CLINICAL TRIALS AND OBSERVATIONS

Randomized multicenter phase 2 study of pomalidomide, cyclophosphamide, and dexamethasone in relapsed refractory myeloma

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Key Points

- PomCyDex results in a higher overall response rate than pomalidomide and dexamethasone.
- PomCyDex is an effective, all oral regimen for refractory myeloma patients.

Pomalidomide and low-dose dexamethasone (PomDex) is standard treatment of lenalidomide refractory myeloma patients who have received >2 prior therapies. We aimed to assess the safety and efficacy of the addition of oral weekly cyclophosphamide to standard PomDex. We first performed a dose escalation phase 1 study to determine the recommended phase 2 dose of cyclophosphamide in combination with PomDex (arm A). A randomized, multicenter phase 2 study followed, enrolling patients with lenalidomide refractory myeloma. Patients were randomized (1:1) to receive pomalidomide 4 mg on days 1 to 21 of a 28-day cycle in combination with weekly dexamethasone (arm B) or pomalidomide, dexamethasone, and cyclophosphamide (PomCyDex) 400 mg orally on days 1, 8, and 15 (arm C). The primary end point was overall response rate (ORR). Eighty patients were enrolled (10 in phase 1 and 70 randomized in phase 2: 36 to arm B and 34 to arm C). The ORR was 38.9% (95% confidence interval [CI], 23-54.8%) and 64.7% (95% CI, 48.6-80.8%) for arms B and C, respectively (P = .035). As of June 2015, 62 of the 70 randomized patients had progressed. The median progression-free survival (PFS) was 4.4 (95% CI, 2.3-5.7) and 9.5 months (95% CI, 4.6-14) for arms B and C, respectively (P = .106). Toxicity was predominantly hematologic in nature but was not statistically higher in arm C. The combination of PomCyDex results in a superior ORR and PFS compared with PomDex in patients with lenalidomide refractory multiple myeloma. The trial was registered at www.clinicaltrials.gov as #NCT01432600. (*Blood*. 2016;127(21):2561-2568)

Introduction

Multiple myeloma is a plasma cell malignancy that accounts for ~1% of all cancers.[1] Despite available therapies, the disease remains uniformly fatal, and patients who have received prior lenalidomide and bortezomib have a median overall survival (OS) of 9 months.[2] Combination therapy is often used in clinical practice in an attempt to overcome drug/clone resistance.

Immunomodulatory agents, such as thalidomide, lenalidomide, and pomalidomide, are active therapies for patients with multiple myeloma.[3-6] Specifically, lenalidomide and dexamethasone are associated with a response rate of ~60% and a median progression-free survival (PFS) of 11 months in patients with relapsed multiple myeloma.[3,4] Richardson et al evaluated pomalidomide with or without dexamethasone in a phase 1/2 trial in patients with prior bortezomib and lenalidomide.[6,7] The study identified a recommended phase 2 dose of pomalidomide of 4 mg given orally days 1 to 21 every 28 days in combination with dexamethasone 40 mg weekly (20 mg in patients >75 years of age).[7] The phase 2 portion determined that pomalidomide-dexamethasone results in an overall response rate (ORR) of 33% and median PFS of 4.2 months in this patient population.[6] Furthermore, a randomized phase 3 trial compared pomalidomide and low-dose dexamethasone to high-dose dexamethasone in patients who had received prior bortezomib and lenalidomide, showing a superior response rate, PFS, and OS with pomalidomide and low-dose dexamethasone.[8] In that setting, pomalidomide and dexamethasone similarly resulted in an ORR of 31% and a median PFS of 4 months.[8] Based on this experience, the US Food and Drug Administration approved pomalidomide in combination with dexamethasone in February 2013 for patients with relapsed and refractory multiple myeloma who had received prior lenalidomide and a proteasome inhibitor.

Alkylating agents (including melphalan and cyclophosphamide) continue to represent standard therapies for patients with multiple myeloma.[9-15] Interestingly, a combination of lenalidomide and continuous cyclophosphamide resulted in an ORR of 50% in lenalidomide refractory patients, suggesting cyclophosphamide may be able to overcome resistance to lenalidomide in the clinic.[16] In addition, Larocca

