

**Phase III trial of lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone in newly diagnosed multiple myeloma (E4A03): a trial coordinated by the Eastern Cooperative Oncology Group**

**S. Vincent Rajkumar, Susanna Jacobus, Natalie Callander, Rafael Fonseca, David Vesole, Michael Williams, Rafat Abonour, David Siegel, and Philip Greipp**

**Mayo Clinic, Rochester, MN; Dana Farber Cancer Institute, Boston, MA; University of Wisconsin, Madison, WI; Mayo Clinic Arizona, Scottsdale, AZ; St. Vincent's Hospital, New York, NY, University of Virginia, Charlottesville, VA, Indiana University, Indianapolis, IN, Hackensack University Medical Center, Hackensack, NJ**

## Thalidomide/Dex in Newly Diagnosed MM

Study	Type of study	No. of patients	Response rate
Rajkumar et al (Mayo Clinic)	Phase II	50	64%
Weber et al (MDACC)	Phase II	40	72%
Cavo et al	Phase II	71	66%
Rajkumar et al (ECOG)	Phase III	207	63%
Rajkumar et al (MM 003)	Phase III	470	63%

# Mayo Phase II Trial Lenalidomide/Dex (Rev/Dex) in New MM

Endpoint	Response Rate
Response rate (PR or better)	<b>91%</b>
CR plus VGPR	<b>56%</b>

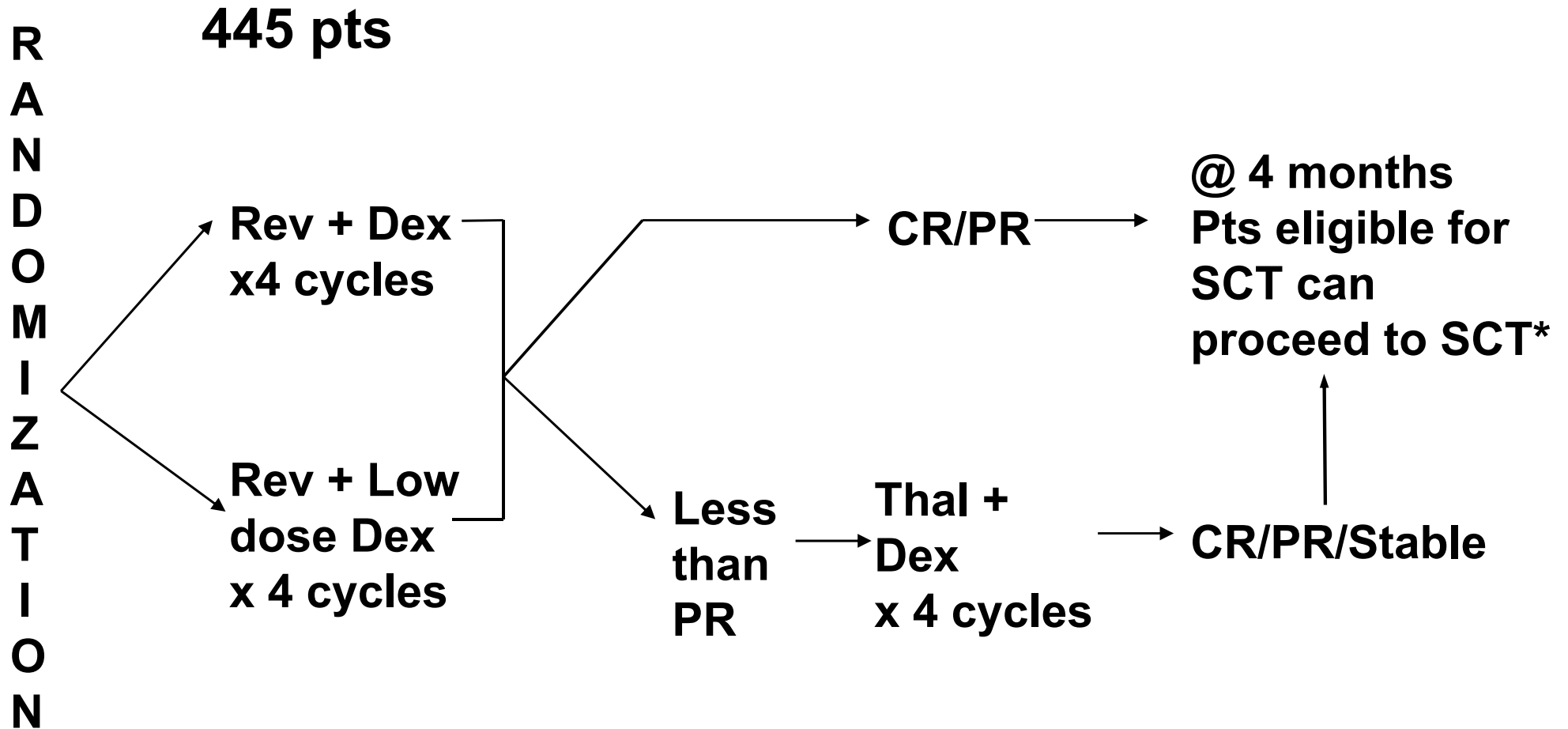
Grade 3-4 non-hematologic toxicities: 55% patients



