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MM-003 Phase 3 Study of Pomalidomide in Combination With Low-Dose Dexamethasone (POM + LoDEX) vs. High-Dose Dexamethasone (HiDEX) in Relapsed/Refractory Multiple Myeloma (RRMM): POM + LoDEX Is Beneficial For Elderly Patients (> 65 Years of Age)

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INTRODUCTION

- In multiple myeloma (MM), patient (pt) survival decreases with increased age[1]
- MM pts refractory to lenalidomide (LEN) or thalidomide and bortezomib (BORT) have a poor prognosis[2]
- POM is a distinct oral IMiD® immunomodulatory agent with a mechanism of action consisting of direct anti-myeloma activity, immune modulation, and microenvironmental effects[3]
- In the phase 2 setting, POM + LoDEX has demonstrated clinical efficacy and acceptable tolerability in elderly pts with RRMM[4]
- POM was recently approved by the US FDA and EU EMA for the treatment (Tx) of RRMM[5,6]
  - US: Pts who have received ≥ 2 prior Tx, including LEN and BORT and have demonstrated disease progression on or within 60 days of last Tx[5]
  - EU: In combination with DEX in RRMM pts who have received ≥ 2 prior Tx, including LEN and BORT and have demonstrated disease progression on last Tx[6]
- MM-003 has demonstrated significant progression-free survival (PFS) and overall survival (OS) benefits for POM + LoDEX vs. HiDEX, despite half of HiDEX pts subsequently receiving POM[7]

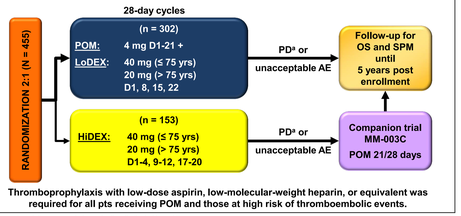
OBJECTIVES

- This analysis examined pt outcomes in MM-003 based on age:
  - ≤ 65 yrs vs. > 65 yrs
  - ≤ 70 yrs vs. > 70 yrs (efficacy only)

METHODS

- MM-003 trial design is shown in Figure 1

Figure 1. MM-003 Trial Design[7]



Thromboprophylaxis with low-dose aspirin, low-molecular-weight heparin, or equivalent was required for all pts receiving POM and those at high risk of thromboembolic events.

[a] Progression of disease was independently adjudicated in real time.
AE, adverse event; HiDEX, high-dose dexamethasone; LoDEX, low-dose dexamethasone; OS, overall survival; PD, progressive disease; POM, pomalidomide; pt, patient; SPM, second primary malignancy.

Study Endpoints

- The primary endpoint was PFS
- Secondary endpoints included OS, overall response rate (ORR; ≥ partial response [PR]), quality of life, and safety

Key Eligibility Criteria

- All pts had to be refractory to last therapy
- All pts must have received at least 2 prior Tx
  - ≥ 2 consecutive cycles of LEN and BORT (alone or in combination)
  - Adequate prior alkylator Tx (stem cell transplant [SCT] or ≥ 6 cycles or progressive disease [PD] following ≥ 2 cycles)
- All pts must have failed BORT and LEN
  - Pt progressed on or within 60 days
  - Pt with PR must have progressed within 6 mos
  - Intolerant to BORT after completing ≥ 2 cycles and achieving ≤ minimal response (MR)
- Refractory or relapsed and refractory disease
  - Primary refractory: Never achieved better than PD to any Tx
  - Relapsed and refractory: Relapsed after having achieved ≥ stable disease (SD) for ≥ 2 cycles of Tx to at least 1 prior regimen and then developed PD ≤ 60 days of completing their last Tx

METHODS (cont)

Assessments

- Response was assessed using IMWG and EBMT criteria (for MR)
- Adverse event (AE) severity was graded according to the NCI CTCAE v 4.0
- Median follow-up: 15.4 mos
  - Last pt enrolled: August 2012
  - Data cut-off: September 1, 2013

