A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma

Andrzej J. Jakubowiak,\textsuperscript{1,2} Dominik Dytfeld,\textsuperscript{2,3} Kent A. Griffith,\textsuperscript{2} Daniel Lebovic,\textsuperscript{2} David H. Vesole,\textsuperscript{4} Sundar Jagannath,\textsuperscript{5} Ammar Al-Zoubi,\textsuperscript{2} Tara Anderson,\textsuperscript{2} Brian Nordgren,\textsuperscript{2} Kristen Detweiler-Short,\textsuperscript{2} Keith Stockerl-Goldstein,\textsuperscript{6} Asra Ahmed,\textsuperscript{2} Terri Jobkar,\textsuperscript{2} Diane Durecki,\textsuperscript{2} Kathryn McDonnell,\textsuperscript{1} Melissa Mietzel,\textsuperscript{2} Daniel Couriel,\textsuperscript{2} Mark Kaminski,\textsuperscript{2} Ravi Vij\textsuperscript{6}

\textsuperscript{1}University of Chicago, Chicago, IL; \textsuperscript{2}University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; \textsuperscript{3}Poznan University of Medical Sciences, Poznan, Poland; \textsuperscript{4}The John Theurer Cancer Center at Hackensack UMC, Hackensack, NJ; \textsuperscript{5}Mount Sinai Medical Center, New York, NY; \textsuperscript{6}Washington University School of Medicine, St. Louis, MO

Corresponding Author:
Andrzej J. Jakubowiak, MD, PhD
Professor of Medicine
Director, Myeloma Program
Section of Hematology/Oncology
University of Chicago Medical Center
5841 S. Maryland Ave, MC 2115
Chicago, IL 60637-6613
773-702-6613 (Office)
773-834-1592 (Direct)
773-702-3002 (Fax)
avjakubowiak@medicine.bsd.uchicago.edu

Short title: Carfilzomib, lenalidomide, and dexamethasone in MM
Abstract

This phase 1/2 study in patients with newly diagnosed multiple myeloma (N=53) assessed CRd—carfilzomib (20, 27, or 36 mg/m\(^2\), days 1, 2, 8, 9, 15, 16 and 1, 2, 15, 16 after Cycle 8), lenalidomide (25 mg/day, days 1–21), and weekly dexamethasone (40/20 mg Cycles 1–4/5+)—in 28-day cycles. After Cycle 4, transplant-eligible candidates underwent stem cell collection (SCC) then continued CRd with the option of transplantation. The maximum planned dose level (carfilzomib 36 mg/m\(^2\)) was expanded in phase 2 (n=36). Thirty-five patients underwent SCC, 7 proceeded to transplantation, and the remainder resumed CRd. Grade 3/4 toxicities included hypophosphatemia (25%), hyperglycemia (23%), anemia (21%), thrombocytopenia (17%), and neutropenia (17%); peripheral neuropathy was limited to Grade 1/2 (23%). Most patients did not require dose modifications. After a median of 12 cycles (range 1–25), 62% (N=53) achieved at least near complete response (nCR) and 42% stringent CR (sCR). Responses were rapid and improved during treatment. In 36 patients completing 8 or more cycles, 78% reached at least nCR and 61% sCR. With median follow-up of 13 months (range 4–25), 24-month progression-free survival estimate was 92%. CRd was well tolerated with exceptional response rates. Registered at www.clinicaltrials.gov (#NCT01029054).
Introduction

Although multiple myeloma (MM) remains incurable, the introduction of targeted therapy with proteasome inhibitors (bortezomib [V]) and immunomodulatory drugs (thalidomide [T] or lenalidomide [R]) has advanced the goals of treatment with significant improvements in long-term outcomes. Initial studies reported good clinical activity when these agents were used either alone or in combination with corticosteroids. As the development of these agents progressed, subsequent studies demonstrated that combination therapies with an immunomodulator, a proteasome inhibitor, and a corticosteroid (eg, low- or high-dose dexamethasone [d or D]) provided rapid, deep, and more durable responses compared with standard treatment approaches and with acceptable tolerability because of non-overlapping toxicity.

Triple-agent regimens that utilize bortezomib, lenalidomide, and/or thalidomide have emerged as a preferred frontline strategy in patients with newly diagnosed MM. The results of two recent randomized phase 3 trials, which compared induction with 3-drug to 2-drug novel regimens (VTD vs TD and VTD vs VD) in transplant-eligible patients, appear to support this approach. Nonetheless, maintaining dose levels over the long-term can be limited by emerging toxicities. After only a short course of 3 cycles of induction with VTD, Grade 3/4 peripheral neuropathy was present in 10% of patients with a rate of 34% for all grades. Treatment with RVD has also been shown to be highly active in the frontline setting and appears to be better tolerated than VTD, but during prolonged treatment (median of 10 cycles), sensory neuropathy developed in 80% of patients although high-grade events were infrequent (2% for Grade 3).

Studies in patients with newly diagnosed MM have also shown that the depth of response (eg, CR or very good partial response [VGPR] with frontline combination regimens is associated with improved
disease control and survival. A retrospective analysis of three phase 3 trials evaluating proteasome inhibitors and immunomodulators in transplant-ineligible newly diagnosed MM showed that CR compared with VGPR was associated with improved progression-free survival (PFS) at 3 years (67% vs 27%; $P<.001$) and overall survival (OS; 91% vs 70%; $P<.001$). Based on these and similar observations, recent investigations have focused on development of novel frontline combinations with a goal to further improve the depth and duration of response compared with established treatment approaches, with improved tolerability and a minimum impact on stem cell collection (SCC).

