Phase 1/2 study of weekly carfilzomib, cyclophosphamide, dexamethasone in newly diagnosed transplant-ineligible myeloma

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ABSTRACT

This multicentre, open-label phase 1/2 trial determined safety and efficacy of weekly carfilzomib plus cyclophosphamide-dexamethasone (wKCyd) in newly diagnosed multiple myeloma (NDMM) patients aged ≥65 years or transplant-ineligible. Patients received wKCyd for up to nine 28-day cycles, followed by maintenance with carfilzomib until progression/intolerance. The phase 1 portion used a 3+3 dose-escalation scheme to determine the maximum tolerated dose (MTD) of weekly carfilzomib: 12 patients received wKCyd with carfilzomib doses of 45 mg/m^2, 56 mg/m^2, and 70 mg/m^2. The MTD was established at 70 mg/m^2 and 54 patients (phase 1 and 2) received weekly carfilzomib 70 mg/m^2: 85% of them achieved ≥ partial response (PR), 66% ≥ very good partial response, 30% ≥ near complete response, and 15% complete response (CR). Responses improved during maintenance: 98% achieved ≥PR, including 29% CR and 10% stringent CR. After a median follow-up of 18 months, the 2-year PFS and OS rates were 53.2% and 81%, respectively. The most frequent grade 3-5 toxicities were neutropenia (22%) and cardiopulmonary adverse events (9%). This is the first study of weekly carfilzomib plus an alkylating agent in elderly patients with NDMM. Of note, wKCyd was effective and safe, thus can be a valid option in this setting.

INTRODUCTION

In the last decade, the increased use of novel agents as initial therapy of multiple myeloma (MM) significantly improved overall survival (OS) in patients ineligible for autologous transplantation.(1) In Europe, bortezomib-melphalan-prednisone and melphalan-prednisone-thalidomide combinations are considered standards of care in elderly patients ineligible for autologous stem cell transplantation.(2,3) Dose-limiting haematological toxicity from melphalan and peripheral neuropathy from bortezomib or thalidomide limit their optimal use.(4,5) Better tolerated alkylating agents, such as cyclophosphamide, which lack the cumulative haematological toxicity of melphalan, have been used successfully in combination with dexamethasone and either thalidomide(6) or bortezomib(7) in elderly newly diagnosed MM (NDMM) patients. Recently, based on the results of MM020 trial, a new standard of care with no alkylating agent has been introduced for the treatment of elderly patients with NDMM. Indeed, that study prospectively compared outcomes of MPT vs lenalidomide and low-dose dexamethasone, and found that treatment with lenalidomide and dexamethasone until disease progression improved PFS and OS compared with MPT.(8)

Carfilzomib, a novel and selective proteasome inhibitor, received accelerated approval in the United States in 2012 for the treatment of patients with relapsed and refractory MM. It is approved in the United States and Europe when used in combination with dexamethasone or lenalidomide plus dexamethasone for patients with relapsed MM (1 to 3 prior lines of therapy).(9) Under the initial approvals, carfilzomib is administered as a 10-minute infusion on a twice-weekly dosing schedule, with a starting dose of 20 mg/m^2 on cycle 1 days 1 and 2, and stepped-up to a target dose of 27 mg/m^2 thereafter. Prolonged infusion over 30 min has been assessed in clinical studies showing that higher carfilzomib doses (56 mg/m^2) in combination with dexamethasone were safe and effective. (10,11) These findings were confirmed with the results of the randomized phase 3 ENDEAVOR trial (RandomizEd, opeN Label, Phase 3 Study of carfilzomib plus DExamethAsone Vs bortezomib plus DexamethasOne in Patients With Relapsed Multiple Myeloma; #NCT01568866) comparing

carfilzomib plus dexamethasone vs bortezomib plus dexamethasone in relapsed/refractory MM, which supported the approval of twice-weekly carfilzomib (at 56 mg/m^2) with dexamethasone for patients with relapsed MM.(12)

Twice-weekly intravenous administration of anti-myeloma therapy can be burdensome for patients, especially for those who are elderly, suffer from myeloma-related symptoms, or who live far from the clinic. Based on results from studies showing that once-weekly bortezomib has similar efficacy and a better safety profile compared to the conventional twice-weekly administration,(13) and to follow up on the CHAMPION-1 study evaluating weekly carfilzomib plus dexamethasone in the relapse setting,(14) we aimed to assess whether the more convenient once-weekly carfilzomib regimen is as effective as the standard twice-weekly dosing schedule in NDMM elderly patients. We previously showed that treatment with twice-weekly carfilzomib in combination with cyclophosphamide and dexamethasone (KCyd) was highly effective and well tolerated in elderly NDMM patients. Responses were rapid and deep, and showed improvement over time. Forty-nine percent of patients achieved ≥nCR, and 20% of patients achieved a sCR. After a median follow-up of 18 months, the 2-year PFS rate was 76%. Severe haematological AEs occurred in <20% of patients and non-haematological AEs occurred in <10% of patients, with a low (18%) rate of discontinuation.(15) Given the improved haematological safety profile of cyclophosphamide and the previous encouraging results with KCyd,(15) we conducted a phase 1/2 study to determine the maximum tolerated dose (MTD), and evaluated the safety and efficacy of once-weekly carfilzomib in combination with cyclophosphamide and dexamethasone (wKCyd) in elderly NDMM patients. We report the safety and efficacy results of the trial herein.

METHODS

Patients

Patients with symptomatic NDMM who were aged ≥65 years or ineligible for autologous transplantation were included in the study. Further eligibility criteria included measurable disease,

ECOG performance status ≤2, creatinine clearance ≥15 mL/minute, platelet count ≥50 × 10^9/L (≥30 × 10^9/L if myeloma involvement in the bone marrow was >50%), and absolute neutrophil count of ≥1 × 10^9/L without the use of growth factors. Patients were excluded from the study if they had non-secretory MM (unless serum free light chains were present, and the ratio was abnormal), grade >2 peripheral neuropathy, active infection, LVEF <40% evaluated with 2D transthoracic ECHO (or Multigated Acquisition Scan if ECHO was not available), myocardial infarction or unstable angina ≤4 months before enrolment, uncontrolled angina, history of severe coronary artery disease, or electrocardiographic evidence of acute ischemia or Grade 3 conduction system abnormalities unless subject had a pacemaker, uncontrolled hypertension, uncontrolled congestive heart failure or uncontrolled diabetes within 14 days prior to enrolment.

