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

UNIVERSITÀ DEGLI STUDI DI TORINO

Pomalidomide, Cyclophosphamide and Prednisone for relapsed/refractory multiple myeloma: a multicenter phase 1/2 open label study

Running head: POMALIDOMIDE FOR RELAPSED/REFRACTORY MYELOMA

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Keypoint

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

Abstract

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 1-2.5 mg/d, cyclophosphamide at 50 mg every other day, prednisone at 50 mg every other day, for six 28-day cycles, followed by pomalidomide-prednisone maintenance therapy. Thromboprophylaxis was recommended.

Sixty-nine patients were enrolled, 55 received the MTD (2.5mg/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, 1-year overall survival was 69%. At the MTD, grade 3-4 toxicities included anemia (9%), thrombocytopenia (11%), neutropenia (42%), neurologic events (7%), dermatologic events (7%), thromboembolism (2%). Grade 3-5 infections occurred in 5 patients (9%). Five patients (9%) discontinued treatment for toxicity. New grade 3-4 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, #NCT01166113.

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 realpse.[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 analogue of thalidomide, showed potent activity against TNF-α secretion and entered clinical studies.[4,5] Pomalidomide at 2-4 mg, combined with low-dose dexamethasone, has shown significant activity in pre-treated patients refractory to lenalidomide and/or bortezomib.[6-10] Partial response (PR) rates were 32-35% and median progression-free survival (PFS) 4.6-6.3 months.[8,9,10] 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 (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, relapsed or relapsed/refractory to lenalidomide, and had received 1-3 prior lines of therapy were eligible. Relapse was defined as reoccurrence of disease requiring the initiation of a salvage therapy, refractory disease was defined as relapse while on salvage therapy or progression within 60 days of the most recent therapy. Patients were required to have measurable disease, Karnofsky performance status ≥60%, platelet count ≥50 x 10^9/L, neutrophil count ≥1.00 x 10^9/L, corrected serum calcium ≤3.5 mmol/L (14 mg/dl), serum hepatic aminotransferase levels ≤2.5-fold of the upper limit of normal (ULN), total bilirubin ≤1.5-fold of the ULN, serum creatinine ≤2 mg/dL, and to agree to use contraception. Patients with clinically relevant active co-morbid 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 >3 days, other grade 4 hematologic toxicity, any ≥grade ≥3 non-hematologic toxicity, febrile neutropenia and/or infection requiring antibiotics, occurring during the first cycle of therapy.

In the phase 2, patients received the MTD of pomalidomide established in the phase 1. Primary endpoint of the phase 2 was the rate of complete response (CR) and very good partial response (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).[15]

Responses were recorded during every cycle, according to the International Myeloma Working Group criteria.[13] Responses among patients refractory to previous novel agents and at high-risk were analysed. 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 the phase 1 and at the MTD in the 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 six 28-day cycles. 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 non-hematologic 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 x 10^9/L, platelet count was ≥50 x 10^9/L, haemoglobin was ≥8 g/dl and non-hematologic adverse events were grade ≤2. If the start of a new cycle was delayed by ≥2 weeks, dose reductions were required. Aspirin 100 mg/day or low-molecular weight heparin was recommended as prophylaxis, according to patient risk.[14]

Statistical analysis

In the phase 1, the continual reassessment method was used as the dose allocation rule in the trial.[16,17] It is based on a mathematical modelling 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, 0.45, respectively. A design with grouped inclusions of four patients per dose-level was chosen and 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]

In the phase 2, we used a Simon optimal two-stage design for the sample size calculation. A 5% response rate was considered not promising, a 20% rate promising. The probability of both type I and II errors was set at 0.05. Accordingly, 24 patients were planned in the first stage, and 31 (total=55) 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 the phase 1 were also included in the phase 2.

All patients meeting the eligibility criteria who had received at least one 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, and the duration of response from response to progressive disease (PD) or death, censored at the date of last assessment for not progressing patients. We evaluated PFS and OS from the start of treatment until PD or death, and 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), 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 (HR) and 95% Confidence Intervals (95%CI). The analyses were performed using SAS software, version 8.2 (SAS Institute, Cary, NC). Data cut-off 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, and 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 the phase 1 and 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). Nine percent, 29% and 62% of patients had received one, two, and three 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 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). 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 four patients: one grade 4 thrombocytopenia with 1.5 mg/d pomalidomide; one grade 3 peripheral neuropathy, one grade 3 hepatic toxicity, and one 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 the phase 1 are reported in table 3.

