Imunomodulační látky a jejich kombinace u mnohočetného myelomu: výhled pro období 2014-2016

Roman Hájek

Hematoonkologická klinika FN Ostrava a LF Ostravské univerzity
Babákova myelomová skupina Kliniky patofyziologie LF Masarykovi univerzity Brno

Mikulov 26. 4. 2013

Úvod
&
co si zapamatovat

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Imunomodulační látky budou v období 2014-2016 patřit mezi klíčové léky u mnohočetného myelomu

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V kombinaci s inhibitory proteasomu a glukokortikoidy budou tvořit nejúčinnější režimy,

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V kombinaci s inhibitory proteasomu a glukokortikoidy budou tvořit nejúčinnější režimy,

a to vše bez významné neuropatie, p.o.

Jaké máme k dispozici IMIDs ?

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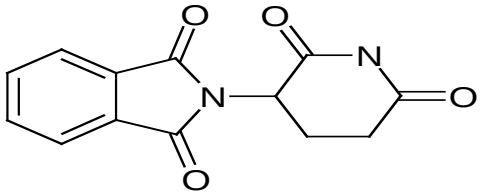
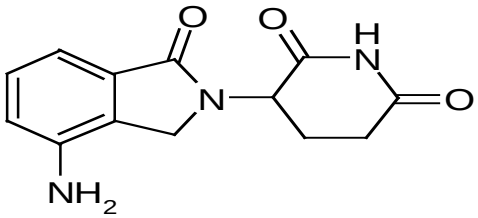


Thalidomide

100-200 mg/d

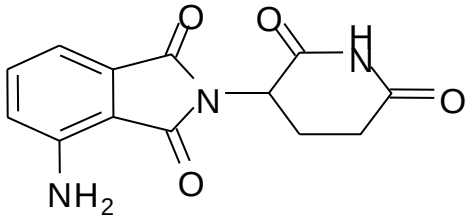
Neuropathy
Constipation
Sedation
DVT
Teratogenní



Lenalidomide

10-25 mg/d

Myelosuppression
Skin rash
DVT
Teratogenní



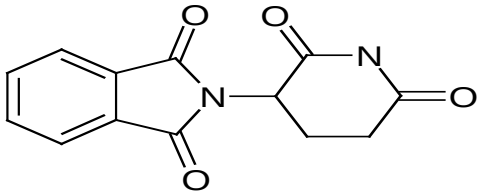
Pomalidomide

1-4 mg/d

Myelosuppression
Fatigue
DVT
Teratogenní

- **Structurally similar, but functionally different both qualitatively and quantitatively**
- **Oral route of administration**

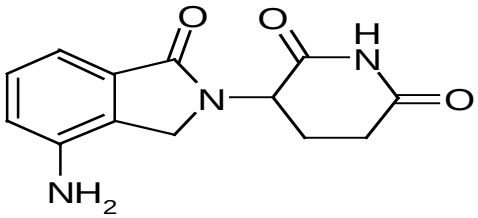
Jaké máme k dispozici IMIDs a jak je můžeme používat?



Thalidomide

100-200 mg/d

Primoléčba
Relaps
Konsolidační l.
Udržovací léčba



Lenalidomide

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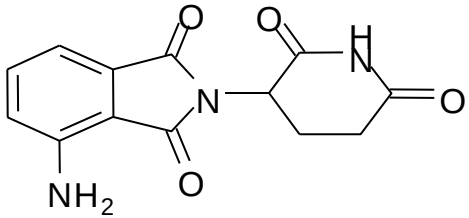


Pomalidomide

1-4 mg/d

Primoléčba
Relaps
Konsolidační l.
Udržovací léčba

- **Nově je možné na paragraf 16 získat Pomalyst**
- **Netrpělivě čekáme na schválení udržovací léčby lenalidomidem**

Jak se budou používat na konci roku 2016?

2.
Pomalidomide
1-4 mg/d

100% relaps

1.
Lenalidomide
10-25 mg/d

20% primoléčba
80% relaps
100% udržovací léčba

3.
Thalidomide
100-200 mg/d

10% primoléčba
90% relaps
0% ÚL

- **PREDIKCE ÚČINNOSTI - CEREBLON a možnost zvýšení šance na účinnost**

Vybrané poznámky k problematice

Pomalidomid

Pomalidomide studies at ASH 2012

- A range of combinations are being tested:

  Pomalidomide +

  - low-dose dex[1,2]
  - cyclophosphamide + prednisone[3]
  - carfilzomib + dex (Car-Pom-d)[4]
  - clarithromycin + dex[5]
  - bortezomib + low-dose dex[6]

- Studies demonstrate activity also in Len-refractory pts
- Primary toxicity: myelosuppression,
- DVT prophylaxis required