Carfilzomib is a next-generation proteasome inhibitor that selectively and irreversibly binds to the proteasome, targeting chymotrypsin-like activity. Carfilzomib provides sustained proteasome inhibition without off-target effects and inhibits proliferation and induces apoptosis in myeloma models. Clinical studies have shown that single-agent carfilzomib provides durable anticancer activity in patients with relapsed and/or refractory MM with an acceptable tolerability profile, including limited neuropathy after prolonged treatment. In a phase 2 study of single-agent carfilzomib (N=266), 24% of evaluable patients with relapsed and refractory MM achieved at least a partial response (PR) with a median duration of response of 7.4 months. In an integrated analysis of three phase 2 studies with single-agent carfilzomib in relapsed and refractory MM (N=526), the most common Grade 3/4 adverse events (AEs) were thrombocytopenia (23%), anemia (22%), and lymphopenia (18%); peripheral neuropathy was 14% for any grade and 1.3% for Grade 3 with no Grade 4 events. Studies have also assessed carfilzomib as part of combination regimens. In an interim analysis of a phase 2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone (CRd) for relapsed MM (N=52), 78% of evaluable patients achieved at least a PR, 40% at least a VGPR, and 18% a CR or stringent CR (sCR) with good tolerability.
Herein we report results from the first prospective phase 1/2 study of the CRd combination in patients with newly diagnosed MM. The primary objectives were to determine the maximum tolerated dose (MTD) of carfilzomib when added to Rd during phase 1 and to assess the safety and activity of CRd in a combined phase 1/2 patient population.

Patients and Methods

Patients

Both transplant-eligible and -ineligible patients with newly diagnosed MM could be enrolled, but the disease had to be symptomatic and measurable per International Myeloma Working Group (IMWG) Criteria. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0–2. Patients were ineligible if they had Grade 3/4 neuropathy, a calculated creatinine clearance <50 mL/min or serum creatinine ≥2 g/dL, absolute neutrophil count (ANC) <1.0 x10^9/L, hemoglobin <8.0 g/dL, platelet count <75 x10^9/L, serious comorbidities, or other plasma cell dyscrasias such as POEMS syndrome, plasma cell leukemia, or Waldenström’s macroglobulinemia.

The study was conducted in accordance with US Food and Drug Administration and International Conference on Harmonisation Guidelines for Good Clinical Practice, the Declaration of Helsinki, and applicable local health authority, Institutional Review Board (IRB), or Independent Ethics Committee requirements. The study protocol was approved by the IRB of participating institutions, and all patients provided written informed consent. The study is registered at ClinicalTrials.gov (NCT01029054).

Study Design and Treatment

This multicenter, open-label, phase 1/2 study was conducted at 4 US centers. Patients received CRd induction therapy in 28-day cycles for up to 8 cycles or until disease progression or unacceptable toxicity
Per protocol design, transplant-eligible patients achieving at least a PR could proceed to SCC any time after Cycle 4 but then were to resume CRd treatment with an option to proceed to autologous stem cell transplantation (ASCT). The acceptance of deferred transplantation was included in eligibility criteria with concept and clinical data thoroughly discussed with patients prior to enrollment and informed consent. However, proceeding to transplant was not mandated with the decision left to the patient and treating physician. After 8 cycles, patients received maintenance CRd. Per initial design, CRd maintenance was planned for an indefinite period of time, but in view of limited progression events and no discontinuation of maintenance due to toxicity, the study was amended to 24 total CRd cycles. After completion of 24 cycles, single-agent lenalidomide was recommended off protocol.

During phase 1, the primary endpoints were to evaluate the safety and determine the MTD of carfilzomib in the context of CRd. Carfilzomib doses were escalated, while lenalidomide and dexamethasone were given at standard low-dose induction levels. Three dose levels for carfilzomib were planned—20, 27 and a maximum planned dose (MPD) of 36 mg/m^2. These dose levels were based in part on initial data from the phase 1/2 study of CRd in relapsed patients, which demonstrated the safety and tolerability of combining carfilzomib 27 mg/m^2 with lenalidomide 25 mg and low-dose dexamethasone using a similar dosing schedule without reaching MTD. Based on this information and emerging data that single-agent carfilzomib appeared to be tolerated at 36 mg/m^2, we designed our dose escalation using 36 mg/m^2 as the MPD. If 20 mg/m^2 was deemed intolerable, then a 15 mg/m^2 dose would be assessed as the MTD. Dose escalation was designed using the Time-to Event Continual Reassessment Method (TITE-CRM). The MTD of carfilzomib was defined by a target probability limit of 20% for dose-limiting toxicities (DLTs).
DLTs included any of the following treatment-related events that occurred during the first cycle to begin Cycle 2 due to drug-related toxicity; ≥Grade 2 neuropathy with pain; any AE ≥Grade 3 (excluding nausea, vomiting, diarrhea, dexamethasone-induced hyperglycemia, lenalidomide-induced maculopapular rash); ≥Grade 3 nausea, vomiting, or diarrhea despite maximal anti-emetic/antidiarrheal therapy; Grade 4 fatigue longer than 7 days; any non-hematologic toxicity requiring dose reduction within Cycle 1 except lenalidomide-induced maculopapular rash; Grade 4 neutropenia (ANC <0.5x10^9/L) longer than 7 days; febrile neutropenia (ANC <1.0x10^9/L with fever ≥100.5°F); Grade 4 thrombocytopenia (platelets <25.0x10^9/L) longer than 7 days despite dose delay; Grade 3/4 thrombocytopenia associated with bleeding; or any hematologic toxicity requiring dose reduction within Cycle 1.

