



**Revlimid®**

**Lenalidomide and  
dexamethasone in  
relapsed/refractory MM  
MM-009, MM-010**



# MM-009 and MM-010: two phase III trials of Len + Dex in relapsed/refractory MM

**North American MM-009 (48 centres USA, Canada): Weber**  
**International MM-010 (50 centres Europe, Australia, Israel): Dimopoulos**

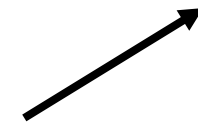
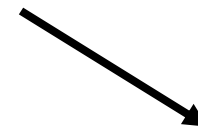
## Inclusion criteria

- $\leq 3$  prior therapies
- No Dex resistance
- Normal hepatic and renal function

Len 25 mg days 1–21  
Placebo days 22–28  
Dex 40 mg days 1–4,  
9–12, 17–20

× 4 courses

Placebo days 1–28  
Dex 40 mg days 1–4,  
9–12, 17–20



**Continue  
until PD**

Same, except  
Dex days 1–4

**Primary end-point:** TTP (by Bladé criteria)

**Secondary end-points:** OS, RR, safety, 1st skeletal-related event, PS

Additional stratification by  $\beta_2$ M concentration ( $\leq 2.5$  mg/ml vs  $> 2.5$  mg/ml), prior transplant (0 vs  $\geq 1$ ), and prior MM treatment regimens ( $< 1$  vs  $\geq 1$ )



# MM-009 and MM-010: patient characteristics

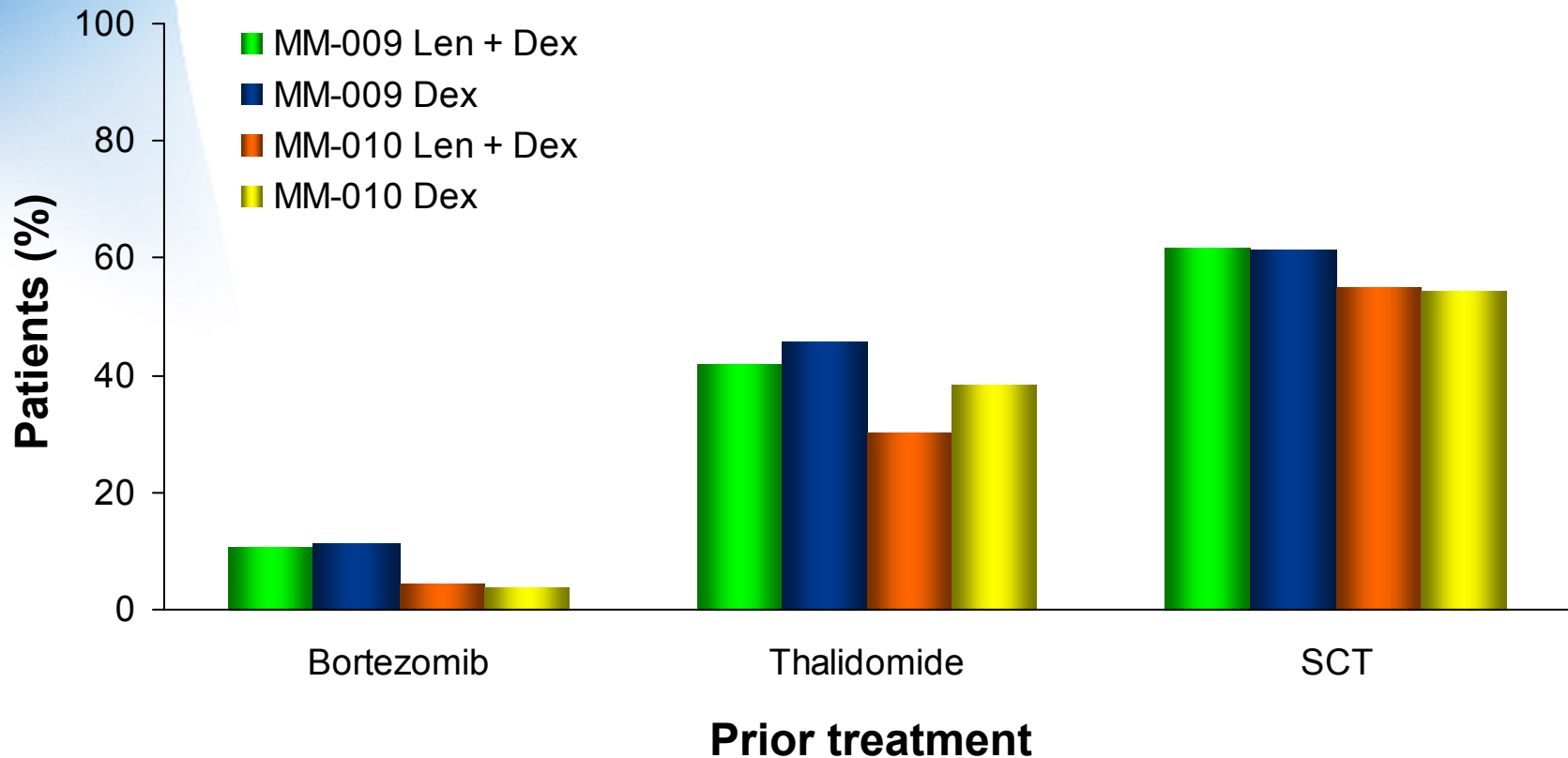
Characteristic	MM-009		MM-010	
	Len + Dex (n = 177)	Dex (n = 176)	Len + Dex (n = 176)	Dex (n = 175)
Median age (range), years	64 (36–86)	62 (37–85)	63 (33.0–84.0)	64 (40.0–82.0)
Males, %	59.9	59.1	59.1	58.9
Lytic bone lesions, n (%)	NR	NR	136 (77.3)	140 (80.0)
Median time from diagnosis (range), years	3.1 (0.5–14.7)	3.1 (0.0–19.7)	3.4 (0.4–15.7)	4.0 (0.3–26.6)
Durie–Salmon stage III, n (%)	114 (64.4)	116 (65.9)	115 (65.3)	110 (62.9)
ECOG PS < 2, n (%)	157 (88.7)	163 (92.9)	150 (85.2)	144 (82.2)
Prior therapy ≥ 2, n (%)	109 (61.6)	109 (61.9)	120 (68.2)	118 (67.4)
β <sub>2</sub> M ≥ 2.5 mg/l, n (%)	125 (70.6)	125 (71.0)	125 (71.0)	127 (72.6)

Dimopoulos M, et al. N Engl J Med. 2007;357:2123-32.

Weber DM, et al. N Engl J Med. 2007;357:2133-42.



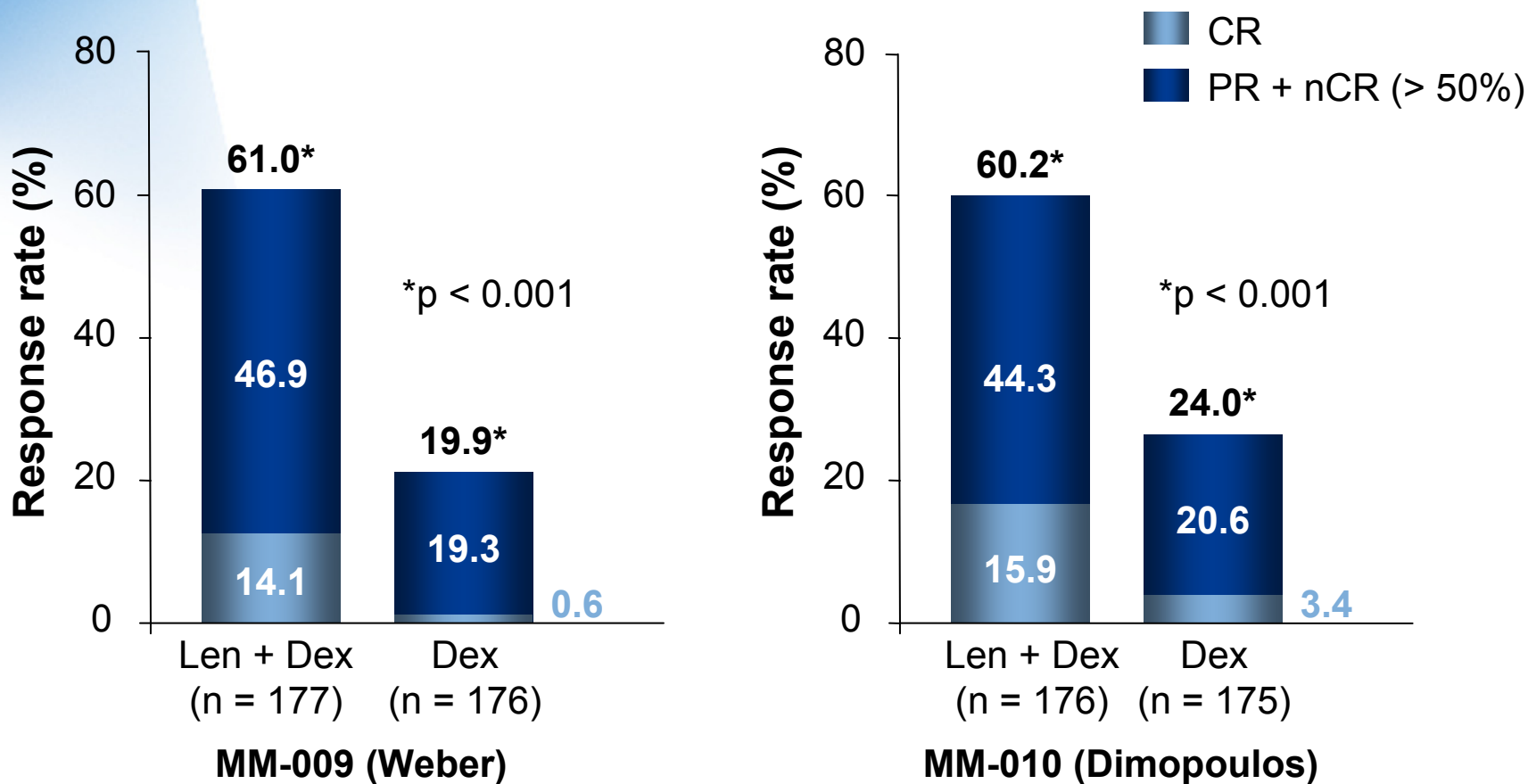
# MM-009 and MM-010 included heavily pretreated patients





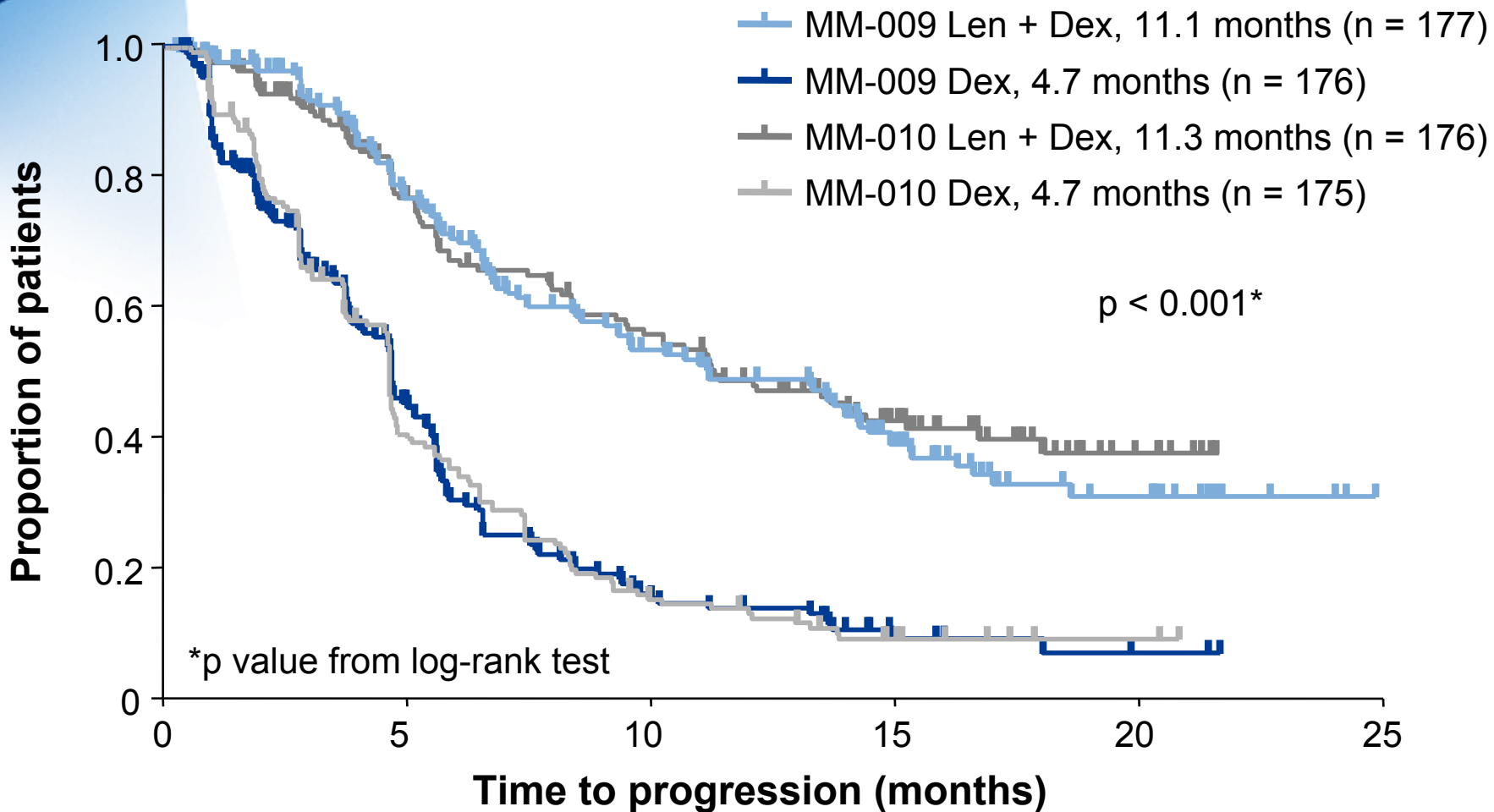
# MM-009 and MM-010: higher response rates with Len + Dex

