



OVERCOMING THROMBOSIS

IN

MM PATIENTS

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Incidence of VTE

		% (95% Confidence Interval) [No. of Patients With VTE/Total No. of Patients Treated With Regimen]									
		Dexamethasone ± Chemotherapy		Doxorubicin ± Chemotherapy		Dexamethasone and Doxorubicin ± Chemotherapy		Melphalan and Prednisone ± Chemotherapy		Monotherapy	
Disease Status	Prophylaxis	Thalido- mide (n = 1544)	Lenalido- mide (n = 712)	Thalido- mide (n = 50)	Lenalido- mide (n = 21)	Thalido- mide (n = 1137)	Lenalido- mide (n = 0)	Thalido- mide (n = 351)	Lenalido- mide (n = 24)	Thalido- mide (n = 986)	Lenalido- mide (n = 324)
Not previously treated	No prophylaxis	14 (11-16) [109/795]	14 (10-18) [38/278]			24 (21-28) [148/610]		15 (11-19) [43/287]		3 (0-6) [2/73]	2 (0.1-4) [4/222]
	Warfarin, 1 mg	15 (9-21) [18/121]									
	Warfarin, 2-3 INR, or LMWH	0 [0/63]				9 (5-13) [19/211]		3 (0-7) [2/64]			
	Aspirin, 325 mg		11 (5-18) [10/88]			7 (0-14) [3/45]		4 (0-12) [1/24]			
Relapsed/ refractory	No prophylaxis	6 (3-8) [25/454]	24 (20-29) [84/346]	12 (3-21) [3/50]		17 (13-22) [47/271]				3 (2-4) [23/913]	0 (0/102)
	Warfarin, 1 mg	9 (3-16) [8/85]									
	Warfarin, 2-3 INR, or LMWH	8 (0-18.0) [2/26]									
	Aspirin, 325 mg				10 (0-22) [2/21]						
Totals for each treatment regimen†		10 (9-12) [162/1544]	19 (16-21) [132/712]	12 (3-21) [3/50]	10 (0-22) [2/21]	19 (17-21) [217/1137]		13 (9-16) [45/351]	4 (0-12) [1/24]	3 (2-4) [25/986]	1 (0.03-2) [4/324]

Thalidomide/Dexamethasone vs Dexamethasone in Newly Diagnosed MM (MM-003)

MM-003 Phase III Multicenter Study Design

Inclusion criteria

- M protein in serum (≥ 1.0 g/dL) or urine (≥ 200 mg/24 h)
- PS: 0–2
- ANC ≥ 1000
- Plt $\geq 50,000/\text{mm}^3$
- SCr ≤ 3.0 mg/dL
- AST/ALT $\leq 3.0 \times$ ULN; BR ≤ 2.0 mg/dL

