Abstract # 8593

Analyzing the Relationship of Response and Survival in Patients With Refractory or Relapsed and Refractory Multiple Myeloma (RRMM) Treated With Pomalidomide Plus Low-Dose Dexamethasone (POM + LoDEX) in the MM-003 Trial

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INTRODUCTION

- Patients (pts) with RRMM who have failed prior treatment (Tx) with bortezomib (BORT) and lenalidomide (LEN) have short overall survival (OS)[1]
- In the phase 3 MM-003 trial (NCT01311687), pts with RRMM treated with POM + LoDEX had significantly longer OS compared to pts treated with high-dose dexamethasone (HiDEX; hazard ratio [HR] = 0.74 [95% CI, 0.56-0.97], *P* = 0.0285)[2]
  - With longer follow-up (median = 15.4 mos), OS benefit of POM + LoDEX was maintained vs HiDEX (13.1 mos vs 8.1 mos, HR = 0.72, *P* = 0.009)[3]
- Overall response (≥ partial response [PR]) was 32% vs 11% and stable disease (SD) rate was 41% vs 46% for pts Tx with POM + LoDEX vs HiDEX, respectively[4]
- Due to the large proportion of pts in MM-003 that had SD,[4] it is important to understand whether any benefit is derived from Tx with POM + LoDEX in these pts

OBJECTIVE

- To investigate OS in pts who achieved SD but no response during Tx in the MM-003 trial

METHODS

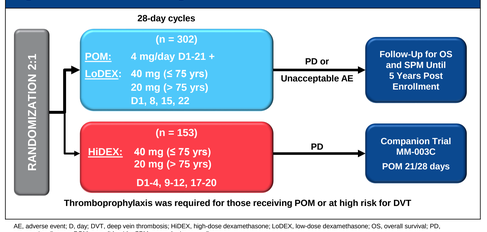
Study design

- The study design is shown in **Figure 1**

Study endpoints

- Primary: Progression-free survival (PFS)
- Secondary included: OS, overall response rate (ORR ≥ PR), duration of response, safety, and health-related quality of life

Figure 1. MM-003 Trial Design



AE, adverse event; D, day; DVT, deep vein thrombosis; HiDEX, high-dose dexamethasone; LoDEX, low-dose dexamethasone; OS, overall survival; PD, progressive disease; POM, pomalidomide; SPM, second primary malignancy.

Key inclusion criteria

- ≥ 18 years of age
- Measurable levels of M protein in serum or urine
- Refractory or relapsed and refractory disease
  - Refractory to last Tx: Documented progressive disease (PD) during or within 60 days of completing their last Tx
  - Failed BORT and LEN: Refractory, progressed within 6 mos following PR, or intolerant (BORT only)
  - ≥ 2 consecutive cycles of LEN and BORT (alone or in combination)
  - Adequate prior alkylator therapy (stem cell transplant or ≥ 6 cycles or PD following ≥ 2 cycles)

METHODS (cont'd)

Key exclusion criteria

- Absolute neutrophil count < 1,000/μL
- Thrombocytopenia
  - Platelets < 75,000/μL for pts in whom < 50% of bone marrow nucleated cells were plasma cells
  - Platelets < 30,000/μL for pts in whom ≥ 50% of bone marrow nucleated cells were plasma cells
- Creatinine clearance < 45 mL/min
- Peripheral neuropathy ≥ grade 2
- Resistance to HiDEX in the last line of Tx

Assessments

- Tumor response, including PD, was assessed by investigators and an Independent Response Adjudication Committee according to International Myeloma Working Group criteria
- OS was based on the intent-to-treat population (all randomized pts)
- Median follow-up: 15.4 mos
  - Last pt enrolled: August 2012
  - Data cut-off: September 1, 2013

Landmark analyses

- Landmark analyses were performed on Day (D) 1 of cycles (C) 3, 5, and 7 using Kaplan-Meier methods and unadjusted Cox regression models
- For both approaches, survival of pts with SD was compared with that of pts who achieved an overall response ≥ PR or had PD at the same landmark point in time

Time-dependent survival analyses

- Time-dependent covariate analysis was conducted to assess the risk of death in each response category (SD, ≥ PR, or PD)

RESULTS

Baseline characteristics

- POM + LoDEX arm (C3, D1):
  - There were no baseline characteristics that showed statistically significant differences across groups **(Table 1)**
- HiDEX Arm (C3, D1):
  - Based on the ITT population, baseline demographics were well balanced
  - There were minor differences in baseline characteristics across response groups, including mean time from diagnosis

