POZVÁNKA

XII. workshop mnohočetný myelom
s mezinárodní účastí a Roční setkání
České myelomové skupiny

Pořadatel:
Lékařská fakulta Masarykovy univerzity

Česká myelomová skupina (CMG)
člen ČHS ČLS JEP

Za podpory:
Celgene s.r.o.

Edukační blok

Současné přístupy a perspektivy v léčbě mnohočetného myelomu imunomodulačními léky

12. dubna 2014, od 14.30 do 16.30 hod
v sále Aurelius, Hotel Galant, Mlýnská 2, Mikulov

FAKULTNÍ NEMOCNICE OSTRAVA

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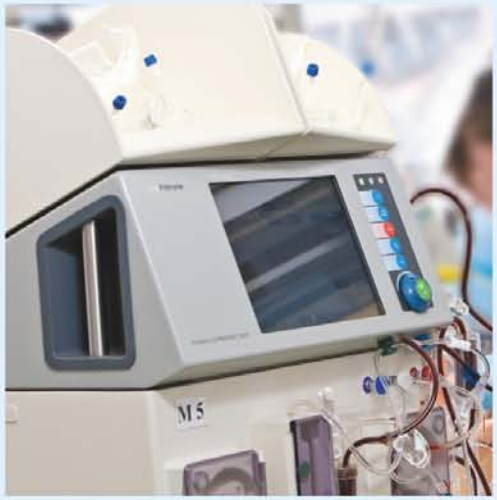
Czech Republic

„Pomalidomid – nový imunomodulační lék v léčbě mnohočetného myelomu



Mikulov 2014

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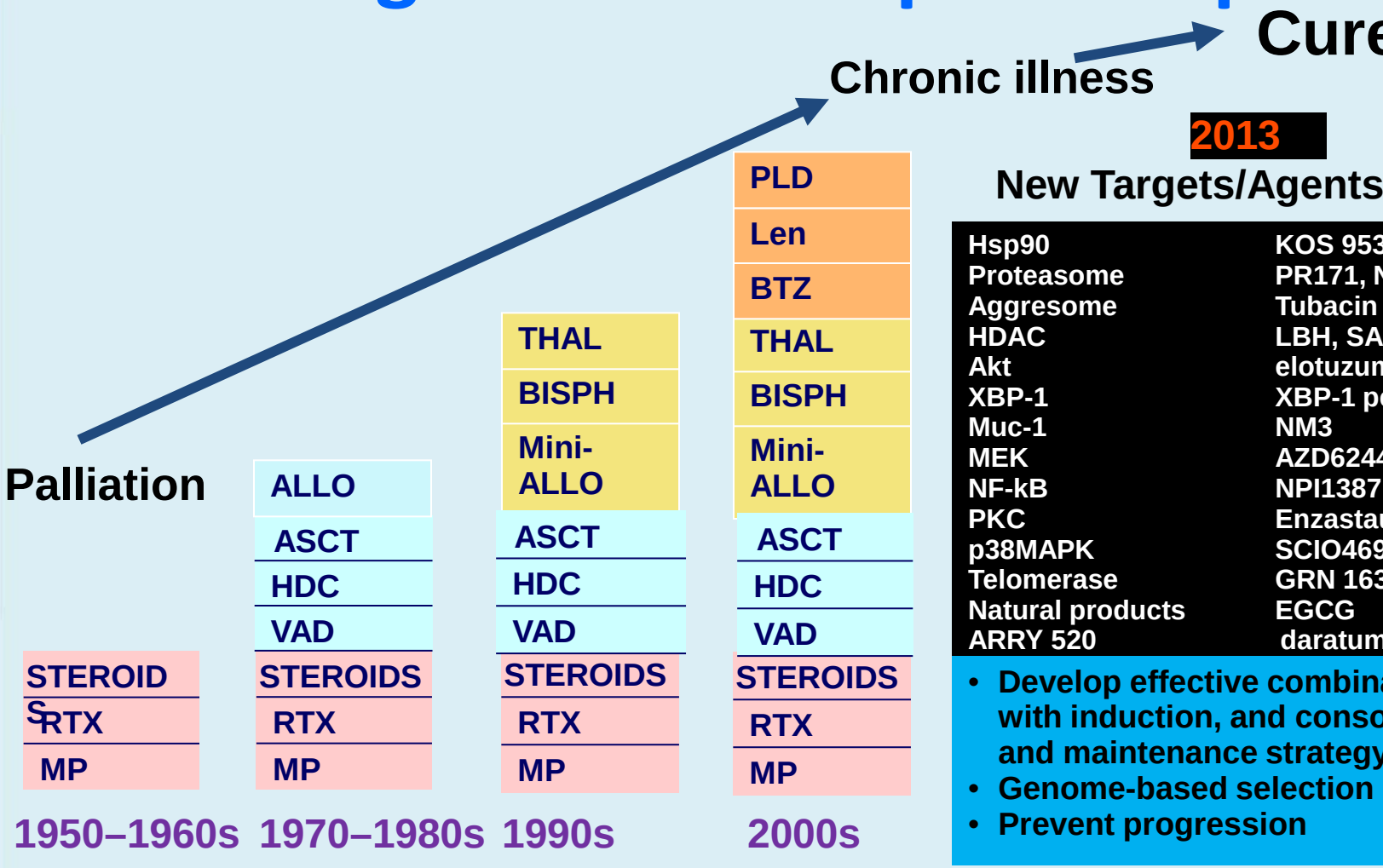
Úvod – aktuální stav

- **Pomalidomid (Imnovid)v kombinaci s dexametazonem je registrovaný v EU**
- **Pomalidomid má schválený SLP v ČR**
- ***Úhradu v ČR jde aktuálně žádat na paragraf 16***

Klíčové účinné léky u MM

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
ARRY 520	daratumumab

- 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
- 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

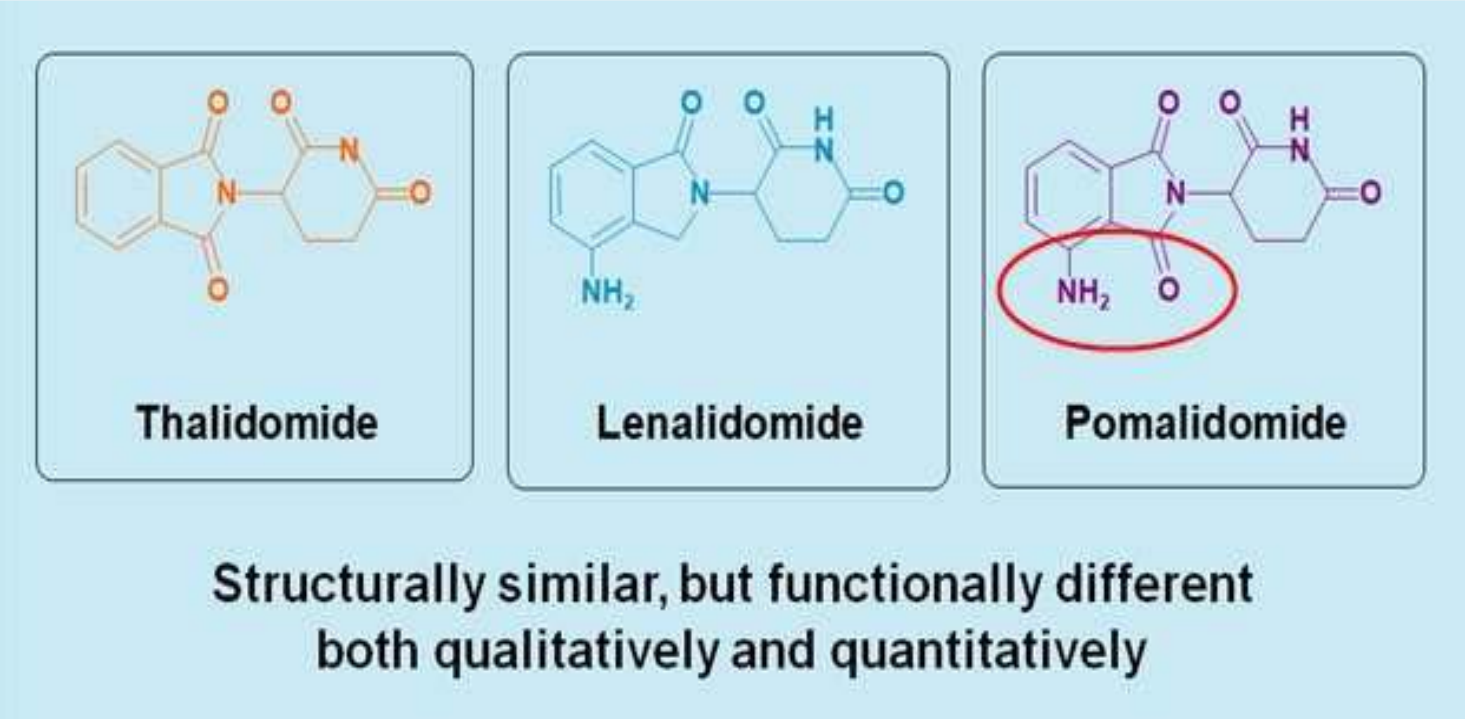
MM: Progress in Therapeutic Options
Key effective drugs

