Institute of Biomedical Research of Salamanca

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Cancer Research Center

IMiDs

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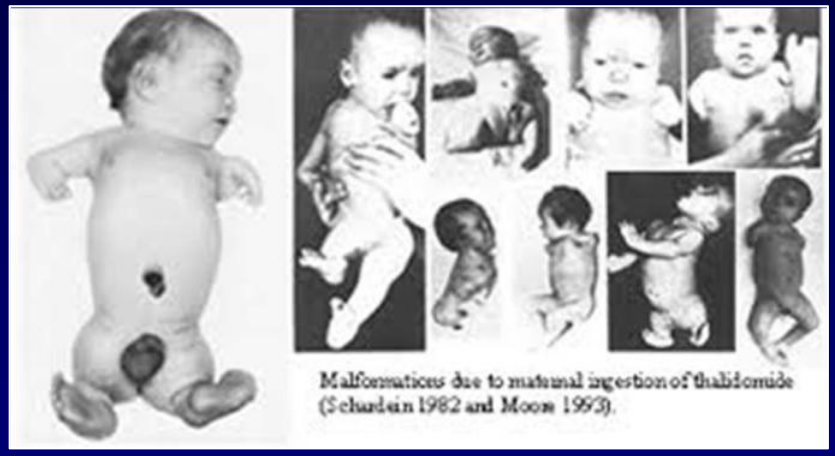
History of Thalidomide, the 1st in class IMiD

- **1954: Non-barbituric hipnotic developed as a sedative used to ameliorate morning sickness in pregnant women.**

- **Thalidomide exposure during the first trimester of pregnancy caused multiple birth defects (e.g. Phocomelia and amelia), affecting > 10.000 children in the late 1950s and early 1960s.**



"One of the greatest medical disasters in the modern era"

Cause unknown for many years

History of Thalidomide, the 1st in class IMiD

- *In the mid-1960's, an Israeli doctor gave it to leprosy patients with trouble sleeping ... Skin lesions cleared up almost overnight*

- **1975: Compassionate use for Leprosy**

- **1998: FDA approved for the acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL) and as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrences.**

Under strict medical control

History of Thalidomide, the 1st in class IMiD

- 1991 → Gilla Kaplan: Thalidomide suppresses TNF-α

  Immune effect?

- 1993 → Dr. Judah Folkman *(Harvard Medical School)*

  Anti-angiogenesis to treat blood cancers at ASH

- 1994 → Robert D'Amato discovered the antiangiogenic properties of Thalidomide.

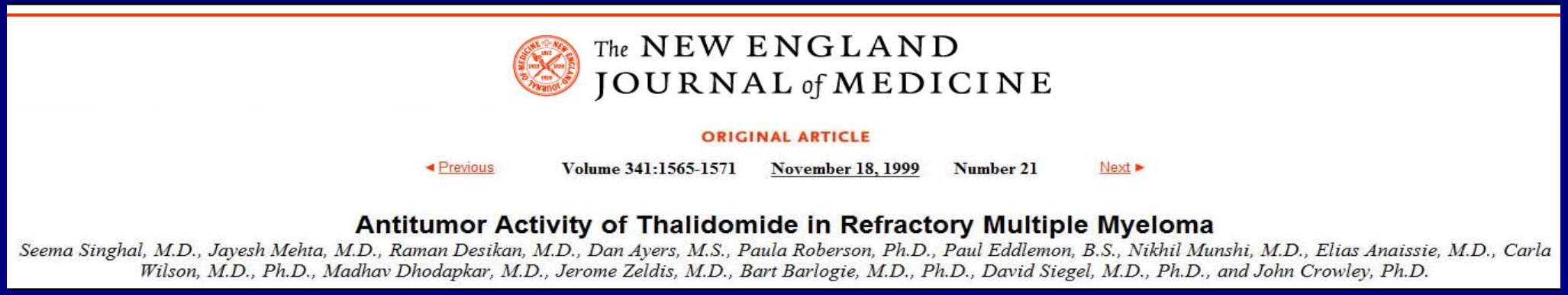
History of Thalidomide, the 1st in class IMiD

"No one was investigating thalidomide for multiple myeloma until Dr. Barlogie was pushed into it by Beth Wolmer, a Manhattan lawyer whose husband, Ira, who had received a diagnosis of multiple myeloma in 1995, at the age of 35. Ira Wolmer, a cardiologist, underwent three bone marrow transplants and tried an experimental vaccine, his wife said, but nothing worked."

"Mrs Wolmer called Dr. Folkman and later told Dr. Barlogie to call Dr. Folkman."

"By the fall of 1997, Dr. Barlogie said, he had obtained permission to test thalidomide in Ira Wolmer. The drug did not work for Dr. Wolmer; he died in March 1998. But when Dr. Barlogie tested it on a second patient, he said, the man "went into almost a complete remission."

New York Times. Nov 18, 1999



The NEW ENGLAND JOURNAL of MEDICINE

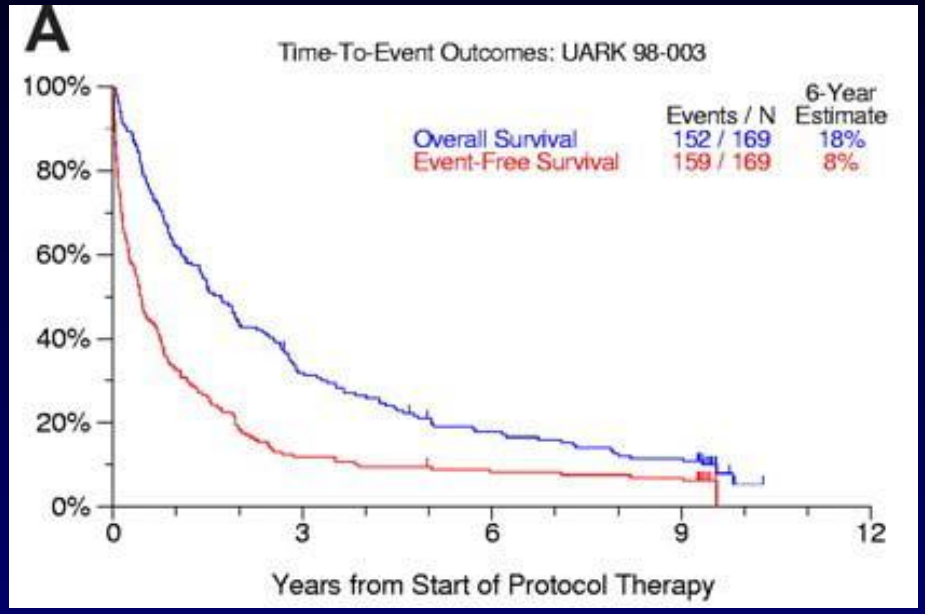
ORIGINAL ARTICLE

◂ Previous Volume 341:1565-1571 November 18, 1999 Number 21 Next ▸

Antitumor Activity of Thalidomide in Refractory Multiple Myeloma

Seema Singhal, M.D., Jayesh Mehta, M.D., Raman Desikan, M.D., Dan Ayers, M.S., Paula Roberson, Ph.D., Paul Eddlemon, B.S., Nikhil Munshi, M.D., Elias Anaissie, M.D., Carla Wilson, M.D., Ph.D., Madhav Dhodapkar, M.D., Jerome Zeldis, M.D., Bart Barlogie, M.D., Ph.D., David Siegel, M.D., Ph.D., and John Crowley, Ph.D.

Thalidomide in R/R MM



The first new drug with single-agent activity in more than 3 decades

84 pts: ORR 32%

After 6 years follow up
10 pts remained event-free and 17 alive

Singhal, S. N Engl J Med. 1999 Nov 18;341(21):1565-71
van Rhee, F. et al. Blood 2008;112:1035-1038

Phase III *n=166*

Thal/Dex

Thal 100 mg/d titrated to 400 mg/d as tolerated, for up to 12 mos

Dex

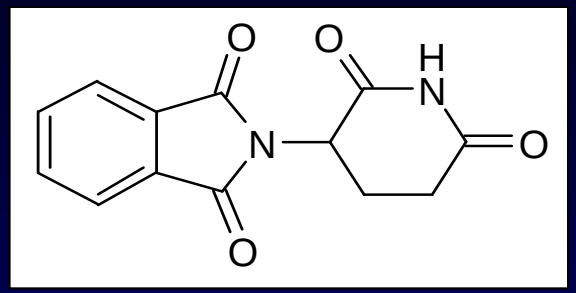
Dex (both arms): 40 mg x 4 d /every other week for 4 cycles, then monthly

	Thal/Dex	Dex	p value
PR	65%	28%	<0.0001
PFS @ 1y	46%	31%	(HR: 1.8, p = 0.004)

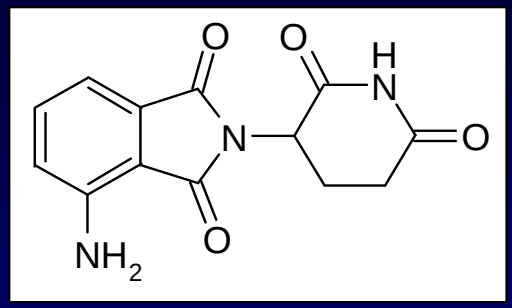
Doxorubicin initially included in both arms; Discontinued after high VTE

Fermand et al. ASH 2006;Abstr.3563.

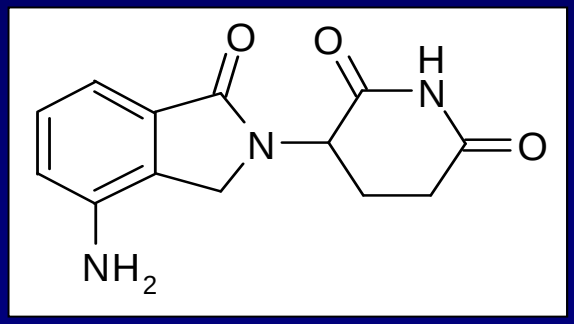
Novel IMiDs in MM



Thalidomide



Actimid™ (pomalidomide)
(CC-4047)

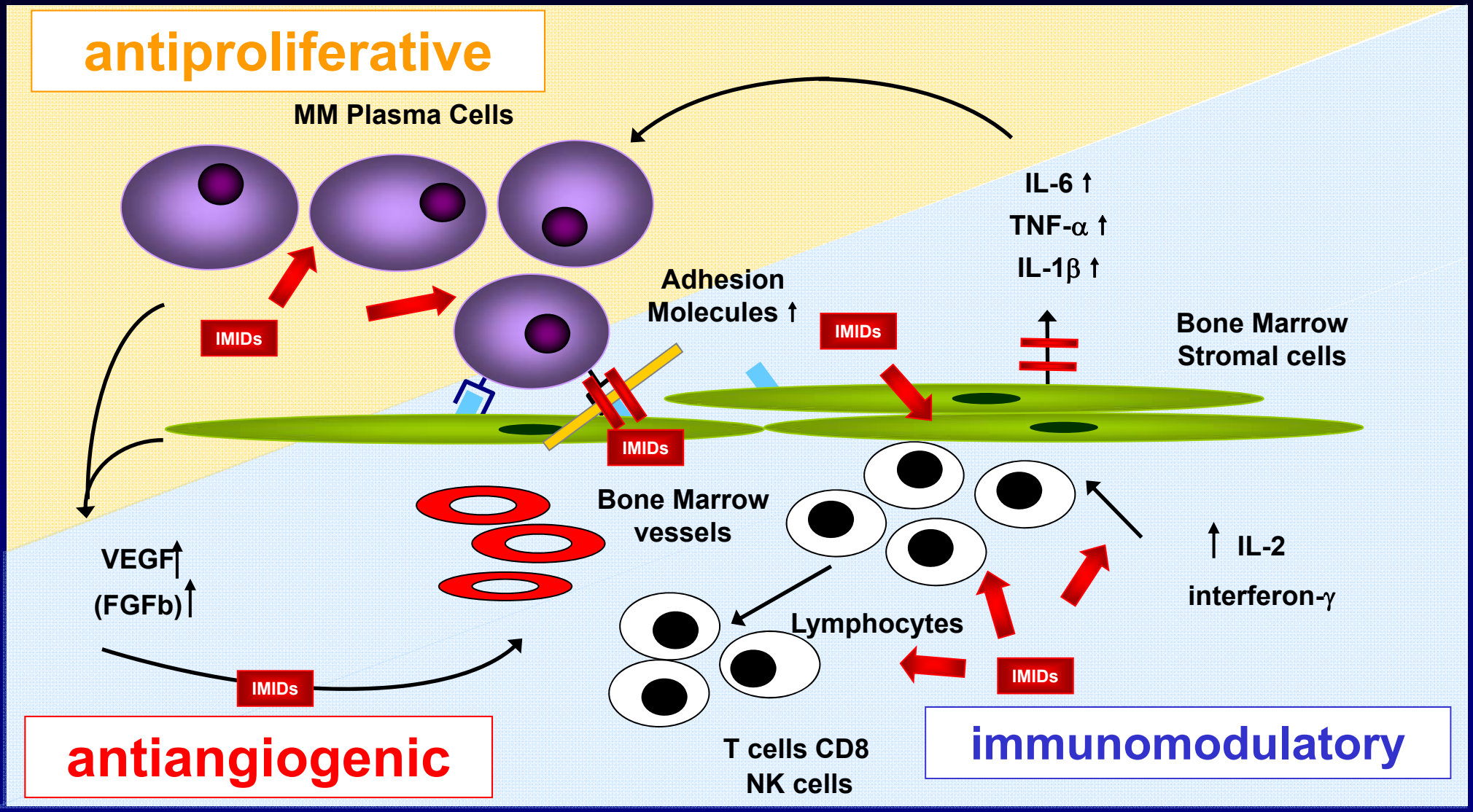


Revlimid™ (lenalidomide)
(CC-5013)

