POZVÁNKA

XII. workshop mnohočetný myelom
s mezinárodní účastí a Roční setkání
České myelomové skupiny

Pořadatel:
Lékařská fakulta Masarykovy univerzity

Česká myelomová skupina (CMG)
člen ČHS ČLS JEP

Za podpory:
Celgene s.r.o.

Edukační blok

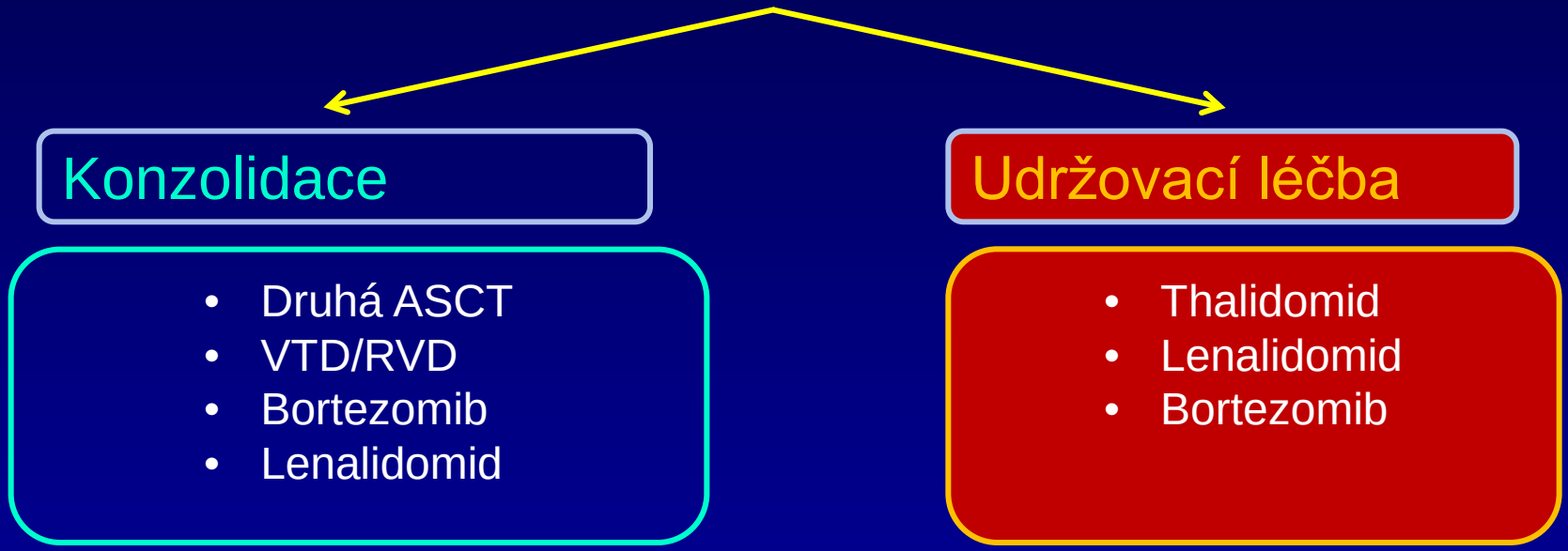
Současné přístupy a perspektivy v léčbě mnohočetného myelomu imunomodulačními léky

12. dubna 2014, od 14.30 do 16.30 hod
v sále Aurelius, Hotel Galant, Mlýnská 2, Mikulov

Kontinuální léčba lenalidomidem – současná data

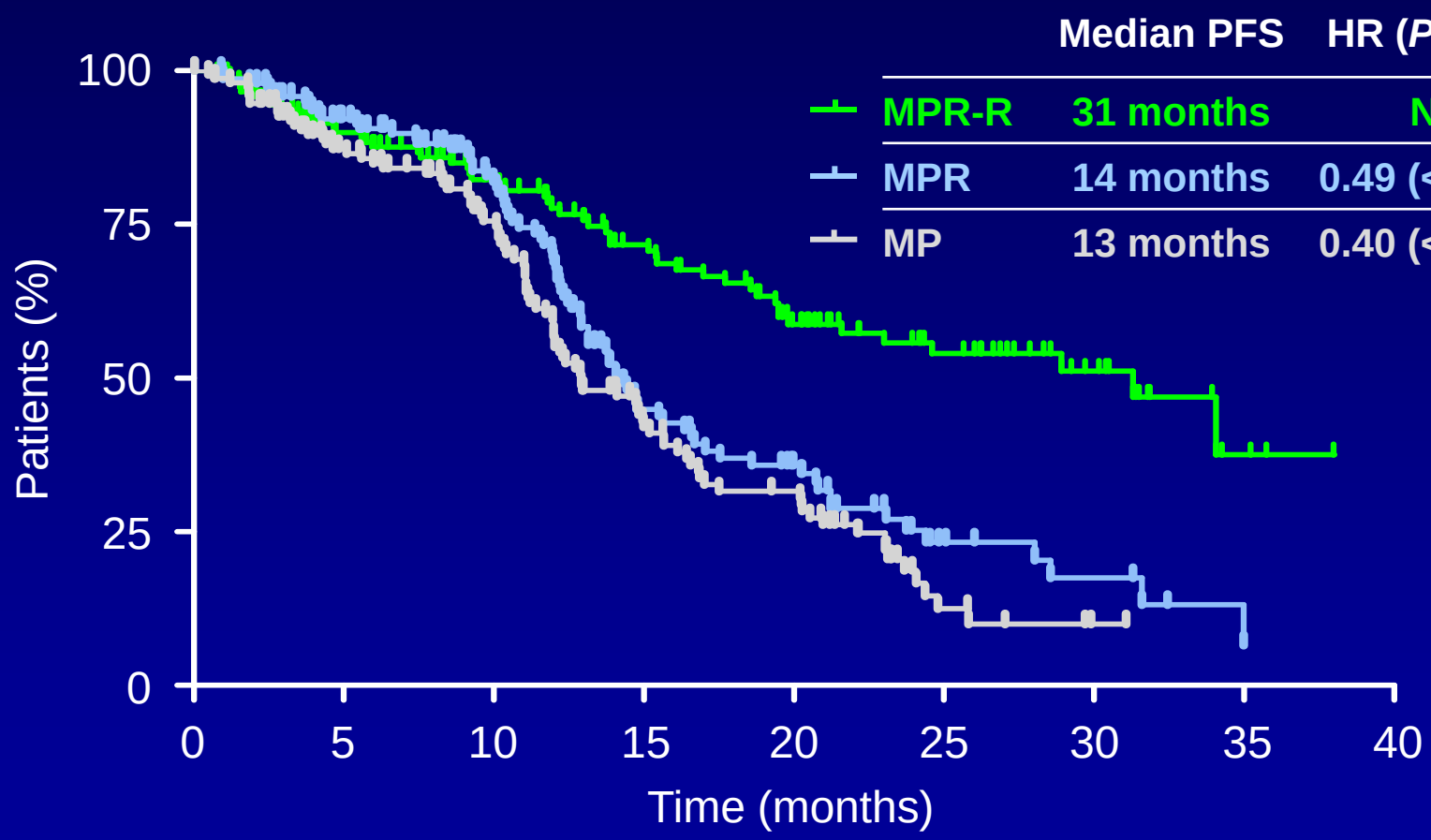
- **Ivan Špička**
- **Univerzita Karlova v Praze**
- **1. lékařská fakulta**
- **I. interní klinika – klinika hematologie 1.LF a VFN**

