Synergy between Proteasome Inhibitors and IMiDs for the treatment of Multiple Myeloma

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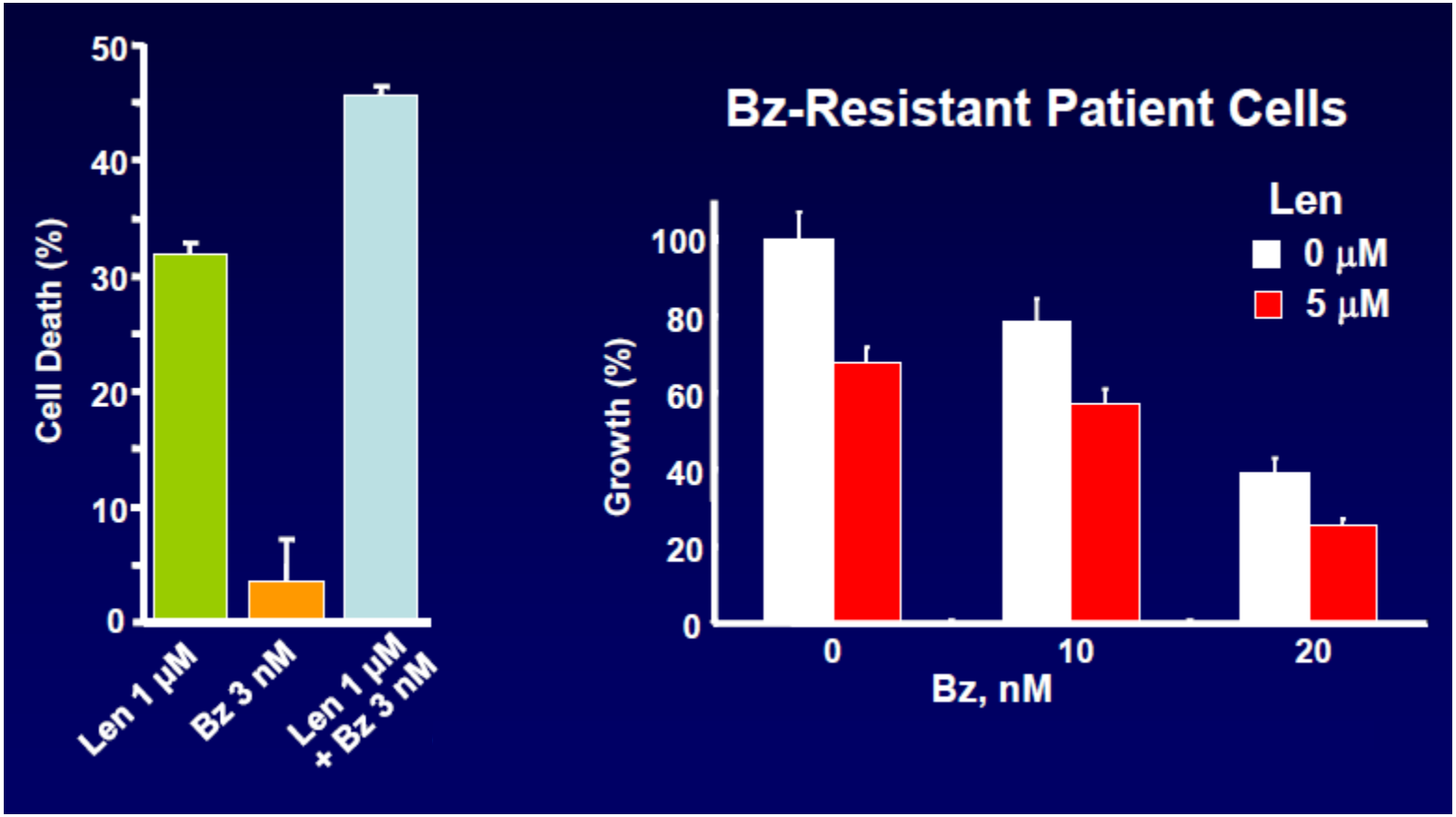
Synergy between Pis and IMiDs was first described in vitro in 2002

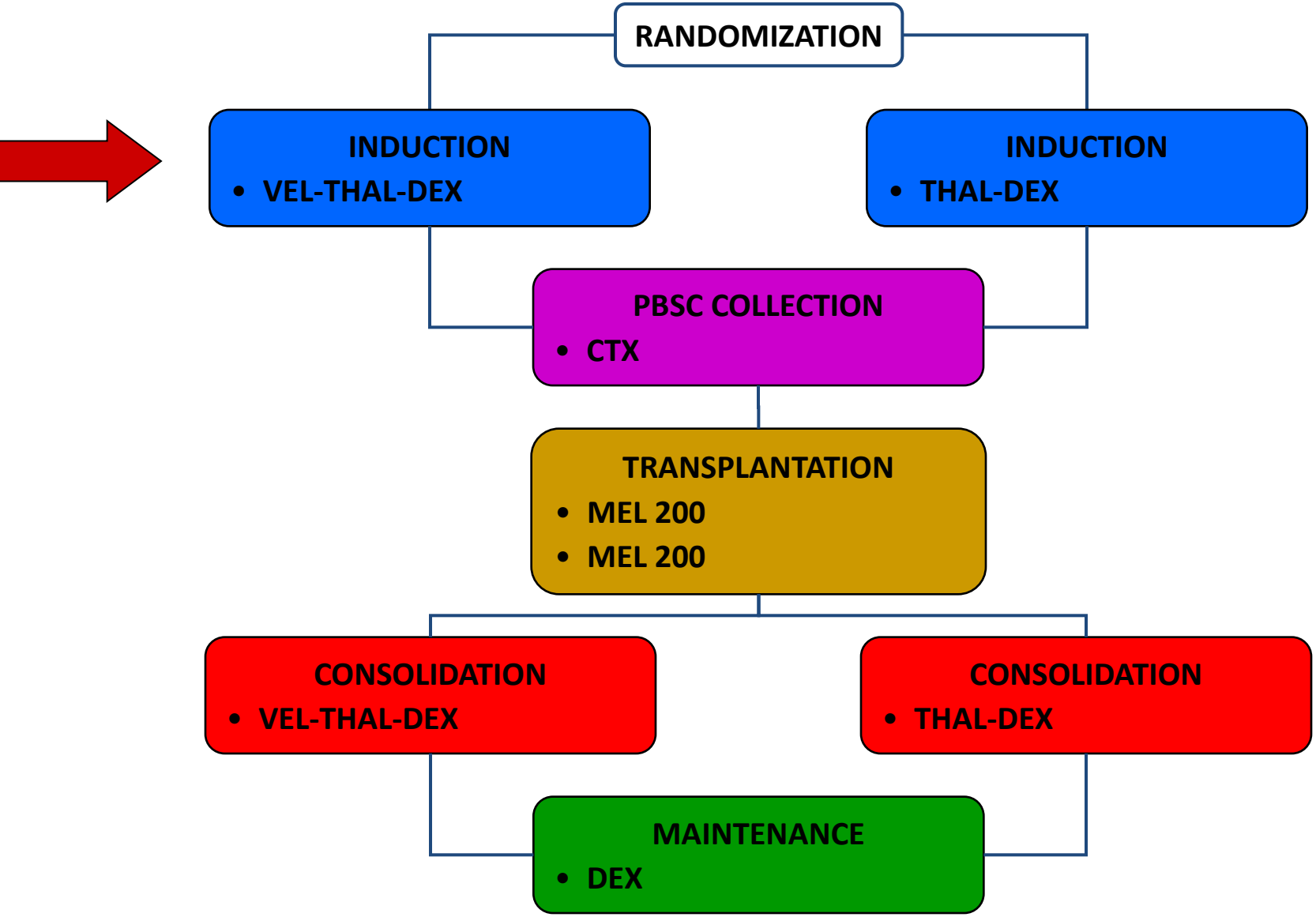
In preclinical studies, bortezomib in combination with lenalidomide triggered synergistic tumour cell death, even in bortezomib-resistant cells



Mitsiades N, et al. *Blood* 2002;99:4525–4530

INDUCTION

Protocol GIMEMA 26866138-MMY-3006
VTD vs TD Incorporated into Double ASCT for MM



Cavo et al, *Lancet* 2010

Response to Induction Therapy

	% of patients		
	VTD (n=226)	TD (n=234)	P value
CR+nCR	33	12	<0.001
VGPR	61	30	<0.001

Cavo M et al, *Lancet* 2010; 376:2075-85

Cavo et al, Lancet 2010

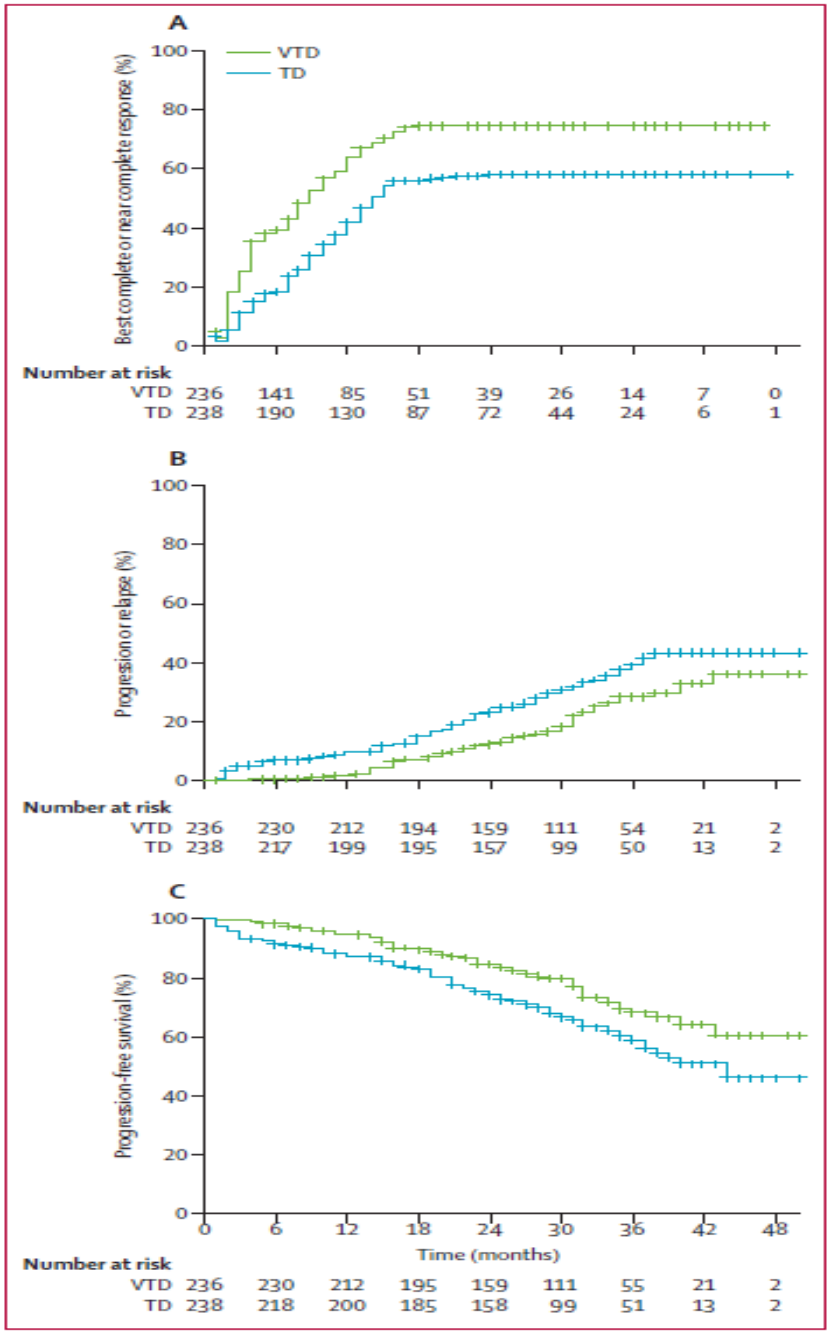


Figure 3: **Kaplan-Meier curves for (A) time to best complete or near complete response, (B) time to progression or relapse, and (C) progression-free survival**
VTD=bortezomib with thalidomide plus dexamethasone. TD= thalidomide plus dexamethasone.

IFM 2007-02: VD vs vTD

4 cycles

VD (IFM 2005/01)

Vel 1.3mg/m2 d1,4,8,11
Dex 40mg d1-4,9-12
Cycles 1 & 2
d1-4, cycles 3 & 4

vTD

Vel 1mg/m2 d1,4,8,11
Thal 100mg/d
Dex idem

increased up to 1.3 & 200mg/day
if response < PR after 2 cycles
+ LMWH

Moreau et al, *Blood* 2011

IFM2007- 02: VD vs vTD
Results Induction Phase

03/2008 → 01/2009, 205 patients < 65 years

	VD	vTD	
%CR	**12**	**14**	**p = 0.68**
% ≥ VGPR	**36**	**50**	**p = 0.047**
% ≥ PR	**81**	**91**	**p = 0.06**
Stable	**12**	**5**	
Prog	**7**	**4**	

Moreau et al, *Blood* 2011

blood®

Prepublished online March 21, 2016;
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VTD is superior to VCD prior to intensive therapy in multiple myeloma: results of the prospective IFM2013-04 trial

Philippe Moreau, Cyrille Hulin, Margaret Macro, Denis Caillot, Carine Chaleteix, Murielle Roussel, Laurent Garderet, Bruno Royer, Sabine Brechignac, Mourad Tiab, Mathieu Puyade, Martine Escoffre, Anne-Marie Stoppa, Thierry Facon, Brigitte Pegourie, Driss Chaoui, Arnaud Jaccard, Borhane Slama, Gerald Marit, Karim Laribi, Pascal Godmer, Odile Luycx, Jean-Claude Eisenmann, Olivier Allangba, Mamoun Dib, Carla Araujo, Jean Fontan, Karim Belhadj, Marc Wetterwald, Véronique Dorvaux, Jean-Paul Fermand, Philippe Rodon, Brigitte Kolb, Sylvie Glaisner, Jean-Valere Malfuson, Pascal Lenain, Laetitia Biron, Lucie Planche, Helene Caillon, Herve Avet-Loiseau, Thomas Dejoie and Michel Attal

Intent-to-treat analysis

	VTD N = 169	VCD N = 169	P value
≥ CR	13.0%	8.9%	0.22
≥ VGPR	**66.3%**	**56.2%**	**0.05**
≥ PR	92.3%	83.4%	0.01

Toxicity

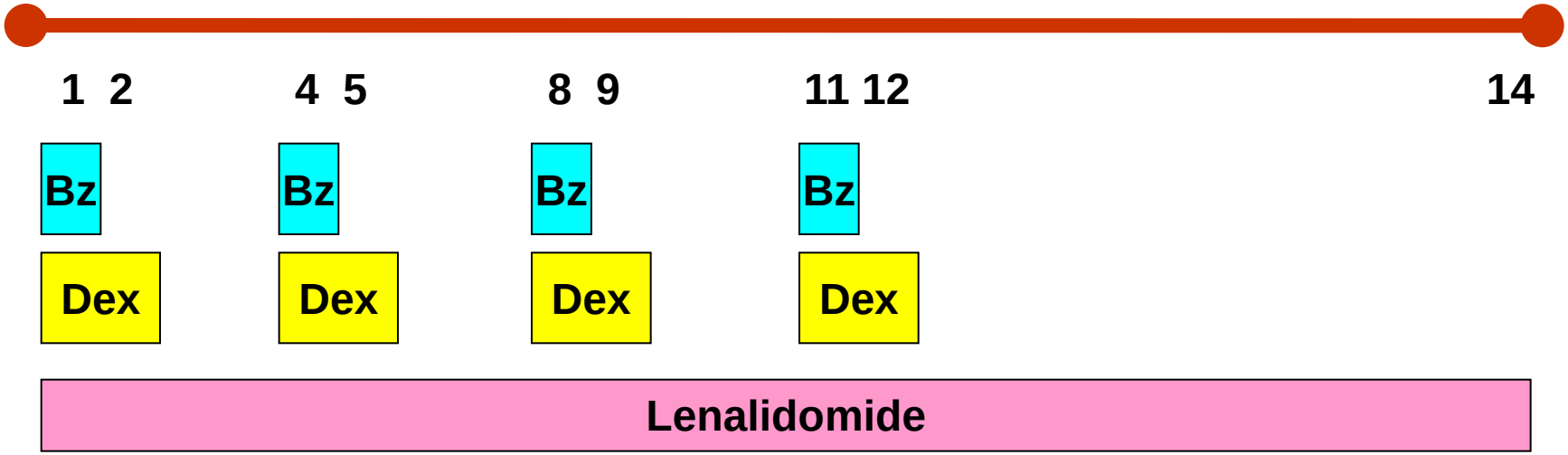
	VTD, n = 169 Grade 3-4 %	VCD, n= 169 Grade 3-4 %	p value
Any Aes	63.9	68.2	0.40
Anemia	**4.1**	**9.5**	**0.05**
Neutropenia	**18.9**	**33.1**	**0.003**
Infection	7.7	10.1	0.45
Thrombocytopenia	**4.7**	**10.6**	**0.04**
Thrombosis	1.8	1.8	0.99
Cardiac disorders	1.2	0	0.16
Cystitis	0	0.6	0.32
GI symptoms	5.3	3.5	0.42
Periph. Neuropathy	**7.7**	**2.9**	**0.05**
PN grade 2-4	**21.9**	**12.9**	**0.008**

Toxicities assessed according to NCI CTCAE, version 4.0.