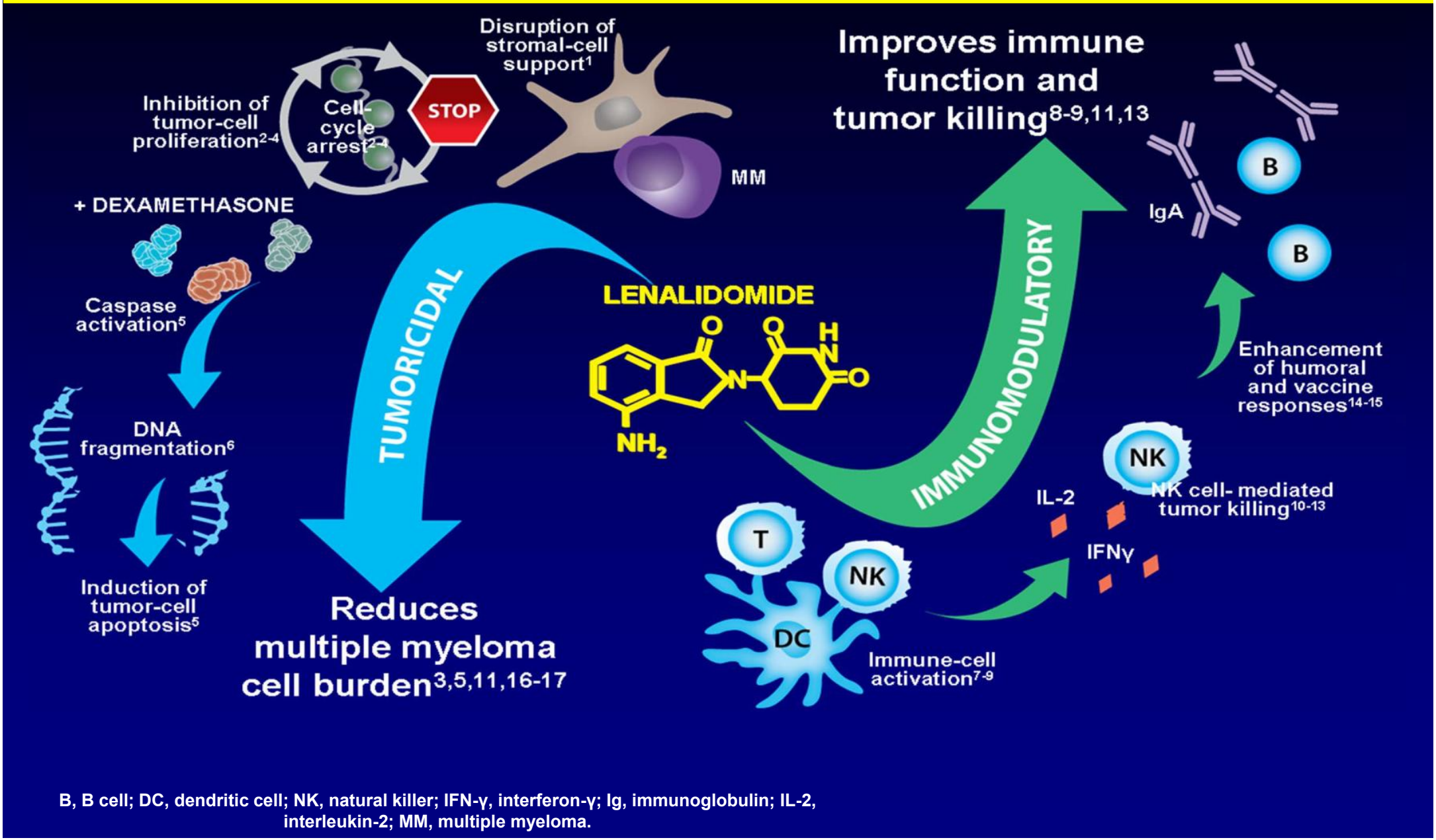
3 main characteristics

- ↑ immunomodulatory effect
- Different toxicity profile
- No theratogenicity

Mech. of action of IMiDs in MM



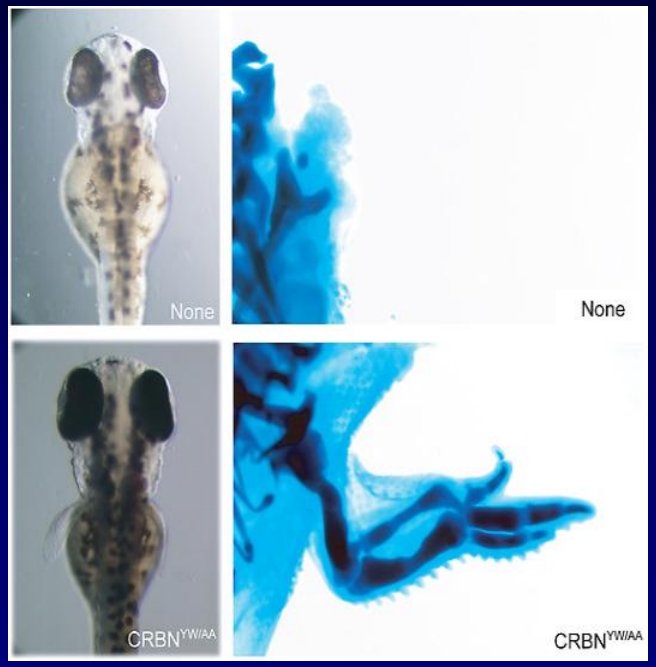
Lenalidomide Mechanism Summary Illustrating Dual Effects



B, B cell; DC, dendritic cell; NK, natural killer; IFN-γ, interferon-γ; Ig, immunoglobulin; IL-2, interleukin-2; MM, multiple myeloma.

Which is the target of IMiDs?

CRBN as the Primary Target of Thalidomide Teratogenicity



Half a century ago, thalidomide was found to be teratogenic, causing multiple birth defects…….

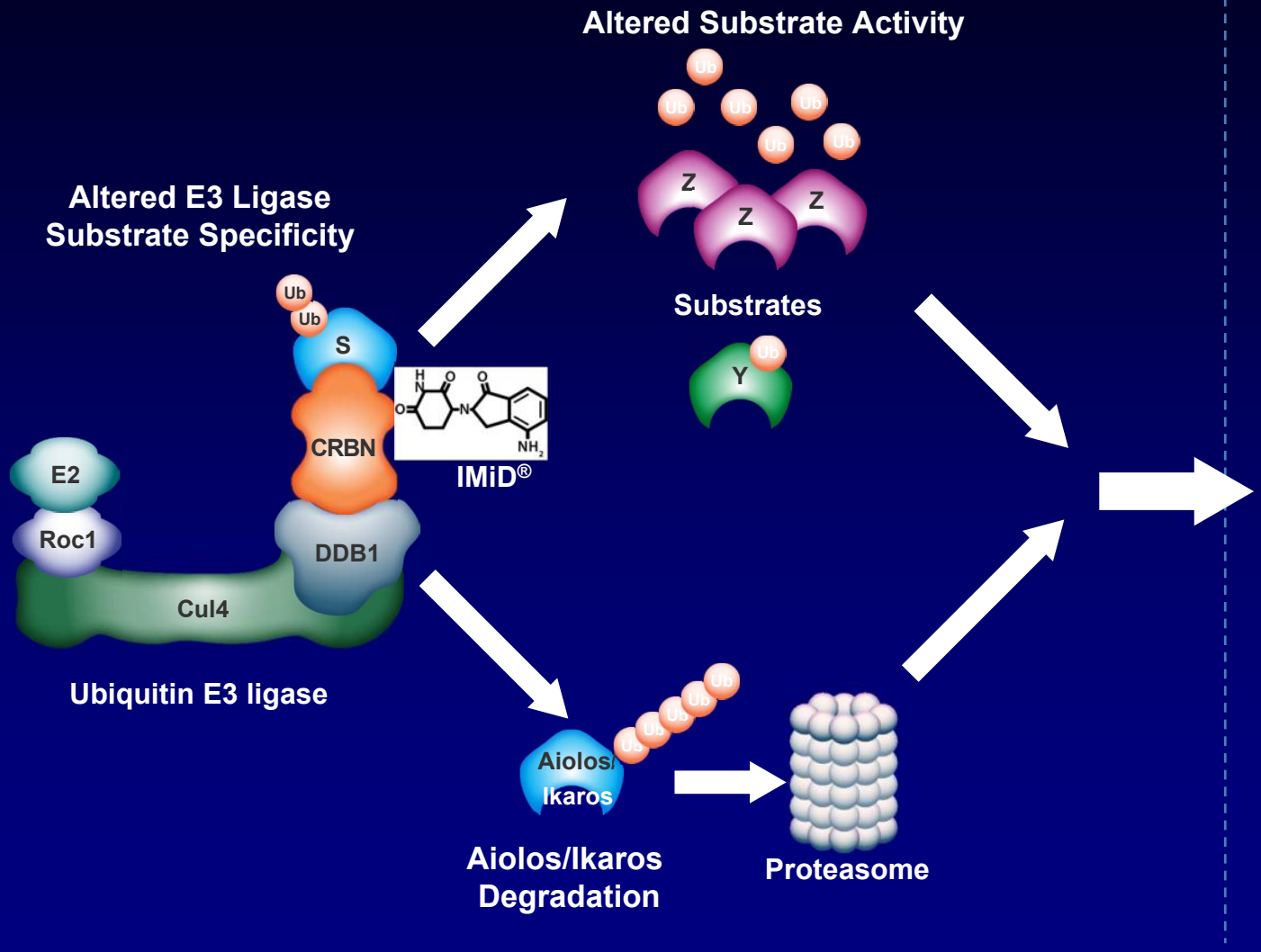
Cereblon (CRBN) was identified as a thalidomide-binding protein.

CRBN forms an E3 ubiquitin ligase complex with damaged DNA binding protein 1 (DDB1) and Cul4A that is important for limb outgrowth.

Thalidomide initiates its teratogenic effects by binding to CRBN and inhibiting the associated ubiquitin ligase activity.

Ito T, et al. Science. 2010;327:1345-50.

IMiD® Agents Bind to a CRBN-Mediated E3 Ligase Resulting in Pleiotropic Clinically Relevant Effects

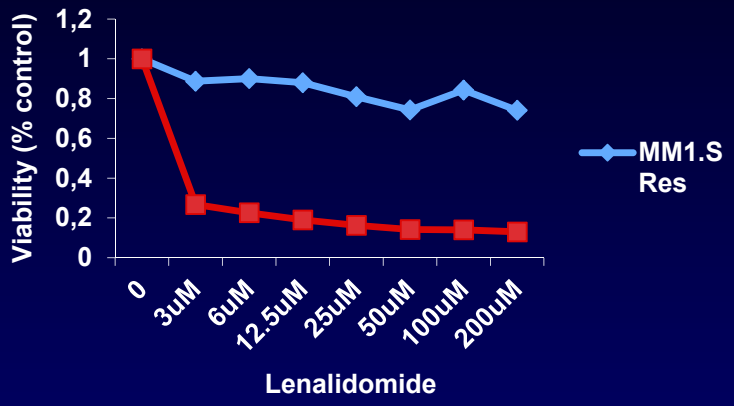


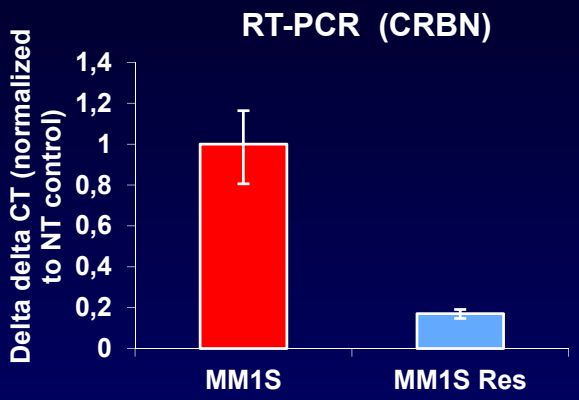
ADCC: antibody-dependent cellular cytotoxicity; Cul: cullin; DDB: DNA damage-binding protein; IFN: interferon; Ig: immunoglobulin; IL: interleukin; NK: natural killer; ROC: regulator of cullins; TNF: tumor necrosis factor; TSG: tumor suppressor gene; ub: ubiquitin.

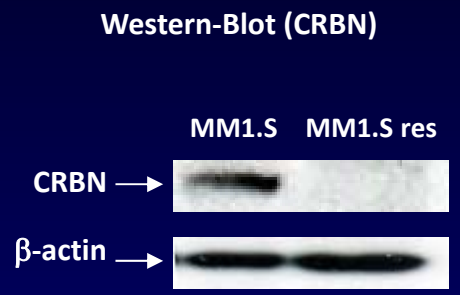
Lopez-Girona A. Leukemia. 2012;26:2326-2325; Schafer PH. Blood. 2012;120:1055[abstract]; Schafer PH. Blood. 2012;120:3279[abstract].

CRBN is required for IMIDs activity

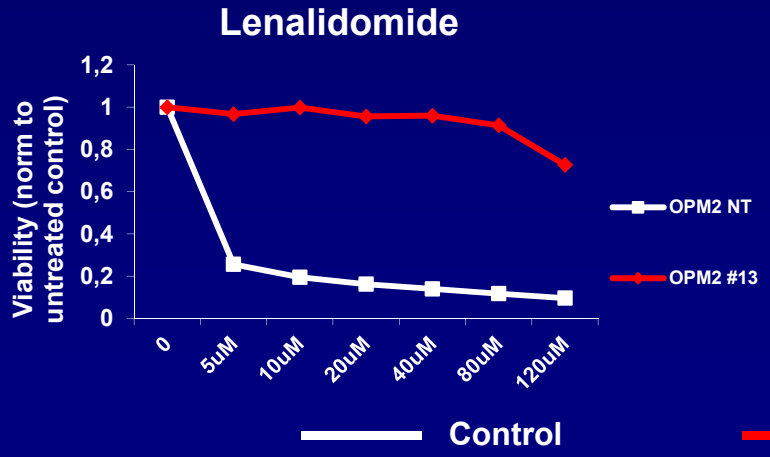
Lenalidomide Resistant Myeloma Cells Lack Cereblon

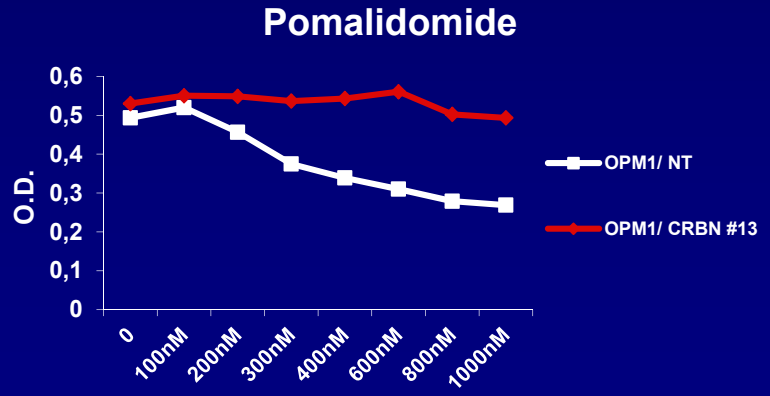






Cereblon KO Confers Complete Len & Pom Resistance





Control

Cereblon knockdown

Zhu YX, et al. Blood. 2011;118:4771-9.

Are all IMiDs the same?