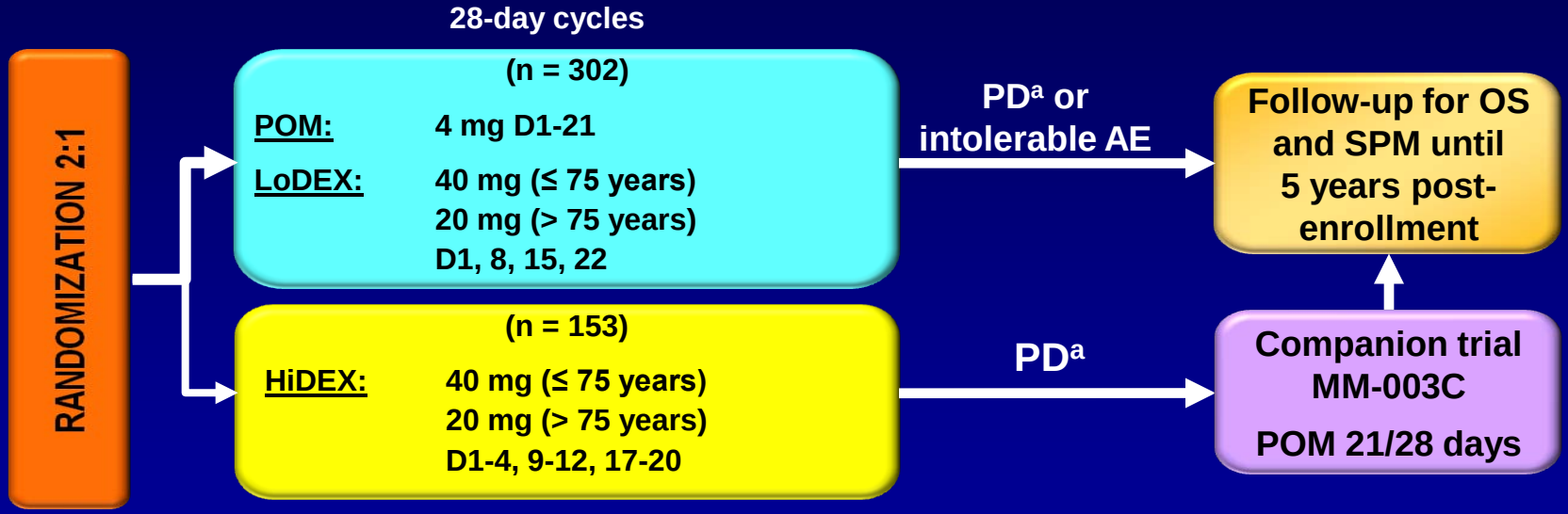
1. *Lacy et al. ASH 2012 (Abstract 201), oral presentation*
2. *Jagannath et al. ASH 2012 (Abstract 450), oral presentation*
3. *Mark et al. ASH 2012 (Abstract 77), oral presentation*
4. *Richardson et al. ASH 2012 (Abstract 727), oral presentation*
5. *Palumbo et al. ASH 2012 (Abstract 446), oral presentation*
6. *Shah et al. ASH 2012 (Abstract 74), oral presentation*

Phase 3 Trial
MM-003: POM + LoDEX vs. HiDEX in Relapsed/Refractory Multiple Myeloma

MM-003 POM + LoDEX in RRMM

Phase 3 —Trial Design

- **Primary endpoint**: PFS
- **Key secondary endpoints**: OS, ORR (≥ PR), DOR, safety



Thromboprophylaxis was indicated for those receiving POM or with DVT history

[a] PD was independently adjudicated in real time.

