# A Phase 1/2 Multi-Center, Randomized, Open-Label, Dose Escalation Study to Determine the Maximum Tolerated Dose, Safety, and Efficacy of Pomalidomide Alone or in Combination With Low-Dose Dexamethasone in Patients With Relapsed and Refractory Multiple Myeloma (MM) Who Have Received Prior Treatment That Includes Lenalidomide and Bortezomib

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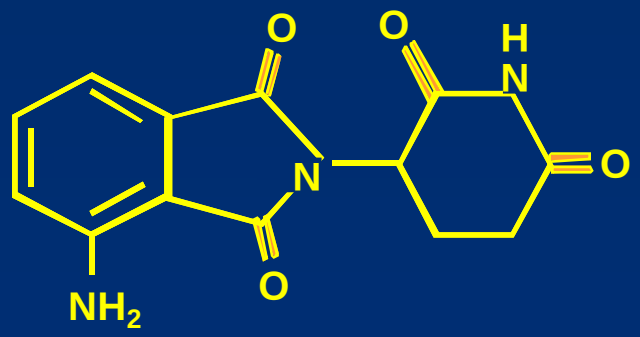
# Disclosures

- **Membership of Advisory Committees:**
  - **Celgene Corporation**
  - **Millennium**
  - **Johnson & Johnson**
- **Research Support / PI:**
  - **Celgene Corporation**
  - **Millennium**

# Introduction

- Pomalidomide (POM) is a distinct immunomodulatory agent that has demonstrated direct anti-myeloma effects in lenalidomide-refractory patients (pts) with significant antiproliferative activity in vitro[1-2]
- POM has promising activity in relapsed multiple myeloma (MM) across a dose range of 2 – 5 mg dosed continuously[3]
- POM at 4 mg for 21 of 28 days as monotherapy and in combination with low-dose dexamethasone (dex) is active and well tolerated in pts with relapsed and refractory MM[4]




Pomalidomide

1. Hideshima et al. Blood. 2000;96(9):2943-50. 2. Mitsiades et al. Blood. 2002;99:4525-30.
3. Schey et al. J Clin Oncol 22:3269-76. 4. Richardson et al. Blood. 2010;116:377-8 [abstract 864].

# Introduction (cont.)

- POM has clinical efficacy in relapsed MM pts following LEN treatment at a dose of 2 mg given continuously with low-dose dex

| Phase 2 Study: POM 2 mg + low-dose dex[1-3] | | | |
|---|---|---|---|
| | ORR | PFS | OS |
| 1-3 prior therapies[1] | 63% | 11.6 mos | 94% at 6 mos |
| Refractory to LEN[2] | 32% | 4.8 mos | 13.9 mos |
| Refractory to LEN & Bz[3] | 26% | 8 mos | 86% at 6 mos |

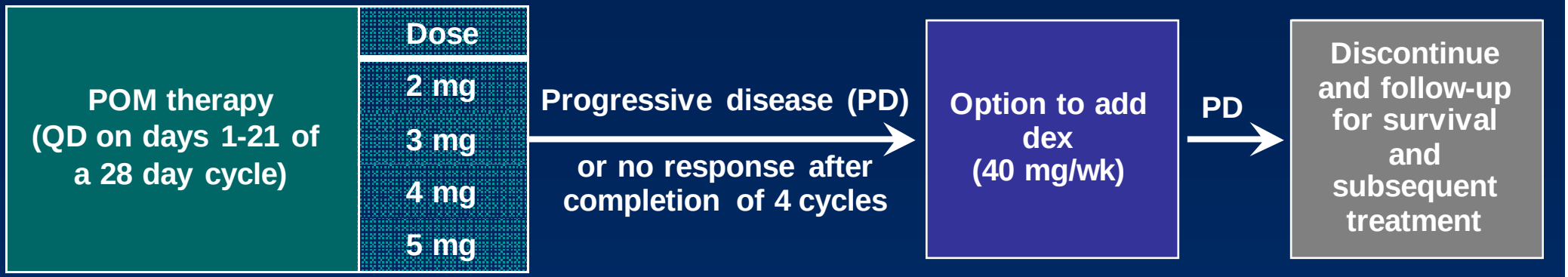
- MM002 (Phase 1) evaluated POM 21 of 28 days ± low-dose dex to explore higher doses ranging from 2 to 5 mg[4]
  - Relapsed and refractory MM
  - Received both LEN & bortezomib (Bz): refractory to last therapy
- MM002: Phase 1 (as of June 2010) and preliminary Phase 2 data (as of October 2010) are presented

1. Lacy et al. J Clin Oncol. 2009;27:5008-14. 2. Lacy et al. Leukemia. 2010;24(11):1934-9. 3. Lacy et al. ASCO 2010 Presentation [Abstract 8002]. 4. Richardson et al. Blood. 2009;114:126-7 [abstract 301].