Možnosti konzolidační a udržovací léčby



MM-015: Progression-Free Survival

- MPR-R significantly extended median PFS vs. MP and MPR



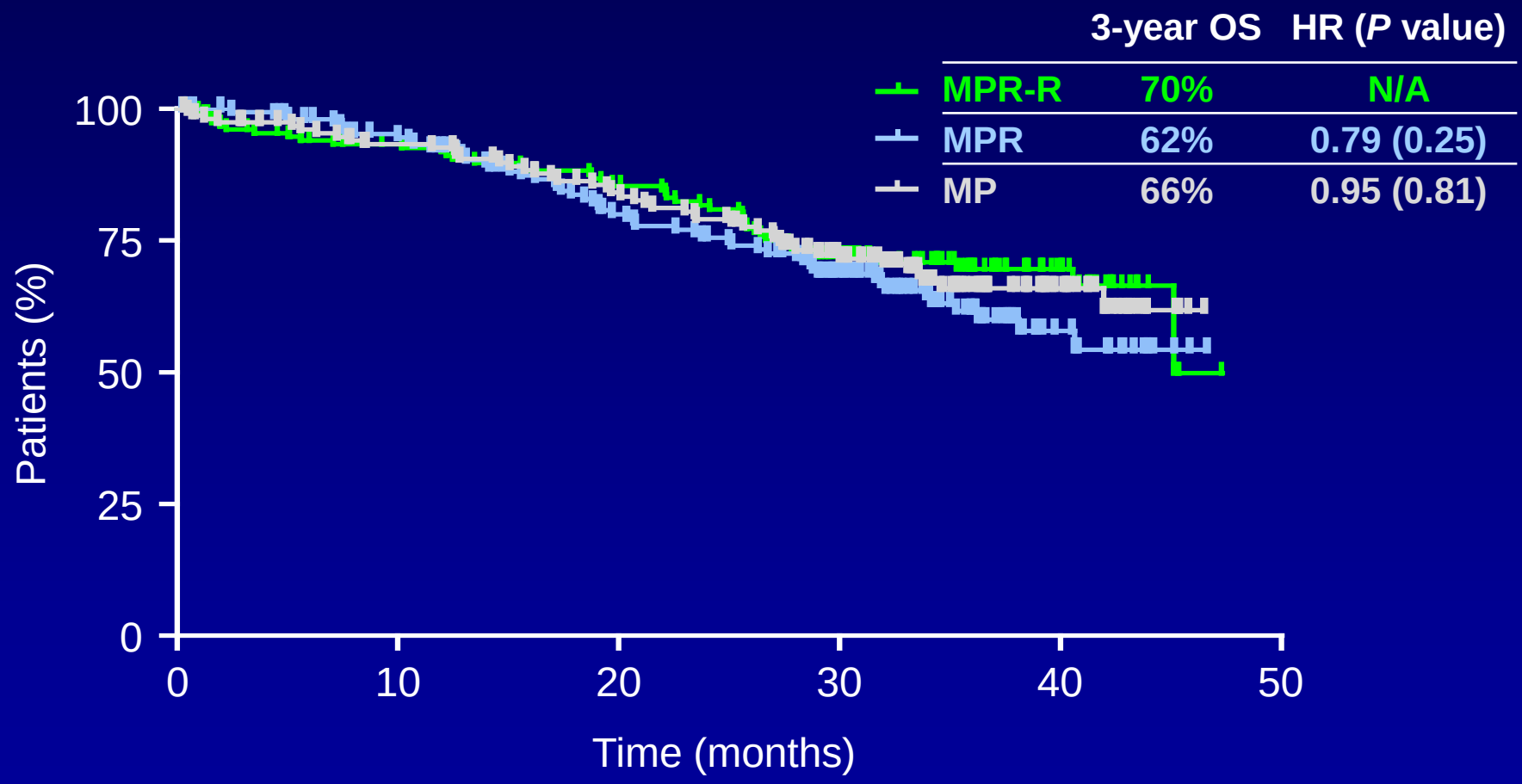
	Median PFS	HR (*P* value)
MPR-R	31 months	N/A
MPR	14 months	0.49 (< 0.001)
MP	13 months	0.40 (< 0.001)

HR: hazard ratio; MP: melphalan-prednisone; MPR: melphalan-prednisone-Lenalidomide; MPR-R: melphalan-prednisone-Lenalidomide followed by Lenalidomide maintenance; N/A: not applicable; PFS: progression-free survival.

Palumbo A. *N Engl J Med*. 2012;366:1759-69.

MM-015: Overall Survival

- After a median follow-up of 30 months, the number of deaths was low (31% event rate) and comparable across all arms



HR: hazard ratio; MP: melphalan-prednisone; MPR: melphalan-prednisone-Lenalidomide; MPR-R: melphalan-prednisone-Lenalidomide followed by Lenalidomide maintenance; N/A: not applicable; OS: overall survival.

Palumbo A. *N Engl J Med*. 2012;366:1759-69.

Lenalidomide Maintenance Therapy

Study details	n	Treatment	Outcome	
IFM 2005-02[1]	307	Lenalidomide	**PFS** 41 months	**5-year OS** 79%
	307	Placebo	24 months $p<10^{-9}$	73%
CALGB 100104[2]	231	Lenalidomide	**TTP** 48 months	**Deaths** n=23
	229	Placebo	30.9 months p<0.0001	n=39

- **Significant improvement in PFS/TTP in both studies**
- **Significant survival advantage in CALGB 100104 study**

[1]Attal et al. Haematologica 2011; 96 (s1): S23; oral presentation at IMW 2011
[2]McCarthy et al. Haematologica 2011; 96 (s1): S23; oral presentation at IMW 2011

2 aktuální otázky pro udržovací léčbu lenalidomidem

- PFS → OS
- SPM
- (Cena, compliance, QoL)

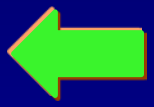
Thalidomide maintenance studies

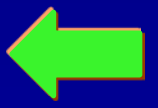
	Significant improvement in PFS with maintenance therapy	Significant improvement in OS with maintenance therapy	Survival after relapse
Spencer	Yes	Yes (3 yrs follow-up)	Similar in all groups
Attal	Yes	Yes (@ 39 m), but OS advantage disappeared with longer follow-up (5.7 yrs)	Similar in all groups
Barlogie	Yes	Yes (7.2 yrs follow-up)	Reduced OS after Thal exposure
Lokhorst	Yes	No	Reduced OS after Thal exposure
Morgan	Yes	No	Reduced OS after Thal exposure
Stewart	Yes	No	Reduced OS after Thal exposure

Spencer A, et al. J Clin Oncol. 2009;27:1788-93. Attal M, et al. Blood. 2006;108:3289-94. Barlogie B, et al. N Engl J Med. 2006;354:1021-30. Barlogie B, et al. Blood. 2008;112:3115-21. Barlogie B, et al. J Clin Oncol. 2010;28:1209-14. Lokhorst HM, et al. Blood. 2010;115:1113-20. Morgan GJ, et al. Blood. 2012;119:7-15. Stewart KA, et al. Blood. 2010;116:[abstract 39].