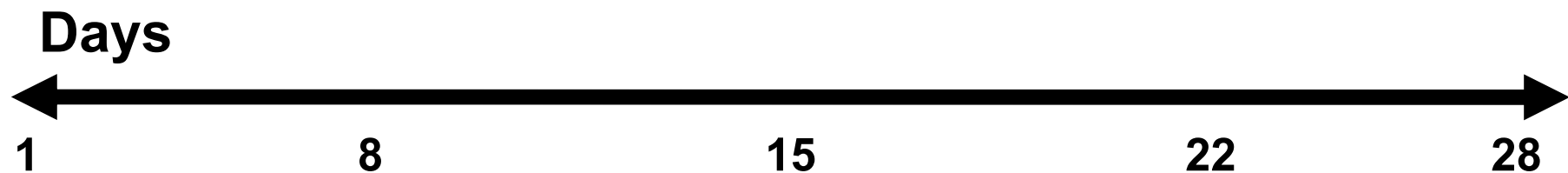
## Aim

- A phase III trial comparing lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as first line therapy in newly diagnosed multiple myeloma

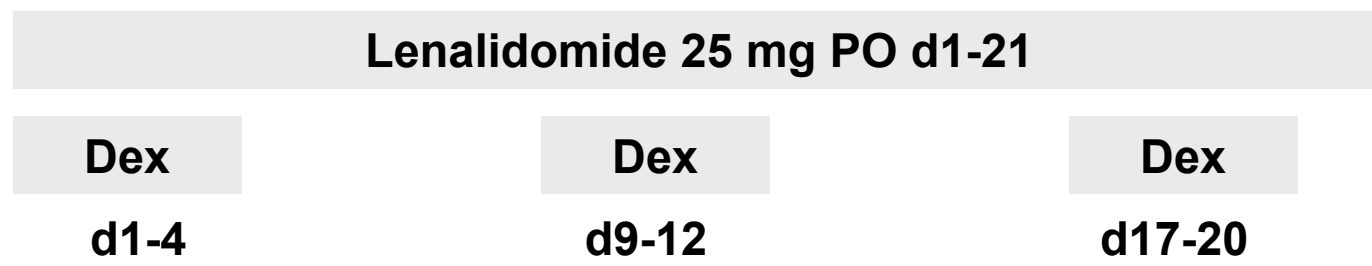
# Schema



# Treatment Schedule

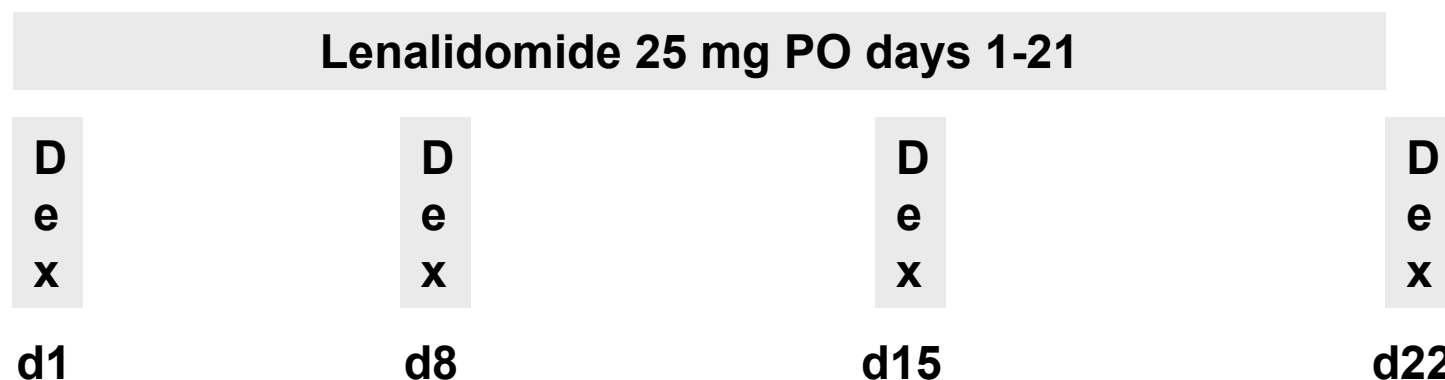


**A**



**Total Dex dose per Cycle = 480 mg**

**B**



**Total Dex dose per Cycle = 160 mg**

## DVT prophylaxis

- Prior to Sept 15, 2005: Thromboprophylaxis with ASA recommended but not mandated
- After Sept 15, 2005: ASA instituted as mandatory thromboprophylaxis; warfarin/LMWH strongly recommended for pts in Arm A

## Patient Characteristics

	<b>Arm A (n=223)</b>	<b>Arm B (n=222)</b>
<b>ISS (%)</b>		
Stage I	30.5	31.5
Stage II	37.8	37.8
Stage III	23.3	23.9

## Patient Characteristics

	<b>Arm A (n=223)</b>	<b>Arm B (n=222)</b>
Male (%)	57.8	54.1
Age (yrs)	66 (36-88)	65 (35-86)
ECOG PS $\leq$ 1 (%)	89.7	89.6
BMPC (%)	44.5	40.0
Serum M protein (g/dL)	3.2	3.1
Hemoglobin (g/dL)	10.9	11.1

## Patient Characteristics

	<b>Arm A (n=223)</b>	<b>Arm B (n=222)</b>
DS Stage III (%)	79.3	75.2
MM Bone Disease (%)	65	60
Albumin (g/dL)	3.5	3.6
LDH (U/L)	155	159
B2 Microglobulin ( $\mu\text{g/mL}$ )	3.75	3.5
Creatinine (mg/dL)	1.1	1.0

