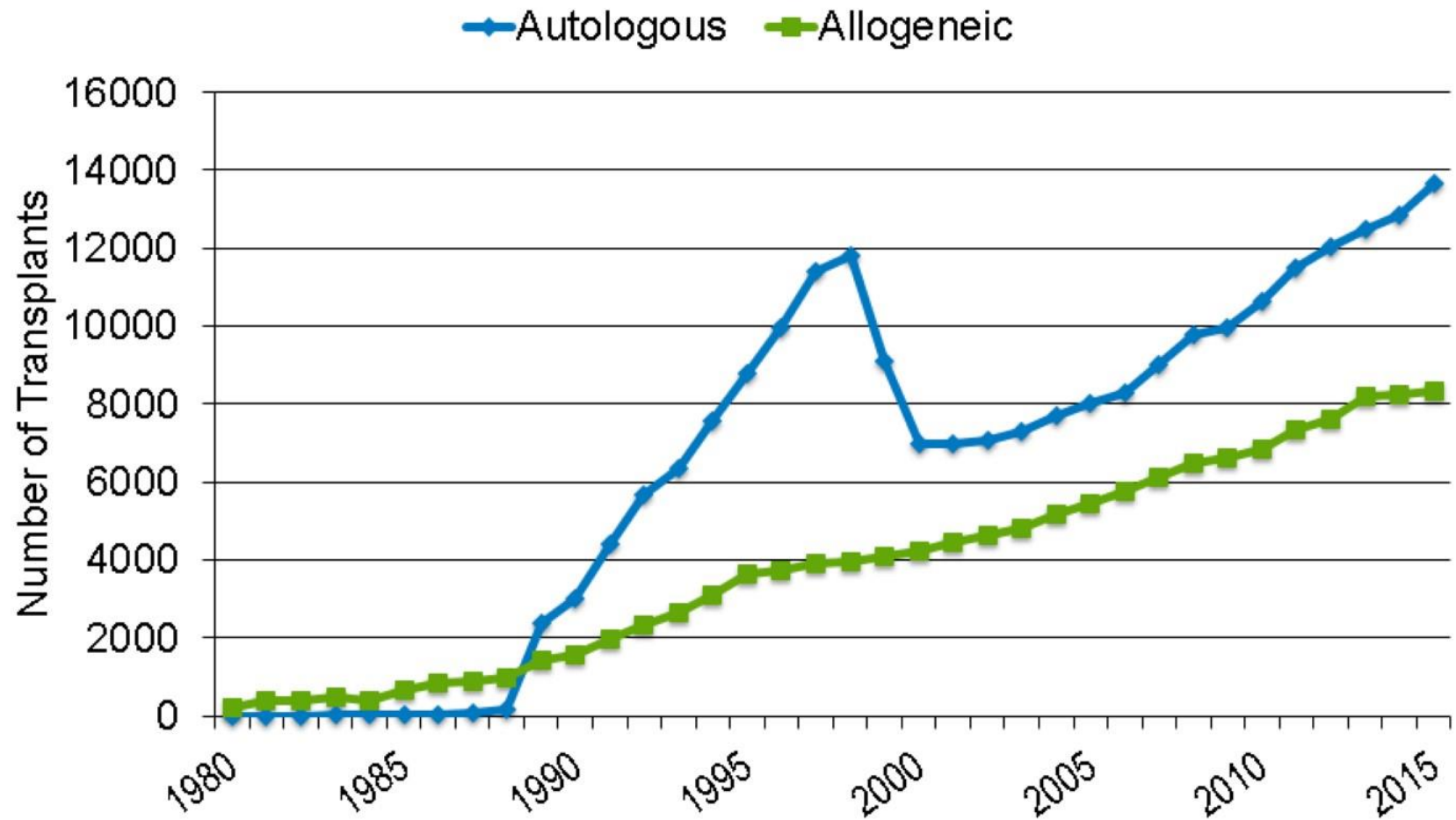


# Transplantácia krvotvorných buniek v liečbe mnohopočetného myelómu

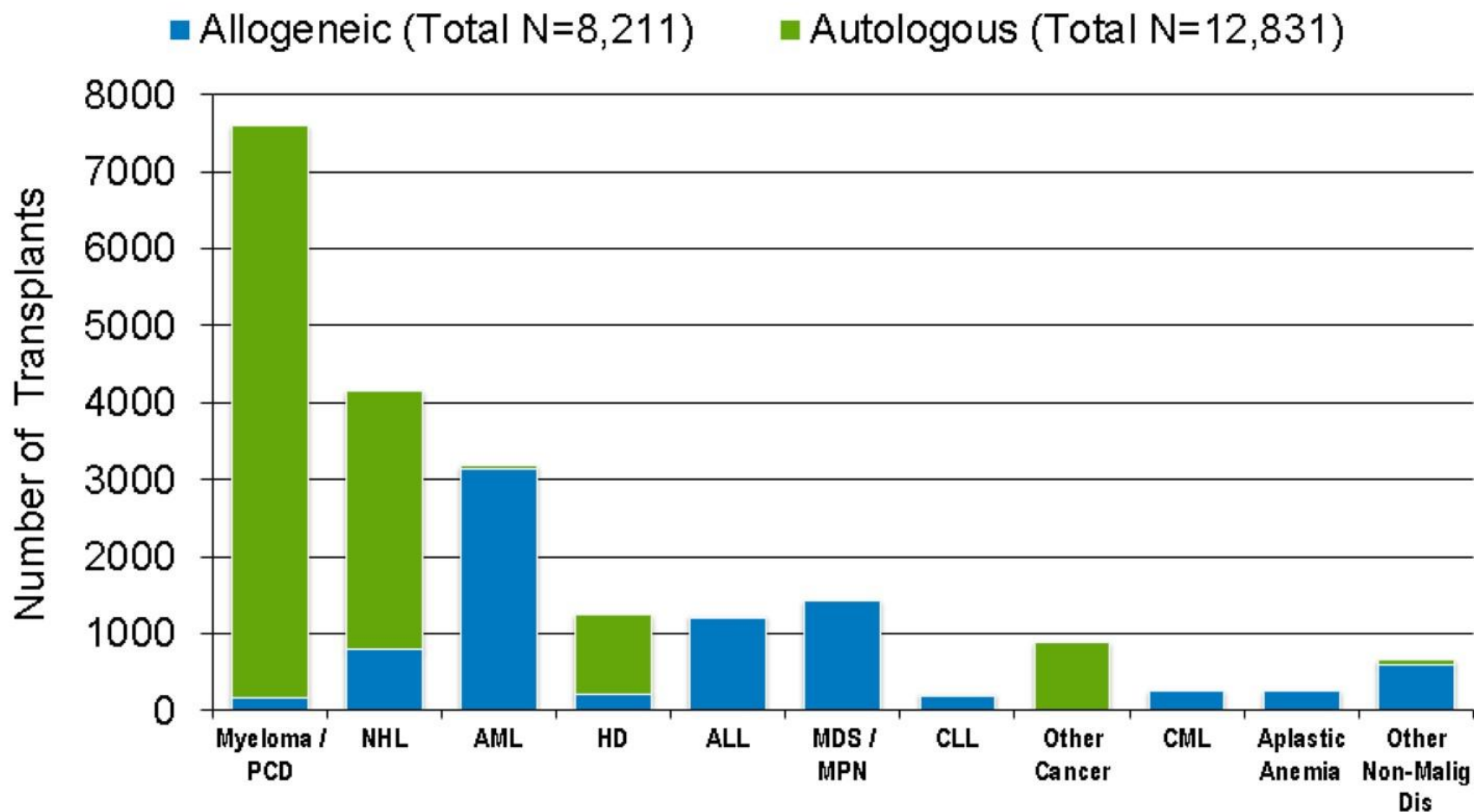
Marti Mistrík

MF máj 2017

# Annual Number of HCT Recipients in the US by Transplant Type

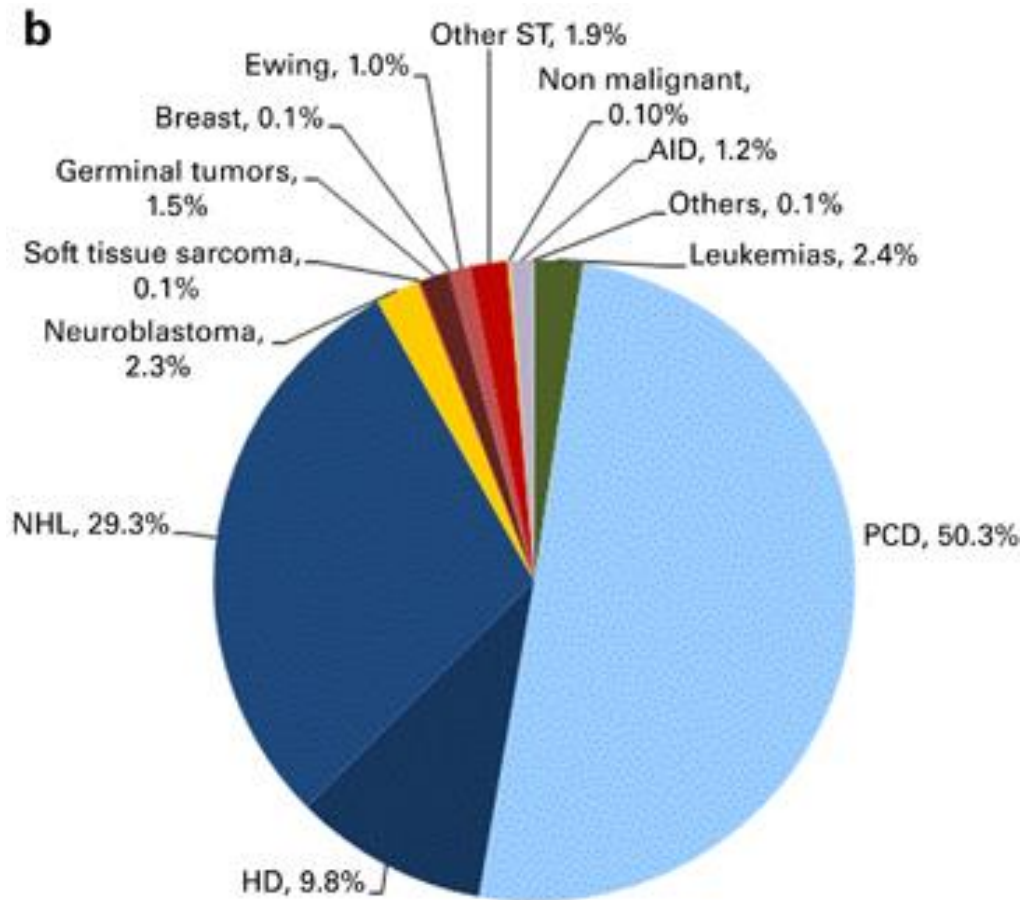


# Indications for Hematopoietic Cell Transplant in the US, 2014

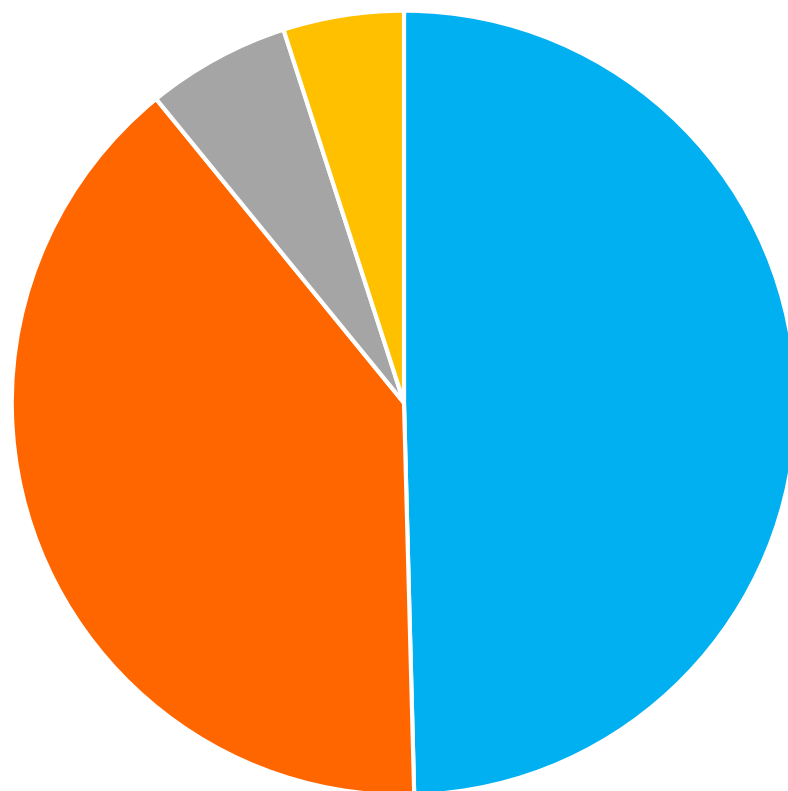


# Indikácie autológnej TKB v Európe v r. 2014

## 1. ATKB



# 845 ATKB v SR (2011-2016)



■ Myelóm ■ Lymfóm ■ solídny Ca ■ Akútna leukémia

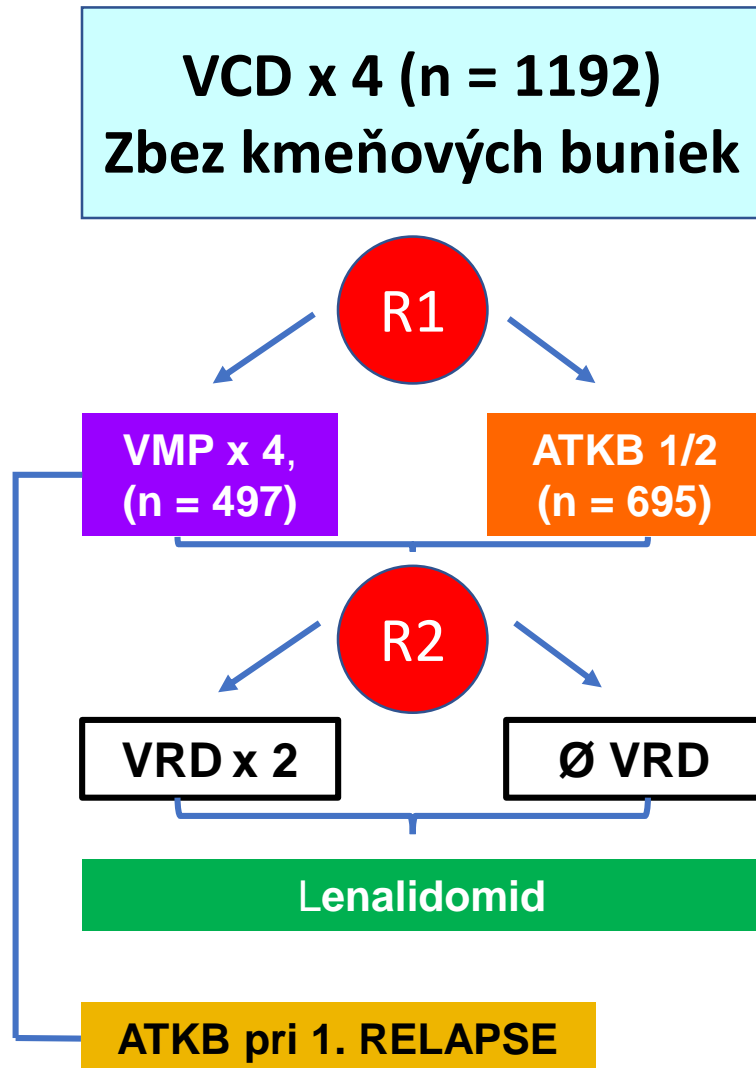
**ATKB v prvej línii: štandard starostlivosti v roku 2017?**

