XI. Workshop Mnohočetný myelom

Doporučené léčebné strategie v roce 2013

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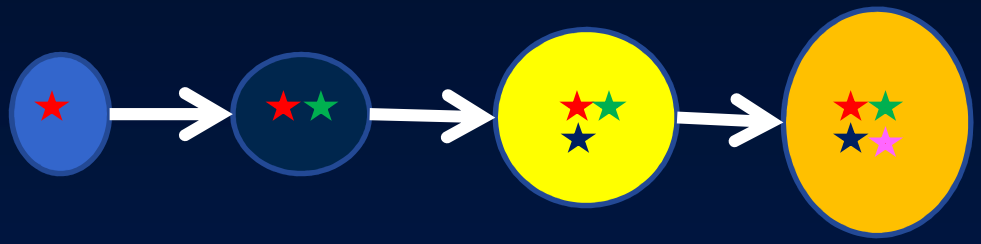
Mikulov, 27. dubna 2013

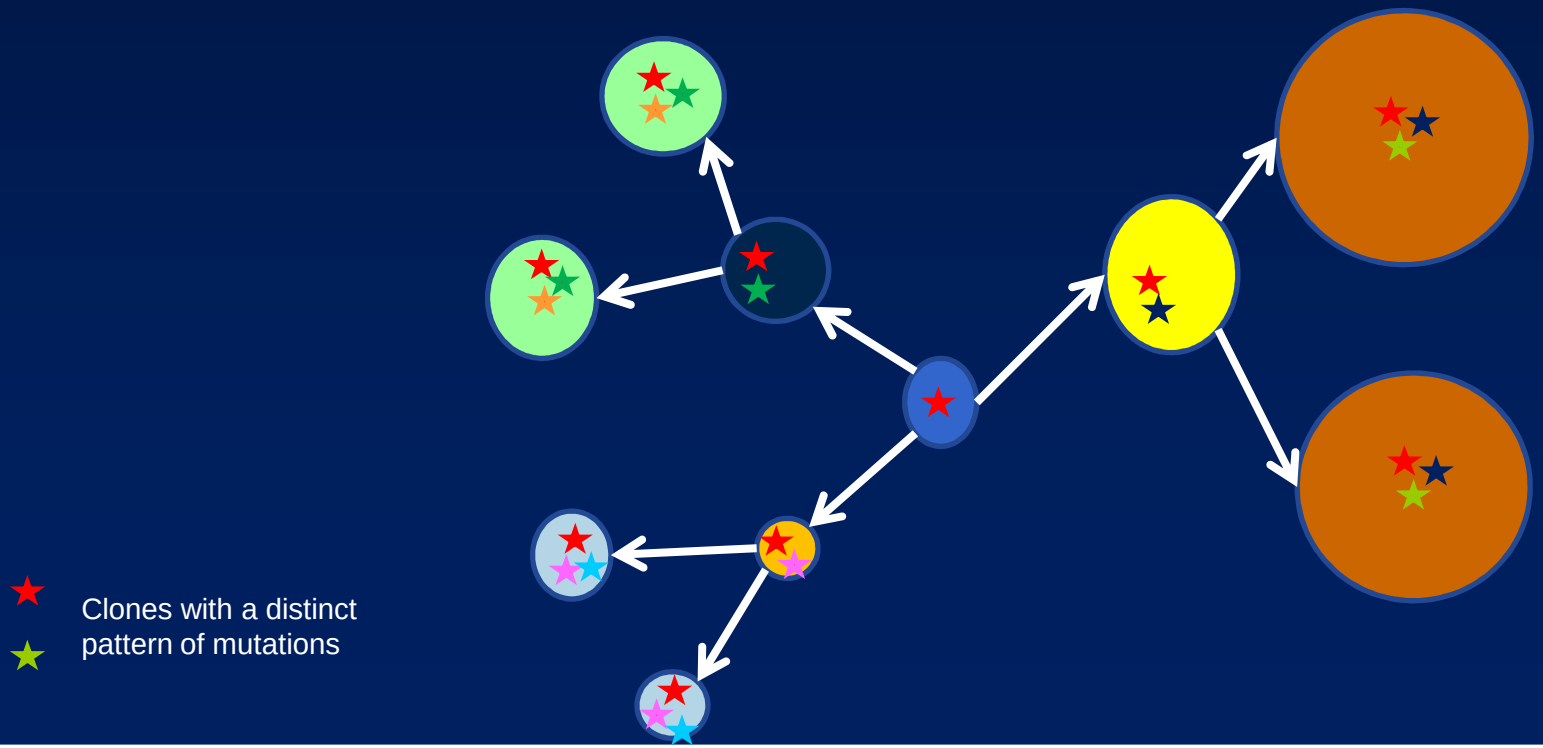
Modely vývoje myelomových klonů

a. **Linear aquisition of genetic change**

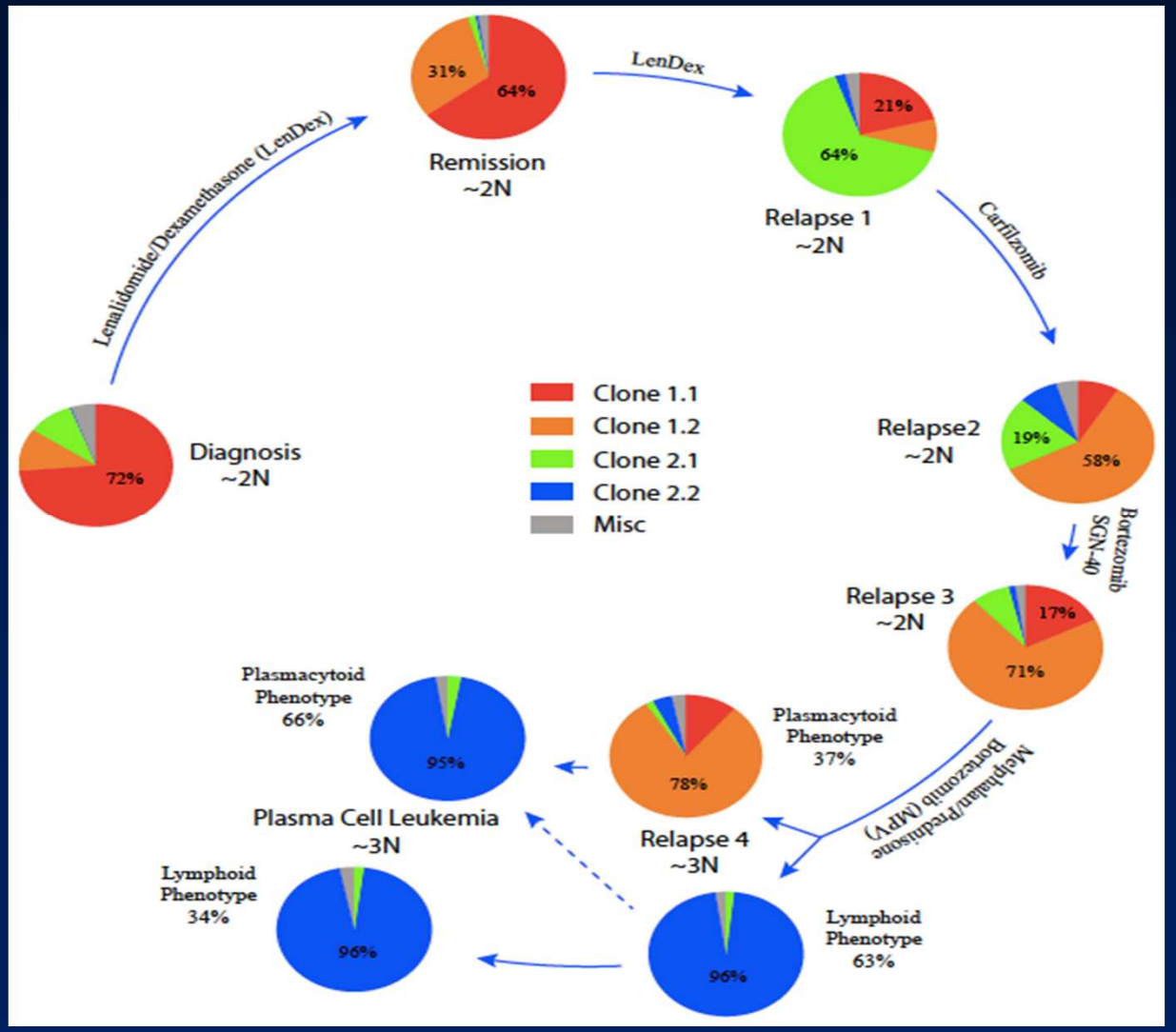


Clonal succession and selective sweeps driving homogeneity

b. **Branching evolutionary aquisition of change**



Dynamika klonálního vývoje v průběhu opakovaných relapsů - příklad t(4;14)

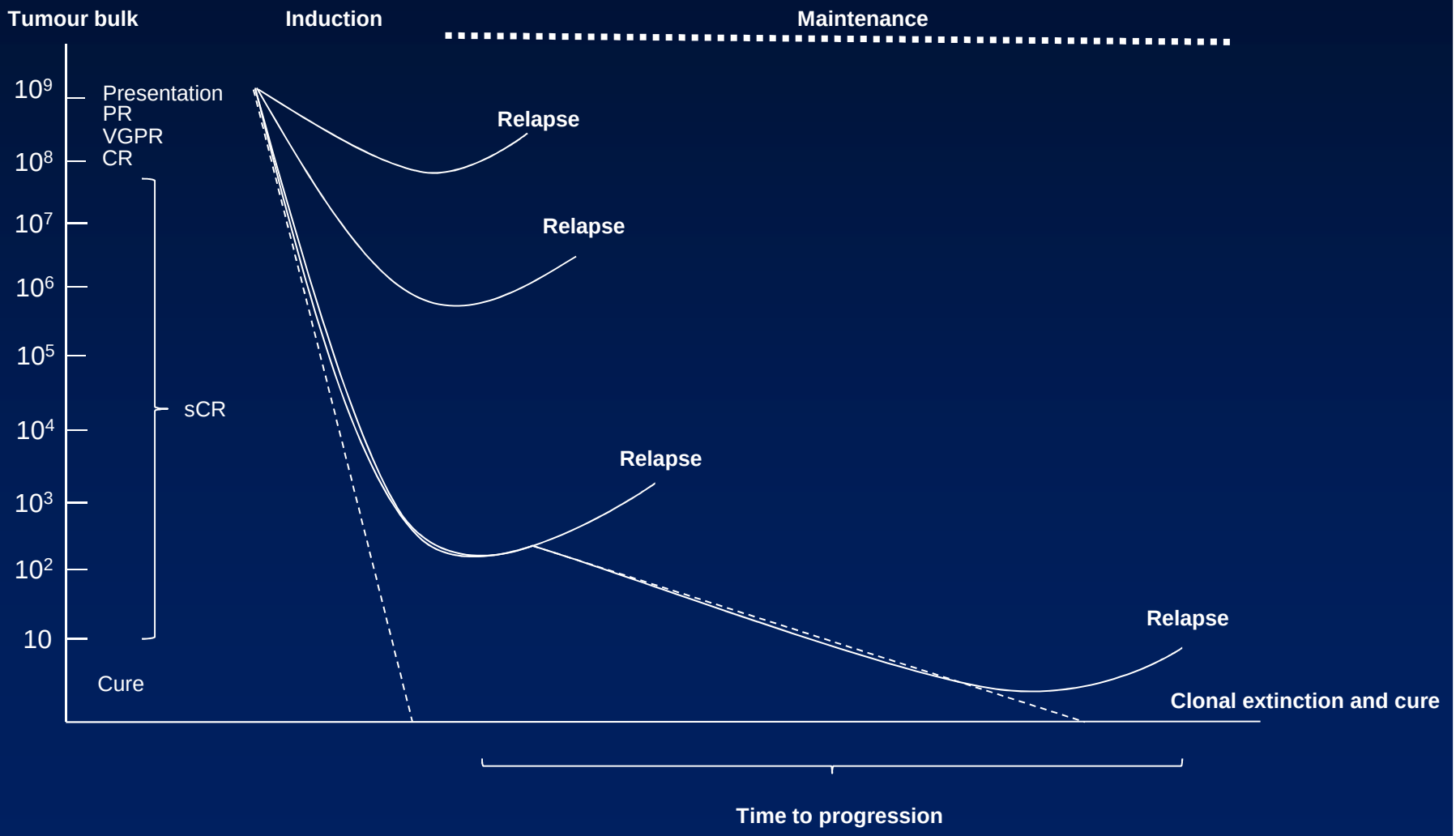


Keats JJ, et al. Blood. 2012;120:1067-76.

Cíl současné léčebné strategie

Cíl současné léčebné strategie

⇒ již ne pouze CR, ale nově iCR = imunofenotypová CR !



1.

Jak reaguje naše léčebná strategie na znalost o možnosti několika klonů u nemocných s MM při stanovení dg.?

Měli bychom dát to nejúčinnější, co máme, hned na začátku = ale to dnes umožňují jen některé klinické studie

Paradox „STOP rules“ v ČR

