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Carfilzomib, cyclophosphamide, and dexamethasone in patients with newly diagnosed multiple myeloma: a multicenter, phase 2 study

Running head: CCyd for elderly patients with NDMM

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KEY POINTS

- This is the first study of carfilzomib-cyclophosphamide-dexamethasone in elderly patients with newly diagnosed multiple myeloma

- Carfilzomib-cyclophosphamide-dexamethasone induced high complete response rates and was associated with a low toxicity

ABSTRACT

This multicenter, open-label phase 2 trial determined the safety and efficacy of carfilzomib, a novel and irreversible proteasome inhibitor, in combination with cyclophosphamide and dexamethasone (CCyd) in patients with newly diagnosed multiple myeloma (NDMM) aged ≥65 years or who were ineligible for autologous stem cell transplantation. Patients (N=58) received CCyd for up to nine 28-day cycles, followed by maintenance with carfilzomib until progression or intolerance. After a median of 9 CCyd induction cycles (range 1–9), 95% of patients achieved at least a partial response, 71% achieved at least a very good partial response, 49% achieved at least a near complete response, and 20% achieved stringent complete response. After a median follow-up of 18 months, the 2-year PFS and OS rates were 76% and 87%, respectively. The most frequent grade 3–5 toxicities were neutropenia (20%), anemia (11%), and cardiopulmonary adverse events (7%). Peripheral neuropathy was limited to grade 1–2 (9%). Fourteen percent of patients discontinued treatment owing to adverse events, and 21% of patients required carfilzomib dose reductions. This is the first study of carfilzomib in combination with an alkylating agent in elderly patients with NDMM; results showed high complete response rates and a good safety profile. This study was registered at clinicaltrials.gov, identifier: NCT01346787.

Introduction

Multiple myeloma (MM) is the second most common hematologic malignancy.[1] In Europe, 33,000 new cases were estimated to be diagnosed in 2013, and MM was estimated to result in approximately 20,300 deaths.[2] The incidence of MM progressively increases with age; the median age at diagnosis is 70 years.[1,3]

In the last decade, the increased use of novel agents as initial therapy significantly improved overall survival (OS) in patients ineligible for autologous transplantation.[3] The 5-year survival improved from 31% (2001–2005) to 56% (2006–2010) (P<.001).[4]

While bortezomib-melphalan-prednisone (VMP) and melphalan-prednisone-thalidomide (MPT) combinations are routinely used in elderly patients,[5,6] dose-limiting hematologic toxicity from melphalan and peripheral neuropathy (PN) from bortezomib- or thalidomide limit their optimal use.[7,8] Better tolerated alkylating agents, such as cyclophosphamide, which lack the cumulative hematologic toxicity of melphalan, have been used successfully in combination with dexamethasone and either thalidomide[9] or bortezomib[10] in elderly NDMM patients.

Carfilzomib, a novel and selective proteasome inhibitor, has demonstrated higher rates of response and lower rates of PN relative to bortezomib or thalidomide.[11] Carfilzomib has been approved in the United States for use as a single agent in the treatment of patients with relapsed and refractory MM, based on the results from the phase 2 PX-171-003-A1 trial.[12,13] Among 257 efficacy-evaluable relapsed and/or refractory patients, 23.7% achieved at least a partial response (PR) with a median survival of 15.6 months. The most common grade 3–4 AEs were thrombocytopenia (29%), anemia (24%), lymphopenia (20%). PN was 12% for any grade and 1% for grade 3.

Given the improved hematologic safety profile of cyclophosphamide and the encouraging efficacy and safety profile of carfilzomib, we initiated a phase 2 trial of carfilzomib-cyclophosphamide-dexamethasone (CCyd) 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 older or who were ineligible for autologous stem cell transplantation (ASCT) were included in the study. Further eligibility criteria included measurable disease, a Karnofsky performance status of least at60%, creatinine clearance 15 mL/minute of higher, platelet count of 50×10^9/L or higher (30×10^9/L or higher if myeloma involvement in the bone marrow was greater than 50%), and an absolute neutrophil count of 1×10^9/L or higher without the use of growth factors. Patients were excluded from the study if they had nonsecretory MM (unless serum free light chains were present, and the ratio was abnormal), peripheral neuropathy (PN) higher than grade 2, active viral infection, myocardial infarction or unstable angina for 4 months or less, or other clinically significant heart disease.

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

Study design and treatment

This multicenter, nonrandomized, open-label, phase 2 study (Clinicaltrials.gov identifier NCT01346787) determined the safety and efficacy of CCyd in NDMM patients. A 2-stage study design according to

Bryant and Day was used.[14] During stage 1, primary end points included evaluation of toxicity and response to obtain the optimal dose of carfilzomib, defined as the dose needed to obtain partial response (PR) in least at 35% of patients with fewer than 45% dose-limiting toxicities (DLTs) at the end of cycle 3. DLTs included any of the following treatment-related events occurring during the first 3 cycles: grade 3 or higher nonhematologic toxicity or grade 4 hematologic toxicity, excluding anemia (grade 4 neutropenia must last longer than 3 days, and grade 4 thrombocytopenia must last longer than 7 days). Nineteen patients were to be enrolled in stage 1. Once the optimal dose was established, 34 additional patients were to be enrolled in stage 2. The dose of cyclophosphamide (900 mg/m^2 per cycle) was chosen based on preliminary experiences with the combination of bortezomib-cyclophosphamide-dexamethasone,[10,15] with the total dose split into 3 separate doses of 300 mg/m^2 to reduce the risk of toxicity in this elderly population. The dose of dexamethasone chosen was the standard low-dose dexamethasone described previously.[16] Nine induction cycles are considered the standard number of induction cycles in patients who are not eligible for autologous stem cell transplantation.[5,17]

Primary end points included evaluation of toxicity and efficacy (PR) at the end of cycle 3. Secondary end points included response rates, progression-free survival (PFS), time to progression (TTP), duration of response (DOR), overall survival (OS), time to next therapy (TNT), rates of PN, 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 nonresponding patients.

