Pomalidomide, Cyclophosphamide, and Dexamethasone Is Superior to Pomalidomide and Dexamethasone in Relapsed and Refractory Myeloma: Results of a Multicenter Randomized Phase II Study


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Background

• Pomalidomide-dexamethasone results in an overall response rate of 33% and median PFS of 4.2 months in patients with prior lenalidomide and bortezomib¹

• Alkylating agents (melphalan, cyclophosphamide) represent standard of care therapy for patients with multiple myeloma with the latter being associated with less myelosuppression

• In addition, a combination of lenalidomide and continuous cyclophosphamide resulted in an ORR of 50% in lenalidomide refractory patients²

• Larocca et al. combined continuous pomalidomide with oral cyclophosphamide³.
  – MTD: pomalidomide 2.5 mg PO daily, cyclophosphamide 50 mg PO QOD, Prednisone 50 mg PO QOD x 6 cycles followed by pomalidomide/pred maintenance
  – ORR 51%, median PFS 10.4 months

Background

Phase I study: Arm A
Dose escalation of oral weekly cyclophosphamide in combination with standard pomalidomide dexamethasone

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Cyclophosphamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1</td>
<td>300 mg PO D1,8</td>
</tr>
<tr>
<td>1</td>
<td>300 mg PO D1,8,15</td>
</tr>
<tr>
<td>2</td>
<td>400 mg PO D1,8,15</td>
</tr>
<tr>
<td>3</td>
<td>500 mg PO D1,8,15</td>
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</tbody>
</table>

Recommended phase II dose

- Pom 4 mg
- Cy 400mg
- Dex 40mg

Baz R et al. Blood (ASH), Nov 2012; 120: 4062
Study Design: Treatment Plan

1:1 Randomization

**Arm B** (28 days cycle)
- Pomalidomide 4mg PO D1-21/28 days
- Dexamethasone 40*mg PO D1,8,15,22

**Arm C** (28 days cycle)
- Pomalidomide 4mg PO D1-21/28 days
- Cyclophosphamide 400 mg PO D1,8,15
- Dexamethasone 40* mg PO D1,8,15,22

**Arm D**: Cross Over for PD at discretion of patient and treating physician

* Dexamethasone 20 mg was given if patient was older than 75 years or unable to tolerate 40 mg of dexamethasone

** Aspirin 81-325 mg daily as prophylactic antithrombotic treatment unless contraindicated. If aspirin is contraindicated, patients will receive another form of anti-thrombotic therapy (low molecular weight heparin or therapeutic anticoagulation with warfarin)
Randomized Phase II trial

• Primary endpoint: Compare the overall response rate (PR or better) of arm B versus C (IMWG response criteria)

• Secondary endpoints:
  – Progression free survival (PFS)
  – OS (overall survival)
  – Safety NCI CTC version 4.0
  – ORR for arm D (IMWG)
Statistical Considerations

• Intent to treat (ITT) analysis:
  – all patients randomized to treatment were analyzed according to the treatment to which they were randomized

• A sample size of 70 patients achieves 78% power to detect the group difference of 30% using the two-sided Fisher’s exact test assuming the response rate of arm B is 30% and arm C 60% with a significant level of 10%
Eligibility

• Key eligibility criteria
  – At least 2 prior therapies and must be lenalidomide refractory (PD while receiving or within 60 days of discontinuing lenalidomide)
  – Measurable disease (Serum M spike ≥ 0.5 g/dL, or Urine M spike ≥ 200 mg/24h, or iFLC>100mg/L and abn ratio)
  – ECOG performance status ≤2
  – Serum creatinine < 3mg/dL
  – ANC ≥ 1000/mm3 (GCSF allowed during screening)
  – Platelet count ≥ 50,000/mm3 (or 30,000/mm3 if greater than 50% BMPC)
  – Washout period 2 weeks from cycle 1 day 1
<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Arm B (N=36)</th>
<th>Arm C (N=34)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median (range)</td>
<td>64 (50-78)</td>
<td>65 (47-80)</td>
<td>0.7</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>23 (64)</td>
<td>18 (53)</td>
<td>0.5</td>
</tr>
<tr>
<td>Number of prior therapies, median (range)</td>
<td>4 (2-12)</td>
<td>4 (2-9)</td>
<td>0.5</td>
</tr>
<tr>
<td>Bortezomib refractory, n (%)</td>
<td>28 (78)</td>
<td>24 (71)</td>
<td>0.4</td>
</tr>
<tr>
<td>Carfilzomib refractory, n (%)</td>
<td>16 (44)</td>
<td>13 (38)</td>
<td>0.6</td>
</tr>
<tr>
<td>Prior high-dose therapy, n (%)</td>
<td>27 (75)</td>
<td>28 (82)</td>
<td>0.7</td>
</tr>
<tr>
<td>Prior alkylating agent, n (%)</td>
<td>32 (89)</td>
<td>32 (94)</td>
<td>1.0</td>
</tr>
<tr>
<td>B2-microglobulin, median (range)</td>
<td>3.2 (1.6-10)</td>
<td>3.6 (1.5-13.9)</td>
<td>0.5</td>
</tr>
<tr>
<td>Serum creatinine, median (range)</td>
<td>1 (0.5-2.3)</td>
<td>0.9 (0.6-2.1)</td>
<td>0.6</td>
</tr>
<tr>
<td>High-risk cytogenetics, n (%)</td>
<td>8 (22)</td>
<td>7 (21)</td>
<td>1.0</td>
</tr>
<tr>
<td>Deletion 17p, n (%)</td>
<td>6 (16)</td>
<td>5 (15)</td>
<td>0.6</td>
</tr>
<tr>
<td>t(4;14), n (%)</td>
<td>4 (11)</td>
<td>3 (9)</td>
<td>0.6</td>
</tr>
<tr>
<td>Trisomy or tetrasomy 1q, n (%)</td>
<td>18 (50)</td>
<td>9 (26)</td>
<td>0.1</td>
</tr>
</tbody>
</table>
Results: IMWG response rate