**Určíte ÁNO!**

**EMN02**

**IFM 2009**

# Štúdia EMN02



*Registrácia  
Indukcia*

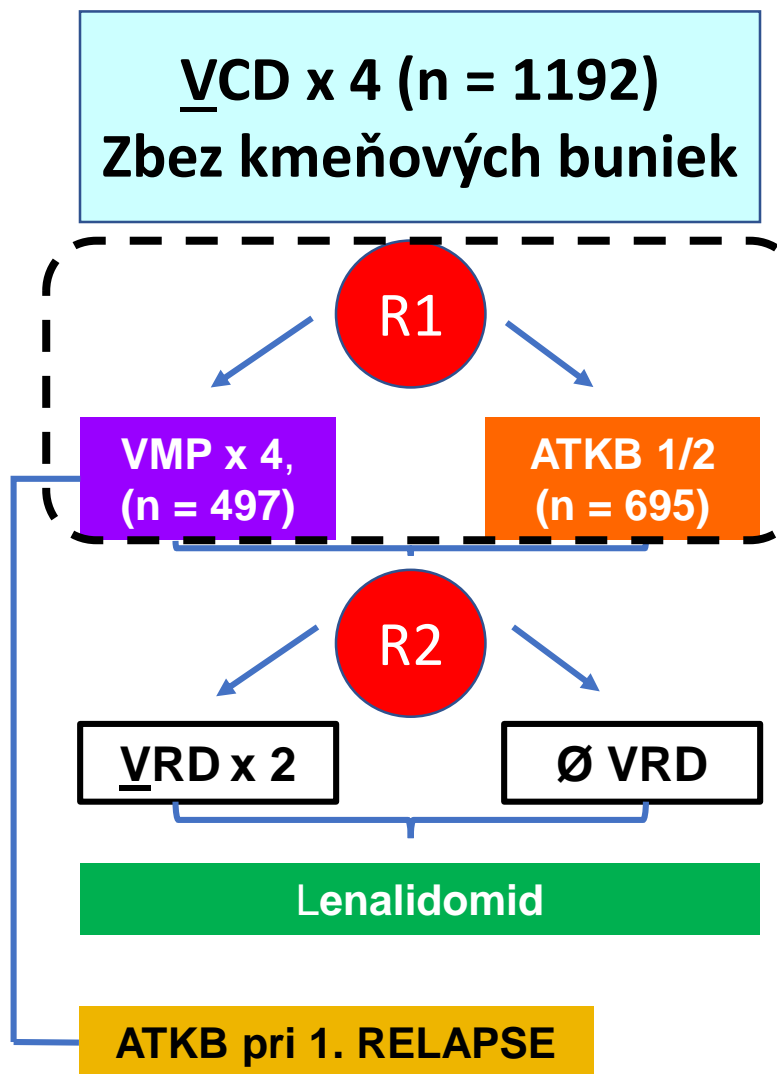
Jedna alebo dve ATKB

*Konsolidácia*

*Udržiavacia liečba do relapsu*



# Štúdiá EMN02



*Registrácia*  
*Indukcia*

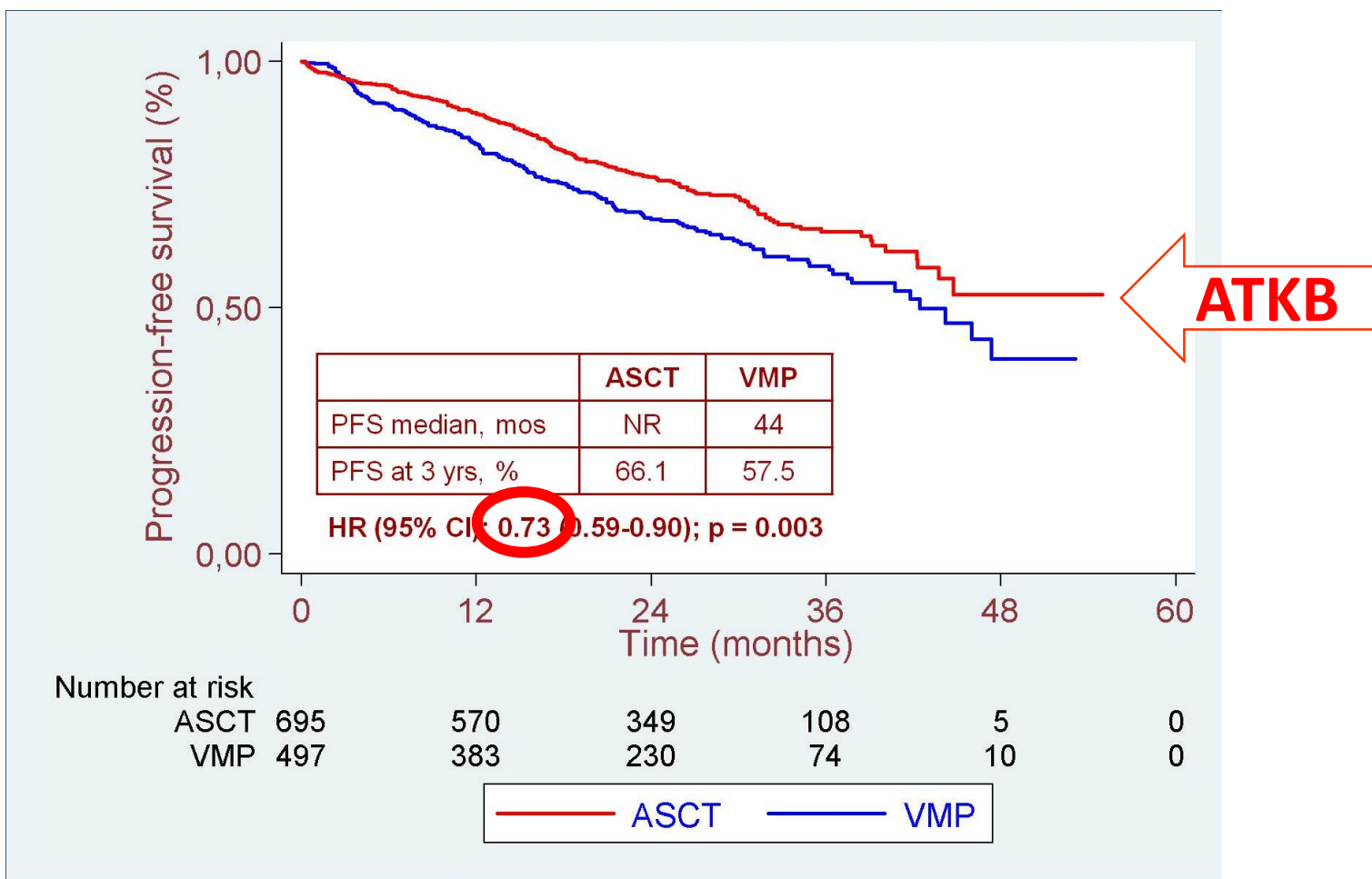
**R1: Je stále potrebná prolíniová  
ATKB v ére nových terapií?**

Jedna alebo dve ATKB

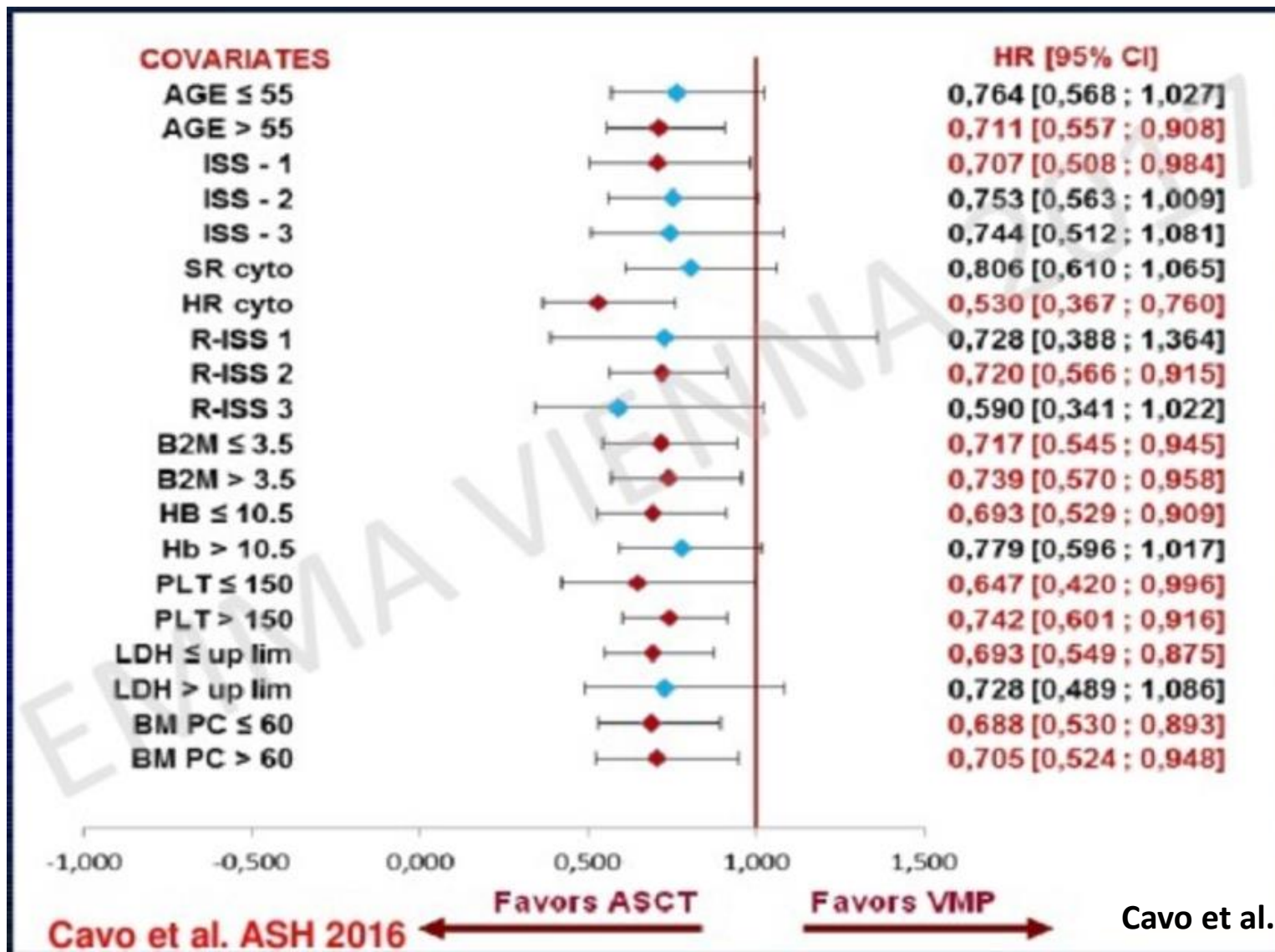
*Konsolidácia*

*Udržiavacia liečba do relapsu*

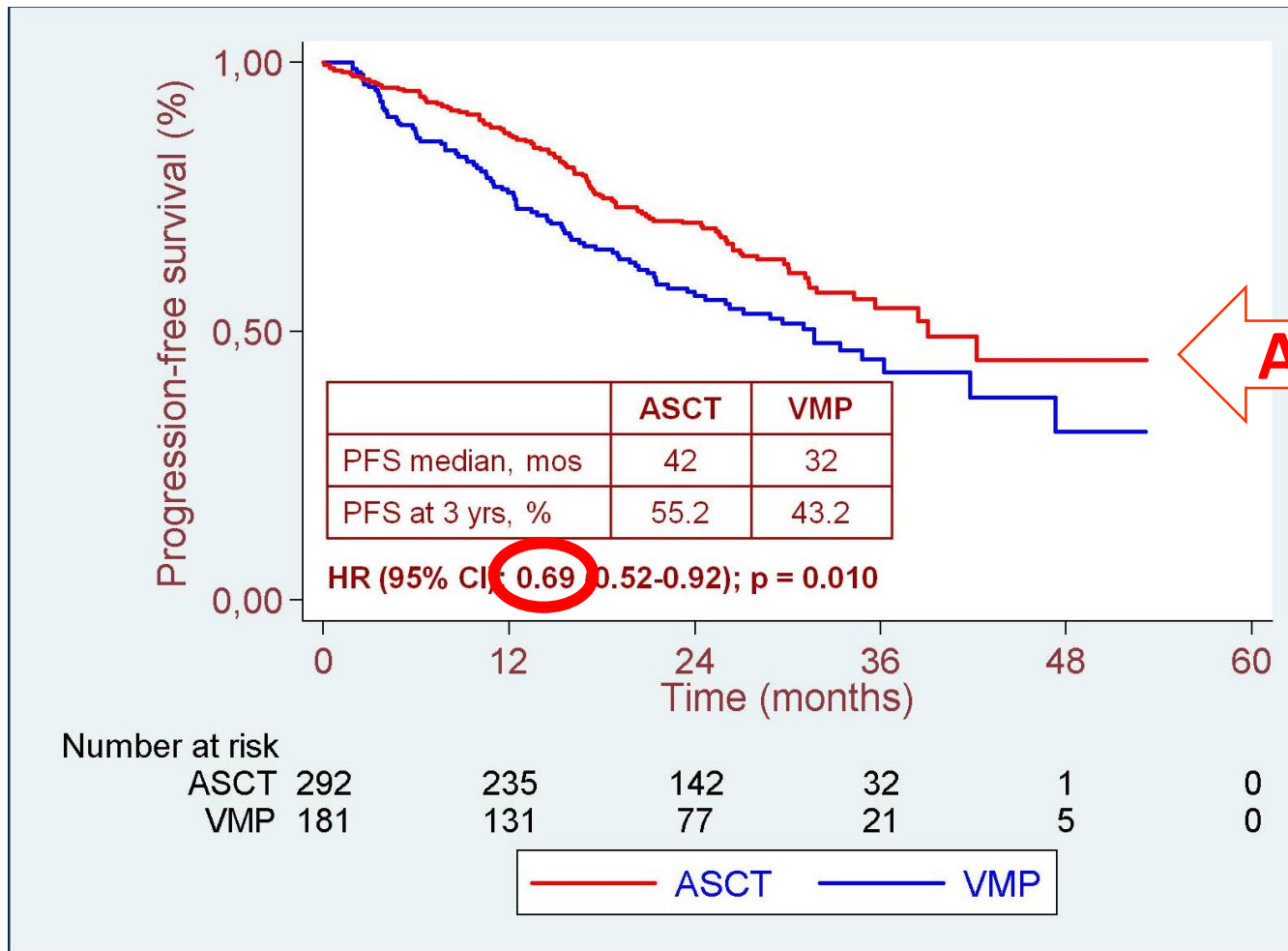
# PFS podľa 1. randomizácie (VMP vs ATKB)



