ASSOCIAZIONE ITALIANA
CONTRO LE LEUCEMIE-LINFOMI E MIELOMA
ONLUS

DIPARTIMENTO DI MEDICINA SPECIALISTICA,
DIAGNOSTICA E SPERIMENTALE

Impiego di Ixazomib nel Mieloma Multiplo di nuova diagnosi

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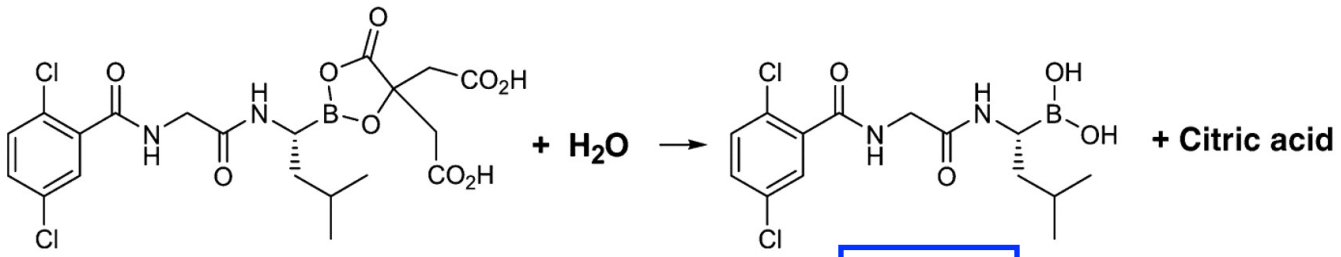
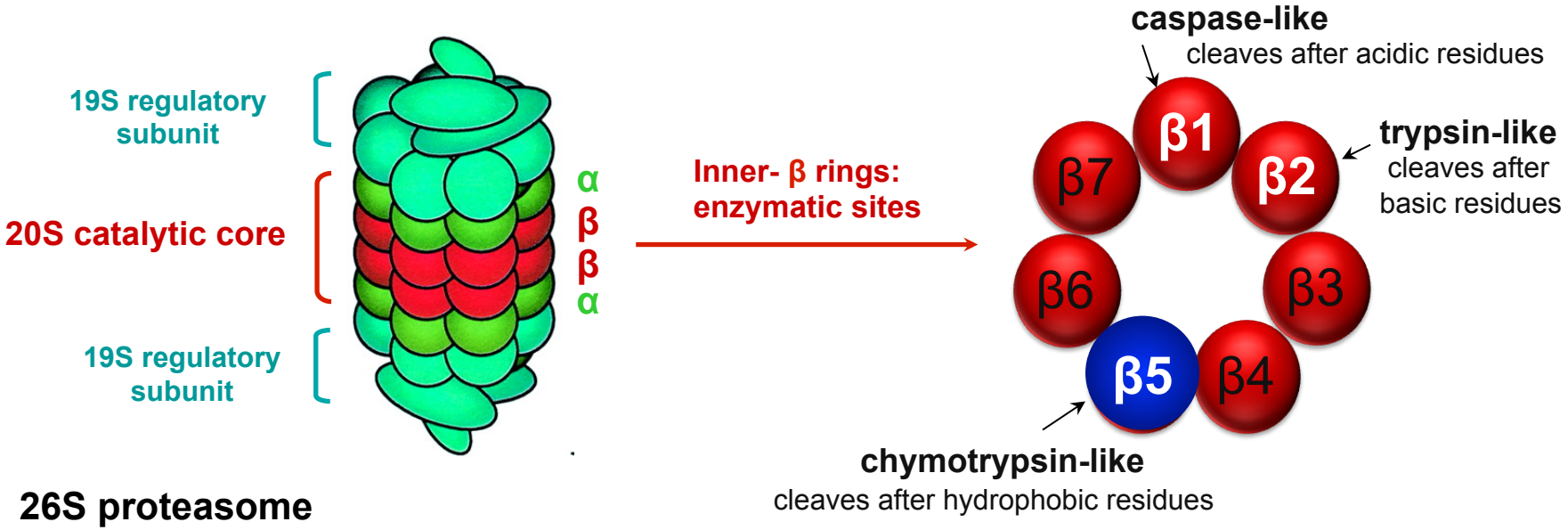
Meldola, 24 Settembre 2016

IXAZOMIB

Ixazomib (MLN9708) is a citrate ester of boronic acid that selectively, reversibly and potently inhibits the β5 site of the 20S proteasome.



MLN9708 | **MLN2238**

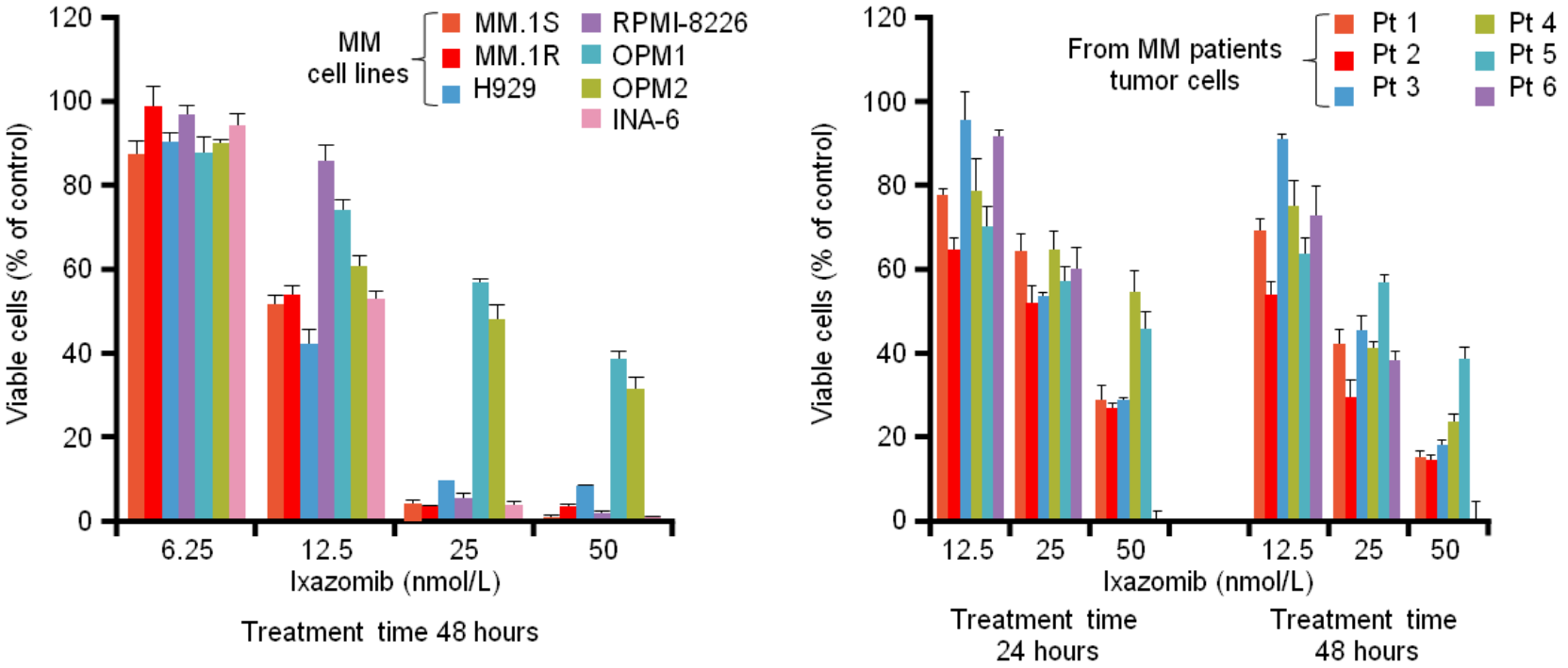


26S proteasome

Ixazomib: Preclinical Background

- In vitro activity against MM cell lines, including cell lines sensitive and resistant to conventional therapies.[1]