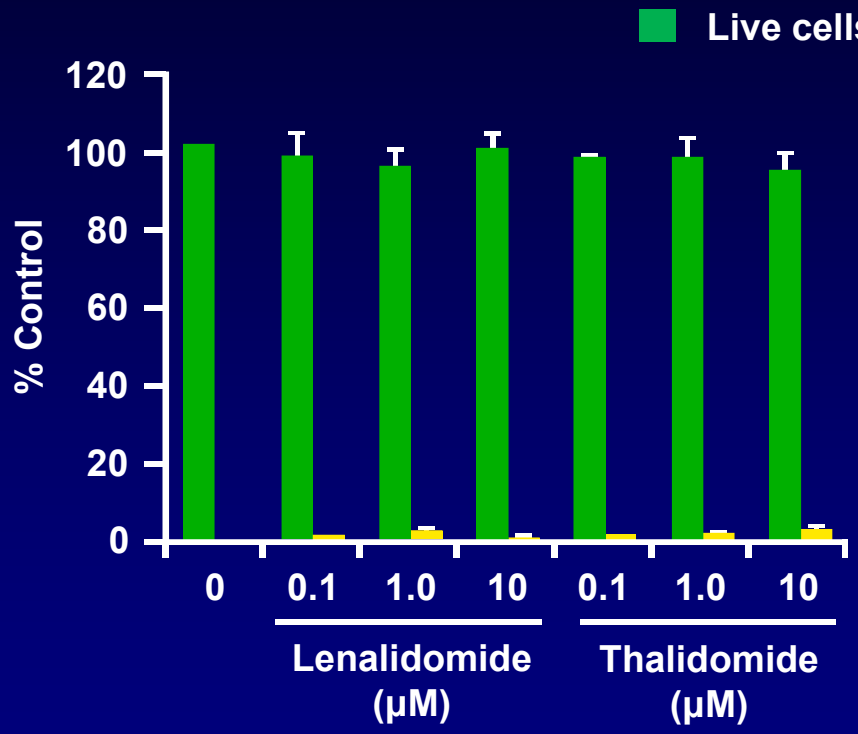
Comparison of the MoA of different IMiDs

	Effect	Relative potency += potency factor of 10 Thalidomide	Lenalidomide	Pomalidomide
Immuno-modulatory	Immune modulation CD4+ and CD8+	+	+ + + +	+ + + + +
	Tregs suppression	_	+	+
	Th1 cytokine production	+	+ + + +	+ + + + +
	NK and NKT cell activation	+	+ + + +	+ + + + +
	Antibody-dependent cellular cytotoxicity (ADCC)	_	+ + + +	+ + + +
Antiangiogenic	Anti-angiogenesis	++++	+ + +	+ + +
	Anti-inflammatory properties	+	+ + + +	+ + + + +
Tumoricidal	Direct anti-tumour effects Anti-proliferative Activity	+	+ + +	+ + +
	Elimination	Primarily urinary excretion; <3% as parent	Primarily urinary excretion; ~80% as parent	Urinary excretion; ~2% as parent
Toxicity	Rate limiting toxicities	PN, constipation, somnolence, DVT	Myelosuppression, DVT	Myelosuppression

Activity in 5q- MDS

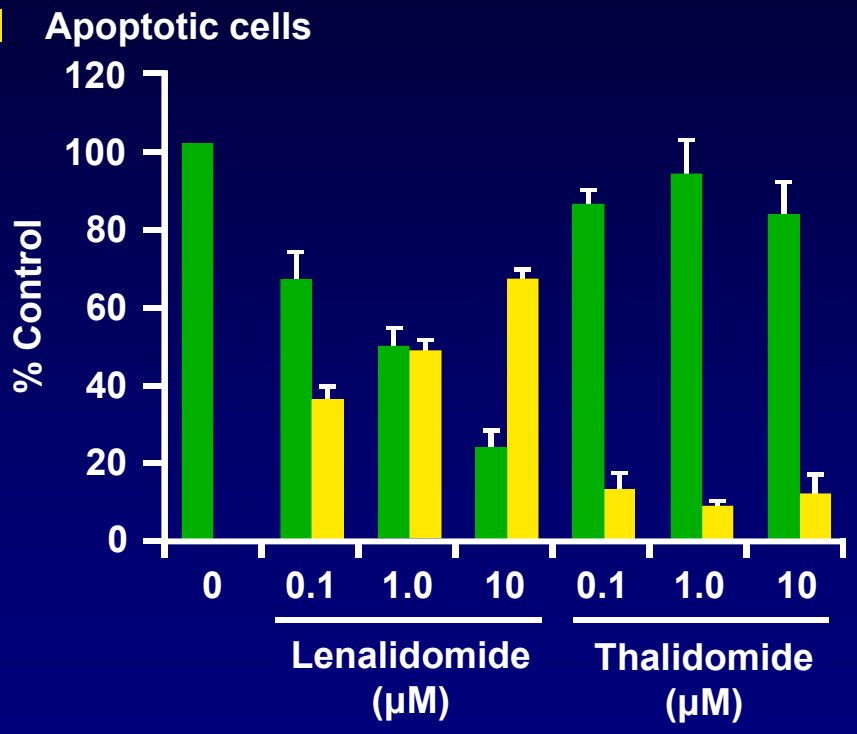
Lenalidomide selectively promotes apoptosis of del(5q) CD34+ cells isolated from patients with MDS

Non-del(5q) CD34+ cells from patients with MDS/AML (n=5)



Lenalidomide had minimal impact on apoptosis of non-del(5q) cells after 48 hours of exposure

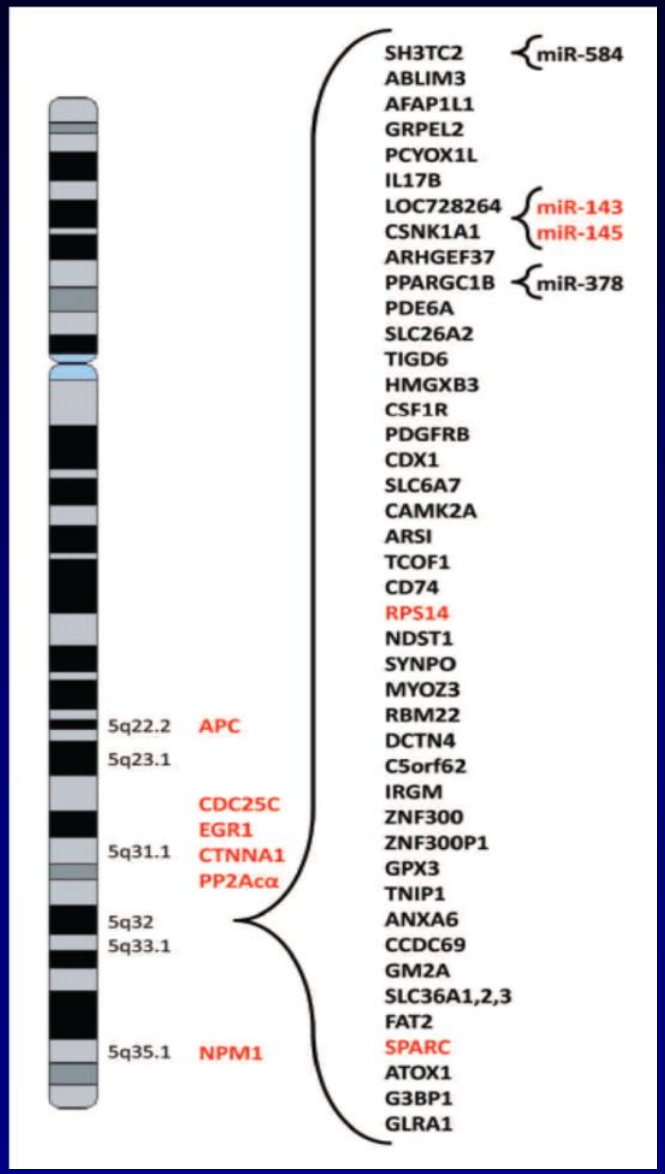
Del(5q) CD34+ cells from patients with MDS/AML (n=5)



Lenalidomide induced a concentration-dependent increase in apoptosis in del(5q) cells after 48 hours'of exposure

Wei S, et al. Proc Natl Acad Sci USA 2009;106:12974–9

Candidate genes within the CDR of chromosome 5q associated with del(5q) MDS



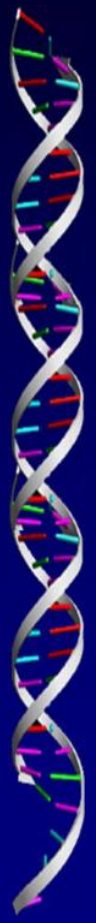
The CDR refers to chromosome band 5q32–33 that is commonly lost in del(5q) clones

Those genes implicated in the pathogenesis of del(5q) MDS are shown in red

CDR = commonly deleted region
RPS14 = ribosomal protein S14

Jädersten M, et al. Haematologica 2011;96:177–80

The role of CDR candidate genes in the pathogenesis of del(5q) MDS: effect of lenalidomide



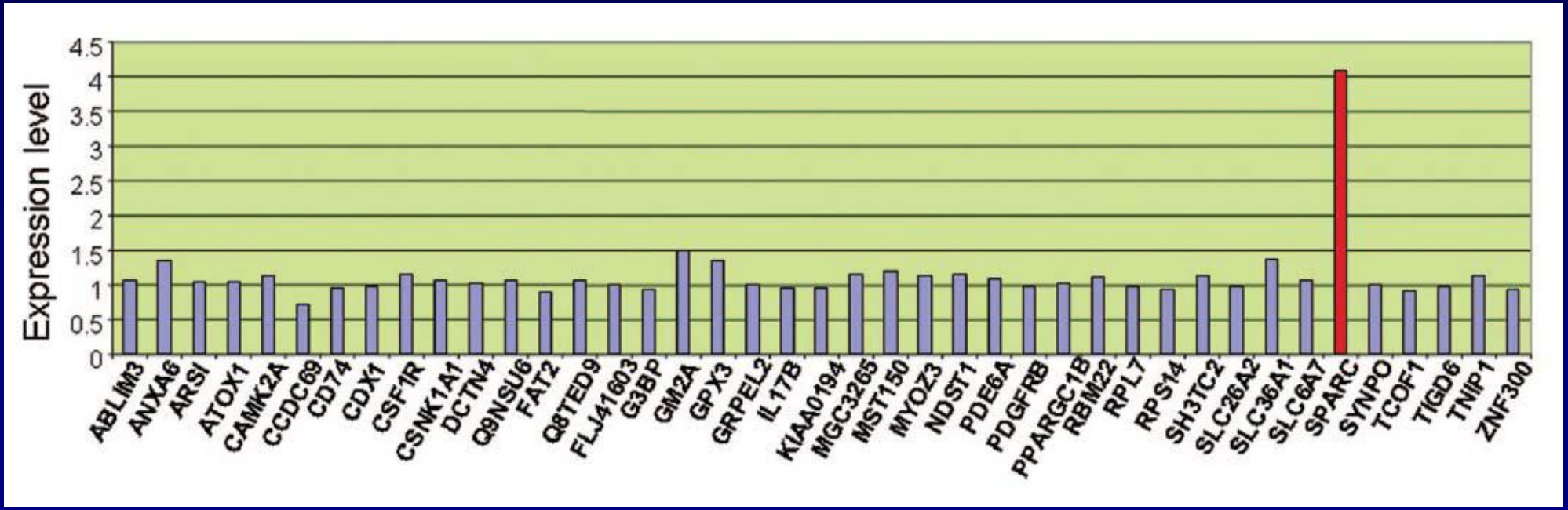
Gene	Effect of lenalidomide	Functional Effect
SPARC	Increased expression in MDS CD34+ cells ex vivo[1]	Inhibits proliferation and adhesion[1,6–7]
EGR1	Increased expression in an MDS-derived del(5q) cell line[2]	Reduced proliferation[2]
CDC25c PP2A	Direct inhibition of CDC25c; indirect inhibition of PP2A[3]	G_1 and G_2–M arrest and apoptosis[3]
RPS14	Increased in patients with del(5q) MDS[4]	Erythroid response[4]
miR-145 miR-146a	Increased expression in patients with del(5q) MDS[5]	Anti inflammatory?
DIAPH1	TBD	Immunomodulatory? Anti-proliferative?

1. Pellagatti A, et al. Proc Natl Acad Sci 2007;104:11406–11; 2. Matsuoka A, et al. Leukemia 2010;24:748–55
3. Wei S, et al. Proc Natl Acad Sci 2009;106:12974–9; 4. Oliva EN, et al. Eur J Haematol 2010;231–5
5. Oliva EN, et al. Poster presentation at ASH 2010. Abstract 3631; 5. Scharenberg C, et al. Poster presentation at EHA 2009. Abstract 246; 6. Zhang L, et al. Poster presentation at ASH 2008. Abstract 2612

Lenalidomide upregulates *SPARC* in CD34+ cells isolated from patients with del(5q) MDS

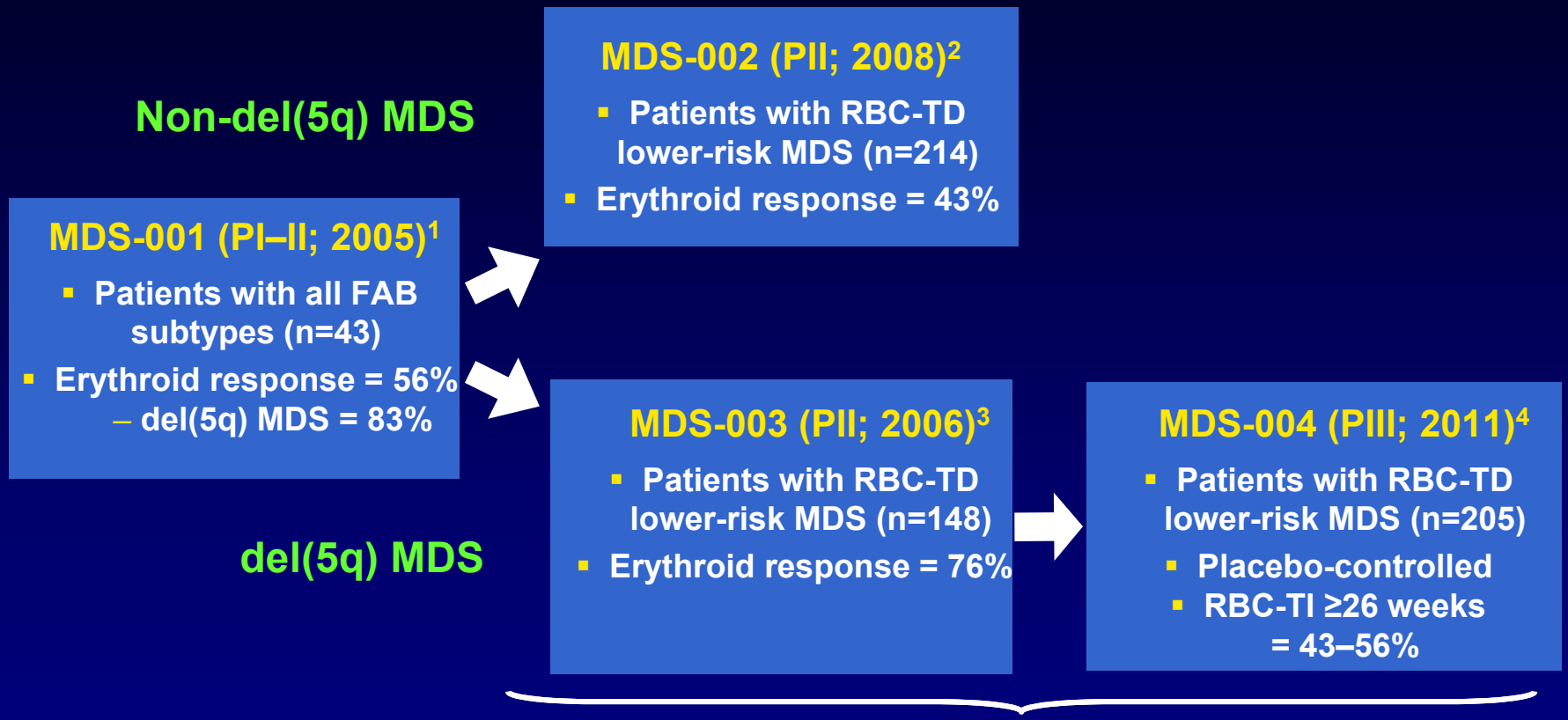
CD34+ cells were isolated from patients with del(5q) MDS (n=9) and cultured for 7 days ± lenalidomide. After this time, del(5q) was still present in ~98% of cells. Therefore any gene expression changes must be due to a direct effect of lenalidomide on del(5q) cells

Effect of lenalidomide on expression of genes within the CDR, based on Affymetrix array analysis (41 of 44 genes in CDR represented on the array)



Pellagatti A, et al. Proc Natl Acad Sci USA 2007;104:11406–11.

