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

- ≤ 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 β_2M concentration (≤ 2.5 mg/ml vs > 2.5 mg/ml), prior transplant (0 vs ≥ 1), and prior MM treatment regimens (< 1 vs ≥ 1)

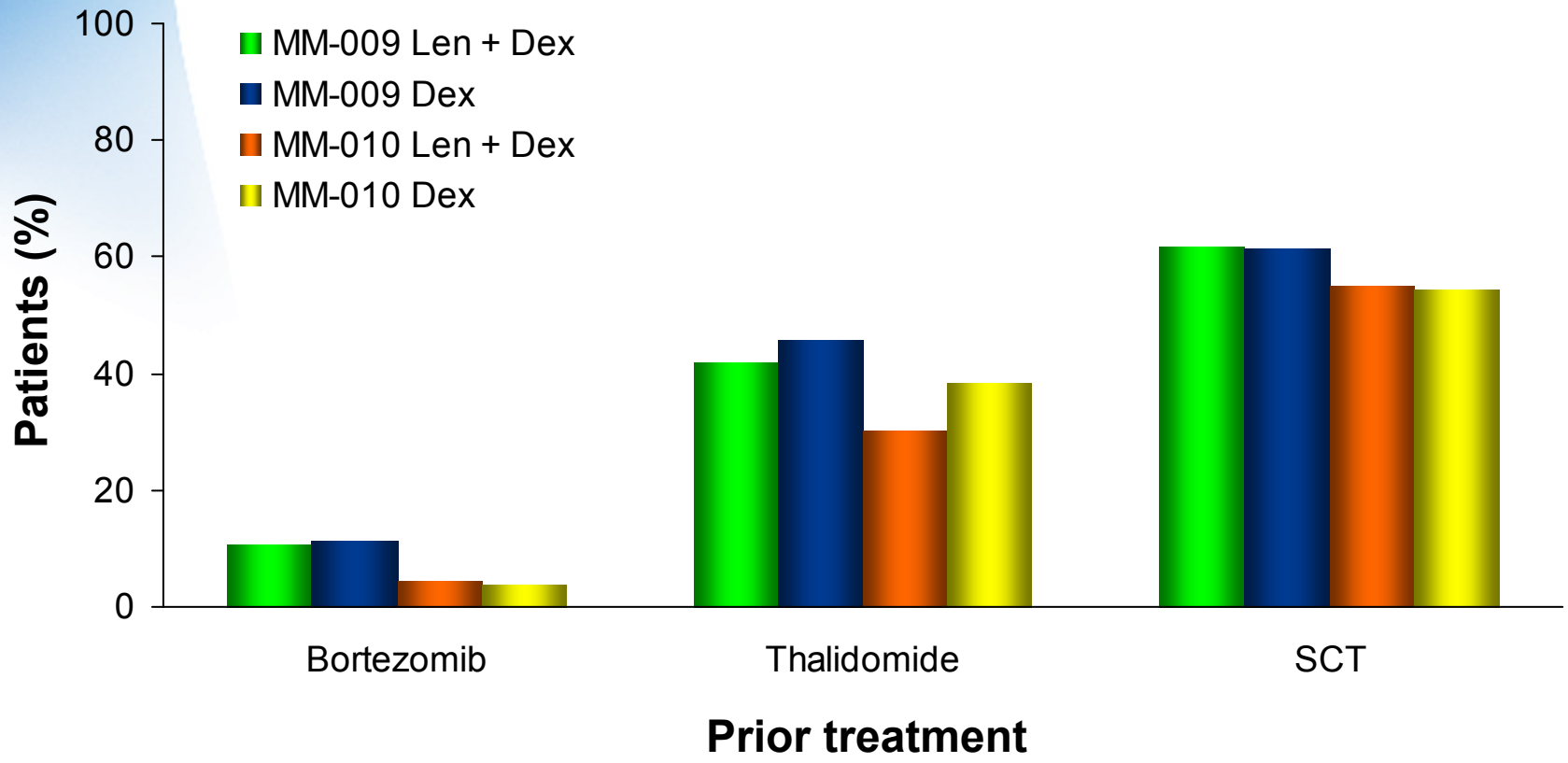
Dimopoulos M, et al. N Engl J Med. 2007;357:2123-32.
Weber DM, et al. N Engl J Med. 2007;357:2133-42.

MM-009 and MM-010: 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_2M ≥ 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.

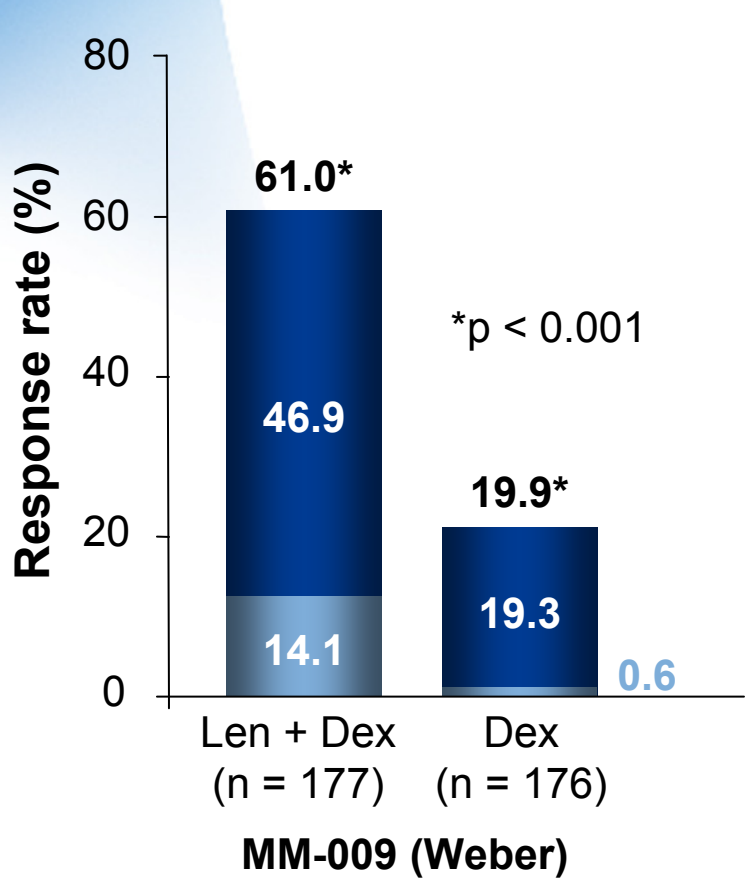
MM-009 and MM-010 included heavily pretreated patients



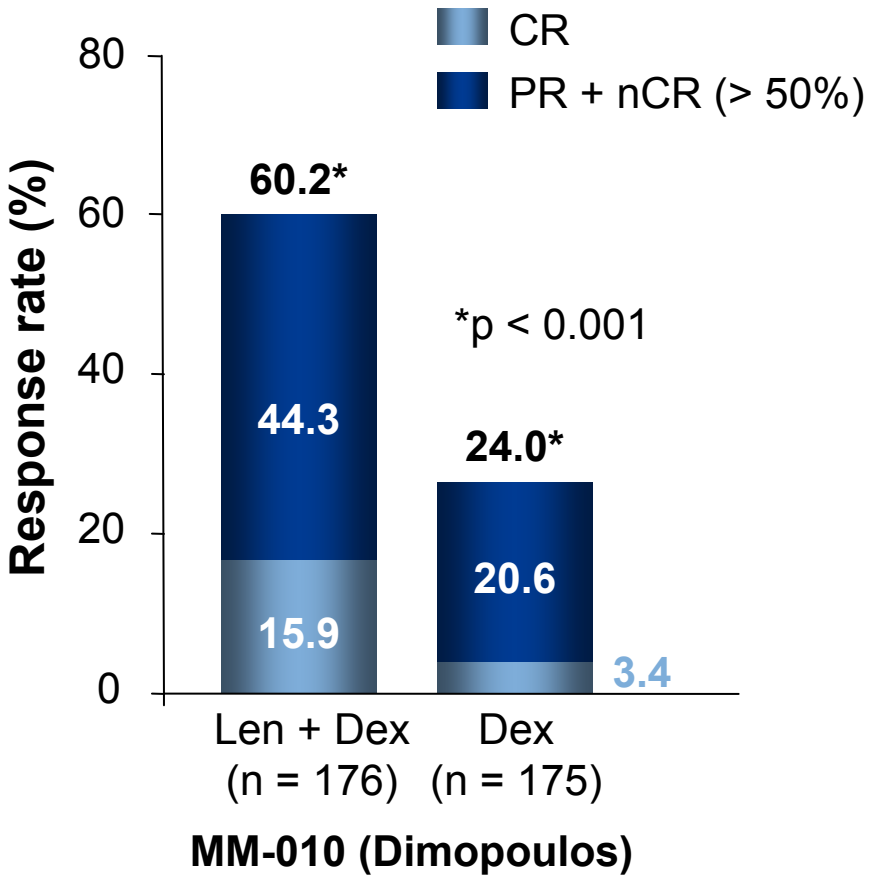
Dimopoulos M, et al. N Engl J Med. 2007;357:2123-32.
Weber DM, et al. N Engl J Med. 2007;357:2133-42.

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

EBMT response data



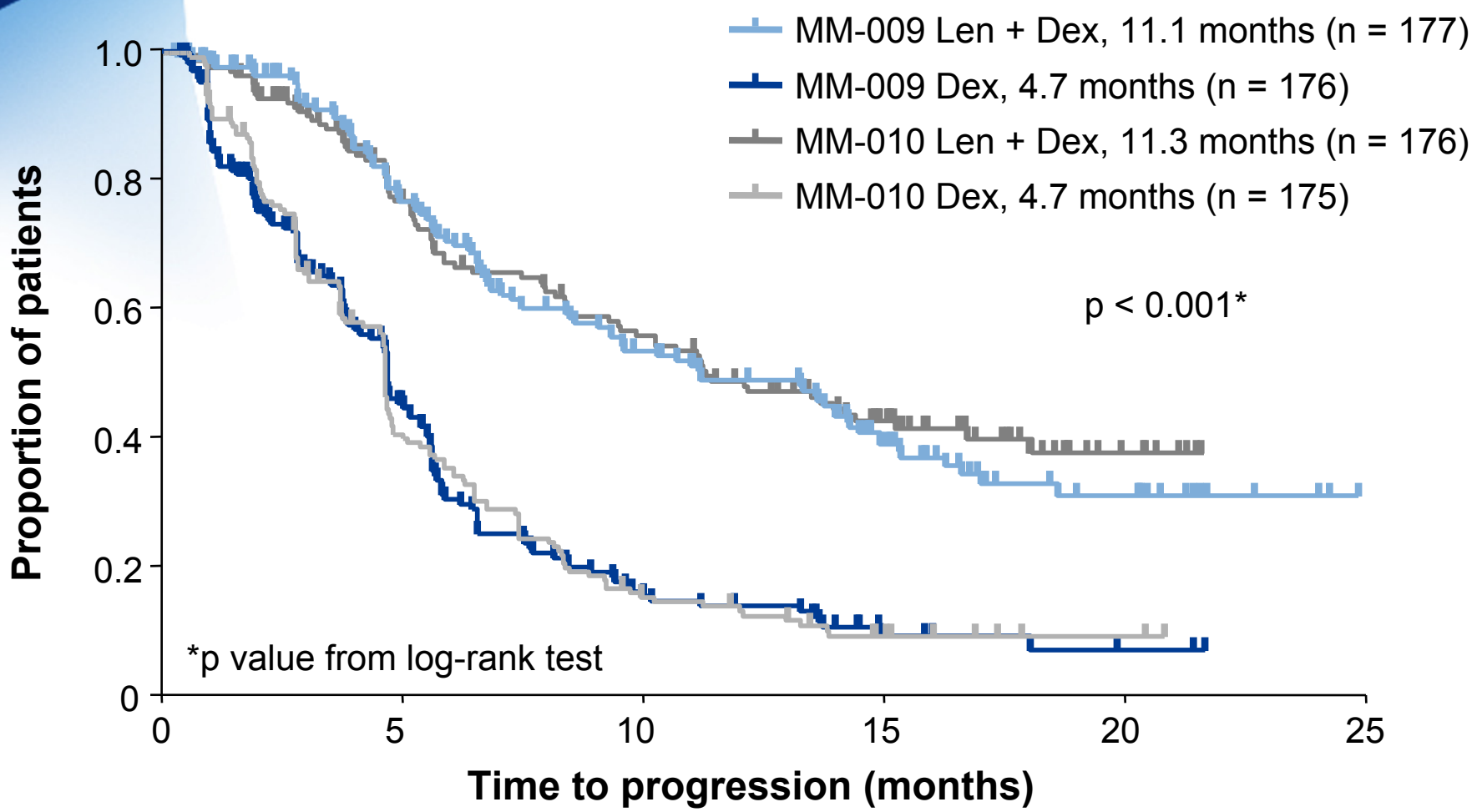
MM-009 (Weber)



MM-010 (Dimopoulos)

