Randomized Multicenter Phase II Study of Pomalidomide, Cyclophosphamide, and Dexamethasone in Relapsed Refractory Myeloma

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• Pomalidomide dexamethasone and cyclophosphamide (PomCyDex) results in a higher overall response rate than pomalidomide and dexamethasone
• PomCyDex is an effective, all oral regimen for refractory myeloma patients
Abstract

Pomalidomide and low dose dexamethasone (PomDex) is standard treatment for lenalidomide refractory myeloma patients who have received more than 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 I study to determine the recommended phase II dose of cyclophosphamide in combination with PomDex (arm A). A randomized, multicenter phase II study followed, enrolling patients with lenalidomide refractory myeloma. Patients were randomized (1:1) to receive pomalidomide 4 mg on days 1-21 of a 28 days cycle in combination with weekly dexamethasone (arm B) or PomDex with cyclophosphamide 400 mg orally on days 1,8,15 (arm C). The primary endpoint was the overall response rate (ORR). Eighty patients were enrolled (ten in the phase I, and 70 randomized in the phase II: 36 to arm B and 34 to arm C). The ORR was 38.9% (95% CI 23-54.8%) and 64.7% (95% CI 48.6-80.8) for arm B and C, respectively (p=0.035). As of June 2015, 62 of the 70 randomized patients had progressed. The median progression free survival (PFS) was 4.4 months (95% CI 2.3-5.7) and 9.5 months (95% CI 4.6-14) for arm B and C, respectively (p=0.106). 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 as compared to PomDex in patients with lenalidomide refractory multiple myeloma. The study is registered at www.clinicaltrials.gov as NCT01432600.
Introduction

Multiple myeloma is a plasma cell malignancy which accounts for about 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 of 9 months\(^2\). Combination therapy is often used in clinical practice in an attempt to overcome drug / clone resistance.

Immunomodulatory agents; thalidomide, lenalidomide and pomalidomide, are active therapies for patients with multiple myeloma\(^3-6\). Specifically, lenalidomide and dexamethasone was associated with a response rate of about 60% and a median progression free survival of 11 month in patients with relapsed multiple myeloma\(^3,4\). Richardson et al. evaluated pomalidomide with or without dexamethasone in a phase I/II trial in patients with prior bortezomib and lenalidomide\(^6,7\). The study identified a recommended phase II dose of pomalidomide of 4 mg given orally days 1-21 every 28 days in combination with dexamethasone 40 mg weekly (20 mg in patients older than 75 years of age)\(^7\). The phase II portion determined that pomalidomide-dexamethasone results in an overall response rate of 33% and median PFS of 4.2 months in this patient population\(^6\). Furthermore, a randomized phase III 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, progression free survival and overall survival 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\textsuperscript{8}. Based on this experience, the United States 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\textsuperscript{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\textsuperscript{16}. In addition, Larocca et al. combined continuous pomalidomide with oral cyclophosphamide\textsuperscript{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 overall response rate was 51\% and the median progression free survival was 10.4 months\textsuperscript{17}.

Based on these encouraging studies, we conducted a phase I to determine the recommended phase II dose of the combination of pomalidomide, dexamethasone and oral weekly cyclophosphamide. We then conducted a randomized phase II study comparing PomCyDex to PomDex in patients with lenalidomide refractory myeloma.

**Patients and Methods**

Patient eligibility
Eligible patients had relapsed and refractory multiple myeloma. Patients had received at least 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 one of the following: serum monoclonal protein $\geq$ 0.5 g/dL; urine monoclonal protein $>$200 mg/24h or serum involved free light chain $\geq$ 10 mg/dL and abnormal serum free light chain ratio. Patients had an ECOG performance status of 0-2 as well as a serum creatinine $<$ 3mg/dL. For the phase I portion, patients were required to have an absolute neutrophil count $\geq$ 1000/mm3, and a platelet count $\geq$ 50,000/mm3. For the phase II portion, patients with greater than 50% bone marrow plasmacytosis were eligible if the platelet count was greater than 30,000/mm3 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 greater than 1000/mm3 during screening. Females of childbearing potential (FCBP) had to have a negative serum or urine pregnancy test within 10 – 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, active hepatitis B or C, patients with
prior pomalidomide (greater than 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 three 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 I (Arm A) portion of the study, patients received pomalidomide at 4 mg orally on days 1-21 of a 28 day cycle, oral weekly cyclophosphamide (dose escalation 300-500 mg) orally on days 1,8,15 (dose level -1 was Cyclophosphamide 300 mg PO D1,8 only). Patients also received dexamethasone 40 mg PO days 1- 4, 15-18 of a 28 days cycle for the first 4 cycles and subsequently 40 mg PO Days 1,8,15, 22. The dose escalation used a standard “3+3” design.

