

2009 Oncology Highlights from ASCO: Multiple Myeloma

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Integration of Novel Therapies Into Myeloma Management

**Bortezomib, Lenalidomide, Thalidomide,
Pegylated Liposomal Doxorubicin**

**Target MM in the BM microenvironment to
overcome conventional drug resistance in vitro
and in vivo**

Effective in Relapsed/Refractory MM

Effective as Induction/First-line Therapy

Transplant/Maintenance

Integration of Novel Therapy Into Myeloma Management

Six FDA/EMEA Drug Approvals
in Last Five Years

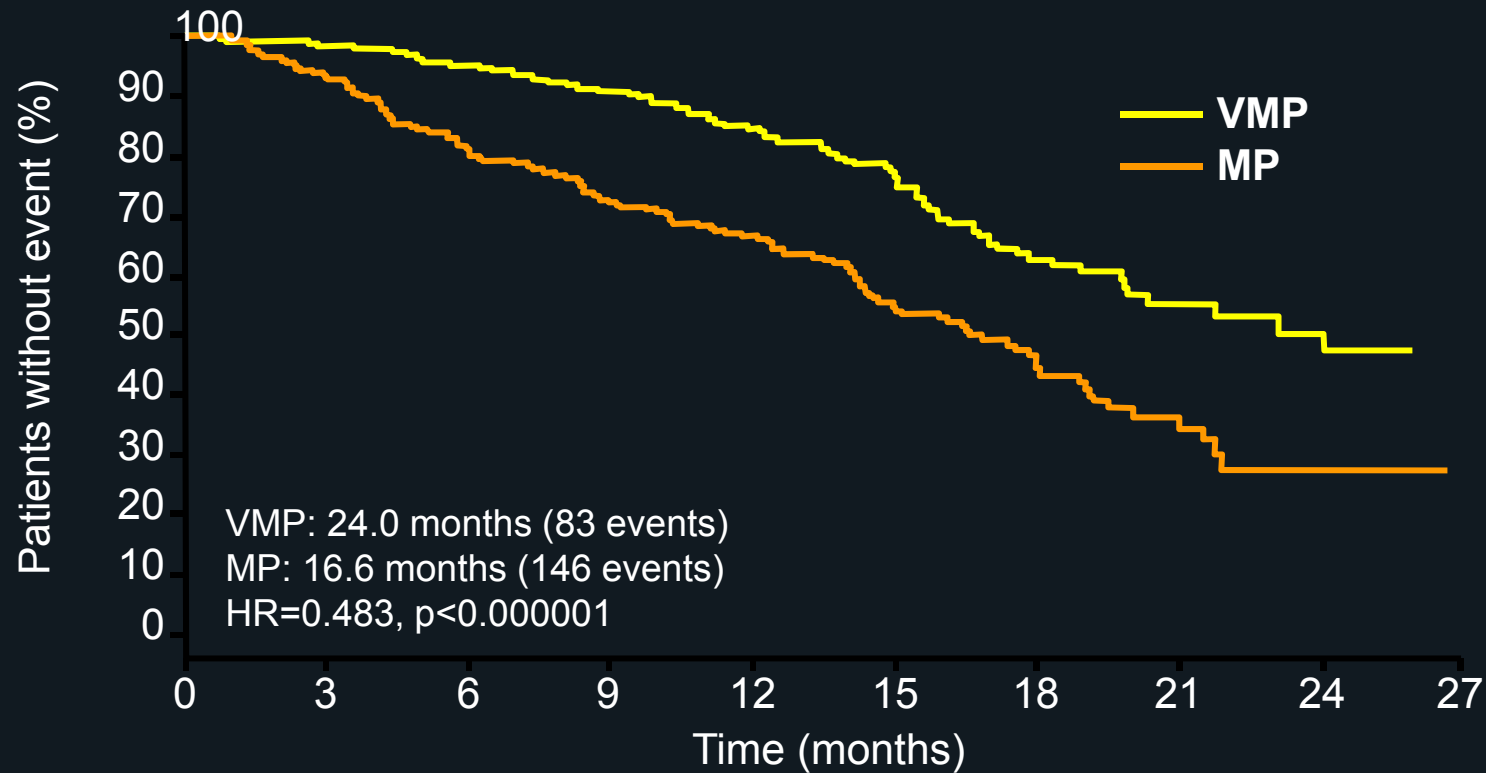
Median survival prolonged from 3-7 years (especially
in younger patients)

Three phase III trials of novel agents
ongoing for FDA approval

VMP versus MP (Vista Trial)

	VMP	MP	p-value
Overall response rate (ORR), %	71	35	<10 ⁻³
Complete response (CR)*	30	4	<10 ⁻³
Median time to first response*, months	1.4	4.2	<10 ⁻³
Median duration of response (DOR), months			
All responders	19.9	13.1	
Patients achieving CR	24.0	12.8	

Time to Progression (Vista Trial)



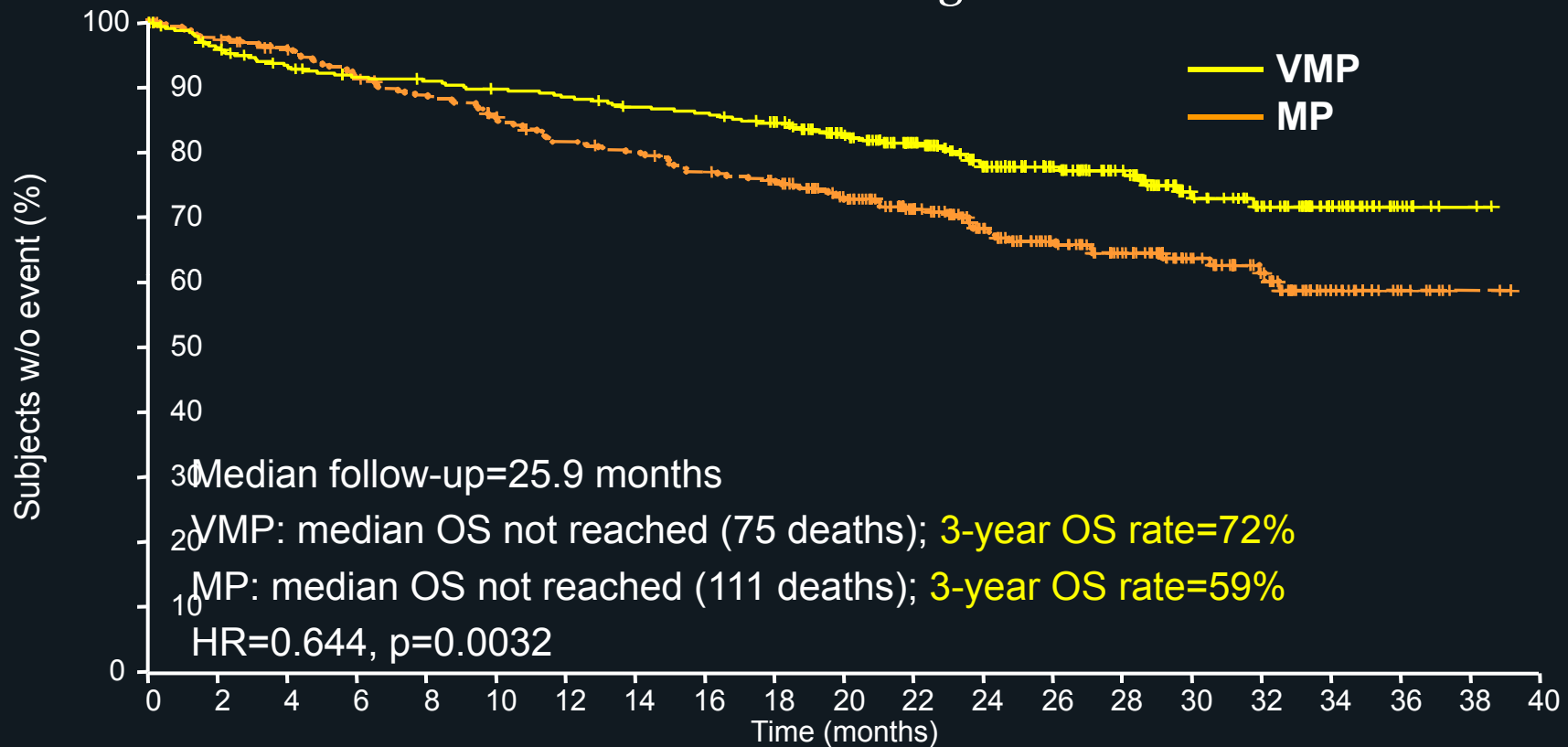
Number of patients at risk:

VMP:	344	295	272	245	185	111	65	31	17
MP:	338	296	241	206	152	86	53	22	5

San Miguel et al, ASH 2008 Abstr 650

Overall Survival (Vista Trial)

San Miguel et al, ASH 2008 Abstr 650



- ▶ 43% of MP patients who received subsequent therapy received bortezomib upon progression
- ▶ Patients received bortezomib >4 cycles: OS at 1 & 2 years: 98.5% & 89%