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

Pomalidomid ?

„Co přináší pomalidomid nemocnému s RRMM?“

Chemická struktura talidomidu a jeho analogů: lenalidomidu a pomalidomidu



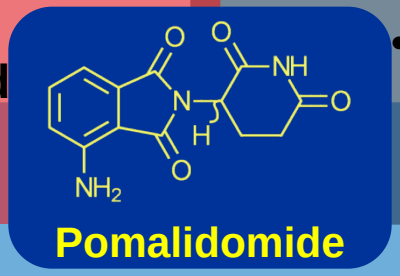
Pomalidomide mechanism of action: Overview

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).

Přehled klinických studií
-
zaměření na překonání rezistence

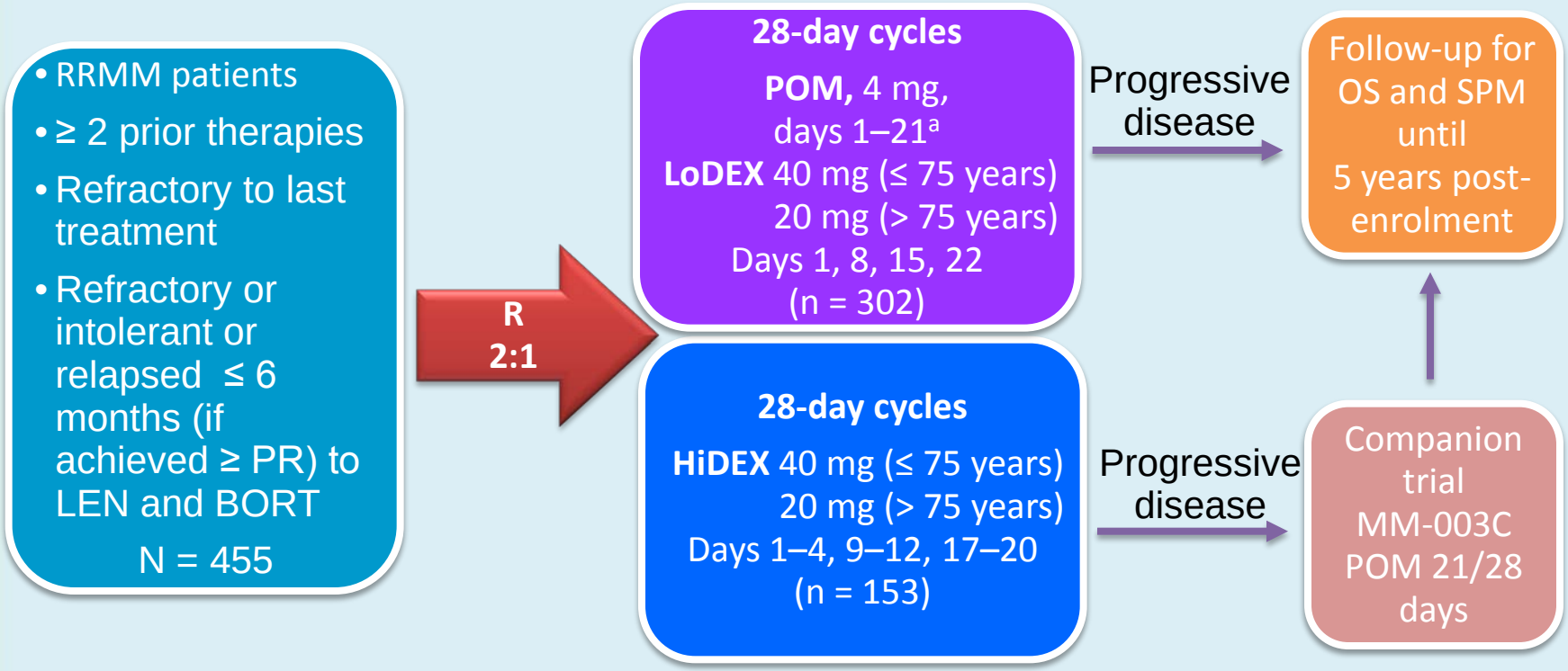
MM-003: Phase 3 trial of pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone in relapsed/refractory multiple myeloma

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.

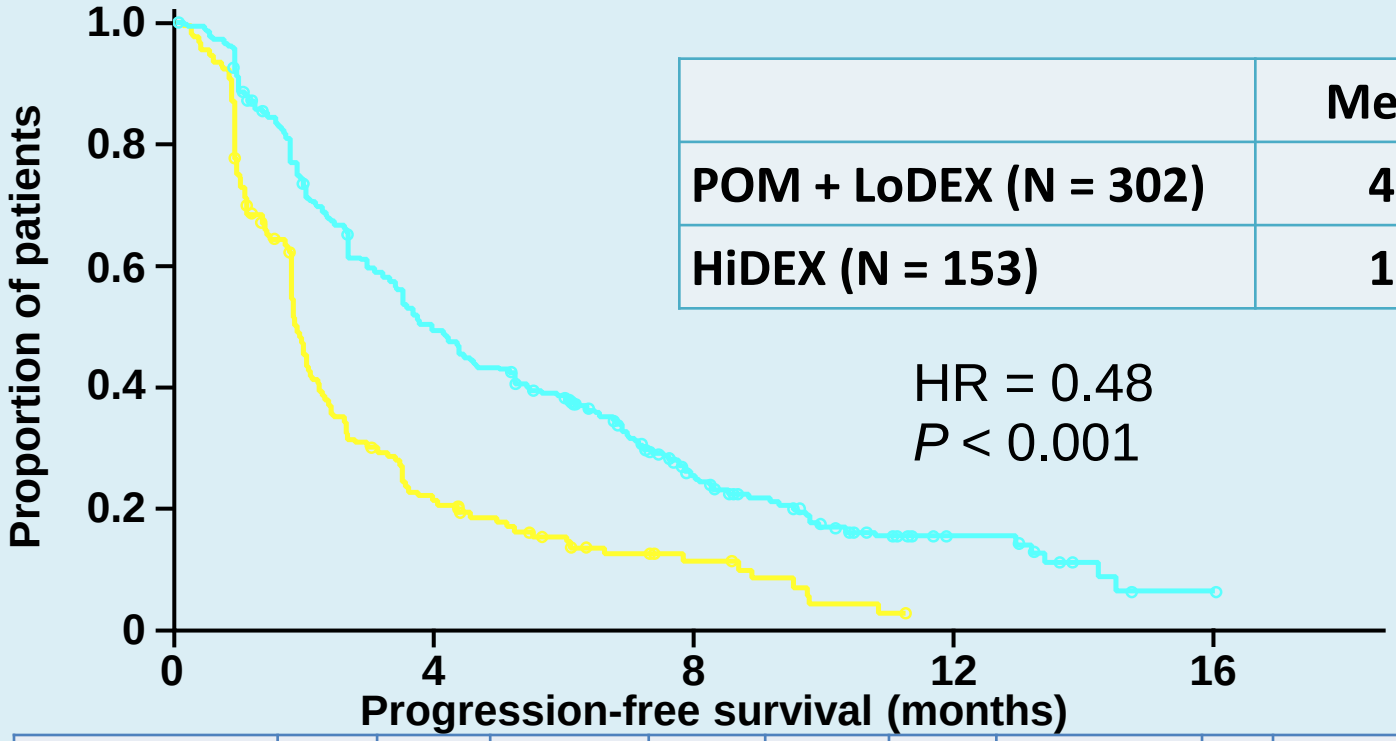
San Miguel JF, et al. *Haematologica.* 2013;98 (suppl, abstr S1151).

