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MM-005: A Phase 1 Trial of Pomalidomide, Bortezomib, and Low-Dose Dexamethasone (PVD) in Relapsed or Relapsed and Refractory Multiple Myeloma (RR MM)

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INTRODUCTION

- Pomalidomide (POM) is a distinct oral immunomodulatory agent whose mechanism of action consists of 3 primary effects[1]:
  - Potent direct anti-myeloma activity
  - Inhibition of stromal cell support
  - Immune modulation
- When combined with low-dose dexamethasone (LoDEX), POM has demonstrated encouraging clinical efficacy in RR MM patients (pts) treated with prior lenalidomide (LEN) and/or bortezomib (BORT)[2]
  - POM was recently approved by the US FDA for RR MM pts who received ≥ 2 prior treatments (Tx), including BORT and LEN and progressed on or within 60 days of last Tx[3]
- Combining an immune modulator (LEN), a proteasome inhibitor (BORT), and dexamethasone (DEX) in RVD triplet therapy has shown preclinical synergy as well as promising efficacy both as frontline and salvage Tx in myeloma patients[4-6]
  - Combination therapy incorporating newer agents may improve outcomes

OBJECTIVE

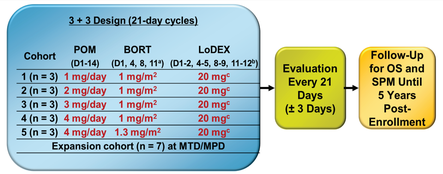
- Identify the optimal POM + BORT + LoDEX (PVD) dose for a phase 3 trial comparing PVD vs. BORT+ LoDEX in RR MM pts

METHODS

Study Design

- MM-005 is a phase 1, multicenter, open-label, dose-escalation study (Figure 1)

Figure 1. MM-005 Study Design: POM + BORT + LoDEX



Concomitant medications

- Required: Thromboprophylaxis (aspirin or low-molecular-weight heparin) and antiviral prophylaxis (eg, acyclovir)
- Supportive care: RBC and platelet transfusions as needed, hematopoietic growth factors (after cycle 1), IV bisphosphonates

[a] For cycles 1-8, then D1 and 8 for cycle 9 and beyond.
[b] For cycles 1-8, then D1-2 and 8-9, for cycles 9 and beyond.
[c] 10mg for patients aged > 75 years.
BORT, bortezomib; IV, intravenous; LoDEX, low-dose dexamethasone; MPD, maximum planned dose; MTD, maximum tolerated dose; OS, overall survival; POM, pomalidomide; RBC, red blood cell; SPM, second primary malignancy.

Key Eligibility Criteria

- Age ≥ 18 years
- Measurable disease by M-protein serum (≥ 0.5 g/dL) or urine protein electrophoresis (≥ 200 mg/dL)
- Relapsed or RR MM with 1-4 prior lines of therapy
- Prior therapy must have included ≥ 2 consecutive cycles of LEN
  - Pts must be LEN-refractory
- Prior therapy must have included ≥ 2 consecutive cycles of a proteasome inhibitor
  - Pts cannot be refractory to BORT (1.3 mg/m² twice weekly)
- No peripheral neuropathy ≥ grade 2
- No significant hematologic or other abnormalities

METHODS (cont)

Safety Assessments

- Dose-limiting toxicities (DLTs) were protocol-defined adverse events (AEs) occurring during the first cycle
- AE severity was graded using NCI CTCAE v4.0
- Peripheral neuropathy (PN) as reported herein included the preferred terms neuropathy peripheral, peripheral motor neuropathy, and peripheral sensory neuropathy

Endpoints

- Primary: Maximum-tolerated dose (MTD)
- Secondary: Safety, response assessment per International Myeloma Working Group (IMWG) criteria,[7] OS, time to response (TTR), and duration of response
- Exploratory: Progression-free survival, time to progression, response assessment per modified European Group for Blood and Marrow Transplant (EBMT) criteria,[8-10] and POM plasma concentration

RESULTS

Patient Characteristics

- Trial is fully enrolled (N = 22)
  - 21 pts were evaluable for baseline characteristics/safety; 20 pts were evaluable for response
- Median number of prior lines of therapy: 2 (1-4; Table 1)
- 100% of pts progressed on or within 60 days of their last LEN regimen
  - 67% of pts had progressed on LEN as their last prior Tx
  - Among the 33% pts (n = 7) whose LEN-containing Tx was not the last regimen prior to the study, nearly one-third of these pts (n = 2) never achieved treatment response
- 100% of pts had relapsed and/or refractory[9,10] disease at study entry