## EBMT response data



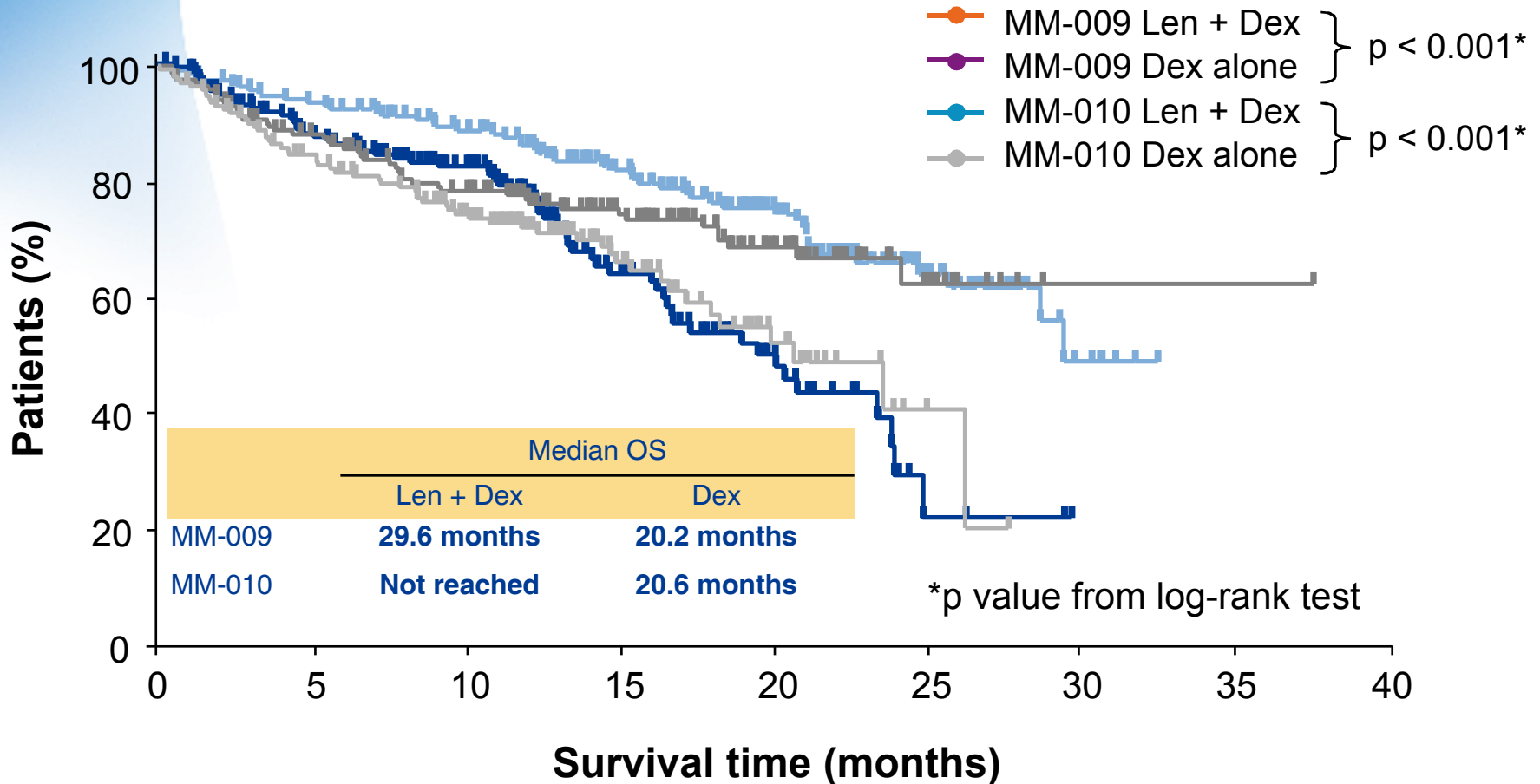


# MM-009 and MM-010: longer time to progression with Len + Dex





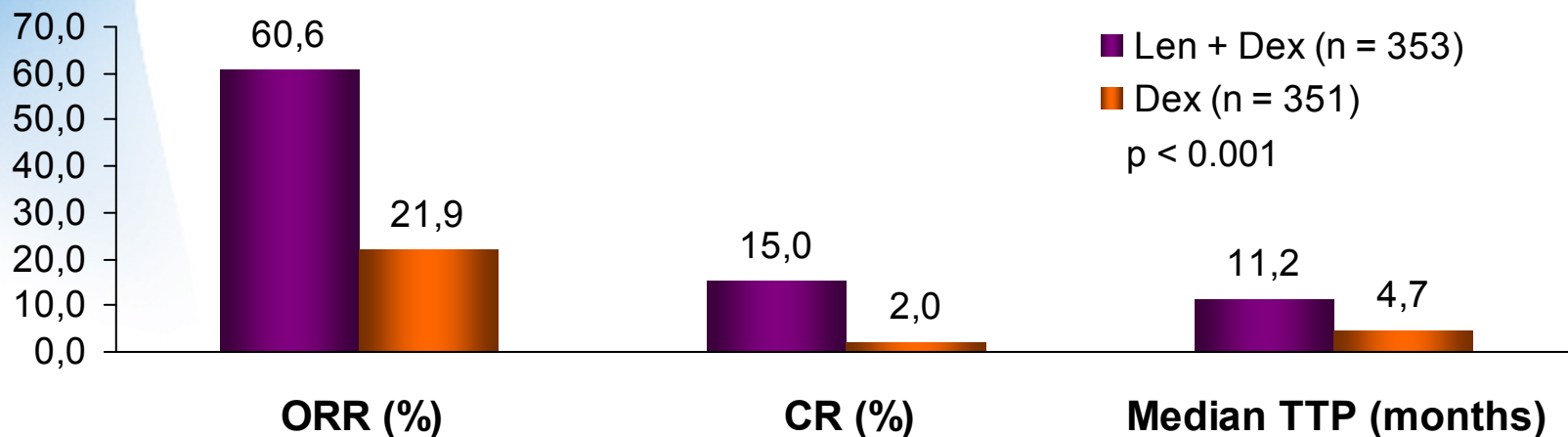
# MM-009 and MM-010: increased overall survival with Len + Dex





# MM-009 and MM-010: pooled response rates

## TTP and OS

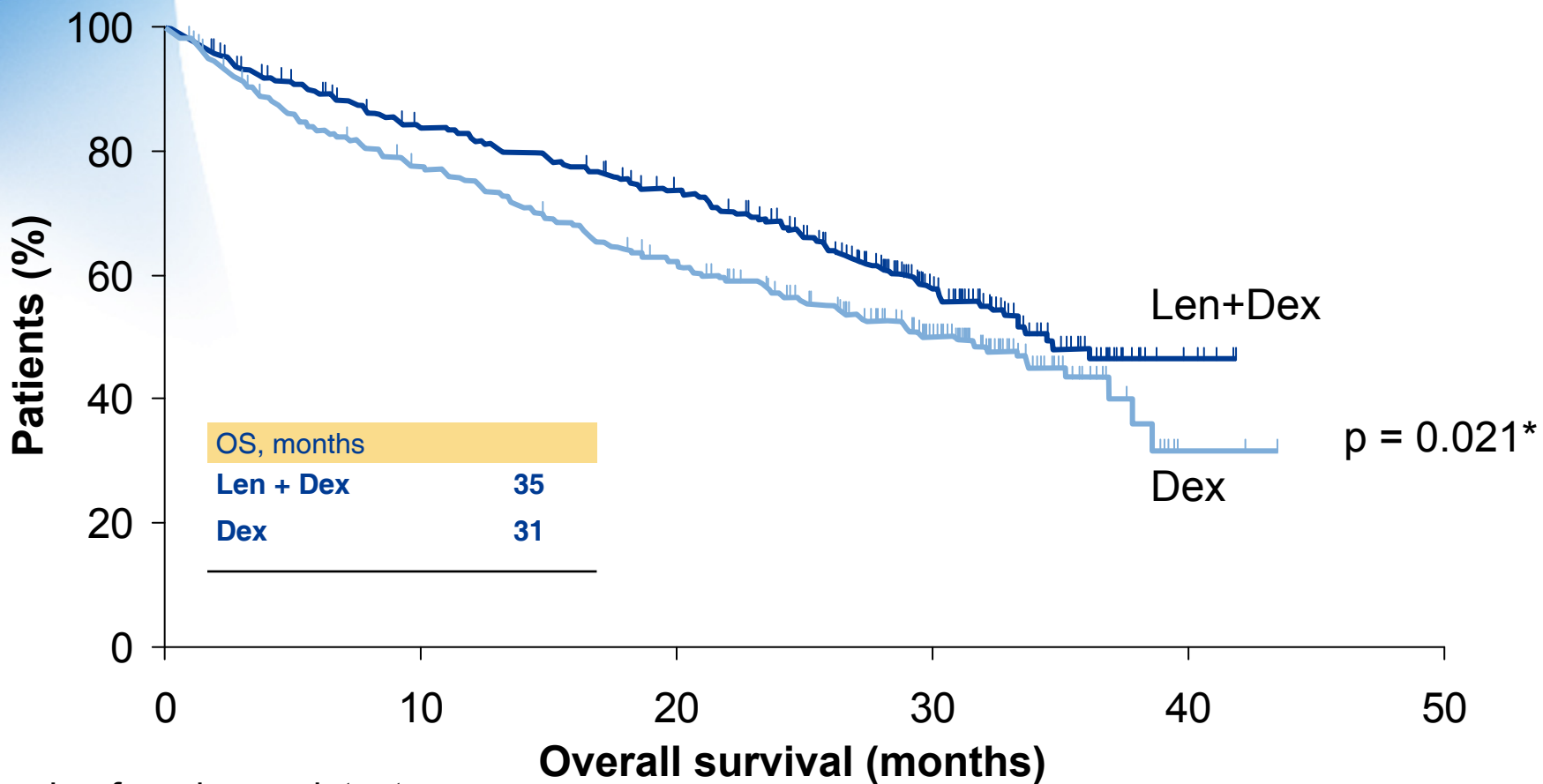


	Len + Dex (n = 353)	Dex (n = 351)	p value
<b>Median OS, months</b>	<b>35.0</b>	<b>31.0</b>	<b>&lt; 0.05</b>
<b>Median OS in patients with 1 prior treatment, months</b>	<b>Not yet reached</b>	<b>35.3</b>	<b>0.24</b>
<b>Median OS in patients with &gt; 1 prior treatment, months</b>	<b>32.4</b>	<b>27.3</b>	<b>&lt; 0.05</b>





# MM-009 and MM-010: pooled overall survival



\*p-value from log-rank test  
Data up to January 2007



# MM-009 and MM-010: overall survival after adjustment for crossover to lenalidomide

## Lifetime simulation model of survival

	Mean survival, life years	
	Dex	Len + Dex
1 prior therapy	2.2	5.6
≥ 2 prior therapies	1.5	4.2

- Lenalidomide delivers significantly larger survival gains when adjustment is made for crossover



# MM-009: grade 3 and 4 adverse events

	Len + Dex (n = 177)		Dex (n = 175)	
	Grade 3	Grade 4	Grade 3	Grade 4
<b>Neutropenia</b>	<b>62 (35.0)</b>	<b>11 (6.2)</b>	<b>6 (3.4)</b>	<b>2 (1.1)</b>
<b>Anaemia</b>	<b>19 (10.7)</b>	<b>4 (2.3)</b>	<b>6 (3.4)</b>	<b>3 (1.7)</b>
<b>Thrombocytopenia</b>	<b>24 (13.6)</b>	<b>2 (1.1)</b>	<b>12 (6.9)</b>	<b>0</b>
<b>Hyperglycaemia</b>	<b>15 (8.5)</b>	<b>4 (2.3)</b>	<b>10 (5.7)</b>	<b>5 (2.9)</b>
<b>Infection</b>	<b>33 (18.6)</b>	<b>5 (2.8)</b>	<b>16 (9.1)</b>	<b>5 (2.9)</b>
<b>Pneumonia</b>	<b>19 (10.7)</b>	<b>3 (1.7)</b>	<b>10 (5.7)</b>	<b>3 (1.7)</b>
<b>VTE</b>	<b>21 (11.9)</b>	<b>5 (2.8)</b>	<b>5 (2.9)</b>	<b>1 (0.6)</b>

## MM-009: effect of VTE on survival

- **177 patients enrolled in the MM-009 study were assigned to lenalidomide plus dexamethasone**
  - median age 64 years
- **Median follow-up was 26 months**
- **31 patients (17.5%) had VTE**
  - baseline characteristics were balanced for patients with and without VTE
  - previous lines of therapy were also evenly distributed
- **No negative effects of VTE were seen on survival ( $p = 0.4$ ) or TTP ( $p = 0.7$ )**

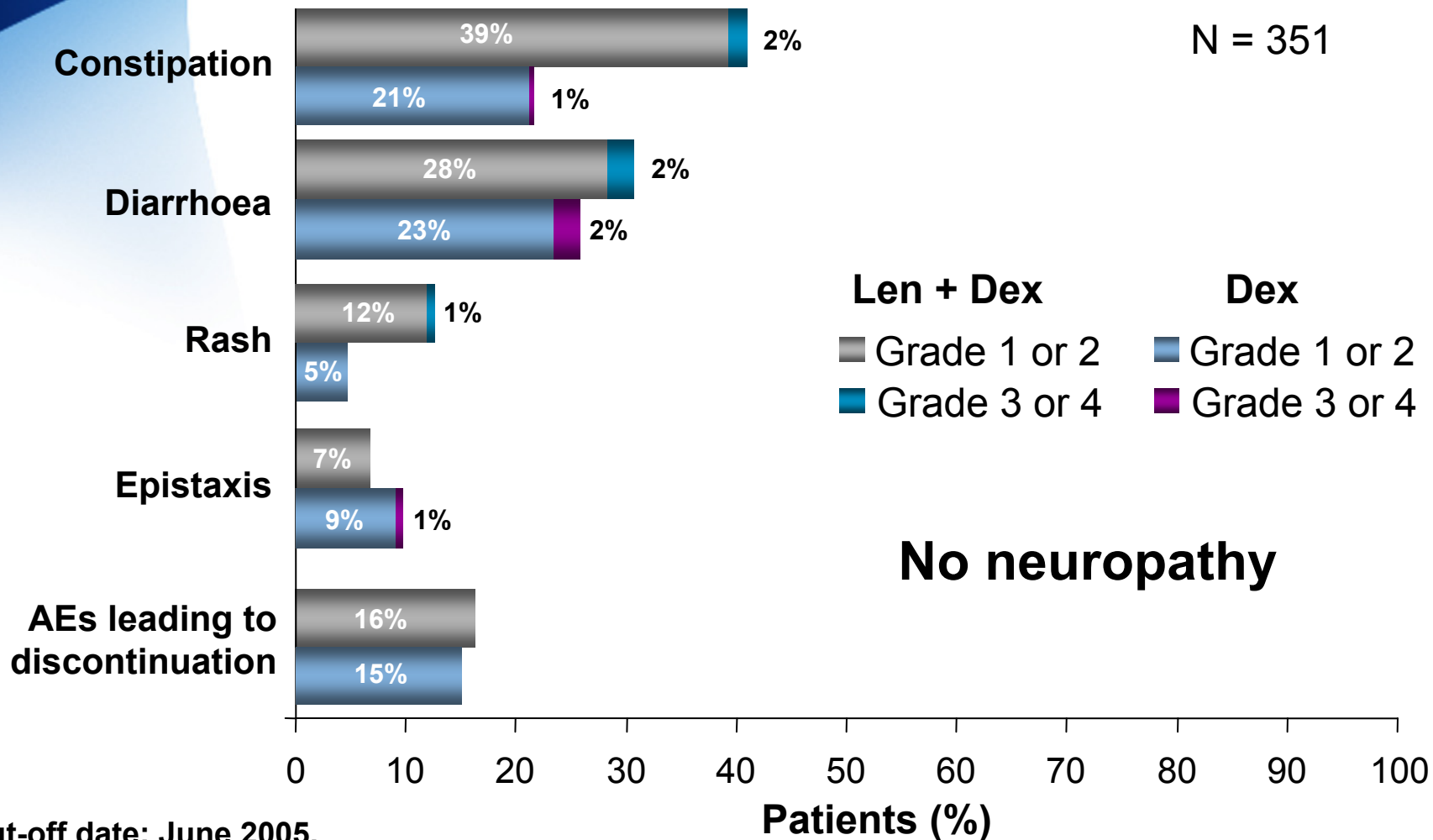


# MM-010: grade 3 and 4 adverse events

Adverse event, n (%)	Len + Dex (n = 176)		Dex (n = 175)	
	Grade 3	Grade 4	Grade 3	Grade 4
<b>Neutropenia</b>	<b>44 (25.0)</b>	<b>8 (4.5)</b>	<b>4 (2.3)</b>	<b>0</b>
<b>Thrombocytopenia</b>	<b>17 (9.7)</b>	<b>3 (1.7)</b>	<b>7 (4)</b>	<b>3 (2)</b>
<b>VTE</b>	<b>13 (7.4)</b>	<b>7 (4)</b>	<b>6 (3)</b>	<b>2 (1)</b>
<b>Infection</b>				
upper respiratory	<b>3 (1.7)</b>	<b>0</b>	<b>0</b>	<b>0</b>
other	<b>15 (8.5)</b>	<b>2 (1.1)</b>	<b>9 (5.1)</b>	<b>2 (1.1)</b>



