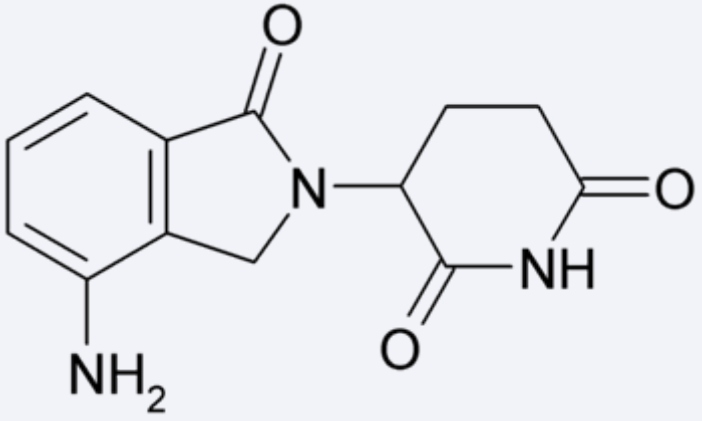
Lenalidomid

Lenalidomid



- Imunomodulační látka patřící mezi sloučeniny zvané IMiDy. Sloučenina strukturou podobná Thalidomidu s účinkem antiangiogenním, imunomodulačním a přímým protinádorovým.

Comparison of response rates in relapsed/refractory MM

Trial	Type of study	CR + PR	Reference
MM009	**Phase III**	**61%**	Weber DM, et al. N Engl J Med. 2007;357:2133-42.
MM010	**Phase III**	**60%**	Dimopoulos M, et al. N Engl J Med. 2007;357:2123-32.
DVd-R	**Phase I/II**	**75%**	Baz R, et al. Annals Oncol. 2006;17:1766-71.
Rev+Vel	**Phase I**	**58%**	Richardson PG, et al. Blood. 2006;108 [abstract 405].
RAD DL1-4	**Phase I**	**60%**	Knop S, et al. Blood. 2007;110 [abstract 2716].
RAD DL5	**Phase I**	**87%**	Knop S, et al. Blood. 2007;110 [abstract 2716].
RCD		**65%**	Morgan G, et al. Br J Haem. 2007;137:268-9.

Comparison of response rates in newly diagnosed MM

Trial	Type of study	CR + PR	Reference
Len+Dex	**Phase II**	**91%**	Lacy MQ, et al. Mayo Clin Proc. 2007;82:1179-84.
RMP	**Phase I/II**	**81%**	Palumbo A, et al. Haematologica. 2007;92(Suppl 2):179 [abstract PO-717].
BIRD	**Phase II**	**89%**	Niesvizky R, et al. Blood. [Epub ahead of print 2007 Nov 7.]

Overview of chosen trials

Trial	Type of study	Reference
MM009	**Phase III**	Weber DM, et al. N Engl J Med. 2007;357:2133-42.
MM010	**Phase III**	Dimopoulos M, et al. N Engl J Med. 2007;357:2123-32.
RCD		Morgan G, et al. Br J Haem. 2007;137:268-9.
ECOG-E4A03	**Phase III**	Rajkumar SV, et al. J Clin Oncol. 2007;25:18S [abstract LBA8025].
RMP	**Phase I/II**	Palumbo A, et al. Haematologica. 2007;92(Suppl 2):179 [abstract PO-717].

Studie proběhlé u pacientů s relabovaným/resistentním mnohočetným myelomem

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)

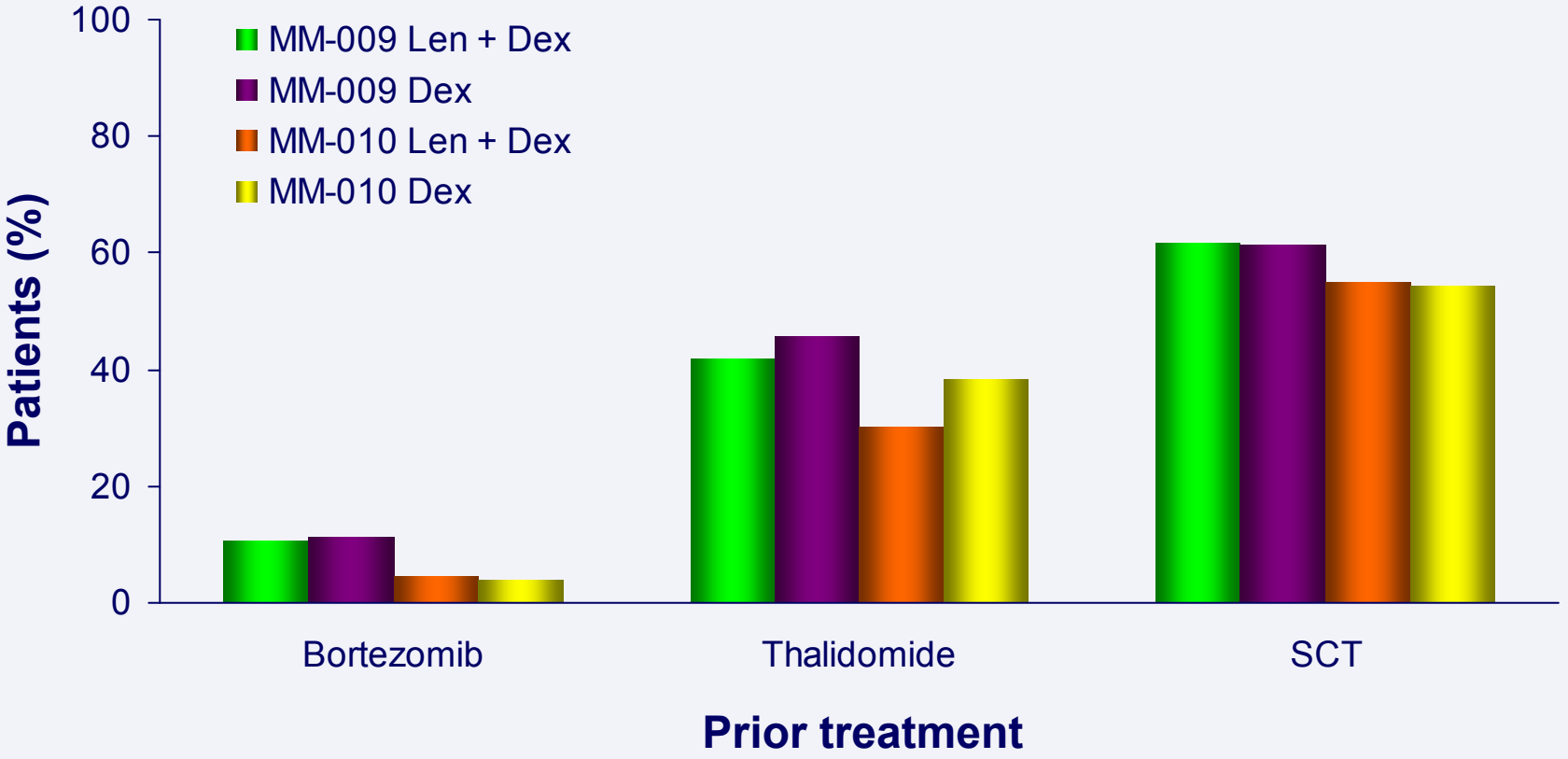
Dimopoulos M, et al. N Engl J Med. 2007;357:2123-32.
Weber DM, et al. N Engl J Med. 2007;357:2133-42.

