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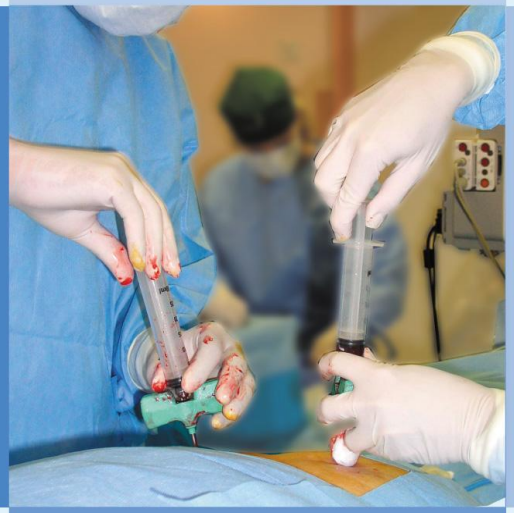
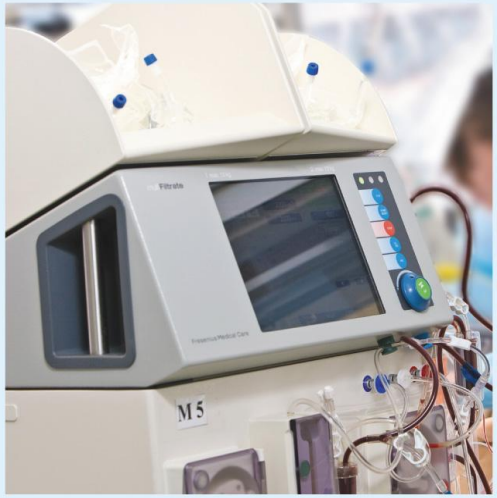


# Pomalidomid
# –
# indikace a logistika v ČR

(US: Pomalyst; EU: Imnomid; 4mg/- 21dnů)



**Farmakoekonomický workshop**
**Brno 29.11.2013**

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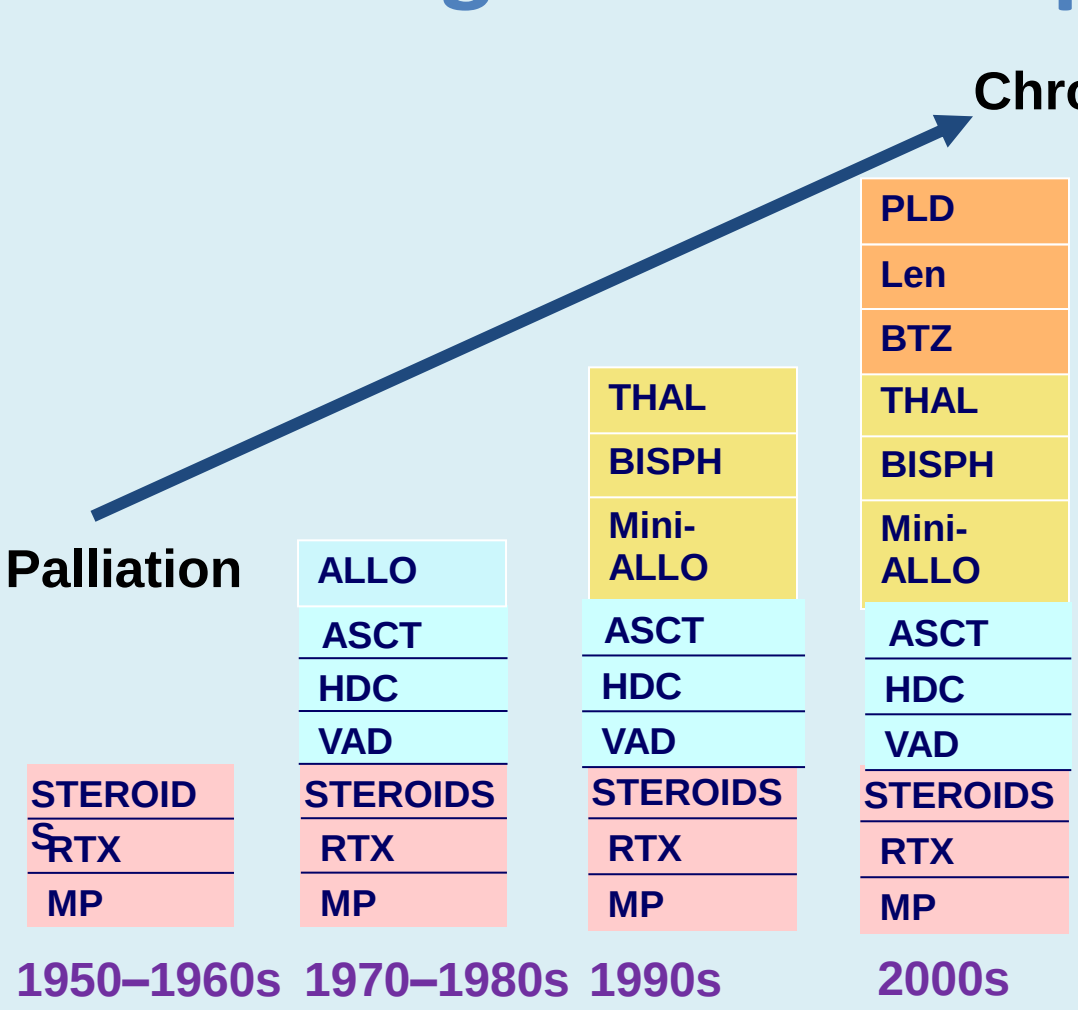
# MM: Progress in Therapeutic Options




**2013**

## New Targets/Agents

| | |
|---|---|
| Hsp90 | KOS 953 |
| Proteasome | PR171, NPI0052 |
| Aggresome | Tubacin |
| HDAC | LBH, SAHA |
| Akt | elotuzumab |
| XBP-1 | XBP-1 peptide |
| Muc-1 | NM3 |
| MEK | AZD6244 |
| NF-kB | NPI1387 |
| PKC | Enzastaurin |
| p38MAPK | SCIO469 |
| Telomerase | GRN 163L |
| Natural products | EGCG |

- Develop effective combination with induction, and consolidation and maintenance strategy
- Genome-based selection
- Prevent progression

BTZ = Bortezomib
BISPH = Bisphosphonates
THAL = Thalidomide

ASCT = Stem cell transplantation
HDC = High-dose chemotherapy
MP = Melphalan + Prednisone

PLD = Pegylated liposomal doxorubicin

# MM: Progress in Therapeutic Options
# Key effective drugs

- Alkylating agens
- Glucocorticoids
- IMIDs
- Proteasome inhibitors

# MM: Progress in Therapeutic Options
# Key effective drugs

| | |
|---|---|
| Alkylating agens | melphalan<br>cyclophosphamid<br>bendamustin |
| Glucocorticoids | prednisolon<br>dexamethason |
| IMIDs | thalidomide<br>lenalidomide<br>pomalidomide |
| Proteasome inhibitors | i.v. : bortezomib, carfilzomib, MLN, marizomib<br>s.c.: bortezomib<br>p.o.: MLN (ixazomib), oprozomib,delanzomib |

# MM: Future in Therapeutic Option
## IMIDs and PI combo regimens for several treatment lines

| | | | |
|---|---|---|---|
| Glucocorticoids | thalidomid | bortezomib | VTD |
| Glucocorticoids | lenalidomide | carfilzomib | CRD |
| Glucocorticoids | pomalidomide | ixazomib | IPD |
| Glucocorticoids | pomalidomide | oprozomib | OPD |

**Kombinace imunomodulačních látek a inhibitorů proteasomu tvoří spolu s glukokortikoidy nejúčinnější režimy současnosti.**

**Tyto léky nemají zkříženou rezistenci a jde je tak rotovat s vysokou účinností v následných léčebných liniích.**

**Jde i o plně perorální režimy**

| | | | |
|---|---|---|---|
| Glucocorticoids | pomalidomide | ixazomib | IPD |
| Glucocorticoids | pomalidomide | oprozomib | OPD |