# MM-010: non-haematological adverse events





# Dex dose adjustments result in better efficacy and tolerability in patients with relapsed/refractory MM (1)

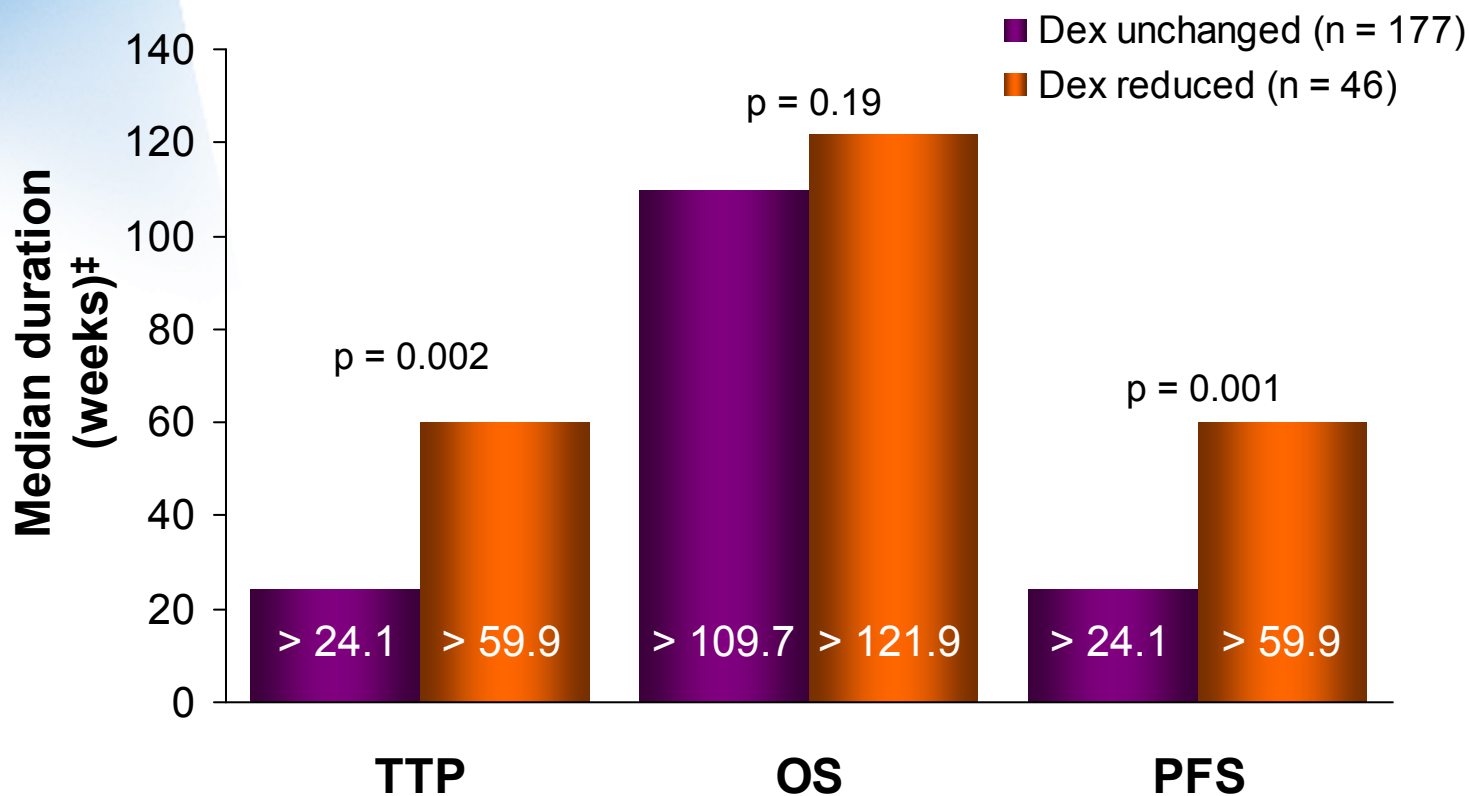
## MM-009 and MM-010: subanalysis

	Len + Dex		p value
	Dex unchanged (n = 177)	Dex reduced (n = 46)*	
Response, %			
OR	50.8	69.6	< 0.05
CR	13.0	23.9	< 0.01
nCR	19.8	37.0	< 0.01
PR	18.1	8.7	< 0.01
Adverse events grade 3 or 4, %			
Neutropenia	32.6	23.7	
Thrombocytopenia	6.8	8.5	
Anaemia	6.2	6.8	

\* Dex dose reductions were 40 mg/day, days 1–4, every 2 weeks (level –1); 40 mg/day, days 1–4, every 4 weeks (level –2); and 20 mg/day, days 1–4, every 4 weeks (level –3).

# Dex dose adjustments result in better efficacy and tolerability in patients with relapsed/refractory MM (2)

## MM-009 and MM-010: subanalysis

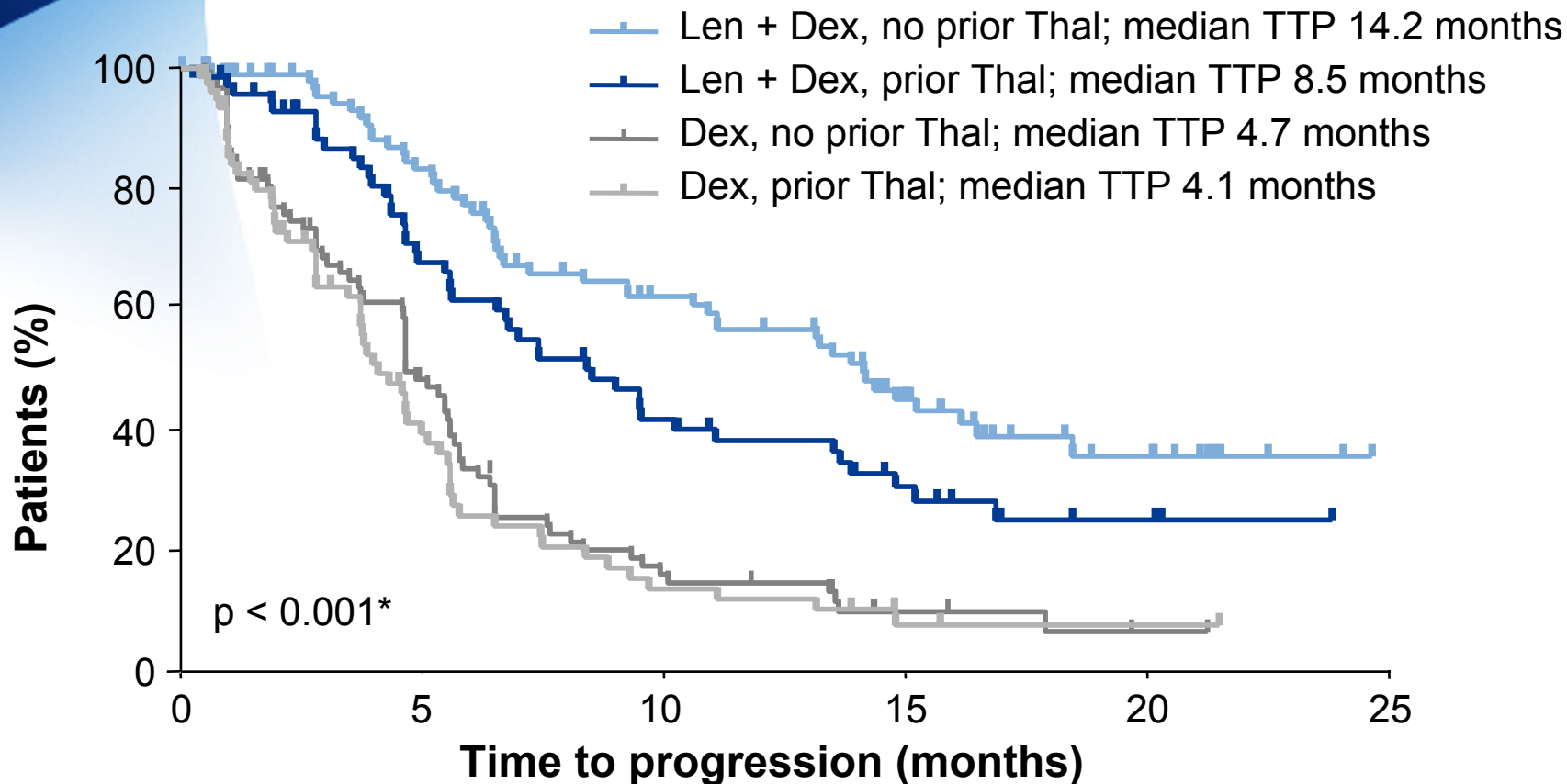


† Most conservative estimate obtained assuming all censored patients die immediately after the censor date.





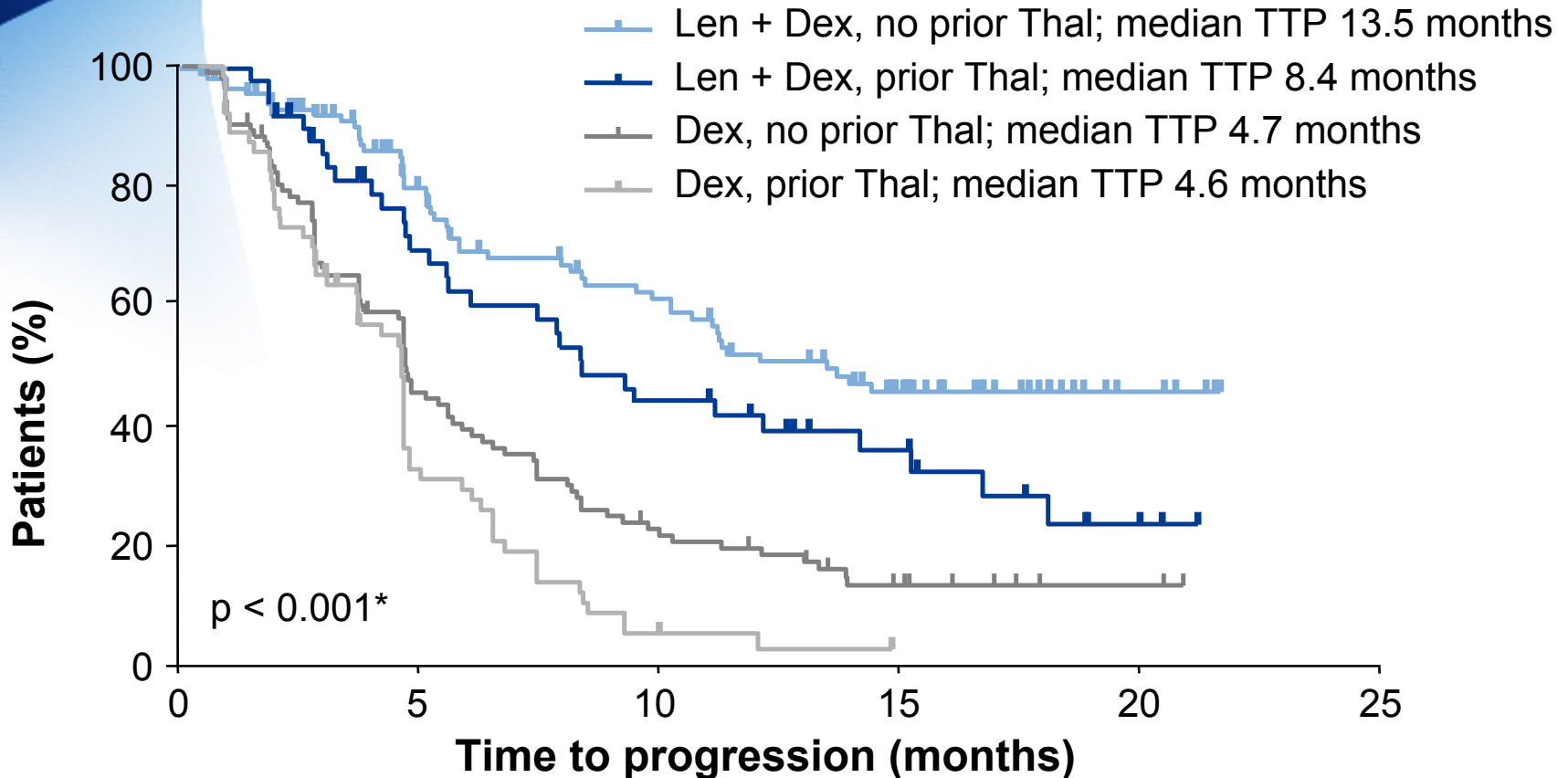
# MM-009: longer time to progression with Len + Dex regardless of prior thalidomide



\*p value from log-rank test comparing Len + Dex (no prior Thal) versus Dex (no prior Thal) and Len + Dex (prior Thal) versus Dex (prior Thal).



# MM-010: longer time to progression with Len + Dex regardless of prior thalidomide



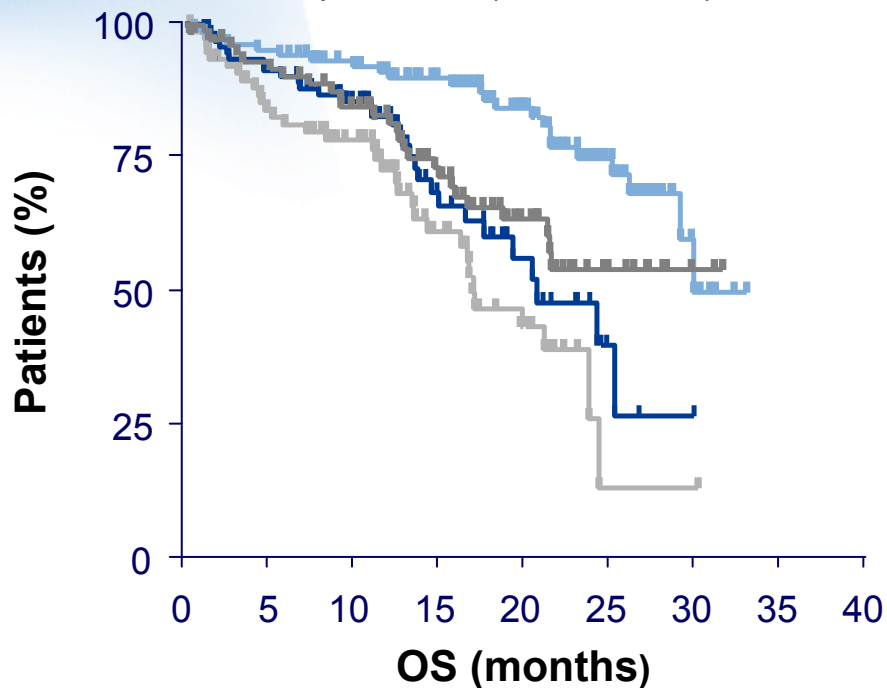
\*p value from log-rank test comparing Len + Dex (no prior Thal) versus Dex (no prior Thal) and Len + Dex (prior Thal) versus Dex (prior Thal).