All patients received oral cyclophosphamide 300 mg/m^2 on days 1, 8, 15; oral dexamethasone 40 mg on days 1, 8, 15, 22; carfilzomib intravenously over 30 minutes on days 1, 2, 8, 9, 15, 16 (20 mg/m^2 on days 1, 2 of cycle 1, and 36 mg/m^2 thereafter) (Figure S1). Treatment was given every 28 days for 9 cycles. Patients then received maintenance therapy with carfilzomib 36 mg/m^2 on days 1, 2, 15, 16 every 28 days until progression or intolerance. Intolerance was defined as any grade 4 neutropenia or febrile

neutropenia, grade 4 lymphopenia persisting for more than 14 days, grade 4 thrombocytopenia with active bleeding, and treatment-related nonhematologic toxicity grade 3 or higher requiring treatment discontinuation. CCyd dosing could be held for up to 2 weeks to resolve toxicity and then restarted at the same dose or at a reduced dose, depending on the type of toxicity.

Assessment

For all patients receiving at least 1 dose of any study drug, toxicity was assessed according to the National Cancer Institute Common Toxicity Criteria, version 4·0.[18] Response was assessed according to the International Myeloma Working Group criteria; assessments were undertaken at the beginning of each treatment cycle (Figure 1) during induction and every 3 cycles during maintenance. Fluorescence in situ hybridization was used for t(4:14), t(11:14), t(14;16), del13, and del 17p.

Statistical analysis

This phase 2 trial sought to consider treatment efficacy and safety by examining error rates.[14] The upper-bound limit for the probability of erroneously accepting treatment when the response rate was inadequate or the toxicity rate was high was set at 0.10. The upper-bound limit for the probability of erroneously failing to accept treatment when the response rate was favorable or the toxicity rate was low was set at 0.2 (80% power). The unacceptable and acceptable probabilities for treatment response were fixed at 0.35 and 0.60, while those for toxicity rates were fixed at 0.45 and 0.30, respectively. According to these parameters, 19 patients were required for stage 1. Progression from stage 1 to stage 2, where an additional 34 patients were to be enrolled (total N=53), was allowed if there were more than 6 patients with PR and fewer than 9 toxicities at the end of cycle 3. Stage 2 results were to be considered positive if there were 23 or more patients with PR and 20 or fewer drug-related toxicities.

Response rates and safety were analyzed in patients who received ≥1 dose of study treatment. Time-to-event end points were determined using the intent-to-treat population, with a censor date of October 31, 2013. The Kaplan–Meier product limit method was used to estimate survivorship functions for time-to-event end points. Cox proportional hazards regression was used to assess the effects of demographic and prognostic variables on relative treatment differences. Continuous and categorical data were summarized 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 the HOVON Foundation, and was co-sponsored by Fondazione Neoplasie Sangue Onlus and supported by funding from Onyx Pharmaceuticals, Inc., and Stichting Hemato-Oncologie voor Volwassenen Nederland. The HOVON Foundation was part of the steering committee of this study and participated in the study design. The sponsor and co-sponsor had no role in the collection, analysis, or interpretation of data. Onyx Pharmaceuticals, Inc., critically reviewed the manuscript for scientific accuracy. Medical writing support was funded by Onyx Pharmaceuticals, Inc. 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 June 21, 2011, to September 15, 2012, in 10 centers in Italy. Fifty-eight patients were enrolled in the study. The median age was 71 years; 31% of patients had an unfavorable chromosomal profile, defined as the presence of t(4;14), del17p, or t(14;16), and 40% were International Staging System (ISS) stage III (Table 1). Fifty-five patients were evaluable for response; 2 were not evaluable because they did not start treatment and 1 because of a missing assessment following cycle 1

(Figure S2). Fifty-six patients received at least 1 dose of study drugs and were evaluable for safety (Figure S2). The median duration of induction treatment was 9 cycles (range, 1–9 cycles). At the time of analysis, 43 patients have proceeded to maintenance therapy; 35 could be assessed for response (Figure S2). The median duration of maintenance treatment was 9 months (range, 2–19 months).

Stage 1

After 3 cycles of CCyd treatment, the first 19 patients were evaluated for response and side effects. Seventeen patients (89%) achieved at least a PR, including 12 (63%) with very good PR (VGPR) and 5 (26%) with near CR (nCR). Five patients (26%) experienced DLTs: 1 grade 4 neutropenia for more than 3 days, 1 grade 3 cardiac event, 2 grade 3 infections, and 1 grade 3 renal event. These data allowed the trial to progress to stage 2.

Efficacy

Overall, 52 of 55 (95%) patients had at least a PR, 39 of 55 (71%) patients had at least a VGPR, 27 of 55 (49%) patients had an nCR or CR, and 11 of 55 (20%) patients had a stringent CR (sCR; Table 2). All sCR were confirmed by multiparametric flow cytometry. The depth of response increased in patients receiving more treatment cycles. At the end of 4 cycles, 41 of 46 (89%) patients achieved at least a PR, including 11 of 46 (24%) patients with an nCR/CR and 1 of 46 (2%) patients with an sCR. Among patients who completed 9 cycles of treatment, 43 of 43 (100%) had at least a PR and 26 of 43 (60%) had an nCR/CR, including 10 of 43 (23%) with an sCR (Table 2). Six of 43 patients (14%) showed further improvement in response during the first 9 months of maintenance with carfilzomib (Figure 1): 2 patients during the first 3 months, 3 between the 4^{th} and 6^{th} month, and 1 thereafter. The median time to achieve PR was 1 month, and 94% of patients with CR achieved CR during induction (Figure 1). The median DOR was 14.0 months (interquartile range [IQR], 11.7–19.2). The DOR was related to the quality

of response. At 2 years, the proportion of patients alive and in remission was 100% in patients who achieved sCR, 74% in those who achieved CR, and 67% in those who achieved PR. Response rates were generally similar across patient groups according to age, ISS stage and chromosomal profile (Table 2).

After a median follow-up of 18 months (IQR, 14–23), the 2-year PFS and OS rates were 76% and 87%, respectively (Figure 2). The risk of progression was slightly higher in patients with ISS III (hazard ratio [HR] 2.81; 95% confidence interval [CI] 0.58–13.56) and with high-risk chromosomal abnormalities (HR 1.85; 95% CI 0.59–5.85).