- Ability to trigger cytotoxicity also against plasma cells from bortezomib-refractory MM patients, without affecting the viability of normal cells.[1]



Human MM cell lines were treated with various concentrations of ixazomib for 48 hours, followed by assessment for cell viability by MTT assays. A significant concentration-dependent decrease in viability of all cell lines was observed in response to treatment with ixazomib ($P < 0.05$; $n = 3$)

[1]Chauhan D, et al. Clin Cancer Res 2011;17:5311–21

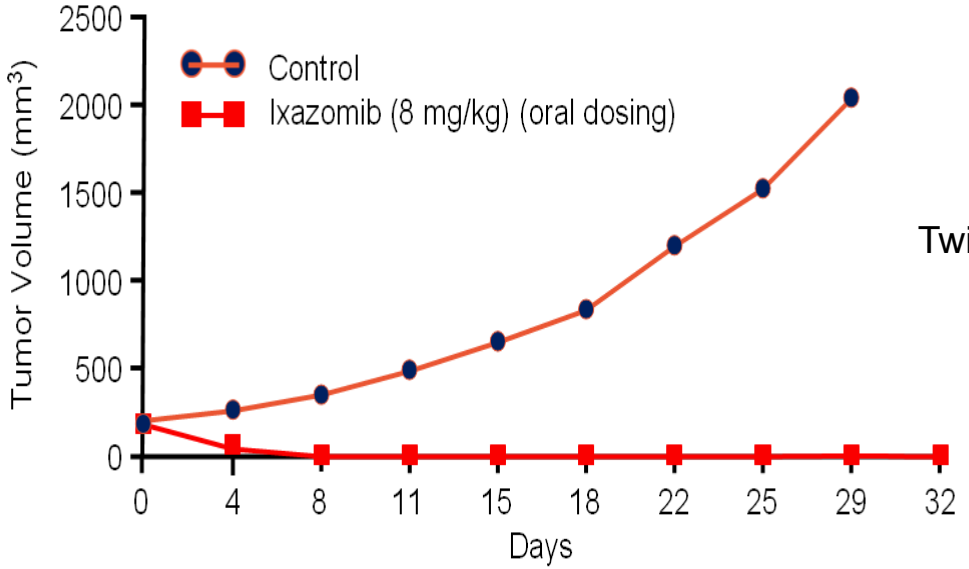
Ixazomib: Preclinical Background

-Antitumor activity in xenograft models of multiple myeloma, lymphoma, and some solid tumors.[1-3]

- Evidence of significantly longer survival in mice treated with MLN2238 vs bortezomib[1,2]

- Synergistic anti-MM activity, triggered by combination of MLN2238 with dex and lenalidomide, both in vitro and in vivo models.[1,2]

- Activity against MM bone disease, including enhanced osteoblast formation and inhibition of osteoclast activity.[4]



Antitumor activity of ixazomib in MM1S human plasmacytoma xenograft-bearing mice

Twice weekly oral dosing of ixazomib for 3 weeks caused complete durable regressions

[1]Chauhan D, et al. Clin Cancer Res 2011;17:5311–21
[2]Kupperman E, et al. Cancer Res 2010;70:1970–80.
[3]Lee EC, et al. Clin Cancer Res 2011; 2011;17:7313–23.
[4]Garcia-Gomez A , et al. Clin Cancer Res 2014; 20(6): 1542-54

Ixazomib: Pharmacokinetic and pharmacodynamic

- Distinct chemical structure and pharmacology compared to bortezomib[1,2]
  - Shorter proteasome dissociation half-life compared to bortezomib, can more readily enter tumor tissues → improved tissue distribution → improved tumor pharmacodynamic response and antitumor activity
  - High oral bioavailability compared to IV formulation (F=67%) → allows ixazomib to be dosed orally[3]

- Population PK studies have shown:[3]
  - Rapid absorption with a median Tmax of 0.5-2.0 hours and a terminal half-life of 3-11 days, supporting both twice-weekly and weekly dosing
  - No effect of sex, race, age, creatinine clearance
  - No impact of body size on exposure → enabling fixed dosing of ixazomib in clinical trials

[1]Kupperman E, et al. Cancer Res 2010;70:1970–80.
[2]Lee EC, et al. Clin Cancer Res 2011; 2011;17:7313–23
[3]Gupta N et al. Br J Clin Pharmacol. 2015 May;79(5):789-800

Safety and tolerability of ixazomib, an oral proteasome inhibitor, in combination with lenalidomide and dexamethasone in patients with previously untreated multiple myeloma: an open-label phase 1/2 study

Shaji K Kumar, Jesus G Berdeja, Ruben Niesvizky, Sagar Lonial, Jacob P Laubach, Mehdi Hamadani, A Keith Stewart, Parameswaran Hari, Vivek Roy, Robert Vescio, Jonathan L Kaufman, Deborah Berg, Eileen Liao, Alessandra Di Bacco, Jose Estevam, Neeraj Gupta, Ai-Min Hui, Vincent Rajkumar, Paul G Richardson

Lancet Oncol 2014; 15: 1503–12

C16005 trial: Phase 1/2 study of weekly oral Ixazomib plus Lenalidomide and Dexamethasone in previously untreated MM

Objectives:

Phase 1: Adverse events, tolerability, MTD, RP2D

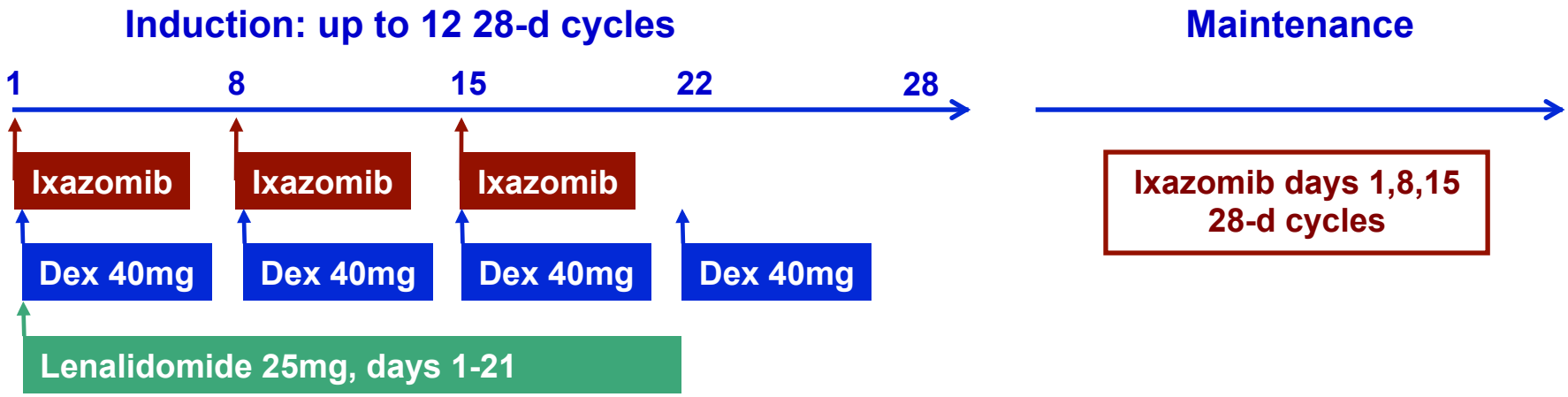
Phase 2: *Primary:* CR+VGPR, adverse events, tolerability;
Secondary: ORR, time to response, duration of response, PFS