Once the MTD of carfilzomib was established, additional patients were enrolled in a phase 2 expansion cohort to reach a sample size of 36 patients treated at the MTD dose; if the MTD was not reached, the MPD could be used. The primary endpoint was the rate of at least nCR after 4 cycles. Secondary endpoints included overall response rate (ORR) defined as PR or better (≥PR), time on study, duration of response, PFS, time to progression (TTP), OS, overall treatment toxicity and tolerability, and the feasibility of SCC after Cycle 4.

For induction (Cycles 1–8), carfilzomib (20, 27, and 36 mg/m^2) was administered intravenously on Days 1, 2, 8, 9, 15, and 16. The 20 and 27 mg/m^2 doses were infused over 5–10 minutes, while the 36 mg/m^2 dose was infused over 30 minutes. Patients slated to receive the 27 or 36 mg/m^2 carfilzomib doses received 20 mg/m^2 on Days 1 and 2 of Cycle 1, and the higher dose thereafter. Lenalidomide (25 mg) was administered orally on days 1–21 of all cycles. Dexamethasone (40 mg Cycles 1–4, 20 mg Cycles 5–8) was administered orally or intravenously on days 1, 8, 15, and 22. During maintenance CRd, Cycles 9–24, individual study drugs were continued at the same dose level as Cycle 8; lenalidomide and
dexamethasone were continued at the same dosing schedule, while carfilzomib was administered less frequently (Days 1, 2, 15, and 16). From Cycles 25+, it was recommended that patients continue maintenance with single-agent lenalidomide at the last tolerated dose.

Dose reductions during Cycle 1 were considered DLTs as described earlier. After Cycle 1, carfilzomib, lenalidomide, and dexamethasone dosing could be held for up to 21 days to resolve toxicity and then restarted at the same dose or the carfilzomib or lenalidomide dose could be reduced depending on the toxicity using dose reduction by 1 dose level (ie, 27, 20, 15, or 11 mg/m$^2$ for carfilzomib and 20, 15, 10, or 5 mg for lenalidomide), or discontinued.

Patients were required to maintain adequate hydration and were treated prophylactically with ciprofloxacin or a similar antibiotic (Cycle 1 only), valacyclovir or a similar antiviral, a proton pump inhibitor or H2 antagonist, and aspirin, a low molecular weight heparin, or clopidogrel. In patients with prior venous thrombosis, low molecular weight heparin or warfarin (INR of 2–3) was required.

**Assessments**

For all patients receiving at least 1 dose of any required study drug, toxicity was assessed according to Common Terminology Criteria for Adverse Events (CTCAE) v3.0.\(^{34}\)

Disease response was assessed by local investigator review according to IMWG criteria, with categorized responses of sCR, CR, VGPR, PR, stable disease, and progressive disease,\(^{30}\) and the addition of nCR\(^{4}\) and minimal response (MR).\(^ {35}\) There was no independent central review of efficacy endpoints. M-protein was measured by serum or urine protein electrophoresis. Additional measurements included quantitative immunoglobulins, serum β2 microglobulin, serum free light chains, plasmacytoma, and
bone marrow aspirate and biopsy as indicated. Assessments were performed at screening, on Days 1 and 15 of Cycle 1, and on Day 1 of subsequent cycles. Bone marrow aspirate and biopsy were conducted at screening to quantify myeloma cell involvement, as well as for cytogenetics (ie, hypodiploidy, del 13) and fluorescence in situ hybridization (FISH) studies for t(4:14), t(11:14), and del 17p, and to confirm CR. Minimal residual disease (MRD) was evaluated in patients with suspected CR using 10-color multiparameter flow cytometry as previously described. Neurologic assessments were performed on Day 1 of each cycle.

**Statistical Analysis**

The sample size for the estimation of the dose-toxicity function (phase 1) was 35 patients. Under the TITE-CRM paradigm, the relationship between dose and toxicity was summarized by a single-parameter (\( \alpha \)) logistic model that represents the assumed relationship prior to data collection. The most current information about the relationship between dose and toxicity, including predictive intervals, was summarized using the distribution of \( \alpha \). The posterior distribution of toxicity, which displays the probability that a future patient will experience toxicity at a given dose based on the current data, was calculated with 95% credible intervals for each dose level. The CRd dose closest to but not exceeding the target rate of toxicity (20%) was estimated as the MTD.

Response was determined at day 15 of Cycle 1 and after each cycle. A rate of at least 45% for nCR or better after 4 cycles was considered promising, while a rate of 25% or lower was considered unworthy of future study. Patients unable to receive 4 cycles were considered nonresponders. This hypothesis was interrogated using a Minimax 2-stage design for patients treated at the phase 2 dose. In the first stage, if at least 5 of 17 patients responded, the trial would continue to the second stage, adding patients for a total sample size of 36. If 14 or more of the 36 patients responded, then the null hypothesis of a 25%
response rate would be rejected in favor of the alternative 45% response rate. The trial was designed to have 80% power for the hypothesis and 5% type I error.

Continuous and categorical data were summarized with descriptive statistics. The product-limit method of Kaplan-Meier was used to analyze time-to-event endpoints. Statistical analyses were conducted using the SAS System, version 9.2 (Cary, NC, USA). All authors had access to clinical data and statistical analyses.

Results

Patients and treatment

Fifty-three patients were enrolled between October 27, 2009, and June 30, 2011. Data cutoff for this analysis was November 30, 2011. Phase 1 dosing cohorts included 4 patients at carfilzomib 20 mg/m$^2$, 13 at 27 mg/m$^2$, and 18 at 36 mg/m$^2$. An additional 18 patients enrolled as part of the phase 2 expansion. The overall population was predominantly male (74%) and ranged in age from 35–81 years with 43% older than 65 years. Of 51 patients with available data, 33% had unfavorable cytogenetics defined as 1 or more abnormalities listed in Table 1.

