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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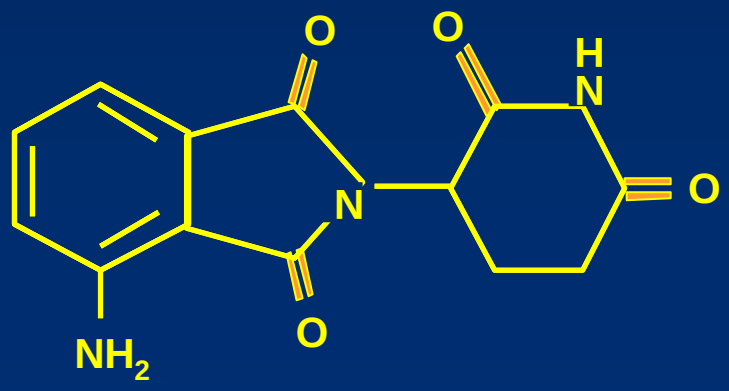
Background

- Pomalidomide (POM) is a distinct immunomodulatory agent that has demonstrated direct anti-myeloma effects in lenalidomide-refractory patients with significant antiproliferative activity in vitro[1-2]
- POM has a different clinical efficacy and safety profile, with MTD of 2mg daily for 28 days of a 28-day cycle in a phase 1 study in relapsed MM[3-4]



Pomalidomide

1. Hideshima et al. Blood. 2000;96(9):2943-50. 2. Mitsiades N, et al. Blood. 2002;99:4525-4530.
3. Schey et al. J Clin Oncol. 2004;22:3269-3276. 4. Streetly et al. Br J Haematol. 2008;141:41-51.

Rationale

- POM: clinical efficacy in heavily pretreated pts following lenalidomide (LEN) treatment at a dose of 2 mg given continuously with dex

Phase 2 IIT study: POM 2 mg + low-dose dexamethasone (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 evaluated POM 21 of 28 days ± low-dose dex to explore higher dose (2 – 5 mg)[4]

- Relapsed and refractory MM
- Received both LEN & bortezomib (Bz): refractory to last therapy

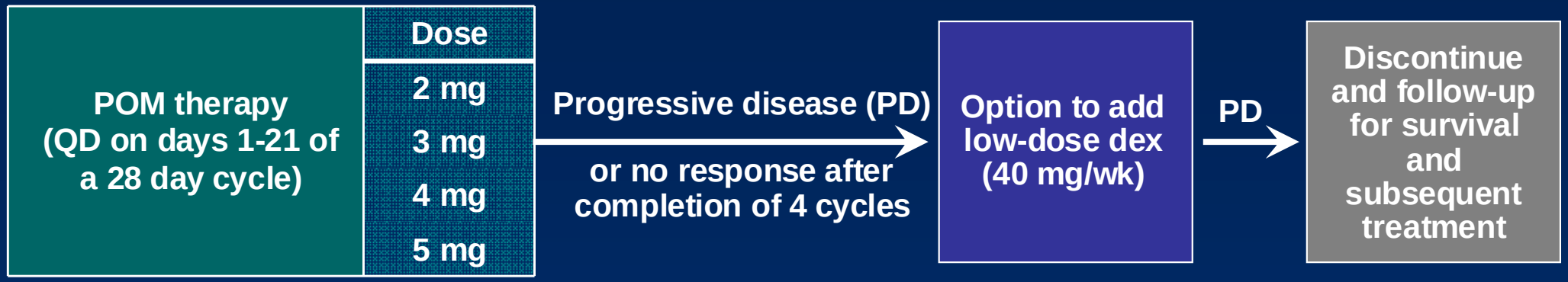
MM002: Final Phase 1 and preliminary Phase 2 data are presented

1. Lacy et al. J Clin Oncol. 2009;27:5008-5014. 2. Lacy et al. Leukemia. 2010;Sept 9:Epub ahead of print. 3. Lacy et al. ASCO 2010 Presentation (Abstract 8002). 4. Richardson P, et al. Blood. 2009;114:126-127[abstract 301].