„Léčba určitým novým lékem je dnes nutné ukončit, pokud po 4. cyklu kombinované léčby nedojde alespoň k parciální remisi, nebo kdykoliv v případě progrese onemocnění.“

= tedy v podstatě při rezistenci klonu na daný lék máme dnes zkusit jiný !

2.

Jak reaguje naše léčebná strategie na znalost o prognostickém riziku?

Nijak!

Zatím jde o informaci pro nemocného a jeho rodinu jakým směrem se onemocnění asi bude ubírat

x „tailoring therapy“ 0

Impact of bortezomib on outcome in pts with high-risk cytogenetics: Results from 3 European trials

	Vel-based regimens	Non Vel-based regimens	*P*
Median PFS			
Overall	**41.5 mos**	**33 mos**	**< 0.001**
Pts with high-risk cytogenetics	**32 mos**	**22 mos**	**< 0.001**
Pts without high-risk cytogenetics	**47 mos**	**38 mos**	**0.01**
Pts with t(4;14), but no del17p	**36 mos**	**24 mos**	**0.001**
Pts with del17p, but no t(4;14)	**27 mos**	**19 mos**	**0.014**

Benefit for standard-risk group and overall population is greater than for high-risk group

Cavo et al. ASH 2012 (Abstract 749), oral presentation

3.

Potřebujeme autologní transplantaci?

ANO!

