de Coca A, de Las Heras N, Mateos MV, López-Berges MC, García-Boyero R, Galende J, Hernández J, Palomera L, Carrera D, Martínez R, de la Rubia J, Martín A, Bladé J, Lahuerta JJ, Orfao A, San Miguel JF; GEM (Grupo Español de MM)/PETHEMA (Programa para el Estudio de la Terapéutica en Hemopatías Malignas) Cooperative Study Groups. Multiparameter flow cytometric remission is the most relevant prognostic factor for multiple myeloma patients who undergo autologous stem cell transplantation. *Blood*. 2008 Nov 15;112(10):4017-23. doi: 10.1182/blood-2008-05-159624. Epub 2008 Jul 31.
33. Compagno M, Mantoan B, Astolfi M, Boccadoro M, Ladetto M. Real-time polymerase chain reaction of immunoglobulin rearrangements for quantitative evaluation of minimal residual disease in myeloma. *Methods Mol Med*. 2005;113:145-63.
34. Sarasquete ME, García-Sanz R, González D, Martínez J, Mateo G, Martínez P, Ribera JM, Hernández JM, Lahuerta JJ, Orfao A, González M, San Miguel JF. Minimal residual disease monitoring in multiple myeloma: a comparison between allelic-specific oligonucleotide real-time quantitative polymerase chain reaction and flow cytometry. *Haematologica*. 2005 Oct;90(10):1365-72.
35. Faham M, Zheng J, Moorhead M, Carlton VE, Stow P, Coustan-Smith E, Pui CH, Campana D. Deepsequencing approach for minimal residual disease detection in acute lymphoblastic leukemia. *Blood*. 2012 Dec 20;120(26):5173-80. doi: 10.1182/blood-2012-07-444042. Epub 2012 Oct 16.
36. Gawad C, Pepin F, Carlton VE, Klinger M, Logan AC, Miklos DB, Faham M, Dahl G, Lacayo N. Massive evolution of the immunoglobulin heavy chain locus in children with B precursor acute lymphoblastic leukemia. *Blood*. 2012 Nov 22;120(22):4407-17. doi: 10.1182/blood-2012-05-429811. Epub 2012 Aug 28.
37. Logan AC, Zhang B, Narasimhan B, Carlton V, Zheng J, Moorhead M, Krampf MR, Jones CD, Waqar AN, Faham M, Zehnder JL, Miklos DB. Minimal residual disease quantification using consensus primers and