# MM-009 and MM-010: increased OS with Len + Dex regardless of prior Thal

## MM-009

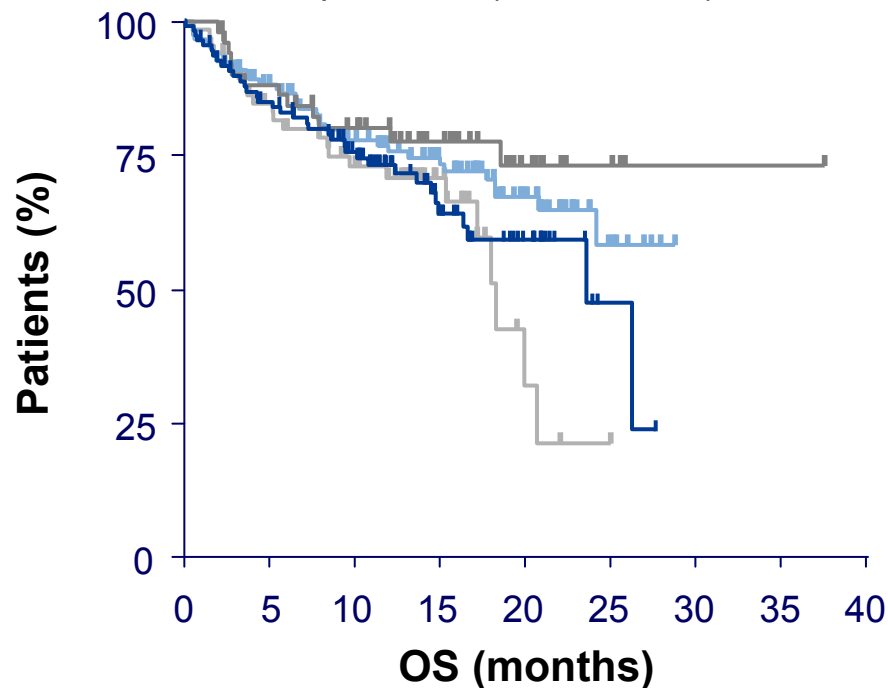
- Len + Dex, no prior Thal (29.6 months)
- Len + Dex, prior Thal (not reached)
- Dex, no prior Thal (20.5 months)
- Dex, prior Thal (16.8 months)



$p < 0.001$  Len + Dex vs Dex, no prior Thal  
 $p = 0.03$  Len + Dex vs Dex, prior Thal

## MM-010

- Len + Dex, no prior Thal (not reached)
- Len + Dex, prior Thal (not reached)
- Dex, no prior Thal (23.5 months)
- Dex, prior Thal (18.2 months)



$p = 0.21$  Len + Dex vs Dex, no prior Thal  
 $p = 0.04$  Len + Dex vs Dex, prior Thal



# Subgroup analyses of MM-009 and MM-010: efficacy of Len + Dex after prior Thal

- **Objective**

- to assess the efficacy and safety of Len + Dex in patients who have previously received treatment with thalidomide

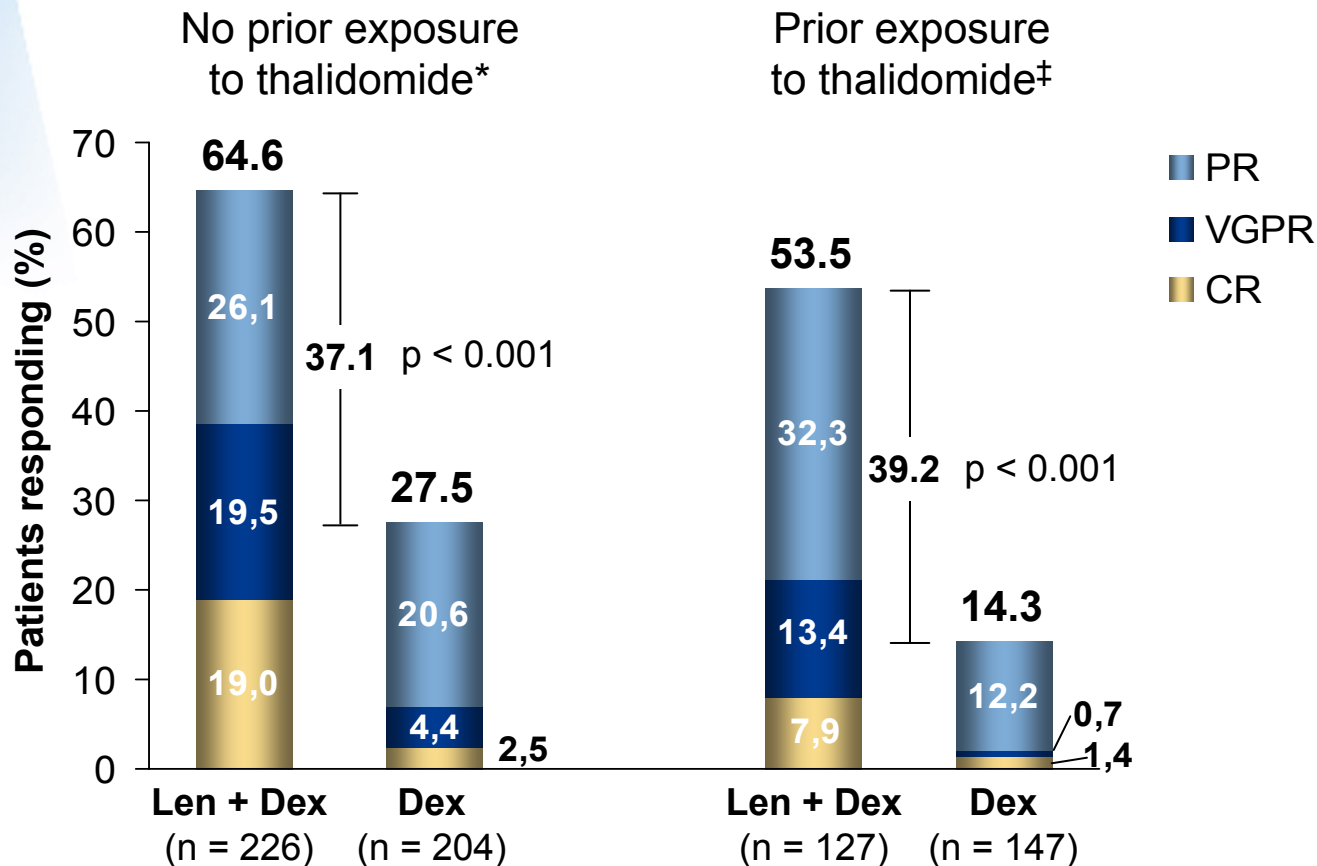
- **Patients**

- a total of 704 patients from MM-009 and MM-010, including 39% who had received prior thalidomide treatment
- those who had received thalidomide had
  - more prior lines of therapy
  - a longer duration of multiple myeloma



# Lenalidomide is effective after prior exposure to thalidomide

## MM-009 and MM-010: prospective subgroup analysis of patients with relapsed/refractory MM



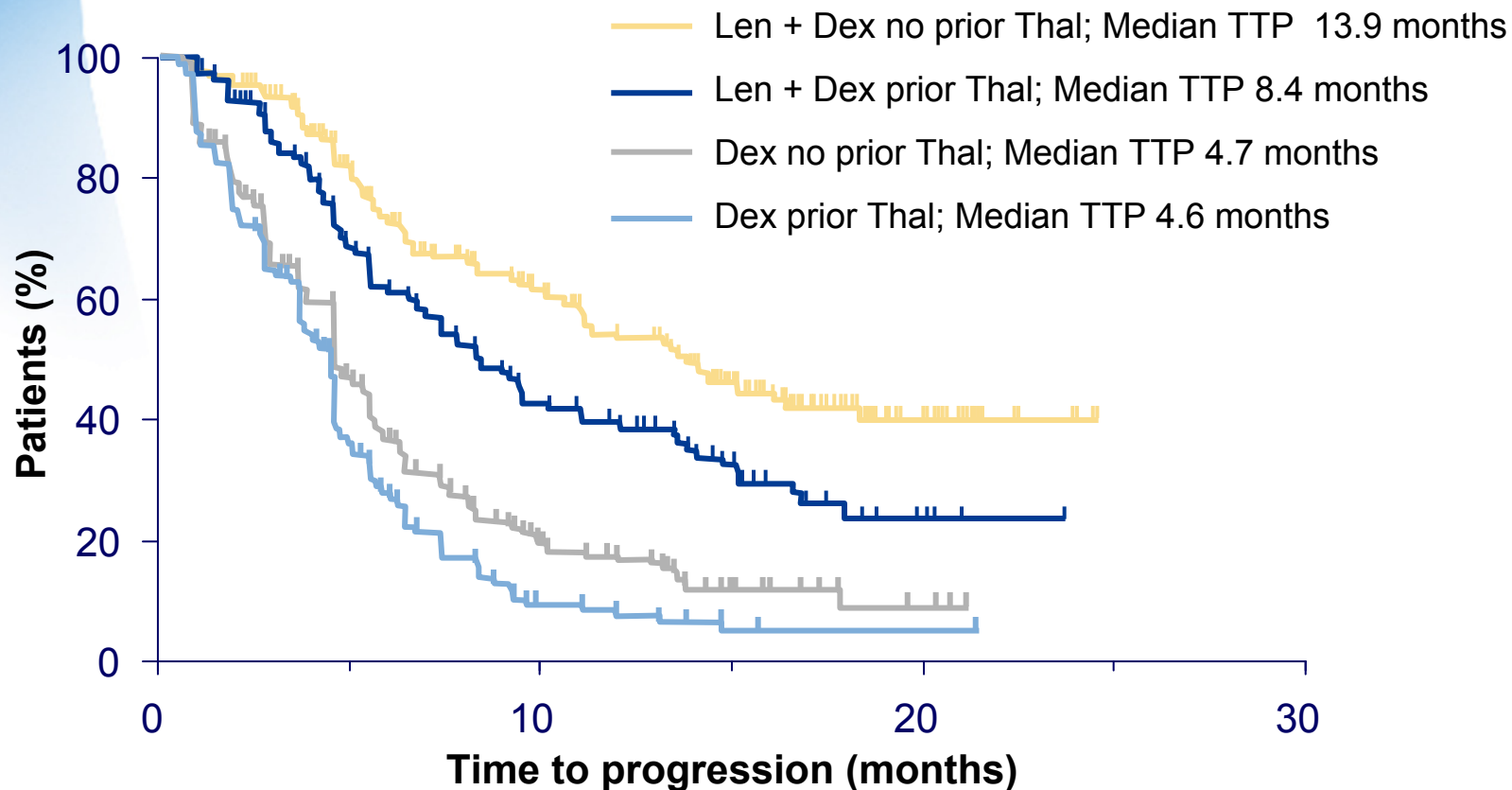
\* Median 2 prior lines of treatment.

‡ Median 3 prior lines of treatment.

Data from Wang M, et al. Blood. 2008;112:4445-51.



# Longer TTP with Len + Dex than with Dex alone regardless of prior Thal





# Len + Dex more effective than Dex despite thalidomide resistance

## MM-009 and MM-010: prospective subgroup analysis

	T1 (n = 124)		T2 (n = 65)		T3 (n = 44)	
	Len + Dex (n = 54)	Dex (n = 70)	Len + Dex (n = 31)	Dex (n = 34)	Len + Dex (n = 20)	Dex (n = 24)
<b>ORR, %</b>	<b>65</b>	<b>17</b>	<b>42</b>	<b>6</b>	<b>50</b>	<b>21</b>
<b>CR</b>	<b>11</b>	<b>1</b>	<b>7</b>	<b>3</b>	<b>5</b>	<b>0</b>
<b>VGPR</b>	<b>13</b>	<b>1</b>	<b>13</b>	<b>3</b>	<b>20</b>	<b>0</b>
<b>PR</b>	<b>41</b>	<b>14</b>	<b>23</b>	<b>0</b>	<b>25</b>	<b>21</b>
<b>Median TTP, months</b>	<b>9.3</b>	<b>4.6</b>	<b>7.8</b>	<b>3.7</b>	<b>7.2</b>	<b>3.7</b>

All differences between Len + Dex and Dex:  $p < 0.05$ .

T1 (thalidomide sensitive): responded to thalidomide; no progression during thalidomide therapy

T2 (thalidomide relapsed): responded to thalidomide; progressed during thalidomide therapy

T3 (thalidomide refractory): no response to thalidomide; progressed during thalidomide therapy



# Len + Dex more effective than Dex alone regardless of prior thalidomide exposure

## MM-009 and MM-010: prospective subgroup analysis

	No prior Thal		Prior Thal	
	Len + Dex (n = 226)	Dex (n = 204)	Len + Dex (n = 127)	Dex (n = 147)
<b>ORR (CR + nCR + PR), %</b>	<b>64.6</b>	<b>27.5</b>	<b>53.5</b>	<b>14.3</b>
<b>CR, %</b>	<b>19.0</b>	<b>2.5</b>	<b>7.9</b>	<b>1.4</b>
<b>Median TTP, months</b>	<b>13.9</b>	<b>4.7</b>	<b>8.4</b>	<b>4.6</b>
<b>Median PFS, months</b>	<b>13.2</b>	<b>4.7</b>	<b>8.4</b>	<b>4.6</b>
<b>Median OS, months</b>	<b>36.1</b>	<b>32.0</b>	<b>33.3</b>	<b>28.7*</b>

For comparisons between Len + Dex and Dex alone:  $p < 0.05$ ; \* = NS.





# Len + Dex is safe in thalidomide-naive and thalidomide-exposed patients

Grade 3 or 4 adverse events	No prior Thal, %		Prior Thal, %	
	Len + Dex (n = 226)	Dex (n = 204)	Len + Dex (n = 127)	Dex (n = 147)
DVT or PE (or both)	9.7	4.4*	15.0	2.7*
Neutropenia	32.3	4.4*	40.9	2.1*
Thrombocytopenia	10.6	5.4	17.3	7.5*
Anaemia	10.2	5.4	11.8	6.9
Febrile neutropenia	2.7	0.0*	1.6	0.0
Infection	15.5	7.4*	14.2	8.9
Fatigue	8.0	3.9	3.9	6.2
Gastrointestinal	5.3	2.0	2.4	1.4
Peripheral neuropathy	0.4	0.5	3.1	0.7

For all comparisons between prior thalidomide exposure and no prior exposure in Len + Dex patients, p was not significant. \* p < 0.05 for Len + Dex vs Dex alone.

Reproduced from Wang M, et al. Blood. 2008;112:445-51

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# Len + Dex more effective than Dex at first relapse and beyond

Prospective subgroup analysis of relapsed/refractory MM patients enrolled in  
MM-009 and MM-010

	1 prior therapy Len + Dex	1 prior therapy Dex	≥ 2 prior therapies Len + Dex	≥ 2 prior therapies Dex
n	120	121	226	225
ORR (CR + nCR + PR), %	63	27	57	20
SD, %	27	54	33	57
PD, %	3	13	1	15
Overall TTP, months	16.5*	4.7	10.2*	4.7
Median OS, months	29.6	25.0	Not reached	18.2

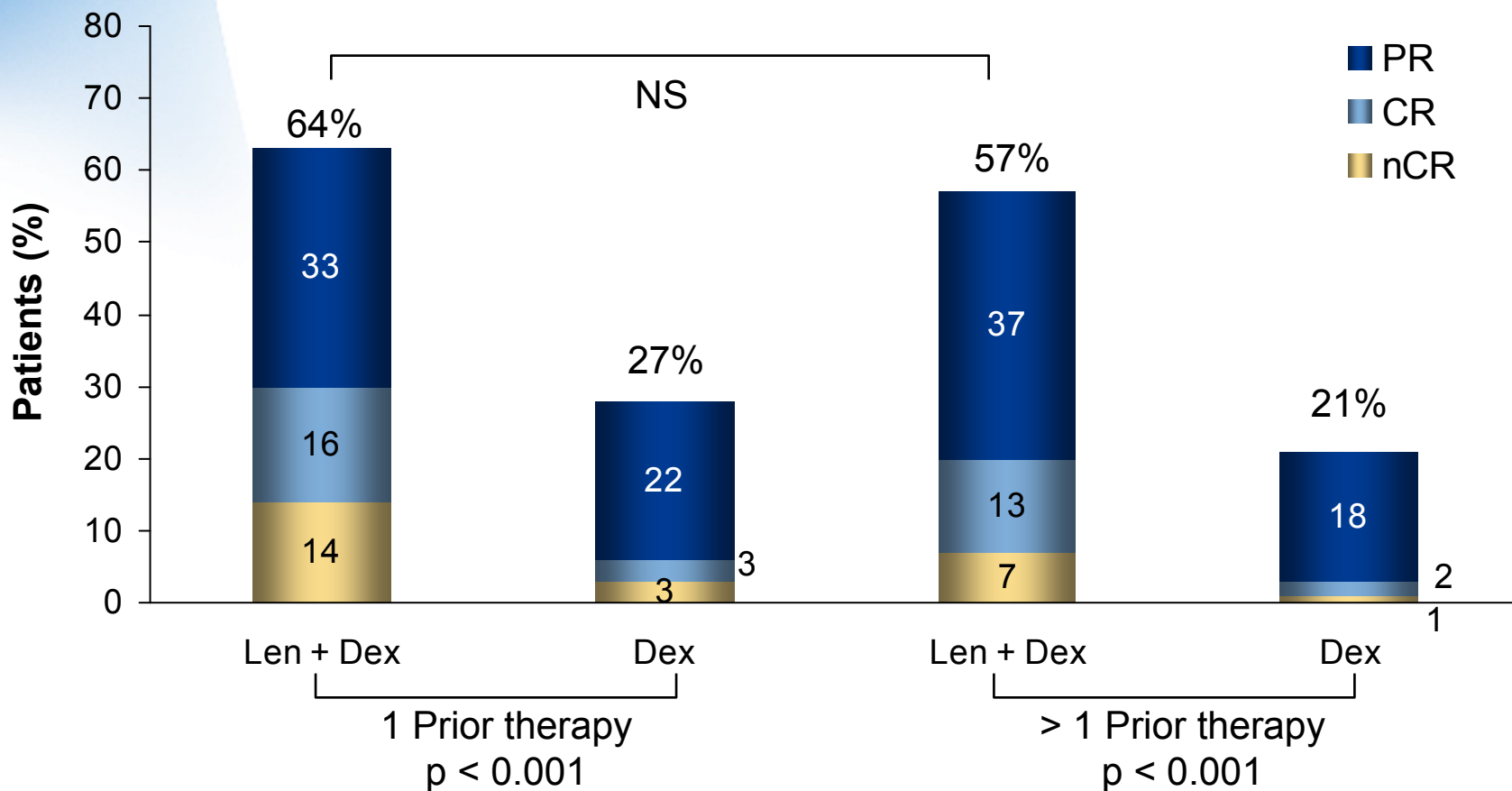
All differences between Len + Dex and Dex for 1 and  $\geq 2$  prior therapies are significant.