All patients gave written informed consent to participate in the study, which had been approved by the institutional ethics committees. The study was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice.

Study design and treatment

This multicentre, non-randomised, open-label, dose escalation phase 1/2 study determined the safety and efficacy of wKCyd in NDMM patients. The primary objective of the phase 1 portion was to determine the MTD of once-weekly carfilzomib with cyclophosphamide and dexamethasone. The primary objective of the phase 2 portion was to determine the overall response rate (ORR). Secondary endpoints included response rates, progression-free survival (PFS), time to progression (TTP), duration of response (DOR), OS, time to next therapy (TNT), subgroup analyses of prognostic factors, the evaluation of the effect of maintenance on PFS and OS, and the relationship between responses and PFS in responding and non-responding patients.

All patients received oral cyclophosphamide 300 mg/m^2 on days 1, 8, 15, and oral dexamethasone 40 mg on days 1, 8, 15, 22. Carfilzomib was administered as a 30-minute, IV infusion on days 1, 8, and 15 of 28-day cycles. In the phase 1, dose-escalation portion, patients received carfilzomib at 20

mg/m^2 on cycle 1, day 1; subsequent doses were escalated in a standard 3+3 dose-escalation scheme at 45, 56, 70 mg/m^2 to determine the MTD. In the phase 2 portion, patients received carfilzomib at the MTD with the same schedule as in the phase 1 portion (Figure S1). Treatment was given every 28 days for nine cycles. Patients then received maintenance therapy with carfilzomib at the MTD on days 1, 15 every 28 days until progression or intolerance.

Dose limiting toxicity (DLT) is defined as the first occurrence in the first cycle of grade ≥2 neuropathy with pain or any severe (grade 3-4) toxicity. A DLT can also be grade ≥3 nausea, vomiting, or diarrhea despite maximal antiemetic/antidiarrheal therapy, grade 4 fatigue lasting for ≥ 7 days, grade 4 neutropenia or thrombocytopenia lasting for ≥ 7 days, febrile neutropenia, grade 3-4 thrombocytopenia associated with bleeding, any toxicity requiring a dose reduction within cycle 1, inability to receive day-1 dose of cycle 2 due to drug related toxicity persisting from cycle 1.

Assessment

For all patients receiving at ≥1 dose of any study drug, toxicity was assessed according to the National Cancer Institute Common Terminology Criteria, version 4.0.(16) Response was assessed according to the International Myeloma Working Group criteria(17) with the addition of near-complete response (nCR), defined as absence of monoclonal component in the serum and/or urine with immunofixation positive. The response assessments were undertaken at the beginning of each treatment cycle (Figure S1) during induction and every three cycles during maintenance.

Fluorescence in situ hybridization was used to detect t(4:14), t(11:14), t(14;16), del13, and del(17p). Bone marrow samples were collected at study entry and investigations were performed at one central laboratory. For the present analysis, the cut-off value of 60% for the proportion of plasma cells with del(17p) was used, according to the recommendation from the International Myeloma Workshop Consensus panel 2.(18)

Statistical analysis

For the sample size of the phase 1 portion of the study, each wKCyd dose level cohort could have a minimum of 3 patients and a maximum of 6 patients. Therefore, a maximum of 18 patients could be recruited in the phase 1. The sample size of the phase 2 portion of the study was estimated according two-stage Simon optimal design, with early stopping rules in case of efficacy lower than a predefined uninteresting response rate. We assumed an ORR p_0 of 0.40, under which further study of the wKCyd combination would not be justified, and an ORR p_1 of 0.60, which could justify additional investigation of this combination. Probability of type I (α) error was set to be 0.05 and type II (β) error 0.20. In the first stage of phase 2, 16 patients had to be accrued. If 7 or less responses had been observed, the trial would have been stopped for futility. Otherwise, 30 additional patients would have been accrued in the second stage: if 23 or fewer responses had been observed by the end of this stage, no further investigation would have been warranted. With this design, the expected number of enrolled patients was 46 and the probability of early termination was 71.6%. Assuming approximately 10% of patients lost to follow-up, an adequate sample size was 53 patients.

Response rates and safety were analysed in patients who received ≥1 dose of study treatment. Time-to-event endpoints were determined using the intent-to-treat population. The Kaplan–Meier product limit method was used to estimate survivorship functions for time-to-event endpoints. Cox proportional hazards regression was used to assess the effects of demographic and prognostic variables on relative treatment differences. Continuous and categorical data were summarised using descriptive statistics. SAS System version 8.2 system (SAS Institute Inc., Cary, NC) was used.

Role of the funding source

The study was sponsored by Hovon Foundation and co-sponsored in Italy by Fo.Ne.Sa. Onlus, and it was supported by funding from Onyx Pharmaceuticals, Inc. first and Amgen afterwards. The funders had no role in the collection, analysis, or interpretation of data. All authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Patients

Patients were enrolled from April 10, 2013, to August 24, 2015, in 8 centres in Italy. Twelve patients were enrolled in the phase 1, dose-escalation portion of the study, 51 patients were enrolled in the phase 2 portion. A total of 54 patients were treated at the recommended phase 2 dose (RP2D) and could be assessed for efficacy and safety. Baseline demographics and disease characteristics for patients enrolled in all study phases are listed in Table 1. Median age of all patients was 72 years (Interquartile range [IQR], 69-74); 14 patients (22%) were ≥75 years; 19 patients (30%) had an unfavourable chromosomal profile, defined as the presence of t(4;14), del17p, or t(14;16), and 20 (32%) had International Staging System (ISS) stage III. All patients could be evaluated for safety and response; the median duration of induction treatment was nine cycles (range, 1–9 cycles). At the time of analysis, 47 patients had proceeded to maintenance therapy, 40 could be assessed for response (Figure S2).

MTD definition

During phase 1, in the dose-escalation portion of the study, no DLTs were observed in the 45 mg/m^2 dose cohort, 1/6 DLT was reported in the 56 mg/m^2 dose cohort (grade 3 creatinine increase) and no DLTs were observed in the 70 mg/m^2 dose cohort. The MTD of once-weekly carfilzomib with cyclophosphamide and dexamethasone was determined to be 70 mg/m^2 (Table S1).