# PFS analýza (VMP vs ATKB)

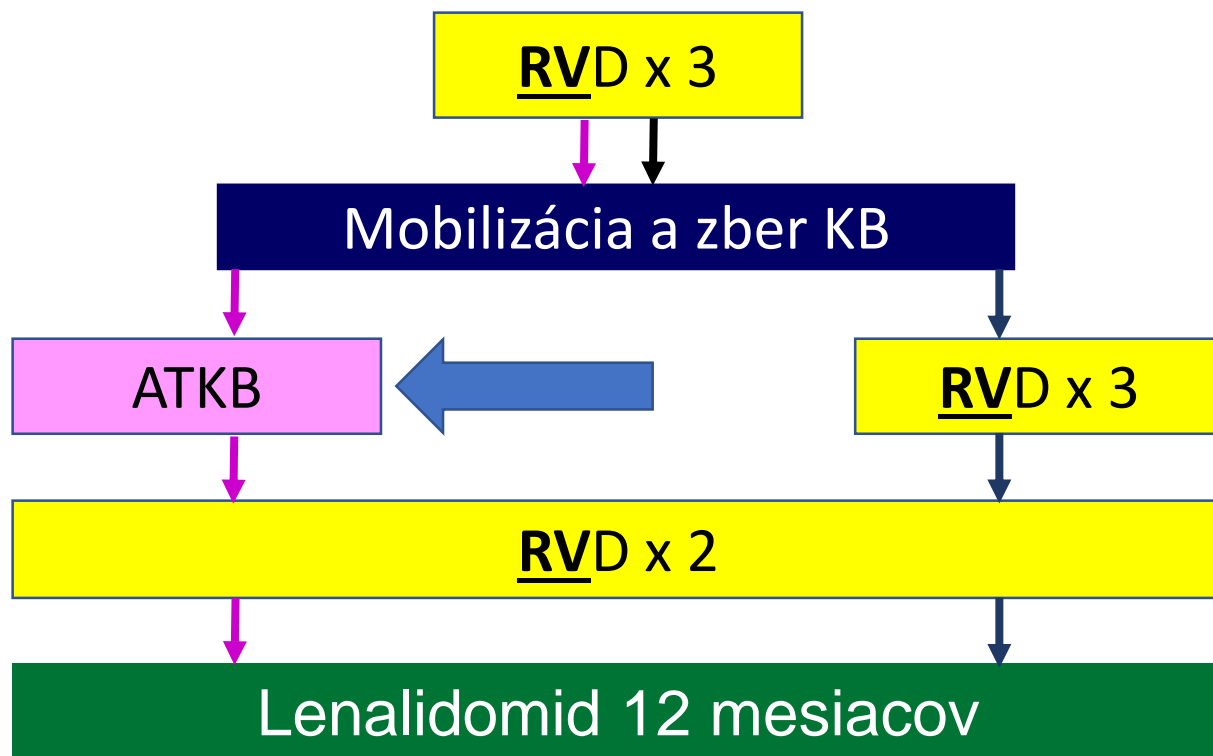


# PFS podľa 1. randomizácie (VMP vs ATKB) VYSOKÉ RIZIKO



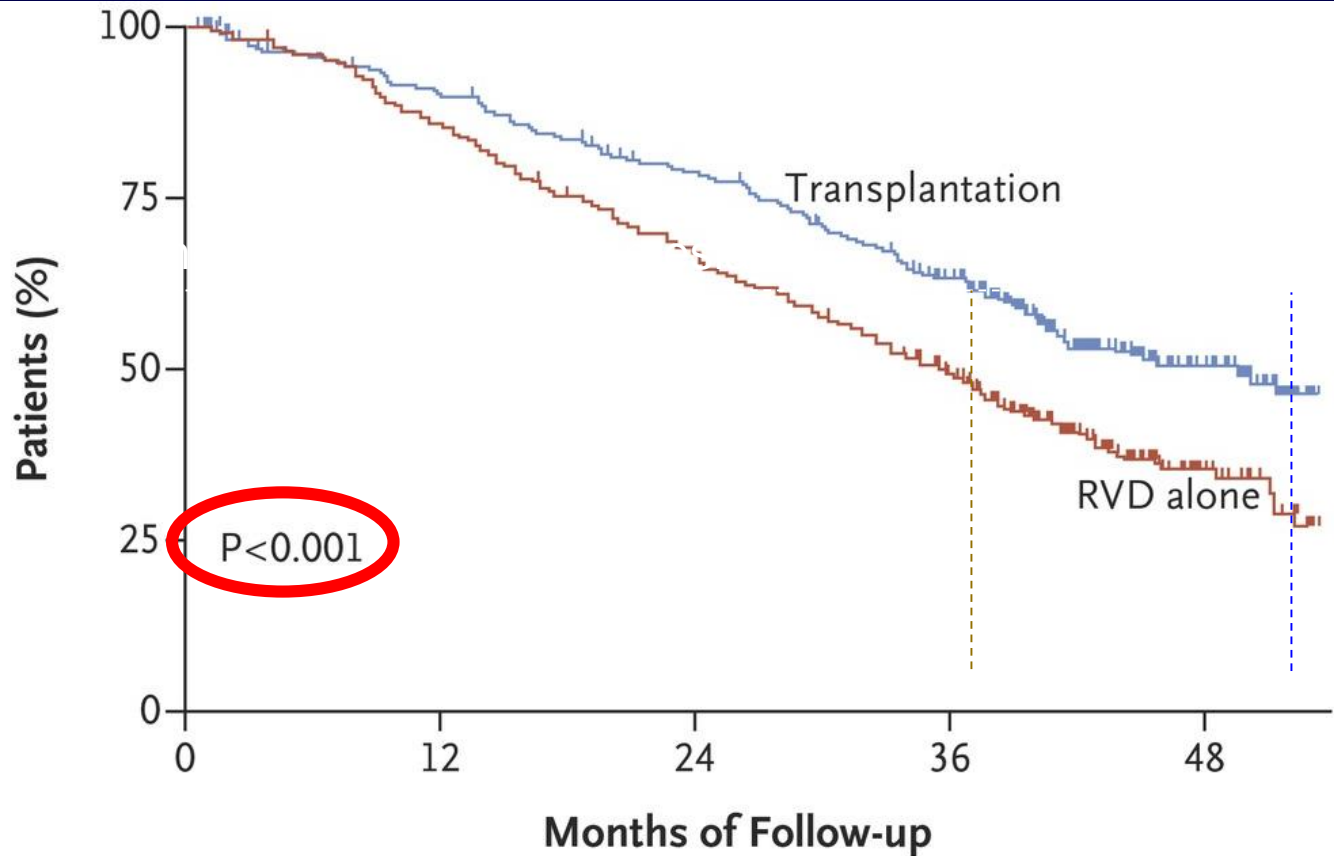
# IFM2009/DFCI štúdia

## RANDOMIZÁCIA



ATKB pri  
RELAPSE

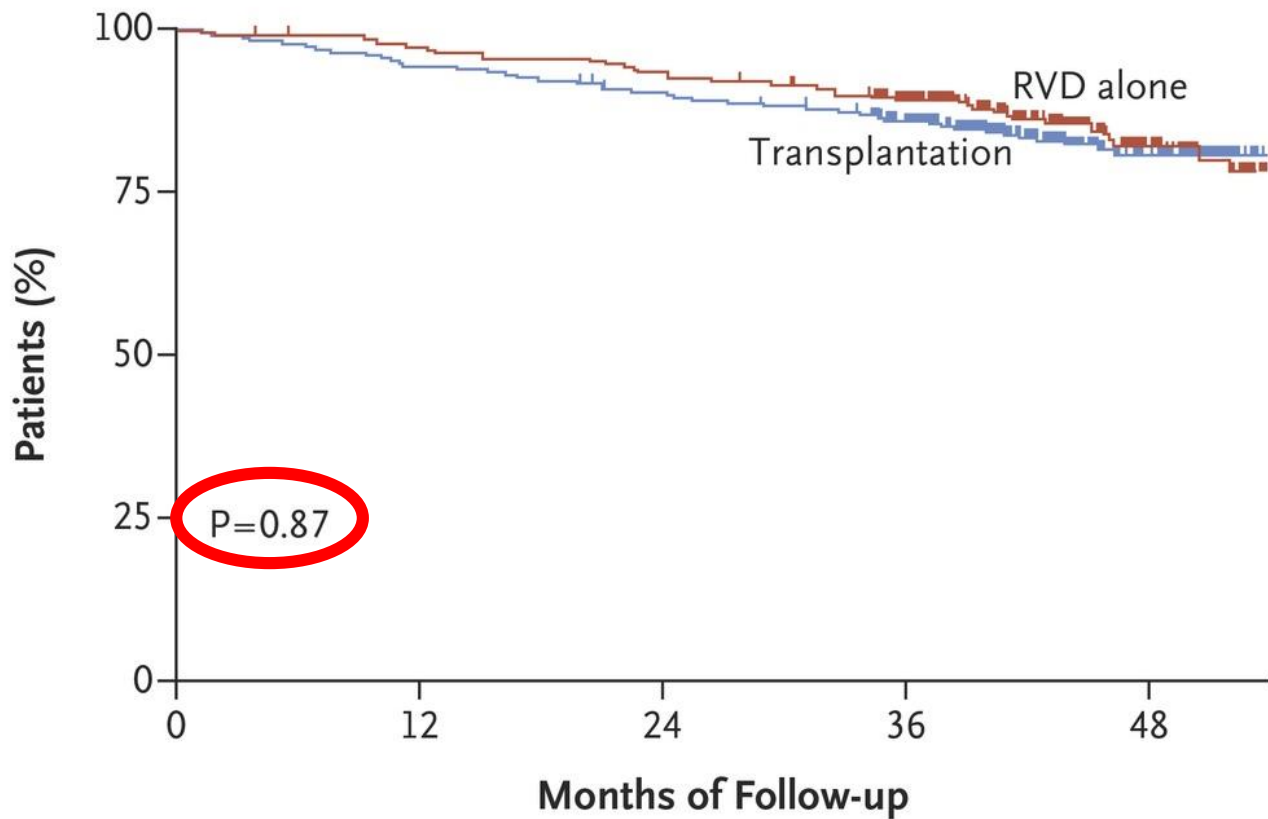
# PFS: ATKB > RVD



## No. at Risk

RVD alone	350	294	228	157	32
Transplantation	350	308	264	196	50

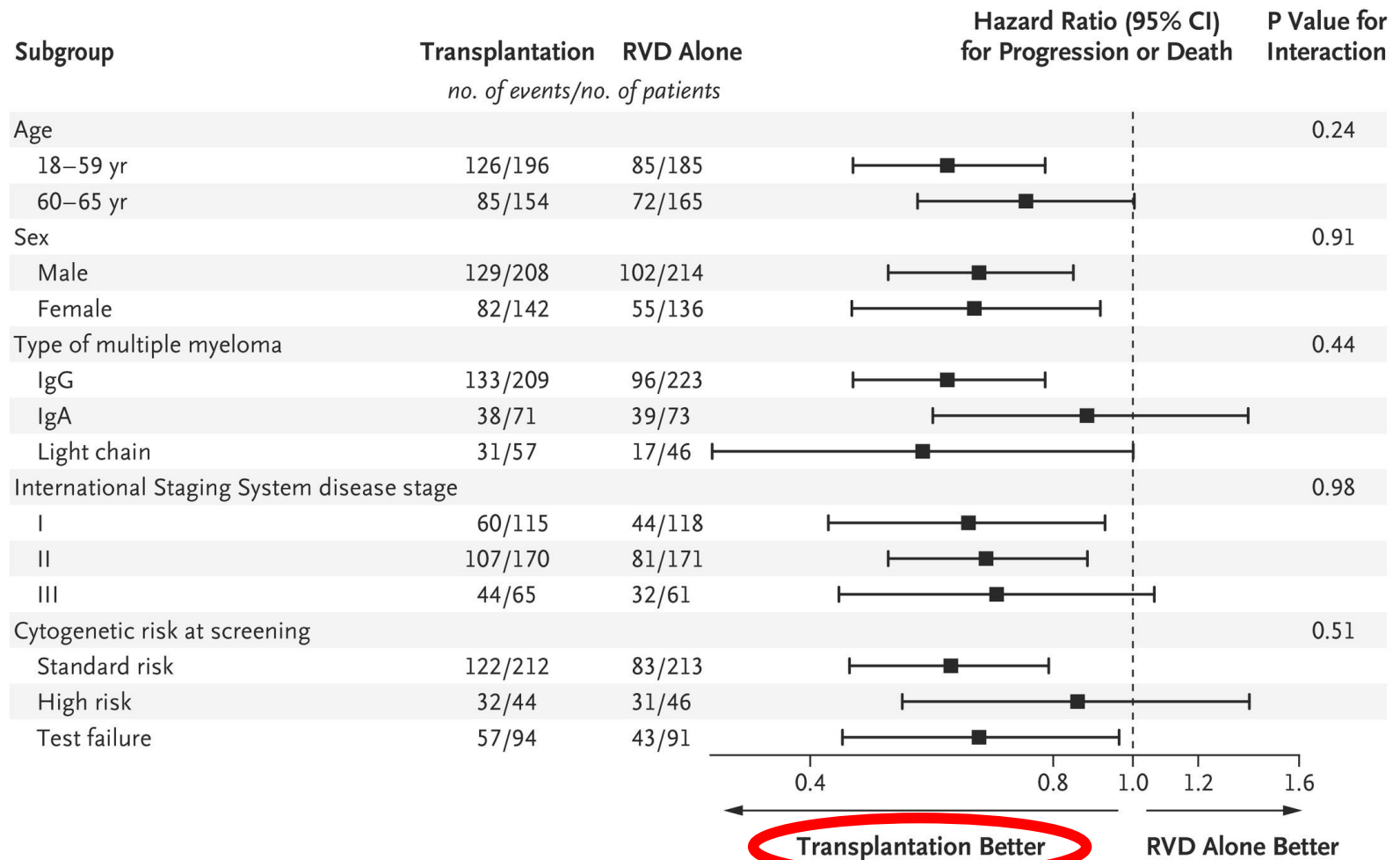
# OS: ATKB = RVD



### No. at Risk

RVD alone	350	339	325	293	95
Transplantation	350	330	313	281	89

# PFS: podľa podskupín





# IFM 2009: PFS, Prognostické Faktory

	Multivariačná analýza	p-hodnota
Liečba Tx/ RVD	0.80	0.02
ISS II vs I	1.33	0.02
III vs II	1.45	0.01
FISH (VR/ŠR)	2.22	< 0.001
KR	0.58	< 0.001
MRD (Flow)	0.39	< 0.001

# IFM 2009: Najlepšia odpoveď

	RVD (N=350)	ATKB (N = 350)	p-hodnota
KR	48%	59%	} 0.004
VGPR	29%	29%	
PR	20%	11%	
< PR	3%	2%	
≥ VGPR	77%	88%	< 0.001
MRD neg (Flow), n (%)	171/265 (65%)	220/278 (80%)	< 0.001

**CIEĽ: najlepšia + trvajúca odpoveď**

# ÚLOHA INDUKCIE

**Odporúča sa PAD, VCD, VTD a RVD, ale:**

**Veľmi málo porovnaní v štúdiách fázy 3!**

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preview](#)[... About AAP](#)[Advance online  
publication](#)[... About AOP](#)[Current issue](#)[Archive](#)[Focus Collections](#)[How to manage](#)[Supplements](#)[Press releases](#)

## Original Article

*Leukemia* (2015) **29**, 1721–1729; doi:10.1038/leu.2015.80; published online 8 May 2015

### Multiple Myeloma

Phase III trial of bortezomib, cyclophosphamide and dexamethasone (VCD) versus bortezomib, doxorubicin and dexamethasone (PAd) in newly diagnosed myeloma

E K Mai<sup>1</sup>, U Bertsch<sup>1</sup>, J Dürig<sup>2</sup>, C Kunz<sup>3</sup>, M Haenel<sup>4</sup>, I W Blau<sup>5</sup>, M Munder<sup>6</sup>, A Jauch<sup>7</sup>, B Schurich<sup>8</sup>, T Hielscher<sup>3</sup>, M Merz<sup>9</sup>, B Huegle-Doerr<sup>1</sup>, A Seckinger<sup>1</sup>, D Hose<sup>1</sup>, J Hillengass<sup>9</sup>, M S Raab<sup>9</sup>, K Neben<sup>9</sup>, H-W Lindemann<sup>10</sup>, M Zeis<sup>11</sup>, C Gerecke<sup>12</sup>, I G H Schmidt-Wolf<sup>13</sup>, K Weisel<sup>14</sup>, C Scheid<sup>15</sup>, H Salwender<sup>16</sup> and H Goldschmidt<sup>1</sup>

**PAD a VCD sú rovnako efektívne: VGPR 34.3% vs 37%,  
p=0.58**

**VCD je menej toxická: vážne vedľajšie účinky, 24% vs  
32.7%, p=0.04**

**VCD > PAd**



**blood**<sup>®</sup>

2016 127: 2569-2574

doi:10.1182/blood-2016-01-693580 originally published  
online March 21, 2016

## **VTD is superior to VCD prior to intensive therapy in multiple myeloma: results of the prospective IFM2013-04 trial**

Philippe Moreau, Cyrille Hulin, Margaret Macro, Denis Caillot, Carine Chaleteix, Murielle Roussel, Laurent Garderet, Bruno Royer, Sabine Brechignac, Mourad Tiab, Mathieu Puyade, Martine Escoffre, Anne-Marie Stoppa, Thierry Facon, Brigitte Pegourie, Driss Chaoui, Arnaud Jaccard, Borhane Slama, Gerald Marit, Karim Laribi, Pascal Godmer, Odile Luycx, Jean-Claude Eisenmann, Olivier Allangba, Mamoun Dib, Carla Araujo, Jean Fontan, Karim Belhadj, Marc Wetterwald, Véronique Dorvaux, Jean-Paul Femand, Philippe Rodon, Brigitte Kolb, Sylvie Glaisner, Jean-Valere Malfuson, Pascal Lenain, Laetitia Biron, Lucie Planche, Helene Caillon, Herve Avet-Loiseau, Thomas Dejoie and Michel Attal

**338 pacientov, prospektívna štúdia**  
**4 cykly VCD vs 4 cykly VTD**

# VTD je účinnější ako VCD

	VTD (N=169)	VCD (N=169)	p-hodnota
≥ KR	13%	9%	0.22
≥ VGPR	<b>66%</b>	<b>56%</b>	<b>0.05</b>
≥ PR	92%	83%	0.01

**VTD > VCD**



# Toxicita

	VTD (n=169) st. 3-4 (%)	VCD (n=169) st. 3-4 (%)	P value
Any AEs	63.9	68.2	.40
Anémia	4.1	9.5	.05
Neutropénia	18.9	33.1	.003
Infekcia	7.7	10.1	.45
Trombocytopénia	4.7	10.6	.04
Trombóza	1.8	1.8	.99
Chor. Srdca	1.2	0	.16
Cystitída	0	0.6	.32
GIT symptómy	5.3	3.5	.42
Perif. neuropatia (PN)	7.7	2.9	.05
PN stupňa 2-4	21.9	12.9	.008

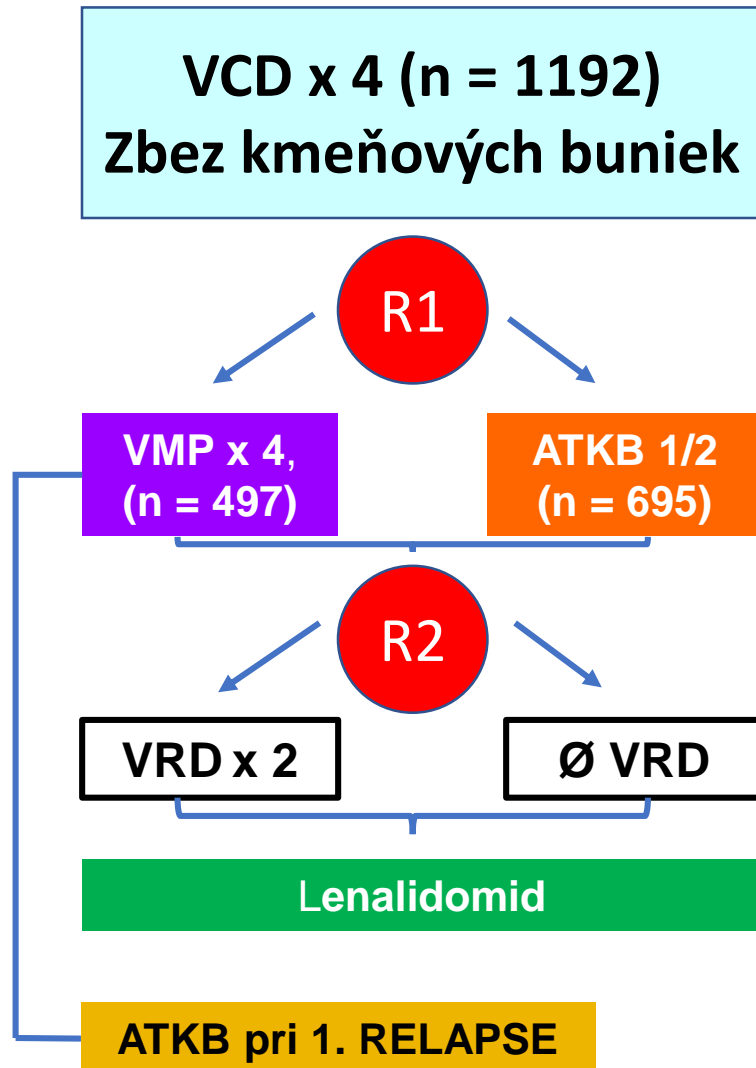
**VTD > VCD > PAd** sa široko používajú v Európe