Safety

During induction, the most common toxicities of any grade were anemia (70%), thrombocytopenia (38%), neutropenia (36%), nausea/vomiting (18%), fever (25%), fatigue (20%), and cardiac events (16%). Hematologic grade 3–5 toxicities included neutropenia (20%), anemia (11%), and thrombocytopenia (4%). The most common grade 3–5 nonhematologic AEs were metabolic events (9%), infections (5%), cardiac events (7%), and renal events (4%) (Table 3). PN was experienced by 9% of patients and was limited in severity to grade 1 and 2. Treatment-emergent serious AEs occurred during induction in 12 (21%) patients and included 4 cardiac events (heart failure, arrhythmia, myocardial infarction, and hypertension [each n=1]), increase in creatinine (n=2), and 1 event each of infection (pneumonia), fever, intestinal perforation, stroke, acute pulmonary edema and pulmonary thromboembolism. A limited number of patients required dose modification during induction: 8 patients (14%) discontinued treatment owing to AEs, and 12 patients (21%) required carfilzomib dose reductions. The cumulative dose intensity was more than 90% (Table S1). The safety profile was generally similar in the 15 patients older than 75 years who received at least 1 dose of study treatment. Hematologic grade 3–5 toxicities included neutropenia only (27%). The most common grade 3–5 nonhematologic AEs were infections,

cardiac events, and vascular events (n=1 [7%] each). Five patients (33%) required carfilzomib dose reductions and 3 patients (20%) discontinued treatment owing to AEs.

During maintenance, the most common toxicities of any grade were anemia (21%), thrombocytopenia (5%), neutropenia (2%), fever (23%), and nausea/vomiting (9%). Hematologic grade 3–5 toxicities included neutropenia (2%), anemia (2%), and thrombocytopenia (2%). Grade 3–5 nonhematologic AEs were rare and occurred in fewer than 5% of patients. Ten patients (23%) experienced grade 1–2 fever not associated with chills, rigors, dyspnea, creatinine increase and/or symptoms of infection. All cases were resolved by administering oral or intravenous dexamethasone 4 mg prior to all subsequent carfilzomib doses, as prophylaxis. PN remained limited in severity to grade 1 and 2 (Table S2). Treatment-emergent serious AEs occurred during maintenance in 3 patients (7%) and included 1 fever, 1 diarrhea, and 1 acute diverticulitis with intestinal perforation. A limited number of patients required dose modification during maintenance: 1 patient (2%) discontinued treatment, and 2 patients (5%) required carfilzomib dose reductions due to AEs (Table S2). The cumulative dose intensity was 100% (Table S1).

Seven patients died while on study: 2 due to disease progression, 1 due to intestinal perforation (considered related to carfilzomib), 1 due to heart failure (considered related to carfilzomib), 1 due to atrial fibrillation (not considered related to carfilzomib), 1 due to pneumonia (not considered related to carfilzomib), and 1 due to an unknown cause.

Discussion

This phase 2 study demonstrated that treatment with CCyd 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 at least an nCR, and 20% of patients achieved an sCR. After a median

follow-up of 18 months, the 2-year PFS rate was 76%. Severe hematologic AEs occurred in fewer than 20% of patients, and nonhematologic AEs occurred in fewer than 10% of patients, with a low (18%) rate of discontinuation.

The achievement of CR has been associated with prolonged PFS and OS, including in elderly patients.[19] Maintenance therapy also improves outcome, and its role has been extensively investigated.[17,20,21] Additionally, drug discontinuation due to AEs has been associated with lower cumulative-delivered dose and shorter OS.[22] The ideal treatment should combine high response rates and continuous therapy to prolong PFS with an optimal safety profile to reduce the rate of treatment discontinuation.

Despite the limitations of cross-trial comparisons, CCyd treatment compares favorably with the current standard treatments for elderly patients. The combination MPT showed a high CR/nCR rate (27%), but a high treatment discontinuation rate (35%) translated to a median PFS of 20.3 months.[8,23] The combination VMP induced a CR rate of 30%, but a discontinuation rate of 33% and the absence of planned maintenance translated to a median PFS of 21 months.[5] Melphalan-prednisone-lenalidomide showed a lower CR/nCR rate (19%), but a drug discontinuation rate of 24%. The continuous lenalidomide treatment translated to a median PFS of 31 months.[17] The combination of lenalidomide and low-dose dexamethasone was associated with a CR/nCR rate of 14%, a drug-discontinuation rate of 19%, and a median PFS of 21 months.[16] In a phase 1/2 dose-escalation study, melphalan-prednisone-carfilzomib showed a that 91% of patients had at least a PR, including 55% achieving at least a VGPR, and a median event-free survival of 21.8 months.[24] In another phase 1/2 dose-escalation study, lenalidomide-dexamethasone-carfilzomib resulted in 64% of patients reaching at least a CR, including 55% achieving an sCR, as well as a 3-year PFS rate of 79% and a 3-year OS rate of 96%.[25,26] The higher CR rate observed in these patients was probably attributable to the combination of a proteasome inhibitor and an immunomodulatory agent, and particularly to the enrollment of younger patients. Indeed, in that

study median age was 59 years—with 57% of patients younger than 65 years and thus potentially transplant-eligible—while in the previous studies the median age was approximately 70 years.

In our study, the CCyd regimen was found to be well tolerated. The most frequently reported AEs were hematologic and mainly grade 1–2. Grade 3–5 neutropenia occurred in 20% of patients. The myelosuppressive effect of this regimen was lower than that reported with other frontline regimens with melphalan, such as VMP, where grade 3–4 neutropenia was reported in 40% of patients.[5] Grade 3–5 thrombocytopenia occurred in 4% of patients, a markedly lower incidence than that reported in the VISTA trial in patients treated with bortezomib (40%).[5]Cyclophosphamide may therefore represent a valid, less toxic alternative to melphalan for elderly patients with NDMM.

No grade 3–4 PN was reported, and only 9% of patients experienced grade 1–2 PN. Historically, grade 3–4 PN has been reported in 6% of patients receiving thalidomide,[8] in 14% of patients receiving twice-weekly bortezomib,[5] and in 6%–8% of patients receiving once-weekly bortezomib or subcutaneous administration.[27,28] A recent study found that carfilzomib and bortezomib have different effects on neurodegeneration, with bortezomib inhibiting several nonproteasomal targets within neurons.[29] This may, in part, explain the lower rates of PN reported with carfilzomib.