## Serious adverse events Hematologic Toxicity

<b>Toxicity (N=433 Ever Reported)</b>	<b>Arm A (N=217)</b>	<b>Arm B (N=216)</b>	<b>P value</b>
Hemoglobin	7.8%	6.0%	0.12
Neutrophils	9.7%	19%	0.002
Platelets	4.1%	5.1%	0.16

## Serious adverse events Non-Hematologic Toxicity

<b>Toxicity (N=433 Ever Reported)</b>	<b>Arm A (N=217)</b>	<b>Arm B (N=216)</b>	<b>P value</b>
DVT/PE (AdEERS*)	23.8%	9.1%	<0.001
Infection/Pneumonia	14.7%	5.1%	<0.001
Hyperglycemia	9.7%	6%	0.05
Cardiac ischemia	2.8%	0.5%	0.05
Atrial fibrillation/flutter	2.3%	0.5%	0.09
Neuropathy	1.4%	0.9%	0.31

# DVT/PE

<b>Toxicity (N=443 Started Treatment)</b>	<b>Arm A N=223 (%)</b>	<b>Arm B N=220 (%)</b>
DVT/PE		
First 4 months	20	7
<b>Any time</b>	<b>24</b>	<b>9</b>
PE	9	4

# DVT/PE

	Arm A		Arm B	
	Before mandatory prophylaxis N=132 (%)	After mandatory prophylaxis N=91(%)	Before mandatory prophylaxis N=132 (%)	After mandatory prophylaxis N=88 (%)
First 4 months	23	14	8	5
<b>All time</b>	<b>26</b>	<b>21</b>	<b>10</b>	<b>8</b>

## Serious adverse events Non-Hematologic Toxicity

<b>Toxicity (N=433 Ever Reported)</b>	<b>Arm A (N=217)</b>	<b>Arm B (N=216)</b>	<b>P value</b>
Any non Hem toxicity (Grade $\geq 3$ )	52.1%	34.3%	$<0.001$
Toxicity of Any Type (Grade $\geq 4$ )	28.6%	18.1%	0.003
Early Deaths ( $< 4$ months)	4.5%	1.4%	0.034