GIMEMA: Italian Myeloma Network

**A Phase III Study of VMPT versus VMP
in newly diagnosed elderly
myeloma patients**

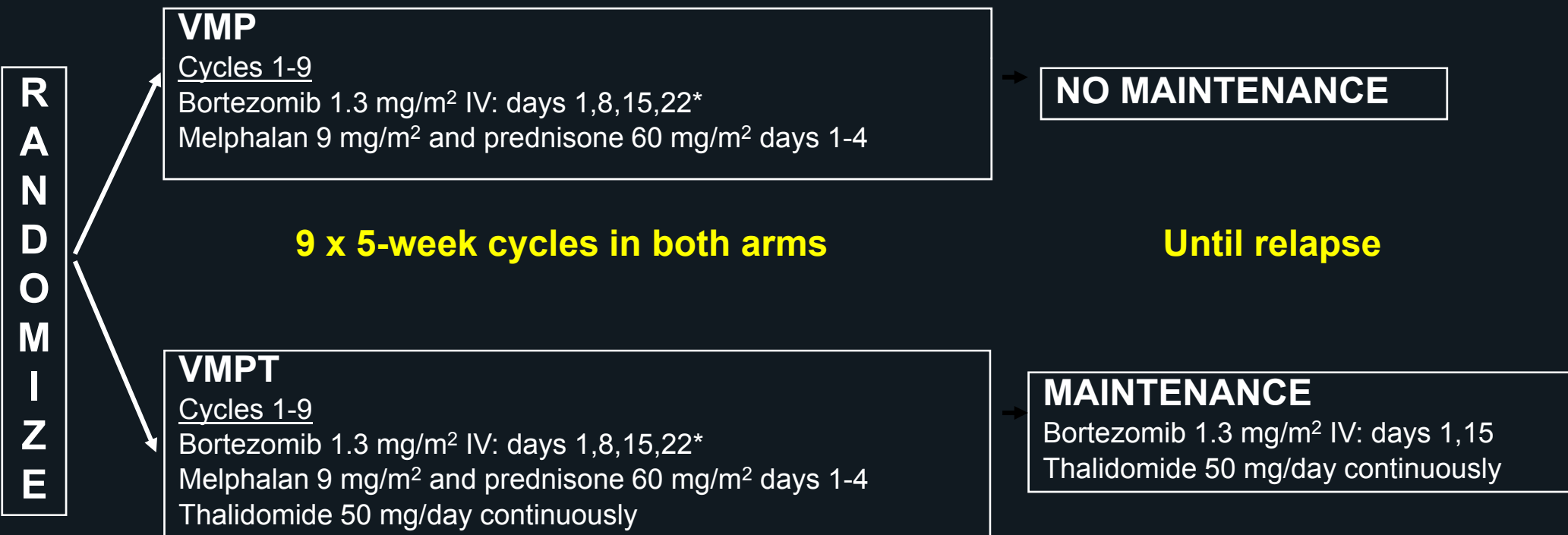
Antonio Palumbo¹, Sara Brinchen¹, Davide Rossi², Salvatore Berretta³, Vittorio Montefusco⁴, Jacopo Peccatori⁵, Monica Galli⁶, Angelo Carella⁷, Paola Omedè¹, Mario Boccadoro¹

¹Divisione di Ematologia dell'Università di Torino, A.O.U. San Giovanni Battista, Torino, Italy; ²Università del Piemonte Orientale Amedeo Avogadro, Novara, Italy; ³Ospedale Ferrarotto, Università di Catania, Catania, Italy; ⁴Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy; ⁵Istituto Scientifico San Raffaele, Milano, Italy; ⁶Ospedali Riuniti, Bergamo, Italy; ⁷A.O.U. San Martino, Genova, Italy.

ASCO Abstract 8515

A Phase III Study of VMPT versus VMP in newly diagnosed elderly myeloma patients

- 511 patients (older than 65 years) randomized from 58 Italian centers
- Patients: Symptomatic multiple myeloma/end organ damage with measurable disease
 - ≥ 65 yrs or < 65 yrs and not transplant-eligible; creatinine ≤ 2.5 mg/dL



Palumbo et al, ASCO 2009

Summary and Conclusions

	VMPT (N=177)	VMP (N=177)	P value
CR	35%	21%	0.06
≥ VGPR	51%	42%	< 0.0001
TTNT @ 3 years	80%	78%	0.30
PFS @ 3 years	71%	56%	0.13
OS @ 3 years	90%	89%	0.81

(Palumbo et al, ASCO 2009)

Efficacy and Toxicity

	VMPT		VMP	
	twice weekly (N=71)	weekly (N=150)	twice weekly (N=64)	weekly (N=165)
CR	38%	32%	27%	20%
Grade 3-4 Peripheral neuropathy	18%	2%	14%	2%
Dose reduction*	42%	11%	35%	13%
Discontinuation*	10%	3%	15%	4%

VMPT improves response rates; weekly infusion decreases bortezomib peripheral neuropathy

Definition of Optimal Multiagent Combination Therapies

Lenalidomide induces caspase 8 mediated apoptosis of MM cells in BM in vitro and in vivo; Dex (caspase 9) enhances response

Synergistic MM cell toxicity of lenalidomide with Bortezomib in vitro and in vivo (dual apoptotic signaling)

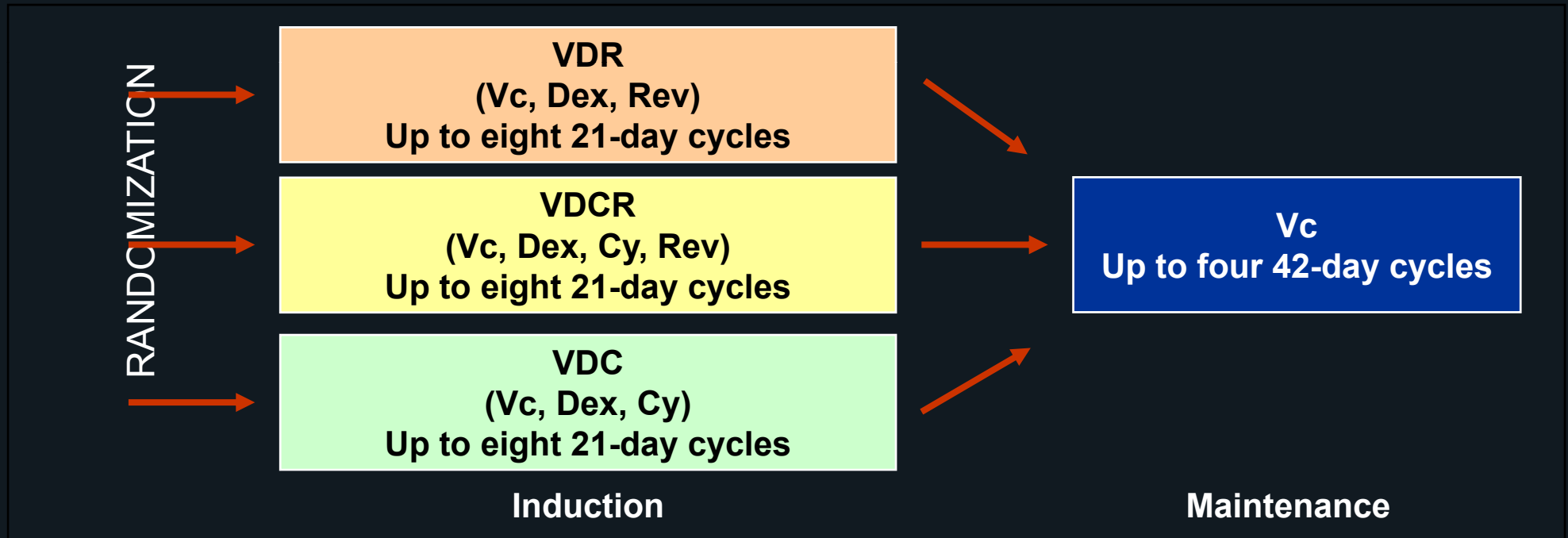
Phase II trial in patients refractory to either agent alone respond to the combination: \geq MR 84%, \geq PR 68%, 21% CR/nCR

Phase I-II trials show 100% response with 71% CR/VGPR when used as initial therapy.

Richardson et al, ASCO 2009, ASH 2008

Defining Multiagent Combination Therapies

Phase II: Evolution Study



- Eligible patients could undergo ASCT after 4 cycles

Kumar et al ASH 2008 Abstr 93



Phase I/II Trial of Lenalidomide, Bortezomib, Doxil® and Dexamethasone (RVDD) in Frontline Multiple Myeloma

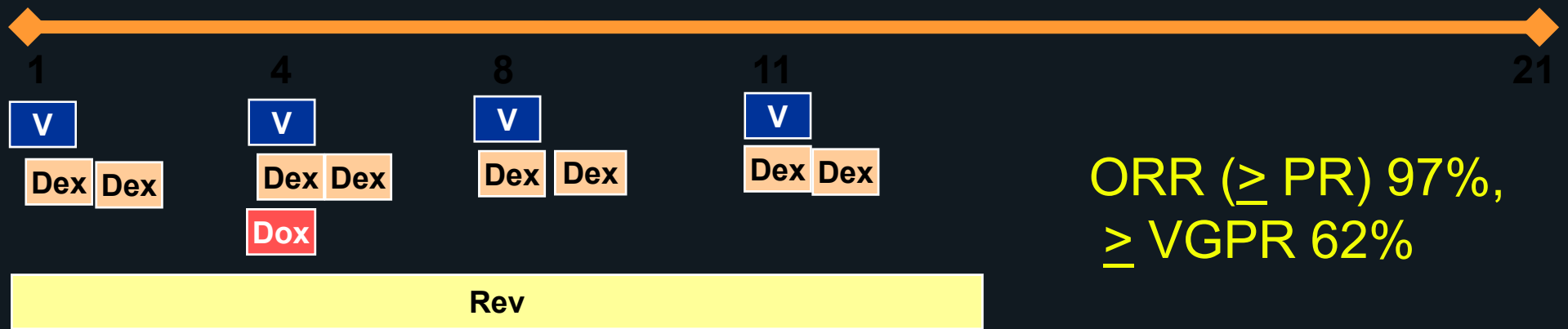
Andrzej J. Jakubowiak¹, Craig Hofmeister², Erica Campagnaro¹, Todd Zimmerman³, Robert Schlossman⁴, Sagar Lonial⁵, Donna Reece⁶, Mark Kaminski¹, Kenneth Anderson⁴, and Paul Richardson⁴