RVD

Richardson et al, *Blood* 2010, online 12 April

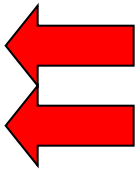
Up to eight 21-day cycles



Phase II : Len 25, Btz 1.3, Dex : 20

Best Response to Treatment Overall and in the Phase II Population

Response, n (%)	All pts (N=66)	Phase II (N=35)
CR	19 (29)	13 (37)
nCR	7 (11)	7 (20)
VGPR	18 (27)	6 (17)
PR	22 (33)	9 (26)
CR+nCR	26 (39)	20 (57)
CR+nCR+VGPR	44 (67)	26 (74)
At least PR	66 (100)	35 (100)

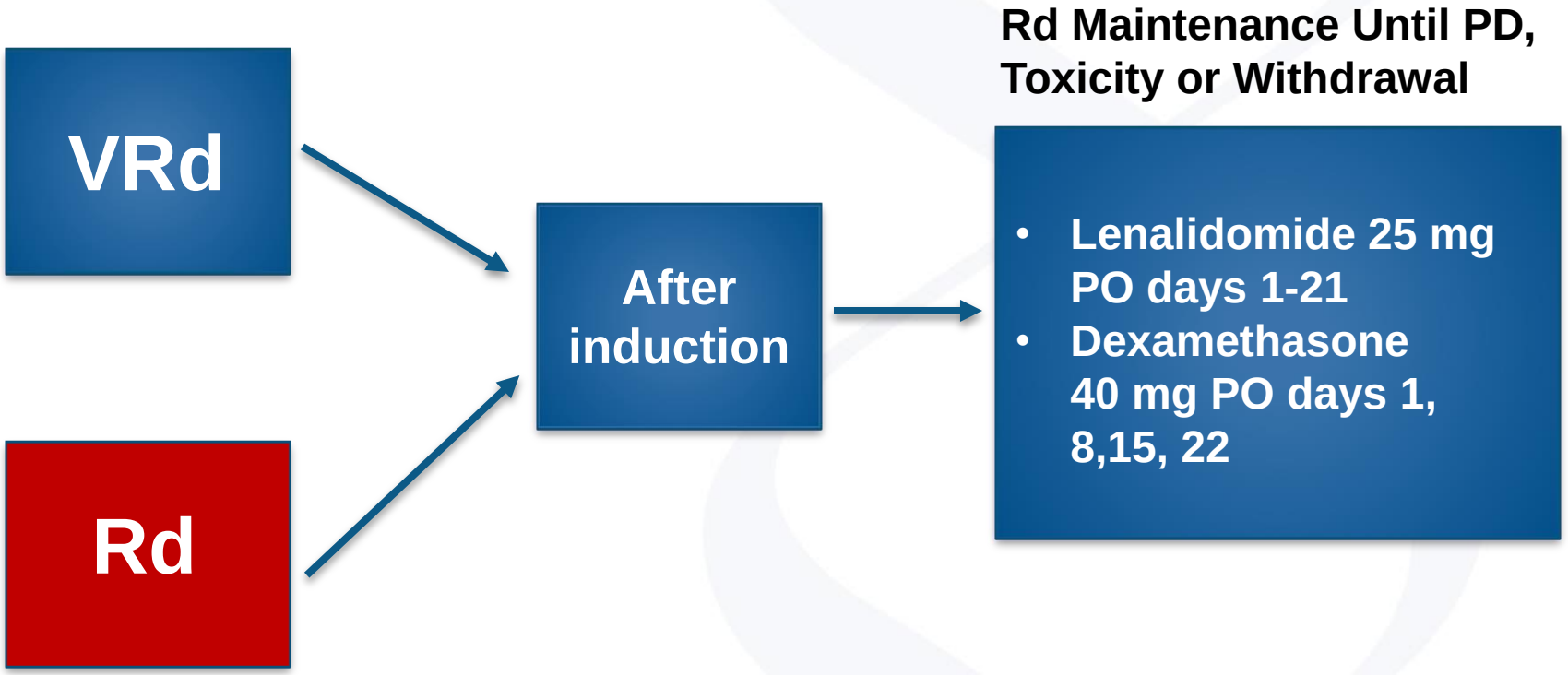


Neuropathy grade > or = 3 : 7%

Bortezomib, Lenalidomide and Dexamethasone vs. Lenalidomide and Dexamethasone in Patients (Pts) with Previously Untreated Multiple Myeloma Without an Intent for Immediate Autologous Stem Cell Transplant (ASCT): Results of the Randomized Phase III Trial SWOG S0777

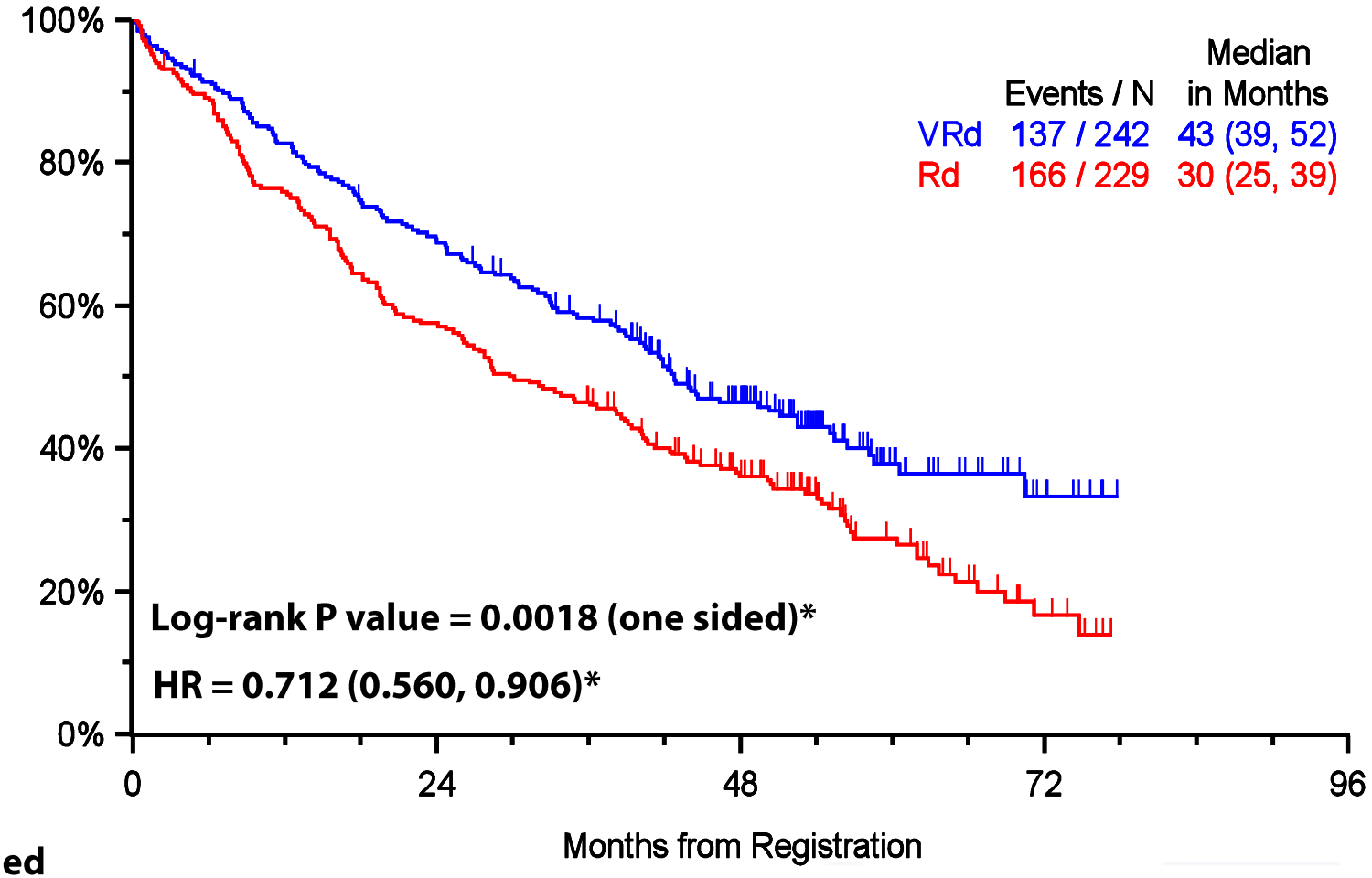
Brian G.M. Durie, MD, Antje Hoering, PhD, S. Vincent Rajkumar, MD, Muneer H. Abidi, MD, Joshua Epstein, DSc, Stephen P. Kahanic, MD, Mohan Thakuri, MD, Frederic Reu, MD, Christopher M. Reynolds, MD, Rachael Sexton, MS, Robert Z. Orlowski, MD, PhD, Bart Barlogie, MD, PhD, Angela Dispenzieri, MD

SWOG S0777 Study Design



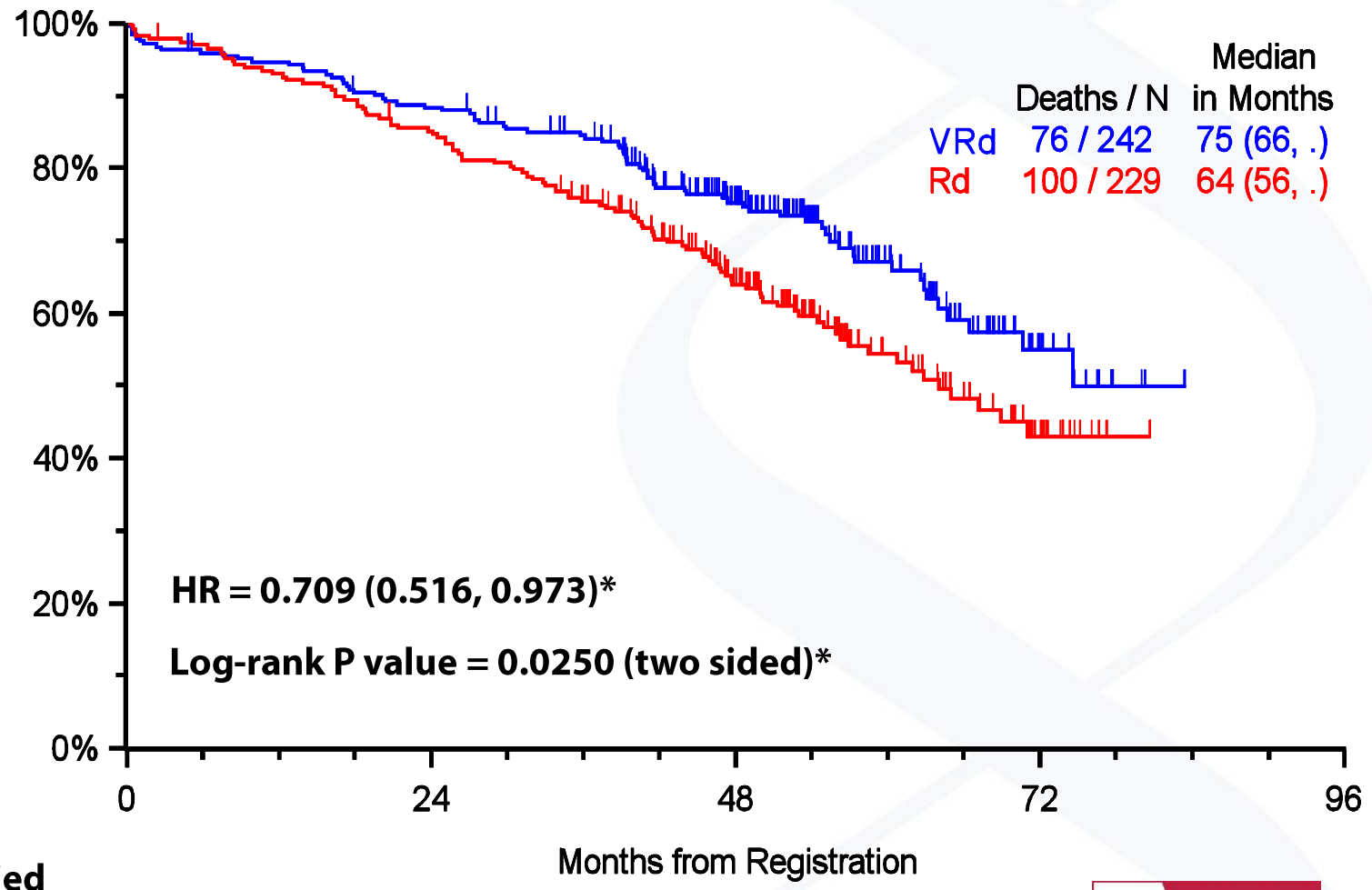
- **All patients received Aspirin 325 mg/day**
- **VRd patients received HSV prophylaxis**

