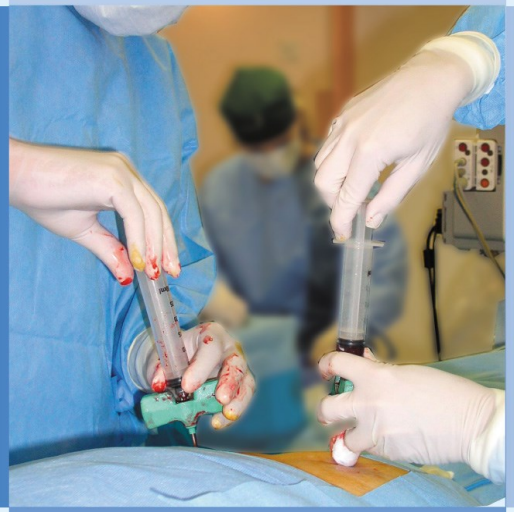
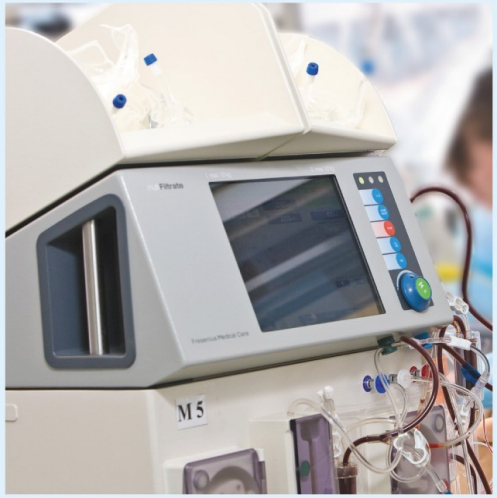
Roman Hájek



Lenalidomid - co máme používat? MPR nebo Rd



www.fno.cz

February 2015

REVLIMID (Lenalidomide) Approved by the European Commission for the Treatment of Adult Patients with Previously Untreated Multiple Myeloma who are Not Eligible for Transplant

Aktuální verze SPC Revlimid

Nová terapeutická indikace

Mnohočetný myelom

Revlimid je indikován k léčbě dospělých pacientů s doposud neléčeným mnohočetným myelomem, kteří nejsou vhodnými kandidáty pro transplantaci

Aktuální verze SPC Revlimid

Dávkování a způsob podání

Nově diagnostikovaný mnohočetný myelom

Lenalidomid v kombinaci s dexamethasonem *až do progrese onemocnění u pacientů, kteří nejsou vhodnými kandidáty pro transplantaci*

Lenalidomid v kombinaci s melfalanem a prednisonem *s následnou udržovací monoterapií u pacientů, kteří nejsou vhodnými kandidáty na transplantaci*