**VRD** v USA, menej toxická a rovnako účinná:  
V budúcnosti po schválení lenalidomidu aj v Európe?

**Najlepšia odpoveď po ATKB je dôležitá**

**→ Úlohou konsolidácie je zlepšiť hĺbku odpovede**

# Štúdiá EMN02



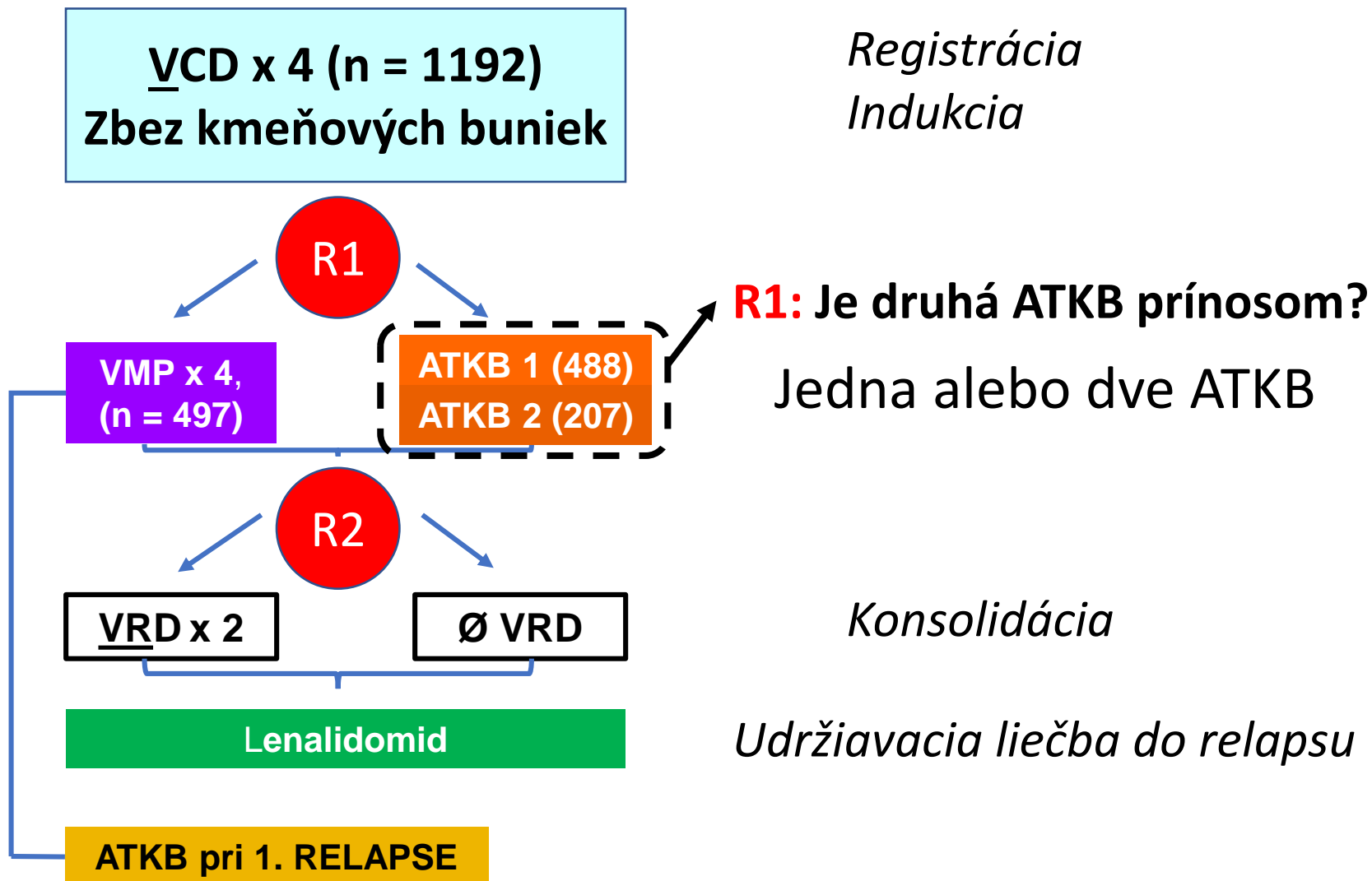
*Registrácia  
Indukcia*

Jedna alebo dve ATKB

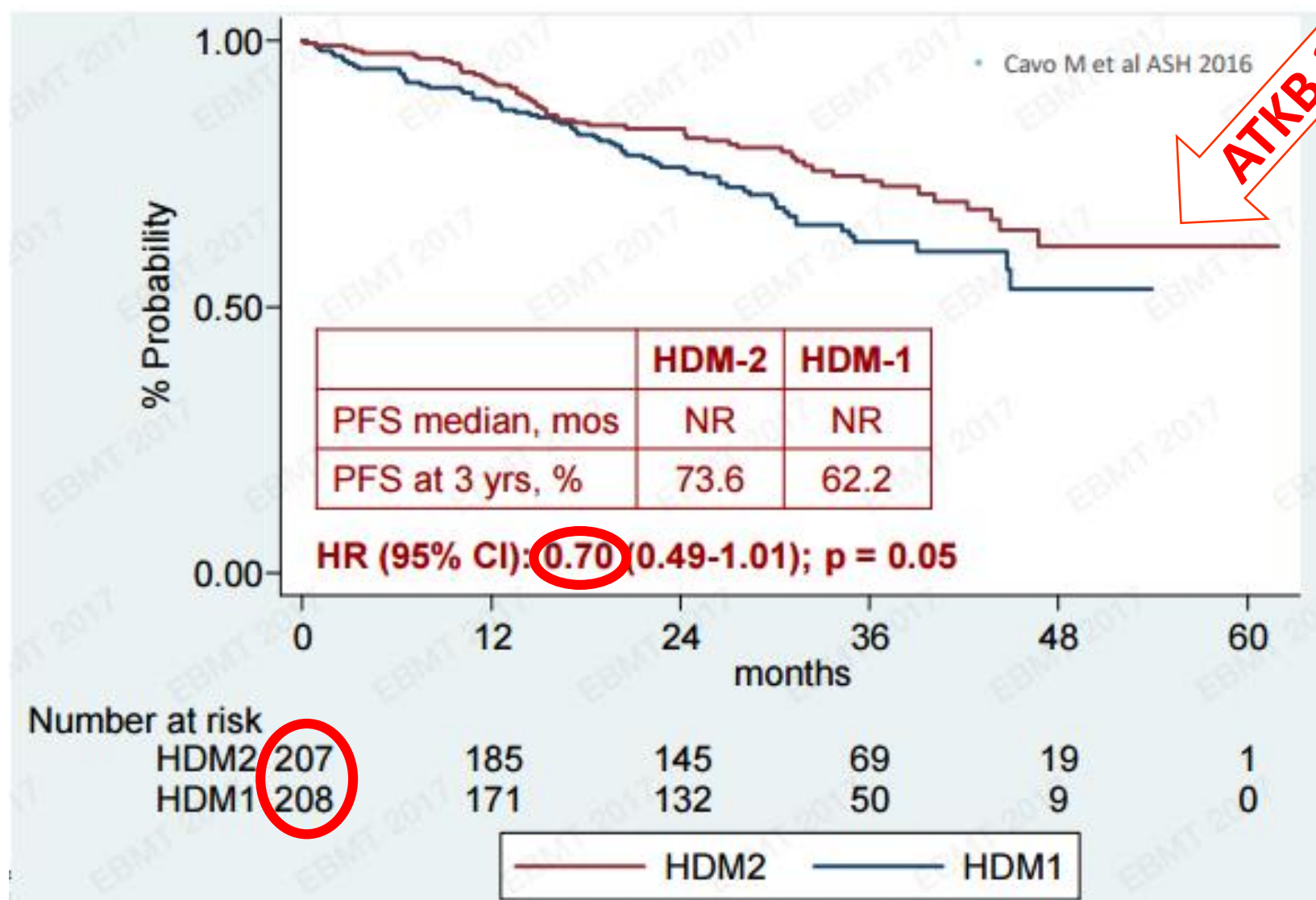
*Konsolidácia*

*Udržiavacia liečba do relapsu*

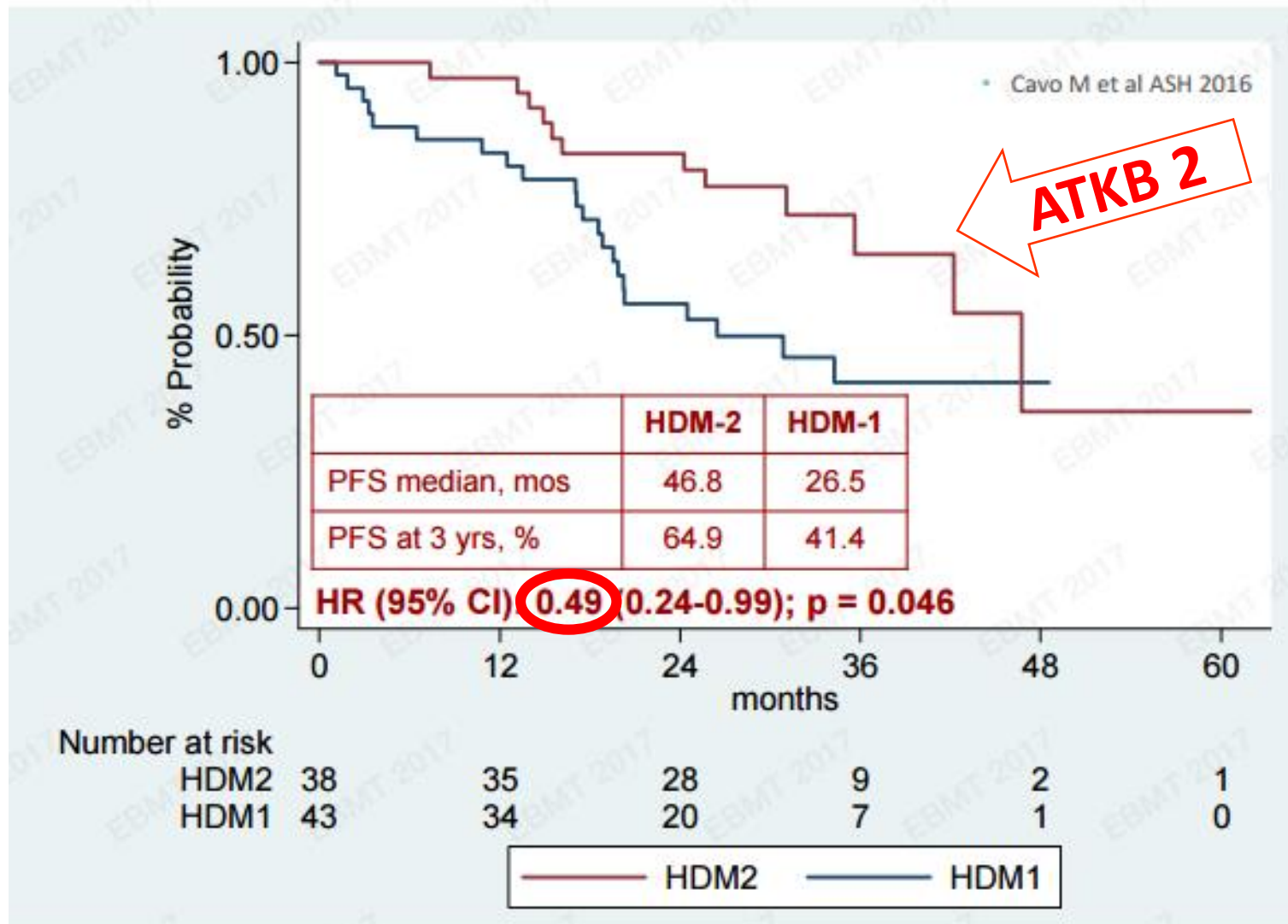
# Štúdiá EMN02



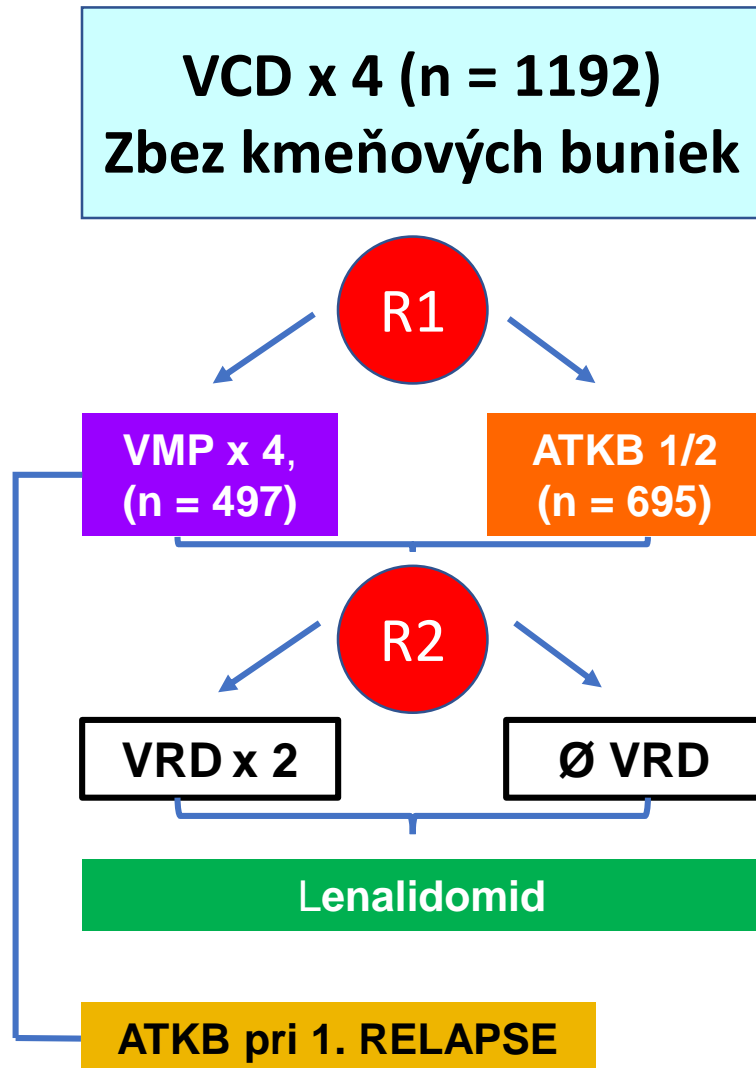
# PFS: ATKB 1 vs 2



# PFS: ATKB 1 vs 2 pri VR cytogenetike



# Štúdiá EMN02



*Registrácia  
Indukcia*

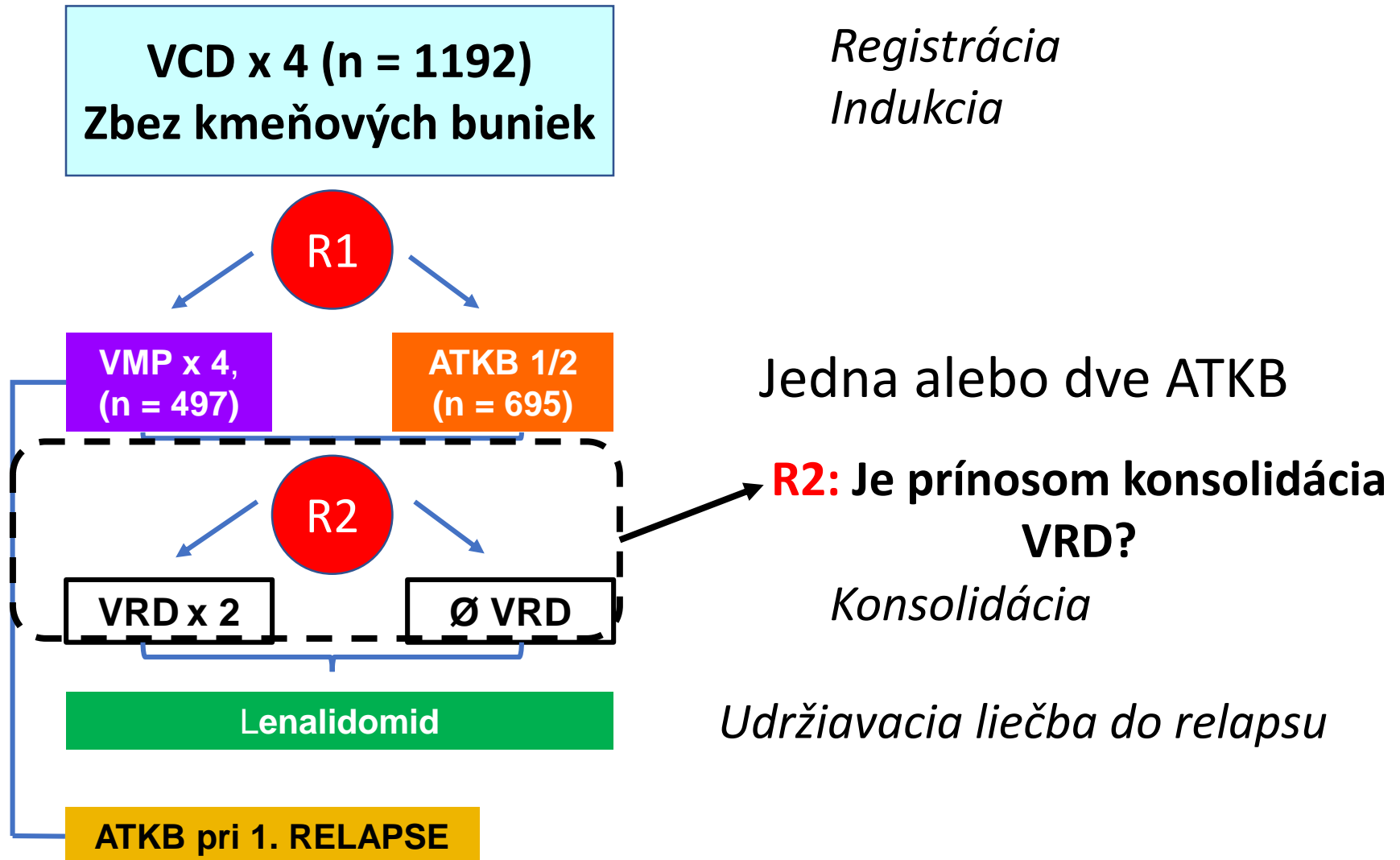
Jedna alebo dve ATKB

*Konsolidácia*

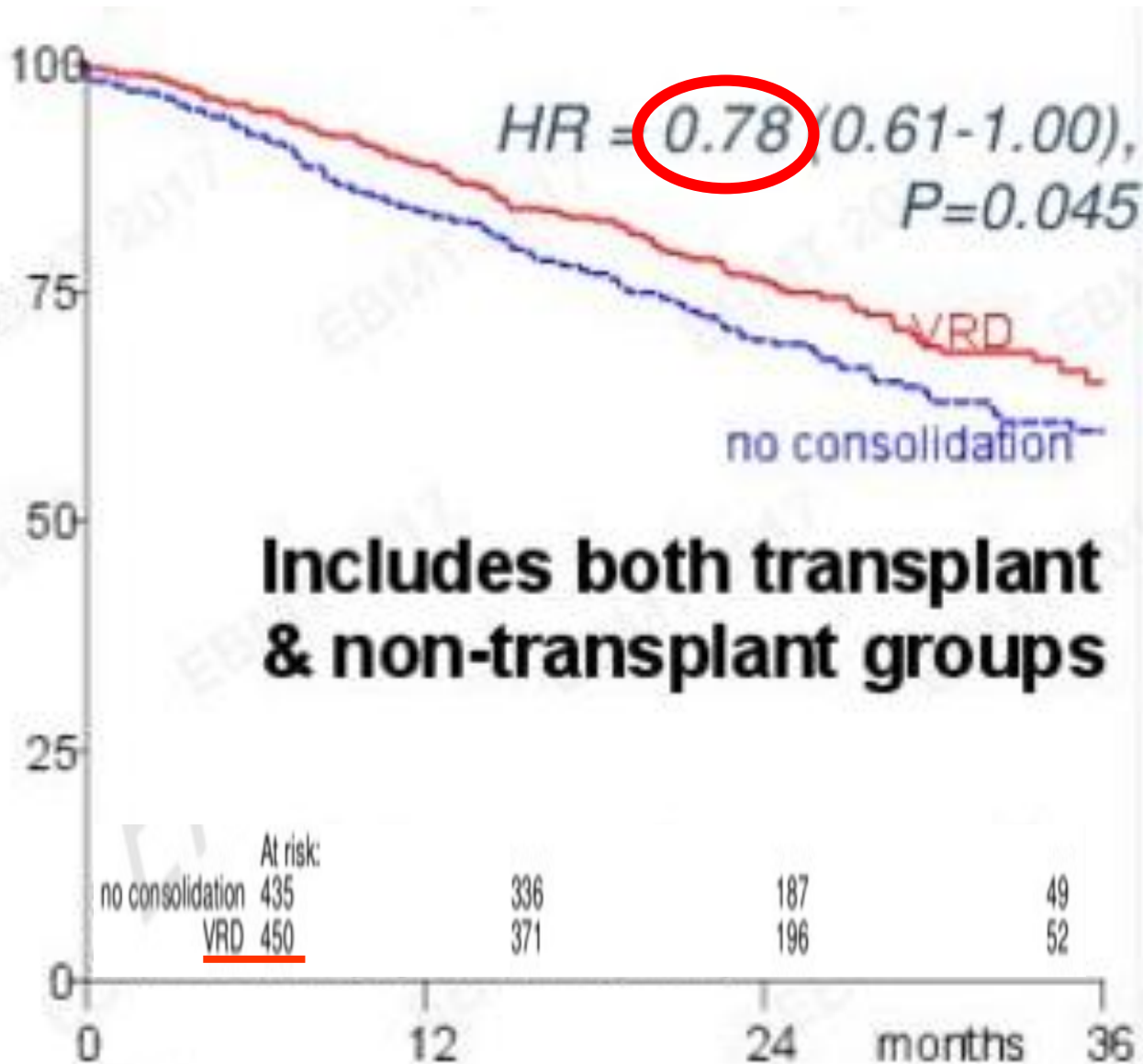
*Udržiavacia liečba do relapsu*



# Štúdia EMN02

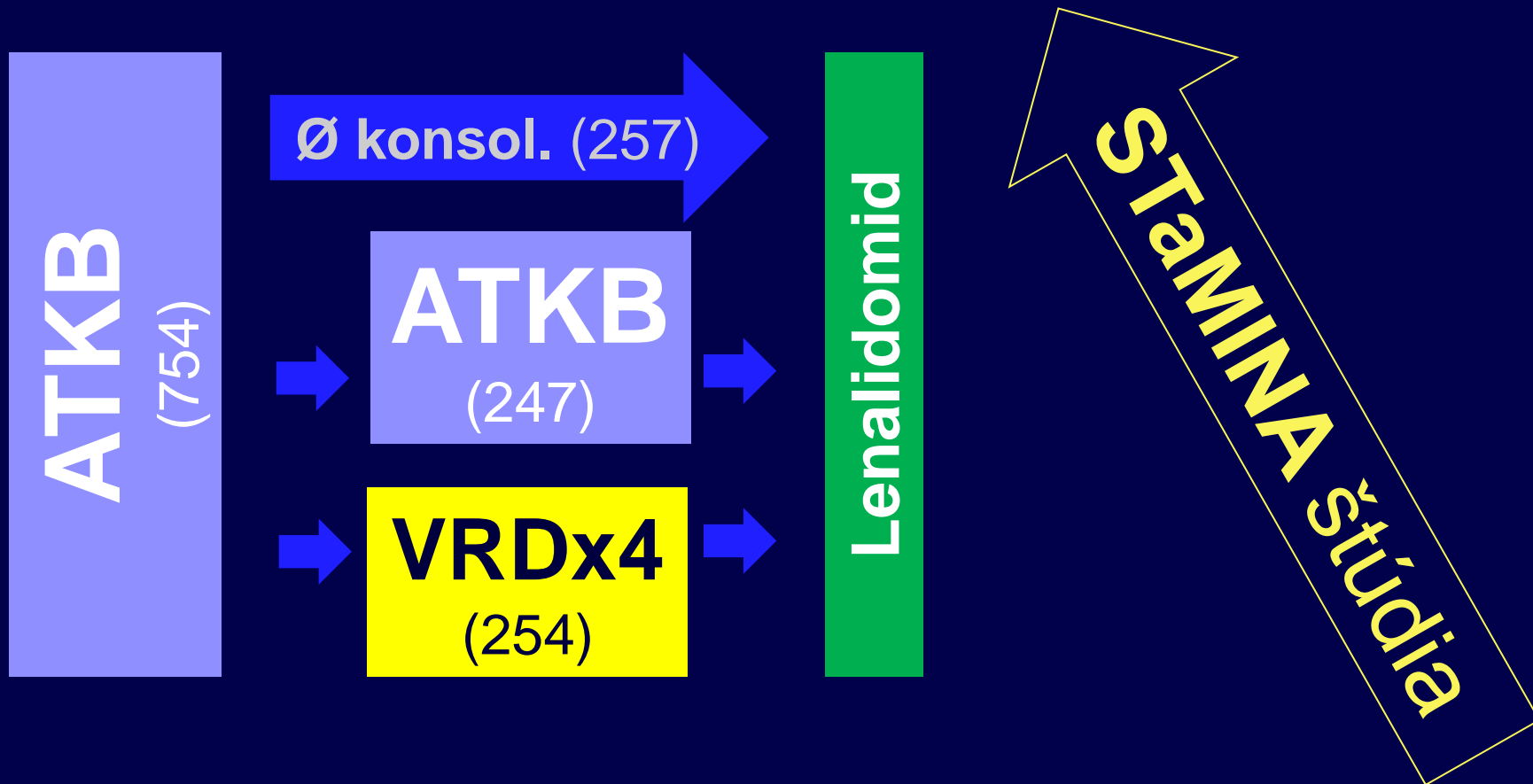


# PFS: konsolidácia VRd > ∅ konsolidácia

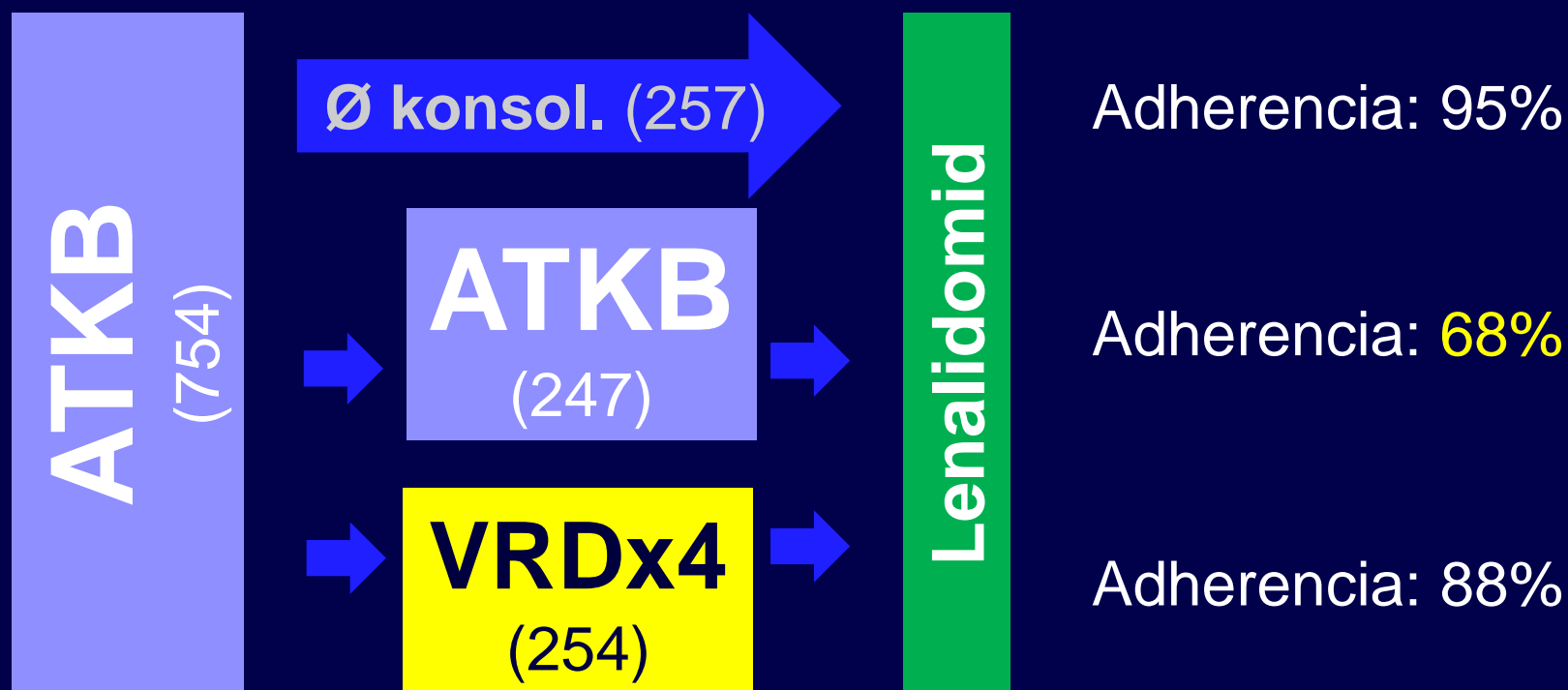


OS  
HR = 1.16 (0.76-1.75)  
P=0.5

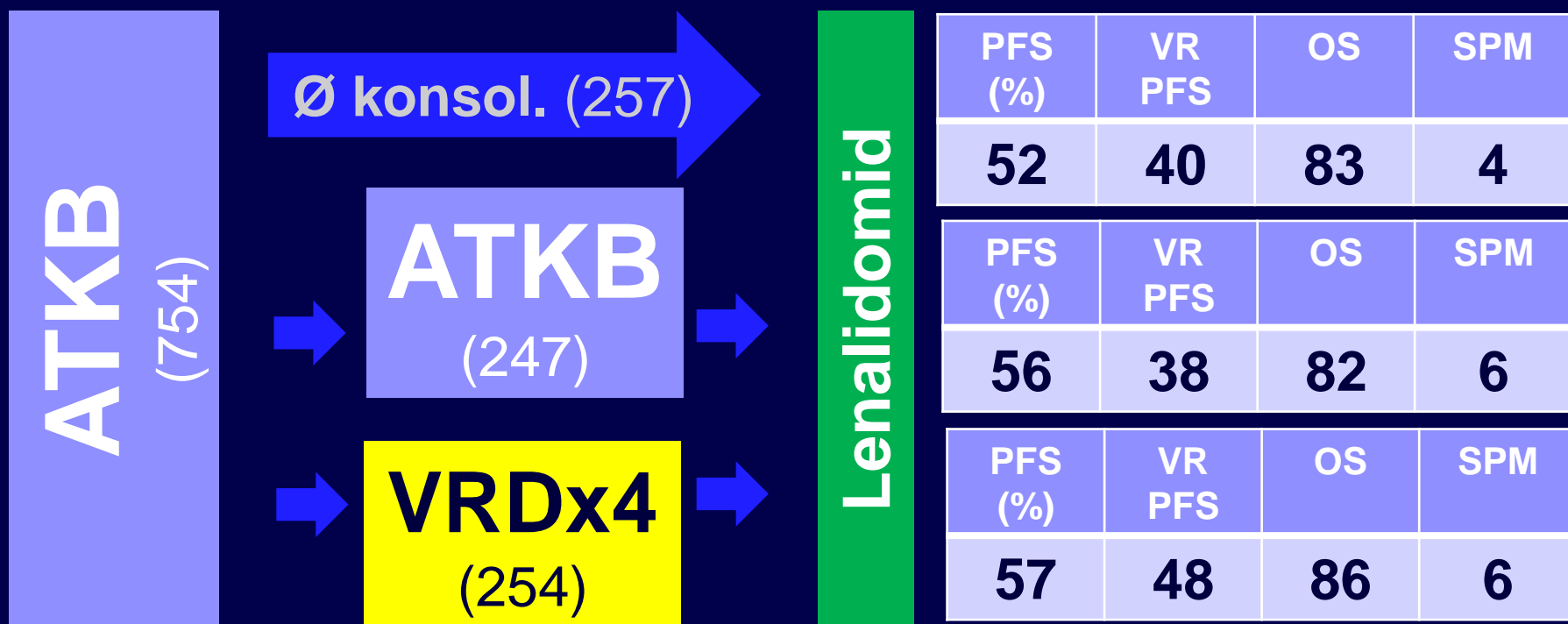
# Stem Cell Transplantation for Multiple Myeloma Incorporating Novel Agents



# STaMINA štúdia



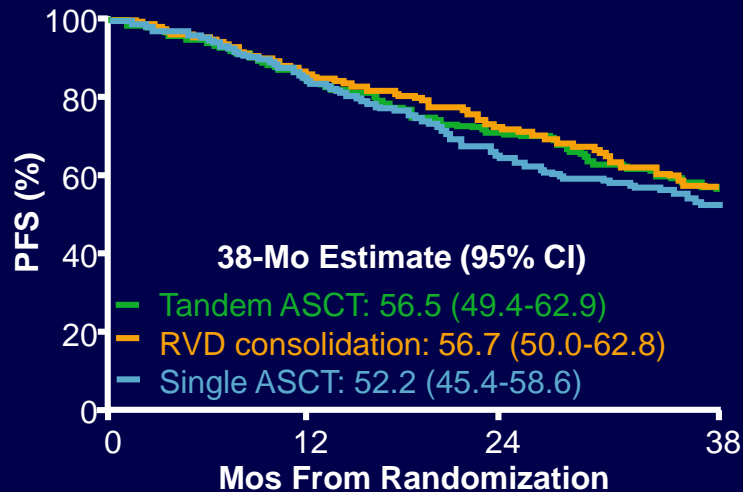