Efficacy of RP2D

Overall, among patients receiving carfilzomib at the MTD, 46/54 (85%) patients had at least a partial response (≥PR), 36/54 (66%) patients had at least a very good partial response (≥VGPR) and 16/54 (30%) patients had at least a near complete response (≥nCR) (Table S1). Depth of response increased with prolonged treatment. At the end of four cycles, 43/48 (90%) patients achieved ≥PR, including

18/48 (38%) patients with ≥nCR. Among patients who completed nine cycles of treatment, 37/40 (93%) had ≥PR and 18/40 (44%) had ≥nCR. Among patients who received maintenance, 39/40 (98%) had ≥PR and 22/40 (54%) had ≥nCR, including 12/40 (29%) CR and 4/40 (10%) stringent CR (sCR) (Table 2). The median time to achieve PR was 2.4 months, but median time to sCR was 12 months and approximately 50% of patients with CR achieved CR during maintenance (Figure 1). The quality of response impacted on long-term outcome. At 2 years, the proportion of patients alive and in remission was 100% in patients who achieved sCR, 60% in those who achieved VGPR or CR, and 44% in those who achieved PR. Response rates were generally similar across patient groups according to ISS stage and chromosomal profile (Table 2).

After a median follow-up of 19.7 months (IQR, 14.3–28.3), the 2-year PFS and OS rates were 53.2% and 81%, respectively (Figure 2). The risk of progression was slightly higher in patients with ISS III (hazard ratio [HR] 2.46; 95% confidence interval [CI] 0·99–6.1, p=0.05) but not with high-risk chromosomal abnormalities. The 2-year PFS was 68% in high-risk patients and 53% in standard-risk ones (HR 0.45; 95% CI 0.12–1.7, p=0.24).

Safety of RP2D

During induction, the most common toxicities of any grade were anaemia (39%), thrombocytopenia (33%), neutropenia (31%), cardiovascular events (24%), nausea/vomiting (19%), fever (13%), infections (13%) and fatigue (9%). Grade 3–5 haematological toxicities included neutropenia (22%), thrombocytopenia (7%) and anaemia (2%). The most common grade 3–5 non-haematological adverse events (AEs) were cardiovascular events (9%), metabolic events (6%), infections (7%), and renal events (4%) (Table 3).

Treatment-emergent serious AEs occurred during induction in 14 patients (26%) and included 4 renal failures, 8 cardiac events (3 heart failures, 3 pulmonary oedemas, 1 sudden death and 1 hypertension), 4 infections (2 pneumonias, 1 sepsis and 1 upper respiratory tract), 1 reversible

posterior leukoencephalopathy, 1 hyponatremia, 1 respiratory failure, 1 adult respiratory distress syndrome and 1 pulmonary thromboembolism. A limited number of patients required dose modification during induction: twelve patients (22%) discontinued treatment owing to AEs, and 5 patients (9%) required carfilzomib dose reductions (Table S2).

A total of 6 patients died during induction; causes of death were disease progression (2 patients) and AEs (pulmonary thromboembolism, acute respiratory failure, pneumonia, and sudden death in 1 patient each) (Table S2).

During maintenance, the most common toxicities of any grade were anaemia (8%), thrombocytopenia (20%), neutropenia (5%), fever (15%), hypertension (15%) and nausea/vomiting (10%). No grade 3–5 haematological toxicities were reported. Grade 3-5 non-haematological AEs were rare and occurred in <5% of patients, with the exception of hypertension, which was reported in 10% and cardiovascular AEs in 5% (1 heart failure and 1 myocardial infarction). Treatment-emergent serious AEs occurred during maintenance in 3 patients and included urinary tract infection, heart failure and myocardial infarction.

DISCUSSION

This trial is the first to investigate carfilzomib on a once-weekly dosing schedule with cyclophosphamide and dexamethasone as part of frontline therapy in patients over 65 years of age with symptomatic MM. The MTD of weekly carfilzomib incorporated into the wKCyd regimen was found to be 70 mg/m^2. Severe haematological AEs occurred in 26% of patients and non-haematological AEs occurred in 35% of patients, with a low rate of discontinuation (22%).

These results compare favourably with other studies assessing twice weekly carfilzomib-based regimens as frontline therapy in elderly patients ineligible for autologous transplantation. The rate of haematological and non-haematological AEs were similar to, or lower than, those reported in our

previous study with twice weekly carfilzomib at the dose of 36 mg/m^2 in combination with cyclophosphamide and dexamethasone.(15) Myelosuppression induced by cyclophosphamide was lower than the one observed with melphalan in combination with twice-weekly carfilzomib and prednisone (KMP), which led to grade 3-4 neutropenia in 38% of patients and grade 3-4 thrombocytopenia in 28%.(19) This lower myelosuppression translated in a lower incidence of infections (13% in our trial versus 53% in the KMP trial).(19) The recent results of CLARION study comparing KMP with bortezomib-melphalan-prednisone showed no difference in PFS between the two regimens. (20) This is probably due to a higher incidence of severe AEs and of toxic deaths in patients receiving KMP. Cyclophosphamide may therefore represent a valid, less toxic alternative to melphalan for elderly patients with NDMM.

During induction, cardiovascular events occurred in 24% of patients, including 9% of grade 3-5 AEs. Among severe cardiac AEs, the most frequent were heart failure and pulmonary oedema. The rate of hypertension was 11% during induction, limited to grade 1-2, but it increased to 15% during maintenance, including 10% of grade 3-4. In the present study, cardiovascular toxicity was higher compared to our previous KCyD trial with twice-weekly carfilzomb at 36 mg/m^2, but similar to that reported in more recent trials, such as the CLARION study (10% of grade 3-4 hypertension).(20) The effect of proteasome-inhibition on cardiovascular system has only recently begun to be understood. Yet, there is some evidence suggesting that the ubiquitine-proteasome system must be considered a modulator of endothelial (dys)-function by interaction with several essential regulatory pathways and regulation of endothelial-dependent contracting and vasodilation factors. Endothelial dysfunction is accompanied by deterioration in this balance, with progressive reduction in vasodilation factors and with an increase in vasoconstriction mediators. Available data suggest that short-term, non-toxic proteasome inhibitors may be beneficial, whereas higher proteasome-inhibitor doses and long-term administration are associated with more disadvantageous effects in the vasculature.(21) These data suggested a time- and dose-dependent effect of carfilzomib. For

patients, especially elderly ones, candidate to treatment with carfilzomib, a full cardiac workup and a careful blood pressure monitoring is suggested to reduce the incidence of severe AEs.