Lenalidomide maintenance therapy

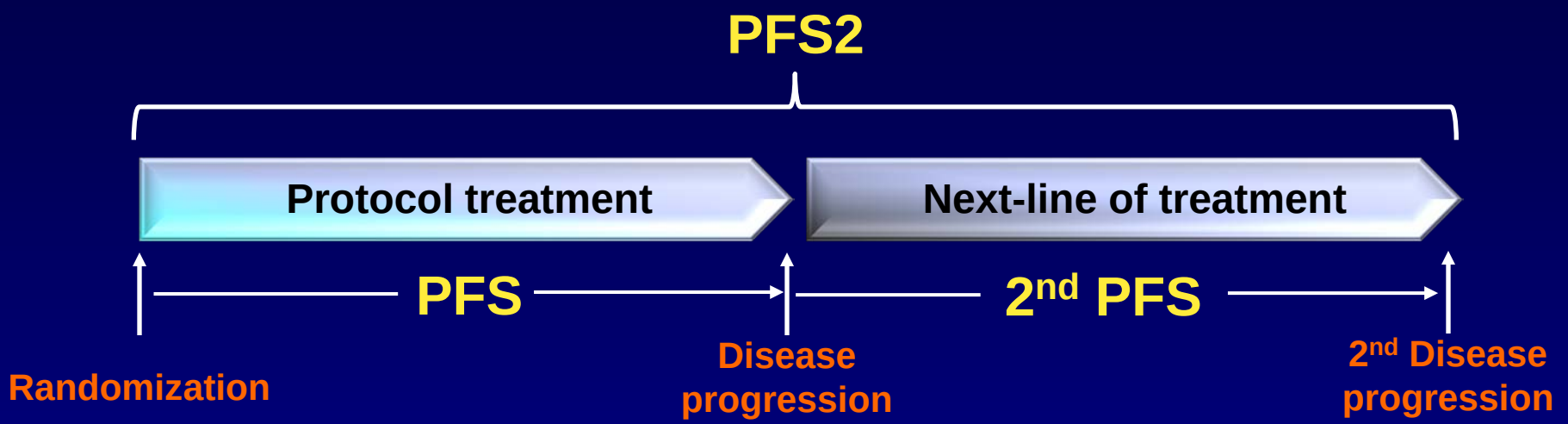
Study details	n	Treatment	Outcome	
IFM 2005-02[1]			PFS	OS
	307	Lenalidomide	46 months	82 months
Median follow-up: 67 months (from random.)	307	Placebo	24 months p<0.001	81 months p=0.8
CALGB 100104[2]			TTP	Deaths
	231	Lenalidomide	50 months	not reached
Median follow-up: 48 months	229	Placebo	27 months p<0.001	73 months p=0.008
GIMEMA[3]			PFS	4-year OS
	198	Lenalidomide	37 months	80%
Median follow-up: 48 months	204	Placebo	26 months p<0.0001	62% p=0.02





[1]Attal et al. ASH 2013 (Abstract 406), oral presentation
[2]McCarthy P. IMW 2013, oral presentation (S15 Consolidation / Maintenance)
[3]Gay et al. ASH 2013 (Abstract 2089), poster presentation

EMA Anticancer Guidance (July 13): PFS2



- Analýza PFS2 byla zavedena EMA[1] se záměrem ukázat, že léčba první linie nevyvolává rezistenci vůči terapii následné.
- PFS2 nelze považovat za náhražku OS.
- Cíl analýzy PFS2 respektuje integritu analýzy ITT – zahrnuje všechny randomizované pacienty

1. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/01/WC500137128.pdf.

PFS: progression-free survival; PFS2: second progression-free survival; Tx: treatment.

Otázky/odpovědi

Znamená prodloužení PFS při udržovací léčba len k prodloužení OS? Neboli – vede tato léčba k selekci rezistentních klonů?

Po ASCT 1x prodl.OS, 1x ne

Bez ASCT – ano

Ještě krátká doba sledování v transplantačních studiích (5-leté přežití u víc než 70% pacientů)

Kombinace ASCT + lenalidomid není dostatečně účinná pro část pac.- tj. v této kombinaci je přínos udržovací léčby malý. Naopak při konveční terapii je udržovací léčba rozhodujícím faktorem OS

Definince druhé PFS přispěje k analýze selekce klonů

Statistické aspekty (USA vs. Evropa)

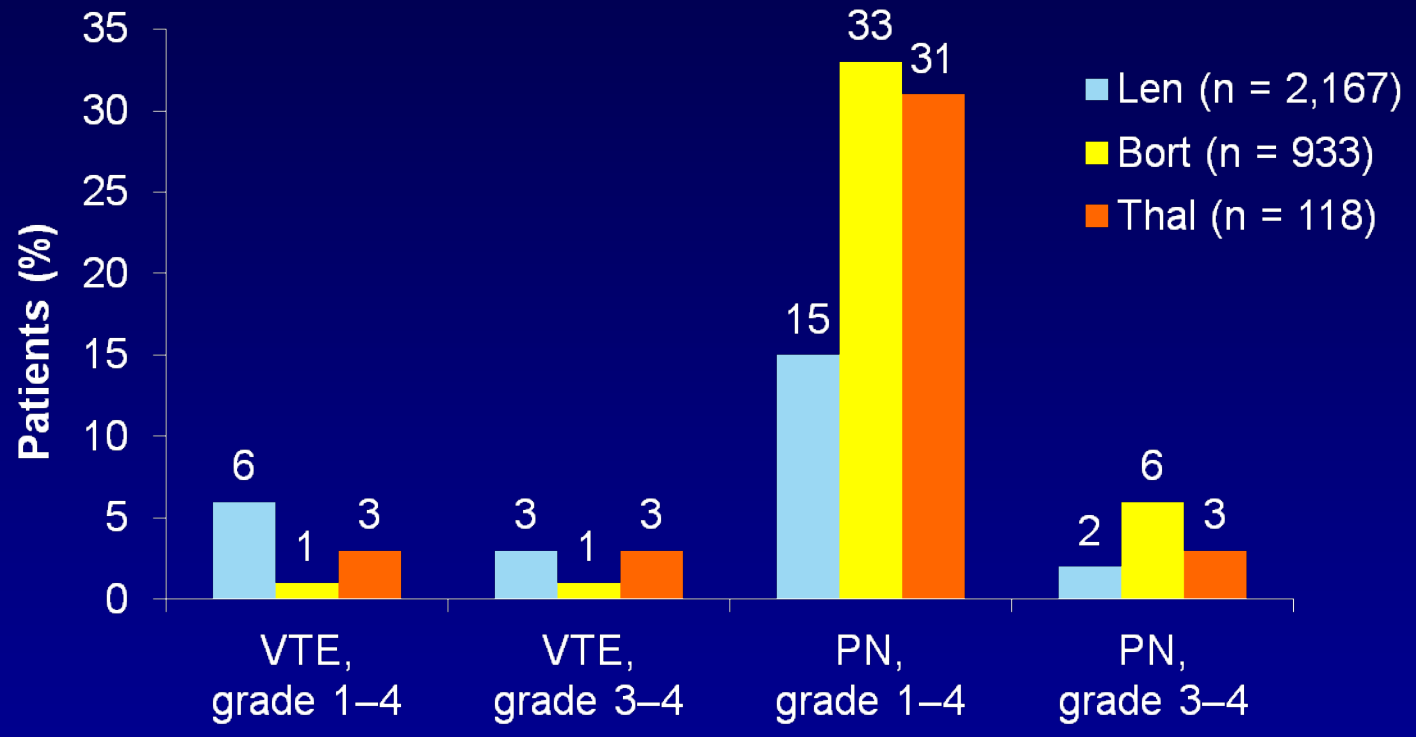
Summary of SPM across the 3 trials (MM-015, IFM 2005-02 and CALGB 100104)

