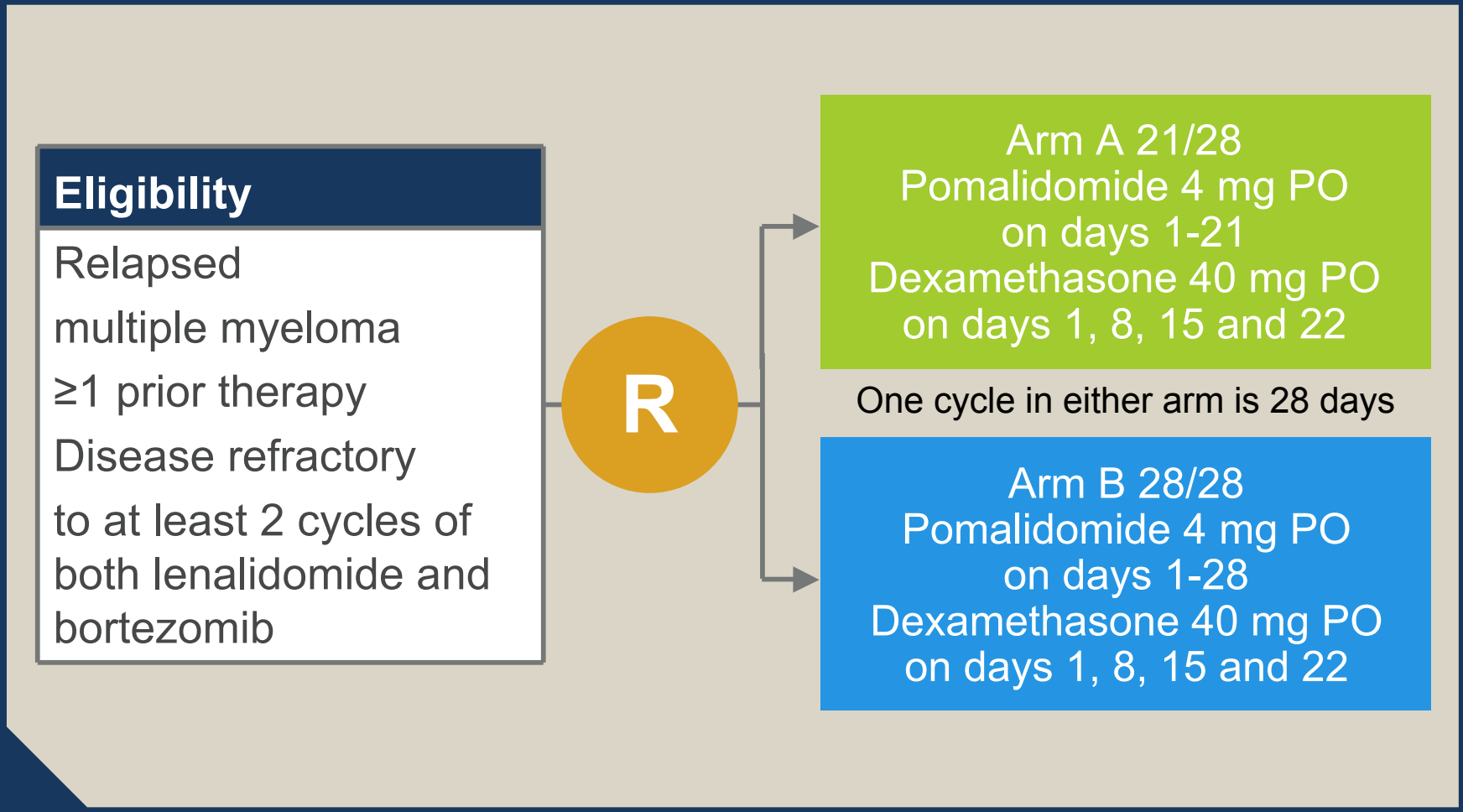
Phase 2 Randomized Open Label Study of 2 Modalities of Pomalidomide plus Low-Dose Dexamethasone in Patients with Multiple Myeloma, Refractory to Both Lenalidomide and Bortezomib. IFM 2009-02

Leleu X et al.

Proc ASH 2010;Abstract 859.

IFM 2009-02 Phase II Study Schema



Leleu X et al. *Proc ASH* 2010;Abstract 859.