¹University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, ²Ohio State University, Columbus, OH, ³University of Chicago Medical Center, ⁴Dana-Farber Cancer Institute, Boston, MA, ⁵Winship Cancer Institute, Atlanta, GA, Chicago, IL, ⁶Princess Margaret Hospital, Toronto, ON

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Phase I/II Trial of Lenalidomide, Bortezomib, Doxil® and Dexamethasone (RVDD) in Frontline Multiple Myeloma (Multiple Myeloma Research Consortium)



Maintenance: 21-day cycles up to progression or toxicity



Treatment to Date – Phase I

- Phase I enrollment is complete (N=40)*

Dose level	Treated**	Patients undergoing ASCT
1	4	3
2	10	7
3	19	7
4	7	1
Total	40	18

*Two patients were not evaluable for MTD per protocol and were replaced

**Median treatment duration: 4.5 cycles (range 1–16)

Summary and Conclusions

- **RVDD is active and is well-tolerated in newly diagnosed MM**
 - **ORR (\geq PR) 97%, \geq VGPR 62%**
- **MTD not reached, recommended Phase II Dose: 25mg/d lenalidomide d1-14, 1.3mg/m² velcade d1,4,8, and 11; dex 20mg day of and after velcade; 30mg/m² doxil d4**
- **Toxicities are manageable – 1 G3 peripheral sensory neuropathy (2.5%), no painful neuropathy and 2 DVT/PE (5.0%). No significant decrease in ANC or platelets from baseline values across patients.**
- **Stem cell mobilization has been successful in all pts, with transplant course unremarkable to date**

Phase II study of pegylated liposomal doxorubicin (PLD), low dose dexamethasone (DEX) and lenalidomide (LEN) in patients with newly diagnosed (ND) multiple myeloma (MM).

Rachid Baz, Mohamad A. Hussein, Dan Sullivan, Jyoti Raychaudhuri, Jose L. Ochoa, Lisa Nardelli, Kara Kosakowski, William Dalton and Melissa Alsina

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Phase II study of pegylated liposomal doxorubicin (PLD), low dose dexamethasone (DEX) and lenalidomide (LEN) in patients with newly diagnosed (ND) multiple myeloma (MM).

ND MM

INDUCTION

PLD 40 mg/m² IV D1

Len 25 mg PO D1-21

Dex 40 mg PO D1-4

MAINTENANCE:

Len 25 mg PO D1-21

Dex 40 mg PO Weekly

Off study HDT

Aspirin 81 mg daily (LMWH or Warfarin if allergy / intolerant to ASA)

Fluoroquinolone and acyclovir prophylaxis recommended

G-CSF allowed at the discretion of the treating physician

Baz et al, ASCO 2009

Summary and Conclusions

- The combination of Lenalidomide, PLD and dexamethasone is an active combination with a ORR of 71% and VGPR rate of 50% after 4 cycles of therapy.
- A high rate of severe fatigue (34%) and grade $\frac{3}{4}$ neutropenia (62%) was noted.
- The protocol was amended to reduce the dose of PLD to 30 mg/m² IV D1 in combination with standard dose of lenalidomide (25 mg D1-21) and low dose dexamethasone (40 mg D1-4).

Impact of PLD in combination with LEN?

	DdR	Rd
ORR after 4 cycles, %	71%	70%
VGPR and better after 4 cycles, %	50%	25%
Gr \geq 3/4 Neutropenia, %	62%	18%
Gr \geq 3/4 Fatigue, %	34%	14%
Gr \geq 3/4 All Infection, %	31%	14%

- Too early to draw definitive conclusions regarding the role of anthracyclines in combination with lenalidomide and dexamethasone in newly diagnosed multiple myeloma.

Baz et al, ASCO 2009; Rajkumar et al, ASH 2009

Results of Primary Therapy beyond 4 cycles with Rd

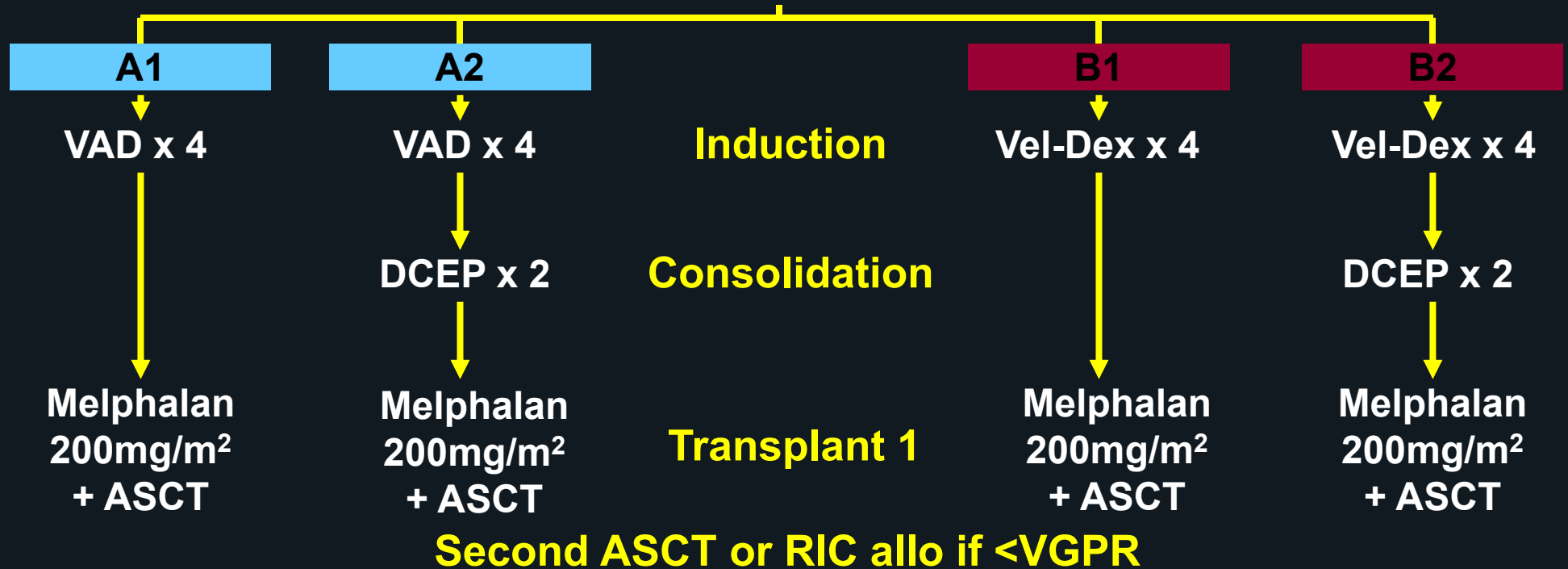
	"Primary Rd" (n=140)
	%
Overall Response Rate	91%
CR* (IF-)	22%
CR + VGPR	57%
Grade \geq 3 non-heme toxicity**	26%

*measured in serum or urine

** 52% with RD

Rajkumar et al, ASH 2008

VD versus VAD Induction Pre Transplant (IFM)