In the phase II 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 II dose determined in arm A). Specifically, arm B patients received pomalidomide at 4 mg orally days 1-21 and dexamethasone 40 mg weekly and arm C patients received pomalidomide 4 mg days 1-21, dexamethasone 40 mg weekly and oral cyclophosphamide 400 mg orally on days 1,8,15 of a 28 day cycle. Patients who experienced progressive disease on arm B
were allowed to cross over to arm D at the discretion of the treating physician in which case oral weekly cyclophosphamide (400 mg orally days 1, 8, 15) was added to their tolerated dose of pomalidomide and dexamethasone (figure 1. Study schema and consort diagram).

In the phase I and phase II, patients who were older than 75 years of age or those who were known to be intolerant to 40 mg of weekly dexamethasone received 20 mg of dexamethasone on the same schedule. In addition, aspirin 81 mg daily was required for thromboprophylaxis (unless the patients had contraindications or were receiving other form of anticoagulation for other indications)\textsuperscript{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 25-49% decrease in serum paraprotein and a 50-89% reduction in urine light chain\textsuperscript{19}. The best response was determined as the highest level of response achieved during an arm of therapy that was confirmed on repeat measurement.

Statistical Considerations
For the phase II portion, the sample size justification was based on the overall response rate, which is the primary endpoint. We estimated the overall response rate was 30% in the arm with pomalidomide and dexamethasone (Arm B) and 60% in the arm with pomalidomide, dexamethasone and oral cyclophosphamide (Arm C). A sample size of 70 patients (35 in each arm) achieved 78% power to detect the group difference of 30% using the two-sided Fisher’s exact test. The significant level of 10% was applied. Randomization was performed by a block size of four 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 I 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 endpoint in phase II trial, we were interested in comparing the overall response rate of pomalidomide dexamethasone with (Arm C) or without cyclophosphamide (Arm B) in patients with relapsed and refractory myeloma. The overall response rate and its 95% confidence were calculated for each study arm using the exact binomial method. The comparison of the overall response rate between the two study groups was evaluated using the Fisher’s exact test. The phase II component of the trial was conducted in a single stage without preplanned interim analysis.

The secondary endpoints included progression-free survival (PFS), overall survival (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% confidence intervals were estimated. The PFS difference between the two study arms were compared using the log-rank test. The same approach was applied for evaluating OS in the two 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. C) on PFS and OS were 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 NCI CTCAE v 4.0. Adverse events leading to death or to discontinuation from treatment, events classified as NCI CTCAE 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 three 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 II had received 5 or more prior therapies. All patients were refractory to lenalidomide, and approximately 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 about 20% of patients while trisomy or tetrasomy 1q was present in nearly 40% of patients. As noted in table 1, baseline characteristic were not significantly different between arm B and arm C.

Phase I

Ten patients were enrolled in the phase I portion. Four patients were enrolled on dose level 1 (cyclophosphamide 300 mg PO D1, 8, 15). One patient was not evaluable for DLT because the patient took a lower than planned dose of cyclophosphamide orally in error. None of the other three 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 PO D1, 8, 15 in combination with pomalidomide 4 mg PO d1-21 and dexamethasone 40 mg weekly in a 28 days cycle) as the recommended phase II dose. Table S1 lists all grade, all cause adverse events while table S2 lists the grade 3 and 4 adverse events reported during the phase I portion of the trial with the most common grade 3 and 4 toxicities being myelosuppression.