In our study, rates of grade 3–5 nonhematologic AEs were low. Severe cardiac events, occurring in 4 patients (7%), were heterogeneous and included congestive heart failure, hypertension, and irregular heart rhythm. One patient had controlled hypertension while the 3 other patients had no pre-existing cardiac co-morbidities. For elderly patients involved in future trials with carfilzomib, a full cardiac workup is suggested to detect cardiac abnormalities that may be exacerbated during treatment.

The results of this study are limited by the relatively small sample size, the single-arm, nonrandomized design, the lack of independent review of response and the short follow-up. Future studies are needed

to determine the most effective strategies for the use of CCyd in the frontline setting. Given the challenges of long-term, twice-weekly infusions of carfilzomib as reported here, more convenient dosing schedules, as well as higher doses of carfilzomib, may be needed.

Our study showed that in elderly patients who are not eligible for transplant, CCyd was highly effective, with excellent CR rates (including sCR), and was well tolerated with a low rate of treatment discontinuation. A longer follow-up is needed to draw more definitive conclusions on long-term outcomes and safety.

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Authorship

Contribution: 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, MB, GC, PS and AP contributed to the study design; SB, LB, GC and AP conducted the data analyses; SB and AP wrote the first draft of the manuscript; MTP, AL, CC, DR, VM, PM, MO, PO, FG, GB, MG, VM, SO, TC and PT provided patients and/or study materials.

Conflict-of-Interest disclosure: SB has received honoraria from Celgene, Janssen-Cilag, and Novartis, and has served on advisory committees for Merck Sharp & Dohme; MTP has received honoraria from Celgene and Janssen-Cilag and has served on the advisory committee for Bristol-Myers Squibb; AL has received honoraria from Celgene and Janssen-Cilag; MO has received honoraria from Celgene and Janssen-Cilag; SO has received honoraria from Celgene; MB declares research support, consultancy, and scientific advisory board participation from Celgene and Janssen-Cilag; PS has received research support from Onyx, Janssen, Celgene, and Millennium, and has participated on advisory boards for Onyx, Janssen, Celgene, Millennium; AP has received consultancy fees and honoraria from Amgen, Bristol-

Myers Squibb, Celgene, Janssen, Millennium, and Onyx. CC, DR, VM, PM, LB, PO, FG, GC, GB, MG, VM, TC, and PT have no conflicts to declare.

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TABLES

Table 1. Patient characteristics at baseline

Characteristic	**N=58**
Male, n (%)	27 (47)
Age	
Median (IQR), years	71 (68–75)
≥75 years, n (%)	17 (29)
ISS stage, n (%)	
I	16 (28)
II	19 (33)
III	23 (40)
Creatinine clearance, mL/min, n (%)	
<30	2 (3)
30–60	29 (50)
>60	27 (47)
Chromosomal abnormalities, n (%)	
t (4;14)	9 (16)
t (14;16)	1 (2)
Del 17	8 (14)
Unfavorable profile[a]	18 (31)
Data missing	7 (12)

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

IQR, interquartile range; ISS, International Staging System.

Table 2. Response to treatment and by patient characteristics

Patient subgroup	n	Response category, n (%)				
		≥PR	≥VGPR	≥nCR	≥CR	sCR
Overall	55	52 (95)	39 (71)	27 (49)	18 (33)	11 (20)
Age						
< 75 years	41	38 (93)	29 (71)	22 (54)	13 (32)	8 (20)
≥ 75 years	14	14 (100)	10 (71)	5 (36)	5 (36)	3 (21)
ISS stage						
I	16	15 (94)	10 (63)	8 (50)	5 (31)	3 (19)
II	18	18 (100)	14 (78)	12 (67)	8 (44)	6 (33)
III	21	20 (95)	15 (71)	7 (33)	5 (24)	2 (10)
Chromosomal abnormalities						
Normal/favorable	31	29 (94)	23 (74)	17 (55)	10 (32)	6 (19)
Unfavorable[a]	17	16 (94)	12 (71)	7 (41)	5 (29)	3 (18)
Treatment duration						
Second cycle	53	40 (75)	16 (30)	3 (6)	-	-
Fourth cycle	46	41 (89)	26 (57)	11 (24)	-	1 (2)
Sixth cycle	43	43 (100)	34 (79)	13 (30)	-	4 (9)
Ninth cycle	43	43 (100)	33 (77)	20 (47)	–	10 (23)

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

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

Table 3. Treatment-related adverse events during induction

Events, n (%)	N=56	
	Any grade	Grades 3–5
Hematologic		
≥1 event	44 (79)	15 (27)
Neutropenia	20 (36)	11 (20)
Thrombocytopenia	21 (38)	2 (4)
Anemia	39 (70)	6 (11)
Nonhematologic		
≥1 event	40 (71)	16 (29)
Cardiac events	9 (16)	4 (7)
Arrhythmia	2 (4)	1 (2)
Myocardial infarction	1 (2)	1 (2)
Heart failure	1 (2)	1 (2)
Hypertension	5 (9)	1 (2)
Vascular events	3 (5)	1 (2)
Pulmonary thromboembolism	1 (2)	1 (2)
Phlebitis	2 (4)	-
Constitutional events	34 (61)	2 (4)
Edema	7 (13)	-
Fever	14 (25)	1 (2)
Fatigue	11 (20)	1 (2)
Dermatologic events	5 (9)	-

Gastrointestinal events	25 (45)	1 (2)
Constipation	3 (5)	-
Diarrhea	8 (14)	-
Nausea/vomiting	11 (20)	-
Intestinal perforation	1 (2)	1 (2)
Other	2 (4)	-
Infections events	10 (18)	3 (5)
Upper respiratory tract	6 (11)	1 (2)
Pneumonia	2 (4)	2 (4)
Febrile neutropenia	1 (2)	1 (2)
Genitourinary tract	1 (2)	-
Neurological events	15 (27)	2 (4)
Sensitive PN	4 (7)	-
Motor PN	1 (2)	-
Mood alteration	1 (2)	1 (2)
Stroke	1 (2)	1 (2)
Other	8 (14)	-
Metabolic events	19 (34)	5 (9)
AST/ALT increase	4 (7)	-
Hyperglycemia	7 (13)	1 (2)
Hypoglycemia	1 (2)	-
Lymphopenia	5 (9)	4 (7)
Other	2 (4)	-

Renal events	3 (5)	2 (4)
Respiratory events	9 (16)	1 (2)
Dyspnea	4 (7)	-
Respiratory failure	1 (2)	-
Acute pulmonary edema	1 (2)	1 (2)
Other	3 (5)	-
Other events	6 (11)	-

ALT, alanine aminotransferase; AST, aspartate aminotransferase; PN, peripheral neuropathy.