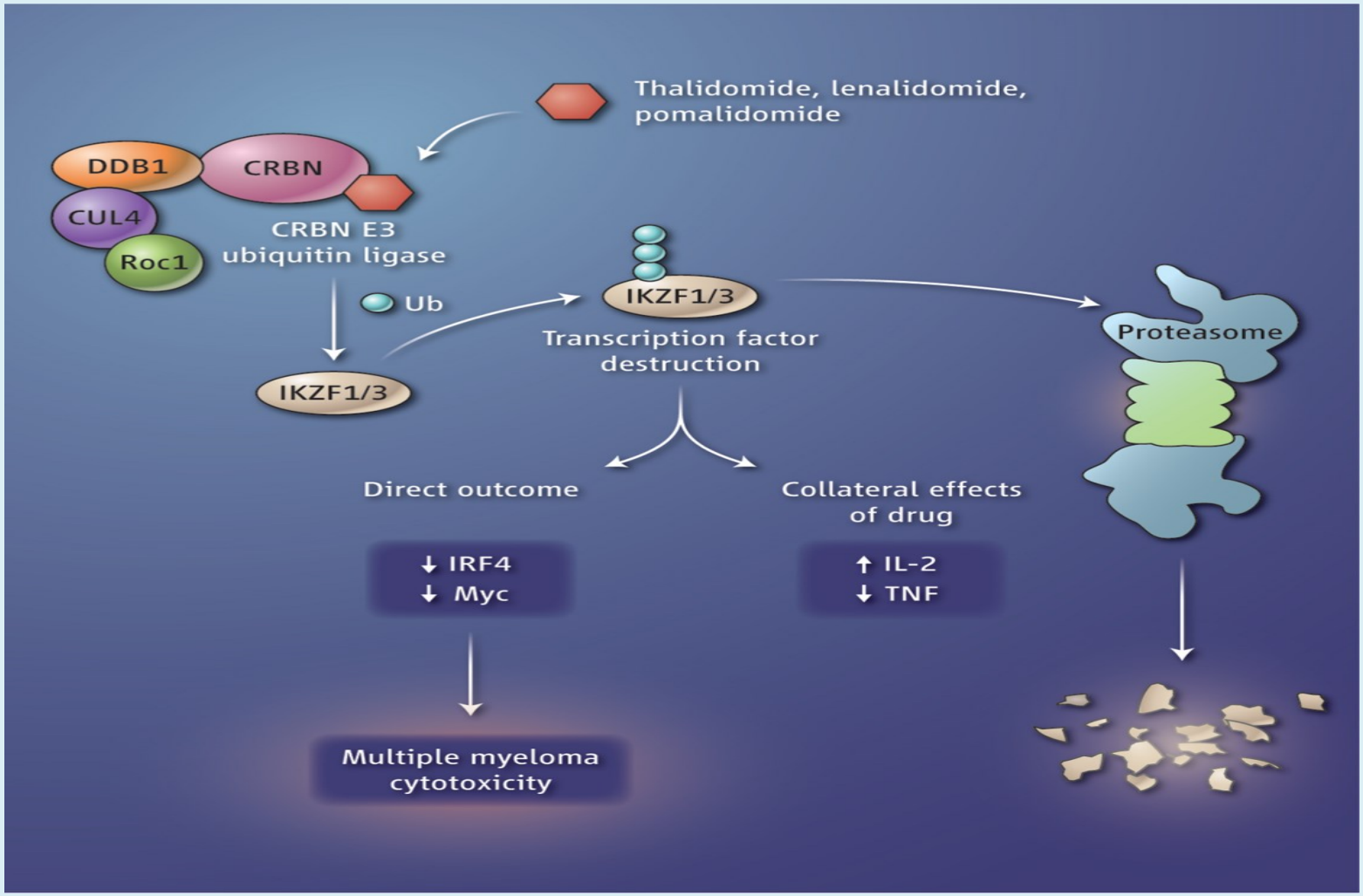
Začneme ale od vědy

Immunomodulatory drugs

- IMiDs agents bind to cereblon, a component of a ubiquitin ligase complex, altering the specificity of the complex to induce the ubiquitylation and degradation of Ikaros (IKZF1) and Aiolos (IKZF3), transcription factors essential for MM growth

Licht *et al*, Cancer Cell, 2014; Lu *et al*, Science, 2014; Krönke *et al*, Science, 2014; Gandhi *et al*, Br J Haematol, 2014

Immunomodulatory drugs



Adopted from: www.sciencemag.com

Začneme ale od vědy

Dnes máme lépe vyjasněno (vědecký podklad) toho, proč působí imunomodulační látky nejen PŘÍMO proti nádoru,

ale

I NEPŘÍMO stimulací imunitního systému

Jestliže tedy budeme diskutovat a v reálné praxi se rozhodovat mezi použitím lenalidomidu v JAKÉMKOLIV REŽIMU, tak nezapomeňme na nejpodstatnější:

Lenalidomid je nejúčinnější, pokud je používán dlouhodobě!

MPR vs. Ld

Toxicita a bezpečnost

IMiDs - toxic profiles

Drug	Thalidomide	Lenalidomide	Pomalidomide
Teratogenicity	+++	+++	+++
Neuropathy	+++	+	+
Frequent AEs	Peripheral polyneuropathy, VTE, obstipation, drowsiness	Neutropenia, thrombocytopenia, VTE, fatigue, skin rash	Neutropenia, anemia, thrombocytopenia, VTE
Prophylaxis of VTE	YES	YES	YES
Metabolic pathway	Non-enzymatic hydrolysis	kidney	liver

IMiDs - toxic profiles

Drug	Thalidomide	Lenalidomide	Pomalidomide
Teratogenicity	+++	+++	+++
Frequent AEs	polyneuropathy, VTE, obstipation, drowsiness	thrombocytopenia, VTE, fatigue, skin rash	anemia, thrombocytopenia, VTE
Prophylaxis of VTE	YES	YES	YES
Metabolic pathway	Non-enzymatic hydrolysis	kidney	liver

Sekundární primární nádory

Sekundární primární nádory

Lenalidomide - safety

- Which drug should not be administered in combination with lenalidomide because of increased risk of haematological second primary malignancies?

Palumbo *et al*, Lancet Oncology, 2014

Lenalidomide - safety

- Which drug should not be administered in combination with lenalidomide because of increased risk of haematological second primary malignancies?

