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 Pts With Relapsed and Refractory Multiple Myeloma Who Have Received Prior Treatment That Includes Lenalidomide and Bortezomib; Preliminary Results

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Background

- Pomalidomide (POM) is a novel IMiD® immunomodulatory compound, a modified chemical structure derived from thalidomide, with improved potency *in vitro*[1]
- Although structurally similar to thalidomide and lenalidomide, POM has a distinctively different clinical efficacy and safety profile[2-4]

Pomalidomide

1. Hideshima et al. Blood. 2000;96(9):2943-50. 2. Schey et al. J Clin Oncol. 2004;22:3269-3276.
3. Streetly et al. Br J Haematol. 2008;141:41-51. 4. Lacy et al. J Clin Oncol. 2009; Epub ahead of print.

Background and Rationale

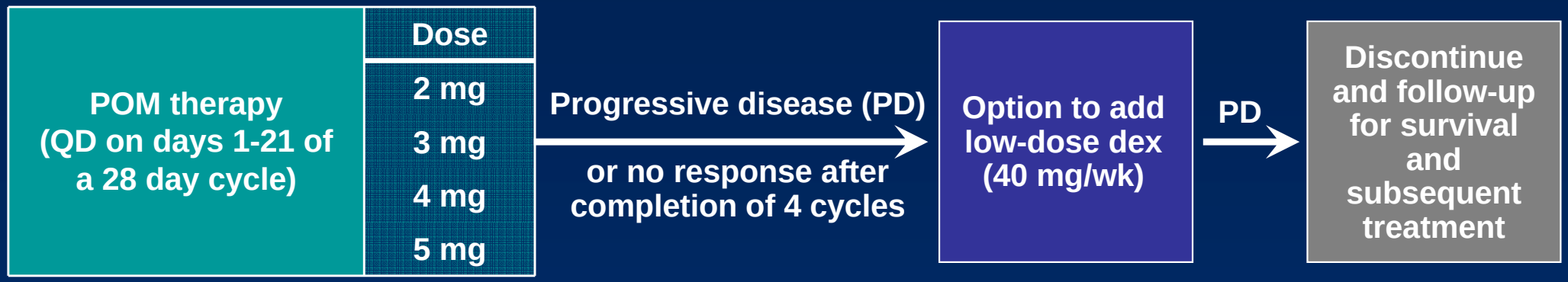
- POM has demonstrated clinical activity following lenalidomide (Len) and bortezomib (Bz) treatment
  - Data from 2 single-center phase 1b clinical studies identified the maximum tolerated dose (MTD) of POM to be 2 mg QD or 5 mg alternate days[1,2]
  - A phase 2 study demonstrated efficacy of POM + low-dose dexamethasone (dex) in pts with relapsed MM[3]
    - 63% overall response rate (ORR)
    - 60% ORR in pts refractory to Bz; 40% in pts refractory to Len
    - 94% OS at 6 mos
    - Median PFS of 11.6 mos
- This phase 1 study evaluated the efficacy and safety of POM, administered for 21 of 28d, alone or in combination with low-dose dex, in pts with relapsed and refractory MM who have received prior treatment including both Len and Bz

1. Schey et al. J Clin Oncol. 2004;22:3269-3276. 2. Streetly et al. Br J Haematol. 2008;141:41-51
3. Lacy et al. J Clin Oncol. 2009; Epub ahead of print.