Of the ten patients that were enrolled in the phase I portion of the trial, one patient achieved a stringent complete response (sCR), one patient a very good partial response (VGPR), three patients a partial response (PR) and two a minimal response (MR). The overall response rate (PR and better) was 50% (table 2).

**Randomized Phase II**

Seventy patients were enrolled in the phase II 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, one in each arm, were randomized but did not receive study therapy and are considered as treatment failures in this intent-to-treat analysis (Consort diagram Figure 1). The overall response rate (PR and better) for arm B was 38.9% (95% CI 23-54.8) while the overall response rate for arm C was 64.7% (95% CI 48.6-80.8), p=0.0355 (table 2). In addition, eight patients (22%) and five patients (15%) achieved a minimal response in arm B and C, respectively.

As of June 2015, 62 patients of the 70 randomized have experienced progressive disease, 33 on arm B and 29 on arm C. The median progression free survival 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 respectively, (log rank p=0.106) (figure 2a). In terms of overall survival, 36 patients have passed away as of June 2015, 21 on arm B and 15 on arm C. The median overall survival 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 respectively (log rank p=0.168) 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 progression free (median PFS 12.1 (95% CI 4.6-16.7) months versus 4.4 (95% CI 2.3-6.6) months, p=0.091) and overall survival (NR (95% CI 18-NR) months versus 16.5 (95% CI 9.3-NR) p=0.02) as compared to arm B respectively (figure 3a and 3b). On the other hand, only 15 patients had high risk cytogenetics although there is a trend for improved overall survival with arm B compared to arm C (17.6 (95% CI 6.2 – NR) months versus 7.5 (95% CI 0-12.5) p=0.09) respectively.

Tables 3 and 4 lists the adverse events reported in arm B and C. While 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, thrombocytopenia were noted in 11%, 31% and 6% of arm B patients versus in 24%, 52%, 15% of arm C patients respectively (for anemia p=0.21, neutropenia p=0.14, thrombocytopenia p=0.25). Importantly, the rate of febrile neutropenia was not meaningfully different (11% versus 12% for arm B and C respectively).
Cross Over Arm (Arm D)

Thirty three patients had progressive disease on arm B. Seventeen patients elected to cross over to arm D and oral weekly cyclophosphamide (400 mg PO D1,8,15) was added to the previously tolerated dose of pomalidomide and dexamethasone. Of the Seventeen patients who crossed over to arm D, one achieved a PR, four patients a MR, and eight had stable disease as their best response (an additional four patients had continued progressive disease) (table 3). The overall response rate for arm D (PR and better) was 6% and the clinical benefit rate was 29%. The median progression free survival 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 to 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 (partial response or better), progression free and overall survival. Treatment assignment (arm C versus arm B) had an adjusted odd ratio of 2.98 (95% CI 0.99-8.99, p=0.052) which neared statistical significance with respect to overall response rate. The adjusted hazard ratio was 0.54(95% CI 0.29-1.00) for progression free survival demonstrated statistical significance. Of note, the number of prior therapies was a statistically significant predictor in the progression free survival 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=0.017) 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 overall survival (p=0.020)(Figure 3A). On the other hand, patients with deletion 17p or t(4;14) have a trend for a worse outcome with the triplet (arm C)(Figure 3C). Treatment effect (Arm B vs. C) on PFS was not significantly modified by cytogenetically defined risk (p=0.118). The number of prior therapies was not associated with a differential benefit (OS: p= 0.790, PFS: p=0.593) from arm B or C in this trial.

Discussion

This randomized phase I/II study identified the recommended phase II 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 dexamethasone alone 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 two treatment arms.
These results would support the conduct of a larger phase III 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\textsuperscript{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 1-3 prior lines of therapy\textsuperscript{17}. In addition, our combination features pomalidomide using the now accepted dose and schedule of 21 dosing day per 28 days cycle.

