CLINICAL TRIALS AND OBSERVATIONS

Pomalidomide, cyclophosphamide, and prednisone for relapsed/refractory multiple myeloma: a multicenter phase 1/2 open-label study

Alessandra Larocca,[1] Vittorio Montefusco,[2] Sara Bringhen,[1] Davide Rossi,[3] Claudia Crippa,[4] Roberto Mina,[1] Monica Galli,[5] Magda Marcatti,[6] Giacinto La Verde,[7] Nicola Giuliani,[8] Valeria Magarotto,[1] Tommasina Guglielmelli,[9] Delia Rota-Scalabrini,[10] Paola Omedé,[1] Alberto Santagostino,[11] Ileana Baldi,[12] Angelo Michele Carella,[13] Mario Boccadoro,[1] Paolo Corradini,[2] and Antonio Palumbo[1]

[1]Myeloma Unit, Division of Hematology, University of Torino, Azienda Ospedaliera Città della Salute e della Scienza di Torino, Torino, Italy; [2]Division of Hematology, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Istituto Nazionale dei Tumori Milano, University of Milano, Milano, Italy; [3]Division of Hematology, Department of Translational Medicine, Amedeo Avogadro University of Eastern Piedmont, Novara, Italy; [4]Struttura Complessa Ematologia e Dipartimento Oncologia Medica, Spedali Civili, Brescia, Italy; [5]Divisione di Ematologia, Ospedale Papa Giovanni XXIII, Bergamo, Italy; [6]Hematology and Bone Marrow Transplant Unit, San Raffaele Scientific Institute, Milano, Italy; [7]Unità Operativa di Supporto Diagnosi e Cura delle Discrasie Plasmacellulari e delle Amiloidosi, Azienda Ospedaliera Sant'Andrea, "Sapienza" Università di Roma, Rome, Italy; [8]Hematology and Blood and Marrow Transplantation Center, University of Parma, Parma, Italy; [9]Unit of Hematology, "S. Luigi Gonzaga" Hospital, Orbassano, Torino, Italy; [10]Fondazione del Piemonte per l'Oncologia Istituto per la Ricerca e Cura del Cancro, Divisione Universitaria di Oncologia, Candiolo, Italy; [11]Struttura Dipartimentale di Onco-Ematologia, Ospedale S. Andrea Vercelli, Vercelli, Italy; [12]Department of Cardiac, Thoracic and Vascular Sciences, University of Padova, Padova, Italy; and [13]Divisione di Ematologia, Istituto di Ricovero e Cura a Carattere Scientifico Azienda San Martino-Ist, Genova, Italy

Key Points

- Pomalidomide-cyclophosphamide-prednisone is an active combination in multiple myeloma patients who are relapsed/refractory to lenalidomide.

We performed a phase 1/2 trial to determine the maximum tolerated dose (MTD) of pomalidomide and to explore its efficacy when combined with cyclophosphamide-prednisone in relapsed/refractory myeloma patients. Pomalidomide was given at 1 to 2.5 mg/d, cyclophosphamide at 50 mg every other day, prednisone at 50 mg every other day, for 6 28-day cycles, followed by pomalidomide-prednisone maintenance therapy. Thromboprophylaxis was recommended. Sixty-nine patients were enrolled, 55 received the MTD (2.5 mg/d) and were evaluated. Best responses included complete response in 3 patients (5%), very good partial response in 10 (18%), partial response in 15 (27%), minimal response in 11 (20%), stable disease in 15 (27%), and progressive disease in 1 (3%), for an overall response rate of 51%. The median time-to-response was 1.83 months. After a median follow-up of 14.8 months, median progression-free survival was 10.4 months and 1-year overall survival was 69%. At the MTD, grade 3 to 4 toxicities included anemia (9%), thrombocytopenia (11%), neutropenia (42%), neurologic events (7%), dermatologic events (7%), and thromboembolism (2%). Grade 3 to 5 infections occurred in 5 patients (9%). Five patients (9%) discontinued treatment for toxicity. New grade 3 to 4 adverse events were low during maintenance. Pomalidomide-cyclophosphamide-prednisone is safe and effective in relapsed/refractory myeloma patients. This trial was registered at www.clinicaltrials.gov as #NCT01166113. (*Blood*. 2013;122(16):2799-2806)

Introduction

Multiple myeloma (MM) is characterized by a clonal proliferation of malignant plasma cells in the bone marrow and osteolytic lesions.[1] The introduction of novel agents, such as thalidomide, lenalidomide, and bortezomib, has considerably improved response rates and survival, both at diagnosis and at relapse.[2]

However, MM remains incurable, and the majority of patients relapse and become refractory to available therapies. The outcome of these patients is very poor, with a median event-free survival of 5 months and overall survival (OS) of 9 months.[3] Newer agents able to overcome drug resistance and achieve a sustained disease control are needed.

Several immunomodulatory derivatives were generated by introducing chemical modifications to the structural backbone of thalidomide. Pomalidomide, a closely related analog of thalidomide, showed potent activity against tumor necrosis factor α secretion and entered clinical studies.[4,5] Pomalidomide at 2 to 4 mg, combined with low-dose dexamethasone, has shown significant activity in pretreated patients refractory to lenalidomide and/or bortezomib.[6-10] Partial response (PR) rates were 32% to 35%, and median progression-free survival (PFS) was 4.6 to 6.3 months.[8-10] Neutropenia and thrombocytopenia were the most frequent adverse events.[11]

The addition of alkylating agents to bortezomib and lenalidomide increased the response rates and, in some cases, prolonged disease-free interval.[12] So far, no data on the role of cyclophosphamide added to pomalidomide are available.

These observations provided the rationale for this phase 1/2 trial. The primary aim of the study was to identify the most appropriate dose of pomalidomide in combination with cyclophosphamide-prednisone

Submitted March 8, 2013; accepted August 2, 2013. Prepublished online as *Blood* First Edition paper, August 16, 2013; DOI 10.1182/blood-2013-03-488676.

P.C. and A.P. contributed equally to this study.

The online version of this article contains a data supplement.

There is an Inside *Blood* commentary on this article in this issue.

The publication costs of this article were defrayed in part by page charge payment. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734.

(PCP) and to determine its safety, tolerability, and efficacy in MM patients relapsed and/or refractory to lenalidomide.