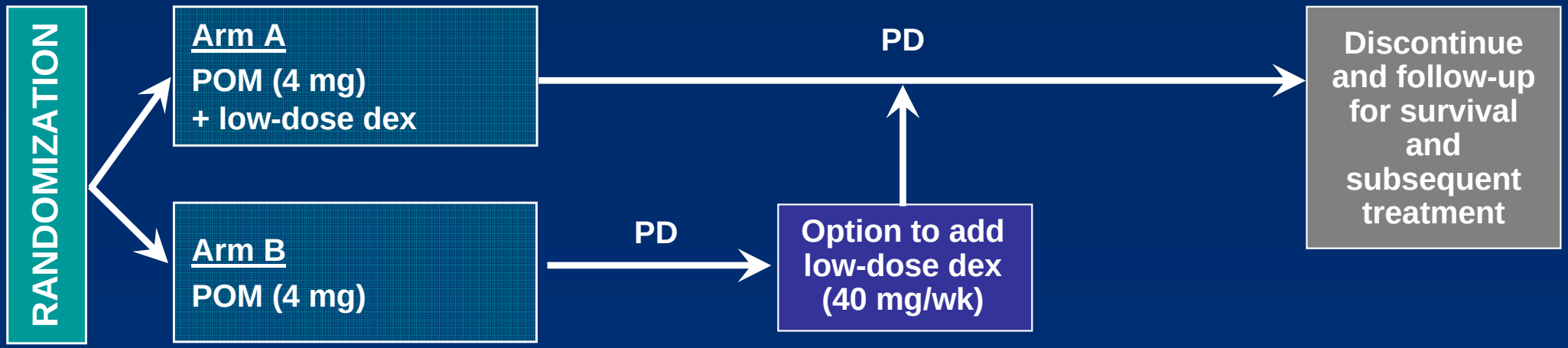
MM-002 Study Schema

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, antibiotics, analgesics, antihistamine, transfusions with platelet, RBC, and fresh frozen plasma as clinically indicated

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

- Phase 1 dose escalation followed by randomized, open label phase 2 segment
- Selected key inclusion criteria:
  - ≥ 18 yrs of age
  - Diagnosed with relapsed and refractory MM
    - Measurable levels of myeloma paraprotein in serum or urine
  - Must have received ≥2 prior therapies
    - 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)[1-3], time to response, duration of response, OS, safety, correlation between response and cytogenetic abnormalities, incl. FISH

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

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

- MTD defined as the highest dose at which more than 2 of 6 pts experienced a DLT within the first 28d cycle
- Phase 1: Statistical Analyses
  - MTD determined using a “3 + 3” design
  - Safety analyses: DLTs summarized at conclusion of each dose level
  - Efficacy analyses: intent-to-treat population
    - Assessments carried out every 28 d following completion of the first cycle
- DMC review of ongoing efficacy and safety data
  - Safety assessed using NCI CTC for Adverse Events v 3.0
- Central Adjudication Committee review of response data and PD (Phase 2 only)

DLT: Dose-limiting toxicity; NCI CTC: National Cancer Institute Common Toxicity Criteria

MM-002 Phase 1
Patient Demographics

	POM Dose				
	2 mg (n = 6)	3 mg (n = 8)	4 mg (n = 8)	5 mg (n = 10)	Total (N = 32)
Male, %	17	38	50	40	38
White, %	83	100	100	80	91
Mean age (range), yrs	65 (55–72)	70 (61–78)	71 (60–80)	61 (38–83)	67 (38–83)
Mean # prior therapies (range)	8 (5–15)	7 (2–12)	6 (2–18)	6 (3–11)	7 (2–18)

- 100% of pts received prior Len, Bz, and dex
- 78% received prior thalidomide
- 59% had undergone prior stem cell transplant

MM-002 Phase 1
Patient Disposition

	POM Dose			
Disposition, n	2 mg (n = 6)	3 mg (n = 8)	4 mg (n = 8)	5 mg (n = 10)
Discontinuation	6	7	3	2
Adverse event[a]	0	1	1	1
Disease progression	5	4	2	1
Withdrew consent	1	1	0	0
Death[b]	0	1	0	0

a. Including renal failure, rash, and neutropenia (with rash reported as drug related, renal failure unrelated);

b. Not related to study drug (GI bleed in the context of progressive MM and pre-existing amyloidosis).