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**

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

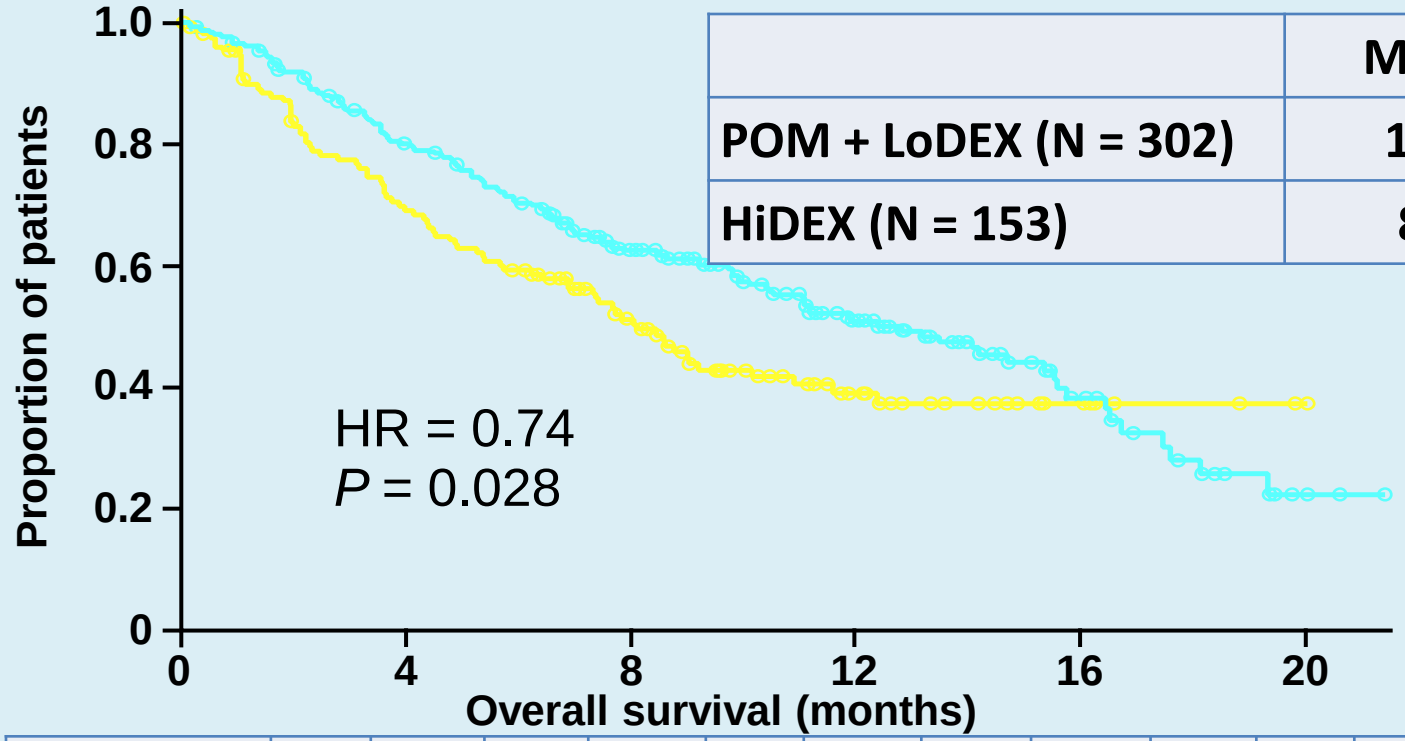
At risk, n										
POM + LoDEX	302		140		63		15		1	
HiDEX	153		29		9		0		0	

- 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

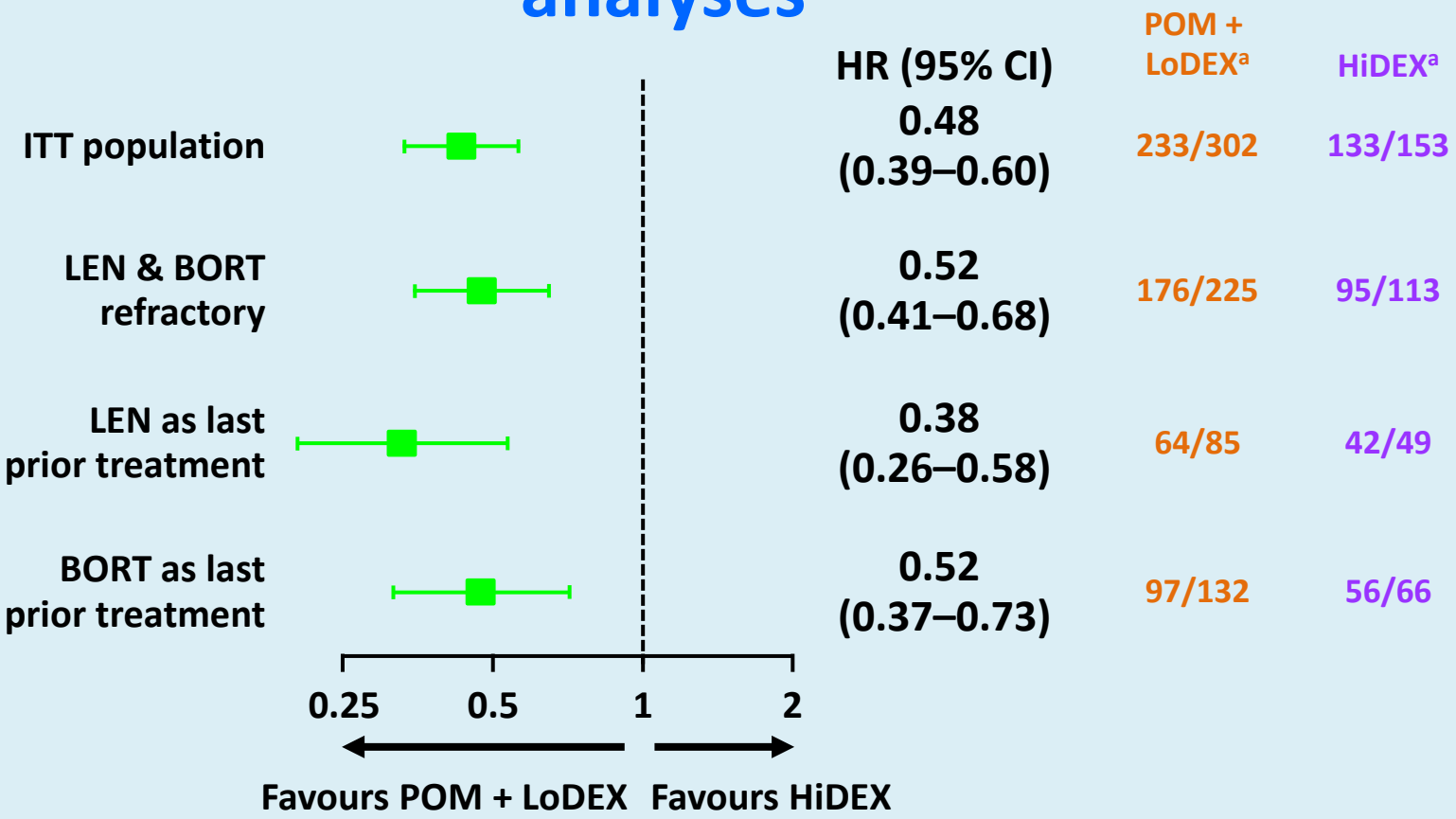
Event	POM + LoDEX (N = 300)	HiDEX (N = 150)
Grade 3/4 haematological AEs, %		
Neutropenia	48	16
Febrile neutropenia	9	0
Anaemia	33	37
Thrombocytopenia	22	26
Grade 3/4 non-haematological AEs, %		
Infection	30	24
Pneumonia	13	8
Bone pain	7	5
Fatigue	5	6
Asthenia	4	6
Glucose intolerance	3	7
Grade 3/4 AEs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