**Thalidomide 50–200 mg days 1–28
Dex 40 mg days 1–4, 9–12, 17–20**

× 4 COURSES



**Continue
until PD**

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

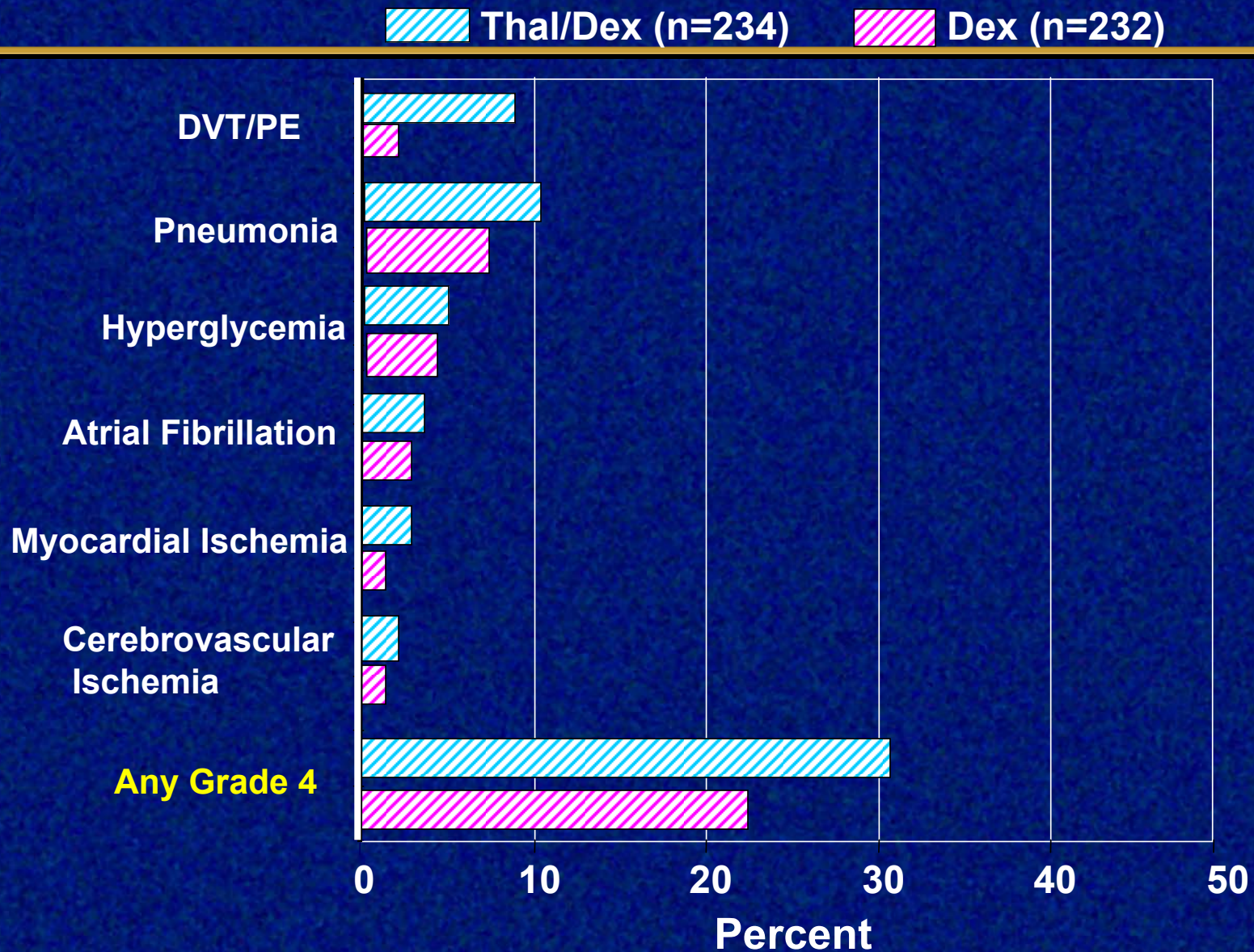
**Same, except
Dex days 1–4**

**Primary endpoints: TTP, OS, response rate
Secondary endpoint: safety**

Rajkumar SV et al. *J Clin Oncol*. 2006;24(suppl 18S):426s [abstract 7517]

Rajkumar SV et al. Presented at ASH Annual Meeting; December 9-12, 2006; Orlando, FL

MM-003: Grade 3 and 4 Toxicities



Rajkumar et al. Presented at: ASH Annual Meeting; December 9-12, 2006; Orlando, FL