Currently, there are 35 pts enrolled and 17 pts are ongoing

MM-002 Phase 1
Safety Profile: POM ± low-dose dex

	POM Dose			
Adverse event, n	2 mg (n = 6)	3 mg (n = 8)	4 mg (n = 8)	5 mg (n = 10)
Neutropenia[a]	8	8	7	9
Thrombocytopenia[a]	2	6	0	0
Anemia[a]	2	7	2	0
VTE	1 (G2)	0	0	1 (G3)
Treatment-emergent SAEs	7	7	4	4
Deaths[b]	2	1	1	0
POM dose reduction	0	1	0	9

SAEs, severe adverse events; VTE, venous thromboembolism.

a. Grade 3/4; b. Includes deaths occurring at least 28d after last treatment (both due to rapid PD).

Most common POM-related all grade AEs included:

- Neutropenia 31%
- Fatigue 31%
- Rash 16%
- Anemia 19%
- Constipation 16%
- Myalgia 13%
- Urticaria 13%
- Thrombocytopenia 13%

MM-002 Phase 1
Dose-Limiting Toxicities

POM Dose	Completed cycles [a] (mean/median/range)	DLTs (reason)
2 mg (n = 6)	17 (2.8 / 0.5 / 0–12)	0
3 mg (n = 8)	38 (4.8 / 4 / 1–11)	0
4 mg (n = 8)	49 (6.1 / 7 / 0–11)	0
5 mg (n = 10)	29 (2.9 / 2.5 / 0–5)	4 (4 drug-related neutropenia)

a. During the dose-escalation phase of the study, G-CSF was not allowed during Cycle 1 (i.e. initial 28d).

MM-002 Phase 1
Safety Summary

- **The MTD of POM was determined to be 4 mg**
  - **There were 4 drug-related DLTs at 5 mg due to grade 4 neutropenia**
- **15 pts received low-dose dex (47%)**
  - **Dex was added at a median of 3 cycles, respectively**
- **Incidence of peripheral neuropathy and VTEs were infrequent**
  - **Peripheral neuropathy (G3: n=1)**
  - **VTE (n=2)**
- **Overall, the frequency of AEs in all dosing cohorts were similar**
  - **Median time to neutropenia (all grades) was 44d with 80% occurring approximately 90d after starting POM**

MM-002 Phase 1
Summary of Response Rates

POM Dose (± Dex)	Best Response[a]
2 mg (n = 6)	1 PR, 1 SD, 1 PD, 3 NE
3 mg (n = 8)	1 CR, 1 MR, 5 SD, 1 NE
4 mg (n = 8)	2 PR, 3 MR, 1 SD, 2 NE
5 mg (n = 10)	3 PR, 2 MR, 3 SD, 1 PD, 1 NE

CR, complete response; MR, minimal response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease. a. As measured using modified EBMT criteria [1,2] every 28d.