Progression-Free Survival By Assigned Treatment Arm

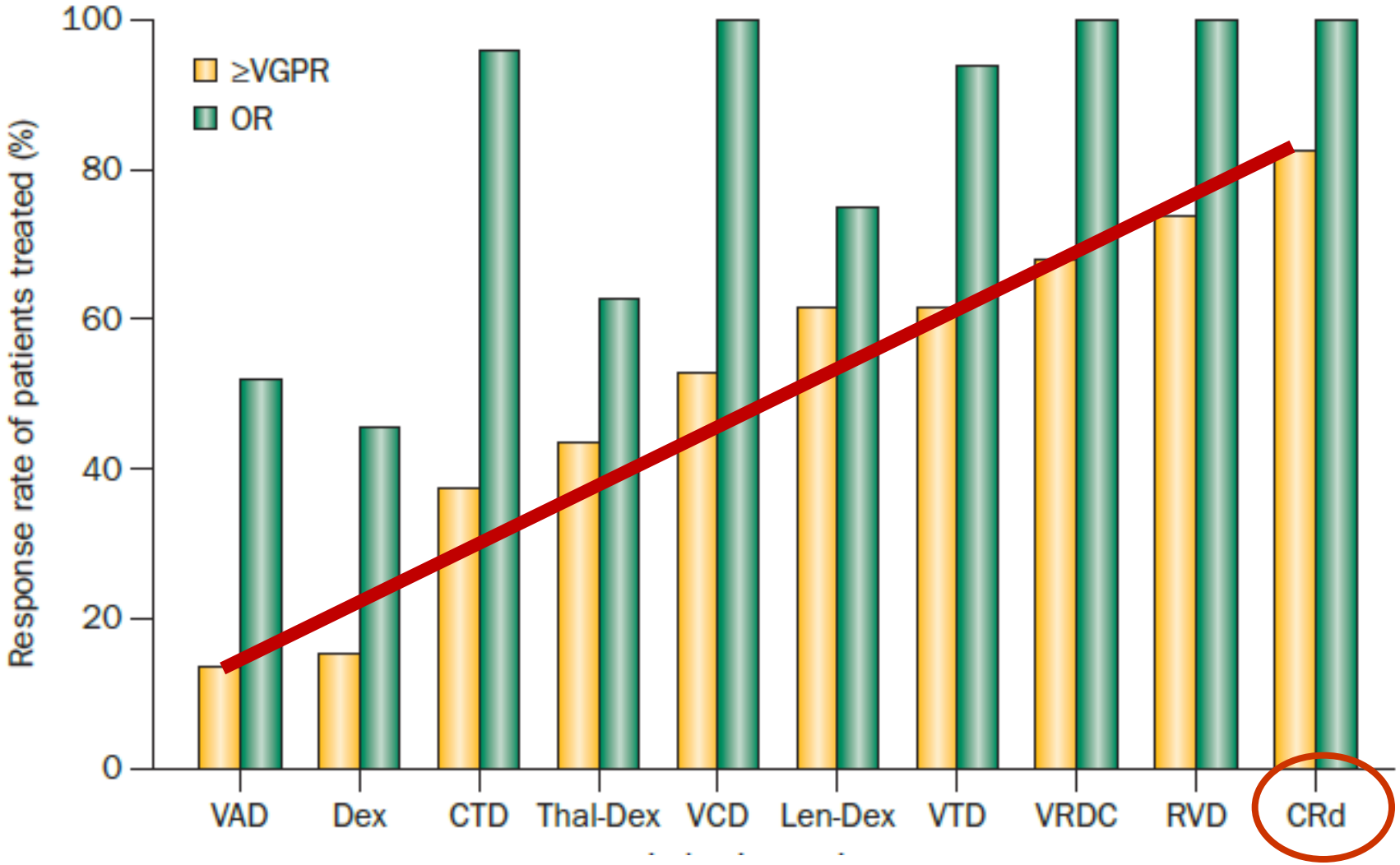


*Stratified

Overall Survival

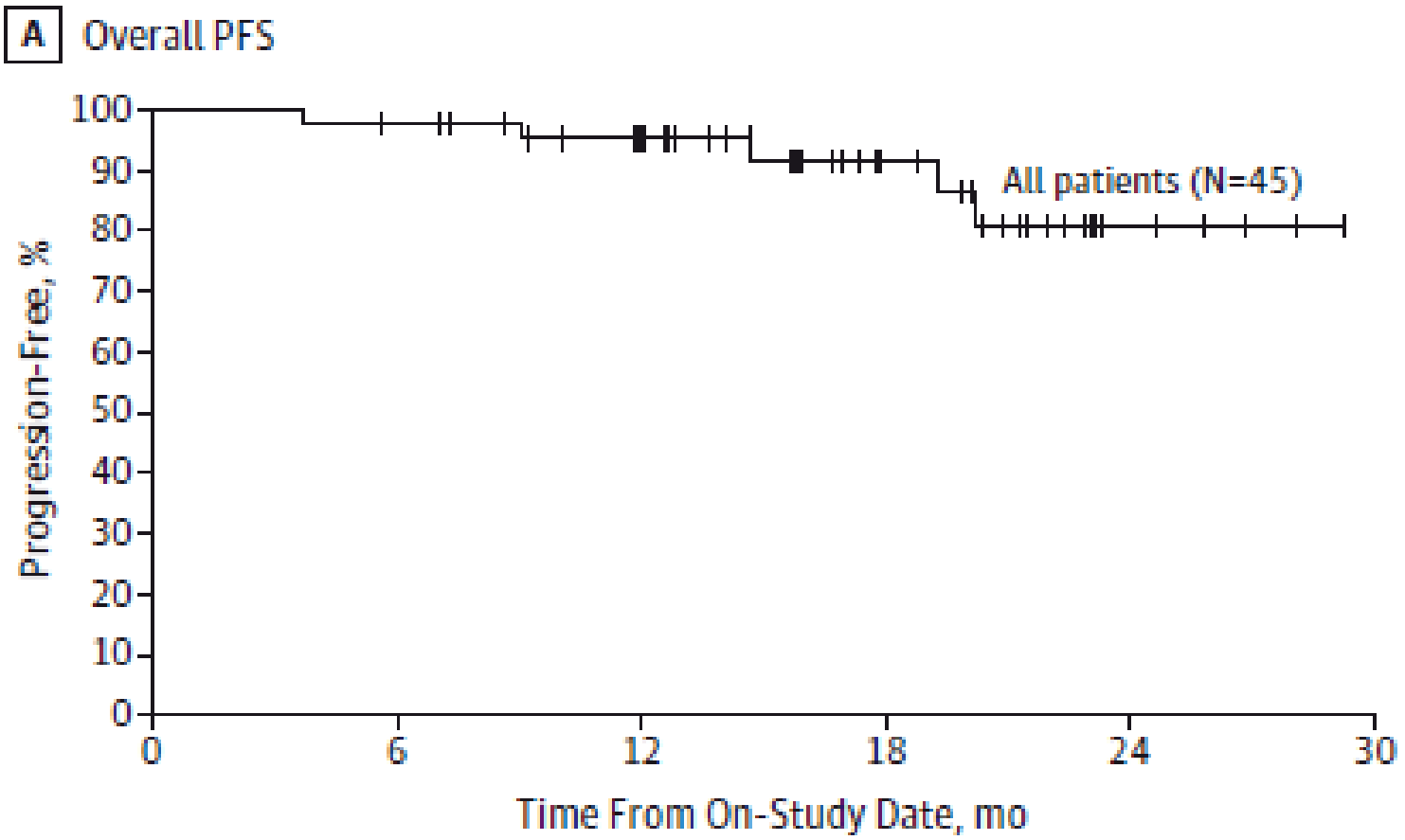


*Stratified



Mailankody, S. *et al. Nat. Rev. Clin. Oncol.* **12**, 286–295 (2015); published online 27 January 2015;

KRd in 45 patients with de novo MM



Korde et al. JAMA Oncology 2015

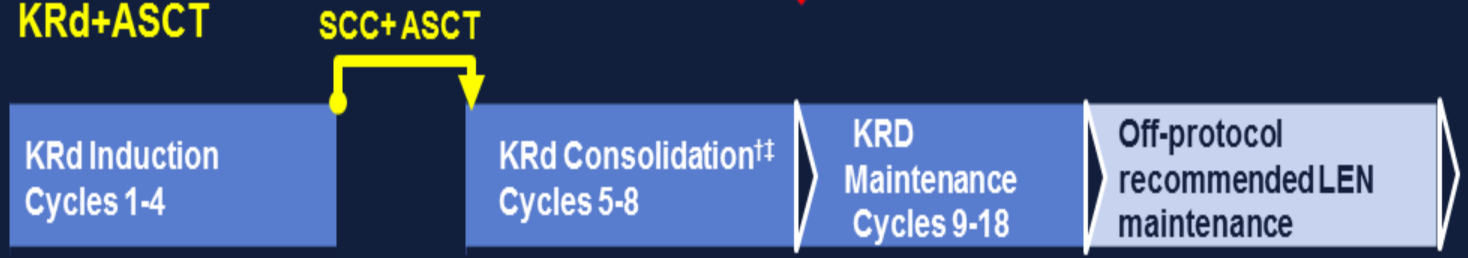
Treatment Schema

Courtesy Dr Jakubowiak

Carfilzomib on days 1-2, 8-9, 15-16 at 20-27-36 mg/m^2* (all patients received 20 mg/m^2 on days 1-2 for cycle 1 only) for cycles 1-8 as tolerated (28-day cycle), and on Days 1-2, 15-16 as tolerated for Cycles 9-24. Lenalidomide on days 1-21 at 25 mg/day for cycles 1-24 or as tolerated, and recommended for single-agent maintenance off protocol. Dexamethasone 40 mg/wk for cycles 1-4, then 20 mg/wk for cycles 5-24 or as tolerated

KRd+ASCT considered promising: improvement of ***sCR at the end of 8 cycles***

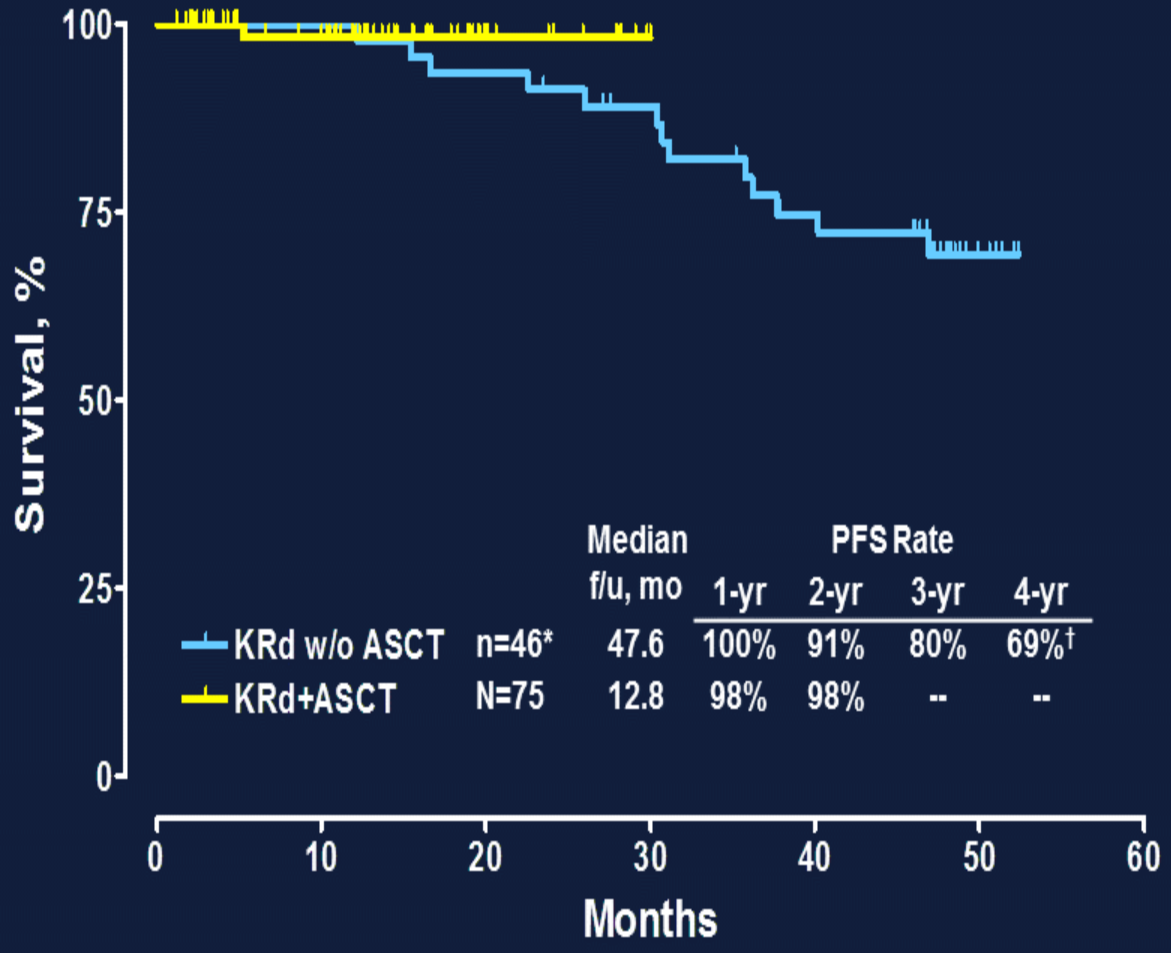
from historical rate of ***30% for KRd w/o transplant*** to ***50% for KRd+ASCT***



Carfilzomib on days 1-2, 8-9, 15-16 at 36 mg/m^2* (20 mg/m^2 on days 1-2 for cycle 1 only) for cycles 1-8 as tolerated (28-day cycle), and on Days 1-2, 15-16 as tolerated for Cycles 9-18. Lenalidomide on days 1-21 at 25 mg/day for cycles 1-18 (15 mg/day for cycle 5) or as tolerated, and recommended for single-agent maintenance off protocol. Dexamethasone 40 mg/wk for cycles 1-4, then 20 mg/wk for cycles 5-18 or as tolerated. KRd restarted 70-90 days and <120 days post-ASCT

Treatment Outcomes – PFS

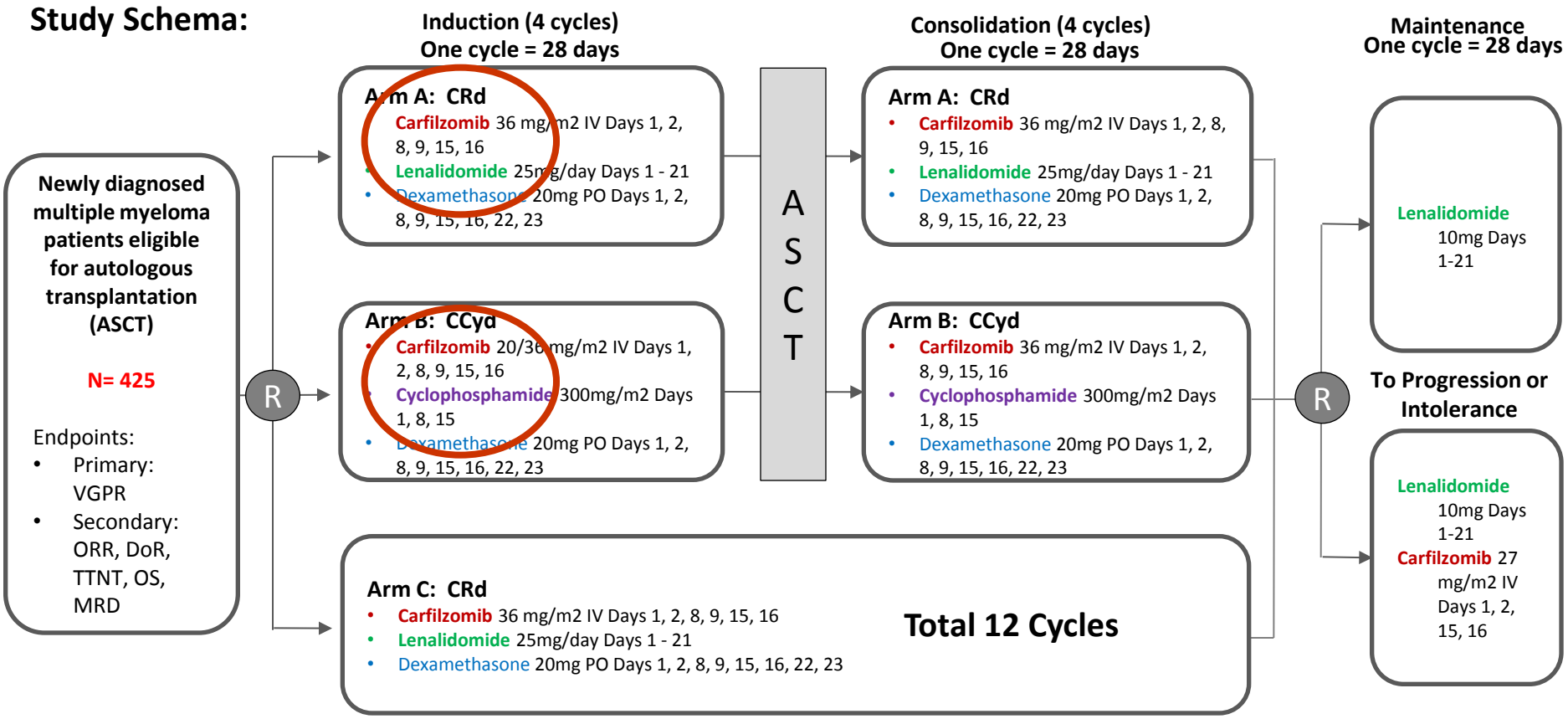
Courtesy Dr Jakubowiak



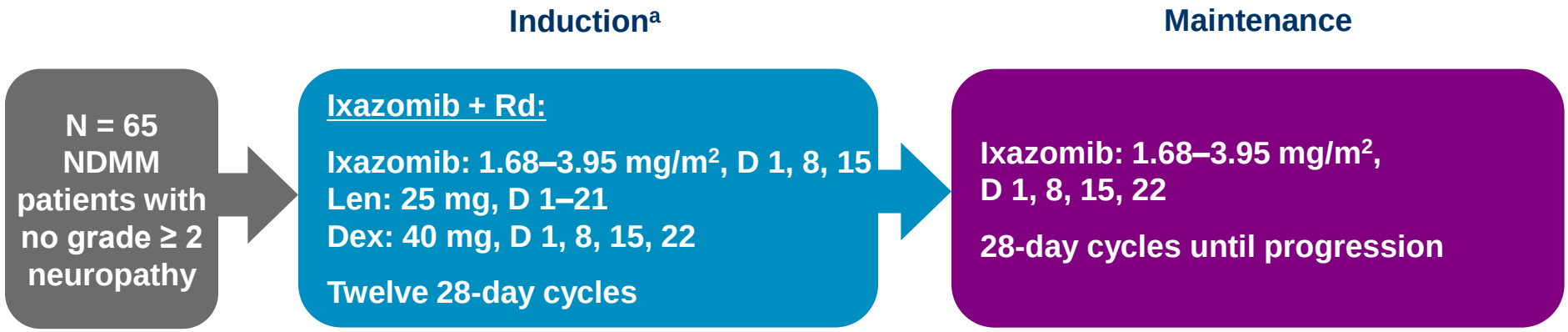
*Excludes 7 pts who discontinued to pursue ASCT