Inclusion criteria:

-Age ≥ 18 years
-ECOG performance status 0-2
-Confirmed diagnosis of symptomatic NDMM
-Measurable disease

Kumar et al. Lancet Oncol 2014;15:1503-1502

C16005 TRIAL: STUDY DESIGN



- Mandatory thromboprophylaxis with aspirin or LMWH
- Stem Cell Collection allowed after 3 cycles, with SCT allowed after 6 cycles
- Pts who proceeded to ASCT did not receive further ixazomib therapy
- Pts who completed 12 cycles of induction were allowed to continue on maintenance (ixazomib given at the last tolerated dose during induction)
- Pts discontinued for progressive disease or unacceptable toxicity

Phase 1 (n=15): Standard 3+3 dose escalation schema; ixazomib 1.68 (n=3), 2.23 (n=3), 2.97 (n=6) or 3.95 (n=3) mg/m2

Phase 2 (n=50): Ixazomib 2.23 mg/m2 (RP2D) → converted to 4.0 mg fixed dose

Kumar et al. Lancet Oncol 2014;15:1503-1502

C16005 TRIAL: SAFETY

- **DLTs/MTD:**
  - 1 patient with DLT at 2.97 mg/m^2: Grade 3 urticarial rash
  - 3 patients with DLTs at 3.95 mg/m^2: Grade 3 nausea, n=2; vomiting, n=3; diarrhea, n=1; syncope, n=1
  - MTD: 2.97 mg/m^2
  - RP2D: 2.23 mg/m^2 (one level below MTD considering the toxicity/efficacy balance across multiple cycles. Converted to 4.0 mg fixed dose based on population PK analysis)

- **Adverse events:**

AE, n (%)	Phase 1 (n=15)	Phase 2 (n=50)	Total (n=65)
Grade ≥3 AE	11 (73)	38 (76)	49 (75)
Drug-related Grade ≥3 AE	9 (60)	32 (64)	42 (63)
SAE	8 (53)	20 (40)	28 (43)
Drug-related SAE	5 (33)	9 (18)	14 (22)
Dose reduction due to AE	8 (53)	29 (58)	37 (57)
AE resulting in discontinuation	1 (7)	4 (8)	5 (8)
Deaths	0	2 (4)	2 (3)

Kumar et al. Lancet Oncol 2014;15:1503-1502

C16005 TRIAL: SAFETY

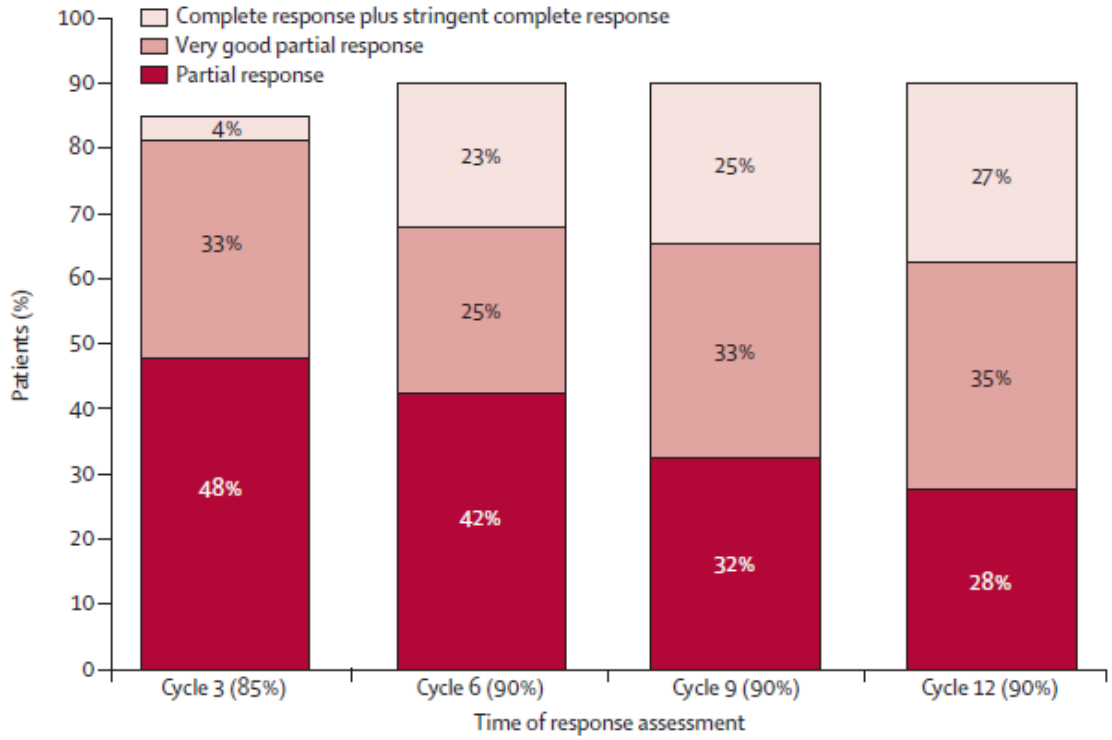
Drug Related Grade ≥ 3 AE, % (N=65)	Phase 1 (n=15)	Phase 2 (n=50)	Total (n=65)
Hematologic toxicity			
Neutropenia	7	14	12
Thrombocytopenia	7	8	8
Lymphopenia	13	4	6
Non-hematologic toxicity			
Skin and subcutaneous tissue disorders	27	14	17
Fatigue	0	12	9
Vomiting	20	2	6
Diarrhoea	7	6	6
PN	13	4	6
Hypokalaemia	0	8	6
Hypertension	20	0	5
Nausea	13	2	5
Syncope	13	0	3
Agitation	7	0	2
Orthostatic hypotension	7	0	2

Kumar et al. Lancet Oncol 2014;15:1503-1502

C16005 TRIAL: RESPONSE

Response, n (%)	Phase 1 (n=15)	Phase 2 (n=49)*	Total (N=64)
ORR (≥PR)	15 (100)	44 (90)	59 (92)
≥ CR	5 (33)	12 (24)	17 (27)
VGPR	3 (20)	17 (35)	20 (31)
≥VGPR	8 (53)	29 (59)	37 (58)
PR	7 (47)	15 (31)	22 (34)

*1 patient was excluded from the response-evaluable population due to having no post-baseline assessments



Kumar et al. Lancet Oncol 2014;15:1503-1502

C16005 TRIAL: MAINTENANCE PHASE

50 pts in ph.2 → 29 discontinued during induction (cycles 1–12) to undergo ASCT (n=14) or due to AEs (n=6) or pt withdrawal (n=4). 21 pts received maintenance (cycle ≥13)

- Median n° cycles (induction+maintenance): 27 (15-32)
- Median treatment duration: 26.6 mos (13.4-29.6)
- Median follow-up for PFS: 31.2 mos; median PFS not reached, 2-yr PFS 57%
- All 21 pts alive after follow-up of 25.1–33.9 months, including a median follow-up from start of maintenance of 19.9 months (range 13.4–22.2)