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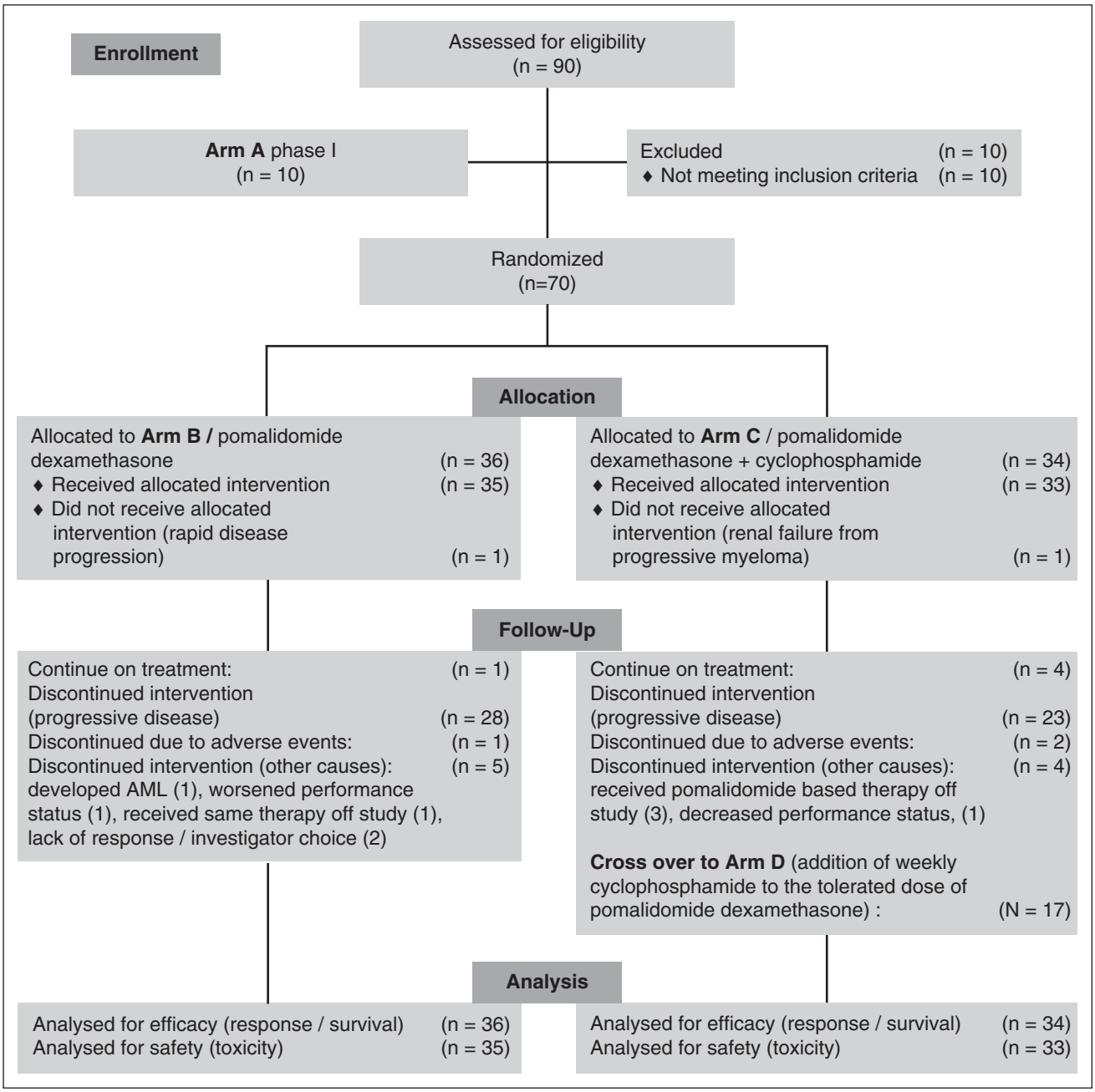


Figure 1. Study scheme and CONSORT flow diagram.

et al combined continuous pomalidomide with oral cyclophosphamide.[17] The maximum tolerated dose was pomalidomide 2.5 mg orally daily, cyclophosphamide 50 mg orally every other day, and prednisone 50 mg orally every other day. Patients received 6 cycles followed by maintenance with pomalidomide and prednisone. The ORR was 51%, and the median PFS was 10.4 months.[17]

Based on these encouraging studies, we conducted a phase 1 trial to determine the recommended phase 2 dose of the combination of pomalidomide, dexamethasone, and oral weekly cyclophosphamide. We then conducted a randomized phase 2 study comparing pomalidomide, dexamethasone, and cyclophosphamide (PomCy-Dex) to pomalidomide and low-dose dexamethasone (PomDex) in patients with lenalidomide refractory myeloma.

Patients and methods

Patient eligibility

Eligible patients had relapsed and refractory multiple myeloma. Patients had received ≥2 prior lines of therapies to include a prior immunomodulatory drug, and patients were required to be refractory to lenalidomide (defined as progressive disease during active therapy or within 60 days of discontinuation of therapy). A line of therapy is defined as a course of therapy that is not interrupted by progressive disease. In addition, patients had measurable disease as defined by the presence of 1 of the following: serum monoclonal protein ≥0.5 g/dL; urine monoclonal protein >200 mg/24 h; or serum-involved free light chain ≥10 mg/dL and abnormal serum free light chain ratio. Patients had an Eastern Cooperative Oncology Group (ECOG)

Table 1. Patient characteristics

	Arm A (N = 10)	Arm B (N = 36)	Arm C (N = 34)	Arm D* (N = 17)	*P* value†
Age, years, median (range)	69 (44-73)	64 (50-78)	65 (47-80)	64 (50-73)	.697
Male, n (%)	7 (70)	23 (64)	18 (53)	12 (71)	.467
Number of prior therapies, median (range)	5 (4-12)	4 (2-12)	4 (2-9)	4 (3-8)	.570
Bortezomib refractory, n (%)	10 (100)	28 (78)	24 (71)	12 (71)	.413
Carfilzomib refractory, n (%)	1 (10)	16 (44)	13 (38)	7 (41)	.632
Prior HDM/ASCT,‡ n (%)	7 (70)	27 (75)	28 (82)	13 (76)	.7
Prior alkylating agent, n (%)	10 (100)	32 (89)	32 (94)	15 (88)	1.0
Serum creatinine (mg/dL), median (range)	1 (1-3)	1 (0.5-2.3)	0.9 (0.6-2.1)	1 (1-2)	.650
High-risk cytogenetics,§ n (%)	3 (30)	8 (22)	7 (21)	4 (23)	1.0
Deletion 17p, n (%)	3 (30)	6 (16)	5 (15)	3 (18)	.6
t(4;14), n (%)	0	4 (11)	3 (9)	3 (18)	.6
Trisomy or tetrasomy 1q, n (%)	3 (30)	18 (50)	9 (26)	9 (53)	.1