\*p < 0.05



# Len + Dex provides higher response rates than Dex at first relapse and beyond

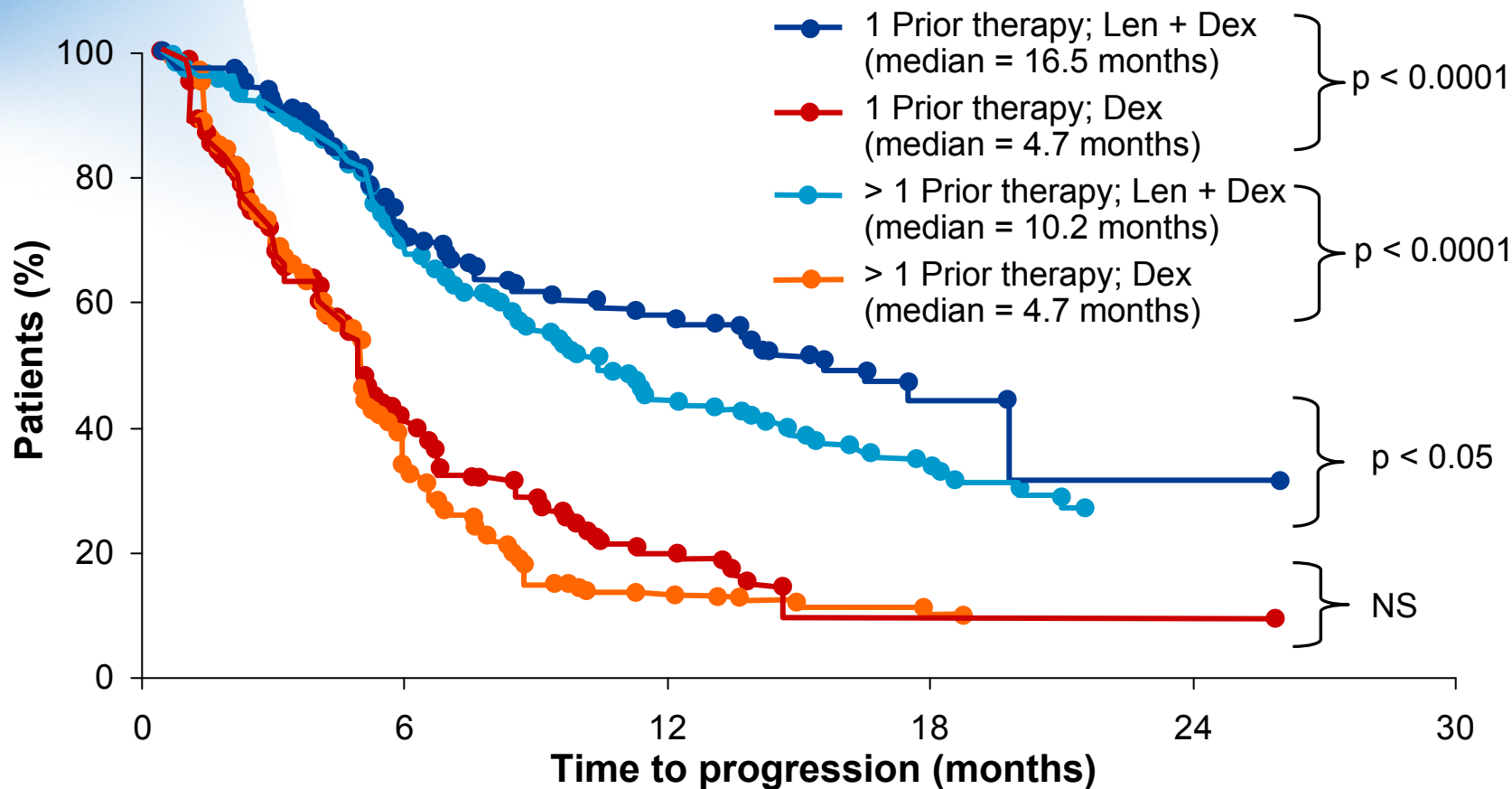
- Prospective subgroup analysis of relapsed/refractory MM patients enrolled in MM-009 and MM-010





# TTP is improved when Len + Dex is used at first relapse compared with use later as salvage therapy

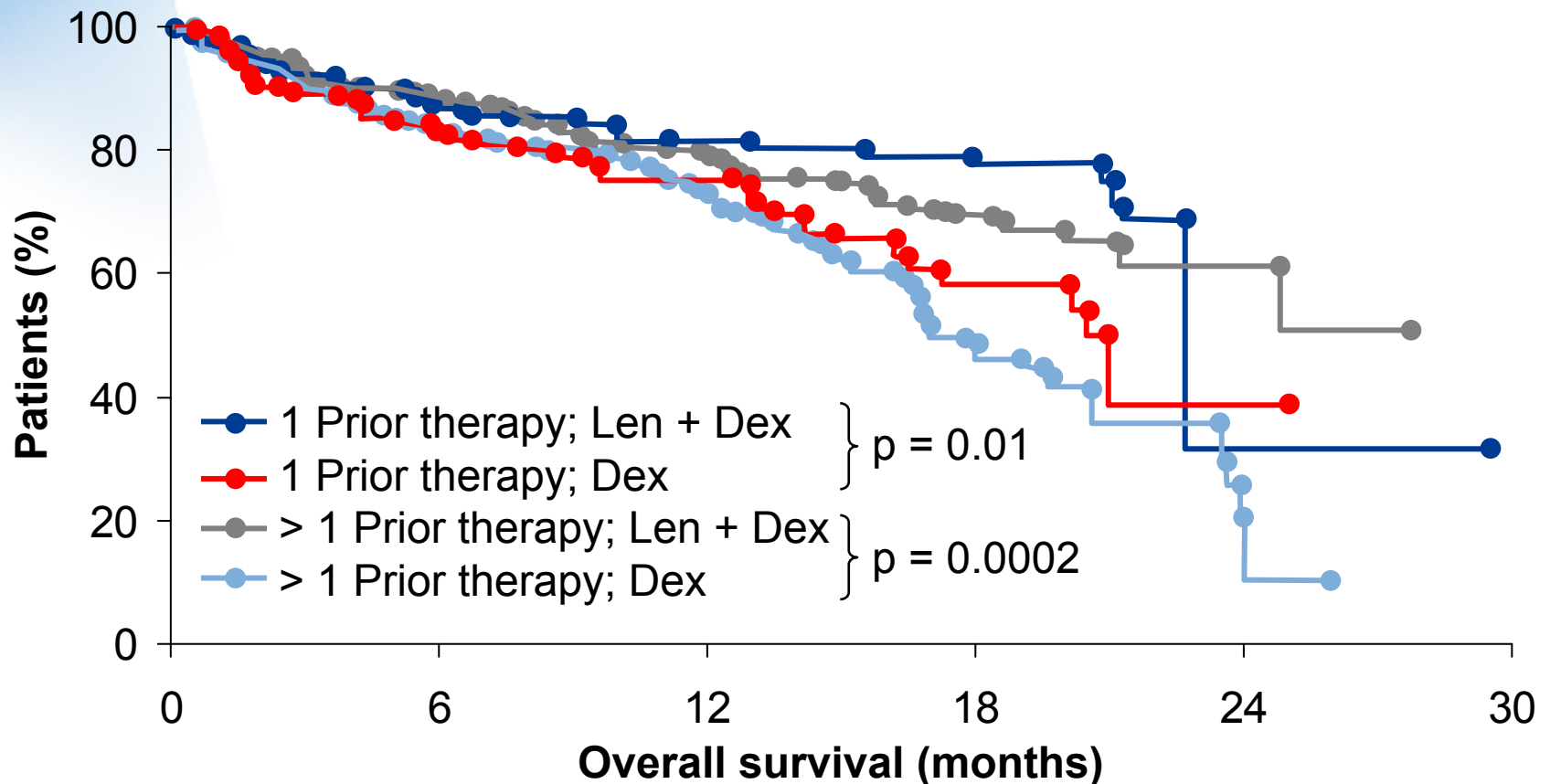
Prospective subgroup analysis of relapsed/refractory MM patients enrolled in MM-009 and MM-010





# Overall survival is improved when Len + Dex is used at first relapse and beyond

- Prospective subgroup analysis of relapsed/refractory MM patients enrolled in MM-009 and MM-010





# Subgroup analysis of MM-009 and MM-010: impact of Len + Dex treatment duration on outcome

- **Objective**
  - to assess survival benefit with long-term Len + Dex therapy
  - to assess the impact of early discontinuation of Len + Dex
- **Survival outcomes analysed according to**
  - duration of treatment, after achievement of best response
    - $\leq 10$  months (n = 223)
    - $> 10$  months (n = 98)
  - early treatment discontinuation because of adverse events (n = 42) or withdrawn consent (n = 30)



# Longer duration of Len + Dex treatment and maintenance of best response prolongs OS

## MM-009 and MM-010: subgroup analyses

Effect of longer duration of Len + Dex treatment after best response

Duration of treatment	≤ 10 months (n = 223)	> 10 months (n = 98)	p value
<b>Median OS, months</b>	<b>23.4</b>	<b>Not reached</b>	<b>&lt; 0.0001</b>
<b>2-year survival, %</b>	<b>48.4</b>	<b>93.8</b>	<b>&lt; 0.0001</b>

Early discontinuation of Len + Dex treatment associated with poor prognosis

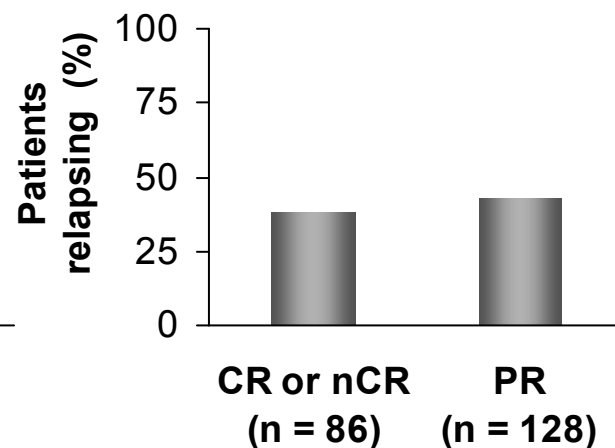
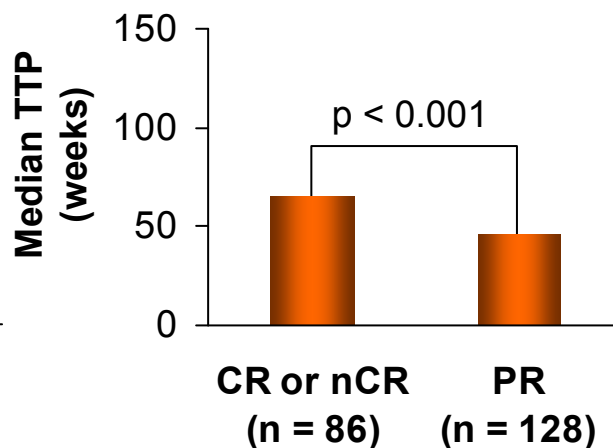
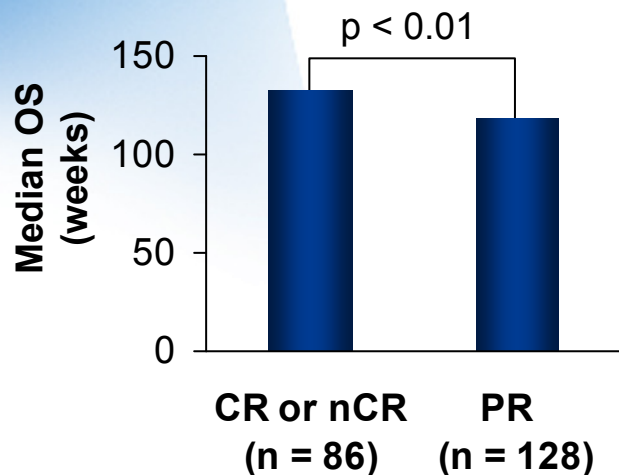
	Discontinued* (n = 72)	Continued (n = 115)	p value
<b>Median TTP, months</b>	<b>13.6</b>	<b>Not reached</b>	<b>&lt; 0.0001</b>
<b>Median OS, months</b>	<b>29.5</b>	<b>Not reached</b>	<b>&lt; 0.0001</b>

\*Discontinued because of adverse events (n = 42) or withdrawn consent (n = 30).



# CR is associated with better OS and TTP than PR after Len + Dex treatment

## Pooled subgroup analysis of relapsed/refractory MM patients enrolled in MM-009 and MM-010



Grade 3 or 4 adverse event, %	CR + nCR (n = 86)	PR (n = 128)
Neutropenia	43	41
Thrombocytopenia	13	16
Anaemia	12	9
Pneumonia	12	6
Febrile neutropenia	1	3





# Len + Dex as effective in MM patients with vs without prior stem cell transplant

- Subgroup analysis of MM-009 and MM-010

	Prior ASCT	Prior ASCT	No prior ASCT	No prior ASCT
	Len + Dex	Dex	Len + Dex	Dex
<b>n</b>	<b>210</b>	<b>204</b>	<b>143</b>	<b>147</b>
<b>ORR (CR + nCR + PR), %</b>	<b>63.3*</b>	<b>23.5</b>	<b>55.2*</b>	<b>20.4</b>
<b>CR, %</b>	<b>13.3‡</b>	<b>2.5</b>	<b>16.1‡</b>	<b>1.4</b>
<b>Median TTP, weeks</b>	<b>44.1</b>	<b>20.1</b>	<b>61.4</b>	<b>20.1</b>

For all differences between Len + Dex and Dex:  $p < 0.001$ .

\* $p = 0.128$  for prior ASCT versus no prior ASCT.