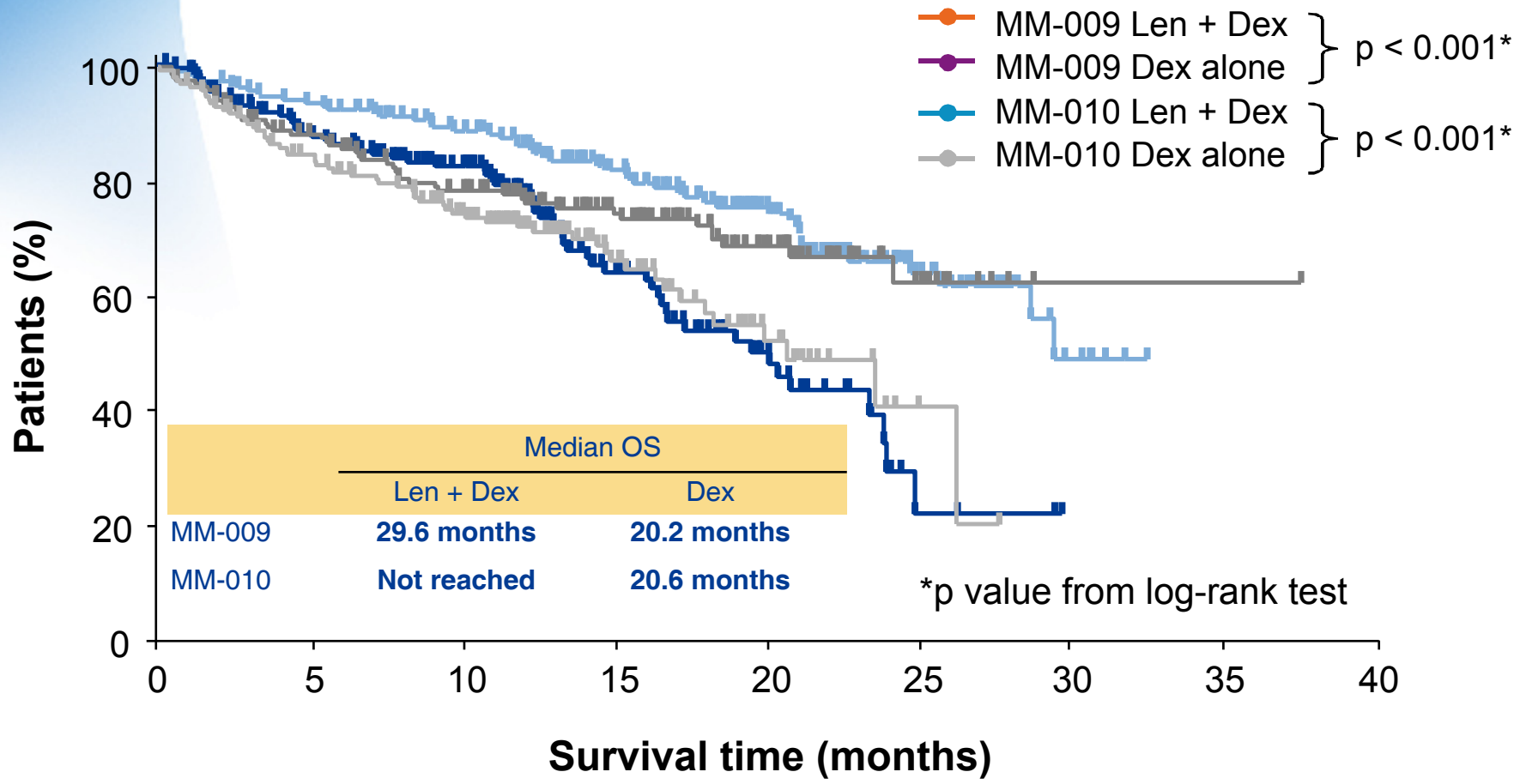
Dimopoulos M, et al. N Engl J Med. 2007;357:2123-32.
Weber DM, et al. N Engl J Med. 2007;357:2133-42.

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



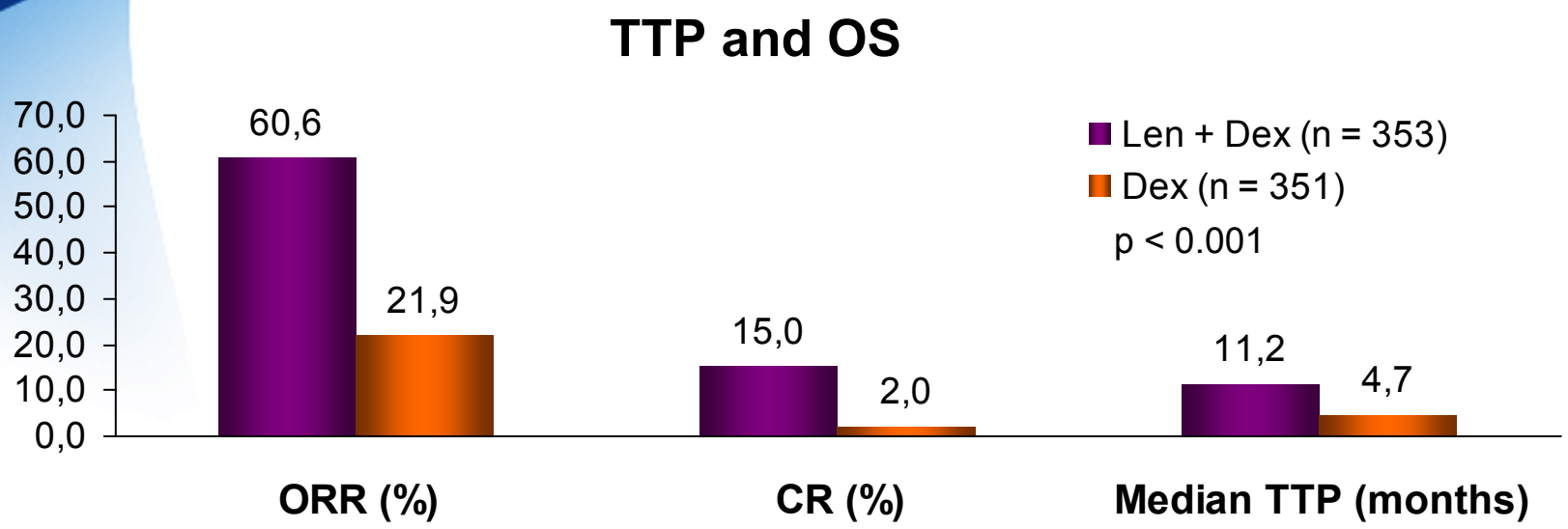
Dimopoulos M, et al. N Engl J Med. 2007;357:2123-32.
Weber DM, et al. N Engl J Med. 2007;357:2133-42.

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



Dimopoulos M, et al. N Engl J Med. 2007;357:2123-32.
Weber DM, et al. N Engl J Med. 2007;357:2133-42.

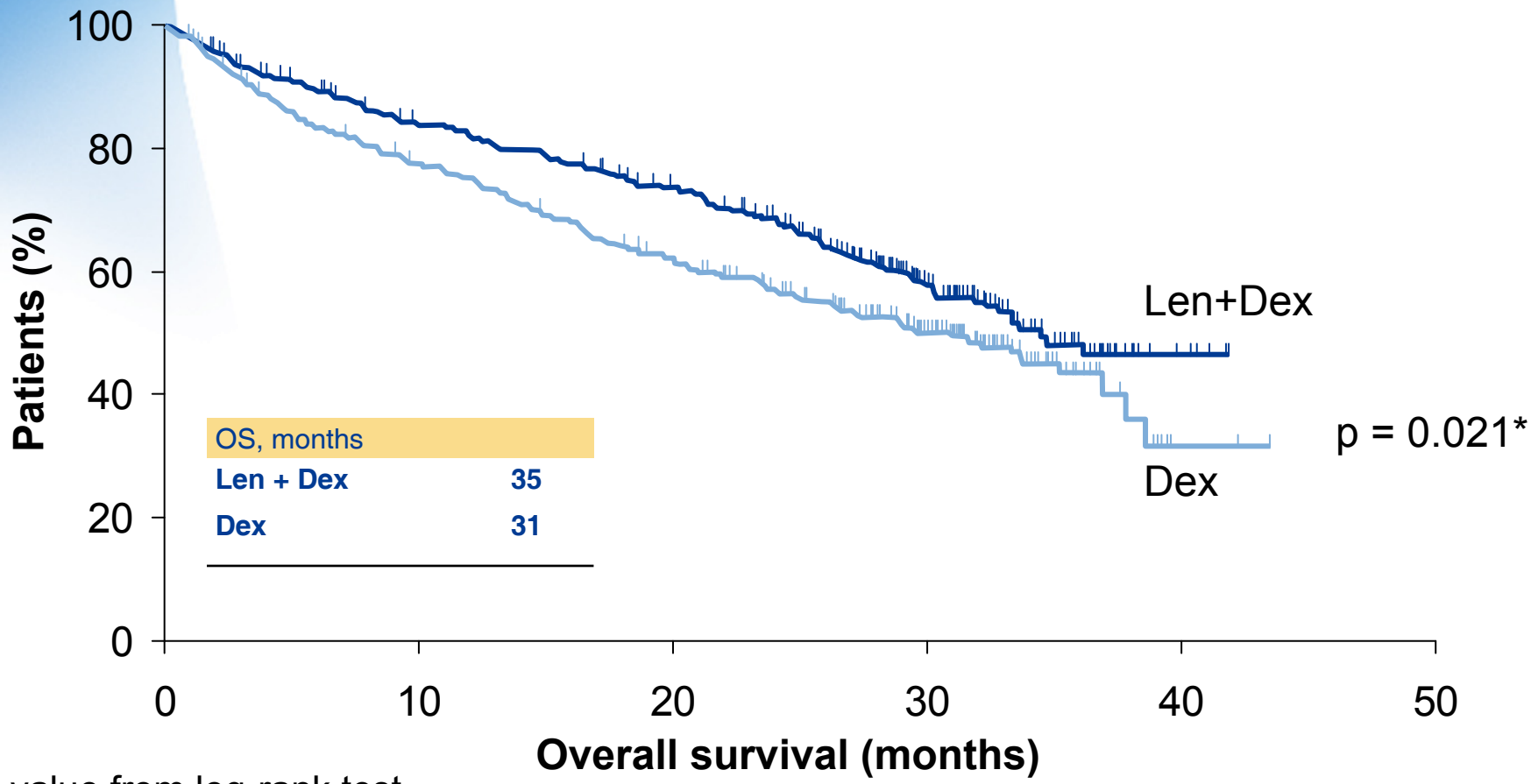
MM-009 and MM-010: pooled response rates



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

Weber DM, et al. Blood. 2007;110 [abstract 412].

MM-009 and MM-010: pooled overall survival



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

Dimopoulos M, et al. Haematologica. 2007;92 (Suppl 2):171 [abstract PO-661].

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

Morgan J, et al. Haematologica. 2008;93(Suppl 1) [abstract 0441].

MM-009: grade 3 and 4 adverse events

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

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

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 ($p = 0.7$)**

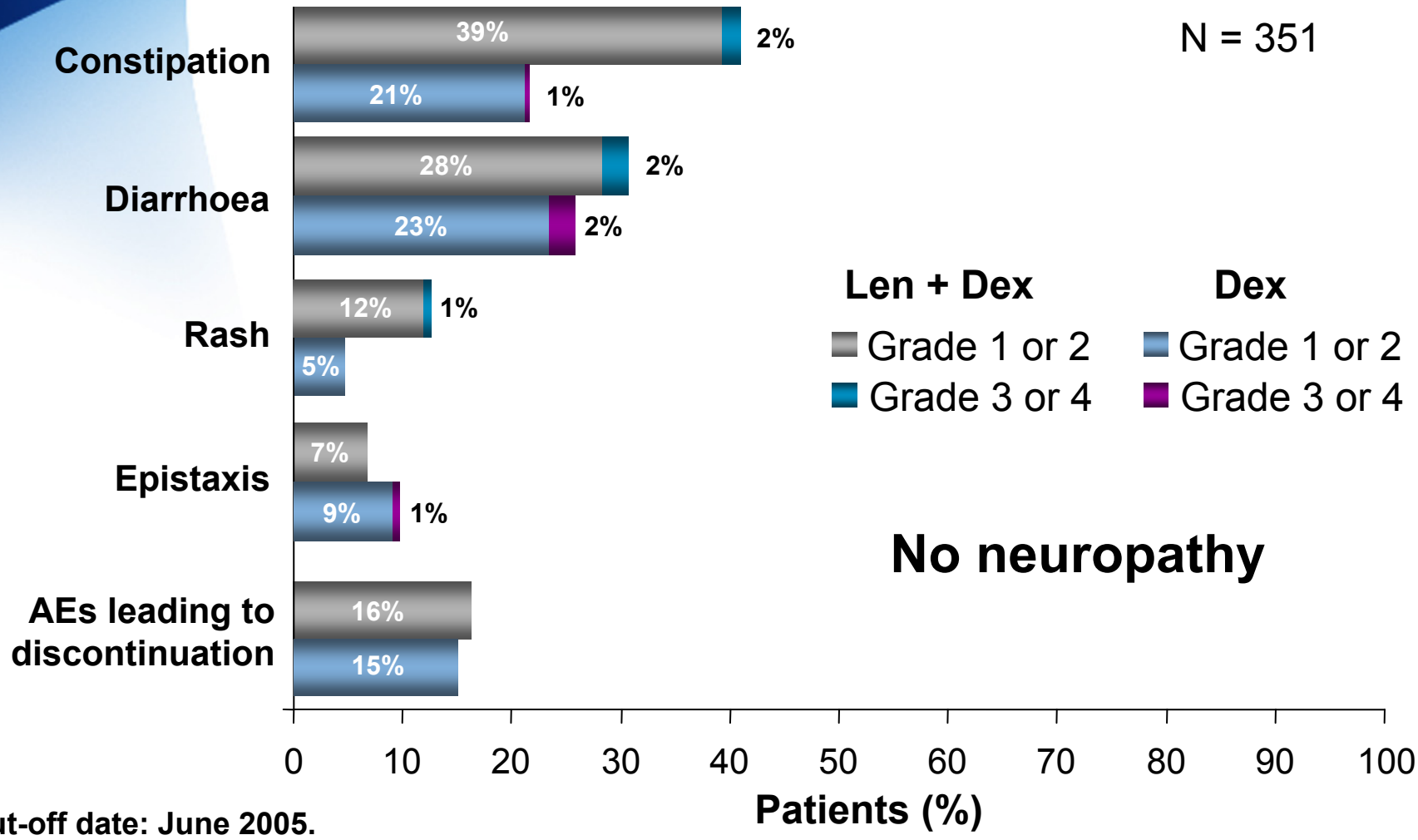
Zangari M, et al. Haematologica. 2008;93(Suppl 1) [abstract 0638].