*Arm D, a crossover group, was part of arm B.
†Comparing arms B and C, the Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables.
‡High-dose melphalan and autologous stem cell transplant.
§High-risk cytogenetics: deletion 17p and/or t(4;14).

performance status of 0 to 2 and a serum creatinine level <3 mg/dL. For the phase 1 portion, patients were required to have an absolute neutrophil count $\geq 1000/mm^3$, and a platelet count $\geq 50\,000/mm^3$. For the phase 2 portion, patients with ≥50% bone marrow plasmacytosis were eligible if the platelet count was $\geq 30\,000/mm^3$ and regardless of baseline absolute neutrophil count if felt to be related to active myeloma in the opinion of the investigator and if growth factor support can result in improvement in the neutrophil count to $\geq 1000/mm^3$ during screening. Females of childbearing potential had to have a negative serum or urine pregnancy test within 10 to 14 days prior to, and within 24 hours of, starting pomalidomide. A washout period of 2 weeks prior to cycle 1 day 1 from prior therapies was required. Exclusion criteria included patients with known hypersensitivity to thalidomide or lenalidomide; patients who had HIV or active hepatitis B or C; patients with prior pomalidomide (>1 cycle); patients with grade 3 or more neuropathy; patients with active malignancy requiring therapy within the next year; and patients within 12 months from allogeneic transplant or with active graft-versus-host disease. All patients were required to sign a written informed consent document per institutional and federal guidelines. Patients were enrolled at 3 academic institutions in the United States (H. Lee Moffitt Cancer Center, Mount Sinai University, and University of California San Francisco) between December 2011 and March 2014.

Treatment

In the phase 1 (arm A) portion of the study, patients received pomalidomide at 4 mg orally on days 1 to 21 of a 28-day cycle, oral weekly cyclophosphamide (dose escalation 300-500 mg) on days 1, 8, and 15 (dose level −1 was cyclophosphamide 300 mg orally on days 1 and 8 only). Patients also received dexamethasone 40 mg orally on days 1 to 4 and 15 to 18 of a 28-day cycle for the first 4 cycles and subsequently 40 mg orally on days 1, 8, 15, and 22. The dose escalation used a standard "3+3" design.

In the phase 2 portion of the study, patients were randomized to either arm B (pomalidomide and low-dose dexamethasone) or arm C (pomalidomide cyclophosphamide, and low-dose dexamethasone at the recommended phase 2 dose determined in arm A). Specifically, arm B patients received pomalidomide at 4 mg orally days 1 to 21 and dexamethasone 40 mg weekly and arm C patients received pomalidomide 4 mg days 1 to 21, dexamethasone 40 mg weekly, and oral cyclophosphamide 400 mg orally on days 1, 8, and 15 of a 28-day cycle. Patients who experienced progressive disease in arm B were allowed to crossover to arm D at the discretion of the treating physician, in which case oral weekly cyclophosphamide (400 mg orally on days 1, 8, and 15) was added to their tolerated dose of pomalidomide and dexamethasone (Figure 1).

In the phase 1 and phase 2 studies, patients who were >75 years of age or those who were known to be intolerant to 40 mg weekly dexamethasone received 20 mg dexamethasone on the same schedule. In addition, aspirin 81 mg daily was required for thromboprophyalxis (unless the patients had contraindications or were receiving other form of anticoagulation for other indications).[18]

Growth factor support was allowed during treatment at the discretion of the treating physician considering the compromised bone marrow function of patients with refractory multiple myeloma. In addition, the use of bisphosphonates, transfusion support, and other approved supportive strategies were allowed per routine standard of care.

Response

The International Myeloma Working group uniform response criteria were used to assess response with the addition of minimal response (MR), which is defined as a 25% to 49% decrease in serum paraprotein and a 50% to 89% reduction in urine light chain.[19] The best response was determined as the highest level of response achieved during an arm of therapy that was confirmed on repeat measurement.

Table 2. International Myeloma Working Group best response on treatment per study arm

Response	Arm A (N = 10) [N (%)]	Arm B (N = 36) [N (%)]	Arm C (N = 34) [N (%)]	Arm D (N = 17) [N (%)]
Complete/stringent complete response	1 (10)	1 (3%)	1 (3)	
Very good partial response	1 (10)	4 (11)	3 (9)	
Partial response	3 (30)	9 (25)	18 (53)	1 (6)
Minimal response	2 (20)	8 (22)	5 (15)	4 (23)
Stable disease	2 (20)	7 (19)	1 (3)	8 (47)
Progressive disease	1 (10)	5 (14)	3 (9)	4 (23)
Not evaluable*		2 (6)	3 (9)	
Overall response rate (≥PR)†		14 (39)	22 (65)	1 (6)

*Two patients were randomized but did not receive study therapy and were included as treatment failure (one was randomized to arm B and the other to arm C). In addition, 3 patients did not complete a cycle of therapy and return for disease assessment and are included as not evaluable (treatment failure based on intent to treat).
†The ORR (PR or better) for arm C was 64.7% (95% CI, 48.6-80.8), whereas the ORR for arm B was 38.9% (95% CI, 23-54.8; $P = .035$).