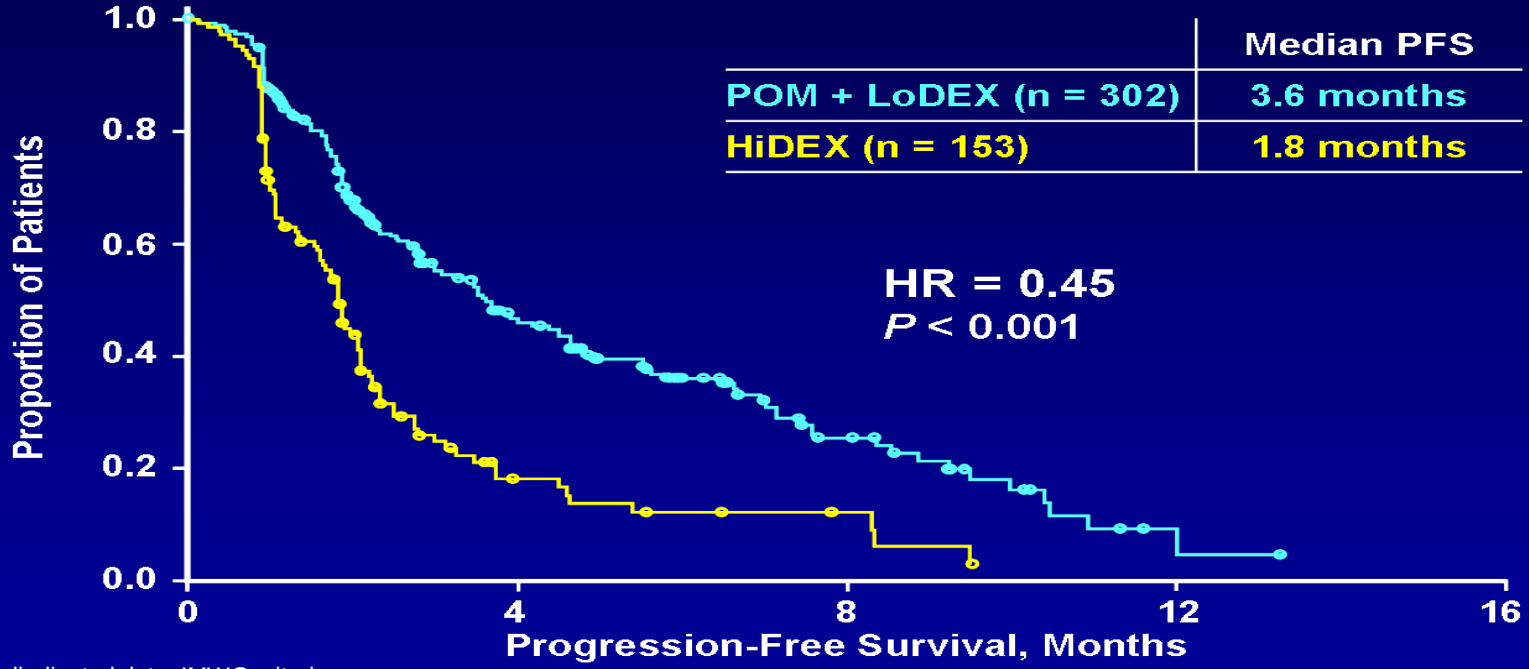
AE: adverse event; D: day; DOR: duration of response; DVT: deep vein thrombosis; HiDEX: high-dose dexamethasone; LoDEX: low-dose dexamethasone; MM: multiple myeloma; ORR: overall response rate; OS: overall survival; PD: progressive disease; PFS: progression-free survival; POM: pomalidomide; PR: partial response; RRMM: relapsed/refractory multiple myeloma; SPM: second primary malignancy.

Dimopoulos MA. *Blood.* 2012;120: [oral presentation, abstract LBA-6].

MM-003 POM + LoDEX in RRMM

Phase 3 — Progression-Free Survival, ITT Population[a]

- PFS was significantly longer with POM + LoDEX vs. HiDEX



	Median PFS
POM + LoDEX (n = 302)	3.6 months
HiDEX (n = 153)	1.8 months

[a] Based on adjudicated data; IMWG criteria.

HiDEX: high-dose dexamethasone; HR: hazard ratio; IMWG: International Myeloma Working Group; ITT: intent-to-treat; LoDEX: low-dose dexamethasone; MM: multiple myeloma; PFS: progression-free survival; POM: pomalidomide; RRMM: relapsed/refractory multiple myeloma.