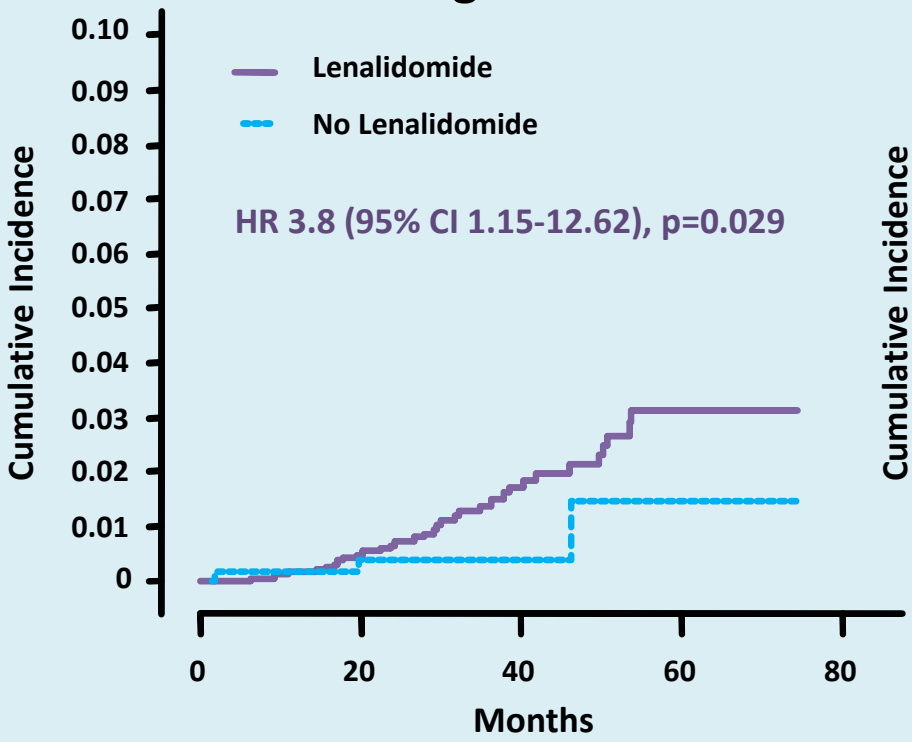
2) **oral melphalan!** (HR: 4, 86)

→ combination of oral melphalan + lenalidomide is **DEAD**!