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.

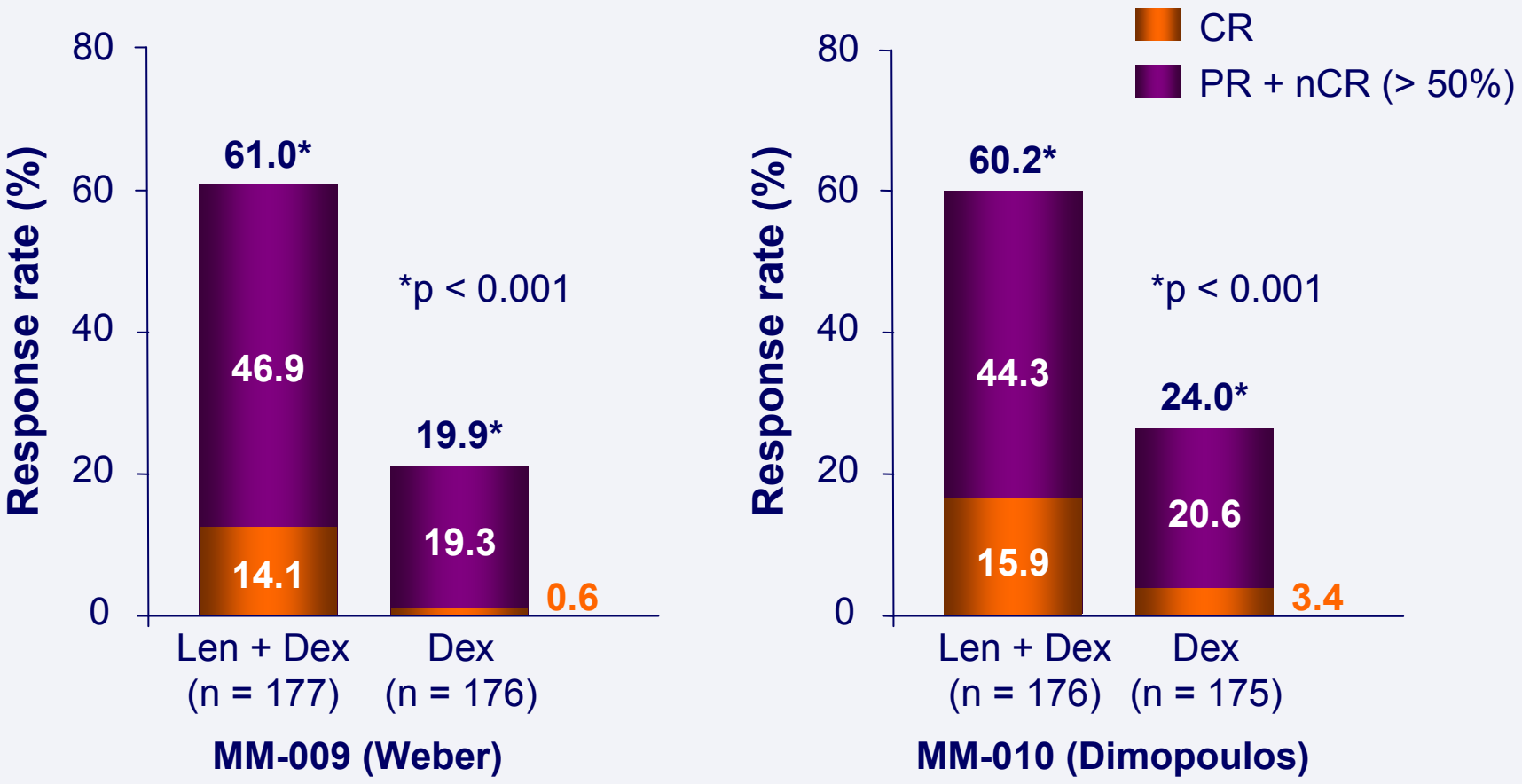
MM-009 and MM-010 included heavily pretreated patients



