Multiple Myeloma

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Faculty

Sagar Lonial, MD
Professor of Hematology and Oncology
Director, Translational Research B-Cell Malignancy Program
The Winship Cancer Institute
Emory University
Atlanta, Georgia

Robert Z. Orlowski, MD, PhD
Director, Myeloma Section
Professor, Department of Lymphoma/Myeloma and of Experimental Therapeutics
Division of Cancer Medicine
The University of Texas M. D. Anderson Cancer Center
Houston, Texas

Disclosures

Sagar Lonial, MD, has disclosed that he has received consulting fees from Bristol-Myers Squibb, Celgene, Merck, Millennium, Novartis, and Onyx.

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Overview

- Carfilzomib combinations in newly diagnosed MM
  - Carfilzomib + melphalan/prednisone in elderly
  - CYCLONE: cyclophosphamide/carfilzomib/thalidomide/dexamethasone
  - Carfilzomib/lenalidomide/dexamethasone
- PANORAMA-2: HDAC inhibitor, panobinostat, to recover response in bortezomib-refractory MM
- Bisphosphonates: long-term efficacy and adverse effects
- Pomalidomide in relapsed/refractory MM
  - Pomalidomide with and without low-dose dexamethasone in lenalidomide- and/or bortezomib-refractory MM
  - Pomalidomide with clarithromycin/dexamethasone in relapsed/refractory MM

Overview

- Ixazomib (MLN9708)
  - Phase I study of twice-weekly ixazomib
  - Combination ixazomib with lenalidomide/dexamethasone
- New monoclonal antibody–mediated therapies
  - Siltuximab (anti–IL-6) plus bortezomib vs bortezomib alone in relapsed/refractory MM
  - Elotuzumab (anti-CD52) plus lenalidomide and low-dose dexamethasone in relapsed/refractory MM
  - Daratumumab (anti-CD38), phase I/II study
- MM disease registry: tracking the incidence of second primary malignancies

Overview

- Follow-up of long-term lenalidomide/dexamethasone in newly diagnosed MM
- Stem cell transplantation
  - Feasibility of risk stratification to determine single vs tandem stem cell transplantation
  - Early stem cell transplantation, followed by lenalidomide/bortezomib/dexamethasone maintenance in high-risk MM

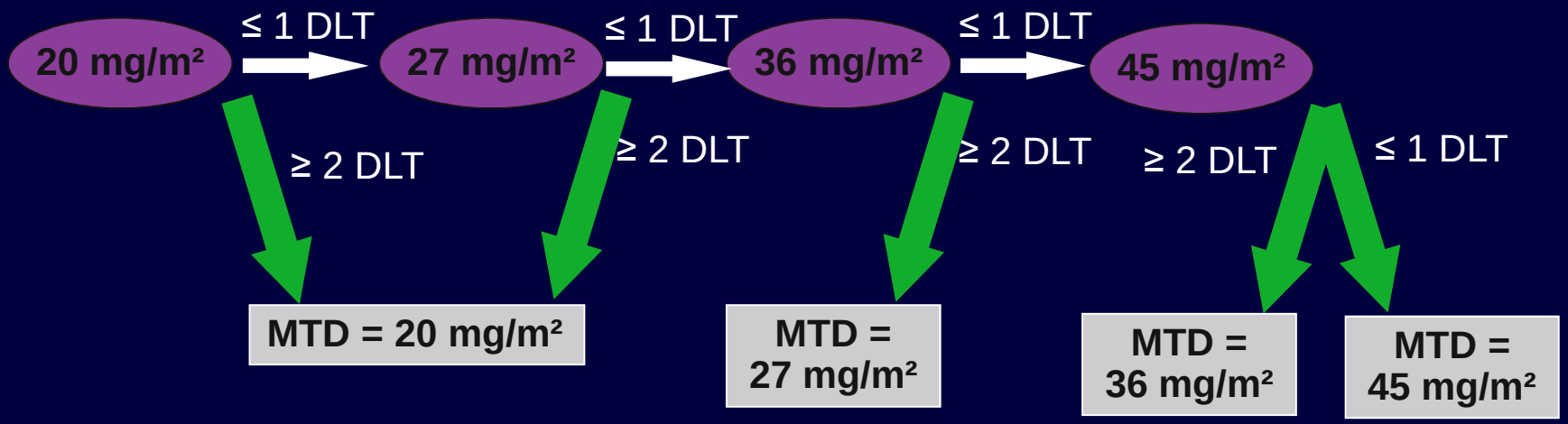
Carfilzomib

Carfilzomib

- Tetrapeptide epoxyketone
- Novel proteasome inhibitor
  - Binds the β5 and $β5_i$ subunits irreversibly
- Active against bortezomib-resistant MM cell lines and samples from pts with bortezomib resistance[1]
- Well tolerated in phase I investigation[2]
- Active alone and in a number of combinations[3] in relapsed/refractory MM

1. Kuhn DJ, et al. Blood. 2007;110:3281-3290. 2. O'Connor OA, et al. Clin Cancer Res. 2009;15:7085-7091. 3. Vij R, et al. Blood. 2012;[Epub ahead of print].

Phase I/II Study: CMP in Elderly Patients With de Novo Symptomatic MM



- CMP for 9 cycles of 6 wks each (N = 43)
  - Carfilzomib 20 mg/m^2 IV on Days 1, 2 of cycle 1, all patients, all arms; then 20, 27, 36, or 45 mg/m^2 on Days 8, 9, 22, 23, 29, 30; then in cycles 2-9 on Days 1, 2, 8, 9, 22, 23, 29, and 30
  - Melphalan 9 mg/m^2/day PO on Days 1-4
  - Prednisone 60 mg/m^2/day PO on Days 1-4

Kolb B, et al. ASCO 2012. Abstract 8009.

CMP in Elderly Patients With de Novo Symptomatic MM: Outcomes

- MTD of carfilzomib in combination with MP defined at 36 mg/m^2

Response, n (%)	Evaluable Patients (n = 35)
ORR (CR + VGPR + PR)	31 (89)
▪ CR	1 (3)
▪ VGPR	14 (40)
▪ PR	16 (46)
MR	1 (3)
SD	2 (6)
PD	1 (3)

- Median follow-up of 12 mos: OS 93.9%, EFS 80.7%
- Tolerable toxicity profile: limited neurotoxicity (single grade 1 event), DVT 6%, infection 15%

Kolb B, et al. ASCO 2012. Abstract 8009.

Conclusions: CMP vs Other Options

- Authors assert that 89% ORR is very promising compared with MPT (76%), MPR (81%), and Rd (76%)
- Comparisons premature at this stage
  - Small cohort with no randomization/stratification
    - 8 patients with ≤ 3 cycles excluded from ORR
  - No information about median age, ISS stage, cytogenetic profiles, and genetic expression profiling risk
  - Different study designs, with other trials (MPT, MPR, VMP) incorporating a maintenance phase

Phase I/II CYCLONE Trial: Overview

Agent	Dose Level	Days
Carfilzomib	Phase I: 15 mg/m^2 first cycle, 20 mg/m^2 subsequent cycles Phase II: 20 mg/m^2 first cycle, 27 mg/m^2 subsequent cycles	1, 2, 8, 9, 15, 16 (of every 28-day cycle)
Thalidomide	100 mg	1-28
Cyclophosphamide	300 mg/m^2	1, 8, 15
Dexamethasone	40 mg	1, 8, 15, 22

- Transplantation-eligible patients (N = 27) with newly diagnosed MM
- Rationale
  - Build on international standard of CTD
  - Add new proteasome inhibitor with less neuropathy in frontline treatment
  - Save lenalidomide and bortezomib for relapse

Mikhael J, et al. ASCO 2012. Abstract 8010.