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). Five patients did not complete the assigned 6 cycles for toxicity: grade 3 cutaneous rash and grade 2 pancreatitis (one patient); grade 2 bradicardia and dispnea (one patient), grade 5 sepsis (one patient), grade 4 deep-vein thrombosis (one patient), and grade 3 liver failure (one patient). Eight patients did not complete salvage therapy for PD, one patient for a concomitant mesothelioma and one patient skipped the last cycle and started maintenance for medical decision. Thirty-four patients started maintenance treatment; 13 of them discontinued therapy for PD and 2 for toxicity, including pulmonary embolism and limbic encephalitis (one patient each) (figure 1).

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

At least PR was achieved in 28/55 patients (51%), at least VGPR in 13/55 patients (24%) and immunofixation negative CR 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 3A). 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 two cycles, in 20 patients after four cycles, and in 23 patients after six 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 for PD (ten patients), pneumonia and respiratory failure (one patient), sudden death (one patient), sepsis (one patient), liver failure (one patient), and mesothelioma (one patient). The 1-year PFS was 48% (95% CI: 33%-62%), with a median of 10.4 months (95%CI, 7.9-15.8; figure 2A). The 1-year OS was 69% (95% CI: 54%-81%), 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=0.22, 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=0.02, figure 3B). The 1-year PFS was 47% in standard-risk and 35% in high-risk patients (p=0.21, figure 3C).

In a multivariable analysis, older age negatively affected PFS (HR=2.65, p=0.035), and the achievement of PR confirmed its positive effect on PFS (HR=0.38, p=0.059) (figure 3B). No differences according to FISH-defined risk were noted (HR=1.36, p=0.48).

At the MTD, the most frequent grade 3-4 adverse events were neutropenia (42%), thrombocytopenia (11%), anemia (9%), neurologic (7%), dermatologic reactions (7%) and infections (5%). Two grade 5 infections were reported (Table 4). 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 one patient, despite low-molecular weight heparin prophylaxis. Pomalidomide dose was reduced in 17 patients for grade 4 hematologic toxicity (4 patients), grade 1-2 non-hematologic toxicity (2 patients), grade 3-4 non-hematologic toxicity (7 patients) and unknown causes (4 patients). During maintenance treatment the frequency of new grade 3-4 adverse events was low and included: grade 4 neutropenia (2 patients); pulmonary embolism (one patient, during aspirin); grade 3 neurologic toxicity (vertigo, peripheral neuropathy, limbic encephalitis, one patient each).

Discussion

In this study, we evaluated dosing, the safety profile, and the efficacy of the combination pomalidomide-cyclophosphamide-prednisone in patients 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 the classical 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 co-morbidities, 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 multi-relapsed/refractory myeloma, median PFS was 3.9 vs. 2 months (p<0.001), and median OS was not reached vs. 8.5 months (p<0.001), in the pomalidomide and in 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, at least PR rate was 40% in patients refractory to lenalidomide, and 60% in those refractory to bortezomib.[6] In our trial, PCP regimen induced at least PR rate of 51% and a clinical benefit, with at least a MR rate of 71%. These results are 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 agent to novel drugs has demonstrated an additive positive effect.[12,27,28] In our study, the median PFS was 10.4 months and the 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, as 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. Since 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 limited, 2.5 mg/d pomalidomide induced better responses and a significant prolonged PFS (p=0.05, data not-shown) as 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 numbers are too limited and larger series are needed to confirm these preliminary findings.

The most common toxicities were hematologic, with grade 3-4 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 where pomalidomide-dexamethasone induced a rate of grade 3-4 adverse events ranging from 38% to 53%.[6,8] Similarly, the 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 3-4 non-hematologic toxicities were neurologic events, infections and dermatologic reactions. The incidence of treatment-related peripheral neuropathy was low (4%), particularly when compared to bortezomib or thalidomide. In our study, grade 3-5 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 3-4 thromboembolic events was low (4%), supporting the need for anticoagulant prophylaxis.