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

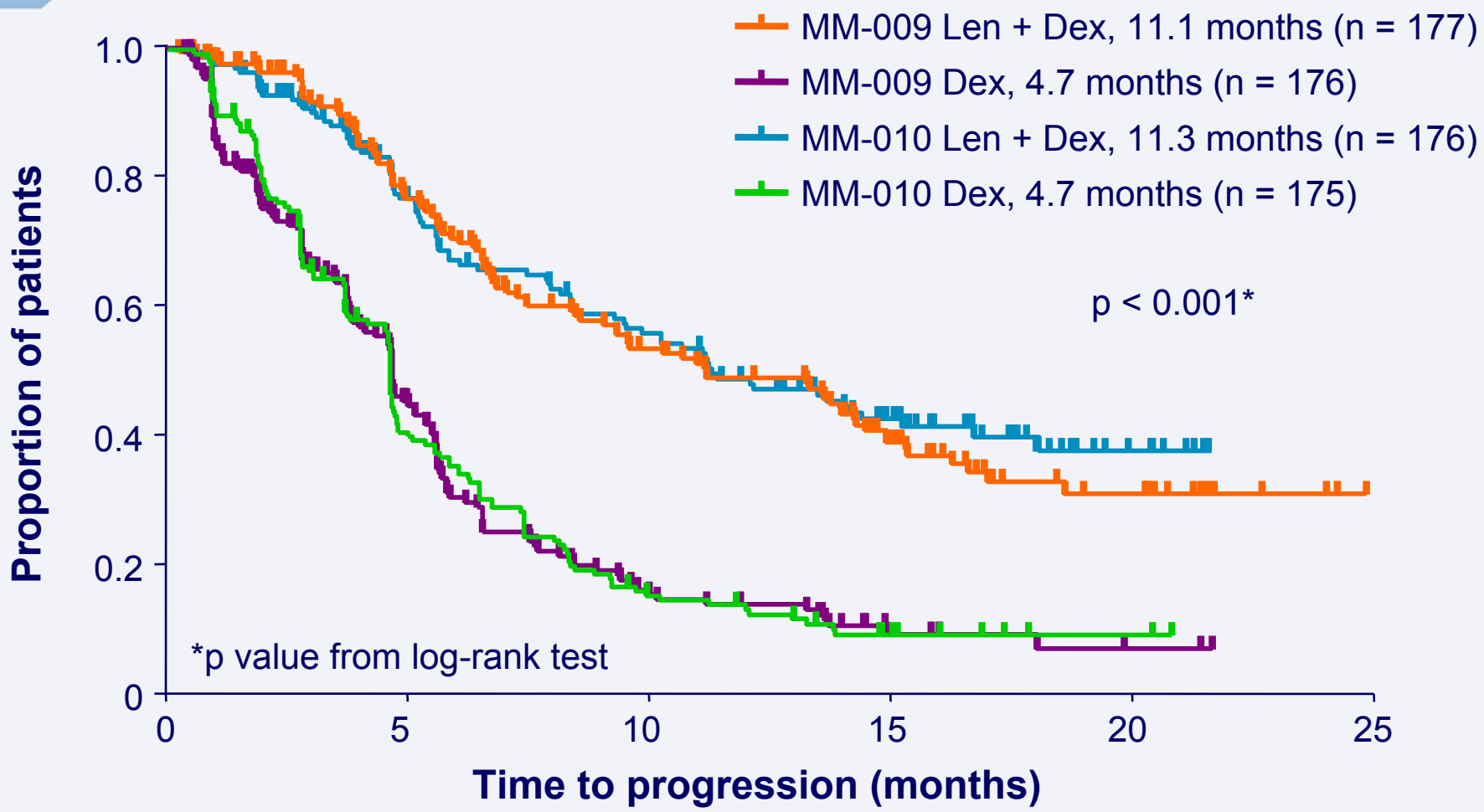
MM-009 and MM-010: higher response rates with Len + Dex