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
Neutropenia	**44 (25.0)**	**8 (4.5)**	**4 (2.3)**	**0**
Thrombocytopenia	**17 (9.7)**	**3 (1.7)**	**7 (4)**	**3 (2)**
VTE	**13 (7.4)**	**7 (4)**	**6 (3)**	**2 (1)**
Infection				
upper respiratory	**3 (1.7)**	**0**	**0**	**0**
other	**15 (8.5)**	**2 (1.1)**	**9 (5.1)**	**2 (1.1)**

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

MM-010: non-haematological adverse events



Cut-off date: June 2005.

Dimopoulos M, et al. Blood. 2005;106:6a.

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

MM-009 and MM-010: subanalysis

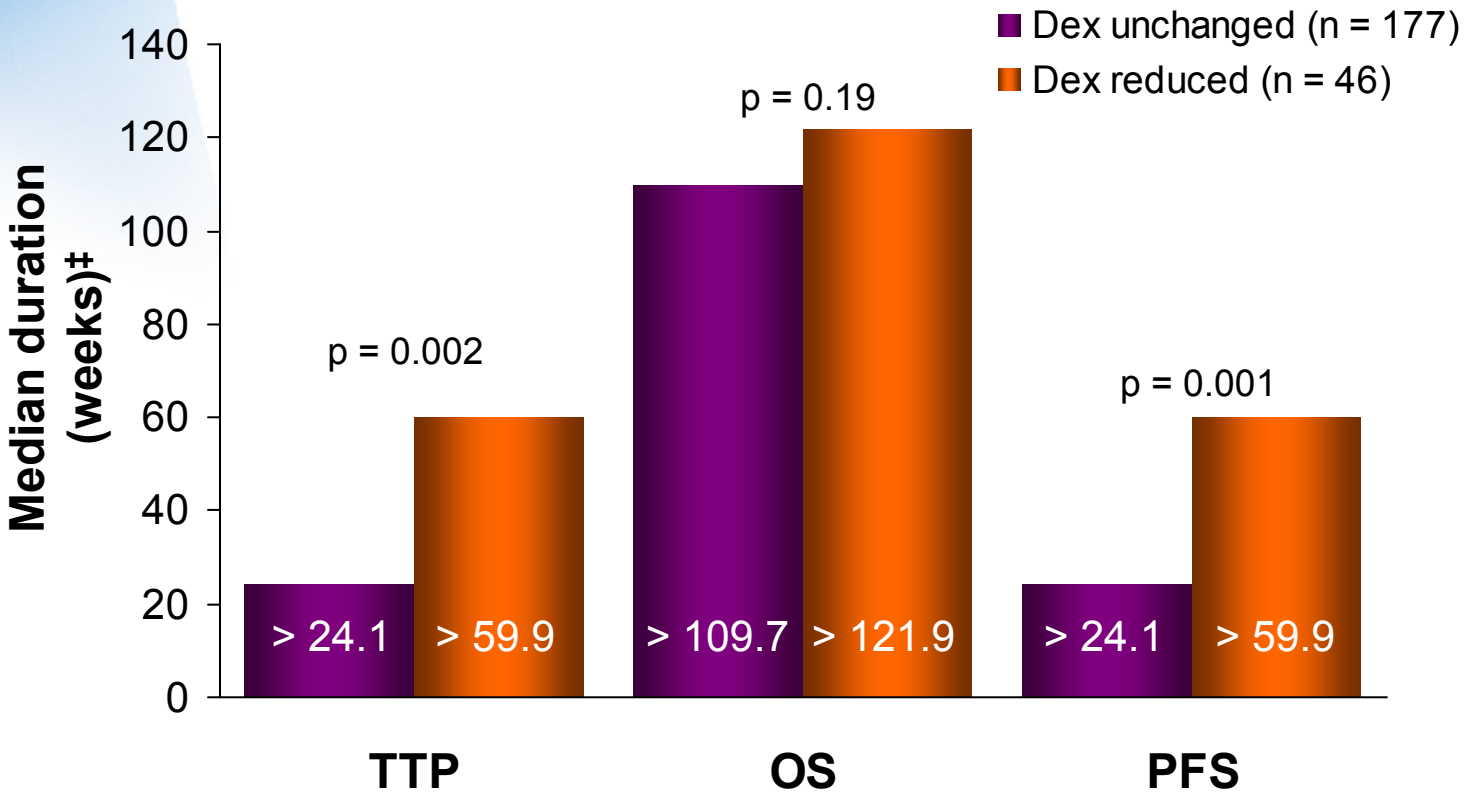
	Len + Dex		
	Dex unchanged (n = 177)	Dex reduced (n = 46)*	p value
Response, %			
OR	**50.8**	**69.6**	**< 0.05**
CR	**13.0**	**23.9**	**< 0.01**
nCR	**19.8**	**37.0**	**< 0.01**
PR	**18.1**	**8.7**	**< 0.01**
Adverse events grade 3 or 4, %			
Neutropenia	**32.6**	**23.7**	
Thrombocytopenia	**6.8**	**8.5**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

San Miguel JF, et al. Blood. 2007;110 [abstract 2712].

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

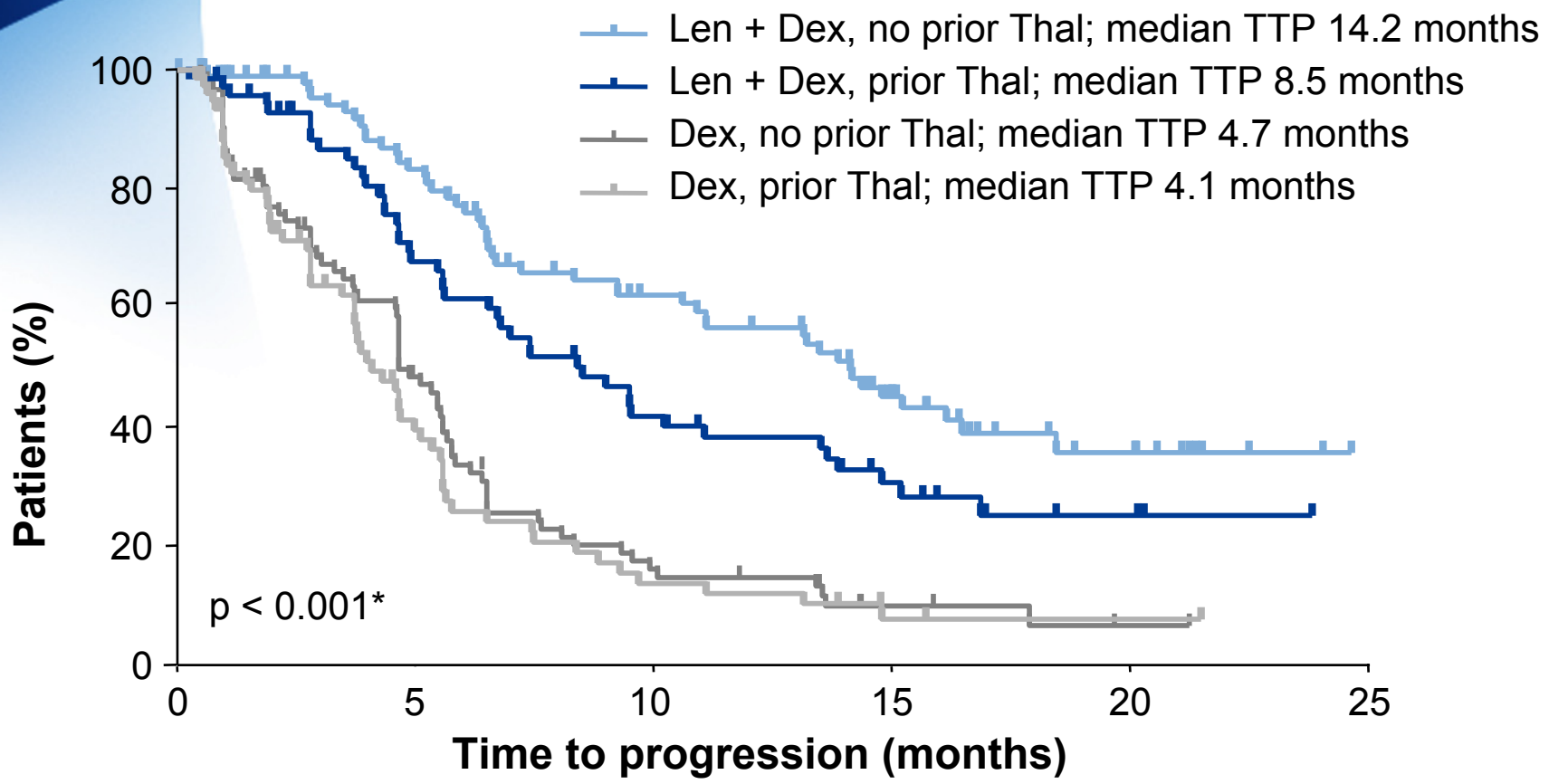
MM-009 and MM-010: subanalysis



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

Data from San Miguel JF, et al. Blood. 2007;110 [abstract 2712].

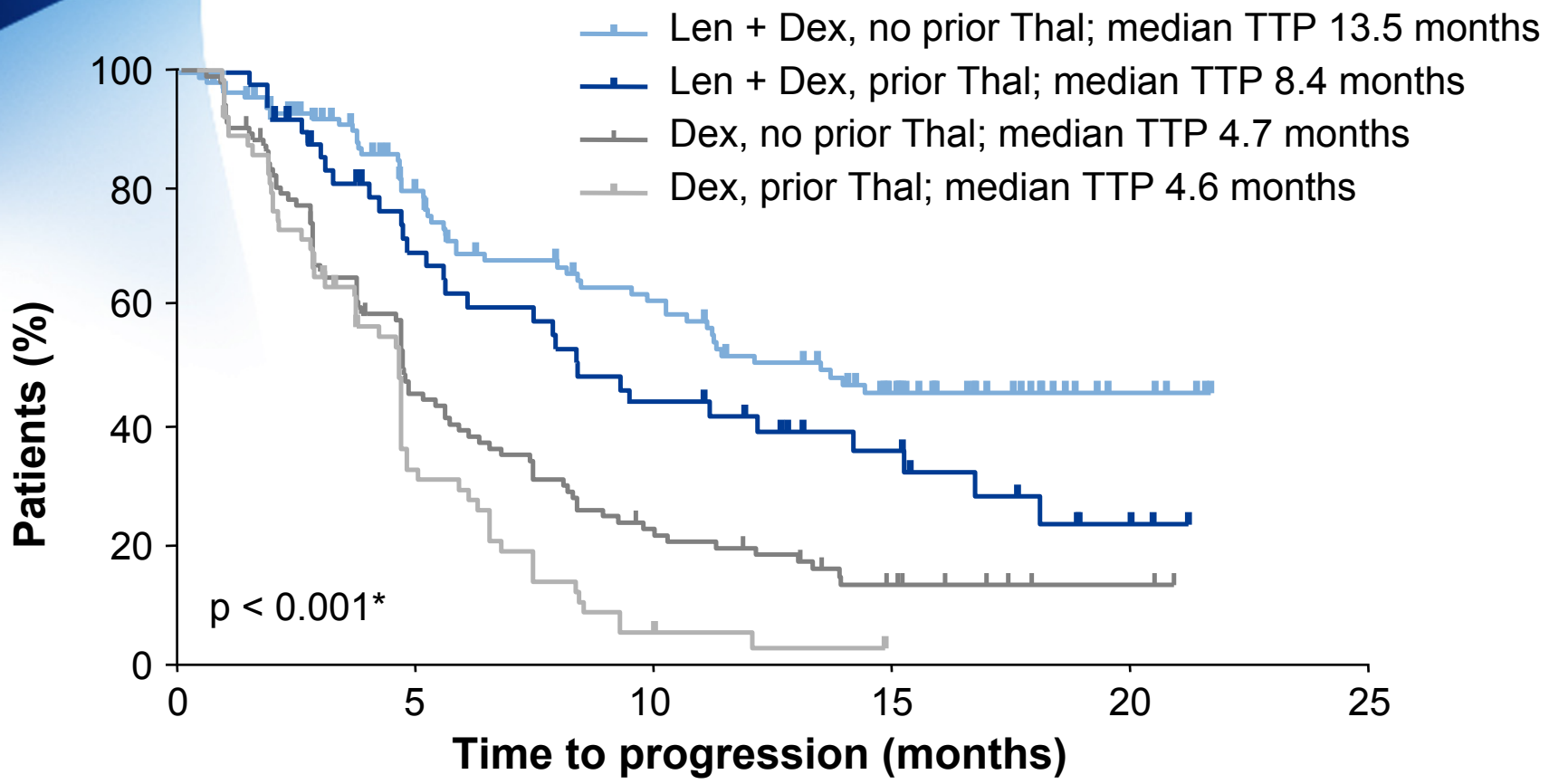
MM-009: longer time to progression with Len + Dex regardless of prior thalidomide



*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).