†Intent-to-treat (N=53), 4-year PFS 64%

KRd study design



Phase 1/2 Ixazomib + Rd in NDMM patients: Design



- Phase 1/2 trial to study efficacy and safety of Lenalidomide + dexamethasone in combination with the novel proteasome inhibitor ixazomib
- Median age (phase 1/2): 66 (range 34–86) years
- MTD: 2.97 mg/m^2; recommended phase 2 dose: 2.23 mg/m^2

[a]Transplant-eligible patients could undergo stem cell collection after Cycle 3 and proceed to stem cell transplantation any time after Cycle 6.
Rd, Lenalidomide, dexamethasone

Kumar SK, et al. Lancet Oncol 2014

Phase 1/2 Ixazomib + Rd in NDMM patients: Results

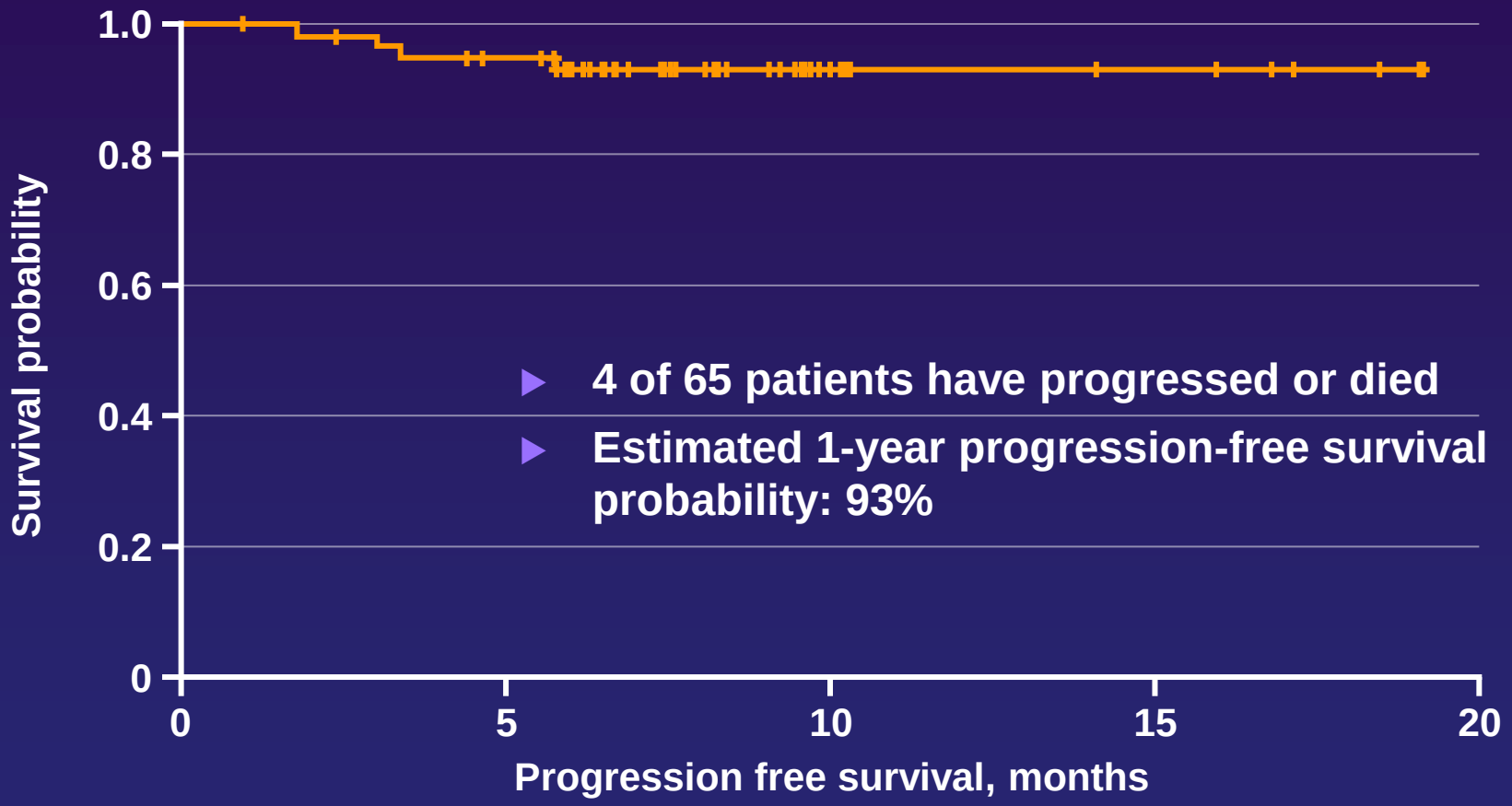
- Estimated PFS probability at 1 year: 93%

	Phase 1 (n=15)	Phase 2 (n=50)	Patients received ≥4 cycles (n=50)
CR, %	33	14	26
≥ VGPR, %	53	36	44
ORR, %	100	84	96

- Duration of response 13.2+ mos
- Safety:
  - grade 3 non-haematological AEs included erythematous rash, nausea, and vomiting (5% each); grade 3 PN at RP2D (1 patient); grade 4 AEs included end-stage renal disease, DVT (1 patient each)
  - 3 patients discontinued due to AEs

Kumar SK, et al. Lancet Oncol 2014

Progression-free survival

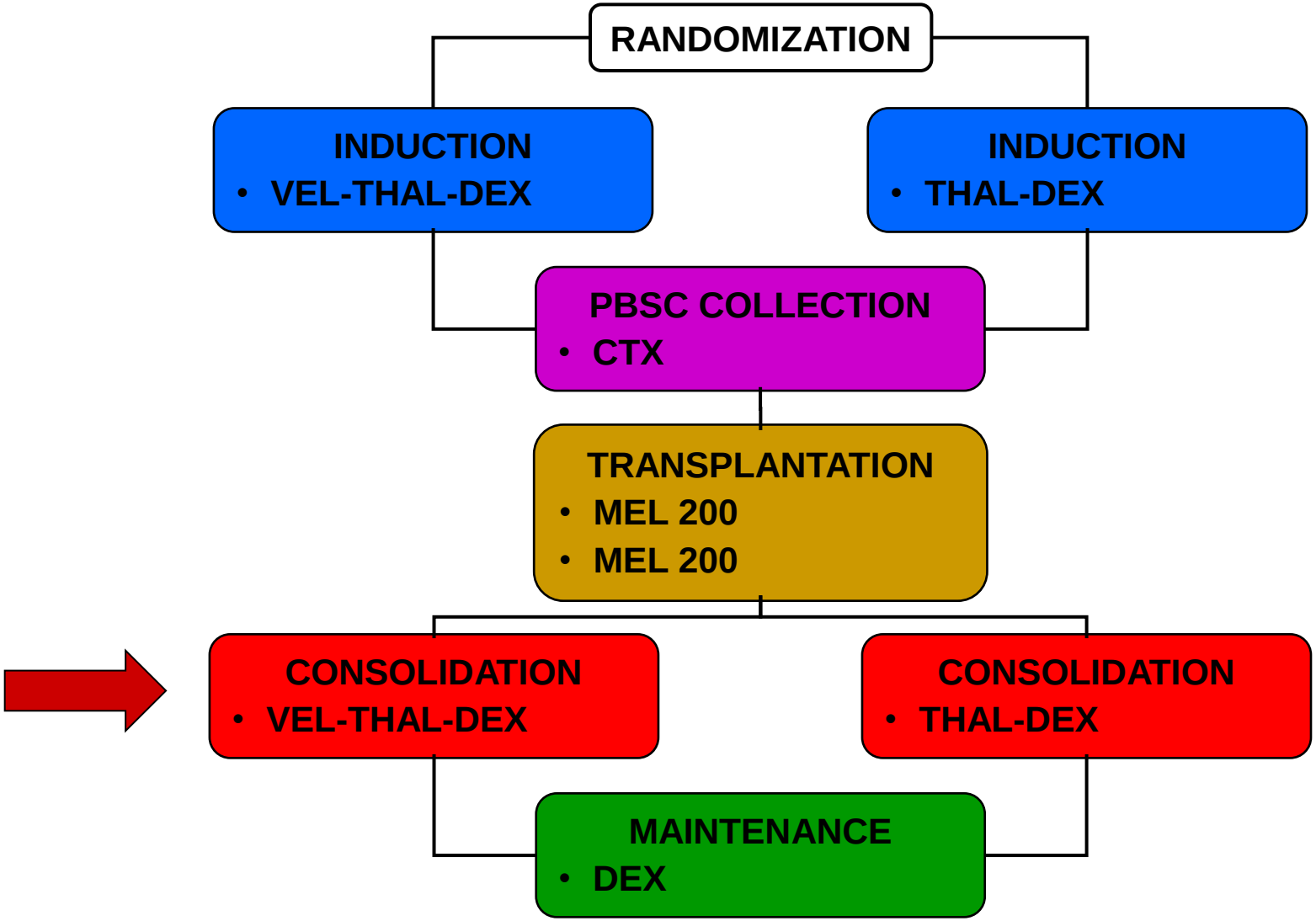


Tourmaline MM2

Rd vs Ird, in patients not eligible for ASCT

CONSOLIDATION

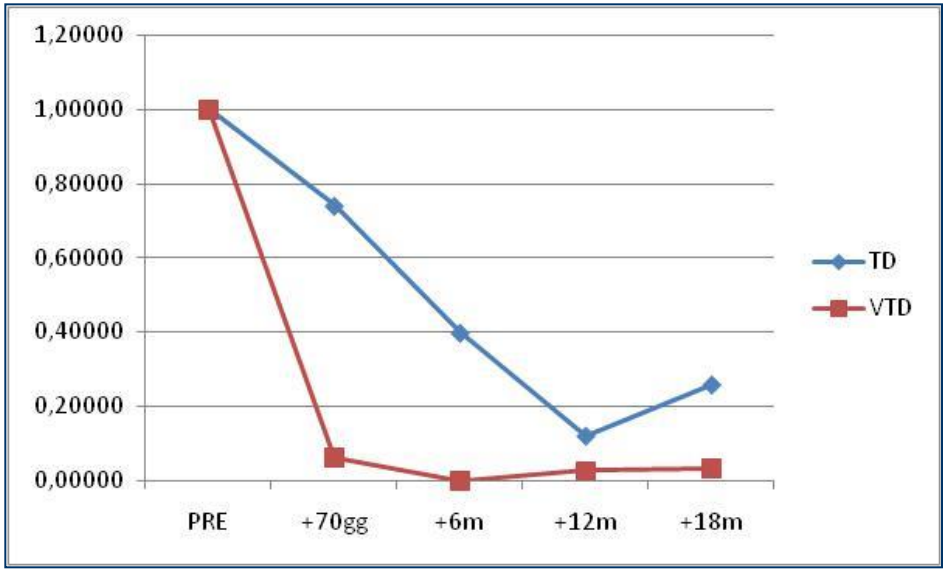
Protocol GIMEMA 26866138-MMY-3006
VTD vs TD Incorporated into Double ASCT for MM



Cavo et al, *Lancet* 2010

VTD Consolidation: PCR (patient-specific) Qualitative and Quantitative Analyses of Molecular Remission

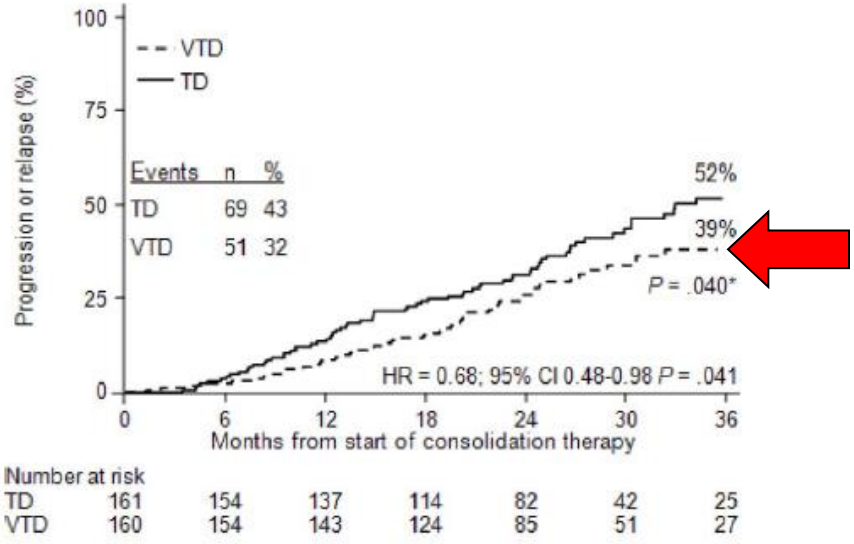
Efficacy	VTD
Pre-consolidation (day 0) PCR neg	39%
Post-consolidation (day +70) PCR neg	64%
P-value (McNemar Test)	0.0078

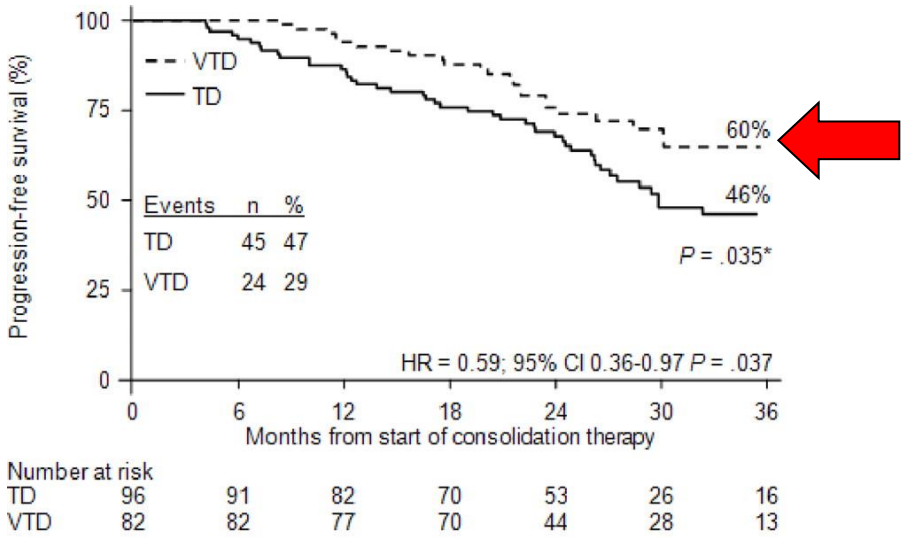


- VTD consolidation following double ASCT significantly increased the rate of molecular remissions up to the 64% value.
- In comparison with TD, VTD consolidation effected more profound reduction in residual tumor burden (1 log vs 5 log reduction).