Methods

Study population

Patients with MM who were 18 years of age or older, were relapsed or relapsed/refractory to lenalidomide, and who had received 1 to 3 prior lines of therapy were eligible. Relapse was defined as the reoccurrence of disease requiring the initiation of a salvage therapy, and refractory disease was defined as relapse while receiving salvage therapy or progression within 60 days of the most recent therapy. Patients were required to have measurable disease, a Karnofsky performance status 60% or higher, a platelet count 50×10^9/L or higher, a neutrophil count of 1.00×10^9/L or higher, a corrected serum calcium 3.5 mmol/L (14 mg/dL) or lower, serum hepatic aminotransferase levels 2.5-fold or less of the upper limit of normal, total bilirubin 1.5-fold or less of the upper limit of normal, and serum creatinine 2 mg/dL or less, and to agree to use contraception. Patients with clinically relevant active comorbid medical or psychiatric conditions or history of malignancy within the last 5 years were excluded. The institutional review board at each participating center approved the study in accordance with the Declaration of Helsinki. All patients provided written informed consent.

Study design

This trial was a phase 1/2, dose-escalating, open-label study. The primary endpoint of the dose-finding phase 1 was to identify the maximum tolerated dose (MTD) of pomalidomide, defined as the dose that achieved a dose-limiting toxicity (DLT) in 25% of patients. DLTs were defined as grade 4 neutropenia lasting more than 3 days, other grade 4 hematologic toxicity, any grade 3 or higher nonhematologic toxicity, febrile neutropenia, and/or infection requiring antibiotics occurring during the first cycle of therapy.

In phase 2, patients received the MTD of pomalidomide established in phase 1. The primary endpoint of phase 2 was the rates of complete response (CR) and very good PR (VGPR). Secondary endpoints were PFS and OS.

All adverse events were assessed during each cycle and graded according to the National Cancer Institute Common Toxicity Criteria (version 3.0).[13]

Responses were recorded during every cycle, according to the International Myeloma Working Group criteria.[14] Responses among patients refractory to previous novel agents and at high risk were analyzed. High risk was defined as the presence of t(4;14), t(14;16), or del 17p13 at enrolment, detected by fluorescence in situ hybridization (FISH).

Procedures

Oral pomalidomide was administered at doses ranging from 1 to 2.5 mg/d in phase 1 and the MTD in phase 2, in combination with cyclophosphamide at 50 mg every other day and prednisone at 50 mg every other day on days 1 to 28, for 6 cycles of 28 days each (see supplemental Appendix 1 available on the *Blood* Web site). Maintenance therapy consisted of pomalidomide 1 mg/d and prednisone 25 mg every other day continuously until any sign of relapse or progression.

Pomalidomide dose reduction (from 2.5 to 2 to 1.5 to 1 to 0.5 mg/d) was allowed if toxicities occurred. Grade 4 neutropenia, or febrile neutropenia with any other hematologic toxicities, or any other grade 4 hematologic or any grade 3 nonhematologic toxicities required immediate interruption of treatment and subsequent dose reduction at the start of the following cycle. A new cycle could be started if the neutrophil count was 1.00×10^9/L or higher, platelet count was 50×10^9/L or higher, hemoglobin was 8 g/dL or higher, and nonhematologic adverse events were grade 2 or lower. If the start of a new cycle were delayed by 2 or more weeks, dose reductions were required. Aspirin 100 mg/day or low-molecular-weight heparin was recommended as prophylaxis, according to patient risk.[15]

Table 1. Baseline characteristics

Variable	Phase 1 (N = 24)	Phase 2 (N = 55)	All patients (N = 69)
Age			
Median-years (range)	71 (50-82)	69 (41-84)	69 (41-84)
Sex			
Female	9 (37.5%)	27 (49%)	33 (48%)
Male	15 (62.5%)	28 (51%)	36 (52%)
International Staging System stage			
I	13 (54%)	28 (51%)	34 (49%)
II	10 (42%)	21 (38%)	27 (39%)
III	1 (4%)	6 (11%)	8 (12%)
Myeloma protein class			
IgG	16 (67%)	34 (62%)	42 (61%)
IgA	4 (17%)	13 (24%)	16 (23%)
Bence-Jones protein	3 (12%)	8 (14%)	10 (15%)
Nonsecretory	1 (4%)	0	1 (1%)
Karnofsky performance status, %			
60-70	3 (12%)	7 (13%)	10 (14%)
80	5 (21%)	9 (16%)	13 (19%)
90-100	16 (67%)	39 (71%)	46 (67%)
Serum β2-microglobulin level			
Median (mg/L)	2.9 (0.03-9)	3 (0.03-9)	3 (1.6-12)
Months from diagnosis to on study			
Median (range)	59 (13-203)	53 (11-203)	53 (11-203)
Prior lines of therapy			
Median (range)	3 (1-3)	3 (1-3)	3 (1-3)
Prior therapies			
Lenalidomide	24 (100%)	55 (100%)	69 (100%)
Bortezomib	20 (83%)	46 (84%)	58 (84%)
Thalidomide	4 (17%)	11 (20%)	14 (20%)
Autologous transplant	7 (29%)	18 (33%)	23 (33%)
Allogeneic transplant	3 (12%)	9 (16%)	10 (15%)
Previous lenalidomide			
Relapsed	9 (37.5%)	18 (33%)	23 (33%)
Refractory	15 (62.5%)	37 (67%)	46 (67%)
Previous bortezomib			
Relapsed	4 (17%)	14 (25%)	17 (25%)
Refractory	10 (42%)	20 (36%)	27 (39%)
Not available	6 (25%)	12 (22%)	14 (20%)
FISH*			
High risk	4 (17%)	13 (24%)	18 (26%)
Standard risk	9 (37%)	31 (56%)	35 (51%)
Not available	11 (46%)	11 (20%)	16 (23%)
Chromosome abnormalities			
Del 13	6 (25%)	18 (33%)	24 (35%)
t(4;14)	2 (8%)	6 (11%)	8 (12%)
t(11;14)	2 (8%)	10 (18%)	12 (17%)
t(14;16)	0	2 (4%)	3 (4%)
Del17	2 (8%)	5 (9%)	8 (12%)

*High-risk FISH was defined as the presence of at least one of the following abnormalities: t(4;14), t(14;16), or del17.