CYCLONE: Outcomes with Carfilzomib + CTD in Newly Diagnosed MM

Response, n (%)	Evaluable Patients in Phase II Portion (n = 24)
ORR (CR + VGPR + PR)	23 (96)
▪ CR	7 (29)
▪ VGPR	11 (46)
▪ PR	5 (21)
MR	1 (4)

- No dose-limiting toxicities found in phase I portion; MTD not reached
- Most frequent low-grade AEs: fatigue, constipation, lethargy
  - Most frequent low-grade hematologic event: grade 1 thrombocytopenia
- Grade 4 AEs: neutropenia 17%, lymphopenia 4%, thrombosis 8%

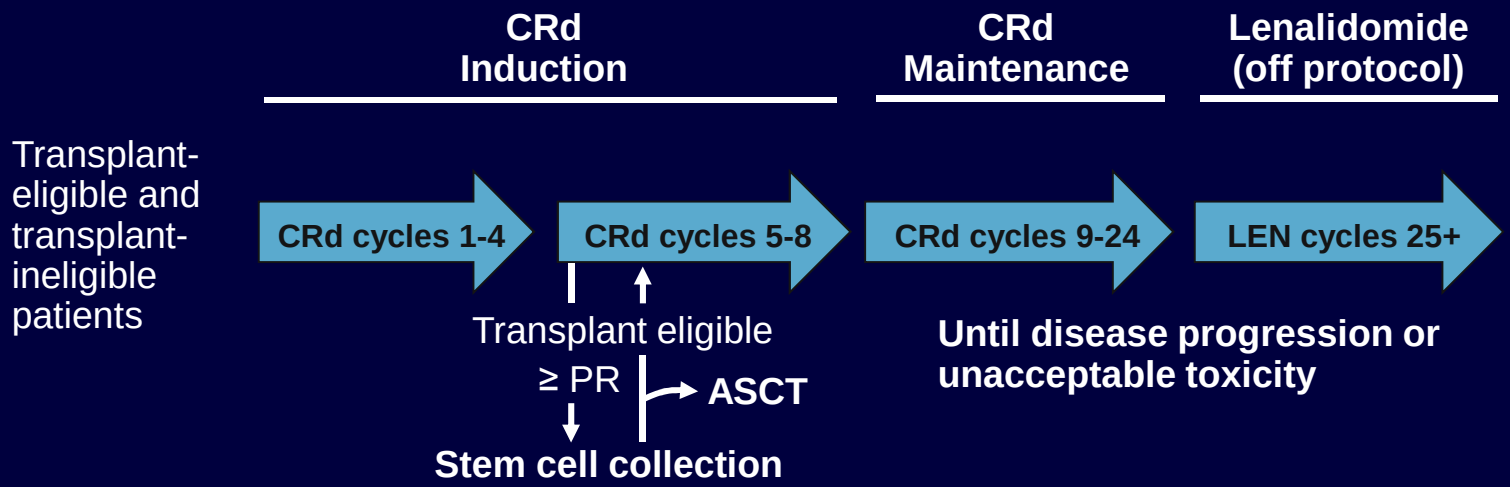
Mikhael J, et al. ASCO 2012. Abstract 8010.

CYCLONE: Conclusions

- Carfilzomib + CTD effective as induction therapy in transplantation-eligible patients with newly diagnosed MM
  - After 4 cycles: ORR of 96%, VGPR of 75%
- Manageable toxicity profile
- All attempted stem cell collections were successful
- Future study goals: extend phase II portion with increasing carfilzomib dose levels to target dose of 45 mg/m^2

Mikhael J, et al. ASCO 2012. Abstract 8010.

Phase I/II Investigation of CRd in Newly Diagnosed MM



- Assessments on Days 1, 15 and cycle 1 and Days 1 thereafter using modified IMWG criteria with nCR

Cycles 1-8

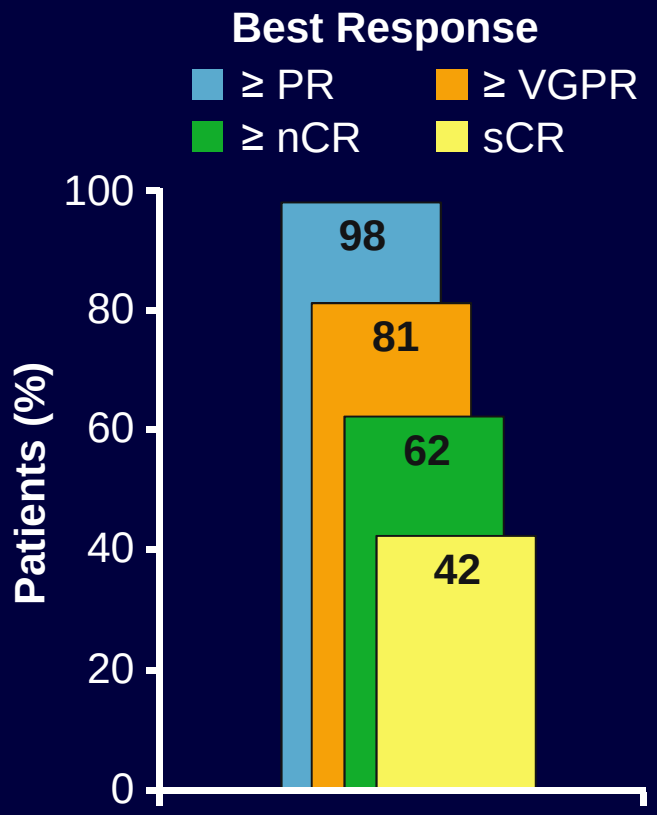
- Carfilzomib 20, 27, or 36 mg/m^2 on Days 1, 2, 8, 9, 15, 16
- Lenalidomide 25 mg/day on Days 1-21
- Dexamethasone 40 mg/day on Days 1, 8, 15, 22 (20 mg/day after cycle 4)

Cycles 9-24

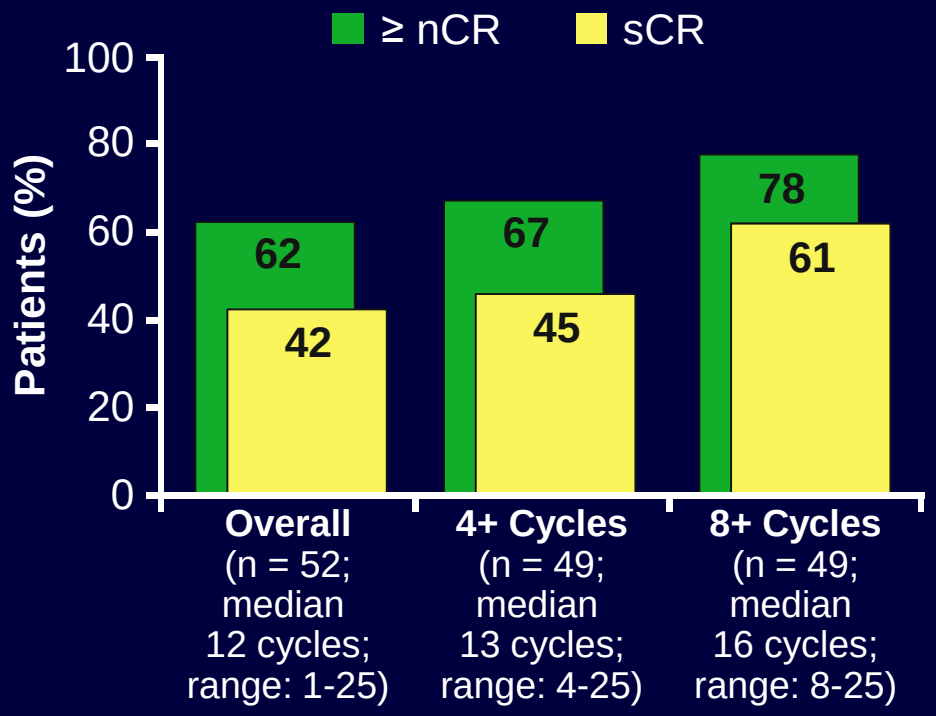
- Carfilzomib at last best tolerated dose on Days 1, 2, 15, 16
- Lenalidomide at last best tolerated dose on Days 1-21
- Dexamethasone at last best tolerated dose on Days 1, 8, 15, 22

Jakubowiak AJ, et al. ASCO 2012. Abstract 8011.