Study	MM-015[1]				IFM 2005-02[2]			CALGB 100104[3]			Combined data from three trials	
	Len induct + main (N = 150)	Len induct (N = 152)	PBO (N = 153)	Total (N = 455)	Len (N = 306)	PBO (N = 302)	Total (N = 608)	Len (N = 231)	PBO (N = 229)	Total (N = 460)	All Len (N = 839)	All PBO (N = 684)
Haematological malignancies (%)	**7 (4.7)**	**5 (3.3)**	**1 (0.7)**	**13 (2.9)**	**13 (4.2)**	**5 (1.7)**	**18 (3.0)**	**8 (3.5)**	**1 (0.4)**	**9 (2.0)**	**33 (3.9)**	**7 (1.0)**
AML/MDS	5	5	1		*5*	*4*		6	0		21 (2.5)	5 (0.7)
ALL‡	1	0	0		*3*	*0*		1	0		5 (0.6)	0
Hodgkin lymphoma	0	0	0		*4*	*0*		1	0		5 (0.6)	0
non-Hodgkin lymphoma	0	0	0		*1*	*1*		0	1		1 (0.1)	2 (0.3)
chronic myelomonocytic leukaemia	1	0	0		0	0		0	0		1 (0.1)	0
Solid tumours (%)	**5 (3.3)**	**4 (2.6)**	**3 (2.0)**	**12 (2.6)**	**10 (3.3)**	**4 (1.3)**	**14 (2.3)**	**10 (4.3)**	**5 (2.2)**	**15 (3.3)**	**29 (3.5)**	**12 (1.8)**
Non-melanoma skin cancers (%)	**NR**	**NR**	**NR**	**NR**	**5 (1.6)**	**3 (1.0)**	**8 (1.3)**	**4 (1.7)**	**3 (1.3)**	**7 (1.5)**	**9 (1.1)**	**6 (0.9)**
Total (%)	**12 (8.0)**	**9 (5.9)**	**4 (2.6)**	**25 (5.5)**	**26* (8.5)**	**11** (3.6)**	**37 (6.1)**	**22 (9.5)**	**9 (3.9)**	**31 (6.7)**		

‡ Includes 1 T-ALL in MM-015 and 4 B-ALL in IFM 2005-02 and CALGB 100104
*26 patients and 32 second primary malignancies in the lenalidomide group.
**11 patients and 12 second primary malignancies reported in the placebo group.

NR = not reported.

EU-PASS: Incidence of Peripheral Neuropathy and Venous Thrombotic Events



- Only 6% of patients with baseline PN reported this AE while receiving Lenalidomide, despite 36.5% of Lenalidomide patients having PN at baseline
- Rates of newly occurring PN in Lenalidomide, bortezomib, and thalidomide groups were 9%, 25% and 25%, respectively

PN, peripheral neuropathy;
VTE, venous thrombotic event.

Cavo M, et al. *Haematologica.* 2013;98:[abstract 792]; poster presentation.

EU-PASS: Second Primary Malignancies

SPM characterization	Len (n = 2,167)	Bort (n = 933)	Thal (n = 118)	Overall[a] (N = 3,345)
Patients with ≥ 1 SPM (invasive and non-invasive), n (%)	44[b] (2.03)	10 (1.07)	1 (0.85)	55 (1.64)
Incidence/100 patient-years, (95% CI)	2.63 (1.95–3.53)	3.03 (1.63–5.64)	1.59 (0.22–11.26)	2.60 (1.99–3.38)
Invasive SPM (haematological or solid tumour) n, (%)	30 (1.38)	10 (1.07)	1 (0.85)	41 (1.23)
Incidence/100 patient-years, (95% CI)	1.79 (1.25–2.56)	3.03 (1.63–5.64)	1.59 (0.22–11.26)	1.94 (1.42–2.63)
Haematological, n (%)	9 (0.42)	3 (0.32)	0	12 (0.36)
Incidence/100 patient-years, (95% CI)	0.54 (0.28–1.03)	0.91 (0.29–2.84)	0	0.57 (0.32–1.00)
Solid tumour, n (%)	21 (0.97)	7 (0.75)	1 (0.85)	29 (0.87)
Incidence/100 patient-years, (95% CI)	1.25 (0.82–1.92)	2.13 (1.02–4.47)	1.59 (0.22–11.26)	1.37 (0.95–1.97)
Non-invasive SPM (NMSC), n (%)	15 (0.69)	0	0	15 (0.45)
Incidence/100 patient-years, (95% CI)	0.89 (0.54–1.48)	–	–	0.71 (0.43–1.17)

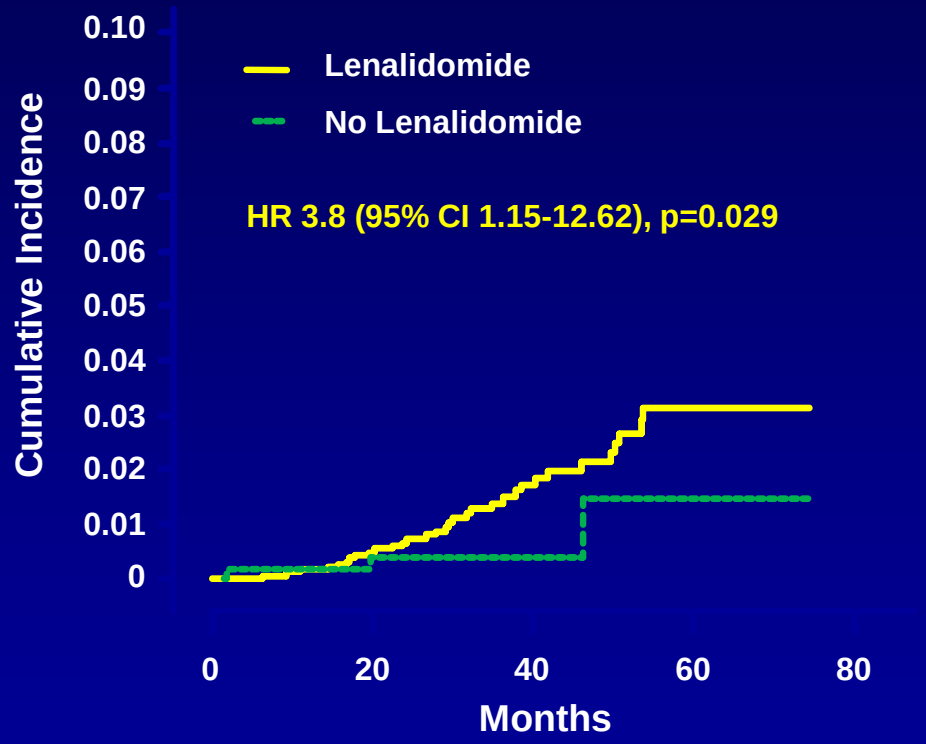
- 55 patients had an SPM; overall SPM incidence rate was 2.60 per 100 patient-years (95% CI, 1.99–3.38)
- Invasive SPM incidence rate was 1.94 per 100 patient-years (95% CI, 1.42–2.63) and was comparable across the cohorts

[a] Includes 127 patients who commenced other therapies or had missing data.
[b] One patient receiving Len developed melanoma and non-melanoma skin cancer.
NMSC, non-melanoma skin cancer; SPM, second primary malignancy.

Cavo M, et al. *Haematologica.* 2013;98:[abstract 792]; poster presentation.

