

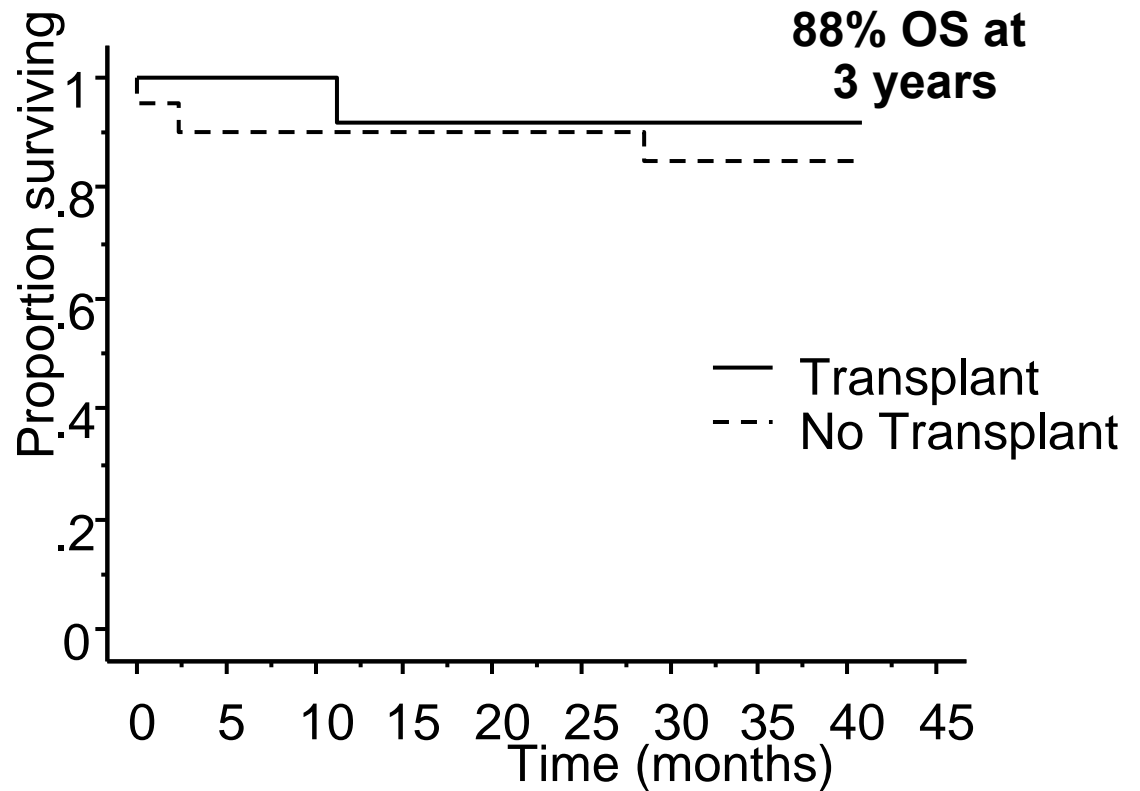
**Phase III trial of lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone in newly diagnosed multiple myeloma (E4A03): a trial coordinated by the Eastern Cooperative Oncology Group**

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# Mayo Phase II trial of Len/Dex in New MM