CRd in Newly Diagnosed MM: Efficacy and Durability



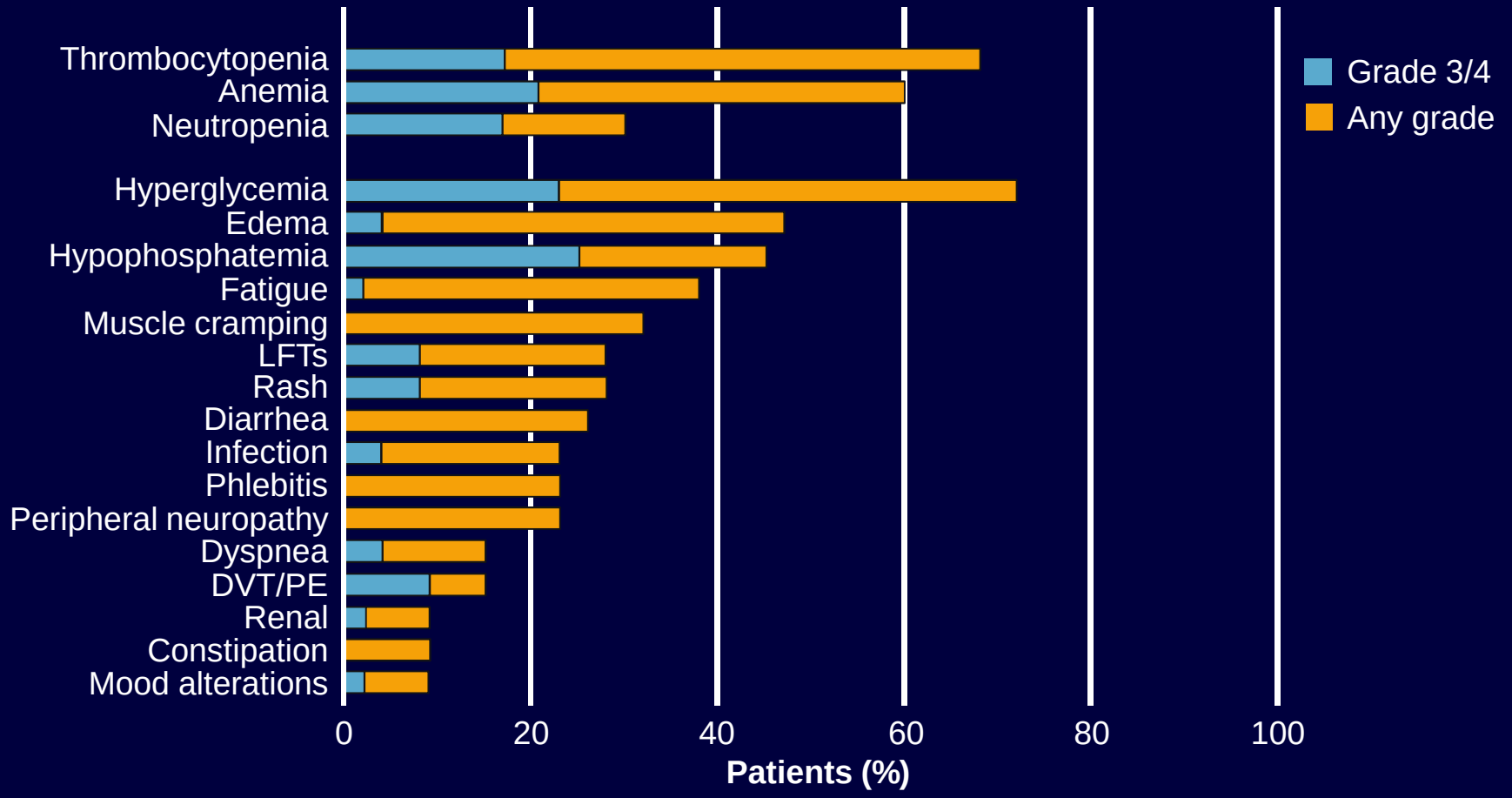
N = 53; median 12 cycles (range: 1-25)



PFS 97% at 12 mos
PFS 92% at 24 mos

Jakubowiak AJ, et al. ASCO 2012. Abstract 8011.

CRd in Newly Diagnosed MM: Toxicity



Jakubowiak AJ, et al. ASCO 2012. Abstract 8011.

CRd in Newly Diagnosed MM: Conclusions

- Clinical responses durable and continue to improve with extended treatment[1]
  - 78% achieved nCR or better after 8 or more treatment cycles
  - Estimated 2-yr PFS: 92%
- High rate of sCR (CR + normal serum free light chains) of 61% after 8+ cycles
  - As sCR is a relatively new parameter, it has not been reported in RVD[2]
  - sCR may not have better outcome than CR[3]
- 91% with suspected CR had no MRD by flow immunophenotyping
  - Immunophenotypic CR associated with prolongation of TTP and EFS compared with less rigorous CR

1. Jakubowiak AJ, et al. ASCO 2012. Abstract 8011. 2. Richardson PG, et al. Blood. 2010;116:679-686.
3. Paiva B, et al. J Clin Oncol. 2011;29:1627-1633.

Rationale for Phase II PANORAMA 2 Study of Panobinostat + BTZ/DEX[1]

- Panobinostat, oral, pan-HDAC inhibitor[1]
  - Low nanomolar activity against classes I, II, IV HDACs
  - Alters transcription of multiple oncogenic pathways
  - Inhibits aggresomes and proteasomes; leads to misfolded protein accumulation and apoptosis
- Panobinostat synergized with BTZ in BTZ-refractory patients in phase Ib trial[2]
  - 50% response rate in BTZ-refractory patients

1. Alsina M, et al. ASCO 2012. Abstract 8012. 2. Atadja P. Cancer Lett. 2009;280:233-241.
3. San Miguel J, et al. Haematologica. 2011;96. Abstract 0314.