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

Contributors: A.P., M.B., 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., P.C. provided study material or recruited patients. I.B. performed statistical analysis. All the authors had access to, commented on, and approved the final manuscript.

Conflicts of interest statement: 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 from Celgene, Janssen-Cilag, Bristol-

Myers Squibb, Millennium, Merck, Onyx, and served on the advisory board for Celgene and Janssen-Cilag. The other authors declare no conflicts of interest.

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 FO.NE.SA Onlus and Celgene.

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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)
Gender			
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%)
Non-secretory	1 (4%)	0	1 (1%)
Kafnofsky 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 trasplant	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%)

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

Table 2. Phase 1: dose limiting toxicity for each cohort of enrolled patients.							
Cohort	**Dose (mg/day)**	**Number of DLTs**	**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**

DLT: dose limiting toxicity. In bold: the dose level closest to the toxicity target (0.25).

Table 3

A) Best responses to combination treatment.

Response	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)
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	-

B) Time to event analysis				
	Median follow-up (months, range)	**Median PFS (months; 95% CI)**	**Median OS (months; 95% CI)**	**12-month 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%)

Table 4 Treatment-related adverse events during salvage therapy.

Events	Phase 2 N=55					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Haematologic						
Neutropenia	6	10	14	9	-	33
Thrombocytopenia	15	5	3	3	-	26
Anaemia	10	22	5	-	-	37
Non-haematologic						
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
Diarrhoea	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

Figure 1. **Flow Diagram. (PCP, pomalidomide-cyclophosphamide-prednisone; PD, progressive disease)**