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

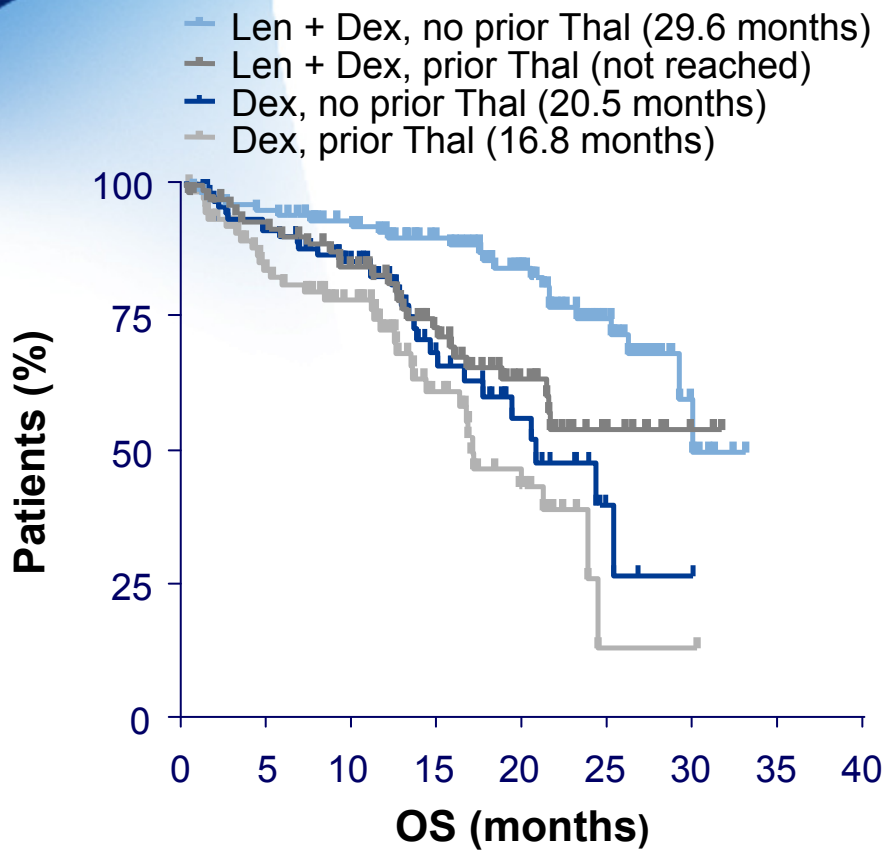
MM-010: longer time to progression with Len + Dex regardless of prior thalidomide



*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).

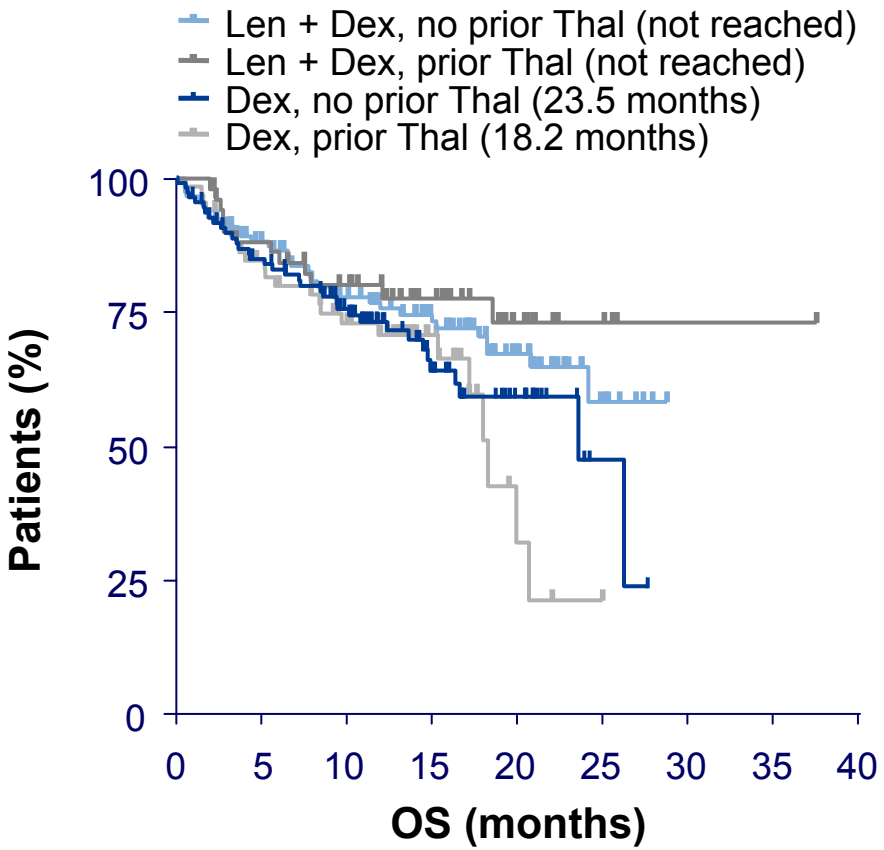
MM-009 and MM-010: increased OS with Len + Dex regardless of prior Thal

MM-009



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

MM-010



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

Dimopoulos M, et al. N Engl J Med. 2007;357:2123-32.
Weber DM, et al. N Engl J Med. 2007;357:2133-42.

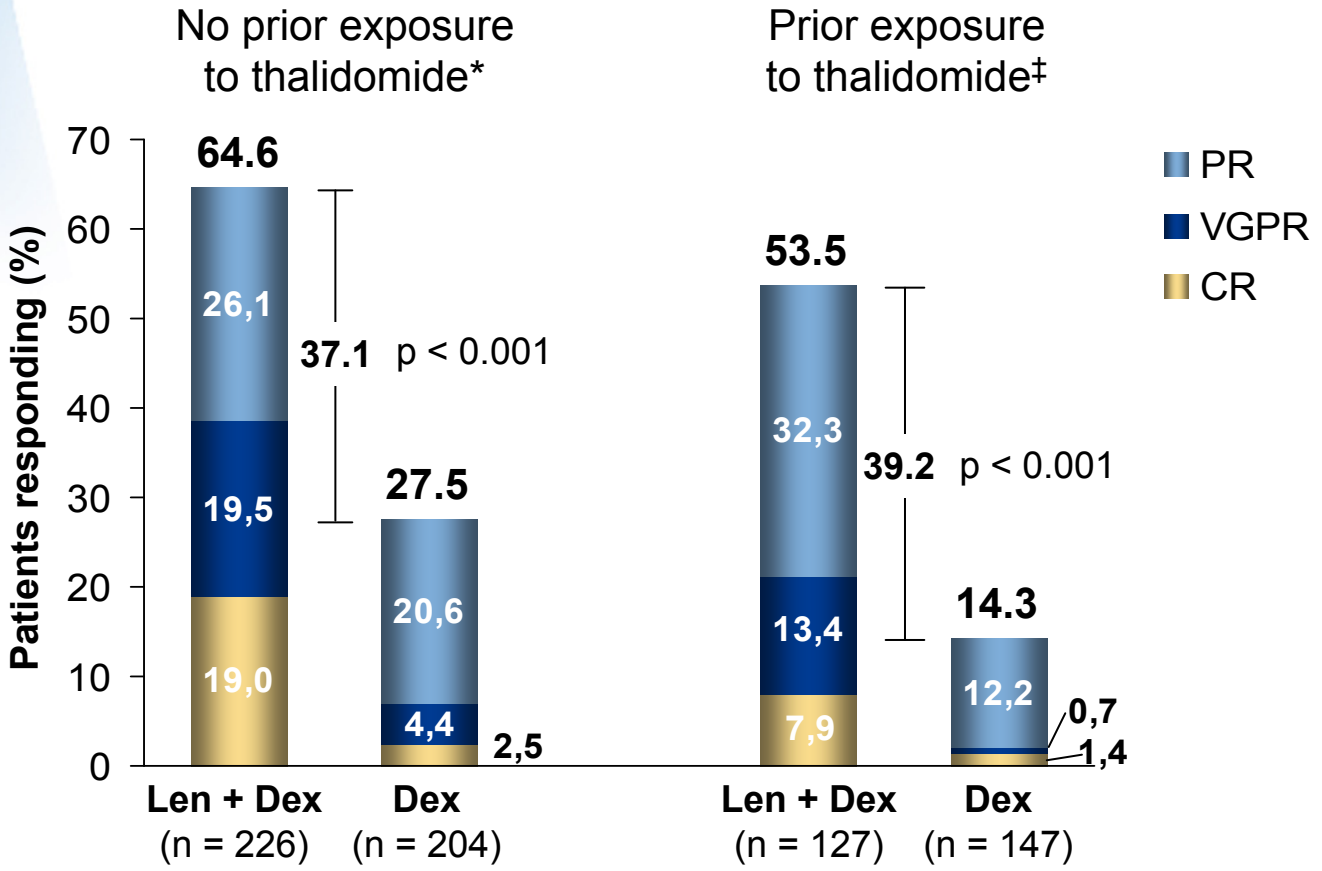
Subgroup analyses of MM-009 and MM-010: efficacy of Len + Dex after prior Thal

- **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

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

Lenalidomide is effective after prior exposure to thalidomide

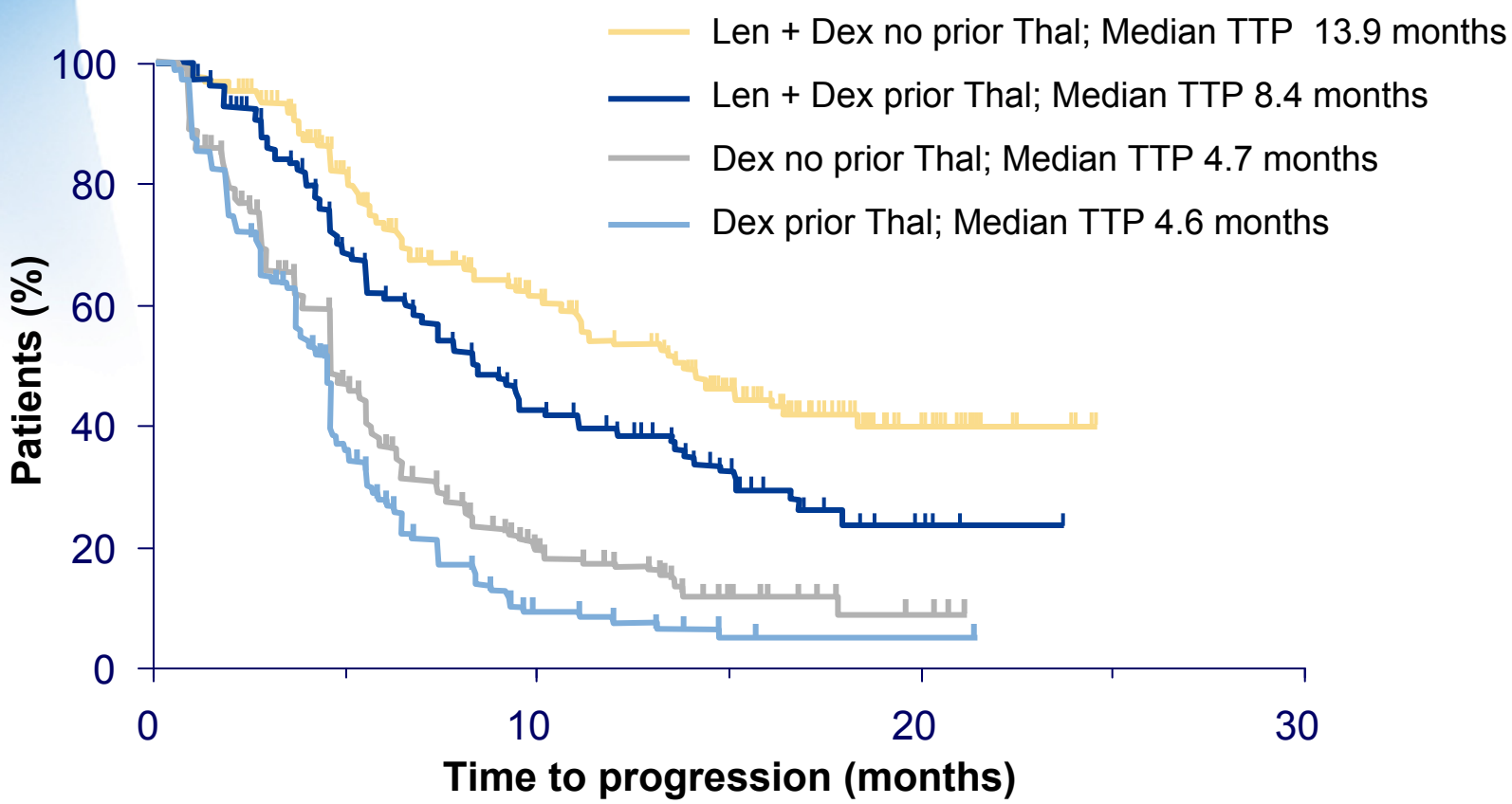
MM-009 and MM-010: prospective subgroup analysis of patients with relapsed/refractory MM



*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



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

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)
ORR, %	65	17	42	6	50	21
CR	11	1	7	3	5	0
VGPR	13	1	13	3	20	0
PR	41	14	23	0	25	21
Median TTP, months	9.3	4.6	7.8	3.7	7.2	3.7

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)
ORR (CR + nCR + PR), %	**64.6**	**27.5**	**53.5**	**14.3**
CR, %	**19.0**	**2.5**	**7.9**	**1.4**
Median TTP, months	**13.9**	**4.7**	**8.4**	**4.6**
Median PFS, months	**13.2**	**4.7**	**8.4**	**4.6**
Median OS, months	**36.1**	**32.0**	**33.3**	**28.7***

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

NS = not significant.