Response to First ASCT

Harousseau et al,
ASH 2008

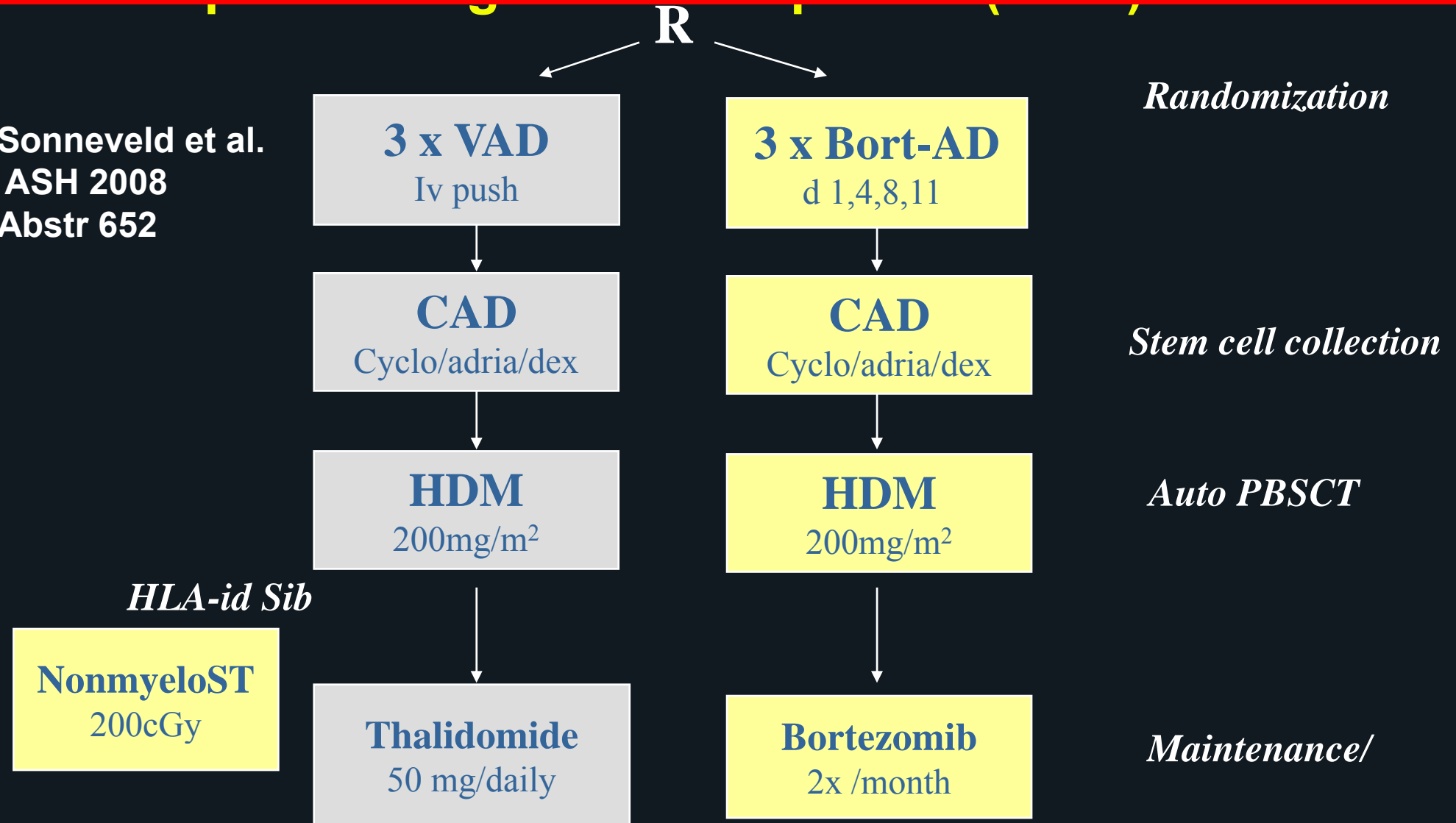
**VAD
(A1+A2)
N=213**

**Vel-Dex
(B1+B2)
N=212**

P value

CR	9%	17%	0.016
CR + nCR	19%	37%	<0.0001
≥ VGPR	38%	57%	0.0003
≥ PR	79%	84%	NS
MR/SD/PD	4%	3%	
No ASCT	17%	13%	

HOVON-65/GMMG-HD4: Bortezomib, Adriamycin, Dexamethasone (PAD) vs VAD prior to High Dose Melphalan (HDM) in MM.



Pre & Post-ASCT Response with VAD vs Bortezomib-AD (PAD) induction

	VAD N=150	PAD N=150	P value
CR/nCR %	1	5	
≥ VGPR	15	42	< 0.000001
≥ PR	59	83	0.000014
	HDM-SCT	HDM-SCT	
CR/nCR %	9	23	0.0015
≥ VGPR	50	80	0.0019
≥ PR	80	93	0.0021

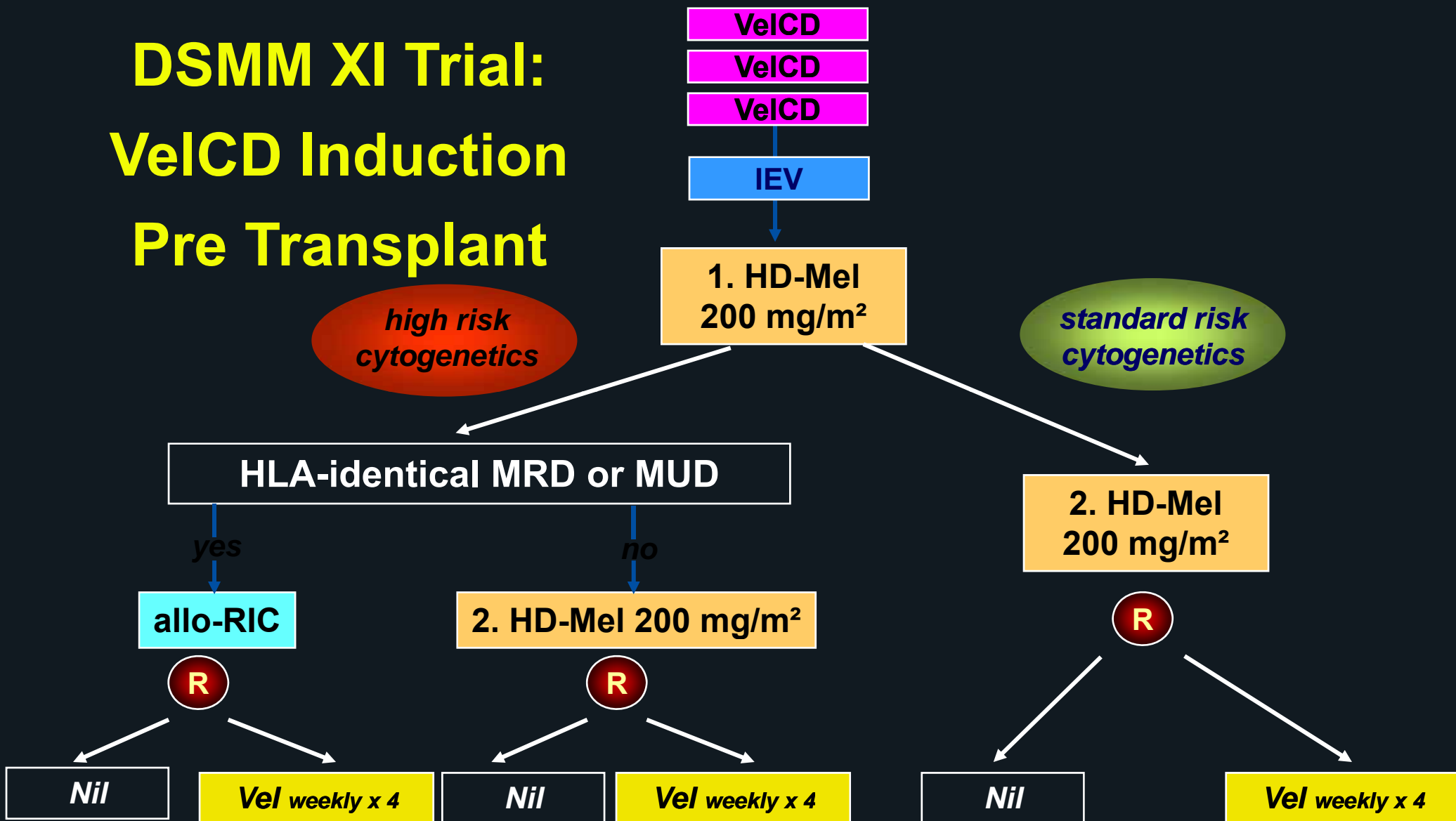
**Bortezomib, IV cyclophosphamide, and
dexamethasone (VelCD) as induction
therapy in newly diagnosed multiple
myeloma: Results of an interim analysis of
the German DSMM XIa trial**

**S Knop, P Liebisch, H Wandt, M Kropff, W
Jung, N Kroeger, O Sezer, C Straka, G
Fingerle Rowson, H Einsele**

on behalf of DSMM

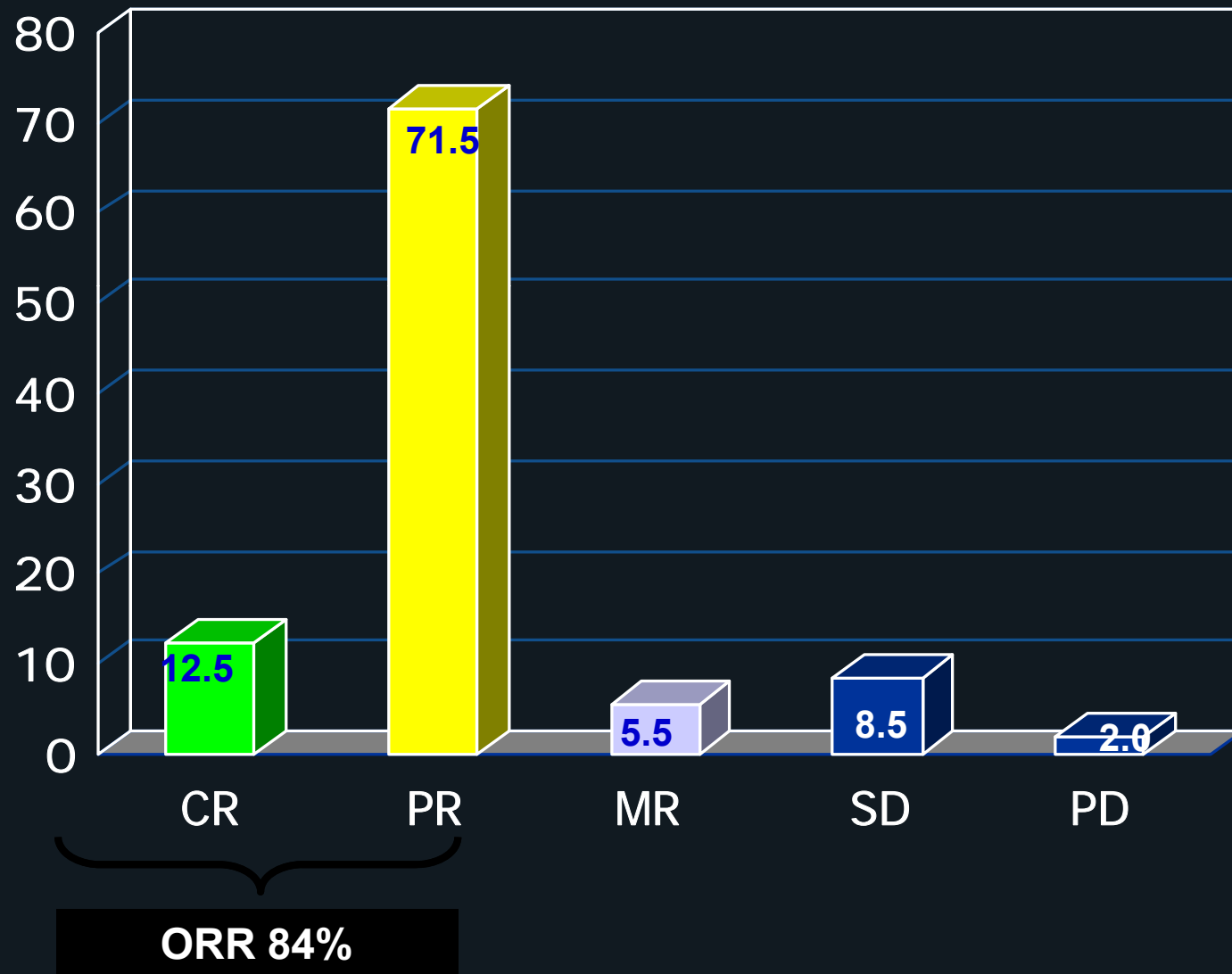
ASCO Abstract 8516

DSMM XI Trial: VelCD Induction Pre Transplant



Knop et al, ASCO 2009

Response to treatment on study day 63 (Interim analysis; n = 200)