FIGURE LEGENDS

Figure 1. Kaplan–Meier analysis of time to response, showing proportion of responding patients achieving their best response over time.

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

Figure 2. Kaplan–Meier analysis of time to events data, showing (A) progression-free survival and (B) overall survival.

Figure 1

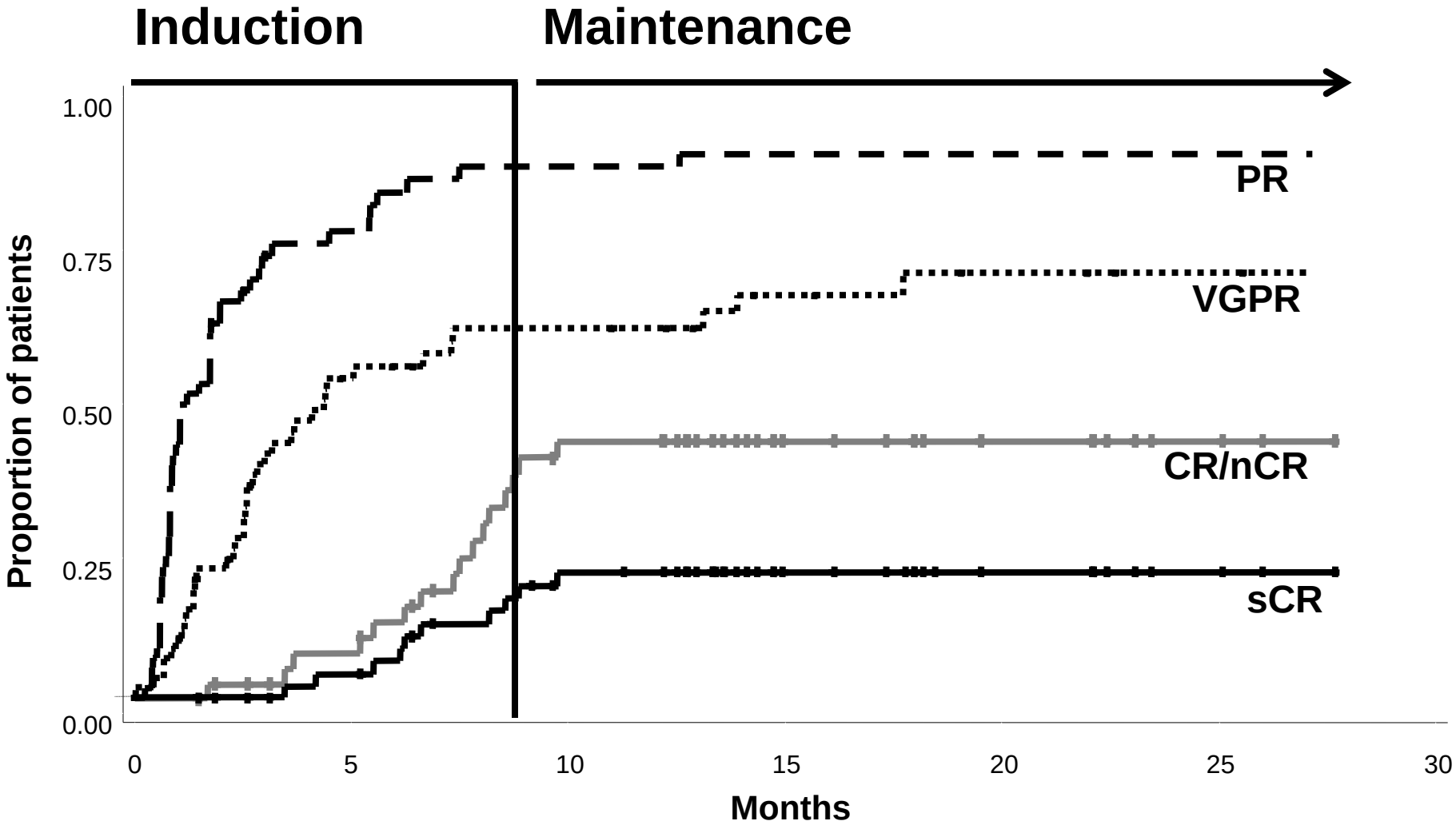

Induction
Maintenance
1.00
0.75
0.50
0.25
0.00
Proportion of patients
PR
VGPR
CR/nCR
sCR
0
5
10
15
20
25
30
Months