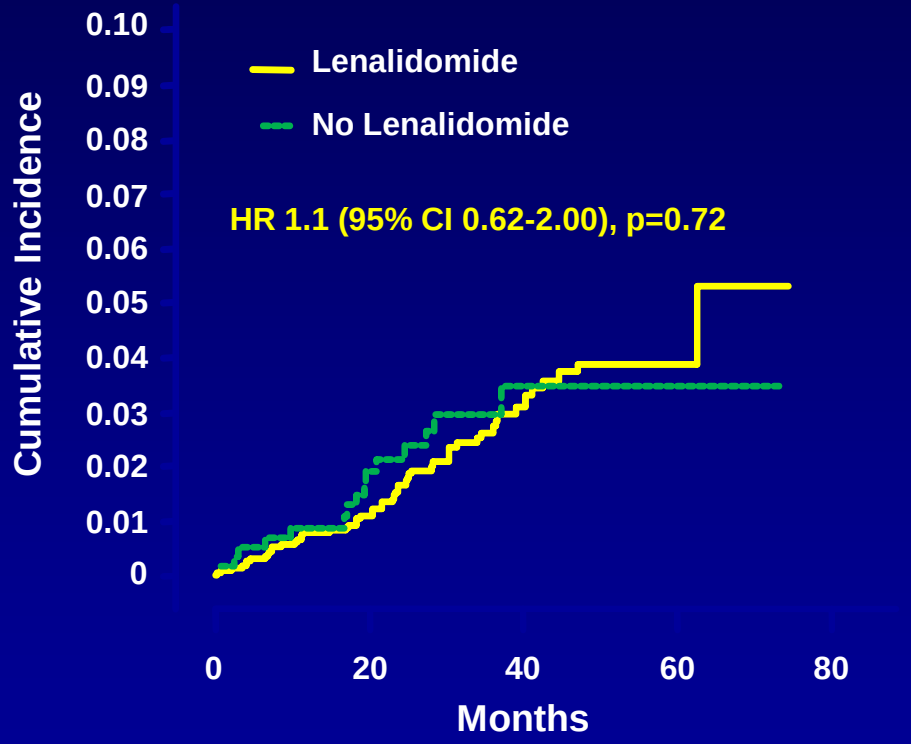
Cumulative incidence of SPMs

Hematologic SPMs



Cumulative incidence (95% CI)	36 months	60 months
Lenalidomide	1.4 (0.8 - 2.0)	3.1 (1.9 - 4.3)
No Lenalidomide	0.4 (0.0 - 0.9)	1.4 (0.0 - 3.6)

Solid SPMs



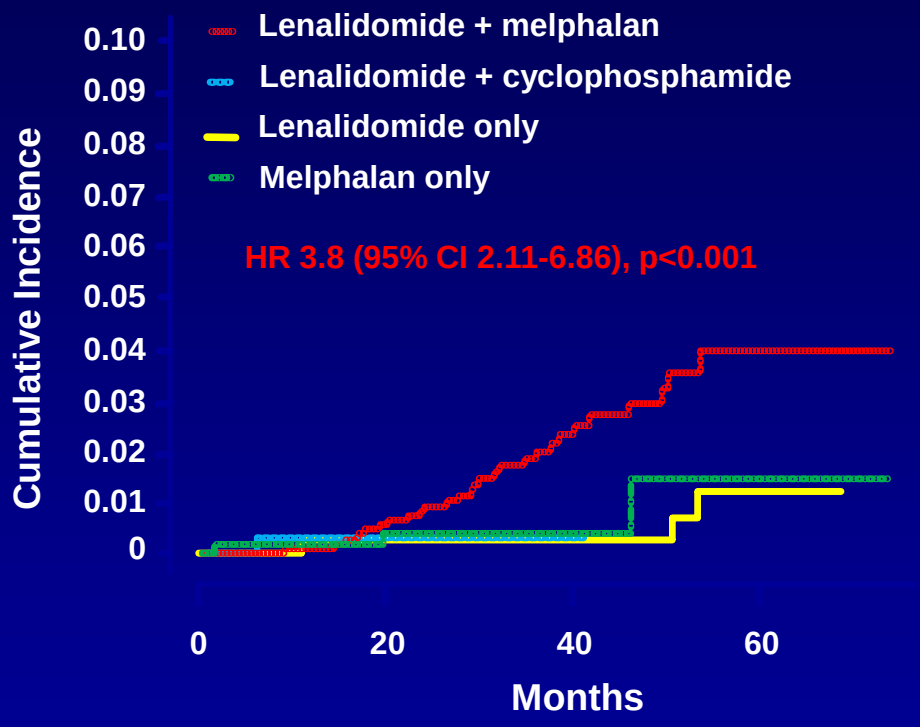
Cumulative incidence (95% CI)	36 months	60 months
Lenalidomide	2.6 (1.8 - 3.3)	3.8 (2.7 - 4.9)
No Lenalidomide	2.9 (1.4 - 4.4)	3.4 (1.6 - 5.2)

Palumbo, ASCO 2013: SECOND PRIMARY MALIGNANCIES IN NDMM TREATED WITH LENALIDOMIDE: META-ANALYSIS OF 6383 PATIENTS

Cumulative incidence of SPMs

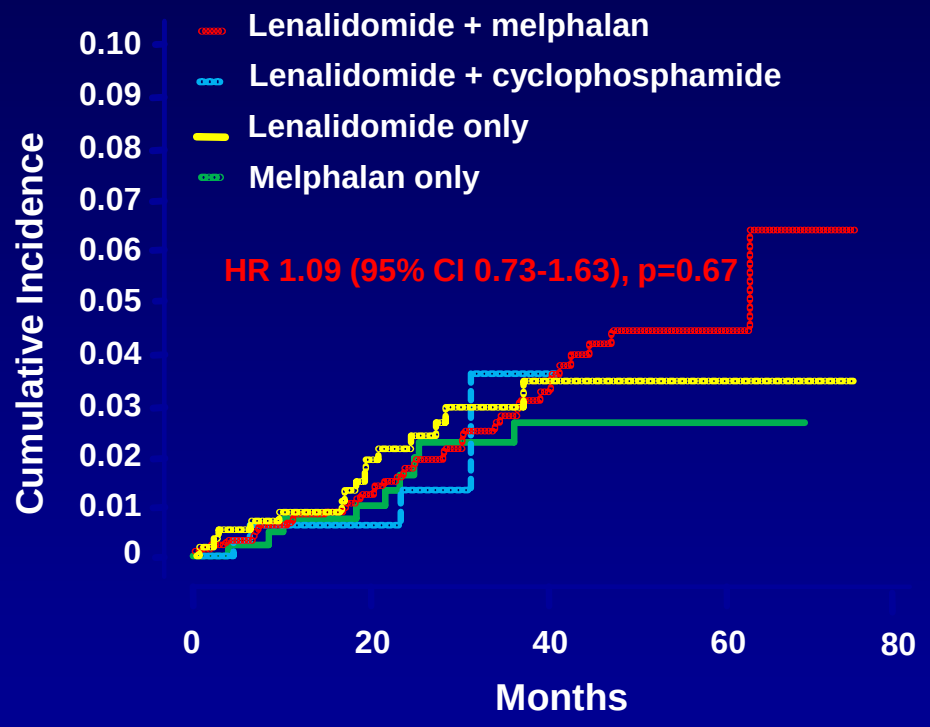
Different lenalidomide combinations

Hematologic SPMs



Cumulative incidence (95% CI)	36 months	60 months
Lenalidomide + melphalan	1.8 (1.0-2.6)	3.9 (2.3-5.5)
Lenalidomide + cyclophosphamide	0.3 (0.0-0.09)	-
Lenalidomide only	0.3 (0.0-0.07)	1.3 (0.0-2.7)
Melphalan only	0.4 (0.0-0.09)	1.4 (0.0-3.6)