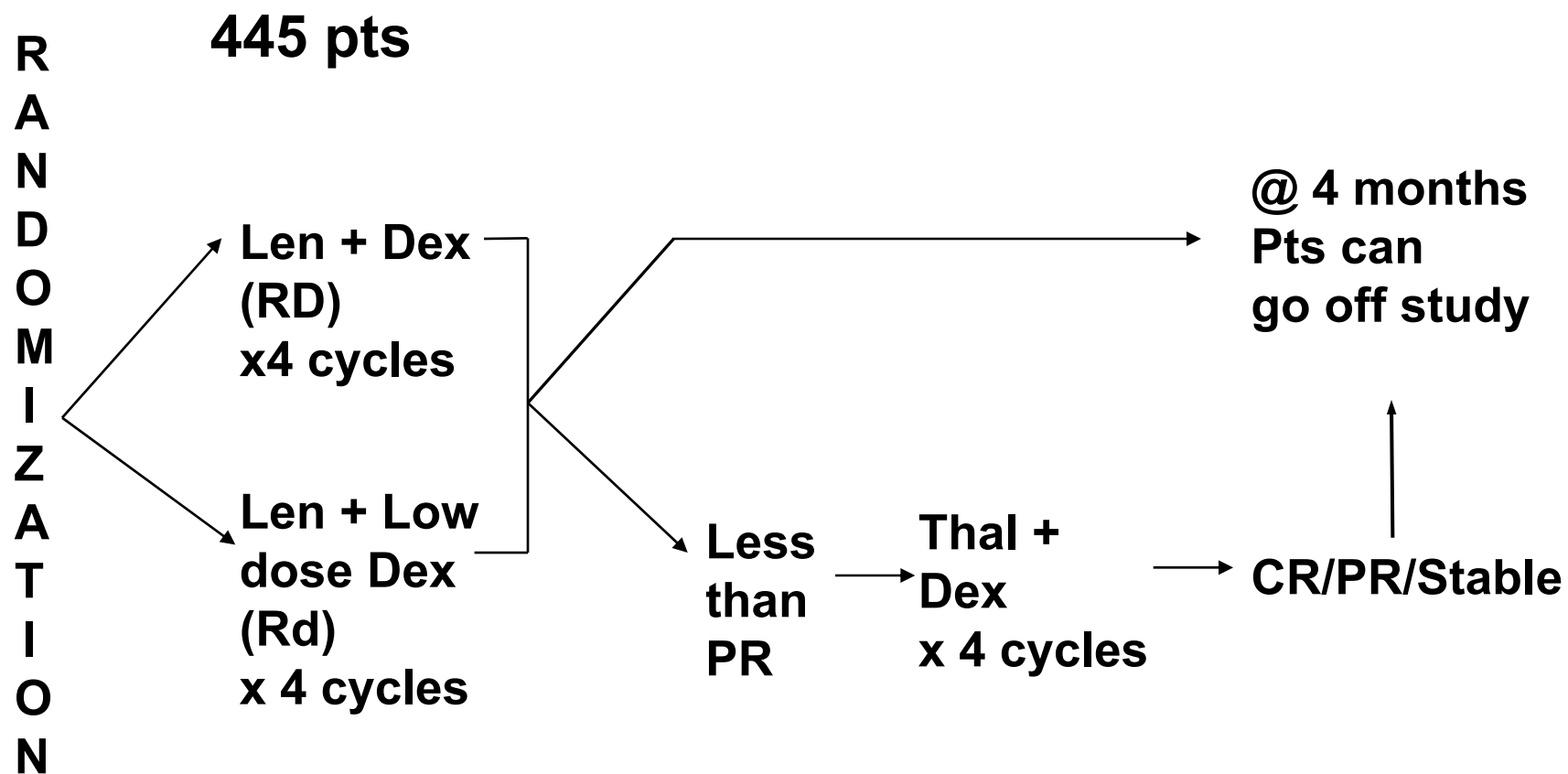
**N=34**  
**RR: 91%**  
**CR/VGPR: 56%**