RESULTS

Baseline Characteristics

- A total of 302 pts received POM + LoDEX; and 153 pts received HiDEX
  - Since only 8% of POM + LoDEX and HiDEX pts were aged > 75 yrs, this analysis focused on pts aged ≤ 65 yrs vs. > 65 yrs
    - An additional cut-off of 70 yrs was included as an exploratory efficacy analysis
  - 45% of POM + LoDEX pts and 47% of HiDEX pts were aged > 65 yrs
- Characteristics were similar across all subgroups with the exception of prior SCT, renal function, and disease stage (Table 1)
  - Pts aged ≤ 65 yrs were more likely to have prior SCT, better renal function (creatinine clearance [CrCl] ≥ 60 mL/min), and less advanced disease than pts aged > 65 yrs
  - For pts aged > 65 yrs, HiDEX pts were more likely to have CrCl < 60 mL/min than POM + LoDEX pts
- Pts were heavily pretreated with a median of 5 prior Tx in all groups

Table 1. Baseline Characteristics

Characteristic	Age ≤ 65 yrs		Age > 65 yrs	
	POM + LoDEX (n = 167)	HiDEX (n = 81)	POM + LoDEX (n = 135)	HiDEX (n = 72)
Median age (range), yrs	59 (35-65)	59 (35-65)	72 (66-84)	71 (66-87)
Male (%)	61	63	59	50
Median time from initial diagnosis (yrs)	5.9	6.3	5.0	5.7
CrCl < 60 mL/min (%)	22	23	44	56
ECOG status 0/1/2/3 (%)	38/47/15/0	30/49/16/2	34/44/20/0	17/64/17/1
ISS stage at study entry I/II/III (%)	29/40/26	27/37/32	24/36/36	19/36/38
Median prior Tx, n (range)	5 (2-14)	5 (2-17)	5 (2-11)	5 (2-10)
Prior LEN/BORT/DEX (%)	100/100/97	100/100/99	100/100/99	100/100/100
Prior SCT (%)	92	90	45	44
LEN refractory (%)	94	93	96	92
BORT refractory (%)	79	80	79	78
LEN and BORT refractory (%)	74	74	75	74
Presence of del(17p)/t(4;14) (%)	26	20	24	26

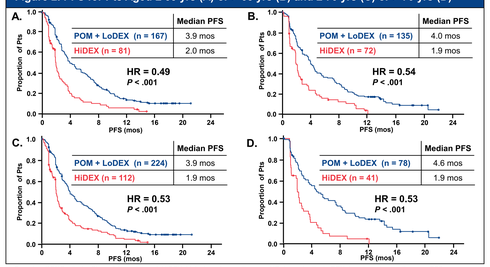
BORT, bortezomib; CrCl, creatinine clearance; del, deletion; DEX, dexamethasone; ECOG, Eastern Cooperative Oncology Group; HiDEX, high-dose dexamethasone; ISS, International Staging System; LEN, lenalidomide; LoDEX, low-dose dexamethasone; POM, pomalidomide; SCT, stem cell transplant; t, translocation; Tx, treatment.

PFS & Survival Outcomes

- POM + LoDEX significantly extended PFS vs. HiDEX regardless of age, consistent with the overall MM-003 population (Figures 2 and 3)
- OS was favorable for POM + LoDEX vs. HiDEX by age (Figures 4 and 5)
- A large proportion of HiDEX pts received POM after HiDEX
  - Pts aged ≤ 65 yrs: 60%
  - Pts aged > 65 yrs: 50%
  - Pts aged ≤ 70 yrs: 58%
  - Pts aged > 70 yrs: 49%

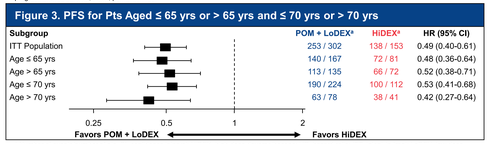
RESULTS (cont)

Figure 2. PFS for Pts Aged ≤ 65 yrs (A) or > 65 yrs (B) and ≤ 70 yrs (C) or > 70 yrs (D)



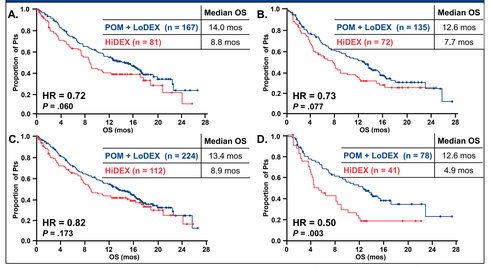
Based on IMWG criteria; CI, confidence interval; HiDEX, high-dose dexamethasone; HR, hazard ratio; LoDEX, low-dose dexamethasone; PFS, progression-free survival; POM, pomalidomide.