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

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.

NS = not significant.

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

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

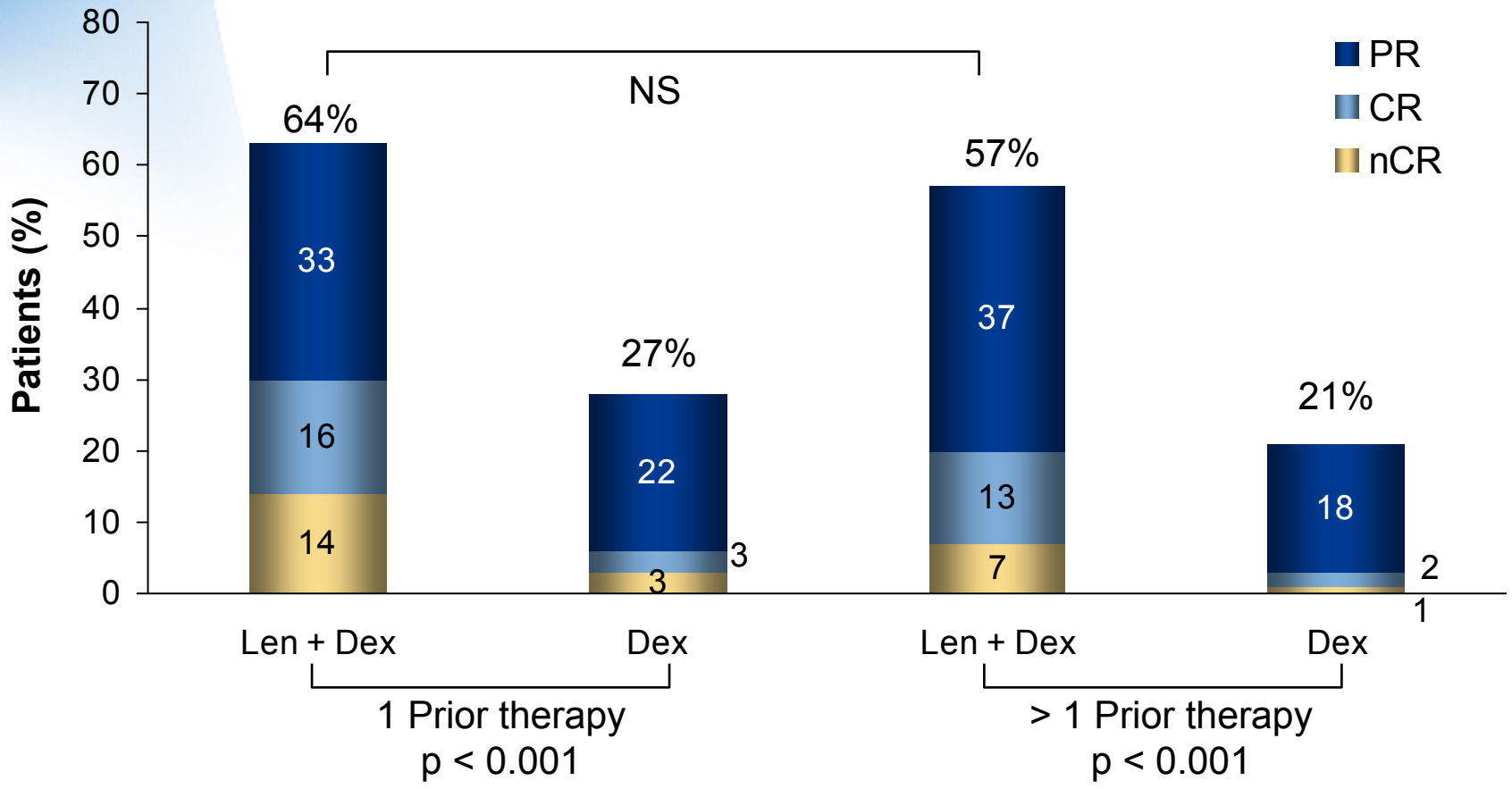
	1 prior therapy Len + Dex	1 prior therapy Dex	≥ 2 prior therapies Len + Dex	≥ 2 prior therapies Dex
n	**120**	**121**	**226**	**225**
ORR (CR + nCR + PR), %	**63**	**27**	**57**	**20**
SD, %	**27**	**54**	**33**	**57**
PD, %	**3**	**13**	**1**	**15**
Overall TTP, months	**16.5***	**4.7**	**10.2***	**4.7**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

All differences between Len + Dex and Dex for 1 and ≥ 2 prior therapies are significant.
*$p < 0.05$

Stadtmauer E, et al. Blood. 2006;108 [abstract 3552].

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

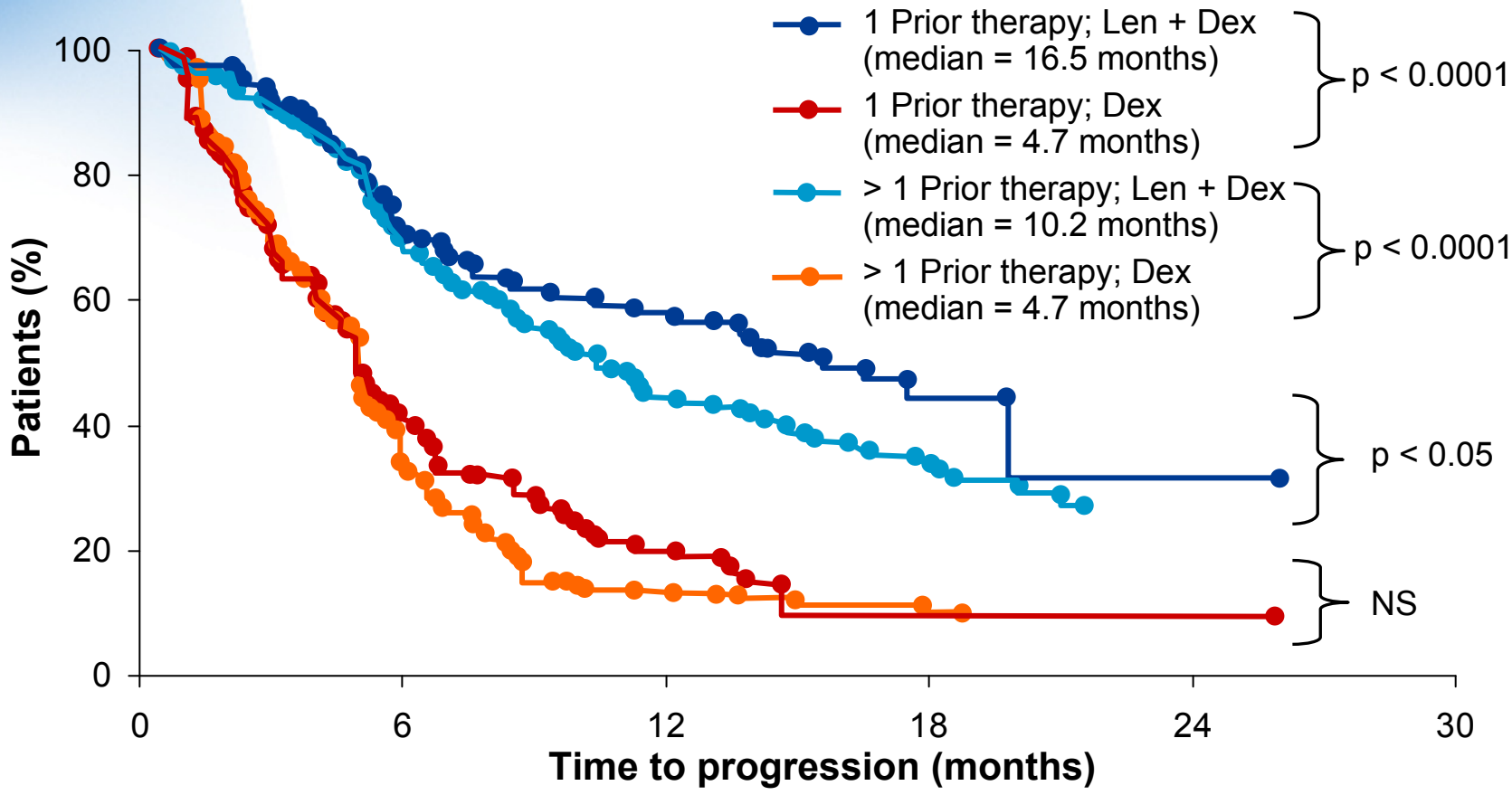
- **Prospective subgroup analysis of relapsed/refractory MM patients enrolled in MM-009 and MM-010**



Stadtmauer E, et al. Blood. 2006;108 [abstract 3552].

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

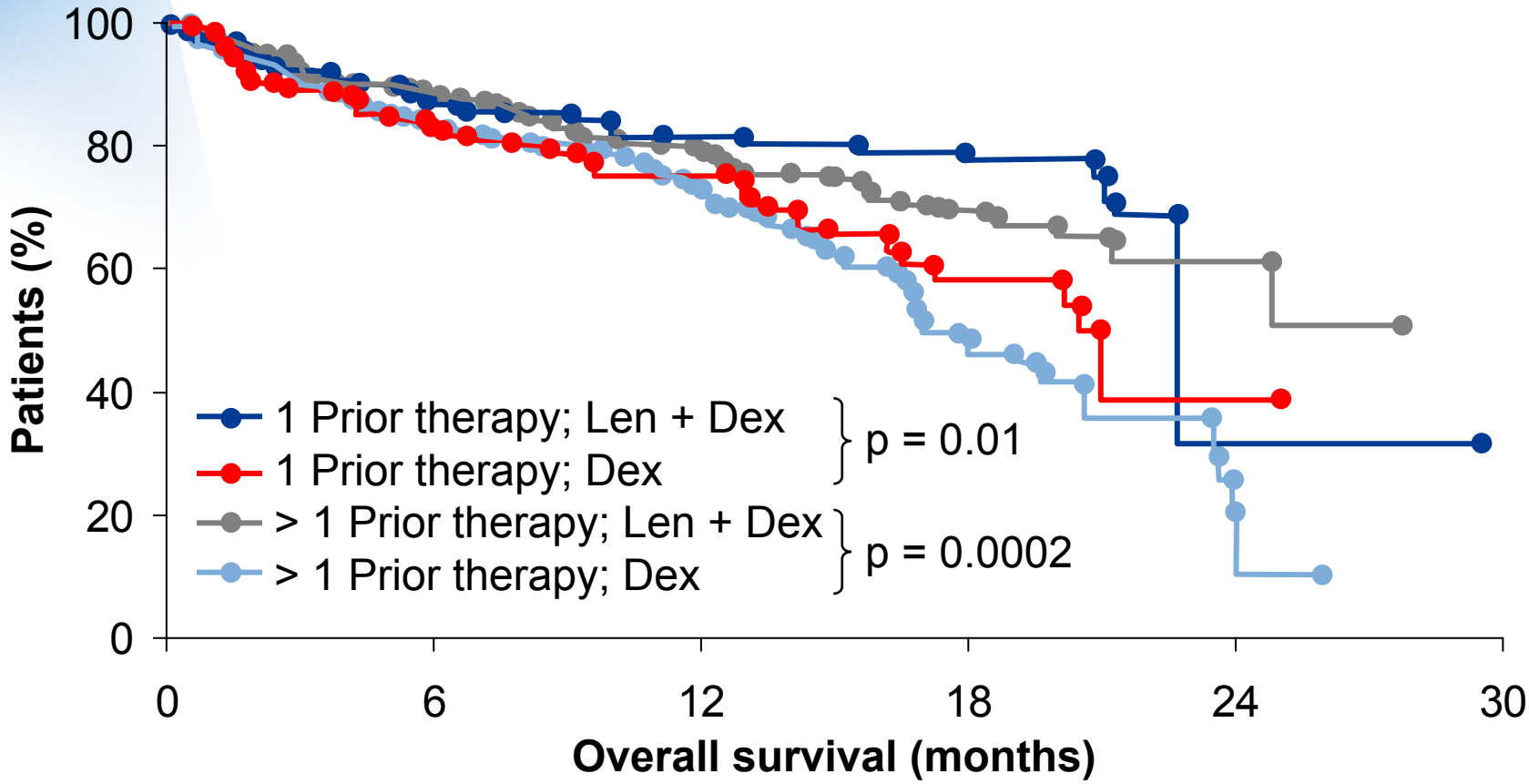
Prospective subgroup analysis of relapsed/refractory MM patients enrolled in MM-009 and MM-010



Stadtmauer E, et al. Blood. 2006;108 [abstract 3552].

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**



Stadtmauer E, et al. Blood. 2006;108 [abstract 3552].

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
    - ≤ 10 months (n = 223)
    - > 10 months (n = 98)
  - early treatment discontinuation because of adverse events (n = 42) or withdrawn consent (n = 30)

San Miguel JF, et al. Blood. 2008;112:[abstract 3702].