2 Phase III Trials of Lenalidomide/Dex in Relapsed or Refractory MM

North American MM-009 (48 Centers USA/Canada): Weber

International MM-010 (51 Centers Europe/Australia/Israel): Dimopoulos

Inclusion criteria
≤3 prior therapies
No Dex resistance
Normal liver/renal function

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

× 4 COURSES



Continue until PD

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

Same, except Dex days 1–4

Primary endpoint: TTP (by Bladé criteria)

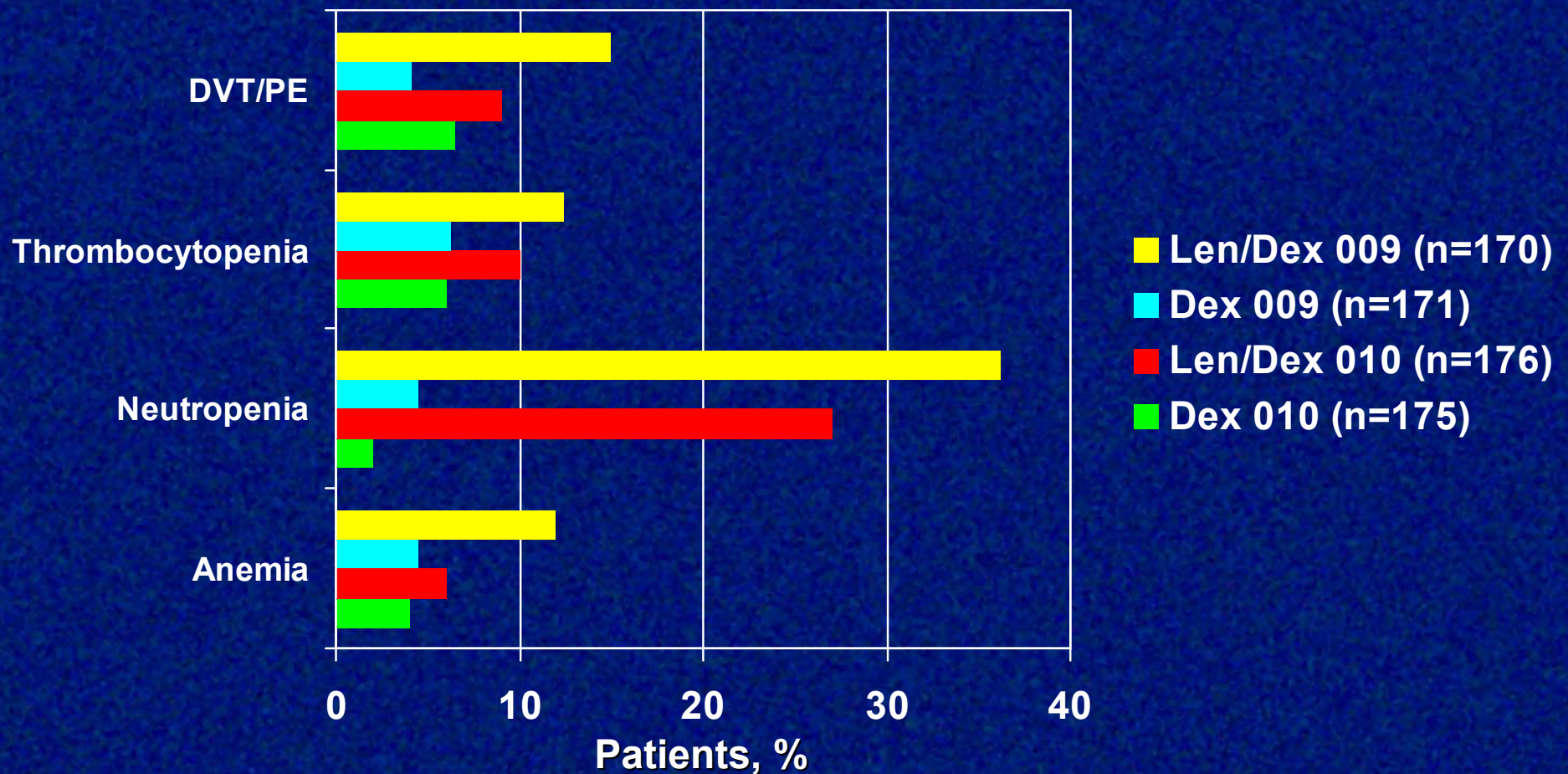
Secondary endpoints: OS, RR, safety, first SRE, PS

