Progress in Multiple Myeloma

Sundar Jagannath, MD

Professor, New York Medical College

Adjunct Professor, New York University

St. Vincent's Comprehensive Cancer Center, NY

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Faculty Disclosure

Advisory Board: Merck, Millennium, and Celgene

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Practice Points from ASH 2009

- ISS staging is relevant in the era of novel agents
  - Obtain β2-microglobulin at start of treatment
- Do we need to consider treatment of high-risk smoldering myeloma?
  - More studies forthcoming (SWOG/ECOG) with lenalidomide
- For frontline therapy triplets are recommended
  - Bortezomib, lenalidomide, dexamethasone
- Maintenance therapy further improves response rate, PFS and OS
- Consider clinical trials for relapsed/refractory myeloma
  - Multiple active drugs in clinical trial:
  - Pomalidomide, carfilzomib, elotuzumab, vorinostat, perifosine

Staging and Prognosis

ISS Stage

Cytogenetics and FISH Analysis

(Flow sorted or cIg FISH)

Impact of Chromosomal Abnormalities on Survival Outcomes in Multiple Myeloma

IMWG Analysis, 9897 patients

Genetic Abnormalities	Positive	Negative	% of total
Any CA	765	1530	33%
Hypodiploidy	162	1551	9.5%
Hyperdiploidy	275	1398	16%
Del 13	294	2015	12.7%
FISH Analysis			
t(4;14)	199	1374	12.6%
Del 13	1380	1846	43%
Del 17	121	1365	8%
t(14;16)	10	356	2.7%
t(11;14)	316	1367	19%

Avet-Loisseau et al. ASH 09, abstract 743.

Impact of Chromosomal Abnormalities on Survival Outcomes in Multiple Myeloma

IMWG Analysis Genetic Abnormalities	**4-Year Estimated OS** Minus vs. Plus Abnormality	Log Rank *P* Value
Any CA	73% vs. 57%	<.0001
t(4;14) ISS I ISS2 ISS3	64% vs. 36% 81% vs. 52% 63% vs. 30% 44% vs. 22%	<.0001 <.0001 <.0001 <.007
Del 17 ISS I ISS2 ISS3	68% vs. 44% 81% vs. 64% 68% vs. 42% 48% vs. 28%	<.0001 <.020 <.0001 <.020
a. ISS I or ISS2, normal FISH	193/610 deaths (76%)	a vs. b <.0001 a vs. c <.0001 b vs. c <.0001
b. ISS I + abnormal FISH / ISS III + normal FISH	140/252 deaths (52%)	
c. ISS II or ISS III + abnormal FISH	146/196 deaths (32%)	

Avet-Loisseau et al., ASH 09, abstract 743.

Smoldering Myeloma
or
Asymptomatic Myeloma

Observe

Or

Observe low risk; treat high risk?

QuiRedex: High-risk smoldering MM

PCs BM ≥ 10% *plus* **M-protein** ≥ 30 g/L

or

PCs BM ≥ 10% *or* **M-protein** ≥ 30 g/L

but **BM aPC/nPC** > 95% plus **immunoparesis**

Time elapsed from diagnosis to inclusion not superior to 5 years

No CRAB (hypercalcemia, anemia, bone lesions, renal impairment) or symptoms

Mateos et al. ASH 2009; abstract 614.

Trial Design for High-risk Smoldering MM

	Treatment arm	Control arm
Induction: Nine 4-wks cycles	**Lenalidomide** 25 mg/daily during 21d every 28 d **Dexamethasone** 20 mg D1-D4 and D12-D15 every 28 d	**Therapeutic Abstention**
Maintenance	**Lenalidomide** 10 mg/daily during 21 d every 2 months	**Therapeutic Abstention**

Randomization according to: diagnosis in the last 6 months
diagnosis more than 6 months

Mateos et al. ASH 2009; abstract 614.

QuiRedex: SUMMARY

Promising efficacy results

Mateos et al, ASH 2009

- ITT analysis: ORR 81%; ≥ VGPR 30%
- Patients who have completed the 9-induction cycles: ORR 91%; ≥ VGPR 38%

Time to Progression to symptomatic MM

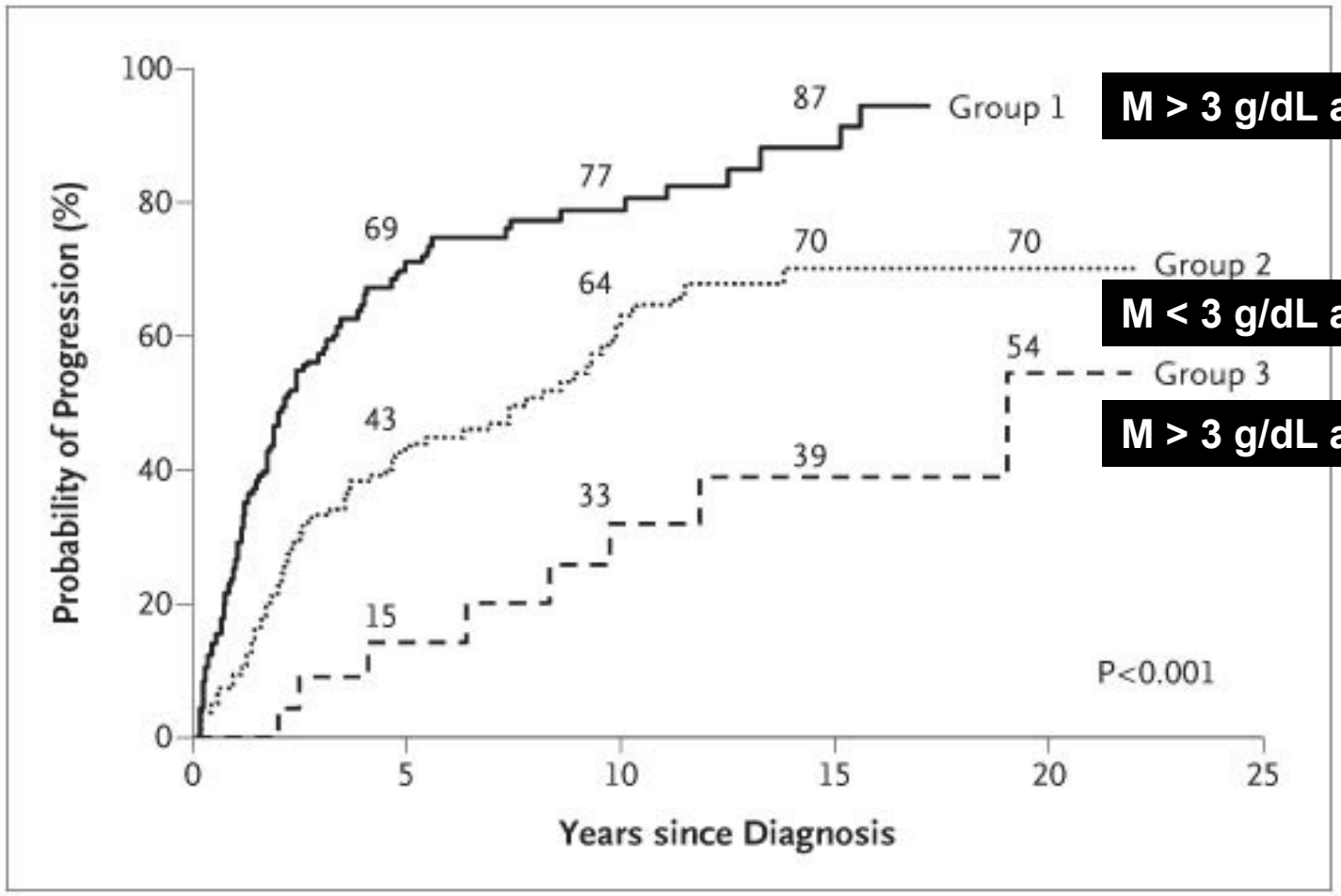
- Median TTP in therapeutic abst arm: 19 months
- 16 out of 47 pts in therapeutic abst arm have already progressed, and 10 out of them presenting bone lessions

Toxicity profile

- Toxicity was manageable. Very low frequency of G3 AEs

Conclusion: In high risk SMM delayed treatment is associated with early progression (17,5m) with bone disease, while len-dex induces high disease control with not only prolonged TTP (no progressions) but also CR and an acceptable & manageable toxicity profile.