PANORAMA 2: Panobinostat + BTZ/DEX in Relapsed/BTZ-Refractory MM

- Relapsed and BTZ refractory; previous IMiDs

Phase I
Panobinostat
Bortezomib
Dexamethasone
8 x 3-wk cycles

- Panobinostat 20 mg PO
  - Days 1, 3, 5, 8, 10, 12
- Bortezomib 1.3 mg/m^2 IV
  - Days 1, 4, 8, 11
- Dexamethasone 20 mg PO
  - Days 1, 2, 4, 5, 8, 9, 11, 12

Patients with clinical benefit

Phase II
Panobinostat
Bortezomib
Dexamethasone
6-wk cycles to PD

- Panobinostat 20 mg PO
  - Days 1, 3, 5 of Wks 1, 2, 4, 5
- Bortezomib 1.3 mg/m^2 IV
  - Days 1, 8, 22, 29
- Dexamethasone 20 mg PO
  - Days 1, 2, 8, 9, 22, 23, 29, 30

Endpoints and assessments

- Primary: ORR
- Secondary: PFS, TTP, OS, MR, TTR, DOR
- Efficacy assessment by modified EBMT criteria

Alsina M, et al. ASCO 2012. Abstract 8012.

PANORAMA 2: Results and Conclusions

Best Confirmed Response (Confirmed at 6 Wks), n (%)	N = 55
Overall response (CR + nCR + PR)	17 (31)
▪ CR	--
▪ nCR	1 (2)
▪ PR	16 (29)
Clinical benefit (CR + nCR + PR + MR)	28 (51)
▪ MR	11 (20)

Adverse Events, n (%)	All Grades	Grade 3/4
Diarrhea	38 (69)	11 (20)
Thrombocytopenia	35 (64)	34 (62)
Nausea	33 (60)	3 (5)
Fatigue	31 (56)	8 (15)
Anemia	24 (44)	8 (15)

Alsina M, et al. ASCO 2012. Abstract 8012.

- Adding panobinostat to bortezomib/dexamethasone can produce clinical responses in patients with heavily pretreated, bortezomib-refractory MM
- No patients discontinued due to thrombocytopenia
- Peripheral neuropathy generally mild
  - 1 grade 3 neuropathy
- No reports of QTc prolongation

MRC Myeloma IX: Extended Follow-up of Long-term Bisphosphonate Use in MM

Patients with newly diagnosed, stage I-III MM (N = 1960)

Zoledronic acid 4 mg IV every 3-4 wks + intensive or nonintensive chemotherapy (n = 981)

Clodronate 1600 mg/day PO + intensive or nonintensive chemotherapy (n = 979)

Bisphosphonate treatment continued at least until disease progression

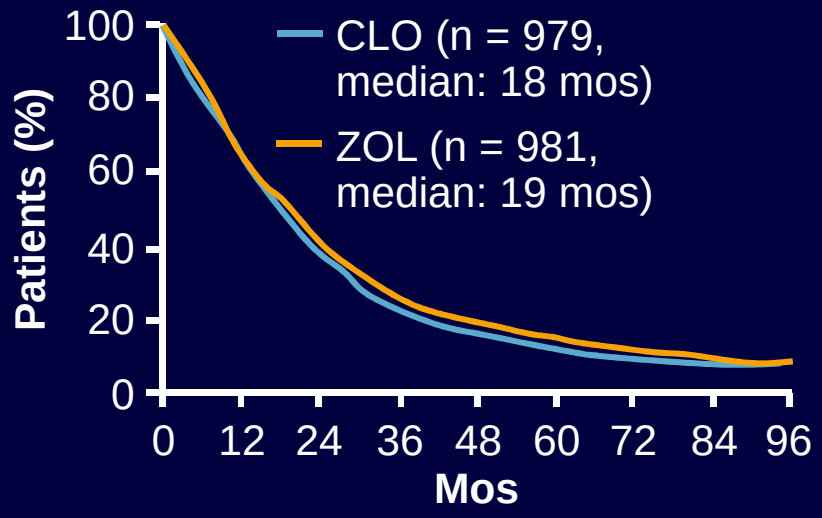
- Endpoints
  - Primary: PFS, OS, response
  - Secondary: SREs (time to first SRE, SRE incidence), safety, QoL

Morgan GJ, et al. ASCO 2012. Abstract 8015.

MRC Myeloma IX: PFS and OS With ZOL vs CLO

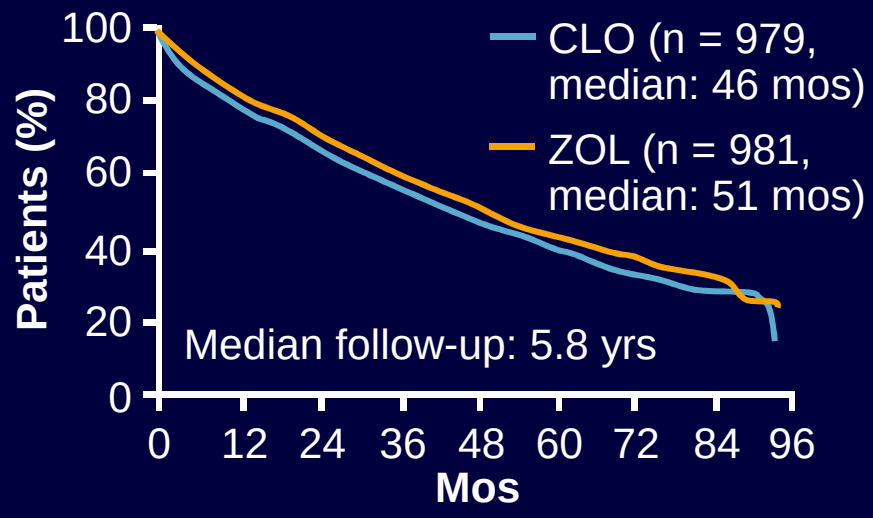
PFS

P = .01 (Cox model)
HR: 0.88 (95% CI: 0.80-0.97)



OS

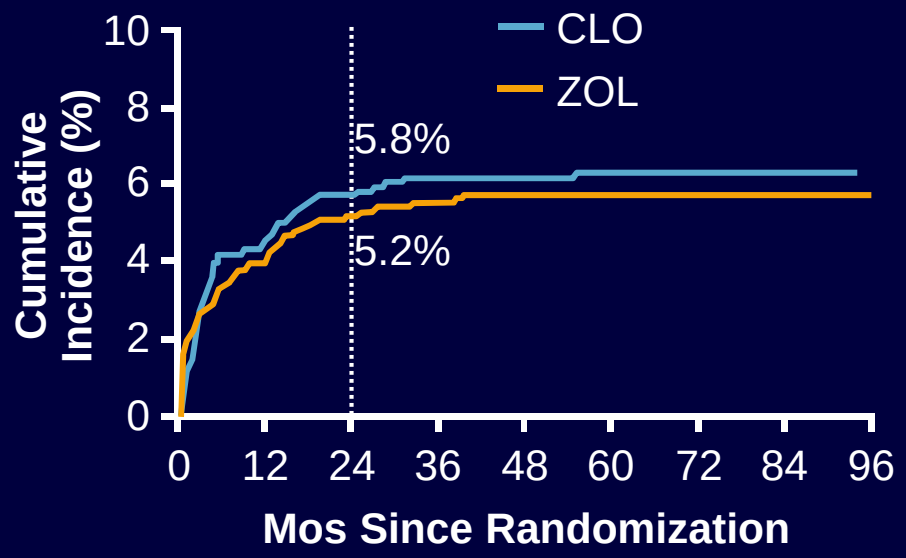
P = .03 (Cox model)
HR: 0.88 (95% CI: 0.78-0.99)



- AEs were similar between arms, except ONJ
- No substantial changes in AEs during long-term follow-up

Morgan GJ, et al. ASCO 2012. Abstract 8015.

