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MM-005: Phase 1 Trial of Pomalidomide, Bortezomib, and Low-Dose Dexamethasone (PVD) in Lenalidomide-Refractory and Proteasome Inhibitor–Exposed Myeloma

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INTRODUCTION

- Pomalidomide (POM) is a distinct oral IMiDs® immunomodulatory agent with direct antimyeloma, stromal-cell support inhibitory, and immunomodulatory effects[1]
- POM + low-dose dexamethasone (LoDEX) has demonstrated clinical benefits in delaying disease progression and extending survival in patients (pts) with relapsed and refractory multiple myeloma (RRMM) treated with prior bortezomib (BORT) and lenalidomide (LEN)[2,3]
- Combination treatment (Tx) with immunomodulatory agents and proteasome inhibitors has demonstrated preclinical synergy and substantial clinical efficacy in early phase trials in myeloma[4-6]

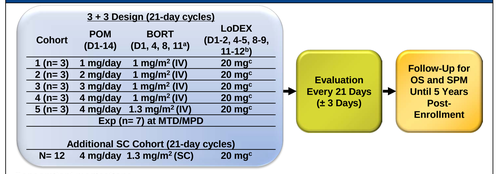
OBJECTIVES

- MM-005 was designed to identify the optimal PVD dose for a phase 3 trial (MM-007) comparing PVD vs. BORT + LoDEX in pts with RRMM
- A secondary objective examined giving BORT subcutaneously (SC) instead of intravenously (IV) as part of PVD Tx

METHODS

- MM-005 is a phase 1, multicenter, open-label, dose-escalation study (Figure 1)
- In April 2013, the study was amended to allow 6 pts to receive BORT SC instead of IV as part of PVD
- In March 2014, the SC BORT PVD cohort was expanded to 12 pts
- The data cutoff for this report is March 7, 2014

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 D8 for cycle 9 and beyond.
[b] For cycles 1-8, then D1-2 and D8-9, for cycles 9 and beyond.
[c] 10 mg for pts aged > 75 years.
BORT, bortezomib; exp, expansion cohort; IV, intravenous; LoDEX, low-dose dexamethasone; MPD, maximum planned dose; MTD, maximum tolerated dose; OS, overall survival; POM, pomalidomide; RBC, red blood cell; SC, subcutaneous; 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/24 h)
- Relapsed or RRMM with 1-4 prior lines of Tx
- Prior Tx must have included ≥ 2 consecutive cycles of LEN
  - Pts must be LEN-refractory
    - Refractory: Disease progression during Tx or within 60 days after the last dose of Tx
- Prior therapy must have included ≥ 2 consecutive cycles of a proteasome inhibitor
  - Pts must not be refractory to BORT (1.3 mg/m² twice weekly)

METHODS (cont)

- No peripheral neuropathy (PN) ≥ grade 2
- No significant hematologic or other abnormalities

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
- PN as reported herein included the preferred terms "neuropathy peripheral," "peripheral motor neuropathy," and "peripheral sensory neuropathy"

Pharmacokinetic (PK) Assessments

- PK sampling:
  - MTD determination cohorts – Cycle 1, day 8: pre-dose and 1, 2, 3, 4, and 6 h after POM administration
  - MTD confirmation cohort – Cycle 1, day 8: pre-dose and 0.5, 1, 2, 3, 4, 6, 8, and 24 h after POM administration

Endpoints

- Primary: maximum tolerated dose (MTD)
- Secondary: safety, response assessment per IMWG criteria, overall survival, time to response (TTR), and duration of response (DOR)
- Exploratory: progression-free survival, time to progression, response assessment per modified EBMT criteria, POM plasma concentration, and use of SC BORT in PVD

RESULTS

Patient Characteristics

- 28 pts have been enrolled (Table 1)
  - POM + IV BORT + LoDEX: n= 22
  - POM + SC BORT + LoDEX: n= 6
- Median number of prior lines of therapy was 2 (range, 1-4) across all cohorts
- 100% of pts had progressed on or within 60 days of their last LEN regimen
  - 71% of pts had progressed on LEN as their last prior Tx
  - Among the 29% of pts (n= 8) whose LEN-containing Tx was not the last regimen prior to the study, 25% (n= 2) never achieved Tx response

Patient Disposition

- 6 of 28 pts (21%) remain on study (Table 2)