Best response, %	21 maintenance pts		
	To induction	Overall	
ORR (≥PR)	100	100	
sCR	5	19	71
CR	19	33	
VGPR	48	10	
nCR	0	10	
PR	29	29	

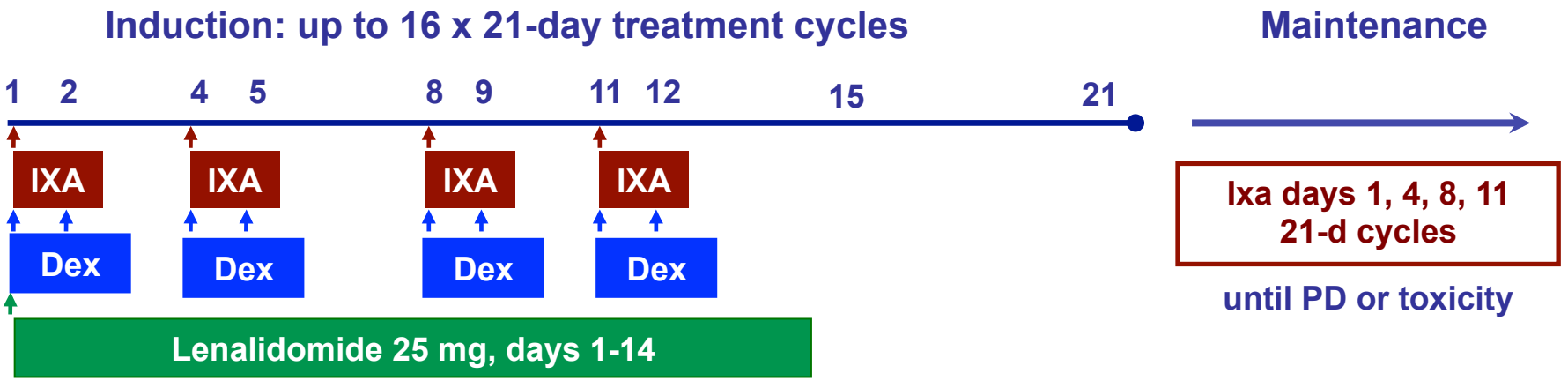
10 (48%) pts improved response during maintenance:
2 VGPR to nCR;
5 VGPR to CR;
1 VGPR to sCR;
2 CR to sCR

15 (71%) pts had drug-related AEs, 2 (10%) pts gr.3 (hypokalemia, thrombocytopenia), no gr.4

Serious AEs were reported in 3 pts, including gr.3 acute myocardial infarction, gr.3 pneumonia, and gr.3 orthostatic hypotension; all were considered not related to treatment

Kumar S, et al. ASH 2014, abstract #82

C16008 trial: Phase 1/2 study of oral Ixazomib plus Lenalidomide and Dexamethasone in previously untreated MM (**Twice-Weekly Dosing**)



- Phase 1: oral ixazomib dose-escalation (standard 3+3 schema, 33% dose increments, based on cycle 1 DLTs)
- Phase 2: oral ixazomib at the RP2D
- LMWH or aspirin prophylaxis mandatory
- Stem cell collection allowed after cycle 4, with ASCT deferred until after 8 cycles

Objectives:

Phase I: safety, tolerability, MTD, RP2D

Phase II: CR+VGPR rate (primary); safety, ORR, DOR, PFS

Richardson PG, et al. ASH 2013, abstract 535

C16008 TRIAL: PHASE I - DLTs and RP2D

Two dose levels: 7 pts enrolled to Ixazomib 3.0 mg; 7 pts to Ixazomib 3.7 mg

DLT: No AE met DLT criteria in cycle 1 at either dose of ixazomib

But all 7 pts enrolled to ixazomib 3.7 mg reported rash-related AE, including 4 pts with grade 3 AE, beyond cycle 1

RP2D: 3.0 mg selected as RP2D based on consideration of overall tolerability, including rate of rash, and efficacy across multiple cycles

C16008 TRIAL: TREATMENT EXPOSURE

Treatment Exposure	Ph.1 (n=14)	Ph.2 (n=57*)	Total (N=64)
Median cycles received, (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)
Pts remaining on treatment (at data cut-off)	3 (21)	15 (26)	16 (25)
Reason for discontinuation, 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)

*Includes 7 phase I pts treated at RP2D

Richardson PG, et al. ASH 2013, abstract 535

C16008 TRIAL: SAFETY

AE, n (%)	Phase I (n=14)	Phase II* (n=57)	Total (n=64)
Any grade ≥3 AE	11 (79)	44 (77)	49 (77)
Any gr. ≥3 drug-related AE	9 (64)	32 (56)	37 (58)
Any serious AE	7 (50)	28 (49)	30 (47)
Any serious drug-related AE	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)
Rash-related AE	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)
Neutropenia	1 (7)	3 (5)	3 (5)
Decreased lymphocyte count	0	3 (5)	3 (5)
Hyponatremia	0	3 (5)	3 (5)
Peripheral neuropathies	1(7)	3 (5)	3 (5)