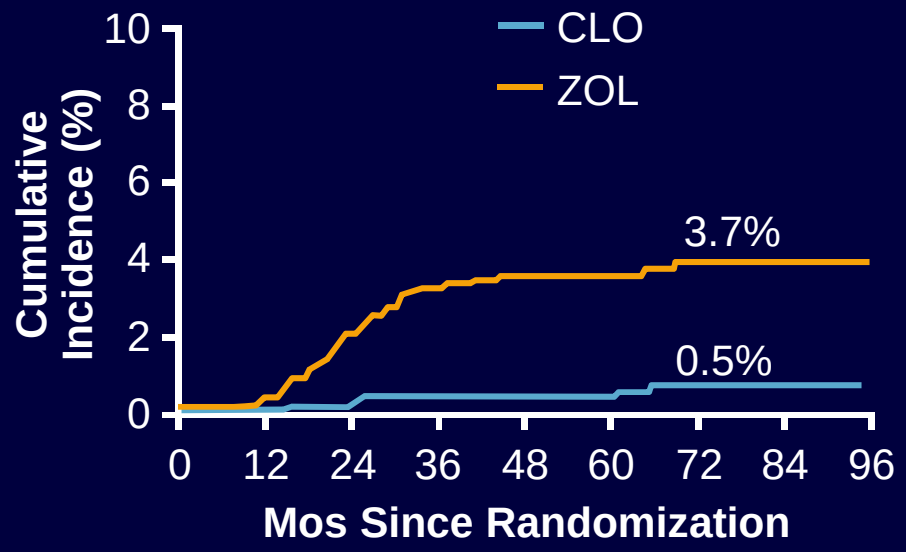
MRC Myeloma IX: Renal Adverse Events With ZOL vs CLO



- Cumulative acute renal failure at 2 yrs was not statistically different

Morgan GJ, et al. ASCO 2012. Abstract 8015.

MRC Myeloma IX: ONJ With ZOL vs CLO



- *P* < .0001
- Most ONJ events occurred at 12-36 mos
- Patients receiving thalidomide experienced fewer ONJ events
- ONJ prevention is important

Morgan GJ, et al. ASCO 2012. Abstract 8015.

Long-term Bisphosphonate Use: Conclusions

- No consensus on optimal duration of bisphosphonate therapy
- NCCN recommends bisphosphonates to all patients receiving primary myeloma therapy to prevent bone loss and preserve skeletal health[1]
  - Potential direct effects on myeloma cell growth and survival
  - Annual bone survey
  - Monitor renal function
  - Monitor for ONJ
- ZOL maintained OS advantage over CLO[2]
- CLO had lower incidence of ONJ than ZOL[2]

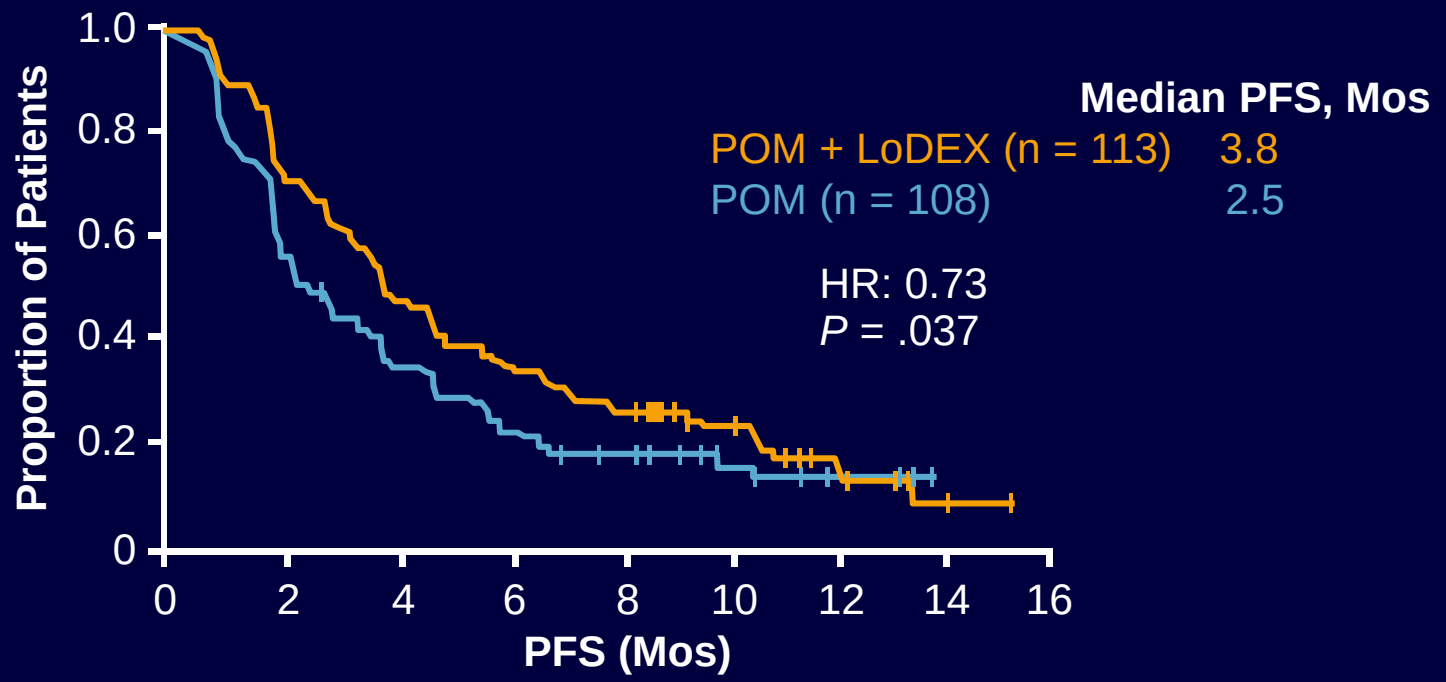
1. NCCN. Clinical practice guidelines in oncology: myeloma. v.1.2012.
2. Morgan GJ, et al. ASCO 2012. Abstract 8015.

Pomalidomide/Low-Dose Dexamethasone in Refractory Patients

- POM: oral immunomodulator
- POM + LoDEX active in LEN- and/or BTZ-refractory patients[1]
- This preplanned subset analysis examines outcomes in LEN- and/or BTZ-refractory disease[2]
- Study design
  - Required previous progression during last LEN or BTZ treatment
  - Randomized to POM 4 mg on Days 1-21 of 28-day cycle, with an option to add LoDEX if disease progresses or to POM plus LoDEX 40 mg/wk
  - Primary endpoint: PFS; secondary: ORR, safety, DOR, OS

1. Lacy MQ, et al. Blood. 2011;118:2970-2975. 2. Vij R, et al. ASCO 2012. Abstract 8016.

POM + LoDEX vs POM Alone: PFS and Adverse Events



- Neutropenia (47%), thrombocytopenia (22%), anemia (22%), leukopenia (6%) were most common hematologic AEs in POM-alone arm
- Pneumonia (14%), fatigue (10%), back pain (12%), dyspnea (7%) were most common nonhematologic AEs in POM-alone arm

Vij R, et al. ASCO 2012. Abstract 8016.

POM + LoDEX Response Rates Stratified by Resistance to LEN or BTZ

Response	LEN Refractory (n = 87)	BTZ Refractory (n = 82)	LEN/BTZ Refractory (n = 69)	LEN/BTZ Refractory + Prior Transplant (n = 47)
ORR (≥ PR), %	25	29	28	34
▪ ≥ MR	41	46	46	53
▪ CR	0	0	0	0
▪ PR	25	29	28	34
▪ MR	16	17	19	19
SD, %	40	33	35	28
PD, %	7	7	7	6
Time to ≥ PR, mos	1.9	1.9	1.8	1.6
Median duration of ≥ PR, mos	7.0	5.8	6.2	5.7
Median duration of MR only, mos	3.4	3.2	3.0	5.7

Vij R, et al. ASCO 2012. Abstract 8016.