Study Objectives

Primary objective:

- Response rate (partial response and better) according to International Myeloma Working Group in either arm

> Secondary objectives (in either arm):

- Safety
- Time to response and duration of response
- Time to disease progression and event-free survival
- Overall survival
- Cytogenetic response in bone marrow plasma cells

Leleu X et al. *Proc ASH* 2010;Abstract 859.

Efficacy Assessment (Intent to Treat)

	Arm A (21/28) (n = 43)	Arm B (28/28) (n = 41)
Overall response rate (≥partial response)	42%	39%
Stable disease	46.5%	51%
Time to best response	2.0 months	1.7 months
Time to progression, median*	7.0 months	9.7 months

* Median follow-up was 6.5 months for Arm A and 7 months for Arm B.

Leleu X et al. *Proc ASH* 2010;Abstract 859.

Hematologic Adverse Events (AEs)

	Arm A (21/28) (n = 43)	Arm B (28/28) (n = 41)
≥Grade 3 events Hematologic events	23.5% 66.0%	26.5% 76.0%
Hemoglobin ≤8 g/dL	11.0%	14.0%
Neutrophils ≤1 x 10^9/L	34.0%	33.5%
Platelets ≤50 x 10^9/L	18.0%	21.0%

Leleu X et al. *Proc ASH* 2010;Abstract 859.

Select Nonhematologic AEs

	Arm A (21/28) (n = 43)	Arm B (28/28) (n = 41)
Percentage nonhematologic AEs out of all AEs	12.0%	9.0%
Neuropathy	0%	0%
Deep vein thrombosis (with prophylactic treatment)	0%	0%
Asthenia	9.3%	4.9%
Cramps	0%	4.9%
Diarrhea	0%	4.9%

Leleu X et al. *Proc ASH* 2010;Abstract 859.

Author Conclusions

- Pomalidomide and dexamethasone combination provides responses in patients with advanced myeloma refractory to bortezomib and lenalidomide.
- Pomalidomide 4 mg once daily is well tolerated.
- Pomalidomide 4 mg once daily x 21 q4wk does not appear inferior to pomalidomide 4 mg once daily x 28 q4wk.

Leleu X et al. *Proc ASH* 2010;Abstract 859.

Faculty Comments

DR BENSINGER: The third-generation IMiD pomalidomide is a promising new agent and is much more potent than prior generations of immunomodulating drugs. The effective doses of pomalidomide (2 to 4 mg daily) are much lower than the typical doses of thalidomide and lenalidomide. Studies have shown that pomalidomide in combination with dexamethasone or alone is effective at controlling disease in patients for whom a proteasome inhibitor or, in many cases, lenalidomide has failed. So pomalidomide can be effective even when a similar immunomodulatory agent has failed. Toxicity profiles appear similar to other IMiDs in that cytopenias seem to be the major toxicities associated with this agent. So reductions in hemoglobin or reductions in platelet levels or neutrophils are common toxicities.

Pomalidomide plus Low-Dose Dexamethasone in Myeloma Refractory to Both Bortezomib and Lenalidomide: Comparison of Two Dosing Strategies in Dual-Refractory Disease

Lacy MQ et al.

Blood 2011;118(11):2970-5.

Introduction

- Pomalidomide/dexamethasone (pom/dex) regimen using a pom dose of 2 mg/day has demonstrated response rates of:
  - 63% in relapsed multiple myeloma (*JCO* 2009;27:5008)
  - 47% in lenalidomide-refractory cohort (*Leukemia* 2010;24:1934)
- Pom has been evaluated at doses of 4 mg, either continuously or for 21 of 28 days as salvage therapy for patients with relapsed myeloma (*Proc ASH* 2010;Abstract 864; *Proc ASH* 2010;Abstract 859).
- Two sequential Phase II trials were opened to evaluate the efficacy of a pom/dex regimen using 2 different doses of pom in patients with multiple myeloma refractory to both lenalidomide and bortezomib.

Lacy MQ et al. *Blood* 2011;118(11):2970-5.