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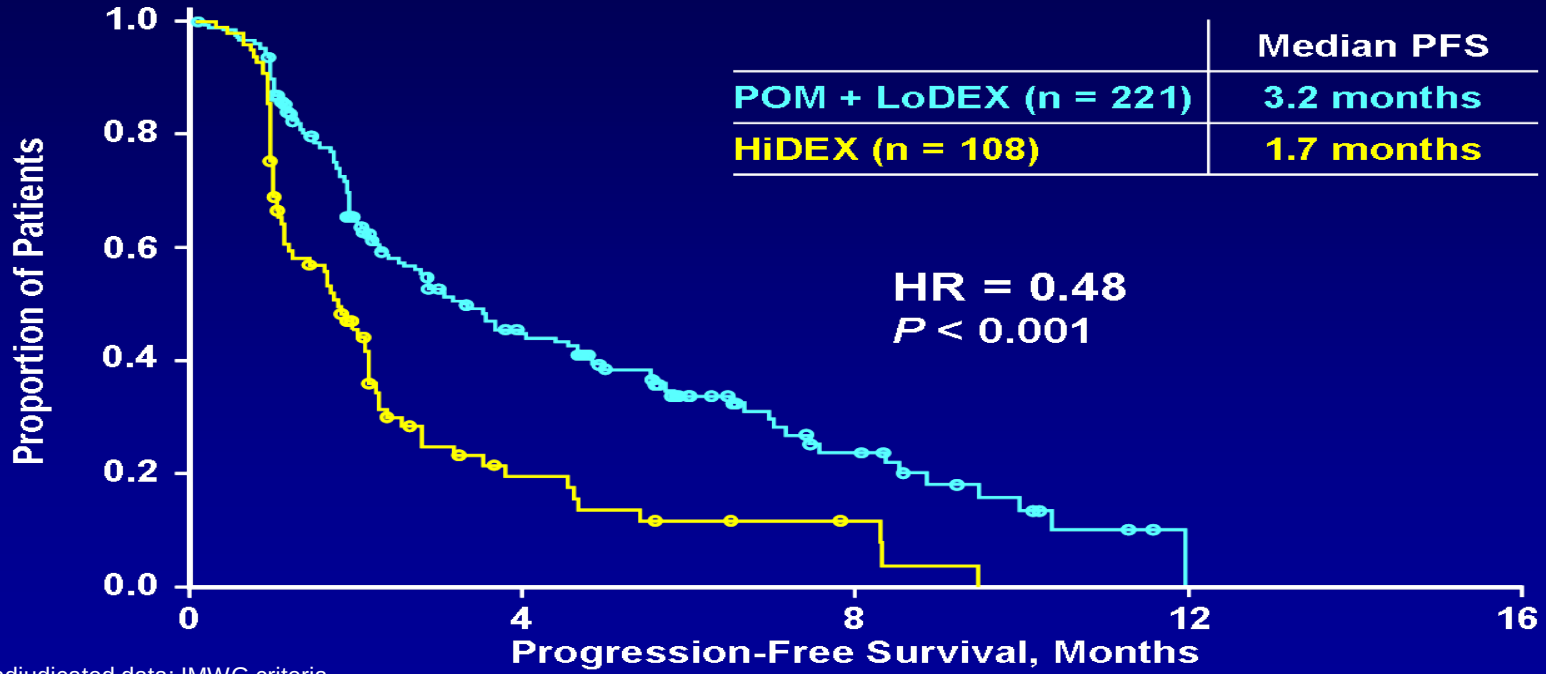
MM-003 POM + LoDEX in RRMM

Phase 3 — Progression-Free Survival, LEN- and BORT-Refractory[a]

- PFS was consistent to the ITT population regardless of refractoriness to LEN and BORT



[a] Based on adjudicated data; IMWG criteria.

BORT: bortezomib; HiDEX: high-dose dexamethasone; HR: hazard ratio; IMWG: International Myeloma Working Group; ITT, intent to treat; LEN: lenalidomide; LoDEX: low-dose dexamethasone; MM: multiple myeloma; PFS: progression-free survival; POM: pomalidomide; RRMM: relapsed/refractory multiple myeloma.

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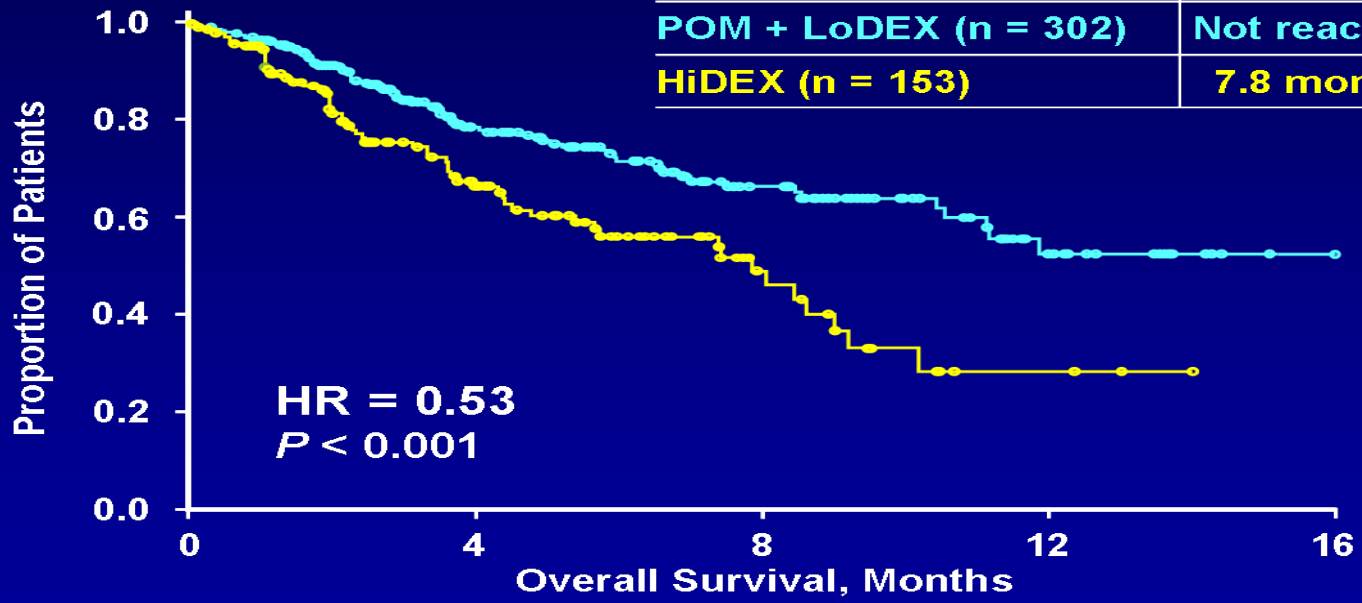
MM-003 POM + LoDEX in RRMM