Risk of Progression to MM or AL According to Risk Group



M > 3 g/dL and BM >10% PC

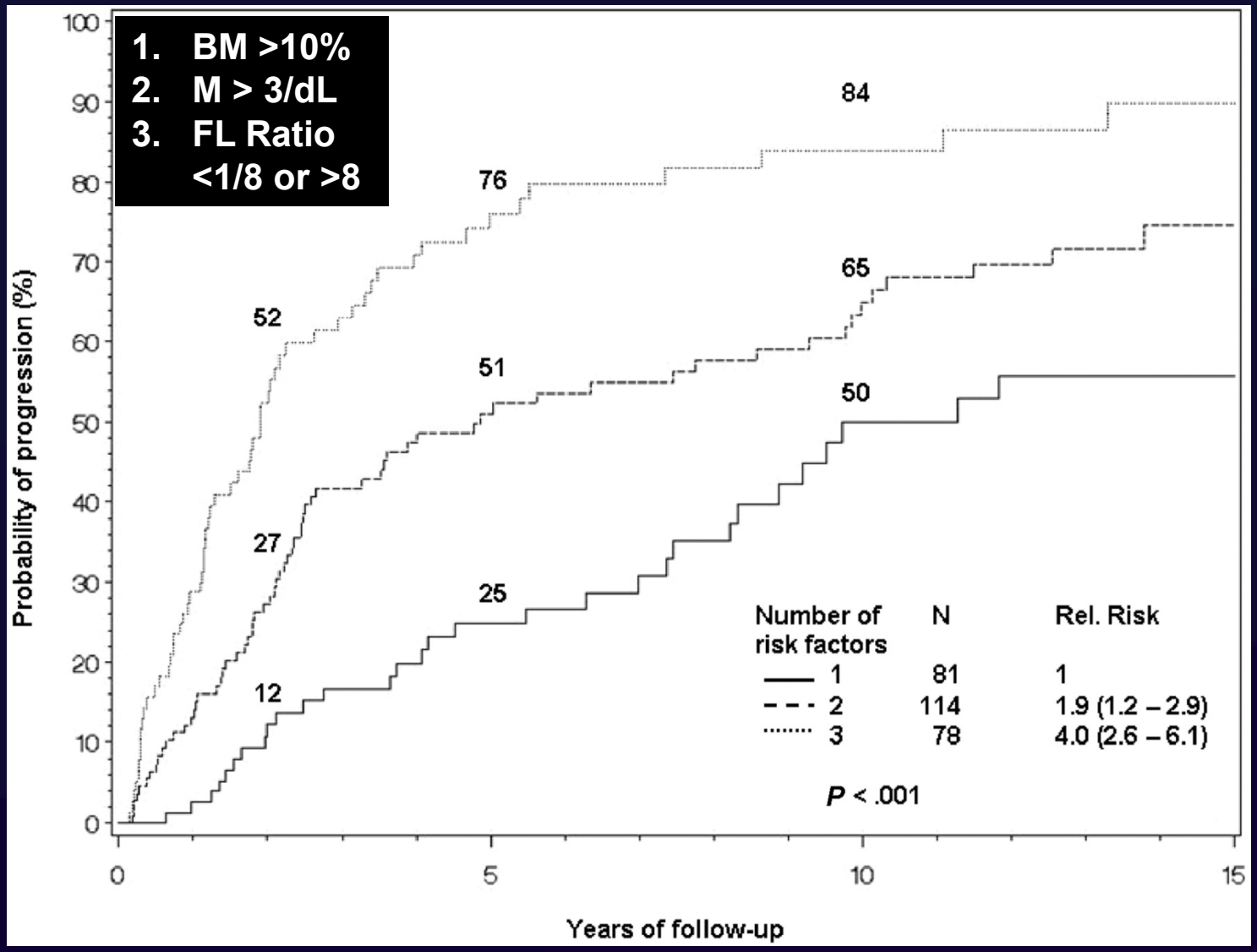
M < 3 g/dL and BM >10% PC

M > 3 g/dL and BM <10% PC

Group 1 = 106
Group 2 = 142
Group 3 = 27

Kyle RA, et al. N Engl J Med. 2007 356(25):2582-90.

Risk of Progression to MM or AL According to Risk Group



Dispenzieri Blood. 111:785, 2008.

Frontline MM: Phase III Trials

Transplant Ineligible

≥ 65 years

VISTA Trial: Melphalan/Prednisone ± Bortezomib in ND MM

Update and Results of Subsequent Therapy

n = 682

Bortezomib 1.3 mg/m^2
Cycle 1-4: days 1, 4, 8, 11, 22, 25, 29, 32
Cycle 5-9: days 1, 8, 22, 29
Melphalan 9 mg/m^2 days 1-4
Prednisone 60 mg/m^2 days 1-4

9 x 6 week cycles (54 weeks)

Melphalan 9 mg/m^2 days 1-4
Prednisone 60 mg/m^2 days 1-4

Stratify: β_2-microglobulin, albumin, region

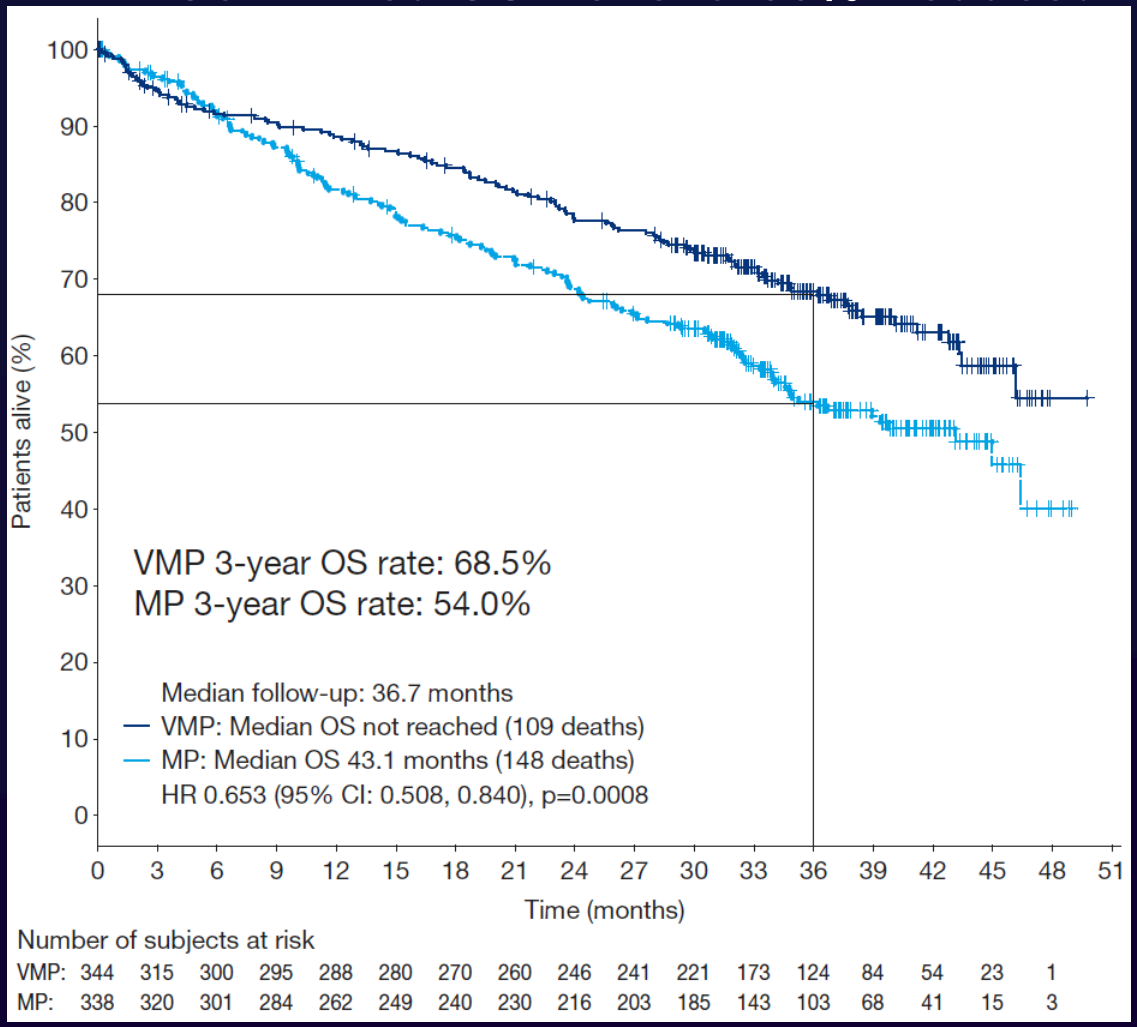
1° endpoint: time to progression
≥ 75 years: 31% in VMP arm, 30% in MP arm

Mateos et al. ASH 2009; abstract 3859.