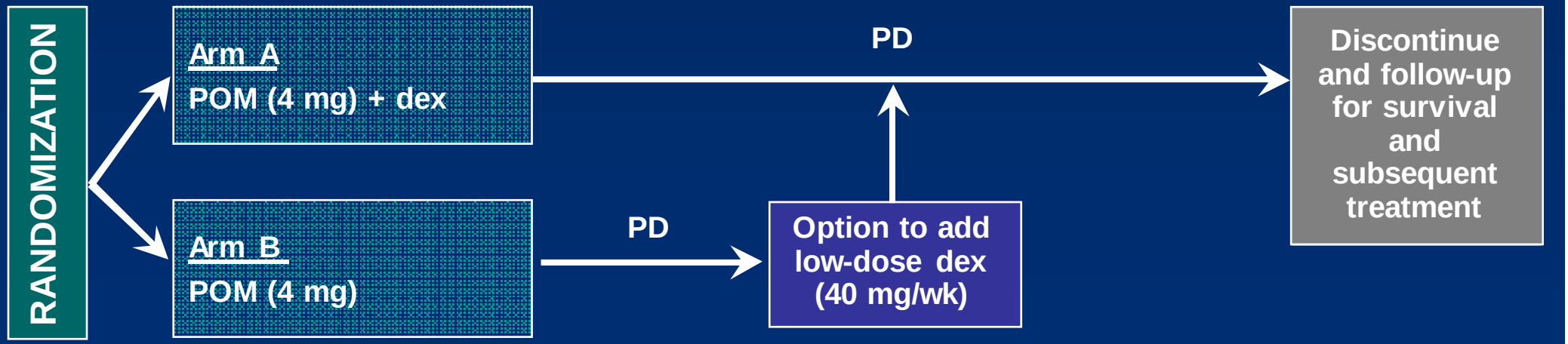
# MM-002 Study Schema

## POM ± low-dose dex in Relapsed and Refractory MM

### Phase 1 (MTD)




### Phase 2 (Open Label)




**Concomitant Medications: anti-coagulants, G-CSF use after Cycle 1, erythroid growth factors, bisphosphonates, transfusions with platelet, RBCs as clinically indicated .**

# MM-002 Study Design
## POM ± low-dose dex in Relapsed and Refractory MM

- Selected key inclusion criteria:
  - ≥ 18 yrs of age
  - Relapsed and refractory MM[1]
    - Measurable levels of M paraprotein in serum or urine
    - ≥ 2 prior therapies: progressing on treatment or within 60 days of last therapy
    - Prior treatment with ≥ 2 cycles of LEN and ≥ 2 cycles of Bz (either in separate regimens or within the same regimen)
- Primary endpoints:
  - Phase 1: MTD
  - Phase 2: PFS
- Secondary endpoints: response (modified EBMT and IMWG criteria)[2-4], time to response, duration of response (DOR), OS, safety

1. Anderson et al. Leukemia. 2008;22(2):231-9. 2. Blade et al. Br J Haematol. 1998;102(5):1115-23. 3. Richardson et al. N Engl J Med. 2003;348(26):2609-17. 4. Durie et al. Leukemia. 2006;20(9):1467-73.

# MM-002: Phase 1
# MTD, Efficacy, Safety, and Statistical Analysis

- MTD - the highest dose at which >2 of 6 pts experienced a DLT within the first 28-day cycle
  - MTD determined using a "3 + 3" design
  - Safety analyses: DLTs summarized at conclusion of each dose level
- Efficacy assessments carried out every 28 days following completion of the first cycle
- DMC review of efficacy and safety data completed
  - Safety assessed using NCI CTC for AE v 3.0

DLT: Dose-limiting toxicity; MTD: Maximum tolerated dose; DMC: Data Monitoring Committee; NCI CTC: National Cancer Institute Common Toxicity Criteria; AE: Adverse event