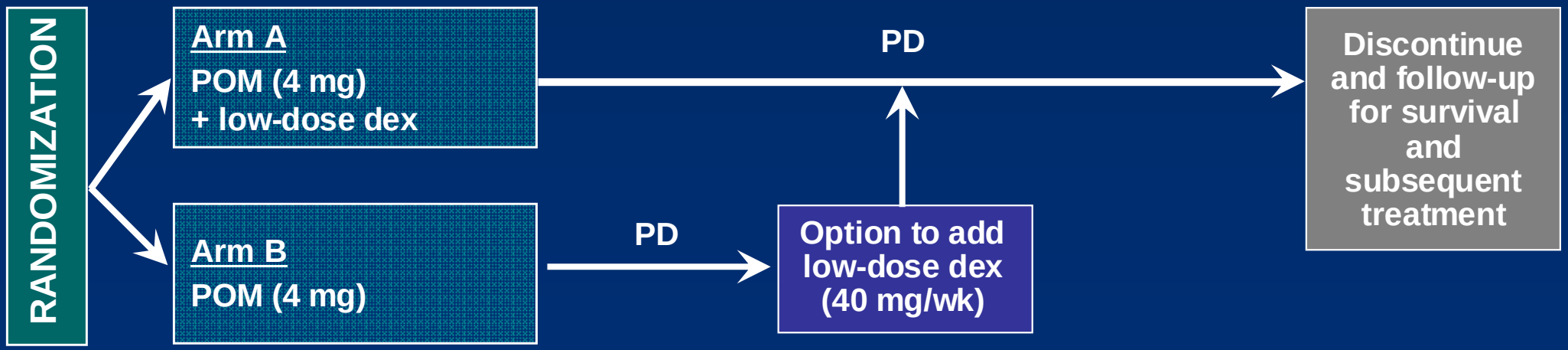
MM-002 Study Schema

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 ongoing efficacy and safety data
  - 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
Patient Demographics and Disposition

	2 mg (n = 6)	3 mg (n = 8)	4 mg (n = 14)	5 mg (n = 10)	Total (N = 38)
Median age (range), yrs	65.5 (55-72)	72 (61-78)	68.5 (45-80)	63.5 (38-83)	67 (38-83)
Male, %	17	38	71	40	47
Caucasian, %	83	100	100	80	92
Median # prior therapies (range)	7.5 (5-14)	6 (2-12)	5.5 (2-17)	5.5 (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

- Majority (84%) were aged ≤ 75 yrs
- 82% had ISS stage II/III disease
- 28% pts had received prior carfilzomib

MM-002: Phase 1
Patient Disposition (continued)

	2 mg (n = 6)	3 mg (n = 8)	4 mg (n = 14)	5 mg (n = 10)	Total (N = 38)
	n	n	n	n	n
Discontinuation	6	8	12	7	33
Disease progression	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

- The rate of discontinuation due to AE was low (10.5%)
- 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
Grade 3/4 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 (grade 3 fatigue)
3 mg (n = 8)	5.0 (2-12)	1 (grade 4 neutropenia)
4 mg (n = 14)	5.5 (1-20)	2 (grade 4 neutropenia)
5 mg (n = 10)	8.0 (1-16)	4 (grade 4 neutropenia)

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

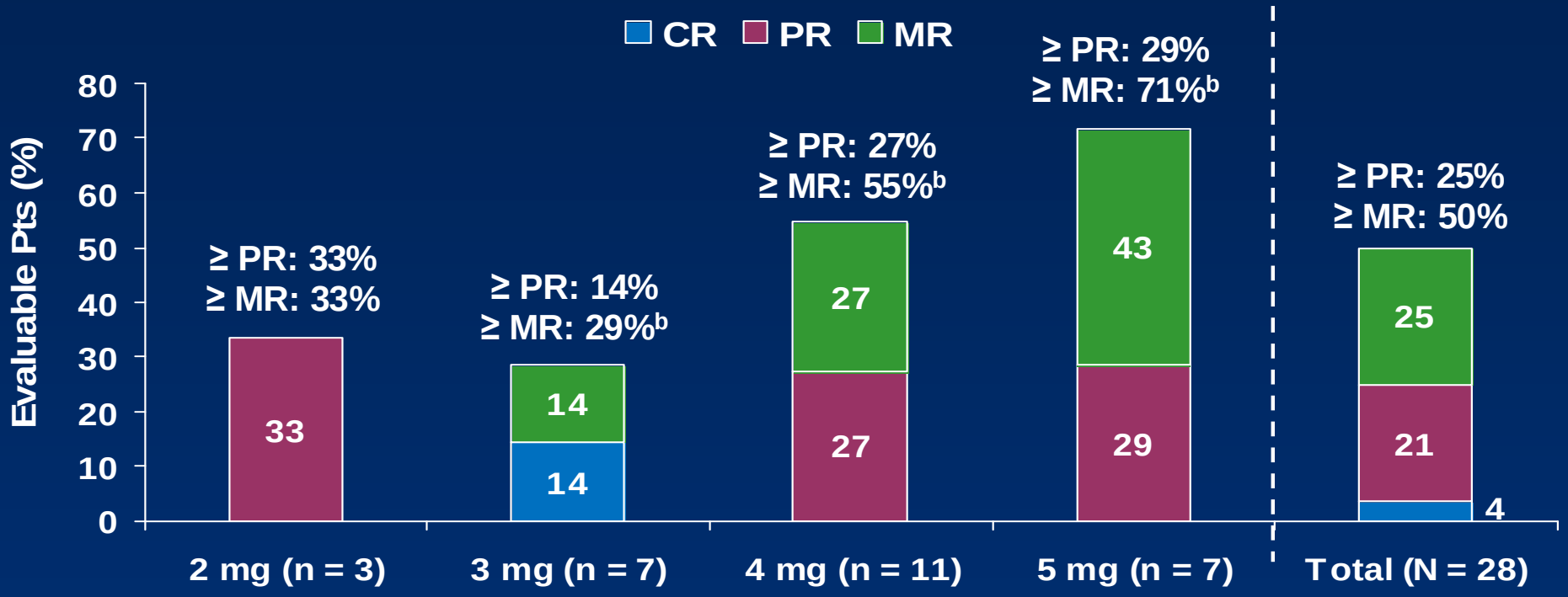
a. During the dose-escalation phase, G-CSF was not allowed during Cycle 1 (ie, initial 28 days).