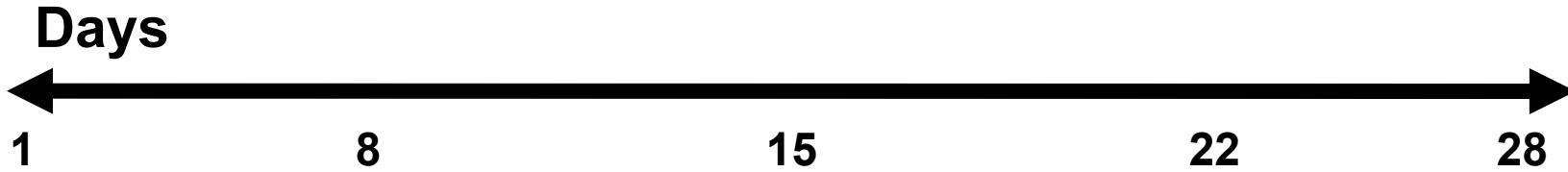
## Aim

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

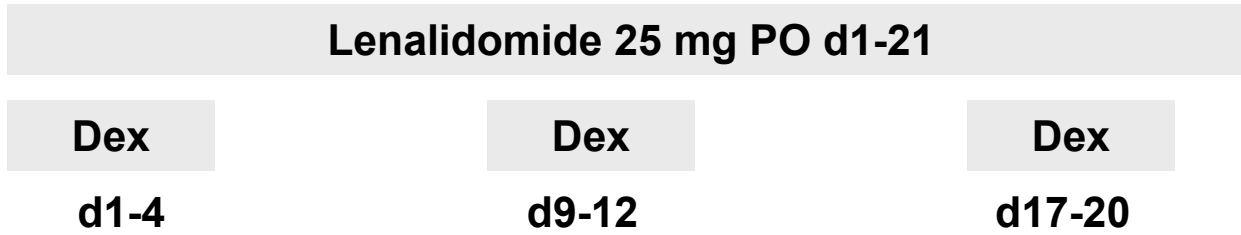
# Schema



# Treatment Schedule

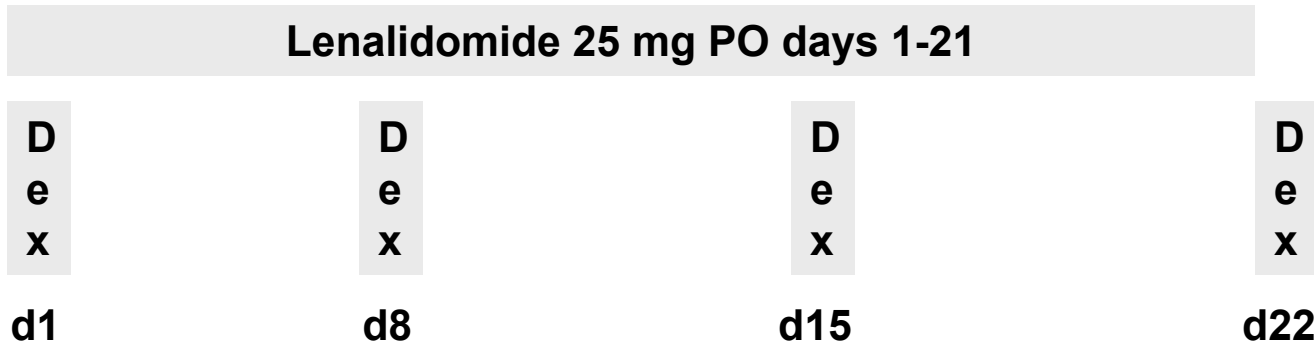


***RD***



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

***Rd***



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

# Study Design

- **Induction trial; Not designed as a trial to test efficacy of long-term lenalidomide/dex**
- **Primary Endpoint: RR @ 4 months**
  - **Equivalence: overall response rate in Rd <15%**

# Eligibility

<b>Status</b>	<b>RD (Arm A) N=223</b>	<b>Rd (Arm B) N=222</b>	<b>Total N=445</b>
<b>Eligible</b>	<b>195</b>	<b>188</b>	<b>383</b>
Not eligible	20	22	42
Questionable eligibility	1	2	3
Missing data for eligibility	7	10	17

## Patient Characteristics

**Arm A  
(n=223)**

**Arm B  
(n=222)**

### **ISS (%)**

Stage I

33.0

33.3

Stage II

41.3

41.4

Stage III

25.7

25.3

## Patient Characteristics

	<b>Arm A (n=223)</b>	<b>Arm B (n=222)</b>
Male (%)	58.3	54.1
Age (yrs)	66 (36-87)	65 (35-85)
ECOG PS $\leq$ 1 (%)	91.0	90.5
BMPC (%)	40.0	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>
MM Bone Disease (%)	65.3	56.8
Albumin (g/dL)	3.5	3.6
LDH (U/L)	156	158
B2 Microglobulin ( $\mu\text{g/mL}$ )	3.8	3.5
Creatinine (mg/dL)	1.1	1.0

## Treatment Administered

- **245 (55%) patients went off study <6months**
- **Median duration of therapy**
  - **Arm A: 4 months**
  - **Arm B: 6 months**

	<b>Arm A</b>	<b>Arm B</b>
	<b>%</b>	<b>%</b>
Len dose reduction @ 4 cycles	23%	26%
Dex dose reduction @ 4 cycles	43%	15%

## Serious adverse events Hematologic Toxicity

	Toxicity		
	Arm A (n=222)	Arm B (n=219)	
Type (Grade 3+)	%	%	Fishers Exact p-value
Hemoglobin	8.1	6.8	0.718
Platelets	5.4	5.5	1.000
Neutrophils	11.7	18.7	0.047

## Serious adverse events: Non-Hematologic

	Toxicity		
	Arm A (n=222)	Arm B (n=219)	
Type (Grade 3+)	%	%	Fishers Exact p-value
<b>DVT/PE</b>	<b>25%</b>	<b>9%</b>	<b>&lt;0.001</b>
<b>Infection/Pneumonia</b>	<b>14%</b>	<b>7%</b>	<b>0.030</b>
<b>Fatigue</b>	<b>13%</b>	<b>10%</b>	<b>0.294</b>
<b>Hyperglycemia</b>	<b>11%</b>	<b>6%</b>	<b>0.126</b>
<b>Nonneuropathic weakness</b>	<b>10%</b>	<b>4%</b>	<b>0.008</b>
<b>Cardiac ischemia</b>	<b>3%</b>	<b>0.5%</b>	<b>0.068</b>
<b>Atrial fib/flutter</b>	<b>3%</b>	<b>0.5%</b>	<b>0.122</b>
<b>Neuropathy</b>	<b>2%</b>	<b>1.5%</b>	<b>1.000</b>

## Serious adverse events Non-Hematologic Toxicity

<b>Toxicity (N=441 Ever Reported)</b>	<b>Arm A (N=222)</b>	<b>Arm B (N=219)</b>	<b>P value</b>
<b>Any non Hem toxicity (Grade <math>\geq 3</math>) in first 4 cycles</b>	<b>50%</b>	<b>30%</b>	<b>&lt;0.001</b>
Any non Hem toxicity (Grade $\geq 3$ )	65%	45%	<0.001
Toxicity of Any Type (Grade $\geq 4$ )	19%	8%	0.001
<b>Early Deaths (&lt; 4 months) All pts</b>	<b>5%</b>	<b>0.5%</b>	<b>0.01</b>
Early Deaths (< 4 months) Pts <65	1%	0%	

## Ability to harvest stem cells

	No. Reporting	% reporting successful harvest	% missing data	% unsuccessful
<b>Harvest</b>	<b>149</b>	<b>97%</b>	<b>1%</b>	<b>2%</b>