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
Median OS, months	**23.4**	**Not reached**	**< 0.0001**
2-year survival, %	**48.4**	**93.8**	**< 0.0001**

Early discontinuation of Len + Dex treatment associated with poor prognosis

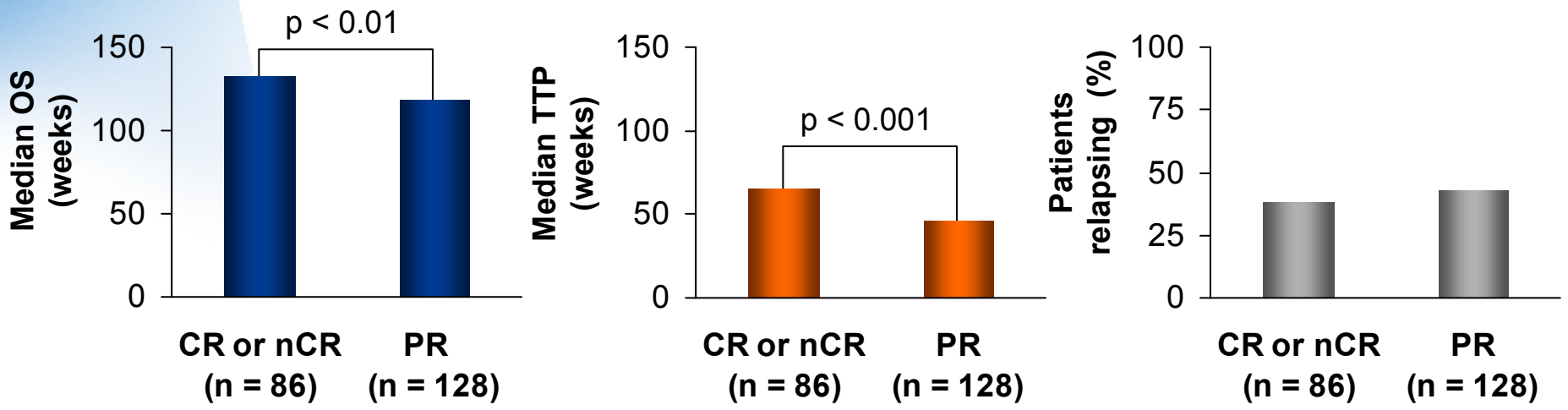
	Discontinued* (n = 72)	Continued (n = 115)	p value
Median TTP, months	**13.6**	**Not reached**	**< 0.0001**
Median OS, months	**29.5**	**Not reached**	**< 0.0001**

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

Data from San Miguel JF, et al. Blood. 2008;112:[abstract 3702].

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**

Harousseau JL, et al. Blood. 2007;110 [abstract 3598].

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

- **Subgroup analysis of MM-009 and MM-010**

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

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.

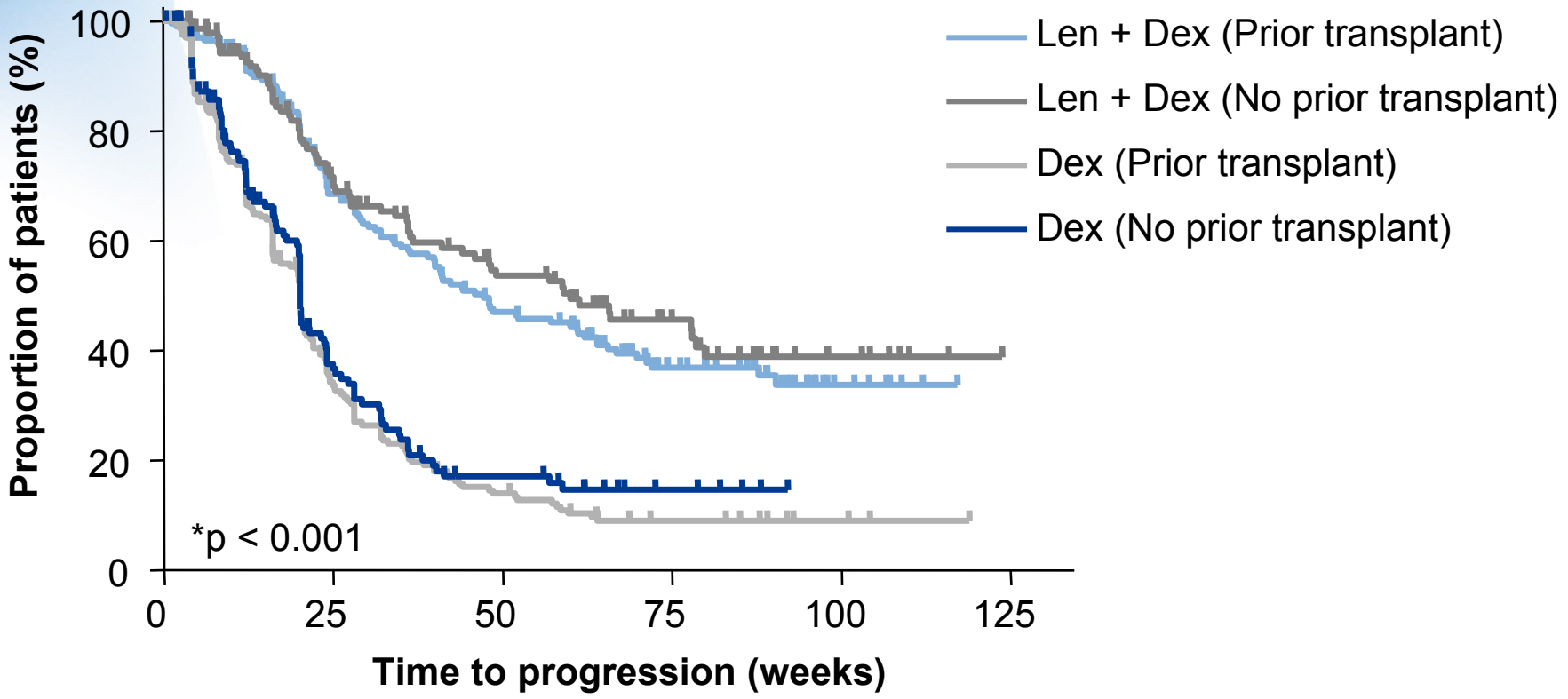
- **In all subgroups, median overall survival had not been reached after a median follow-up of 16.8 months**

ASCT = autologous stem cell transplantation.

Chanan-Khan A, et al. Blood. 2006;108 [abstract 3554].

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

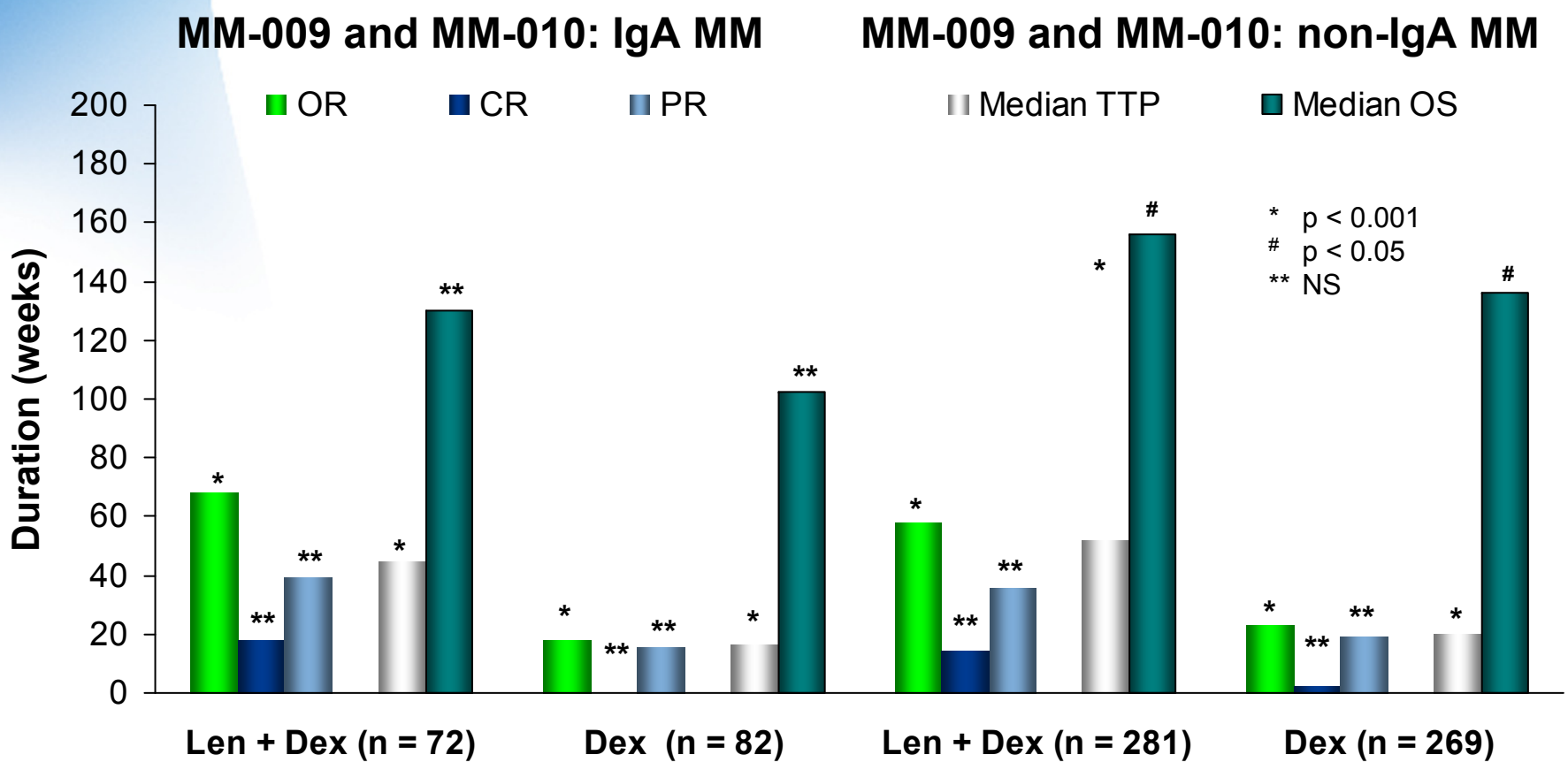
- **Subgroup analysis of MM-009 and MM-010**



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

Chanan-Khan A, et al. Blood. 2006;108 [abstract 3554].

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



Foa R, et al. Blood. 2007;110 [abstract 4839].

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)
Neutropenia	**37.5**	**2.4**	**46.5**	**14.5**
Thrombocytopenia	**16.7**	**8.5**	**12.1**	**5.7**
Anaemia	**11.1**	**7.3**	**11.0**	**5.7**

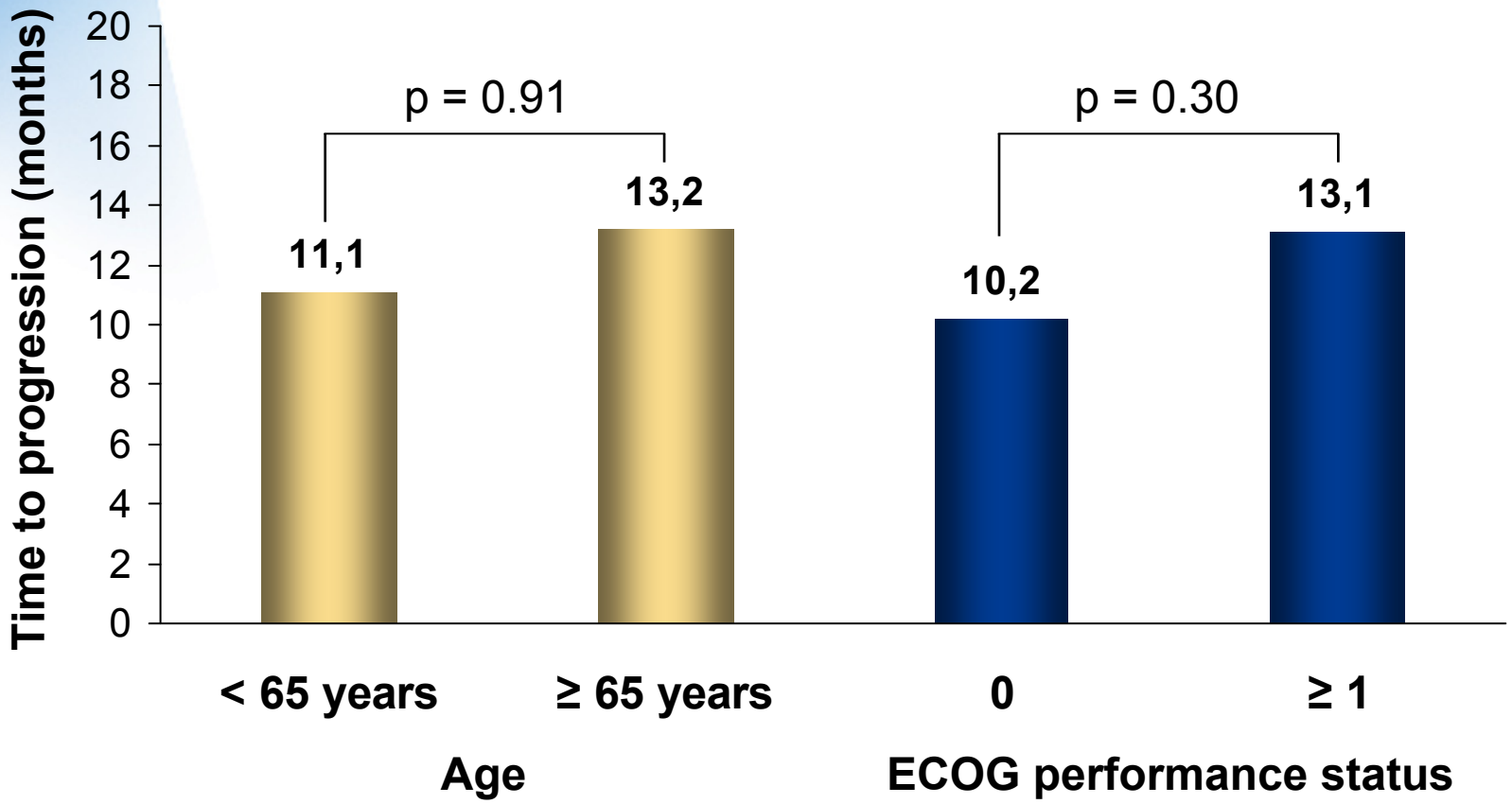
Foa R, et al. Blood. 2007;110 [abstract 4839].