VTD

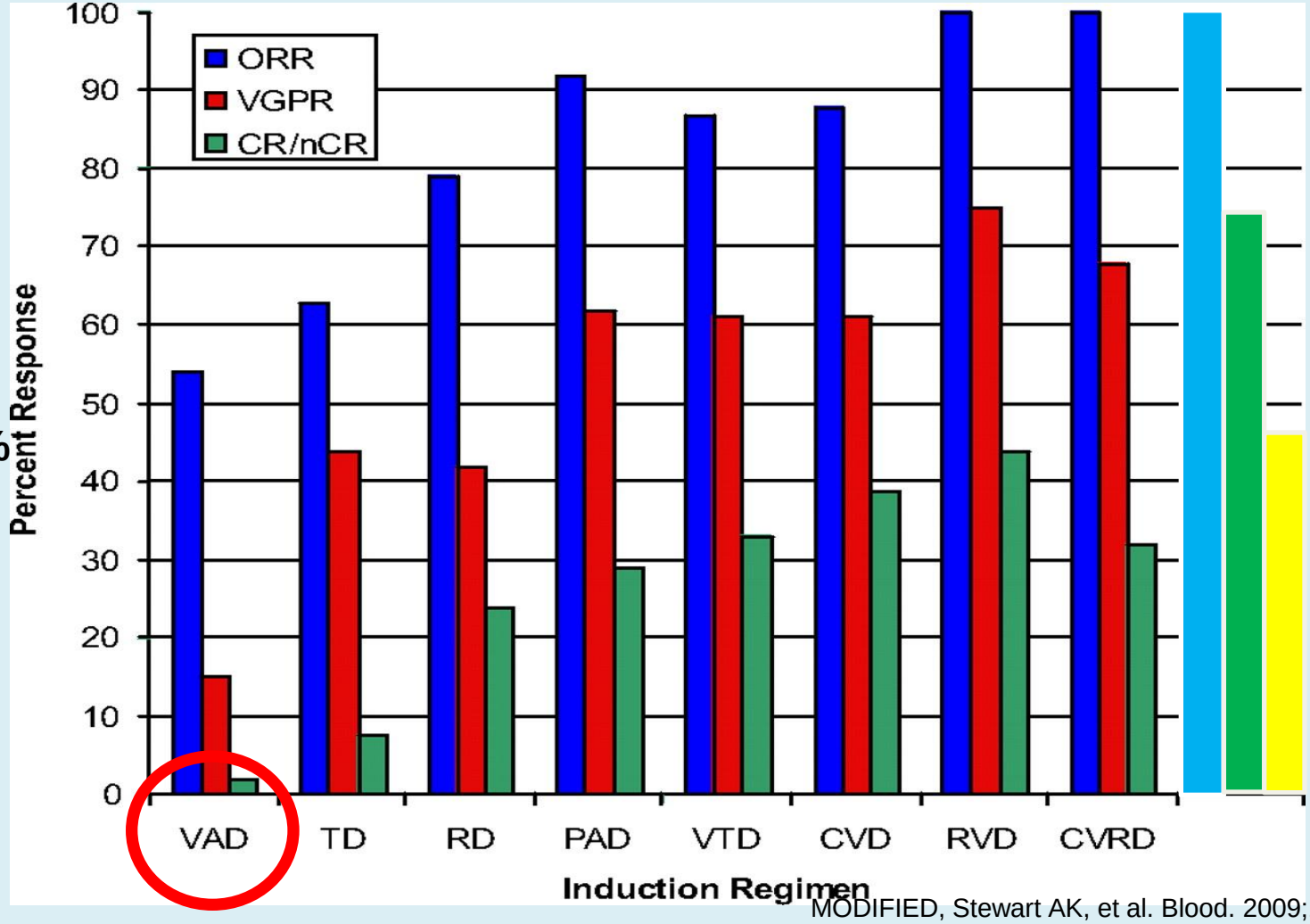
CRD

# Combinations in the upfront treatment of MM – near perspective

**50-60% ORR**

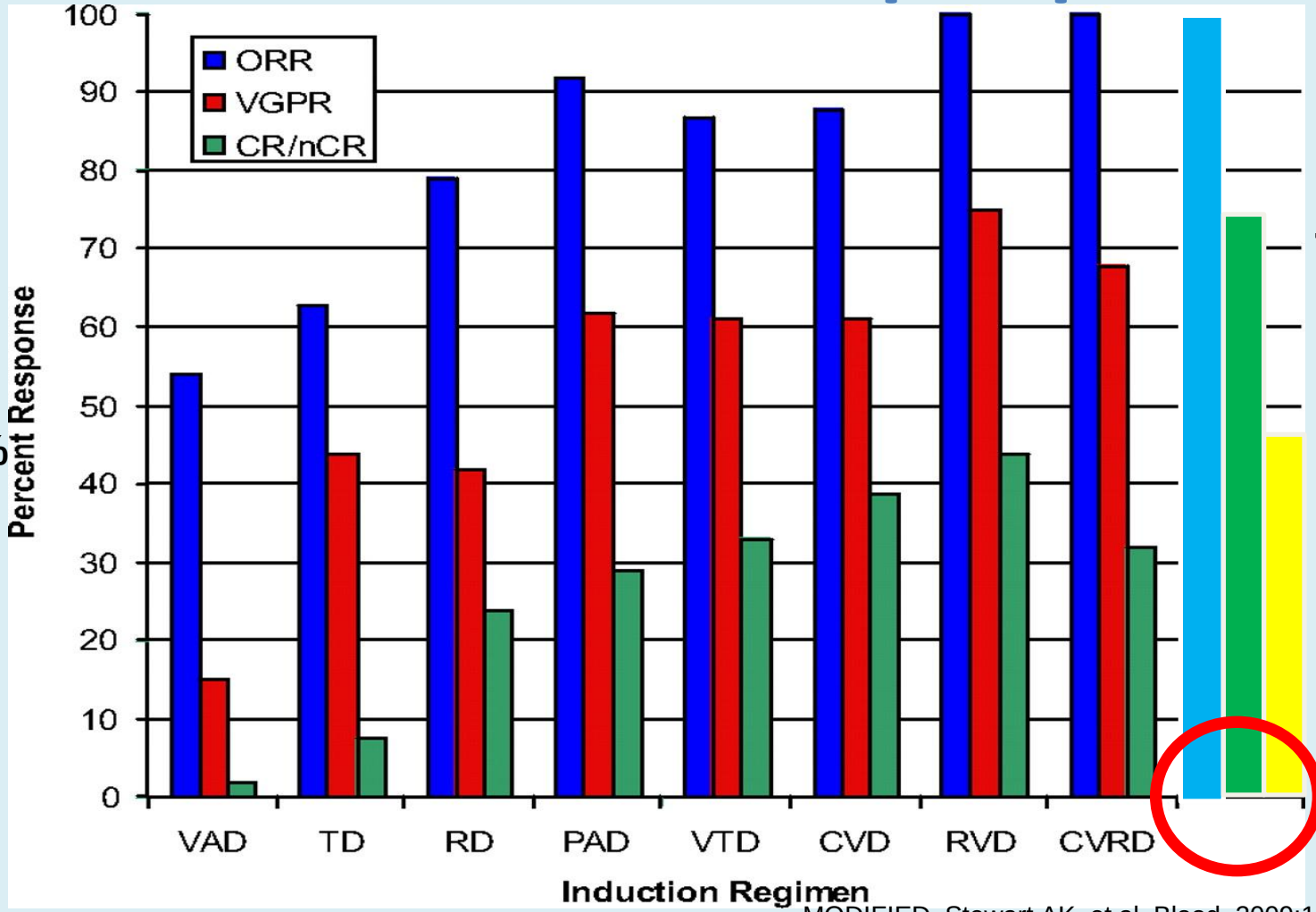
**< 5% CR**

**? % i/mCR?**




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

# Combinations in the upfront treatment of MM – near perspective




50-60% ORR

< 5% CR

? % i/mCR?