Summary of key clinical trials of lenalidomide in patients with MDS

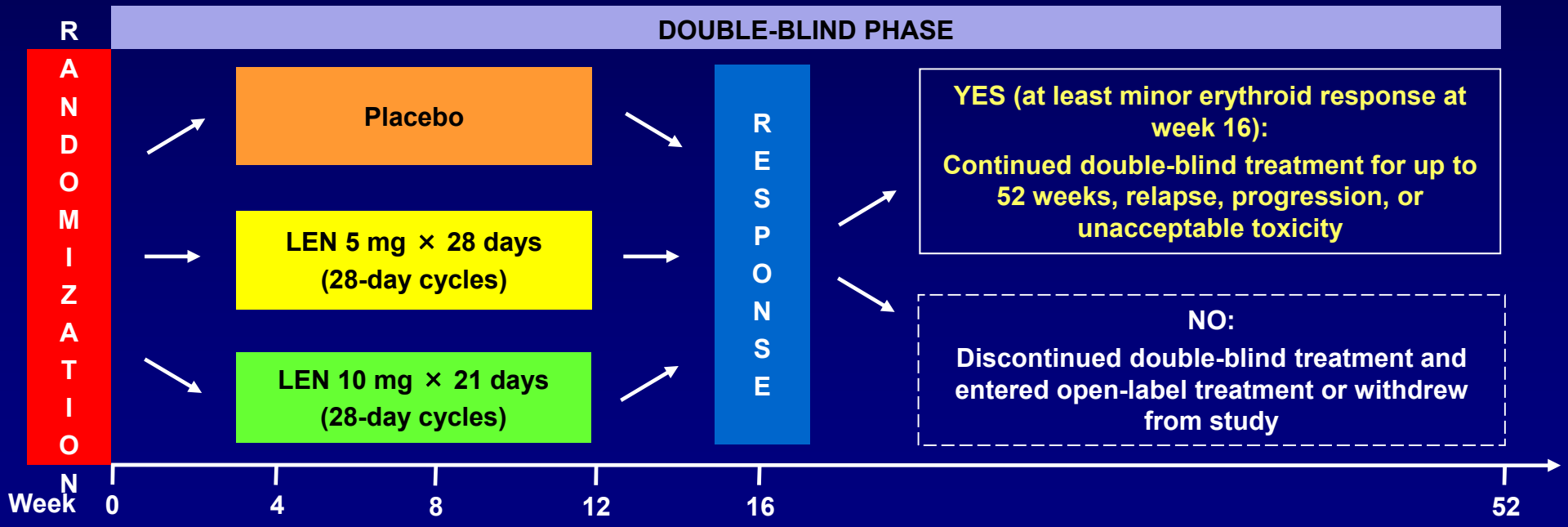


FAB = French–American–British
RBC-TD = RBC transfusion dependence
OS = overall survival

1. List A, et al. N Engl J Med 2005;352:549–57; 2. Raza A, et al. Blood 2008;111:86–93
3. List A, et al. N Engl J Med 2006;355:1456–65; 4. Fenaux P, et al. Blood 2011;epub ahead of print
5. Giagounidis A, et al. Oral presentation at 11th International Symposium on MDS 2011, Edinburgh, UK

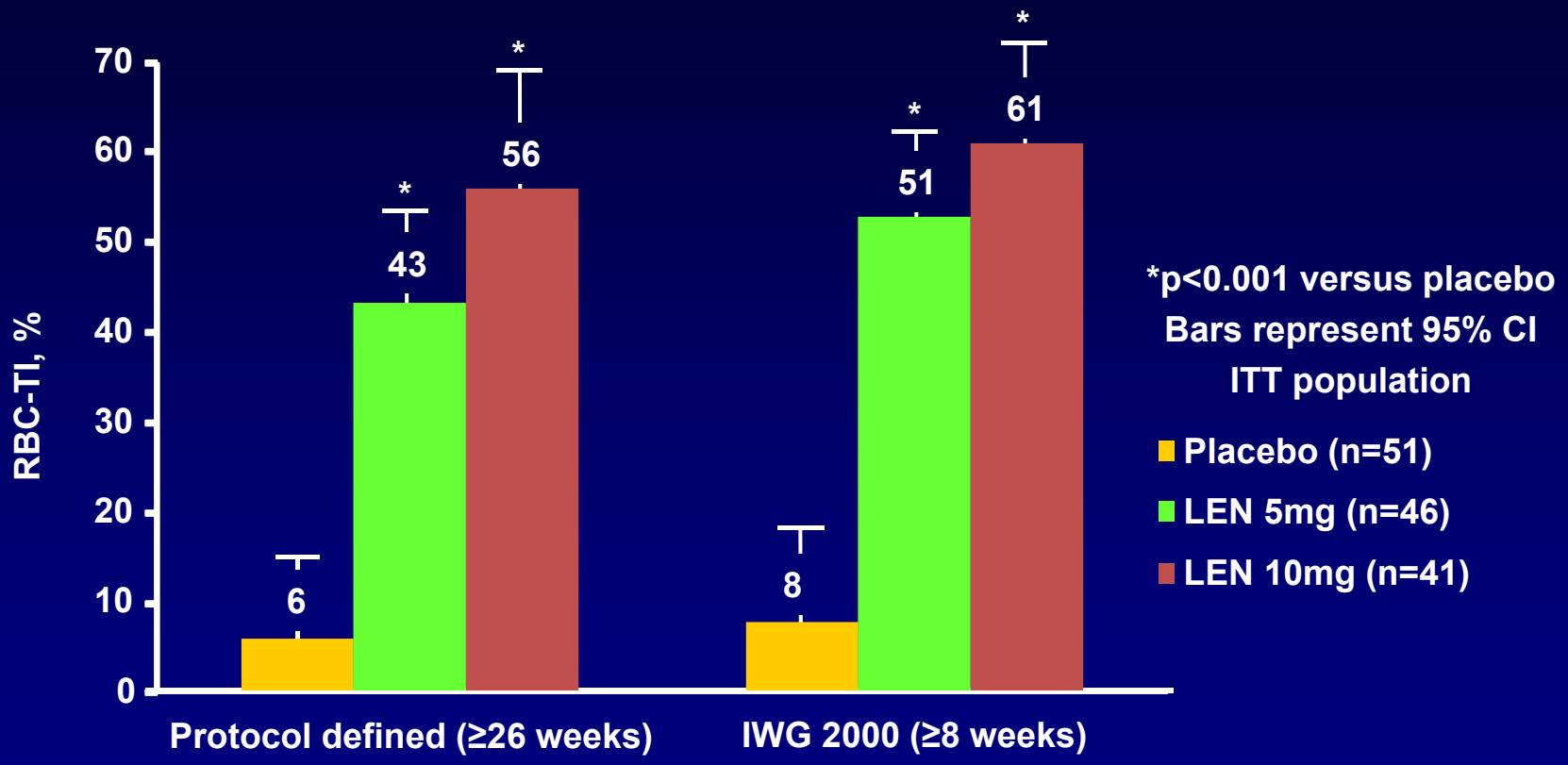
MDS-004: study design (n=205)

- Phase 3, multicenter, randomized, double-blind, placebo-controlled
- Conducted at 37 study sites in the UK, France, Germany, Italy, Spain, Belgium, Netherlands, Sweden, and Israel
- Key inclusion criteria
  - IPSS Low- or Int-1-risk MDS with del5q, with or without additional cytogenetic abnormalities
  - no 8 consecutive weeks without RBC transfusion/prior 16 weeks



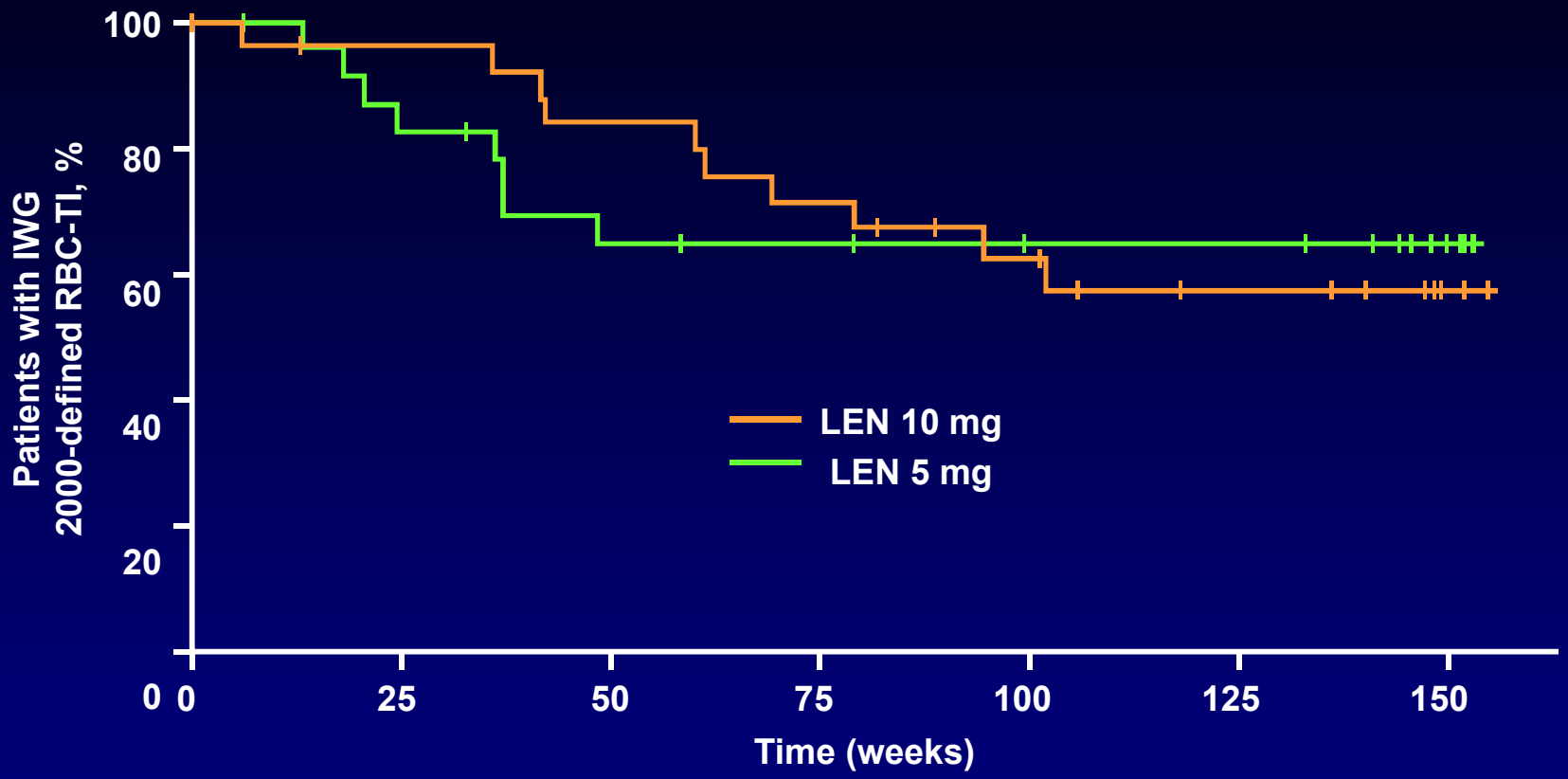
Double-blind phase was up to 52 weeks; open label was up to 2 years; total follow-up was up to 3 years.
56 (84%) nonresponders in the placebo group crossed over to LEN 5 mg.

MDS-004: significant improvements in RBC-TI in patients randomised to lenalidomide versus placebo



Fenaux P, et al. Blood 2011;118:3765–76

MDS-004: durable response to lenalidomide

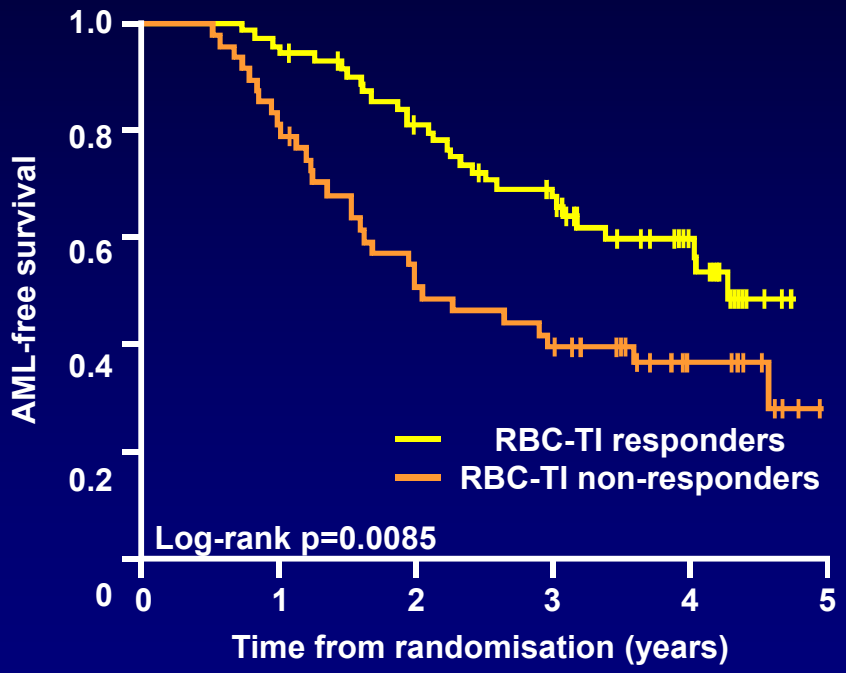


- In patients who achieved RBC-TI (≥ 8 weeks) during the double blind phase of the study, median duration of response had not been reached after a median follow-up of 1.55 years
  - Median duration of protocol-defined RBC-TI (≥ 26 weeks) was not reached

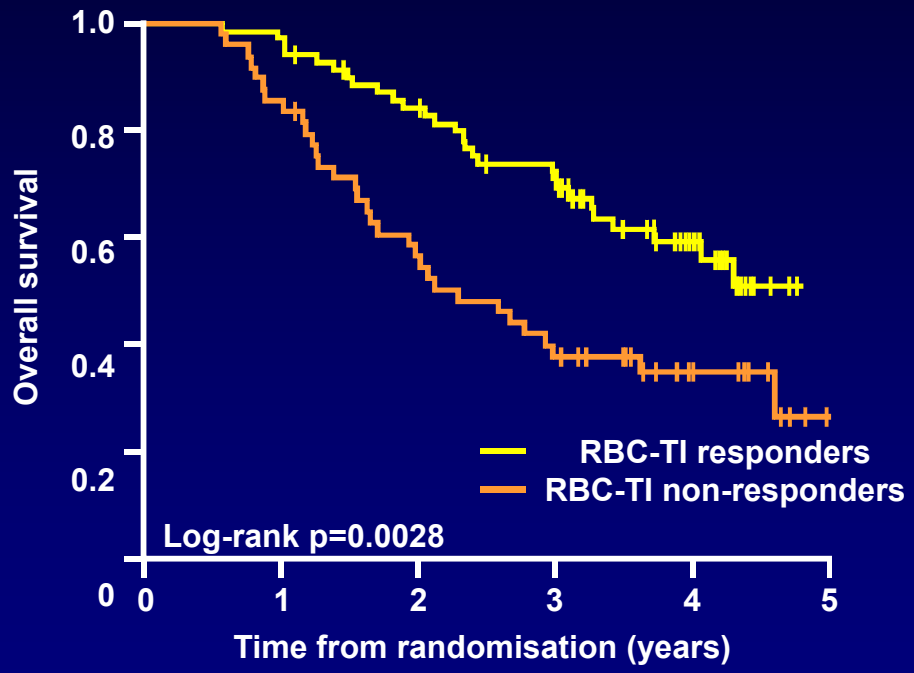
Fenaux P, et al. Blood 2011;118:3765–76

MDS-004: OS and progression to AML in patients who achieved RBC-TI

AML-free survival by RBC-TI for ≥8 weeks in patients randomised to lenalidomide*



OS by RBC-TI for ≥8 weeks in patients randomised to lenalidomide*



In patients treated with lenalidomide, achievement of RBC-TI for ≥8 weeks was associated with improved OS and reduced risk of AML progression