Median follow-up was 13 months (range, 4–25 months) with all 53 patients on treatment for more than 1 month and evaluable for response (Figure 2). Median treatment duration was 12 cycles (range, 1–25 cycles). Ten patients discontinued treatment during induction—1 due to CRd toxicity at dose level 3 (pulmonary edema), 7 proceeded to ASCT, and 2 due to patient/investigator preference. Patients who proceeded to ASCT continue to be followed for TTP, PFS, and OS. Thirty-six patients proceeded to maintenance CRd with 1 patient discontinuing treatment due to PD and 1 patient preferring to discontinue treatment while in VGPR, which subsequently progressed. At the data cut-off date, 29
patients were on maintenance CRd and 5 patients proceeded to single-agent lenalidomide (median duration of 1 cycle).

The CRd regimen did not appear to have an adverse impact on SCC. Thirty five transplant-eligible patients who achieved at least a PR after Cycle 4 underwent SCC. Three additional patients were considered for SCC but declined or did not proceed for insurance reasons. Median number of completed cycles prior to collection was 4 (range, 2–9 cycles) with 1 patient preferring to discontinue CRd after 2 cycles to undergo SCC and pursue alternative treatment. SCC was conducted with only growth factors in 30 patients, of whom 2 required the addition of cyclophosphamide, and with chemotherapy and growth factors in 5 patients. SCC was unsuccessful in one patient who was over 70 years of age and underwent the procedure after 8 cycles of CRd. The median number of CD34+ cells harvested was $6.9 \times 10^6$/kg (range 0.6–27.8 $\times 10^6$/kg). Of 7 patients who underwent ASCT, all proceeded after initial induction per the participating center’s preference (1 in the 27 mg/m$^2$ cohort and 6 in the 36 mg/m$^2$ cohort).

**Determination of Phase 2 Dosing**

There were no DLTs in the 20 mg/m$^2$ dose cohort (**Table 2**). One patient in the 27 mg/m$^2$ dose cohort experienced a DLT of Grade 3 asymptomatic neutropenia, which resolved within a few days. Two patients experienced a DLT in the 36 mg/m$^2$ dose cohort, including Grade 4 pulmonary edema and Grade 3 dyspnea. The probability of a DLT estimated using the TITE-CRM algorithm was 5.9% at 20 mg/m$^2$, 8.1% at 27 mg/m$^2$, and 12% at 36 mg/m$^2$. Although the DLT probability was less than the 20% set for MTD, these data indicated a dose dependent trend of increasing DLTs.

Based on the tolerability of this regimen, the trend in the DLT probability estimate with increasing doses of carfilzomib, initial response data that showed high activity at all 3 dose levels, the limited clinical
experience with carfilzomib at higher dose levels, and the limitations of adding dose cohorts during an ongoing trial with TITE-CRM design in a post-hoc fashion, phase 2 proceeded using carfilzomib at MPD of 36 mg/m² without determination of the MTD.

**Efficacy**

In the overall population (N=53), 62% of patients achieved at least a nCR (42% sCR), 81% at least a VGPR, and 98% at least a PR after a median of 12 cycles (range, 1–25 cycles) (Table 3). In general, responses were rapid, improved with continued treatment, and durable. At the end of Cycle 1, the mean M-protein level was reduced by 67% from baseline, and at the end of Cycle 2, the mean level was reduced by 81% from baseline (Figure 3). Prolonged treatment with CRd increased the proportion of patients in at least nCR. At the end of 4 cycles, 38% of patients were in at least nCR with 6% in sCR. In patients who received 8 or more treatment cycles, 78% achieved at least a nCR with 61% in sCR. In the subset of patients who did not proceed to transplantation (n=46), 67% achieved at least a nCR (48% sCR), 83% at least a VGPR, and 100% at least a PR after a median of 12 cycles (range, 1–25). Of the 7 patients who proceeded to ASCT, best responses prior to transplant were 2 CR, 1 VGPR, 3 PR and 1 MR. In 22 patients with CR or suspected CR (including 2 in nCR), there was no evidence of MRD in 20 (91%). Of 2 patients with positive MRD, 1 was in CR and the other was in nCR.

ISS stage and cytogenetics did not impact rate or depth of responses (Table 4), but these analyses are limited by patient numbers. Although response rates in the 36 mg/m² cohort were lower compared with the 20 and 27 mg/m² dose cohorts combined, the median duration of treatment at data cut-off was 8 cycles (range, 1–19 cycles) versus 21 cycles (range, 4–25 cycles), respectively. At equivalent time points, response rates were generally comparable across the 20, 27 and 36 mg/m² dose cohorts, although achieving sCR appeared to be dose dependent (Supplemental Table).
Assessment of time-to-event endpoints was limited because of the small number of events. Only 2 patients progressed, 1 after discontinuation of treatment while in VGPR after completion of 8 cycles as noted earlier, and another after completion of 15 cycles while in PR. The PFS rate was 97% at 12 months and 92% at 24 months (Figure 4). All patients who achieved sCR have maintained response for a median of 9 months (range 1–20 months). The patient who progressed after discontinuing treatment eventually died due to disease progression; all others are alive.

Safety and Tolerability

Table 5 summarizes the incidence of adverse events (AEs) that occurred during induction (Cycles 1–8). The most common toxicities of any grade were hyperglycemia (72%), thrombocytopenia (68%), anemia (60%), edema (47%), hypophosphatemia (45%), and fatigue (38%). Grade 3/4 non-hematologic AEs included hypophosphatemia (25%), hyperglycemia (23%), deep vein thrombosis/pulmonary embolism (DVT/PE) (9%), rash (8%), and elevated liver function test (8%). Hematologic Grade 3/4 toxicities included anemia (21%), thrombocytopenia (17%), and neutropenia (17%). Peripheral neuropathy was experienced by 23% and was limited in severity to Grades 1 (17%) and 2 (6%).