100% ORR

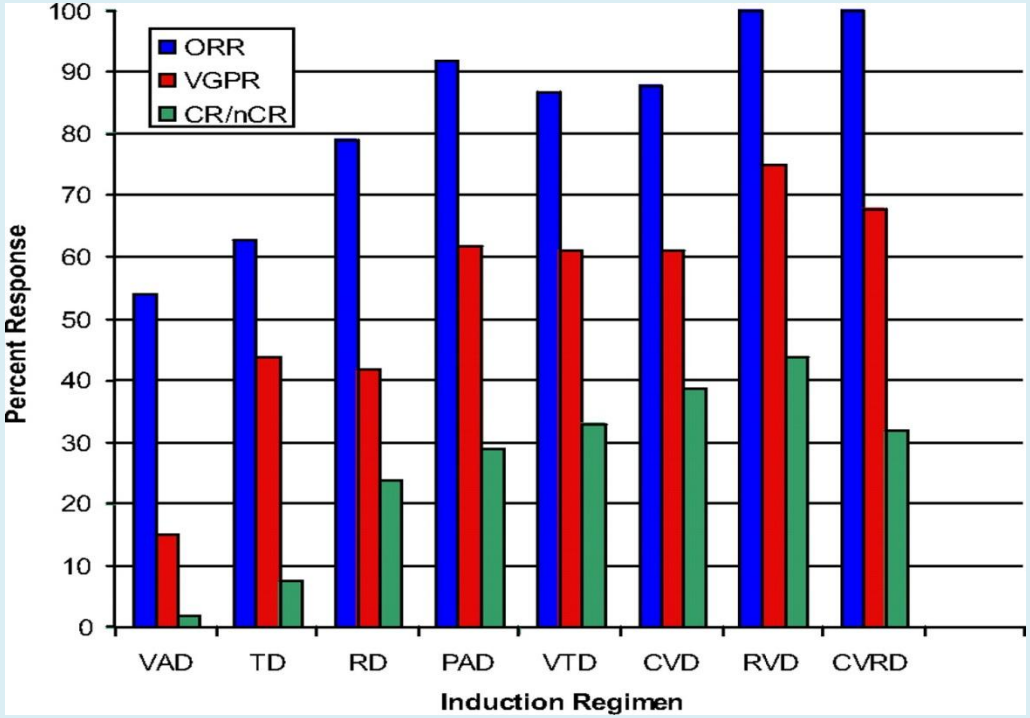
70-80% CR

30-40% i/mCR?

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

# MM: Progress in Therapeutic Options
# Key effective drugs

- Alkylating agens
- Glucocorticoids
- IMIDs
- Proteasome inhibitors



# MM: Progress in Therapeutic Options
# Key effective drugs

- Alkylating agens
- Glucocorticoids
- IMIDs
- Proteasome inhibitors

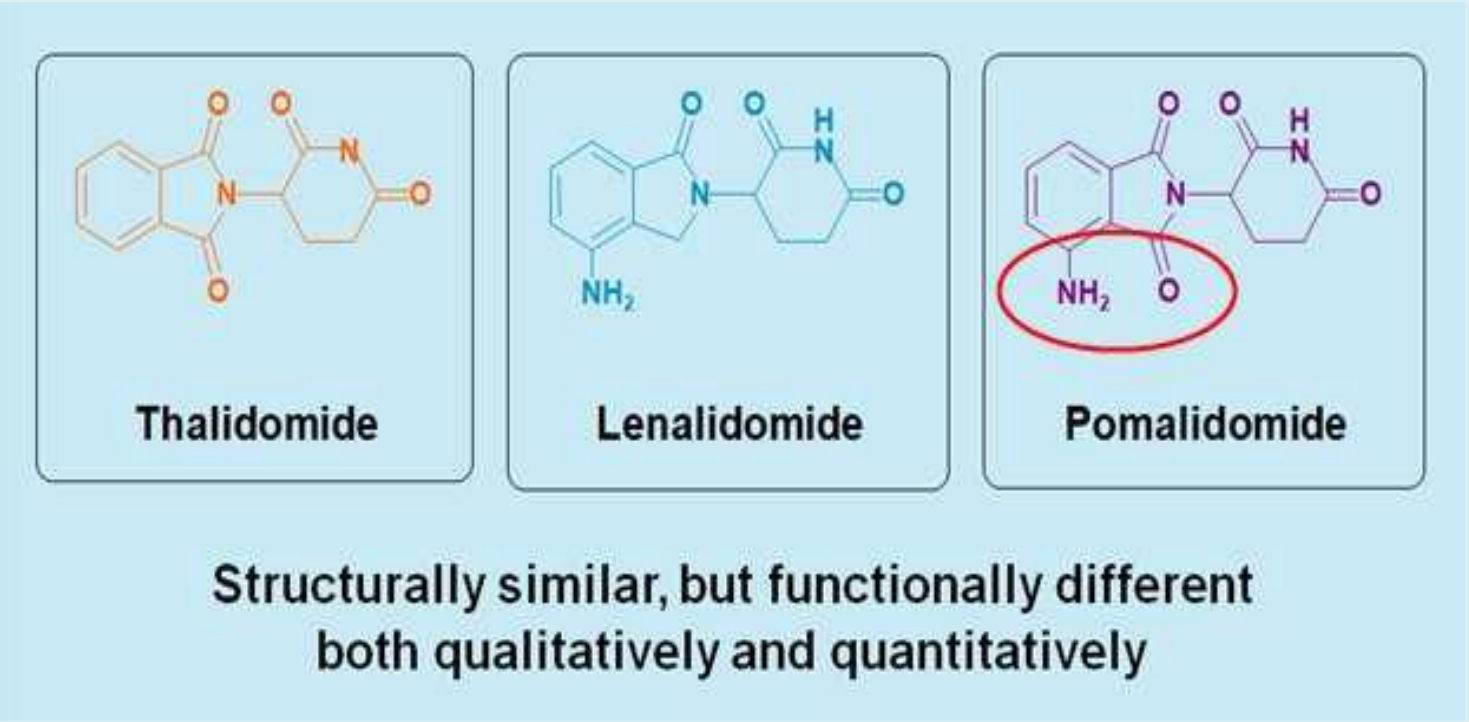
**Přes obrovský vývoj nových molekul potenciálně účinných u MM patří a ještě delší dobu budou patřit tyto 3 (USA) 4 (EU) klíčové skupiny léků mezi „NEJ„ u MM**

# MM: Progress in Therapeutic Options
# Key effective drugs

- Alkylating agens
- Glucocorticoids
- **IMIDs**
  - thalidomide
  - lenalidomide
  - pomalidomide
- Proteasome inhibitors

# Pomalidomid
# –
# Co od něj očekávat ?

# Chemická struktura thalidomidu a jeho analogů: lenalidomidu a pomalidomidu



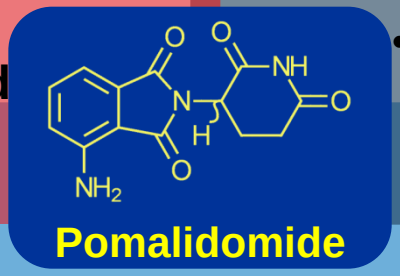
# Pomalidomide mechanism of action: Overview

## Anti-myeloma

- Tumour suppressor gene upregulation and oncogene inhibition[1–4]
- Induction of cell-cycle arrest and apoptosis[1–5]
- Effects in drug-sensitive and drug-resistant cells[1–5]

## Stromal inhibition

- Inhibition of osteoclast differentiation[6,7]
- Inhibition of growth factor production[8]
- Inhibition of angiogenesis[9]




Pomalidomide

## Immunomodulatory

- Enhanced immune function[8,10–14]
- Increased NK-mediated MM lysis[14,15]

References in slide notes.