VISTA: VMP vs MP Updated Follow-Up and Results of Subsequent Therapy

Updated median follow-up of 36.7 mos

Confirmed OS Benefit: 35% Reduced Risk of Death with VMP



VMP Arm

- **Subgroup analyses of 3-yr OS:**
  - Longer OS in pts aged <75 (74%) vs ≥75 (56%) (HR= 1.664, *p*=0.011)
  - No difference in OS between pts with CrCl ≥60 mL/min (75%) vs <60 mL/min (63%) (HR=1.291, *p*=0.238)
  - No difference in OS between standard-risk (72%) vs high-risk cytogenetics (56%) (HR 1.346, *p*=0.399)

Mateos MV, et al. ASH 2009, abstract #3859.

Bortezomib/Melphalan/Prednisone/ Thalidomide (VMPT) vs. Bortezomib/ Melphalan/Prednisone (VMP) in ND MM

n = 511

RANDOMIZE

≥ 65 years or transplant ineligible

VMPT [n=254; Age ≥75 = 27%]
Bortezomib* 1.3 mg/m^2 IV; days 1, 8, 15, 22
Melphalan 9 mg/m^2; days 1-4
Prednisone 60 mg/m^2; days 1-4
Thalidomide 50 mg/d; continuously

9 x 5 week cycles

VMP [n=257; Age ≥75 = 27%]
Bortezomib* 1.3 mg/m^2 IV; days 1, 8, 15, 22
Melphalan 9 mg/m^2; days 1-4
Prednisone 60 mg/m^2; days 1-4

Maintenance

Bortezomib
1.3 mg/m^2 q 15 days
Thalidomide 50 mg/day

Until relapse

No Maintenance

*Twice-weekly Btz: VMP, 66 pts; VMPT, 73 pts

Primary endpoint: PFS

Palumbo et al. ASH 09; abstract 128.

VMPT→ VT vs. VMP in ND MM: Efficacy & Toxicity

Endpoint	VMPT→VT (n = 250)	VMP (n = 253)	*P* Value
Best Overall Response	89%	81%	.01
CR	38%	24%	.0008
≥ VGPR	59%	50%	.03
Median follow-up 21.6 months	n = 254	n = 257	
3-year time-to-next-treatment	75%	60%	.0029
3-year progression-free survival	60%	42%	.007
3-year overall survival	89%	89%	.96

Grade 3/4 Adverse Events

Significantly higher on VMPT→VT arm

Neutropenia (*P* = .02)

Cardiologic (*P* = .04)

Maintenance Improves PFS

Palumbo et al. ASH 09; abstract 128.

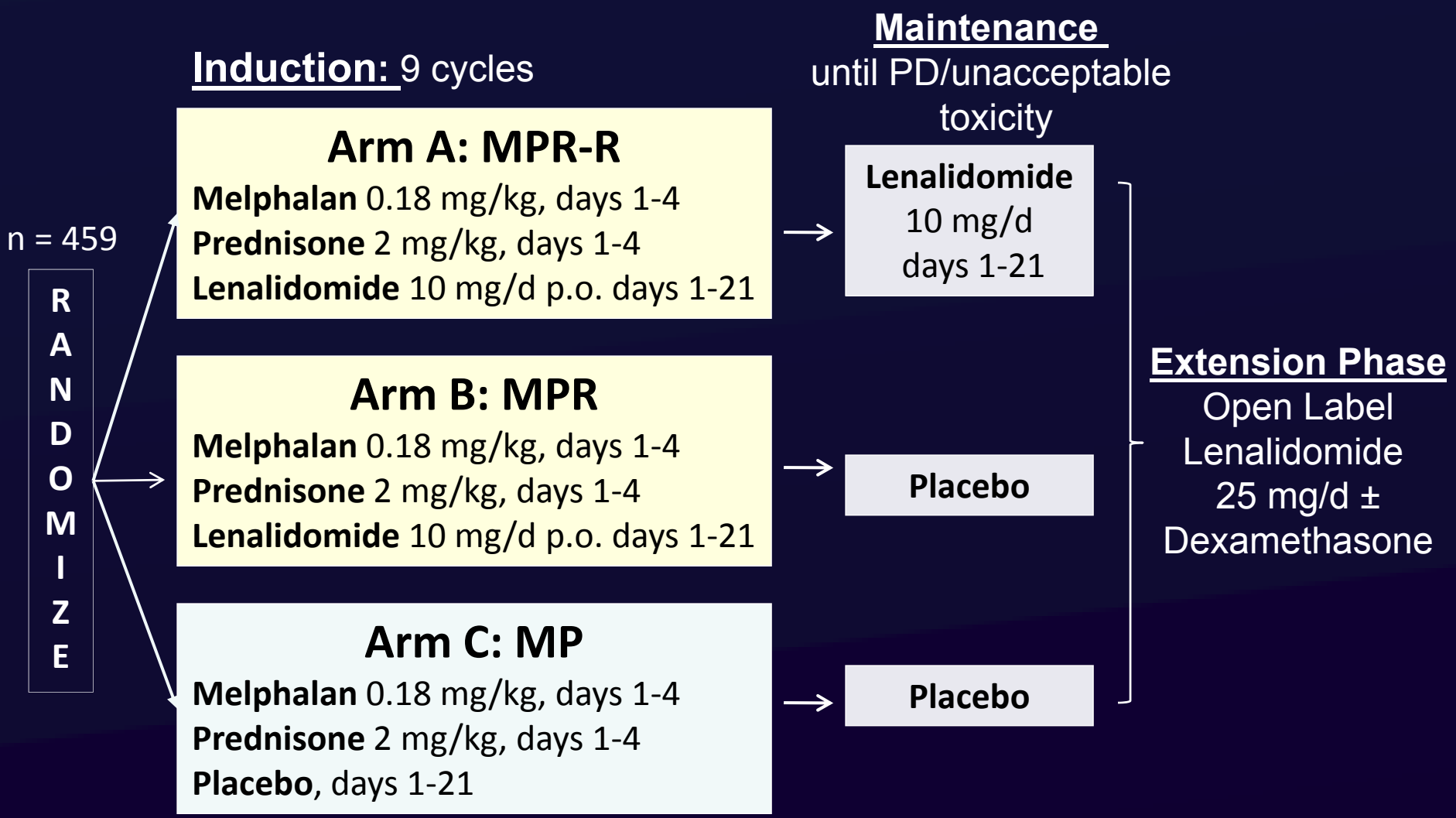
VMPT→ VT vs. VMP in ND MM: Efficacy & Toxicity by Bortezomib Schedule

	VMP Weekly (n = 190)	VMP Twice-weekly (n = 63)
CR	23%	25%
Progression-free survival, 2 year	58%	56%
Sensory Neuropathy Any grade Grade 3/4	 21% 2%	 43% 14%
Discontinuation due to PN	4%	16%
Total planned dose Total delivered dose	46.8 mg/m^2 40.0 mg/m^2	67.6 mg/m^2 41.0 mg/m^2

Weekly Bortezomib is better tolerated with same outcome

Palumbo et al. ASH 09; abstract 128.

Lenalidomide/MP (MPR) vs. MP in Elderly Patients With ND MM



Primary endpoint: PFS

Palumbo et al. ASH 2009; abstract 613.

MPR vs. MP in Elderly ND MM: Efficacy

Best Response	MPR-R (n = 152)	MPR (n = 153)	MP (n = 154)
ORR	77%	67%	49%†
CR/IF⁻	18%	13%	5%†
≥ VGPR rate	32%	33%	11%†
Time to First Response	1.9 months	1.9 months	2.8 months†