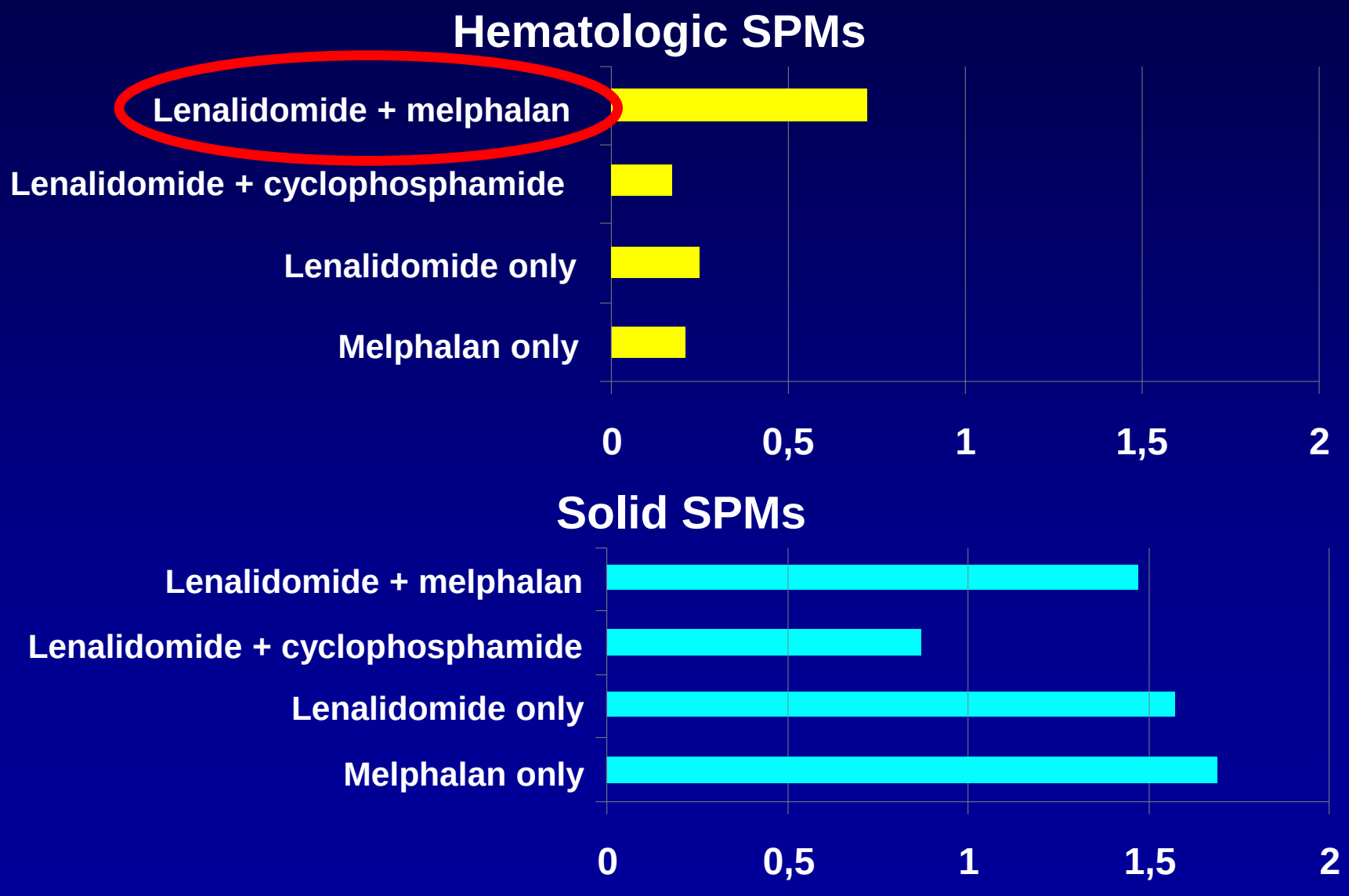
Solid SPMs



Cumulative incidence (95% CI)	36 months	60 months
Lenalidomide + melphalan	2.7 (1.8-3.7)	4.4 (2.9-5.8)
Lenalidomide + cyclophosphamide	3.5 (0.0-8.3)	-
Lenalidomide only	2.2 (0.7-3.7)	2.6 (0.9-4.3)
Melphalan only	2.9 (1.4-4.4)	3.4 (1.6-5.2)

