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Analysis of Patients With Refractory or Relapsed and Refractory Multiple Myeloma and Renal Impairment Treated With Pomalidomide + Low-Dose Dexamethasone in the Phase 3b STRATUS™ Trial (MM-010)

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INTRODUCTION

- Overall survival (OS) of patients (pts) with refractory or relapsed and refractory multiple myeloma (RRMM) has been extended by treatment (Tx) with newer agents, such as lenalidomide (LEN) and bortezomib (BORT)[1]
- Renal impairment (RI), a major cause of death in this pt population, occurs in ≈ 20% - 40% of pts with MM[2,3]
- In pts with RRMM that was not successfully treated with LEN and BORT, pomalidomide (POM) + low-dose dexamethasone (LoDEX) extended progression-free survival (PFS) and OS vs high-dose dexamethasone in the phase 3 MM-003 trial, which included pts with moderate RI (creatinine clearance [CrCl] = ≥ 45 to < 60 mL/min)[4]
  - Efficacy of POM + LoDEX was similar across renal function subgroups in the MM-002 trial, in which pts with serum creatinine ≥ 3 mg/dL were excluded[5]
- Here, we examine the safety and efficacy of POM + LoDEX in pts with RRMM based on their RI status in the phase 3b STRATUS trial (MM-010)

OBJECTIVE

- To further evaluate the safety and efficacy of POM + LoDEX in pts with RRMM, including those pts with varying degrees of RI

METHODS

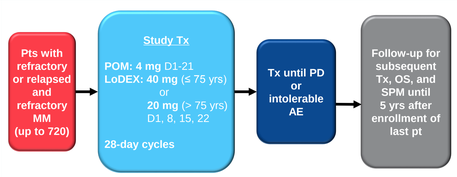
Study Design

- STRATUS is a multicenter, single-arm, open-label phase 3b trial of POM + LoDEX in a large RRMM pt population with 91 centers across Europe **(Figure 1)**

Study Endpoints

- **Primary:** Safety
- **Secondary included:** Overall response rate (ORR; ≥ partial response [PR]), duration of response (DOR), PFS, OS, and POM exposure

Figure 1. MM-010 Trial Design



Thromboprophylaxis with low-dose aspirin, low-molecular-weight heparin, or equivalent was required for all pts

Registered at ClinicalTrials.gov as NCT01712789 and at EudraCT as 2012-001888-78.
AE, adverse event; LoDEX, low-dose dexamethasone; MM, multiple myeloma; OS, overall survival; PD, progressive disease; POM, pomalidomide; pt, patient; SPM, second primary malignancy; Tx, treatment.

METHODS (cont)

Key Eligibility Criteria

- All pts had to be refractory to last therapy
- ≥ 2 prior therapies
  - ≥ 2 consecutive cycles of LEN and BORT (alone or in combination)
  - Adequate prior alkylator therapy (stem cell transplant [SCT] or ≥ 4 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
- Refractory or relapsed and refractory disease
  - Primary refractory: never achieved better than PD to any therapy
  - Relapsed and refractory: relapsed after having achieved ≥ stable disease for ≥ 2 cycles of Tx to ≥ one prior regimen and then developed PD ≤ 60 days of completing last therapy

Assessments

- Response was assessed using International Myeloma Working Group Criteria according to investigator assessment
- Renal function was calculated using the Cockcroft-Gault method
- Adverse event (AE) severity was graded according to NCI CTCAE v 4.0

RESULTS

Baseline Characteristics

- As of January 23, 2015, 682 pts have been enrolled and 676 have received POM + LoDEX
  - 35% of pts had moderate RI (CrCl < 60 mL/min)
- Baseline characteristics were similar across subgroups with the exception of age, sex, and performance status **(Table 1)**
  - Pts with CrCl ≥ 60 mL/min were more likely to be younger, male, have better performance status and have had prior SCT vs pts with CrCl < 60 mL/min
  - Pts were heavily pretreated, with a median of 4 prior Tx regimens

Safety

- Grade (Gr) 3/4 hematologic and non-hematologic treatment-emergent AEs (TEAEs) were similar in pts with vs those without moderate RI **(Table 2)**
  - Gr 3/4 deep vein thrombosis and peripheral neuropathy were infrequent
- 8% of pts with moderate RI and 5% of pts without moderate RI required discontinuation of POM due to TEAEs **(Table 3)**
- Median relative POM dose intensity was consistent between subgroups (93% in each group, **Table 3**)

RESULTS (cont)

Table 1. Patient Characteristics

Characteristic	With Moderate RI CrCl < 60 mL/min (n = 239)	Without Moderate RI CrCl ≥ 60 mL/min (n = 443)
Median age (range), yrs	72 (44-88)	63 (37-85)
Male, %	45	62
ECOG performance status 0/1/2, %	36/53/11	47/44/9
ISS stage at study entry I/II/III/missing, %	11/38/46/5	27/42/27/5
Median time since diagnosis (range), yrs	5.0 (0.5-28.1)	5.3 (0.6-21.3)
Median prior Tx regimens (range)	4 (2-15)	4 (2-18)
Prior LEN, %	100	100
Prior BORT, %	100	100
Prior THAL, %	49	57
Prior CFZ, %	4	3
Prior SCT, %	48	76
LEN refractory, %	95	96
BORT refractory, %	85	83
LEN and BORT refractory, %	80	80

BORT, bortezomib; CFZ, carfilzomib; CrCl, creatinine clearance; ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; LEN, lenalidomide; RI, renal impairment; SCT, stem cell transplant; THAL, thalidomide; Tx, treatment.

Table 2. Safety Profile

TEAE, %	With Moderate RI CrCl < 60 mL/min (n = 235)	Without Moderate RI CrCl ≥ 60 mL/min (n = 441)
Grade 3/4 hematologic TEAEs occurring in ≥ 10% of pts		
Neutropenia	45	49
Febrile neutropenia	4	6
Anemia	36	28
Thrombocytopenia	23	23
Grade 3-4 non-hematologic TEAEs occurring in ≥ 10% of pts		
Infections	30	31
Pneumonia	12	11
Grade 3-4 TEAEs of interest		
DVT/PE	3	1
Peripheral neuropathy[a]	1	1

[a] Includes the preferred terms: neuropathy peripheral, peripheral sensory neuropathy, paraesthesia, hypoesthesia, polyneuropathy, peripheral sensorimotor neuropathy, peripheral motor neuropathy, and dysesthesia.
CrCl , creatinine clearance; DVT, deep vein thrombosis; PE, pulmonary embolism; pt, patient; RI, renal impairment; TEAE, treatment-emergent adverse event.

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

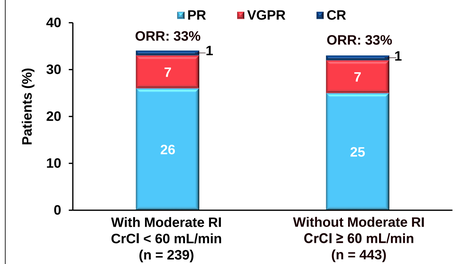
	With Moderate RI CrCl < 60 mL/min (n = 235)	Without Moderate RI CrCl ≥ 60 mL/min (n = 441)
Median Tx duration range, weeks	16.7 (1-93)	20.3 (1-106)
Median relative dose intensity[a]	0.927	0.933
Discontinuation due to TEAE, %	8	5
Reduction due to TEAE, %	20	18
Interruption due to TEAE, %	60	62

[a] Relative dose intensity = dose intensity/planned dose intensity.
CrCl, creatinine clearance; POM, pomalidomide; RI, renal impairment; TEAE, treatment-emergent adverse event; Tx, treatment.

Response

- Responses were not different across subgroups, with a median follow-up of 12.8 mos **(Figure 2)**
  - With moderate RI (CrCl < 60 mL/min): ORR = 33%; median DOR = 6.7 mos
  - Without moderate RI (CrCl ≥ 60 mL/min): ORR = 33%; median DOR = 8.4 mos

Figure 2. Response (IMWG Criteria)

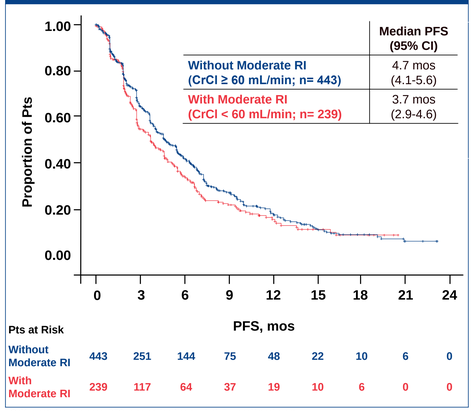


Values may not add up to ORR due to rounding.
CR, complete response; CrCl, creatinine clearance; DOR, duration of response; IMWG, International Myeloma Working Group; ORR, overall response rate; PR, partial response; RI, renal impairment; VGPR, very good partial response.

PFS

- Median PFS was 3.7 mos for pts with moderate RI (CrCl < 60 mL/min) vs 4.7 mos for pts without moderate RI (CrCl ≥ 60 mL/min, *P* = .1644; **Figure 3**)

Figure 3. PFS by Renal Function Status



CrCl, creatinine clearance; PFS, progression-free survival; RI, renal impairment.

CONCLUSIONS

- The STRATUS trial demonstrated that in pts with moderate RI, POM + LoDEX had a manageable safety profile and was efficacious
- Tolerability was similar in pts with or without moderate RI and consistent with results from the pivotal MM-002 and MM-003 trials
- ORRs with POM + LoDEX were consistent between pt groups, despite differences in renal function
- There was a slightly longer median PFS in pts without moderate RI, but this did not meet statistical significance (*P* = .1644)
- Two ongoing trials, MM-008 (US) and MM-013 (EU), are currently evaluating POM in pts with RRMM and severe RI

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