We showed that treatment with wKCyd was highly effective in elderly NDMM patients. Responses were rapid and deep, and improved over time. During induction, 66% of patients achieved ≥VGPR, including 30% nCR and 15% CR. During maintenance, 88% of patients achieved ≥VGPR, including 54% nCR and 29% CR. Fifty percent of CR/sCR patients achieved CR/sCR during maintenance with a mean time to CR/sCR >12 months. After a median follow-up of 19.7 months, the 2-year PFS and OS rates were 53.2% and 81%, respectively. The achievement of CR has been associated with prolonged PFS and OS, also in elderly patients.(22) In addition, maintenance therapy improves outcome, and its role has been extensively investigated.(23–25)The ideal treatment should combine high response rates and continuous therapy to prolong long-term outcome. Despite the limitations of cross-trial comparisons, the promising antitumor activity observed with weekly carfilzomib in this study was similar to – or even better than – that reported in our prior study with twice weekly carfilzomib, and also to the one observed in the French phase 1/2 trial and in the CLARION trial, both with twice weekly carfilzomib plus melphalan-prednisone.(19,20) The improved results with wKCyd were probably due to the better safety profile and the continuous treatment with carfilzomib. Nevertheless, better results were seen with carfilzomib-lenalidomide-dexamethasone combination which induced an at least nCR rate of 62-63%, including a sCR rate of 42%, and a 2-year PFS rate of 92%.(26,27) The higher CR rate observed in these patients was probably attributable to the combination of a proteasome inhibitor and an immunomodulatory agent, and to the enrolment of younger patients. Indeed, in that studies, median age was 59-60 years—with 57-58% of patients <65 years and thus potentially transplant-eligible. Of note, the combination KCyd has the advantage of a lower cost, providing good efficacy. Furthermore, as survival continues to improve in MM patients, it is essential to consider subsequent treatment options when choosing therapy at diagnosis. As KCyd regimen does not use bortezomib or lenalidomide, patients initially treated with KCyd may still receive these other agents at relapse.

No statistically significant PFS difference was observed in patients with high risk cytogenetic status compared with those with standard risk (2-year PFS 68% versus 53%, HR 0.45, p=0.24). Although the number of patients in this subgroup analysis was limited and definitive conclusions cannot be drawn, these data are consistent with those reported in the subgroup analysis of the ASPIRE trial. This pre-planned analysis showed that carfilzomib-lenalidomide-dexamethasone in relapsed/refractory patients improved the poor prognosis associated with high-risk cytogenetics.(28) Similar results were reported in two phase 2 studies with carfilzomib-lenalidomide-dexamethasone in NDMM.(26,27). These data, if confirmed on a larger number of patients, may have important implications regarding risk-adapted therapy.

In conclusion, our study showed that in elderly patients ineligible for transplant, the more convenient dosing schedule wKCyd was highly effective with excellent CR rates and was well tolerated with a low rate of treatment discontinuation.

ACKNOWLEDGEMENTS

The authors wish to thank all patients who took part in the study; the nurses Montanaro Vincenza and Puccio Loredana; Federica Leotta, Marta Santoro and Giorgio Schirripa from the coordinating site in Torino for their assistance with the study.

CONFLICTS OF INTEREST

SB has received honoraria from BMS, Celgene, Janssen-Cilag, and served on the advisory board for Amgen, Mundipharma, Karyopharm; LDP has received honoraria from Amgen, Celgene, Abbvie and Janssen; VM has received speaker's bureau and advisory board for Amgen; PG has served on the advisory board for Takeda; MO gas received honoraria from Celgene; MTP has received honoraraia from Celgene, Janssen-Cilag, BMS, Takeda, Amgen; GG has served on the advisory board for Amgen, Janssen, Gilead, Abbvie, Morphosys, Roche; AP is currently a Takeda employee; PS has received research support from Amgen, Celgene, Janssen, Karyopharm, and honoraria from Amgen, Celgene, Janssen, Karyopharm and BMS; MB has received honoraria from Sanofi, Celgene, Amgen, Janssen, Novartis, Abbivie, BMS; research funding from Celgene, Janssen, Amgen, BMS, Mundipharma, Novartis, Sanofi.

AUTHOR CONTRIBUTIONS

All authors participated in the interpretation of data and reviewed and approved of all drafts of the manuscript, including the decision to submit for publication. SB, LDP, PS, MB, contributed to the study design; SB conducted the data analyses; SB and MB wrote the first draft of the manuscript; all authors provided patients and/or study materials.

References

1. Palumbo A, Anderson K. Multiple myeloma. N Engl J Med. 2011 Mar 17;364(11):1046–60.
2. Palumbo A, Bringhen S, Caravita T, Merla E, Capparella V, Callea V, et al. Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. Lancet. 2006 Mar 11;367(9513):825–31.
3. San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M, et al. Bortezomib plus Melphalan and Prednisone for Initial Treatment of Multiple Myeloma. N Engl J Med. 2008 Aug 28;359(9):906–17.
4. Richardson PG, Briemberg H, Jagannath S, Wen PY, Barlogie B, Berenson J, et al. Frequency, characteristics, and reversibility of peripheral neuropathy during treatment of advanced multiple myeloma with bortezomib. J Clin Oncol. 2006 Jul;24(19):3113–20.
5. Palumbo A, Waage A, Hulin C, Beksac M, Zweegman S, Gay F, et al. Safety of thalidomide in newly diagnosed elderly myeloma patients: a meta-analysis of data from individual patients in six randomized trials. Haematologica. 2013 Jan;98(1):87–94.
6. Morgan GJ, Davies FE, Gregory WM, Russell NH, Bell SE, Szubert AJ, et al. Cyclophosphamide, thalidomide, and dexamethasone (CTD) as initial therapy for patients with multiple myeloma unsuitable for autologous transplantation. Blood. 2011 Aug 4;118(5):1231–8.
7. Kumar S, Flinn I, Richardson PG, Hari P, Callander N, Noga SJ, et al. Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. Blood. 2012 May 10;119(19):4375–82.
8. Benboubker L, Dimopoulos MA, Dispenzieri A, Catalano J, Belch AR, Cavo M, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med. 2014 Sep 4;371(10):906–17.
9. Onyx Pharmaceuticals Inc. Kyprolis^TM (carfilzomib) for Injection Full Prescribing

Information. FDA. 2012.