*Landmark 6-month analysis

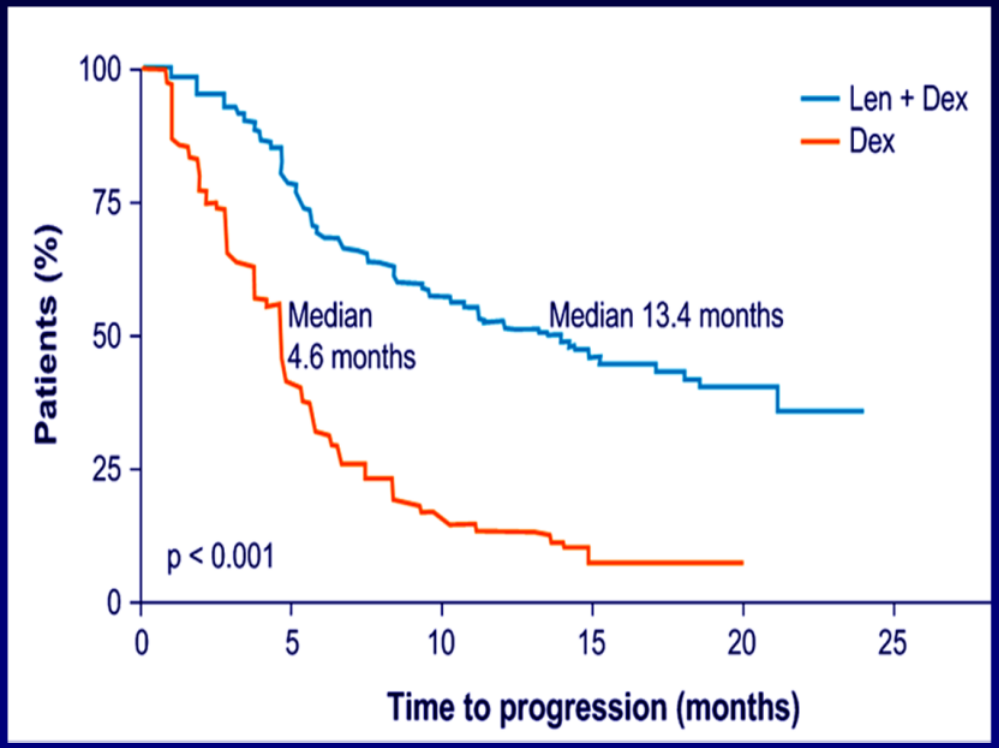
Fenaux P, et al. Blood 2011;118:3765–76

Activity in MM

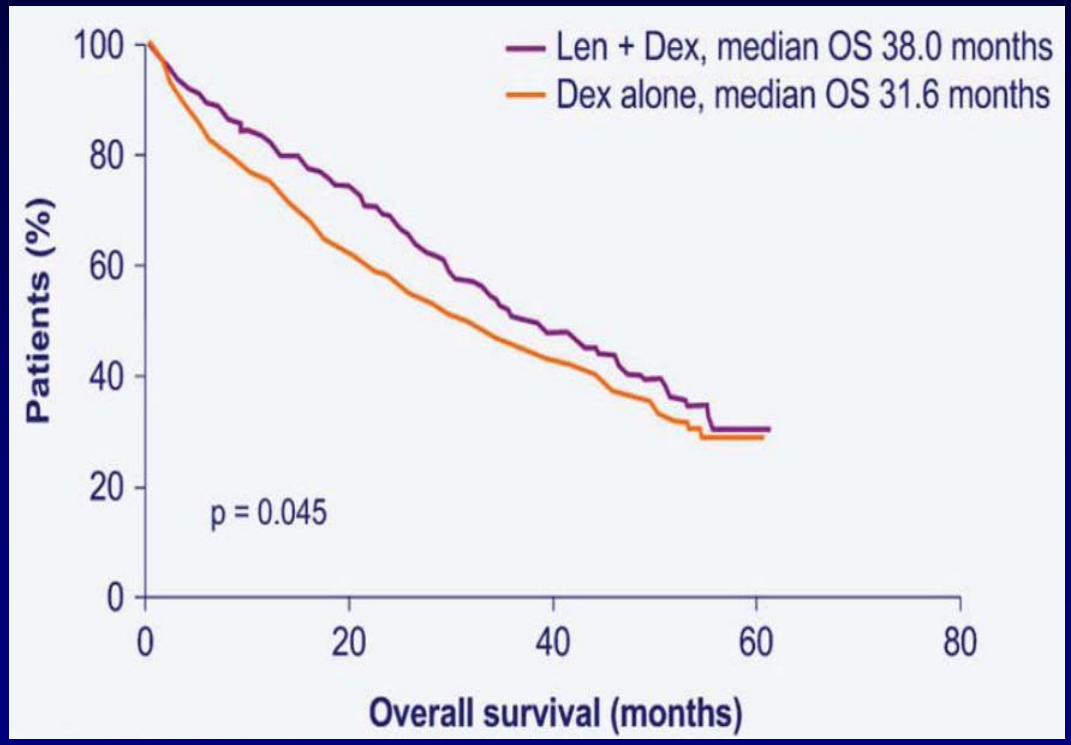
Lenalidomide + Dex vs Dex (MM 009/010)

Response (≥ PR): 60% (15% CR) vs 22% (2% CR)

TTP: 13.4 vs 4.6 m



OS: 38 vs 32 m*



* 48% Crossed over

Weber D. & Dimopoulos M, NEJM 2007; Updated Dimopoulos M. Leukemia 2009

FIRST: Phase 3 trial of Lenalidomide + low-dose Dex vs MPT (IFM 07-01; MM-020)

Inclusion criteria

N = 1,623

- Previously untreated MM
- Age ≥ 65 years or not eligible for a transplant
- No neuropathy of grade > 2

RANDOMIZATION

Rd (28-day cycle; until disease progression)
Lenalidomide 25 mg/day, days 1–21
Dexamethasone* 40 mg/day, days 1, 8, 15, and 22

Rd (28-day cycle; up to 18 cycles)
Lenalidomide 25 mg/day, days 1–21
Dexamethasone* 40 mg/day, days 1, 8, 15, and 22

MPT (6-week cycle; up to 12 cycles)
Melphalan* 0.25 mg/kg/day, days 1–4
Prednisone 2.0 mg/kg/day, days 1–4
Thalidomide* 200 mg/day

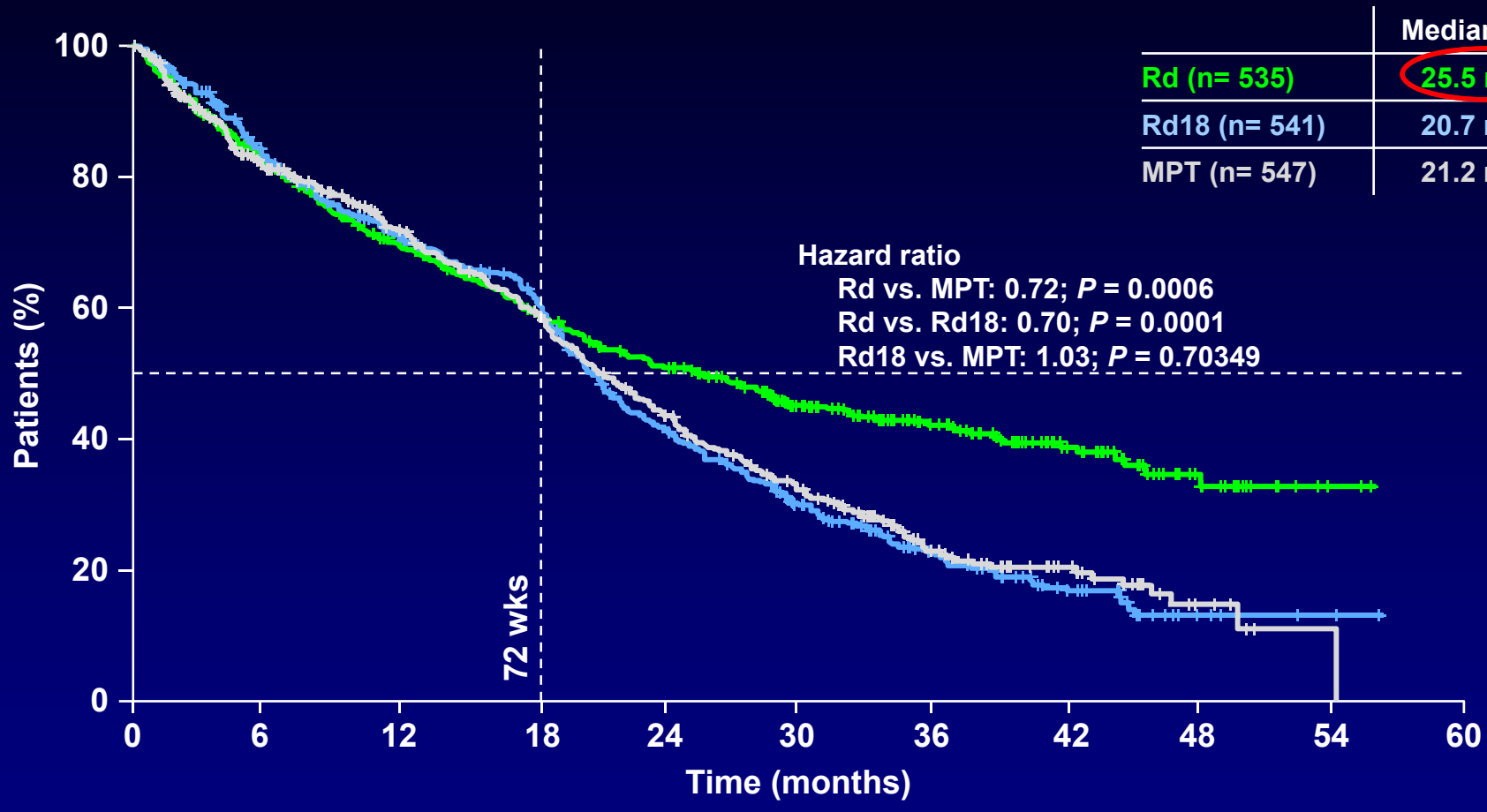
Primary end-point: PFS

**In patients aged > 75 years: Dex 20 mg/day, melphalan 0.20 mg/kg/day, thalidomide 100 mg/day*

Facon T, NEJM 2014

FIRST trial: PFS

Continuous Rd reduced the risk of disease progression by 28% vs. MPT



	Median PFS
Rd (n= 535)	25.5 mos
Rd18 (n= 541)	20.7 mos
MPT (n= 547)	21.2 mos

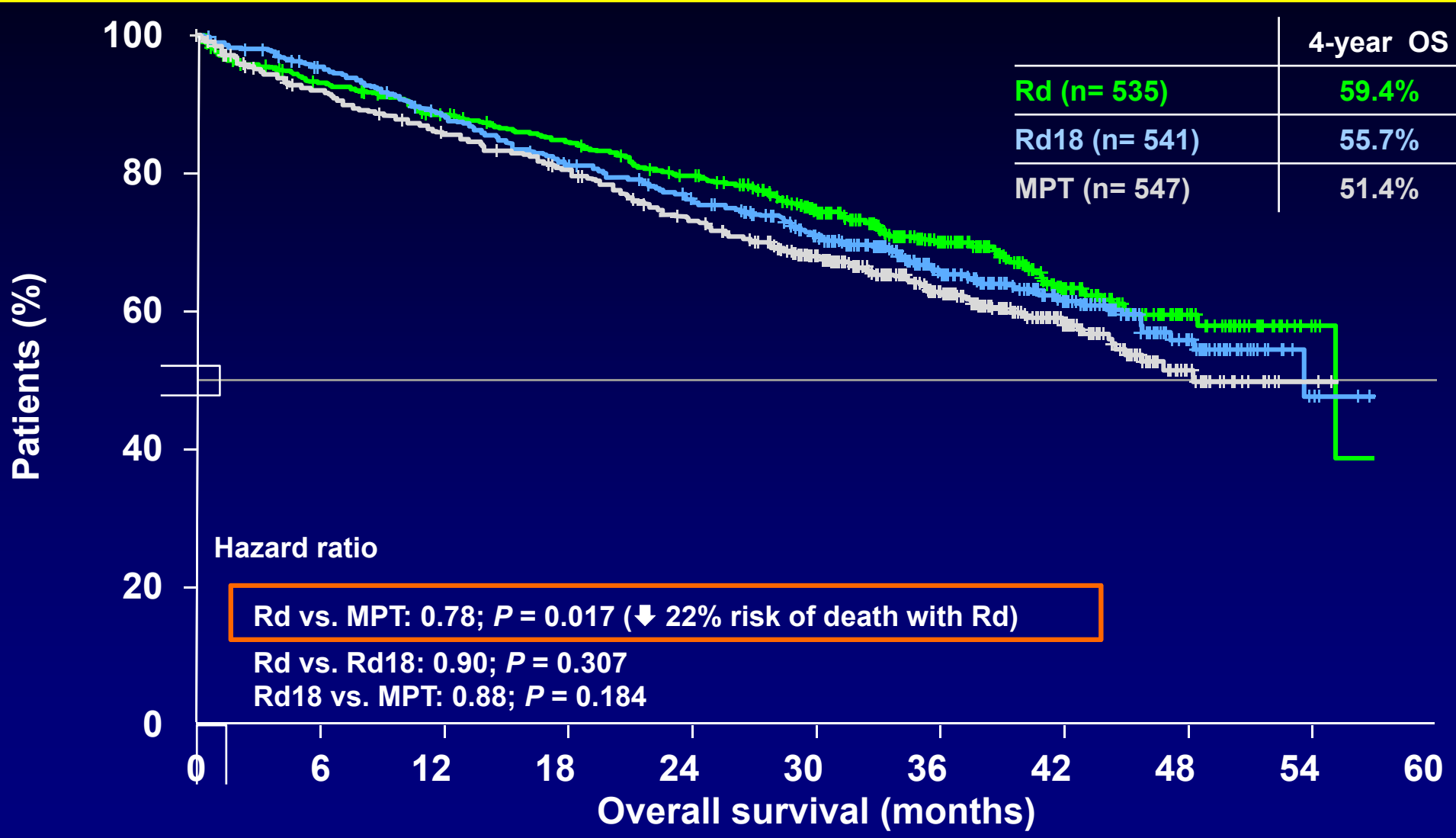
Hazard ratio
Rd vs. MPT: 0.72; *P* = 0.0006
Rd vs. Rd18: 0.70; *P* = 0.0001
Rd18 vs. MPT: 1.03; *P* = 0.70349

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

mos, months; MPT, melphalan, prednisolone, thalidomide; PFS, progression-free survival; Rd, Lenalidomide plus low-dose dexamethasone.