Overall, the CRd regimen was well tolerated during induction. Dose modifications were limited (31%), and more than 50% of patients remained on originally assigned doses. Generally, AEs were effectively managed with supportive measures. As noted earlier, only 1 patient discontinued treatment due to toxicity (pulmonary edema). Grade 3/4 dyspnea was observed only during phase 1 and within the first 3 cycles. All but one case of dyspnea were associated with vigorous hydration, and patients promptly responded to diuresis; one case was associated with the development of methemoglobinemia secondary to dapsone given as Pneumocystis carinii pneumonia prophylaxis. No cases of dyspnea were
reported after vigorous hydration was discontinued. Most cases of hyperglycemia and hypophosphatemia (65% and 61% of all respective events) were observed after dexamethasone dosing (ie, on Days 2, 9, and 16) and had no clinical implications. All cases of DVT/PE developed while on aspirin prophylaxis and after the first few cycles. One patient who experienced a DVT had 2 risk factors (prior DVT and ongoing smoking), and DVT was deemed possibly related to carfilzomib infusion in 2 patients. All 3 cases of PE required hospitalization.

Extended treatment in the CRd maintenance phase (9–24 cycles) was also generally well tolerated. The most common toxicities (all grades) during maintenance were lymphopenia (30%), leukopenia (26%), and fatigue (25%). Peripheral neuropathy remained limited (11%, all grade 1/2) as did dose modifications (19% carfilzomib, 28% lenalidomide, and 31% dexamethasone). Throughout the duration of treatment, there were no treatment-related deaths, no incidents of acute renal failure and only limited Grade 1 and 2 transient changes in serum creatinine, and only one incident of febrile neutropenia.

**Discussion**

This phase 1/2 study demonstrated that CRd is well tolerated and highly active in patients with newly diagnosed MM. During phase 1, all 3 dose levels of carfilzomib were safely combined with standard doses of Rd. Response rates were excellent at all carfilzomib dose levels with no apparent dosee-response relationship. Given the safety and high activity of the CRd regimen with the MPD of carfilzomib (36 mg/m$^2$), the dose-dependent trend of DLTs, the limited experience with carfilzomib at higher dose levels, and the limitations of adding additional dose cohorts during an ongoing trial using the TITE-CRM design, it was decided to proceed with phase 2 using the 36 mg/m$^2$ dose rather than amending the protocol to escalate the dose further.
The efficacy data from the combined phase 1 and 2 populations indicated a rapid and deep response with CRd. Analysis of response demonstrated a significant and rapid decline in M-protein levels within the first few cycles. Responses improved as patients continued treatment with the majority achieving nCR or better, which exceeded 75% after treatment of 8 cycles or more. The impact of prolonged treatment on the sCR rate was notable with an exceptional rate of 61% in patients who completed at least 8 cycles. In addition, the depth of response included a significant number of patients suspected to be in CR without evidence of MRD. While time-to-event data continue to mature, the lack of disease progression in all but 2 patients after a median of 13 months of follow-up as well as all patients who achieved sCR remaining in remission for a median of 9 months suggest that responses were also durable.

There was no notable difference in response when assessed by ISS stage or the presence of unfavorable cytogenetic factors. Although the proportion of patients achieving at least nCR appears to be lower in the 36 mg/m² cohort compared with the other dose cohorts, this was likely impacted by the shorter duration of treatment for the MPD cohort, higher proportion of patients proceeding early to transplant, and the limited number of patients. Response trends during the study suggest that as patients are treated longer with carfilzomib 36 mg/m², best response data will improve. However, given the sample size, we cannot preclude that as more patients are treated for a longer duration that this trend will dissipate. The response data also suggested that achievement of sCR was dose dependent but with the small number of patients in the lower dose cohorts and limited follow-up in the 36 mg/m² dose cohort it is difficult to definitively establish such a relationship.
Although direct comparison between studies should be viewed cautiously, these response data with frontline CRd compare favorably with results from studies with frontline Rd and RVD. In the phase 3 ECOG E4A03 study, transplant-eligible and -ineligible patients with newly diagnosed MM (N=445) were randomized to receive at least 4 cycles of treatment with lenalidomide (25 mg) in combination with high-dose dexamethasone or low-dose dexamethasone and followed for a median of 35.8 months. After 4 cycles, the rate of patients achieving at least a VGPR was 50% in the high-dose group and 40% in the low-dose group (P=.04) and the rate of at least a PR was 81% and 70% (P=.009). Of 140 patients in the low-dose group who continued Rd after 4 cycles, 57% achieved at least a VGPR and 91% at least a PR with a median duration of treatment of 11.2 months. The PFS rate was 50% at 3 years. In a phase 1/2 dose escalation study of RVD for newly diagnosed MM (N=66), 39% of patients in the overall population achieved at least a nCR, 67% at least a VGPR, and 100% at least a PR with a median of 10 cycles of treatment; corresponding values in the phase 2 population (n=35) who received the MTD were 57%, 74%, and 100%. Of note, 28 patients (42%) proceeded to ASCT (13 prior to the end of Cycle 8). With a median follow-up of 21 months, the 18-month PFS rate was 75%.