EBMT response data



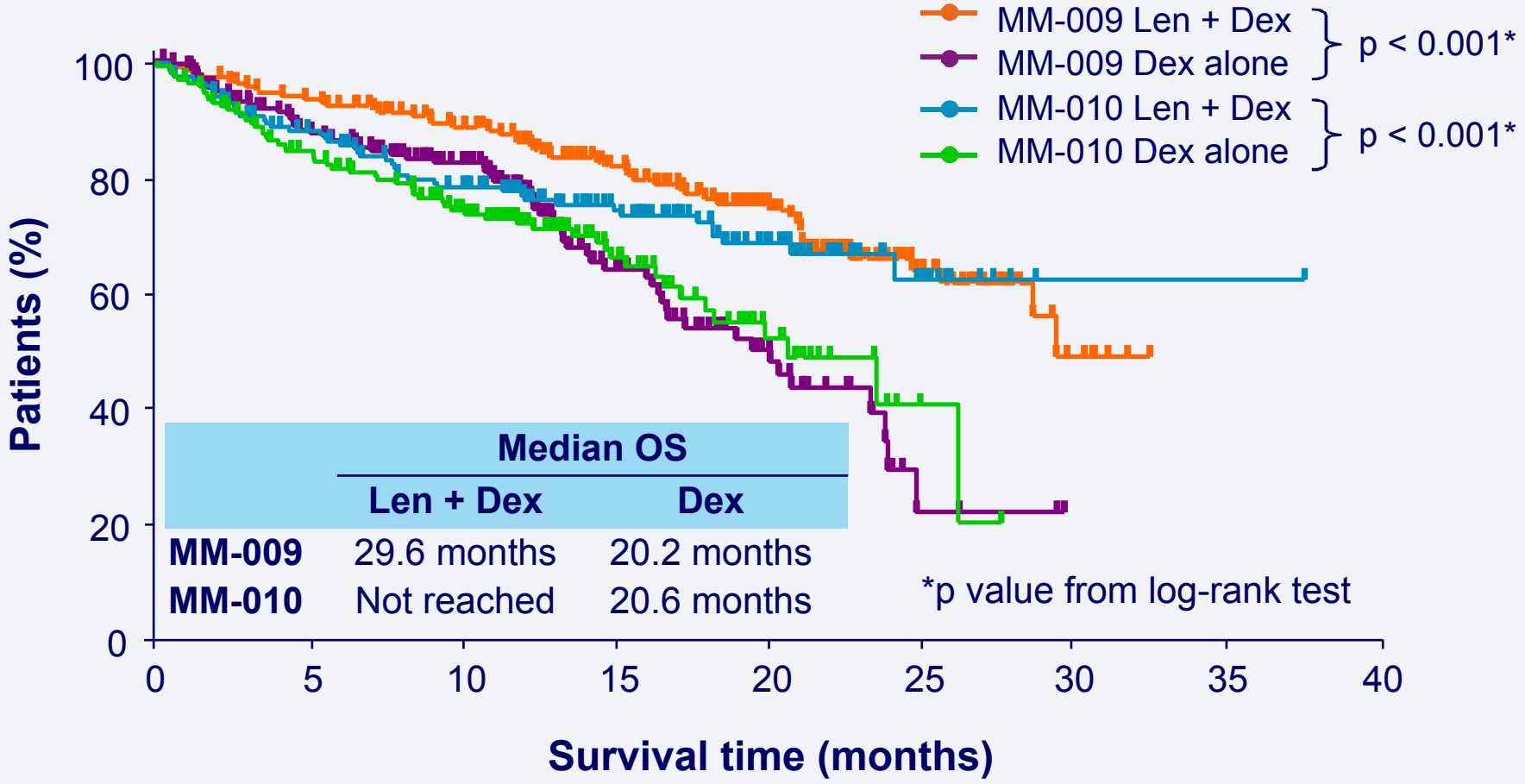
Dimopoulos M, et al. N Engl J Med. 2007;357:2123-32.
Weber DM, et al. N Engl J Med. 2007;357:2133-42.

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



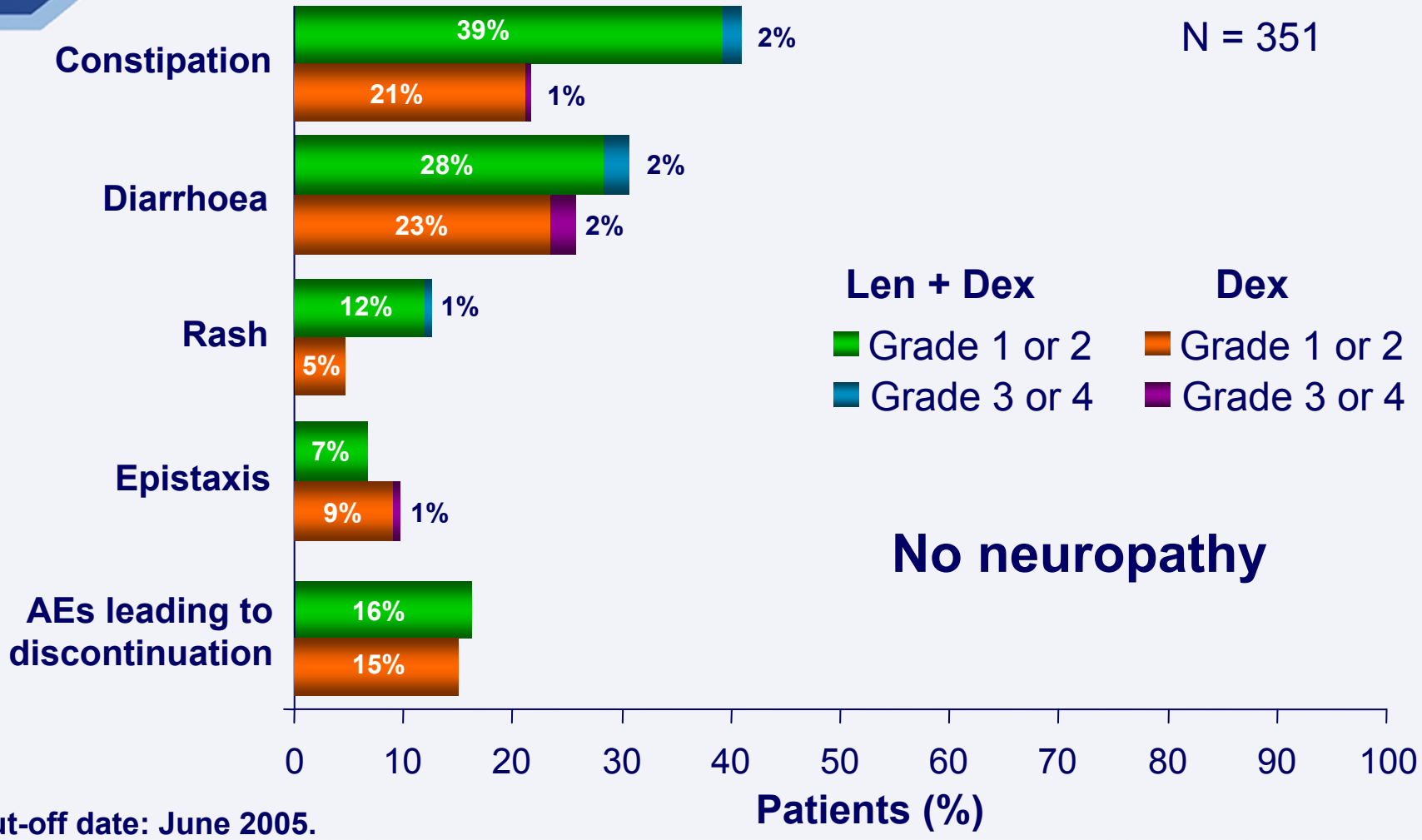
Dimopoulos M, et al. N Engl J Med. 2007;357:2123-32.
Weber DM, et al. N Engl J Med. 2007;357:2133-42.