10. Jakubowiak AJ. Evolution of carfilzomib dose and schedule in patients with multiple myeloma: A historical overview. Cancer Treat Rev. 2014;40(6):781–90.

11. Papadopoulos KP, Siegel DS, Vesole DH, Lee P, Rosen ST, Zojwalla N, et al. Phase I study of 30-minute infusion of carfilzomib as single agent or in combination with low-dose dexamethasone in patients with relapsed and/or refractory multiple myeloma. J Clin Oncol. 2015 Mar;33(7):732–9.

12. Dimopoulos MA, Moreau P, Palumbo A, Joshua D, Pour L, Hájek R, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. Lancet Oncol. 2016 Jan;17(1):27–38.

13. Bringhen S, Larocca A, Rossi D, Cavalli M, Genuardi M, Ria R, et al. Efficacy and safety of once-weekly bortezomib in multiple myeloma patients. Blood. 2010 Dec 2;116(23):4745–53.

14. Berenson JR, Cartmell A, Bessudo A, Lyons RM, Harb W, Tzachanis D, 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.

15. Bringhen S, Petrucci MT, Larocca A, Conticello C, Rossi D, Magarotto V, et al. Carfilzomib, cyclophosphamide, and dexamethasone in patients with newly diagnosed multiple myeloma: a multicenter, phase 2 study. Blood. 2014 Jul;124(1):63–9.

16. US Dept of Health and Human Services - National Institutes of Health - National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) v.4. 2017.

17. Rajkumar SV, Harousseau J-L, Durie B, Anderson KC, Dimopoulos M, Kyle R, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood. 2011 May;117(18):4691–5.

18. Munshi NC, Anderson KC, Bergsagel PL, Shaughnessy J, Palumbo A, Durie B, et al. Consensus recommendations for risk stratification in multiple myeloma: report of the International

396 Myeloma Workshop Consensus Panel 2. Blood. 2011 May;117(18):4696–700.
397 19. Moreau P, Kolb B, Attal M, Caillot D, Benboubker L, Tiab M, et al. Phase 1/2 study of
398 carfilzomib plus melphalan and prednisone in patients aged over 65 years with newly
399 diagnosed multiple myeloma. Blood. 2015 May;125(20):3100–4.
400 20. Facon T, Lee JH, Moreau P, Niesvizky R, Dimopoulos MA, Hajek R, et al. Phase 3 Study
401 (CLARION) of Carfilzomib, Melphalan, Prednisone (KMP) v Bortezomib, Melphalan,
402 Prednisone (VMP) in Newly Diagnosed Multiple Myeloma (NDMM). In: International
403 Myeloma Workshop. 2017. p. abstract OP – 044; e37–8.
404 21. Stangl K, Stangl V. The ubiquitin-proteasome pathway and endothelial (dys)function.
405 Cardiovasc Res. 2010 Jan;85(2):281–90.
406 22. Gay F, Larocca A, Wijermans P, Cavallo F, Rossi D, Schaafsma R, et al. Complete response
407 correlates with long-term progression-free and overall survival in elderly myeloma treated
408 with novel agents: analysis of 1175 patients. Blood. 2011 Mar 17;117(11):3025–31.
409 23. Ludwig H, Durie BGM, McCarthy P, Palumbo A, San Miguel J, Barlogie B, et al. IMWG
410 consensus on maintenance therapy in multiple myeloma. Blood. 2012 Mar 29;119(13):3003–
411 15.
412 24. Sonneveld P, Schmidt-Wolf IGH, van der Holt B, El Jarari L, Bertsch U, Salwender H, et al.
413 Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple
414 myeloma: results of the randomized phase III HOVON-65/ GMMG-HD4 trial. J Clin Oncol.
415 2012 Aug 20;30(24):2946–55.
416 25. Palumbo A, Hajek R, Delforge M, Kropff M, Petrucci MT, Catalano J, et al. Continuous
417 lenalidomide treatment for newly diagnosed multiple myeloma. N Engl J Med. 2012 May
418 10;366(19):1759–69.
419 26. Jakubowiak AJ, Dytfeld D, Griffith KA, Lebovic D, Vesole DH, Jagannath S, et al. A phase 1/2
420 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a
421 frontline treatment for multiple myeloma. Blood. 2012 Aug 30;120(9):1801–9.

27. Korde N, Roschewski M, Zingone A, Kwok M, Manasanch EE, Bhutani M, et al. Treatment With Carfilzomib-Lenalidomide-Dexamethasone With Lenalidomide Extension in Patients With Smoldering or Newly Diagnosed Multiple Myeloma. JAMA Oncol. 2015 Sep;1(6):746.