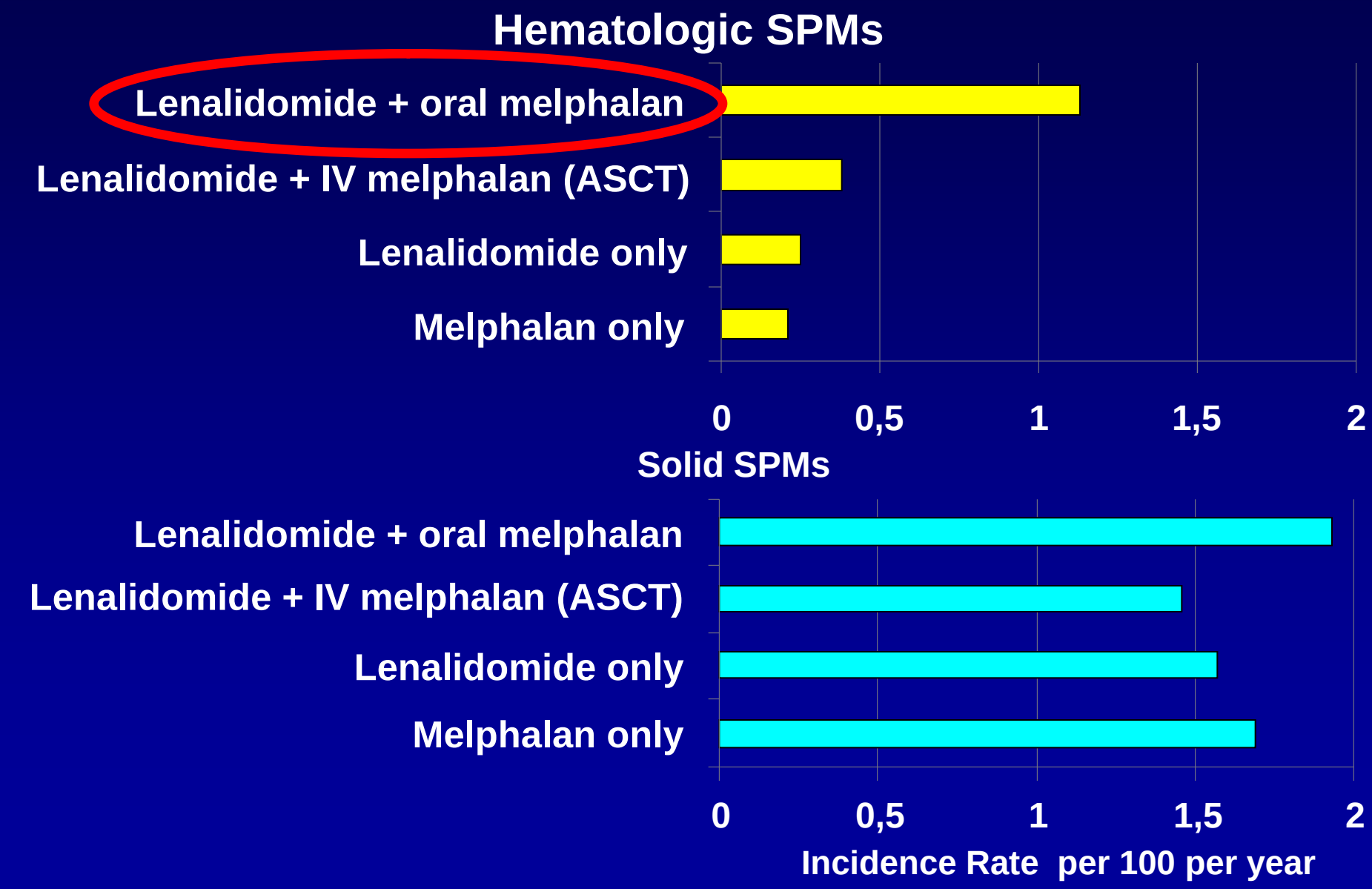
Incidence rate per 100 per year

Different lenalidomide combinations



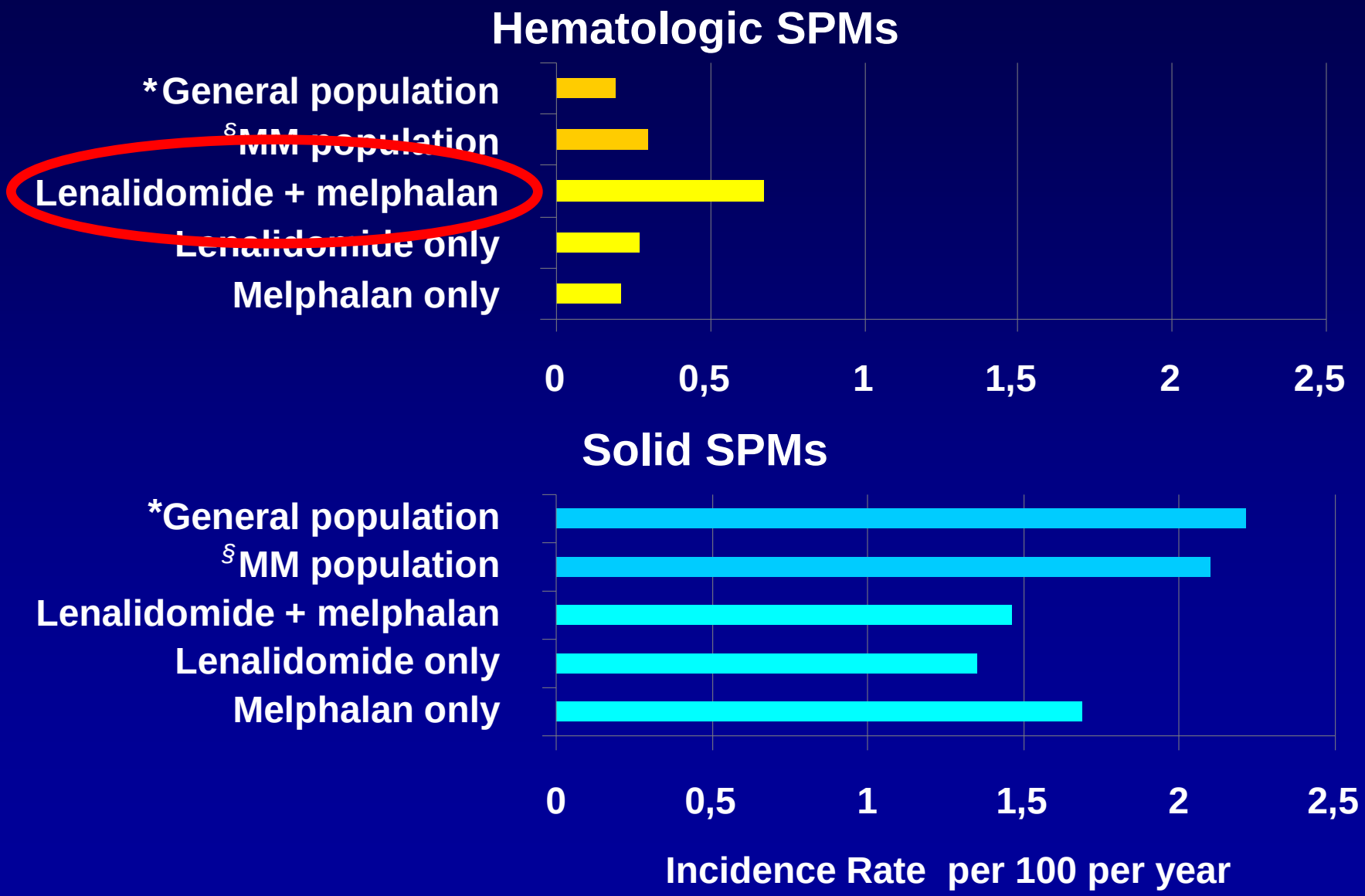
Incidence rate per 100 per year

Oral *versus* high-dose intravenous melphalan



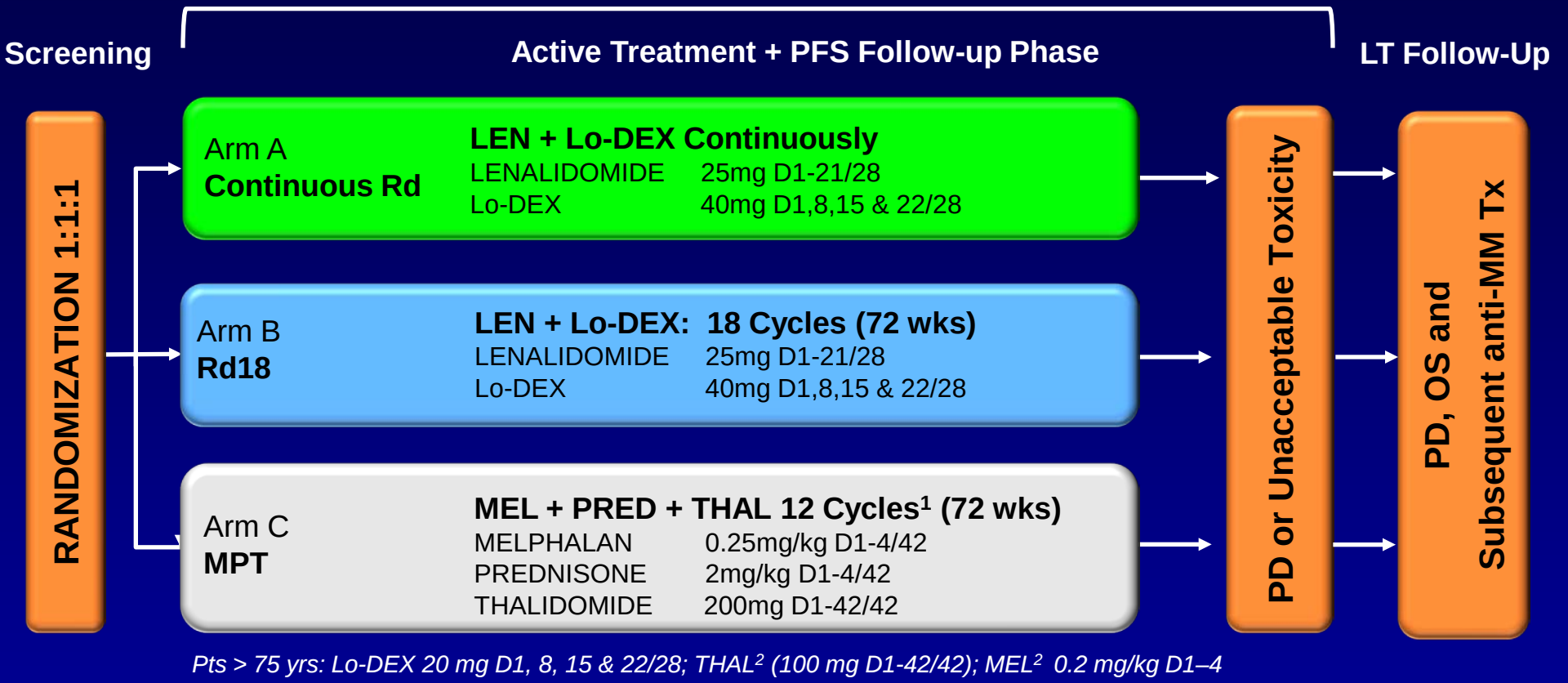
Summary SPMs - 1

Incidence rate per 100 per year



** Mailankody et al., 2011; § Chakraborty et al., 2012*

FIRST Trial: Study Design



Pts > 75 yrs: Lo-DEX 20 mg D1, 8, 15 & 22/28; THAL[2] (100 mg D1-42/42); MEL[2] 0.2 mg/kg D1–4