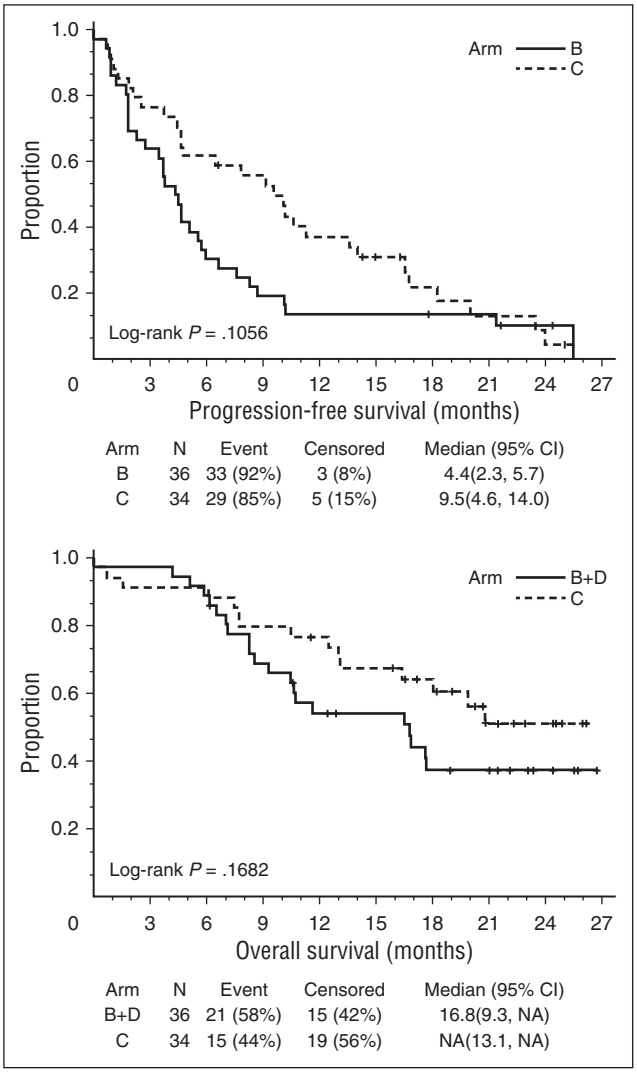


Figure 2. PFS and OS comparing arms B and C. (A) PFS and (B) OS comparing arms B and C.

Statistical considerations

For the phase 2 portion, the sample size justification was based on the ORR, which is the primary end point. We estimated the overall response rate was 30% in the PomDex (arm B) and 60% in the arm with PomCyDex (arm C). A sample size of 70 patients (35 in each arm) achieved 78% power to detect the group difference of 30% using the 2-sided Fisher's exact test. The significant level of 10% was applied. Randomization was performed by a block size of 4 to assign in a 1:1 ratio to arm B or arm C.

Patients' demographic and clinical characteristics were summarized using descriptive statistics. For the phase 1 trial, the primary objective was to determine the maximum tolerated dose of oral weekly cyclophosphamide in combination with pomalidomide and dexamethasone. All toxicities and dose-limiting toxicities (DLTs) were summarized based on dose levels and toxicity grades.

For the primary end point in the phase 2 trial, we were interested in comparing the ORR of pomalidomide dexamethasone with (arm C) or without cyclophosphamide (arm B) in patients with relapsed and refractory myeloma. The ORR and its 95% confidence interval (CI) were calculated for each study arm using the exact binomial method. The comparison of the ORR between the 2 study groups was evaluated using the Fisher's exact test. The phase 2 component of the trial was conducted in a single stage without preplanned interim analysis.

The secondary end points included PFS, OS, and safety. PFS was defined as the duration of time from start of treatment to the first occurrence of disease progression or death, whichever occurred earlier. OS was defined as the time from start of treatment to death. For each study arm, the PFS curves were estimated using the Kaplan-Meier method. The median of PFS and its 95% CIs were estimated. The PFS difference between the 2 study arms were compared using the log-rank test. The same approach was applied for evaluating OS in the 2 study arms. The treatment effect adjusting for age, number of prior therapies, β2-microglobulin, and high-risk cytogenetics was analyzed on overall response using logistic regression and on PFS and OS using the Cox model. For exploratory, we evaluated whether treatment effect (arm B vs arm C) on PFS and OS was modified by the number of prior therapies and cytogenetically defined risk by adding the interaction of treatment and the variable of interest in the multivariable main effect models.

All efficacy analyses were performed on an intent-to-treat basis

The safety analyses were performed using data from all subjects who received any study drug. Toxicities were characterized and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v 4.0. Adverse events leading to death or to discontinuation from treatment, events classified as National Cancer Institute Common Terminology Criteria for Adverse Events v 4.0 grade 3 or higher, study drug–related events, and serious adverse events were listed separately. Cross-tabulations were provided to summarize frequencies of abnormalities. This study was approved by the institutional review board of all 3 participating institutions.