A první srovnávací studie naznačují, že nové léky ji nemají potenciál nahradit x běží další studie

Cyclophosphamide-Lenalidomide-Dexamethasone vs Autologous transplant in newly diagnosed myeloma: a Phase III trial

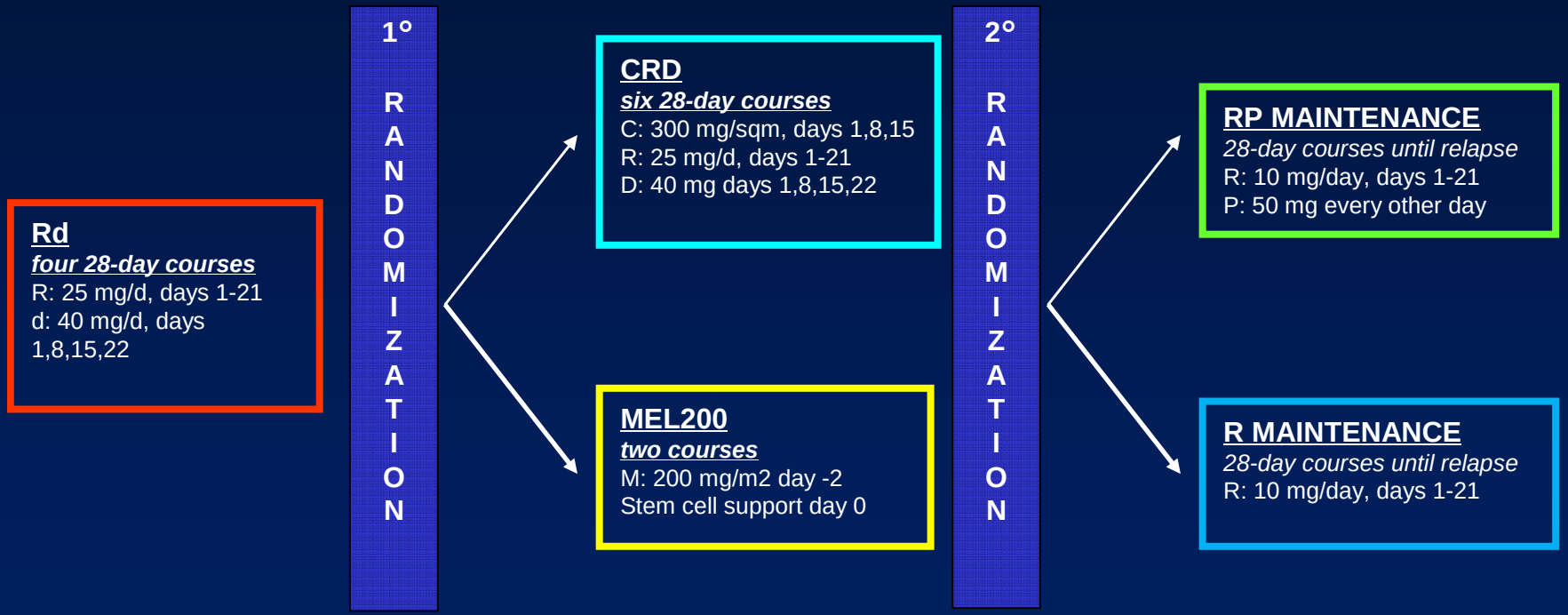
Gay F,1 Hajek R,2 Di Raimondo F,3 Genuardi M,1 Krejci M,2 Falcone A,3 Catalano L,3 Levi A,3 Pika T,4 Ciccone G,5 Offidani M,3 Liberati M,3 Carella A,3 Maisnar V,6 Rocci A,3 Caravita T,3 Montefusco V,3 Ria R,3 Pulini S,3 Stocchi R,3 Conticello C,3 Petrucci M,3 Spencer A,6 Palumbo A1

1 Myeloma Unit, Division of Hematology, University of Torino, 2 Czech myeloma Group, 3 Italian Multiple Myeloma Network, GIMEMA , 4 3rd Department of Internal Medicine, University of Hospital Olomouk, Olomouk, 5Tumor Epidemiology Unit, Citta della Salute e della Scienza, Torino, 6 Department of Medicine - Hematology, Charles University Faculty Hospital, Hradec Kralove, 7 Department of Clinical Haematology, The Alfred Hospital, Monash University, Melbourne

EMN
Trialist Group

Treatment schedule

- 389 patients (younger than 65 years) randomized from 59 centers
- Patients: Symptomatic disease, organ damage, measurable disease



R, lenalidomide; D, dexamethasone; C, cyclophosphamide; P, prednisone; MEL200, melphalan 200 mg/m^2

Patient Characteristics

	CRD (N=194)	MEL200 (N=195)
Age (median)	57	57
≥ 60 y	36%	37%
ISS Stage I/II/III	43%/ 38%/ 19%	44%/ 38%/ 17%
Chromosomal Abnormalities		
t(4;14)	23%	16%
t(14;16)	7%	13%
del17	10%	8%

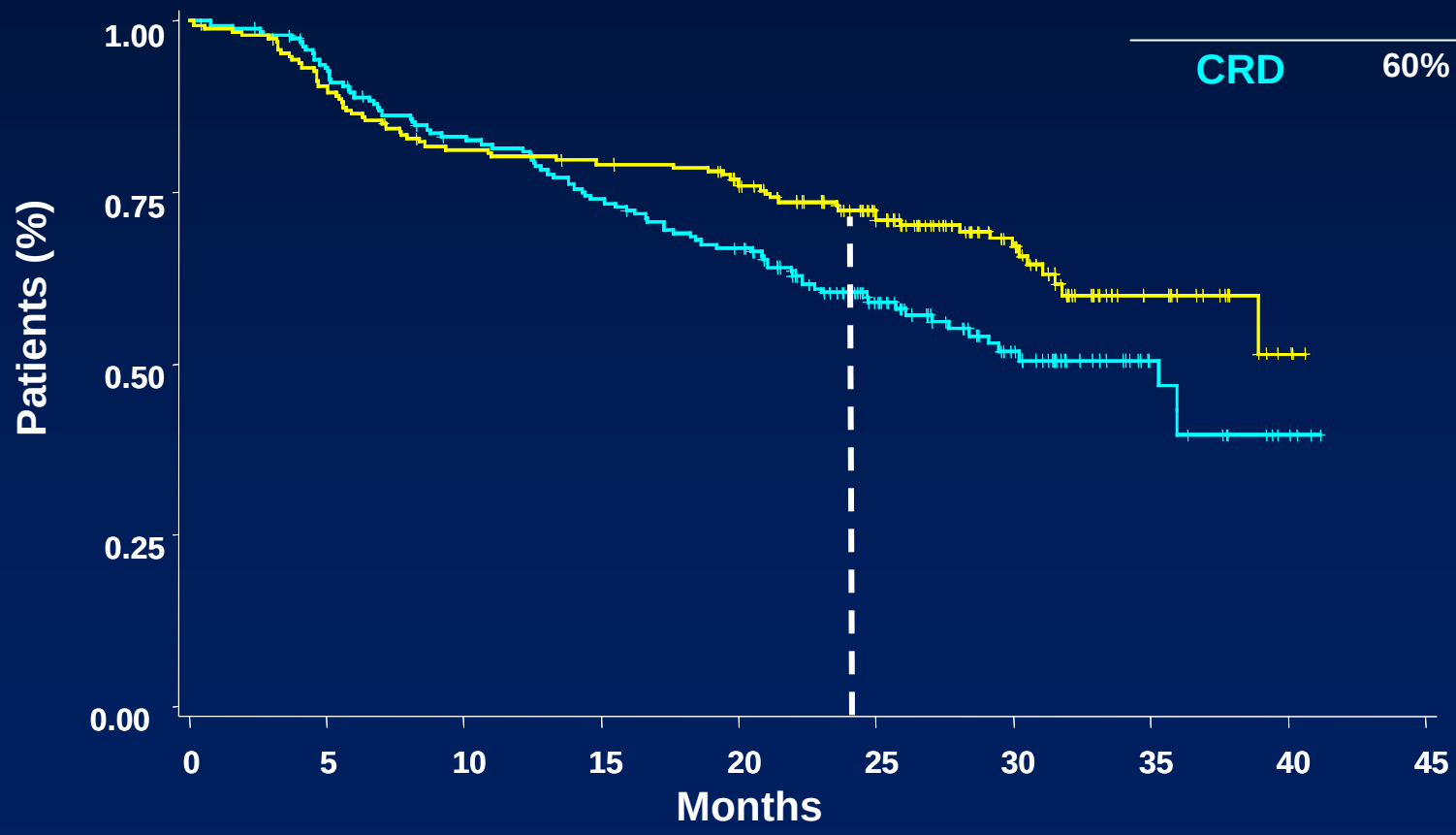
CRD, cyclophosphamide-lenalidomide-dexamethasone; MEL200, melphalan 200 mg/m^2; ISS, International Staging System;