Phase 3 — Overall Survival, ITT Population

- OS was significantly longer with POM + LoDEX vs. HiDEX, despite 29% of pts receiving POM after progression on HiDEX

	Median OS (95% CI)
POM + LoDEX (n = 302)	Not reached (11.1-NE)
HiDEX (n = 153)	7.8 months (5.4-9.2)



CI: confidence interval; HiDEX: high-dose dexamethasone; HR: hazard ratio; ITT: intent-to-treat; LoDEX: low-dose dexamethasone; MM: multiple myeloma; NE: not estimable; OS: overall survival; POM: pomalidomide; pts: patients; RRMM: relapsed/refractory multiple myeloma.

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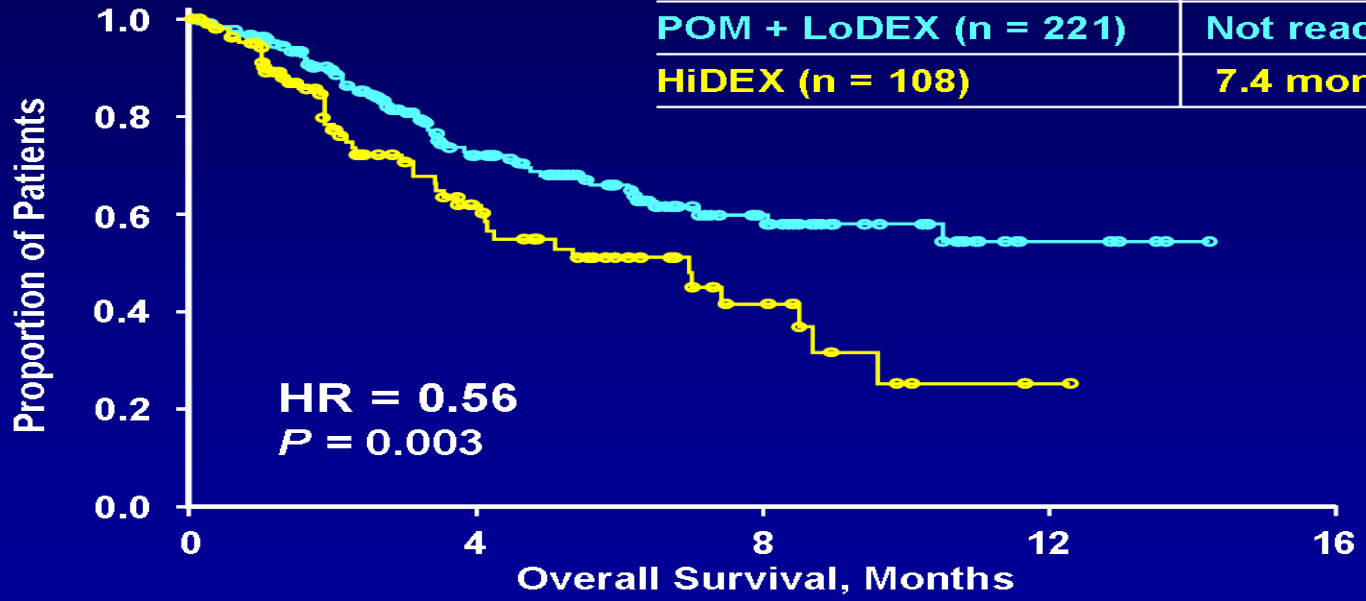
MM-003 POM + LoDEX in RRMM

Phase 3 — Overall Survival, LEN- and BORT-Refractory

- OS was consistent to the ITT population regardless of refractoriness to LEN and BORT

	Median OS (95% CI)
POM + LoDEX (n = 221)	Not reached (8.5-NE)
HiDEX (n = 108)	7.4 months (4.3-9.2)



BORT: bortezomib; CI: confidence interval; HiDEX: high-dose dexamethasone; HR: hazard ratio; ITT, intent to treat; LEN: lenalidomide; LoDEX: low-dose dexamethasone; MM: multiple myeloma; NE: not estimable; OS: overall survival; POM: pomalidomide; RRMM: relapsed/refractory multiple myeloma.