[a] Peripheral neuropathy includes the preferred terms hyperaesthesia, neuropathy peripheral, peripheral sensory neuropathy, paraesthesia, hypoaesthesia, and polyneuropathy.

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

MM-003: Subgroup analyses by prior treatment

MM-003: Progression-free survival subgroup analyses

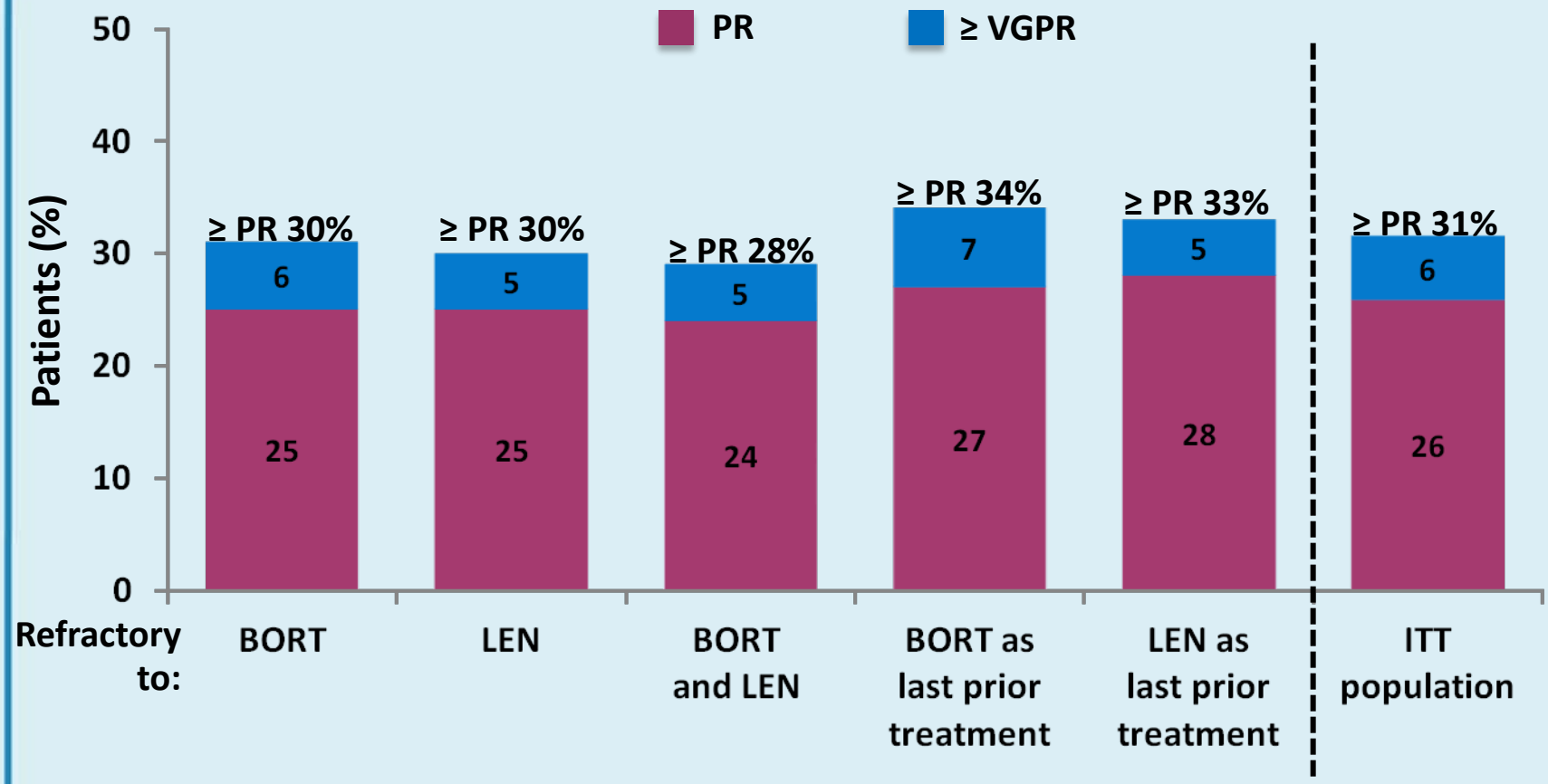


- POM + LoDEX was associated with favourable PFS compared with HiDEX regardless of whether the last prior treatment was LEN or BORT, and regardless of refractoriness to LEN + BORT

[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) 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) DEX: 40 mg/wk	LEN-refractory	4 (1–14)[2]	**32%**	8.2	33	5
35	POM: 2 mg (28/28d) DEX: 40 mg/wk	LEN- and BORT-refractory	6 (3–9)[2]	**26%**	15.6	16	6.4
35	POM: 4 mg (28/28d) 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) 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) 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