# STaMINA štúdia



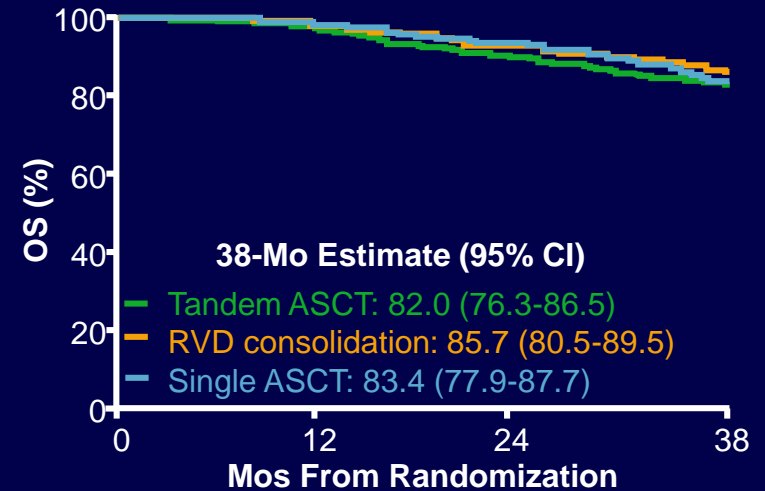
Všetky p-hodnoty = nesignifikantné

# STaMINA: PFS and OS for Overall Population

**PFS (Primary Endpoint)**



**OS**



**Pts at Risk, n**

	0	12	24	38
Tandem ASCT	247	200	153	87
RVD consolidation	254	215	172	99
Single ASCT	257	213	158	80

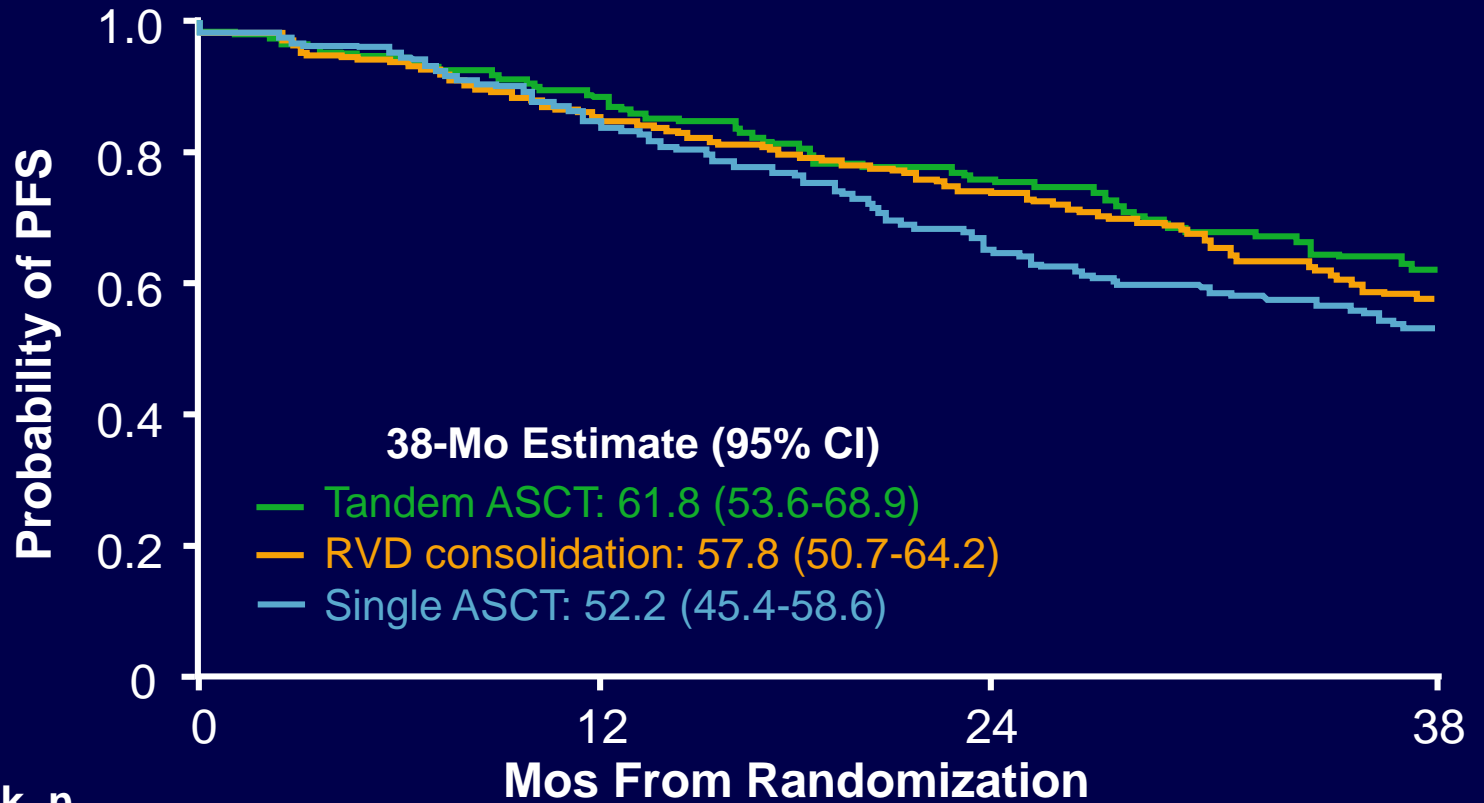
**Pts at Risk, n**

	0	12	24	38
Tandem ASCT	247	231	204	147
RVD consolidation	254	246	229	166
Single ASCT	257	247	227	148



Slide credit: [clinicaloptions.com](http://clinicaloptions.com)

# STaMINA: PFS as Treated/Per Protocol Analysis



PTs at Risk, n	0	12	24	38
Tandem ASCT	247	149	121	70
RVD consolidation	254	195	160	91
Single ASCT	257	212	157	79

**Potrebujeme trvalé odpovede po ATKB a konsolidácii:**

**Vplyv udržiavacej liečby**

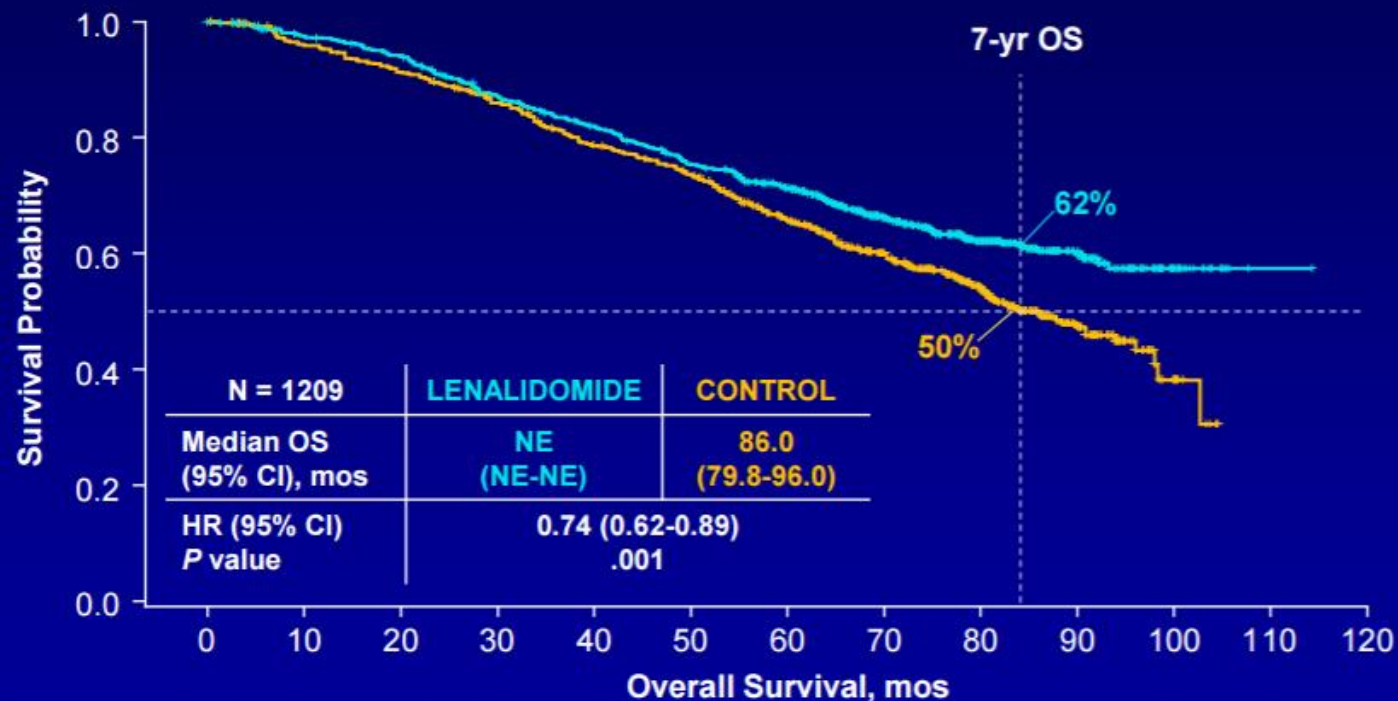


# **Lenalidomide Maintenance After High-Dose Melphalan and Autologous Stem Cell Transplant in Multiple Myeloma: A Meta-Analysis of Overall Survival**