# IMIDs: mechanisms of action

| Effect | Thalidomide | Lenalidomide | Pomalidomide |
|---|---|---|---|
| Immune modulation CD4+ and CD8+ | + | + + + + | + + + + + |
| Tregs suppression | _ | + | + |
| Th1 cytokine production | + | + + + + | + + + + + |
| NK and NKT cell activation | + | + + + + | + + + + + |
| Antibody-dependent cellular cytotoxicity (ADCC) | _ | + + + + | + + + + |
| Anti-angiogenesis | ++++ | + + + | + + + |
| Anti-inflammatory properties | + | + + + + | + + + + + |
| Direct anti-tumor effects Anti-proliferative activity | + | + + + | + + + |
| Elimination | Primarily urinary excretion; <3% as parent | Primarily urinary excretion; ~ 80% as parent | Urinary excretion; ~ 2% as parent |
| Rate-limiting toxicities | PN, constipation, somnolence, DVT | Myelosuppression, DVT | Myelosuppression |

San Miguel JF, et al. *Haematologica.* 2013;98 (suppl, abstr S1151).

# IMIDs: mechanisms of action

| Effect | Thalidomide | Lenalidomide | Pomalidomide |
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| Immune modulation CD4+ and CD8+ | + | + + + + | + + + + + |
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| NK and NKT cell activation | + | + + + + | + + + + + |
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San Miguel JF, et al. *Haematologica.* 2013;98 (suppl, abstr S1151).

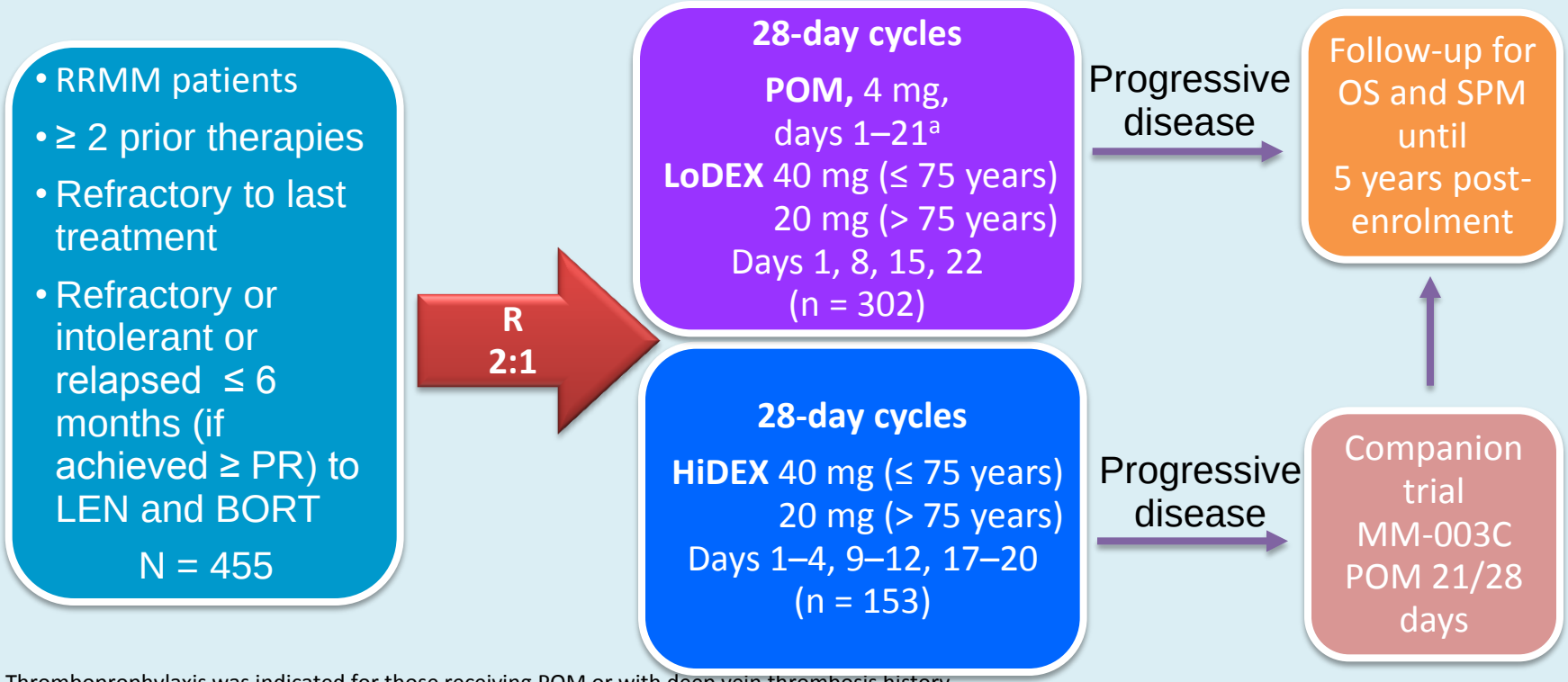
# Přehled klinických studií
# -
# zaměření na překonání rezistence

# MM-003: Phase 3 trial of pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone in relapsed/refractory multiple myeloma

# MM-003: Study design

- Phase 3, open-label, multicentre study
- Primary endpoint: PFS
- Secondary endpoints: OS, ORR (≥ PR), DoR, safety

**Stratification**
- Age (≤ 75 years vs > 75 years)
- Number of prior treatments (2 vs > 2)
- Primary refractory vs relapsed/refractory vs intolerance/failure




[a] Thromboprophylaxis was indicated for those receiving POM or with deep vein thrombosis history.
BORT, bortezomib; DoR, duration of response; HiDEX, high-dose dexamethasone;
LEN, lenalidomide; LoDEX, low-dose dexamethasone; ORR, overall response rate;
OS, overall survival; PFS, progression-free survival; POM, pomalidomide;
PR, partial response; R, randomised; RRMM, relapsed/refractory multiple myeloma;
SPM, second primary malignancy.

San Miguel JF, et al. *Haematologica.* 2013;98 (suppl, abstr S1151).