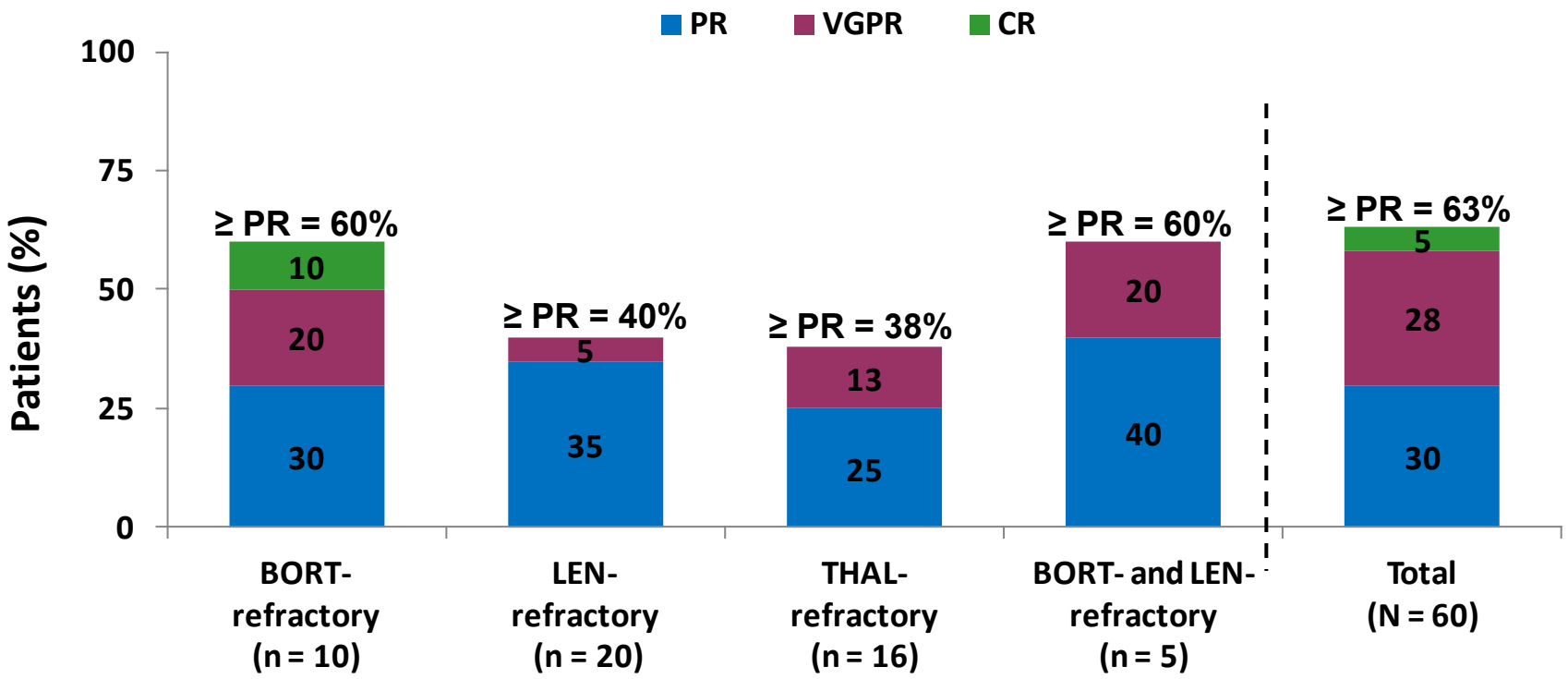
- Venous thromboembolism was reported in 10 patients (3%)

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

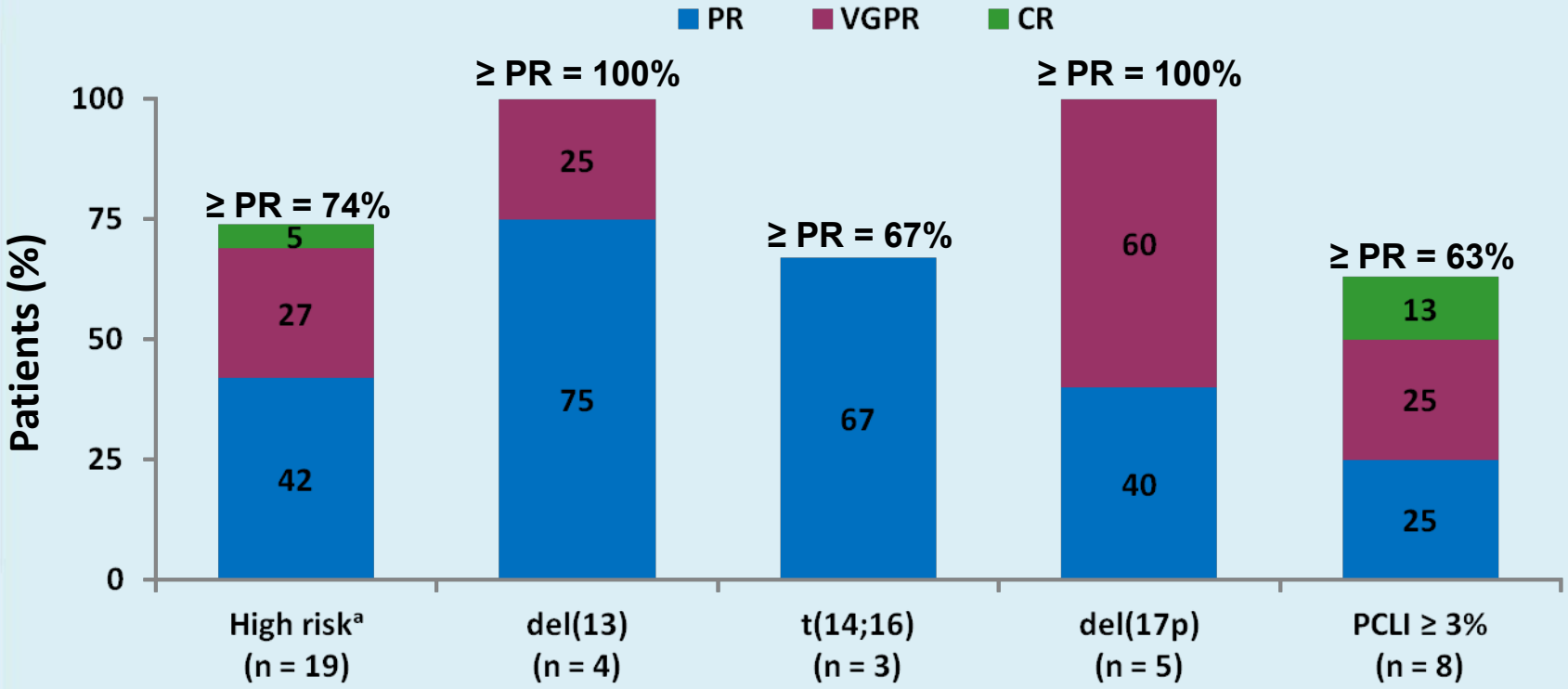


- Median DoR was not achieved
  - 97% of responders maintained response for at least 6 months

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: Responses in patients with high-risk disease or cytogenetic abnormalities