**Michel Attal,<sup>1</sup> Antonio Palumbo,<sup>2</sup> Sarah A. Holstein,<sup>3</sup>  
Valérie Lauwers-Cances,<sup>1</sup> Maria Teresa Petrucci,<sup>4</sup> Paul Richardson,<sup>5</sup> Cyrille Hulin,<sup>6</sup>  
Patrizia Tosi,<sup>7</sup> Kenneth C. Anderson,<sup>5</sup> Denis Caillot,<sup>8</sup> Valeria Magarotto,<sup>9</sup>  
Philippe Moreau,<sup>10</sup> Gerald Marit,<sup>11</sup> Zhinuan Yu,<sup>12</sup> Philip L. McCarthy<sup>13</sup>**

# Overall Survival: Median Follow-Up of 80 Months

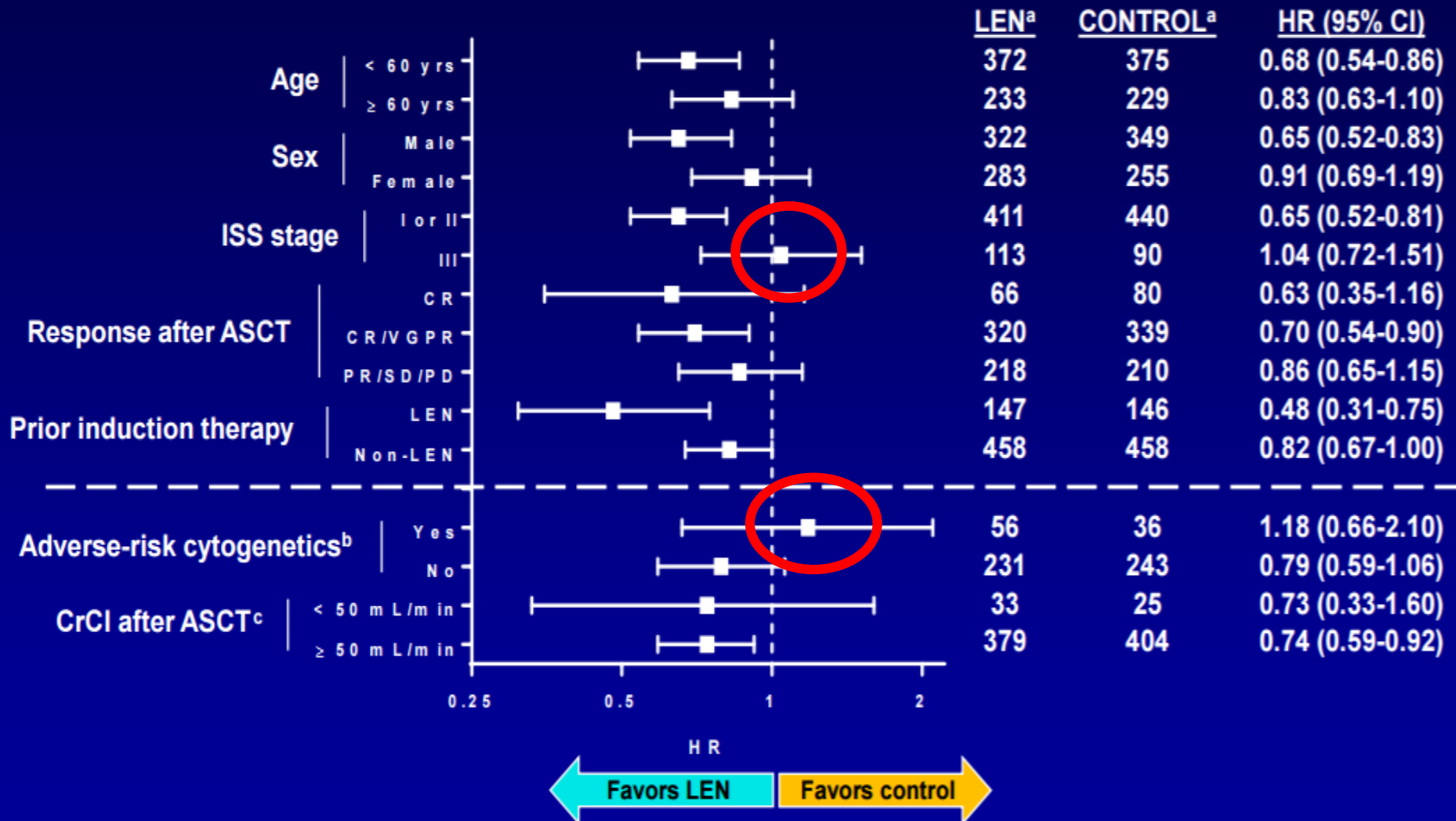
There is a 26% reduction in risk of death, representing an estimated 2.5-year increase in median survival<sup>a</sup>



Patients at risk	605	578	555	509	474	431	385	282	200	95	20	1	0
	604	569	542	505	458	425	350	271	174	71	10	0	

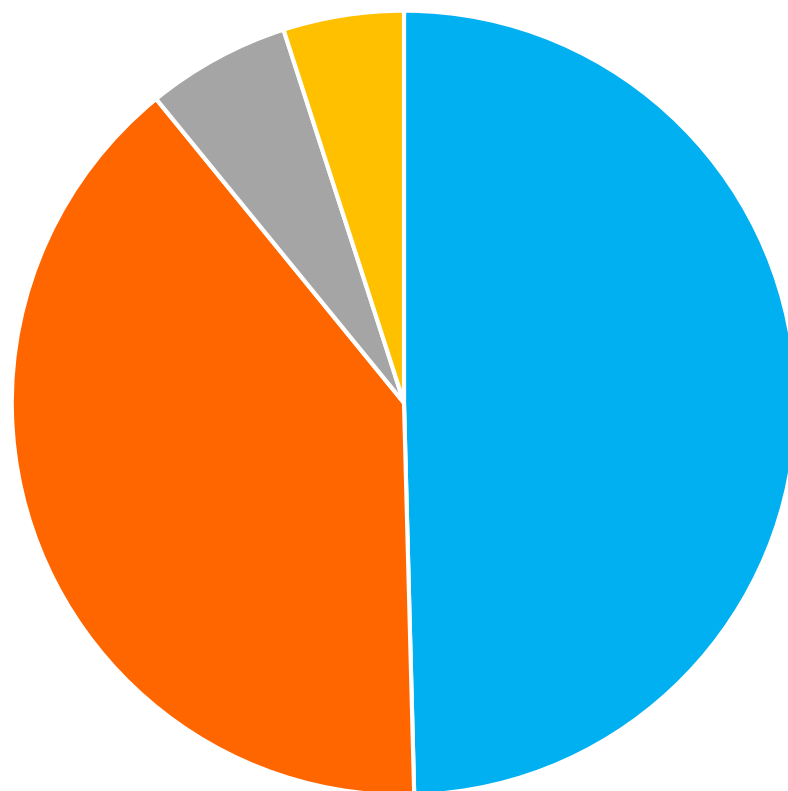
<sup>a</sup> Median for lenalidomide treatment arm was extrapolated to be 116 months based on median of the control arm and HR (median, 86 months; HR = 0.74). HR, hazard ratio; NE, not estimable; OS, overall survival.

# Overall Survival: Subgroup Analysis



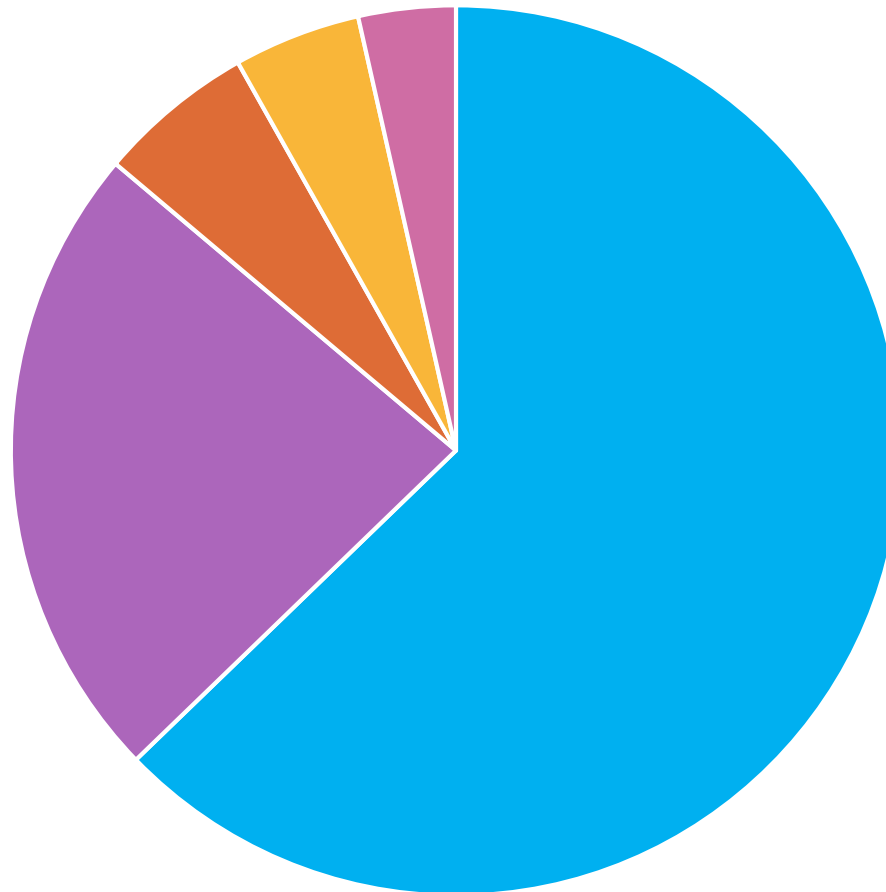
**Dôverujeme ATKB pri MM?**

# 845 ATKB v SR (2011-2016)



■ Myelóm ■ Lymfóm ■ solídny Ca ■ Akútna leukémia

# 368 ATKB 1996-4/2016

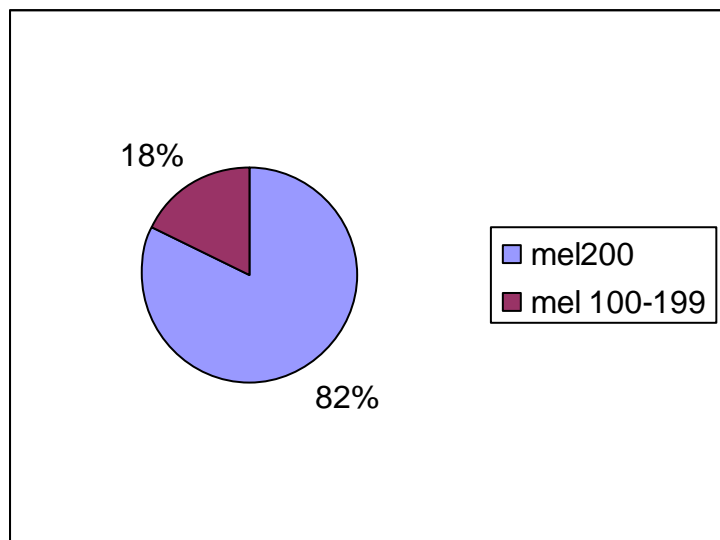


■ Myelóm ■ AML ■ CML ■ ALL ■ iné

# PRÍPRAVNÝ REŽIM A TRM 1.ATKB PRE MM

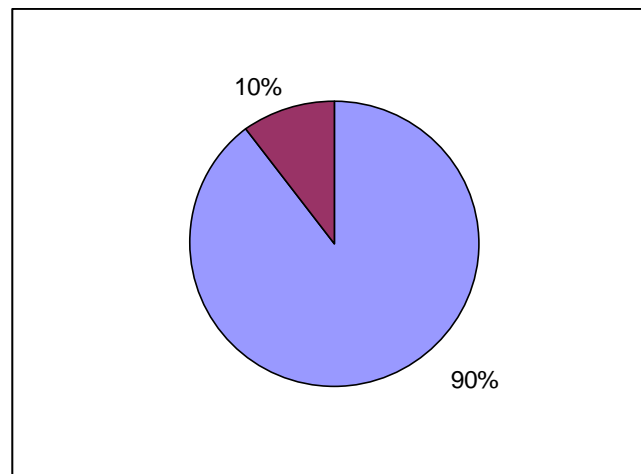
192 pacientov

Vek (r): medián 61 (33-69)



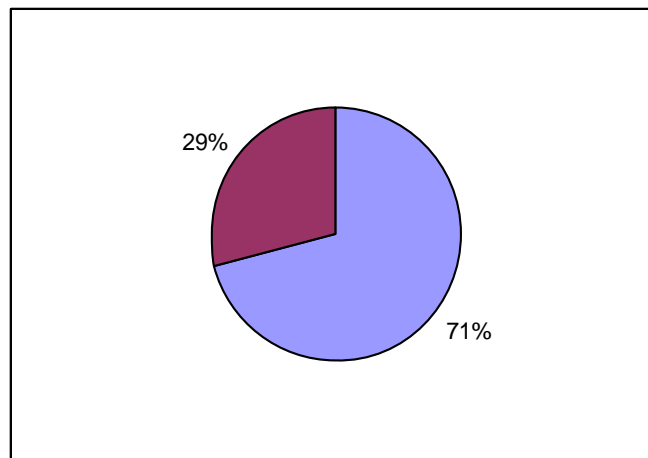
Mortalita do 100 dní:  
**1,56%** (3/192)

< 60 rokov



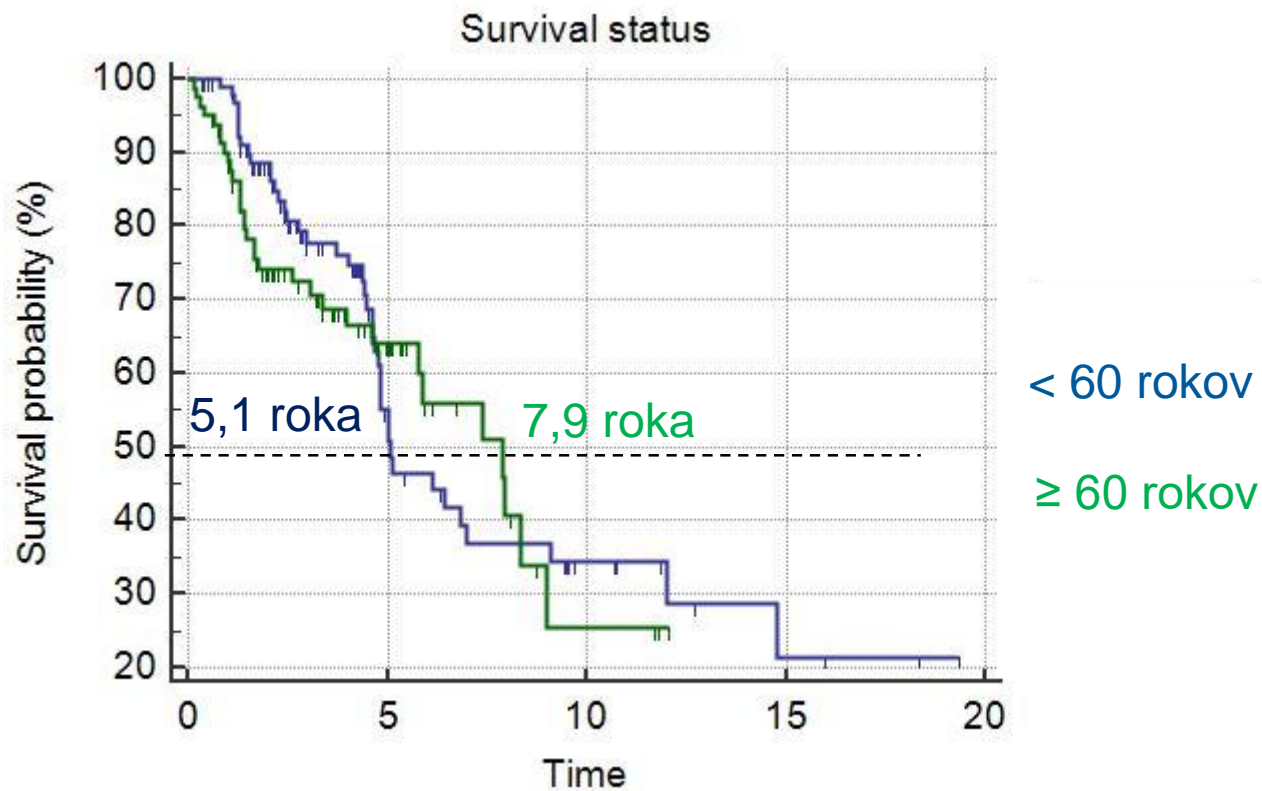
Mortalita do 100 dní: **0%**  
(0/106)

> 60 rokov



Mortalita do 100 dní: **3.5%**  
(3/86)