Study Methods

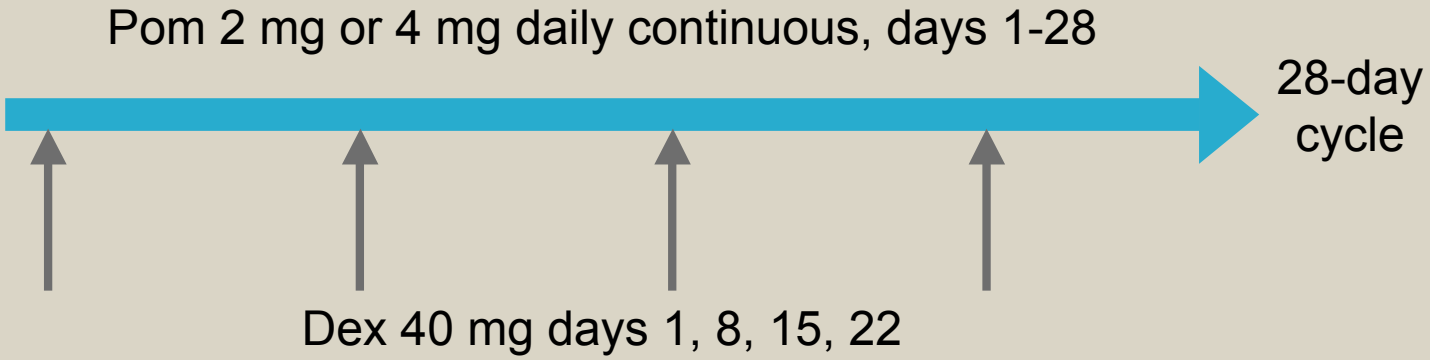
- Two sequential Phase II trials opened with 35 patients each:
  - May 2009-Nov 2009: 2 mg/day pom cohort
  - Nov 2009-Apr 2010: 4 mg/day pom cohort
- Efficacy rule for 2 mg pom cohort:
  - Cohort considered ineffective if a maximum 18 confirmed responders observed in the first 33 evaluable patients
- Efficacy rule for 4 mg pom cohort:
  - Cohort considered ineffective if a maximum 11 confirmed responders observed in the first 33 evaluable patients
- Responses were assessed according to IMWG criteria.

Lacy MQ et al. *Blood* 2011;118(11):2970-5.

Treatment Schema

Eligibility

> Previously treated multiple myeloma refractory to lenalidomide and bortezomib



Lacy MQ et al. *Blood* 2011;118(11):2970-5.

Efficacy Assessment

Clinical variable	Pom 2 mg (n = 35)	Pom 4 mg (n = 35)
Confirmed response (≥PR)	26% (9)	28% (10)
≥MR	49%	43%
Median time to response	1 mo	2 mo
Median duration of response	Not reached	3.9 mo
Survival rate at 6 months	78%	67%

PR = partial response; MR = minimal response

- Prespecified efficacy rule for study design was not met by either cohort.
- Of 62 patients with cytogenetics/FISH data available, responses were seen in 13 patients considered to be at high risk (21%).

Lacy MQ et al. *Blood* 2011;118(11):2970-5.

Select Grade 3/4 Adverse Events

Clinical variable	Pom 2 mg (n = 35)	Pom 4 mg (n = 35)
Anemia	26%	26%
Neutropenia	51%	65%
Peripheral sensory neuropathy	0%	3%
Thrombosis	3%	3%
Fatigue	9%	9%

Lacy MQ et al. *Blood* 2011;118(11):2970-5.

Author Conclusions

- Although the study design goals were not met for either cohort, pom/dex was significantly active in dual-refractory myeloma at both dosing levels, and responses were durable.
- Pom/dex demonstrated activity in patients with dual-refractory multiple myeloma who were considered to be at high risk.
- Myelosuppression was the most common toxicity.
- It is not clear whether an advantage exists with the higher 4-mg dose of pom versus the 2-mg dose using the day 1-28 schedule.
- Additional studies are ongoing exploring whether a regimen of 4 mg of pom for 21 of 28 days is superior to 2 mg continuously.

Lacy MQ et al. *Blood* 2011;118(11):2970-5.

Faculty Comments

DR WOLF: I believe that pomalidomide will be another important drug for the treatment of multiple myeloma. It is a tolerable drug that shows responses in patients with disease that is refractory to lenalidomide. It may be slightly better than lenalidomide in the sense that little neuropathy was observed with pomalidomide.

I don't believe, however, that this study established the correct dose of the drug as being 4 or 2 mg. In the future, it would be interesting to address whether pomalidomide has activity if used before or instead of lenalidomide for patients with multiple myeloma.