Palumbo *et al*, Lancet Oncology, 2014

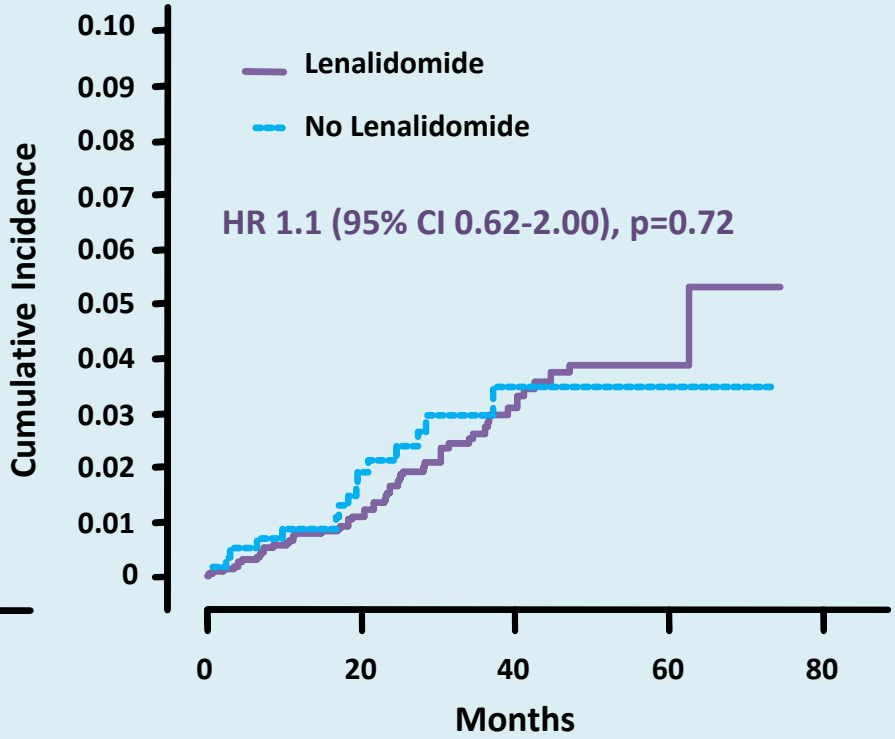
Cumulative incidence of SPMs

Haematologic 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



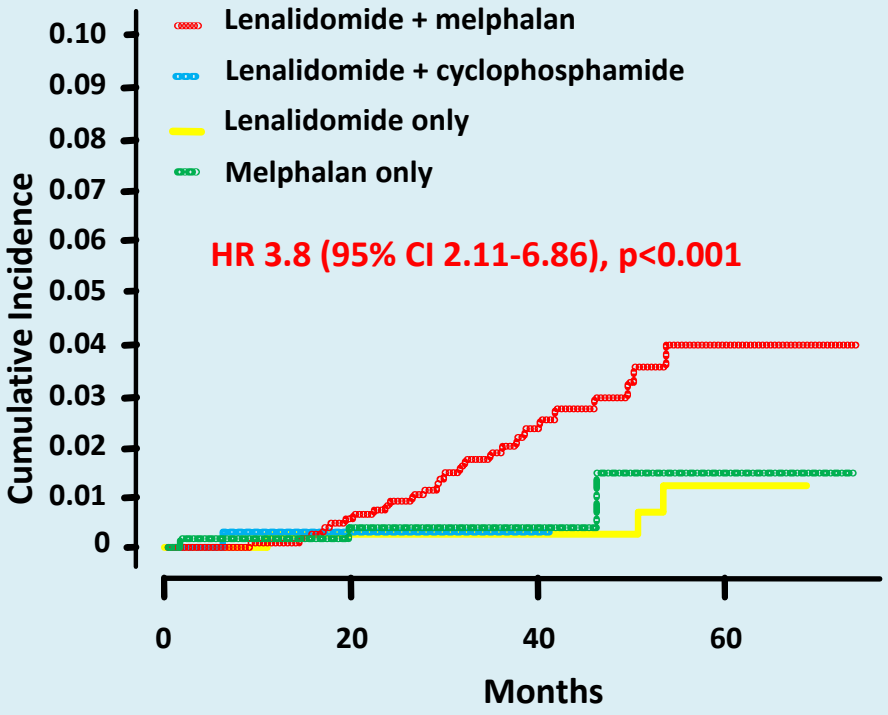
Cumulative incidence (95% CI)	36 months	60 months
Lenalidomide	2.6 (1.8 - 3.3)	3.8 (2.7 - 4.9)
No Lenalidomide	2.9 (1.4 - 4.4)	3.4 (1.6 - 5.2)

Palumbo, ASCO 2013: Second primary malignancies in NDMM treated with lenalidomide: meta-analysis of 6383..

Cumulative incidence of SPMs

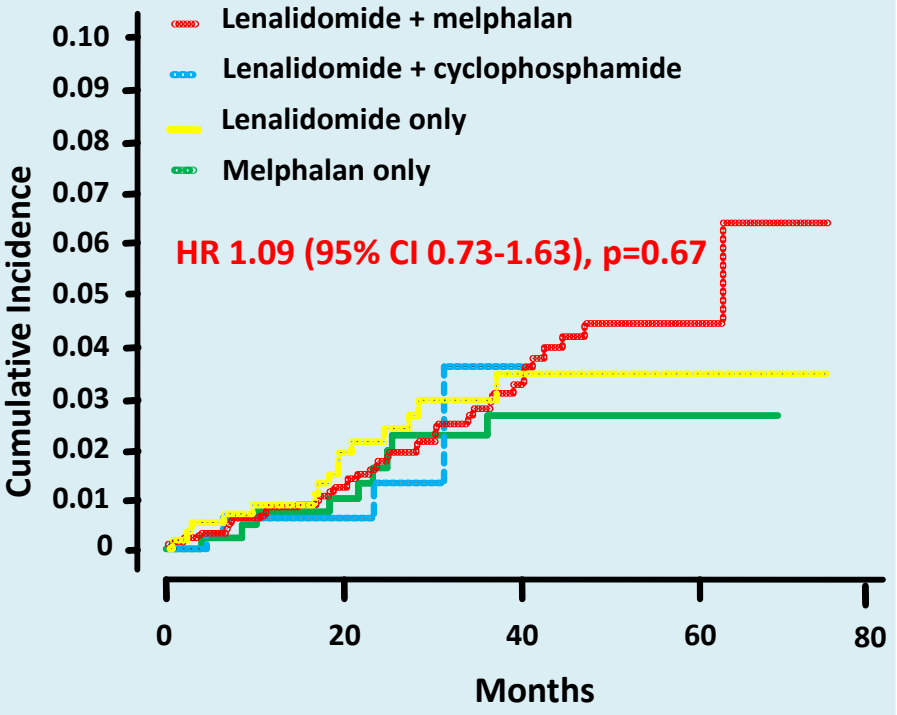
Different lenalidomide combinations

Haematologic 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)