# MM-002: Phase 1 Demographics

| | 2 mg (n = 6) | 3 mg (n = 8) | 4 mg (n = 14) | 5 mg (n = 10) | Total (N = 38) |
|---|---|---|---|---|---|
| Median age (range), yrs | 66 (55-72) | 72 (61-78) | 69 (45-80) | 64 (38-83) | 67 (38-83) |
| Male, % | 17 | 38 | 71 | 40 | 47 |
| Caucasian, % | 83 | 100 | 100 | 80 | 92 |
| Median # prior therapies (range) | 8 (5-14) | 6 (2-12) | 6 (2-17) | 6 (3-10) | 6 (2-17) |
| Prior LEN and Bz, % | 100 | 100 | 100 | 100 | 100 |
| Prior dexamethasone, % | 100 | 100 | 100 | 100 | 100 |
| Prior thalidomide, % | 67 | 75 | 79 | 90 | 79 |
| Prior SCT, % | 67 | 75 | 79 | 60 | 66 |

- 84% aged ≤ 75 yrs
- 82% ISS stage II/III disease
- 28% pts received prior carfilzomib

# MM-002: Phase 1 Disposition

| | 2 mg (n = 6) n | 3 mg (n = 8) n | 4 mg (n = 14) n | 5 mg (n = 10) n | Total (N = 38) n |
|---|---|---|---|---|---|
| Discontinuation | 6 | 8 | 12 | 7 | 33 |
| PD | 2 | 3 | 5 | 3 | 13 |
| AE[a] | 1 | 0 | 2 | 1 | 4 |
| Withdrew consent | 1 | 1 | 2 | 2 | 6 |
| Death[b] | 0 | 1 | 2 | 0 | 3 |

- Rate of discontinuation due to AE was low (11%)
- No treatment-related mortality

a. Includes thrombocytopenia, anemia, gastrointestinal hemorrhage, vomiting, chills, fatigue, pyrexia, metastases to meninges, renal failure, and rash.
b. Not related to study drug (pneumonia due to infection; gastrointestinal hemorrhage; bacterial meningitis and subarachnoid hemorrhage).

# MM-002: Phase 1 Adverse Events

| | 2 mg (n = 6) n | 3 mg (n = 8) n | 4 mg (n = 14) n | 5 mg (n = 10) n | Total (N = 38) n |
|---|---|---|---|---|---|
| **G3/4 AE** | | | | | |
| Neutropenia | 1 | 4 | 7 | 8 | 20 |
| Anemia | 4 | 2 | 2 | 0 | 8 |
| Thrombocytopenia | 1 | 2 | 1 | 2 | 6 |
| Fatigue | 2 | 1 | 3 | 1 | 7 |
| Peripheral neuropathy | 1 | 0 | 1 | 3 | 5 |
| VTE | 2 | 0 | 1 | 1 | 4 |
| **SAE and dose reductions** | | | | | |
| SAEs | 3 | 4 | 8 | 4 | 19 |
| POM dose reduction | 0 | 1 | 3 | 10 | 14 |

- Manageable toxicity
  - Most common AEs (all grades): neutropenia (47%), fatigue (32%), anemia (24%), and muscle spasms (18%)

SAEs, severe adverse events; VTE, venous thromboembolism

# MM-002: Phase 1 Dose-Limiting Toxicities

| POM Dose | Completed Cycles,[a] Median (range) | DLTs (Reason) |
|---|---|---|
| 2 mg (n = 6) | 1.5 (1-12) | 1 (G3 fatigue) |
| 3 mg (n = 8) | 5.0 (2-12) | 1 (G4 neutropenia) |
| 4 mg (n = 14) | 5.5 (1-20) | 2 (G4 neutropenia) |
| 5 mg (n = 10) | 8.0 (1-16) | 4 (G4 neutropenia) |