## Response within 4 cycles

	<b>Arm A N=196</b>	<b>Arm B N=190</b>	<b>Total N=386</b>
	<b>%</b>	<b>%</b>	<b>%</b>
Complete Response	2%	1%	2%
Partial Response	80%	69%	75%
	<b>82%</b>	<b>70%</b>	
Minimal Response	5%	15%	10%
No Response/Stable	6%	8%	7%
Progressive Disease	3%	2%	3%
Unevaluable	4%	5%	5%
Missing (no. of pts)	5	9	14

## Response within 4 cycles

	<b>Arm A N=196</b>	<b>Arm B N=190</b>	<b>Total N=386</b>	<b>Fisher's Exact p-value 2-sided</b>
	%	%	%	
$\geq$ PR	80%	67%	74%	0.004
	82%	70%	76%	0.007
CR+VGPR	44%	26%	35%	<0.001

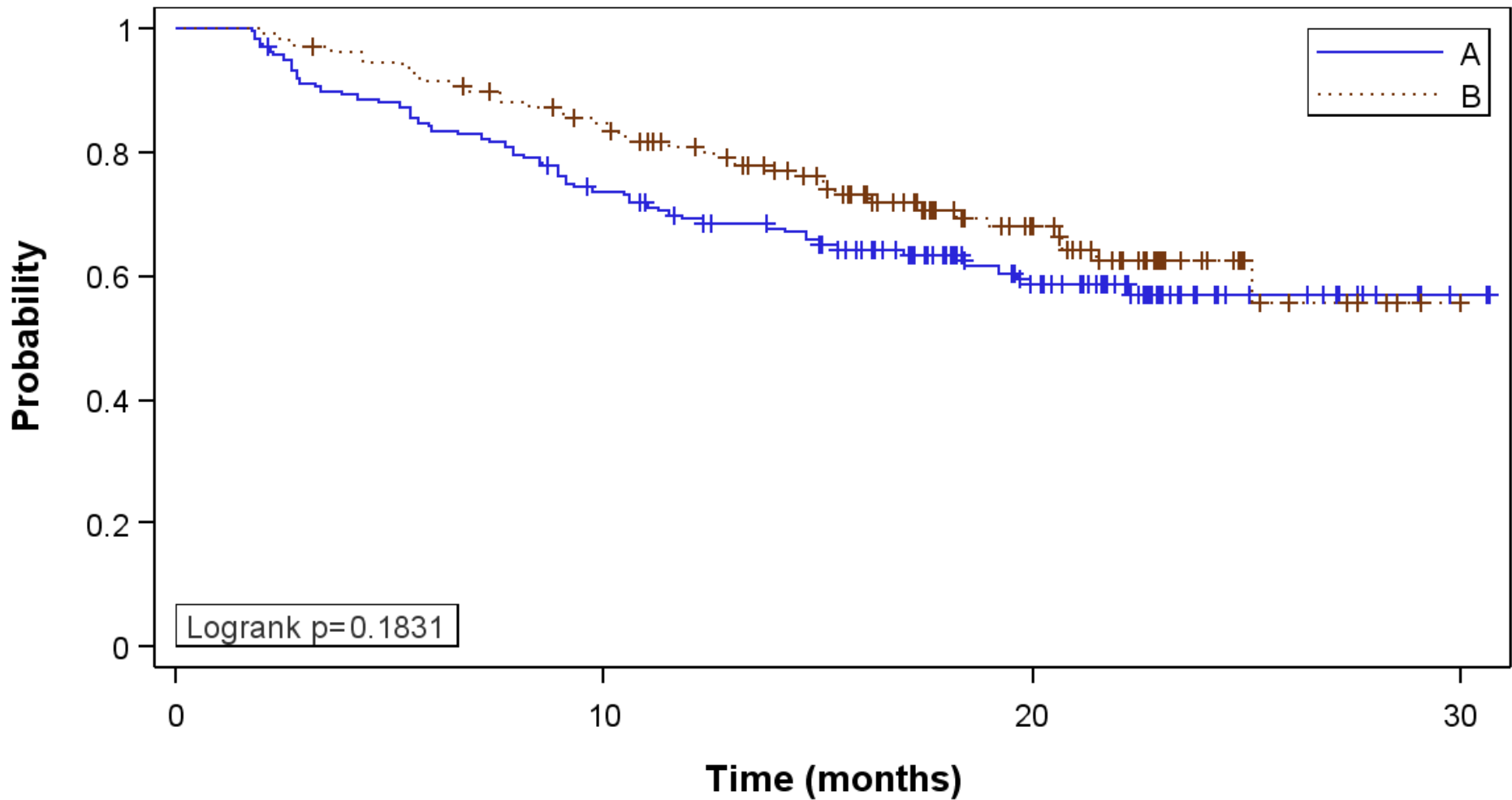
## Best Overall Response

	<b>Arm A</b> <b>N=196</b>	<b>Arm B</b> <b>N=190</b>	<b>Total</b> <b>N=386</b>
	<b>N (%)</b>	<b>N (%)</b>	<b>N (%)</b>
Complete Response	4% } <b>52%</b>	2% } <b>42%</b>	3%
VGPR	48% }	40% }	44%
Partial Response	30%	29%	29%
Minimal Response	4%	14%	9%
No Response/Stable	7%	8%	7%
Progressive Disease	3%	3%	3%
Unevaluable	4%	5%	4%
Missing (no. of pts)	3	6	9