Patients who experienced progressive disease on pomalidomide and dexamethasone were allowed to cross over 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 cross over arm was overall low (6\%) and the overall survival curves also suggests this is not an effective salvage strategy. This 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 Pomalidomide cyclophosphamide and dexamethasone) in patients who have received more than 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 overall survival 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 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 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 regimens6, 20-23. Acknowledging the limitation of comparisons across different phase II studies, this regimen results in comparable efficacy. Moreover, the present study is the only randomized trial which 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 II nature of the design which may have limited the power to detect statistically significance difference in efficacy outcomes and toxicity measures. Nevertheless we were able to demonstrate a statistically significant improvement in overall response rate and progression free survival 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, pomalidomide cyclophosphamide and dexamethasone (PomCyDex) is well tolerated and results in increased overall response rate and progression free survival as compared to pomalidomide and dexamethasone in patients with lenalidomide refractory myeloma.
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Authorship Contributions:

Conception and design: RB, KS, MA, AC, TM, SJ
Collection and assembly of data: RB, HC, XZ, AM, JW, LN, KL, TM
Data analysis and interpretation: RB, DS, XZ, JW, KS, MA, AC, HYL, TM
Manuscript writing: all authors
Final approval of the manuscript: all authors

Conflict of Interest Disclosures:

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Hui-Yi Lin: no conflict
Xiuhua Zhao: no conflict
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References:


**Figures and Tables**

**Figure 1. Study Scheme and Consort flow diagram**

**CONSORT Flow Diagram**

**Enrollment**

- Assessed for eligibility (n=90)
  - Excluded (n=10)
    - Not meeting inclusion criteria (n=10)
  - Randomized (n=70)

**Allocation**

- Arm A phase I (n=10)
  - Received allocated intervention (n=35)
  - Did not receive allocated intervention (rapid disease progression) (n=1)
- Allocated to Arm B / pomalidomide dexamethasone (n=36)
  - Received allocated intervention (n=35)
  - Did not receive allocated intervention (renal failure from progressive myeloma) (n=1)
  - Continue on treatment: n=4
  - Discontinued intervention (progressive disease) n=23
  - Discontinued due to adverse events: n=2
  - Discontinued intervention (other causes): n=4 received pomalidomide based therapy off study (3), decreased performance status, (1)
  - Cross over to Arm D (addition of weekly cyclophosphamide to the tolerated dose of Pomalidomide dexamethasone) : N=17

**Follow-Up**

- Arm C / pomalidomide dexamethasone + cyclophosphamide (n=34)
  - Received allocated intervention (n=33)
  - Did not receive allocated intervention (renal failure from progressive myeloma) (n=1)
  - Continue on treatment: n=4
  - Discontinued intervention (progressive disease) n=23
  - Discontinued due to adverse events: n=2
  - Discontinued intervention (other causes): n=4 received pomalidomide based therapy off study (3), decreased performance status, (1)

**Analysis**

- Analysed for efficacy (response / survival) (n=36)
- Analysed for safety (toxicity) (n=35)

- Analysed for efficacy (response / survival) (n=34)
- Analysed for safety (toxicity) (n=33)
Figure 2. Progression free (a) and overall survival (b) comparing arms B and C.

Progression-free survival (months)

<table>
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<tr>
<th>Arm</th>
<th>N</th>
<th>Event</th>
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<tr>
<td>B</td>
<td>36</td>
<td>33 (92%)</td>
<td>3 (8%)</td>
<td>4.4 (2.3, 5.7)</td>
</tr>
<tr>
<td>C</td>
<td>34</td>
<td>29 (85%)</td>
<td>5 (15%)</td>
<td>9.5 (4.6, 14.0)</td>
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Overall survival (months)

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<th>Arm</th>
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<tr>
<td>B+D</td>
<td>36</td>
<td>21 (58%)</td>
<td>15 (42%)</td>
<td>16.8 (9.3, NA)</td>
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<tr>
<td>C</td>
<td>34</td>
<td>15 (44%)</td>
<td>19 (56%)</td>
<td>NA (13.1, NA)</td>
</tr>
</tbody>
</table>

Log-rank p = 0.1056

Log-rank p = 0.1682
Figure 3. Progression free survival and overall survival of patients with high risk cytogenetics with arm B and C respectively. High risk cytogenetics is defined as the presence of deletion 17p and/or t(4;14).