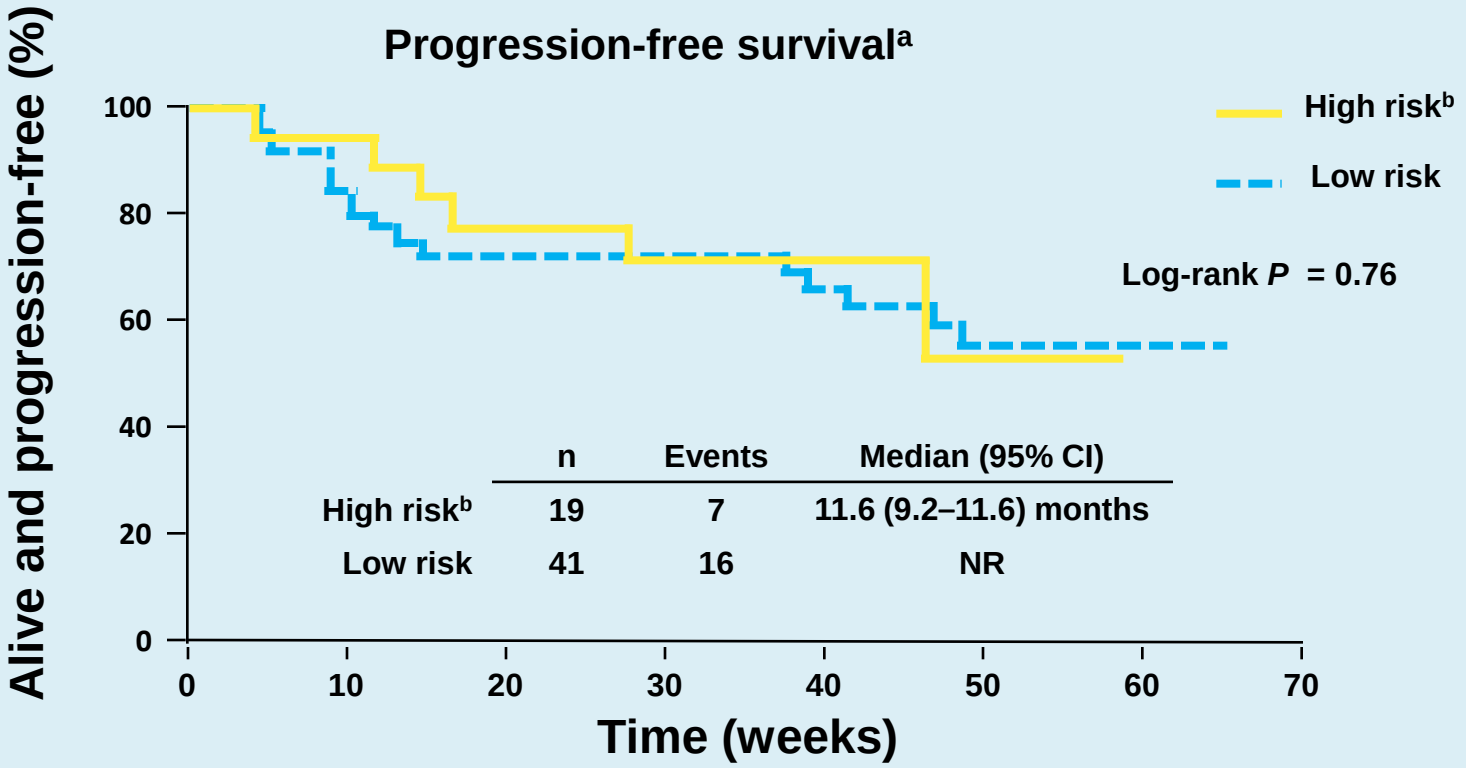


- The majority of patients with high-risk disease and/or unfavourable cytogenetics[a] responded to POM
  - One patient presented with t(4;14) and exhibited SD

[a] 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.

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.

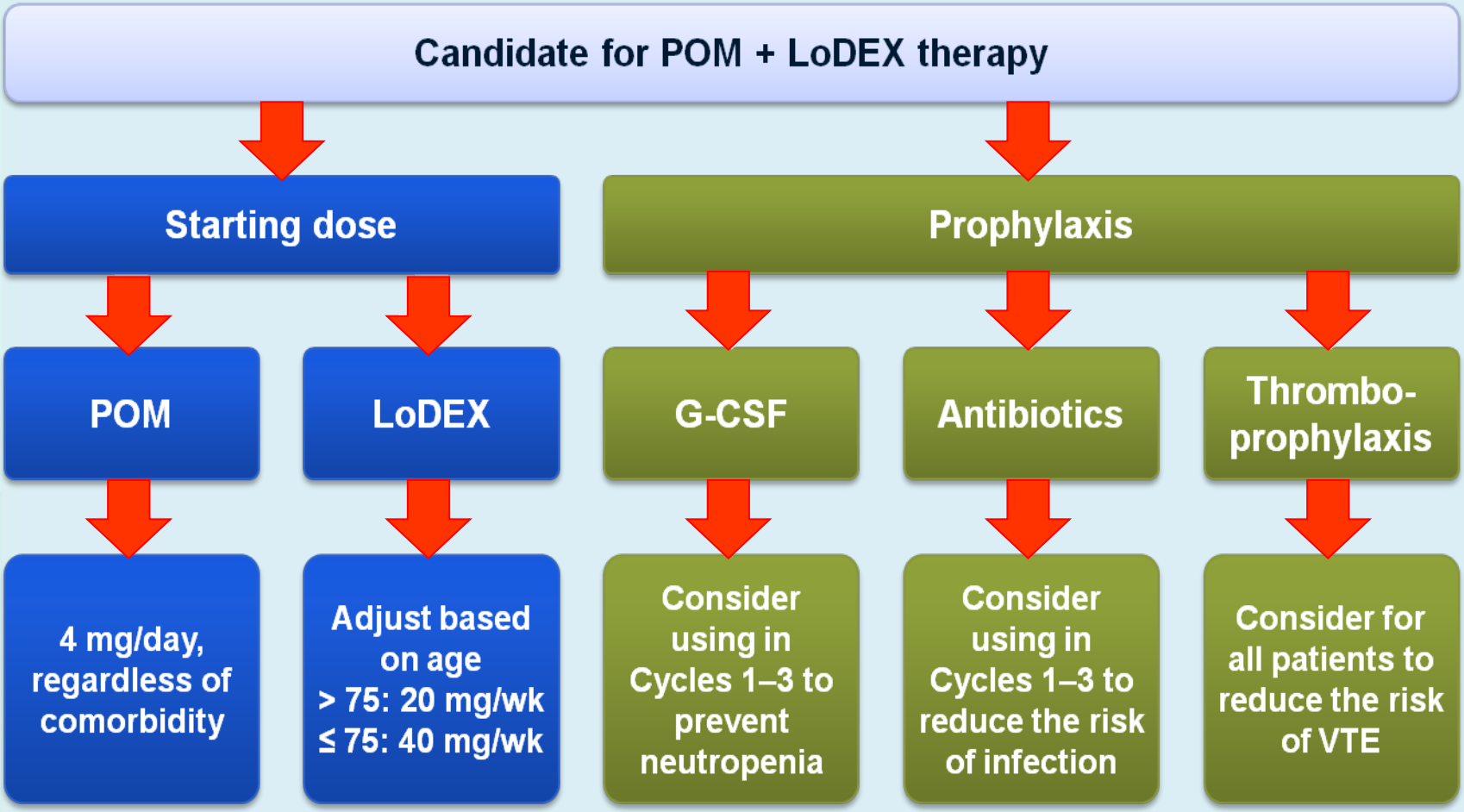
Expert panel consensus statement on the optimal use of pomalidomide in relapsed and refractory multiple myeloma

Dimopoulos MA, Leleu X, Palumbo A, Moreau P, Delforge M, Cavo M, Ludwig H, Morgan GJ, Davies FE, Sonneveld P, Schey SA, Zweegman S, Hansson M, Weisel K, Mateos MV, Facon T, San Miguel JF

Leukemia. 2014; [Epub ahead of print].