- highthroughput IGH sequencing predicts post-transplant relapse in chronic lymphocytic leukemia. *Leukemia*. 2013 Feb 19. doi: 10.1038/leu.2013.52. [Epub ahead of print].
38. Joaquin Martinez-Lopez, Ramon Garcia-Sanz, Francois Pepin, Rosa Ayala, Maria Angeles Montalban, Bruno Paiva, Li Weng, Santiago Barrio, Laura Montejano, Immaculada Rapado, Rafael Martinez, Maria Jesus Blachard, Pedro Sanchez-Godoy, Joan Blade, Jesús F. San-Miguel, Malek Faham, Juan José Lahuerta; Hematology, Hospital 12 de Octubre, Madrid, Spain; University Hospital of Salamanca, Salamanca, Spain; Sequentia, Inc., South San Francisco, CA; Hospital 12 de Octubre, Madrid, Spain; Hospital Clinic of Madrid, Madrid, Spain; Hospital Ramon y Cajal, Madrid, Spain; Hospital Severo Ochoa de Leganes, Madrid, Spain; Hospital Clinic de Barcelona, Barcelona, Spain; Hematology, Hospital Universitario de Salamanca, Salamanca, Spain. Prognostic value of deep sequencing method for minimal residual disease (MRD) detection in multiple myeloma. *J Clin Oncol* 31, 2013 (suppl; abstr 8511).
 39. Brinthen S, Cerrato C, Petrucci MT, M Genuardi, F Gentilini, C Conticello, S Oliva, L Pantani, M Offidani, C Palladino, G Benevolo, V Montefusco, M Astolfi, O Villani, A Siniscalchi, A Rocci, L De Paoli, M Boccadoro, P Sonneveld and A Palumbo. A Phase II Study With Carfilzomib, Cyclophosphamide and Dexamethasone (CCd) For Newly Diagnosed Multiple Myeloma. *Blood* November 15, 2013 vol. 122 no. 21 685.
 40. Siegel D, Martin T, Nooka A, et al. Integrated safety profile of single-agent carfilzomib: experience from 526 patients enrolled in 4 phase II clinical studies. *Haematologica*. 2013 Nov;98(11):1753-61. doi: 10.3324/haematol.2013.089334. Epub 2013 Aug 9.
 41. Enrico O, Gabriele B, Nadia C, et al. Unexpected cardiotoxicity in haematological bortezomib treated patients. *Br J Haematol*. 2007;138:396–397.
 42. Willis MS, Patterson C. Into the heart: the emerging role of the ubiquitin-proteasome system. *J Mol Cell Cardiol*. 2006;41:567–579.
 43. Li YF, Wang X. The role of the proteasome in heart disease. *Biochim Biophys Acta*. 2011;1809:141–149.
 44. Stangl K, Satngl V. The ubiquitin-proteasome pathway and endothelial (dys)function. *Cardiovascular Research*. 2010; 85:281-290.
 45. Maitland ML, Bakris GL, Black HR, et al. Initial assessment, surveillance and management of blood pressure in patients receiving vascular endothelial growth factor signaling pathway inhibitors. *J Natl Cancer Inst*. 2010; 102:596-604.
 46. C hobanian AV, Bakris GL, Black HR, et al. JNC 7: Complete Report. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003; 42: 1206-1252.
 47. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension. The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Journal of Hypertension*. 2013; 31:1925-1938.
 48. James, P.A., S. Oparil, B.L. Carter, and et al., 2014 evidence-based guideline for the management of high blood pressure in adults: Report from the panel members appointed to the eighth joint national committee (jnc 8). *Jama*, 2013
 49. Berdeja J, Rifkin R, Lyons R, et al. Efficacy and Safety of Once-Weekly Carfilzomib and Dexamethasone in Patients With Relapsed or Refractory Multiple Myeloma: Secondary Analysis from the CHAMPION-1 Study by Prior Lines of Therapy. *Clinical Lymphoma, Myeloma and Leukemia*, 17(1), e58-e59.
 50. Berenson JR, Cartmell A, Bessudo A, et al. CHAMPION-1: a phase 1/2 study of once-weekly carfilzomib and dexamethasone for relapsed or refractory multiple myeloma. *Blood*. 2016 Jun 30;127(26):3360-8
 51. Lonial S, San-Miguel JF, Martínez-Lopez S, et al. Daratumumab in Combination with Carfilzomib and Dexamethasone in Patients (pts) with Relapsed Multiple Myeloma (MMY1001): An Open-Label, Phase 1b Study. *Blood (ASH Annual Meeting Abstracts)* 2017 Abstract 1869.
 52. Biran N, Siegel DS, Berdeja GJ, et al. A Phase 1b Study Investigating Carfilzomib Administered Once Weekly in Combination with Lenalidomide and Dexamethasone in Patients with Multiple Myeloma. *Blood (ASH Annual Meeting Abstracts)* 2016 Abstract 3322.

53. N. C. Munshi et al., “Association of minimal residual disease with superior survival outcomes in patients with multiple myeloma: A meta-analysis,” *JAMA Oncol.*, vol. 3, no. 1, pp. 28–35, 2017.
54. O. Landgren, S. Devlin, M. Boulad, and S. Mailankody, “Role of MRD status in relation to clinical outcomes in newly diagnosed multiple myeloma patients: A meta-analysis,” *Bone Marrow Transplant.*, vol. 51, no. 12, pp. 1565–1568, 2016.
55. C. Mazzotti et al., “Myeloma MRD by deep sequencing from circulating tumor DNA does not correlate with results obtained in the bone marrow,” *Blood Adv.*, vol. 2, no. 21, pp. 2811–2813, 2018.
56. J. R. Mills, D. R. Barnidge, A. Dispenzieri, and D. L. Murray, “High sensitivity blood-based M-protein detection in sCR patients with multiple myeloma,” *Blood Cancer J.*, vol. 7, no. 8, pp. 1–5, 2017.
57. N. Puig et al., “Qip-Mass Spectrometry in High Risk Smoldering Multiple Myeloma Patients Included in the GEM-CESAR Trial: Comparison with Conventional and Minimal Residual Disease IMWG Response Assessment,” *Blood*, vol. 134, no. Supplement_1, p. 581, Nov. 2019.
58. S. Jaiswal et al., “Age-related clonal hematopoiesis associated with adverse outcomes,” *N. Engl. J. Med.*, vol. 371, no. 26, pp. 2488–98, 2014.
59. M. Xie et al., “Age-related mutations associated with clonal hematopoietic expansion and malignancies,” *Nat. Med.*, vol. 20, no. 12, pp. 1472–1478, 2014.
60. H. P. Koefler and G. Leong, “Preleukemia: One name, many meanings,” *Leukemia*, vol. 31, no. 3, pp. 534–542, 2017.
61. G. Genovese et al., “Clonal Hematopoiesis and Blood-Cancer Risk Inferred from Blood DNA Sequence,” *N. Engl. J. Med.*, vol. 371, no. 26, pp. 2477–2487, 2014.
62. S. Chitre et al., “Clonal hematopoiesis in patients with multiple myeloma undergoing autologous stem cell transplantation,” *Leukemia*, vol. 32, no. 9, pp. 2020–2024, 2018.
63. C. A. Ortmann et al., “Functional Dominance of CHIP-Mutated Hematopoietic Stem Cells in Patients Undergoing Autologous Transplantation,” *Cell Rep.*, vol. 27, no. 7, pp. 2022–2028.e3, 2019.
64. T. H. Mouhieddine et al., “The Role of Clonal Hematopoiesis of Indeterminate Potential (CHIP) in Multiple Myeloma: Immunomodulator Maintenance Post Autologous Stem Cell Transplant (ASCT) Predicts Better Outcome,” *Blood*, vol. 132:749, 2018.
65. P. Musto et al., “Second primary malignancies in multiple myeloma: An overview and IMWG consensus,” *Ann. Oncol.*, vol. 28, no. 2, pp. 228–245, 2017.
66. A. Palumbo et al., “Continuous Lenalidomide Treatment for Newly Diagnosed Multiple Myeloma,” *N. Engl. J. Med.*, vol. 366, no. 19, pp. 1759–1769, 2012.
67. M. Attal et al., “Lenalidomide Maintenance after Stem-Cell Transplantation for Multiple Myeloma,” *N. Engl. J. Med.*, vol. 366, no. 19, pp. 1782–1791, 2012.
68. P. L. McCarthy et al., “Lenalidomide after Stem-Cell Transplantation for Multiple Myeloma,” *N. Engl. J. Med.*, vol. 366, no. 19, pp. 1770–1781, 2012.