Additional stratification by β_2 M (≤ 2.5 mg/dL vs > 2.5 mg/dL), prior transplant (0 vs > 1), and prior MM treatment regimens (< 1 vs > 1)

Dimopoulos MA et al. *Blood*. 2005;106:6a [abstract 6]

Weber DM et al. *J Clin Oncol*. 2006;24(suppl 18S):427s [abstract 7521]

Phase III Trials of Lenalidomide/Dex in Relapsed or Refractory MM: Grade 3/4 AEs

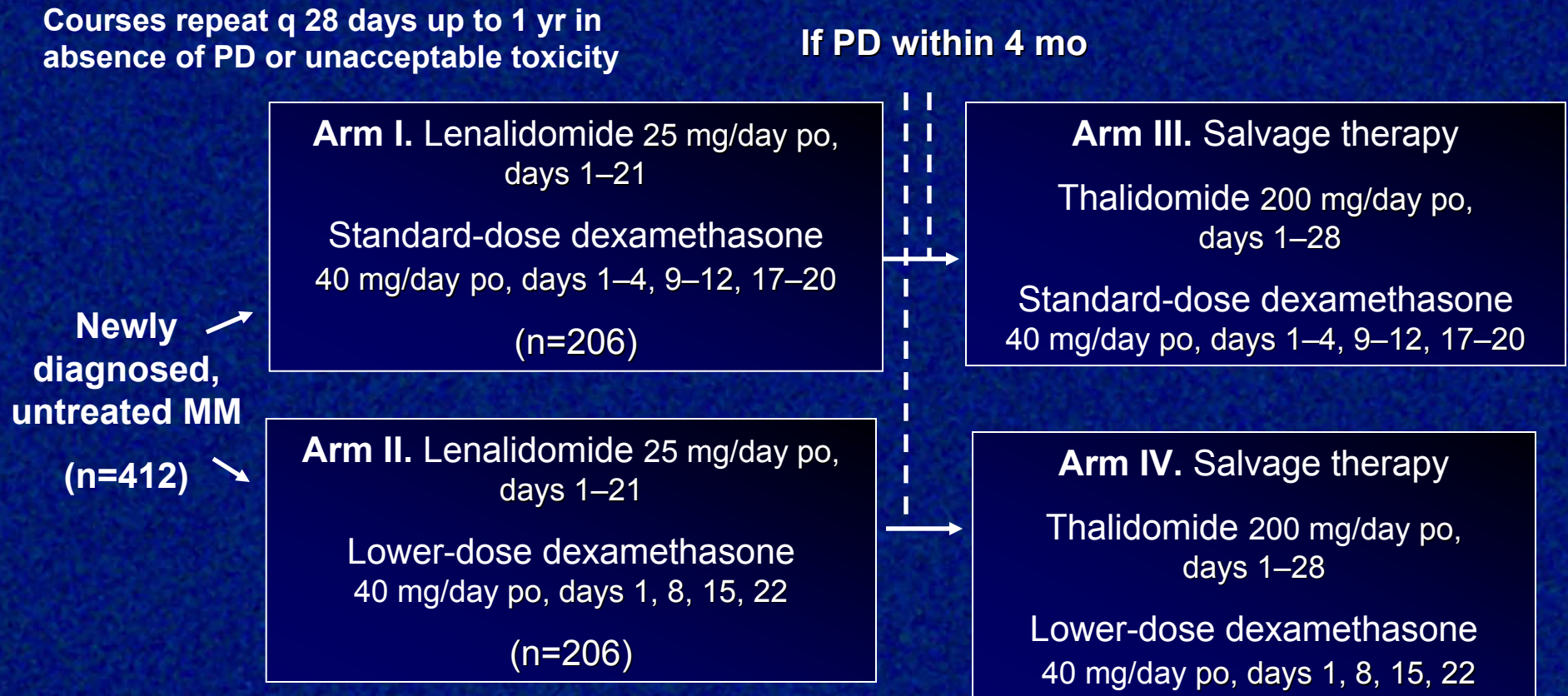


Dimopoulos MA et al. *Blood*. 2005;106:6a [abstract 6]

Weber DM et al. *J Clin Oncol*. 2006;24(suppl 18S):427s [abstract 7521]

Lenalidomide Plus Standard or Low-Dose Dexamethasone in Newly Diagnosed MM

ECOG 4A03: Phase III Randomized Study



Endpoints: Response Rate, Safety in Arms I, II; Response Rate in Arms III, IV

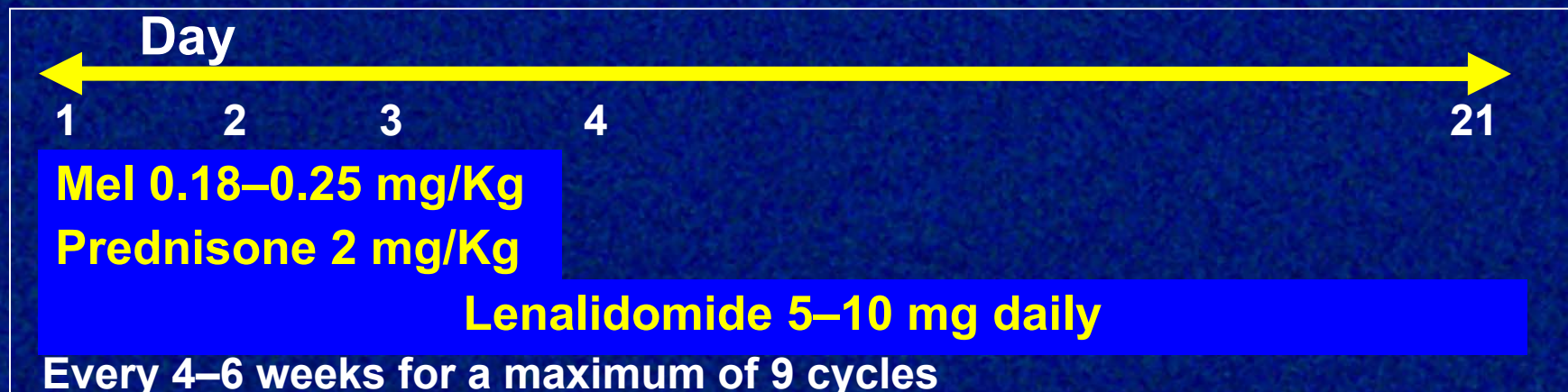
EA403: Non-Hematologic Grade 3 or 4 Adverse Events During The First 4 Months of Therapy

Adverse Event (Grade \geq 3)	Len/ Std-dose Dex (N=223)	Len/ Low-dose Dex (N=222)	P-value
Infection/Pneumonia	16.1%	9.0%	0.031
DVT/PE	18.4%	6.3%	<0.001
Atrial fibrillation/flutter	3.1%	0.0%	0.015
Cardiac ischemia	1.8%	0.5%	0.372

DVT/PE

Toxicity	Len High-dose Dex	Len Low-dose Dex
DVT/PE (445 pts)	18.4%	6.3%
Grade \geq4	8.0%	3.2%

Oral Lenalidomide plus Melphalan and Prednisone (R-MP) for Newly Diagnosed MM: Treatment Schedule