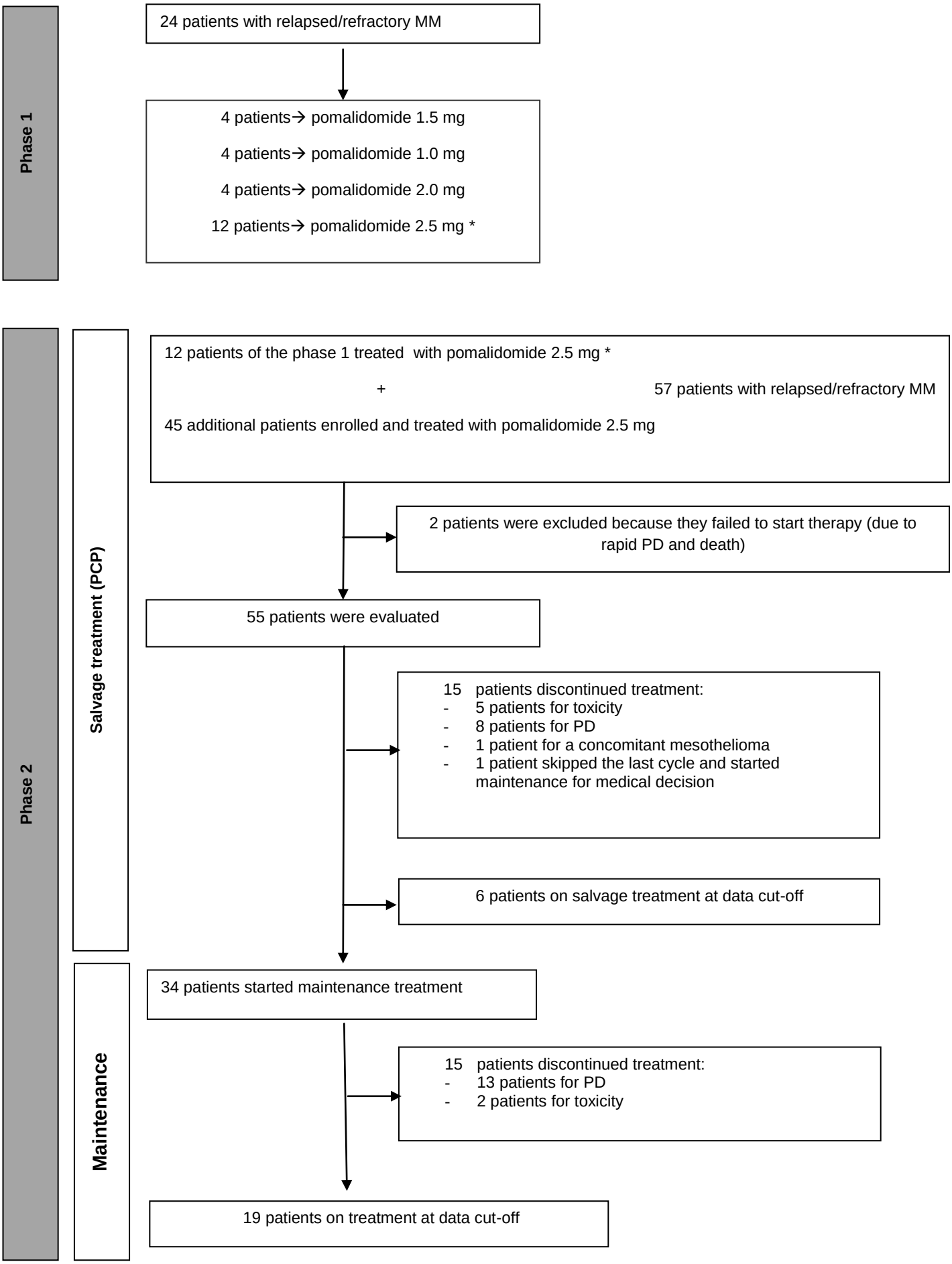
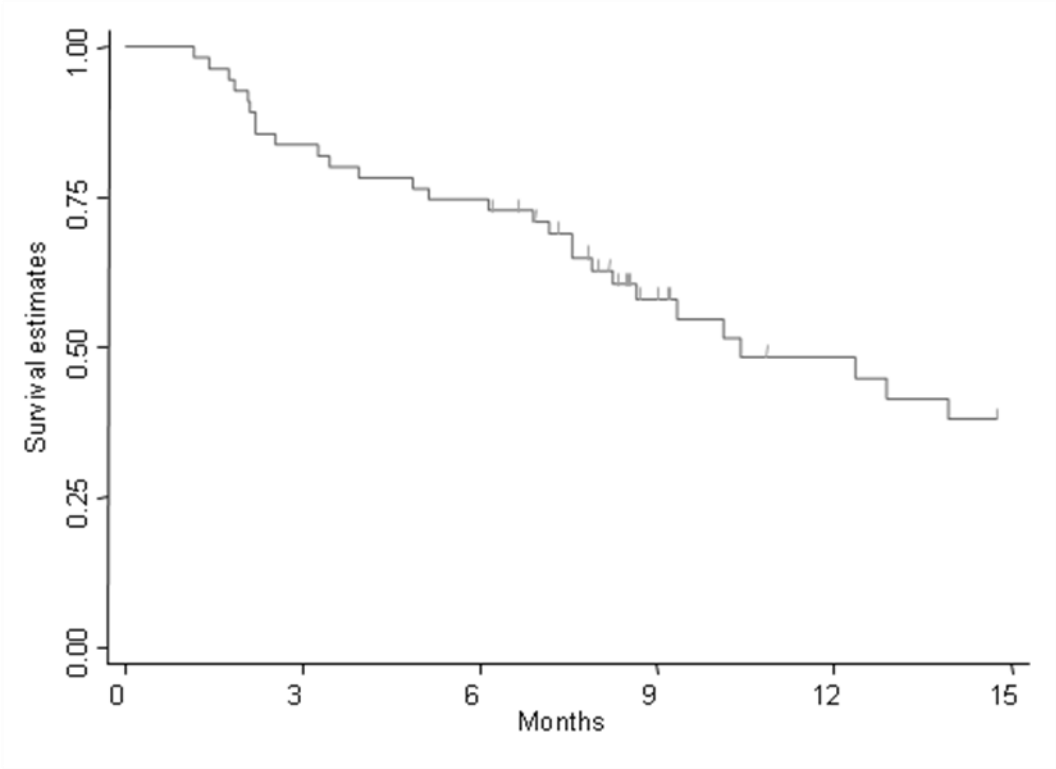


Figure 2 Time-to-event analysis.