3A: Overall survival of Arm B versus C in patients without high risk cytogenetic

3B: Progression free survival of Arm B versus C in patients without high risk cytogenetics
3C Overall survival of Arm B versus C in patients with high risk cytogenetics

![Survival Curve](image)

- **Arm B/High**:
  - Median (95% CI): 17.6 (6.2, NA)
  - Event: 4 (50%)
  - Censored: 4 (50%)

- **Arm C/High**:
  - Median (95% CI): 7.5 (0.0, 12.5)
  - Event: 6 (86%)
  - Censored: 1 (14%)

Log-rank p = 0.0922

3D : Progression free survival of Arm B versus C in patients with high risk cytogenetics

![Survival Curve](image)

- **Arm B/High**:
  - Median (95% CI): 5.3 (0.7, 8.3)
  - Event: 7 (88%)
  - Censored: 1 (13%)

- **Arm C/High**:
  - Median (95% CI): 1.3 (0.0, 7.8)
  - Event: 6 (86%)
  - Censored: 1 (14%)

Log-rank p = 0.4022
Table 1. Patient characteristics

<table>
<thead>
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<th>Arm A (N=10)</th>
<th>Arm B (N=36)</th>
<th>Arm C (N=34)</th>
<th>Arm D** (N=17)</th>
<th>P value*</th>
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<td>Age, years, median (range)</td>
<td>69 (44-73)</td>
<td>64 (50-78)</td>
<td>65 (47-80)</td>
<td>64 (50-73)</td>
<td>0.697</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>7 (70)</td>
<td>23 (64)</td>
<td>18 (53)</td>
<td>12 (71)</td>
<td>0.467</td>
</tr>
<tr>
<td>Number of prior therapies, median (range)</td>
<td>5 (4-12)</td>
<td>4 (2-12)</td>
<td>4 (2-9)</td>
<td>4 (3-8)</td>
<td>0.570</td>
</tr>
<tr>
<td>Bortezomib refractory, n (%)</td>
<td>10 (100)</td>
<td>28 (78)</td>
<td>24 (71)</td>
<td>12 (71)</td>
<td>0.413</td>
</tr>
<tr>
<td>Carfilzomib refractory, n (%)</td>
<td>1 (10)</td>
<td>16 (44)</td>
<td>13 (38)</td>
<td>7 (41)</td>
<td>0.632</td>
</tr>
<tr>
<td>Prior HDM/ASCT†, n (%)</td>
<td>7 (70)</td>
<td>27 (75)</td>
<td>28 (82)</td>
<td>13 (76)</td>
<td>0.7</td>
</tr>
<tr>
<td>Prior alkylating agent, n (%)</td>
<td>10 (100)</td>
<td>32 (89)</td>
<td>32 (94)</td>
<td>15 (88)</td>
<td>1.0</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL), median (range)</td>
<td>1 (1-3)</td>
<td>1 (0.5-2.3)</td>
<td>0.9 (0.6-2.1)</td>
<td>1 (1-2)</td>
<td>0.650</td>
</tr>
<tr>
<td>High-risk cytogenetics¥, n (%)</td>
<td>3 (30)</td>
<td>8 (22)</td>
<td>7 (21)</td>
<td>4 (23)</td>
<td>1.0</td>
</tr>
<tr>
<td>Deletion 17p, n (%)</td>
<td>3 (30)</td>
<td>6 (16)</td>
<td>5 (15)</td>
<td>3 (18)</td>
<td>0.6</td>
</tr>
<tr>
<td>t(4;14), n (%)</td>
<td>0</td>
<td>4 (11)</td>
<td>3 (9)</td>
<td>3 (18)</td>
<td>0.6</td>
</tr>
<tr>
<td>Trisomy or tetrasomy 1q, n (%)</td>
<td>3 (30)</td>
<td>18 (50)</td>
<td>9 (26)</td>
<td>9 (53)</td>
<td>0.1</td>
</tr>
</tbody>
</table>