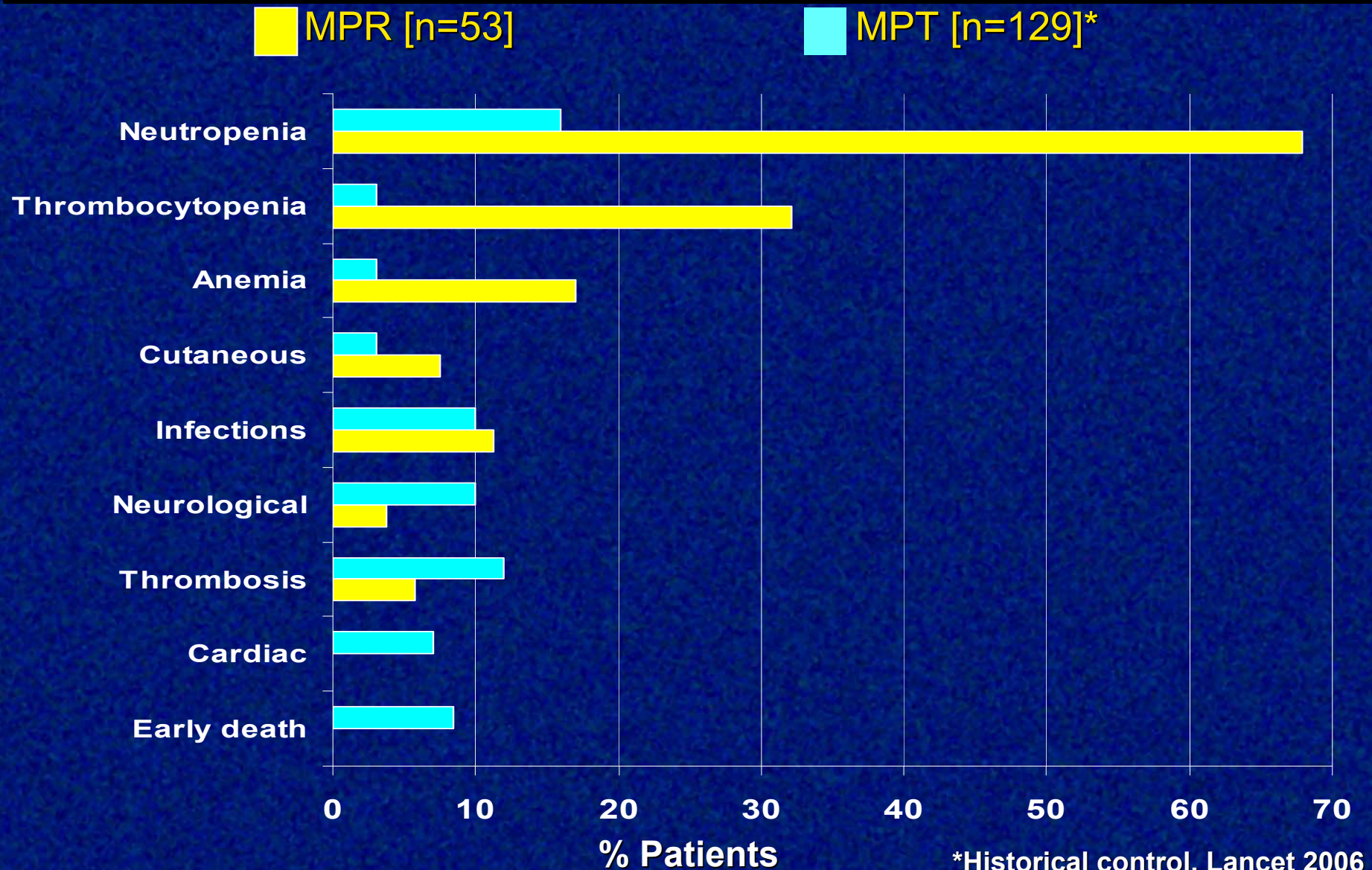


Aspirin 100 mg/d continuously

	Melphalan mg/kg/d	Lenalidomide mg/d	Patients
Cohort 1	0.18	5	6
Cohort 2	0.25	5	6
Cohort 3	0.18	10	6+15
Cohort 4	0.25	10	6+15

6 patients in each cohort ; additional 15 pts in cohort 3 and 4

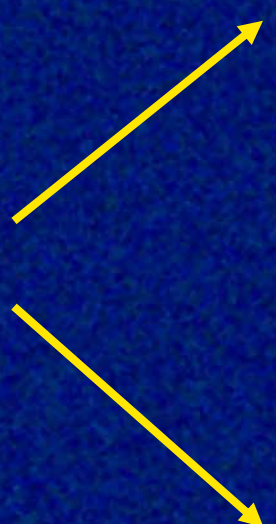
MPR vs MPT: Grade 3–4 Adverse Events



MPT vs MP in Elderly Patients With MM

Phase III Randomized, Controlled Trial

Newly diagnosed MM
patients, aged >65 yr
(n=255[†])



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graph LR; A["Newly diagnosed MM patients, aged >65 yr (n=255†)"] --> B["MPT* arm (median age 72)"]; A --> C["MP arm (median age 72)"]; B --> D["→ × 6 courses"]; C --> D;
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MPT* arm (median age 72)

Melphalan, 4 mg/m² (7 days/mo)

Prednisone, 40 mg/m² (7 days/mo)

Thalidomide, 100 mg/d (continuously)*

(n=129[†])

→ × 6 courses

MP arm (median age 72)