Statistical analysis

In phase 1, the continual reassessment method was used as the dose allocation rule in the trial.[16,17] It is based on a mathematical modeling of dose–DLT relationship, iteratively updated using Bayes theorem. Before trial onset, prior opinions about DLT probability at each dose level were elicited from expert clinicians and were fixed at 0.15, 0.20, 0.30, and 0.45, respectively. A design with grouped inclusions of 4 patients per dose level was chosen; the starting dose was 1.5 mg. The dose level associated with an updated DLT probability close to 25% was administered to the next cohort. All this process was re-run until the fixed sample size (N = 24) was reached,[18] using the BPCT software.[19]

Table 2. Phase 1: DLT for each cohort of enrolled patients

Cohort	Dose (mg/day)	DLTs, n	Type of DLTs	Updated estimated probability of DLT per dose level			
				1 mg	1.5 mg	2 mg	2.5 mg
1	1.5	1	Grade 4 thrombocytopenia	**0.237**	0.298	0.409	0.553
2	1.0	0	—	0.104	0.145	**0.232**	0.376
3	2.0	0	—	0.051	0.076	0.136	**0.255**
4	2.5	1	Grade 3 neuropathy	0.052	0.078	0.139	**0.259**
5	2.5	1	Grade 3 hepatic	0.052	0.078	0.139	**0.259**
6	2.5	1	Grade 4 thrombocytopenia	0.052	0.077	0.138	**0.258**

The dose level closest to the toxicity target (0.25) is in bold.

In phase 2, we used a Simon optimal 2-stage design for the sample size calculation. A 5% response rate was considered not promising, a 20% rate was promising. The probability of both type I and type II errors was set at 0.05. Accordingly, 24 patients were planned in the first stage, and 31 (total = 55) were planned in the second stage. Our design required VGPR or better in at least 2 patients in the first stage to proceed to the second stage, and at least 5 patients for the treatment to be worth further consideration. Patients enrolled at the MTD in phase 1 were also included in phase 2.

All patients meeting the eligibility criteria who had received at least a single dose of pomalidomide were evaluated for response, toxicity, and survival. For responding patients, we measured the median time to response from the start of treatment to the date of the first response, as well as the duration of response from response to PD or death, censored at the date of last assessment for patients not progressing. We evaluated PFS and OS from the start of treatment until PD or death and until death, respectively.

Survival curves were estimated with the Kaplan-Meier method and compared with log-rank test.[20] The individual effects on PFS of age (>75 vs ≤75 years), FISH-defined risk (high vs standard), and achievement of at least PR (treated as a time-dependent variable) were evaluated using a Cox's model. Results are presented as hazard ratios (HRs) and 95% confidence intervals (95% CIs). The analyses were performed using SAS software, version 8.2 (SAS Institute). Data cutoff was October 16, 2012.

Role of the funding source

The pharmaceutical sponsor was not involved in the study design, collection, analysis, or interpretation of the data or the writing of the report. Celgene supplied pomalidomide free of charge. The corresponding author had full access to all the data and had final responsibility for the decision to submit this manuscript for publication.

Results

Patient characteristics

Between August 2010 and May 2012, 69 patients were enrolled at 12 Italian centers. In the phase 1 study, 24 patients were accrued. In the phase 2 study, 12 patients who received the MTD during phase 1 and an additional 45 patients were enrolled. Two patients who rapidly developed PD and died were excluded from the analysis because they failed to start therapy.

Patient characteristics are listed in Table 1. The median age was 69 years (range, 41-84 years). The median number of previous treatments was 3 (range, 1-3 treatments). Nine percent, 29%, and 62% of patients had received 1, 2, and 3 prior regimens, respectively. All patients (100%) had previously received lenalidomide, 84% bortezomib, 20% thalidomide, 33% autologous transplantation, and 14% allogeneic stem-cell transplantation. Twenty-three patients were relapsed and 46 were refractory to lenalidomide; 22 were refractory to both lenalidomide and bortezomib. The median time from diagnosis to study entry was 53 months (range, 11-203 months). Eighteen patients (26%) were classified as high-risk by FISH.

Phase 1

Table 2 lists the assigned pomalidomide dose levels and the observed DLTs. The dose level 2.5 mg/d was defined as the MTD, with an estimated probability of DLT of 0.258 (95% credibility interval, 0.101-0.468). DLTs were recorded in 4 patients: 1 grade 4 thrombocytopenia with 1.5 mg/d pomalidomide, 1 grade 3 peripheral neuropathy, 1 grade 3 hepatic toxicity, and 1 grade 4 thrombocytopenia, with 2.5 mg/d pomalidomide. The dose of pomalidomide maintenance was increased to the identified MTD.

Responses and time to event analysis during phase 1 are reported in Table 3 and Table 4.

Phase 2

Fifty-five patients treated at the MTD (2.5 mg/d) were evaluated. Patients received a median of 6 cycles (range, 1-6 cycles). Five patients did not complete the assigned 6 cycles for toxicity: grade 3 cutaneous rash and grade 2 pancreatitis (1 patient), grade 2 bradycardia and dyspnea (1 patient), grade 5 sepsis (1 patient), grade 4

Table 3. Best responses to combination treatment

	1 mg (N = 4)	1.5 mg (N = 4)	2 mg (N = 4)	2.5 mg (N = 55)	Relapsed after lenalidomide 2.5 mg (N = 18)	Refractory to lenalidomide 2.5 mg (N = 37)	Refractory to both lenalidomide and bortezomib 2.5 mg (N = 16)
Response							
Complete or partial	1 (25%)	2 (50%)	2 (50%)	28 (51%)	11 (61%)	17 (46%)	8 (50%)
Complete response	—	—	—	3	1	2	2
Very good partial response	—	—	—	10	6	4	1
Partial response	1	2	2	15	4	11	5
Minimal response	1	—	1	11	2	9	5
Stable disease	1	1	1	15	5	10	3
Progressive disease	1	1	—	1	0	1	—