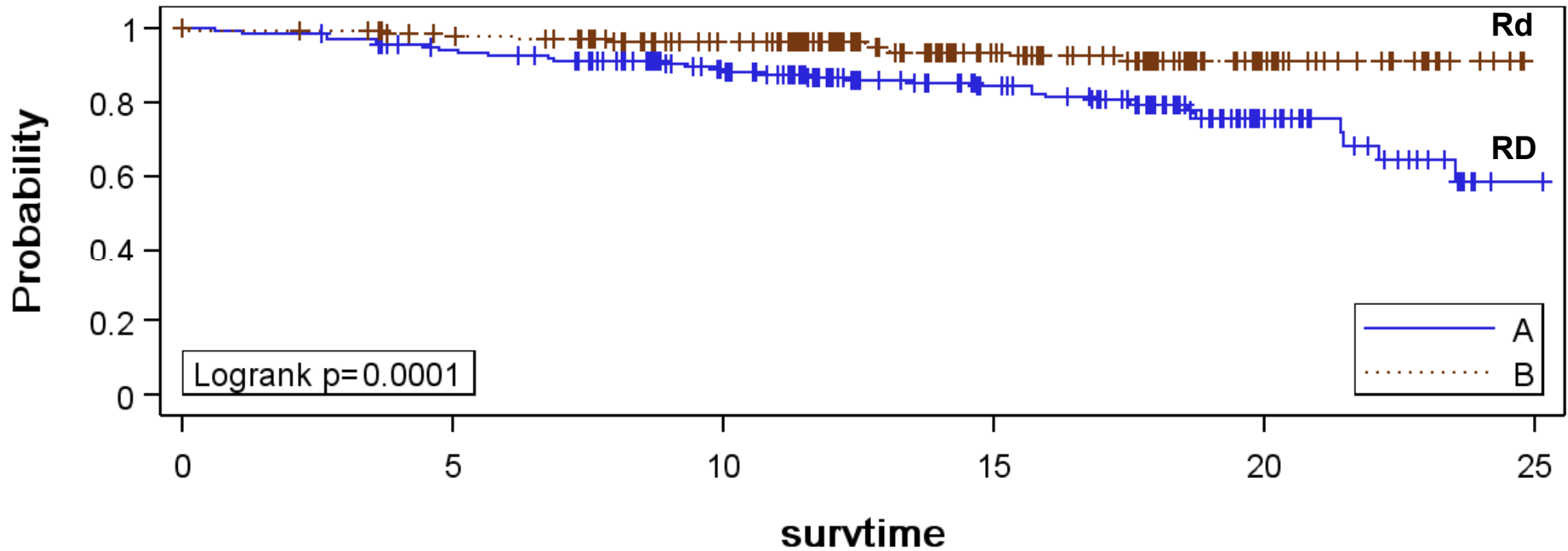
# Preliminary data on stem cell harvest, transplant

	<b>% Reporting</b>	<b>% reporting successful harvest/SCT</b>	<b>% missing data</b>	<b>% unsuccessful</b>
<b>Harvest</b>	<b>26%</b>	<b>94%</b>	<b>3.4%</b>	<b>2.6%</b>
<b>Transplant</b>	<b>24%</b>	<b>93.3%</b>	<b>4.8%</b>	<b>1.9%</b>

## One-year Survival Rate

	<b>N</b>	<b>Events</b>	<b>Survival Probability (95%CI)</b>
Len-High Dex(RD)	223	26	<b>0.87</b> (0.82, 0.92)
Len-Low Dex(Rd)	222	8	<b>0.96</b> (0.94, 0.99)