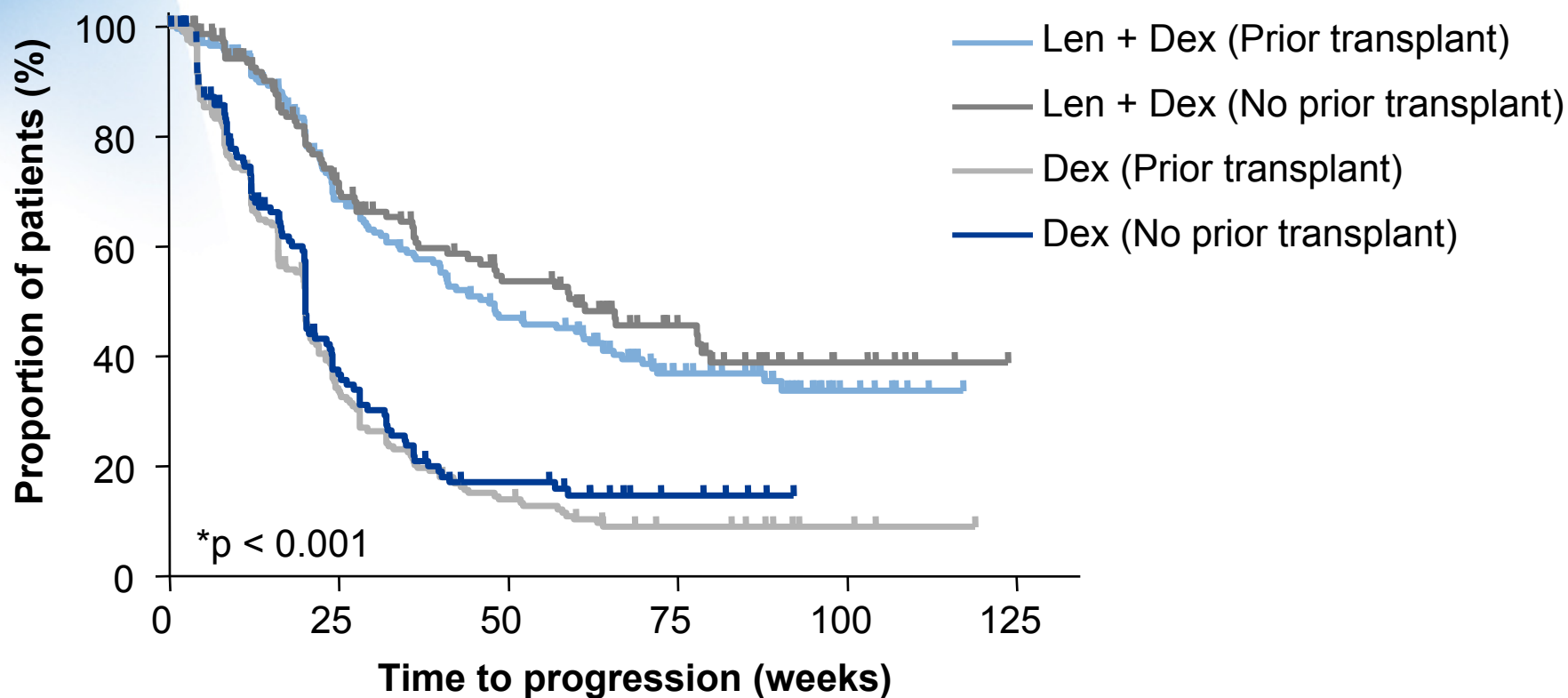
‡ $p = 0.483$  for prior ASCT versus no prior ASCT.

- In all subgroups, median overall survival had not been reached after a median follow-up of 16.8 months



# Longer TTP in MM patients treated with Len + Dex vs Dex regardless of prior transplant

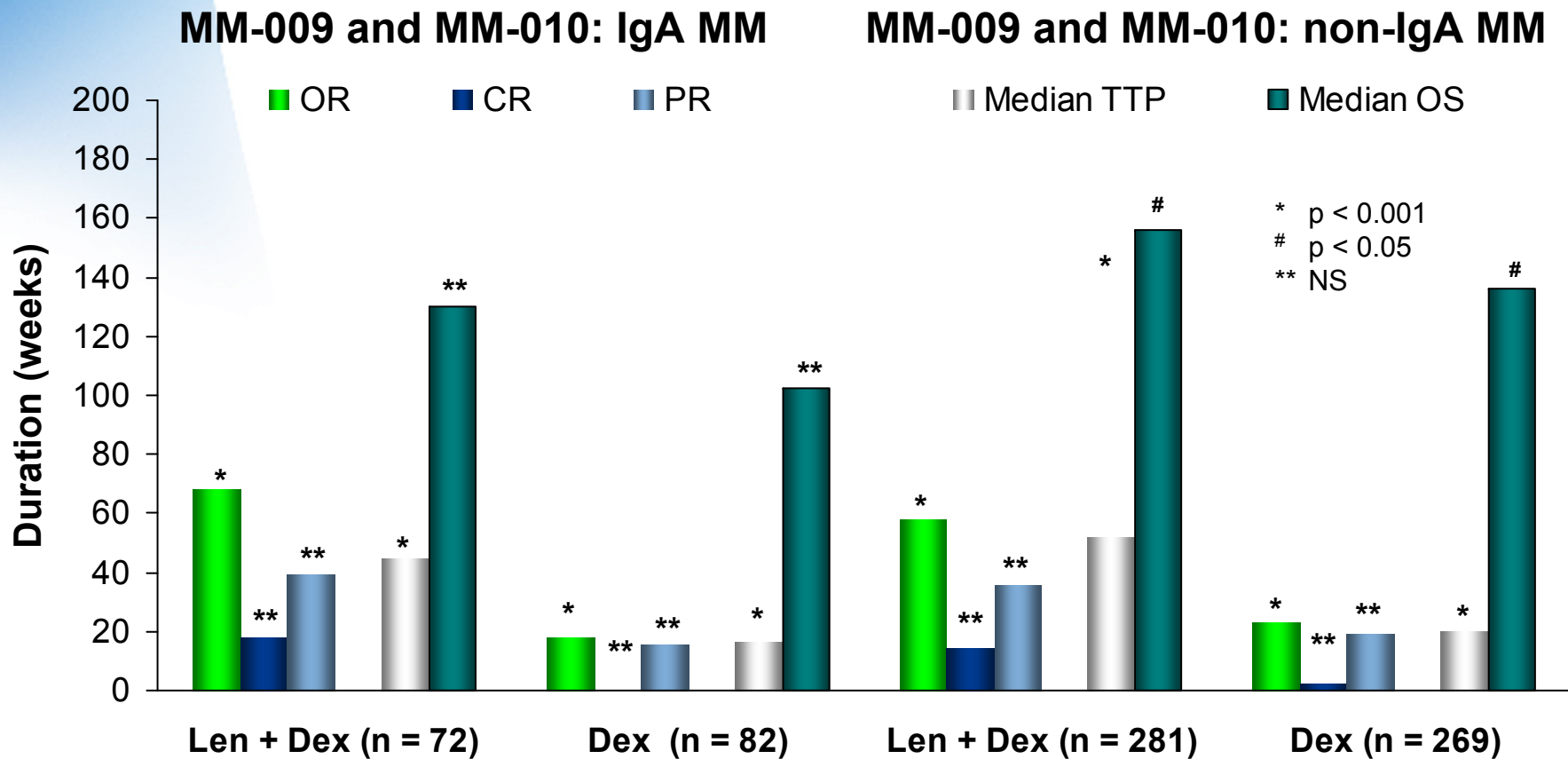
- Subgroup analysis of MM-009 and MM-010



\*p value from log-rank test for Len + Dex and Dex comparison



# Len + Dex significantly improves response and prolongs TTP in patients with IgA MM (1)





# Len + Dex significantly improves response and prolongs TTP in patients with IgA MM (2)

## MM-009 and MM-010: IgA MM versus non-IgA MM

Grade 3 or 4 adverse event, %	IgA MM		Non-IgA MM	
	Len + Dex (n = 72)	Dex (n = 82)	Len + Dex (n = 281)	Dex (n = 269)
<b>Neutropenia</b>	<b>37.5</b>	<b>2.4</b>	<b>46.5</b>	<b>14.5</b>
<b>Thrombocytopenia</b>	<b>16.7</b>	<b>8.5</b>	<b>12.1</b>	<b>5.7</b>
<b>Anaemia</b>	<b>11.1</b>	<b>7.3</b>	<b>11.0</b>	<b>5.7</b>



# Subgroup analyses of MM-009 and MM-010: efficacy of Len + Dex in high- and low-risk patients

- **Objective**

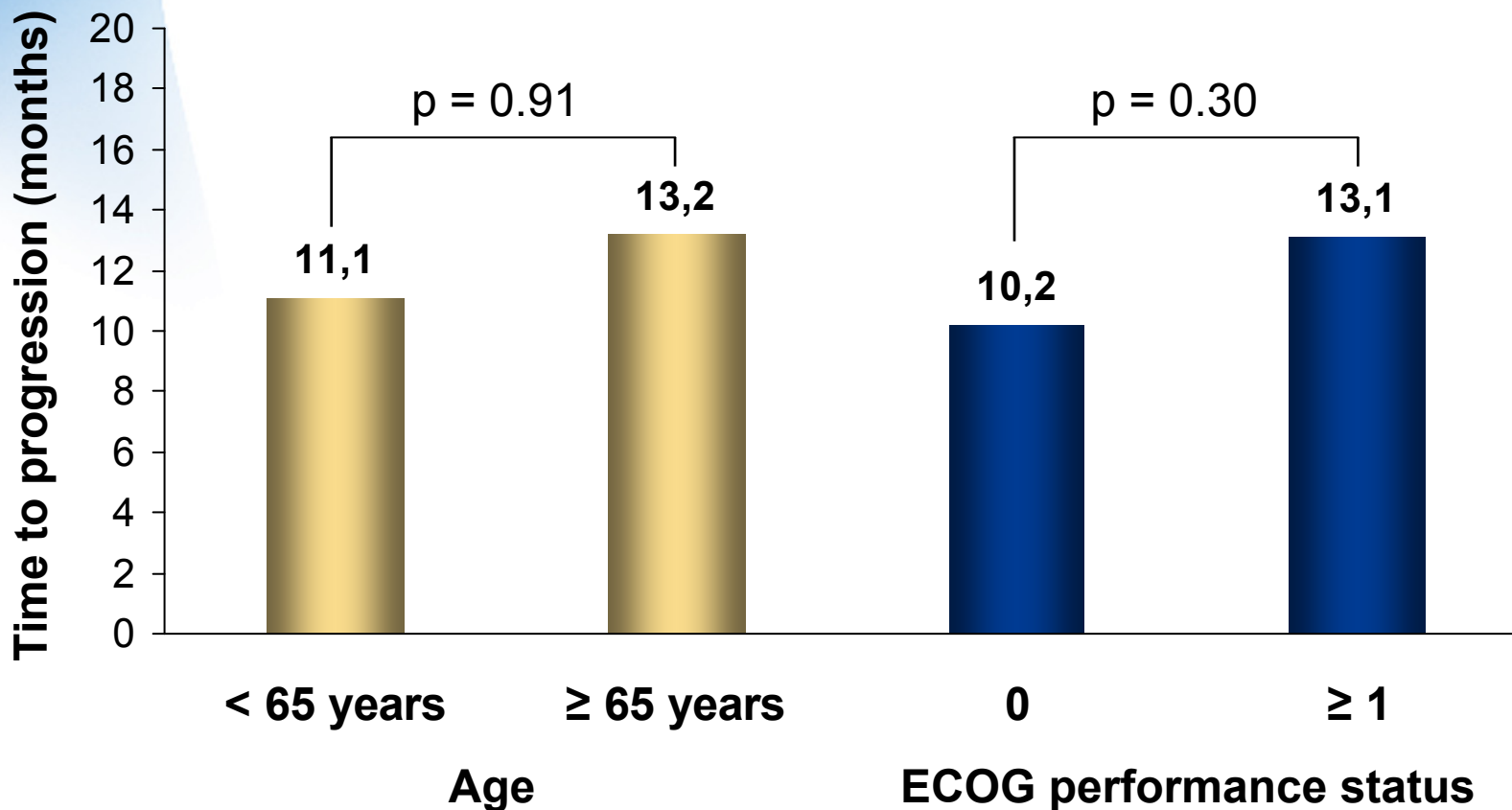
- to assess efficacy of lenalidomide + dexamethasone in high-risk and low-risk patients
- high-risk patients: age  $\geq$  65 years, Eastern Cooperative Oncology Group score  $\geq$  1, IgA multiple myeloma, Durie-Salmon stage III, and b<sub>2</sub>-microglobulin > 2.5 mg/L

- **Patients**

- all those who had received lenalidomide + dexamethasone in MM-009 and MM-010



# TTP is similar in low- and high-risk patients who received Len + Dex



Data from

ECOG = Eastern Cooperative Oncology Group.

Chanan-Khan A, et al. Blood. 2008;112:[abstract 3701].



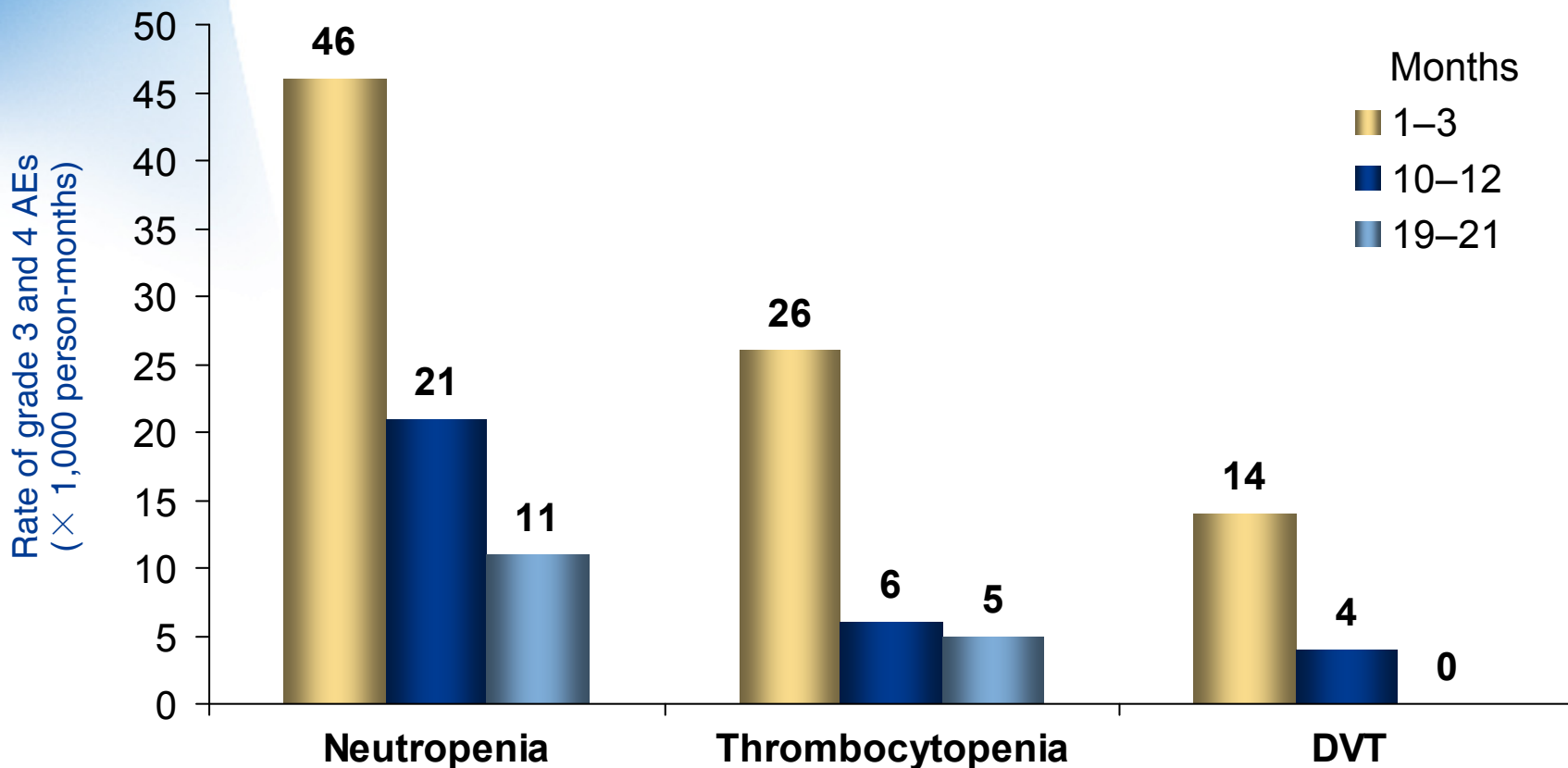
# Len + Dex is safe in high- and low-risk patients: grade 3 or 4 AEs are similar in each group