Carfilzomib, Lenalidomide, and Dexamethasone in Newly Diagnosed Multiple Myeloma: Initial Results of Phase I/II MMRC Trial

Jakubowiak AJ et al.

Proc ASH 2010;Abstract 862.

Introduction

- Carfilzomib is a novel, irreversible proteasome inhibitor with promising single-agent activity and a favorable toxicity profile in relapsed/refractory multiple myeloma (MM) (*Proc ASCO* 2009;Abstract 8504).
- Additive anti-MM effects have been reported with carfilzomib in combination with lenalidomide and dexamethasone (CRd) in preclinical studies (*Proc ASH* 2009;Abstract 304).
- Lack of overlapping toxicity allows for the use of these agents at full doses and for extended durations in relapsed/refractory MM (*Proc ASH* 2009;Abstract 304).
- Current study goals: To determine the maximum tolerated dose (MTD) and to assess safety and efficacy of CRd in newly diagnosed MM.

Jakubowiak AJ et al. *Proc ASH* 2010;Abstract 862.

Methods

- Phase I carfilzomib dose-escalation trial
- Carfilzomib as only dose-escalating agent (IV on days 1, 2, 8, 9, 15, 16 in 28-day cycles)
  - Level 1: 20 mg/m^2
  - Level 2: 27 mg/m^2 (initial maximal planned dose)
  - Level -1: 15 mg/m^2 (if needed)
  - Level 3: 36 mg/m^2 (study amendment inclusion after toxicity assessment)
- Lenalidomide 25 mg PO (days 1-21) for all dose levels
- Dexamethasone 40/20 mg PO weekly (cycles 1-4/5-8) for all dose levels

Jakubowiak AJ et al. *Proc ASH* 2010;Abstract 862.

Methods (continued)

- Phase I/II (target accrual = 36)
- After ≥4 cycles, patients achieving ≥partial response (PR) proceed to stem cell collection (SCC) and autologous stem cell transplant (ASCT).
  - ASCT candidates offered continued CRd treatment after SCC
  - After completion of 8 cycles, patients receive 28-day maintenance cycles.
  - Carfilzomib (days 1, 2, 15, 16), lenalidomide days 1-21 and dexamethasone weekly at the doses tolerated at the end of 8 cycles

Jakubowiak AJ et al. *Proc ASH* 2010;Abstract 862.

Best Responses to Date

Clinical response	CRd (n = 27*)
≥PR	96%
≥Very good PR (VGPR)	70%
Complete response (CR)/near CR (nCR)/stringent CR	55%

* 4 patients not evaluable for response

Jakubowiak AJ et al. *Proc ASH* 2010;Abstract 862.

Select Adverse Events (Abstract)

Hematologic	CRd (n = 21)
Neutropenia (Grade 3 or 4)	14%
Thrombocytopenia (Grade 3 or 4)	14%
Anemia (Grade 3)	10%
Nonhematologic (Grade 3)	
Peripheral neuropathy (Grade 3 or 4)	0%
Fatigue	5%
Mood alteration	5%
Glucose elevations	24%
Deep vein thrombosis (while receiving aspirin prophylaxis)	5%

Jakubowiak AJ et al. *Proc ASH* 2010;Abstract 862.

Author Conclusions

- The MTD of carfilzomib was not reached (data not shown).
- CRd is well tolerated and highly active in newly diagnosed MM.
  - ≥PR = 96%
  - ≥VGPR = 70%
  - CR/nCR = 33%
- These data represent the first report to date on treatment of front-line myeloma with carfilzomib and add support to the Phase III trial of CRd versus Rd in relapsed MM (NCT01080391).

Jakubowiak AJ et al. *Proc ASH* 2010;Abstract 862.

Faculty Comments

DR BENSINGER: Carfilzomib is a promising second-generation proteasome inhibitor. It is more target specific and probably has a lower incidence of off-target side effects, the most notable being peripheral neuropathy. This trial evaluated carfilzomib at the maximum preferred dose of 27 mg/m^2 in combination with lenalidomide and dexamethasone in about 24 patients with newly diagnosed myeloma. Basically, almost 100% of patients responded to treatment. Of the patients enrolled, 23 have remained on the trial. A major degree of peripheral neuropathy has not been reported in this trial. So this regimen yields a high response rate, a high degree of efficacy and a high degree of tolerance. Carfilzomib will be an important agent to add to our armamentarium.