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 ≥ 65 years, Eastern Cooperative Oncology Group score ≥ 1, IgA multiple myeloma, Durie-Salmon stage III, and b_2-microglobulin > 2.5 mg/L
- **Patients**
  - all those who had received lenalidomide + dexamethasone in MM-009 and MM-010

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

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



ECOG = Eastern Cooperative Oncology Group.

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

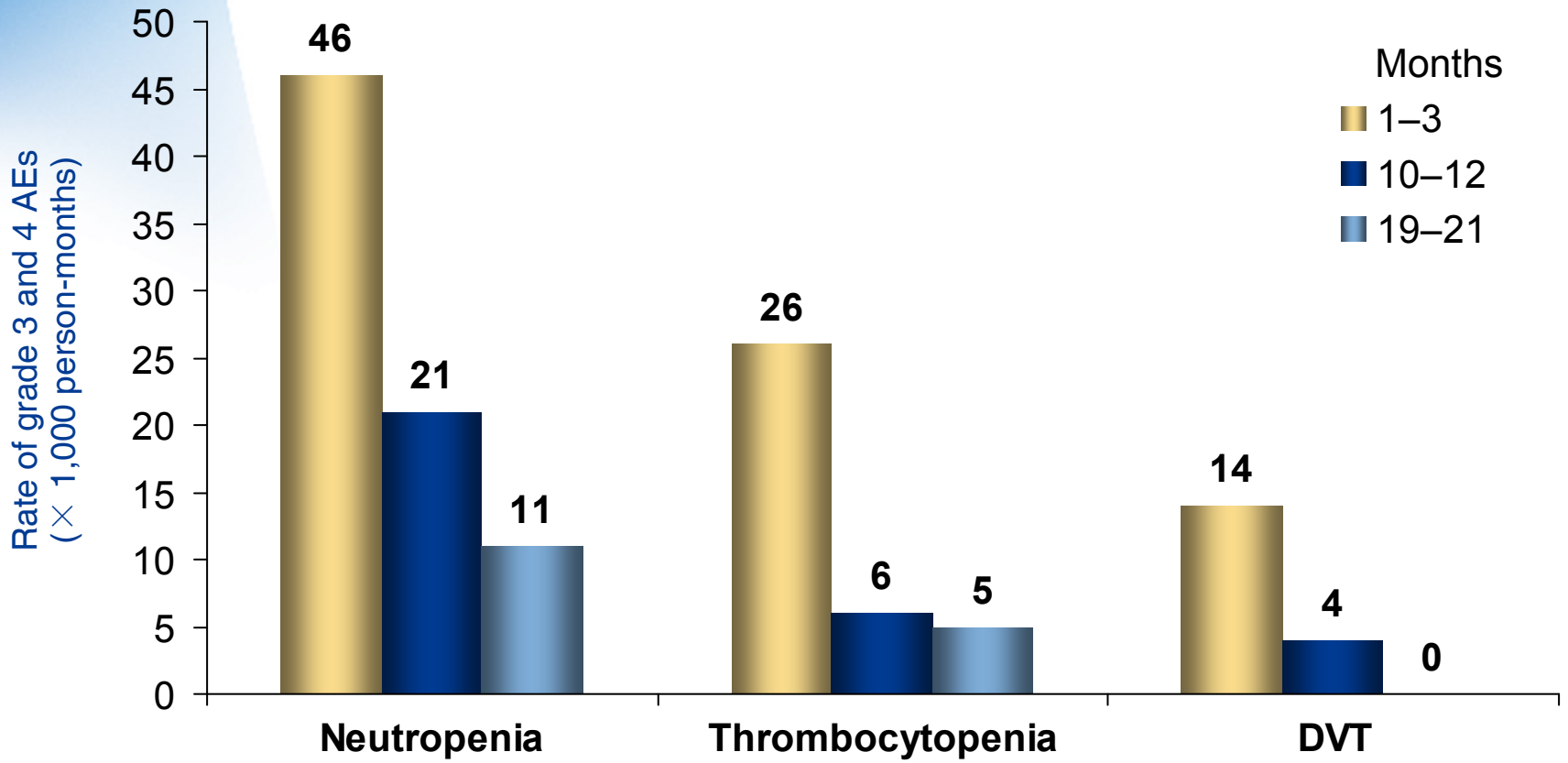
Len + Dex is safe in high- and low-risk patients: grade 3 or 4 AEs are similar in each group

- **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_2-microglobulin ≤ 2.5 mg/L, 16%; > 2.5 mg/L, 7% (p = 0.03)
  - anaemia
    - b_2-microglobulin ≤ 2.5 mg/L, 15%; > 2.5 mg/L, 1% (p = 0.0001)

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

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

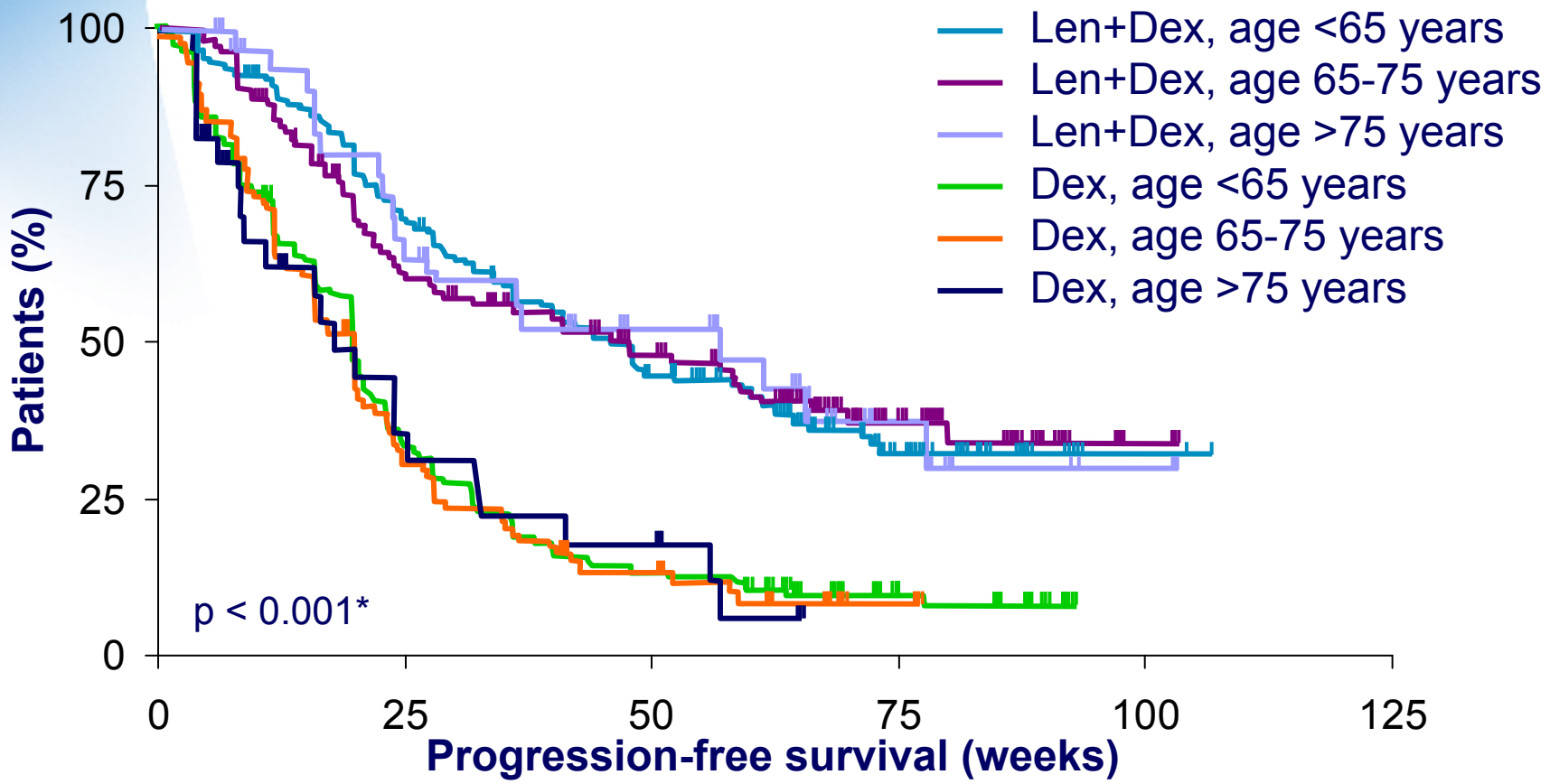
Grade 3 or 4 adverse events in patients receiving long-term treatment with Len + Dex



Treatment interruptions and dose reductions also declined during follow-up

Data from Ishak J, et al. Blood. 2008;112:[abstract 3708].

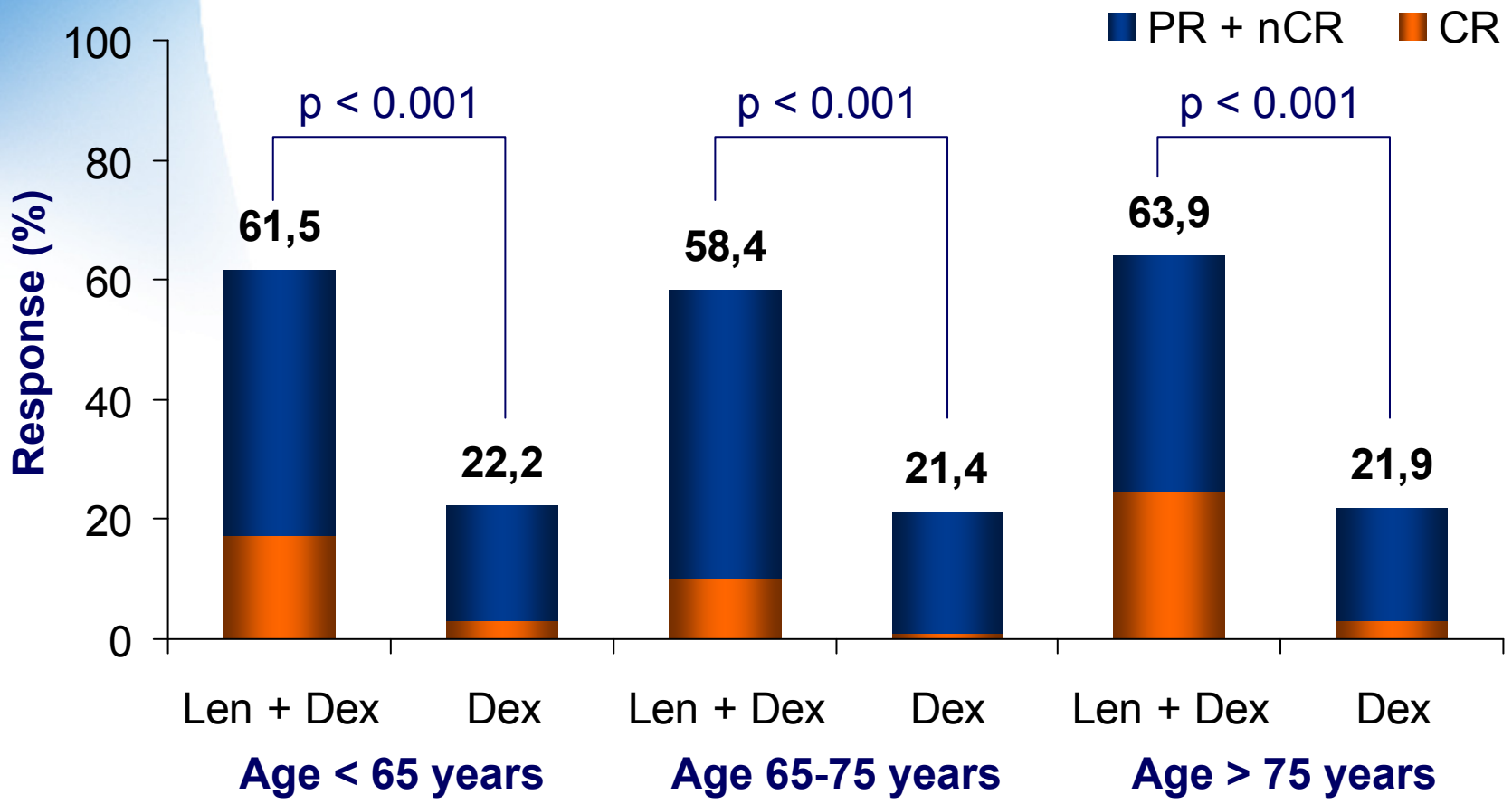
Progression-free survival by age group of Len + Dex vs Dex in relapsed/refractory MM



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

Lonial S, et al. Haematologica. 2007;92(Suppl 2):172 [abstract PO-663].