Terragna et al. Blood 2010; 116(21). Abstract 861

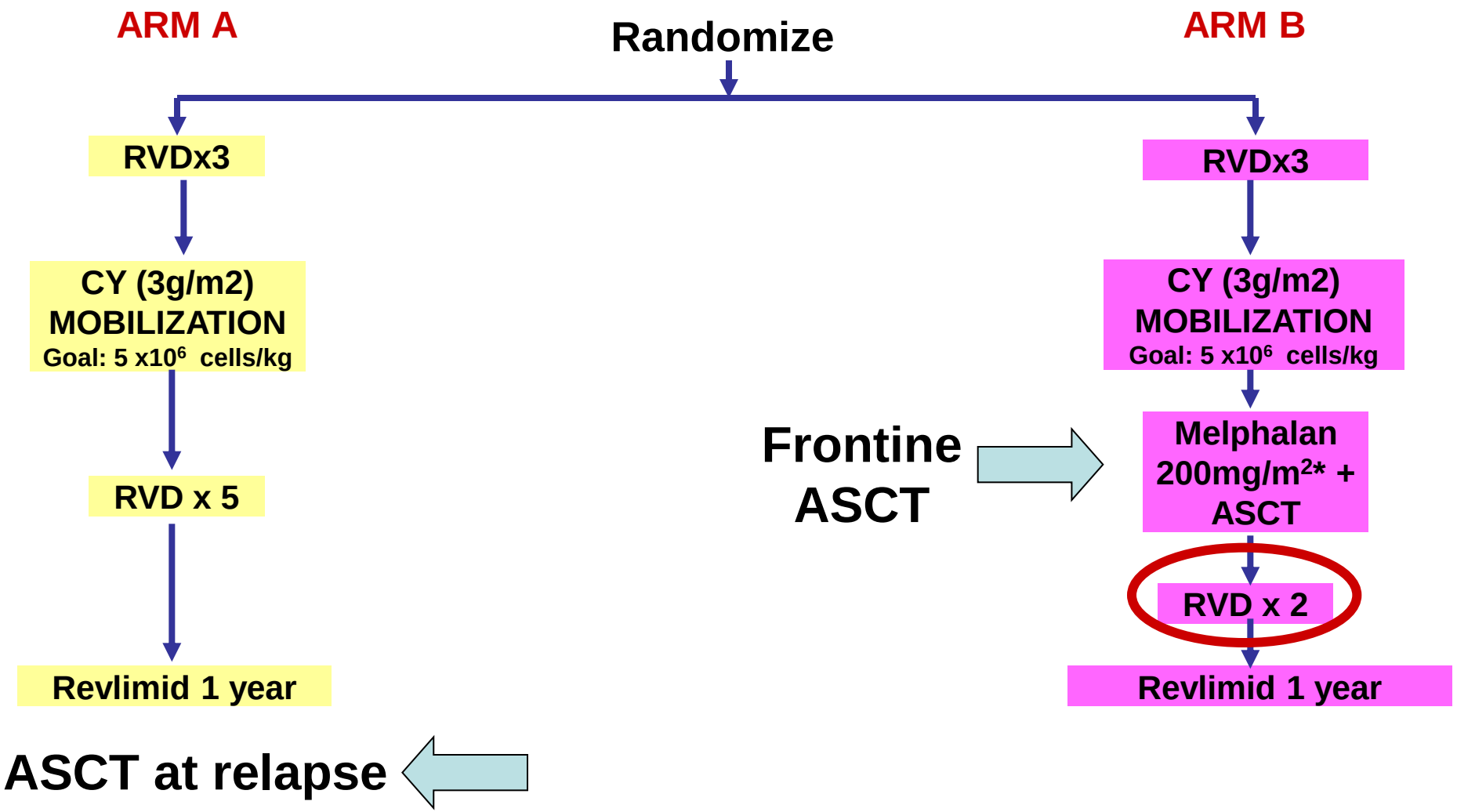
Phase 3 GIMEMA trial: TTP and PFS with VTD vs TD as consolidation





Cavo et al , *Blood* 2012;120:9-19

IFM/DFCI 2009 Study
Newly Diagnosed MM Pts (SCT candidates)



IFM 2009: VGPR rate During each Treatment Phase.

	RVD arm N=350	Transplant arm N=350	p-value
Post induction	47%	50%	NS
Post transplant or at C4	55%	73%	<0.0001
Post consolidation	71%	81%	<0.006
Post maintenance	78%	88%	<0.001

ORIGINAL ARTICLE

Consolidation and maintenance therapy with lenalidomide, bortezomib and dexamethasone (RVD) in high-risk myeloma patients

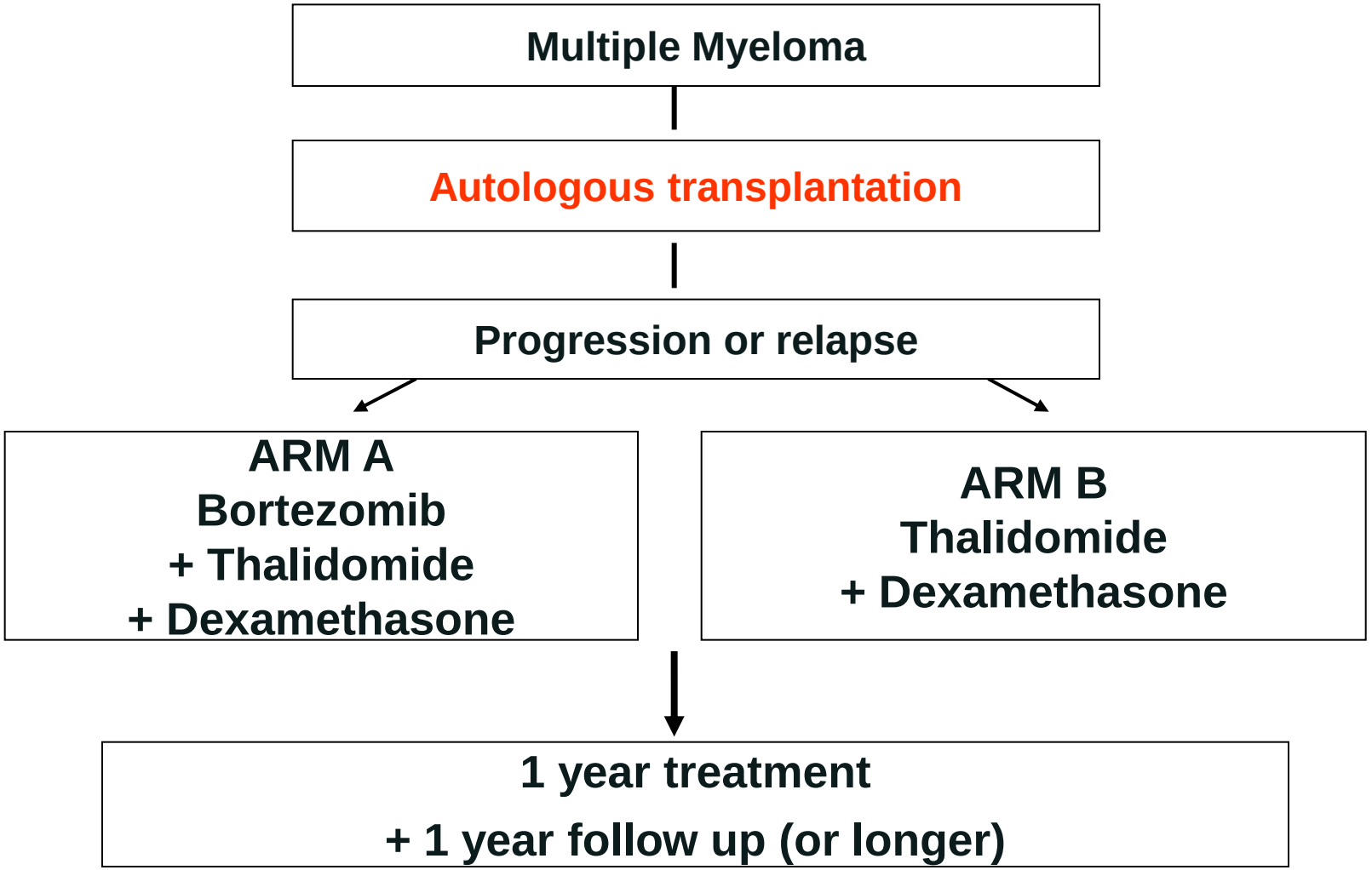
AK Nooka[1], JL Kaufman[1], S Muppidi[1], A Langston[1], LT Heffner[1], C Gleason[1], D Casbourne[1], D Saxe[2], LH Boise[1] and S Lonial[1]

Leukemia 2015

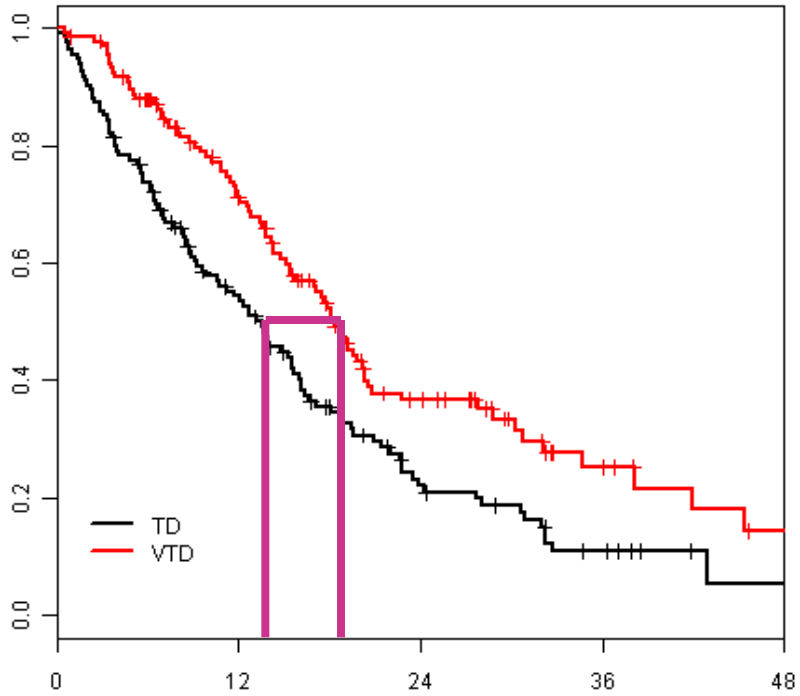
RELAPSE

Garderet L, et al. *J Clin Oncol*. 2012;30(20):2475-82

Study schema



Time-to-progression

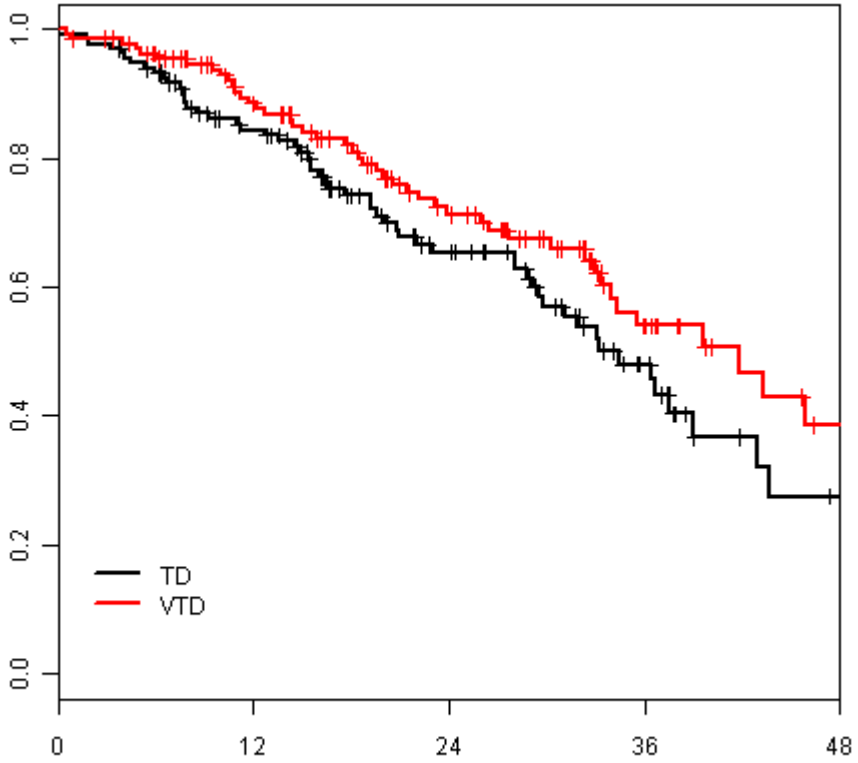


19.5 vs 13.8 mos
P= 0.0007, HR= 0.6

No. of patients at risk:				
VTD (N=135)	84	31	10	3
TD (N=134)	63	20	7	1

Garderet L, et al. *J Clin Oncol*. 2012;30(20):2475-82.

Overall survival



P= 0.09

At 2 years
VTD : 71%
TD : 65%

No. of patients at risk:				
VTD (N=135)	101	62	23	8
TD (N=134)	99	55	21	5

Garderet L, et al. *J Clin Oncol*. 2012;30(20):2475-82.

ASPIRE Study Design

Randomization

N=792

Stratification:

- **β_2-microglobulin**
- **Prior bortezomib**
- **Prior lenalidomide**

28-day cycles

KRd

Carfilzomib 27 mg/m^2 IV (10 min)

Days 1, 2, 8, 9, 15, 16 (20 mg/m^2 days 1, 2, cycle 1 only)

Lenalidomide 25 mg *Days 1–21*

Dexamethasone 40 mg *Days 1, 8, 15, 22*

After cycle 12, carfilzomib given on days 1, 2, 15, 16

After cycle 18, carfilzomib discontinued

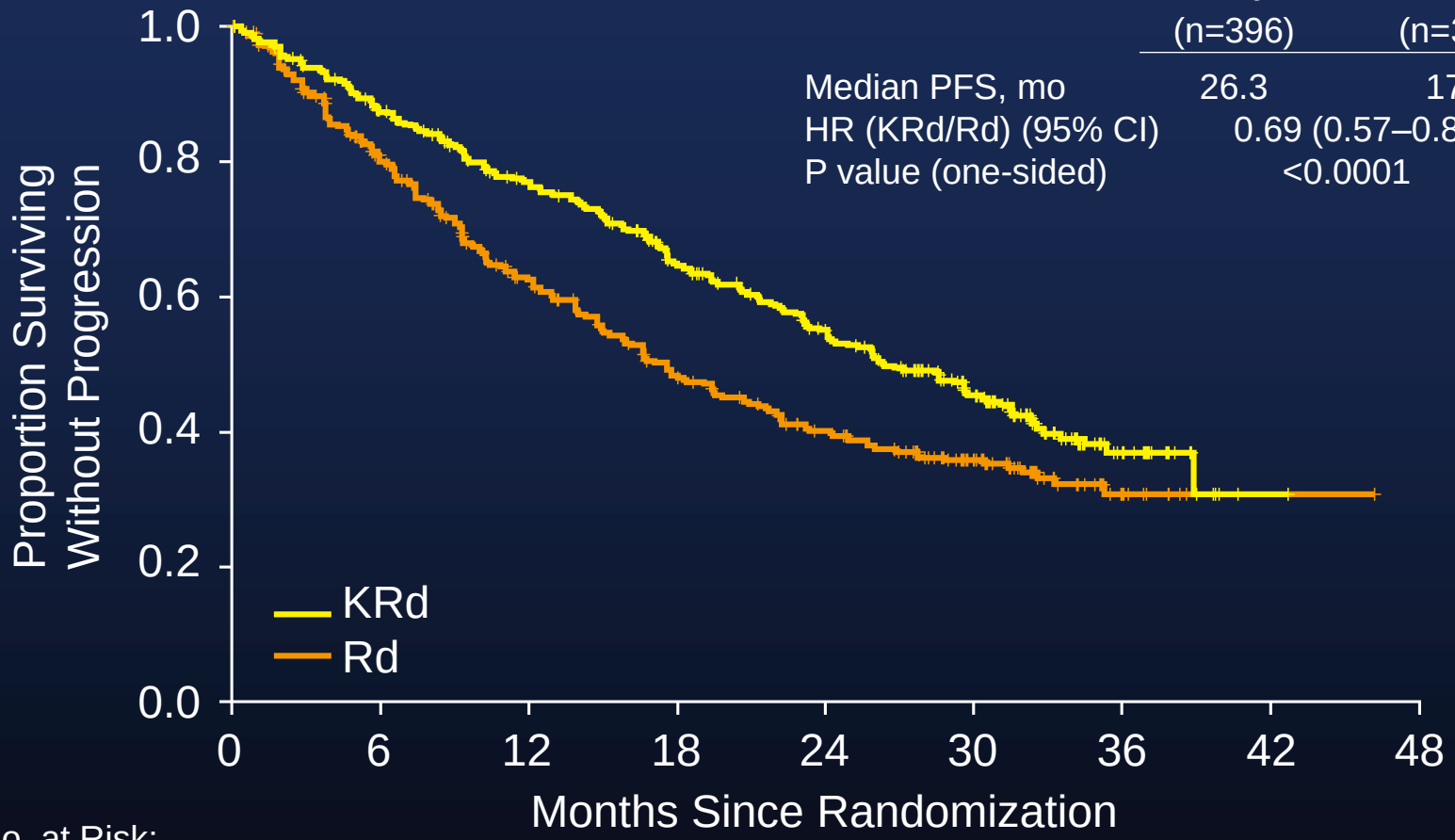
Rd

Lenalidomide 25 mg *Days 1–21*

Dexamethasone 40 mg *Days 1, 8, 15, 22*

Stewart et al. N Engl J Med 2014

Primary Endpoint: Progression-Free Survival
ITT Population (N=792)