Table 1. Baseline Characteristics for Pts in the POM + LoDEX Arm (C3, D1)

Baseline Characteristic		≥ PR n = 58	PD n = 44	SD n = 116
Age, n (%)	≤ 75 yrs	51 (87.9)	41 (93.2)	106 (91.4)
	> 75 yrs	7 (12.1)	3 (6.8)	10 (8.6)
Disease population, n (%)[a]	Disease group 1	48 (82.8)	38 (86.4)	92 (79.3)
	Disease group 2	1 (1.7)	0	3 (2.6)
	Disease group 3	9 (15.5)	6 (13.6)	21 (18.1)
ECOG performance status, n (%)	0-1	44 (75.9)	34 (77.3)	103 (88.8)
	1-2	14 (24.1)	10 (22.7)	12 (10.3)
	Missing	0	0	1 (0.9)
Sex, n (%)	F	24 (41.4)	19 (43.2)	45 (38.8)
	M	34 (58.6)	25 (56.8)	71 (61.2)
ISS stage, n (%)	I	20 (34.5)	12 (27.3)	37 (31.9)
	II	26 (44.8)	14 (31.8)	39 (33.6)
	III	12 (20.7)	16 (36.4)	31 (26.7)
	Missing	0	2 (4.5)	9 (7.8)
Cytogenetic status, n (%)	Low-risk	22 (37.9)	12 (27.3)	35 (30.2)
	Modified high-risk[b]	12 (20.7)	12 (27.3)	33 (28.4)
Prior anti-MM Tx, n (%)	2	6 (10.3)	3 (6.8)	4 (3.4)
	> 2	52 (89.7)	41 (93.2)	112 (96.6)
Refractory to BORT, n (%)		43 (74.1)	38 (86.4)	90 (77.6)
Refractory to LEN, n (%)		52 (89.7)	44 (100.0)	111 (95.7)
Refractory to both LEN and BORT, n (%)		38 (65.5)	38 (86.4)	86 (74.1)
Time from diagnosis, yrs	Mean	6.7	5.3	6.5
	Std Deviation	4.5	2.8	4.5

[a] Disease Group 1 is defined as refractory pts who have progressed on or within 60 days of both LEN- and BORT-based Tx. Disease Group 2 is defined as relapsed and refractory pts who achieved a PR and progressed within 6 months after stopping Tx with LEN and/or BORT. Disease Group 3 is defined as refractory/intolerant pts who have developed intolerance/toxicity after ≥ 2 cycles of BORT.
[b] Modified high-risk is defined as presence of del(17p) and/or t(4;14).
BORT, bortezomib; C, cycle; D, day; ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; LEN, lenalidomide; LoDEX, low-dose dexamethasone; MM, multiple myeloma, PD, progressive disease; POM, pomalidomide; PR, partial response; pt, patient; Q, quartile; SD, stable disease; Tx, treatment.

RESULTS (cont'd)

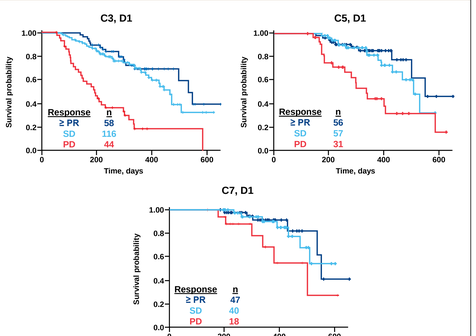
Landmark OS analysis for POM + LoDEX

- Pts who had SD at the start of C3, 5, and 7 and were treated with POM + LoDEX had similar OS to pts who achieved ≥ PR at these same time points **(Figure 2; Table 2)**
- On D1 of C3, 5, and 7, pts who had SD had significantly different OS compared with pts with PD at the same time points **(Figure 2; Table 2)**

Landmark PFS analysis for POM + LoDEX

- PFS was similar for pts who had SD or ≥ PR at the start of C5 or 7

Figure 2. Landmark OS Analysis of POM + LoDEX



C, cycle; D, day; LoDEX, low-dose dexamethasone; OS, overall survival; PD, progressive disease; POM, pomalidomide; PR, partial response; SD, stable disease.