Table 4. Time to event analysis

	Median follow-up (months, range)	Median PFS (months; 95% CI)	Median OS (months; 95% CI)	12-mo OS (95% CI)
All patients (N = 67)	15.0 (3.7-26.4)	8.6 (7.5-13.9)	Not reached	65% (51-76%)
Dose level 1, 1.5, 2 mg (N = 12)	24.1 (3.7-26.4)	4.6 (3.3-8.0)	9 (5.2-not reached)	44% (15-70%)
Dose level 2.5 mg (N = 55)	14.8 (6.1-21.4)	10.4 (7.8-15.8)	Not reached	69% (54-81%)
Relapsed after lenalidomide (N = 18)	12.7 (7.2-21.4)	15.7 (12.8-20.7)	Not reached	88% (60-97%)
Refractory to lenalidomide (N = 37)	15.3 (6.1-21.4)	8.6 (7.5-13.9)	Not reached	60% (41-75%)
Refractory to lenalidomide and bortezomib (N = 16)	15.8 (6.6-21.4)	8.6 (4.8-not reached)	Not reached	67% (37-85%)

deep vein thrombosis (1 patient), and grade 3 liver failure (1 patient). Eight patients did not complete salvage therapy for PD, 1 patient for a concomitant mesothelioma, and 1 patient skipped the last cycle and started maintenance for medical reasons. Thirty-four patients started maintenance treatment; 13 of them discontinued therapy for PD and 2 for toxicity, including pulmonary embolism and limbic encephalitis (1 patient each) (Figure 1).

At the end of the first stage of the phase 2 portion, 2 CRs and 3 VGPRs were observed, allowing us to proceed with the second stage.

At least PR was achieved in 28/55 patients (51%), at least VGPR was achieved in 13/55 patients (24%), and immunofixation-negative CR was achieved in 3/55 patients (5%). A high proportion of patients achieved a clinical benefit, with at least a minimal response (MR) in 39/55 patients (71%) and at least stable disease in 54/55 patients (98%) (Table 3). The median time to at least PR was 1.83 months (range, 0.65-6.4 months); at least PR was achieved in 19 patients after 2 cycles, in 20 patients after 4 cycles, and in 23 patients after 6 cycles. The median duration of response for the 28 responding patients has not been achieved yet.

The median follow-up from study entry was 14.8 months (range, 6-21 months). At the time of the analysis, 40 patients were alive, 26 had progressed, and 15 had died from PD (10 patients), pneumonia and respiratory failure (1 patient), sudden death (1 patient), sepsis (1 patient), liver failure (1 patient), and mesothelioma (1 patient). The 1-year PFS was 48% (95% CI, 33%-62%), with a median of 10.4 months (95% CI, 7.9-15.8 months; Figure 2A). The 1-year OS was 69% (95% CI, 54%-81%), and the median value was not reached (Figure 2B).

The 1-year PFS was 72% for patients relapsed after lenalidomide and 37% for those refractory to lenalidomide ($P = .22$; Figure 3A). The 1-year PFS was 68% in patients who achieved at least PR and 26% in those who achieved less than PR ($P = .02$; Figure 3B). The 1-year PFS was 47% in standard-risk and 35% in high-risk patients ($P = .21$; Figure 3C).

In a multivariable analysis, older age negatively affected PFS (HR, 2.65; $P = .035$), and the achievement of PR confirmed its positive effect on PFS (HR, 0.38; $P = .059$) (Figure 3B). No differences according to FISH-defined risk were noted (HR, 1.36; $P = .48$).

At the MTD, the most frequent grade 3 to 4 adverse events were neutropenia (42%), thrombocytopenia (11%), anemia (9%), neurologic (7%), dermatologic reactions (7%), and infections (5%). Two grade 5 infections were reported (Table 5). Grade 3 peripheral neuropathy was detected in 2 patients. Dermatologic events were mild to moderate and were manageable with pomalidomide dose reduction and corticosteroids. Grade 4 deep vein thrombosis was reported in 1 patient, despite low-molecular-weight heparin prophylaxis. Pomalidomide dose was reduced in 17 patients for grade 4 hematologic toxicity (4 patients), grade 1 to 2 nonhematologic toxicity (2 patients), grade 3 to 4 nonhematologic toxicity (7 patients), and unknown causes (4 patients). During maintenance treatment, the frequency of new grade 3 to 4 adverse events was low and included grade 4 neutropenia (2 patients), pulmonary embolism (1 patient, while receiving aspirin), and grade 3 neurologic toxicity (vertigo, peripheral neuropathy, and limbic encephalitis, 1 patient each).

Discussion

In this study, we evaluated dosing, the safety profile, and the efficacy of the combination of PCP in patients who were relapsed/refractory to multiple lines of treatment, including lenalidomide. At the MTD (2.5 mg/d pomalidomide), the at least PR rate was 51%, and the median PFS was 10.4 months. Adverse events were mainly hematologic: the rate of grade 4 neutropenia was 16%, and the rate of grade 4 thrombocytopenia was 5%. A Bayesian adaptive design for dose finding was implemented. This approach is expected to replace classic dose-finding schemes because it enables more patients be treated at near-optimal doses while controlling excessive toxicities.

Patients who experience multiple relapses and become refractory to current salvage treatments have virtually no treatment options. Responses after relapse are generally short-lived, and outcomes can be affected by comorbidities, adverse chromosomal abnormalities, and the toxicity of the previous treatments.[21-23] A recent survey on 286 relapsed myeloma patients who were refractory to bortezomib and relapsed/refractory to an immunomodulatory drug reported at least MR in 44% of patients, including 32% PR, and median event-free survival and OS of 5 and 9 months, respectively.[3]

Initial reports demonstrated encouraging activity with pomalidomide alone or with low-dose dexamethasone in relapsed/refractory myeloma.[6-12,24,25] In a phase 3 study comparing pomalidomide (4 mg/d for 21 days in a 28-day cycle) plus low-dose dexamethasone (160 mg monthly) with high-dose dexamethasone (480 mg monthly) in multirelapsed/refractory myeloma, median PFS was 3.9 vs 2 months ($P < .001$), and median OS was not reached vs 8.5 months ($P < .001$), in the pomalidomide and the high-dose dexamethasone groups, respectively.[26]

In a previous study, pomalidomide-dexamethasone induced at least PR rate of 32%, at least MR rate of 47%, and median PFS of 4.8 months in patients refractory to lenalidomide.[8] In another phase 2 trial, the at least PR rate was 40% in patients refractory to lenalidomide and 60% in those refractory to bortezomib.[6] In our trial, the PCP regimen induced an at least PR rate of 51% and a clinical benefit, with an at least MR rate of 71%. These results are