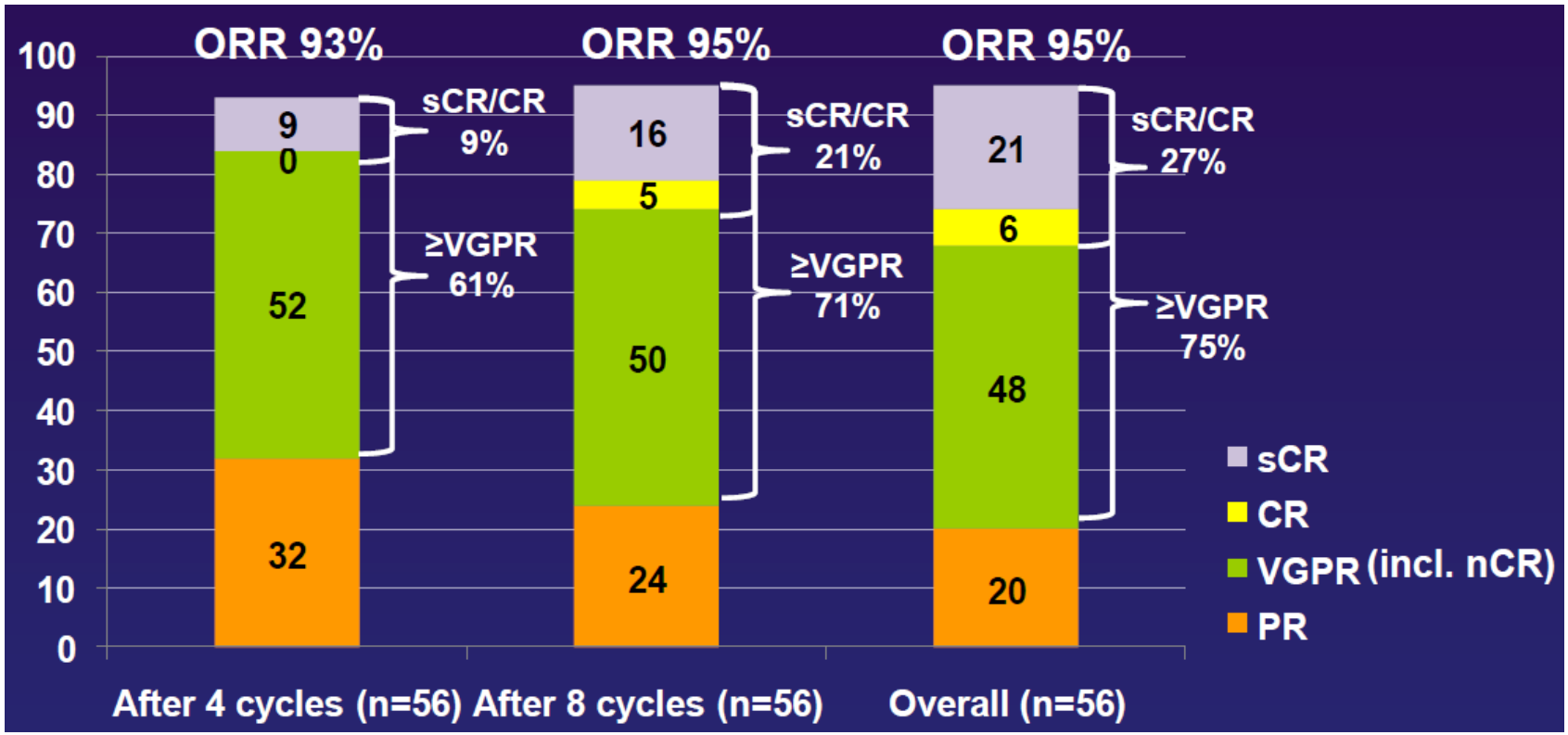
No gr.4 drug-related AEs

Richardson PG, et al. ASH 2013, abstract 535

C16008 TRIAL: RESPONSE

Response, n (%)	Phase I (n=13)	RP2D (n=56)	Total* (n=62)
Overall response (≥PR)	12 (92)	53 (95)	58 (94)
CR+VGPR	10 (77)	42 (75)	46 (76)
CR (including sCR)	2 (15)	15 (27)	16 (26)
VGPR (including nCR)	8 (62)	27 (48)	30 (48)

*2 pts excluded due to having no post-baseline assessments



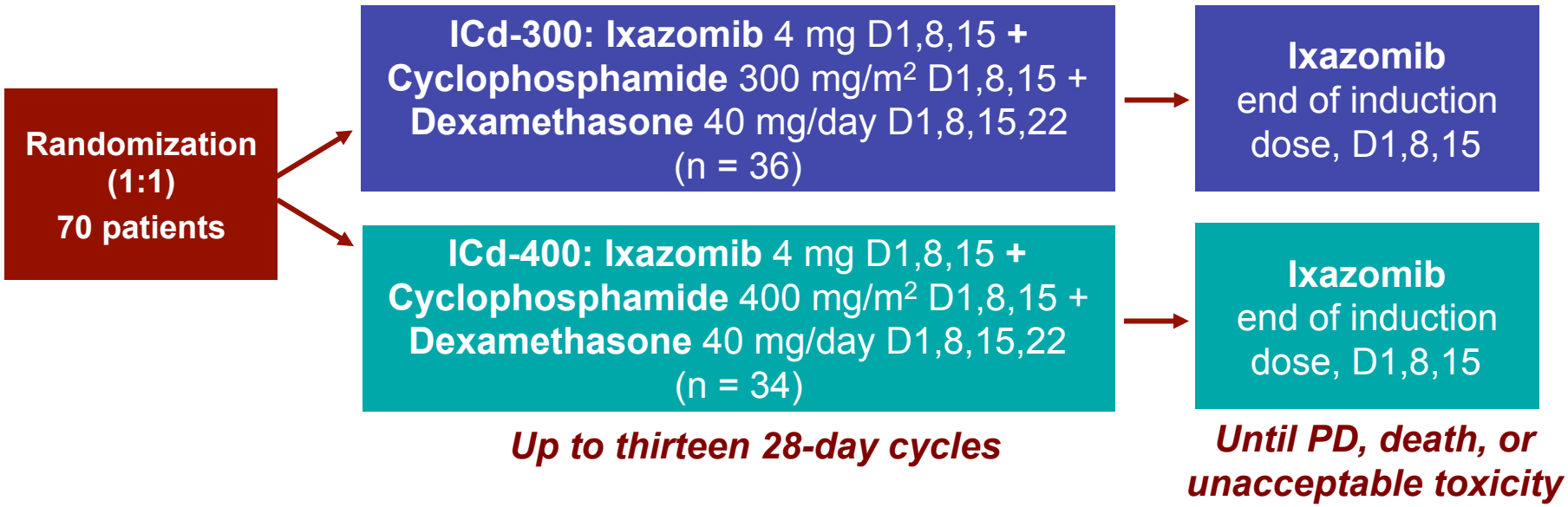
Median DOR to date is 13.8 mos, ranging up to 18.8+ mos

Richardson PG, et al. ASH 2013, abstract 535

Phase II study of ixazomib plus Cy and low-dose Dex (ICd) in transplant-ineligible, newly diagnosed MM

C16020: Randomized, open-label, multicenter phase II trial

NDMM with symptomatic, measureable disease and ineligible for transplant



Progressed to maintenance if SD or better and acceptable toxicity profile

Primary endpoint: CR + VGPR during induction

Secondary endpoints: ORR (CR + VGPR + PR), PFS, safety

Dimopoulos MA, et al. ASH 2015. Abstract 26.

C16020: Efficacy

Treatment exposure	ICd-300 (n = 36)	ICd-400 (n = 34)
Median nr cycles, (range)	9 (1-18)	9 (1-16)
Completed all 13 planned cycles, %	22	18
Still on treatment, %	67	68

Response§, n (%)	ICd-300 (n=32*)	ICd-400 (n=34*)
CR + VGPR	10 (28)	7 (21)
ORR (CR + VGPR + PR)	25 (78)	22 (65)
CR	3 (10)	3 (9)
VGPR	7 (22)	4 (12)
PR	15 (47)	15 (44)

§Best confirmed response (IMWG criteria)

*Evaluable for response.

Median time to ≥ PR (both arms): 1.3 cycles

Median follow-up: 9.2 mos

Median TTP: not reached

12-mo PFS: 80% overall, 68% in ICd-300 arm; 91% in ICd-400 arm

Dimopoulos MA, et al. ASH 2015. Abstract 26.

C16020: Safety

AE	ICd-300 (n=36)	ICd-400 (n=34)
Gr ≥3 AE,* %	64	68
Drug-related Gr ≥3 AE, %	39	56
SAE,%	39	50
AE leading to treatment discontinuation, %	14	18
AE leading to dose reduction of any study drug, %	19	21
On-treatment deaths, n†	3	1

†Deaths due to cardiac arrest, upper GI hemorrhage, pulmonary edema (ICd-300), and pneumonia (ICd-400), all deemed not drug related by investigator

Most Common Gr ≥3 AE, %	ICd-300 (n=36)	ICd-400 (n=34)
Neutropenia	14	35
Anemia	11	15
Thrombocytopenia	3	10
Diarrhea	6	0
Constipation	3	3
Nausea-Vomiting	6	0
Pneumonia	8	9
Fatigue	0	3
PN	0	3
Cardiac SOC	8	9
Rash	8	0
Renal impairment	3	6