## Best Overall Response

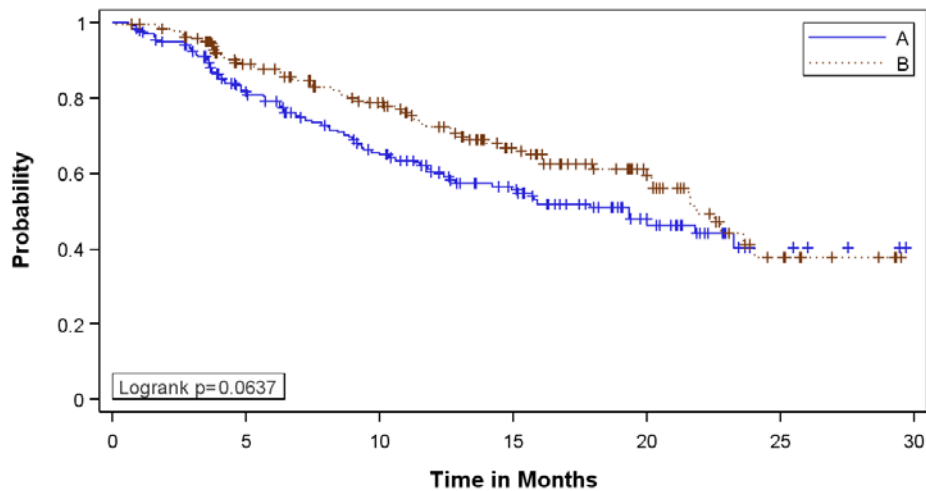
	Arm A N=196	Arm B N=190	Total N=386	Fisher's Exact p-value 2-sided
	%	%	%	
$\geq$ PR	82%	71%	76%	0.01
<b>CR+VGPR</b>	<b>52%</b>	<b>42%</b>	<b>47%</b>	<b>0.06</b>

# Response Duration



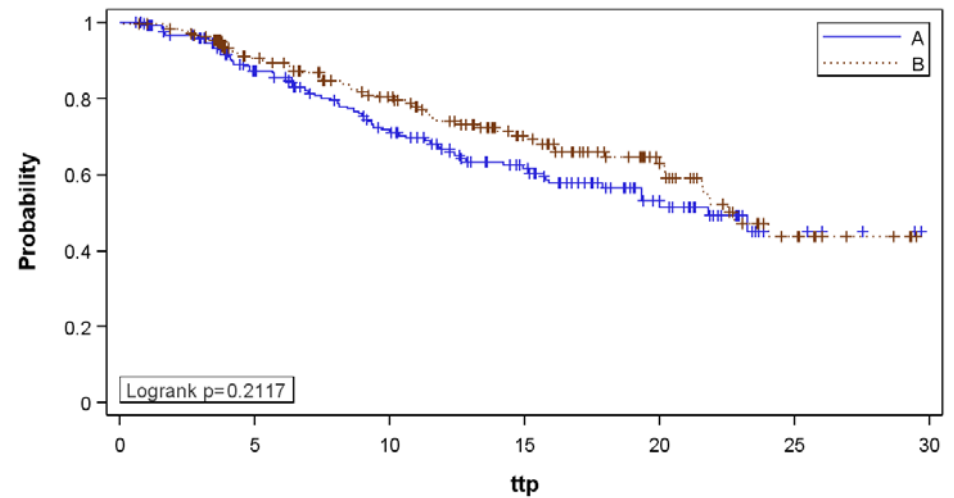
	No. of Subjects	Event	Censored	Median (95% CL)
A	157	39% (62)	61% (95)	NA ( 22.31 NA )
B	127	31% (40)	69% (87)	NA ( 25.13 NA )

# PFS and TTP



	No. of Subjects	Event	Censored	Median (95% CL)
A	193	42% (81)	58% (112)	19.32 ( 12.81 NA )
B	181	35% (63)	65% (118)	21.85 ( 20.17 NA )