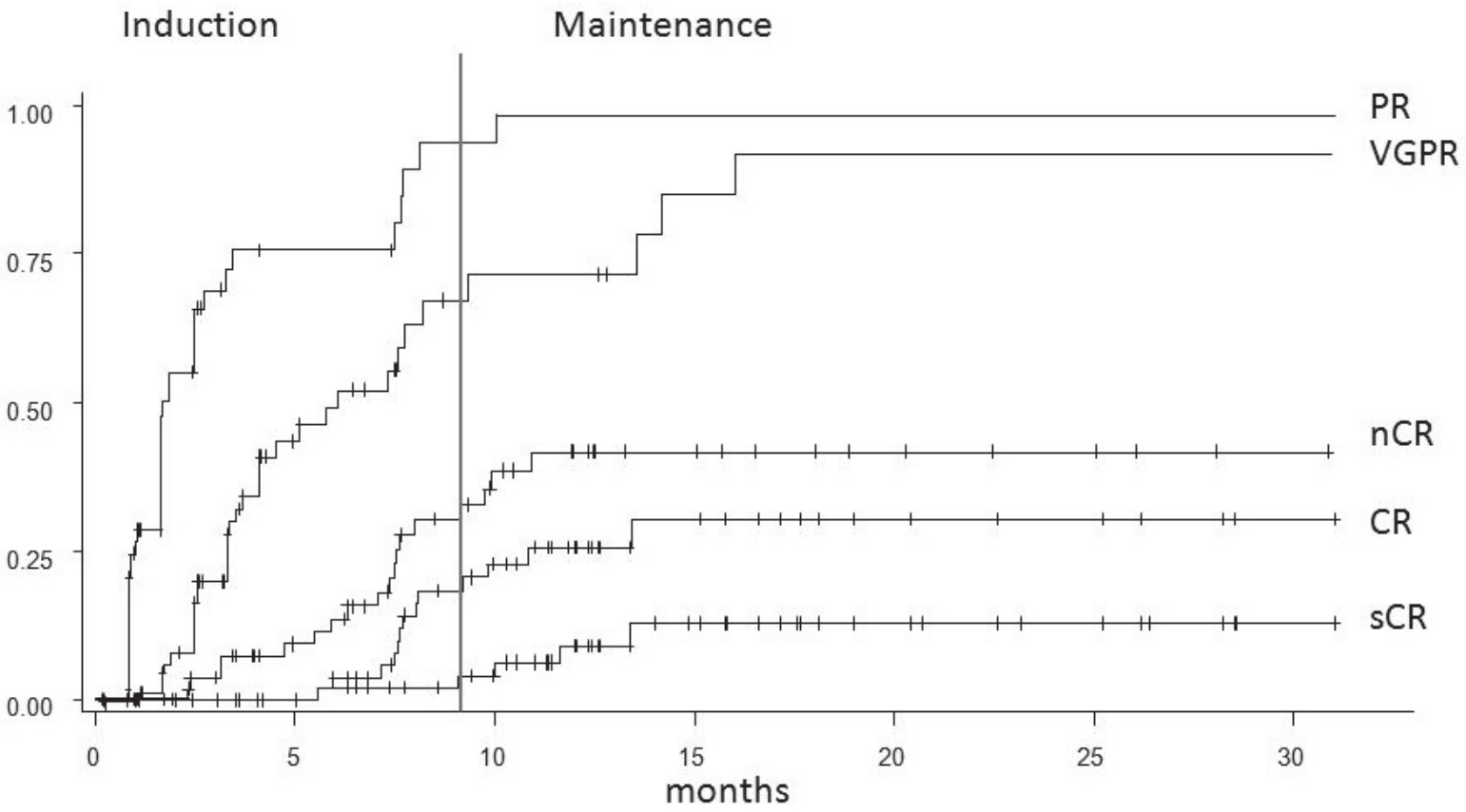
28. Avet-Loiseau H, Fonseca R, Siegel D, Dimopoulos MA, pi ka I, Masszi T, et al. Carfilzomib significantly improves the progression-free survival of high-risk patients in multiple myeloma. Blood. 2016 Sep;128(9):1174–80.

Figure Legend

Figure 1: Time to response onset.

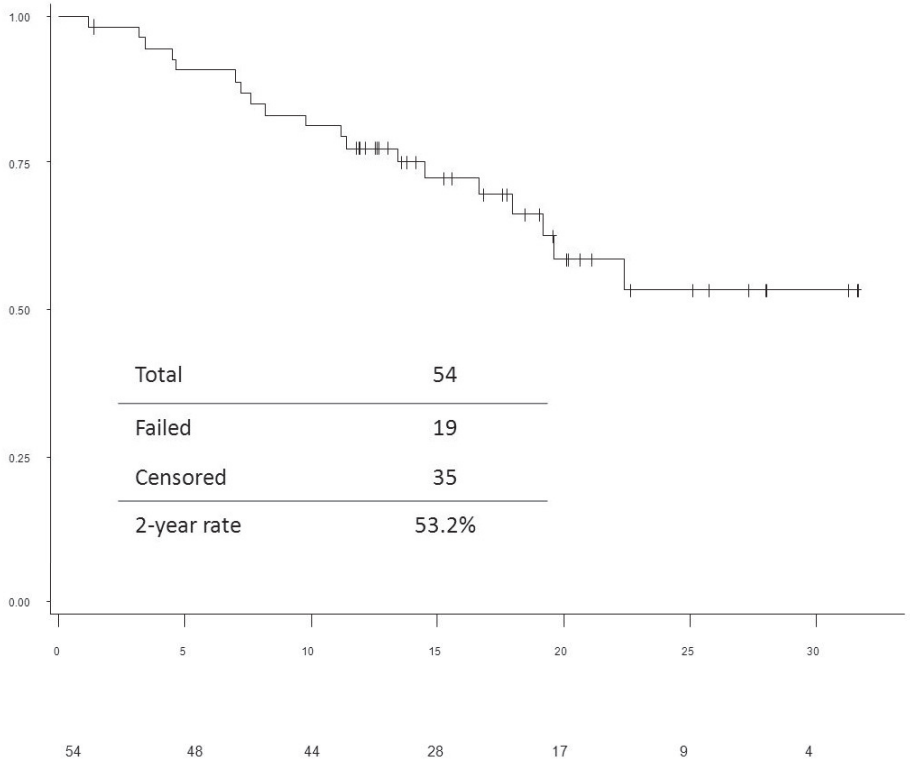
Figure 2: Treatment outcome: A) Progression-free survival and B) overall survival in patients treated with the recommended phase 2 dose (RP2D) schedule.

Figure 1. Time to onset response.



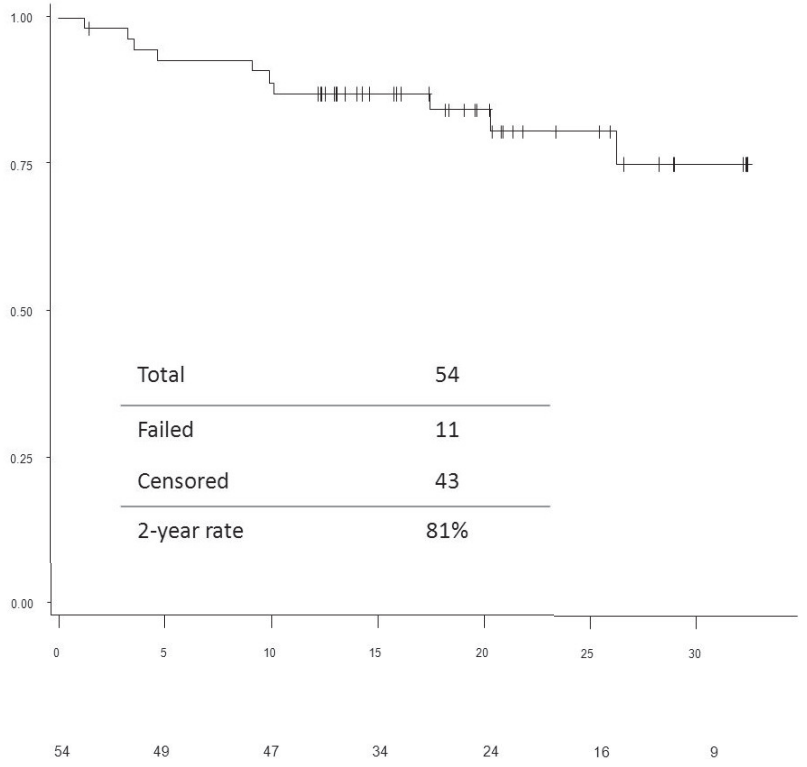
PR, partial response; VGPR, very good partial response; nCR, near complete response; CR, complete response; sCR, stringent complete response.