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



Lonial S, et al. Haematologica. 2007;92(Suppl 2):172 [abstract PO-663].

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

Updated data from Lonial S, et al. Haematologica. 2007;92(Suppl 2):172 [abstract PO-663].

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

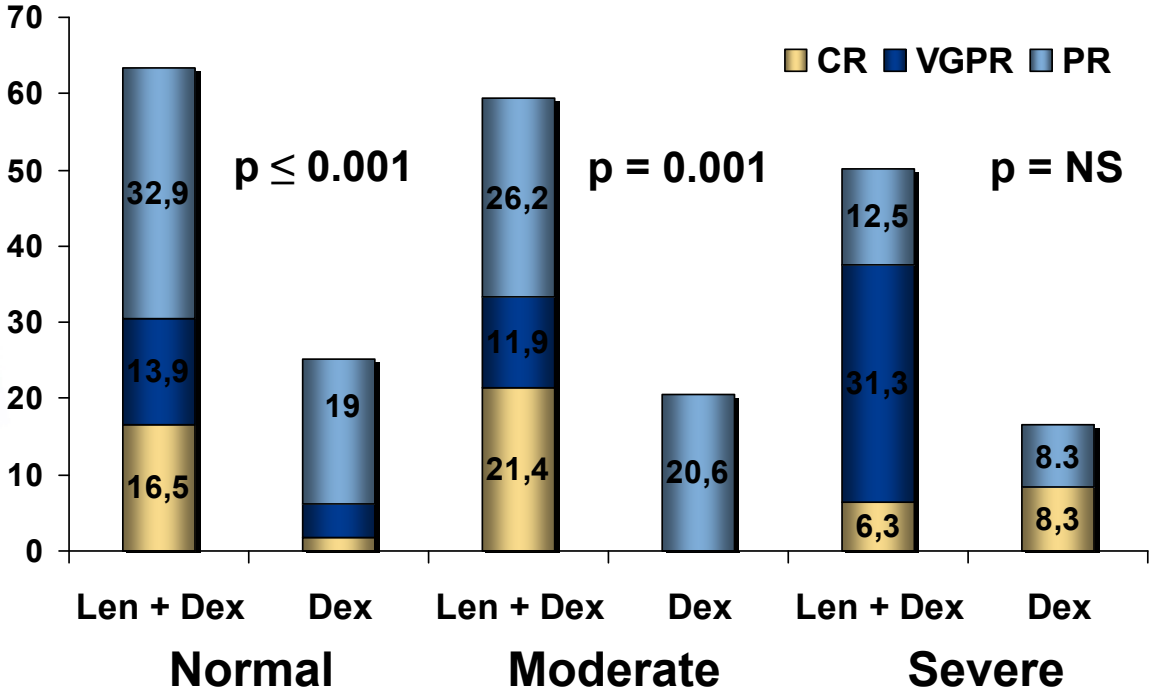
- **Analysis of patients treated with lenalidomide ± corticosteroids within the Extended Access Program Canada**
- **64% of patients were treated with Len + Dex, 10% with Len + prednisone, 7% with Len + Dex + prednisone, and 19% with lenalidomide only**

	≥ 65 years Len + corticosteroids (n = 41)	< 65 years Len + corticosteroids (n = 28)
PR, %	**58**	**56**
PFS, %	**43**	**43**
OS, %	**74**	**76**

Differences between elderly and younger patients were not significant.

Reece DE, et al. Blood. 2006;108 [abstract 3550].

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



	Normal (> 80 ml/min)		Moderate (≥ 30 < 50 ml/min)		Severe (< 30 ml/min)	
Months	**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**

Weber D, et al. Blood. 2006;108 [abstract 3547].
Weber DM, et al. J Clin Oncol. 2008;26(Suppl) [abstract 8542].

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

	Normal (> 80 ml/min)		Moderate (≥ 30 < 50 ml/min)		Severe (< 30 ml/min)	
Adverse events, %	**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**

Weber D, et al. Blood. 2006;108 [abstract 3547].
Weber DM, et al. J Clin Oncol. 2008;26(Suppl) [abstract 8542].

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
n	**23**	**46**
nCR/PR, %	**61**	**54**
PFS, %	**30**	**50**
OS, %	**72**	**76**

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

Reece DE, et al. Blood. 2006;108 [abstract 3548].

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

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

	n (%)
Neutropenia	**6 (1.4)**
Pneumonia	**5 (1.2)**
Febrile neutropenia	**4 (0.9)**
Pancytopenia	**4 (0.9)**

Chen C, et al. Blood. 2006;108 [abstract 3556].

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

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

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

Chen C, et al. Blood. 2006;108 [abstract 3556].

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%)

Palumbo A, et al. Haematologica. 2008;93(Suppl 1) [abstract 0639].

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

Bahlis NJ, et al. Blood. 2008;112:[abstract 1731].

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)
Patients, n	**130**	**54**	**28**	**12**
ORR, %	**83.1**	**76.4**	**78.6**	**58.3**

- **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

Data from Bahlis NJ, et al. Blood. 2008;112:[abstract 1731].

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

Avet-Loiseau H, et al. Blood. 2008;112:[abstract 3685].

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

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

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

Data from Avet-Loiseau H, et al. Blood. 2008;112:[abstract 3685].

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 β_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 then 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.

Dimopoulos M, et al. Haematologica. 2007;92(Suppl 2):171 [abstract PO-659].

Economic evaluation of lenalidomide in patients with ≥ 1 prior therapy

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

	1 prior therapy		≥ 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

Palumbo A, et al. Haematologica. 2007;92(Suppl 2):217 [abstract PO-1121].

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)

Palumbo A, et al. Haematologica. 2007;92(Suppl 2):217 [abstract PO-1121].

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)

- **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

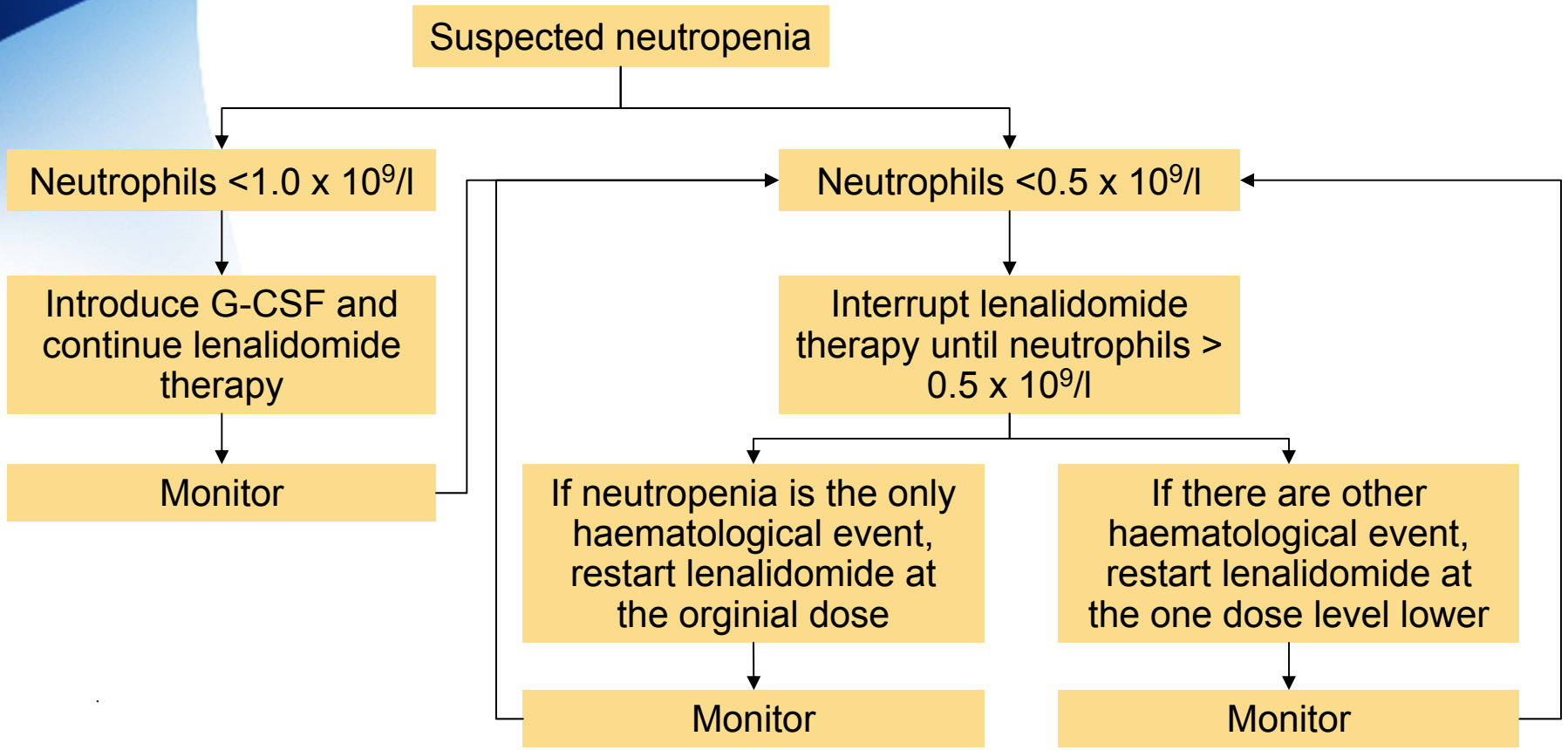
Sonneveld P, et al. Haematologica. 2007;92(Suppl 2);217 [abstract PO-1123].

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

Sonneveld P, et al. Haematologica. 2007;92(Suppl 2);217 [abstract PO-1123].

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 × 10^9/l, the lenalidomide dose should be resumed at the next lower dose.

Palumbo A. Presented at EHA Annual Meeting, 2007 [abstract 265].

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

- **Rash (grades ≥ 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

Attal M, et al. Haematologica. 2007;92(Suppl 2):217 [abstract PO-1122].

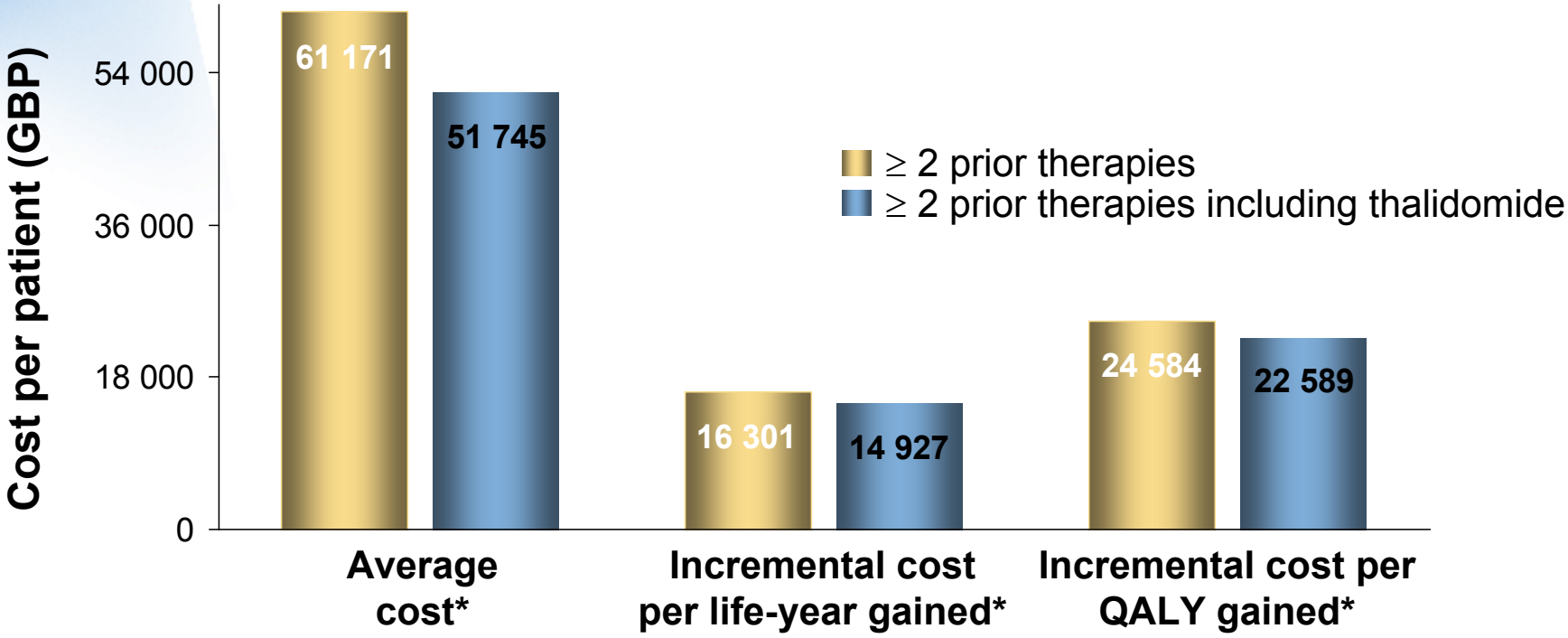
Economic evaluation of Len and Dex for the treatment of relapsed/refractory MM

- Objective
  - to estimate long-term health and cost consequences of Len + Dex versus Dex alone in MM patients with ≥ 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

Deniz B, et al. Blood. 2008;112:[abstract 2400].

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

Len + Dex delivers substantial improvements in quality-adjusted survival



*Discounted

Data from Deniz B, et al. Blood. 2008;112:[abstract 2400].

Revlimid®

Lenalidomide and dexamethasone in relapsed/refractory MM

MM-009, MM-010