Figure 3. PFS for Pts Aged ≤ 65 yrs or > 65 yrs and ≤ 70 yrs or > 70 yrs



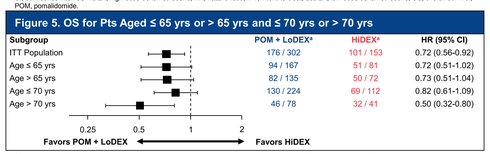
[a] Number of events/number of pts. CI, confidence interval; HiDEX, high-dose dexamethasone; HR, hazard ratio; ITT, intent-to-treat; LoDEX, low-dose dexamethasone; PFS, progression-free survival; POM, pomalidomide.

Figure 4. OS for Pts Aged ≤ 65 yrs (A) or > 65 yrs (B) and ≤ 70 yrs (C) or > 70 yrs (D)



CI, confidence interval; HiDEX, high-dose dexamethasone; HR, hazard ratio; ITT, intent-to-treat; LoDEX, low-dose dexamethasone; OS, overall survival; POM, pomalidomide.

Figure 5. OS for Pts Aged ≤ 65 yrs or > 65 yrs and ≤ 70 yrs or > 70 yrs



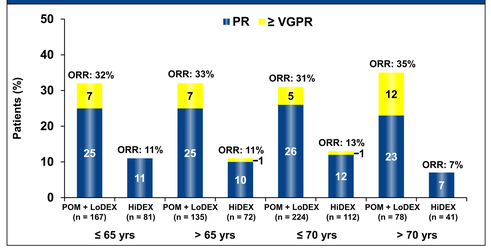
[a] Number of events/number of pts. CI, confidence interval; HiDEX, high-dose dexamethasone; HR, hazard ratio; ITT, intent-to-treat; LoDEX, low-dose dexamethasone; OS, overall survival; POM, pomalidomide.

RESULTS (cont)

Response

- POM + LoDEX significantly improved ORR vs. HiDEX regardless of age (Figure 6; *P* < .001 for all comparisons)
- Duration of response (≥ PR) was consistent by age and significantly longer for POM + LoDEX vs. HiDEX in pts aged > 65 yrs and > 70 yrs
  - Pts aged ≤ 65 yrs: 7.5 mos vs. 6.1 mos (*P* = .320)
  - Pts aged > 65 yrs: 7.6 mos vs. 5.1 (*P* = .038)
  - Pts aged ≤ 70 yrs: 7.4 mos vs. 6.1 mos (*P* = .177)
  - Pts aged > 70 yrs: 9.7 mos vs. 5.1 (*P* = .029)

Figure 6. Overall Response Rate (IMWG)



Note: Numbers may not sum due to rounding.
HiDEX, high-dose dexamethasone; LoDEX, low-dose dexamethasone; ORR, overall response rate; POM, pomalidomide; PR, partial response; VGPR, very good partial response.

Adverse Events (AEs)

- The most common grade 3/4 AEs for both age groups (≤ 65 yrs and > 65 yrs) were neutropenia, anemia, and infections (Table 2)
- The POM + LoDEX safety profile was generally consistent by age
  - Thrombocytopenia appeared to be higher for pts aged ≤ 65 yrs vs. pts aged > 65 yrs
  - Incidence of pneumonia appeared to be lower in the younger age group
- Study discontinuation due to AE in the POM + LoDEX arm was 6% for pts aged ≤ 65 yrs vs. 13% for pts aged > 65 yrs