Melphalan, 4 mg/m² (7 days/mo)

Prednisone, 40 mg/m² (7 days/mo)

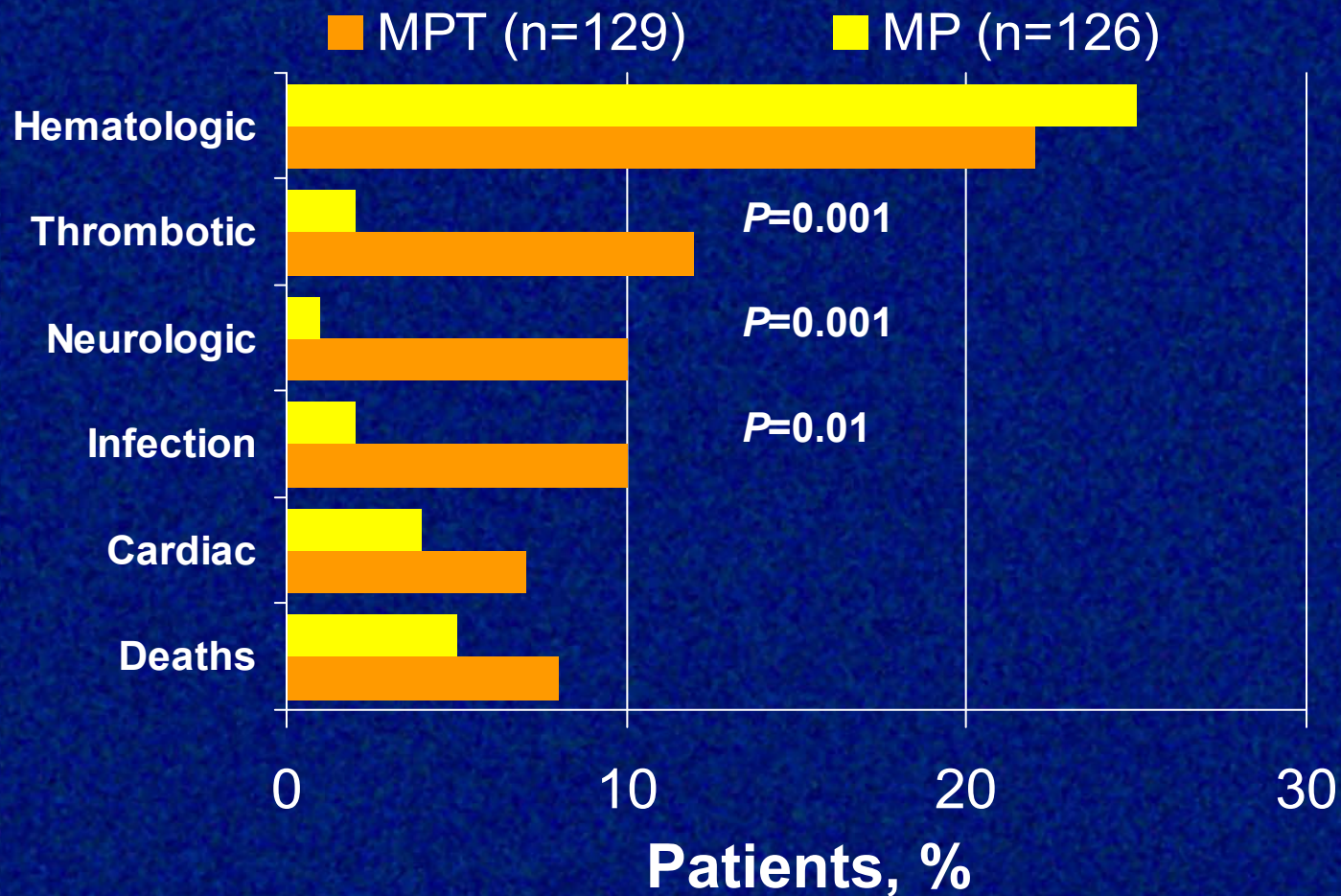
(n=126[†])

*Thalidomide dose reduced to 50% if grade 2 toxicity; enoxaparin prophylaxis added to protocol December 2003