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MM-003 POM + LoDEX in RRMM

Phase 3 — Adverse Events

- Discontinuation due to AEs: 7% POM + LoDEX; 6% HiDEX
- VTE, all grades: 3% POM + LoDEX; 2% HiDEX
- Peripheral neuropathy, all grades: 12% POM + LoDEX; 11% HiDEX

Grade 3-4 AEs, %	POM + LoDEX (n = 300)	HiDEX (n = 149)
Neutropenia	42	15
Febrile neutropenia	7	0
Anemia	27	29
Thrombocytopenia	21	24
Infections	24	23
Pneumonia	9	7
Hemorrhage	3	5
Glucose intolerance	3	7
Fatigue	5	5

AE: adverse event; HiDEX: high-dose dexamethasone; LoDEX: low-dose dexamethasone; MM: multiple myeloma; POM: pomalidomide; RRMM: relapsed/refractory multiple myeloma; VTE: venous thromboembolism.

Dimopoulos MA. *Blood.* 2012;120: [oral presentation, abstract LBA-6].

MM-003 POM + LoDEX u RRMM

Fáze 3 — Závěry autorů

- POM + LoDEX významně zlepšil PFS and OS vs. HiDEX
- Srovnatelný prospěch u refrakterních pacientů léčených jak LEN tak BORT
- U těchto těžce předléčených pacientů POM + LoDEX byl obecně dobře tolerován
- POM + LoDEX by měl být zvažován jako možná volba léčby pro tyto pacienty

BORT: bortezomib; HiDEX: high-dose dexamethasone; LEN: lenalidomide; LoDEX: low-dose dexamethasone; MM: multiple myeloma; OS: overall survival; PFS: progression-free survival; POM: pomalidomide; pts: patients; RRMM: relapsed/refractory multiple myeloma.

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Vybrané poznámky k problematice

Thalidomid

Carfilzomib + Thal + Dex (CTD) as Induction and Consolidation in newly diagnosed MM

- n=50
- Treatment
  - **4 cycles induction CTD,**
  - **transplant,**
  - **4 cycles consolidation CTD**
  - **Thal dose: 200 mg/d during induction, 50 mg/d during consolidation**
- Results
  - 39/50 pts completed treatment according to protocol

Adverse events	Grade 1-2	Grade 3
PN	19%	2%
Azotemia	0	4%
GI	22%	6%
Skin	8%	12%
Cardiac	2%	6%

  - No DLTs

Sonneveld et al. ASH 2012 (Abstract 333), oral presentation

Carfilzomib + Thal + Dex (CTD) as Induction and Consolidation in newly diagnosed MM

- Response following induction
  - ORR 91%, VGPR 60%, CR 18%
- Median follow-up: 14 mos
- Responses are upgraded following consolidation

	High-risk MM	Standard-risk MM	All pts
CR/sCR	**55%**	**45%**	**44%**
≥ VGPR	**90%**	**77%**	**84%**
≥PR	**95%**	**92%**	**94%**

Sonneveld et al. ASH 2012 (Abstract 333), oral presentation

Vybrané poznámky k problematice

Lenalidomid a udržovací léčba

Lenalidomide maintenance therapy

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

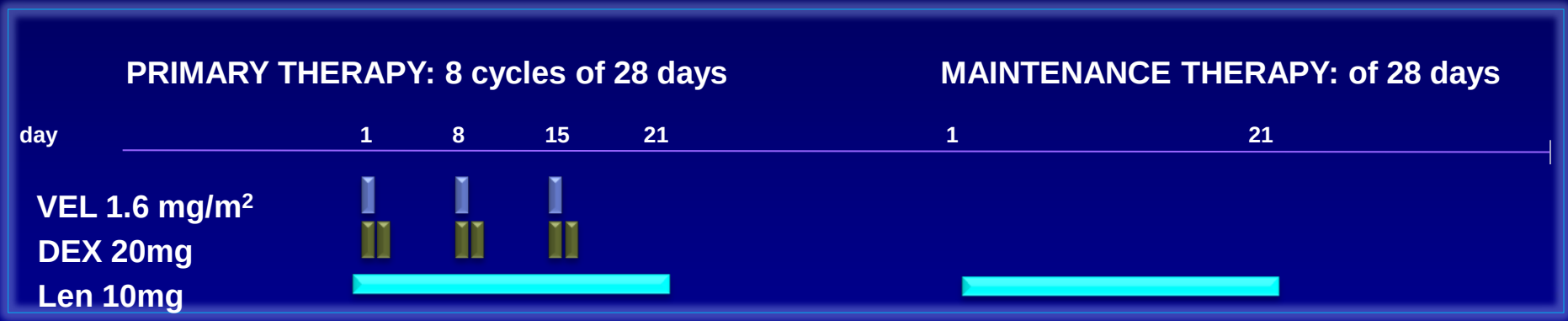
Occurrence of secondary primary malignancies (SPMs) requires monitoring