Figure 2A

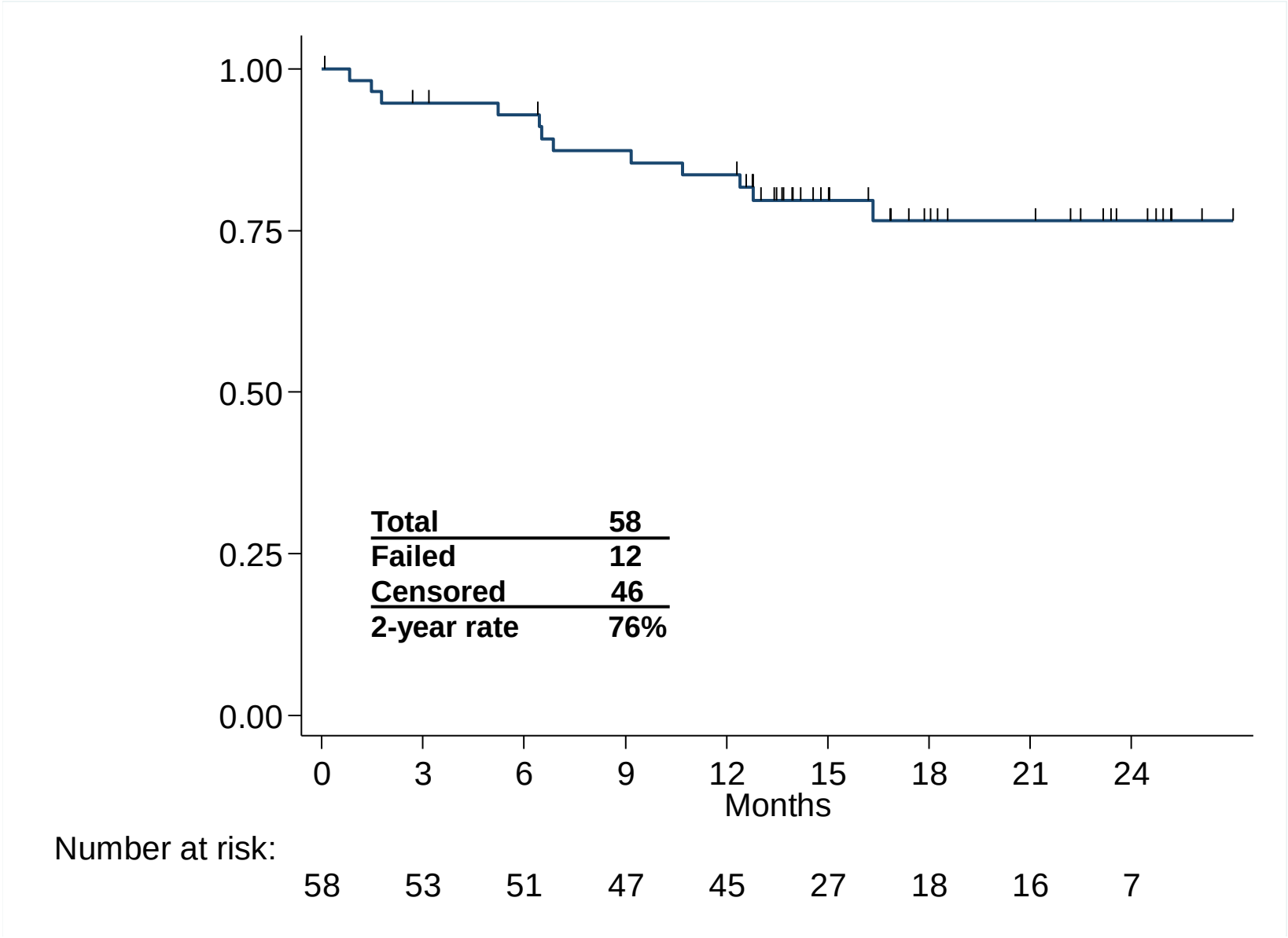
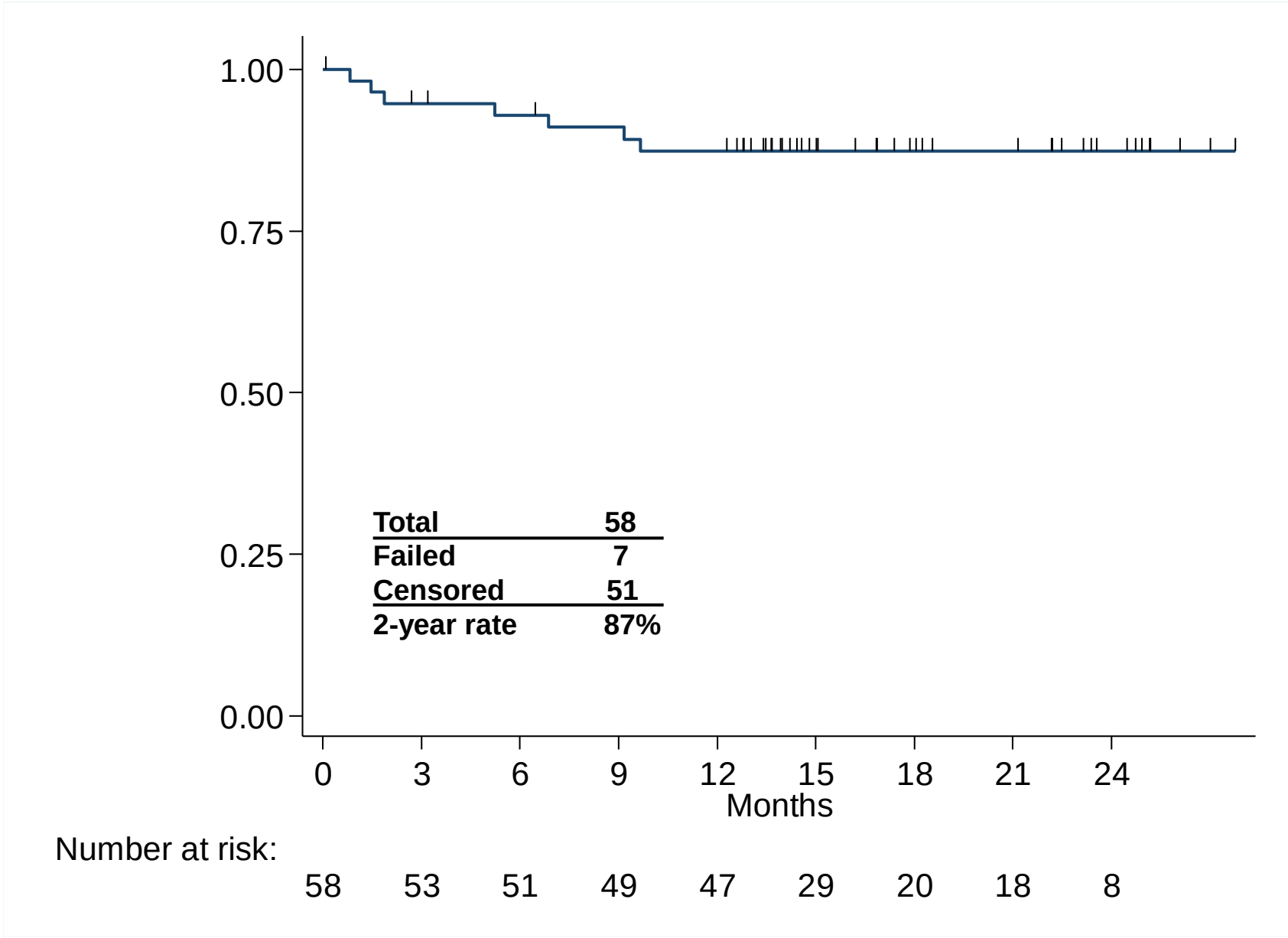

1.00
0.75
0.50
0.25
0.00
Total 58
Failed 12
Censored 46
2-year rate 76%
0
3
6
9
12
15
18
21
24
Months
Number at risk:
58
53
51
47
45
27
18
16
7

Figure 2B


1.00
0.75
0.50
0.25
0.00
Total 58
Failed 7
Censored 51
2-year rate 87%
0
3
6
9
12
15
18
21
24
Months
Number at risk:
58
53
51
49
47
29
20
18
8

SUPPLEMENTAL FIGURE LEGENDS

Figure S1. Study design and treatment schema. CCyd, cyclophosphamide and dexamethasone.