[†]No. of patients with ≥6 mo follow-up

Palumbo A et al. *Lancet*. 2006;367:825

MPT vs MP in Elderly Patients With MM: Grade 3/4 AEs



MPT in Elderly Patients With MM: Thromboembolic Events

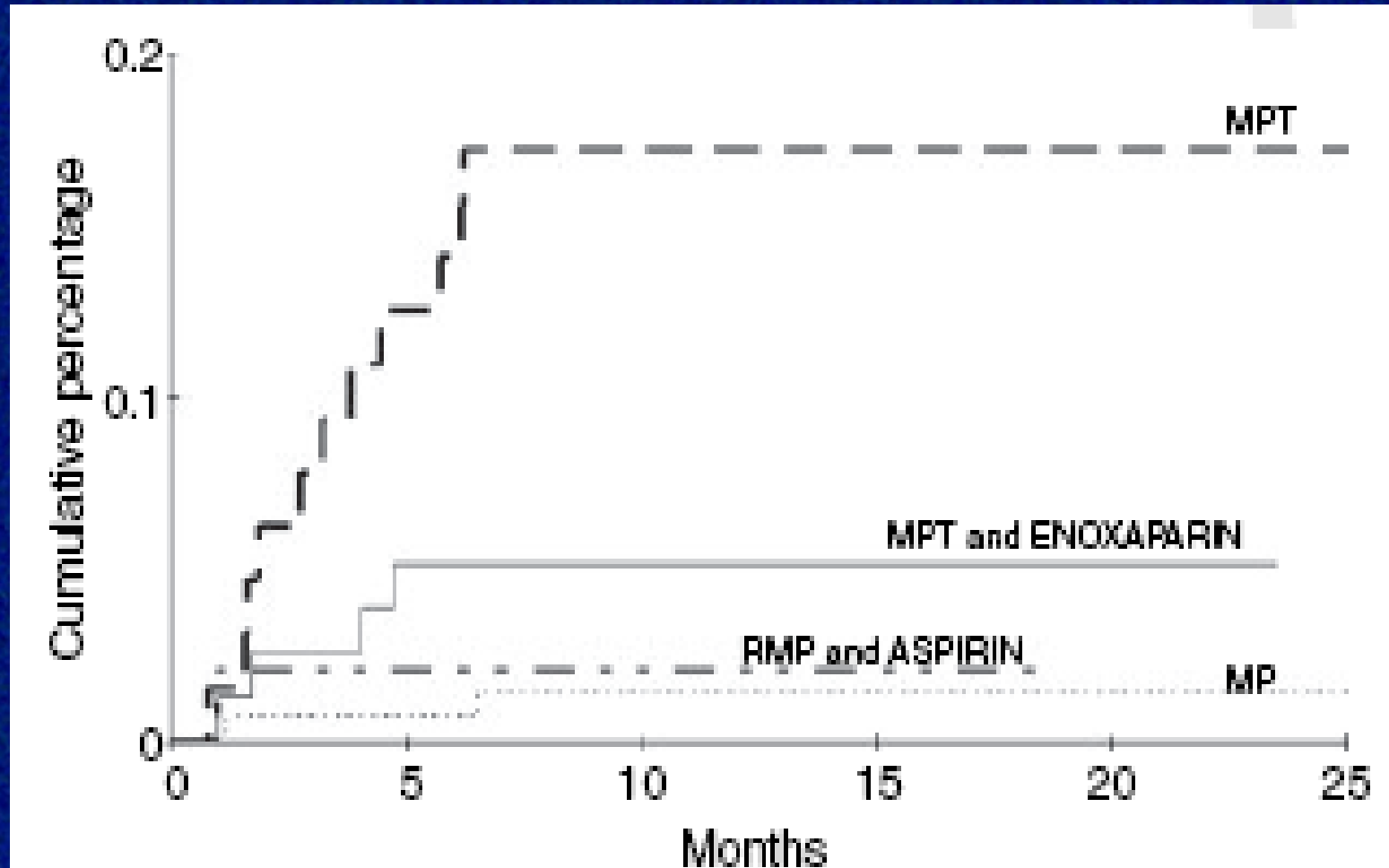
- MPT with no prophylaxis (n=65)
 - 56.9% (37/65) grade 3/4 adverse events*
 - 16.9% (11/65) thromboembolism[†]
- MPT + enoxaparin (40 mg/day for 4 mo) (n=64)
 - 39.1% (25/64) grade 3/4 adverse events*
 - 3.1% (2/64) thromboembolism[†]
 - Both patients had evidence of thromboembolism within 2 mo of discontinuing enoxaparin