[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*

Vybrané poznámky k problematice

Lenalidomid a nejúčinnější kombinace

Escalated-dose bortezomib once weekly + Len + Dex (eVRD) followed by Len maintenance in First Relapse (HOVON 86 Phase 2 Trial)



Sonneveld et al. ASH 2012 (Abstract 1853), poster presentation

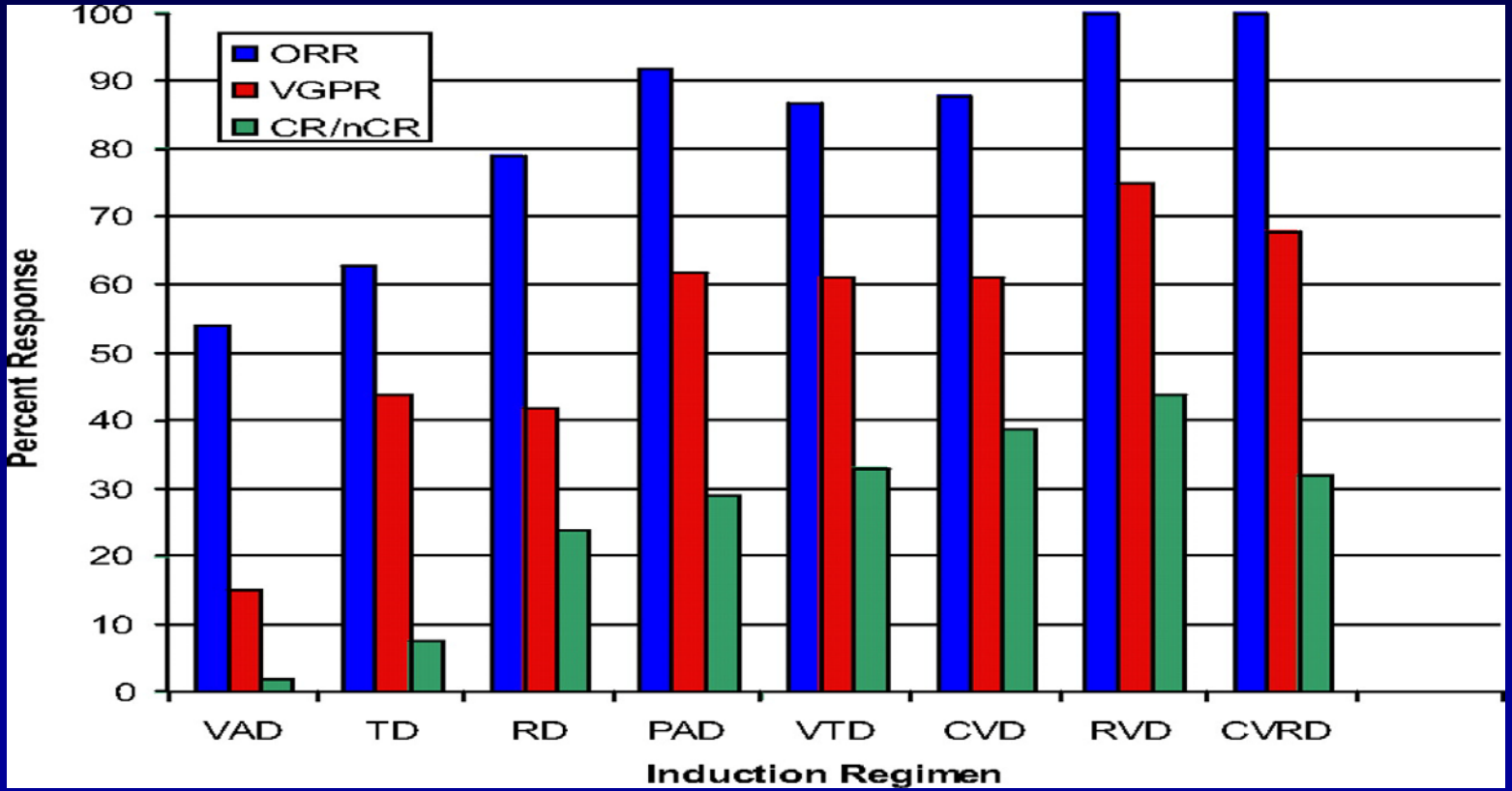
Escalated-dose bortezomib once weekly + Len + Dex (eVRD) followed by Len maintenance in First Relapse
(HOVON 86 Phase 2 Trial)

Median follow-up: 13.6 months	Median time to response 1.1 cycles
ORR/≥ VGPR/CR/nCR	92/64/30%
PFS @ 18 months	52%
OS	76%
significant factors associated with PFS (p<0.001) and OS (p<0.001	ISS stage, prior HDM/ASCT, depth of response
Toxicity Grade 3/4	
PN	19%
Hematological	29%