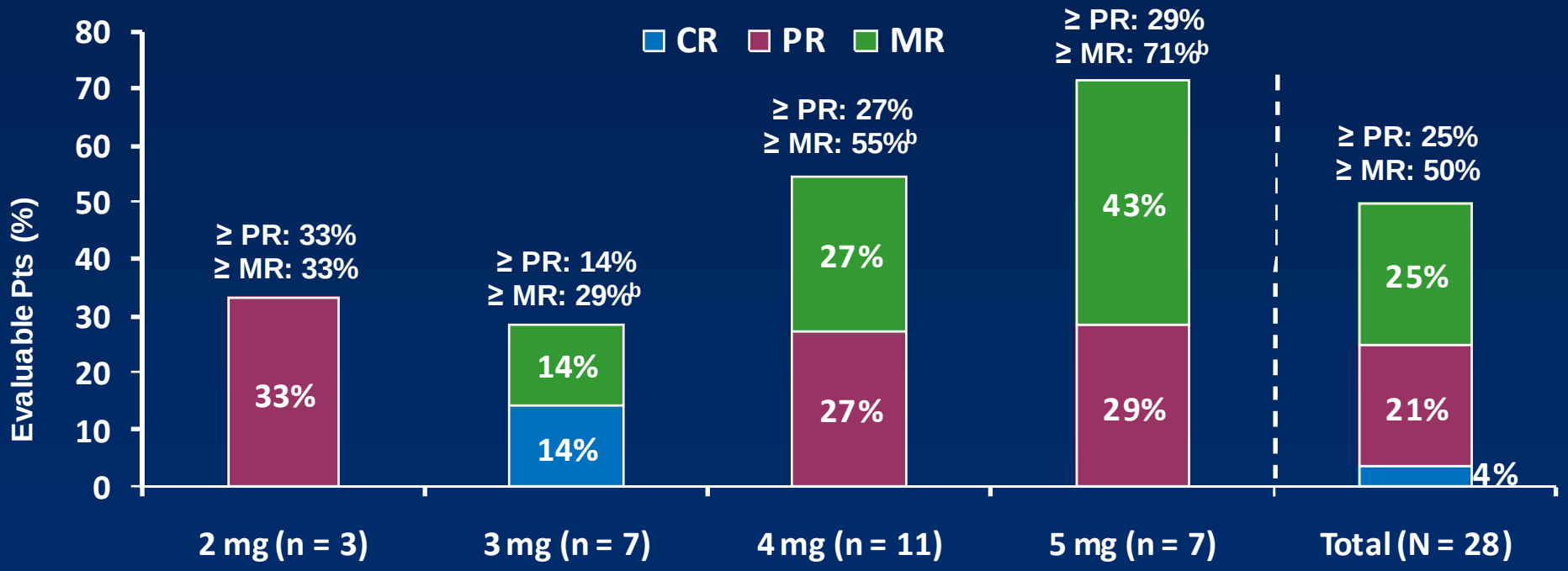
- Pts received a median of 5 (range 1-20) cycles of POM
- All but 1 of the DLTs due to G4 neutropenia
- MTD determined to be 4 mg

a. During the dose-escalation phase, G-CSF was not allowed during Cycle 1 (ie, initial 28 days).

# MM-002: Phase 1

## Best Response & Clinical Outcome: POM ± low-dose dex

### (Evaluable Pts[a])




| | | | | | |
|---|---|---|---|---|---|
| DOR[c], median wks | 20 | 24 | 16 | Not reached | 20 |
| PFS, median wks | 31 | 36 | 12 | 20 | 20 |
| OS, median wks | 81 | 80 | Not reached | Not reached | 80 |

- Pts who received POM 4 or 5 mg achieved higher response rates compared to those who received 2 or 3 mg

a. Includes eligible, treated and evaluable for efficacy assessment; b. Discrepancies in totals due to rounding
c. Assessed for responders only: 2mg (1); 3mg (1); 4mg (3); 5mg (2); total (7)

# MM-002: Phase 2
# Status and Update

- Study ongoing: Phase 2 enrollment completed in September 2010 (N=221)
- Data analysis performed on first 120 efficacy evaluable pts (enrolled by April 30, 2010)
- Central Adjudication Committee review of Phase 2 response data in process
- Aggregate data on response results based on investigator assessment (Oct 29, 2010 cut-off)

# MM-002: Phase 2 Preliminary Results Demographics

| Relapsed and Refractory Myeloma | Total N=120 |
|---|---|
| Median age, yrs (range) | 63 (34 - 88) |
| ≤75, % | 89 |
| >75, % | 11 |
| Male, % | 55 |
| Caucasian, % | 79 |
| Median time since diagnosis, yrs (range) | 6 (1 - 18) |
| Median # prior therapies (range) | 5 (2 - 13) |
| Prior LEN & Bz, % | 100 |
| Prior thalidomide, % | 74 |
| Prior SCT, % | 79 |
| Double refractory to both prior LEN & Bz, n (%) | 38 (32) |
| ECOG performance status score, % | |
| 0 | 23 |
| 1 | 64 |
| 2 | 10 |
| Pending | 3 |

# MM-002: Phase 2 Preliminary Results Efficacy (Aggregate Data)

| Best Response in Efficacy Evaluable Pts (Modified EBMT Criteria) | |
|---|---|
| N = 120 | n (%) |
| ≥PR | 30 (25) |
| CR | 1 (1) |
| PR | 29 (24) |
| MR | 16 (13) |
| SD | 64 (53) |
| PD | 10 (8) |

CR: complete response; PR: partial response; MR: minimal response; SD: stable disease; PD: progressive disease