Conclusions and Future Directions

- **3 cycles of VelCD induction in MM before HD-MEL**
 - is among the most active regimens
 - may overcome traditional poor-risk cytogenetics except
17p-
 - is safe
 - low mortality of 1%
 - low risk of hospitalization due to infection
 - low incidence of severe, acceptable rates of mild/moderate polyneuropathy
 - very low risk of thromboembolism
 - is feasible in an outpatient setting

Defining the Role of Stem Cell Transplantation

IFM/DFCI 2009 Study

Newly Diagnosed MM Pts (SCT candidates)

Randomize

Induction

Collection

Consolidation

Maintenance

RVDx3

CY (3g/m²)
MOBILIZATION
Goal: 5 x10⁶ cells/kg

Melphalan
200mg/m²* +
ASCT

RVD x 2

Revlimid 18 mos

RVDx3

CY (3g/m²)
MOBILIZATION
Goal: 5 x10⁶ cells/kg

RVD x 5

Revlimid 18 mos

SCT at relapse

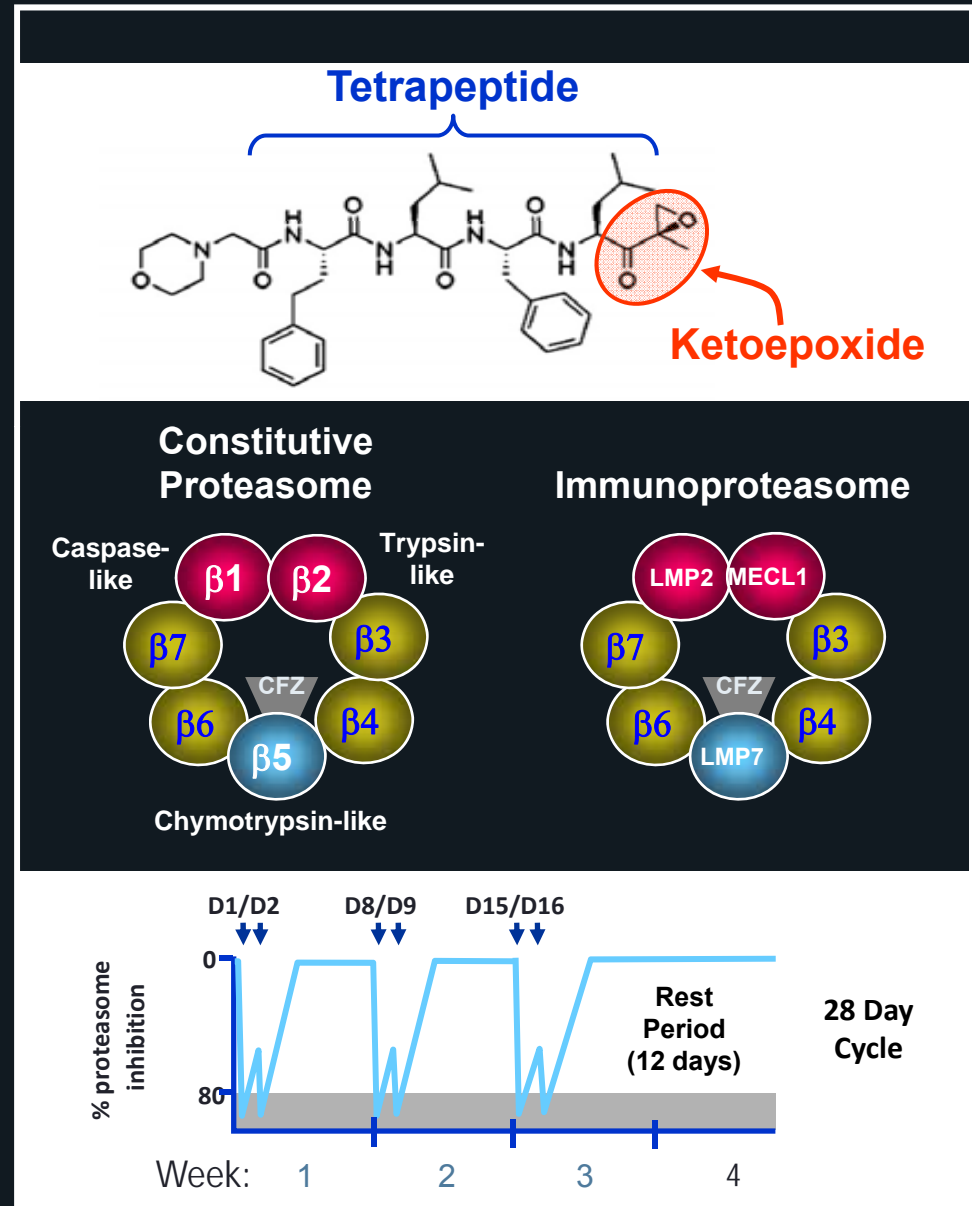
**PX-171-003-A0: Final Results of an
Open-Label, Single-Arm, Phase 2 Study of
Carfilzomib in Patients With Relapsed and Refractory
Multiple Myeloma**

Sundar Jagannath, MD; Ravi Vij, MD; A. Keith Stewart,
MBChB; George Somlo, MD; Andrzej Jakubowski, MD,
PhD; Suzanne Trudel, MD; Richard Schwartz, MD, Lori
Kunkel, MD; David Siegel, MD, PhD

ASCO Abstract 8504

Carfilzomib

- Irreversibly inhibits chymotrypsin-like activity
- At MTD >80% inhibition of proteasome
- Consecutive day dosing allows protracted proteasome inhibition



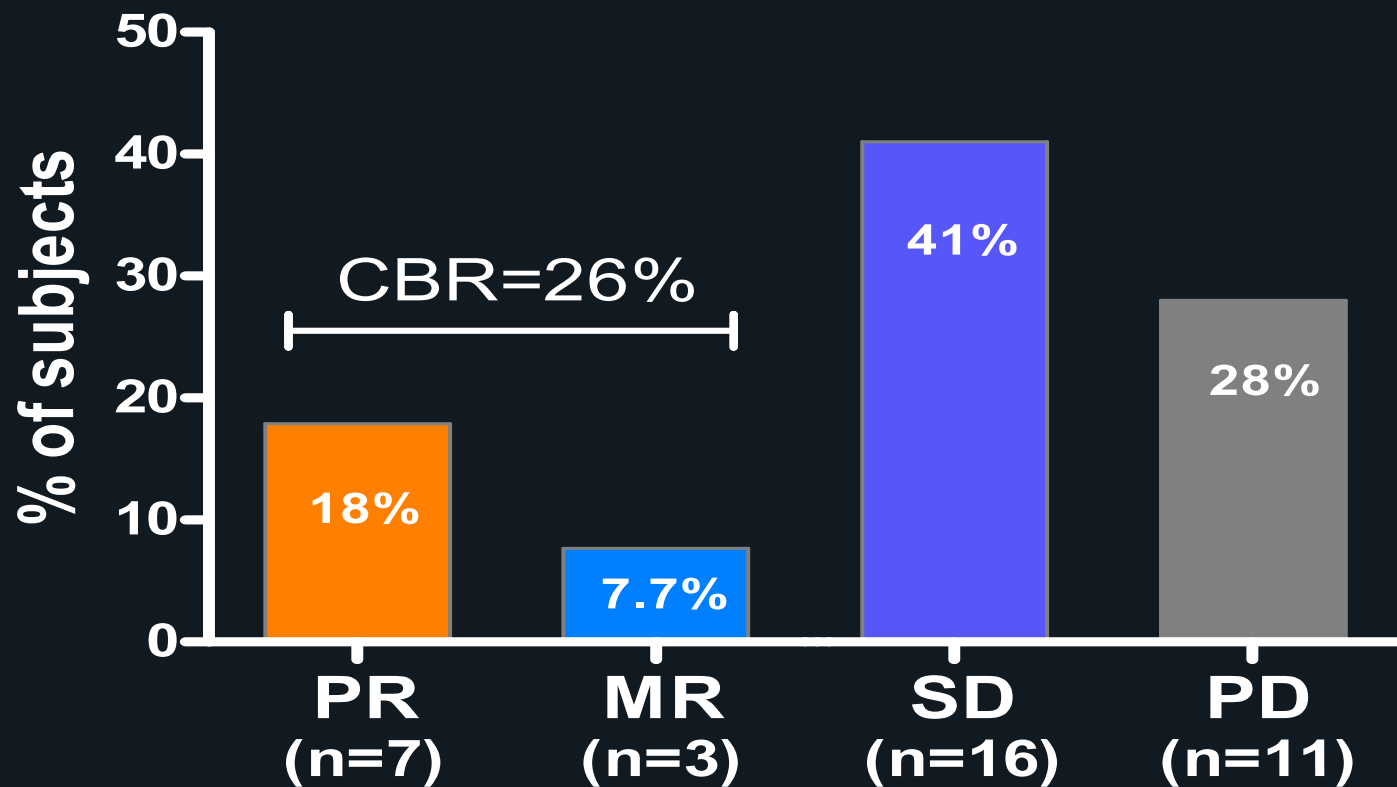
PX-171-003-A0: Prior Therapies (N = 46)