MM-009: 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-010: non-haematological adverse events



Cut-off date: June 2005.

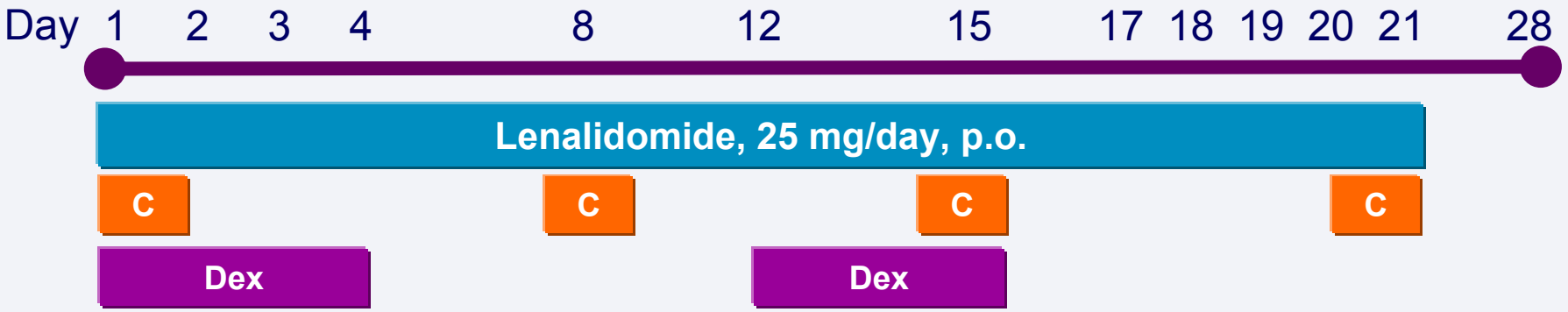
Dimopoulos M, et al. Blood. 2005;106:6a.

Léčba Len + Dex u relabovaného/refrakterního MM

- Léčba Lenalidomidem v kombinaci s Dexamethasonem oproti monoterapii Dexamethasonem prodlužuje čas do progrese, celkové přežití a je při ní zřejmý větší podíl léčebných odpovědí.
- Léčebný přínos kombinace Len+ Dex je prokazatelný bez ohledu na věk,stadium nemoci či délku jejího trvání.
- Léčebný přínos kombinace Len +Dex je též prokazatelný ve všech skupinách předléčených pacientů i když je zřejmý nižší podíl léčebných odpovědí u pacientů resistentních na Thalidomid.
- Nižší dávky Dexamethasonu v kombinaci s Lenalidomidem vedou ke snížení četnosti nežádoucích účinků stejně jako k vyššímu podílu léčebných odpovědí.

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

Lenalidomide (R), cyclophosphamide, and dexamethasone (RCD) in relapsed/refractory MM



Lenalidomide: 25 mg/day, p.o., days 1–21

C = cyclophosphamide: 500 mg/day, p.o. on days 1, 8, 15, and 21

Dex = dexamethasone: 40 mg/day, p.o., days 1–4 and 12–15

Maximum of 9 cycles of 28 days each

Morgan G, et al. Br J Haem. 2007;137:268-9.

RCD trial: baseline patient characteristics

Characteristic	N = 21
Median age, years (range)	59 (34–76)
Prior therapies	
Median number, n (range)	4 (1–8)
High-dose melphalan, n	14
Thalidomide	21
Bortezomib	17
Allogeneic BMT	2
Median time from diagnosis, months (range)	54 (11–122)

Morgan G, et al. Br J Haem. 2007;137:268-9.

RCD trial: efficacy and safety

Response (EBMT criteria)	n = 20
ORR (CR + PR), n (%)	15 (65)
CR	1
VGPR	3
PR	9
MR	2
Median time to response, days (range)	31 (15–68)

Adverse events, n	n = 20
Neutropenia	8 (38)

Morgan G, et al. Br J Haem. 2007;137:268-9.

Lenalidomide

Studie proběhlé u pacientů s nově diagnostikovaným mnohočetným myelomem

ECOG-E4A03: lenalidomide and standard- or low-dose dexamethasone in newly diagnosed MM

Phase III, randomized study – dexamethasone

Four courses, every 28 days

Newly diagnosed MM

(N = 445)

Arm 1:
lenalidomide 25 mg/day p.o., days 1–21
standard-dose **dexamethasone**
40 mg/day p.o., days 1–4, 9–12, 17–20
Dex/cycle 480 mg (n = 223)

Arm 2:
lenalidomide 25 mg/day p.o., days 1–21
lower-dose **dexamethasone**
40 mg/day p.o., days 1, 8, 15, 22
Dex/cycle 160 mg (n = 222)

If PD within 4 months

Salvage therapy:
thalidomide 200 mg/day p.o., days 1–28
standard-dose **dexamethasone**
40 mg/day p.o., days 1–4, 9–12, 17–20

Salvage therapy:
thalidomide 200 mg/day p.o., days 1–28
lower-dose **dexamethasone**
40 mg/day p.o., days 1, 8, 15, 22

When CR or PR response is reached, eligible patients proceed to stem cell transplant.