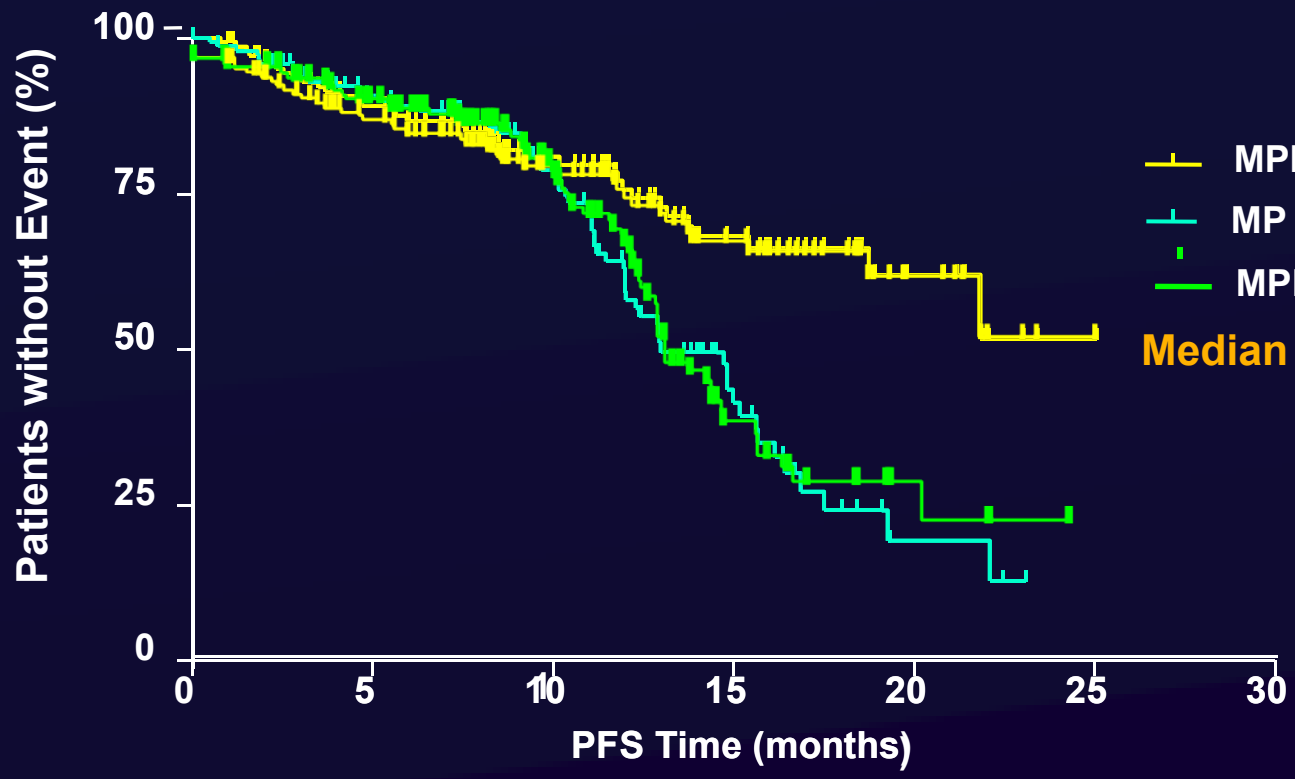
† *P* <.001 for MPR-R vs. MP

Survival	HR	95% CI	*P* Value
MPR-R vs. MP			
PFS, 1st interim analysis	0.499	0.330-0.755	< .001
TTNT	0.369	0.243-0.559	< .001
MPR-R vs. MPR			
PFS	0.530	0.350-0.802	.002
PFS, after cycle 9	0.245	0.126-0.476	< .001

1-year OS, 92% for MPR-R and MP arms

Palumbo et al. ASH 2009; abstract 613.

Progression-Free Survival
First Interim Analysis
50% Reduced Risk in PFS



Maintenance improves PFS

Palumbo et al. ASH 2009; abstract 613.

Frontline MM: Phase III Trials

Transplant Eligible

≤ 65 years

VD vs. VAD as Induction Therapy: Efficacy

Best Response by Phase	VD (n = 223)	VAD (n = 218)	*P* Value
≥ nCR rate			
Induction	15%	7%	.003
Post -ASCT I	35%	18%	< .0001
Post -ASCT 2	39%	32%	< .0001
≥ VGPR rate			
Induction	39%	16%	< .0001
Post -ASCT I	54%	57%	< .0003
Post- ASCT 2	68%	47%	< .0001

Harousseau et al. ASH 2009; abstract 353.

VD vs. VAD Induction Therapy: PFS

* Median follow-up 32 months

Median PFS	VD	VAD	*P* Value
	(n = 240)	**(n = 242)**	
All pts*	36 months	30 months	.057
	(n = 133)	**(n = 136)**	
Pts with ISS 2-3	33 months	23 months	.006
	(n = 40)	**(n = 29)**	
Pts with t(4;14) ± del (17p)	33.5 months	24 months	.113
	≥ VGPR	**< VGPR**	
All pts*	**(n = 117)**	**(n = 324)**	
	41 months	30 months	< .0001
Pts with ISS 2-3	**(n = 65)**	**(n = 204)**	
	Not reached	23 months	< .0001
Pts with t(4;14) ± del (17p)	**(n = 21)**	**(n = 48)**	
	37 months	24 months	.0036

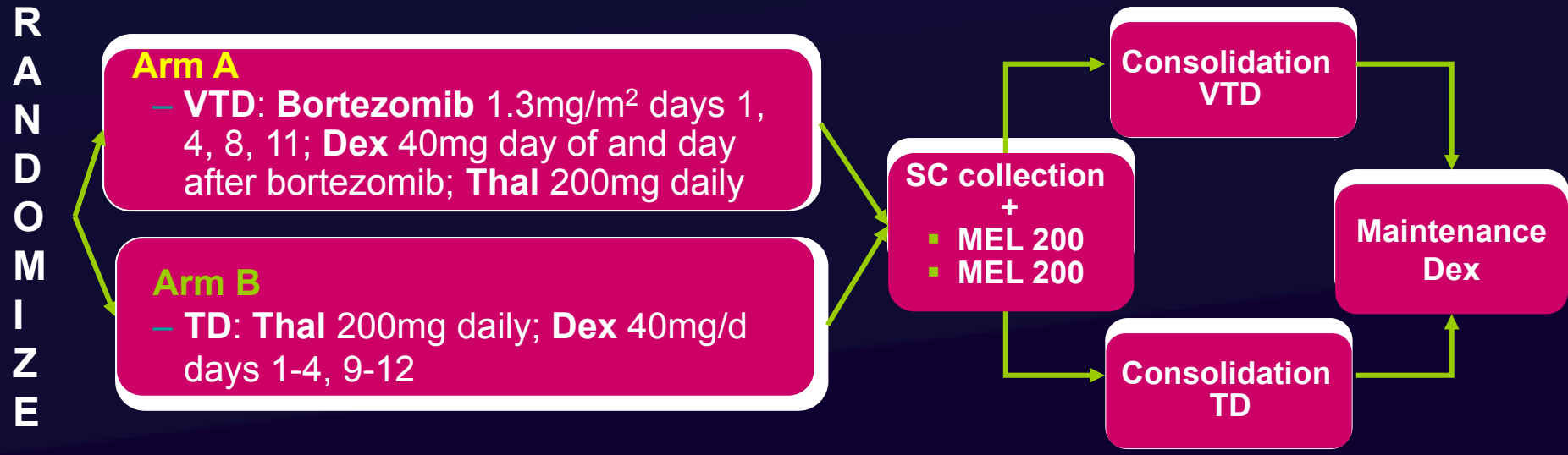
Depth of response predicts for better outcome

Harousseau et al. ASH 2009; abstract 353.

VTD vs TD for SCT Induction

Phase III study: Updated results

- **Endpoints:** Primary was CR/nCR post-induction: Secondary include: CR/nCR post- SCT and consolidation, TTP, EFS, PFS, OS, Stem cell yield, and Safety
- **Patients:** 450 planned patients: 474 enrolled (Arm A n=236, Arm B n=238)
- **Dose:** Three 21-day cycles



– **DVT Prophylaxis:** Pts randomized to LMWH (enoxaparin 40mg/d), Aspirin (100mg/d), or warfarin 1.25mg/d

Cavo et al. ASH 2009; abstract 351.

VTD vs. TD Induction → ASCT: Efficacy

Efficacy*		VTD (n = 241)	TD (n = 239)	*P* Value
Induction	ORR ≥ nCR ≥ VGPR	92% 26% 61%	79% 9% 28%	< .0001 < .0001 < .0001
Double ASCT	≥ nCR ≥ VGPR	52% 79%	41% 64%	.01 .0004
Consolidation	≥ nCR ≥ VGPR	59% 82%	43% 67%	.0009 .0005
PFS	30 month†	76%	58%	.009
OS	Median	Not reached		.6

* ≥ nCR and ≥ VGPR by central assessment
† n = 236 (VTD) and n = 238 (TD)

Cavo et al. ASH 2009; abstract 351.

VTD vs. TD Induction → ASCT: PFS in Poor-Prognosis Subgroups

Cox Regression Analysis

Variable	Hazard Ratio (95% CI)	*P* Value
del(13q)	0.554 (0.308-0.997)	.04
t(4;14) ± del(17p)	0.454 (0.210-0.979)	.04
LDH > 190 U/L	0.573 (0.353-0.930)	.02
Age > 60 Years	0.460 (0.231-0.915)	.02

Bortezomib improves outcome in high risk

Cavo et al. ASH 2009; abstract 351.

VTD vs. TD Induction → ASCT: Toxicity

Selected Grade 3/4 Adverse Events	VTD (n = 236)	TD (n = 238)	*P* Value
Induction			
Peripheral neuropathy	9.7%	2.1%	.0004
Skin rash	10%	1.7%	.0001
DVT	4.2%	5.5%	.5
Herpes zoster	0.4%	0	.3
Consolidation			
Peripheral neuropathy	1.3%	0	.1
Skin rash	0.6%	1%	.9
DVT	0.6%	0	.3
Herpes zoster	1%	1%	.9

Twice weekly Bortezomib has grade III neuropathy (painful neuropathy) ~10%

Cavo et al. ASH 2009; abstract 351.