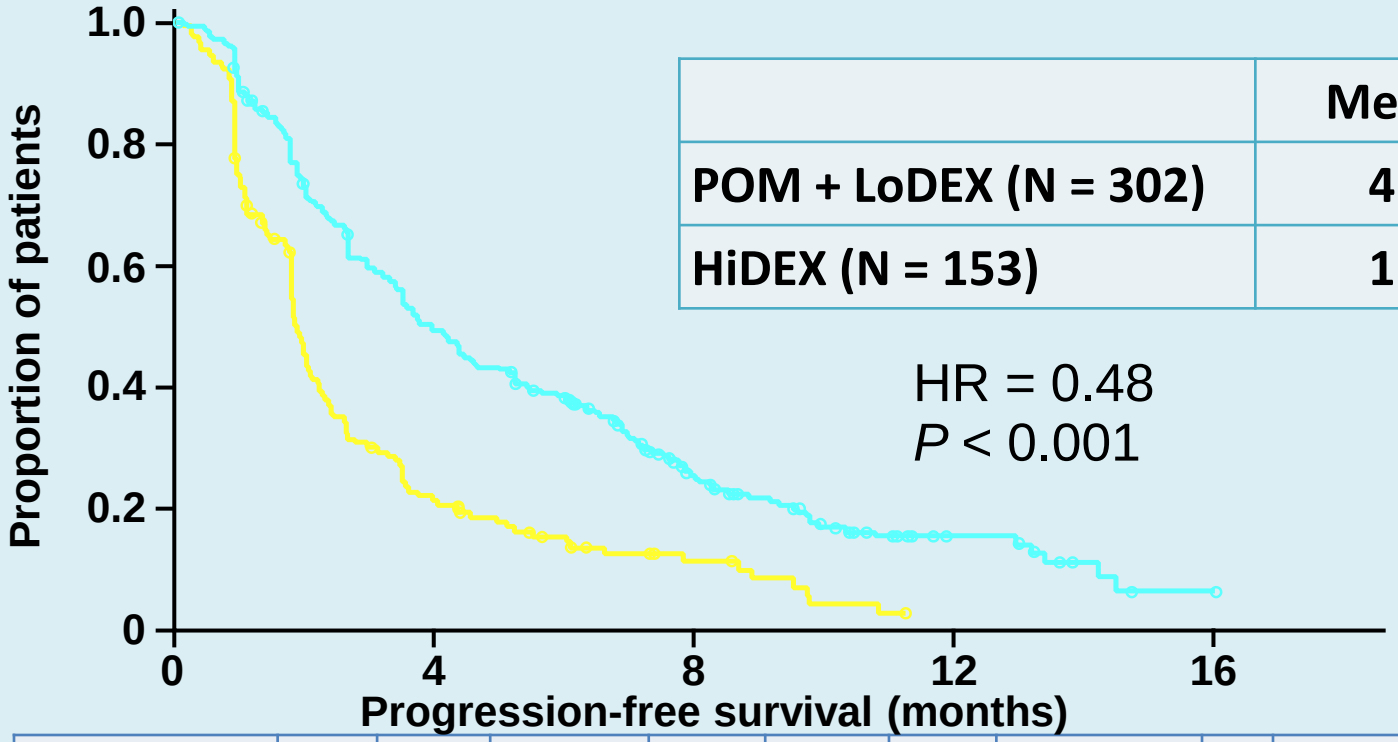
# MM-003: Baseline characteristics

| | POM + LoDEX (N = 302) | HiDEX (N = 153) |
|---|---|---|
| Median age, years (range) | 64 (35–84) | 65 (35–87) |
| Median time from initial diagnosis, years | 5.3 | 6.1 |
| ECOG status 0/1/2, % | 36/46/17 | 24/56/16 |
| ISS I/II/III, % | 27/38/31 | 24/37/35 |
| CrCl, < 60 mL/min, % | 31 | 39 |
| Median number of prior therapies, n (range) | **5** (2–14) | **5** (2–17) |
| Prior DEX, % | 98 | 99 |
| Prior THAL, % | 57 | 61 |
| Prior SCT, % | 71 | 69 |
| Prior LEN, % | 100 | 100 |
| Prior BORT, % | 100 | 100 |
| Prior alkylator, % | 100 | 100 |
| **LEN-refractory, %** | **95** | **92** |
| **BORT-refractory, %** | **79** | **79** |
| **LEN- and BORT-refractory, %** | **75** | **74** |

151).

# MM-003: Key efficacy and safety data

# MM-003: Progression-free survival – ITT population (median follow-up 10 months)




| | Median PFS |
|---|---|
| POM + LoDEX (N = 302) | 4.0 mos |
| HiDEX (N = 153) | 1.9 mos |

HR = 0.48
*P* < 0.001

| At risk, n | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| POM + LoDEX | 302 | | 140 | | 63 | | 15 | | 1 | |
| HiDEX | 153 | | 29 | | 9 | | 0 | | 0 | |

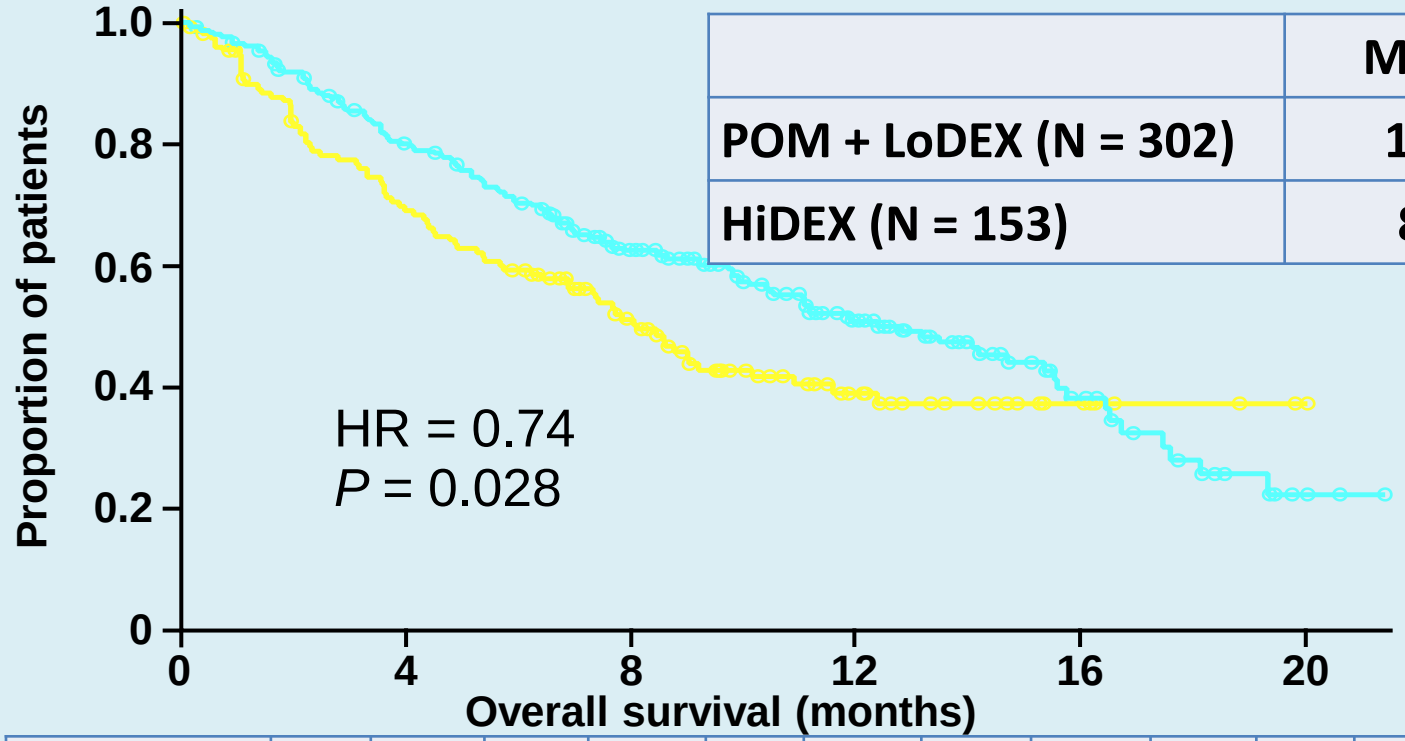
- POM + LoDEX significantly improved PFS compared with HiDEX (4.0 vs 1.9 months; *P* = 0.001), with a 52% reduction in the risk of progression

Based on IMWG criteria. Data cut-off 1 March 2013.
HiDEX, high-dose dexamethasone; ITT, intent-to-treat; LoDEX, low-dose dexamethasone; PFS, progression-free survival; POM, pomalidomide.

San Miguel JF, et al. *Haematologica.* 2013;98 (suppl, abstr S1151).

# MM-003: Overall survival – ITT population (median follow-up 10 months)

| | Median OS |
|---|---|
| POM + LoDEX (N = 302) | 12.7 mos |
| HiDEX (N = 153) | 8.1 mos |




| At risk, n | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| POM + LoDEX | 302 | | 231 | | 145 | | 71 | | 24 | | 2 |
| HiDEX | 153 | | 100 | | 59 | | 26 | | 7 | | 0 |

- At a median follow-up of 10 months, POM + LoDEX significantly improved OS compared with HiDEX (12.7 vs 8.1 months; *P* = 0.028)
- This was despite 76 patients (50%) in the HiDEX arm receiving POM

Data cut-off 1 March 2013.

San Miguel JF, et al. *Haematologica.* 2013;98 (suppl, abstr S1151).

# MM-003: Response – ITT population

- PFS for patients achieving ≥ MR in the POM + LoDEX arm was 8 months

| Response | POM + LoDEX (N = 302) | HiDEX (N = 153) |
|---|---|---|
| ORR (≥ PR), n (%) | 95 **(31%)** | 15 **(10%)** |
| ≥ VGPR | 17 (6) | 1 (1) |
| sCR/CR | 3 (1) | 0 (0) |
| ≥ MR, n (%) | 118 (39) | 24 (16) |
| ≥ SD, n (%) | 247 (82) | 94 (61) |
| Median DoR,[a] months (95% CI) | 7.0 (6.0–9.0) | 6.1 (1.4–8.5) |

Response based on investigator assessment and IMWG criteria, except for MR (based on EBMT criteria).
[a] Based on Kaplan–Meier analysis of patients with ≥ PR only. Data cut-off 1 March 2013.