MM-002: Phase 1

POM ± Low-Dose Dex in Relapsed and Refractory MM

Best Response & Clinical Outcome

(Evaluable Pts[a] [n=28])



- Best response (≥ PR) to POM alone: 18%
- Median time to best response[c]: 16.1 wks
- Median DOR: 20.1 wks (assessed for responders only)
- Median PFS: 20.1 wks (95% CI: 12.0, 36.0)
- Median OS: 79.6 wks (95% CI: 61.9, NE)

a. Includes eligible, treated and evaluable for efficacy assessment; b. Discrepancies in totals due to rounding
c. Response rates based on EBMT criteria; includes pts on POM alone (n=9), pts who had dex added for SD (n=7), and pts who had dex added for PD (n=12)

MM-002: Phase 2
Status and Update

- **Study ongoing: Phase 2 enrollment completed in September 2010 (N=221)**
- **Data analysis performed to date on first 120 efficacy evaluable pts (enrolled by April 30, 2010)**
- **Central Adjudication Committee with review of Phase 2 response data planned**

MM-002: Phase 2 Preliminary Results
Patient Demographics

Relapsed and Refractory Myeloma	Total (N=120)
Median age (range), yrs	63 (34.0, 88.0)
≤75, %	89
>75, %	11
Male, %	55
Caucasian, %	79
Median time since diagnosis (yrs)	6 (1.0, 18.1)
Median # prior therapies (range)	5 (2.0, 13.0)
Prior LEN & Bz, %	120 (100)
Prior thalidomide, %	89 (74)
Prior SCT, %	95 (79)
ECOG performance status score	
0	27 (23)
1	77 (64)
2	12 (10)
Pending	4 (3)

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

	Assessment of Best Response	
N = 120	EBMT n (%)	IMWG n (%)
≥PR	30 (25)	33 (28)
CR	1 (1)	1 (1)
VGPR	N/A	6 (5)
PR	29 (24)	26 (22)
MR	16 (13)	N/A
SD	64 (53)	76 (63)
PD	10 (8)	11 (9)

CR: complete response; VGPR: very good partial response; PR: partial response; MR: minimal response; SD: stable disease; progressive disease

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

Grade 3/4 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 therapy
  - MTD: 4 mg days 1-21 of a 28-day cycle
  - Most common hematologic G 3/4 AE: myelosuppression
- Very low incidence of G 3/4 PN and DVT
- Clinically meaningful responses in heavily pretreated relapsed and refractory pts who have received prior 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: 20.1 wks
    - Median PFS: 20.1 wks
    - Median OS: 79.6 wks
  - Phase 2 (aggregated data):
    - ≥PR 25%; ≥MR 38%
    - Median DOR not reached

Future Directions

- Final analysis of Phase 2 (N=221)
- Analysis of GEP/surrogates
- Additional studies in relapsed and refractory MM
- Further dose exploration in less heavily pre-treated patients
- Novel combinations (e.g. POM/Bz/dex, second-generation proteasome inhibitors, alkylating agents, clarithromycin/dex, other small molecules, MoABs)

Acknowledgements

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Our Patients and Families