Frontline MM:
Selected Early Trials

Phase I/II: Lenalidomide/ Bortezomib/Dexamethasone in ND MM

Induction q 3 weeks × 8

Lenalidomide 15-25 mg, d1-14
Bortezomib 1.0 / 1.3 mg/m^2
d1, 4, 8, 11
Dexamethasone 40/20 mg
d1-2, 4-5, 8-9, 11-12

Responders →

Maintenance q 3 weeks

Lenalidomide d1-14
Bortezomib d1, 8
Dexamethasone
10 mg d1-2, 8-9

→ ≥ PR at ≥ 4 cycles may proceed to ASCT

Phase II Dose: Bortezomib 1.3 mg/m^2; lenalidomide 25 mg; dex 20/10

Richardson et al. ASH 09, abstract 1218.

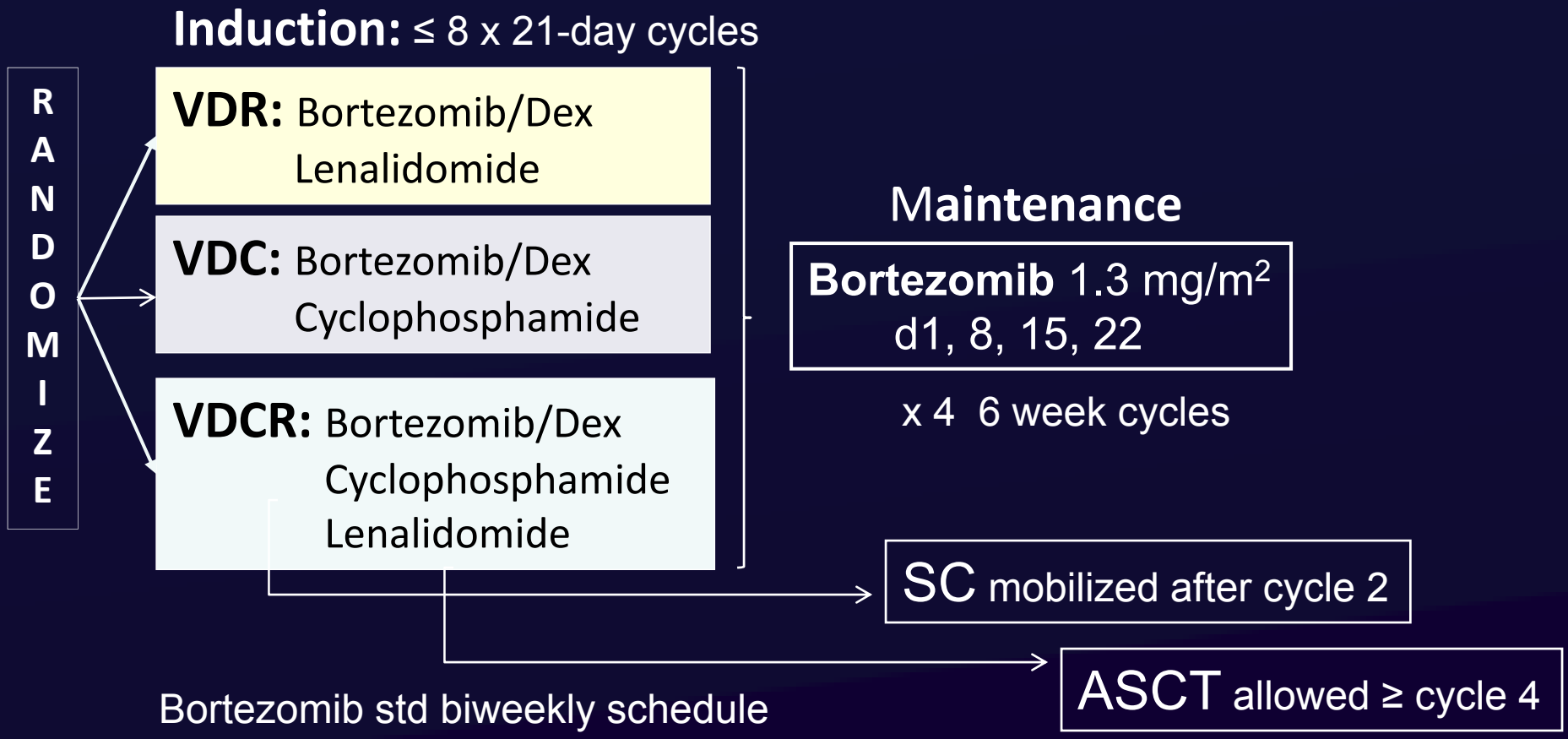
Phase I/II: Lenalidomide/ Bortezomib/Dexamethasone in ND MM

Efficacy (n=66)	Cycle 4	Cycle 8	Best
ORR ≥ nCR ≥ VGPR	74% 6% 11%	95% 23% 53%	100% 39% 67%
$CD34^+$ Stem cells x 10^6/kg (n = 28)	Median 5.6 (range, 2.3 – 20.1)		
Progression-free Survival Progression-free at 18 months ISS stage II/III vs. stage I	Median: Not reached 75% 65% vs. 89%		
Overall Survival	Median: Not reached		
Adverse Events			
Grade 3 sensory PN[a] Grade 3 neuropathic pain Grade 3 motor PN	1 (2%) 2 (3%) 1 (2%)		
Grade 3/4 neutropenia Grade 3/4 thrombocytopenia	9% 6%		

[a] No grade 4 PN

Richardson et al. ASH 09, abstract 1218.

Evolution: Phase II Randomized Trial of 3- and 4-Drug Combinations*



Bortezomib std biweekly schedule
Dex 120 mg/cycle
Cyclophosphamide 500 mg/m^2 d1, 8;
Lenalidomide 25 mg (VDR) or
15 mg (VDCR), d1-14

Kumar et al. ASH 2009, abstract 127.

Evolution: Phase II Randomized Trial of 3- and 4-Drug Combinations[a]

Median Duration of followup: 7.3 months

Efficacy	VDCR Btz/Dex/Cyc/Len n = 41	VDR Btz/Dex/Len n = 42	VDC Btz/Dex/Cyc n = 32	VDC mod[a] n = 15
ORR	93%	93%	91%	93%
CR / sCR	20% /2%	24% /10%	22% /3%	40% /0
≥ nCR	32%	38%	25%	40%
≥ VGPR	59%	55%	47%	60%
$CD34^+$ SC Mobilization	n = 13	n = 18	n = 13	n = 2
Median (range) x 10^6/kg	8.5 (0.3-11.7)	6.05 (0-26)	7.7 (3.1-17.6)	7.3 (4.5-10.1)
Toxicity				
1 or more ≥ grade 3 AE	75%[b]	76%	76%	73%
AE → discontinuation	17%	17%	12%	7
All Grade				
Neutropenia	<80%	<60%	<80%	<100%
Thrombocytopenia	<80%	<100%	<100%	<90%
PN, grade 3/4	<15%	<15%	<10%	≈20%