Figure S2. Patient disposition.

Figure S1

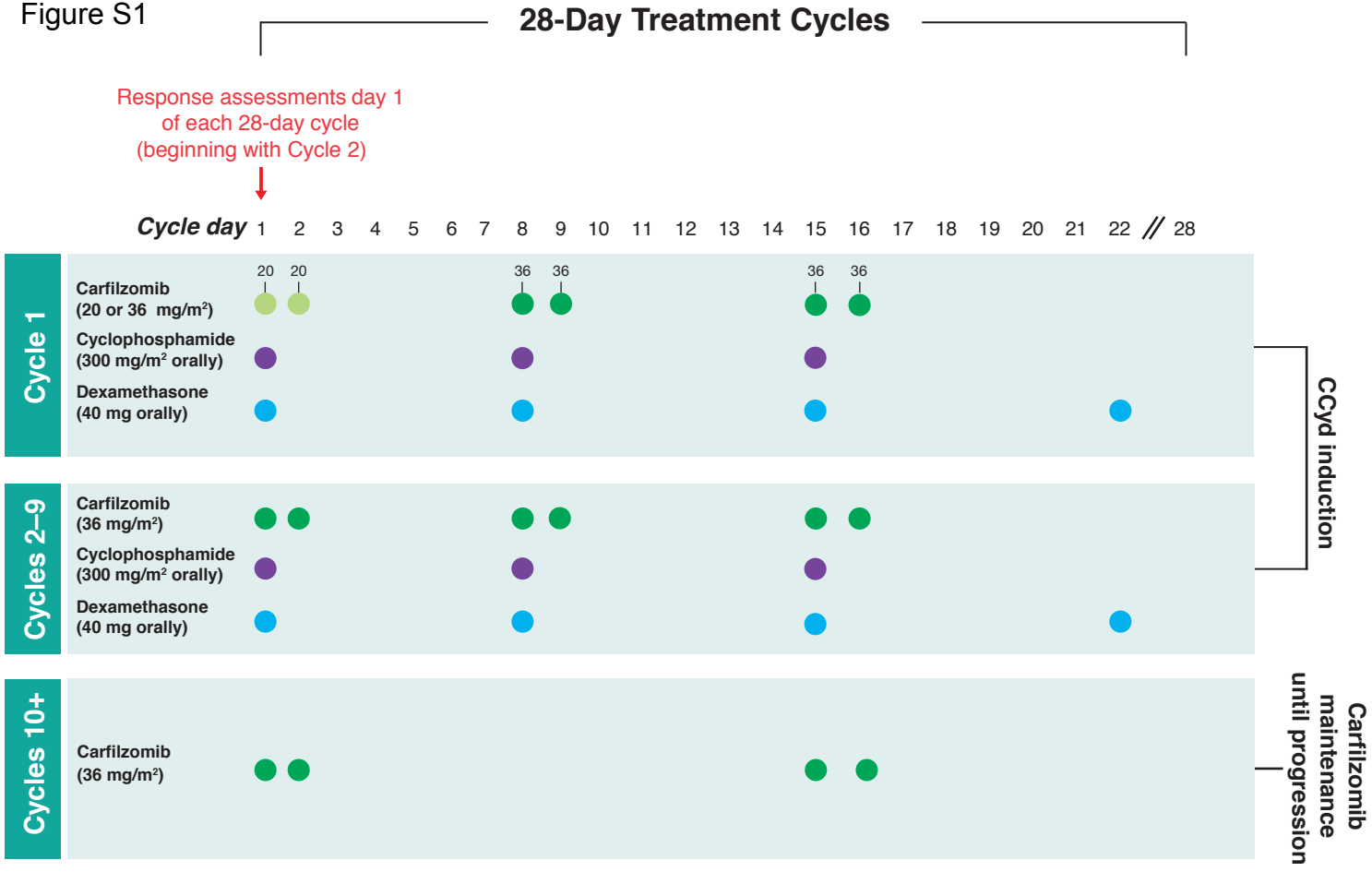
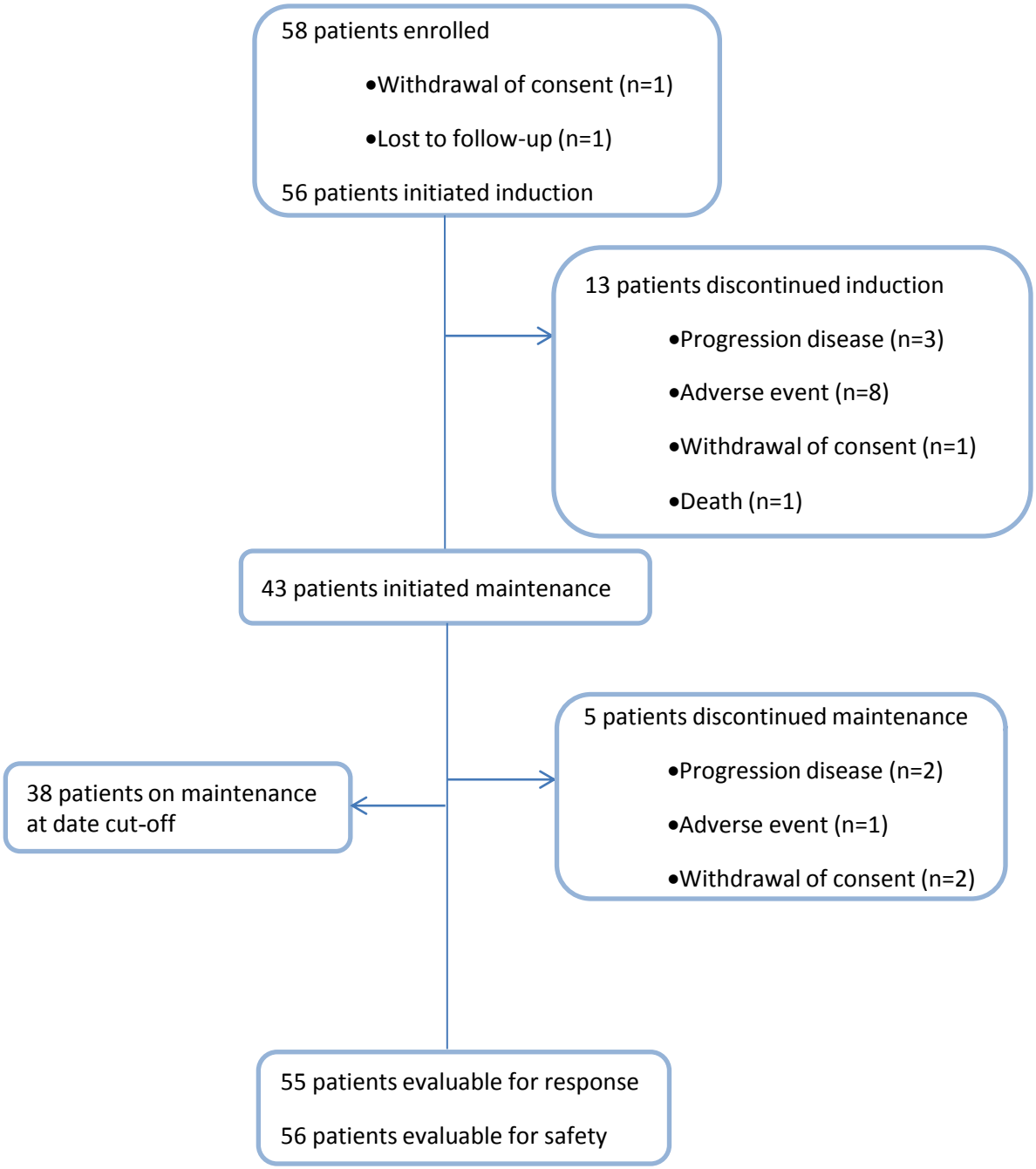