DoR, duration of response; HiDEX, high-dose dexamethasone; ITT, intent-to-treat; LoDEX, low-dose dexamethasone; MR, minimal response; ORR, overall response rate; PFS, progression-free survival; POM, pomalidomide; PR, partial response; SD, stable disease; VGPR, very good partial response.

San Miguel JF, et al. *Haematologica.* 2013;98 (suppl, abstr S1151).

# MM-003: Adverse events

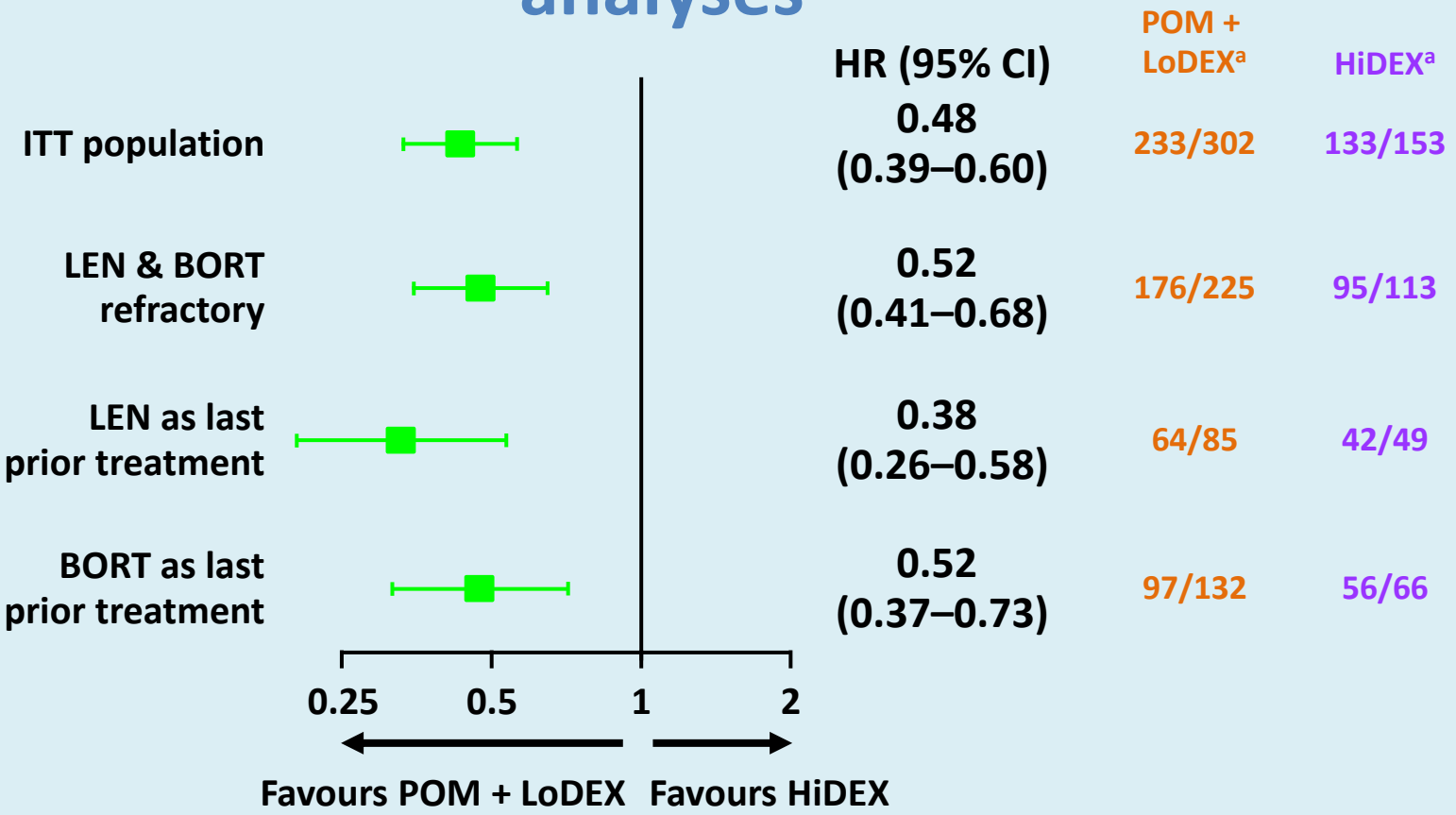
| Event | POM + LoDEX (N = 300) | HiDEX (N = 150) |
|---|---|---|
| **Grade 3/4 haematological AEs, %** | | |
| Neutropenia | **48** | **16** |
| Febrile neutropenia | 9 | 0 |
| Anaemia | 33 | 37 |
| Thrombocytopenia | 22 | 26 |
| **Grade 3/4 non-haematological AEs, %** | | |
| Infection | **30** | **24** |
| Pneumonia | 13 | 8 |
| Bone pain | 7 | 5 |
| Fatigue | 5 | 6 |
| Asthenia | 4 | 6 |
| Glucose intolerance | 3 | 7 |
| **Grade 3/4 AEs of interest, %** | | |
| DVT/PE | 1 | 0 |
| Peripheral neuropathy[a] | **1** | **1** |
| **Discontinuation due to AEs, %** | **9** | **10** |

[a] p

51).

# MM-003: Subgroup analyses by prior treatment

# MM-003: Progression-free survival subgroup analyses

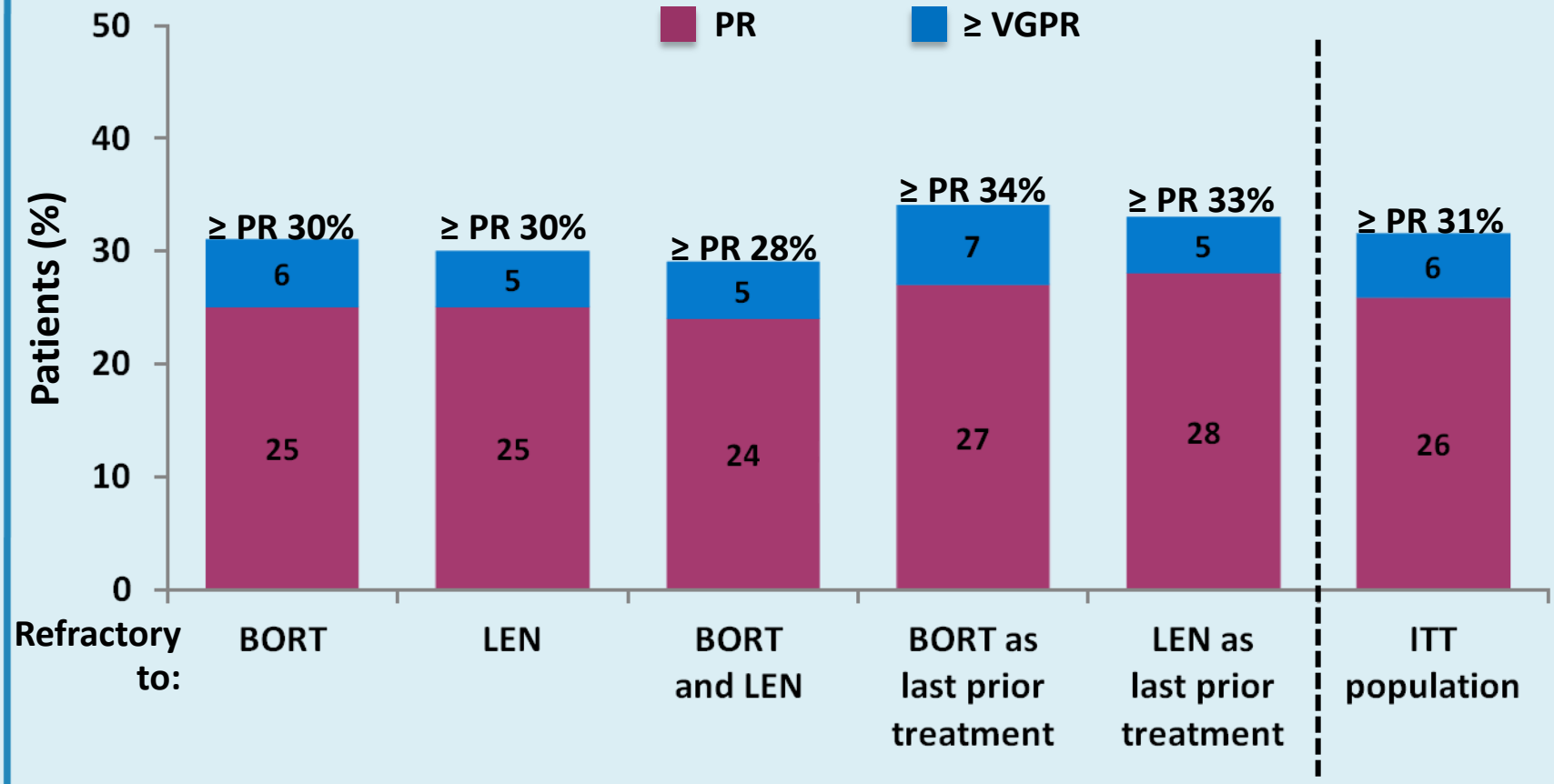



- POM + LoDEX was associated with favourable PFS compared with HiDEX regardless of whether the last prior treatment was LEN or BORT, and regardless of refractoriness to LEN + BORT