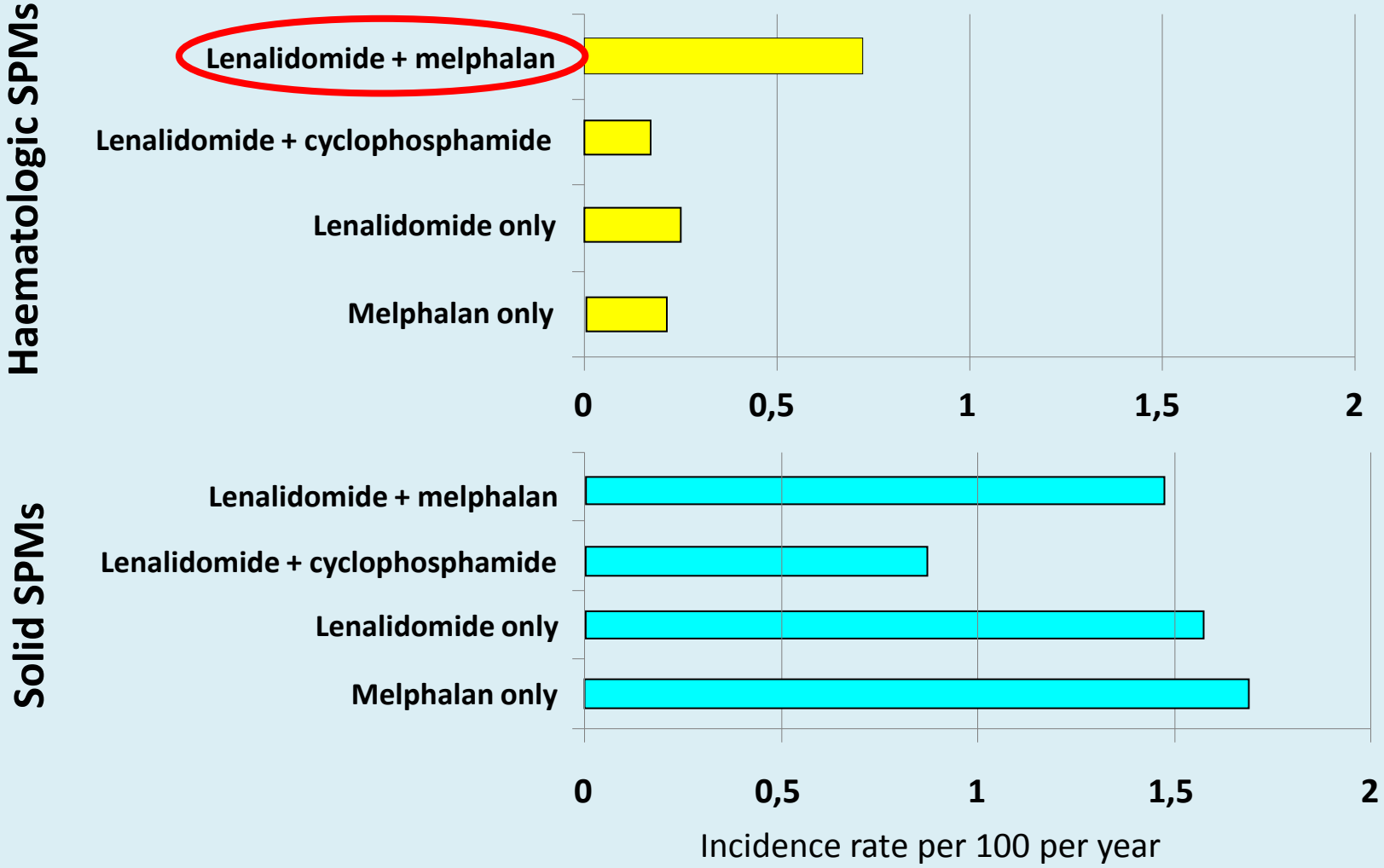
Solid SPMs



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)