Prior Therapies, median (range)

5 (2-15)

	%
≥4 prior therapies	80
Bortezomib	100
As last therapy	57
Immunomodulatory agent	100
Lenalidomide	89
Thalidomide	91
Corticosteroid	100
Alkylator	
(Melphalan, cyclophosphamide, carmustine)	94
Stem cell transplant	83
Anthracycline	80

PX-171-003-A0: Results (N = 39)*



CBR = 19% (5/26) in bortezomib refractory patients (2 PR, 3 MR)

PX-171-003-A0 Adverse Events

Adverse Event	003-A0 (N=46)	
	All Grades (%)	Grade 3/4 (%)
Hematologic ($\geq 15\%$)		
Anemia	75	37
Thrombocytopenia	50	26
Neutropenia	22	4.3
Non-Hematologic ($\geq 20\%$)		
Fatigue	67	8.7
Dyspnea	28	8.7
Renal Impairment	43	15
Nausea	37	0
Constipation	13	0
Diarrhea	33	0
Hyperglycemia	26	0
Upper respiratory tract infection	37	4.3
Other		
Peripheral neuropathy	17	2.2
Tumor Lysis Syndrome	4.3	4.3

PX-171-003-A0 Conclusions

- Single-agent carfilzomib is active in heavily pretreated refractory MM patients who have failed all proven agents
 - 18% PR and 8% MR
- Carfilzomib is active in bortezomib refractory patients
 - PR+MR in 5/26 (19%)
- Response is durable
 - Median PFS was 5.1 months
 - Response duration was 7.4 months
- Carfilzomib is well tolerated
 - Low rate of peripheral neuropathy
 - 10% (4/39) patients completed 12 cycles

Tanespimycin + Bortezomib in Relapsed and Refractory Multiple Myeloma: Final Results of a Phase 1/2 Study

PG Richardson,¹ A Chanan-Khan,² S Lonial,³ A Krishnan,⁴ M Carroll,⁵ M Alsina,⁶ M Albitar,⁷ D Berman,⁸ S Kaplita,⁸ KC Anderson¹

¹Dana-Farber Cancer Institute, Boston, MA, USA; ²Roswell Park Cancer Institute, Buffalo, NY, USA;

³Emory University, Winship Cancer Institute, Atlanta, GA, USA; ⁴City of Hope, Duarte, CA, USA;

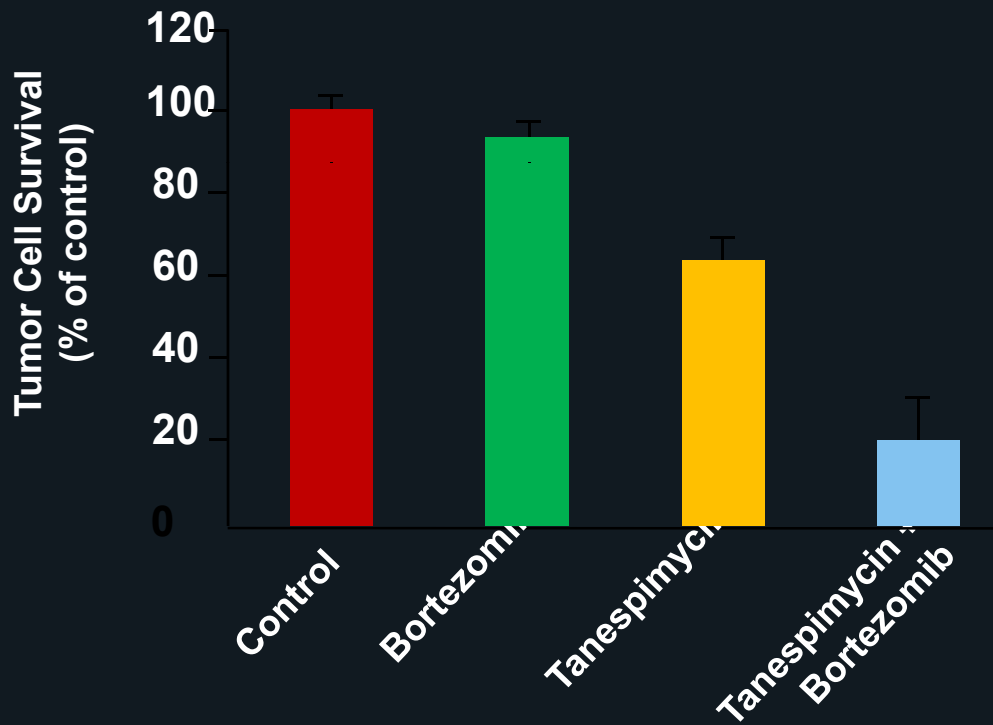
⁵Sutter Regional Cancer Institute, Sacramento, CA, USA; ⁶H. Lee Moffitt Cancer Center, Tampa, FL, USA;

⁷Quest Hematopathology, San Juan Capistrano, CA, USA; ⁸Bristol-Myers Squibb, Princeton, NJ, USA

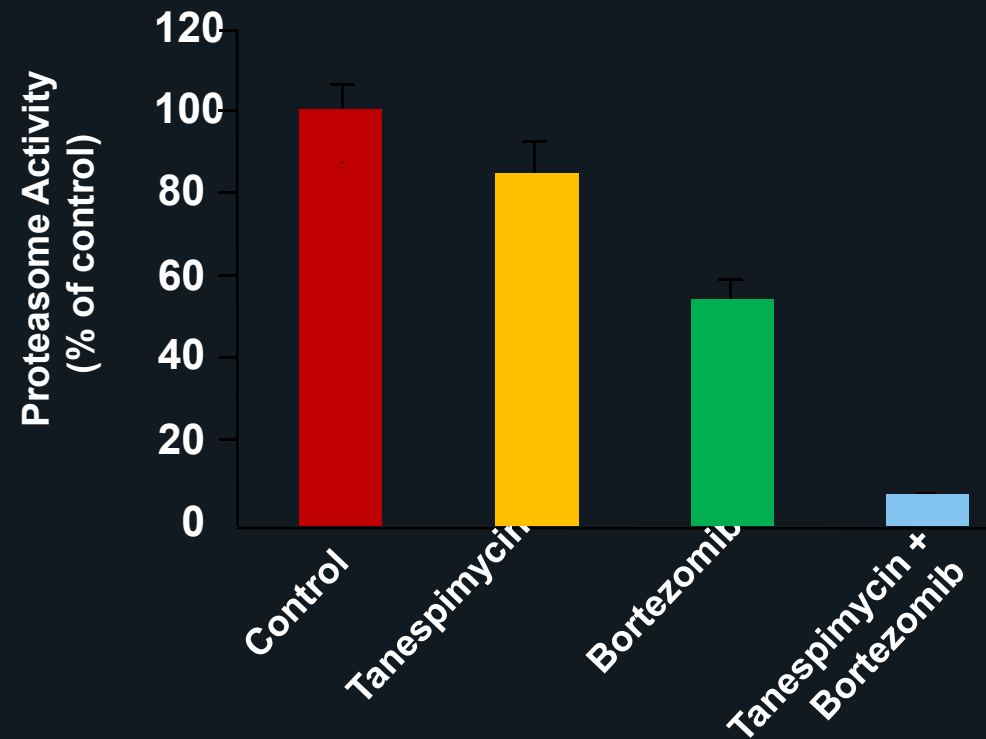


Tanespimycin + Bortezomib: Preclinical Rationale in MM

Synergistic Antitumor Activity*

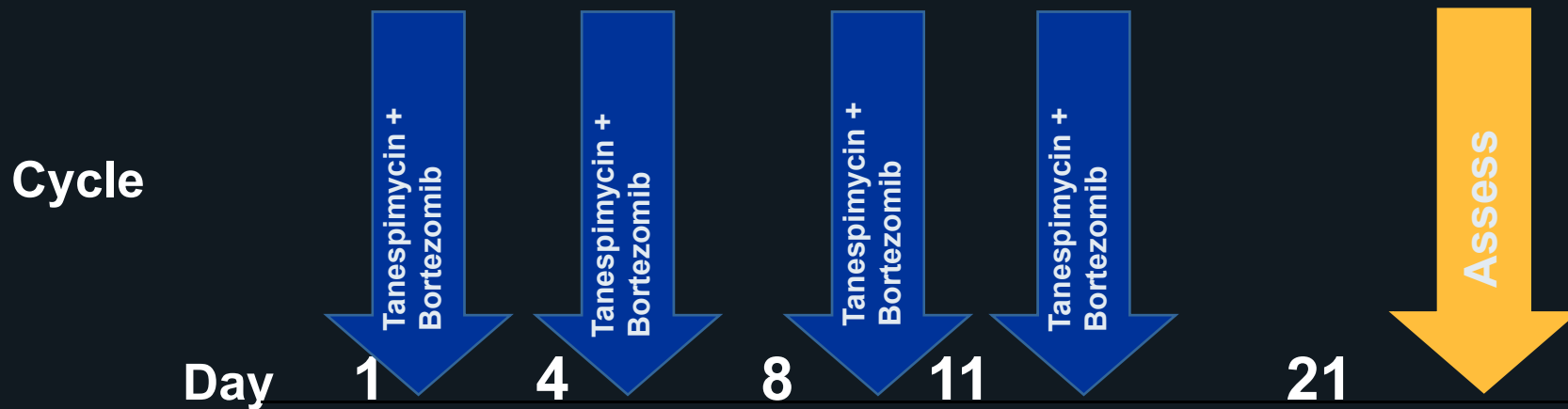


Enhanced Proteasome Inhibition*



*These assays were performed on bortezomib-resistant MM cells.