28-Day Treatment Cycles
Response assessments day 1 of each 28-day cycle (beginning with Cycle 2)
Cycle day 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 // 28
Cycle 1
Carfilzomib (20 or 36 mg/m²)
20 20 36 36 36 36
Cyclophosphamide (300 mg/m² orally)
Dexamethasone (40 mg orally)
Cycles 2–9
Carfilzomib (36 mg/m²)
Cyclophosphamide (300 mg/m² orally)
Dexamethasone (40 mg orally)
Cycles 10+
Carfilzomib (36 mg/m²)
CCyd induction
Carfilzomib maintenance until progression

Figure S2


58 patients enrolled
•Withdrawal of consent (n=1)
•Lost to follow-up (n=1)
56 patients initiated induction
13 patients discontinued induction
•Progression disease (n=3)
•Adverse event (n=8)
•Withdrawal of consent (n=1)
•Death (n=1)
43 patients initiated maintenance
5 patients discontinued maintenance
•Progression disease (n=2)
•Adverse event (n=1)
•Withdrawal of consent (n=2)
38 patients on maintenance at date cut-off
55 patients evaluable for response
56 patients evaluable for safety

Supplementary Materials

Table S1. Dose modifications and dose intensity during induction and maintenance

Parameter	All patients (N=56)	Induction (n=56)	Maintenance (n=43)
Dose reduction due to AEs, n (%)			
≥1 drug	21 (38)	21 (38)	-
Carfilzomib	14 (25)	12 (21)	2 (5)
Carfilzomib discontinuation due to AEs, n (%)	9 (16)	8 (14)	1 (2)
Regimen dose intensity			
Carfilzomib			
Median relative dose intensity, %	95	93	100
Median cumulative dose, mg	4413	2904	1722
IQR cumulative dose, mg	2245–4499	2265–3130	1122–1722
Cyclophosphamide			
Median relative dose intensity, %	96	96	-
Median cumulative dose, mg	12150	12150	-
IQR cumulative dose, mg	9600–13500	9600–13500	-
Dexamethasone			
Median relative dose intensity, %	96	96	-
Median cumulative dose, mg	1360	1360	-
IQR cumulative dose, mg	840–1440	840–1440	-

"Relative dose intensity" is defined as the cumulative delivered dose divided by the planned dose × 100.

AE, adverse event; IQR, interquartile range.

Table S2. Treatment-related adverse events during maintenance (N=43)

Events	n (%)	
	Any grade	Grades 3-5
Hematologic		
≥1 event	12 (28)	2 (5)
Neutropenia	1 (2)	1 (2)
Thrombocytopenia	2 (5)	1 (2)
Anemia	9 (21)	1 (2)
Nonhematologic		
≥1 event	18 (42)	3 (7)
Cardiac events	1 (2)	-
Arrhythmia	1 (2)	-
Myocardial infarction	-	-
Hypertension	-	-
Vascular events	1 (2)	-
Phlebitis	-	-
Constitutional events	12 (28)	1 (2)
Edema	-	-
Fever	10 (23)	1 (2)
Fatigue	-	-
Dermatologic events	3 (7)	-

Gastrointestinal events	6 (14)	1 (2)
Constipation	-	-
Diarrhea	-	-
Nausea/vomiting	4 (9)	1 (2)
Intestinal perforation	-	-
Other	2 (5)	-
Infections events	2 (5)	-
Upper respiratory tract	1 (2)	-
Pneumonia	-	-
Genitourinary tract	-	-
Neurological events	4 (9)	1 (2)
Sensitive PN	2 (5)	-
Motor PN	1 (2)	-
Mood alteration	1 (2)	1 (2)
Other	-	-
Metabolic events	1 (2)	-
AST/ALT increase	-	-
Hyperglycemia	-	-
Hypoglycemia	-	-
Lymphopenia	-	-
Other	1 (2)	-
Renal events	2 (5)	1 (2)
Respiratory events	-	-
Dyspnea	-	-
Respiratory failure	-	-
Other	-	-
Other events	2 (5)	-

ALT, alanine aminotransferase; AST, aspartate aminotransferase; PN, peripheral neuropathy.