- Stratification: age, country and ISS stage

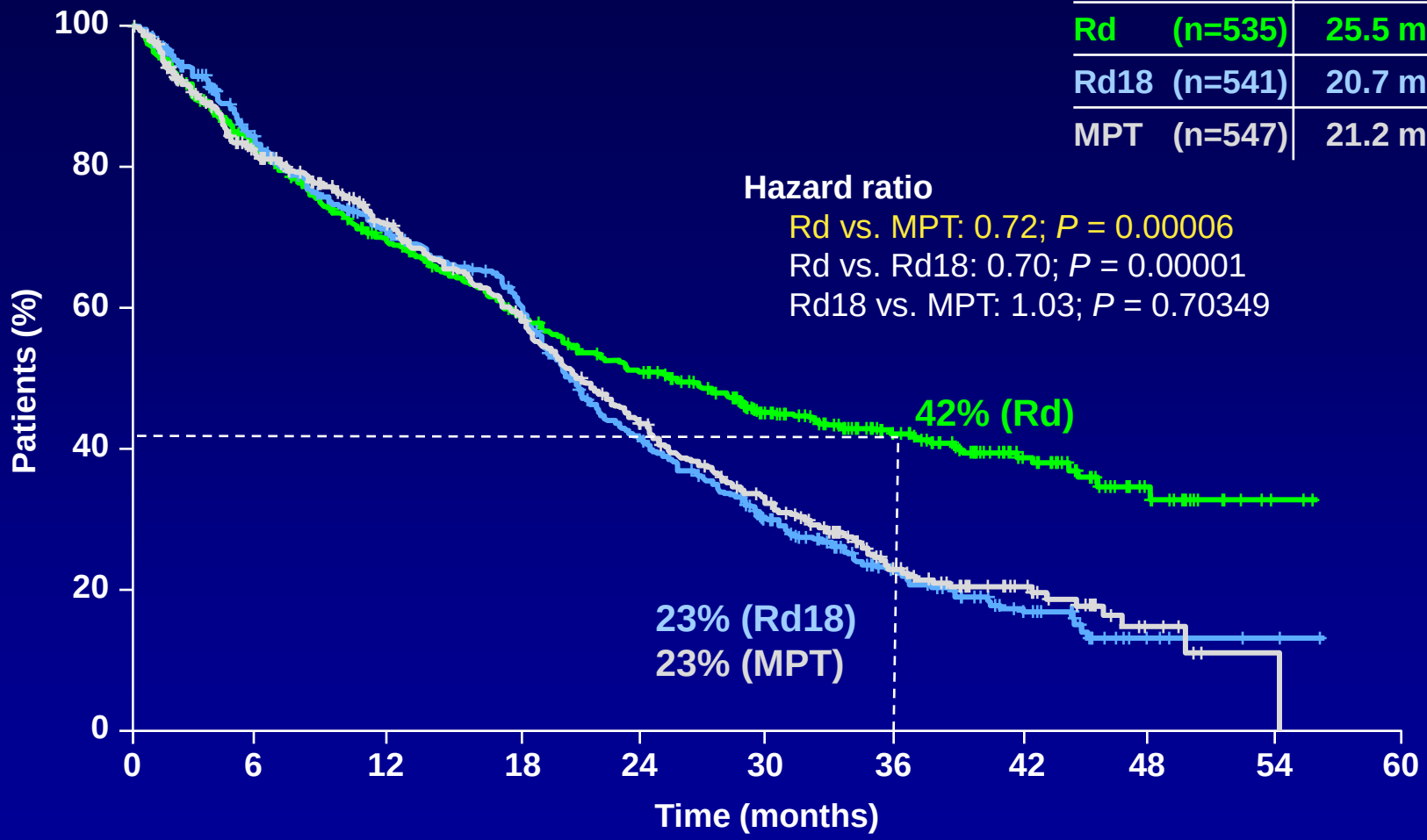
ISS, International Staging System; LT, long-term; PD, progressive disease; OS, overall survival

[1]Facon T, et al. Lancet 2007;370:1209-18; [2]Hulin C, et al. JCO. 2009;27:3664-70.

Facon T, et al. Blood. 2013;122:abstract 2.

FIRST Trial: Final Progression-free Survival

		Median PFS
Rd	(n=535)	25.5 mos
Rd18	(n=541)	20.7 mos
MPT	(n=547)	21.2 mos



Rd	535	400	319	265	218	168	105	55	19	2	0
Rd18	541	391	319	265	167	108	56	30	7	2	0
MPT	547	380	304	244	170	116	58	28	6	1	0

mos, months; MPT, melphalan, prednisolone, thalidomide; PFS, progression-free survival; Rd, lenalidomide plus low-dose dexamethasone.

Facon T, et al. Blood. 2013;122:abstract 2.

FIRST Trial: Second Primary Malignancy

	Continuous Rd (n=532)	Rd 18 (n=540)	MPT (n=541)
Hematological malignancies, n (%)	**2 (0.4)**	**2 (0.4)**	**12 (2.2)**
AML	1 (0.2)	1 (0.2)	4 (0.7)
MDS	1 (0.2)	1 (0.2)	6 (1.1)
MDS to AML	0 (0.0)	0 (0.0)	2 (0.4)
B-cell	0 (0.0)	0 (0.0)	0 (0.0)
Solid tumors, n (%)	**15 (2.8)**	**29 (5.4)**	**15 (2.8)**
Invasive SPM, n (%)	**17 (3.2)**	**30 (5.6)**	**27 (5.0)**
Patients with ≥ 1 NMSC (non-invasive), n (%)	22 (4.1)	17 (3.1)	21 (3.9)
Total patients with SPM, n (%)	**37 (7.0)**	**44 (8.1)**	**47 (8.7)**

AML, acute myeloid leukemia; MDS, myelodysplastic syndromes; MPT, melphalan, prednisolone, thalidomide; NMSC; nonmelanoma skin cancer; Rd, lenalidomide plus low-dose dexamethasone; SPM, second primary malignancy.

Facon T, et al. Blood. 2013;122:abstract 2.

FIRST Trial: Závěry

- Kontinuální th.Rd signifikantně prodloužila PFS, a zlepšila OS vs. MPT
  - PFS:
    - HR= 0.72 (*P*= 0.00006)
    - Konzistentní benefit ve většině podskupin
    - Rd lepší než Rd18 (HR= 0.70, *P*= 0.00001)
    - 3 yr PFS: 42% Rd vs 23% Rd18 a MPT
  - Plánovaná interim analýza OS: HR= 0.78 (*P*= 0.0168)
  - Rd režim byl lepší než MPT ve všech dalších sekundárních parametrech účinnosti

- Bezpečnostní profil kontinuálního Rd byl uspokojivý
  - Hematologické a ne-hematologické AEs byly očekávatelné pro Rd a MPT
  - Incidence hematologických SPM byla nižší u kontinuálního Rd vs. MPT

- U NDMM pacientů nevhodných k ASCT **FIRST Trial** ustanovil kontinuální Rd za nový léčebný standard

Facon T, et al. Blood. 2013;122:abstract 2.

Otázky / výzvy

- Konzolidace vs maintenance nebo obě?
- Všichni pacienti?
  - MRD-based post-ASCT strategie?
  - High-risk choroba?
- Doba trvání léčby
  - Tolerabilita
  - Vznik rezistentních klonů
  - Progóza při relapsu/relapsech?
- Vliv na QoL
  - Délka treatment-free intervalu (TFI) je spojena s lepším QoL*
- Compliance (pacient,systém, cena)

**Acaster et al. Support Care Cancer 2013;21(2):599-607*

Místo rozloučení a děkování: Lenalidomide Related Diarrhea Correlates With Survival In Multiple Myeloma

Beth Faiman, Surbhi Sidana,Paul Elson et al.

- In multivariable analyses, development of LRD (HR 0.46, 95% C.I. 0.21-1.00, p=0.05) was associated with improved OS as were the number of prior therapies (0-2, vs >2, HR 0.16, 95% C.I. 0.08-0.32, p<0.0001) and no use of antineoplastic therapy other than corticosteroids during len therapy (HR 0.52, 95% C.I. 0.29-0.93, p=0.03), while age and prior ASCT (p=0.52 and 0.49, respectively) were not.

Blood 2013 122:5397