## PFS



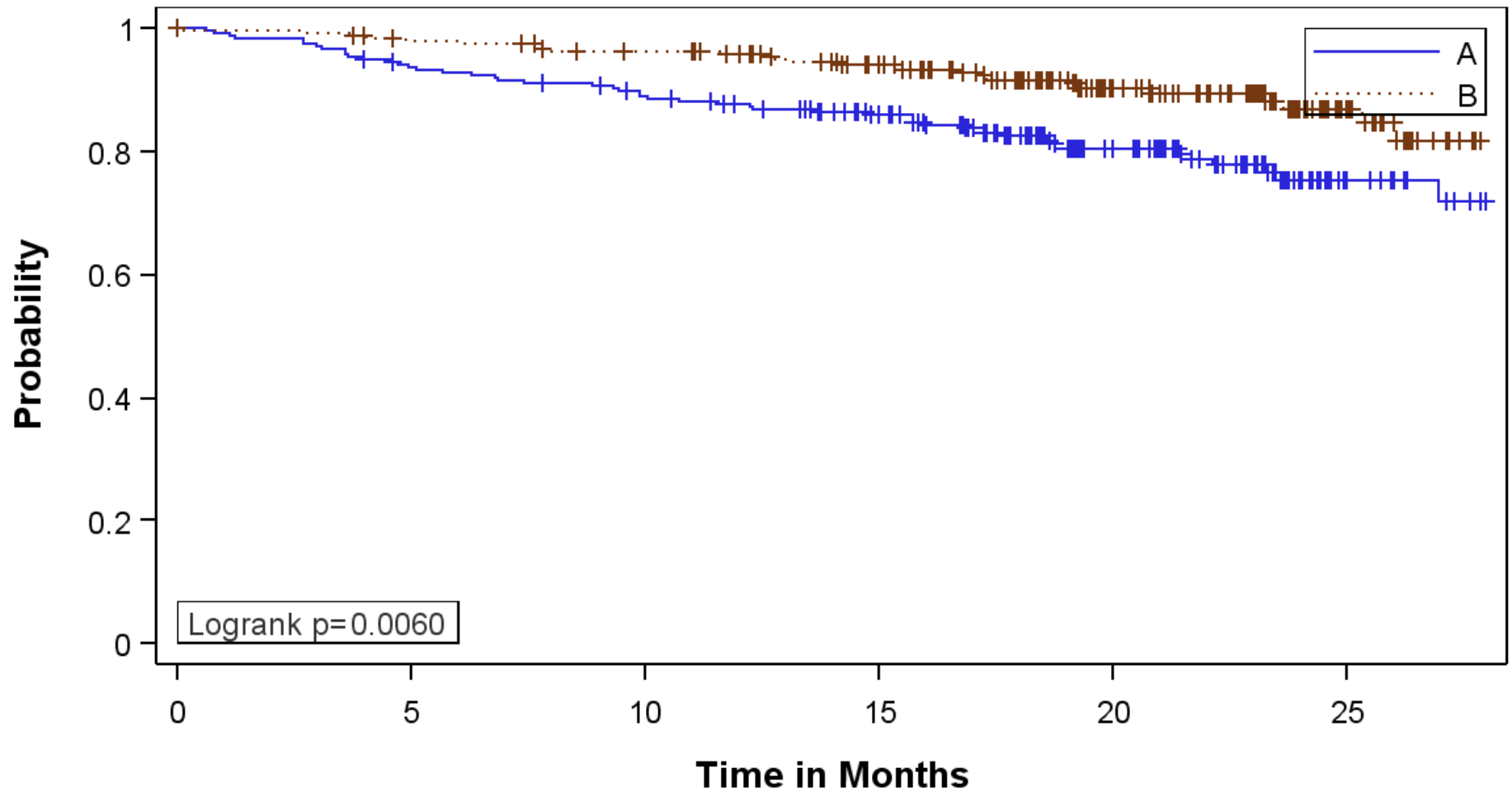
	No. of Subjects	Event	Censored	Median (95% CL)
A	193	35% (68)	65% (125)	21.78 ( 15.93 NA )
B	181	31% (57)	69% (124)	22.54 ( 20.24 NA )

## TTP

## Survival Rate

	<b>N</b>	<b>12 month Survival Probability (95%CI)</b>	<b>24 month survival Probability (95%CI)</b>
<b>Len-High Dex(RD)</b>	223	<b>0.88</b> (0.83-0.92)	<b>0.75</b> (0.68-0.82)
<b>Len-Low Dex(Rd)</b>	222	<b>0.96</b> (0.93-0.99)	<b>0.87</b> (0.81-0.93)
		<i>P=0.003</i>	<i>P=0.009</i>