# PREŽÍVANIE PO 1.TKB



5-ročné prežívanie 55%

5-ročné prežívanie 63%



# HOSPITALIZÁCIA PO TKB

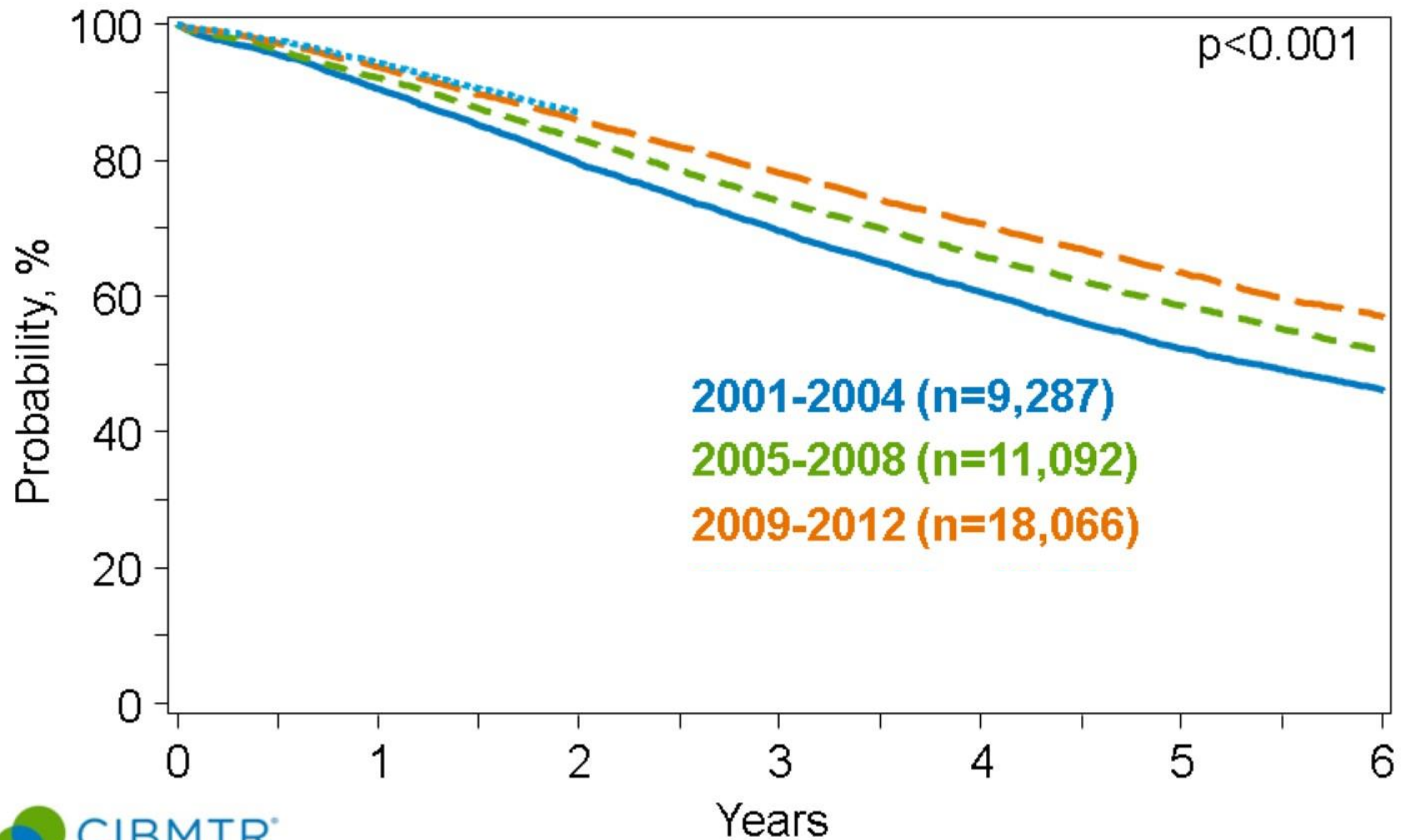
	<b>median (dni)</b>	min	max	valid cases	
CML	<b>34</b>	15	90	85	
AML	<b>24</b>	9	93	215	
<b>MM</b>	<b>13</b>	<b>0</b>	<b>32</b>	<b>202</b>	
ALL	<b>28</b>	10	99	89	
AA	<b>31</b>	14	57	27	
APL	<b>29</b>	14	47	9	
MPO/MDS	<b>23,5</b>	14	70	33	
OMF	<b>27,5</b>	20	69	12	štatistika malých čísel
PNH	<b>34</b>	19	42	7	
NHL	<b>14,5</b>	11	29	6	
HL	<b>24</b>			3	
CLL	<b>21</b>	18	45	10	

# NEUTROFILNÉ SEGMENTY $>0.5 \times 10^9/l$

	median (dni)	min	max	valid cases
CML	<b>21</b>	3	63	113
AML	<b>16</b>	7	69	242
MM	<b>11</b>	4	27	211
ALL	<b>19</b>	5	34	40
AA	<b>19</b>	12	40	27
APL	<b>17</b>	13	25	9
NHL	<b>12</b>	10	28	13
OMF	<b>18</b>	13	42	12
PNH	<b>19</b>	13	23	7
HL	<b>15</b>	30	34	5
CLL	<b>16</b>	12	31	10

štatistika  
malých  
čísel

# Trends in survival after Autologous HCT for Multiple Myeloma, 2001-2014

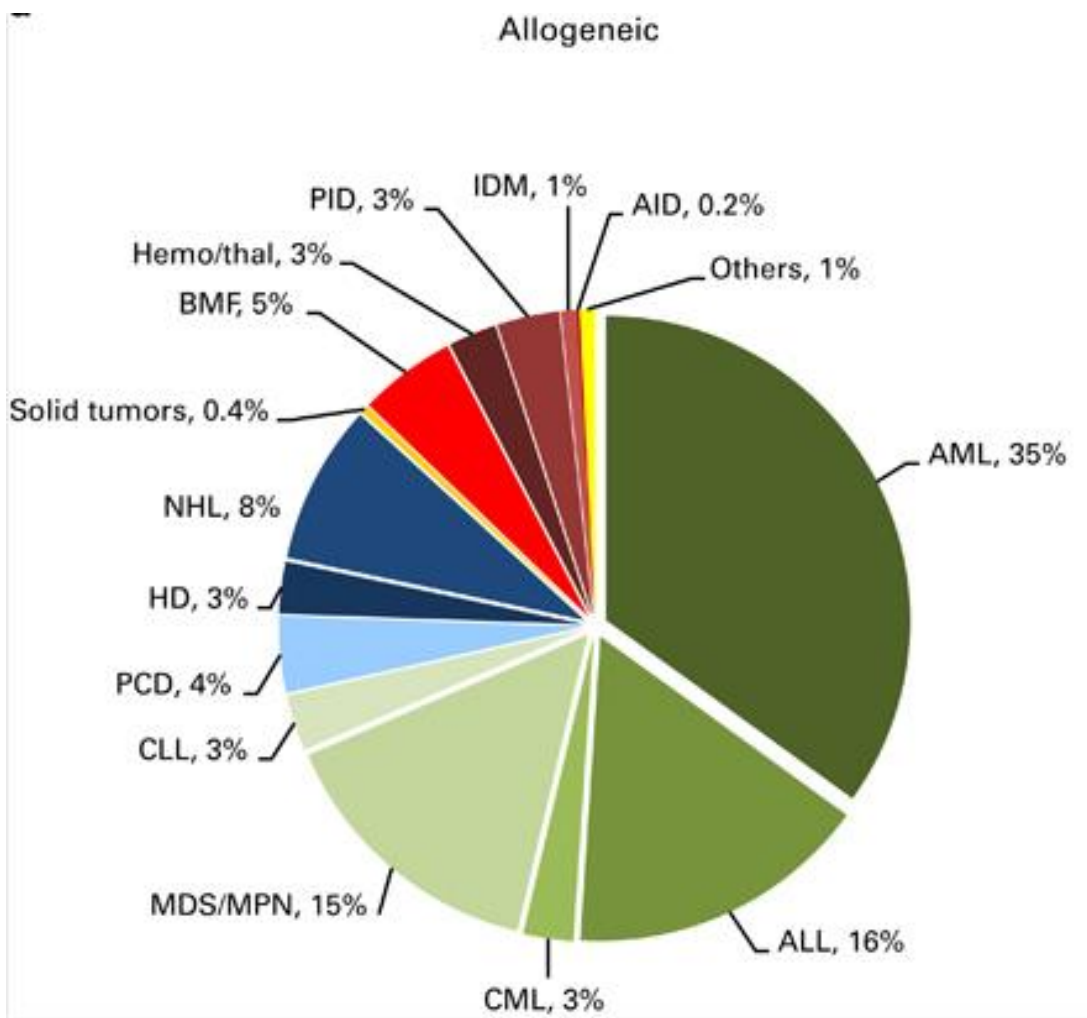


# Záver

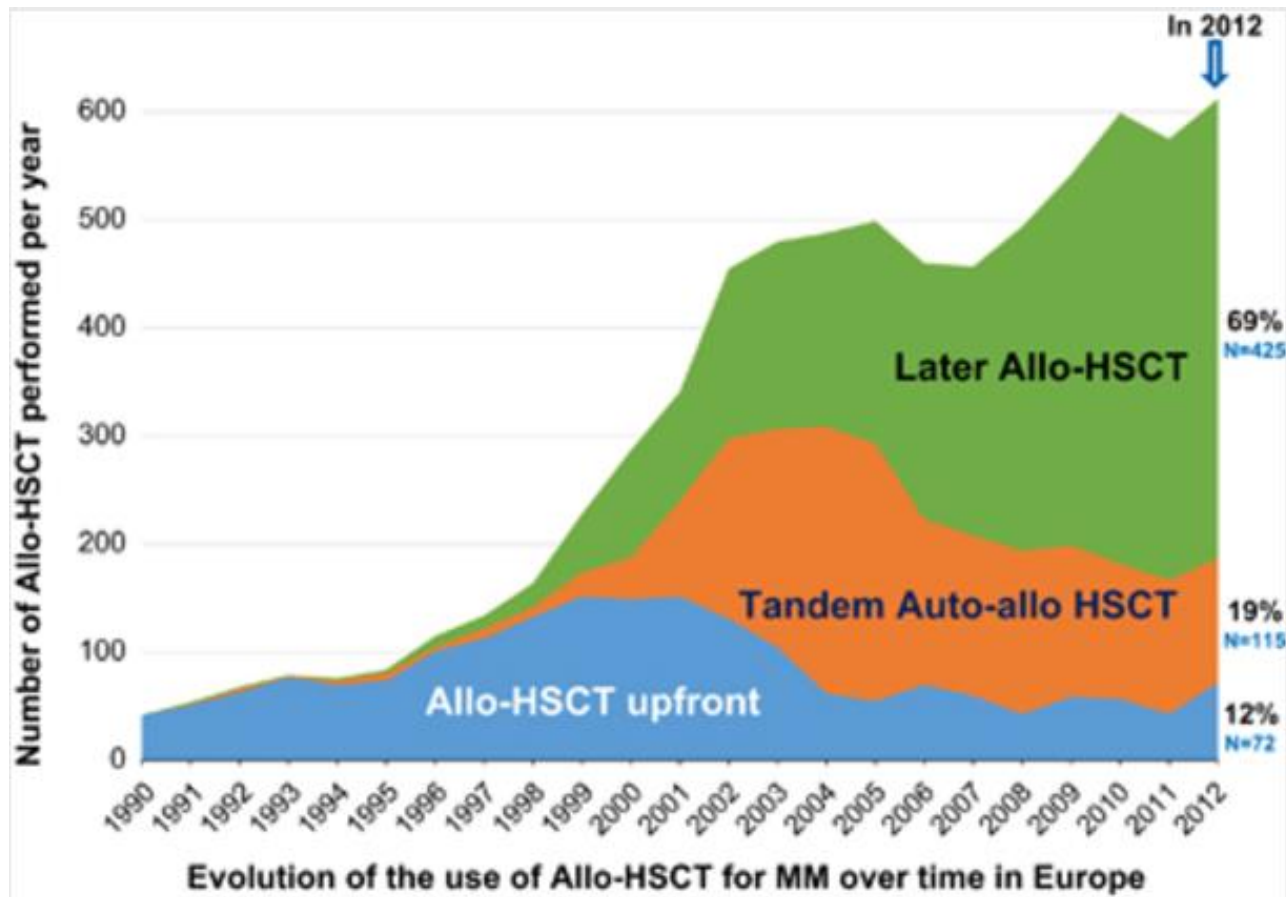
- **ATKB v prvej línii++** VS odložená: IFM2009, EMN02
- **Jedna alebo tandemová ATKB**: MM s vysokým rizikom,...
- **Konsolidácia: ÁNO** alebo nie?
- **Udržiavacia liečba: ÁNO** pre všetkých?

**Aké má postavenie alogénna TKB  
pri MM?**

# Podiel indikácií aloTx v Európe v r 2013



# Vývoj stratégií alogénnej TKB pre MM



# **Alogénna TKB pre MM**

Účinná záchranná liečba



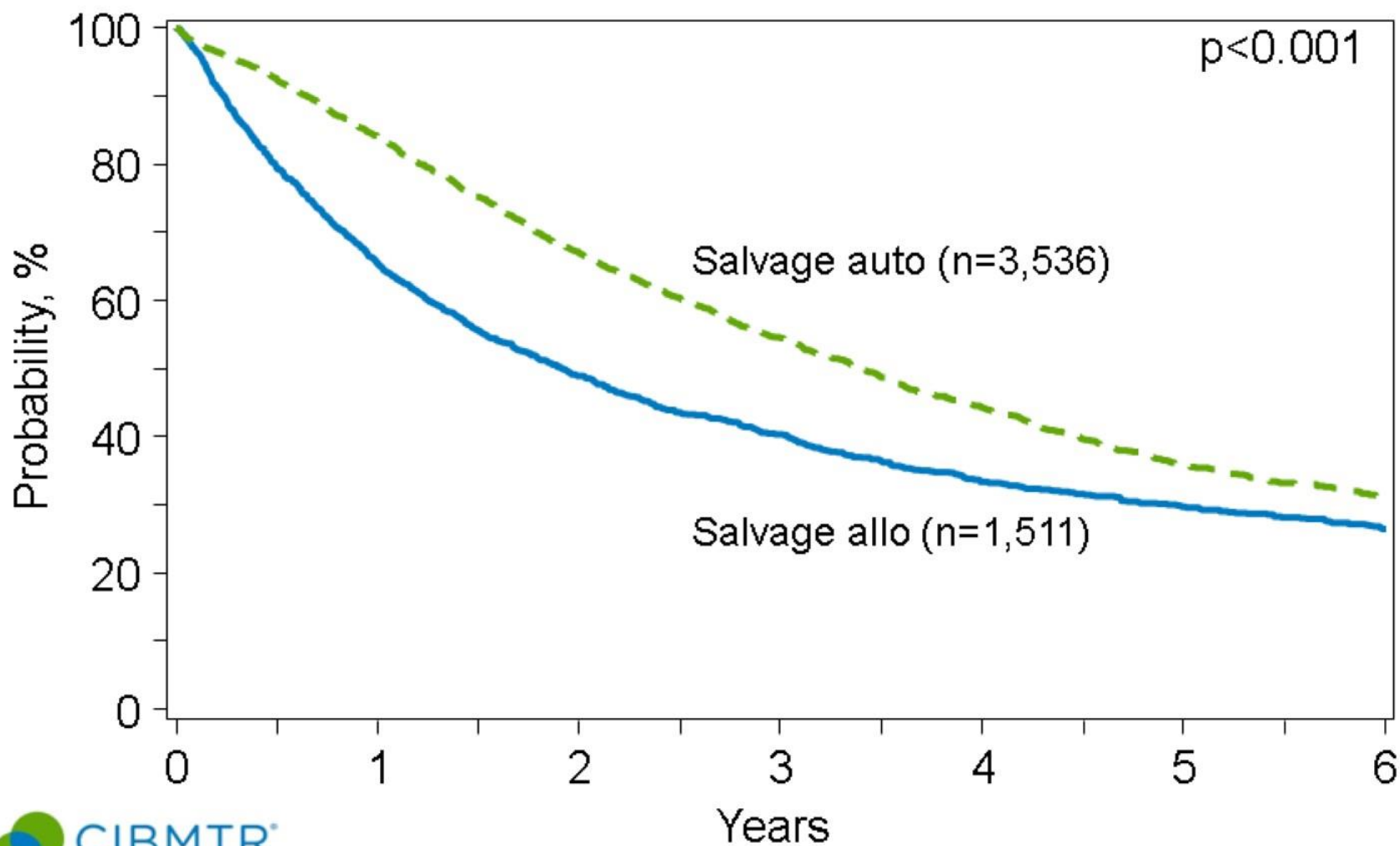
# Alogénna TKB pre MM

Účinná záchranná liečba

RIC-aloTKB 2 r PFS 42% a OS 54%

Smith E, Devlin SM, Kosuri S et al. CD34-Selected Allogeneic Hematopoietic Stem Cell Transplantation for Patients with Relapsed, High-Risk Multiple Myeloma. Biol Blood Marrow Transplant 2016;22:258-267.

# Survival after Salvage HCT for Multiple Myeloma, 2004-2014



# Alogénna TKB pre MM

Účinná záchranná liečba

RIC-aloTKB 2 r PFS 42% a OS 54%

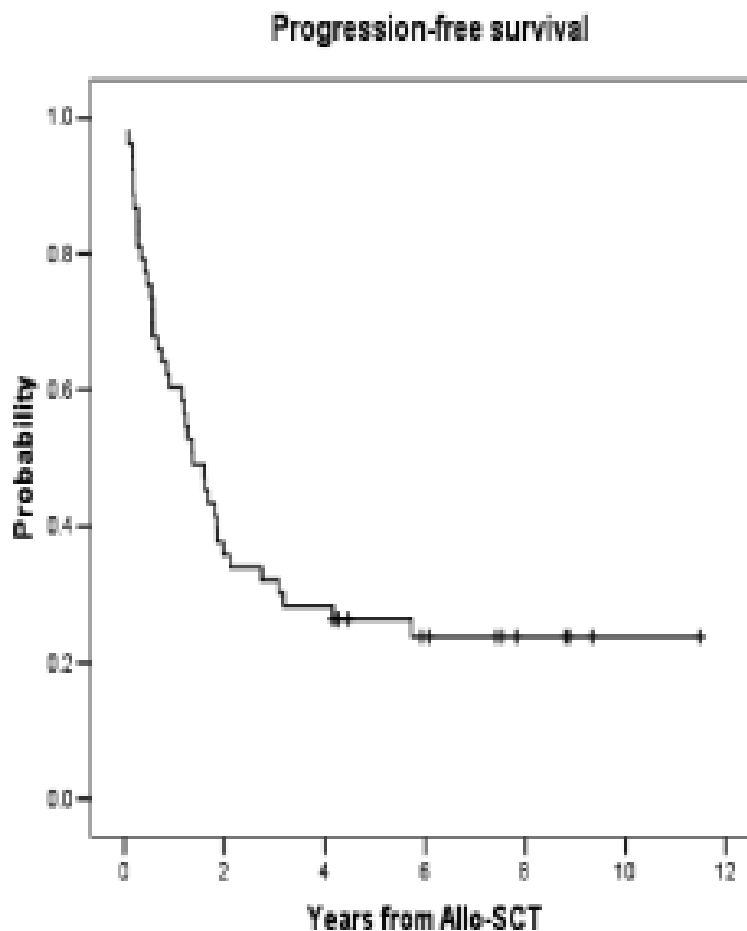
Máme dôkazy o reakcii štepu voči  
myelómu (GVM)

# Dôkazy GVM

- Plateau po RIC

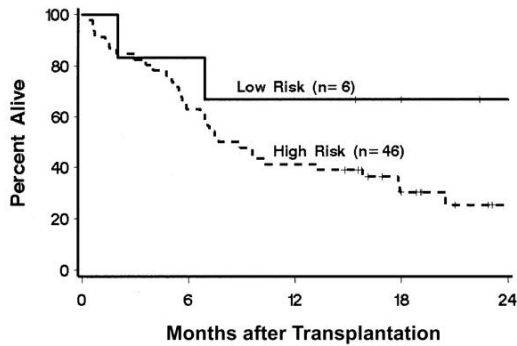
?