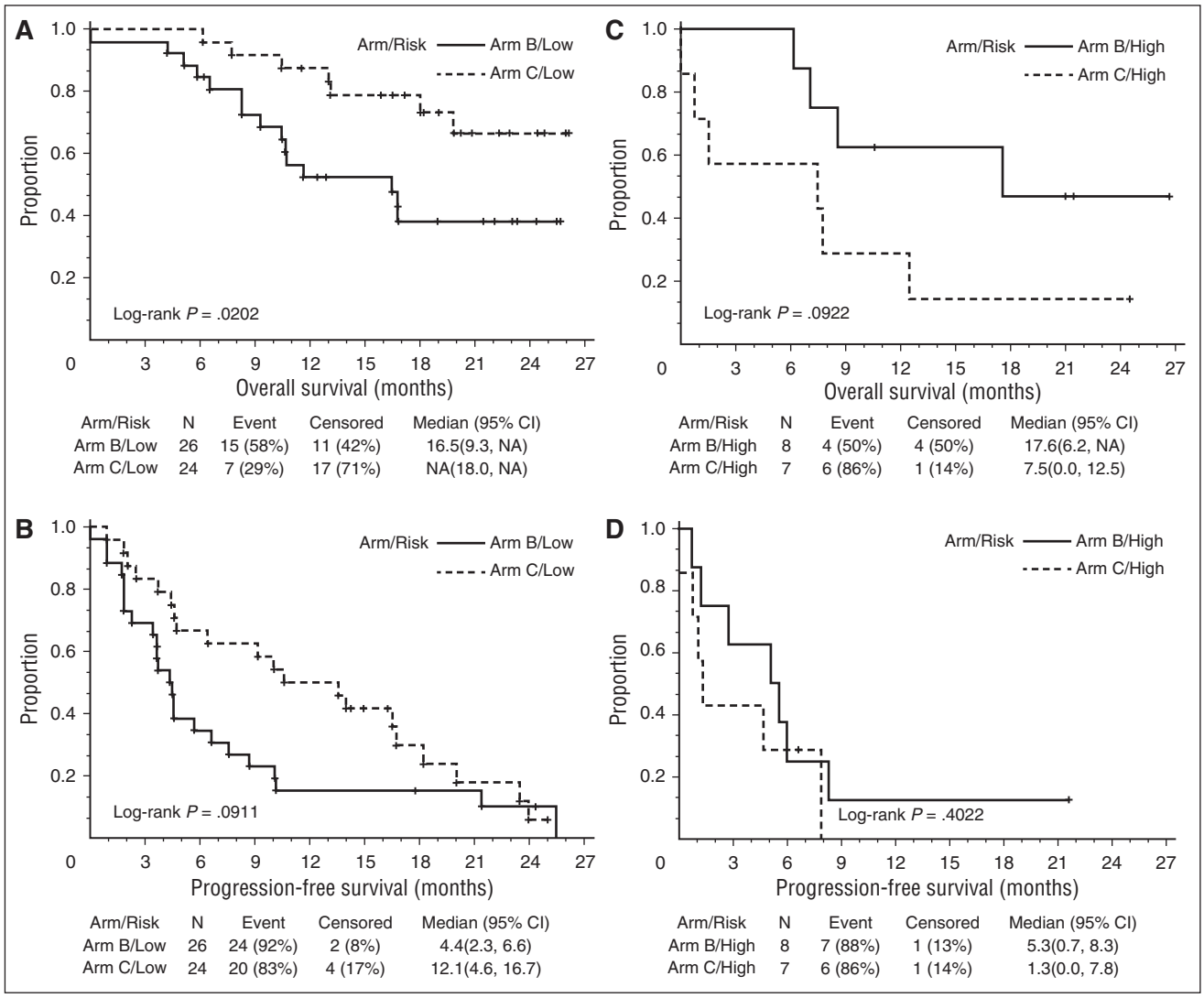
Results

Patient characteristics

Between December 2011 and March 2014, 80 patients were enrolled. Table 1 lists the patient characteristics according to the treatment group. Overall, patients had advanced multiple myeloma and had received a median of 4 prior therapies (range, 2-12). Of note, 29 patients (42%) in the phase 2 trial had received ≥5 prior therapies. All patients were refractory to lenalidomide, and ~75% were refractory to bortezomib. More than 90% of patients had prior alkylating agents. High-risk cytogenetics [defined as deletion 17p and/or t(4;14)] were noted in ~20% of patients, whereas trisomy or tetrasomy 1q was present in nearly 40% of patients. As noted in Table 1, baseline characteristics were not significantly different between arm B and arm C.

Phase 1

Ten patients were enrolled in the phase 1 portion. Four patients were enrolled on dose level 1 (cyclophosphamide 300 mg orally on days 1, 8, and 15). One patient was not evaluable for DLT because the patient took a lower than planned dose of cyclophophamide orally in error. None of the other 3 patients experienced a DLT. Three patients were enrolled on dose level 2, and a patient developed an upper extremity deep venous thrombosis (catheter associated while on aspirin prophylaxis), which was considered a DLT. An additional 3 patients were enrolled without a DLT. In dose level 2, Grade 3/4 neutropenia and thrombocytopenia occurred in 5 (83%), and 3 (50%) patients, respectively, which resulted in no further dose escalation and the determination of dose level 2 (cyclophosphamide 400 mg orally on days 1, 8, and 15 in combination with pomalidomide 4 mg orally on days 1-21 and dexamethasone 40 mg weekly in a 28-day cycle) as the recommended phase 2 dose. Supplemental Table 1 (available on the *Blood* Web site) lists all-grade, all-cause adverse events, whereas supplemental Table 2 lists the grade 3 and 4 adverse events reported during the phase 1 portion of the trial, with the most common grade 3 and 4 toxicities being myelosuppression.