Figure 2A. Progression free survival in RP2D patients.



Number at risk							
	54	48	44	28	17	9	4

Figure 2B. Overall survival in RP2D patients.



Number at risk							
	54	49	47	34	24	16	9

Table 1: Patient characteristics at baseline

Characteristic	Phase 1 patients N=12	RP2D patients N=54	All patients N=63
Male, n (%)	5 (42)	22 (41)	26 (41)
Age			
Median (IQR), years	73 (68-75)	72 (69-74)	72 (69–74)
≥75 years, n (%)	4 (33)	11 (20)	14 (22)
ISS stage, n (%)			
I	4 (33)	20 (37)	24 (38)
II	4 (33)	16 (30)	19 (30)
III	4 (33)	18 (33)	20 (32)
Creatinine clearance, mL/min, n (%)			
<30	1 (8)	3 (6)	4 (6)
30–60	4 (33)	11 (20)	14 (22)
>60	7 (59)	40 (74)	45 (71)
Chromosomal abnormalities, n (%)			
t (4;14)	0	3 (6)	3 (5)
t (14;16)	1 (8)	2 (4)	3 (5)
Del 17	3 (25)	11 (20)	14 (22)
Unfavourable profile[a]	3 (25)	16 (30)	19 (30)
Data missing	3 (25)	17 (31)	19 (30)

IQR=interquartile range. ISS=International Staging System. RP2D=Recommended Phase 2 Dose.

[a]Unfavourable profile was defined as the presence of t(4;14) or t(14;16) or deletion of chromosome 17.

***Table 2*:** Response to treatment, by patient characteristics and by treatment duration in RP2D patients

Patient subgroup	**n**	**Response category, n (%)**				
		≥PR	**≥VGPR**	**≥nCR**	**≥CR**	**sCR**
Overall – Induction	54	46 (85)	36 (66)	16 (30)	7 (13)	1 (2)
Overall – Induction + Maintenance	54	48 (89)	37 (69)	22 (41)	12 (22)	4 (7)
ISS stage						
I	20	18 (90)	17 (85)	11 (55)	6 (30)	3 (15)
II	16	16 (100)	11 (69)	7 (44)	2 (13)	1 (6)
III	18	14 (78)	9 (50)	4 (22)	4 (22)	0
Chromosomal abnormalities						
Normal/favourable	21	17 (81)	12 (57)	6 (29)	3 (14)	0
Unfavourable[a]	16	16 (100)	11 (69)	7 (44)	4 (25)	2 (13)
Treatment duration						
Second cycle	50	45 (90)	36 (72)	18 (36)	7 (14)	1 (2)
Fourth cycle	48	43 (90)	36 (75)	18 (38)	7 (15)	1 (2)
Sixth cycle	44	40 (91)	36 (82)	18 (41)	7 (16)	1 (2)
Ninth cycle	40	37 (93)	34 (85)	18 (44)	7 (18)	1 (3)
Maintenance	40	39 (98)	35 (88)	22 (54)	12 (29)	4 (10)

CR=complete response. nCR=near complete response. PR=partial response. sCR=stringent complete response. VGPR=very good partial response. ISS=International Staging System.

[a]Presence of t(4;14) or t(14;16) or deletion chromosome 17.

***Table 3*:** Treatment-related adverse events during induction in RP2D patients

Events, n (%)	N=54	
	Any grade	Grades 3–5
Hematological		
≥1 event	39 (72)	14 (26)
Neutropenia	17 (31)	12 (22)
Thrombocytopenia	18 (33)	4 (7)
Anaemia	21 (39)	1 (2)
Non-hematological		
≥1 event	50 (92)	19 (35)
Cardiac events	13 (24)	5 (9)
Hypertension	6	-
Acute pulmonary oedema	3	3
Heart failure	3	2
Arrhythmia	1	-
Vascular events	2 (4)	1 (2)
Pulmonary thromboembolism	1	1
Other	1	-
Constitutional events	16 (30)	2 (4)
Oedema	2	-
Fever	7	1
Fatigue	5	1
Other	2	-
Dermatological events	0	0
Gastrointestinal events	21 (39)	2 (4)
Constipation	4	1
Diarrhoea	4	-
Nausea/vomiting	10	-
Other	3	1
Infections events	7 (13)	4 (7)
Upper respiratory tract	4	1
Pneumonia	2	2
Sepsis	1	1
Neurological events	10 (18)	3 (6)

Insomnia	2	-
Reversible posterior leukoencephalopathy	1	1
Mood alteration	4	1
Headache	2	1
Other	1	-
Metabolic events	10 (18)	3 (6)
AST/ALT increase	4	2
Hyperglycaemia	1	-
Hyponatriemia	1	1
Hyperkaliemia	1	-
Renal events	6 (11)	2 (4)
Acute renal failure	3	1
Chronic renal failure	1	-
Creatinine increase	1	1
Other	1	-
Respiratory events	4 (7)	1 (2)
Dyspnoea	1	-
Adult respiratory distress syndrome	1	1
Other	2	-
Other events	2 (4)	0

Supplementary material

Table S1: Safety and efficacy of Phase 1 portion of the trial.