Table 1. Patient Characteristics

Characteristic	Cohort 1 (n = 3)	Cohort 2 (n = 3)	Cohort 3 (n = 3)	Cohort 4 (n = 3)	Cohort 5 (n = 3)	Exp (n = 6)	Total (N = 21)
Median age, y (range)	58 (57-61)	65 (36-75)	61 (47-73)	48 (41-57)	65 (60-66)	55.5 (49-67)	57 (36-75)
Male (%)	67	33	0	100	33	67	52
ECOG PS (0/1) (%)	100	100	100	100	100	100	100
ISS stage (I/II/III/NA) (n)	1/0/1/1	0/0/0/3	0/1/1/1	0/0/1/2	2/0/1/0	2/1/0/3	5/2/4/10
Median prior lines Tx (range)	2 (2-4)	3 (1-4)	2 (1-3)	1 (1-3)	2 (2-4)	2 (1-2)	2 (1-4)
Prior LEN and BORT (%)	100	100	100	100	100	100	100
Prior DEX (%)	100	100	100	100	100	100	100
Prior THAL (%)	33	67	33	33	0	33	33
Prior SCT (%)	100	100	100	100	100	67	90

BORT, bortezomib; DEX, dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; Exp, expansion; ISS, International Staging System; LEN, lenalidomide; NA, not applicable; SCT, stem cell transplant; THAL, thalidomide; Tx, treatment.

Patient Disposition

- 14 of 22 (64%) pts remain on study (Table 2)

Table 2. Patient Disposition

Disposition, n (%)	Cohort 1 (n = 3)	Cohort 2 (n = 3)	Cohort 3 (n = 3)	Cohort 4 (n = 3)	Cohort 5 (n = 3)	Exp (n = 7)	Total (N = 22)
On treatment	0	1 (33)	2 (67)	2 (67)	3 (100)	6 (86)	14 (64)
Discontinued	3 (100)	2 (67)	1 (33)	1 (33)	0	1 (14)	8 (36)
PD	2 (67)	2 (67)	1 (33)	1 (33)	0	0	6 (27)
Consent withdrawn	1 (33)	0	0	0	0	0	1 (5)
Adverse event	0	0	0	0	0	1 (14)[a]	1 (5)

[a] One patient discontinued study treatment in cycle 2 due to treatment-unrelated metastatic pancreatic cancer.
Exp; expansion; PD, progressive disease; pt: patient.

RESULTS (cont)

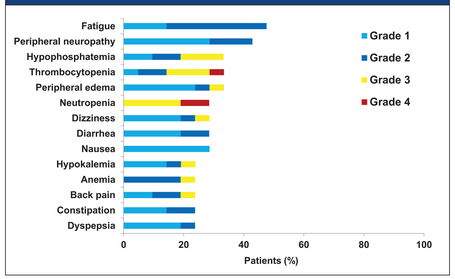
Dose-Limiting Toxicities (Cycle 1)

- No DLTs were observed at any dose escalation level
- Thus, the MTD/maximum planned dose (MPD) for PVD is:
  - POM: 4 mg (D1-14)
  - BORT: 1.3 mg/m² (days 1, 4, 8, 11) for cycles 1-8; days 1 and 8 for cycles 9+
  - DEX: 20 mg (days 1-2, 4-5, 8-9, 11-12) for cycles 1-8; days 1-2, 8-9 for cycles 9+
    - 10 mg DEX administered for pts aged > 75 years

Adverse Events

- The most common grade 3/4 AE was neutropenia (Figure 2)
- No grade 3/4 PN was observed
  - Grade 1 and 2 PN reported for 29% and 14% pts, respectively
  - 62% of pts with AE of PN had prior history of PN or prior Tx with THAL
- No deep vein thrombosis was observed (any grade)
- One pt discontinued study Tx in cycle 2 due to treatment-unrelated metastatic pancreatic cancer

Figure 2. Adverse Events Occurring in ≥ 20% of Patients



Dose Modifications Due to Adverse Events

- With appropriate dose adjustments, no pts discontinued study treatment due to AEs (Table 3)
  - One pt discontinued BORT due to persistent grade 2 PN without discontinuing POM or DEX, as per protocol

Table 3. Dose Modifications Due to Adverse Events

Patients (n)	Dose Interruption POM/BORT/DEX	Dose Reduction POM/BORT/DEX	Discontinuation POM/BORT/DEX
Cohort 1 (n = 3)	2/2/2	0/2/2	0/1/0
Cohort 2 (n = 3)	1/1/2	0/0/2	0/0/0
Cohort 3 (n = 3)	1/2/1	1/1/2	0/0/0
Cohort 4 (n = 3)	2/2/2	0/1/3	0/0/0
Cohort 5 (n = 3)	3/3/2	2/1/2	0/0/0
Expansion cohort (n = 6)	3/3/3	0/0/2	1/1/1[a]
Total (n = 21)	12/13/12	3/5/13	1/2/1[a]

[a] One patient discontinued study treatment in cycle 2 due to treatment-unrelated metastatic pancreatic cancer.
BORT, bortezomib; DEX, dexamethasone; POM, pomalidomide.