Clarithromycin + POM/DEX in Relapsed/ Refractory MM: Phase II Study

- CLA enhances LEN + DEX in first-line MM treatment[1]
- Phase II trial POM + CLA + DEX[2]
  - All patients received ≥ 3 previous therapies, of which ≥ 1 was LEN therapy
  - POM 4 mg/day on Days 1-21 of 28-day cycle, CLA 500 mg BID, DEX 40 mg/wk
  - Evaluation: immunoelectrophoresis, free light chain analysis; bone marrow biopsy and skeletal imaging to confirm response
- Median number of cycles: 6 (range: 1-17)

1. Gay F, et al. Am J Hematol. 2010;85:664-669. 2. Rossi AC, et al. ASCO 2012. Abstract 8036.

Clarithromycin + POM/DEX in Heavily Pretreated Relapsed/Refractory MM

- Phase II study (N = 66)
- Median PFS: 5 mos
- ORR not affected by LEN or BTZ resistance
- Grade ≥ 3 AEs: fatigue (n = 1), muscular weakness (n = 1)

Response, %	Rate
ORR	56
≥ VGPR	23
▪ sCR	5
▪ VGPR	18
▪ PR	33
▪ MR	12
▪ SD	21

Response, %	Refractory to		
	LEN	BTZ	LEN + BTZ
ORR	85	82	76

Rossi AC, et al. ASCO 2012. Abstract 8036.

Conclusions: Pomalidomide

- Pomalidomide/low-dose dexamethasone was active in lenalidomide- and bortezomib-refractory disease
- Adverse events are manageable
- Addition of clarithromycin may improve pomalidomide/dexamethasone therapy
- Potential future option in MM

Vij R, et al. ASCO 2012. Abstract 8016. Rossi AC, et al. ASCO 2012. Abstract 8036.

Oral Proteasome Inhibitor Ixazomib in Relapsed/Refractory MM: Phase I Study

- Ixazomib (MLN9708): orally bioavailable, potent, reversible, specific inhibitor of 20S proteasome
- Greater tissue penetration, faster dissociation from proteasome vs BTZ[1]
- Phase I study[2]
  - Primary endpoints: safety, MTD; secondary: ORR, plasma pharmacokinetics, pharmacodynamics
  - Ixazomib on Days 1, 4, 8, 11 of 21-day cycle
  - Patients: relapsed/refractory MM, ≥ 2 previous therapies (must include BTZ, thalidomide, or LEN and corticosteroids)
  - Blood samples collected after dosing on Days 1 and 11 of cycle 1
  - Response assessed using IMWG criteria, with the addition of MR and nCR
- MTD determined to be 2.0 mg/m^2

1. Fisher RI, et al. J Clin Oncol. 2006;24:4867-4874. 2. Lonial S, et al. ASCO 2012. Abstract 8017.

Oral Ixazomib in Relapsed/Refractory MM: Responses and Adverse Events

- Grade 3/4 adverse events
  - Hematologic: thrombocytopenia (34%; 21% grade 4), neutropenia (14%), anemia (5%), leukopenia (3%)
  - Peripheral neuropathy: no grade ≥ 3 (10% grade 1/2)
  - Nonhematologic: fatigue (9%), rash (7%), abdominal pain (3%), hypophosphatemia (3%), hypotension (3%)
  - 38% required dose reductions, 12% discontinued due to adverse events
- Data support twice-weekly dosing
  - MLN9708 rapidly absorbed, terminal half-life: 4-6 days, dose-dependent whole blood 20S proteasome inhibition
- Responses achieved in relapsed/refractory MM
  - ≥ PR in 6 patients (1 sCR, 1 nCR, 1 VGPR, 3 PRs)
  - 2 patients achieved MR
  - Durable SD in 32 patients, up to 17.3 mos

Lonial S, et al. ASCO 2012. Abstract 8017.

Ixazomib + Lenalidomide/Dexamethasone

- Bortezomib currently used with LEN and DEX
- Phase I trial in untreated MM, 28-day cycle
  - Primary endpoints: safety, MTD, recommended phase II dose, CR + VGPR rate
  - Previously untreated patients
  - Ixazomib 1.68-3.95 mg/m^2 on Days 1, 8, 15
  - LEN 25 mg/day on Days 1-21, DEX 40 mg/day on Days 1, 8, 15, 22

Gerard P, et al. ASCO 2012. Abstract 8033.

Ixazomib/LEN/DEX: Responses and Adverse Events

- Ixazomib MTD: 2.97 mg/m^2; RP2D: 2.23 mg/m^2
- Grade 3/4 adverse events
  - Hematologic: anemia (n = 2), thrombocytopenia (n = 1)
  - Nonhematologic (n = 2 each): erythematous rash, syncope, vomiting
  - Peripheral neuropathy 21% (n = 6); no grade ≥ 3
- Responses in patients with untreated MM
  - All 19 evaluable patients achieved ≥ PR
  - 1 sCR, 4 CR, 4 VGPR, 10 PR

Gerard P, et al. ASCO 2012. Abstract 8033.

Potential Immunotherapy Targets in MM

APRIL	CD74	IGF-1	SDF-1α
BAFF	CD200	IGR1R	TGFB
BSF-3	CS1 (elotuzumab)	IL-6 (siltuximab)	TNFα
CD126	FGFR	IL-6R	VACM-1
CD20	GFGR3	KIR	VEGF
CD38 (daratumumab)	GM-2	LFA-1	VEGFR
CD40	ICAM-1	MUC-1	VLA-4
CD56			

Hideshima T, et al. Nat Rev Cancer. 2002;2:927-937.
Hideshima T, et al. Blood. 2004;104:607-618.

Siltuximab + BTZ vs BTZ Alone in Relapsed/Refractory MM

- Siltuximab: chimeric $IgG_1\kappa$ anti–human IL-6 antibody
  - High affinity, half-life ≈ 3 wks
  - Tolerability: no DLT up to ≥ 15 mg/kg
- Study design: phase II, randomized, double-blind, placebo-controlled
  - Patients:1-3 previous lines of therapy; no previous BTZ
  - Treatment
    - BTZ 1.3 mg/m^2, 8 x 42-day cycles on Days 1, 4, 8, 11, 22, 25, 29, 32 followed by maintenance, 4 x 35-day cycles on Days 1, 8, 15, 22
    - Placebo or siltuximab 6 mg/kg every 2 wks
  - Patients progressing had option to end BTZ and start DEX 40 mg on Days 1-4, 9-12, 17-20 and maintenance therapy at 40 mg on Days 1-4

Orlowski R, et al. ASCO 2012. Abstract 8018.

Siltuximab + BTZ Efficacy

- Nonsignificant trend toward improved ORR with siltuximab
- Nonsignificant, marginal effect on overall PFS
- Regional differences in PFS noted
  - Significant increase in NA and WE (*P* = .01) vs no effect for rest of world
  - Patients outside of NA and WE less often pretreated, which was thought to obviate benefit of adding siltuximab
- Siltuximab continues to be developed for frontline therapy

Orlowski R, et al. ASCO 2012. Abstract 8018.