Progression Free Survival

32% Reduced Risk of Progression

Median follow-up 28 months

	2-years PFS	Median PFS
MEL200	73%	Not reached
CRD	60%	35 months



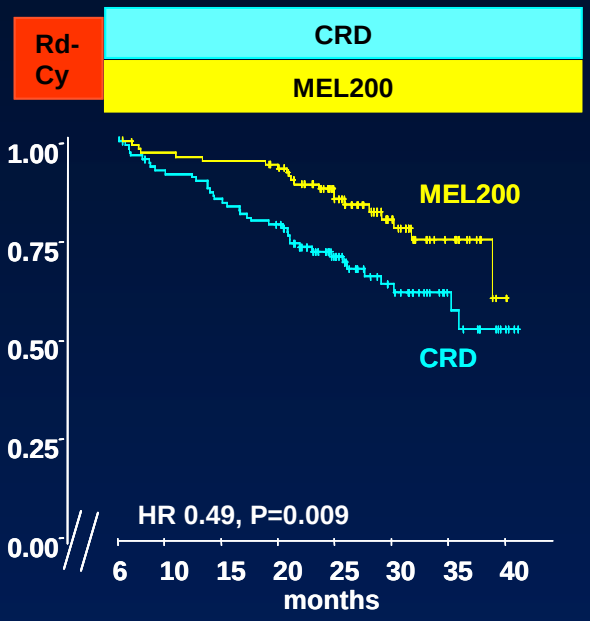
HR 0.68

P = 0.02

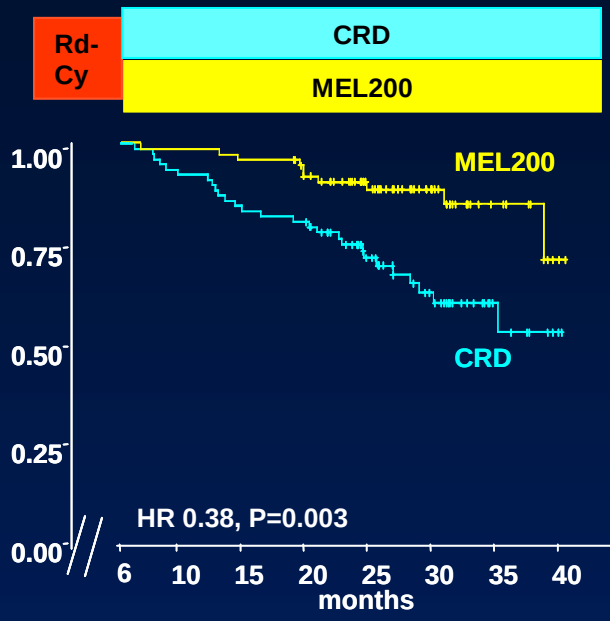
CRD, Cyclophosphamide-lenalidomide-dexamethasone; MEL200, melphalan 200 mg/m^2; PFS, progression free survival; HR, hazard ratio