# MM-002: Phase 2 Preliminary Results Efficacy (Aggregate Data)

| Best Response According to Refractoriness to Prior Therapy* (Modified EBMT Criteria) | | | |
|---|---|---|---|
| | Refractory to LEN N = 64 | Refractory to Bz N = 51 | Double Refractory (LEN & Bz) N = 38 |
| | n (%) | | |
| ≥PR | 15 (23) | 13 (26) | 11 (29) |
| ≥MR | 21 (33) | 19 (37) | 13 (34) |
| CR | 0 | 1 (2) | 0 |
| PR | 15 (23) | 12 (24) | 11 (29) |
| MR | 6 (9) | 6 (11) | 2 (5) |
| SD | 36 (56) | 25 (49) | 20 (53) |
| PD | 7 (10) | 7 (14) | 5 (13) |

* Among the 120 efficacy evaluable pts, 64 were refractory to LEN, 51 refractory to Bz, 38 were refractory to both LEN and Bz

# MM-002: Phase 2 Preliminary Results Efficacy with or without Cytogenetic Abnormalities (Aggregate Data)

| | Best Response (Modified EBMT Criteria) | |
|---|---|---|
| | With Cytogenetic Abnormalities* N = 45 n (%) | Without Cytogenetic Abnormalities N = 74 n (%) |
| ≥PR | 8 (18) | 22 (30) |
| CR | 0 (0) | 1 (1) |
| PR | 8 (18) | 21 (28) |
| MR | 8 (18) | 8 (11) |
| SD | 25 (56) | 38 (51) |
| PD | 4 (9) | 6 (8) |

*Presence of at least one of the following at baseline: del13q14, del17p13, t(4p13;14q32), t(14q32;16q23)

# MM-002: Phase 2 Preliminary Results Safety (Aggregate Data)

| G3/4 Events of Clinical Importance | Total N = 120 % |
|---|---|
| **Hematologic** | |
| Neutropenia | 42 |
| Thrombocytopenia | 22 |
| Anemia | 20 |
| Febrile neutropenia | 5 |
| **Non-Hematologic** | |
| Infections | 31 |
| Fatigue | 12 |
| Renal failure | 7 |
| Cardiac disorders[a] | 4 |
| DVT | 1 |
| Peripheral neuropathy | 0 |

a. Cardiac disorders include: atrial fibrillation, myocardial ischemia, CHF

# MM-002: Conclusions

## POM ± low-dose dex in Relapsed and Refractory MM

- Manageable toxicity profile in heavily pretreated pts status-post LEN & Bz
  - MTD: 4 mg days 1-21 of a 28-day cycle
  - Most common hematologic G3/4 AE: myelosuppression
- Very low incidence of G3/4 PN and DVT
- Clinically meaningful responses in relapsed and refractory pts status-post LEN & Bz
  - Median lines of prior therapy:
    - 6 in Phase 1
    - 5 in Phase 2
  - Phase 1 (evaluable pts):
    - ≥PR: 25%; ≥MR: 50%
    - Median DOR: 20 wks
    - Median PFS: 20 wks
    - Median OS: 80 wks

# MM-002: Conclusions
# POM ± low-dose dex in
# Relapsed and Refractory MM

- Phase 2 (aggregate data):
  - ≥PR 25%; ≥MR 38%
  - Median DOR: not reached
- Double refractory to both LEN & Bz
  - ≥PR 29%; ≥MR 34%
  - Median DOR: not reached
- POM has activity in pts who have cytogenetic abnormalities

# Future Directions

- Final analysis of Phase 2 (N=221)
- Analysis of gene expression profiling/surrogates
- Additional study in relapsed and refractory MM now enrolling
- Future studies to use 4 mg on days 1-21 of each 28-day cycle
- Further dose exploration in less heavily pre-treated pts
- Novel combinations (e.g. POM/Bz/dex, second-generation proteasome inhibitors, alkylating agents, clarithromycin/dex, other small molecules, MoABs)

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**Institutions with Study Sites**

The Cancer Center - Hackensack University Medical Center
H. Lee Moffitt Cancer and Research Institute
Massachusetts General Hospital
Mayo Clinic Arizona
Mayo Clinic Minnesota
Roswell Park Cancer Institute
The Ohio State University - James Cancer Hospital
University of Michigan Comprehensive Cancer Center
Washington University - Siteman Cancer Center
St. Vincent's Comprehensive Cancer Center
University of Pittsburgh Cancer Institute
Emory University
Princess Margaret Hospital - UHN
Cross Cancer Center
University of Calgary - Tom Baker Cancer Center
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**Our Patients and Families**