Table 2. Safety Profile

Event	Age ≤ 65 yrs		Age > 65 yrs	
	POM + LoDEX (n = 167)	HiDEX[a] (n = 79)	POM + LoDEX (n = 133)	HiDEX[a] (n = 71)
Grade 3/4 hematologic AEs in ≥ 10% of pts (%)				
Neutropenia	51	22	45	13
Febrile neutropenia	12	0	6	0
Anemia	35	41	30	37
Thrombocytopenia	28	27	16	25
Grade 3/4 nonhematologic AEs in ≥ 10% of pts (%)				
Infections	34	20	31	30
Pneumonia	12	5	17	11
Grade 3/4 AEs of interest (%)				
DVT/PE	1	0	2	0
Peripheral neuropathy[b]	1	3	2	0
Discontinuation due to AEs (%)	6	10	13	11

[a] Pts may have received POM + LoDEX following crossover.
[b] Peripheral neuropathy includes the preferred terms "hyperaesthesia," "neuropathy peripheral," "peripheral sensory neuropathy," "paraesthesia," "hypoaesthesia," and polyneuropathy.
AE, adverse event; DVT, deep vein thrombosis; HiDEX, high-dose dexamethasone; LoDEX, low-dose dexamethasone; PE, pulmonary embolism; POM, pomalidomide; pt, patient.

POM Duration of Tx and Dose Modifications Due to AEs

- Median duration of POM Tx was similar in pts aged ≤ 65 yrs (4.4 mos) and > 65 yrs (4.0 mos) (Table 3)
- Frequency of dose reductions and interruptions was not affected by age
- Median relative dose intensity was consistent at 90% for both age groups

RESULTS (cont)

Table 3. POM Dose Modification Due to AEs and Dose Intensity

Variable	≤ 65 yrs (n = 167)	> 65 yrs (n = 133)
POM dose modifications due to AEs (%)		
Interruption	63	73
Reduction	26	30
Discontinuation	7	11
POM dose intensity		
Planned POM dose/day, mg	4	4
Median relative dose intensity,[a] mg (range)	0.9 (0.3-1.3)	0.9 (0.3-1.3)
Median duration of treatment, mos (range)	4.4 (0.1-25.6)	4.0 (0.1-26.3)

[a] Relative dose intensity = dose intensity/planned dose intensity.
AE, adverse event; POM, pomalidomide.

CONCLUSIONS

- POM + LoDEX significantly extended PFS compared with HiDEX with similar benefits across age groups
- OS results were similar to those of the overall pt population, and favored POM + LoDEX in age subgroups
- Duration of treatment and dose intensity were not affected by age
- Tolerability profiles were consistent for pts ≤ 65 yrs and > 65 yrs
- There is no need for upfront dose reduction in pts aged > 65 yrs
  - POM at 4 mg is an appropriate starting dose for elderly pts
- These data support using POM + LoDEX as a standard Tx option in RRMM pts regardless of age

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DISCLOSURES

- KW: Consultant – Celgene, Janssen; Honoraria – Celgene and Janssen; Research funding – Celgene
- JFSM: Consultant – Celgene, Janssen, Millennium, Novartis, and Onyx; Honoraria – Celgene, Janssen, Millenium, Novartis, and Onyx; Member of board of directors or advisory committee – Celgene, Janssen, Millennium, Novartis, and Onyx
- KWS: Honoraria – Celgene; Member of board of directors or advisory committee – Celgene; Research funding – Celgene; Member of speakers bureau – Celgene
- MD: Honoraria – Celgene
- LK: Member of export board committee – Celgene; Honoraria – Celgene, Janssen
- HG: Consultant – Celgene, Janssen, and Novartis; Honoraria – Celgene, Janssen, and Novartis; Research funding – Celgene, Janssen, and Novartis
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- AA: Member of board of directors or advisory committee – Celgene, Janssen
- JML: Honoraria – Celgene; Research funding – Celgene
- CIC: Consultant – Celgene; Honoraria – Celgene; Research funding – Celgene
- SK: Honoraria – Celgene
- XY, LW, LS, MHZ, CJ: Employed by Celgene; owns equity in Celgene
- MAD: Honoraria – Celgene; Member of board of directors or advisory committee – Celgene

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