# Overall Survival

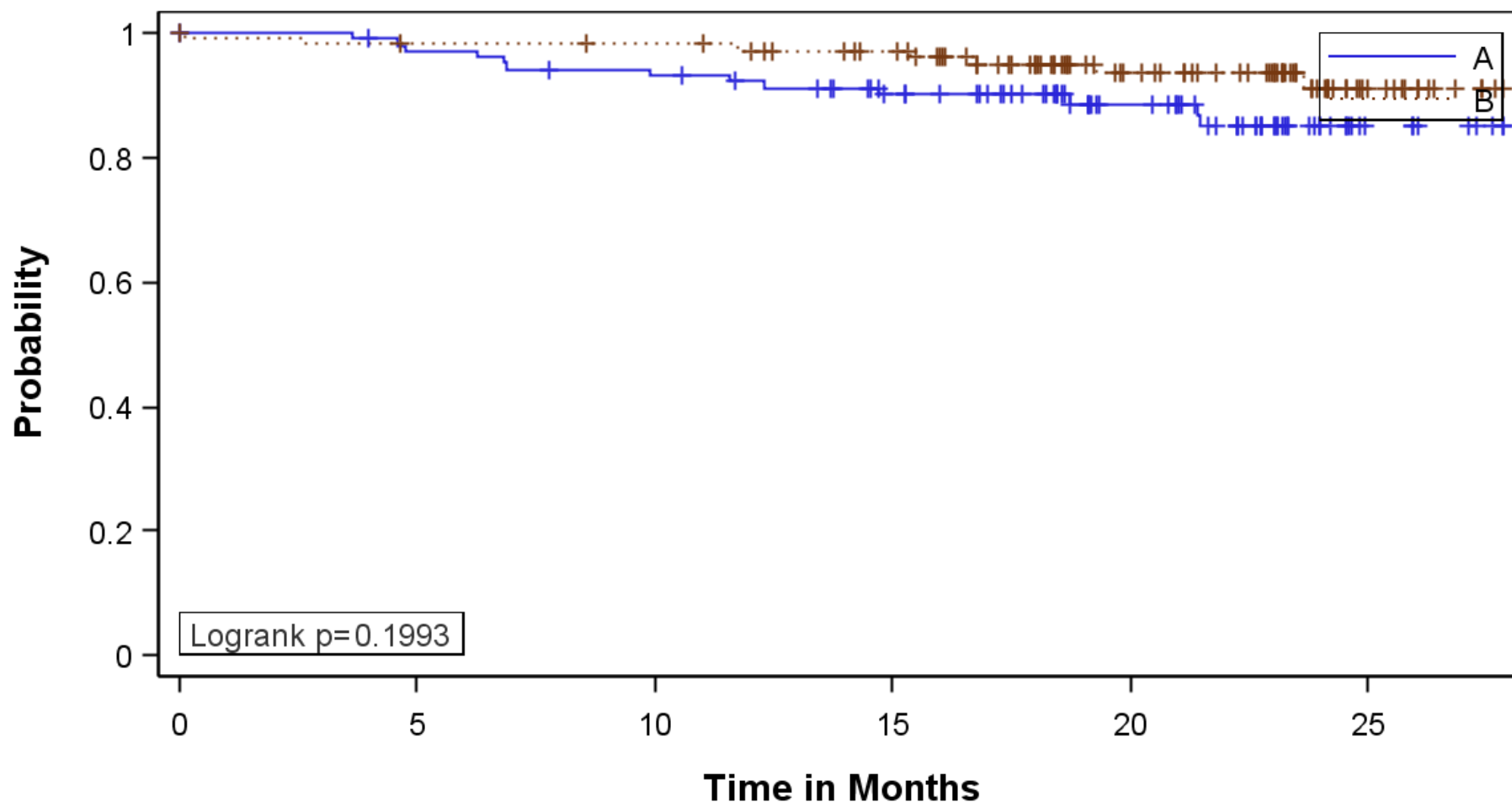


	No. of Subjects	Event	Censored	Median (95% CL)
A	223	21% (46)	79% (177)	NA ( NA NA )
B	222	11% (25)	89% (197)	NA ( 30.55 NA )