PFS: subgroup analysis

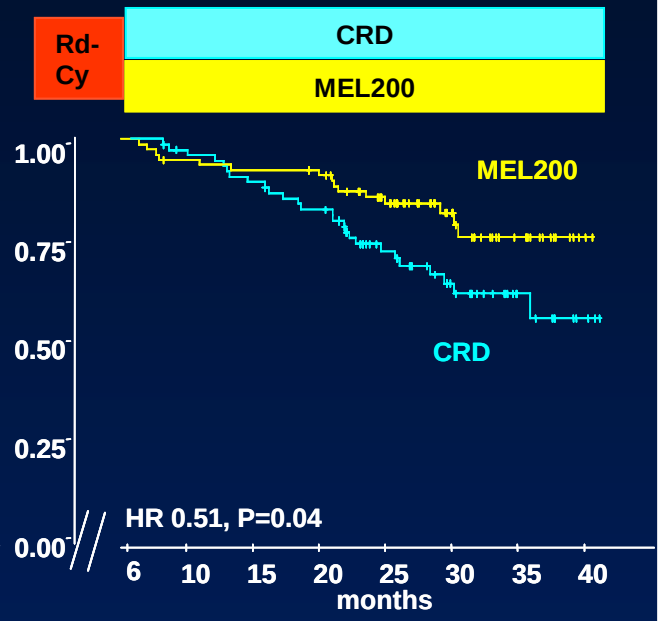
Age < 60 years



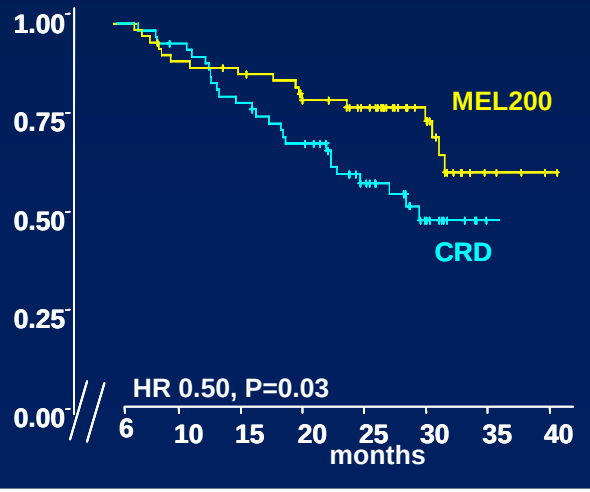
ISS Stage I



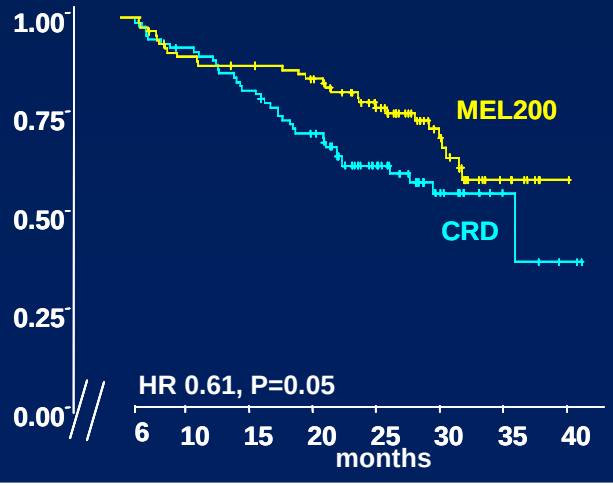
Absence of t(4;14), t(14,16) del17



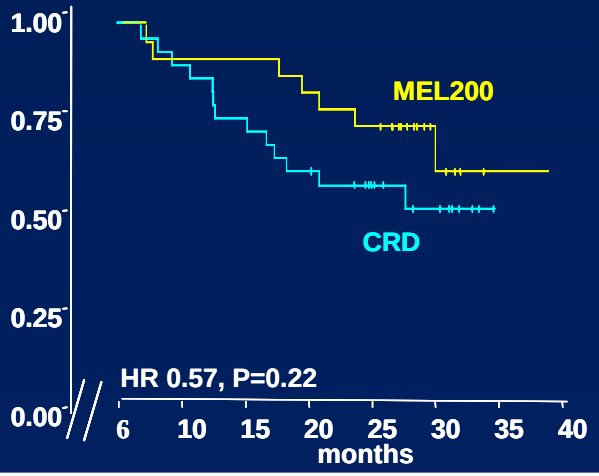
Age ≥ 60 years



ISS Stage II/III

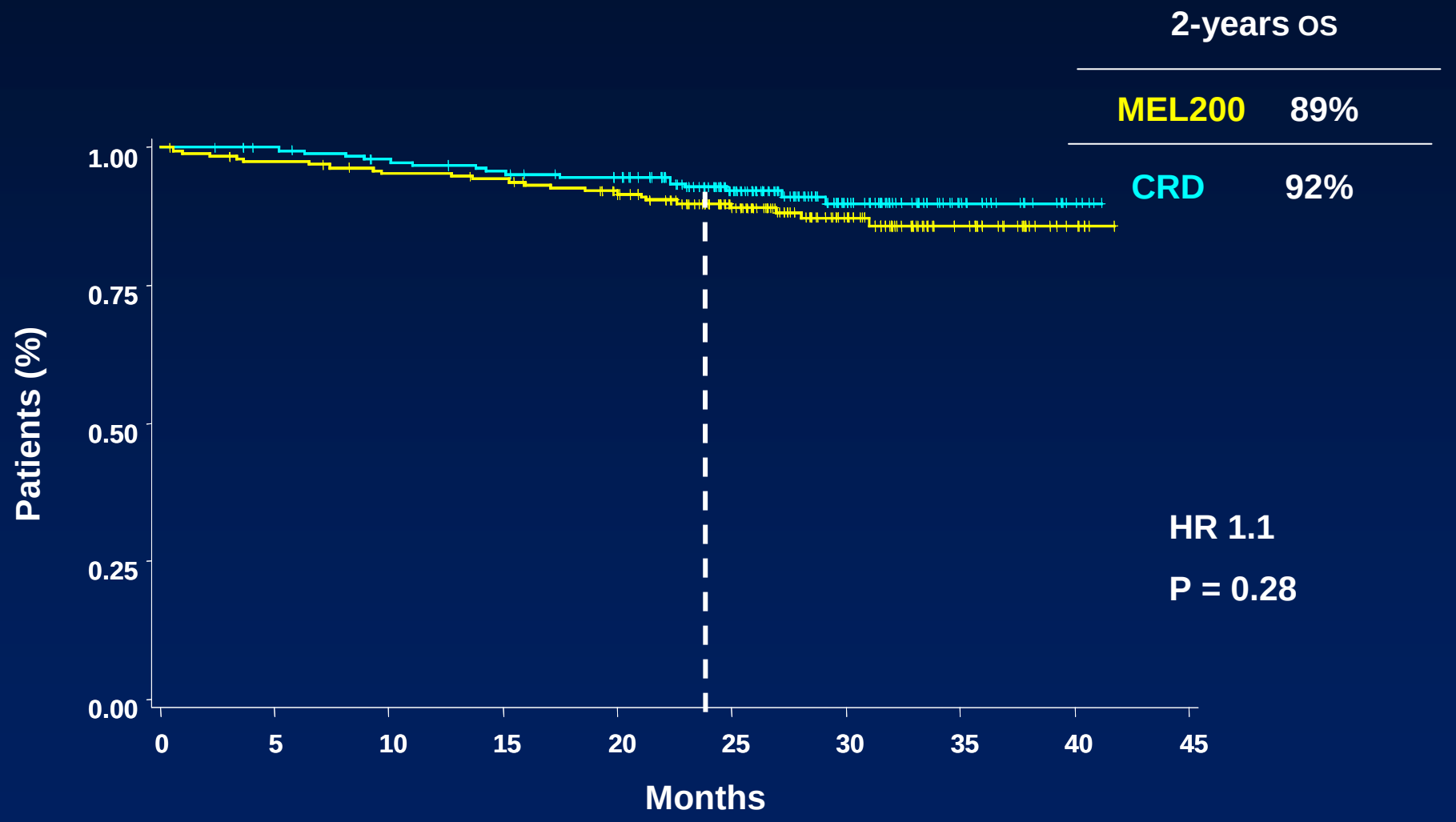


Presence of t(4;14) or t(14,16) or del17



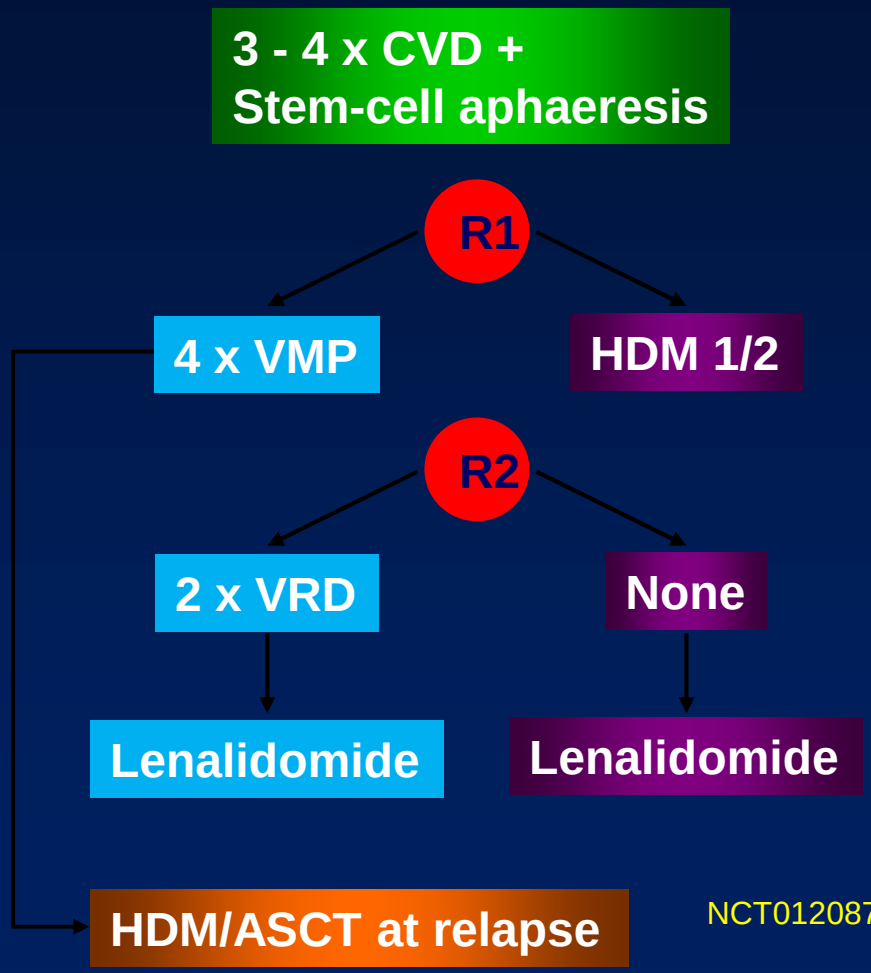
Overall Survival

Median follow-up 28 months



CRD, cyclophosphamide-lenalidomide-dexamethasone; MEL200, melphalan 200 mg/m^2; OS, overall survival; HR, hazard ratio

Novel agents alone
versus
intensive therapy + novel agents:



Induction
Stem-cell mobilization in all patients

Consolidation

Maintenance until replacement

NCT01208766. Available from: http://clinicaltrials.gov. Accessed October 2011.