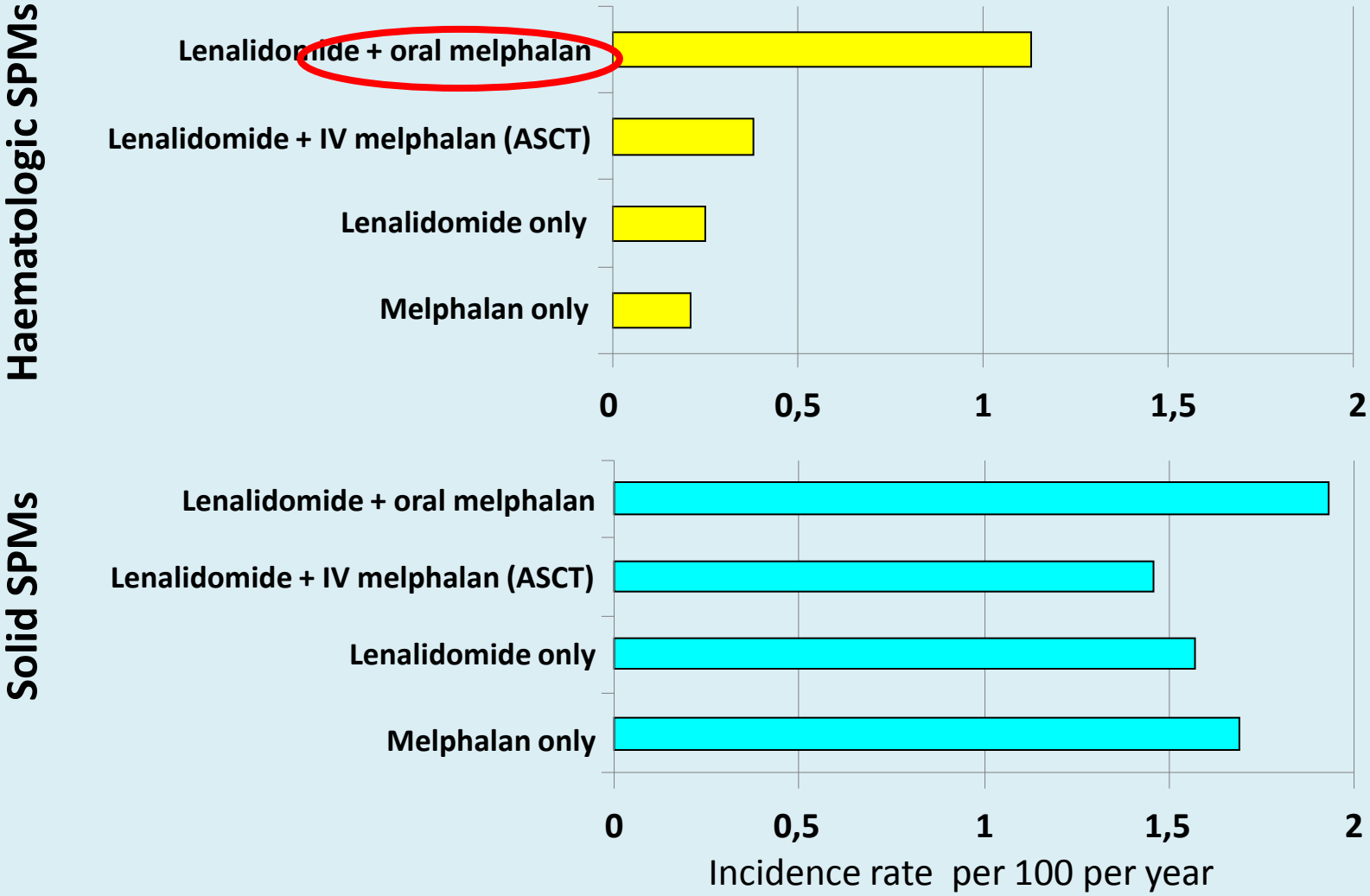
Incidence rate per 100 per year

Different lenalidomide combinations



Incidence rate per 100 per year

Oral *versus* high-dose intravenous melphalan



Bezpečnost lenalidomidu

–

shrnutí pro praxi

NEPOUŽÍVAT NIKDY KOMBINACI LEN – MELFALAN p.o.