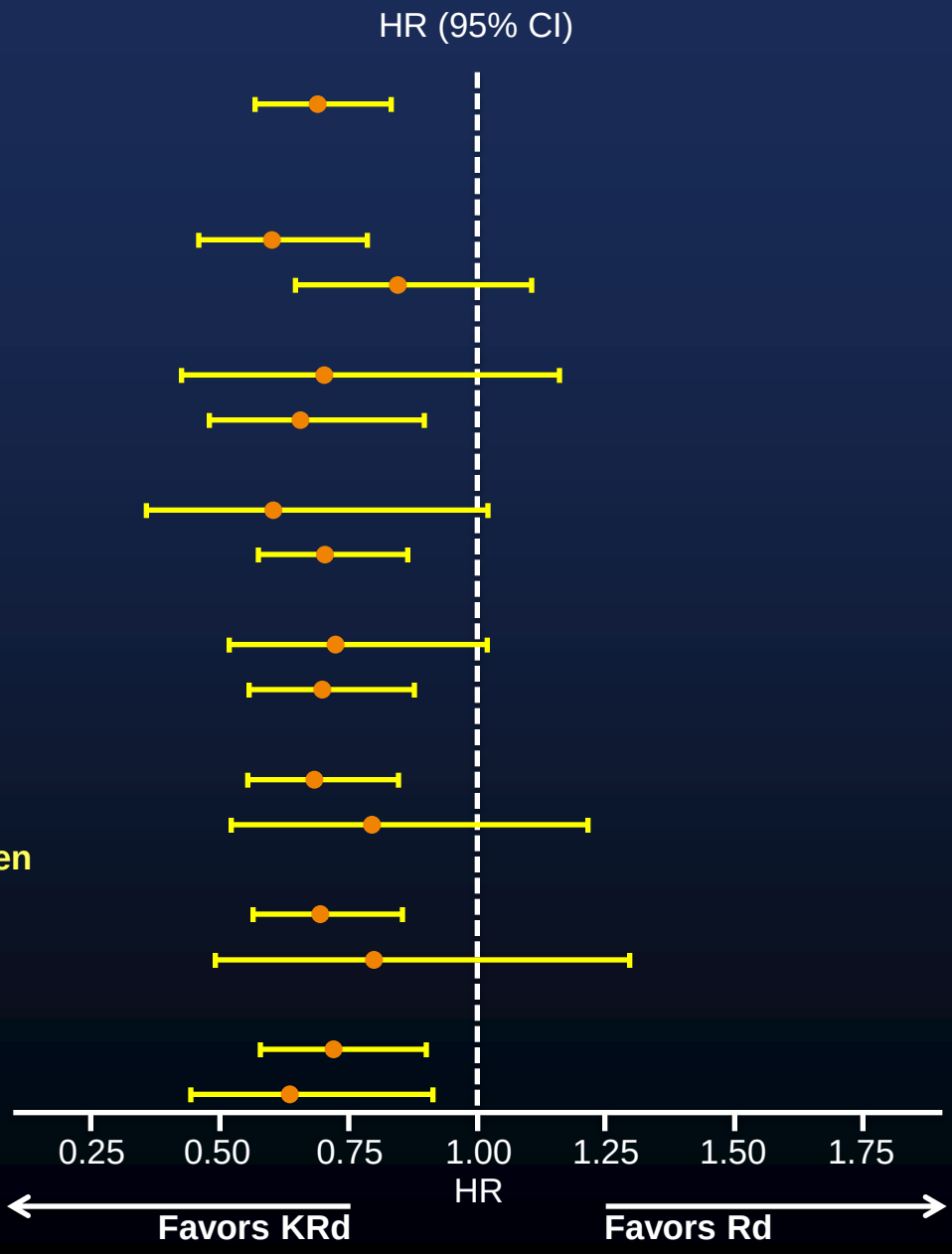


No. at Risk:

KRd	396	332	279	222	179	112	24	1
Rd	396	287	206	151	117	72	18	1

Primary Endpoint: Progression-Free Survival by Subgroup

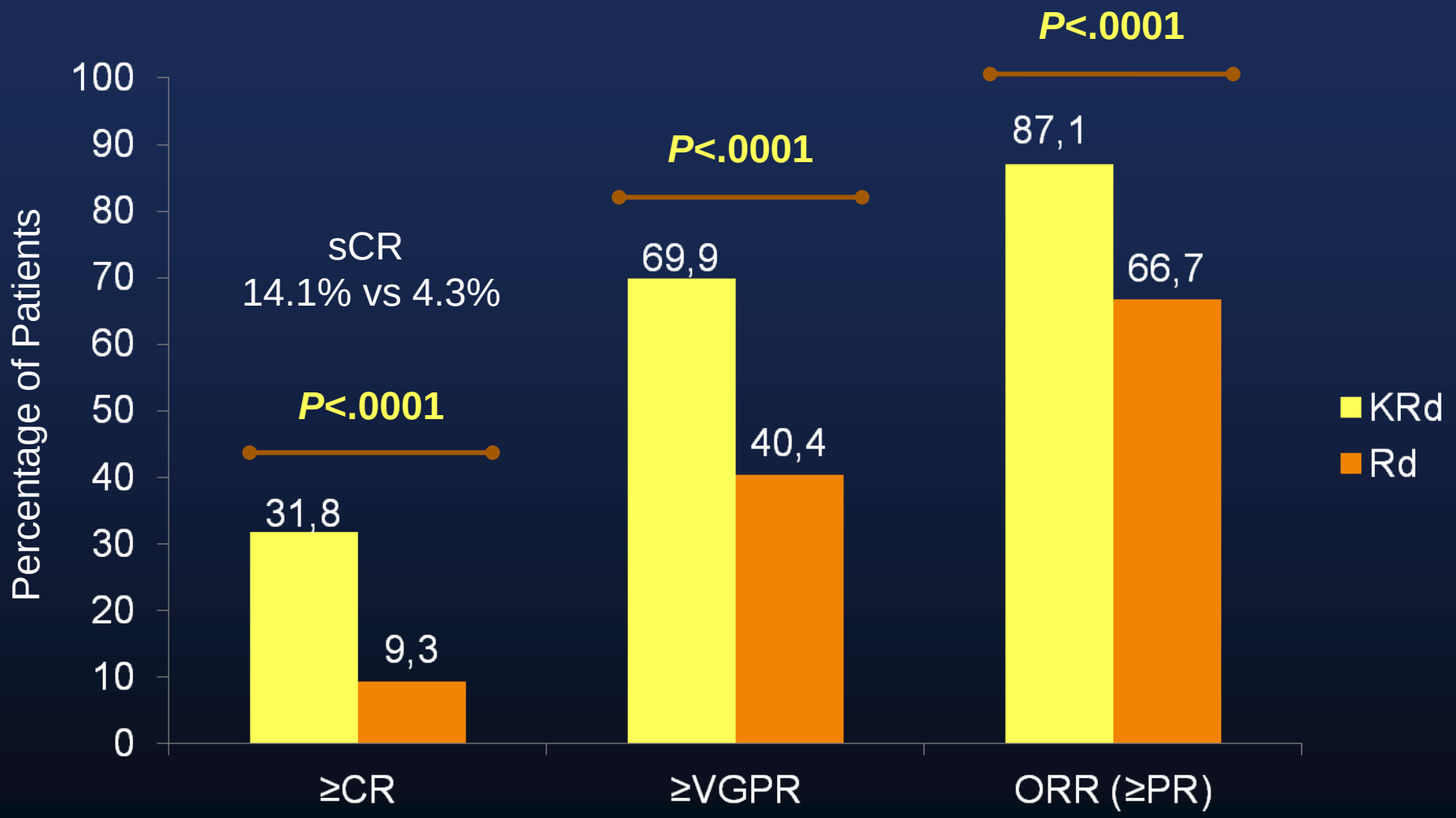
Intent-to-treat group	KRd (n)	Rd (n)
Overall	396	396
Subgroup		
Age, years		
18–64	211	188
≥65	185	208
Risk group by FISH		
High-risk	48	52
Standard-risk	147	170
$ß_2$-microglobulin, mg/L		
<2.5	68	71
≥2.5	324	319
Prior treatment with bortezomib		
No	135	136
Yes	261	260
Prior treatment with lenalidomide		
No	317	318
Yes	79	78
Non-responsive to bortezomib in any prior regimen		
No	336	338
Yes	60	58
Refractory to IMiD in any prior regimen		
No	311	308
Yes	85	88



PFS by Risk Group

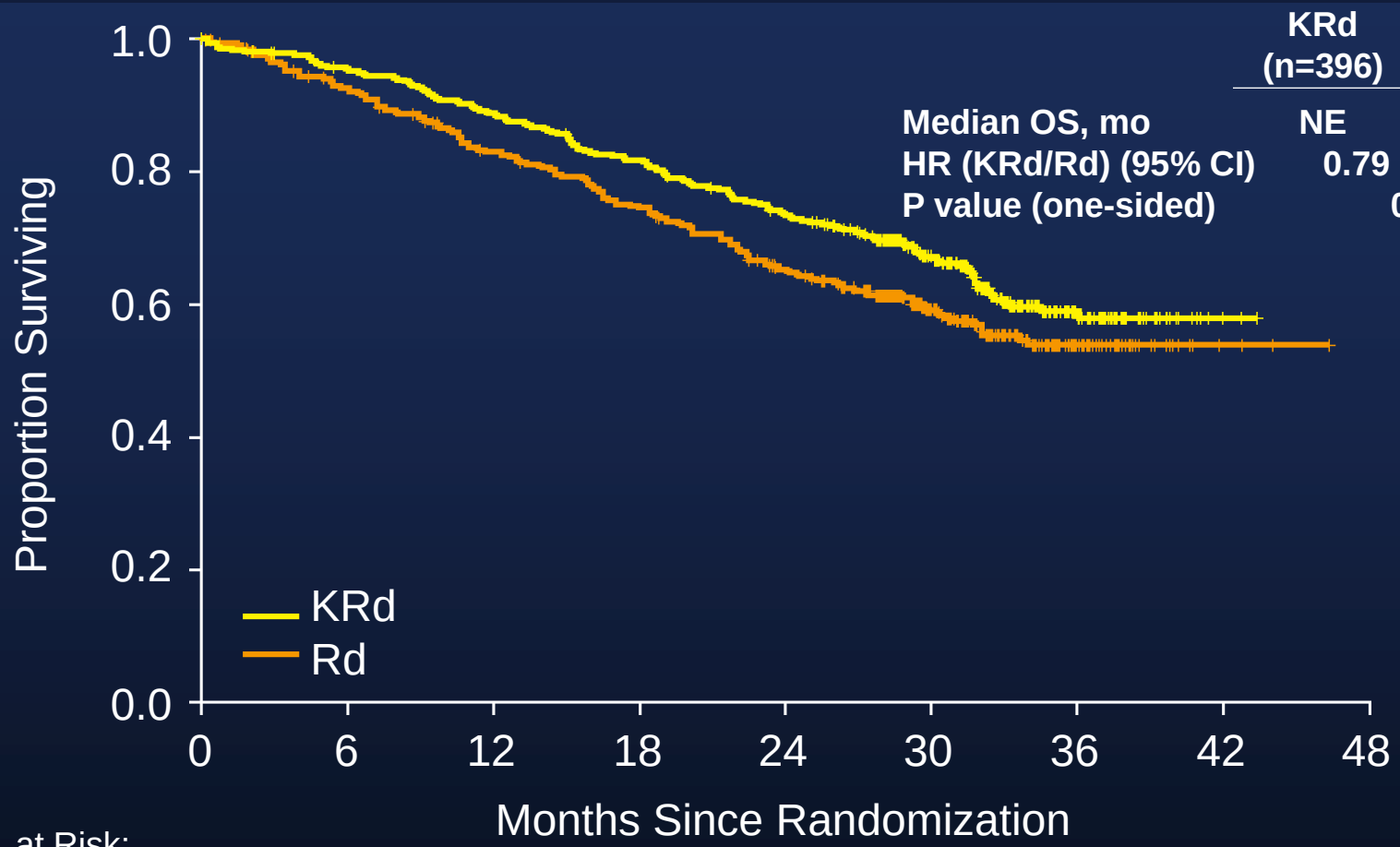
	KRd (n=396)		Rd (n=396)			
Risk Group by FISH	N	Median, months	N	Median, months	HR	P-value (one-sided)
High	48	23.1	52	13.9	0.70	0.083
Standard	147	29.6	170	19.5	0.66	0.004

Secondary Endpoints: Response



- **Median duration of response was 28.6 months in the KRd group and 21.2 months in the Rd group**

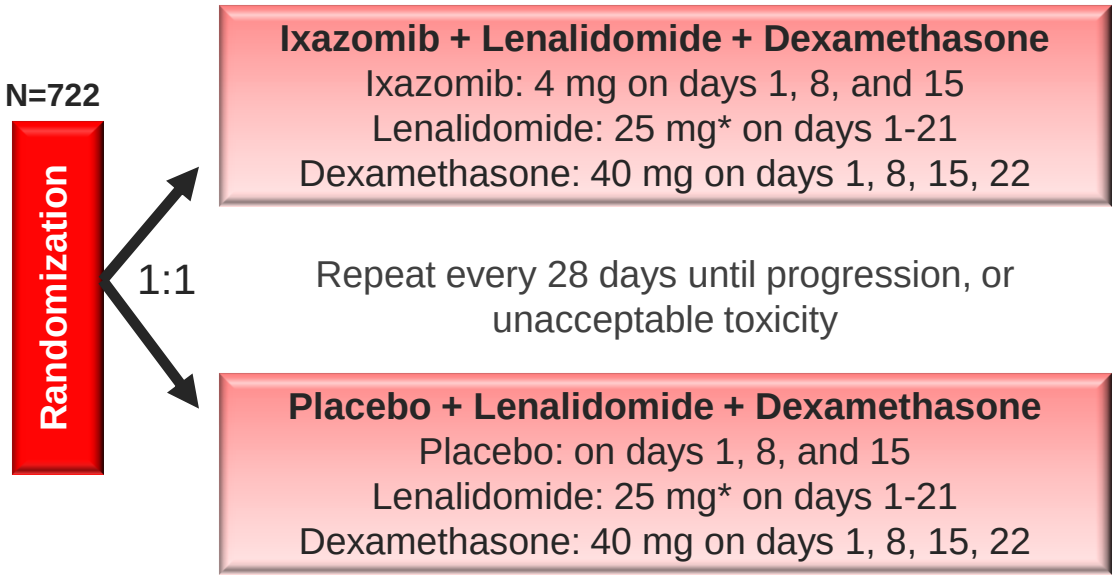
Secondary Endpoints: Interim Overall Survival Analysis
Median Follow-Up 32 Months