Rajkumar SV, et al. J Clin Oncol. 2007;25:18S [abstract LBA8025].

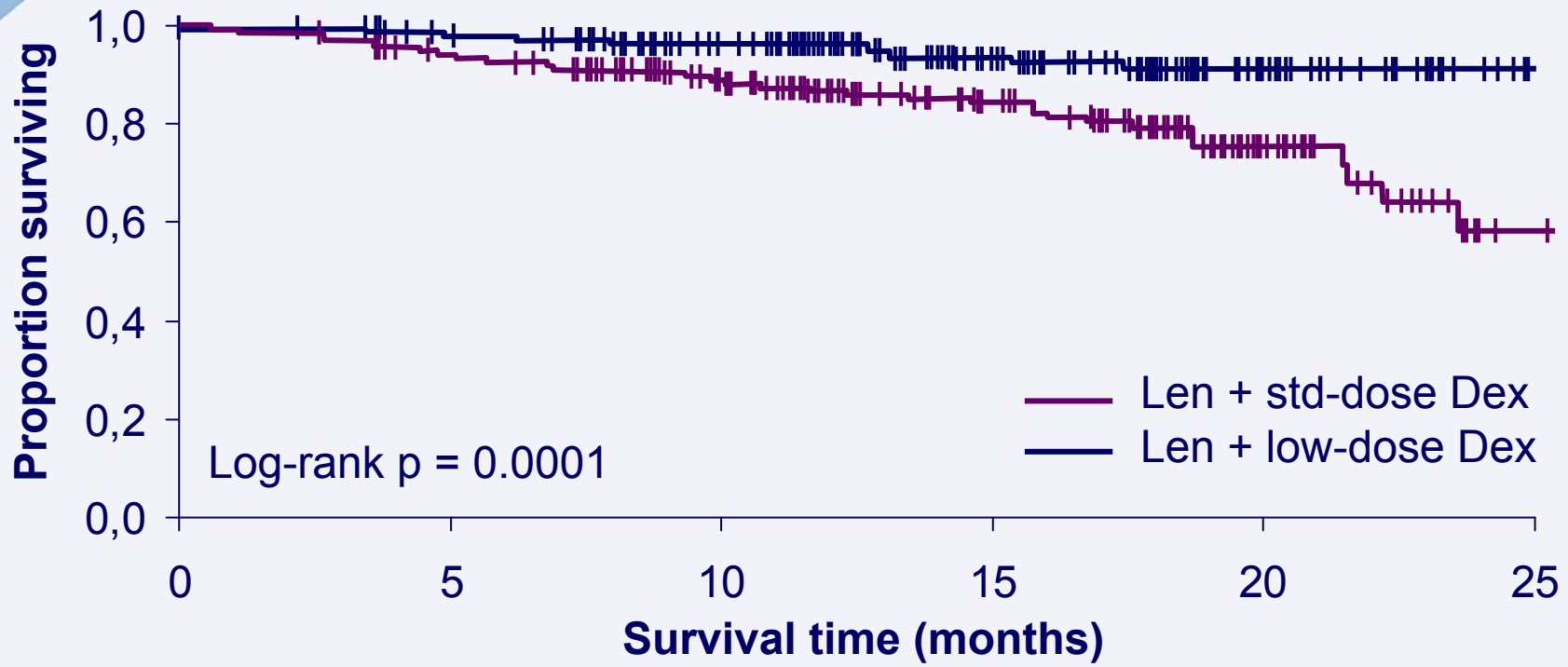
ECOG-E4A03: co-administration of low-dose dex leads to fewer adverse events

Patients with newly diagnosed MM (N = 445)

Grade 3 or 4 adverse events and deaths during first 4 months of therapy	Len + high-dose Dex, % (n = 223)	Len + low-dose dex, % (n = 222)	p value
Neutropenia	10	19	0.01
DVT/PE	**25**	**9**	< 0.001
Infections	16	6	< 0.001
Any grade 3 or higher non-haematological AE	49	32	< 0.001
Any grade 4 non-haematological AE	20	9	< 0.001
Death in first 4 months	**5**	**0.5**	0.006

Rajkumar SV, et al. Blood. 2007;110 [abstract 74].

ECOG-E4A03: superior overall survival rate with low- vs standard-dose Dex



	n	Event, % (n)	Censored, % (n)	Median survival (95% CI)
Len + std-dose Dex	223	18 (41)	82 (182)	NR (23.56–NR)
Len + low-dose Dex	222	6 (13)	94 (209)	NR