Facon T, NEJM 2014

FIRST trial: OS interim analysis (574 deaths. 34%)



Facon T, NEJM 2014

FIRST trial: Safety – Selected Gr 3-4 TEAEs

	Rd (n=535)	Rd 18 (n=541)	MPT (n=545)
Hematological (%)			
Anemia	18.2	15.7	18.9
Neutropenia	27.8	26.5	44.9
Thrombocytopenia	8.3	8.0	11.1
Febrile neutropenia	1.1	0.9	2.6
Non-hematological (%)			
Infections	28.9	21.9	17.2
Pneumonia	8.1	8.3	5.7
Diarrhea	3.9	3.3	1.5
Constipation	2.3	1.9	5.4
Peripheral sensory neuropathy	1.1	0.4	9.4
Rash	8.8	6.7	5.5
Deep vein thrombosis	5.5	3.7	2.6
Cataract	5.8	2.6	0.6

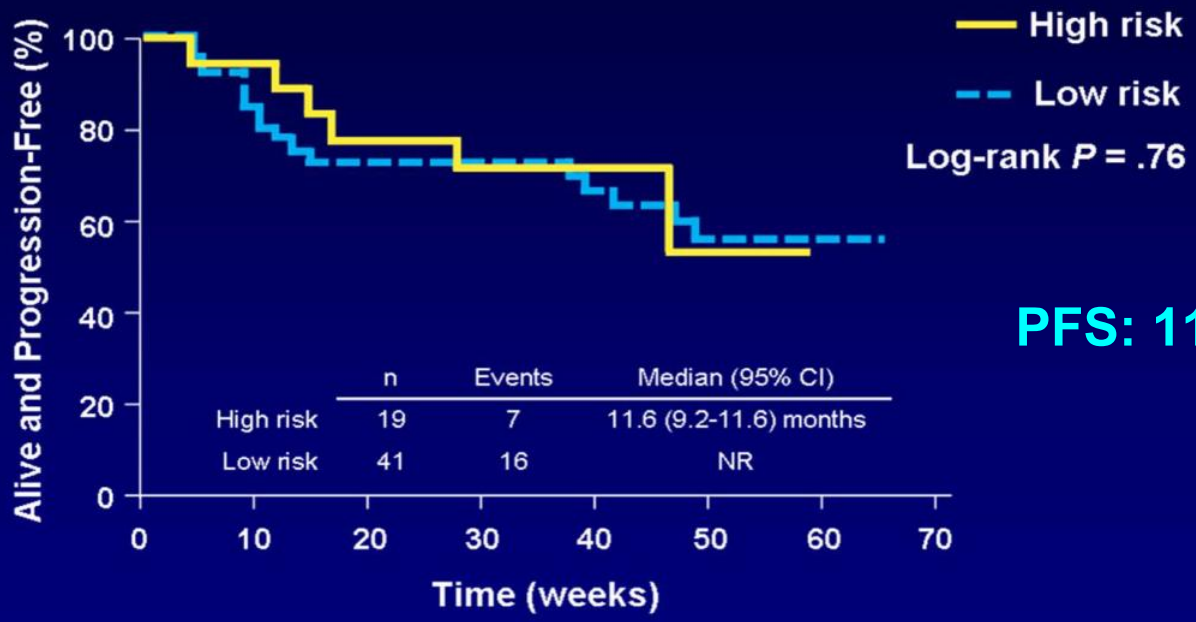
TEAEs: treatment emerging adverse events

Facon T, NEJM 2014

POM + LoDEX in RRMM Pts With 1-3 Prior Therapies

n= 60 R/R pts 35% previous Len & 47% previous Thal

ORR 63%: 5% CR + 28% VGPR + 30 % PR



PFS: 11.6 m

Update ASH 2012: ORR 65%; PFS: 13 m; OS 40 m

POM: 2 mg (1-28) + LoDEX: 40 mg (1, 8, 15, 22)

Len + Dex[2,3] ≥ PR: 60% (15% CR) TTP: 11.2 m

1. Lacy MQ. *J Clin Oncol.* 2009;27:5008-5014. Updated ASH 2012. Abs 201

*2. Weber D, NEJM 2007, *Updated ASH 2007, Abstr 412*

*3. Dimopoulos M, NEJM 2007, *Upd. ASH 2007, Abstr 412*

Activity of Pomalidomide + Dex in Len refr. pts

	n	Population	Dose	≥ *PR*	PFS/TTP/DOR
Lacy[1,2]	34	Len refr	2 mg (1-28)	32 %	PFS 4.7 m
Lacy[2]	60	Len refr	4 mg (1-28)	38%	PFS 7.9 m
Leleu[3]	84	Len & Btz refr	4 mg (1-21)	35 %	PFS 5.4 m
			4 mg (1-28)	34 %	PFS 3.7 m
Lacy[2,4]	70	Len & Btz refr	2 mg (1-28)	26 %	PFS 6.5 m
			4 mg (1-28)	29 %	PFS 3.3 m

Dex 40 mg weekly

1. Lacy. Leukemia. 2010

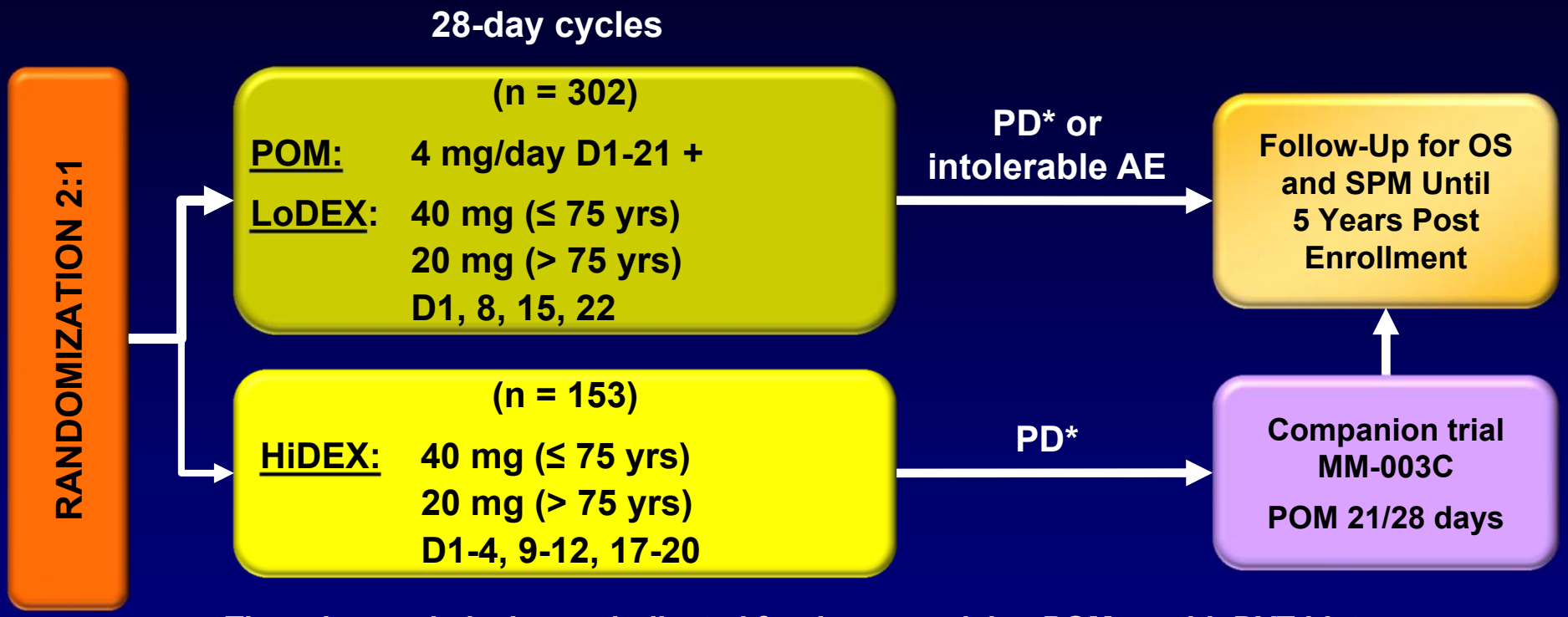
2. Lacy. ASH 2012. Abst 201

3. Leleu . Blood 2013

4. Lacy Blood 2011

MM-003 Design: POM + LoDEX vs HiDEX

455 pts Refractory MM Pts Who Have Failed BORT and LEN



Thromboprophylaxis was indicated for those receiving POM or with DVT history

Stratification

- Age (≤ 75 vs > 75 yrs)
- Number of prior Tx (2 vs > 2)
- Disease population

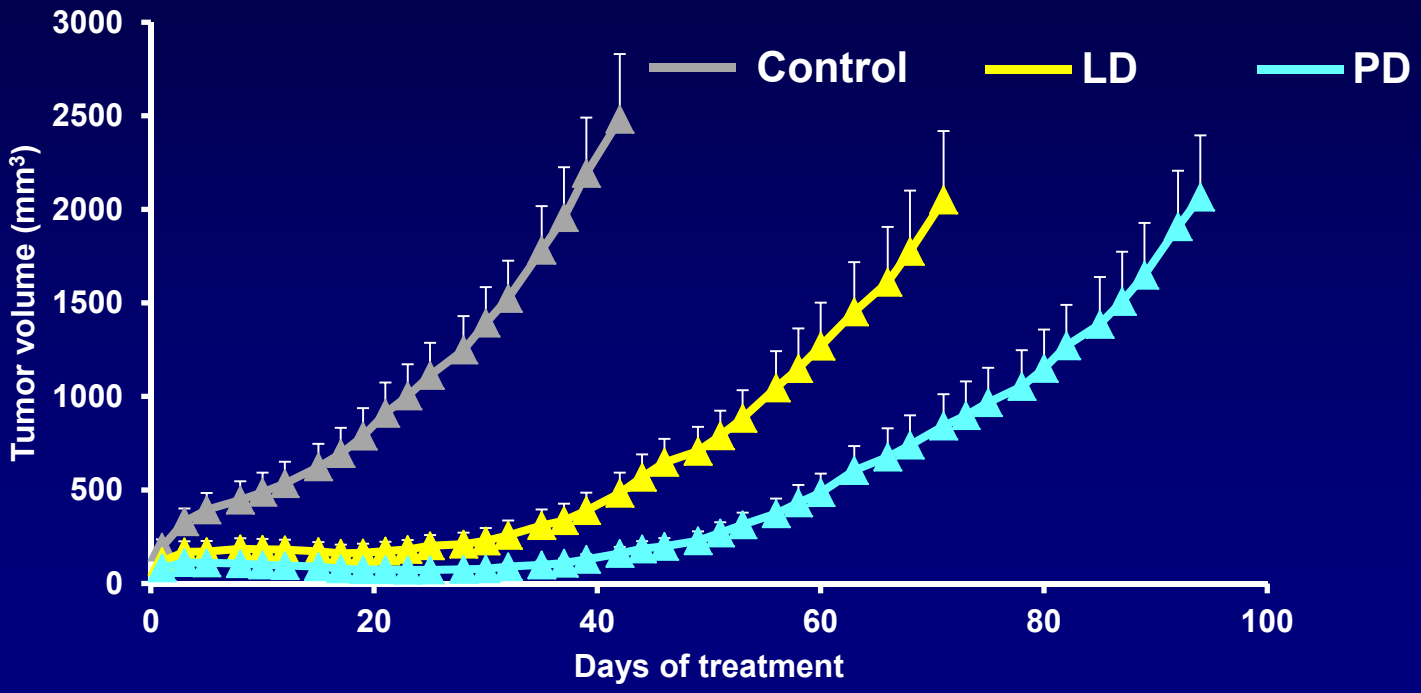
- Len: Prior (100%); Refr (93%)
- Btz: Prior (100%); Refr (78%)

San Miguel, Lancet Oncology 2013

Are all IMiDs the same?

Develop MM cells in vivo resistant to IMIDs

- Human subcutaneous plasmacytoma of MM1S in CB17-SCID mice
- Mice were randomized to
  - Vehicle (control)
  - LD: Len 25 mg/Kg x 5/w + Dex 1 mg/Kg x 2/w
  - PD: Pom 7 mg/Kg x 5/w + Dex 1 mg/Kg x 2/w

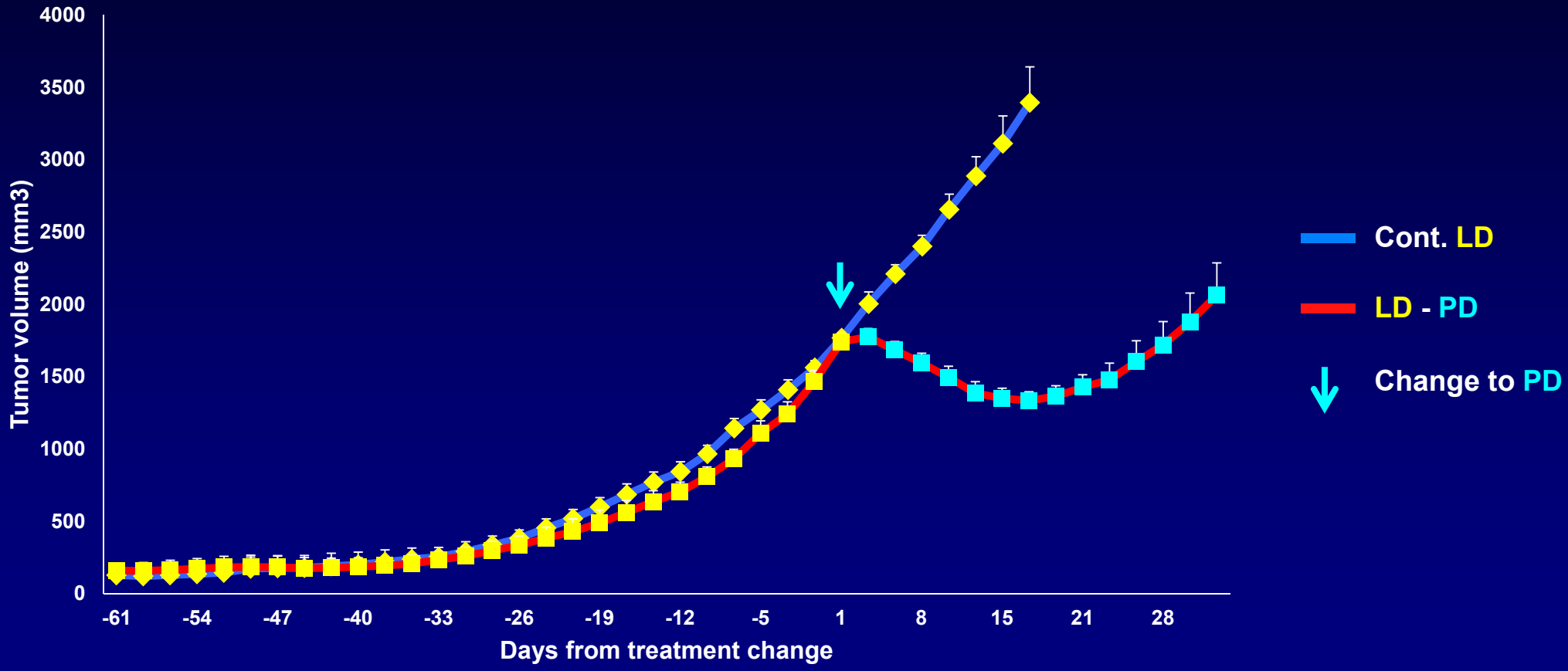


After 30 days of sensitivity tumors develop resistance to LD & PD

Ocio EM, et al. Leukemia 2014.