4.

Je vhodná konsolidace či udržovací léčba MM?

ANO!

Lenalidomid jistě. Která jiná léčba dokud nebude povolen lenalidomid v UL není jasné. Bortezomib má lepší výsledky než thalidomid !

Phase 3: VTD vs TD (GIMEMA study)
Impact of VTD consolidation

Per-protocol analysis of 321 patients who received entire treatment program

	VTD	TD	p
CR post-consolidation	61%	47%	0.012
CR/nCR post-consolidation	73%	61%	0.02
Landmark analysis from start of consolidation (30 months median follow up)			
3-yr probability of relapse or progression	38%	52%	0.039
3-yr PFS	62%	46%	0.025

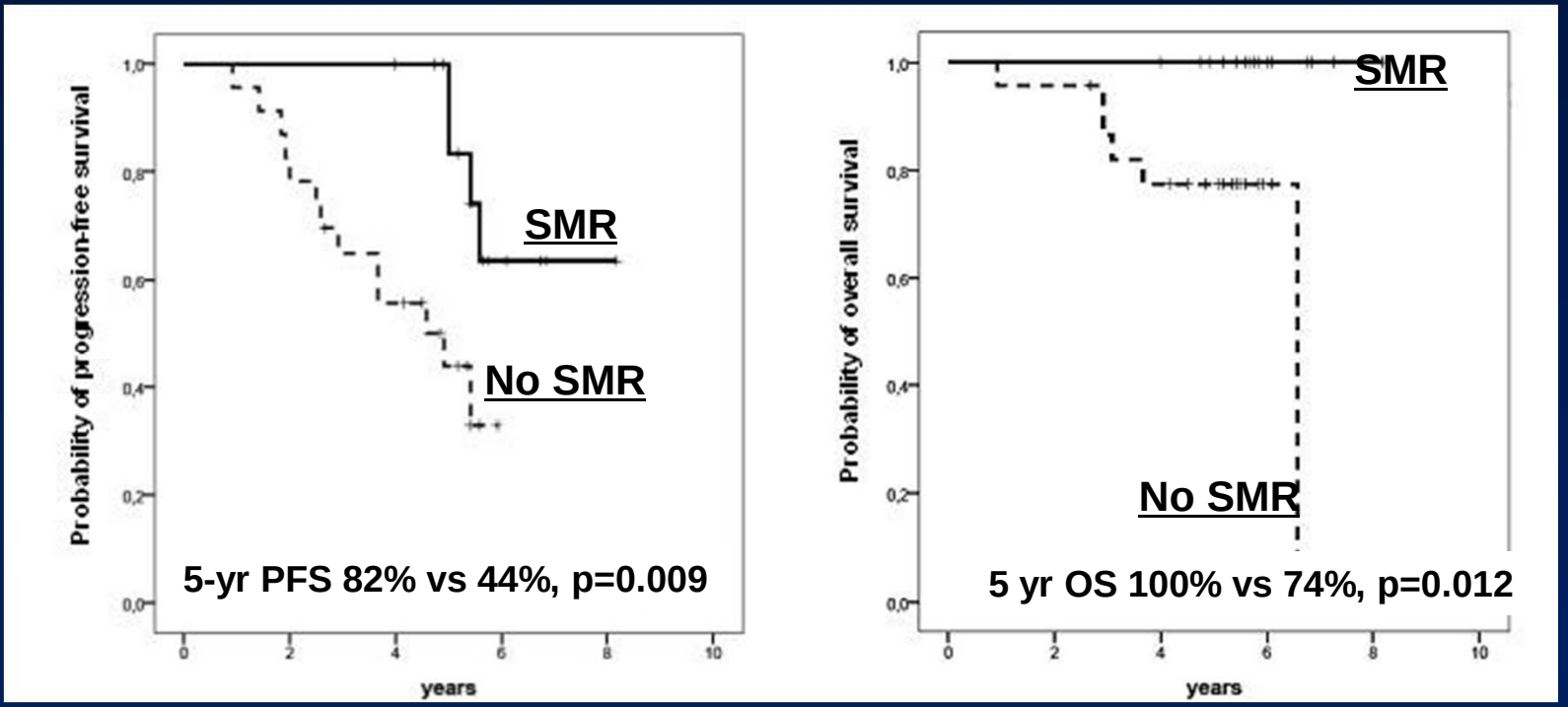
- **Superior PFS with VTD vs TD consolidation retained across poor prognosis subgroups (t(4;14) and/or del(17q), del(13q), β_2-M >3.5 mg/L, LDH >190 U/L, ISS stage 2 and 3)**
- **No OS difference between two groups**
- **Both treatments well tolerated**
  - **Frequency of grade 3-4 AEs comparable in both groups (9.3% VTD, 8.6% TD)**
  - **PN with VTD 0.6%, skin rash and DVT 0.6% in each group**
  - **Patients treated with VTD received 93% of planned doses of bortezomib and thalidomide**

Cavo *et al.* ASH 2011 (Abstract 1871), oral presentation

VTD consolidation: long-term follow up

- **Aim: Assess impact of minimal residual disease (MRD) detection by real time quantitative PCR on late recurrences and OS**
- **Patients (n=39) ≥ VGPR post ASCT received VTD consolidation***