* comparing arm B and C, the Fisher’s exact test for categorical variables, the Wilcoxon rank-sum test for continuous variables
** Arm D, a cross-over group, was part of Arm B
†: High dose melphalan and autologous stem cell transplant
¥: high risk cytogenetics: deletion 17p and / or t(4 ;14)
Table 2. International Myeloma Working Group (IMWG) best response on treatment per study arm

<table>
<thead>
<tr>
<th>Response</th>
<th>Arm A (N=10)</th>
<th>Arm B (N=36)</th>
<th>Arm C (N=34)</th>
<th>Arm D (N=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Complete / stringent complete response</td>
<td>1 (10%)</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
<td></td>
</tr>
<tr>
<td>Very Good Partial response</td>
<td>1 (10%)</td>
<td>4 (11%)</td>
<td>3 (9%)</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>3 (30%)</td>
<td>9 (25%)</td>
<td>18 (53%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Minimal response</td>
<td>2 (20%)</td>
<td>8 (22%)</td>
<td>5 (15%)</td>
<td>4 (23%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>2 (20%)</td>
<td>7 (19%)</td>
<td>1 (3%)</td>
<td>8 (47%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>1 (10%)</td>
<td>5 (14%)</td>
<td>3 (9%)</td>
<td>4 (23%)</td>
</tr>
<tr>
<td>Not evaluable*</td>
<td></td>
<td></td>
<td></td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Overall response rate (≥ PR)‡</td>
<td>14 (39%)</td>
<td>22 (65%)</td>
<td>1 (6%)</td>
<td></td>
</tr>
</tbody>
</table>

* 2 patients were randomized but did not receive study therapy and were included as treatment failure (one was randomized to arm B while 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 overall response rate (partial response or better) for arm C was 64.7% (95% CI 48.6-80.8) while the overall response rate for arm B was 38.9% (95% CI 23-54.8), p=0.035
Table 3. Grade 3/4 adverse events at least possibly related to the study treatment in 5% or greater of patients in the phase II portion

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Arm_B N=35</th>
<th>Arm_C N=33</th>
<th>Arm_D N=17</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>4(11.4)</td>
<td>8(24.2)</td>
<td>1(5.9)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>4(11.4)</td>
<td>4(12.1)</td>
<td>-</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3(8.6)</td>
<td>4(12.1)</td>
<td>-</td>
</tr>
<tr>
<td>Flu like symptoms</td>
<td>-</td>
<td>-</td>
<td>1(5.9)</td>
</tr>
<tr>
<td>Lung infection</td>
<td>4(11.4)</td>
<td>3(9.1)</td>
<td>1(5.9)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>-</td>
<td>3(9.1)</td>
<td>0.109</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>-</td>
<td>2(6.1)</td>
<td>0.232</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>4(11.4)</td>
<td>3(9.1)</td>
<td>2(11.8)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>11(31.4)</td>
<td>17(51.5)</td>
<td>4(23.5)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2(5.7)</td>
<td>5(15.2)</td>
<td>-</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>5(14.3)</td>
<td>4(12.1)</td>
<td>1(5.9)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>-</td>
<td>2(6.1)</td>
<td>0.232</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>-</td>
<td>2(6.1)</td>
<td>0.232</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>-</td>
<td>-</td>
<td>1(5.9)</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>-</td>
<td>-</td>
<td>1(5.9)</td>
</tr>
<tr>
<td>Confusion</td>
<td>-</td>
<td>2(6.1)</td>
<td>0.232</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>-</td>
<td>3(9.1)</td>
<td>0.109</td>
</tr>
<tr>
<td>Thromboembolic event</td>
<td>-</td>
<td>2(6.1)</td>
<td>0.232</td>
</tr>
</tbody>
</table>

* compared arm B to arm C using the Fisher's exact test
Table 4. All cause, all grade non-hematologic adverse events in >15% of patients regardless of attribution