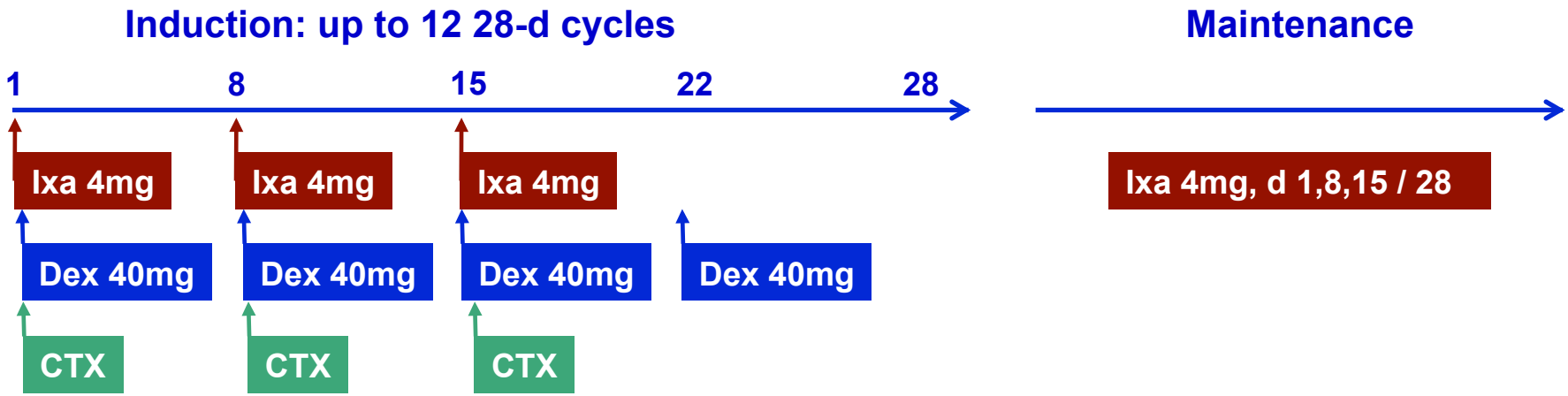
Dimopoulos MA, et al. ASH 2015. Abstract 26.

Phase 1/2 trial of ixazomib, cyclophosphamide, and dexamethasone in patients with previously untreated symptomatic multiple myeloma

Inclusion criteria: NDMM, measurable disease, ECOG 0-2, adequate organ function

Primary objectives: **Phase 1**: MTD of cyclophosphamide
Phase 2: CR+VGPR rate

Secondary objectives: PFS, OS, toxicity



Phase I: CTX dose-escalation (300 mg/m^2 → 400 mg/m^2)
Phase II: CTX at the RP2D from phase I
Stem cell collection allowed after 4 cycles

Lacy M, et al. ASCO 2016

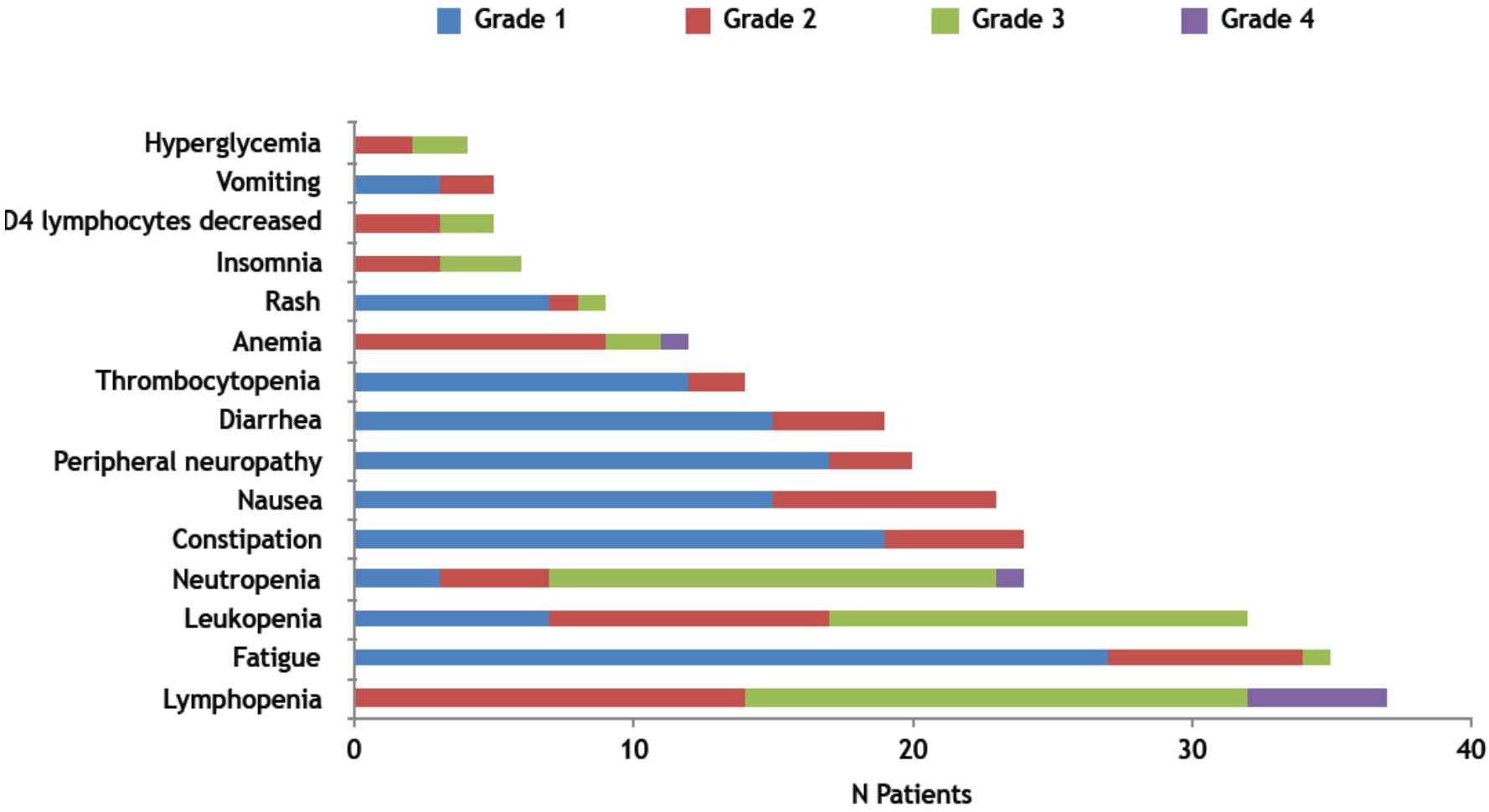
Characteristics and outcomes

	All pts* (n=48)	Phase II dose (n=45)
Median age, (range)	64.5 (41-88)	64 (41-88)
Male, n (%)	25 (52.1%)	24 (53.3%)
Nr still on treatment	17	16
Reason for discontinuation, n (%)		
refused further treatment	3 (9.7)	2 (6.9)
adverse event	2 (6.5)	2 (6.9)
disease progression	5 (16.1)	5 (17.2)
alternative treatment	16 (51.6)	15 (51.7)
other	5 (16.1)	5 (17.2)
Overall response rate	77%	78%
≥ VGPR response rate	35%	38%
Median follow up, mos	13.4 (3.9 - 32.2)	12.8 (3.9 - 30.4)
12-mos PFS, (95%CI)	92% (80-100)	91% (78-100)
12-mos OS	100%	100%

*Evaluable patients.