# Overall Survival (months)

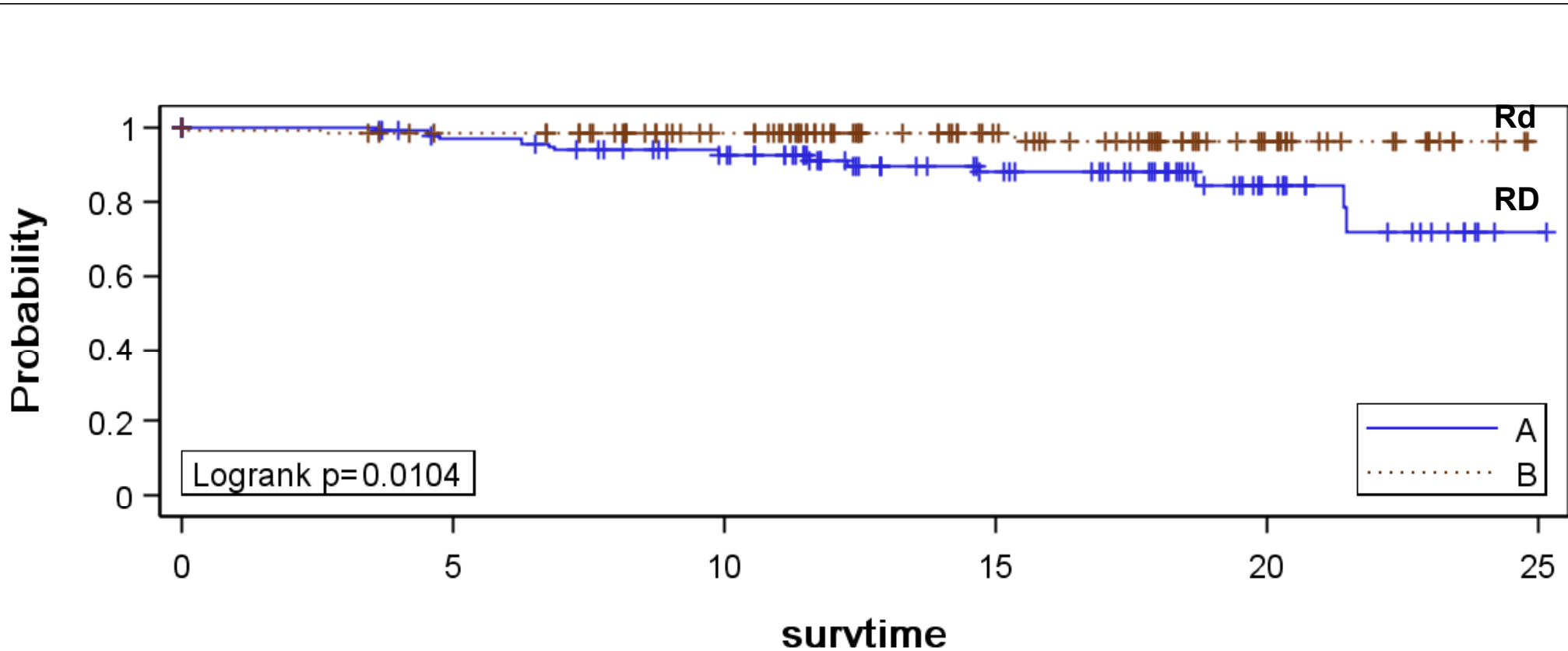


	No. of Subjects	Event	Censored	Median Survival (95% CL)
A	223	18% (41)	82% (182)	NA ( 23.56 NA )
B	222	6% (13)	94% (209)	NA ( NA NA )