A) Progression-free survival in phase 2 patients



B) Overall survival in phase 2 patients

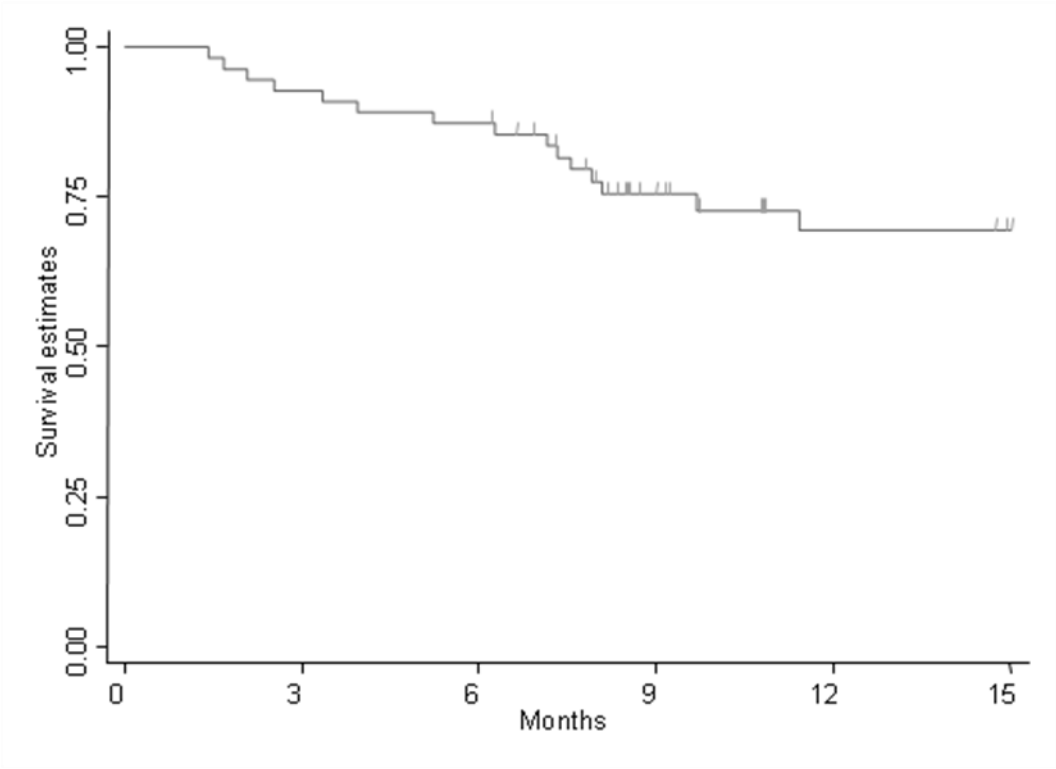
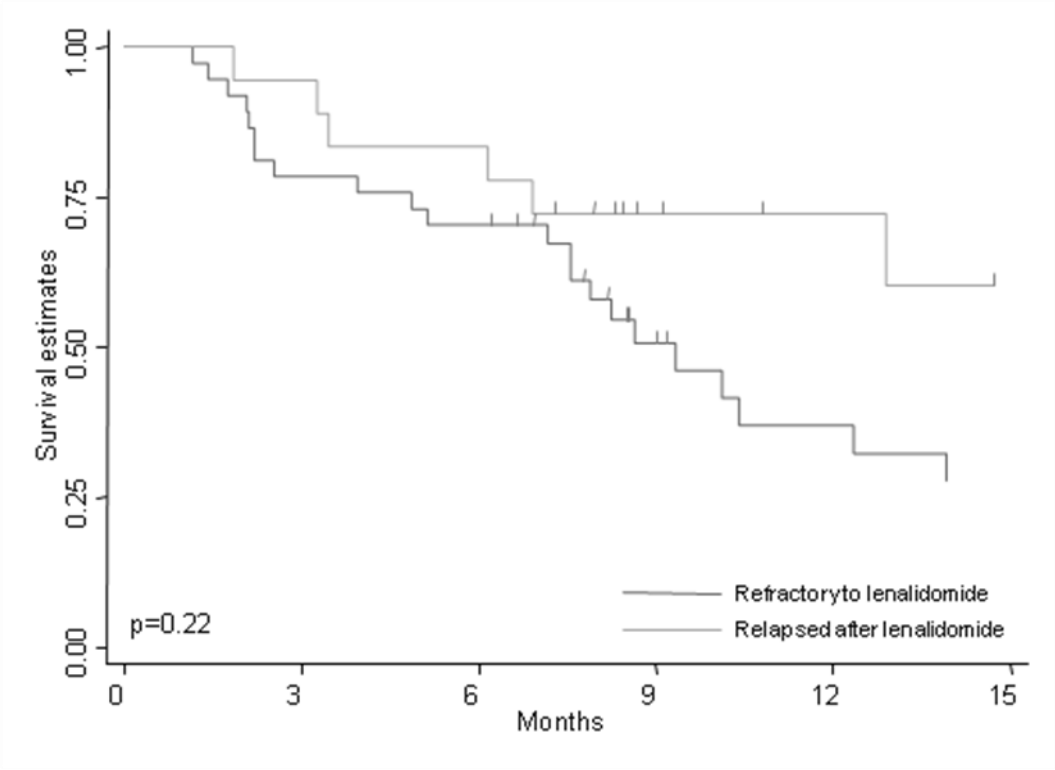
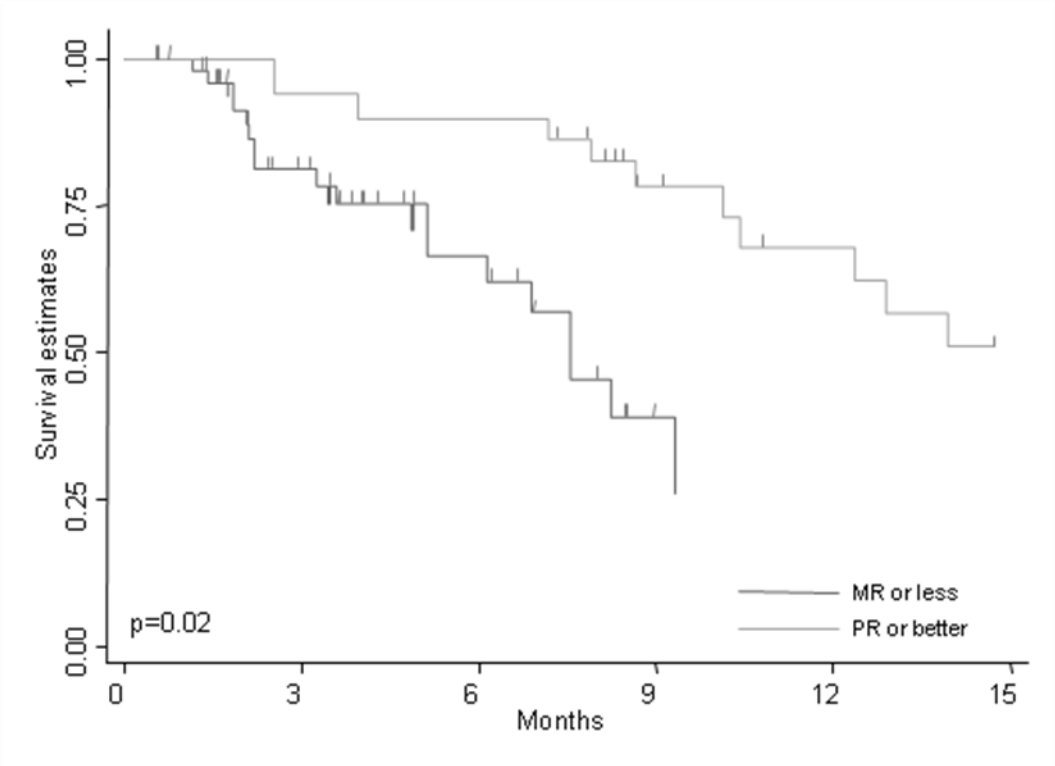


Figure 3

A) Progression-free survival in phase 2 patients refractory (N=18) or relapsed (N=37) after lenalidomide.



B) Progression-free survival in phase 2 patients according to best response*.



*** treated as time-dependent covariate**

C) Progression-free survival in phase 2 patients with standard-risk or high-risk FISH abnormalities.