Arm/Risk	N	Event	Censored	Median (95% CI)
Arm B/Low	26	15 (58%)	11 (42%)	16.5(9.3, NA)
Arm C/Low	24	7 (29%)	17 (71%)	NA(18.0, NA)

Arm/Risk	N	Event	Censored	Median (95% CI)
Arm B/High	8	4 (50%)	4 (50%)	17.6(6.2, NA)
Arm C/High	7	6 (86%)	1 (14%)	7.5(0.0, 12.5)

Arm/Risk	N	Event	Censored	Median (95% CI)
Arm B/Low	26	24 (92%)	2 (8%)	4.4(2.3, 6.6)
Arm C/Low	24	20 (83%)	4 (17%)	12.1(4.6, 16.7)

Arm/Risk	N	Event	Censored	Median (95% CI)
Arm B/High	8	7 (88%)	1 (13%)	5.3(0.7, 8.3)
Arm C/High	7	6 (86%)	1 (14%)	1.3(0.0, 7.8)

Figure 3. PFS and OS of patients with high-risk cytogenetics with arms B and C, respectively. High-risk cytogenetics is defined as the presence of deletion 17p and/or t(4;14). (A) OS of arm B vs arm C in patients without high-risk cytogenetics. (B) PFS of arm B vs arm C in patients without high-risk cytogenetics. (C) OS of arm B vs arm C in patients with high-risk cytogenetics. (D) PFS of arm B vs arm C in patients with high-risk cytogenetics.

Of the 10 patients who were enrolled in the phase 1 portion of the trial, 1 patient achieved a stringent complete response, 1 patient had a very good partial response, 3 patients a partial response (PR), and 2 had a MR. The ORR (PR and better) was 50% (Table 2).

Randomized phase 2

Seventy patients were enrolled in the phase 2 portion of the trial, with 36 randomized to arm B (pomalidomide and dexamethasone) and 34 to arm C (pomalidomide and dexamethasone with oral weekly cyclophosphamide). Two patients, 1 in each arm, were randomized but did not receive study therapy and are considered as treatment failures in this intent-to-treat analysis (Figure 1). The ORR (PR and better) for arm B was 38.9% (95% CI, 23-54.8), whereas the overall response rate for arm C was 64.7% (95% CI, 48.6-80.8; $P = .0355$; Table 2). In addition, 8 patients (22%) and 5 patients (15%) achieved an MR in arms B and C, respectively.

As of June 2015, 62 patients of the 70 randomized have experienced progressive disease: 33 in arm B and 29 in arm C. The median PFS was 4.4 months (95% CI, 2.3-5.7) for arm B and 9.5 months (95% CI, 4.6-14) for arm C (log rank, $P = .106$; Figure 2A). In terms of OS, 36 patients have died as of June 2015: 21 in arm B and 15 in arm C. The median OS was 16.8 months (95% CI, 9.3-not reached) for arm B and not reached (95% CI, 13.1-not reached) for arm C (log rank, $P = .168$; Figure 2B). These survival differences (albeit not statistically significant) were noted despite 17 patients crossing over from arm B and receiving added oral weekly cyclophosphamide (arm D).

In patients without high-risk cytogenetics [t(4;14) or deletion 17p], arm C was associated with improved PFS (median PFS, 12.1 [95% CI, 4.6-16.7] vs 4.4 months [95% CI, 2.3-6.6]; $P = .091$) and OS (not reached [95% CI, 18-not reached] vs 16.5 months [95% CI, 9.3-not reached]; $P = .02$) compared with arm B (Figure 3A-B). On the other hand, only 15 patients had high-risk cytogenetics, although there is a trend for improved OS with arm B compared with arm C (17.6 [95% CI, 6.2-not reached] vs 7.5 months [95% CI, 0-12.5]; $P = .09$).

Tables 3 and 4 lists the adverse events reported in arms B and C. Although myelosuppression was greater with arm C (as would be expected with the use of cyclophosphamide), these differences were not statistically significant. Specifically, grade 3 and 4 anemia, neutropenia, and thrombocytopenia were noted in 11%, 31%, and 6%

Table 3. Grade 3/4 adverse events at least possibly related to the study treatment in ≥5% of patients in the phase 2 portion

Adverse event	Arm B (N = 35) [N (%)]	Arm C (N = 33) [N (%)]	*P* value*	Arm D (N = 17) [N (%)]
Anemia	4 (11.4)	8 (24.2)	.211	1 (5.9)
Febrile neutropenia	4 (11.4)	4 (12.1)	1.000	—
Fatigue	3 (8.6)	4 (12.1)	.705	—
Flu-like symptoms	—	—	—	1 (5.9)
Lung infection	4 (11.4)	3 (9.1)	1.000	1 (5.9)
Sepsis	—	3 (9.1)	.109	—
Upper respiratory infection	—	2 (6.1)	.232	—
Lymphopenia	4 (11.4)	3 (9.1)	1.000	2 (11.8)
Neutropenia	11 (31.4)	17 (51.5)	.139	4 (23.5)
Thrombocytopenia	2 (5.7)	5 (15.2)	.252	—
Leukopenia	5 (14.3)	4 (12.1)	1.000	1 (5.9)
Hyperglycemia	—	2 (6.1)	.232	—
Hyponatremia	—	2 (6.1)	.232	—
Hypophosphatemia	—	—	—	1 (5.9)
Hypoxia	—	—	—	1 (5.9)
Confusion	—	2 (6.1)	.232	—
Pneumonitis	—	3 (9.1)	.109	—
Thromboembolic event	—	2 (6.1)	.232	—

*Comparing arm B to arm C using Fisher's exact test.

of arm B patients vs in 24%, 52%, and 15% of arm C patients, respectively (anemia, $P = .21$; neutropenia, $P = .14$; thrombocytopenia, $P = .25$). Importantly, the rate of febrile neutropenia was not meaningfully different (11% vs 12% for arms B and C, respectively).