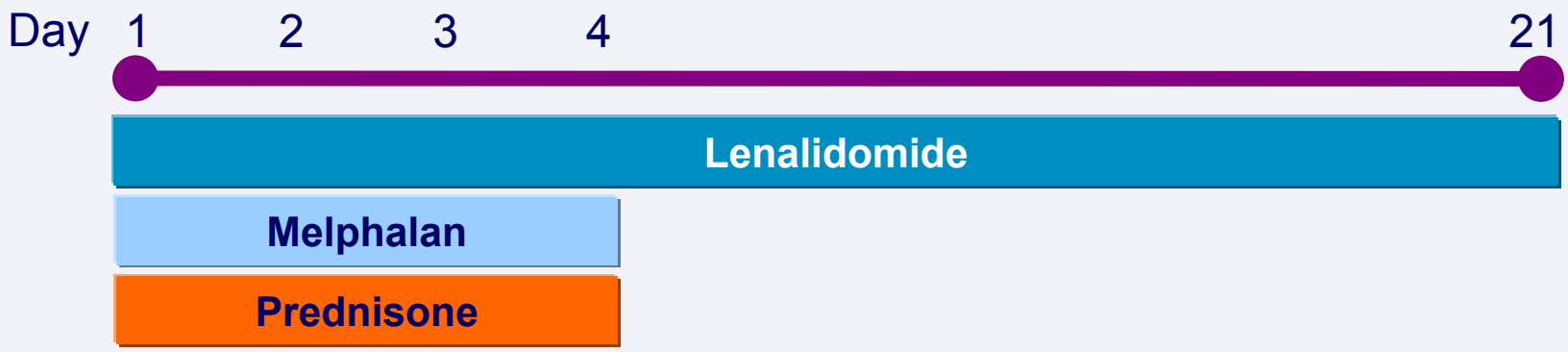
Overall survival was significantly superior in the low-dose Dex arm p < 0.001

Rajkumar SV, et al. J Clin Oncol. 2007;25:18S [abstract LBA8025].

Phase I/II trial of lenalidomide, melphalan, and prednisone (RMP) in newly diagnosed MM

Median age 71 years (range 57–77)

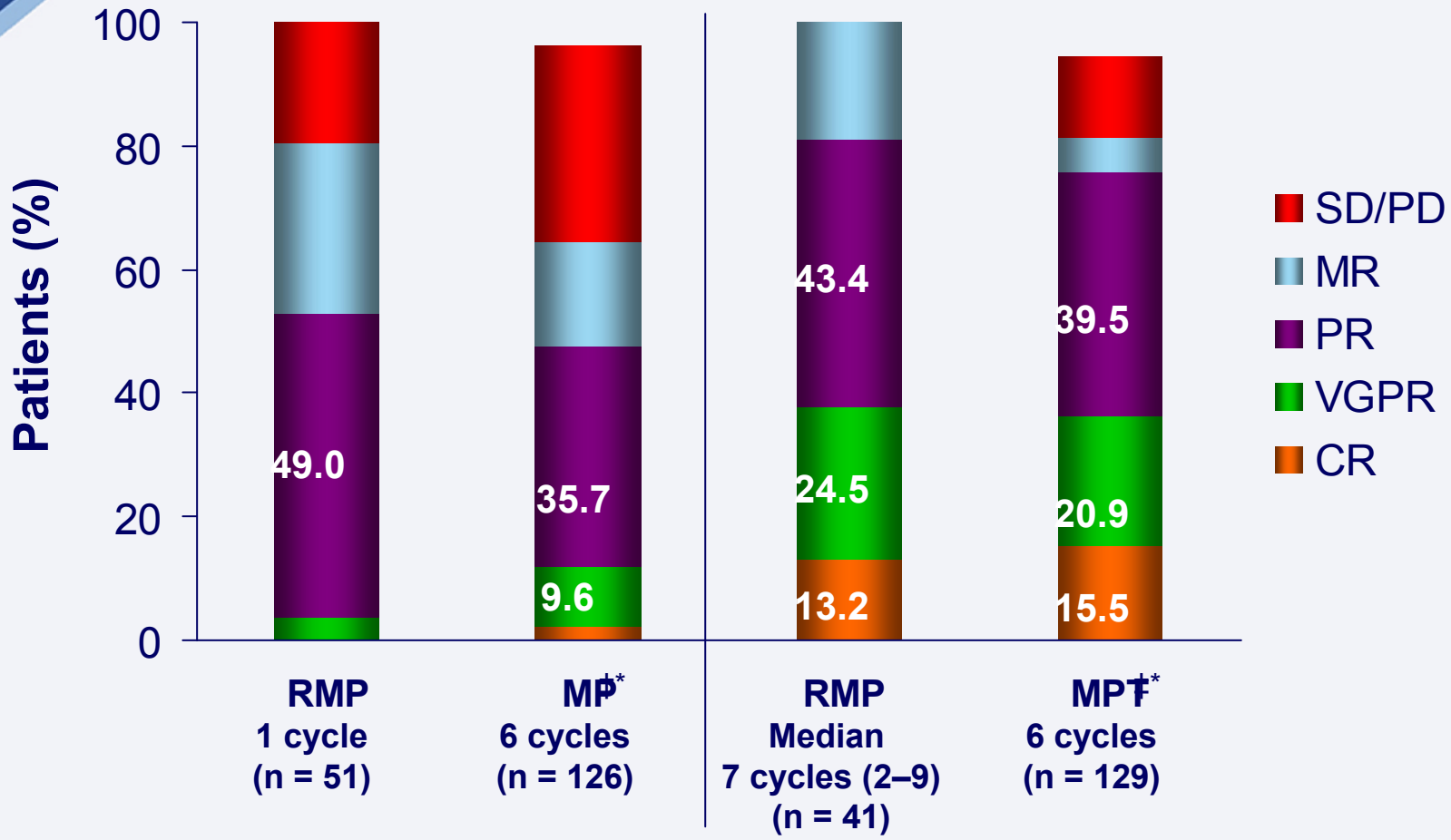
Cohort	Lenalidomide (R) (mg/day)	Melphalan (mg/kg/day)	Prednisone (mg/kg/day)
1 (n = 6)	5	0.18	2
2 (n = 6)	5	0.25	2
3 (n = 6 + 15)	10	0.18	2
4 (n = 6 + 15)	10	0.25	2



Every 4–6 weeks for maximum of 9 cycles.
Aspirin (100 mg/day) given as VTE prophylaxis.