Arm B (Pom Dex)
- ORR (≥PR): 38.9
- CBR (≥MR): 61.1
- ≥ VGPR: 13.8

Arm C (Pom Cy Dex)
- ORR (≥PR): 64.7
- CBR (≥MR): 79.4
- ≥ VGPR: 11.8

P=0.03
P=0.1
Results: PFS

<table>
<thead>
<tr>
<th>Arm</th>
<th>N</th>
<th>Event (%)</th>
<th>Censored (%)</th>
<th>Median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>36</td>
<td>30 (83%)</td>
<td>6 (17%)</td>
<td>4.4(2.3, 6.0)</td>
</tr>
<tr>
<td>C</td>
<td>34</td>
<td>26 (76%)</td>
<td>8 (24%)</td>
<td>9.5(4.6, 13.6)</td>
</tr>
</tbody>
</table>

Log-rank p = 0.1078
Results: OS

<table>
<thead>
<tr>
<th>Arm</th>
<th>N</th>
<th>Event</th>
<th>Censored</th>
<th>Median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B+D</td>
<td>36</td>
<td>20 (56%)</td>
<td>16 (44%)</td>
<td>16.8 (9.3, NA)</td>
</tr>
<tr>
<td>C</td>
<td>34</td>
<td>13 (38%)</td>
<td>21 (62%)</td>
<td>NA (13.0, NA)</td>
</tr>
</tbody>
</table>

Log-rank p = 0.1308
### Results: Gr3/4 AE in >5% of patients (at least possibly related)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Arm C (Pom Cy Dex)</th>
<th>Arm B (Pom Dex)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphopenia</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Other infections</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>11</td>
<td>17</td>
</tr>
<tr>
<td>Pneumonia (incl pneumonitis)</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>Anemia</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>33</td>
<td>49</td>
</tr>
</tbody>
</table>

* Includes 1 patient with grade 5 pneumonia.
Results: Allcause, all grade non-hematologic AE in >15% of patients

- Fever
- Weakness (muscle)
- Edema
- Lung Infection
- URI
- Fatigue
- Diarrhea
- Nausea
- Constipation
- Hyperglycemia
- Tremors

Percent of patients

Arm C (Pom Cy Dex)
Arm B (Pom Dex)
As of 11/2014, 15 patients (out of 30 eligible) crossed over from Arm B to arm D (addition of oral weekly cyclophosphamide to the tolerated dose of pomalidomide dexamethasone).

Safety: the percent of patients with grade 3 / 4 at least possibly related adverse events is as follows:

- Neutropenia 33%, Febrile neutropenia 13%, Anemia 6%, pneumonia / pneumonitis 6%, fatigue 6%, fever 6%.

IMWG responses: ORR (≥ PR) was 13% with 2 PR, 2 MR, 7 SD, 3 PD, 1 NE. 14/15 have progressed with a median PFS of 3 months (range 1-9 months).
## Pomalidomide combinations

<table>
<thead>
<tr>
<th>N</th>
<th>Dose / Schedule</th>
<th>ORR</th>
<th>PFS</th>
</tr>
</thead>
</table>
| Pomalidomide Dex | Pom 4 mg D1-21  
Dex 40 mg weekly                          | 33%  | 4.7  |
| + Clarithromycin¹  | Pom 4 mg D1-21  
Dex 40 mg weekly  
Clarithromycin 500 mg BID                      | 61.4%| 8.1  |
| + Bortezomib²     | Bort: 1.3 mg/m2 D1,4,8,11  
Pom: 4 mg D1-14  
Dex: 20mg D1,2,4,5,8,9,11,12                         | 75%  | N/A  |
| + Carfilzomib³    | Carfil: 20/27 mg/m2 D1,2,8,9,15,16  
Pom: 4 mg D1-21  
Dex: 40 mg weekly                                    | 64%  | 12   |
| + Liposomal Doxorubicin⁴ | PLD: 5 mg/m2 IVD1,4,8,11  
Pom: 4 mg D1-21  
Dex: 40 mg weekly                                   | 34.5%| N/A  |
| + Cyclophosphamide⁵ | Cy: 50 mg PO QOD  
Pom 2.5 mg 28/28  
Pred 50 mg QOD                                          | 51%  | 10.4 |
| +/- Cyclophosphamide⁶ | Pom 4 mg D1-21  
Dex 40 mg weekly  
+/- Cy 400 mg PO D1,8,15                           | 39%  | 4.4  |

Conclusions and future directions

- As compared to pomalidomide dexamethasone, Pom Cy Dex results in
  - A superior response rate (ORR 65% versus 39%)
  - An improvement in progression free and overall survival of borderline significance.
- Pom Cy Dex was well tolerated with possible increased hematologic adverse events which are manageable.
- This regimen compares favorably with other pomalidomide based regimens in terms of efficacy, toxicities and cost.
- The addition of cyclophosphamide for patients progressing on pomalidomide and dexamethasone results in minimal clinical benefits.
- Baseline levels of Cereblon, Ikaros and Aiolos will be correlated with clinical benefits.
Acknowledgments

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• Moffitt biostatistic team

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