Conclusion: Escalated VRD followed by Len maintenance is effective and feasible in patients with first relapse MM

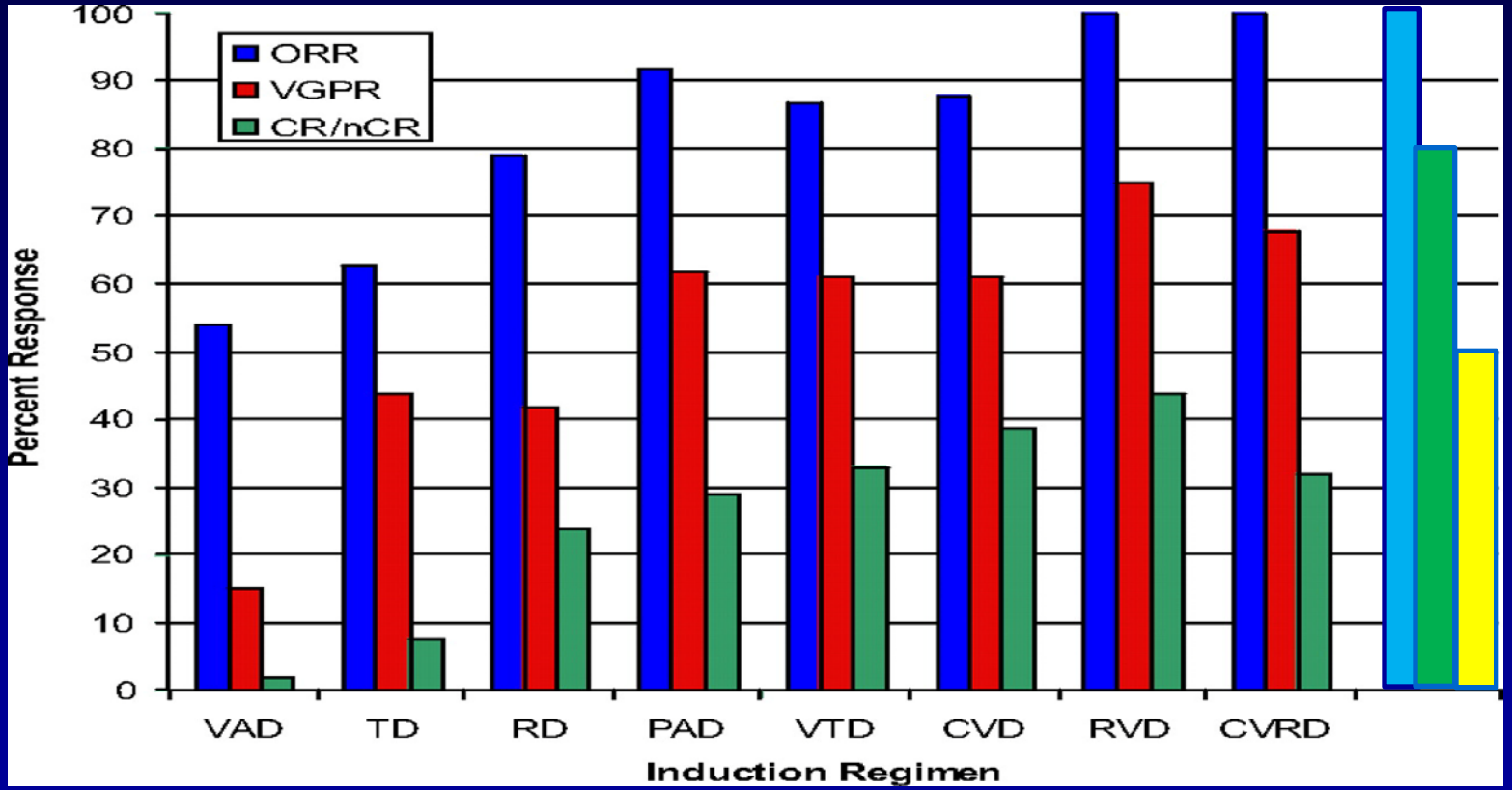
Sonneveld et al. ASH 2012 (Abstract 1853), poster presentation

Combinations in the upfront treatment of MM



Stewart AK, et al. Blood. 2009;114:5436-43.

Combinations in the upfront treatment of MM



100% ORR

70-80% CR

30-40% i/mCR ?

Stewart AK, et al. Blood. 2009;114:5436-43.

Combination therapy vs. single agent

QoL/$$$

Intensive treatment in the first relapse

- carfilzomib-lenalidomid-dex
- MLN9708-lenalidomid/pomalidomid-dex
  +- ASCT

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