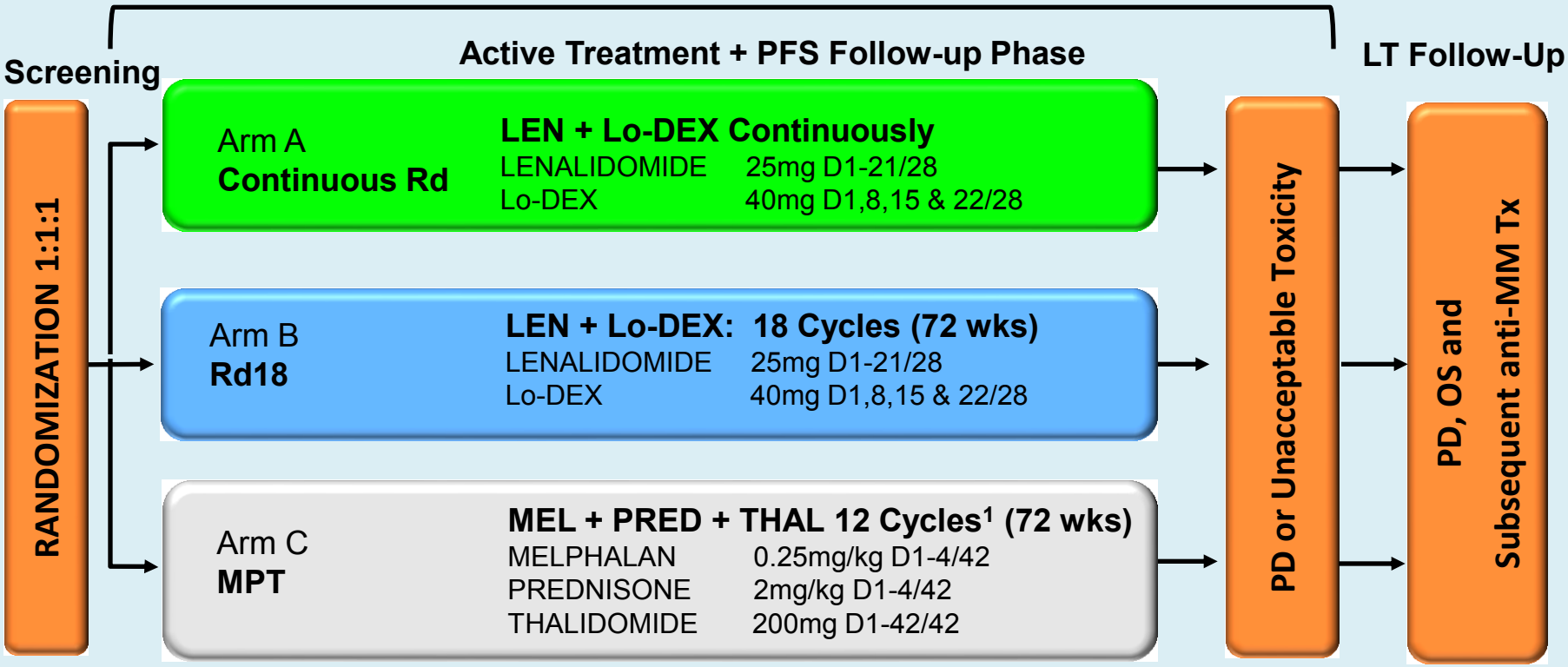
Platí obecně, třebaže analyzovaná data jsou jen z primoléčby

Continuous Lenalidomide and Low-dose Dexamethasone Demonstrates a Significant PFS and OS Advantage in Transplant Ineligible NDMM Patients – The FIRST Trial: MM-020/IFM 0701

- Thierry Facon, Meletios A. Dimopoulos, Angela Dispenzieri, John V. Catalano, Andrew R. Belch, Cyrille Hulin, Michele Cavo, Antonello Pinto, Katja Weisel, Heinz Ludwig, Nizar J. Bahlis, Anne Banos, Mourad Tiab, Michel Delforge, James D. Cavenagh, Catarina Geraldes, Je-Jung Lee, Christine I. Chen, Albert Oriol, Javier De La Rubia, Lugui Qiu, Darrell J. White, Daniel Binder, Kenneth C. Anderson, Philippe Moreau, Michel Attal, Robert Knight, Guang Chen, Jason Van Oostendorp, Christian J. Jacques, Annette Ervin-Haynes, Lotfi Benboubker

Facon T, et al. Continuous Lenalidomide and Low-dose Dexamethasone Demonstrates a Significant PFS and OS Advantage in Transplant Ineligible NDMM Patients – The FIRST Trial: MM-020/IFM 0701. *Plenary presentation at: American Society of Hematology*. 2013; December 7-10; New Orleans, LA.