LD & PD do not present Cross-Resistance

Tumors that had developed resistance to LD & reached 1.700 mm^3, where switched to receive PD

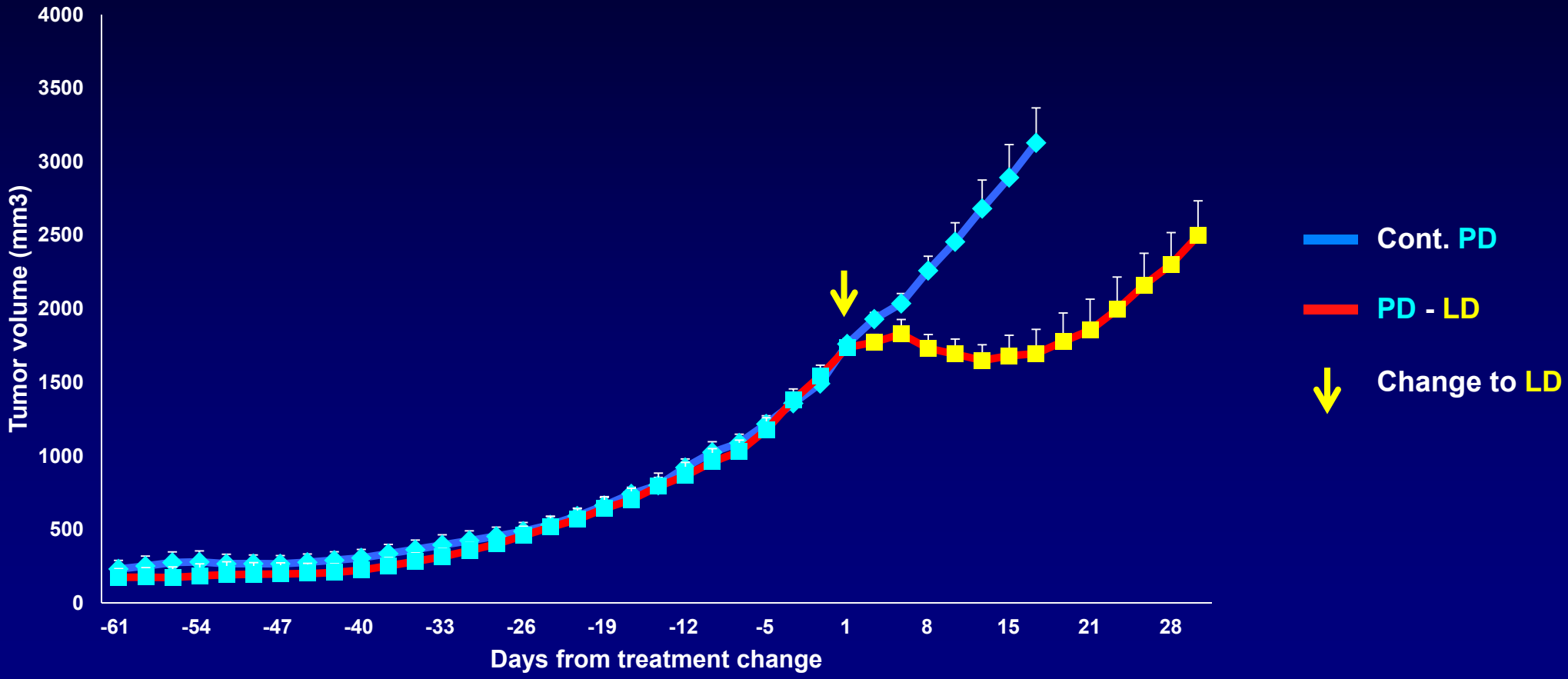


PD overcomes resistance to LD

Ocio EM, et al. Leukemia 2014.

LD & PD do not present Cross-Resistance

Tumors that had developed resistance to PD & reached 1.700 mm^3, where switched to receive LD

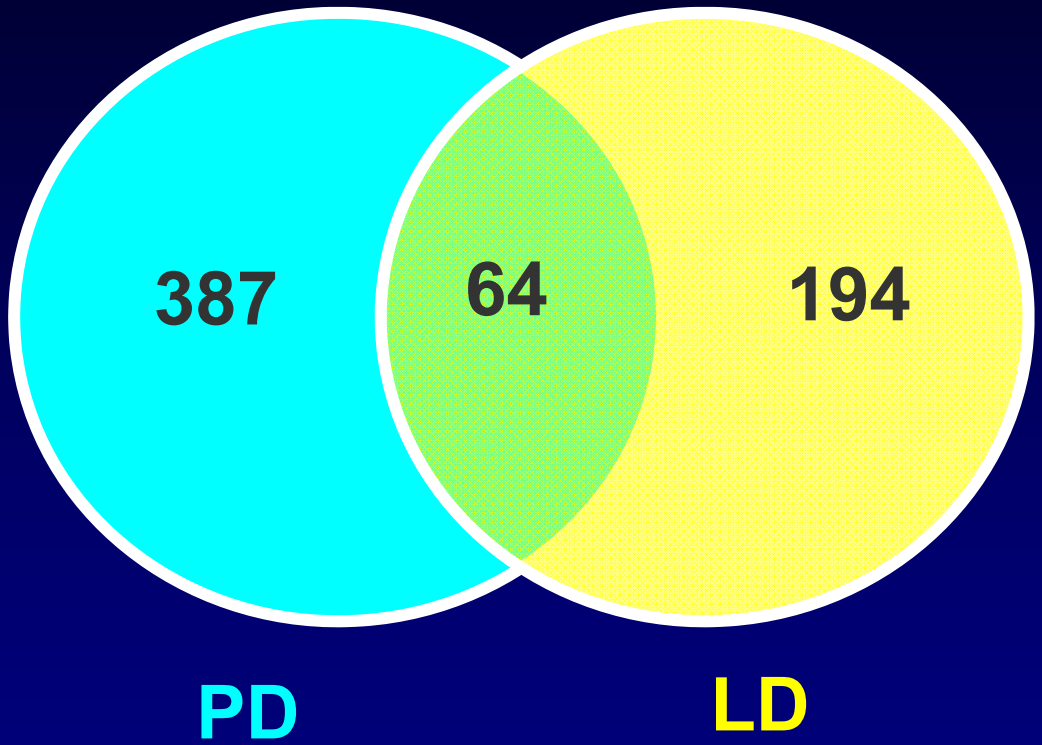


LD overcomes resistance to PD

Ocio EM, et al. Leukemia 2014.

GEP associated with resistance to IMiDs + Dex

GEP of cells excised from control & resistant tumors



Out of a total of 645 genes deregulated in resistant cells, only 10% were common to RLD and RPD.

Resistance to LD and to PD is associated with quite different genomic changes, what supports the absence of cross resistance

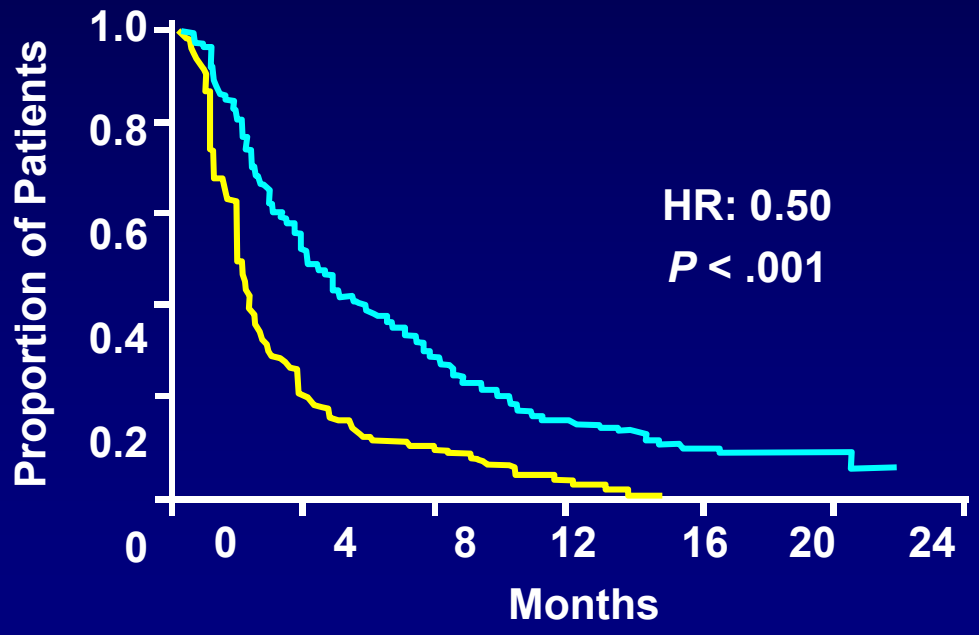
Ocio EM, et al. Leukemia 2014.

MM-003 Final Analysis: Pomalidomide/ LoDex vs HiDex: PFS and OS

ORR (≥ PR): 31% vs 3%; (≥ MR): 39% vs 16%

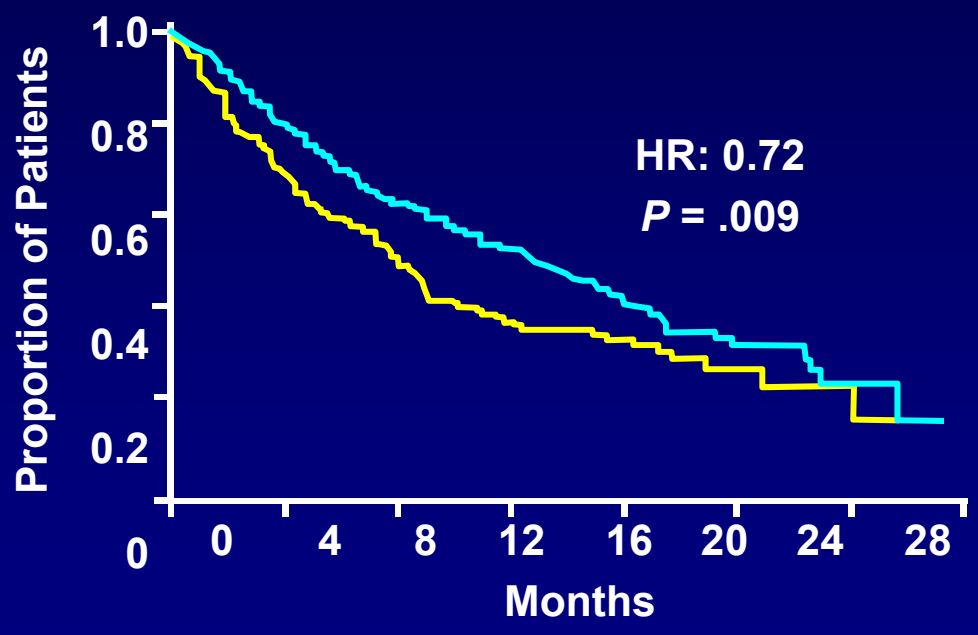
Median PFS, months

POM + LoDex (n = 302)	4.0
HiDex† (n = 153)	1.9



Median OS, months

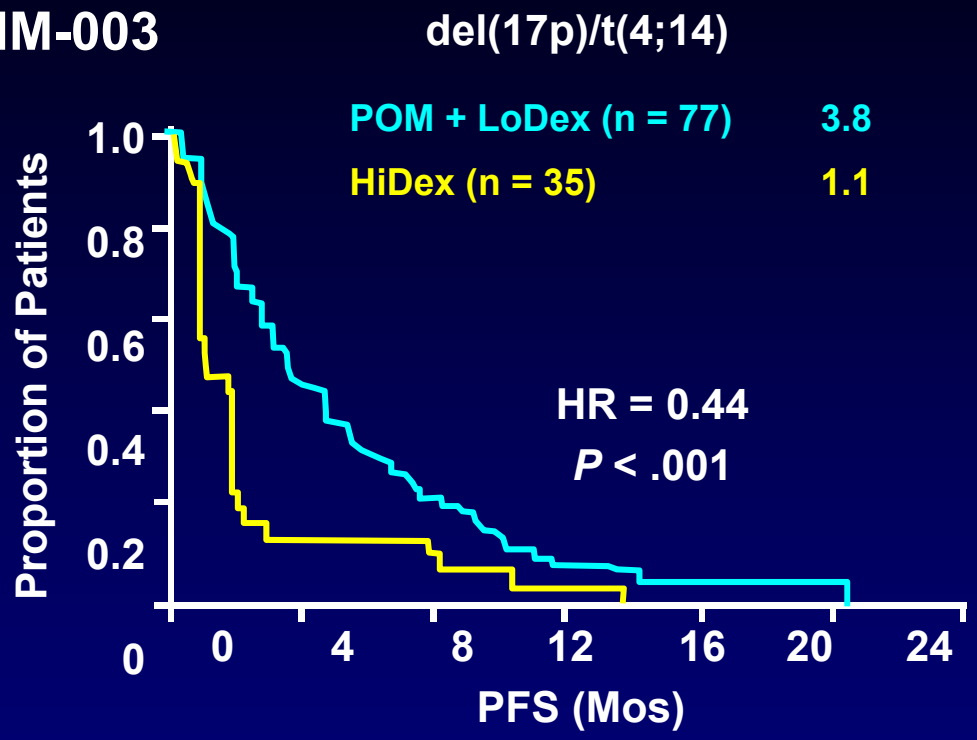
POM + LoDex (n = 302)	13.1
HiDex† (n = 153)	8.1

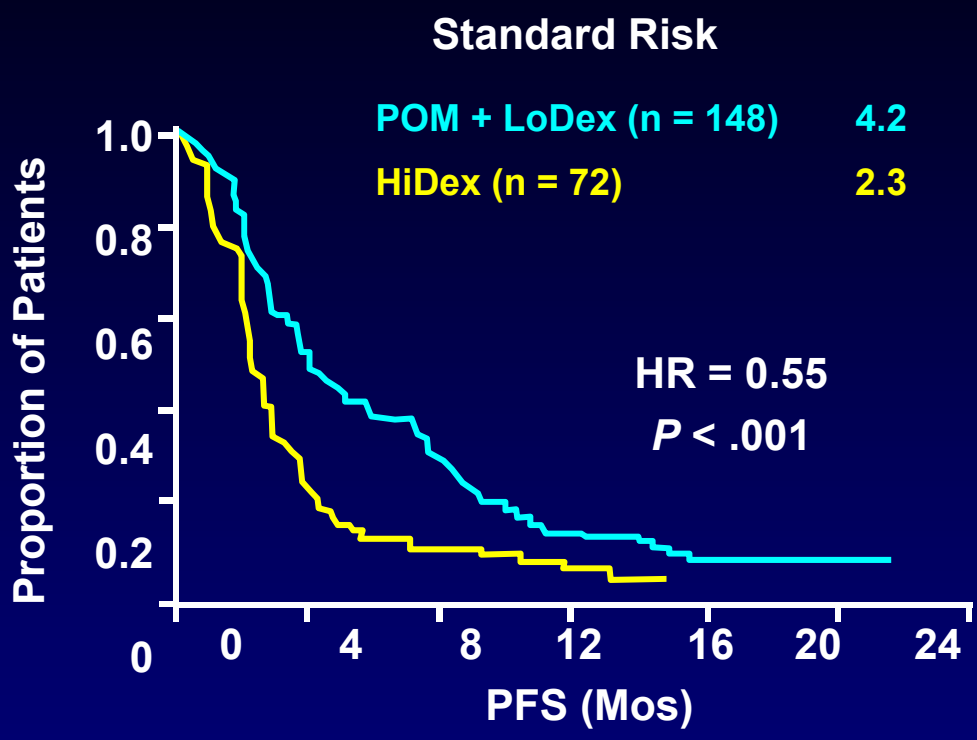


*Primary endpoint.
†85 pts (56%) on the HiDex arm received subsequent POM.