Lacy M, et al. ASCO 2016

Common toxicities



A grade 3 or higher adverse events (AE), considered possibly related was seen in 73%. Most common AE included cytopenias, fatigue and GI side effects

Lacy M, et al. ASCO 2016

Ongoing Clinical Trials in NDMM

Agent	Sponsor	Trial	Phase	Condition	Status
Ixazomib or placebo **+** lenalidomide + dexamethasone	Millennium	C16014 NCT01850524 TOURMALINE-MM2	3	Newly diagnosed MM	Active, not recruiting
Ixazomib	Millennium	C16019 NCT02181413 TOURMALINE-MM3	3	Maintenance post-ASCT in MM	Active, not recruiting
Ixazomib	Millennium	C16021 NCT02312258 TOURMALINE-MM4	3	Maintenance (non-SCT)	Recruiting
Lenalidomide + dexamethasone ± **Ixazomib**	PETHEMA	NCT02406144	3	Maintenance post-SCT in MM	Recruiting
Ixazomib + lenalidomide + dexamethasone	IFM	IFM2013-06 NCT01936532	2	Newly diagnosed MM	Active, not recruiting
Ixazomib + lenalidomide	MD Anderson Cancer Center	NCT01718743	2	Maintenance post-SCT in MM	Active, not recruiting

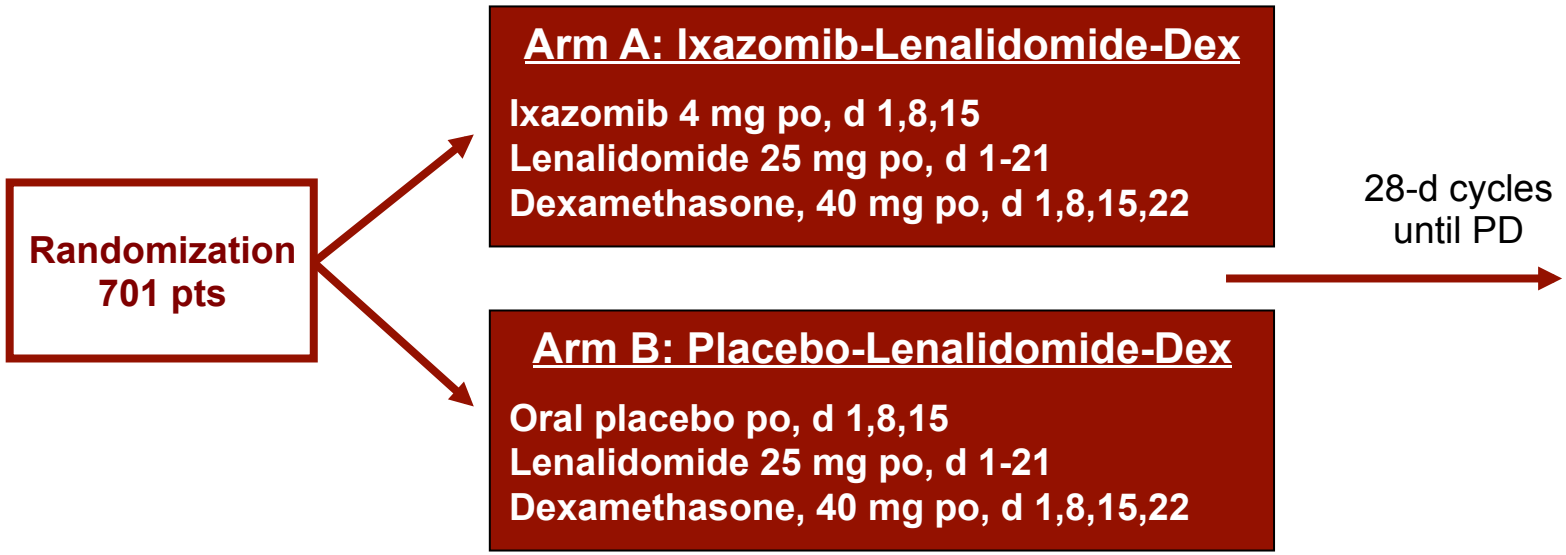
www.clinicaltrials.gov; accessed September 2016

Agent	Sponsor	Trial	Phase	Condition	Status
Ixazomib + lenalidomide + dexamethasone	Washington Univ.	NCT02253316	2	Consolidation post-ASCT, followed by maintenance with ixazomib/lenalidomide	Recruiting
Ixazomib + cyclophosphamide + dexamethasone	Brown Univ.	NCT02412228	2	Newly diagnosed MM	Recruiting
Ixazomib + Lenalidomide	National Cancer Institute	NCT02619682	2	Alternating Ixazomib and lenalidomide as maintenance post ASCT	Recruiting
Ixazomib + cyclophosphamide + dexamethasone	Millennium	C16020 NCT02046070	2	Newly diagnosed MM, relapsed/refractory MM	Active, not recruiting
Lenalidomide ± **ixazomib +** dexamethasone	Univ. of Chicago	NCT02389517	2	Consolidation/maintenance after allogenic SCT	Recruiting
Ixazomib	Millennium	NCT02168101	2	Maintenance after allogenic SCT	Recruiting
Ixazomib + melphalan + prednisone	Millennium	C16006 NCT01335685	1/2	Newly diagnosed MM	Active, not recruiting
Ixazomib + cyclophosphamide + dexamethasone	Mayo Clinic	NCT01864018	1/2	Previously untreated symptomatic MM	Active, not recruiting

www.clinicaltrials.gov; accessed September 2016

TOURMALINE MM-2 (C16014):
Ixazomib plus lenalidomide and dexamethasone in NDMM

A Phase 3, Randomized, Double-Blind, Multicenter Study Comparing Oral IXAZOMIB (MLN9708) Plus Lenalidomide and Dexamethasone vs Placebo plus Lenalidomide and Dexamethasone in Adult Patients with Newly Diagnosed Multiple Myeloma



Select Inclusion/Exclusion Criteria:

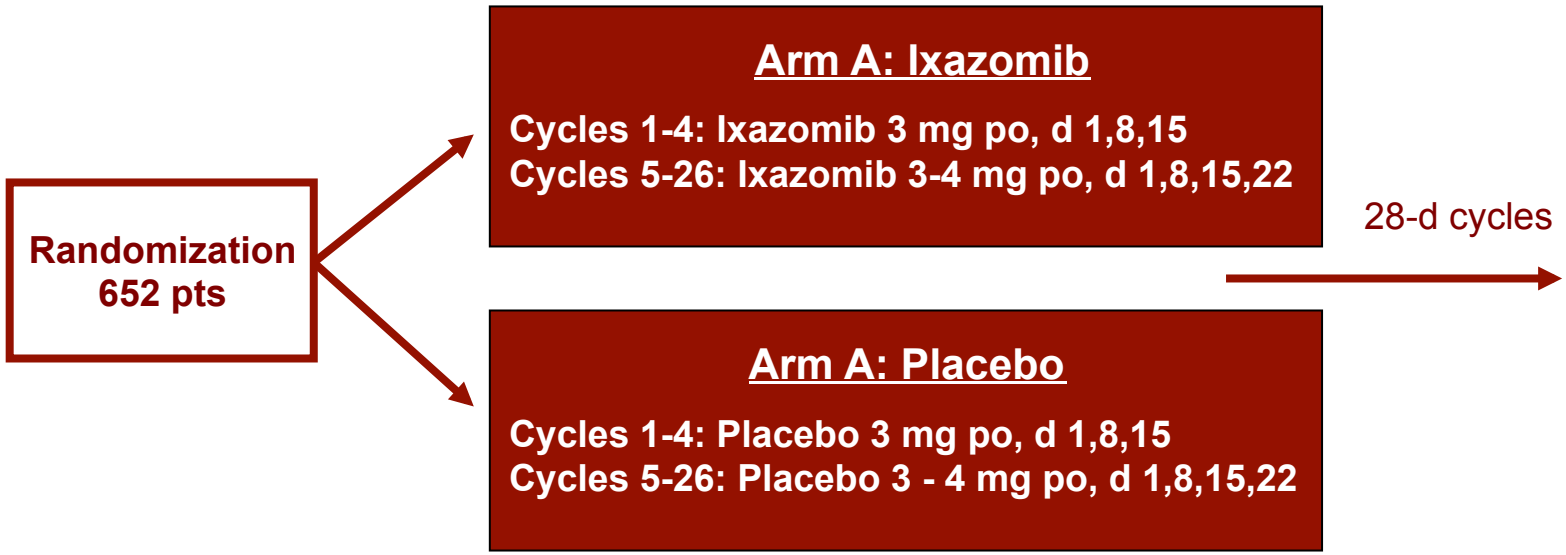
- Newly diagnosed MM
- No prior treatment for MM
- Ineligible for HDT followed by SCT due to age ≥ 65 or significant co-morbid conditions
- Measurable disease
- ECOG performance status 0-2