Probability of PFS



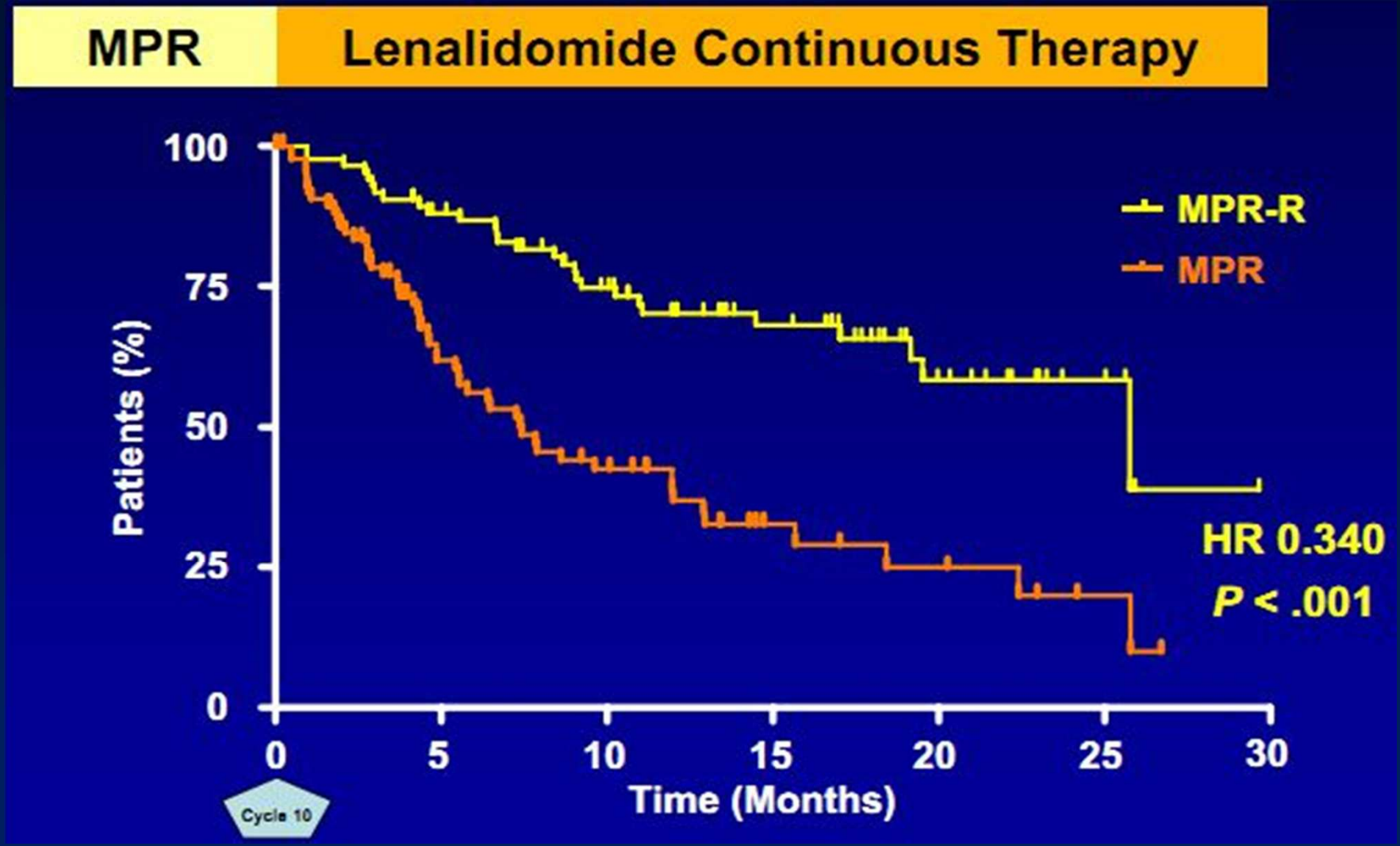
Probability of OS

SMR: Standard molecular remission (MRD negativity on two consecutive samples by RQ-PCR)

**Ladetto et al. J Clin Oncol 2010 ;28(12):2077-84*

Ladetto et al. ASH 2011 (Abstract 827), oral presentation

Významně delší PFS v rameni s UL lenalidomidem



HR, hazard ratio; MP, melphalan, prednison; MPR-R, melphalan, prednison, lenalidomid s udržovací léčbou lenalidomidem; PR, částečná odpověď; VGPR, velmi dobrá částečná odpověď

Lenalidomide maintenance therapy

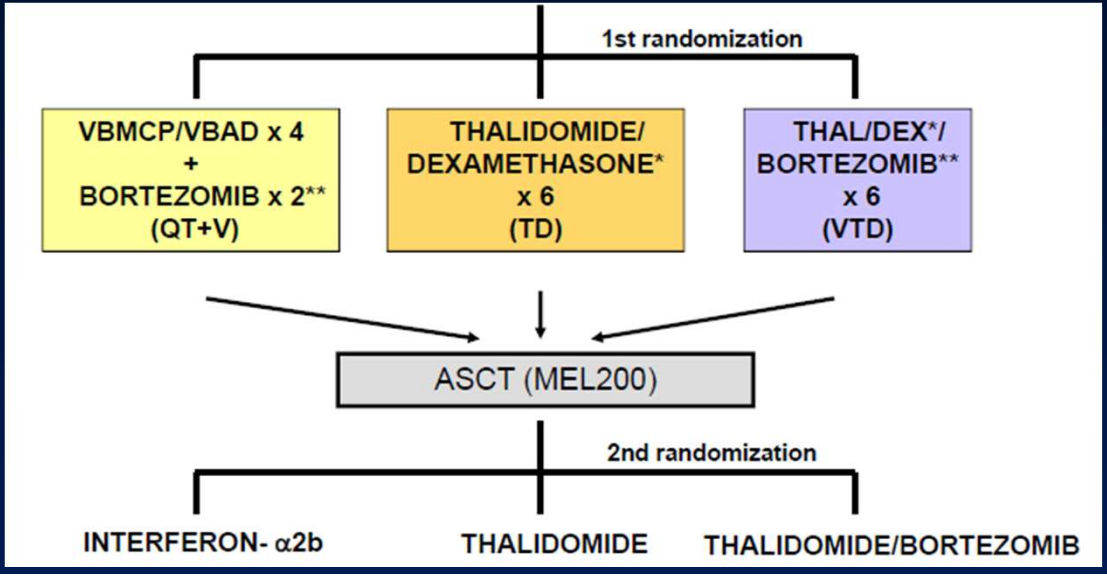
Study details	n	Treatment	Outcome	
			PFS	4-year OS
IFM 2005-02[1]	307	Lenalidomide	41 months	73%
Median follow-up: 45 months	307	Placebo	23 months p<0.001	75% p=ns
			TTP	Deaths
CALGB 100104[2]	231	Lenalidomide	46 months	n=35
Median follow-up: 34 months	229	Placebo	27 months p<0.001	n=53 p=0.03

Occurrence of secondary primary malignancies (SPMs) requires monitoring

[1]*Attal et al. N Engl J Med 2012;366(19):1782-91*
[2]*McCarthy et al. N Engl J Med 2012;366:1770-81*

Post-ASCT maintenance: VT versus Thal versus Interferon-α2b

Phase III PETHEMA/GEM randomized trial



	IFN	Thal	VT
n	90	87	89
Response			
Status prior to maintenance			
CR	53%	49%	53%
VGPR	13%	11%	12%
Status after maintenance			
CR	70%	64%	72%

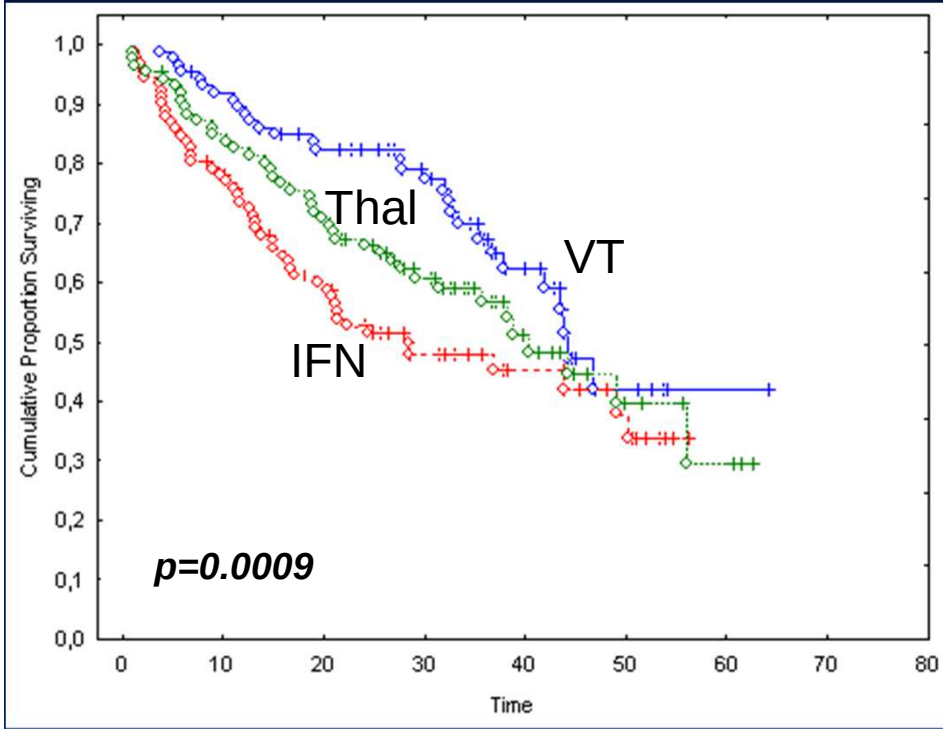
IFN: Interferon-α2b

Rosinol et al. ASH 2012 (Abstract 334), oral presentation

Post-ASCT maintenance: VT versus Thal versus Interferon alfa2b

Median follow-up: 34.9 months

PFS from maintenance



	IFN	Thal	VT
n	90	87	89
PFS			
overall group	Significant benefit for VT, p=0.0009		
pts with high-risk MM	PFS poor for all arms		
pts with standard-risk MM	Significant benefit with VT, p=0.02		
OS			
overall group	No significant difference between arms, p=0.47		
pts with high-risk MM	Poor for all arms		