# Krivka PFS po RIC-TKB pre MM sa stabilizuje po 6 rokoch od aloTKB

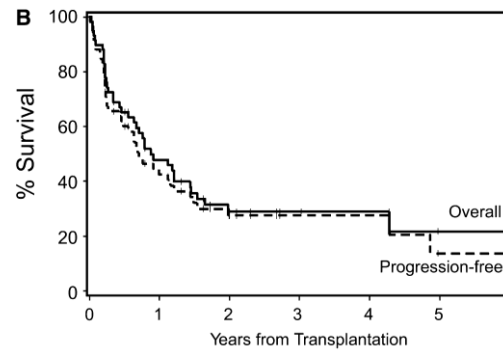


# Celkové prežívanie po RIC – TKB pre MM

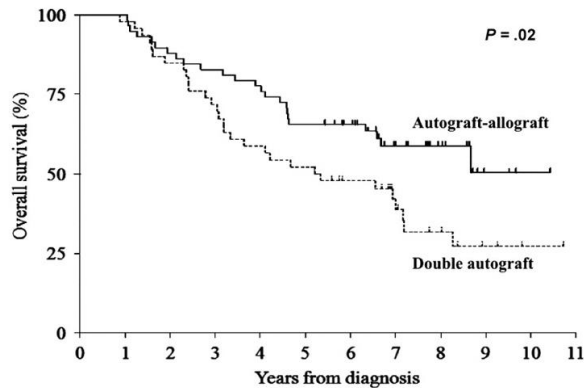
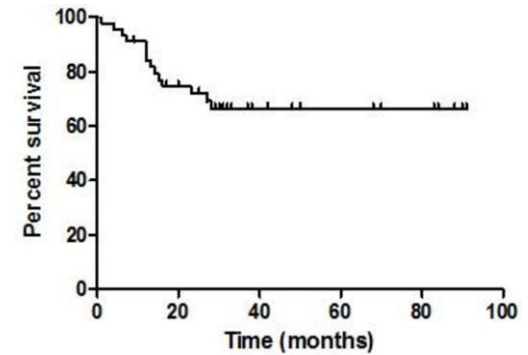
Niederwieser et al. Blood 2003



Nakamae et al., BBMT 2010

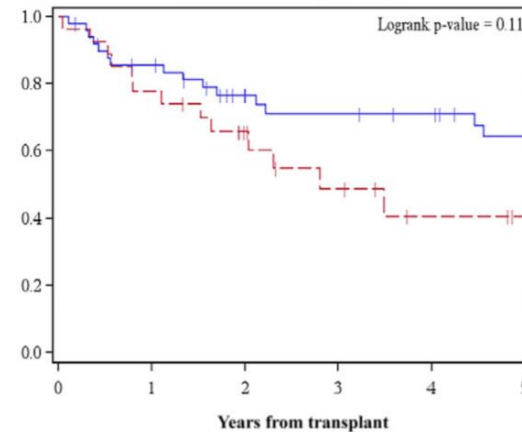


Shipton et al. Blood 2015



Giaccone et al. Blood 2011

Overall survival by FISH risk



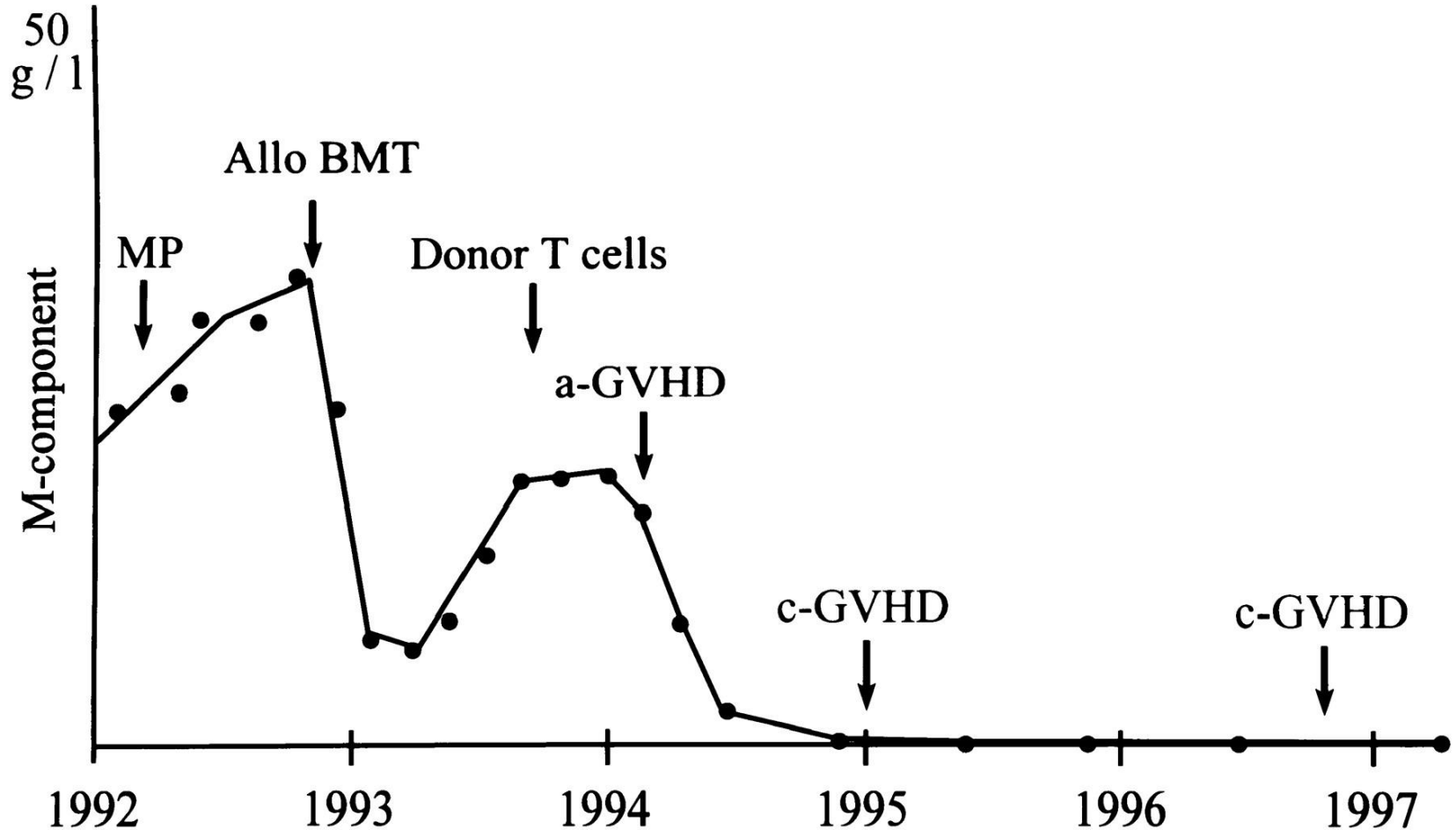
Dhakar et al., ClinLyMMLeuk 2016

# Dôkazy GVM

- Plateau po RIC ✓
- Efektivita transfúzie darcových lymfocytov ?

# Odpoved' M proteínu na DLI

## Pacient s relapsom MM po alogénnej TKD





# DLI pri MM

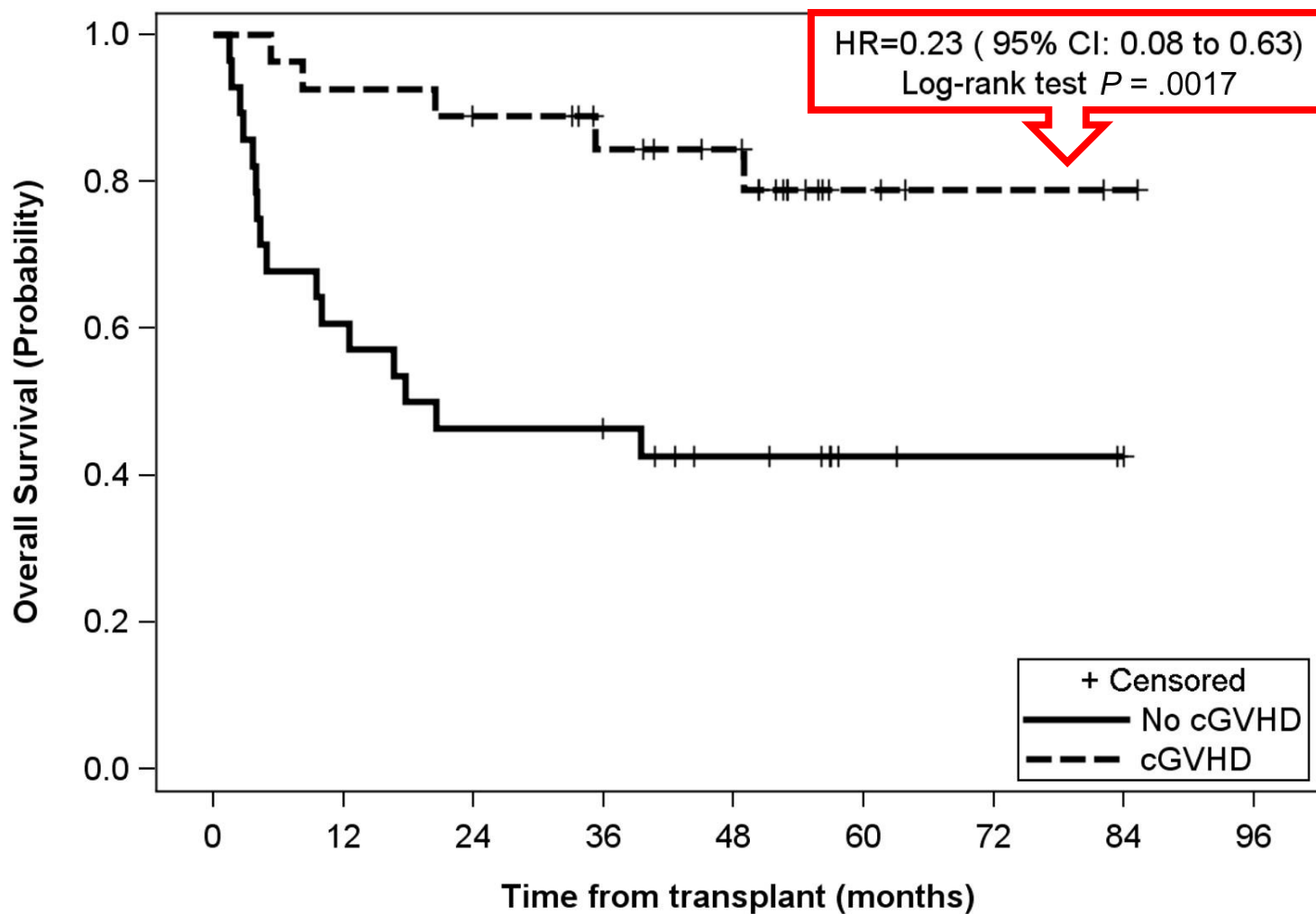
- EBMT register
- 70 pacientov preemptívne (chimérizmus/ zvyšková choroba): KR 23% a PR 40% = **ORR 63%**
- 46 pacientov pre RELAPS/ PROGRESIU: KR 15% a PR 37% = **ORR 52%**

Crawley C, Lalancette M, Szydlo K, et al. Outcomes for reduced intensity allogeneic transplantation for multiple myeloma: an analysis of prognostic factors from the Chronic Leukaemia Working Party of the EBMT. Blood. 2005;105:4532-4539.

# Dôkazy GVM

- Plateau po RIC ✓
- Efektivita transfúzie darcových lymfocytov ✓
- Ochranný účinok chronickej GVHD ?

# Chronická GVHD má ochranný účinek



# Dôkazy GVM

- Plateau po RIC ✓
- Efektivita transfúzie darcových lymfocytov ✓
- Ochranný účinok chronickej GVHD ✓
  
- Vysadenie imunosupresie
- Kinetika minimálnej zvyšnej choroby
- Škodlivý vplyv T bunkovej deplécie

# Alogénna TKB pre MM

Účinná záchranná liečba

RIC-aloTKB 2 r PFS 68% a OS 85%

Máme dôkazy o reakcii štepu voči leukémii (GVL)

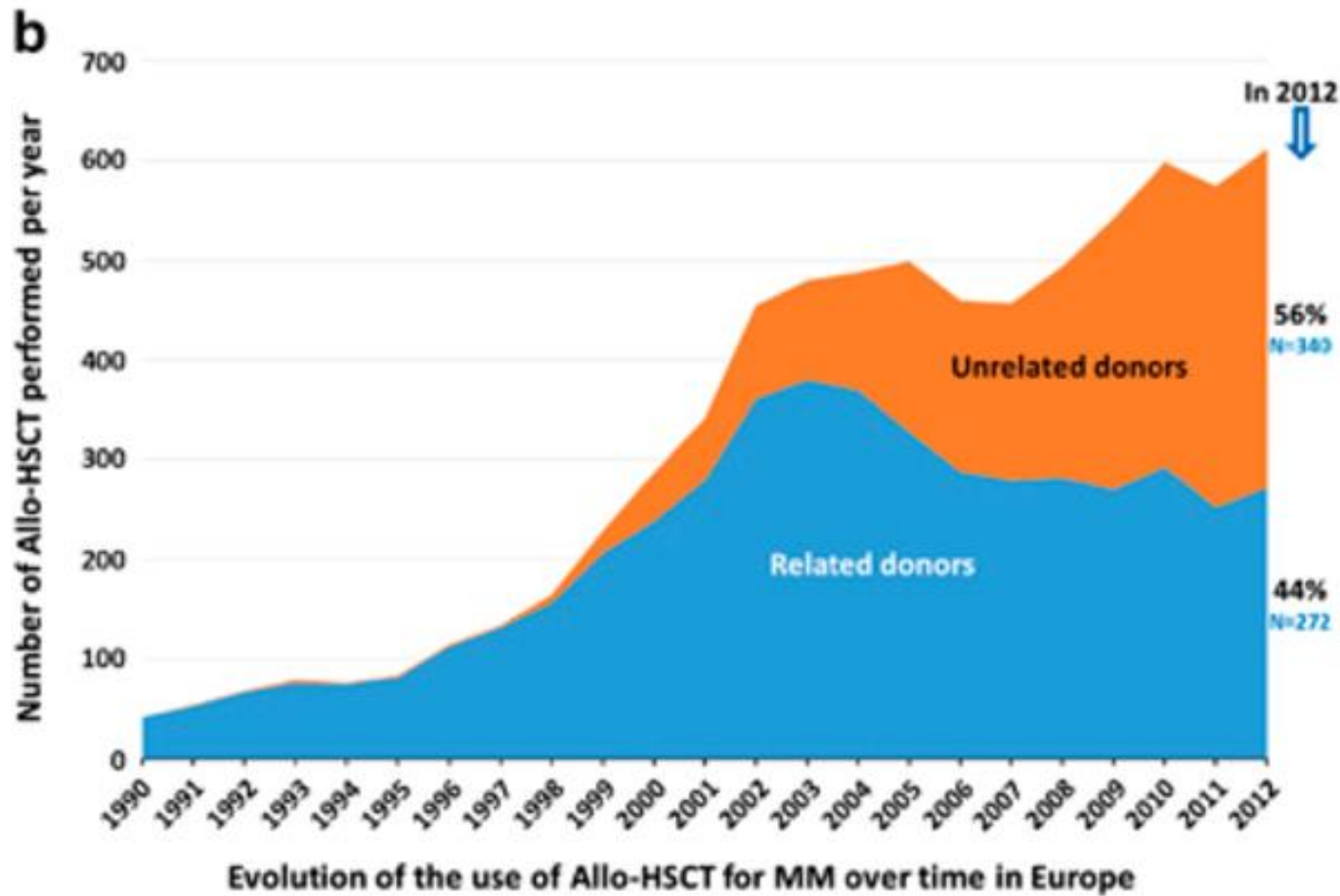
ALE.....

Mnohí chorí s MM sú príliš krehkí/ postarší na TKB

Menej ako 30% pacientov má súrodeneckého darcu

Zvýšené použitie alternatívnych darcov

# Ročný počet alotransplantácií pre MM



**Kedy alogénna TKB pri MM?**

# Alogénna TKB pre MM

- Mladší pacienti: do 65 rokov
- Vhodní na aloTKB
- WHO výkonnostný stav 0-2





# Alogénna TKB pre MM

Pri RELAPSE (všetky body!):

- 1. včasný 1. relaps** (< 18 mesiacov od prvolíniovej liečby aj s ATKB = **rezistencia na vysoké dávky melfalanu**)
- 2. dosiahnutie  $\geq$  VGPR** záchrannou liečbou
- 3. maximálne 3 línie** záchrannej liečby RELAPSU dosiahli  $\geq$  VGPR
- 4. Pred aloTKB** radioterapia PET/CT ložísk

# V PRVEJ LÍNII auto-alo vs auto-auto

Autori	No. Pacientov	CR (%)	PFS	OS	NRM (%)
Bruno NEJM 2007 Giaccone Blood 2011	58/46 súrodenec	55 vs 26	35 vs 29 mes  39 vs 33 mes	80 vs 54 mes  8 r vs 5.3 r	10 vs 2
Krishnan Lancet Oncol 2011	226/484 súrodenec		SR: 3r 43% vs 46% VR: 3r 40% vs 33%	SR: 3r 77% vs 80% VR: 3r 59% vs 67%	11 vs 4
Bjorkstrand JCO 2011 Gahrton Blood 2013	108/249 súrodenec		8 r 22% vs 12% VR: 21% vs 5%	8 r 49% vs 36% VR: 47% vs 31%	13 vs 3

# Alogénna TKB pre MM: konsenzus?

V prvej línii môže prichádzať do úvahy (všetky body):

1. Pacient  $\leq$  50 rokov
2. ak ATKB 1 dosiahla  $\geq$ VGPR
3. VR MM:
  - t(4;14), t(14;16), t(14;20), del 17p, del 1p, amp 1q;alebo
  - LDH x 2 a ISS III

# Záver - aloTKB

**Záchranná AloTKB = pri prvom včasnom RELAPSE**

**Musí sa navodiť minimálne VGPR (maximálne 3 línie reindukcie)**

**Mladší chorý, výborne spolupracujúci, so súrodeneckým darcom, dobré rodinné zázemie,....**