- **Grade 3 or 4 AEs in high- and low-risk patients are similar to those reported in the overall study population**
- **Grade 3 and 4 AEs were similar in high- and low-risk groups receiving Len + Dex, except**
  - neutropenia  
Durie-Salmon stage III, 40%; stage I or II, 28% (p = 0.03)
  - thrombocytopenia  
≥ 65 years, 17%; < 65 years, 9% (p = 0.03)  
b<sub>2</sub>-microglobulin ≤ 2.5 mg/L, 16%; > 2.5 mg/L, 7% (p = 0.03)
  - anaemia  
b<sub>2</sub>-microglobulin ≤ 2.5 mg/L, 15%; > 2.5 mg/L, 1% (p = 0.0001)



# Subgroup analysis of MM-009 and MM-010: incidences of haematosuppression and DVT decline over time

## Grade 3 or 4 adverse events in patients receiving long-term treatment with Len + Dex

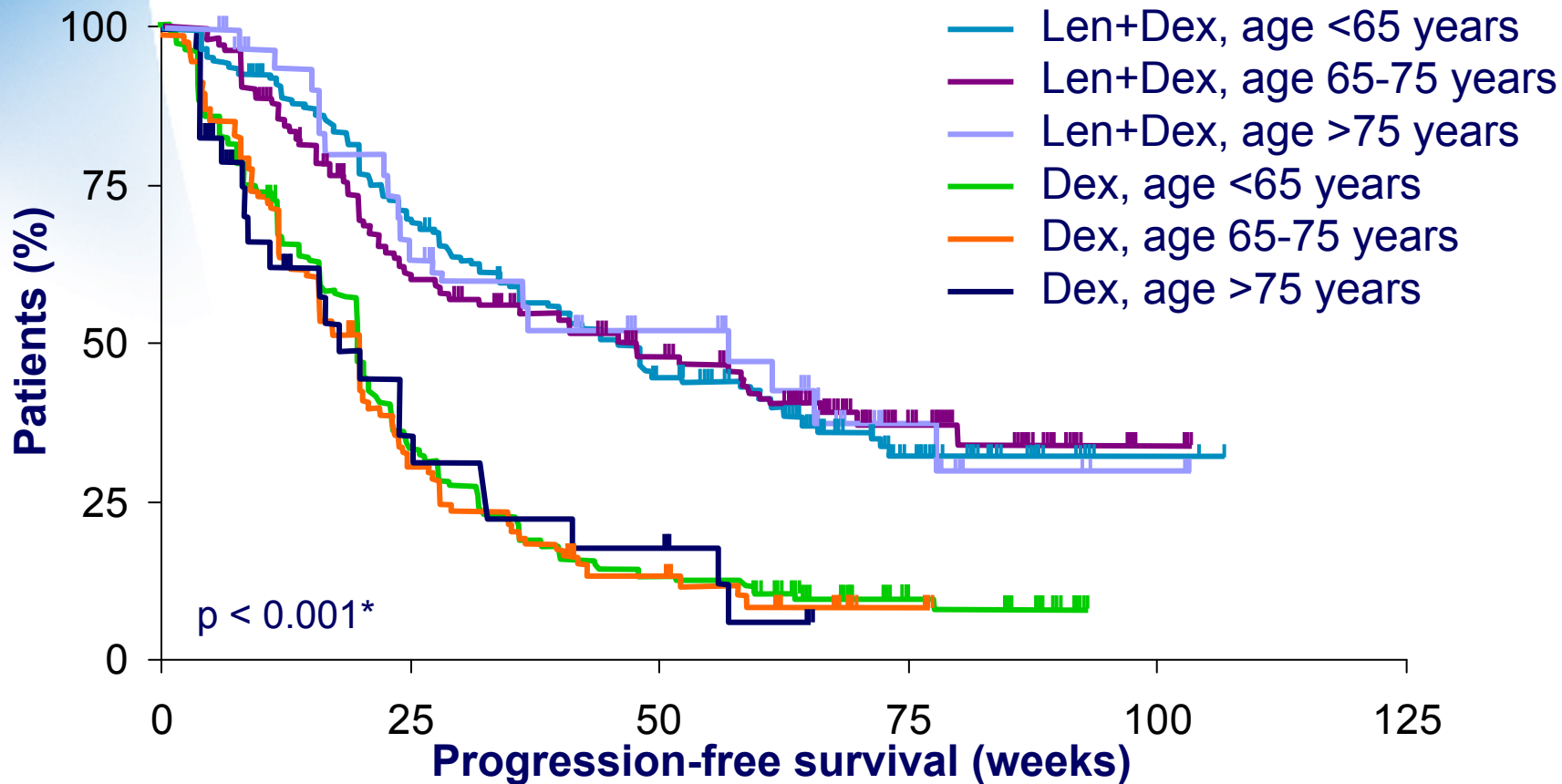


Treatment interruptions and dose reductions also declined during follow-up



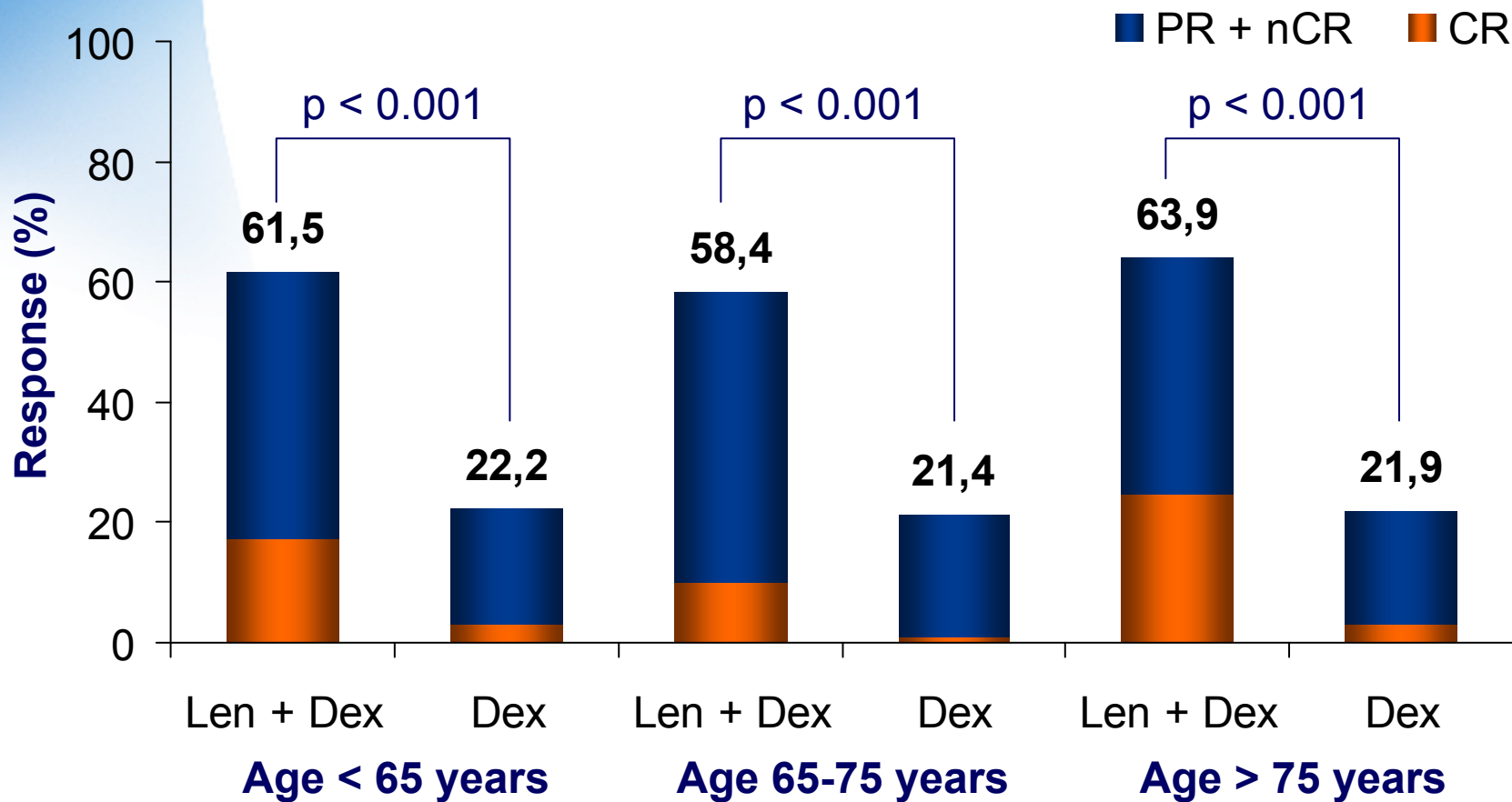


# Progression-free survival by age group of Len + Dex vs Dex in relapsed/refractory MM



\*p value is for comparison between Len/Dex vs Dex for each of the age groups

# Response rates by age group of Len + Dex vs Dex in relapsed/refractory MM





# Adverse events by age group of Len + Dex vs Dex in relapsed/refractory MM

## Subanalysis of MM-009 and MM-010

Adverse events (all grades), %	Age (< 65 years)		Age (65–75 years)		Age (> 75 years)	
	Len + Dex (n = 192)	Dex (n = 198)	Len + Dex (n = 125)	Dex (n = 121)	Len + Dex (n = 36)	Dex (n = 32)
Neutropenia	40.6*	8.6	47.2*	4.1	41.7*	3.2
Thrombocytopenia	18.2	12.6	29.6*	7.4	22.2	9.7
Anaemia	22.0	18.7	43.2*	28.9	58.3	35.5
Febrile neutropenia	1.6	0.0	3.2	0.0	2.8	0.0

\*p < 0.05 for Len + Dex versus Dex using Fisher's exact test.

- Age did not affect the incidence of adverse events
- For all three age groups, grade 3 or 4 cytopenia was more common in the Len + Dex group compared with the Dex group



# Equal clinical benefit of Len + corticosteroids in elderly and younger relapsed/refractory MM patients

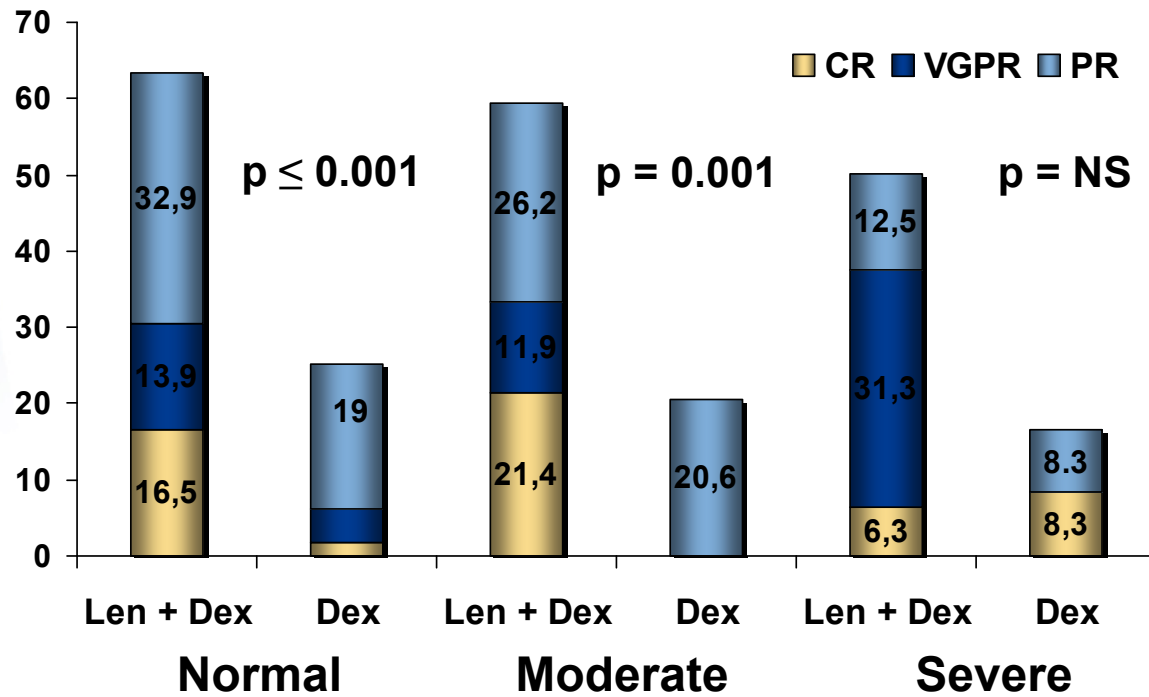
- **Analysis of patients treated with lenalidomide ± corticosteroids within the Extended Access Program Canada**
- **64% of patients were treated with Len + Dex, 10% with Len + prednisone, 7% with Len + Dex + prednisone, and 19% with lenalidomide only**

	<b>≥ 65 years Len + corticosteroids (n = 41)</b>	<b>&lt; 65 years Len + corticosteroids (n = 28)</b>
<b>PR, %</b>	<b>58</b>	<b>56</b>
<b>PFS, %</b>	<b>43</b>	<b>43</b>
<b>OS, %</b>	<b>74</b>	<b>76</b>

Differences between elderly and younger patients were not significant.



# Len + Dex is superior to Dex alone in patients with normal or impaired renal function



Months	Normal (> 80 ml/min)		Moderate (≥ 30 < 50 ml/min)		Severe (< 30 ml/min)	
	Len + Dex	Dex	Len + Dex	Dex	Len + Dex	Dex
Median TTP	11.3	4.7	11.4	2.8	7.9	4.7
Median OS	NR	101.2	30.4	12.5	18.6	16.9



# Impaired renal function is linked to grade 3 and 4 thrombocytopenia in relapsed / refractory MM

Retrospective subgroup analysis of patients with impaired renal function enrolled in MM-009 and MM-010

Adverse events, %	Normal (> 80 ml/min)		Moderate (≥ 30 < 50 ml/min)		Severe (< 30 ml/min)	
	Len + Dex	Dex	Len + Dex	Dex	Len + Dex	Dex
Neutropenia	31.0	4.3	42.9	5.9	37.5	8.3
Thrombocytopenia	7.0	5.5	19.0	17.6	37.5	>0.0
VTE	11.4	1.8	14.3	2.9	6.3	8.3



# Len + corticosteroids equally effective in patients with elevated vs normal serum creatinine levels

Patients treated with lenalidomide ± corticosteroids within the Extended Access Program Canada, stratified by baseline serum creatinine levels

	Elevated serum creatinine levels (> 89 µmol/l for females and > 109 µmol/l for males)	Normal serum creatinine levels
<b>n</b>	<b>23</b>	<b>46</b>
<b>nCR/PR, %</b>	<b>61</b>	<b>54</b>
<b>PFS, %</b>	<b>30</b>	<b>50</b>
<b>OS, %</b>	<b>72</b>	<b>76</b>

Differences in responses between patients with elevated vs normal serum creatinine levels were not significant.