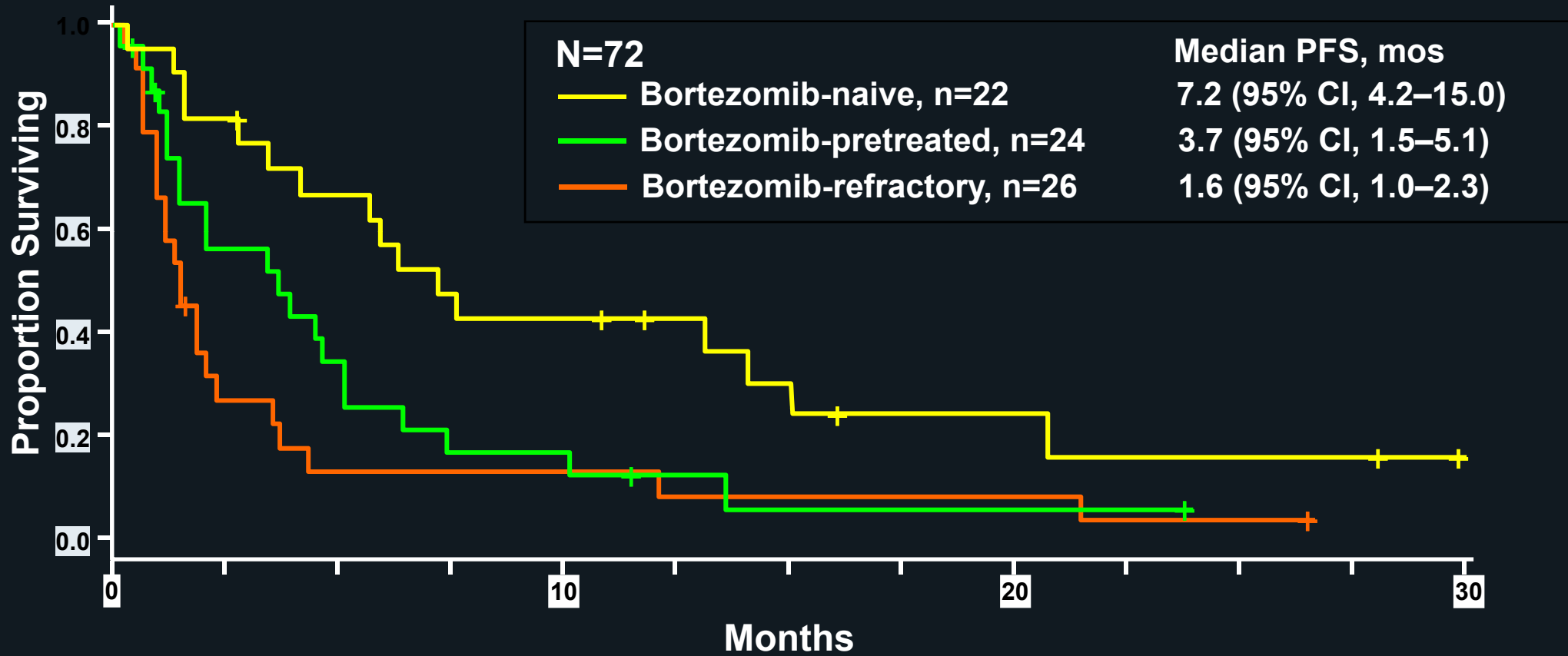
Tanespimycin + Bortezomib Study Design



Best Response

	CR + PR + MR, n (%)
Total, N=67*	18 (27)
Bortezomib Status at Study Entry	
Naive, n=21	10 (48)
≤3 prior regimens, n=11	7 (64)
≥4 prior regimens, n=10	3 (30)**
Pretreated, n=23	5 (22)
Refractory, n=23	3 (13)

Progression-free Survival



Summary

- **Tanespimycin + bortezomib induces durable responses in relapsed/refractory MM, including bortezomib-refractory pts.**
- **Tanespimycin neuroprotective in animal models, reverses bortezomib-induced PN**
 - **No severe PN observed in this study, c/w preclinical models**
- **Tanespimycin + bortezomib as long-term therapy is well tolerated.**
 - **Low rate of neutropenia**
 - **Low rates of constipation, anorexia**
 - **LFT elevation and other AEs manageable and reversible**

Clinical Value of Minor Responses After 4
Doses of Rituximab in Waldenström
Macroglobulinemia: A Follow-Up of the Eastern
Cooperative Oncology Group E3A98 Trial

Morie A. Gertz, MD Rafat Abonour, MD L. Thomas Heffner,
MD Philip R. Greipp, MD Hajime Uno, PhD S. Vincent
Rajkumar, MD

ASCO Abstract 8513

Questions posed by the Study

- Should patients with a less than 50% decline in IgM be monitored for progression or receive alternate therapy in an effort to achieve a better (i.e. objective, >50%) response?

Patients E3A98

- All were rituximab naive
- 34 untreated median dx to R 0.1 yrs
- 35 treated median dx to R 2.5 yrs
- 4 doses at 375/M2
- Eligibility IgM > 1000 (response required a decline of 500. Minor response required a decline of 250)
- Hb <11 g/dL

Response Data

n=66

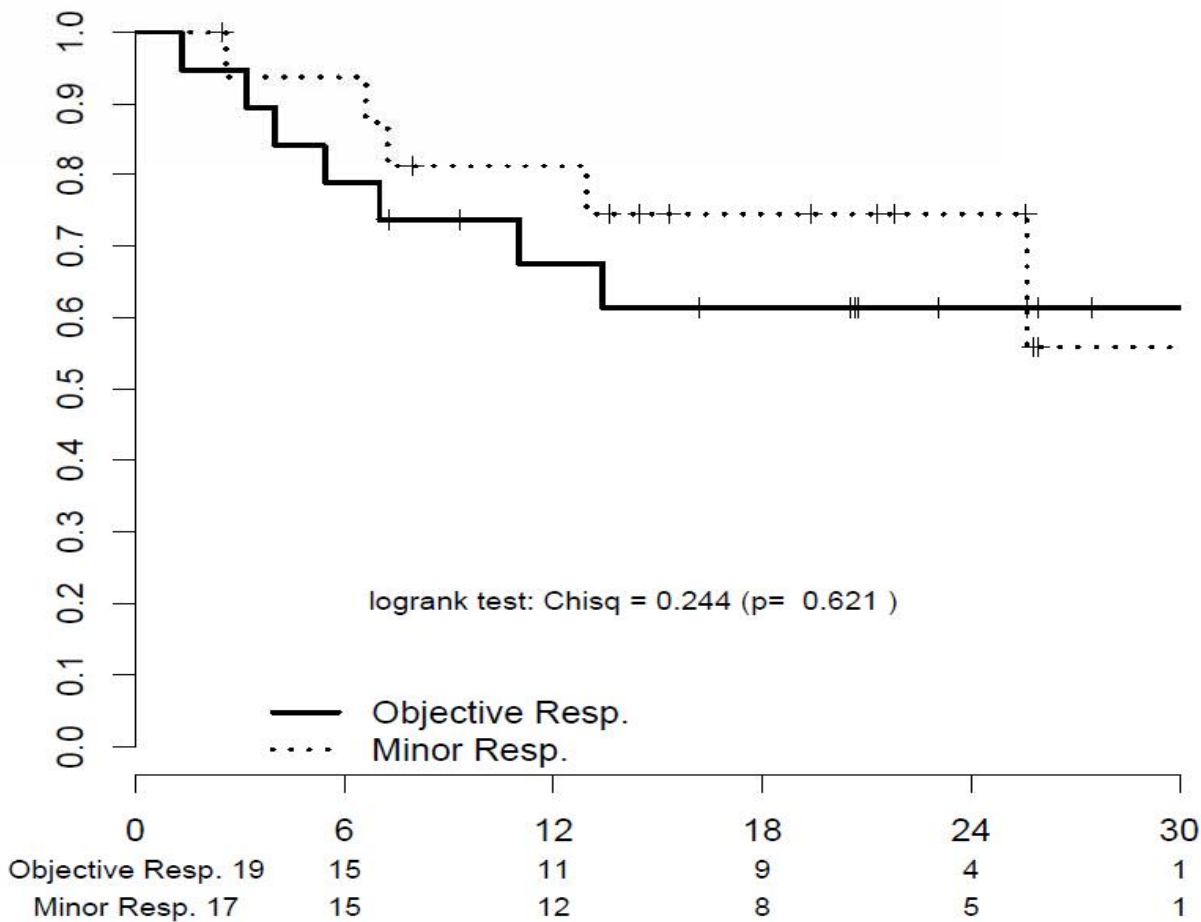
- 22 (33%) had a best response >50%-PR
 - 7 at 3 mos
 - 7 at 3-6 mos
 - 3 at 6-9 mos
 - 5 at >9 mos
- 16 (24%) had a best response 25-50%MR
 - 2 at 3 mos
 - 9 at 3-6 mos
 - 2 at 6-9 mos
 - 3 at >9 mos