[a] Number of events/number of pts.Based on IMWG criteria. Data cut-off 1 March 2013.

San Miguel JF, et al. *Haematologica.* 2013;98 (suppl, abstr S1151).

# MM-003: Response by prior treatment in the pomalidomide + LoDEX arm




- Response rate was consistent amongst all subgroups, including LEN and BORT as last prior treatment

Percentages may not sum due to rounding. Data cut-off 1 March 2013.

San Miguel JF, et al. *Haematologica.* 2013;98 (suppl, abstr S1151).

# Mayo Clinic Phase 2 studies: Pomalidomide + low-dose dexamethasone in patients with relapsed/refractory multiple myeloma

# Mayo Clinic combined cohorts: Response rates and survival outcomes per cohort

| N | Treatment | Population | Median prior Tx | ≥ PR | DoR months | OS months | PFS months |
|---|---|---|---|---|---|---|---|
| 60 | POM: 2 mg (28/28d)<br>DEX: 40 mg/wk | 1-3 prior treatments, relapsed/ refractory | 2 (1–3)[2] | **65%** | 21.3 | NR | 13 |
| 34 | POM: 2 mg (28/28d)<br>DEX: 40 mg/wk | LEN-refractory | 4 (1–14)[2] | **32%** | 8.2 | 33 | 5 |
| 35 | POM: 2 mg (28/28d)<br>DEX: 40 mg/wk | LEN- and BORT-refractory | 6 (3–9)[2] | **26%** | 15.6 | 16 | 6.4 |
| 35 | POM: 4 mg (28/28d)<br>DEX: 40 mg/wk | LEN- and BORT-refractory | 6 (2–11)[2] | **29%** | 3.1 | 9.2 | 3.3 |
| 60 | POM: 4 mg (28/28d)<br>DEX: 40 mg/wk | 1-3 prior treatments, LEN-refractory | 2 (1–3)[2] | **38%** | NR | NR | 7.7 |
| 120 | POM: 4 mg (21/28d)<br>DEX: 40 mg/wk | LEN-refractory | NR | **21%** | 8.3 | NR | 4.3 |

BORT, bortezomib; d, day; DEX, dexamethasone, DoR, duration of response; LEN, lenalidomide; NR, not reported; OS, overall survival; PFS, progression-free survival; POM, pomalidomide; PR, partial response; wk, week.

1. Lacy MQ, et al. *Blood.* 2012;120 (suppl; abstr 201).
2. Lacy MQ, et al. *Blood*. 2011;118 (suppl; abstr 3963).

# Mayo Clinic combined cohorts: Response rates and survival outcomes

- In the combined cohort analysis, ORR was 34%
- In patients with mSMART* high-risk status, ORR was 30.6%
- After a median follow-up of 10.4 months (5.4–34):
  - 67% of patients were alive
  - 32% of patients were progression free
  - 46 patients remained on treatment

* mSMART high risk defined in these studies as del(17p), t(4;14), or t(14;16) by FISH or del(13) by conventional cytogenetics or myeloma cells > 3%.

Lacy MQ, et al. *Blood.* 2012;120 (suppl; abstr 201)

# Mayo Clinic combined cohorts: Adverse events

| Most common grade 3/4 adverse events in patients receiving POM 2 mg or 4 mg, % | N = 345 |
|---|---|
| **Haematological** | |
| Neutropenia | 31 |
| Anaemia | 16 |
| Thrombocytopenia | 12 |
| **Non-haematological** | |
| Pneumonia | 8 |
| Fatigue | 8 |

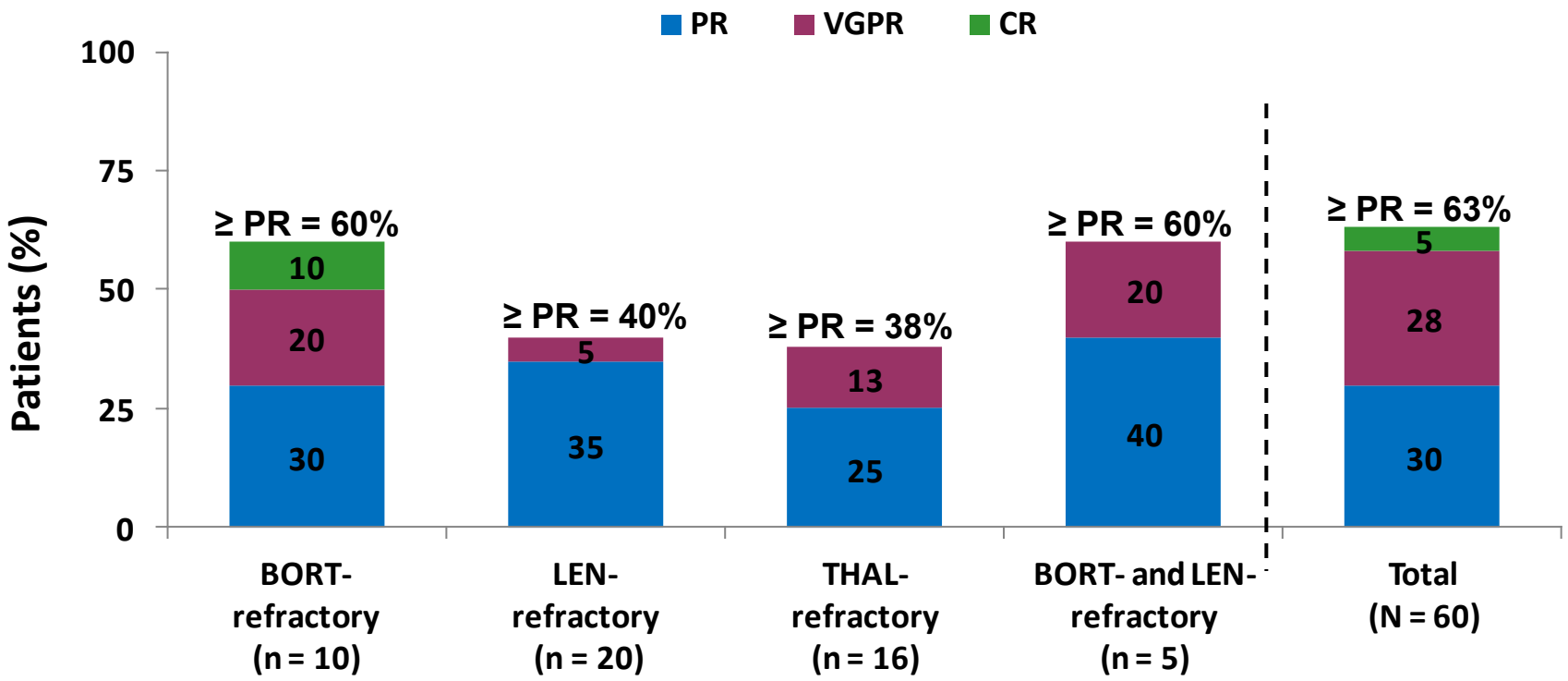
- Venous thromboembolism was reported in 10 patients (3%)

POM, pomalidomide.