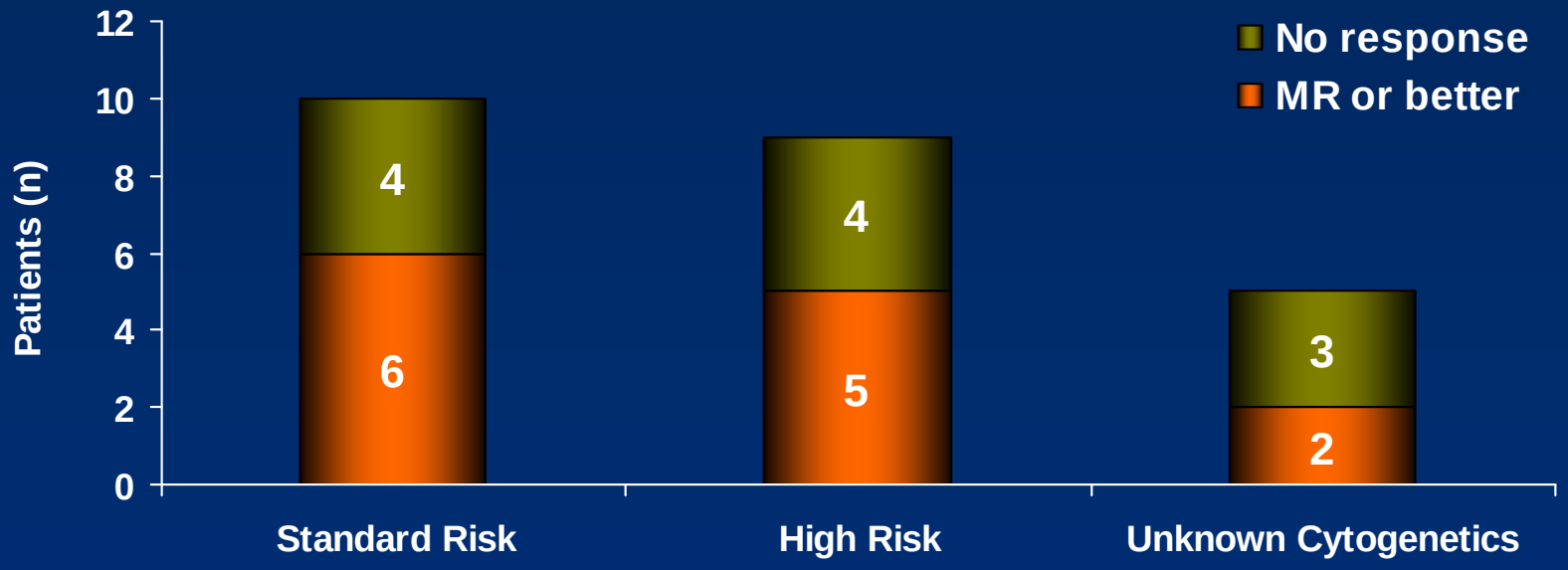
7/25 evaluable pts (28%) ≥PR; 13/25 pts (52%) ≥MR[3]

15 pts received dex in addition to POM for either lack of response or PD; 8/15 pts (53%) improved response after dex was added, with durability of response also improved from 13.5 to 16.9 weeks

1. Bladé et al. Br J Haematol. 1998;102:1115-1123. 2. Richardson et al. N Engl J Med. 2003;348(26):2609-17. 3. Anderson et al. Leukemia. 2008;22(2):231-9.

Cytogenetics Risk Subgroups: Preliminary Response Analysis

	POM Dose				
	2 mg (n = 6)	3 mg (n = 8)	4 mg (n = 8)	5 mg (n = 10)	Total (N = 32)
Cytogenetic risk, n (high / standard/ unknown)	4 / 1 / 1	3 / 2 / 3	5 / 3 / 0	2 / 5 / 3	14 / 11 / 7



- High risk defined as cytogenetic studies showing hypodiploidy or karyotypic deletion of chromosome 13, fluorescent in situ hybridization (FISH) showing presence of translocations t(4:14) or t(14;16) or deletion of 17p.[1]
- Unevaluable high risk n=5; unknown cytogenetics n=3

1. Kyle and Rajkumar. Clin Lymphoma Myeloma. 2009;9(4):278-88.

Conclusions

- 4 mg D1-21 q28d is the recommended dose for phase 2
- Safety profile favorable
  - Most frequent toxicity was neutropenia, minimal non-hematologic toxicity (DVT 6%, PN 3%)
  - Increased incidence of neutropenia at POM 5 mg, G-CSF will be allowed during cycle 1 in phase 2 of the study
- POM MTD given on 21 days of each 28-day cycle is similar to that of prior phase 1/2 study finding[1]
- POM achieves clinically significant responses in heavily-pretreated MM and specifically in pts who are Len and Bz-refractory
  - POM achieves response as a single agent, with responses observed at each dose level; PR 28%; MR 52%
  - Addition of low-dose dex was feasible and safe, as well as improving quality of response, suggesting synergy
- Phase 2 of the study is ongoing

1. Streetly et al. Br J Haematol. 2008;141:41-51

Future Directions

- **Complete phase 2 (anticipated completion Q4 2010, n=200)**
- **Analysis of GEP**
- **Randomized studies in Relapsed /Refractory MM**
- **Novel Combinations**

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