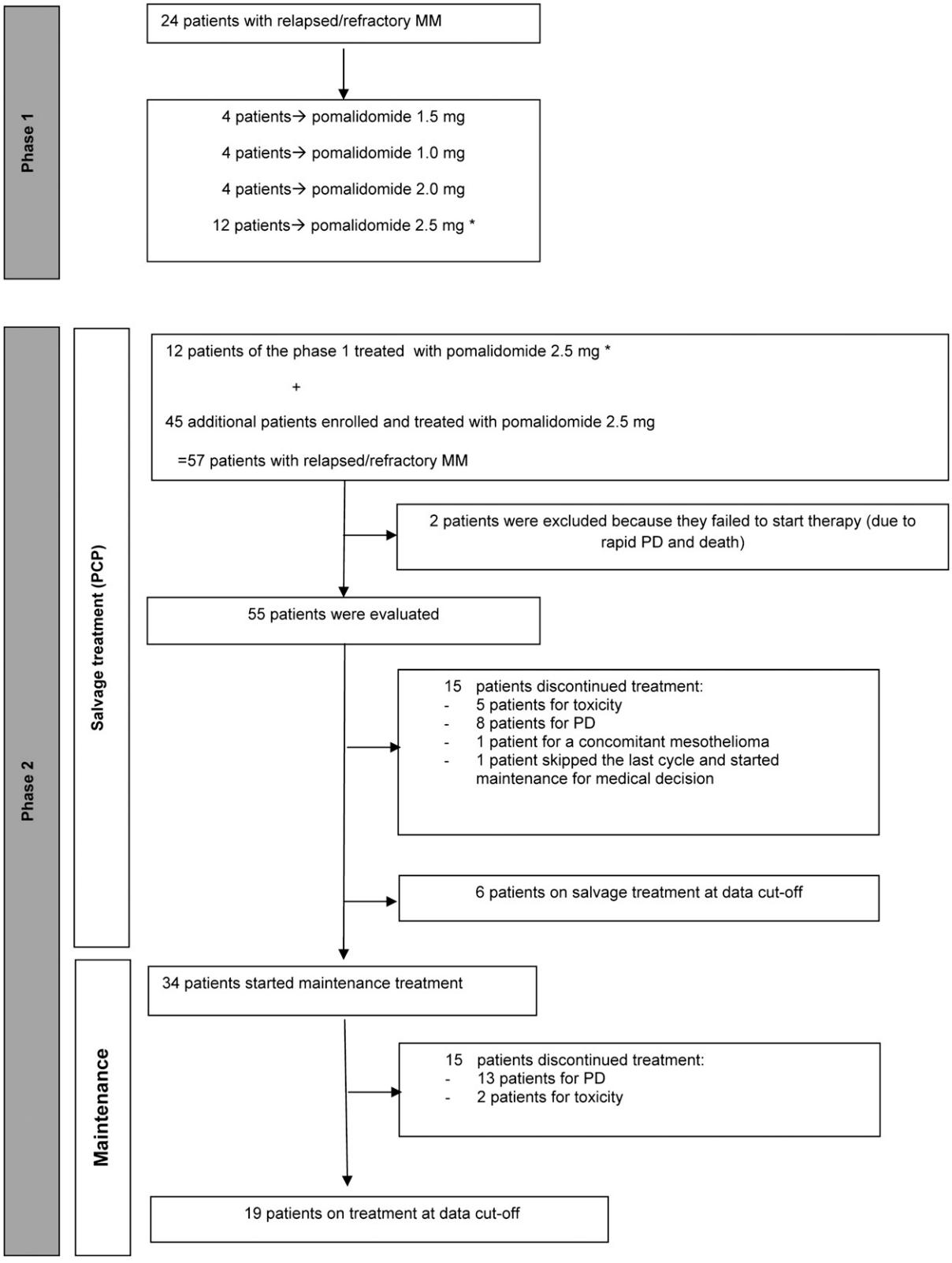

Figure 1. Flow diagram.

clinically meaningful in patients who had received most of the available therapies. Furthermore, patients were mostly refractory to lenalidomide (67%) or bortezomib (39%), and a subgroup was refractory to both these agents (29%). At least PR was reported in 46% of patients refractory to lenalidomide and in 50% of those refractory to bortezomib-lenalidomide. The addition of an alkylating

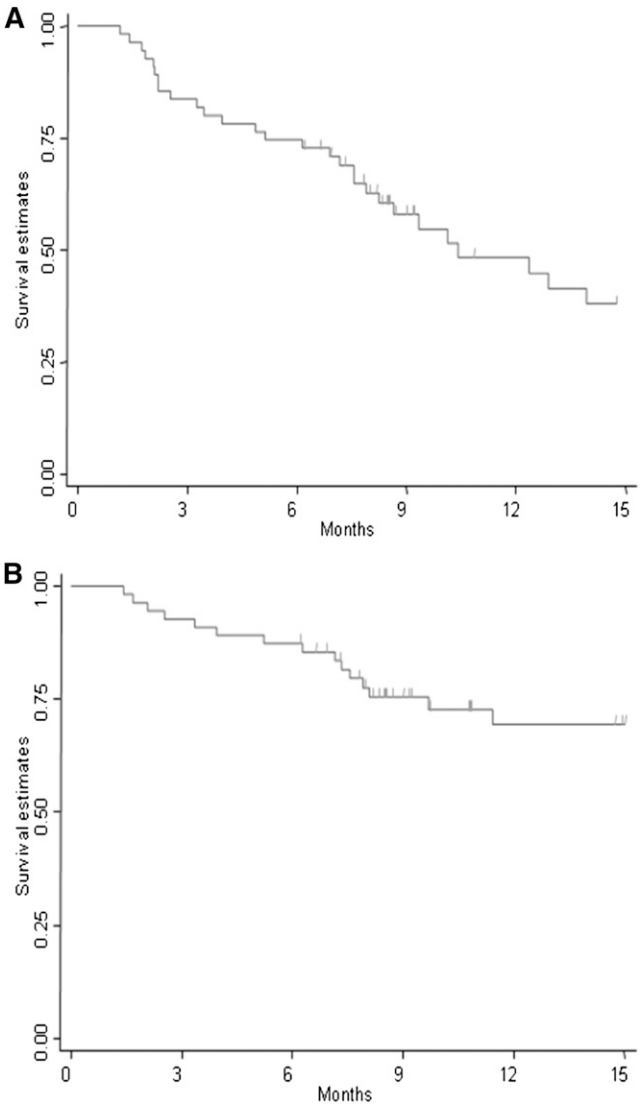

Figure 2. Time-to-event analysis. (A) PFS in phase 2 patients. (B) OS in phase 2 patients.

agent to novel drugs has demonstrated an additive positive effect.[12,27,28] In our study, median PFS was 10.4 months and median OS was not reached, supporting the hypothesis that cyclophosphamide increased the clinical efficacy of pomalidomide.