ORR=PR+MR= 57%

**8/38 (21%) best
response > 9 mos.**

**Progression-free survival, stratified by degree of response.
PFS was calculated (landmark analysis) starting 4 months
after trial enrollment. @2 yrs PFS 58 vs 46 % P=NS**

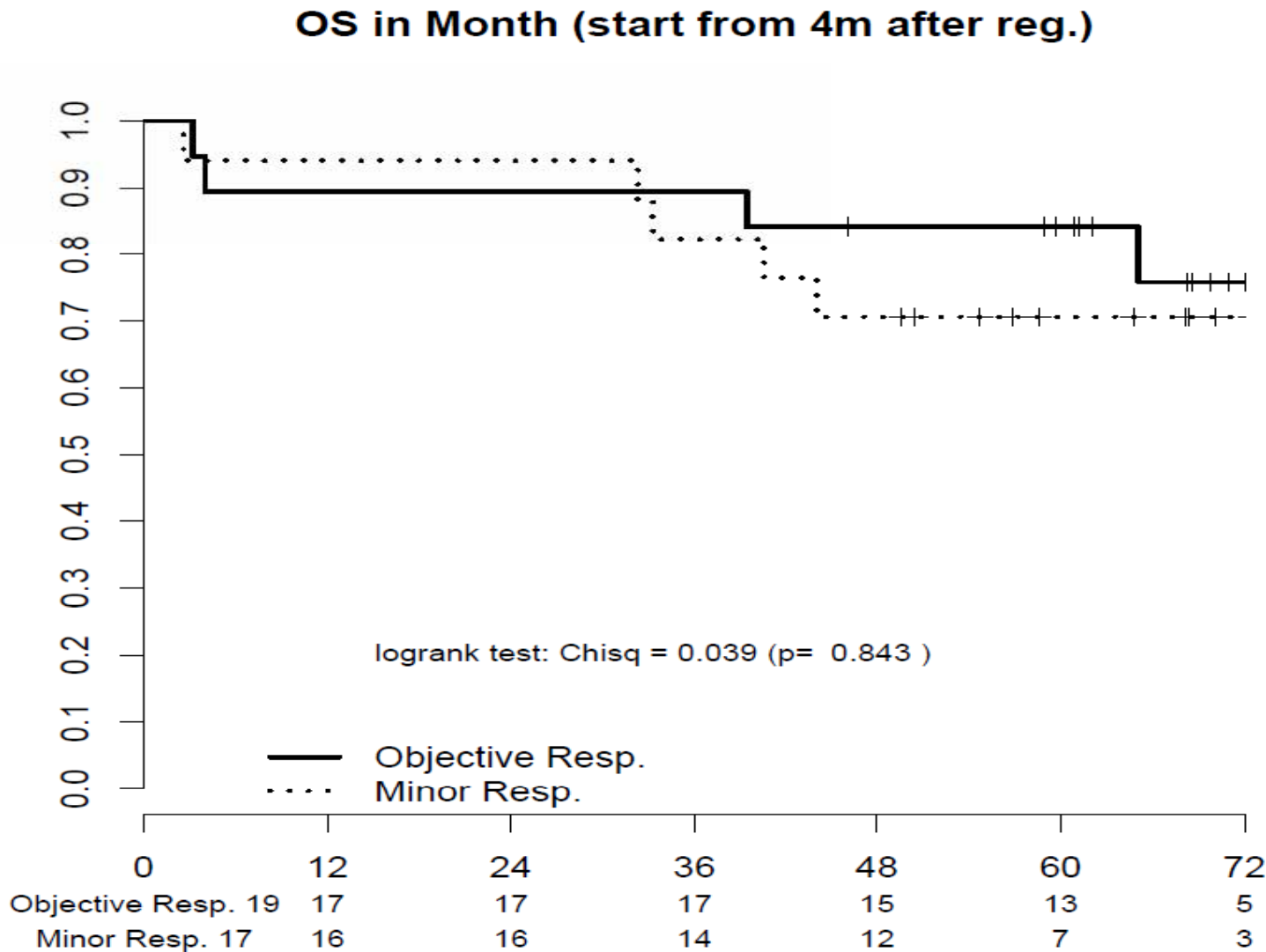
PFS in Month (start from 4m after reg.)



**Response
duration
unrelated to
response depth**

No difference if
landmark 4, 6, 9 or 12
mos

OS of responders, stratified by degree of response. Survival was calculated (landmark analysis) starting 4 months after trial enrollment. @5 yrs 75 vs 71 %



No difference if landmark 4, 6, 9 or 12 mos

Deeper response did not translate into improved survival

Conclusions

- More aggressive or intensive therapy for minor responders is not required
- Minor responses are associated with clinically meaningful benefits
- Response rate to Rituxan as a single agent not associated with the pre therapy IgM level so no threshold exists requiring therapy
- Responses are slow median of 6 mos (21%>9 mos) despite therapy completion at 4 weeks-implications for no. of Rituxan doses

Phase II trial of bortezomib and rituximab in relapsed or relapsed/refractory WM

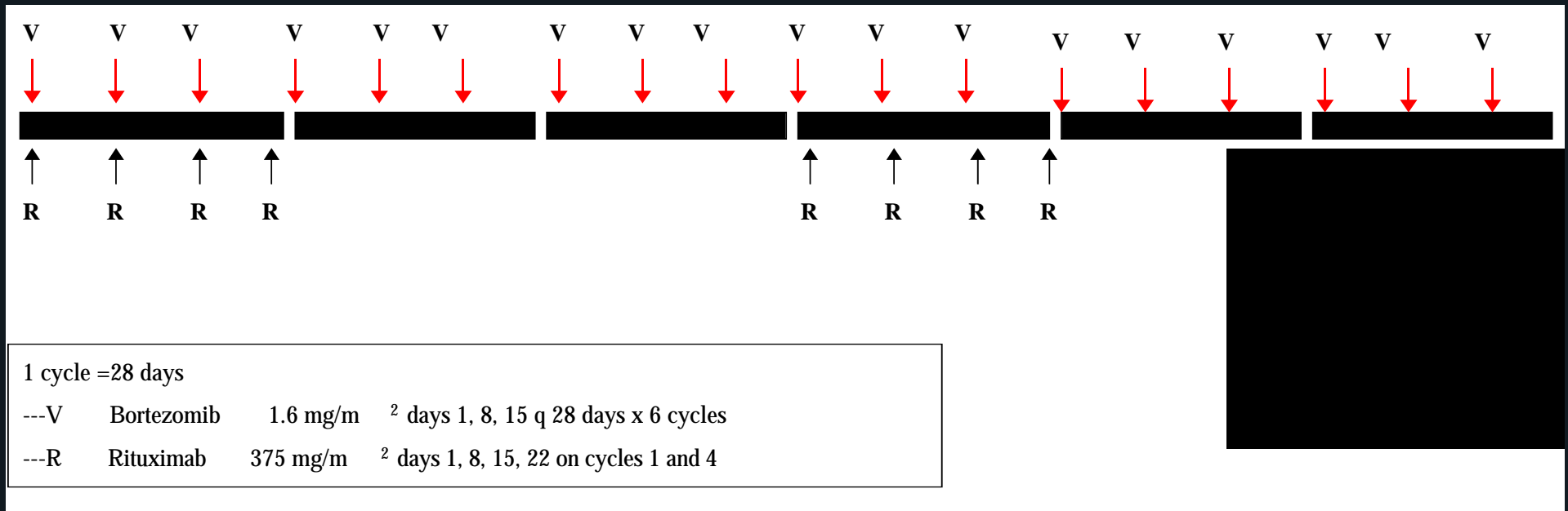
Irene M. Ghobrial¹, Fangxin Hong¹, Jeffrey Matous², Swaminathan Padmanabhan³, Ashraf Badros⁴, Robert Schlossman¹, Stacey Chuma¹, Renee Leduc¹, Meghan Rourke¹, Brianna Harris¹, Amy Sam¹, Diane Warren,¹ Kenneth C. Anderson¹, Paul Richardson¹

ASCO Abstract 8535

Objectives

- Primary Objective:
 - Assess response rate (CR+PR+MR) in patients treated with bortezomib and rituximab
- Secondary Objectives:
 - 1- Evaluate toxicity specifically neurotoxicity
 - 2- Role of serum free light chain in assessing response
 - 3- Correlative studies on tumor cells before/after therapy
 - 4- Duration of response and time to progression

Treatment Schema



- A total of 6 cycles, a cycle= 28 days
- No rituximab maintenance
- No dexamethasone with therapy except for rituximab reactions

Results

- **Types of prior therapy:** Chlorambucil, 2CDA, Fludarabine, CHOP, CVP, rituximab, bortezomib, and others
 - All received prior rituximab alone or in combination
 - 5 patients had received bortezomib
- **35/37 pts are evaluable for response**
 - 1 pt withdrew consent in the first cycle
 - 1 pt passed away in the first cycle due to viral pneumonia and hospice

Conclusion

- The combination of bortezomib and rituximab using weekly bortezomib was well tolerated
- Demonstrated CR (6%)+ PR (48%) + MR (29%) in 83% of patients
- No significant peripheral neuropathy was observed with this regimen
- Upfront clinical trial using the same regimen is ongoing

Overall Conclusions and Future Directions

1. Novel therapies have increased extent and frequency of response, as well as prolonged event free and overall survival.
2. Integration of novel therapies into the transplant paradigm has already resulted in sustained complete responses.
3. Randomized trials will define the optimal combination of novel therapies, as well as the role of transplantation in the era of novel therapies
4. Combination therapies in myeloma, as in NHL, HD, and testicular cancer, offer the promise of long-term disease free survival and cure.