Palumbo A, et al. Haematologica. 2007;92(Suppl 2):179 [abstract PO-717].

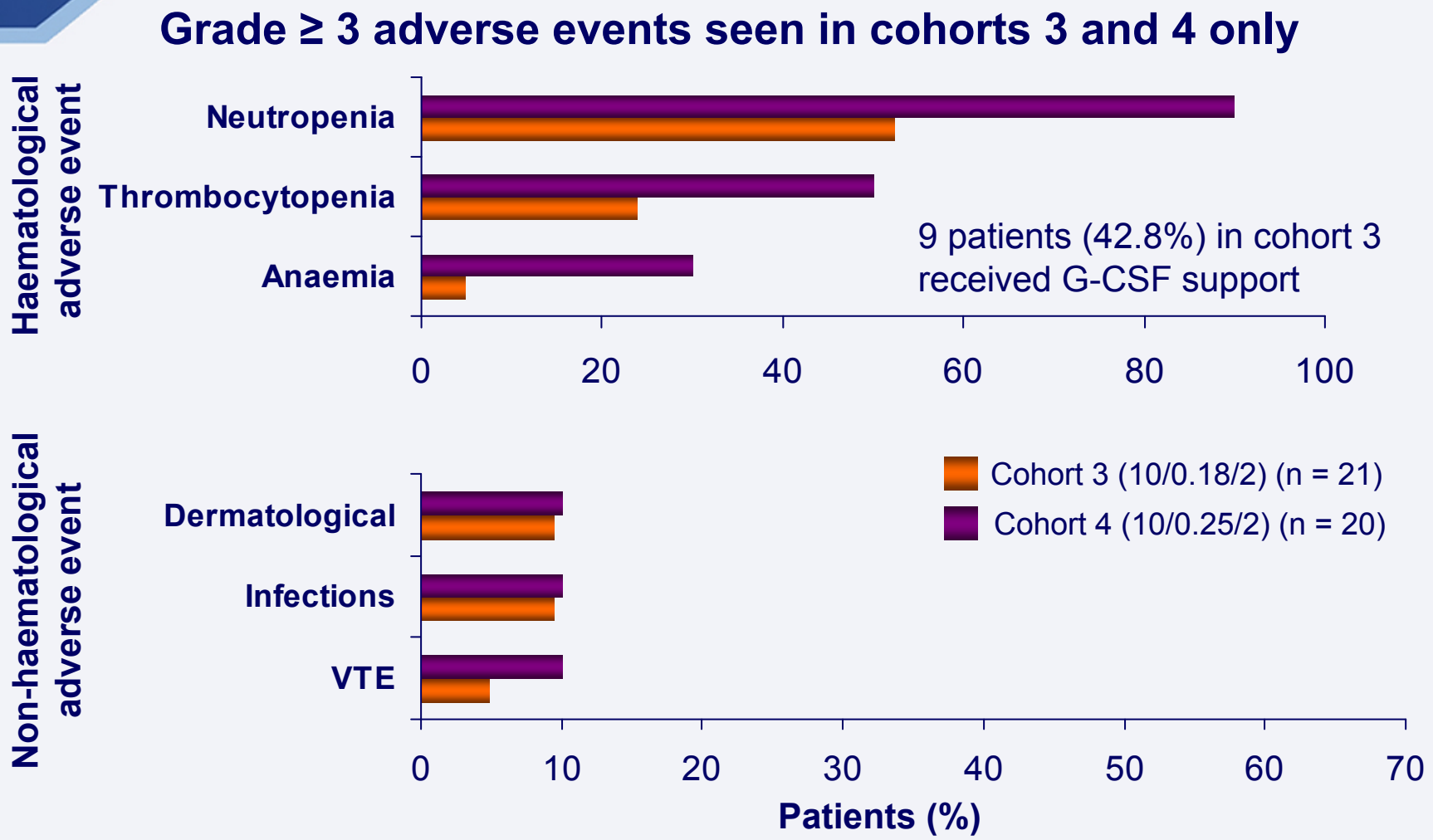
RMP vs MP and MPT: EBMT-defined response



‡4% (MP) and 4.5% (MPT) of the patients were not evaluable for response.

*Historical control; Palumbo A, et al. Lancet. 2006;367:825-31.
Palumbo A, et al. Blood. 2006;108 [abstract 800].

RMP in newly diagnosed MM: adverse events



Palumbo A, et al. J Clin Oncol. 2007;25:4459-65.

Souhrn toxicit Lenalidomidu v jednotlivých studiích

Toxicity of Lenalidomid in trials

	MM009 Len+dex	RCD	ECOG-E4A03-high dex	ECOG-E4A03-low dex	RMP-cohort 3
Neutropenia	41%	38%	10%	19%	55%
Trombocytopenia	15%	unknown	unknown	unknown	55%
Infection	21%	29%	16%	6%	10%
VTE/PE	14%	14%	25%	9%	5%
Neuropathy	NO	NO	NO	NO	unknown

Teratogenita- nově prokázána jako velice pravděpodobná na opičích modelech.

Závěr

- Studie MM009 a MM010 byli klíčové pro celosvětové schválení preparátu k užívání v léčbě pacientů s mnohočetným myelomem.
- RCD kombinace Lenalidomidu s alkylační látkou a kortikoidem která je plánována k použití u pacientů s relabovaným mnohočetným myelomem.
- RMP I/II studie která určila design studie RMP/MP která nyní probíhá v ČR za účelem uznání Revlimidu v primoléčbě mnohočetného myelomu.
- ECOG –E4A03 revoluční svým omezení používání Dexamethasonu a důrazem na nově používaný lék.

Thank you for your attention