The results obtained with PCP are impressive considering the dose and schedule used compared with the most recent trials.[9,10,12,29] In our study, the monthly dose of cyclophosphamide was 700 mg, which is inferior to the most commonly used doses. The monthly dose of pomalidomide (2.5 mg daily, 70 mg in a 28-day cycle) is slightly inferior to the standard schedule (4 mg/d for 21 days in a 28-day cycle, 84 mg monthly). This suggests that the positive results obtained with PCP are mainly related to the synergistic activity of the combination. Because PCP was well-tolerated, increasing dose intensity of pomalidomide to 4 mg for 21 days might further improve its efficacy without a major increase in toxicity.[9,10,12,29] We planned 6 cycles of PCP, but prolonging the treatment up to 9 cycles might also improve response rate and outcome. Future phase 3 trials should investigate higher doses of pomalidomide (4 mg/day) in a less-intensive 21-day schedule to minimize both the acute and the cumulative toxicity.

A dose-response relationship of pomalidomide is difficult to establish because the trial was not powered to evaluate it. Although the number of patients enrolled at different dose levels was quite

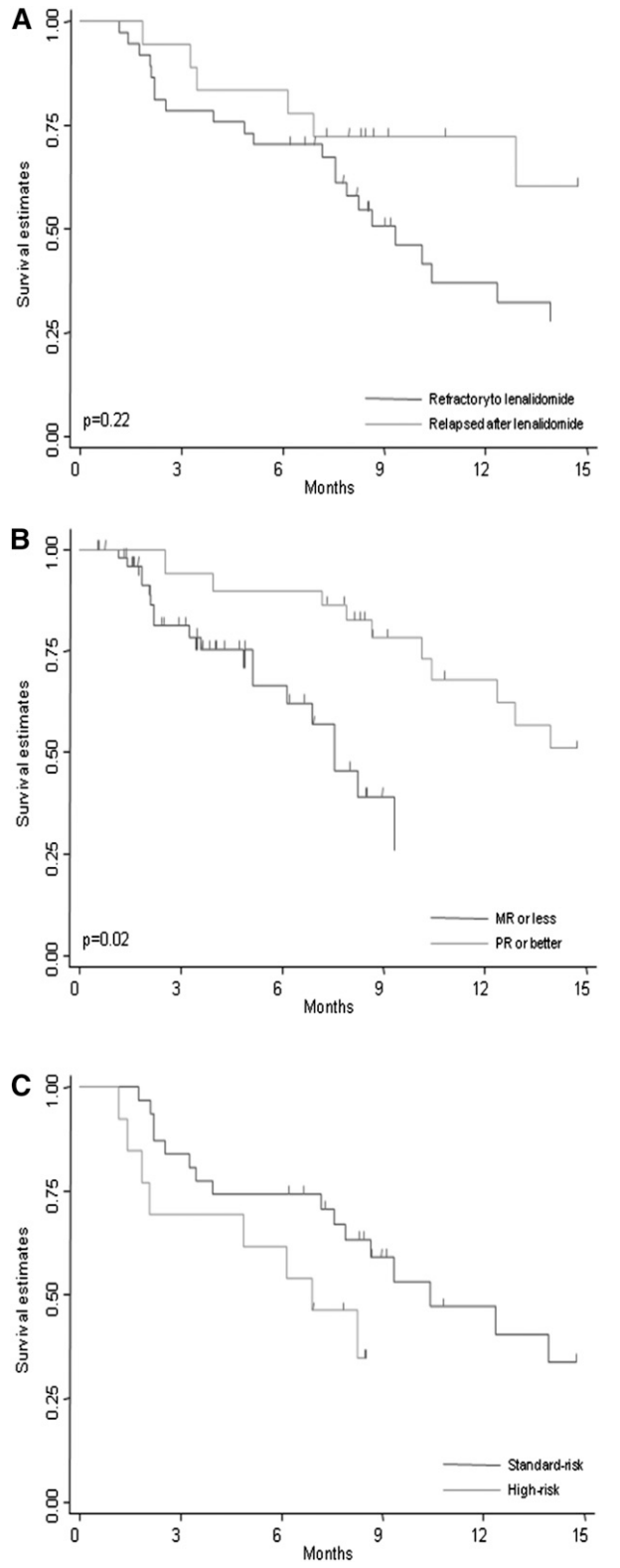

Figure 3. Progression-free survival. (A) PFS in phase 2 patients refractory (N = 18) or relapsed (N = 37) after lenalidomide. (B) PFS in phase 2 patients according to best response (treated as time-dependent covariate). (C) PFS in phase 2 patients with standard-risk or high-risk FISH abnormalities.