Crossover arm (arm D)

Thirty-three patients had progressive disease in arm B. Seventeen patients elected to crossover to arm D, and oral weekly cyclophosphamide (400 mg orally on days 1, 8 and 15) was added to the previously tolerated dose of pomalidomide and dexamethasone. Of the 17 patients who crossed over to arm D, 1 achieved a PR, 4 patients achieved an MR, and 8 had stable disease as their best response (an additional 4 patients had continued progressive disease; Table 3). The ORR for arm D (PR and better) was 6%, and the clinical benefit rate was 29%. The median PFS from the start of arm D was 4.4 months (95% CI, 0.9-8). As of the data cutoff, all patients have had progressive disease on arm D (range, 0.9-8 months). Table 3 lists the adverse events in arm D.

Multivariable analysis of factors associated with response, PFS, and OS

Table 5 summarizes the results of the multivariable analysis of the factors associated with overall response (PRe or better), PFS, and OS. Treatment assignment (arm C vs arm B) had an adjusted odds ratio of 2.98 (95% CI, 0.99-8.99; $P = .052$), which neared statistical significance with respect to ORR. The adjusted hazard ratio was 0.54 (95% CI, 0.29-1.00) for PFS and demonstrated statistical significance. Of note, the number of prior therapies was a statistically significant predictor in the PFS model. Importantly, as noted above, an interaction between treatment arms and the presence of high-risk cytogenetics was noted.

There was a significant interaction between cytogenetically defined risk and treatment arm ($P = .017$) on OS after adjusting for age, number of prior therapies, and β2-microglobulin. Patients without deletion 17p or t(4;14) seem to derive greatest benefit from the triplet (arm C) and even have a statistically significant improvement in OS ($P = .020$; Figure 3A). On the other hand, patients with deletion 17p or t(4;14)

Table 4. All-cause, all-grade nonhematologic adverse events in >15% of patients regardless of attribution

Adverse event	Grade	Arm B (N = 35) [N (%)]	Arm C (N = 33) [N (%)]	*P* value*
Anemia	1/2	12 (34.3)	9 (27.3)	.6049
Constipation	1/2	8 (22.9)	6 (18.2)	.7669
Diarrhea	1/2	6 (17.1)	9 (27.3)	.3866
Nausea	1/2	6 (17.1)	9 (27.3)	.3866
Edema	1/2	4 (11.4)	6 (18.2)	.5066
Fatigue	1/2	9 (25.7)	3 (9.1)	.1114
Fever	1/2	6 (17.1)	4 (12.1)	.7350
Pain	1/2	2 (5.7)	10 (30.3)	.0105
Thrombocytopenia	1/2	8 (22.9)	11 (33.3)	.4209
Generalized muscle weakness	1/2	7 (20)	2 (6.1)	.1515
Peripheral sensory neuropathy	1/2	6 (17.1)	4 (12.1)	.7350
Tremor	1/2	7 (20)	5 (15.2)	.7531
Dyspnea	1/2	5 (14.3)	5 (15.2)	1.0000
Skin / subcutaneous tissue disorders	1/2	2 (5.7)	5 (15.2)	.2522
Anemia	3/4/5	4 (11.4)	9 (27.3)	.1277
Lung infection	3/4/5	6 (17.1)	3 (9.1)	.4783
Neutropenia	3/4/5	11 (31.4)	17 (51.5)	.1389
Thrombocytopenia	3/4/5	2 (5.7)	5 (15.2)	.2522
Hyperglycemia	3/4/5	1 (2.9)	6 (18.2)	.0513

*Based on Fisher's exact test.

Table 5. Factors associated with overall response, PFS, and OS

	Overall response		PFS		OS	
	Unadjusted [OR (95% CI)]	Adjusted [OR (95% CI)]	Unadjusted [HR (95% CI)]	Adjusted [HR (95% CI)]	Unadjusted [HR (95% CI)]	Adjusted [HR (95% CI)]
Age (in 10-year increments)	1.16 (0.64-2.11)	1.22 (0.62-2.40)	0.80 (0.59-1.10)	0.72 (0.50-1.04)	0.83 (0.56-1.24)	0.88 (0.51-1.49)
Number of prior therapies (≥5 vs <5)	1.23 (0.47-3.21)	1.77 (0.56-5.60)	0.79 (0.47-1.33)	0.54 (0.29-0.99)*	0.94 (0.48-1.85)	0.66 (0.32-1.38)
B2-microglobulin (mg/L)	1.03 (0.84-1.25)	0.99 (0.80-1.23)	1.09 (0.99-1.20)	1.15 (1.03-1.28)*	1.30 (1.15-1.47)*	1.38 (1.21-1.58)*
High-risk cytogenetics	0.36 (0.11-1.22)	0.33 (0.09-1.22)	1.73 (0.92-3.27)	1.77 (0.88-3.55)	2.12 (1.00-4.48)	2.21 (0.98-4.98)
Study arm* (arm C vs B)	2.88 (1.09-7.61)*	2.98 (0.99-8.99)	0.66 (0.40-1.10)	0.54 (0.29-1.00)*	0.63 (0.32-1.22)	0.54 (0.25-1.17)

HR, hazard ratio; OR, odds ratio.
Overall response is defined as partial response or better; study arm $P = .052$ in the multivariable overall response model. *$P < .05$.

have a trend for a worse outcome with the triplet (arm C; Figure 3C). Treatment effect (arm B vs arm C) on PFS was not significantly modified by cytogenetically defined risk ($P = .118$). The number of prior therapies was not associated with a differential benefit (OS: $P = .790$; PFS: $P = .593$) from arm B or C in this trial.