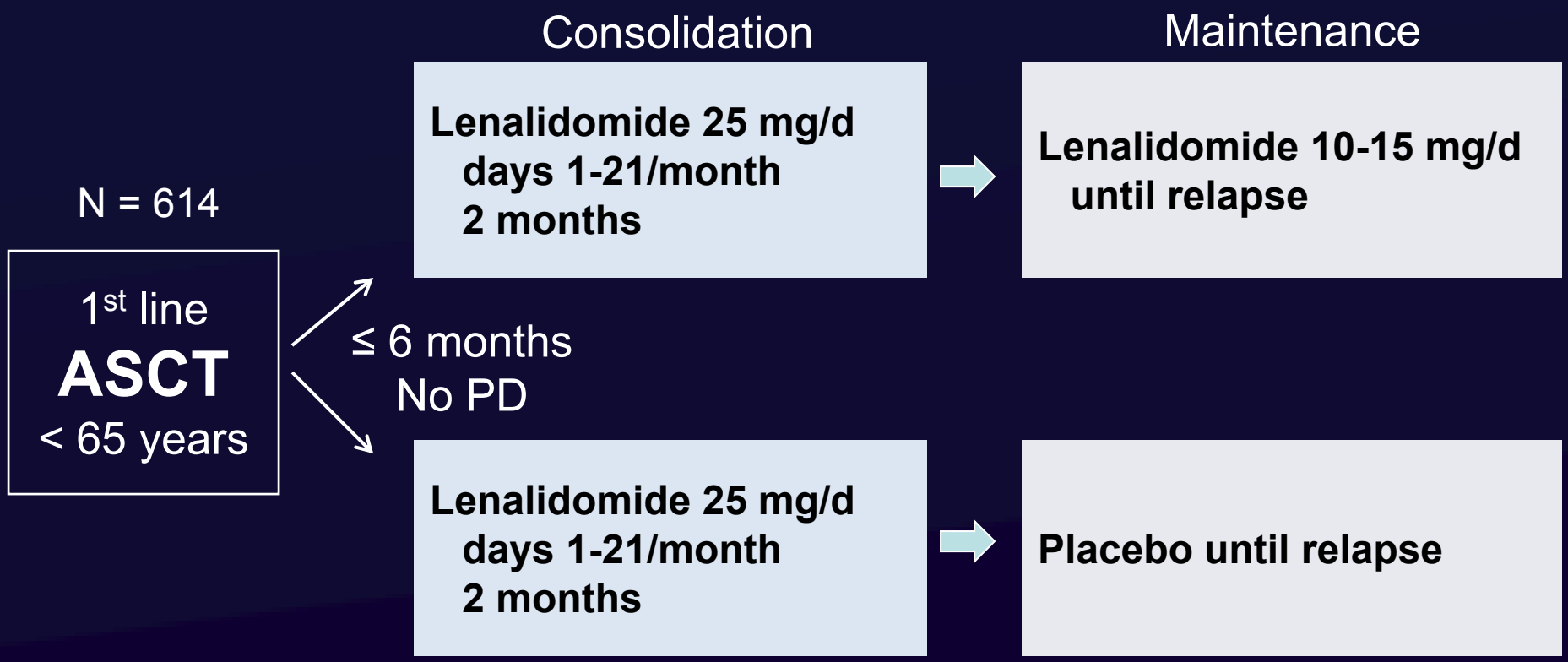
[a] VCD mod: VCD + cyclophosphamide d15

[b] 2 deaths on study: 1 treatment-related renal failure

Kumar et al. ASH 2009, abstract 127.

Maintenance / Consolidation
Transplant Eligible

Phase III IFM 2005-02: Lenalidomide as Consolidation/Maintenance Post-ASCT



Primary endpoint: Progression-free survival

Attal et al. ASH 09; abstract 529.

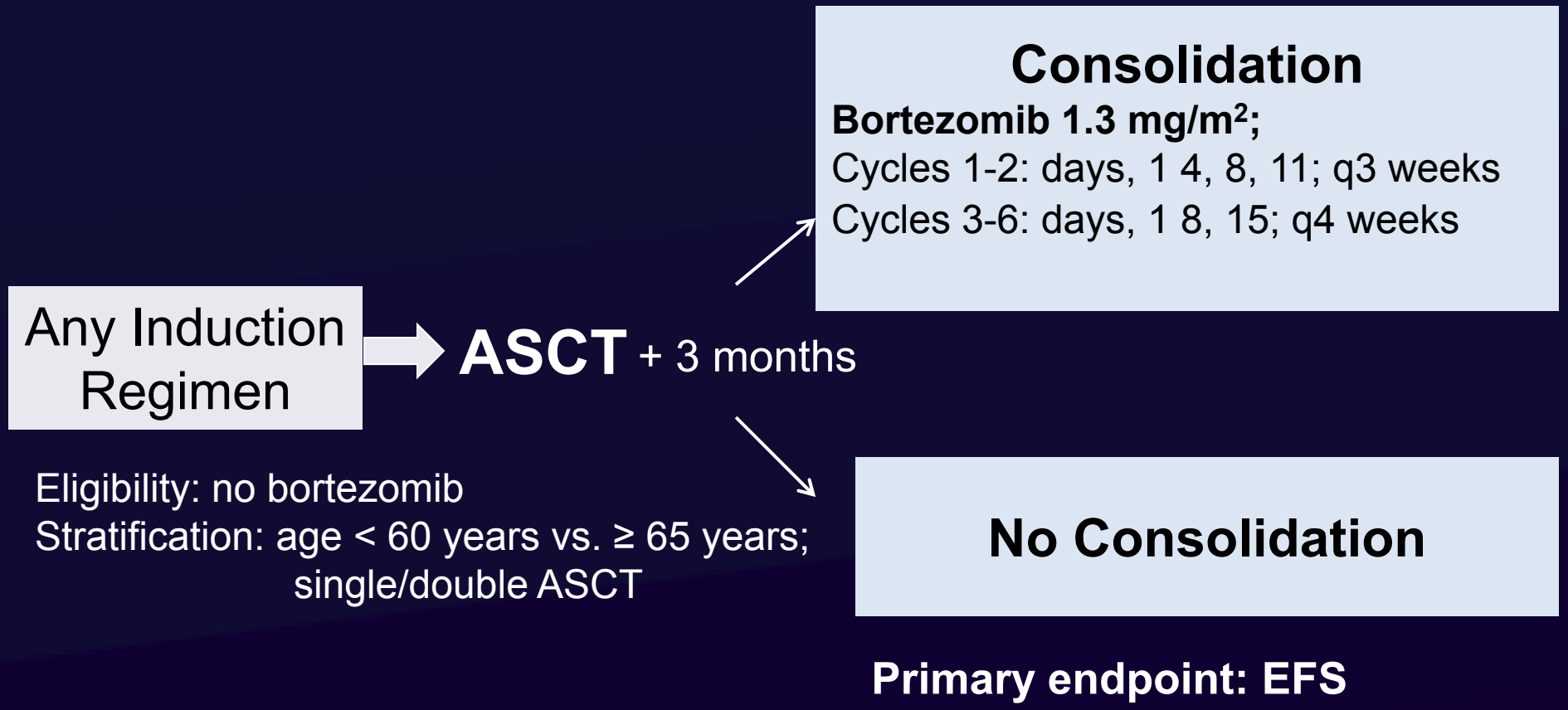
IFM 2005 02: Lenalidomide as Consolidation/Maintenance Post-ASCT—1st Analysis of Consolidation Phase

	Response by Independent Review Committee Assessment during Consolidation (n = 361)			
Response after consolidation	**CR IF- (n = 16 [4%])**	**nCR (n = 63 [18%])**	**VGPR (n = 129 [36%])**	**PR/SD (n = 153 [42%])**
Improvement: Complete Response, IF- Near Complete Response Very Good PR / PR	NA	14	12 34	4 12 31 / 1
No change Progressive Disease	16 0	48 1	82 1	102 3

	IRC Assessment Consolidation Response (n = 361)		
	Pre	**Post**	***P* Value**
Complete Response, IF- ≥ Very Good PR	4% 58%	13% 70%	<.0001 <.0001

Attal et al. ASH 09; abstract 529.

NMSG 15/05: Bortezomib Consolidation Post-ASCT



Primary endpoint: EFS

Mellqvist et al. ASH 09; abstract 530.

NMSG 15/05: Bortezomib Consolidation Post-ASCT

1st Analysis: 330 randomized patients at 3-9 months post ASCT

Median doses given to 168 patients, 19

Response	Bortezomib	Control	*P* Value
CR/nCR			
At 3 months	20%	19%	.9
At 9 months	49%	33%	.01
Progressive disease			
3 – 9 months	6%	12%	.08