Response

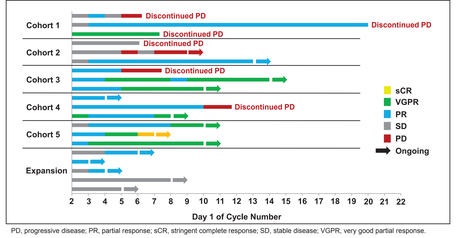
- Overall response rate (≥ partial response [PR]): 75% (15/20; Table 4)
  - ≥ Very good partial response (VGPR): 30% (6/20)
- Median TTR: 1 cycle (range 1-3)
- Median number of cycles: 6 (range 2-16)
- Most responses are ongoing (Figure 3)
- Responses were observed in pts with adverse cytogenetics (Table 5)

Table 4. Summary of Best Response (IMWG)

Patients (n)	Best Response	Median (range) Treatment cycles
Cohort 1 (n = 3)	1 VGPR, 1 PR, 1 SD	5 (4-16)
Cohort 2 (n = 3)	1 PR, 2 SD	7 (4-13)
Cohort 3 (n = 3)	2 VGPR, 1 PR	9 (5-13)
Cohort 4 (n = 3)	3 PR	9 (3-10)
Cohort 5 (n = 3)	1 sCR, 2 VGPR	8 (6-9)
Expansion cohort (n = 5 evaluable[a])	3 PR, 2 SD	5 (2-7)

[a] Assessment of response ongoing.
IMWG, International Myeloma Working Group; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

Figure 3. Duration of Response



PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

Table 5. Response by Cytogenetic Profile

Cohort	Patient	Cytogenetic Profile	Best Response (IMWG)
Cohort 1 (n = 3)	Patient 1	1q21	SD
	Patient 2	+1, +11, +19	PR
	Patient 3	del(13q), del(17p)	VGPR
Cohort 2 (n = 3)	Patient 1	+11q, +19p	SD
	Patient 2	del(13q), t(4;14)	SD
	Patient 3	Not available	PR
Cohort 3 (n = 3)	Patient 1	IgH-BA+, p53 deletion, RB1 deletion, D13S319+	PR
	Patient 2	Abnormal (details pending)	VGPR
	Patient 3	del(17p)	VGPR
Cohort 4 (n = 3)	Patient 1	del(13q), +1q, +19p, +5, ++11q	PR
	Patient 2	Normal	PR
	Patient 3	Not available	VGPR
Cohort 5 (n = 3)	Patient 1	del(13q), del(17p), +3, +7, +15	PR
	Patient 2	del(13), del(14)	sCR
	Patient 3	Not available	VGPR
Expansion cohort (n = 5)	Patient 1	Trisomy 3, 9, 15	PR
	Patient 2	Not available	PR
	Patient 3	Hyperdiploid clone	PR
	Patient 4	Normal	SD
	Patient 5	Normal	SD

del, deletion; IMWG, International Myeloma Working Group; PR, partial response; sCR, stringent complete response; SD, stable disease; t, translocation; VGPR, very good partial response.

CONCLUSIONS

- PVD was well tolerated in pts with RR MM
  - No DLTs observed at any of 5 escalating dose levels tested
- PVD is active, with responses in RR MM across all cohorts
  - Responses were rapid; majority are ongoing
- Efficacy is encouraging, with favorable tolerability observed in this population including those with adverse cytogenetics and relapsed/refractory disease
- An additional cohort of 6 pts using subcutaneous BORT is planned
- MPD identified with this trial will serve as the recommended dose for the recently activated phase 3 trial comparing PVD vs. BORT + LoDEX (VD) [MM-007]
  - Estimated sample size: 782 RR MM pts
  - Enrollment is anticipated to begin shortly
- Observed activity of PVD in RR MM provides a strong rationale for the use of POM in different combinations
- Phase 1/2 trials are ongoing in RR MM evaluating POM + steroids in combination with carfilzomib, cyclophosphamide, clarithromycin, and pegylated liposomal doxorubicin

REFERENCES

1. Quach H, et al. *Leukemia*. 2010;24:22-32.
2. Jagannath S, et al. *Blood*. 2012;120 [oral presentation; abstract 450].
3. Pomalyst (pomalidomide) [prescribing information]. Summit, NJ: Celgene Corporation; 2013.
4. Mitsiades N, et al. *Blood*. 2002;99:4525-4530.
5. Richardson PG, et al. *J Clin Oncol*. 2009;27:5713-5719.
6. Richardson PG, et al. *Blood*. 2010;116:679-686.
7. Durie BGM, et al. *Leukemia*. 2006;20:1467-1473.
8. Bladé J, et al. *Br J Haematol*. 1998;102:1115-1123.
9. Richardson PG, et al. *N Engl J Med*. 2003;348:2609-2617.
10. Anderson K, et al. *Leukemia*. 2008;22:231-239.

DISCLOSURES

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- DSDS: Received honoraria from Celgene, Millennium, Onyx, Merck
- SL: Consultant/advisor for Celgene, Millennium, Johnson & Johnson, Novartis, Onyx, Bristol-Myers Squibb, sanofi
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- NSR: Consultant/advisor for Celgene, Millennium, Amgen, and Onyx; research finding from Acetylon and Eli Lilly
- MHZ, YH, SS, JW: Employment and equity ownership – Celgene
- KCA: Consultant/advisor for Celgene, Gilead, Sanofi, Onyx; founder of Acetylon, Oncopep

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