- **Median OS was not reached; results did not cross the prespecified stopping boundary (P=0.005) at the interim analysis**

TOURMALINE-MM1: Phase 3 study of weekly oral ixazomib plus lenalidomide-dexamethasone

Global, double-blind, randomized, placebo-controlled study design



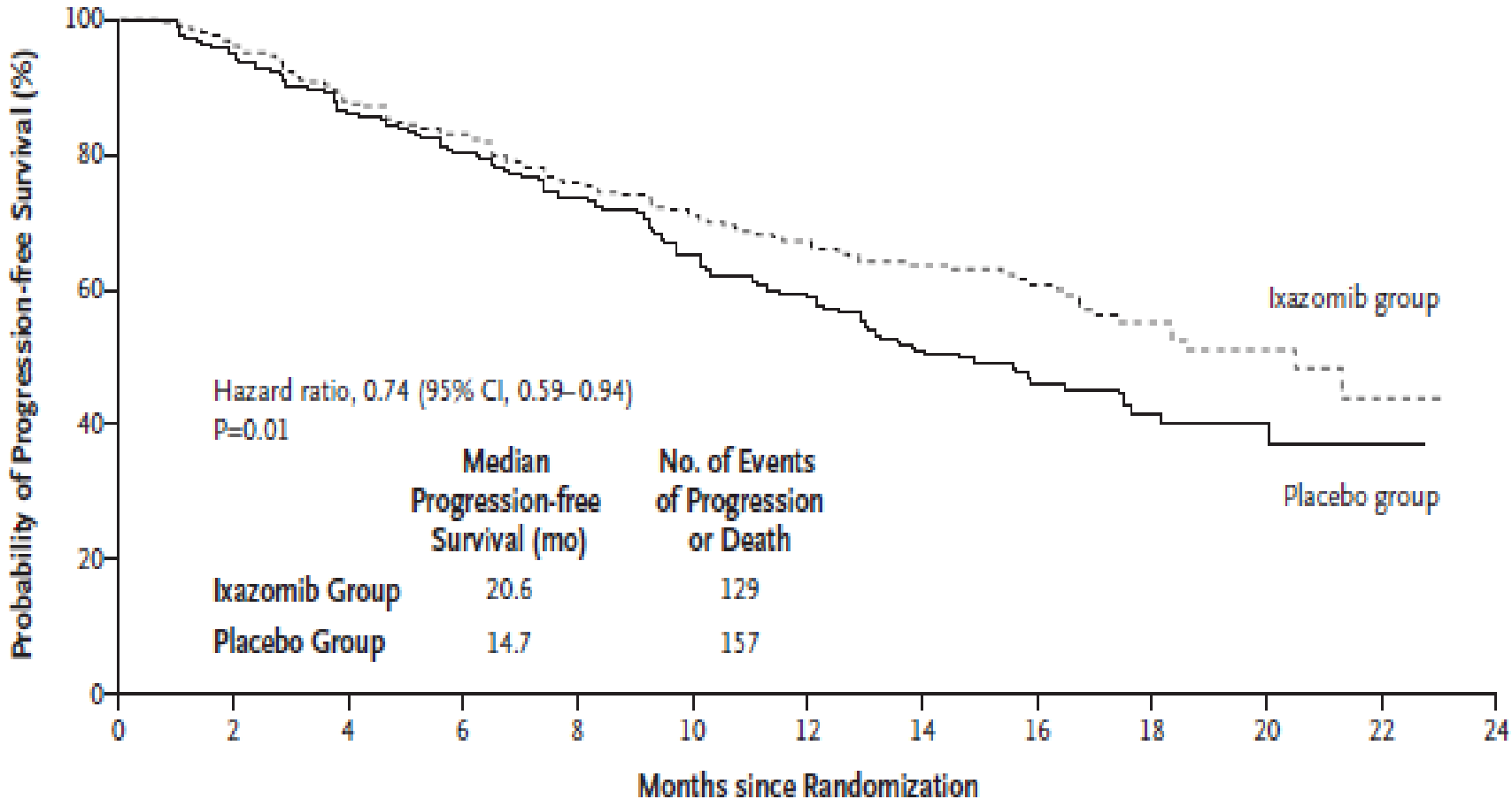
Stratification:
- Prior therapy: 1 vs 2 or 3
- ISS: I or II vs III
- PI exposure: yes vs no

Primary endpoint:
- PFS

Key secondary endpoints:
- OS
- OS in patients with del(17p)

Response and progression (IMWG 2011 criteria[1]) assessed by an independent review committee (IRC) blinded to both treatment and investigator assessment

A Progression-free Survival in the Intention-to-Treat Population



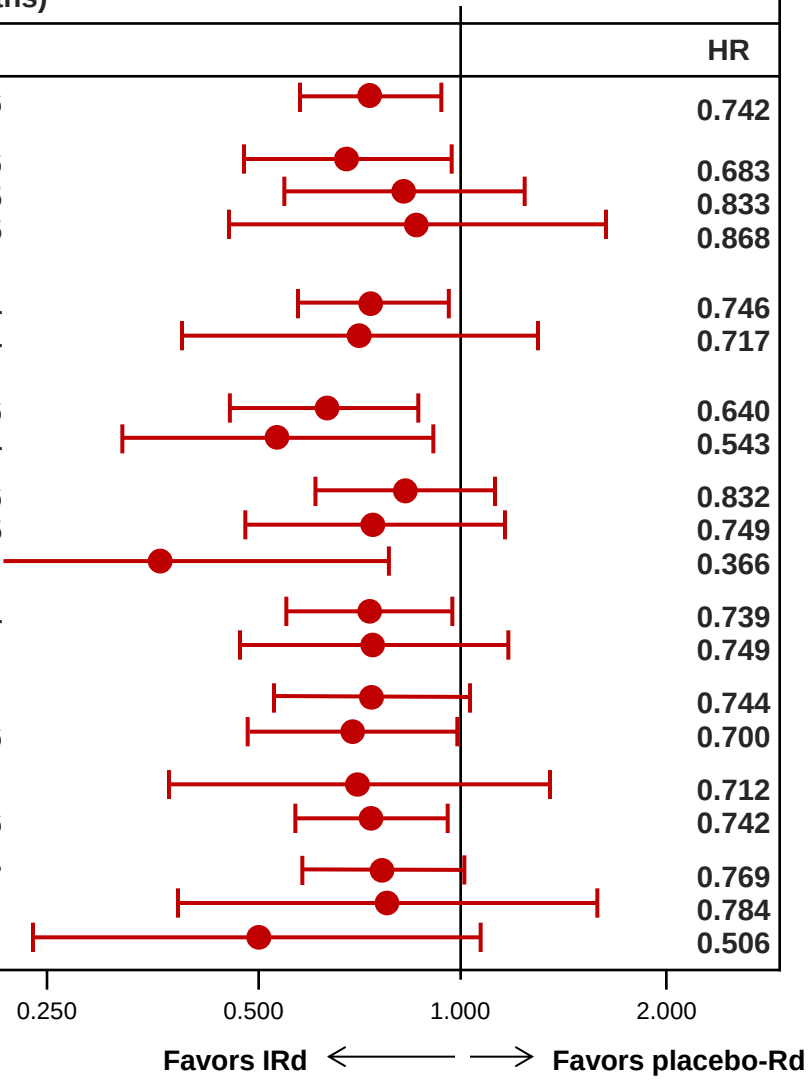
No. at Risk

Ixazomib group	360	345	332	315	298	283	270	248	233	224	206	182	145	119	111	95	72	58	44	34	26	14	9	1	0
Placebo group	362	340	325	308	288	274	254	237	218	208	188	157	130	101	85	71	58	46	31	22	15	5	3	0	0

Moreau et al. N Engl J Med 2016, online Apr28

Consistent PFS benefit across pre-specified patient subgroups

		N		Median PFS (months)		
Variable	Subgroup	Placebo-Rd	IRd	Placebo-Rd	IRd	HR
All patients	ALL	360	362	14.7	20.6	0.742
Age (yrs)	≤65	176	168	14.1	20.6	0.683
	>65-75	125	145	17.6	17.5	0.833
	>75	61	47	13.1	18.5	0.868
ISS stage (stratification factor)	I or II	318	314	15.7	21.4	0.746
	III	44	46	10.1	18.4	0.717
Cytogenetic risk	Standard-risk	216	199	15.6	20.6	0.640
	High-risk	62	75	9.7	21.4	0.543
Number of prior therapies	1	217	224	15.9	20.6	0.832
	2	111	97	14.1	17.5	0.749
	3	34	39	10.2	NE	0.366
Proteasome inhibitor	Exposed	253	250	13.6	18.4	0.739
	Naive	109	110	15.7	NE	0.749
Prior IMiD therapy	Exposed	204	193	17.5	NE	0.744
	Naïve	158	167	13.6	20.6	0.700
Refractory to last prior therapy	Yes	55	59	NE	NE	0.712
	No	307	301	14.1	20.6	0.742
Relapsed or refractory	Relapsed	280	276	15.6	18.7	0.769
	Refractory	40	42	13.0	NE	0.784
	Ref & rel	42	41	13.1	NE	0.506



Outcomes by cytogenetic risk group

	ORR, %		≥VGPR, %		≥CR, %		Median PFS, months		
	IRd	Placebo-Rd	IRd	Placebo-Rd	IRd	Placebo-Rd	IRd	Placebo-Rd	HR
All patients	78.3*	71.5	48.1*	39	11.7*	6.6	20.6	14.7	0.742*
Standard-risk patients	80	73	51	44	12	7	20.6	15.6	0.640*
All high-risk patients	79*	60	45*	21	12*	2	21.4	9.7	0.543
Patients with del(17p)†	72	48	39	15	11*	0	21.4	9.7	0.596
Patients with t(4;14) alone	89	76	53	28	14	4	18.5	12.0	0.645

*p<0.05 for comparison between regimens. †Alone or in combination with t(4;14 or t(14;16).
Data not included on patients with t(14:16) alone due to small numbers (n=7).

- Median OS was not reached in either arm
- In the IRd arm, median PFS in high-risk patients was similar to that in the overall patient population and in patients with standard-risk cytogenetics

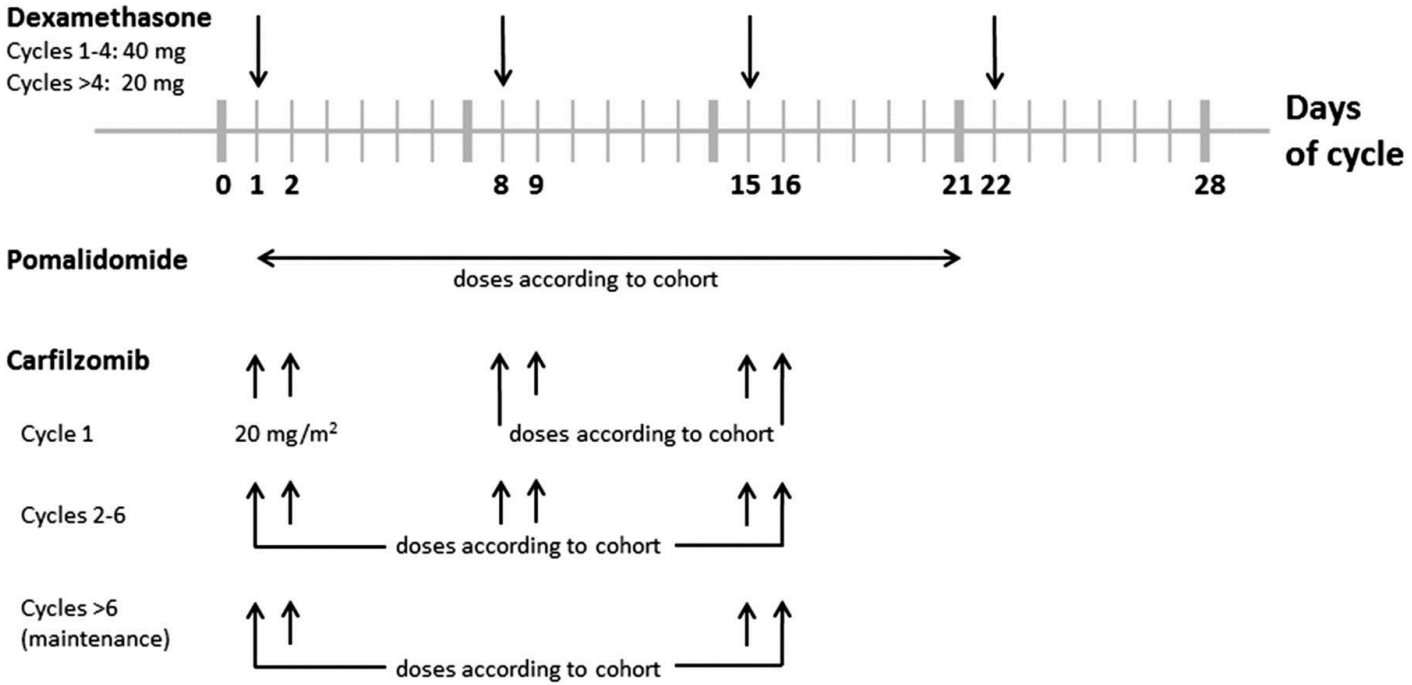
Burden to patient, caregiver, and healthcare system

	IRd	KRd
Route of administration	PO	IV
Minimum clinic visits based on 18 cycles	18	96
Dosing schedule	Days 1, 8, and 15 of 28-day cycle	Days 1, 2, 8, 9, 15, and 16 of 28-day cycle. Additional IV hydration needed especially before each dose in Cycle 1, but may be in other cycles also
Hospital/clinic visit	Every 4 weeks	Twice a week
Premedication	N	N
Prehydration	N	Y
Minimum administration time in clinic/ hospital per visit	0 hours	Over 2 hours (130 minutes)