## Adverse events leading to Len + Dex discontinuation in the Expanded Access Program

- Safety population: N = 422
- $\geq 1$  prior therapy
- Median time on study: 7.1 weeks (0.1–24.4)
- Median daily dose: 20.5 mg

	n (%)
<b>Neutropenia</b>	<b>6 (1.4)</b>
<b>Pneumonia</b>	<b>5 (1.2)</b>
<b>Febrile neutropenia</b>	<b>4 (0.9)</b>
<b>Pancytopenia</b>	<b>4 (0.9)</b>





# Adverse events leading to dose reduction or interruption in the Expanded Access Program

- Safety population: N = 422
- $\geq 1$  prior therapy
- Median time on study: 7.1 weeks (0.1–24.4)
- Median daily dose: 20.5 mg

	n (%)
<b>Neutropenia</b>	<b>47 (11.1)</b>
<b>Thrombocytopenia</b>	<b>33 (7.8)</b>
<b>Fatigue</b>	<b>16 (3.8)</b>
<b>Pneumonia</b>	<b>10 (2.4)</b>
<b>Febrile neutropenia</b>	<b>9 (2.1)</b>
<b>Anaemia</b>	<b>9 (2.1)</b>



# Preliminary data from the Italian Expanded Access Program (EAP)

- **The EAP was for patients with progressive disease**
- **Patients were given:**
  - lenalidomide 25 mg/day for 21 days of every 28-day cycle
  - dexamethasone 40 mg/day on days 1–4, 9–12, and 17–20 of every 28 day cycle for the first 4 cycles; then on days 1–4 only
  - treatment continued until disease progression or discontinuation
- **221 patients were enrolled at 55 centres**
  - median age 68 years (range 43–85 years)
  - median time since diagnosis 5 years (range 1–21 years)
  - median number therapies 3 (range 1–12)
  - prior therapies included bortezomib (27%), thalidomide (27%), and SCT (17%)



# Subgroup analysis of MM-016: Len + Dex efficacy in patients with poor cytogenetic prognosis

- **Lenalidomide 25 mg per day p.o. days 1–21 and dexamethasone 40 mg per day p.o. days 1–4, 9–12, and 17–20, then days 1–4 only from cycle 5 of each 28-day cycle**
- **N = 130 patients with FISH data on del(13q), t(4;14), del(17p13)**
- **Baseline cytogenetics**
  - 41.5% with del(13q)
  - 21.5% with t(4;14)
  - 9.2% with del(17p13)
- **Prior therapy**
  - 53.8% had received thalidomide
  - 45.9% had received bortezomib
  - 73.3% had received a stem cell transplant



# MM-016: Len + Dex treatment overcomes the negative prognosis associated with most cytogenetic abnormalities

## ORR according to baseline cytogenetics

Cytogenetic group	Overall	del(13q)	t(4;14)	del(17p13)
<b>Patients, n</b>	<b>130</b>	<b>54</b>	<b>28</b>	<b>12</b>
<b>ORR, %</b>	<b>83.1</b>	<b>76.4</b>	<b>78.6</b>	<b>58.3</b>

- **Multivariate analysis**
  - the longer TTP and OS achieved with Len + Dex treatment are not adversely affected by del(13q) or t(4;14)
  - del(17p13) remains a predictor of poor treatment outcome



# Effect of adverse cytogenetics on the outcome of Len + Dex treatment in heavily pretreated patients\*

- **Lenalidomide 25 mg per day p.o. days 1–21 and dexamethasone 40 mg per day p.o. days 1–4, 9–12, and 17–20, then days 1–4 only from cycle 5 of each 28-day cycle**
- **N = 207 patients**
- **Baseline cytogenetics**
  - 41% with del(13q)
  - 14% with t(4;14)
  - 5% with del(17p13)
- **Prior therapy**
  - 87% had received thalidomide
  - 81% had received bortezomib



# Predictors of response to Len + Dex in heavily pretreated patients\*

Cytogenetic status	ORR, %	PFS, months	OS, months
<b>With del(13q)</b>	<b>43</b>	<b>5.0</b>	<b>10.4</b>
<b>Without del(13q)</b>	<b>71</b>	<b>12.5</b>	<b>17.4</b>
<b>With t(4;14)</b>	<b>39</b>	<b>5.5</b>	<b>9.4</b>
<b>Without t(4;14)</b>	<b>62</b>	<b>10.6</b>	<b>15.4</b>

For all comparisons (with vs without),  $p < 0.04$ .

**Haemoglobin < 10 g/dL, progression on thalidomide, and del(13q) were identified as independent predictors of reduced progression-free survival**



## **Eligibility for Len + Dex treatment in relapsed/refractory MM**

- **Len + Dex shown to be superior to Dex alone**
- **This benefit of Len + Dex was seen in all groups of patients, independent of age, disease stage, duration of disease, ECOG performance status, cytogenetics, level of  $\beta_2$ -microglobulin, and renal or hepatic impairment**
- **This benefit is also independent of type of therapy**
- **None of the baseline factors are exclusion criteria**
- **Patients with one previous therapy had greater survival advantages than patients with more than one previous therapy**
- **Lower doses of Dex result in fewer adverse events**
- **Reduction of lenalidomide dose is dependent on severity of renal impairment**
- **Adjustments for mild or moderate hepatic dysfunction or potential drug reactions are not required.**



# Economic evaluation of lenalidomide in patients with $\geq 1$ prior therapy

Use of Len + Dex improves survival and QALYs compared with Dex alone

	1 prior therapy		$\geq 2$ prior therapies	
	Len + Dex	Dex	Len + Dex	Dex
Life years (projected mean)	4.54	2.00	3.61	1.41
QALYs	3.20	1.39	2.50	1.00
Average cost, (per patient)	£54,499	£2,126	£44,169	£1,896
Incremental cost per life-year gained	£20,617		£19,218	
Incremental cost per QALY gained	£28,943		£28,184	





# VTE management recommendations for Len + Dex in relapsed/refractory MM

## **Risk factors for VTE during Len + Dex treatment**

- Central venous line
- Concomitant chemotherapy
- Doxorubicin use
- Erythropoietin use
- High-dose dexamethasone use
- High tumour mass
- Immobilization
- Ongoing infection/inflammation
- Older age
- Previous VTE
- Pre-existing coagulation disorder(s)
- Thrombophilia



# VTE management recommendations for Len + Dex in relapsed/refractory MM

## Screening

- No baseline coagulation studies nor screening recommended
- In symptomatic patients sonography for VTE diagnosis recommended

## VTE prophylaxis

- 4–6 months prophylaxis for patients with risk factors
- No evidence for best prophylaxis
- Low dose aspirin (81–100 mg) or prophylactic dose of LMWH is recommended
- Low-dose warfarin not recommended (risk severe haemorrhage)

## VTE treatment

- Patients can be continued on treatment with Len + Dex or re-treated after stabilization dependent on severity of VTE
- Therapeutic anticoagulation: switch patients on aspirin prophylaxis to LMWH and patients on LMWH prophylaxis to therapeutic doses (6 months therapeutic dose LMWH after which prophylaxis can be re-started)



# Cytopenia management recommendations for Len + Dex in relapsed/refractory MM

Occurrence, n/N (%)

**13/346 (3.8)**

**4/436 (1.2)**

**4/436 (1.2)**

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- **Monitoring of FBC**

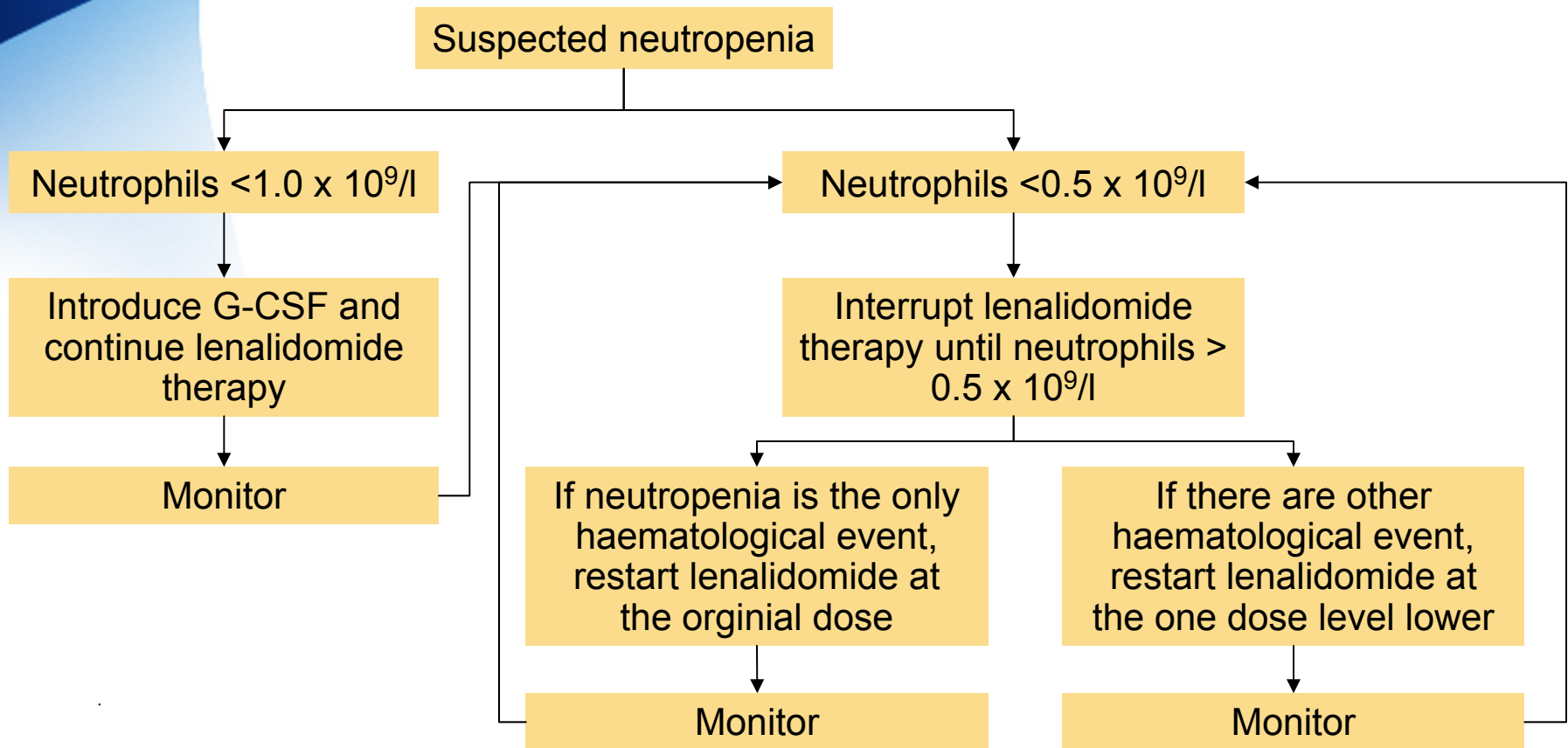
- biweekly monitoring is necessary in patients with a normal FBC
- if FBC is abnormal as a result of MM infiltration: full-dose Len + Dex should be tried and at least weekly monitoring
- standard dose reductions for all other causes of abnormal FBC



# Cytopenia management recommendations for Len + Dex in relapsed/refractory MM

- **Management of febrile neutropenia**
  - consider **antibiotic prophylaxis** if Len plus high-dose Dex is used
  - patient should receive clear instructions to seek medical care within 3 hours if febrile while neutropenic
- **Management of neutropenia**
  - as a general rule, in case of neutrophils  $< 1 \times 10^9/l$ , G-CSF is recommended to prevent dose reduction and febrile neutropenia, aiming at  $> 0.5 \times 10^9/l$  neutrophils
  - if ANC  $< 0.5 \times 10^9/l$ : interrupt lenalidomide treatment; restart at lower dose once ANC  $> 0.5 \times 10^9/l$
- **Management of thrombocytopenia**
  - platelets  $< 50 \times 10^9/l$ : anticoagulation should be stopped
  - platelets  $< 30 \times 10^9/l$ : lenalidomide treatment should be interrupted and restarted at lower dose once platelets  $> 30 \times 10^9/l$
- **Management of anaemia:**
  - erythropoiesis-stimulating agents should be used in patients with Hb  $< 10$  g/dl and in those who are symptomatic and present with Hb  $< 12$  g/dl. The target is Hb 12 g/dl and should not be exceeded

# Neutropenia management recommendations for Len + Dex in relapsed/refractory MM



\*For each subsequent drop and return to a neutrophil count of at least  $0.5 \times 10^9/l$ , the lenalidomide dose should be resumed at the next lower dose.



# Non-haematological AE management recommendations for Len + Dex in relapsed/refractory MM

- **Rash (grades  $\geq 2$ )**
  - antihistamine treatment recommended; if rash persists, continuous low-dose prednisone (10–20 mg/day for 14 days) should be added
  - rash usually self-limiting, lasting for several weeks
  - in some cases, lenalidomide dose reduction or interruption is necessary
- **Fatigue**
  - other causes such as anaemia, infection, depression or hypothyroidism should be ruled out
  - patients benefit from counselling
  - dose reduction may be considered for severe fatigue
- **Dexamethasone treatment may predispose patients to infection**
  - routine antibiotic prophylaxis is recommended upon starting Len + Dex treatment
  - vaccinations against influenza, pneumococci, meningococci, and haemophilus should be considered



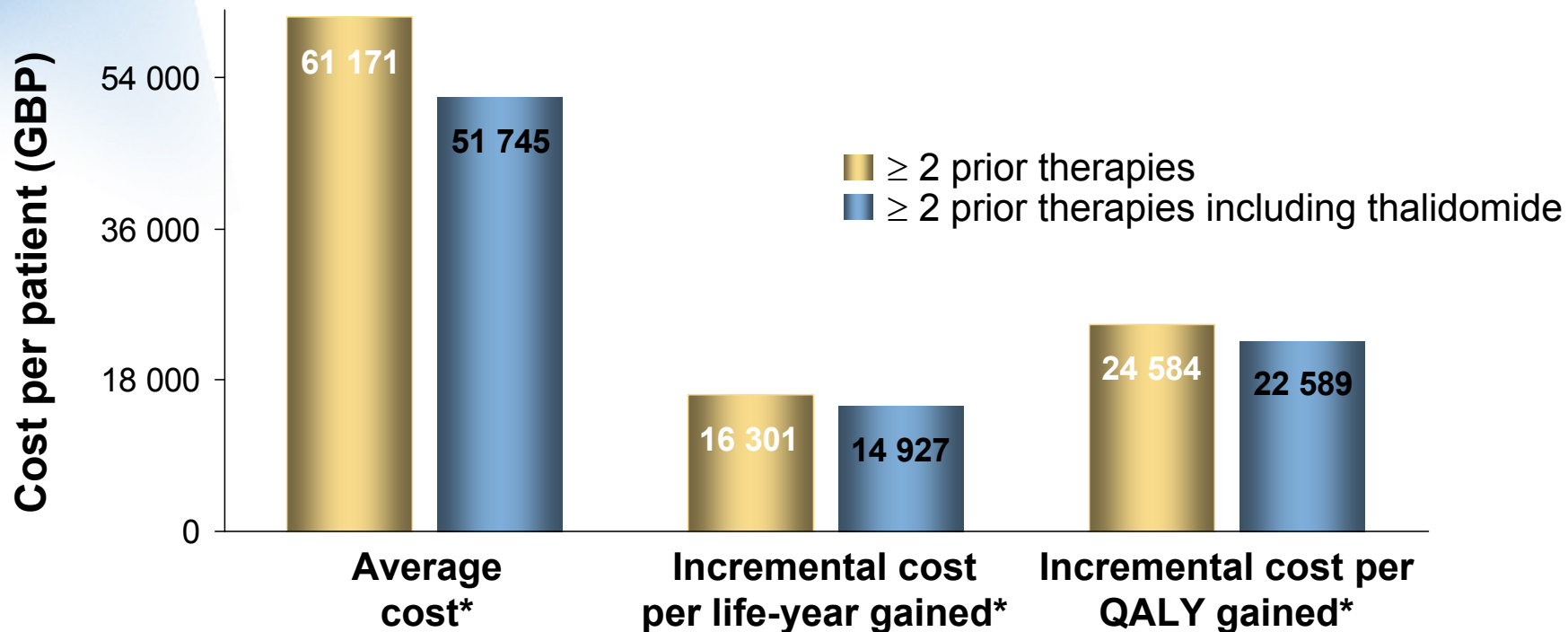
# Economic evaluation of Len and Dex for the treatment of relapsed/refractory MM

- Objective
  - to estimate long-term health and cost consequences of Len + Dex versus Dex alone in MM patients with  $\geq 2$  prior therapies
- Methods
  - discrete-event simulation of disease course by using response, TTP, and OS estimates based on pooled data from trials MM-009 and MM-010
  - disease-management costs reflective of clinical practice in UK NHS
  - lifetime horizon used to model costs and health outcomes, including survival and QALYs



# Len + Dex is cost effective in the treatment of relapsed/refractory MM

**Len + Dex delivers substantial improvements in quality-adjusted survival**



\*Discounted





**Revlimid®**

**Lenalidomide and  
dexamethasone in  
relapsed/refractory MM  
MM-009, MM-010**