Siltuximab + BTZ: Adverse Events

- Modest increase in adverse events observed with the addition of siltuximab

Adverse Events, n (%)	BTZ + Siltuximab (n = 142)	BTZ + Placebo (n = 139)
Grade ≥ 3	129 (91)	103 (74)
▪ Blood and lymphatic system disorders	79	52
• Neutropenia	49	30
• Thrombocytopenia	48	34
• Anemia	11	15
▪ Infections	16	14
▪ Gastrointestinal disorders	13	4
▪ Peripheral sensory neuropathy	12	10

Orlowski R, et al. ASCO 2012. Abstract 8018.

Daratumumab: Phase I/II Study in Relapsed/Refractory MM

- Daratumumab: anti-CD38 antibody; kills MM cells via ADCC, CDC, and induction of apoptosis
- Patients: relapsed/refractory MM (≥ 2 different therapies), not eligible for ASCT; 3 patients/dosing group
- Efficacy based on serum and/or urine M-component analyses
- At the highest dose (4 mg/kg), patients had a 49%, 55%, and 64% reduction in serum M-component and a 80%, 89%, and 97% reduction in plasma cells
- Adverse events were manageable

Plesner T, et al. ASCO 2012. Abstract 8019.

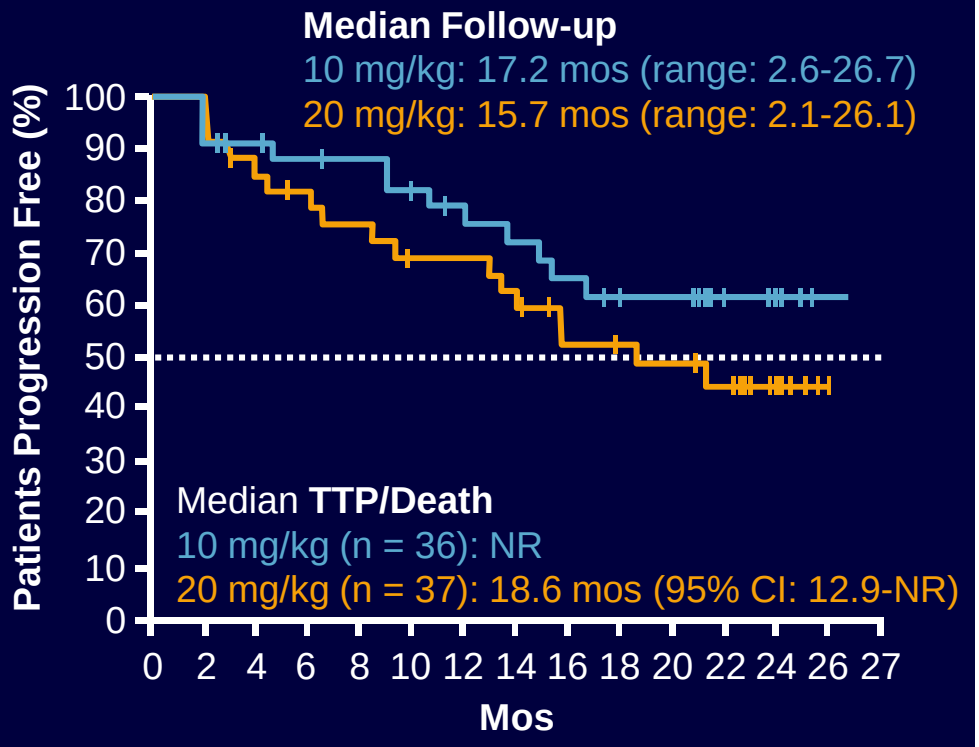
Phase II Study: Elotuzumab + LEN and Low-Dose DEX in Relapsed/Refractory MM

- Elotuzumab, humanized, anti-CS1 IgG_1 antibody[1]
  - CS1 is highly expressed on MM cells, much less on NK cells, and has very little to no expression on normal cells
  - MOA of elotuzumab is postulated to be through NK-mediated ADCC
- Phase I/II study in relapsed/refractory MM[2]
  - Primary endpoint: ORR; secondary endpoint: PFS, safety
  - 1-3 previous therapies, no LEN
  - Elotuzumab 10 or 20 mg IV on Days 1, 8, 15, 22 (2 x 28-day cycles), then every 2 wks until disease progression or unacceptable adverse events
  - LEN 25 mg/day PO on Days 1-21 (28-day cycle)
  - Low-dose DEX 40 mg/wk PO

1. Hsi ED, et al. Clin Cancer Res. 2008;14:2775-2784. 2. Moreau P, et al. ASCO 2012. Abstract 8020.

Elotuzumab + LEN/Low-Dose DEX in Relapsed/Refractory MM

	Elotuzumab 10 mg/kg	Elotuzumab 20 mg/kg
Patients, n	36	37
ORR (≥ PR), n (%)	**33 (92)**	**28 (76)**
▪ CR/stringent CR, n (%)	5 (14)	4 (11)
▪ VGPR, n (%)	17 (47)	13 (35)
▪ PR, n (%)	11 (31)	11 (30)
< PR, n (%)	3 (8)	9 (24)



- PFS by cytogenetics: 9 mos for high-risk patients vs not reached for standard-risk

Moreau P, et al. ASCO 2012. Abstract 8020.

Elotuzumab + LEN/Low-Dose DEX AEs

- No DLTs observed
- MTD not reached

	Elotuzumab 10 mg/kg	Elotuzumab 20 mg/kg
Total enrolled (ITT population), n	36	37
Treatment cessation, n (%)	18 (50)	24 (65)
▪ Disease progression	12	12
▪ AE	2	9
▪ Other	4	3

- Elotuzumab + LEN/low-dose DEX is active in relapsed/ refractory MM with manageable AEs

AE, n (%)	Elotuzumab 10 mg/kg (n = 36)		Elotuzumab 20 mg/kg (n = 37)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Diarrhea	20 (56)	3 (8)	21 (57)	2 (5)
Muscle spasms	19 (53)	2 (6)	22 (60)	0
Fatigue	21 (58)	3 (8)	16 (43)	2(5)
Constipation	17 (47)	0	19 (51)	0
Anemia	14 (39)	4 (11)	12 (32)	5 (14)
Lymphopenia	11 (31)	9 (26)	8 (22)	5 (14)
Neutropenia	11 (31)	5 (14)	8 (22)	7 (19)
Thrombo-cytopenia	12 (33)	6 (17)	7 (19)	6 (16)
Leukopenia	8 (22)	2 (6)	5 (14)	4 (11)

Moreau P, et al. ASCO 2012. Abstract 8020.