Endpoints:
Primary: PFS
Secondary: CR, pain response, OS

www.clinicaltrials.gov; accessed September 2016

TOURMALINE MM-3 (C16019):
Ixazomib maintenance therapy following ASCT

A Phase 3, Randomized, Placebo-Controlled, Double-Blind Study of Oral Ixazomib Citrate (MLN9708) Maintenance Therapy in Patients with Multiple Myeloma Following Autologous Stem Cell Transplant



Select Inclusion/Exclusion Criteria:

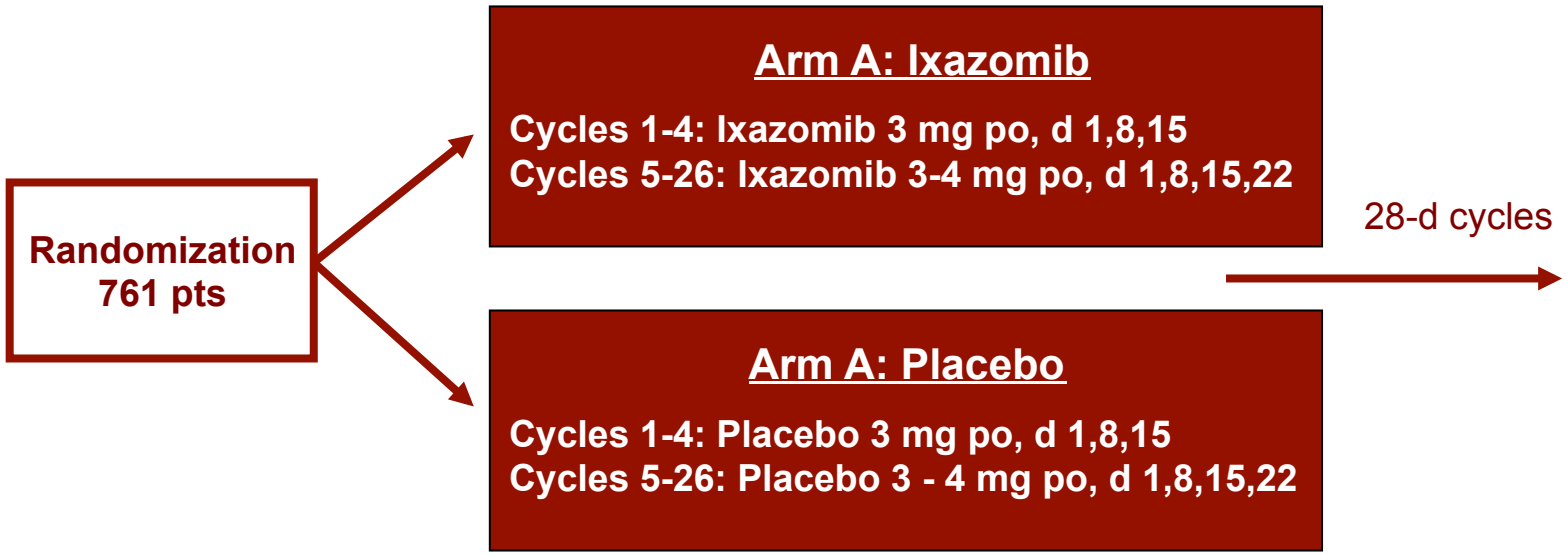
- Symptomatic MM
- Received standard of care induction therapy (including proteasome inhibitor and/or IMiD) followed by single SCT within 12 months of diagnosis, w/o consolidation therapy
- Documented response (≥PR) to SCT, with no relapse
- ECOG performance status 0-2

Select Endpoints:
Primary: PFS
Secondary: OS, ORR, TTP, 2nd PFS

www.clinicaltrials.gov; accessed September 2016

TOURMALINE MM-4 (C16021):
Ixazomib maintenance therapy without stem cell transplant

A Phase 3, Randomized, Placebo-Controlled, Double-Blind Study of Oral Ixazomib Maintenance Therapy After Initial Therapy in Patients With Newly Diagnosed Multiple Myeloma Not Treated With Stem Cell Transplantation



Select Inclusion/Exclusion Criteria:

- Symptomatic newly diagnosed MM
- Documented response (≥PR) to initial therapy, without relapse
- No prior SCT
- ECOG performance status 0-2

Select Endpoints:
Primary: PFS
Secondary: OS, ORR, TTP, 2nd PFS

www.clinicaltrials.gov; accessed September 2016

Conclusions

- Ixazomib is the first available oral proteasome inhibitor to evaluated for the treatment of MM
- Represents a more practical option than other PI, being a once-weekly oral drug
- Enables the combination of PI and IMiDs in an all-oral regimen
- Phase I-II studies demonstrated feasibility and efficacy of ixazomib in combination with Lenalidomide-Dex and Cyclophosphamide-Dex in pts with NDMM
- Additional toxic effects with this regimens were limited
- The manageable safety profile enables long-term treatment
- Results from ongoing phase III trial (comparing ixazomib vs placebo either in combination with lenalidomide/dexamethasone in pts with NDMM, or as single-agent maintenance treatment) are eagerly awaited

C16005 TRIAL: SUBSET ANALYSIS IN ELDERLY PATIENTS

	<65 years (n=25)	≥65 years (n=25)	≥75 years (n=9)
Median number of treatment cycles (range)	9 (2–17)	10 (1–19)	5 (1–18)
Received ≥12 cycles, n (%)	10 (40)	12 (48)	2 (22)
Remain on treatment, n (%)	8 (32)	10 (40)	2 (22)
Proceeded to ASCT, n (%)	11 (44)	2 (8)	1 (11)
Discontinued due to AE, n (%)	2 (8)	2 (8)	1 (11)
Dose reductions, any drug, n (%)	12 (48)	16 (64)	6 (67)
SAEs, all-cause, n (%)	10 (40)	9 (36)	3 (33)
Grade ≥3 AEs, all-cause , n (%)	18 (72)	19 (76)	8 (89)
Grade 3 AE in ≥4 patients, %			
Neutropenia	28	8	22
Thrombocytopenia	8	12	11
Anemia	4	8	11
Rash	12	28	33
Fatigue	12	11	11
Hyponatremia	4	8	11
ORR, %	92	88	75
CR+VGPR	56	71	75

At data cut-off (April 24, 2013), 12 of the 65 patients who were enrolled in the C16005 study had progressed or died, including 3, 9, and 4 patients aged <65, ≥65, and ≥75 years, respectively

Richardson PG, et al. EHA 2013, abstract P236