Table 1. Patient Characteristics

Characteristic	Escalation Cohorts (n= 12)	MTD Cohorts (n= 10)	SC Cohort (n= 6)	Total (N= 28)
Median age (range) (y)	58 (36-75)	59 (49-67)	61 (54-76)	58 (36-76)
Male (%)	50	60	50	54
ECOG PS (0/1) (%)	42/58	60/40	67/33	54/46
ISS stage (I/II/III/NA) (n)	1/1/3/7	5/1/1/3	3/2/0/1	9/4/4/11
High-risk cytogenetics[a] (%)	33	10	17	21
Not available (%)	17	20	33	21
No. median prior Tx (range)	2 (1-4)	2 (1-3)	1 (1-2)	2 (1-4)
Prior LEN and PI (%)	100	100	100	100
LEN in last prior Tx (%)	67	80	83	75
Prior DEX (%)	100	100	100	100
Prior THAL (%)	50	30	17	36
Prior SCT (%)	100	80	17	75

[a] Del(13q) and/or del(17p) and/or t(4;14) and/or t(14;16).
DEX, dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System; LEN, lenalidomide; MTD, maximum tolerated dose; NA, not available; PI, proteasome inhibitor; SC, subcutaneous; SCT, stem cell transplant; THAL, thalidomide; Tx, treatment.

RESULTS (cont)

Table 2. Patient Disposition

Disposition, n (%)	Escalation Cohorts (n= 12)	MTD Cohorts (n= 10)	SC Cohort (n= 6)	Total (N= 28)
On treatment	2 (17)	1 (10)	3 (50)	6 (21)
Discontinued	10 (83)	9 (90)	3 (50)	22 (79)
PD	8 (67)	6 (60)	1 (17)	15 (54)
Consent withdrawn	2 (17)	0	0	2 (7)
AE	0	1 (10)[a]	0	1 (4)
Death	0	0	1 (17)[b]	1 (4)
Other	0	2 (20)[c,d]	1 (17)[d]	3 (11)

[a] One patient discontinued study treatment in cycle 2 due to treatment-unrelated metastatic pancreatic cancer; [b] One patient experienced grade 5 treatment-unrelated cardiac arrest in cycle 3; [c] One patient discontinued for non-compliance; [d] One patient proceeded to transplant.
AE, adverse event; MTD, maximum tolerated dose; PD, progressive disease; SC, subcutaneous.

Dose-Limiting Toxicities (Cycle 1)

- No DLTs were observed with any level of PVD dose
- The recommended dose is the maximum planned dose (MPD) for PVD
  - POM: 4 mg (D1-14)
  - IV 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
- No DLTs have been observed in the first 6 pts treated in the SC cohort

Adverse Events

- The most common grade 3-4 AE was neutropenia (Table 3)
- No grade 3-4 PN was observed
  - 25% of patients had grade 1 and 18% had grade 2 PN
    - One pt had grade 2 PN within the SC cohort
  - 70% of pts with PN had a prior history or previous Tx with THAL
- One pt developed deep vein thrombosis (grade 2)
- One pt discontinued study Tx in cycle 2 due to treatment-unrelated metastatic pancreatic cancer
- One pt experienced grade 5 Tx-unrelated cardiac arrest in cycle 3

Table 3. Grade 3-4 Adverse Events Occurring in > 5% of All Patients

Adverse event (%)	Escalation Cohorts (n= 12)	MTD Cohorts (n= 10)	SC Cohort (n= 6)	Total (N= 28)
Neutropenia	25	70	17	39
Thrombocytopenia	25	40	0	25
Pneumonia	17	30	0	18
Blood CPK increased	17	0	17	11
Hypophosphatemia	17	10	0	11
WBC count decreased	0	30	0	11
Hyperglycemia	8	10	0	7
Hypokalemia	0	20	0	7
Tremor	8	10	0	7

CPK, creatinine phosphokinase; MTD, maximum tolerated dose; SC, subcutaneous; WBC, white blood cell.

Dose Reductions and Discontinuations Due to AEs

- With appropriate dose adjustments, there were no study discontinuations due to treatment-related AEs (Table 4)
- One pt discontinued BORT due to persistent grade 2 PN without discontinuing POM or DEX, per protocol

RESULTS (cont)

Table 4. Dose Modifications Due to AEs

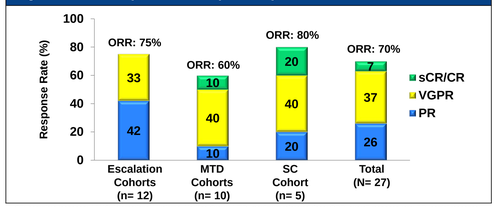
Patients	Dose Reduction POM / BORT / DEX	Discontinuation POM/BORT/DEX
Escalation cohorts (n= 12)	3 / 5 / 9	0 / 1 / 0
MTD cohorts (n= 10)	3 / 3 / 5	1 / 1 / 1[a]
SC cohort (n= 6)	3 / 2 / 4	1 / 1 / 2[b]
Total (N= 28)	9 / 10 / 18	2 / 3 / 3

[a] One patient discontinued study treatment in cycle 2 due to treatment-unrelated metastatic pancreatic cancer.
[b] One patient discontinued study treatment in cycle 3 due to grade 5 treatment-unrelated cardiac arrest.
AE, adverse event; BORT, bortezomib; DEX, dexamethasone; MTD, maximum tolerated dose; POM, pomalidomide; SC, subcutaneous.