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

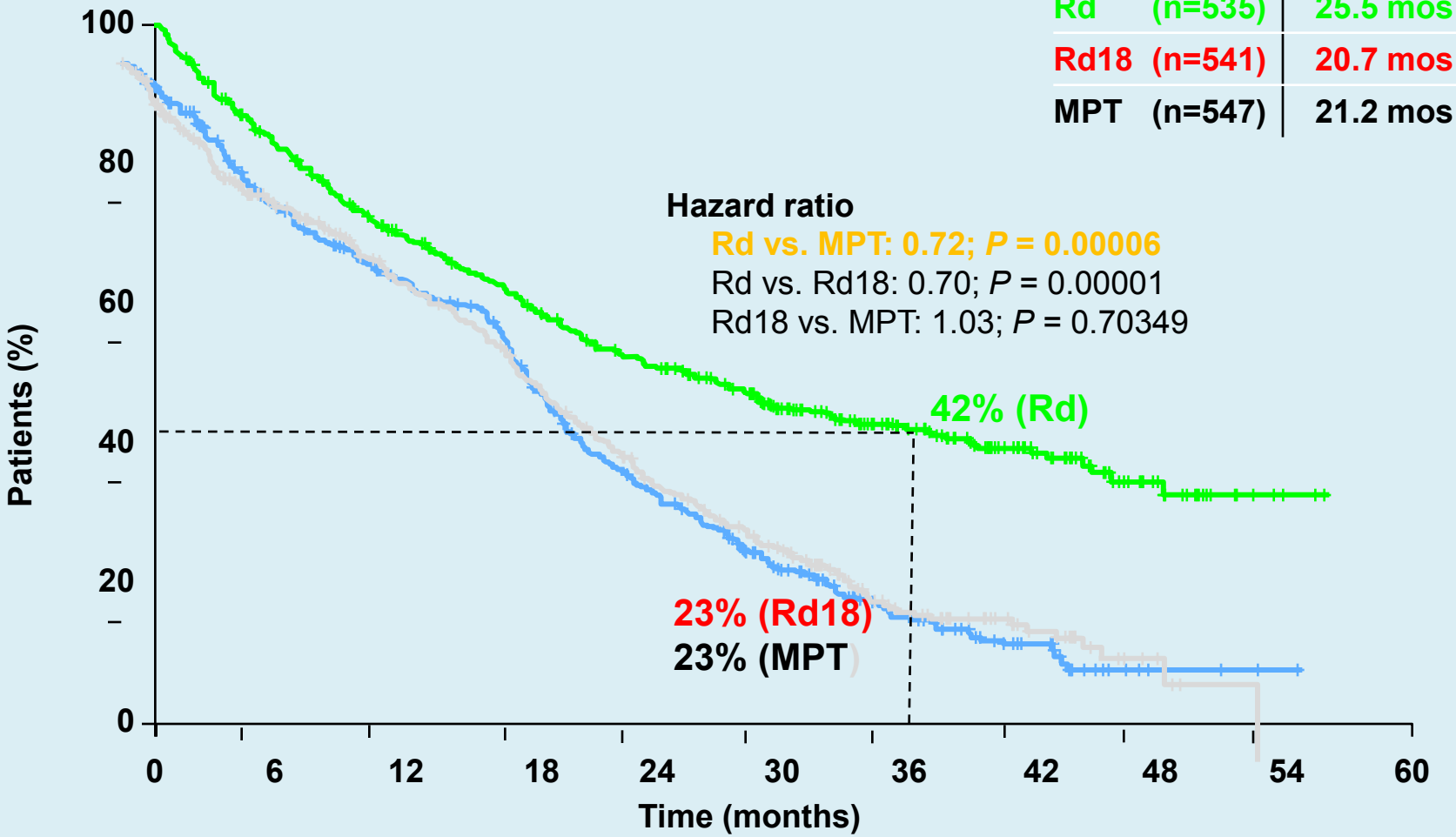
ISS, International Staging System; LT, long-term; PD, progressive disease; OS, overall survival

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

Facon T, et al. Continuous Lenalidomide and Low-dose Dexamethasone Demonstrates a Significant PFS and OS Advantage in Transplant Ineligible NDMM Patients – The FIRST Trial: MM-020/IFM 0701. *Plenary presentation at: American Society of Hematology*. 2013; December 7-10; New Orleans, LA.

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

Facon T, et al. Continuous Lenalidomide and Low-dose Dexamethasone Demonstrates a Significant PFS and OS Advantage in Transplant Ineligible NDMM Patients – The FIRST Trial: MM-020/IFM 0701. *Plenary presentation at: American Society of Hematology*. 2013; December 7-10; New Orleans, LA.

FAKULTNÍ NEMOCNICE OSTRAVA

Změna pozice lenalidomidu v léčebné strategii

Shrnutí

Lenalidomid má jasné místo v léčebné strategii MM:

VE VŠECH LINIÍCH LÉČBY

Lenalidomid přestal být nejdražší lék u MM

Lenalidomid v primoléčbě:

Klíčové je dlouhodobé podání

Režim první volby

Lenalidomid – Dexametazon (LD)

Bezpečnost lenalidomidu

–

shrnutí pro praxi

NEPOUŽÍVAT NIKDY KOMBINACI LEN – MELFALAN p.o.

Platí obecně, třebaže analyzovaná data jsou jen z primoléčby

Děkuji za pozornost