Summary of considerations for initiating POM + LoDEX therapy

Expert panel opinion



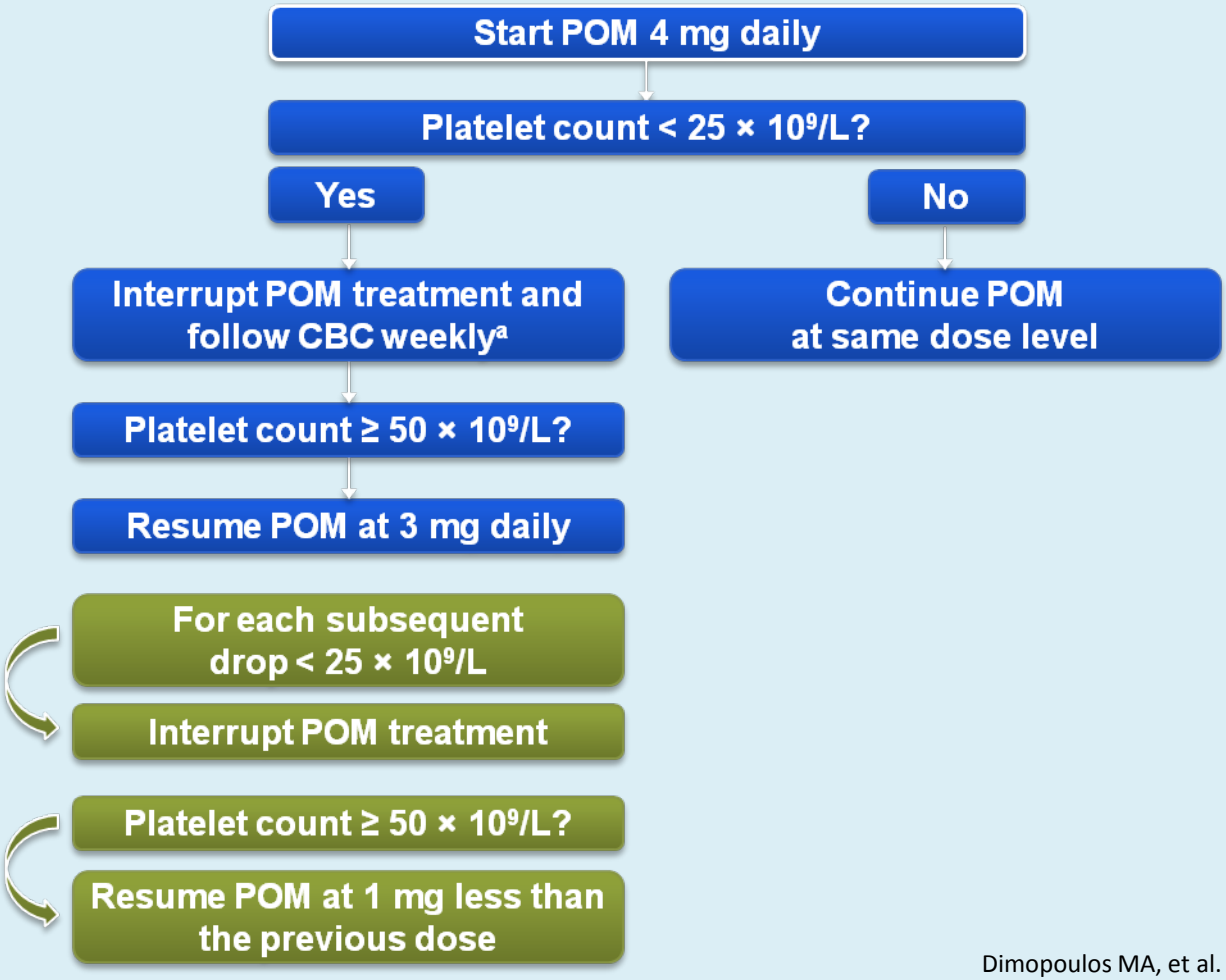
G-CSF, granulocyte colony-stimulating factor; LoDEX, low-dose dexamethasone; POM, pomalidomide; wk, week; VTE, venous thromboembolism.

Dimopoulos MA, et al. *Leukemia*. 2014; Feb 5 [Epub].

FAKULTNÍ NEMOCNICE OSTRAVA

Managing thrombocytopenia with POM + LoDEX

Expert panel opinion



Dimopoulos MA, et al. *Leukemia*. 2014; Feb 5 [Epub].
Imnovid® SmPC. Celgene Europe Ltd. 2013.

Minimum blood levels required to start treatment with POM at the full 4 mg dose are: ANC ≥ 1 × 10^9/L and platelets ≥ 75 × 10^9/L (or ≥ 30 × 10^9/L if ≥ 50% of bone marrow nucleated cells are plasma cells). POM doses < 1 mg are not recommended.

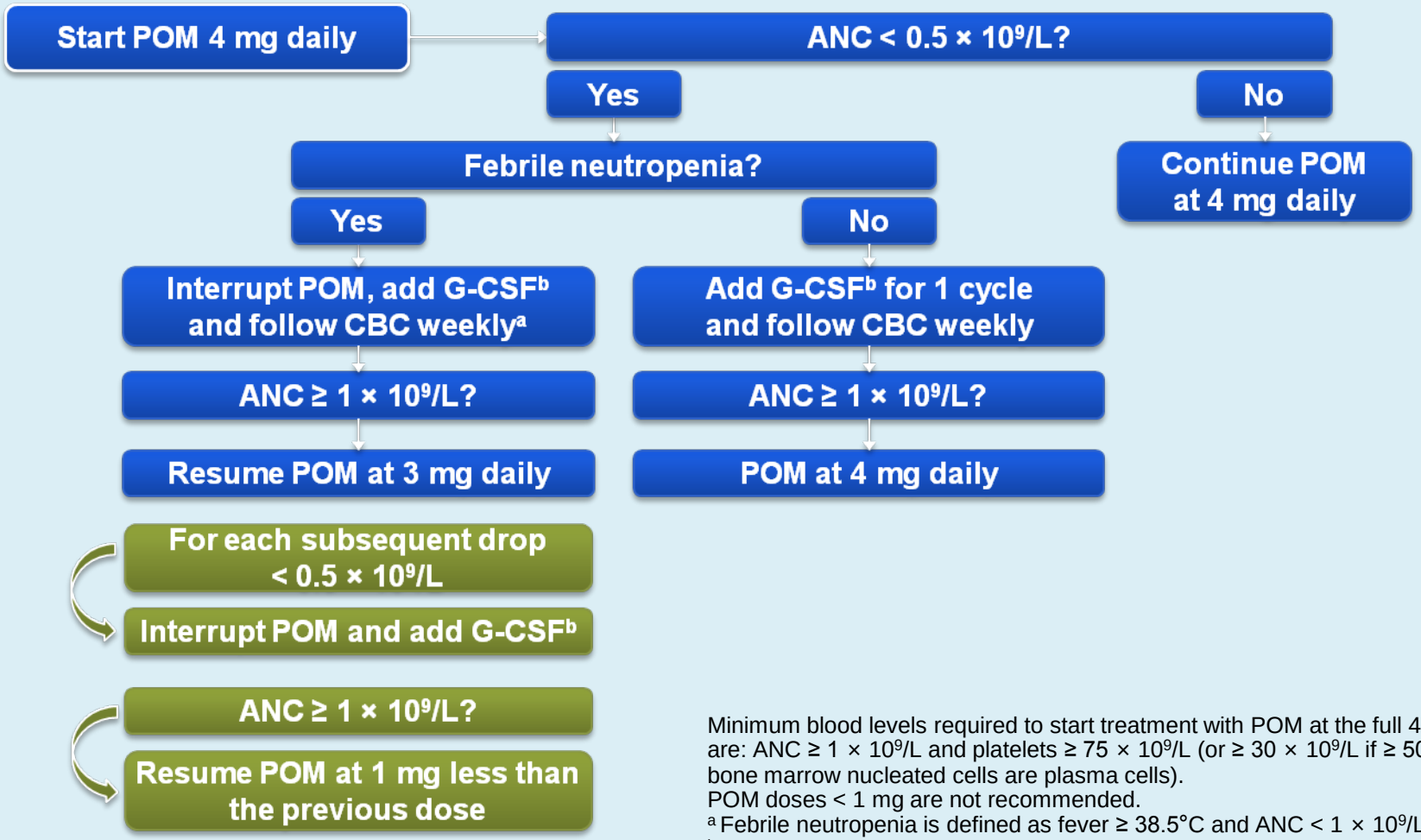
[a] Consider frequent platelet transfusions.