Response

- The overall response rate (≥ partial response) for all cohorts combined was 70% (Figure 2)
- 43% achieved ≥ very good partial response
- Responses were observed in pts regardless of adverse cytogenetics
- Median TTR: 1.1 months (range, 0.7-3.4)
- Median DOR: 7.4 months (95% CI, 3.3-11.1)
- Median number of cycles received: 9 (range, 1-21)

Figure 2. Summary of Best Response by IMWG Criteria



CR, complete response; IMWG, International Myeloma Working Group; MTD, maximum tolerated dose; ORR, overall response rate; PR, partial response; SC, subcutaneous; sCR, stringent complete response; VGPR, very good partial response.

Pharmacokinetics

- Dose-dependent increases in POM exposures from cohort 1 (1 mg) to cohort 4 (4 mg) were observed (Table 5)
- BORT administration route (IV or SC) did not appear to impact POM exposure (Cohort 5 versus SC Cohort)
- POM exposure from MM-005 was within the range observed in previous studies

Table 5. Summary of POM Exposure by Cohort

Cohort	Drug Administration	$AUC_{[0-t]}$ h·ng/mL (CV%)	C_{max} ng/mL (CV%)
1 (n= 3)	1 mg POM + 1 mg/m² BORT (IV) + LoDEX	87.8 (35)	19.0 (28)
2 (n= 3)	2 mg POM + 1 mg/m² BORT (IV) + LoDEX	131.3 (41)	31.1 (54)
3 (n= 3)	3 mg POM + 1 mg/m² BORT (IV) + LoDEX	222.9 (50)	48.5 (41)
4 (n= 3)	4 mg POM + 1 mg/m² BORT (IV) + LoDEX	274.8 (28)	58.8 (17)
5 (n= 3)	4 mg POM + 1.3 mg/m² BORT (IV) + LoDEX	326.9 (25)	71.8 (23)
Exp (n= 7)	4 mg POM + 1.3 mg/m² BORT (IV) + LoDEX	596.4[a] (48)	59.5 (40)
SC (n= 5)	4 mg POM + 1.3 mg/m² BORT (SC) + LoDEX	341.9 (48)	78.7 (44)

[a] $AUC_{[0-24]}$ was used due to different PK sampling schedules for the confirmation cohort. N = 6 for AUC calculation.
Geometric mean (geometric CV%) data are presented.
AUC, area under the plasma concentration-time curve; BORT, bortezomib; C_{max}, maximum plasma concentration; DEX, dexamethasone; exp, expansion cohort; IV, intravenous; POM, pomalidomide; SC, subcutaneous.

CONCLUSIONS

- PVD was effective and well tolerated in LEN-refractory and BORT-exposed pts, with no DLTs or discontinuations due to treatment-related AEs reported in any cohort to date
- Maturing data from PVD with SC BORT show efficacy and safety profiles similar to those of PVD with IV BORT
  - MM-005 has been amended to include an additional cohort of 6 pts receiving SC BORT to verify these findings
  - POM exposure does not appear to be affected by BORT administration route
- PVD is now under evaluation vs. BORT + LoDEX in the MM-007 phase 3 trial (N= 782)
- These results support the use of other POM-containing combinations for the treatment of RRMM
  - Phase 1/2 trials are currently investigating combinations with carfilzomib, cyclophosphamide, clarithromycin, and pegylated liposomal doxorubicin

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DISCLOSURES

- PGR: Consultant/advisor for Celgene, Millennium, Johnson & Johnson
- CCH: Consultant/advisor for Celgene; received research funding from Celgene and Millennium
- NSR: Consultant/advisor for Celgene
- DSS: Consultant/advisor for and received honoraria from Celgene, Onyx, Millennium, and Merck
- SL: Consultant/advisor for Celgene, Millennium, Novartis, and Bristol-Myers Squibb
- JL: Received research funding from Novartis and Onyx
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- DHV: Consultant/advisor for Celgene; received honoraria from Celgene and Millennium
- YL: Employment with Celgene
- MHZ, SS, JW: Employment and equity ownership with Celgene
- KCA: Consultant/advisor for Celgene and Millennium

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