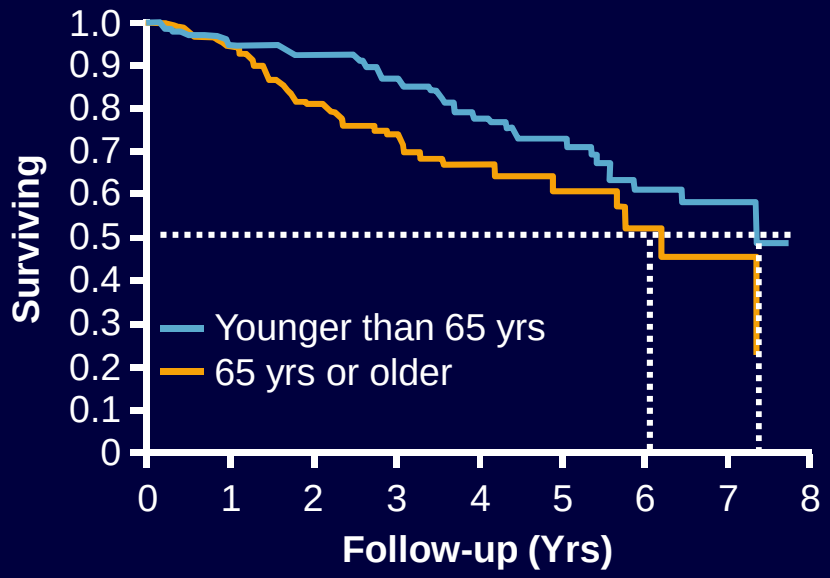
Second Primary Malignancies in Newly Diagnosed MM by Age and Regimen

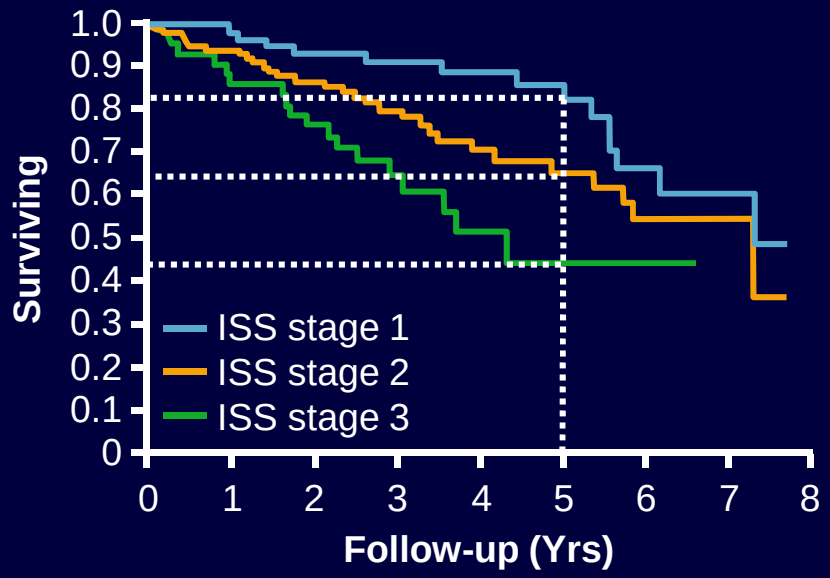
Malignancy Type	Aged < 65 Yrs (n = 519)	Aged ≥ 65 Yrs (n = 656)	All Patients (N = 1175)
Invasive SPM (hematologic and solid tumor), n (%)	7 (1.3)	8 (1.2)	15 (1.3)
Incidence per 100 pt-yrs (CI)	1.21 (0.57-2.53)	1.16 (0.58-2.33)	1.18 (0.71-1.96)
▪ Hematologic, n (%)	4 (0.8)	2 (0.3)	6 (0.5)
• Incidence per 100 pt-yrs (CI)	0.69 (0.26-1.83)	0.29 (0.07-1.15)	0.47 (0.21-1.05)
▪ Solid tumor, n (%)	3 (0.6)	6 (0.9)	9 (0.8)
• Incidence per 100 pt-yrs (CI)	0.51 (0.17-1.59)	0.87 (0.39-1.94)	0.71 (0.37-1.36)
Non-invasive SPM, n (%)	0	7 (1.1)	7 (0.6)
• Incidence per 100 pt-yrs (CI)	0	1.02 (0.48-2.13)	0.55 (0.26-1.15)

- SPMs: AML, melanoma, bronchus (2 each); MDS, CMML, NHL, DLBCL, breast, prostate, tonsil, renal, gastric (1 each)
- 9 unique regimens (drugs included: bortezomib, carfilzomib, doxorubicin, melphalan, lenalidomide, thalidomide, dexamethasone, prednisone)
- Causal relationship between SPM and therapy inconclusive

Rifkin R, et al. ASCO 2012. Abstract 8037.

Long-term Follow-up With Lenalidomide/ Dexamethasone in Newly Diagnosed MM





- Median OS: 7.4 and 6.2 yrs (< 65 and ≥ 65 yrs of age, respectively)
- Median OS at 5 yrs: 82%, 65%, 44% (ISS stage 1, 2, 3, respectively)

Srivastava G, et al. ASCO 2012. Abstract 8096.

Tandem vs Single SCT in High- and Standard-Risk MM: Time to Relapse

- Tandem SCT in high-risk patients compared vs single SCT in high-risk and standard-risk MM patients at a single center
- Risk-stratified SCT allocation (129 patients: 22% HRT, 36% HRS, 43% SRS); most patients in each group received maintenance therapy

Response, %	HRT	HRS	SRS
≥ VGPR	68	72	80
1-yr relapse	7	29	7
2-yr survival	91	81	97

- Greater depth of remission in HRT patients may result in better outcomes vs single SCT in high-risk patients

Risendal M, et al. ASCO 2012. Abstract e18550.

Early ASCT Followed by RVD Maintenance in High-Risk Patients With MM

High-risk patients receive ASCT (N = 37)

60-day rest

Lenalidomide 10 mg/day on Days 1-21 of 28-day cycle +
Bortezomib 1.3 mg/m^2 on Days 1, 8, 15 +
Dexamethasone 40 mg/wk

- Patients with high-risk cytogenetic features (del[17p], t(4;14), t(14;16), complex karyotype) have poor outcomes with a median PFS of 18.5 mos
- Median PFS and OS have not been reached
  - Subset patients with < VGPR, pre-ASCT have median PFS of 28 mos
  - Subset patients with < VGPR on maintenance have median PFS of 11 mos

Kaufman JL, et al. ASCO 2012. Abstract 8100.

Early ASCT + RVD Maintenance: Efficacy

- Median PFS and OS have not been reached
  - Subset patients with < VGPR, pre-ASCT have median PFS of 28 mos
  - Subset patients with < VGPR on maintenance have median PFS of 11 mos
- No thrombotic events (DVT prophylaxis used)
- No second primary malignancies
- No grade 3/4 adverse events

Response, %	Patients
sCR + CR	51
▪ sCR	47
▪ CR	14
≥ VGPR	73
▪ VGPR	22
≥ PR	81
▪ PR	8
▪ SD	0
▪ PD	8

Kaufman JL, et al. ASCO 2012. Abstract 8100.

Conclusions

- Carfilzomib, second-generation proteasome inhibitor, had efficacy in newly diagnosed patients; grade 3/4 AEs primarily hematologic and manageable; high-grade peripheral neuropathy uncommon
- Panobinostat, histone deacetylase inhibitor, showed activity in bortezomib-refractory patients
- No consensus on optimal duration of bisphosphonate therapy; however, in the MRC Myeloma IX trial, zoledronic acid maintained OS advantage over clodronate after a median follow-up of nearly 6 yrs
- Pomalidomide had activity in relapsed/refractory MM, including lenalidomide-refractory disease

Conclusions

- Ixazomib (MLN9708) active in MM with no peripheral neuropathy
- Siltuximab active in combination with bortezomib; extent of pretreatment may affect benefit
- Daratumumab reduced serum M-component plasma cells in a phase I/II study
- Elotuzumab active in combination with lenalidomide/low-dose dexamethasone, encouraging PFS among high-risk patients

Conclusions

- Increased second primary malignancy as a result of MM therapy could not be conclusively proven or disproven
- Long-term follow-up of patients receiving LEN/DEX maintenance revealed a longer PFS and OS in younger patients and those of lower ISS stage
- Early autologous stem cell transplantation in high-risk patients improved outcomes in small study
- Tandem stem cell transplantation in high-risk patients was more effective than single stem cell transplantation in this patient population in a single-center trial

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