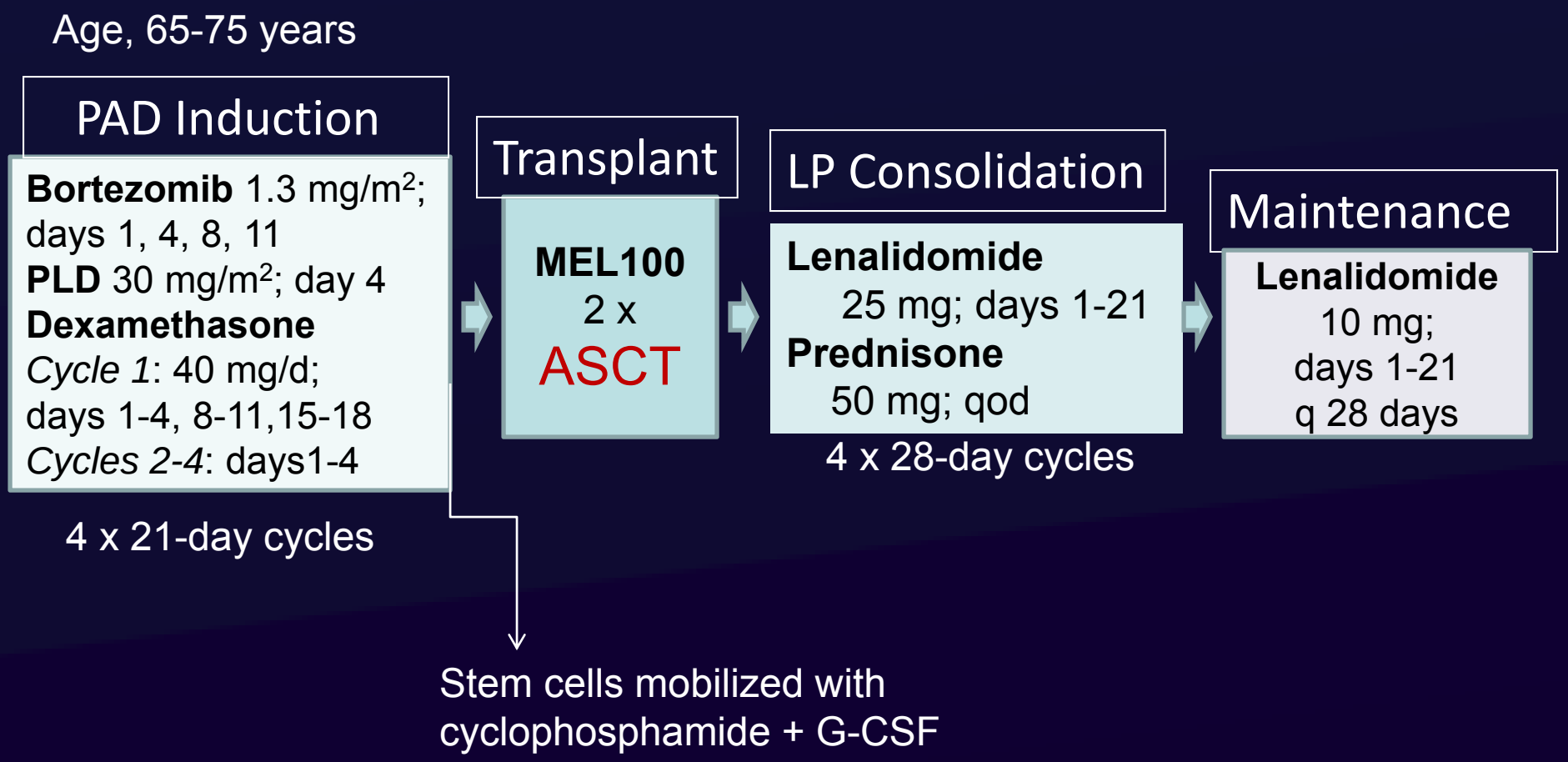
Toxicity:

Cyclical neutropenia and thrombocytopenia occurred in cycles 1, 2

Grade 3/4 neuropathic pain (5%) and PN (3%) in bortezomib arm

Mellqvist et al., ASH 09; abstract 530

Bortezomib/PLD/Dex (PAD) → RIC/ASCT → Lenalidomide Consolidation/Maintenance



Gay et al. ASH 2009; abstract 3419.

Bortezomib/PLD/Dex (PAD) → RIC/ASCT → Lenalidomide Consolidation/Maintenance

Response	PAD (n = 94)	PAD-MEL 100 (n = 83)	MEL 100 – LP – L (n = 50)
CR	13%	38%	66%
VGPR	46%	43%	20%
PR	34%	13%	10%

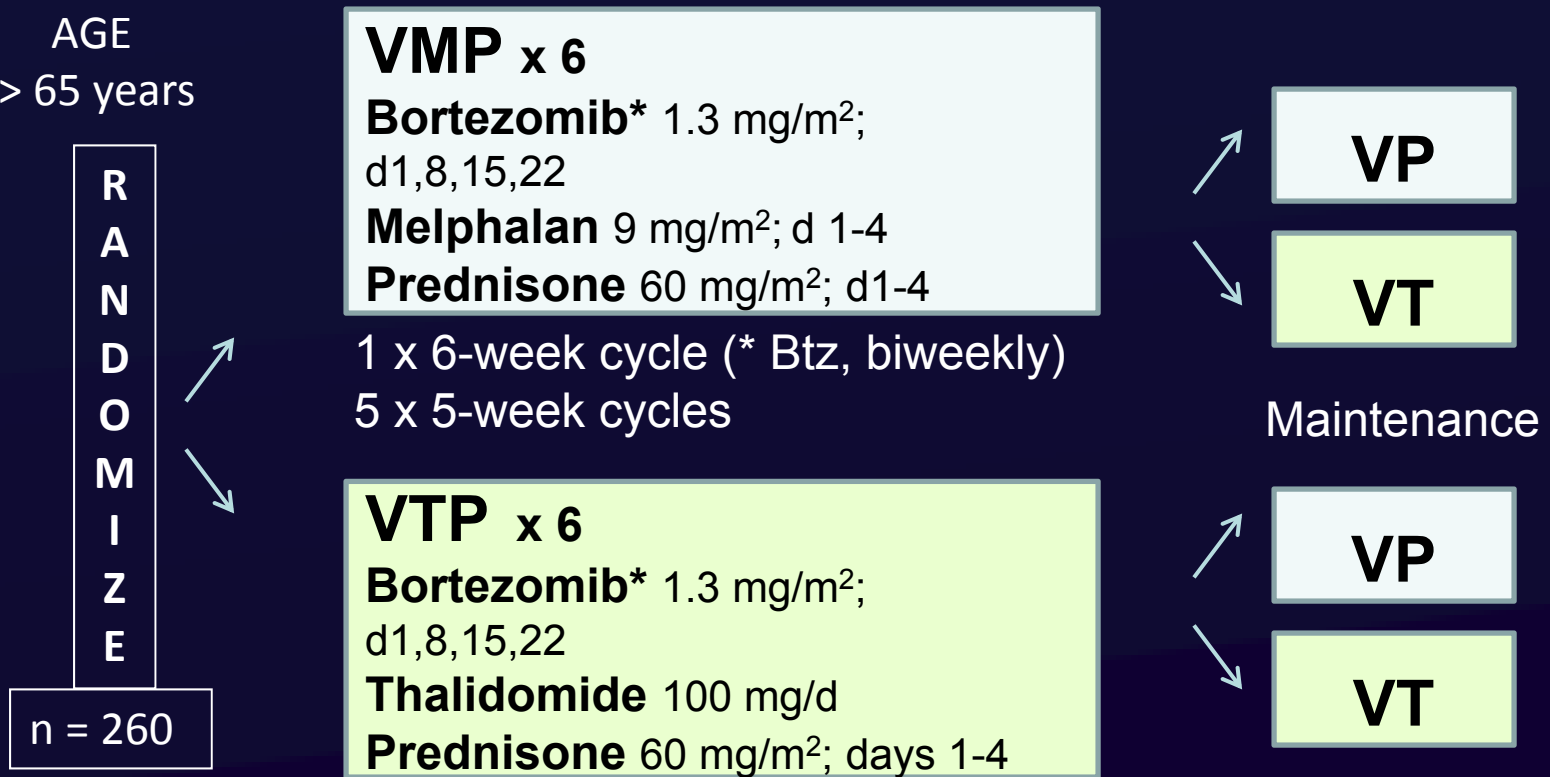
Survival	MEL 100 – LP – L	
Median follow-up 2 years	12 Month	24 Month
Progression-free survival	88%	69%
Time-to-progression	93%	75%
Overall survival	91%	86%

Is consolidation important? maintenance is enough?

Gay et al. ASH 2009; abstract 3419.

Maintenance for Transplant Ineligible

Bortezomib/Melphalan/Prednisone (VMP) vs. Bortezomib/Thalidomide/Prednisone (VTP) in Elderly ND MM



Mateos et al. ASH 2009; abstract 3.

VMP vs. VTP in Elderly ND MM: Efficacy

Response to Induction	VMP (n = 130)	VTP (n = 130)
ORR CR IF⁻/CR IF⁺	80% 20%/12%	81% 27%/10%
Median Time: First response Median Time: CR	1.6 months 4.4 months	1.6 months 4.9 months
Response to Maintenance	**VT (n = 91)**	**VP (n = 87)**
ORR CR IF⁻/CR IF⁺	98% 44%/15%	99% 39%/16%

Survival, median follow-up 24 months	Intent-to-Treat
Time to Progression Progression-free Survival Overall Survival	3-year rate: 53% Median: 33 months 3-year rate: 75%

Mateos et al. ASH 2009; abstract 3.

VMP vs. VTP in Elderly ND MM: Efficacy

Regimen	Median PFS	2-Year OS rate
VMP vs. VTP Survival from 1st rx	34 months vs. 23 months HR = 1.3; *P* = .1	3 year: 80% vs. 64% HR = 1.4; *P* = .1
VT vs. VP Survival from 2nd rx	Not reached vs. 23 months HR = 1.7; *P* = .05	86% vs. 81% HR = 1.1; *P* = .7
VMP→ VT vs. VP	Not reached vs. 32 months HR = 1.7; *P* = .1	88% vs. 88%
VTP→ VT vs. VP	Not reached vs. 26.5 months HR = 1.7; *P* = .1	84% vs. 81%
VTP→ VP vs. VMP→VT	HR = 1.6; *P* = .008	Not reported

Thalidomide is equivalent to melphalan
Maintenance further improves outcome
Maintenance with VT appears better

Mateos et al. ASH 2009; abstract 3.