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Grade</th>
<th>Arm_B (N=35)</th>
<th>Arm_C (N=33)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>1/2</td>
<td>12(34.3)</td>
<td>9(27.3)</td>
<td>0.6049</td>
</tr>
<tr>
<td>Constipation</td>
<td>1/2</td>
<td>8(22.9)</td>
<td>6(18.2)</td>
<td>0.7669</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1/2</td>
<td>6(17.1)</td>
<td>9(27.3)</td>
<td>0.3866</td>
</tr>
<tr>
<td>Nausea</td>
<td>1/2</td>
<td>6(17.1)</td>
<td>9(27.3)</td>
<td>0.3866</td>
</tr>
<tr>
<td>Edema</td>
<td>1/2</td>
<td>4(11.4)</td>
<td>6(18.2)</td>
<td>0.5066</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1/2</td>
<td>9(25.7)</td>
<td>3(9.1)</td>
<td>0.1114</td>
</tr>
<tr>
<td>Fever</td>
<td>1/2</td>
<td>6(17.1)</td>
<td>4(12.1)</td>
<td>0.7350</td>
</tr>
<tr>
<td>Pain</td>
<td>1/2</td>
<td>2(5.7)</td>
<td>10(30.3)</td>
<td>0.0105</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1/2</td>
<td>8(22.9)</td>
<td>11(33.3)</td>
<td>0.4209</td>
</tr>
<tr>
<td>Generalized muscle weakness</td>
<td>1/2</td>
<td>7(20)</td>
<td>2(6.1)</td>
<td>0.1515</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>1/2</td>
<td>6(17.1)</td>
<td>4(12.1)</td>
<td>0.7350</td>
</tr>
<tr>
<td>Tremor</td>
<td>1/2</td>
<td>7(20)</td>
<td>5(15.2)</td>
<td>0.7531</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1/2</td>
<td>5(14.3)</td>
<td>5(15.2)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Skin / subcutaneous tissue disorders</td>
<td>1/2</td>
<td>2(5.7)</td>
<td>5(15.2)</td>
<td>0.2522</td>
</tr>
<tr>
<td>Anemia</td>
<td>3/4/5</td>
<td>4(11.4)</td>
<td>9(27.3)</td>
<td>0.1277</td>
</tr>
<tr>
<td>Lung infection</td>
<td>3/4/5</td>
<td>6(17.1)</td>
<td>3(9.1)</td>
<td>0.4783</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3/4/5</td>
<td>11(31.4)</td>
<td>17(51.5)</td>
<td>0.1389</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3/4/5</td>
<td>2(5.7)</td>
<td>5(15.2)</td>
<td>0.2522</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>3/4/5</td>
<td>1(2.9)</td>
<td>6(18.2)</td>
<td>0.0513</td>
</tr>
</tbody>
</table>

* based on the Fisher’s exact test
Table 5. Factors associated with overall response, progression survival (PFS) and overall survival (OS)

<table>
<thead>
<tr>
<th>Overall response#</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted OR (95% CI)</td>
<td>Adjusted OR (95% CI)</td>
</tr>
<tr>
<td>Age (in 10 yrs increment)</td>
<td>1.16 (0.64-2.11)</td>
<td>1.22 (0.62-2.40)</td>
</tr>
<tr>
<td>Number of prior therapies (≥5 vs. &lt;5)</td>
<td>1.23 (0.47-3.21)</td>
<td>1.77 (0.56-5.60)</td>
</tr>
<tr>
<td>B2-microglobulin (mg/L)</td>
<td>1.03 (0.84-1.25)</td>
<td>0.99 (0.80-1.23)</td>
</tr>
<tr>
<td>High-risk Cytogenetics</td>
<td>0.36 (0.11-1.22)</td>
<td>0.33 (0.09-1.22)</td>
</tr>
<tr>
<td>Study arm# (Arm C vs B)</td>
<td>2.88 (1.09-7.61)*</td>
<td>2.98 (0.99-8.99)</td>
</tr>
</tbody>
</table>

#Overall response is defined as partial response or better, study arm p-value=0.052 in the multivariable overall response model

*OR: odds ratio, HR: hazard ratio
Randomized multicenter phase II study of pomalidomide, cyclophosphamide, and dexamethasone in relapsed refractory myeloma