Table 5. Treatment-related adverse events during salvage therapy

	Phase 2 (N = 55)					
Events	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Hematologic						
Neutropenia	6	10	14	9	—	33
Thrombocytopenia	15	5	3	3	—	26
Anemia	10	22	5	—	—	37
Nonhematologic						
Cardiologic	—	3	—	1	—	4
Ischemia	—	—	—	1	—	1
Arrhythmia	—	3	—	—	—	3
Neurologic	11	6	3	1	—	21
Sensory neuropathy	6	2	—	—	—	8
Neuralgia	2	1	1	—	—	4
Motor neuropathy	—	—	1	—	—	1
Tremor	—	1	—	—	—	1
Confusion	—	1	—	1	—	2
Mood depression	—	1	—	—	—	1
Other	3	—	1	—	—	4
Infective	5	14	3	0	2	24
Upper respiratory	2	5	—	—	—	7
Pneumonia	2	5	3	—	1	11
Sepsis	—	—	—	—	1	1
Other	1	4	—	—	—	5
Gastrointestinal	3	7	1	0	—	11
Diarrhea	1	—	—	—	—	1
Constipation	—	5	—	—	—	5
Nausea/Vomiting	1	—	—	—	—	1
Other	1	2	1	—	—	4
Hepatic/pancreatic	2	2	1	0	—	5
Increased transaminase	2	1	—	—	—	3
Liver failure	—	—	1	—	—	1
Pancreatitis	—	1	—	—	—	1
Vascular	1	1	0	1	—	3
Deep-vein thrombosis	—	1	—	1	—	2
Phlebitis	1	—	—	—	—	1
Systemic	8	8	2	0	—	18
Fatigue	5	7	2	—	—	14
Fever	2	—	—	—	—	2
Drowsiness	1	—	—	—	—	1
Weight gain	—	1	—	—	—	1
Dermatologic	—	3	4	0	—	7
Rash	—	2	4	—	—	6
Other	—	1	—	—	—	1
Other	7	6	3	—	—	16

limited, 2.5 mg/d pomalidomide induced better responses and a significant prolonged PFS ($P = .05$; data not shown) compared with lower doses.

The quality of response and the amount of cytoreduction seem to be predictive factors of longer remission duration. In our study, patients with at least PR showed a significantly prolonged PFS compared with patients achieving less than PR, suggesting a potential clinical benefit of a more intense cytoreduction in fit patients. Older age negatively affects PFS, demonstrating that dose adjustments are needed in vulnerable patients. Chromosomal abnormalities are the major prognostic factors for MM. A quarter of the patients in this study were classified as high risk at enrolment. PFS was not significantly different between standard- and high-risk patients, but the numbers are too limited and larger series are needed to confirm these preliminary findings.

The most common toxicities were hematologic, with grade 3 to 4 toxicities occurring in 25 patients (45%) at the MTD. Neutropenia was seen mainly in the first cycles, suggesting a concomitant role of the disease and the toxicity of the regimen. Hematologic toxicities were consistent with previous studies in which pomalidomide-dexamethasone induced a rate of grade 3 to 4 adverse events ranging from 38% to 53%.[6,8] Similarly, hematologic toxicity reported with PCP was comparable to the rates reported with lenalidomide-dexamethasone (52%).[30] These data suggest that cyclophosphamide at 50 mg every other day does not significantly increase hematologic toxicity.

The most frequent grade 3 to 4 nonhematologic toxicities were neurologic events, infections, and dermatologic reactions. The incidence of treatment-related peripheral neuropathy was low (4%), particularly when compared with bortezomib or thalidomide. In our study, grade 3 to 5 infections were noted in 9% of patients. In these patients, antibiotic prophylaxis may be recommended. A careful management of fever and neutropenia with the prompt institution of antibiotics is also suggested to reduce the incidence of infections. The incidence of grade 3 to 4 thromboembolic events was low (4%), supporting the need for anticoagulant prophylaxis.

This is the first study to establish that a novel combination, PCP, induces encouraging responses and outcomes in refractory MM. Data from this phase 1/2 study justify further exploration of this combination.

Acknowledgments

The authors thank the patients who took part in the study; the nurses, D'Ambrosio Luisella and Mastropasqua Gianmauro; the data managers, Antonella Fiorillo and Jessica Mastrovito; and the editorial assistant, Giorgio Schirripa.

The study was supported by Fondazione Neoplasie Sangue Onlus and Celgene.

Authorship

Contribution: A.P., M.B., and P.C. designed the study, supervised its conduct and data analysis; A.L. and A.P. wrote the manuscript; A.L., V.M., S.B., D.R., C.C., R.M., M.G., M.M., G.L.V., N.G., V.M., T.G., D.R-S., P.O., A.S., A.M.C., and P.C. provided study material or recruited patients; I.B. performed statistical analysis; and all the authors had access to, commented on, and approved the final manuscript.

Conflict-of-interest disclosure: A.L. has received honoraria from Celgene and Janssen-Cilag. S.B. has received honoraria from Celgene, Janssen-Cilag, and Novartis and served on the advisory committee for Merck Sharp & Dohme. M.B. has received research support from and served on the scientific advisory board for Celgene and Janssen-Cilag. A.P. has received honoraria and consultancy fees from Celgene, Janssen-Cilag, Bristol-Myers Squibb, Millennium, Amgen, and Onyx. The remaining authors declare no competing financial interests.

Correspondence: Antonio Palumbo, Myeloma Unit, Division of Hematology, Azienda Ospedaliera Città della Salute e della Scienza di Torino, Via Genova 3, 10126, Torino, Italy; e-mail: appalumbo@yahoo.com.