The CRd regimen was well tolerated with only 1 patient discontinuing treatment due to toxicity after 1 cycle. Some patients required dose modifications, but the majority were able to maintain dose intensity. It is possible that the ability to tolerate the CRd regimen allowed for prolonged treatment at or near the assigned dose, effectively reducing the disease to nondetectable levels and ultimately reaching rates of CR and sCR that are close to or that possibly exceed rates observed after sequential therapy, including transplant and post-transplant consolidation. The types of AEs were generally consistent with those reported in previous studies with Rd in newly diagnosed multiple myeloma, single-agent carfilzomib in relapsed and relapsed/refractory myeloma, and CRd in relapsed/refractory myeloma.
There were no AEs that would preclude the use of the CRd regimen with carfilzomib dosed at 36 mg/m². The myelosuppressive effect of the regimen was limited and tolerable, with a small proportion of patients requiring dose modifications to manage these events. Despite prolonged use of lenalidomide at the originally assigned dose of 25 mg, only 4 patients required lenalidomide dose reduction due to myelosuppression, and there was only one case of neutropenic fever. Renal toxicity was infrequent and transient. Dyspnea occurred early during the study and appeared to correspond to fluid overload. Once overhydration was addressed, the incidence of dyspnea declined and no Grade 3/4 dyspnea was reported during phase 2. The incidence of DVT/PE may also be mitigated in the future with improved risk stratification and use of heparin or full-dose warfarin as per current guidelines. Most patients experiencing an event were receiving only aspirin (81 mg) prophylaxis from the start of treatment and in at least 3 cases additional risk factors were retrospectively noted.

Comparison of tolerability and AEs between CRd and RVD or other frontline regimens should also be viewed with caution, but the difference in peripheral neuropathy is notable. In the frontline RVD phase 1/2 study, the rate of sensory neuropathy was 80% for all grades and 2% for Grade 3 with rates of 18% and 2%, respectively, for motor neuropathy, whereas in our study the rate for any grade of peripheral neuropathy was only 23% with no Grade 3 events. Furthermore, the study investigators attributed most neuropathic events to lenalidomide, although it was deemed to be related to carfilzomib in 1 patient.

The results of this phase 1/2 study are very encouraging but are limited by the sample size, the single-arm non-randomized design, the lack of independent central review of response results, and a study population that included both transplant-eligible and -ineligible patients. These results will require validation in the randomized controlled setting to definitively demonstrate the benefit of adding
carfilzomib to Rd. A phase 3 trial of CRd compared with Rd for the treatment of patients with relapsed multiple myeloma (ASPIRE) is ongoing (ClinicalTrials.gov NCT01080391).

It is worth noting that only 7 of the 35 transplant-eligible patients proceeded to ASCT. It appears that with the depth and duration of responses observed with frontline combination therapy with a proteasome inhibitor, immunomodulatory drug, and corticosteroid, select patients may opt to defer ASCT for a maintenance regimen until disease progression or intolerable toxicity. This approach is being evaluated in an ongoing Intergroupe Francophone du Myelome/Dana-Farber Cancer Institute randomized study with RVD (ClinicalTrials.gov NCT01191060) and in a study conducted by the European Network using a sequence of combination regimens (ClinicalTrials.gov NCT01208766). The tolerability and efficacy data reported here support a similar study with CRd. Conversely, it is of clinical interest to evaluate whether incorporating ASCT into sequential treatment with CRd pre- and post-transplant may further improve outcomes beyond those reported here. Our observation that CRd does not appear to adversely impact SCC is the first for a carfilzomib combination in the frontline setting and consistent with similar reports of bortezomib regimens. Long follow-up from our study and results from separate studies will help to determine the most effective strategies for CRd in the frontline setting. Given the challenges of long-term twice-weekly infusions of carfilzomib in the CRd regimen reported here, more convenient dosing schedules will likely be explored in future studies.

In conclusion, the CRd regimen was well tolerated and highly active as frontline therapy in patients with newly diagnosed MM. Long-term follow-up will help to better characterize the durability of the response with this regimen, and the relationship of response to PFS and OS, as well as long-term tolerability. Based on our study results, a carfilzomib dose of 36 mg/m² for CRd treatment appears appropriately tolerated in the frontline setting and should be considered for future studies. The CRd regimen would be
a welcomed addition to frontline treatment options. These data support a phase 3 trial to validate the
benefit of adding carfilzomib to Rd as a frontline therapy for MM.
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Authorship Contributions and Disclosure of Conflicts of Interest

Authorship contributions: A.J.J. designed research, performed research, contributed vital new reagents or analytical tools, analyzed data, and wrote the paper. D.D. performed research, contributed vital new reagents or analytical tools, and analyzed data. K.A.G. designed research, analyzed data and wrote the paper. D.L. performed research and contributed vital new reagents or analytical tools. D.H.V. performed research and contributed vital new reagents or analytical tools. S.J. performed research and contributed vital new reagents or analytical tools. A.A.Z. performed research. T.A. performed research. B.N. performed research. K.D.S. performed research. K.S.G. performed research. A.A. performed research.
T.J. performed research. D.D. contributed vital new reagents or analytical tools and analyzed data. K.M. contributed vital new reagents or analytical tools and analyzed data. M.M. performed research and contributed vital new reagents or analytical tools. D.C. performed research. M.K. performed research. R.V. performed research and contributed vital new reagents or analytical tools.

Conflict of interest disclosure:

Andrej Jakubowiak: Consultancy for Ortho Biotech, Celgene, Millennium, Onyx Pharmaceuticals, Bristol-Myers Squibb, and Exelixis; Honoraria for Ortho Biotech, Celgene, Millennium, Bristol-Myers Squibb, and Exelixis; Speakers Bureau for Ortho Biotech, Celgene, and Millennium; Board of Directors membership for Millennium, Onyx Pharmaceuticals, and Bristol-Myers Squibb; Advisory committee membership for Onyx Pharmaceuticals and Bristol-Myers Squibb. Dominik Dytfeld: No relevant financial relationship(s) to disclose. Kent A. Griffith: No relevant financial relationship(s) to disclose. Daniel Lebovic: No relevant financial relationship(s) to disclose. David H. Vesole: Advisory Board, Honorarium, Speakers Bureau for Celgene. Sundar Jagannath: Consultancy and honoraria for Celgene, Consultancy for Millenium/Takeda and Merck. Ammar Al-Zoubi: No relevant financial relationship(s) to disclose. Tara Anderson: No relevant financial relationship(s) to disclose. Brian Nordgren: No relevant financial relationship(s) to disclose. Kristen Detweiler-Short: No relevant financial relationship(s) to disclose. Keith Stockerl-Goldstein: No relevant financial relationship(s) to disclose. Asra Ahmed: No relevant financial relationship(s) to disclose. Terri Jobkar: No relevant financial relationship(s) to disclose. Diane Durecki: No relevant financial relationship(s) to disclose. Kathryn McDonnell: No relevant financial relationship(s) to disclose. Daniel Couriel: No relevant financial relationship(s) to disclose. Melissa Mietzel: No relevant financial relationship(s) to disclose. Mark Kaminski: No relevant financial relationship(s) to disclose. Ravi Vij: Consultancy and research funding for Onyx Pharmaceuticals.
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### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=53</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>Median, years (range)</td>
<td>59 (35–81)</td>
</tr>
<tr>
<td>≥65 years, n (%)</td>
<td>23 (43)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>39 (74)</td>
</tr>
<tr>
<td>Female</td>
<td>14 (26)</td>
</tr>
<tr>
<td><strong>ISS stage, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>21 (40)</td>
</tr>
<tr>
<td>II</td>
<td>18 (34)</td>
</tr>
<tr>
<td>III</td>
<td>14 (26)</td>
</tr>
<tr>
<td><strong>Durie-Salmon stage, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>7 (13)</td>
</tr>
<tr>
<td>II</td>
<td>12 (24)</td>
</tr>
<tr>
<td>III</td>
<td>34 (63)</td>
</tr>
<tr>
<td><strong>Unfavorable cytogenetics, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>del 13(^\text{†})/hypodiploidy</td>
<td>17/51 (33)</td>
</tr>
<tr>
<td>t(4;14)</td>
<td>10/50 (20)</td>
</tr>
<tr>
<td>t(14;16)</td>
<td>5/49 (10)</td>
</tr>
<tr>
<td>del 17p</td>
<td>0/48 (0)</td>
</tr>
<tr>
<td>del 17p</td>
<td>7/48 (15)</td>
</tr>
</tbody>
</table>

*1 or more of the abnormalities listed
\(^\text{†}\) del 13 by metaphase only

ISS, International Staging System
Table 2. Determination of the MTD During Phase 1

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Carfilzomib Dose, mg/m²</th>
<th>N=35</th>
<th>n</th>
<th>DLT probability estimate*</th>
<th>95% Credible Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>4</td>
<td>0</td>
<td>5.9%</td>
<td>1.7–15.3</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
<td>13</td>
<td>1</td>
<td>8.1%</td>
<td>2.6–19.4</td>
</tr>
<tr>
<td>3</td>
<td>36</td>
<td>18</td>
<td>2</td>
<td>12.0%</td>
<td>4.3–25.4</td>
</tr>
</tbody>
</table>

* Time-to Event Continual Reassessment Method (TITE-CRM) single-parameter logistic model

† Neutropenia, Grade 3, asymptomatic, resolved within a few days

‡ One patient with Grade 4 pulmonary edema, resolved with diuresis but patient withdrew consent and switched to alternate therapy achieving CR; the second patient with Grade 3 dyspnea responded to diuresis, resumed treatment at lower carfilzomib dose level, and continued on this dose without difficulty in subsequent cycles.
Table 3. Best Response to Treatment in Evaluable Patients

<table>
<thead>
<tr>
<th>Response, n (%)*</th>
<th>≥PR</th>
<th>≥VGPR</th>
<th>≥nCR</th>
<th>sCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (N=53)</td>
<td>52 (98)</td>
<td>43 (81)</td>
<td>33 (62)</td>
<td>22 (42)</td>
</tr>
<tr>
<td>Treatment duration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4+ cycles (n=49)</td>
<td>49 (100)</td>
<td>43 (88)</td>
<td>33 (67)</td>
<td>22 (45)</td>
</tr>
<tr>
<td>8+ cycles (n=36)</td>
<td>36 (100)</td>
<td>33 (92)</td>
<td>28 (78)</td>
<td>22 (61)</td>
</tr>
<tr>
<td>12+ cycles (n=29)</td>
<td>29 (100)</td>
<td>25 (86)</td>
<td>21 (72)</td>
<td>18 (62)</td>
</tr>
</tbody>
</table>

*Assessed by Modified IMWG Uniform Criteria with the addition of nCR

nCR, near complete response; PR, partial response; sCR, stringent complete response; VGPR, very good partial response
Table 4. Best Response to Treatment by Carfilzomib Dose, ISS Stage, and Cytogenetics (N=53)

<table>
<thead>
<tr>
<th>Response, n (%)*</th>
<th>≥PR</th>
<th>≥VGPR</th>
<th>≥nCR</th>
<th>sCR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carfilzomib dose, mg/m²</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 (n=4)</td>
<td>4 (100)</td>
<td>4 (100)</td>
<td>3 (75)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>27 (n=13)</td>
<td>13 (100)</td>
<td>13 (100)</td>
<td>11 (85)</td>
<td>7 (54)</td>
</tr>
<tr>
<td>36 (n=36)</td>
<td>35 (97)</td>
<td>25 (69)</td>
<td>20 (55)</td>
<td>14 (39)</td>
</tr>
<tr>
<td><strong>ISS stage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I (n=21)</td>
<td>21 (100)</td>
<td>15 (71)</td>
<td>11 (52)</td>
<td>7 (33)</td>
</tr>
<tr>
<td>II (n=18)</td>
<td>18 (100)</td>
<td>15 (75)</td>
<td>10 (55)</td>
<td>8 (44)</td>
</tr>
<tr>
<td>III (n=14)</td>
<td>13 (93)</td>
<td>11 (79)</td>
<td>10 (71)</td>
<td>7 (50)</td>
</tr>
<tr>
<td><strong>Cytogenetics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal/favorable† (n=34)</td>
<td>34 (100)</td>
<td>26 (76)</td>
<td>20 (59)</td>
<td>13 (38)</td>
</tr>
<tr>
<td>Unfavorable (n=17)†</td>
<td>16 (94)</td>
<td>13 (76)</td>
<td>11 (65)</td>
<td>9 (53)</td>
</tr>
</tbody>
</table>