VMP vs. VTP in Elderly: Toxicity

Grade 3/4 Toxicity	VMP (n = 130)	VTP (n = 130)	VP* (n = 87)	VT* (n = 91)
Anemia	11%	8%	2%[a]	2%[a]
Neutropenia	39%[b]	22%	1%[a]	3%[a]
Thrombocytopenia	27%[b]	12%	1%[a]	1%[a]
Gastrointestinal	7%	2%	1%	4%
Peripheral neuropathy	5%	9%	2%	5%
Infections	7%[b]	<1%	1%	2%
DVT/thromboembolism	<1%	2%	0	1%
Cardiac toxicity	0	8%[b]	1%	2%
Discontinuations due to AEs	11%	17%	5%	7%
Deaths	7	7	1	1

[a] Only grade 1/2 hematologic AEs during maintenance

[b] Significantly different AEs

Deaths: VMP, 5/7 due to infection; VTP, 5/7 due to cardiac complications

Mateos et al. ASH 2009; abstract 3.

Relapsed/Refractory MM: Early Trials

MM-002: Phase I/II of Pomalidomide ± Low-Dose Dex in Relapsed/Refractory MM

Pomalidomide dose escalated from 2 to 5 mg in 4 patient cohorts

Efficacy	**Pomalidomide 2-5 mg (n = 32[a])**
Best ORR	7 (28%)
Complete response	1
Partial response	6
Clinical benefit rate (≥ MR)	13 (52%)
Patients given additional dexamethasone	**(n = 15)**
Patients attaining improved response	8 (53%)
Selected Pomalidomide-Related AEs (All Grades)	
Neutropenia	31%
Anemia	19%
Thrombocytopenia	13%
Venous thromboembolism	1, grade 2; 1, grade 3
Peripheral neuropathy	1, grade 3

[a] 25 response-evaluable patients

Maximum tolerated dose: 4 mg/day, days 1-21, q 28 days
Dose-limiting toxicity: 4 grade 4 events of neutropenia (at 5-mg dose)

Richardson et al. ASH 2009; abstract 301.

Phase II: Pomalidomide/Low-Dose Dex in Lenalidomide-Resistant/Refractory MM

Pomalidomide: 2 mg/day p.o., days 1-28, 4 mg/day after cycle 2 if no response or PD
Dexamethasone: 40 mg p.o., days 1, 8, 15, 22
Aspirin: 325 mg p.o., days 1-28

	Number of Patients (%) (n = 34)
Efficacy	
ORR	11 (32%)
Partial response (PR)	10 (29%)
Clinical benefit rate (≥ MR)	17 (50%)
≥ PR: high-risk patients (n = 14)	4 (29%)
≥ PR: standard-risk patients (n = 20)	7 (35%)
Progression (median follow-up 6 months)	18 (53%)
Selected Grade 3/4 Adverse Events	
Neutropenia	9 (26%)
Anemia	4 (12%)
Thrombocytopenia	3 (9%)
Deep vein thrombosis/PE	0 (any grade)
Peripheral neuropathy	All grade 1/2, 8 (23%)

Lacy et al. ASH 2009; abstract 429.

PX-171-004: Phase II Trial of Single-Agent Carfilzomib in Relapsed/Refractory MM

Carfilzomib 20 mg/m^2 I.V., days 1 and 2 × 3 weeks q 28 days × ≤ 12 cycles

Efficacy	Bortezomib-Naive Pts (n = 54[a])	Bortezomib-Treated Pts (n = 33[a])
ORR	46%	18%
Complete response	1 (2%)	1 (3%)
Very good partial response	5 (9%)	1 (3%)
Partial response	19 (35%)	4 (12%)
Disease control rate (≥ SD)	45 (83%)	23 (70%)
Duration of response (≥ PR), median	8.4 months	10.6 months
Time to progression, median[b]	7.6 months	5.3 months
Grade ≥ 3 Adverse Events		
Thrombocytopenia	7 (12%)	2 (6%)
Neutropenia	5 (9%)	4 (11%)
Pneumonia	6 (10%)	2 (6%)
Treatment-emergent PN all grade	14%	12%
Grade 3 (no ≥ grade 4)	1 (2%)	1 (3%)

[a] Evaluable patients

[b] Median follow-up: 9.2 months, bortezomib naive; 11.5 months, bortezomib treated

Wang et al. ASH 2009, abstract 302; Siegel et al. ASH 2009, abstract 303.

Phase I: Vorinostat Plus Bortezomib in Relapsed/Refractory MM

MTD: not reached

Recommended: bortezomib 1.3 mg/m^2, days 1, 4, 8, 11 plus vorinostat 400 mg/day, days 1-14, q 21 days

Efficacy	All Patients (n = 33)	Bortezomib Refractory (n = 7)	Therapy for ≥ 12 Weeks (n = 9)
ORR (all PRs) Minor response	10 (30%) 7 (21%)	2 (29%) 2 (29%)	5 (56%) 2(22%)
Median duration of PR	22 weeks	14.3 weeks	Range, 169-694 days
Selected Grade 3/4 AEs	**(n = 34)**		
Thrombocytopenia Neutropenia Peripheral neuropathy	15 (5 grade 4) 3 (2 grade 4) 3 (all grade 3)		

Vantage 095: Open-label phase IIb trial with target enrollment of 142

Eligibility: ≥ 2 prior therapies; refractory to bortezomib; relapsed, refractory, intolerant, or ineligible to other therapies including immunomodulators

DMC: 38 patients evaluated—trial sufficient to continue unchanged

Jagannath et al, ASH 2009, abstract 3886; Siegel et al., ASH 2009, abstract 3890.

Phase I/II: Perifosine/Bortezomib/ Dexamethasone in Relapsed/Refractory MM

Phase I: define MTD (n = 18)
Phase II: response rate (n = 66)

Phase II: Perifosine: 50 mg/day
Bortezomib: 1.3 mg/m^2, days 1, 4, 8, 11
Dexamethasone: 20 mg/day, 4 days/week

Efficacy	All Response Evaluable (n = 73)	Bortezomib Relapsed (n = 20)	Bortezomib Refractory (n = 53)
Complete response (CR)/near CR	3 (4%)	2 (10%)	1 (2%)
Partial response (PR)	13 (18%)	7 (35%)	6 (11%)
≥ Minor response	30 (41%)	13 (65%)	17 (32%)
Median progression-free survival	6.4 months	8.8 months	5.7 months
Median overall survival	25 months	Not reached	22.5 months
Selected Grade 3/4 AEs ≥ 10%	**(n = 84)**		
Thrombocytopenia	23%		
Neutropenia	15%		
Pneumonia	12%		
Peripheral neuropathy	2% (grade 3 only)		

Phase III: Perifosine/bortezomib/dexamethasone vs. bortezomib/dexamethasone pending commencement

Richardson et al. ASH 2009; abstract 1869.

Phase I/II: Elotuzumab/Lenalidomide/Dex in Relapsed/Refractory MM

Elotuzumab: 5, 10, or 20 mg/kg, days 1, 8, 15, 22 (cycles 1, 2); days 1,15 (cycles ≥ 3)
Lenalidomide: 25 mg/day, days 1-21
Dexamethasone: 40 mg/week p.o.
q 28-days
MTD not reached

Efficacy	**All Treated Patients[a] (n = 28)**	**Refractory to Most Recent Treatment (n = 12)**
ORR Very good PR Partial response (PR)	23 (82%) 5 (18%) 18 (64%)	10 (83%) 3 (25%) 7 (58%)
Time to progression (median follow-up 4.5 months	Median TTP not reached 4/28 progressed	
Selected Grade 3/4 AEs (≥ 10%)	**(n = 28)**	
Neutropenia Thrombocytopenia Anaphylactic reaction	≈ 20% ≈15% 2 patients	

[a] Median lines of prior MM therapy 3 (range, 1-10)

Phase II expansion under way with elotuzumab 10 and 20 mg

Lonial et al. ASH 2009; abstract 432.

Practice Points from ASH 2009

- ISS staging is relevant in the era of novel agents
  - Obtain β2-microglobulin at start of treatment
- Do we need to consider treatment of high-risk smoldering myeloma
  - More studies forthcoming (SWOG/ECOG) with lenalidomide
- For frontline therapy triplets are recommended
  - Bortezomib, lenalidomide, dexamethasone
- Maintenance therapy further improves response rate, PFS and OS
- Consider clinical trials for relapsed/refractory myeloma
  - Multiple active drugs in clinical trial:
  - Pomalidomide, carfilzomib, elotuzumab, vorinostat, perifosine