CBC, complete blood count; LoDEX, low-dose dexamethasone; POM, pomalidomide.

FAKULTNÍ NEMOCNICE OSTRAVA

Managing neutropenia with POM + LoDEX

Expert panel opinion



Minimum blood levels required to start treatment with POM at the full 4 mg dose are: ANC ≥ 1 × 10^9/L and platelets ≥ 75 × 10^9/L (or ≥ 30 × 10^9/L if ≥ 50% of bone marrow nucleated cells are plasma cells).
POM doses < 1 mg are not recommended.
[a] Febrile neutropenia is defined as fever ≥ 38.5°C and ANC < 1 × 10^9/L.
[b] G-CSF cycle: 300 µg/kg for 3 days (Days 22, 23 and 24 of each 28-day cycle).

ANC, absolute neutrophil count; CBC, complete blood count;
G-CSF, granulocyte colony-stimulating factor;
LoDEX, low-dose dexamethasone; POM, pomalidomide.

Dimopoulos MA, et al. *Leukemia*. 2014; Feb 5 [Epub].

FAKULTNÍ NEMOCNICE OSTRAVA

Managing infection with POM + LoDEX

Expert panel opinion

- Antibiotická profylaxe by měla být zvažována pro první 3 cykly léčby pomalidomidem u všech pacientů kvůli vysokému riziku infekce v tomto období

- Pro pacienty s vysokým rizikem infekce (nízký počet krvinek, předchozí historie infekce) zvážit antibiotickou profylaxi po celou dobu léčby pomalidomidem

Dimopoulos MA, et al. *Leukemia*. 2014; Feb 5 [Epub].

AE, adverse event; LoDEX, low-dose dexamethasone; POM, pomalidomide.

FAKULTNÍ NEMOCNICE OSTRAVA

Managing infection with POM + LoDEX

Expert panel opinion

- Zaručit opatrnost, pokud je pomalidomid podáván současně se silnými inhibitory CYP1A2 jako jsou ciprofloxacin a enoxacin, jelikož tyto látky mohou zvýšit působení pomalidomidu a proto i zvýšit riziko nežádoucích účinků

- Pro pacienty, u kterých se objeví infekce, zaručit včasný zásah, včetně přerušení léčby a okamžitého zahájení antibiotické léčby

Dimopoulos MA, et al. *Leukemia*. 2014; Feb 5 [Epub].

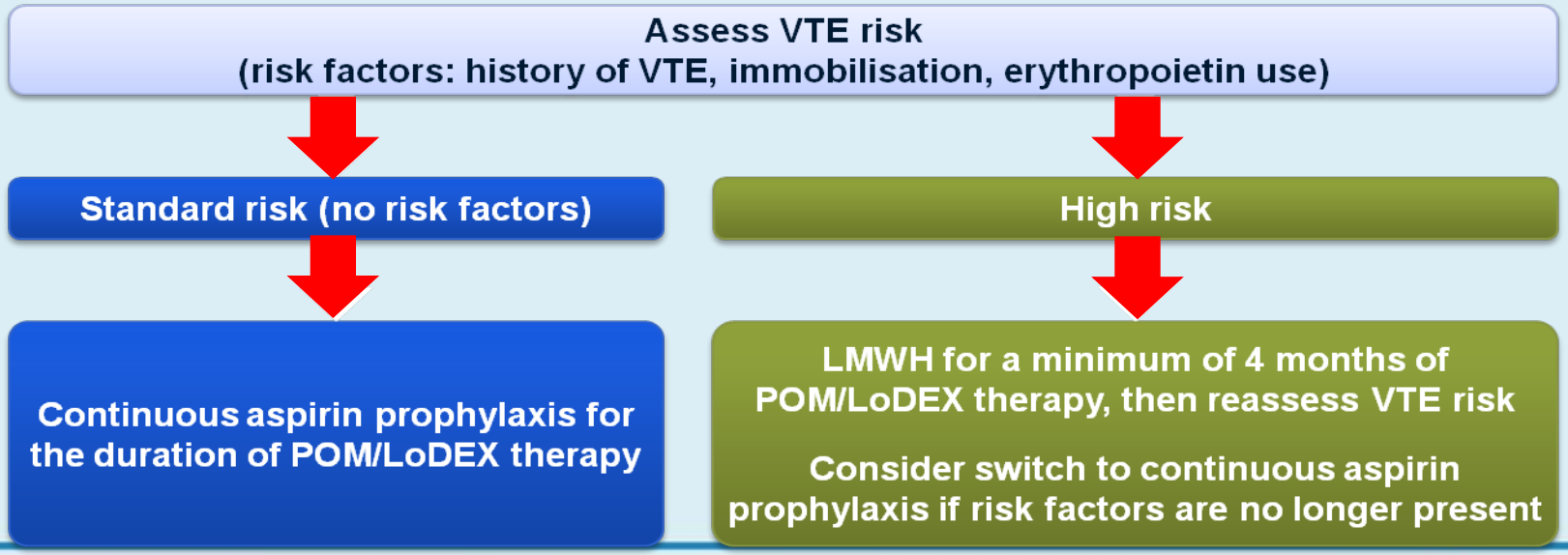
AE, adverse event; LoDEX, low-dose dexamethasone; POM, pomalidomide.

FAKULTNÍ NEMOCNICE OSTRAVA

Managing VTE with POM + LoDEX

Expert panel opinion

- Z existujících doporučení pro tromboprofylaxi během léčby imunomodulačními látkami vyplývá, že např. profylaxe aspirinem pro pacienty se standardním rizikem a LMWH pro pacienty s nejméně jedním rizikovým faktorem, snižuje výskyt VTE na < 5%
- Pacienti s vysokým rizikem VTE by kvůli doprovodným léčebným okolnostem měli pokračovat v předepsané antikoagulační léčbě
- U pacientů s vysokým rizikem z jiných důvodů než komorbidit může být riziko VTE po 4 měsících přehodnoceno a u pacientů se standardním rizikem pak změněno na aspirin



DVT, deep vein thrombosis; IMiD, immunomodulatory drug; LMWH, low-molecular-weight heparin; LoDEX, low-dose dexamethasone; POM, pomalidomide; VTE, venous thromboembolism.

FAKULTNÍ NEMOCNICE OSTRAVA

Dimopoulos MA, et al. *Leukemia*. 2014; Feb 5 [Epub].

POM + LoDEX use in patients with renal impairment

Expert panel opinion

- U pacientů se střední poruchou ledvin (clearance kreatinin ≥ 45ml/min) není potřeba dávku pomalidomidu 4 mg upravovat

- U pacientů s těžkou poruchou ledvin je pro použití pomalidomidu + nízkodávkového dexamethasonu potřeba více dat

- U pacientů s poruchou funkce ledvin, kteří jsou léčeni pomalidomidem, je třeba sledovat nežádoucí účinky

AE, adverse event; CrCl, creatinine clearance;
LoDEX, low-dose dexamethasone; POM, pomalidomide.

Dimopoulos MA, et al. *Leukemia*. 2014; Feb 5 [Epub].

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Pomalidomid ?

„Co přináší pomalidomid nemocnému s RRMM?“

„Co přináší pomalidomid pacientovi s RRMM?“

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

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

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

Děkuji za pozornost