Lacy MQ, et al. *Blood.* 2012;120 (suppl; abstr 201).

# Mayo Clinic Phase 2 study: Pomalidomide + low-dose dexamethasone in patients with 1–3 prior therapies

# Mayo Clinic, 1–3 prior therapies: Response rates

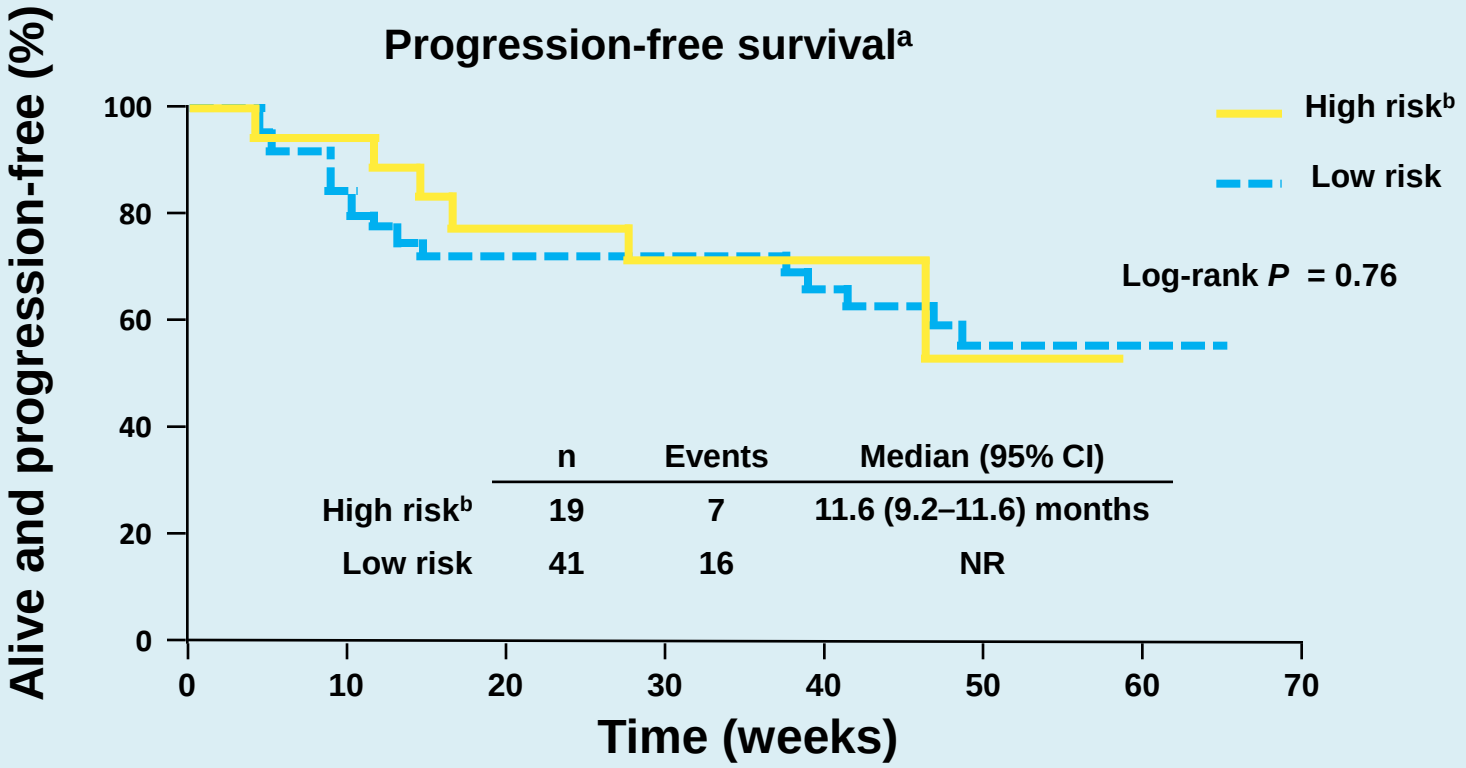



- Median DoR was not achieved
  - 97% of responders maintained response for at least 6 months

BORT, bortezomib; CR, complete response; DoR, duration of response;
LEN, lenalidomide; PR, partial response;
THAL, thalidomide; VGPR, very good partial response.

Lacy MQ, et al. *J Clin Oncol.* 2009;27:5008–5014.

# Mayo Clinic, 1–3 prior therapies: Progression-free survival




- Median PFS was 11.6 months (9.2–NR) with no significant difference observed between patients with low-risk or high-risk disease[b]
- 94% of patients were alive at 6 months

[a] Median follow-up time of 7.4 months

[b] Defined in the manuscript as PCLI ≥ 3%, del(17p), t(4;14), or t(14;16), by FISH or del(13) by conventional cytogenetics.

Lacy MQ, et al. *J Clin Oncol.* 2009;27:5008–5014.

# Souhrn

## Účinnost

Nejméně 1/3 nemocných refrakterní
na dostupnou léčbu dosáhne parciální remisi

Přínos na celkové přežití: 1 rok
Přínos - doba do relapsu u nemocných reagujících na léčbu: 1 rok

## Nežádoucí účinky

- neutropenie (první tři cykly), slabost
- téměř žádná polyneuropatie

# MM: Progress in Therapeutic Options
# Key effective drugs

- Alkylating agens
- Glucocorticoids
- **IMIDs**
  - thalidomide
  - lenalidomide
  - pomalidomide
- Proteasome inhibitors

**Nemá zkříženou rezistenci ani s IMIDs, ani s PI;**
**Podobný profil jako lenalidomid**
**PLUS**
- **bez redukce u renálního selhání**
- **bez neg .vlivu na ledviny u typu s LŘ**

**Kombinace imunomodulačních látek a inhibitorů proteasomu tvoří spolu s glukokortikoidy nejúčinnější režimy současnosti.**

**Tyto léky nemají zkříženou rezistenci a jde je tak rotovat s vysokou účinností v následných léčebných liniích.**

**Jde i o plně perorální režimy**

| | | | |
|---|---|---|---|
| Glucocorticoids | pomalidomide | ixazomib | IPD |
| Glucocorticoids | pomalidomide | oprozomib | OPD |

VTD

CRD

# Pomalidomid
# –
# indikace

# EMA – terapeutické indikace

**Imnovid** je v kombinaci s dexamethasonem indikován k léčbě dospělých pacientů s relabovaným a refrakterním mnohočetným myelomem, kteří absolvovali alespoň dvě předchozí léčebná schémata,zahrnující jak lenalidomid, tak bortezomib, a při poslední terapii vykazovali progresi onemocnění.

## FDA - therapeutic indication

**Pomalyst** is indicated for patients with multiple myeloma who have received at least two prior thearpies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy.

# Pomalidomid

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# Schválení EMA
# Logistika-§16,cena
# Poznámka o SLP

# Schválení EMA

**Datum první registrace:**

5.srpna 2013 (pod názvem Pomalidomide Celgene)

**Datum revize textu:**

27.srpna 2013 (pod názvem Imnovid)

# •Logistika

•o hrazení jednotlivých pacientů se musí žádat jednotlivě na §16

• lékárna pošle vyplněný formulář do Celgene

• dodání z UK přímo do nemocnice – lékárny

Zatím není dostupný „český“ Imnovid , dodává se americký Pomalyst (cca do března 2014)

Prodejní cena přípravku Pomalyst cps 21x2 mg i 21x4mg v ČR je 9562 Euro (250 tis. Kč; bez DPH a marže lékárny)

# Specifický léčebný program- Pomalyst

## **Pomalyst 2mg** (por cps dur 21x2mg)

**Datum schválení:** 16.8.2013
**Platnost programu:** 31.8.2014
**Počet povolených balení:** 50

## **Pomalyst 4 mg** (por cps dur 21x4 mg)

**Datum schválení.** 16.8. 2013
**Platnost programu:** 30.8. 2014
**Počet povolených balení:** 110

# Thank you for your attention.