## Survival Rate by Age

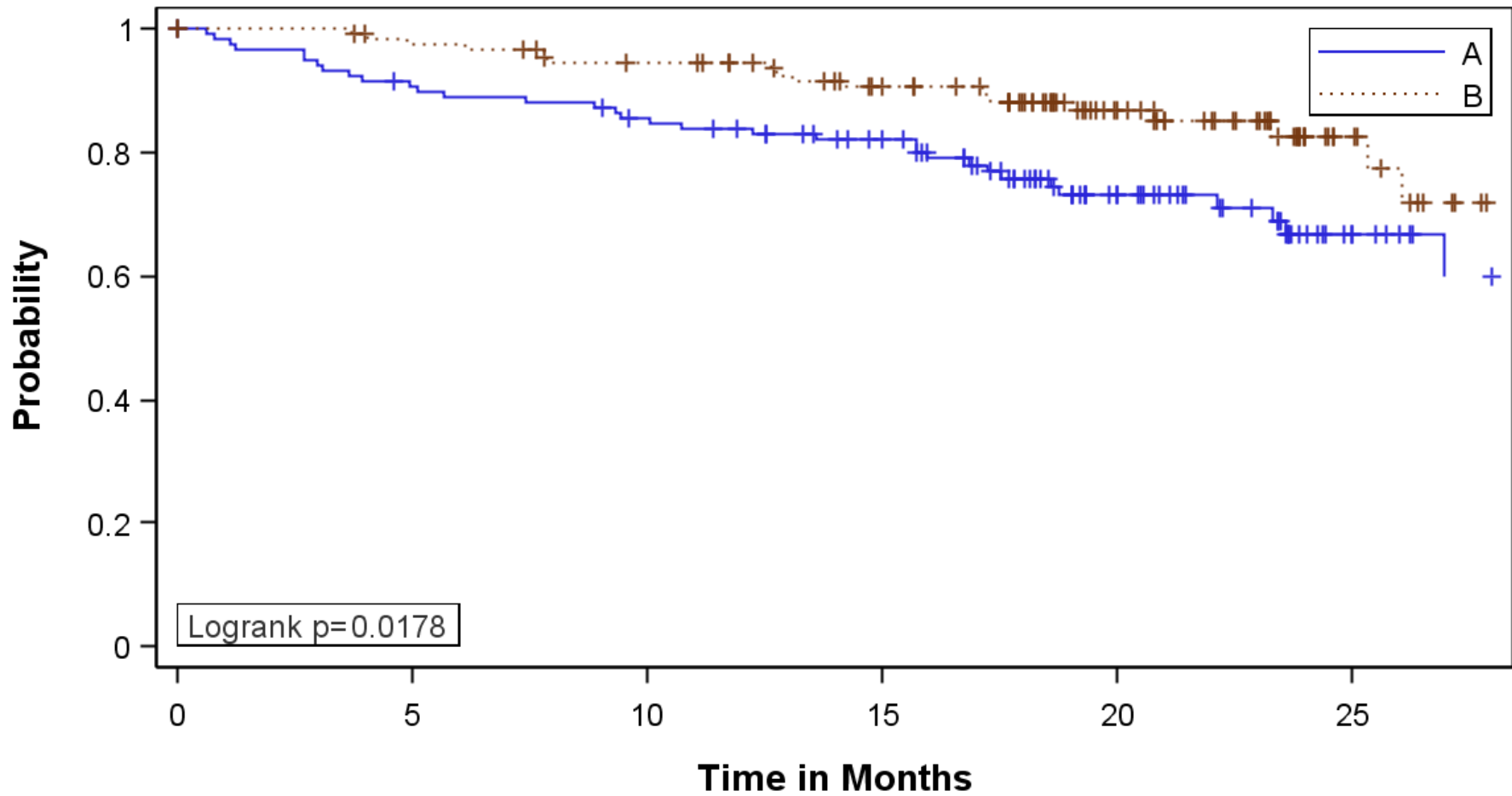
	<b>N</b>	<b>12 month survival probability (95%CI)</b>	<b>24 month survival probability (95%CI)</b>
<b>Age &lt;65</b>			
Len-High Dex	104	<b>0.92</b> (0.87-0.97)	<b>0.85</b> (0.78-0.93)
Len-Low Dex	108	<b>0.97</b> (0.94-1.00)	<b>0.91</b> (0.84-0.98)
<b>Age ≥65</b>		<i>P=0.13</i>	<i>P=0.16</i>
Len-High Dex	119	<b>0.84</b> (0.77-0.91)	<b>0.67</b> (0.56-0.77)
Len-Low Dex	114	<b>0.95</b> (0.84-1.00)	<b>0.82</b> (0.74-0.91)
		<i>P=0.01</i>	<i>P=0.009</i>

# Overall Survival: Age <65



	No. of Subjects	Event	Censored	Median (95% CL)
A	104	13% (13)	88% (91)	NA ( NA NA )
B	108	7% (8)	93% (100)	30.55 ( 30.55 NA )

# Overall Survival: Age $\geq 65$



	No. of Subjects	Event	Censored	Median (95% CL)
A	119	28% (33)	72% (86)	NA ( 26.94 NA )
B	114	15% (17)	85% (97)	NA ( NA NA )

## Survival Rate

	12 month Survival (95%CI) Pts off study <6 months N=245	12 month survival (95%CI) Rx $\geq$ 6months N=192
Len-High Dex(RD)	<b>0.83</b> (0.75-0.88)	<b>0.97</b> (0.90-0.99)
Len-Low Dex(Rd)	<b>0.93</b> (0.86-0.97)  <i>P=0.02</i>	<b>0.99</b> (0.94-0.99)  <i>P=0.15</i>

# Cause of Death

**Median Follow up 21 mos**

	<b>Arm A</b>	<b>Arm B</b>
	<b>N=46</b>	<b>N=25</b>
	<b>N</b>	<b>N</b>
Progressive Disease	26	17
Thromboembolic	5	1
Infection	4	3
Cardiac	6	2
Stroke	1	1
Resp Failure	1	0
Second Cancer	1	0
Unknown	2	1

# Conclusions

- RD and Rd are highly active in newly diagnosed MM
- Rd had lower response rates than RD, but this was within the 15% limit that was defined in study design as clinically equivalent
- Rd is associated with superior OS compared to RD
- Response duration, TTP or PFS with Rd not inferior to RD
- The excess mortality in the high-dose dex arm was due to both disease progression (myeloma deaths) as well as increased toxicity.
- This study has major implications for the use of high-dose dexamethasone in the treatment of newly diagnosed MM.