Vd vs Vd-pomalidomide
MM007 ongoing

Carfilzomib-pomalidomide-dexamethasone

Phase I/II study of RRMM patients

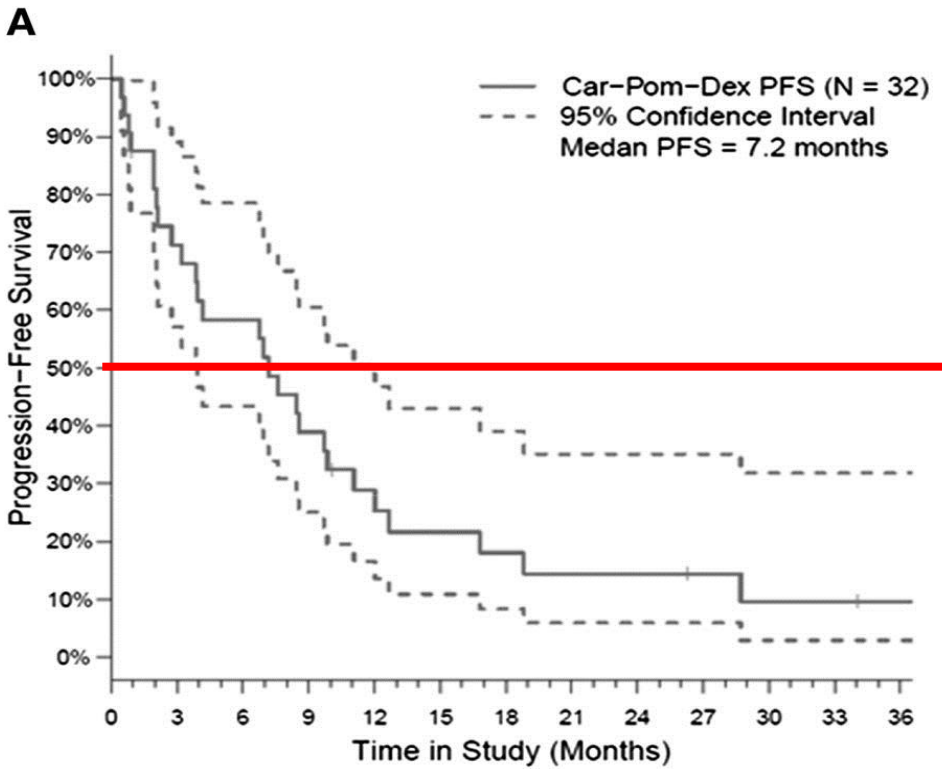


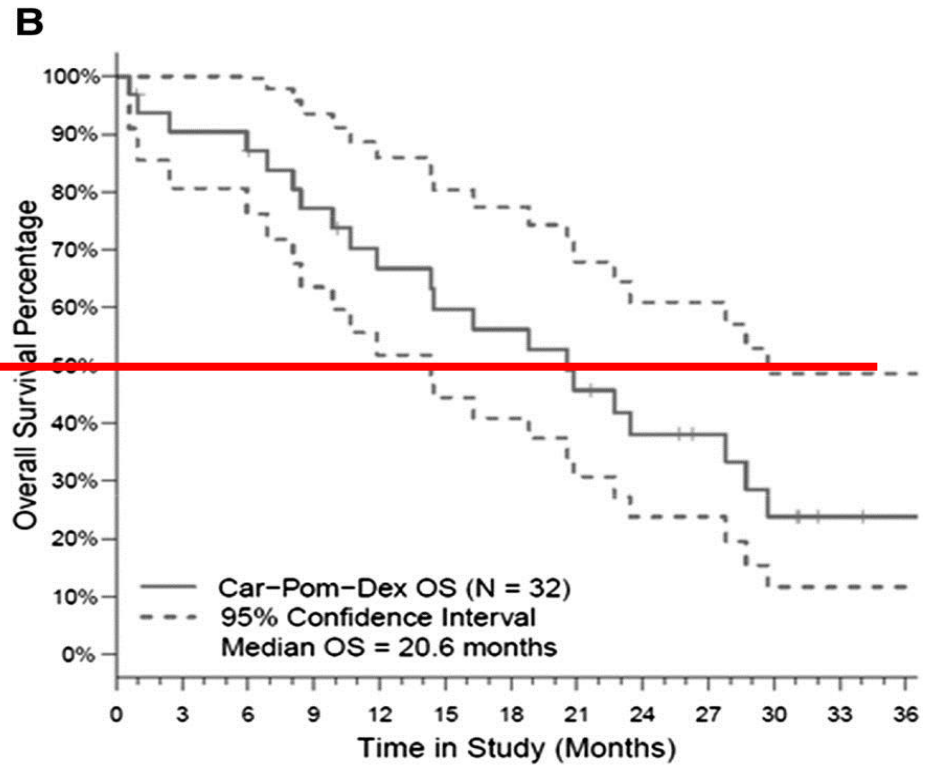
- Primary endpoints: safety and MTD
- Secondary endpoints: ORR, TTP, PFS and OS

Shah JJ, et al. *Blood* 2015;126:2284–2290

Carfilzomib-pomalidomide-dexamethasone

CPD is highly active in RRMM patients





Shah JJ, et al. *Blood* 2015;126:2284–2290

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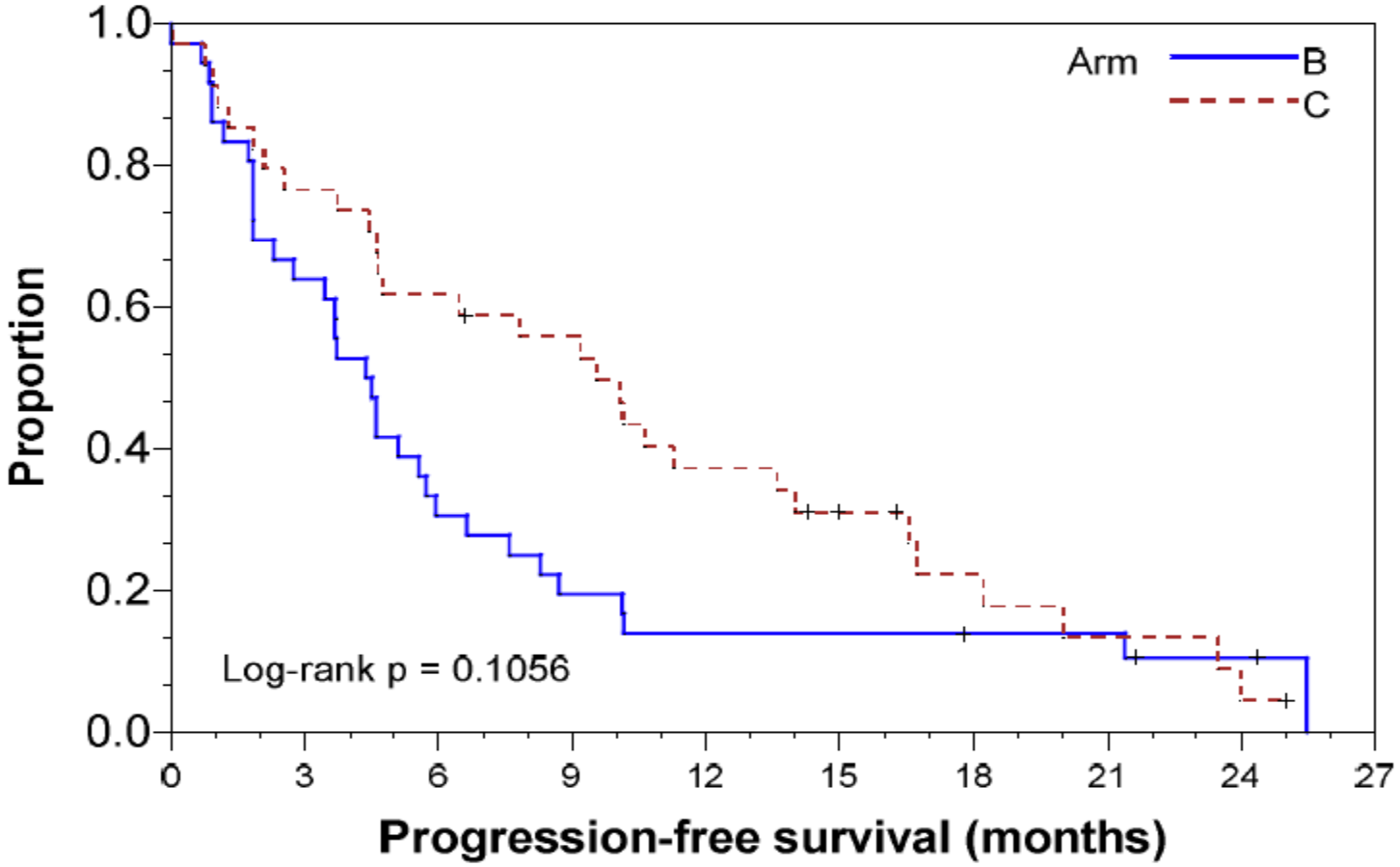
Randomized multicenter phase II study of pomalidomide, cyclophosphamide, and dexamethasone in relapsed refractory myeloma

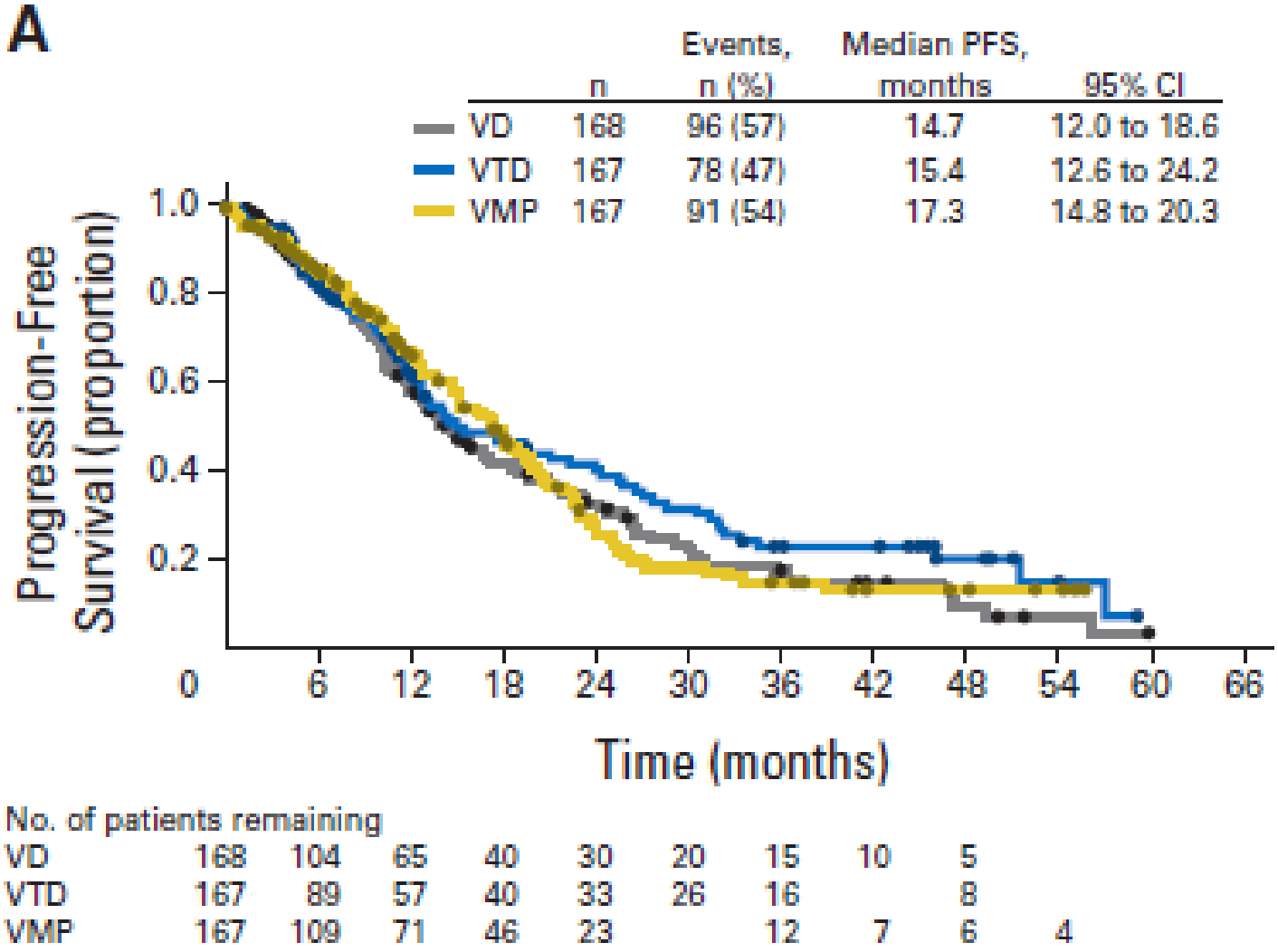
Rachid C. Baz, Thomas G. Martin III, Hui-Yi Lin, Xiuhua Zhao, Kenneth H. Shain, Hearn J. Cho, Jeffrey L. Wolf, Anuj Mahindra, Ajai Chari, Daniel M. Sullivan, Lisa A. Nardelli, Kenneth Lau, Melissa Alsina and Sundar Jagannath

Figure 2. Progression free (a) and overall survival (b) comparing arms B and



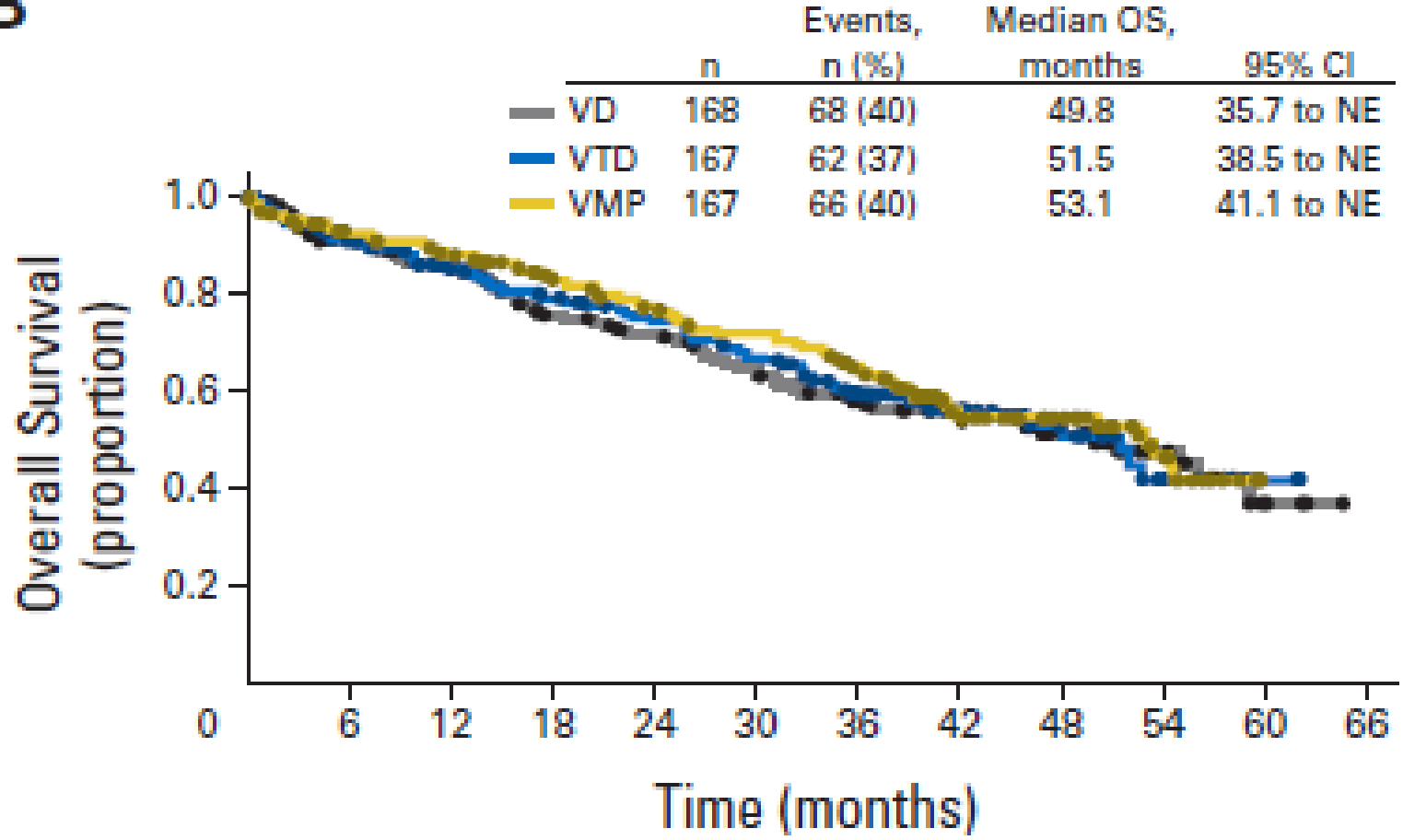
Arm	N	Event	Censored	Median (95% CI)
B	36	33 (92%)	3 (8%)	4.4(2.3, 5.7)
C	34	29 (85%)	5 (15%)	9.5(4.6, 14.0)

Cyclophosphamide : 400 mg oral D1, D8, D15



Niesvisky et al. JCO 2015

B



No. of patients remaining

VD	168	136	122	99	91	79	66	54	35	20	5
VTD	167	132	115	103	93	83	64	44	26	12	3
VMP	167	143	133	113	104		78	50	36	21	

Niesvisky et al. JCO 2015

Conclusions

- PI + IMiD : standard of care, upfront and relapse

- VRD: prior to ASCT, in patients not eligible for ASCT as well

Frontline eligible for ASCT : KRd ?

Ird in elderly patients ?

- In the relapse setting: KRd or Ird ?

- Effective in patients with high-risk cytogenetics

- No biomarkers

! Cautious : IMiDs / PIs + cyclophosphamide, IMiDs / PIs + MoAbs ?