## One-year Survival Rate by Age

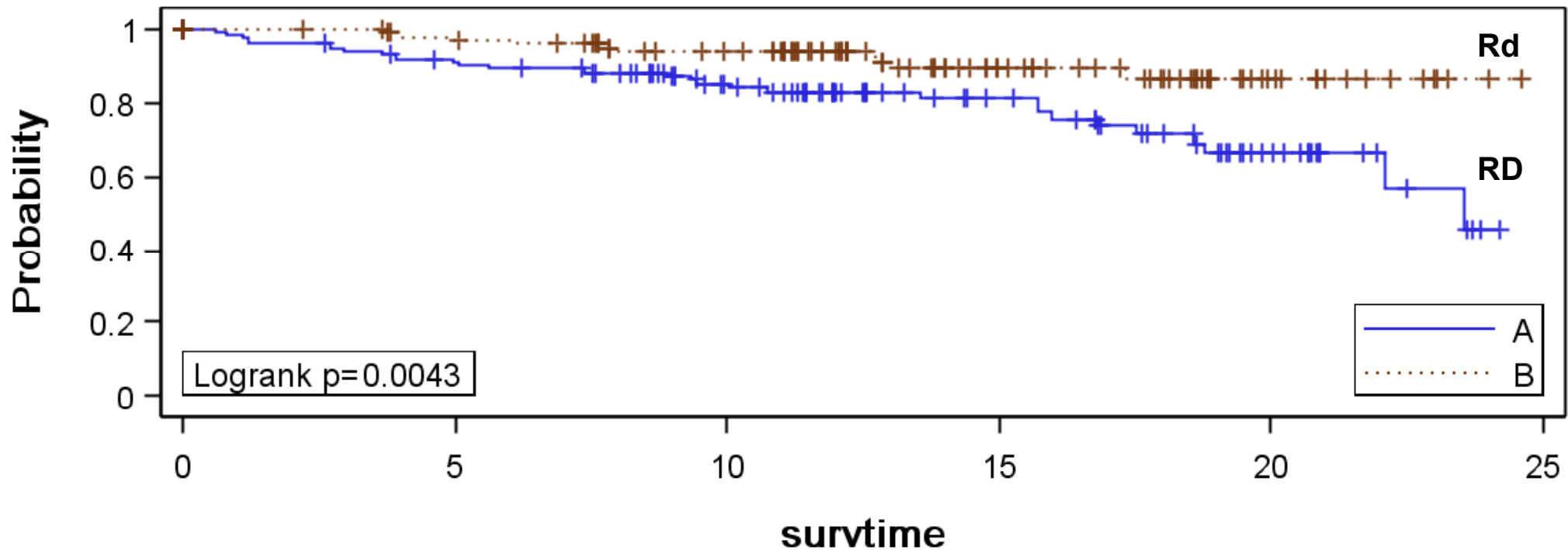
	<b>N</b>	<b>Events</b>	<b>Survival Probability (95%CI)</b>
<b>Age &lt;65</b>			
Len-High Dex	104	8	<b>0.91</b> (0.85, 0.97)
Len-Low Dex	108	2	<b>0.98</b> (0.96, 1.00)
<b>Age ≥65</b>			
Len-High Dex	119	18	<b>0.83</b> (0.76, 0.90)
Len-Low Dex	114	6	<b>0.94</b> (0.89, 0.99)

# Overall Survival (months): Age <65



	No. of Subjects	Event	Censored	Median Survival (95% CL)
A	104	13% (13)	88% (91)	NA ( NA NA )
B	108	3% (3)	97% (105)	NA ( NA NA )

# Overall Survival (months): Age ≥65



	No. of Subjects	Event	Censored	Median Survival (95% CL)
A	119	24% (28)	76% (91)	23.56 ( 22.11 NA )
B	114	9% (10)	91% (104)	NA ( NA NA )

# One-year Survival rate in Phase III Newly Diagnosed MM Trials

Study	Age	Phase	N	Regimen	1-yr Survival rate	Ref
Rajkumar, E1A00	Median=65	III	103	Thal Dex vs Dex	80%	JCO 2006
Rajkumar, MM003	Median=65	III	470	Thal Dex vs Dex	80%	ASH 06
Palumbo	Median=72	III	255	MPT vs MP	87%~	Lancet 06
Attal, IFM	<65	III	200	Auto vs Chemo	88%~	NEJM 1996
Child, MRC	<65	III	401	Auto vs Chemo	87%~	NEJM 2003
Barlogie, S9321	<=70	III	516	Auto vs Chemo	84%*	JCO 06
Attal, IFM	<60	III	399	Single vs Double Auto	90%~	NEJM 2003
<b>Barlogie, TT II</b>	<b>&lt;75**</b>	<b>III</b>	<b>668</b>	<b>TT2 +/-Thal</b>	<b>92%</b>	<b>NEJM 2006</b>
E4A03 Arm A	Median=65	223	223	Len + high-dose dex	87%	ASCO 2007
<b>E4A03 Arm B</b>	<b>Median=65</b>	<b>222</b>	<b>222</b>	<b>Len + low-dose dex</b>	<b>96%</b>	<b>ASCO 2007</b>

\*intent to treat population; \*\*80% age <65

Rajkumar, ASCO 2007

## Conclusions

- Lenalidomide plus low-dose dexamethasone is associated with significantly superior survival and lower toxicity compared to lenalidomide plus high-dose dexamethasone
- High one-year survival rate with lenalidomide plus low-dose dexamethasone
- DVT risk is 5-8% with lenalidomide plus low-dose dexamethasone with routine aspirin prophylaxis
- Response, TTP, and PFS assessment is ongoing
- Major implications for use of high-dose dexamethasone in myeloma