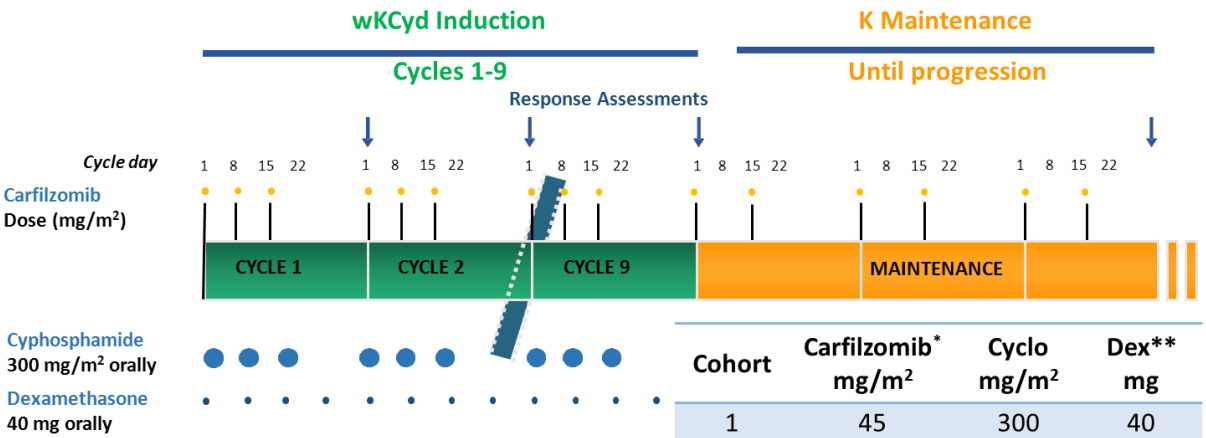
	Dose level 0 20/45 mg/m^2 N=3	Dose level +1 20/56 mg/m^2 N=6	Dose level +2 20/70 mg/m^2 N=3
Safety			
DLTs – n	0	1	0
DLTs – type	-	Creatinine increase	-
Efficacy – Best response – n (%)			
sCR	0	1 (17)	0
CR	1 (33)	0	1 (33)
nCR	0	1 (17)	0
VGPR	2 (67)	3 (50)	1 (33)
PR	0	1 (17)	0
ORR	3 (100)	6 (100)	2 (67)

Table S2: Serious adverse events, drug discontinuation and dose reduction in RP2D patients.

	wKCyd (n=54)
Median treatment duration – mos (IQR)	14.0 (8.5-20.3)
AE, %	
Any grade non-hematologic AEs – n (%)	50 (92)
Grade ≥3 non-hematologic AEs – n (%)	19 (35)
Serious AEs – n (%)	9 (17)
Dose reduction due to an AE - n (%)	5 (9)
Treatment discontinuations	
Discontinuation due to disease progression – n (%)	8 (15)
Discontinuation due to AE – n (%)	12 (22)
Deaths during induction	
Deaths due to disease progression – n (%)	2 (4)
Deaths due to AEs* – n (%)	4 (7)

*One each: pulmonary thromboembolism, acute respiratory failure, pneumonia, sudden death.

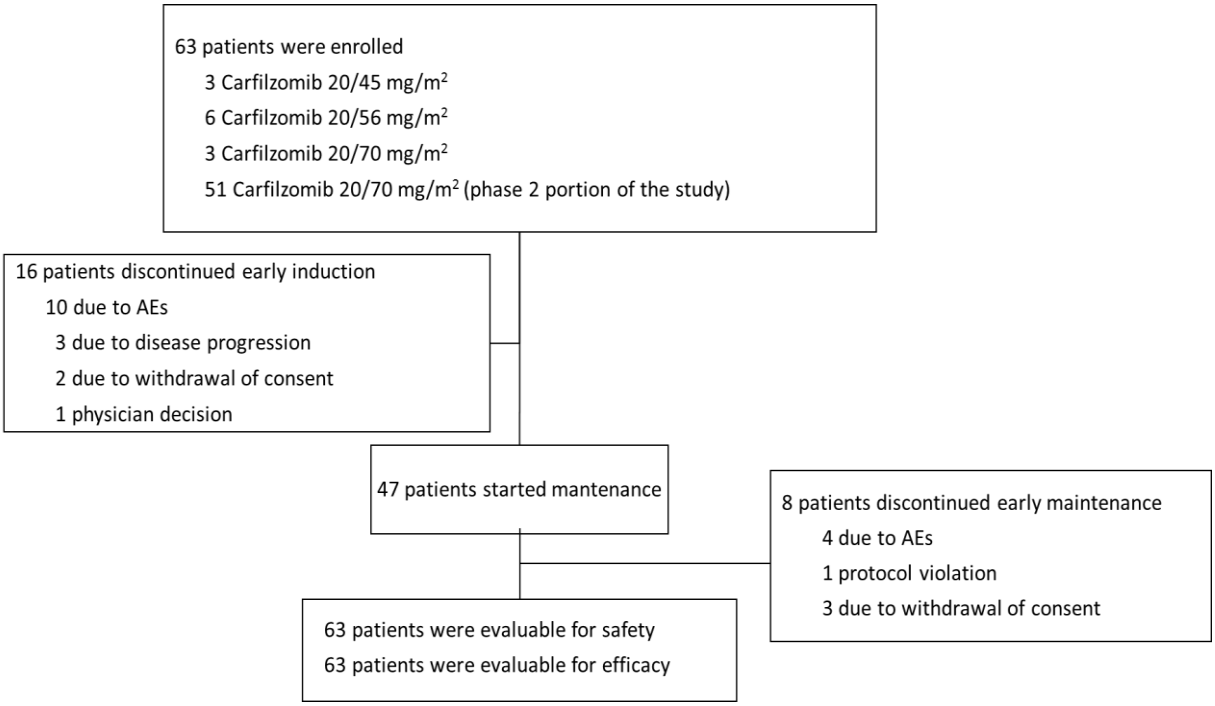
***Figure S1*:** Treatment schema



Cohort	Carfilzomib* mg/m²	Cyclo mg/m²	Dex** mg
1	45	300	40
2	56	300	40
3	70	300	40

wKCyd, weekly carfilzomib plus cyclophosphamide and dexamethasone; K, carfilzomib; Cyclo, cyclophosphamide; Dex, dexamethasone; *All patients received 20 mg/m2 carfilzomib on D1 of cycle 1; subsequent doses were escalated to the indicated levels; **or 20 mg of Dexamethasone on days 1,2,8,9,15,16,22,23.

***Figure S2*:** Patient flow



AEs, adverse events