* $P=0.042$ comparing MPT with MP

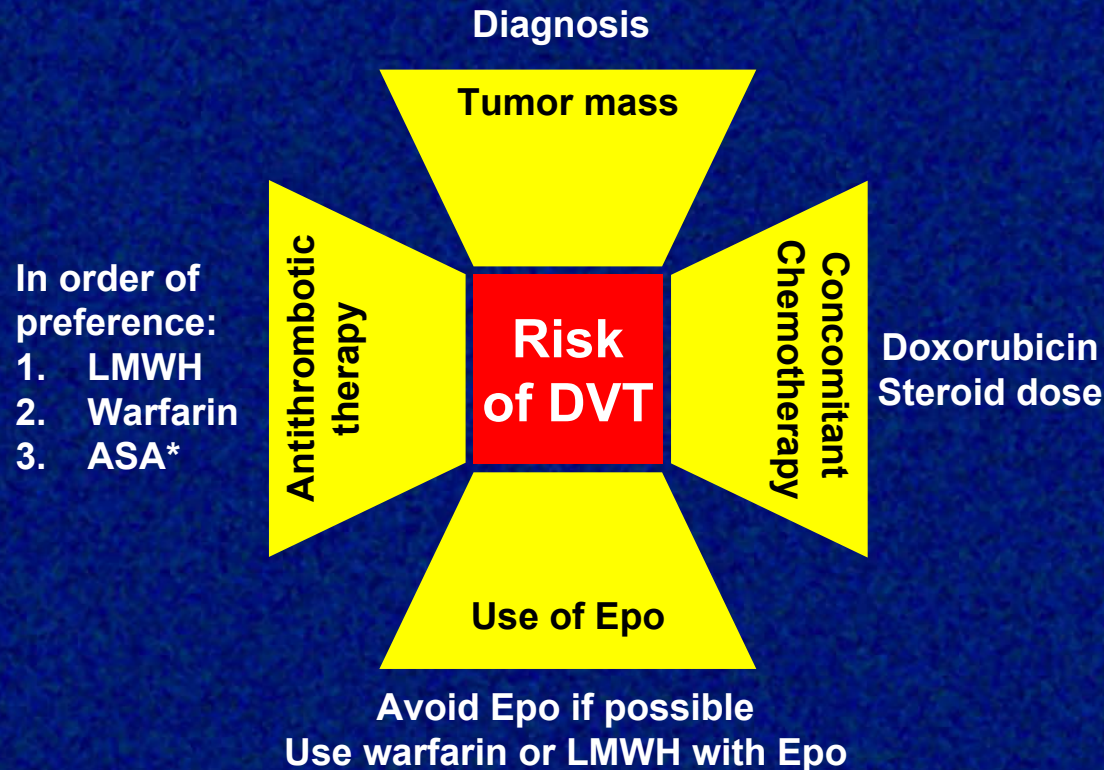
[†] $P=0.005$ comparing MPT with MP

Palumbo A et al. *Lancet*. 2006;367:825

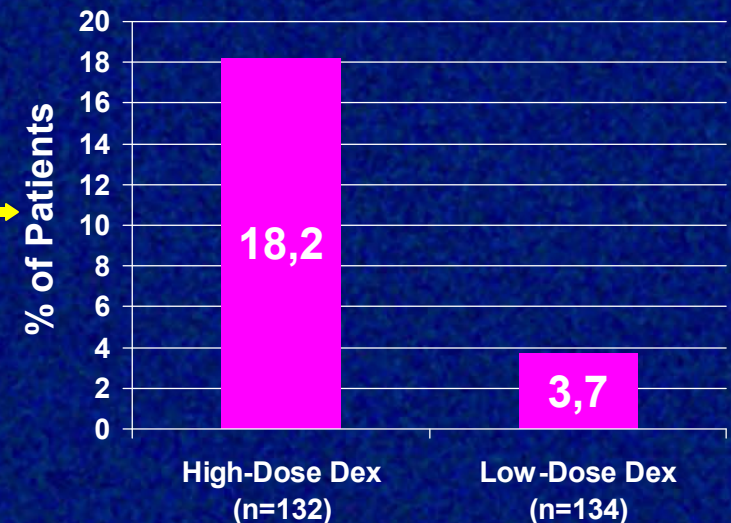
Cumulative risk of VTE



Thrombotic Risk Factors and Risk Reduction With Thalidomide and Lenalidomide



Thromboembolic events among 266 patients enrolled in ECOG 4A03 as of 11/15/05



*ASA is effective with lenalidomide/dexamethasone or thalidomide/dexamethasone combinations
 Knight R et al. *N Engl J Med.* 2006;354:2079; Rajkumar SV et al. *N Engl J Med.* 2006;354:2080
 Zonder JA et al. *Blood.* 2006;108:403; Rajkumar SV, Gertz MA. *Blood.* 2006;108:404
 Rajkumar SV et al. Presented at: ASCO Annual Meeting; June 2–6, 2006; Atlanta, GA

Factors increasing the risk of VTE

- diagnosis
- high-tumour mass

- concomitant chemotherapy
- doxorubicin
- high-dose dexamethasone
- use of erythropoietin

- infection/inflammation
- higher age

- previous VTE
- pre-existing coagulation disorders

Management of VTE

- patients need to receive instructions in case VTE occur
- no baseline coagulation studies
- no screening for VTE in asymptomatic patients
- sonography for diagnosis of VTE

Prophylactic anticoagulation

No evidence of the best prophylaxis:

- daily aspirin (low or high-dose)
- low-molecular-weight heparin (LMWH)
- warfarin (therapeutic doses or low-doses)

- low-dose aspirin (ASA) (81-100 mg) or
- prophylactic dose of LMWH
- therapeutic-dose warfarin (increased risk of haemorrhage)

The risk of VTE is high in the first 4–6 months of therapy.

When VTE occurs

- therapeutic doses of LMWH are recommended
- patient can be continued on treatment after stabilization depending on the severity of the VTE.

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