Discussion

This randomized phase 1/2 study identified the recommended phase 2 dose for the combination of pomalidomide, cyclophosphamide, and dexamethasone and, importantly, has shown that pomalidomide in combination with dexamethasone and oral weekly cyclophosphamide results in a superior response rate than pomalidomide and dexamethasone in patients with lenalidomide refractory multiple myeloma. In addition, the combination of oral weekly cyclophosphamide with pomalidomide and dexamethasone was well tolerated, with only a modest increase in hematologic toxicity detected, although these did not reach the level of statistical significance. Neutropenia was commonly managed with the use of growth factor support. Gastrointestinal toxicity including nausea, vomiting, and diarrhea was also similar in the 2 treatment arms. These results would support the conduct of a larger phase 3 study, although this is not likely to be performed.

The eligibility criteria were generally consistent with the clinical use of pomalidomide and dexamethasone in the United States and included patients with grade 3 thrombocytopenia and neutropenia, who are often excluded from many clinical trials. Importantly, the outcome of patients treated with PomDex is not different from other studies of this combination.[6-8]

This combination of cyclophosphamide and pomalidomide/dexamethasone compares favorably with and confirms the published reports of a similar combination by Larocca et al using continuous pomalidomide dosing and every other day oral cyclophosphamide, where the ORR was 51% and the median was 10.4 months in patients who had less advanced myeloma and had received 1 to 3 prior lines of therapy.[17] In addition, our combination features pomalidomide using the now accepted dose and schedule of 21 dosing days per 28-day cycle.

Patients who experienced progressive disease on pomalidomide and dexamethasone were allowed to crossover at the discretion of the patient and treating physician to arm D, which resulted in the addition of oral weekly cyclophosphamide to the tolerated dose of pomalidomide and dexamethasone. It is noteworthy that the response rate to this crossover arm was overall low (6%), and the OS curves also suggest this is not an effective salvage strategy. These data would argue that, in patients with advanced myeloma refractory to lenalidomide, it may be preferable to initiate therapy with the triplet combination of pomalidomide, dexamethasone, and cyclophosphamide rather than a sequential therapy, although this was not rigorously evaluated in this trial (arm D was not mandated). Despite the approval in the United States of monoclonal antibodies (elotuzumab, daratumumab) for myeloma, such therapy may not yet be available in other countries, highlighting the importance of more effective salvage strategies (such as PomCyDex) in patients who have received >4 prior therapies.

Interestingly, patients without high-risk cytogenetics appear to derive a greater benefit from the combination of pomalidomide, cyclophosphamide, and dexamethasone, whereas patients with high-risk cytogenetics had a trend consistent with a worse OS with this combination, as opposed to pomalidomide and dexamethasone. This observation is, however, tempered by the small sample size of high-risk patients (15) and the fact that this was an unplanned subgroup analysis. Future studies are needed to validate this observation. It is, however, possible that treatment of patients with high-risk cytogenetics with alkylating agents could further increase the genomic instability and contribute to worse outcomes with the cyclophosphamide-based combination. This finding does not preclude the possibility that other triplet regimens (without alkylating agents) may be superior to pomalidomide and dexamethasone in high-risk patients.

In an attempt to increase the overall response rate of a pomalidomide-based regimen in patients with advanced myeloma, others have investigated different pomalidomide combination regimens.[6,20-23] Acknowledging the limitation of comparisons across different phase 2 studies, this regimen results in comparable efficacy. Moreover, the present study is the only randomized trial that establishes the superiority of this regimen over the pomalidomide and dexamethasone backbone. In addition, this all-oral regimen is more convenient for patients and likely associated with a lower cost of care than combinations of pomalidomide and proteasome inhibitors.

One limitation of this study is the phase 2 nature of the design, which may have limited the power to detect statistically significance differences in efficacy outcomes and toxicity measures. Nevertheless, we were able to demonstrate a statistically significant improvement in ORR and PFS using the predefined 10% significance level. Differences in the rates of meaningful adverse events could not be demonstrated; however, one can anticipate that cyclophosphamide would result in additional hematologic toxicities.

In conclusion, PomCyDex is well tolerated and results in increased ORR and PFS compared with PomDex in patients with lenalidomide refractory myeloma.

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Authorship

Contribution: R.C.B., K.H.S., M.A., A.C., T.G.M., and S.J. conceived and designed the study; R.C.B., H.J.C., X.Z., A.M., J.L.W., L.A.N., K.L., and T.G.M. collected and assembled the data; R.C.B., D.M.S., X.Z., J.L.W., K.H.S., M.A., A.C., H.-Y.L., and T.G.M. analyzed and interpreted the data; and all authors wrote and provided final approval for the manuscript.

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