References

1. Palumbo A, Anderson K. Multiple myeloma. *N Engl J Med.* 2011;364(11):1046-1060.
2. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood.* 2008;111(5): 2516-2520.
3. Kumar SK, Lee JH, Lahuerta JJ, et al; International Myeloma Working Group. Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: a multicenter international myeloma working group study. *Leukemia.* 2012;26(1):149-157.
4. Bartlett JB, Dredge K, Dalgleish AG. The evolution of thalidomide and its IMiD derivatives as anticancer agents. *Nat Rev Cancer.* 2004;4(4): 314-322.
5. Schey S, Ramasamy K. Pomalidomide therapy for myeloma. *Expert Opin Investig Drugs.* 2011; 20(5):691-700.
6. Lacy MQ, Hayman SR, Gertz MA, et al. Pomalidomide (CC4047) plus low-dose dexamethasone as therapy for relapsed multiple myeloma. *J Clin Oncol.* 2009;27(30):5008-5014.
7. Lacy MQ, Allred JB, Gertz MA, et al. Pomalidomide plus low-dose dexamethasone in myeloma refractory to both bortezomib and lenalidomide: comparison of 2 dosing strategies in dual-refractory disease. *Blood.* 2011;118(11): 2970-2975.
8. Lacy MQ, Hayman SR, Gertz MA, et al. Pomalidomide (CC4047) plus low dose dexamethasone (Pom/dex) is active and well tolerated in lenalidomide refractory multiple myeloma (MM) *Leukemia.* 2010;24(11):1934-1939.
9. Leleu X, Attal M, Arnulf B, et al. High Response Rates to Pomalidomide and Dexamethasone in Patients with Refractory Myeloma, Final Analysis of IFM 2009-02. In: 53rd ASH Annual Meeting and Exposition; December 10-13, 2011; San Diego, CA. Abstract 812.
10. Richardson PG, Siegel D, Vij R, et al. Randomized, Open Label Phase 1/2 Study of Pomalidomide (POM) Alone or in Combination with Low-Dose Dexamethasone (LoDex) in Patients (Pts) with Relapsed and Refractory Multiple Myeloma Who Have Received Prior Treatment That Includes Lenalidomide (LEN) and Bortezomib (BORT): Phase 2 Results. In: 53rd ASH Annual Meeting and Exposition; December 10-13, 2011; San Diego, CA. Abstract 634.
11. McCarthy DA, Macey MG, Streetly M, Schey SA, Brown KA. The neutropenia induced by the thalidomide analogue CC-4047 in patients with multiple myeloma is associated with an increased percentage of neutrophils bearing CD64. *Int Immunopharmacol.* 2006;6(7):1194-1203.
12. Schey SA, Morgan GJ, Ramasamy K, et al. The addition of cyclophosphamide to lenalidomide and dexamethasone in multiply relapsed/refractory myeloma patients; a phase I/II study. *Br J Haematol.* 2010;150(3):326-333.
13. Cancer Therapy Evaluation Program. Common terminology criteria for adverse events, version 3.0, DCTD, NCI, NIH, DHHS March 31, 2003. http://ctep.cancer.gov.
14. Kyle RA, Rajkumar SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. *Leukemia.* 2009;23(1):3-9.
15. Palumbo A, Rajkumar SV, Dimopoulos MA, et al; International Myeloma Working Group. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. *Leukemia.* 2008;22(2):414-423.
16. O'Quigley J, Pepe M, Fisher L. Continual reassessment method: a practical design for phase 1 clinical trials in cancer. *Biometrics.* 1990; 46(1):33-48.
17. O'Quigley J, Zohar S. Experimental designs for phase I and phase I/II dose-finding studies. *Br J Cancer.* 2006;94(5):609-613.
18. Zohar S, Chevret S. The continual reassessment method: comparison of Bayesian stopping rules for dose-ranging studies. *Stat Med.* 2001;20(19): 2827-2843.
19. Zohar S, Latouche A, Taconnet M, Chevret S. Software to compute and conduct sequential Bayesian phase I or II dose-ranging clinical trials with stopping rules. *Comput Methods Programs Biomed.* 2003;72(2):117-125.
20. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc.* 1958;53(282):457-481.
21. Augustson BM, Begum G, Dunn JA, et al. Early mortality after diagnosis of multiple myeloma: analysis of patients entered onto the United kingdom Medical Research Council trials between 1980 and 2002—Medical Research Council Adult Leukaemia Working Party. *J Clin Oncol.* 2005; 23(36):9219-9226.
22. Quach H, Mileshkin L, Seymour JF, et al. Predicting durable remissions following thalidomide therapy for relapsed myeloma. *Leuk Lymphoma.* 2009;50(2):223-229.
23. Gertz MA, Kumar S, Lacy MQ, et al. Stem cell transplantation in multiple myeloma: impact of response failure with thalidomide or lenalidomide induction. *Blood.* 2010;115(12):2348-2353, quiz 2560.
24. Schey SA, Fields P, Bartlett JB, et al. Phase I study of an immunomodulatory thalidomide analog, CC-4047, in relapsed or refractory multiple myeloma. *J Clin Oncol.* 2004;22(16): 3269-3276.
25. Streetly MJ, Gyertson K, Daniel Y, Zeldis JB, Kazmi M, Schey SA. Alternate day pomalidomide retains anti-myeloma effect with reduced adverse events and evidence of in vivo immunomodulation. *Br J Haematol.* 2008;141(1): 41-51.
26. Dimopoulos MA, Lacy MQ, Moreau P, et al. Pomalidomide in Combination with Low-Dose Dexamethasone: Demonstrates a Significant Progression Free Survival and Overall Survival Advantage, in Relapsed/Refractory MM: A Phase 3, Multicenter, Randomized, Open-Label Study. In: 54th ASH Annual Meeting and Exposition; December 8-11, 2012; Atlanta, GA. Abstract LBA-6.
27. Reece D, Masih-Khan E, Khan A, et al. Phase I-II Trial of Oral Cyclophosphamide, Prednisone and Lenalidomide (Revlimid®) (CPR) for the Treatment of Patients with Relapsed and Refractory Multiple Myeloma. In: 51st ASH Annual Meeting and Exposition; December 5-8, 2009; New Orleans, LA. Abstract 1874.
28. Sidra G, Williams CD, Russell NH, Zaman S, Myers B, Byrne JL. Combination chemotherapy with cyclophosphamide, thalidomide and dexamethasone for patients with refractory, newly diagnosed or relapsed myeloma. *Haematologica.* 2006;91(6):862-863.
29. Baz R, Shain KH, Alsina M, et al. Oral Weekly Cyclophosphamide in Combination with Pomalidomide and Dexamethasone for Relapsed and Refractory Myeloma: Report of the Dose Escalation Cohort. In: 54th ASH Annual Meeting and Exposition; December 8-11, 2012; Atlanta, GA. Abstract 4062.
30. Weber DM, Chen C, Niesvizky R, et al; Multiple Myeloma (009) Study Investigators. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med.* 2007; 357(21):2133-2142.

2013 122: 2799-2806
doi:10.1182/blood-2013-03-488676 originally published online August 16, 2013

Pomalidomide, cyclophosphamide, and prednisone for relapsed/refractory multiple myeloma: a multicenter phase 1/2 open-label study

Alessandra Larocca, Vittorio Montefusco, Sara Bringhen, Davide Rossi, Claudia Crippa, Roberto Mina, Monica Galli, Magda Marcatti, Giacinto La Verde, Nicola Giuliani, Valeria Magarotto, Tommasina Guglielmelli, Delia Rota-Scalabrini, Paola Omedé, Alberto Santagostino, Ileana Baldi, Angelo Michele Carella, Mario Boccadoro, Paolo Corradini and Antonio Palumbo

Blood (print ISSN 0006-4971, online ISSN 1528-0020), is published weekly by the American Society of Hematology, 2021 L St, NW, Suite 900, Washington DC 20036.