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

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Protocol UNITO-MM-01/FORTE

Version 6.0, 12.05.2019

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APPENDIX B: MULTIPLE MYELOMA DIAGNOSTIC CRITERIA

THE INTERNATIONAL MYELOMA WORKING GROUP DIAGNOSTIC CRITERIA:

Clonal bone marrow plasma cells $\geq 10\%$ 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 μ mol/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* $\geq 60\%$
- 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

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- 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 \geq 3.5 g/dL

- Stage II Neither Stage I or Stage III

- Stage III Serum β_2 -microglobulin >5.5 mg/L

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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

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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 $\geq 90\%$ decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria
Partial Response (PR)	$\geq 50\%$ reduction of serum M-protein and reduction in 24-h urinary Mprotein by $\geq 90\%$ or < 200mg per 24 h If the serum and urine M-protein are unmeasurable ^d a $\geq 50\%$ 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, $\geq 50\%$ reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was $\geq 30\%$

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	In addition to the above listed criteria, if present at baseline, a $\geq 50\%$ 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 endpoints for all patients including those in CR (includes primary progressive disease and disease progression on or off therapy)	<p>Progressive disease: required one or more of the following:</p> <p>Increase of $\geq 25\%$ from nadir in</p> <p>Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dl)^e</p> <p>Urine M-component and/or (the absolute increase must be ≥ 200 mg/24 h</p> <p>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.</p> <p>Bone marrow plasma cell percentage: the absolute % must be $\geq 10\%$^f</p> <p>Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas.</p> <p>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</p>

Clinical Relapse ^a	<p>Clinical relapse requires one or more of:</p> <p>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</p>
	<ol style="list-style-type: none"> 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

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

^fRelapse from CR has the 5% cutoff versus 10% for other categories of relapse.

^gFor 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 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 to the end of the study, have not progressed, and are still alive will also be censored at the time of last contact.

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• 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

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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

Intrauterine device (IUD)

Hormonal (birth control pills, injections, implants)

Tubal ligation

Partner's vasectomy

Additional Effective Methods

Latex condom

Diaphragm

Cervical Cap

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 carfilzomib.

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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)

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During maintenance (every 3 months until clinical progression)

10 ml peripheral blood in Na citrate

7 ml peripheral blood in red top (serum)

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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 starting treatment			X	X
6 months after starting treatment	X	X	X	X
9 months after starting 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

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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 treatment**

APPENDIX 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:

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1=Asymptomatic or mild symptoms, clinical or diagnostic observations only, intervention not indicated;

2=Moderate; minimal, local or noninvasive 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:

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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 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 Committees 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.

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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): _____

	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

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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:

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	Not 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

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15. Have you vomited?	1	2	3	4
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During the past week:

	Not All at	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

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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

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

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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

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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

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

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- 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