Table 2. Comparison of OS With ≥ PR or PD vs SD in Pts Treated With POM + LoDEX

Cycle	Response	HR (95% CI)	*P* value
C3, D1	≥ PR vs SD	0.75 (0.43-1.31)	0.3200
	PD vs SD	3.83 (2.39-6.14)	< 0.0001
C5, D1	≥ PR vs SD	0.74 (0.33-1.66)	0.4622
	PD vs SD	2.81 (1.38-5.71)	0.0044
C7, D1	≥ PR vs SD	0.90 (0.30-2.67)	0.8426
	PD vs SD	2.66 (0.89-7.94)	0.0799

C, cycle; D, day; HR, hazard ratio; LoDEX, low-dose dexamethasone; OS, overall survival; PD, progressive disease; POM, pomalidomide; PR, partial response; Pt, patient; SD, stable disease.

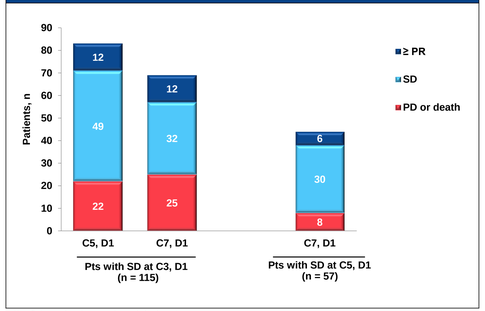
Landmark OS analysis for HiDEX

- For pts treated with HiDEX, OS was similar between pts who had SD on C3, D1 and pts with ≥ PR at the same time point
  - OS in pts with SD treated with HiDEX was significantly different from that in pts with PD at cycle 3
- Later analyses were complicated by the fact that most pts in the HiDEX arm had died, and no conclusions could be drawn

Improvement in response

- Some pts with SD showed improved response after 2 or 4 cycles of SD **(Figure 3)**
  - 17% of pts treated with POM + LoDEX who had SD on D1, C3 went on to demonstrate a response by D1, C7
  - Approximately 14% of pts treated with POM + LoDEX who had SD for ≥ 4 cycles went on to demonstrate a response by D1, C7 (vs no pts in the HiDEX arm)

Figure 3. Response Status of Pts With Prior SD



Note: Patient numbers do not sum due to missing data points.
C, cycle; D, day; PD, progressive disease; PR, partial response; Pt, patient; SD, stable disease.

Time-dependent covariate analysis

- When looking at death in each response state (≥ PR, SD, or PD) over the course of the trial, pts had a greater likelihood of death during PD compared with SD, and a greater likelihood of death during either PD or SD compared with ≥ PR **(Table 3)**
- There was a trend toward a difference in risk of death in each response state across Tx arms, but this did not reach statistical significance (*P* = 0.0924)

Table 3. Summary of Survival Events by Response State in Pts Treated With POM + LoDEX

Response state	N	Total time at risk, yrs	Median time at risk (Q1-, 2), yrs	Total number of events	Events per yr at risk
≥ PR	94	47.7	0.48 (0.3, 0.71)	4	0.08
PD	191	76.8	0.35 (0.15, 0.62)	105	1.37
SD	302	83.7	0.18 (0.1, 0.37)	38	0.45

LoDEX, low-dose dexamethasone; PD, progressive disease; POM, pomalidomide; PR, partial response; Pt, patient; Q, quarter; SD, stable disease.

CONCLUSIONS

- Pts treated with POM + LoDEX with SD at the start of C3, 5, and 7 had similar OS as pts who had ≥ PR at these time points
- Pts with either SD or ≥ PR had a longer OS vs pts who achieved PD at the same time points
- Some pts with SD improved their response status even after only achieving SD through ≥ 4 cycles of Tx
- By time-dependent covariate analysis, pts have a greater risk of death during PD than during SD or ≥ PR
- Overall, there may be benefit in continuing POM + LoDEX Tx in pts who maintain SD for a long period of time

REFERENCES

1. Kumar SK, et al. *Leukemia.* 2012;26:149-157.
2. San Miguel J, et al. *Lancet Oncol.* 2013;14:1055-1066.
3. Dimopoulos MA, et al. *Blood.* 2013;122:408 [oral presentation].
4. San Miguel J, et al. *Blood.* 2013;122:686 [oral presentation].

ACKNOWLEDGEMENTS

- The authors thank the patients, nurses, and study personnel who were involved in this clinical trial
- The authors acknowledge the financial support for this study from Celgene Corporation. The authors received editorial assistance from MediTech Media (Daniel Sinsimer, PhD, and Nicola Hanson, PhD), and printing support from MediTech Media, sponsored by Celgene Corporation

Presented at the ASCO 2015 Annual Meeting; May 29-June 2, 2015; Chicago, IL.