*Assessed by Modified IMWG Uniform Criteria with the Addition of nCR

†Any of del 13 by metaphase or hypodiploidy or t(4;14) or t(14;16) or del 17p considered as unfavorable, all others considered normal/favorable

ISS, International Staging System; nCR, near complete response; PR, partial response; VGPR, very good partial response
Table 5. Treatment-emergent Adverse Events During Induction (Cycles 1–8) (N=53)

<table>
<thead>
<tr>
<th></th>
<th>Any Grade</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td><strong>Non-hematologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>38 (72)</td>
<td>12 (23)</td>
</tr>
<tr>
<td>Edema</td>
<td>25 (47)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>24 (45)</td>
<td>13 (25)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>20 (38)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Muscle cramping</td>
<td>17 (32)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Rash</td>
<td>15 (28)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Elevated liver function test</td>
<td>15 (28)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14 (26)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Infection*</td>
<td>12 (23)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Phlebitis</td>
<td>12 (23)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>12 (23)†</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>8 (15)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>6 (11)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>3 (6)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (13)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Renal</td>
<td>5 (9)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Constipation</td>
<td>5 (9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Mood alterations</td>
<td>5 (9)</td>
<td>1 (2)</td>
</tr>
<tr>
<td><strong>Hematologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>36 (68)</td>
<td>9 (17)</td>
</tr>
<tr>
<td>Anemia</td>
<td>32 (60)</td>
<td>11 (21)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>16 (30)</td>
<td>9 (17)</td>
</tr>
</tbody>
</table>

* Grade 3/4 events were pneumonia, and Grade 1/2 events were upper respiratory infections

†3 (6%) Grade 2, remaining Grade 1
Figure 1. Study design and treatment schema

Until disease progression* or unacceptable toxicity

<table>
<thead>
<tr>
<th></th>
<th>Cycles 1–4</th>
<th>Cycles 5–8</th>
<th>Cycles 9–24</th>
<th>Cycles 25+</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carfilzomib</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment days</td>
<td>1–2, 8–9, 15–16</td>
<td>1–2, 8–9, 15–16</td>
<td>1–2, 15–16</td>
<td></td>
</tr>
<tr>
<td><strong>Lenalidomide</strong></td>
<td>25 mg</td>
<td>25 mg</td>
<td>25 mg(^a)</td>
<td>25 mg(^a)</td>
</tr>
<tr>
<td>Treatment days</td>
<td>1–21</td>
<td>1–21</td>
<td>1–21</td>
<td>1–21</td>
</tr>
<tr>
<td><strong>Dexamethasone</strong></td>
<td>40 mg(^b)</td>
<td>20 mg</td>
<td>20 mg(^a)</td>
<td>20 mg(^a)</td>
</tr>
<tr>
<td>Treatment days</td>
<td>1, 8, 15, 22</td>
<td>1, 8, 15, 22</td>
<td>1, 8, 15, 22</td>
<td>1, 8, 15, 22</td>
</tr>
</tbody>
</table>

*Assessment on Days 1 and 15 of Cycle 1 and Day 1 of each subsequent cycle using modified IMWG Uniform Criteria with the addition of near complete response; \(^a\)patients achieving a PR after cycle 4 underwent stem cell collection and then continued CRd with the option to proceed to ASCT; \(^b\)Initial dose of 20 mg/m\(^2\) during Cycle 1 Days 1–2 for all patients regardless of dose cohort; \(^a\)at the discretion of the investigator, patients could receive 4 mg dexamethasone PO or IV on Days 2, 9 and 16 (Cycles 1 and 2) prior to carfilzomib infusion if signs of tumor flare were present; \(^a\)or the last tolerated dose

ASCT, autologous stem cell transplant; CRd, carfilzomib, lenalidomide, dexamethasone; LEN, lenalidomide monotherapy; PR, partial response
**Figure 2. Patient flow**

53 patients initiated induction CRd
4 carfilzomib 20 mg/m² (phase 1)
13 carfilzomib 27 mg/m² (phase 1)
36 carfilzomib 36 mg/m² (18 phase 1 and 18 phase 2)

10 patients discontinued induction CRd
7 proceeded to ASCT
2 patient/investigator preference
1 toxicity

36 patients initiated maintenance CRd

2 patients discontinued maintenance CRd
1 disease progression
1 patient/investigator preference

29 patients on maintenance CRd at data cut-off

5 patients initiated LEN maintenance

5 patients on LEN maintenance at data cut-off

53 patients evaluable for response
53 patients evaluable for safety

Median duration of treatment (N=53): 12 cycles (range, 1–25)
1 cycle=28 days
ASCT, autologous stem cell transplant; CRd, carfilzomib, lenalidomide, dexamethasone; LEN, lenalidomide monotherapy; SCC, stem cell collection
Figure 3. Change in M-protein levels compare with baseline

Error bars = standard deviation
Figure 4. Progression-free survival (N=53)

12-month rate 97%
24-month rate 92%
A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma