Twice-weekly Oral MLN9708, an Investigational Proteasome Inhibitor, in Combination with Lenalidomide (Len) and Dexamethasone (Dex) in Patients (Pts) with Newly Diagnosed Multiple Myeloma (MM): Final Phase 1 Results and Phase 2 Data

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MLN9708

- MLN9708 (ixazomib citrate) is an investigational oral proteasome inhibitor that is being investigated in multiple Phase 3 trials
- Phase 1 studies using weekly and twice-weekly dosing have demonstrated that oral MLN9708 has single-agent activity, with responses also seen in pts with heavily pre-treated relapsed and/or refractory MM[1,2]
- In pts with newly diagnosed MM, a study of weekly oral MLN9708 in combination with len and dex has demonstrated activity, as evidenced by high response rates, including CRs, VGPRs, and MRD-negativity[3]
- Here we report final phase 1 results and phase 2 data of a phase 1/2 study of twice-weekly oral MLN9708 in combination with len and dex (triplet oral combination) in pts with newly diagnosed MM (NCT01383928)
  - Trial conducted in collaboration with the Multiple Myeloma Research Consortium

1. Lonial S, et al. Oral presentation at ASCO 2012, Chicago, IL
2. Kumar S, et al. Oral presentation at ASCO 2013, Chicago, IL
3. Kumar S, et al. Oral presentation at ASH 2012, Atlanta, GA

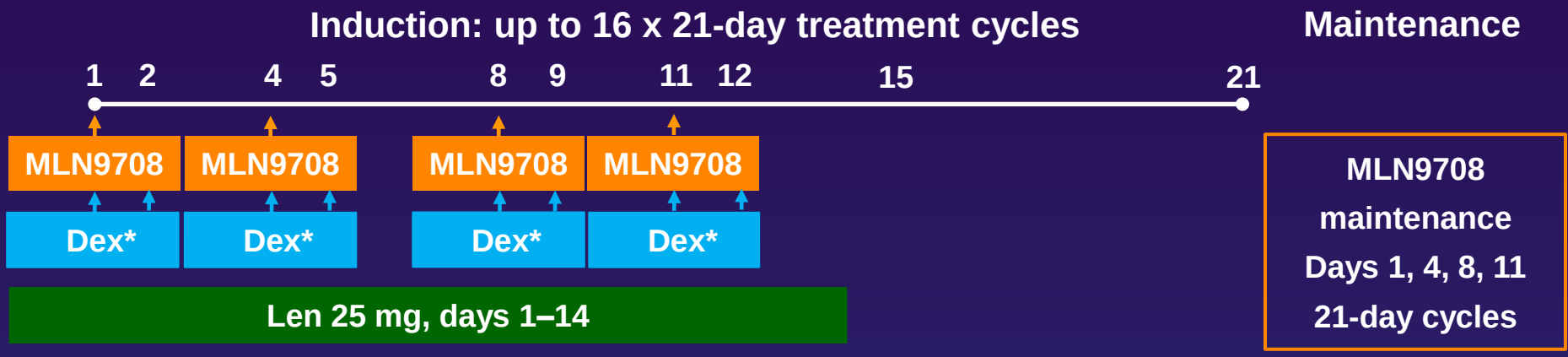
Key objectives

- **Phase 1 objectives:**
  - **Primary: determine the safety, tolerability, maximum tolerated dose (MTD), and recommended phase 2 dose (RP2D)**
  - **Secondary: characterize the pharmacokinetics (PK) of MLN2238 (the pharmacologically active hydrolysis product of MLN9708)**
- **Phase 2 objectives:**
  - **Primary: determine combined CR+VGPR rate; further evaluate tolerability and toxicity**
  - **Secondary: determine overall response rate (ORR; ≥PR), duration of response, and progression-free survival**

Patients

- Key inclusion criteria:
  - Age ≥18 years
  - ECOG performance status 0–2
  - Adequate renal, hepatic, and hematologic function
  - Newly diagnosed MM
  - Measurable disease (at least one of the following):
    - Serum M-protein ≥1 g/dL
    - Urine M-protein ≥200 mg/24 hours
    - Involved free light chain (FLC) ≥10 mg/dL, provided the serum FLC ratio is abnormal
- Key exclusion criteria:
  - Grade ≥2 peripheral neuropathy
  - Prior/concurrent deep vein thrombosis/pulmonary embolism

Study design



*Dex 20/10 mg cycles 1–8 / 9–16
All patients required thromboembolism prophylaxis with aspirin 81–325 mg QD or LMWH while receiving len–dex

- Phase 1: oral MLN9708 dose-escalation
  - Standard 3+3 schema, 33% dose increments, based on cycle 1 DLTs
- Phase 2: oral MLN9708 at the RP2D from phase 1
- Protocol allows for stem cell collection after cycle 4, with ASCT deferred until after 8 cycles
- MLN9708 maintenance continued at the last tolerated dose level until progression or unacceptable toxicity

Patient demographics and baseline disease characteristics

	Phase 1 (n=14)	RP2D* (n=57)	Total (N=64)
Median age, years (range)	63 (42–78)	64 (34–82)	63.5 (34–82)
Male, n (%)	9 (64)	36 (63)	40 (63)
White / African American / Other, n†	12 / 1 / 1	47 / 8 / 1	54 / 8 / 1
ISS stage at diagnosis, n (%)			
I	8 (57)	24 (42)	30 (47)
II	5 (36)	22 (39)	23 (36)
III	1 (7)	11 (19)	11 (17)

*RP2D cohort includes 50 phase 2 pts and 7 phase 1 pts treated at MLN9708 3.0 mg
†Data not provided for 1 pt in phase 2

Phase 1: DLTs and RP2D

- Two dose levels in this study:
  - 7 pts enrolled to MLN9708 3.0 mg
  - 7 pts enrolled to MLN9708 3.7 mg
- No AEs met DLT criteria in cycle 1 at either dose of MLN9708
- RP2D was chosen as 3.0 mg
  - Determined based on consideration of the balance between overall tolerability, including rate of rash that was higher than expected with either single-agent MLN9708 or lenalidomide, and efficacy across multiple cycles
    - All 7 pts enrolled to MLN9708 3.7 mg reported rash-related AEs (including 4 pts with grade 3 AEs)

DLTs, dose-limiting toxicites

Treatment exposure

	Phase 1 (n=14)	RP2D* (n=57)	Total (N=64)
Median cycles received, n (range)	10.5 (1–30)	9 (1–30)	9 (1–30)
Pts who received ≥8 cycles, n (%)	10 (71)	45 (79)	49 (77)
Pts who received ≥16 cycles, n (%)	5 (36)	9 (16)	11 (17)
Median relative dose intensity,[#] %			
MLN9708	90	97	95
Len	74	96	93
Dex	94	94	95
Pts remaining on treatment,[†] n (%)	3 (21)	15 (26)	16 (25)
Reason for going off treatment, n (%)			
Proceeding to ASCT	3 (21)	20 (35)	21 (33)
Adverse event	3 (21)	9 (16)	11 (17)
Progressive disease	1 (7)	6 (11)	6 (9)
Other[‡]	4 (29)	7 (12)	10 (16)

*RP2D cohort includes all 50 phase 2 pts and 7 phase 1 pts treated at MLN9708 3.0 mg; [#]Dose taken/dose prescribed; [†]At data cut-off (Oct 9, 2013); [‡]Other included subject preference (n=5), investigator discretion (n=2), health complications unrelated to study drug, unsatisfactory response, syngeneic stem cell transplant (each n=1)

Stem cell mobilization

- At data cut-off (October 9, 2013), 18 (28%) pts had stem cells harvested
- Median cycle of first stem cell mobilization: 6 (range 4–13)
- Sites used institutional standard mobilization regimens, which included:
    - Plerixafor + G-CSF (n=8)
    - Cyclophosphamide (n=2)
    - Cyclophosphamide + G-CSF (n=2)
    - G-CSF (n=1)
    - Other (n=5)
- Median number of apheresis procedures: 2
    - 6 and 12 pts underwent 1 and 2 procedures, respectively
- Median number of harvested CD34+ cells: 10.8 x 10^6/L (range 6–100 x 10^6)
- MLN9708 plus len and dex did not appear to have an adverse impact on stem cell mobilization

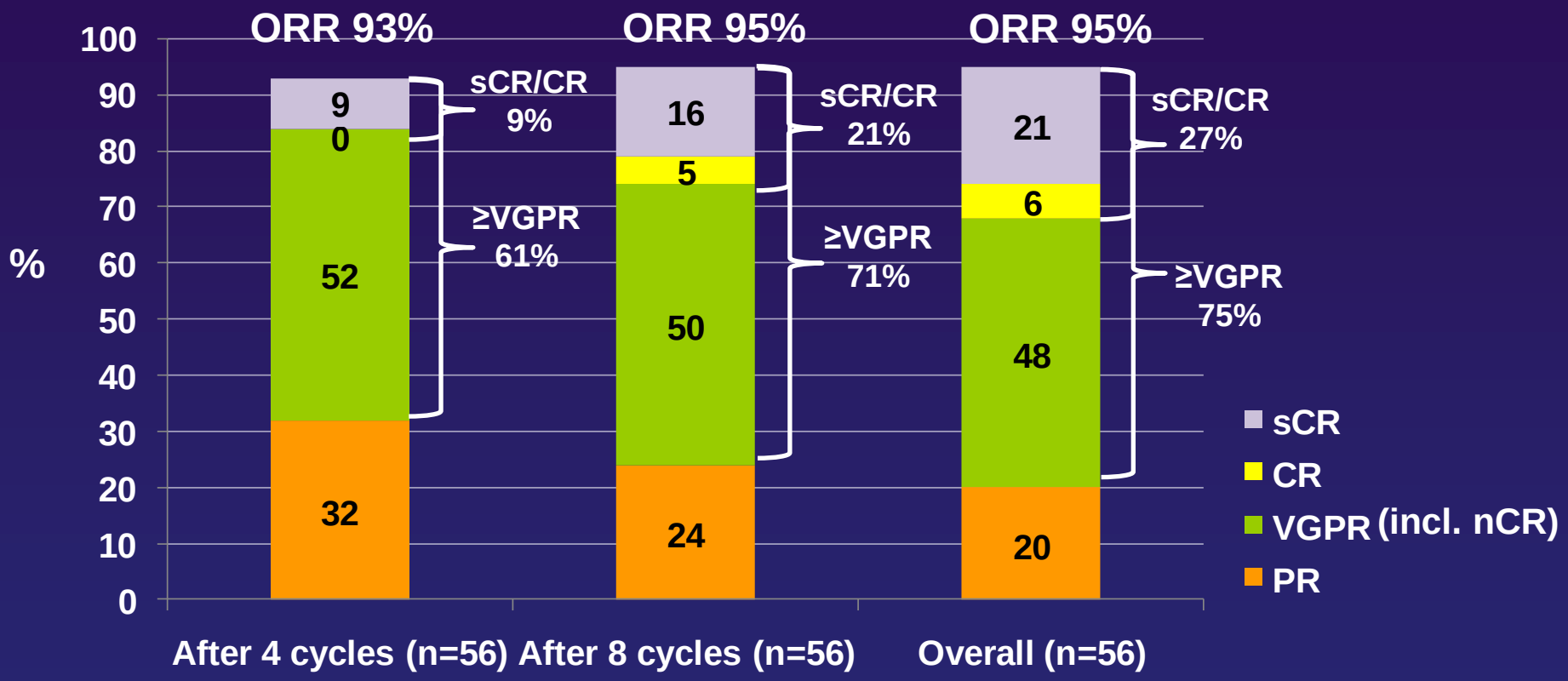
Preliminary response data

Response, n (%)*	Phase 1 (n=13)	RP2D† (n=56)	Total (n=62)
ORR (≥PR)	12 (92)	53 (95)	58 (94)
CR+VGPR	10 (77)	42 (75)	46 (76)
CR	2 (15)	15 (27)	16 (26)
sCR	0	12 (21)	12 (19)
nCR	3 (23)	5 (9)	6 (10)
VGPR (incl. nCR)	8 (62)	27 (48)	30 (48)

- 62 of 64 pts were evaluable for response (2 patients did not have post-baseline response assessments thus were not evaluable)
- Median follow-up of 10.9 months

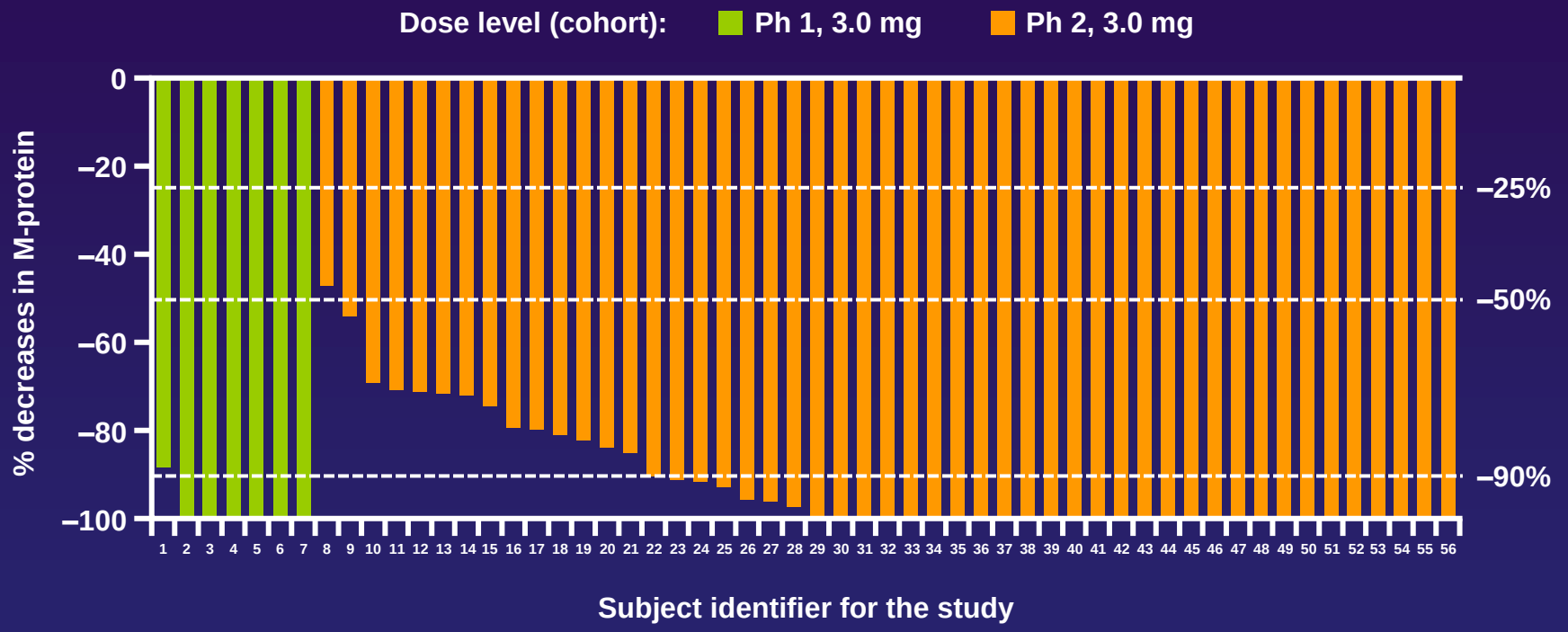
*Best confirmed/unconfirmed response by investigator assessment using IMWG uniform response criteria;
†Includes 7 phase 1 pts treated at MLN9708 3.0 mg

Preliminary response data show deepening responses over course of treatment (pts treated at RP2D)



- Depth of response increased over the course of treatment
  - Median time to first response: 0.69 months
  - Median time to best response to date: 1.96 months
- Median duration of response to date is 13.8 months, ranging up to 18.8+ months

Individual best M-protein or serum FLC response to treatment (pts treated at RP2D)



- 56 patients treated at the RP2D were evaluable for response (7 phase 1, 49 phase 2)
- 61% of pts had 100% decreases in M-protein or serum free light chain from baseline

MRD evaluation

Feasibility of MRD assessment

Response achieved	Expected MRD samples, N	MRD samples received, n	MRD sample collection compliance, %
sCR + CR	16	12	75

MRD status in patients providing samples

Response/status	MRD-negative, n	MRD-positive, n	MRD inevaluable, n
sCR + CR, n=12	9	2	1
Ongoing on treatment, n	4	0	1

Safety profile

AE,* n (%)	Phase 1 (n=14)	RP2D† (n=57)	Total (N=64)
Any AE	14 (100)	57 (100)	64 (100)
Any drug-related AE#	14 (100)	56 (98)	63 (98)
Any grade ≥3 AE	11 (79)	44 (77)	49 (77)
Any grade ≥3 drug-related AE#	9 (64)	32 (56)	37 (58)
Any serious AE (SAE)	7 (50)	28 (49)	30 (47)
Any drug-related SAE†	4 (29)	16 (28)	18 (28)
Dose reduction due to AEs	10 (71)	32 (56)	37 (58)
Discontinuation due to AEs	3 (21)	7 (12)	9 (14)

- One pt (phase 2) died due to cardio-respiratory arrest, likely a pulmonary embolism, considered by the investigator to be unrelated to MLN9708 or dex but probably related to len

*AEs graded using NCI-CTCAE v4.03; †Includes 7 phase 1 pts treated at MLN9708 3.0 mg; #Drug-related is defined as related to any drug in the combination

Drug-related* AEs, all grades (≥20% of total)

AE, n (%)	Phase 1 (n=14)	RP2D (n=57)†	Total (N=64)
Peripheral neuropathies‡	9 (64)	30 (53)	34 (53)
Rash-related AEs#	10 (70)	25 (44)	32 (50)
Fatigue	9 (64)	27 (47)	31 (48)
Peripheral edema	7 (50)	22 (39)	25 (39)
Dysgeusia	3 (21)	18 (32)	20 (31)
Diarrhea	5 (36)	17 (30)	19 (30)
Insomnia	6 (43)	15 (26)	19 (30)
Constipation	4 (29)	14 (25)	17 (27)
Nausea	4 (29)	15 (26)	17 (27)
Dizziness	2 (14)	14 (25)	14 (22)

*Drug-related defined as related to any drug in the combination; †Includes 7 phase 1 pts treated at MLN9708 3.0 mg; #Any rash-related AE within the MedDRA System Organ Class, includes rash maculo-papular (n=17), rash macular (n=7), pruritus, rash papular (n=5), rash pruritic, dermatitis acneiform, dry skin (n=3), dermatitis exfoliative, rash erythematous, acne, erythema multiforme, rash vesicular, Stevens-Johnson syndrome; ‡Includes peripheral neuropathy and peripheral sensory neuropathy

Drug-related* AEs, grade 3 (≥5% of total)

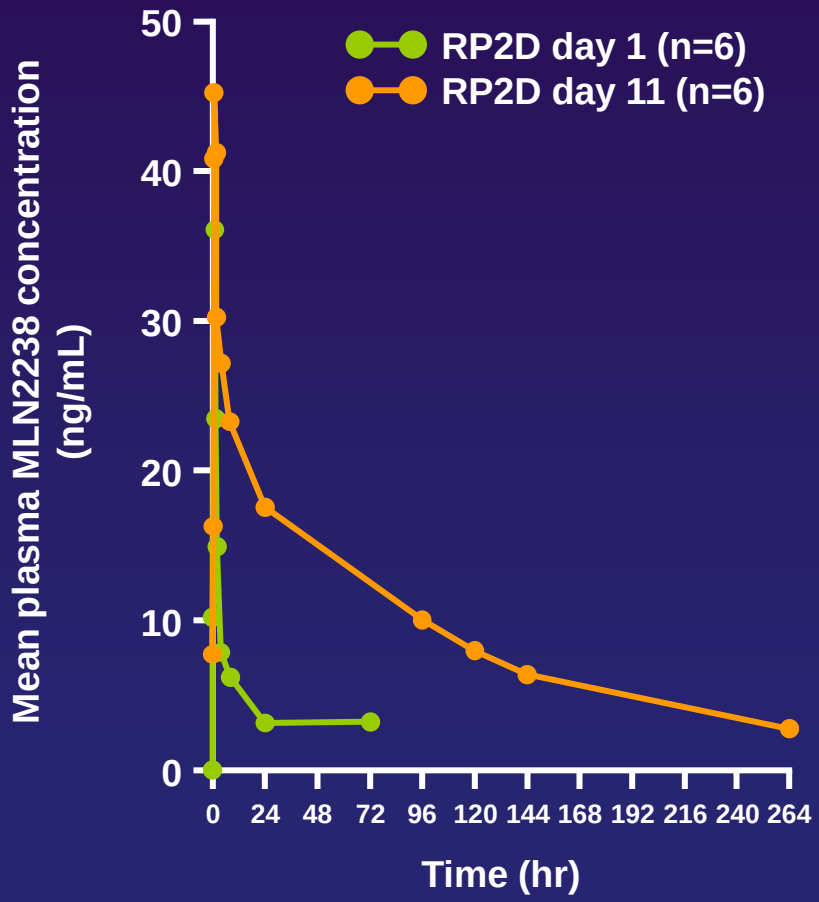
AE, n (%)	Phase 1 (n=14)	RP2D (n=57)†	Total (N=64)
Rash-related AEs#	5 (36)	6 (11)	10 (16)
Hyperglycemia	3 (21)	5 (9)	5 (8)
Pneumonia	1 (7)	4 (7)	4 (6)
Thrombocytopenia	2 (14)	3 (5)	4 (6)
Decreased lymphocyte count	0	3 (5)	3 (5)
Hyponatremia	0	3 (5)	3 (5)
Neutropenia	1 (7)	3 (5)	3 (5)
Peripheral neuropathies‡	1 (7)	3 (5)	3 (5)

- There were no drug-related grade 4 AEs

*Drug-related defined as related to any drug in the combination; †Includes 7 phase 1 pts treated at MLN9708 3.0 mg; #Any rash-related AE within the MedDRA System Organ Class, includes rash maculo-papular, rash papular (n=3), dermatitis exfoliative, erythema multiforme, rash macular, Stevens-Johnson syndrome (n=1); ‡Includes peripheral neuropathy and peripheral sensory neuropathy

Phase 1 PK data

- Based on phase 1 preliminary PK data, MLN2238 was absorbed quickly with a T_{max} of 0.5–4 hours
- Terminal half-life was 2–8 days
- PK data were similar to single-agent twice-weekly dosing studies,[1] suggesting no MLN2238 PK interaction with len or dex



1. Lonial S, et al. Oral presentation at ASCO 2012, Chicago, IL

Conclusions / Future Directions

- MLN9708 plus len–dex is the first completely oral combination regimen including an IMiD and a proteasome inhibitor for patients with newly diagnosed MM
- Data suggest that twice-weekly oral MLN9708 plus len–dex is feasible and active
  - 25% of patients remain on therapy
- However, rates of rash, PN, and dose reductions appear lower in the parallel study using weekly MLN9708, with similar response rates and better convenience[1]
  - Supports the use of weekly dosing in ongoing phase 3 trials
    - Phase 3 trial of weekly MLN9708, len, and dex in pts with relapsed/refractory MM (NCT01564537, TOURMALINE-MM1)
    - Phase 3 trial of weekly MLN9708, len, and dex in pts with newly diagnosed MM (NCT01850524, TOURMALINE-MM2)
    - Phase 3 trial of weekly MLN9708/ dex in pts with relapsed or refractory AL amyloidosis (NCT01659658, TOURMALINE-AL1)
- An abstract presented at this meeting (Mateos et al, #1968) shows that greater proteasome inhibitor exposure produces better outcomes
  - MLN9708 administered orally may be best positioned to provide patients with this benefit in the future

1. Kumar S, et al. Oral presentation at ASH 2012, Atlanta, GA

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