IFN: Interferon-α2b

Rosinol et al. ASH 2012 (Abstract 334), oral presentation

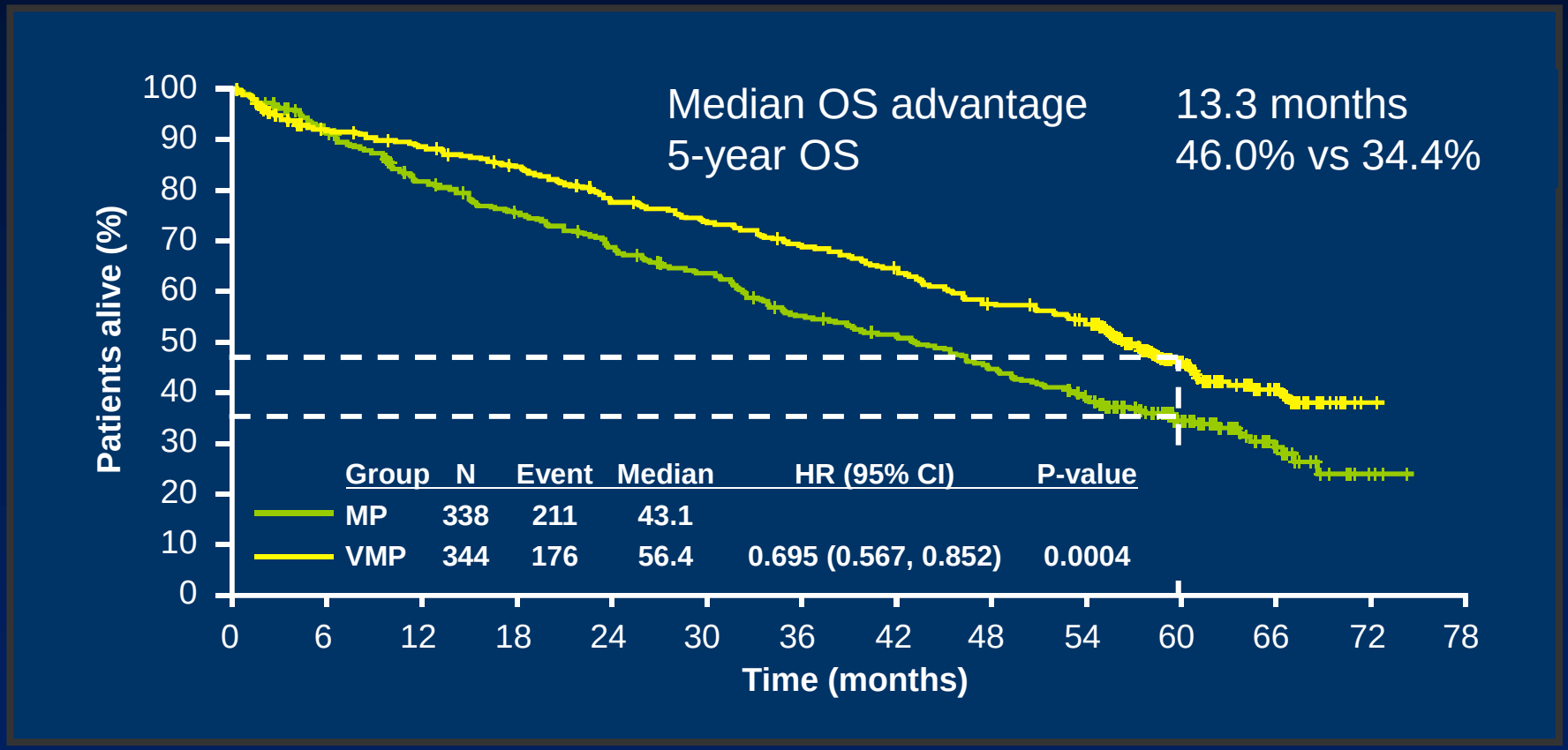
5.

Který režim je optimální u seniorů?

V primoléčbě nepochybně bortezomib based indukce, zvláště když je nyní optimalizována v týdenním režimu + s možností s.c. podání

OS advantage MPV versus MP

compares favorably to 6.6 months OS advantage of MPT versus MP, no OS advantage of MPR-R [yet?]



V = Velcade, M = Melphalan, P = Prednisone

San Miguel et al. J Clin Oncol 2013;31(4):448-55

Bortezomib i.v. versus s.c.

- 222 patients with relapsed and/or refractory MM
- Bortezomib given at conventional dose and scheme

	Bortezomib i.v. (n=73)		**Bortezomib s.c. (n=145)**	
Primary endpoint: response after 4 / 8cycles (single agent bortezomib or +/-dex)				
ORR	42% / 52%		42% / 52%	
CR	8% / 12%		6% / 10%	
TTP	9.4 m		10.4 m	
Peripheral Neuropathy	All grades 53%	Grade ≥3 16%	All grades 38%	Grade ≥3 6% *P=0.04 and 0.03*

Comparable pharmakokinetic data

Moreau et al. Lancet Oncology 2011; 12(5): 431-40
Arnulf et al. Haematologica 2012;97(12):1925-8

6.

Jak postupovat u starších a křehkých nemocných?

Individuálně, s plánovanou redukcí léčby umožňující dobrou toleranci. Je lepší kumulativní dávku podat nemocnému v delším časovém období.

Redukce dávek s ohledem na věk

	< 65 years	65-75 years	> 75 years or 65-75 years with comorbidities
Prednisone	2 mg/kg	1 mg/kg	1 mg/kg
Dexamethasone	40 mg day 1, 8, 15, 22	40 mg day 1, 8, 15, 22	20 mg day 1, 8, 15, 22
Melphalan	0.18 mg/kg days 1-4	0.18 mg/kg days 1-4	0.13 mg/kg days 1-4
Thalidomide	200 mg/day	100-200 mg/day	50-100 mg/day
Lenalidomide	25 mg days 1-21	15-25 mg days 1-21	10-25 mg days 1-21
Bortezomib	1.3 mg/m^2 2 x per week	1.3 mg/m^2 1-2 x week	1.3 mg/m^2 1 x week

Palumbo & Anderson. N Engl J Med 2011;364(11):1046-60

Shrnutí:

- **použít nejúčinnější režim hned v úvodu onemocnění ve snaze dosáhnout co nejlepší léčebné odpovědi**
  = pokud dojde k relapsu, vždy už bude léčebná odpověď horší
- **cílem léčby je dnes imunofenotypová CR (iCR), již ne „pouze“ CR !**
- **stratifikace léčby dle rizika**
  – **využívat v praxi známé PF (ISS a FISH)**
- **léčbu přizpůsobit stavu+věku nemocného**

Děkuji za pozornost !