San Miguel, Lancet Oncology 2013

Pomalidomide overcomes high risk cytogenetics





Dimopoulos MA, et al. ASH 2013.

Pomalidomide in pts with relapsed/refractory MM with del(17p) and/or t(4;14)

n=50 17p (22 pts), t(4;14) (32 pts)

- Median follow-up 8.2 months

	ORR	TTP (m)	OS (m)
All pts (n=50)	22%	2.9	12
del(17p) (n=22)	32%	7.3	12
t(4;14) (n=32)	16%	2.8	9.2

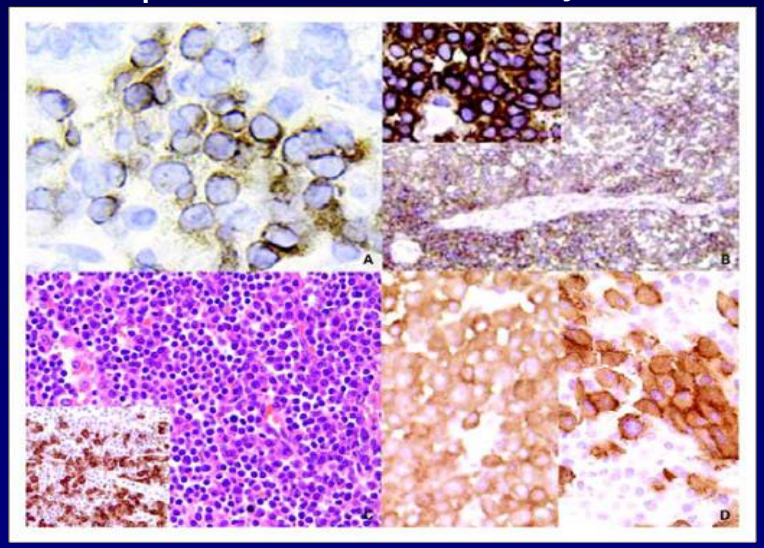
Leleu et al. ASH 2013

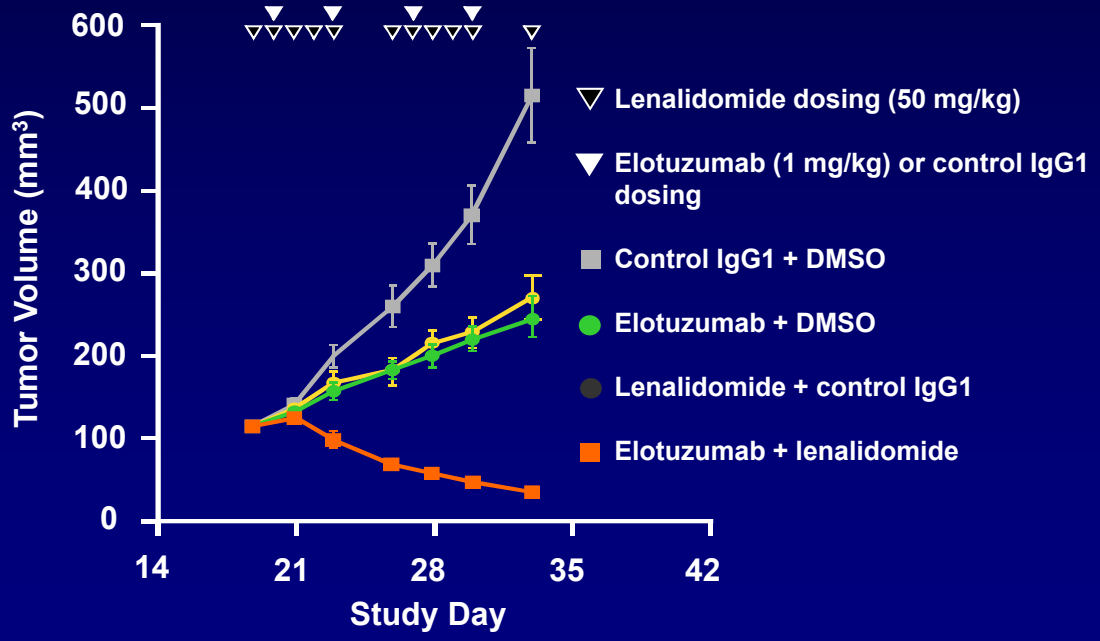
IMiDs are good partners for combination

Specially Immune-related combinations

Elotuzumab (Anti-CS1 MoAb) in MM

- Elotuzumab is a humanized IgG1 mAb targeting human CS1, a cell surface glycoprotein[1,2]
- CS1 is highly expressed on >95% of MM cells[1-3]
  - Lower expression on NK cells
  - Little to no expression on normal tissues
- MoA of elotuzumab is primarily through NK cell-mediated ADCC against myeloma cells[1,2]
- In a MM xenograft mouse model, the combination of elotuzumab + lenalidomide significantly reduced tumor volume compared with either agent alone[4]

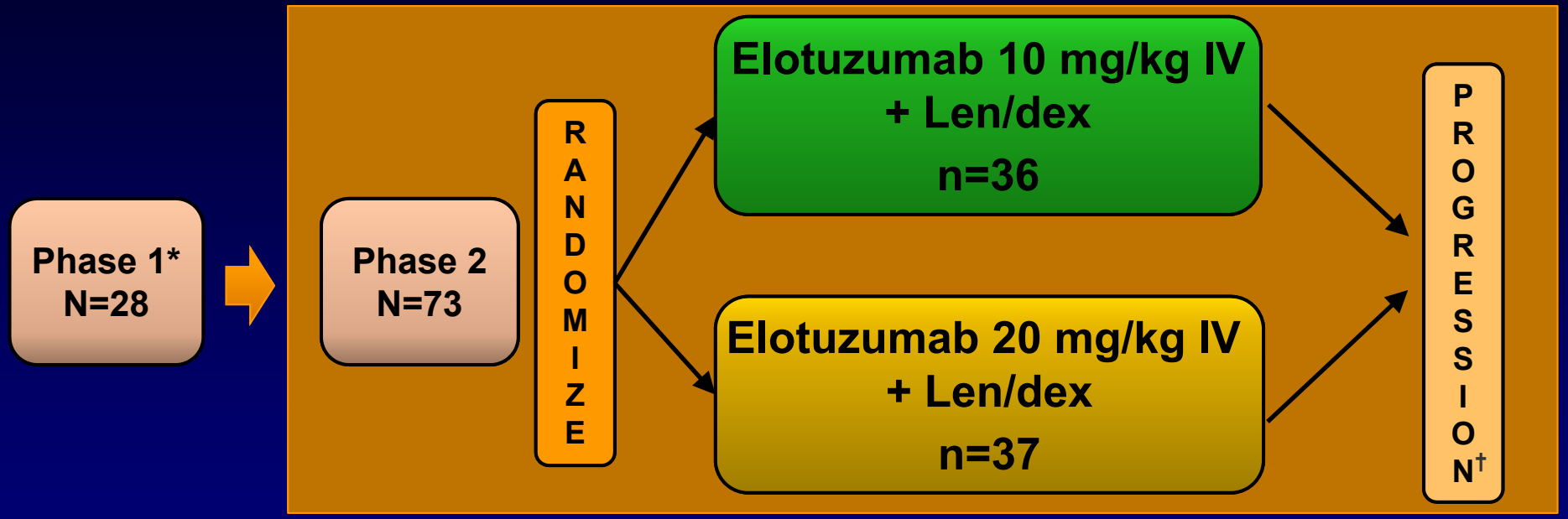




ADCC = antibody-dependent cellular cytotoxicity; DMSO = dimethyl sulfoxide;
mAb = monoclonal antibody; MED = maximum efficacious dose; MM = multiple myeloma; MoA = mechanism of action; NK = natural killer

1. Hsi ED et al. *Clin Cancer Res*. 2008;14:2775-2784; 2. Tai YT et al. *Blood*. 2008;112:1329-1337
3. Van Rhee F et al. *Mol Cancer Ther*. 2009;8:2616-2624; 4. Lonial S et al. *Blood*. 2009;114:Abstract 432

Phase II: Elotuzumab + Len + Low-Dose Dex in Rel/Ref MM (Study 1703)



- Phase 2: Pts (n=73) with relapsed and/or refractory MM with 1-3 prior therapies & Len naive
- Endpoints
  - Primary: ORR (≥PR per IMWG Criteria)
  - Key secondary endpoints: PFS and safety

Lonial et al. J Clin Oncol. 2012

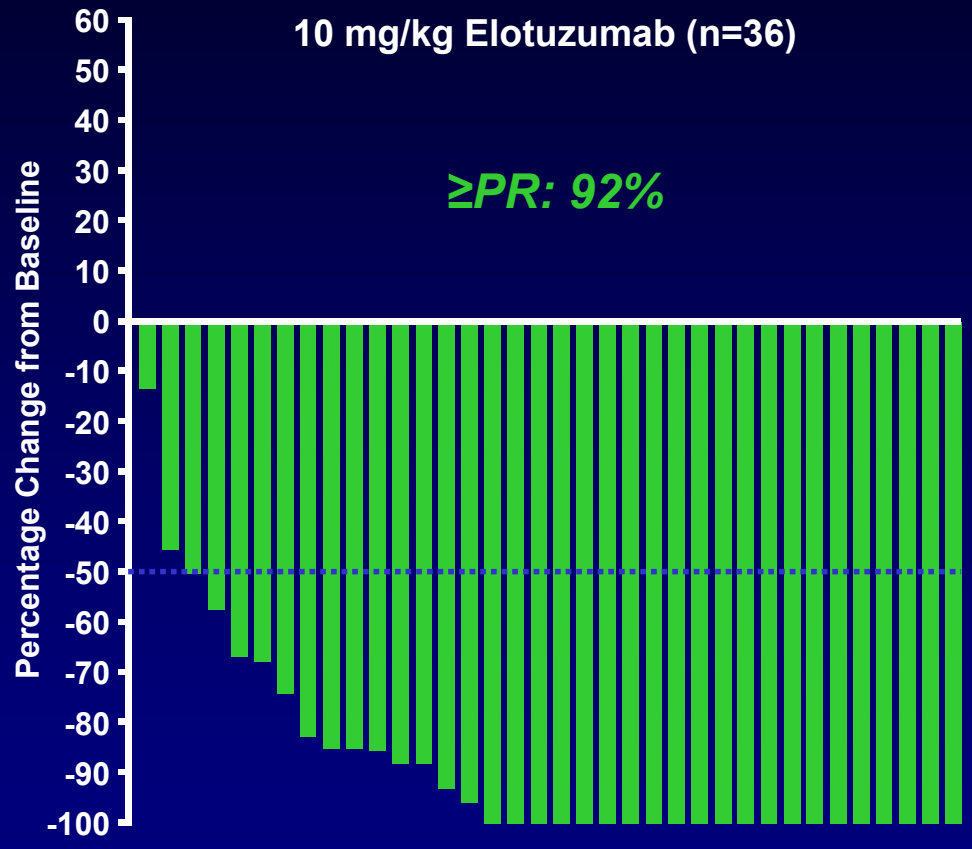
Len/dex: lenalidomide plus low dose dexamethasone

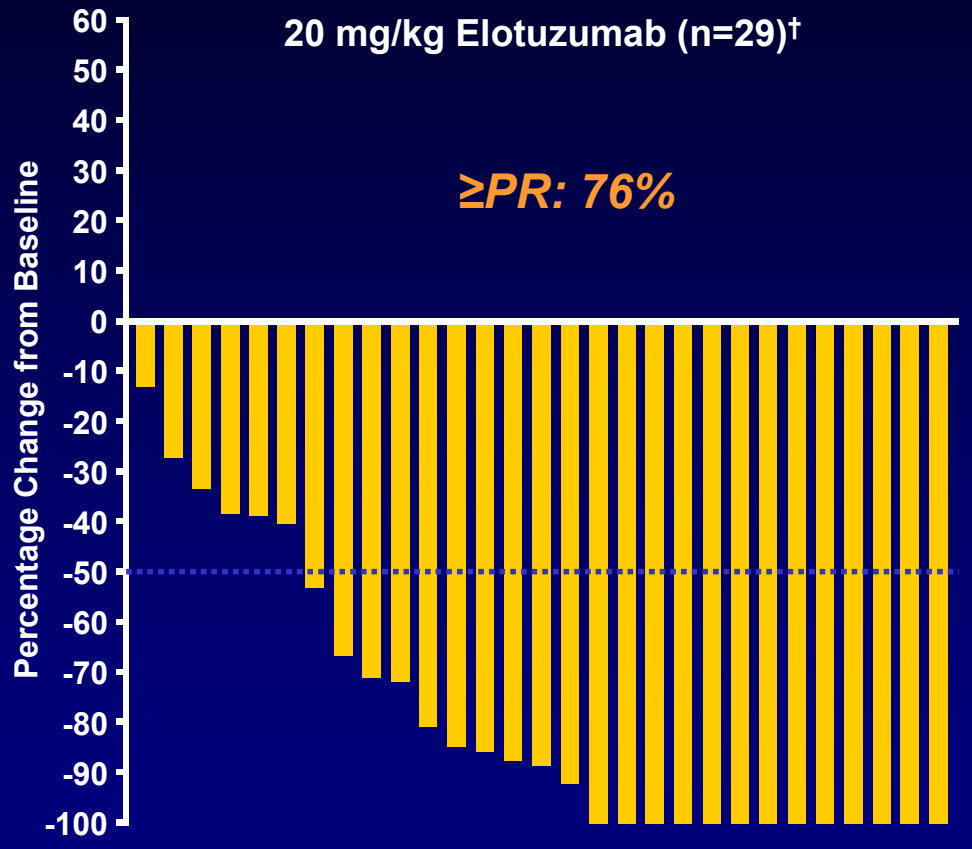
†Progression defined by IMWG Criteria.

Richardson. ASH 2012. Abs 202 & IMW 2013 (P-214)

Response Rate of Elotuzumab + Len-Dex

Phase 2: Pts (n=73) with relapsed and/or refractory MM with 1-3 prior therapies & Len naive



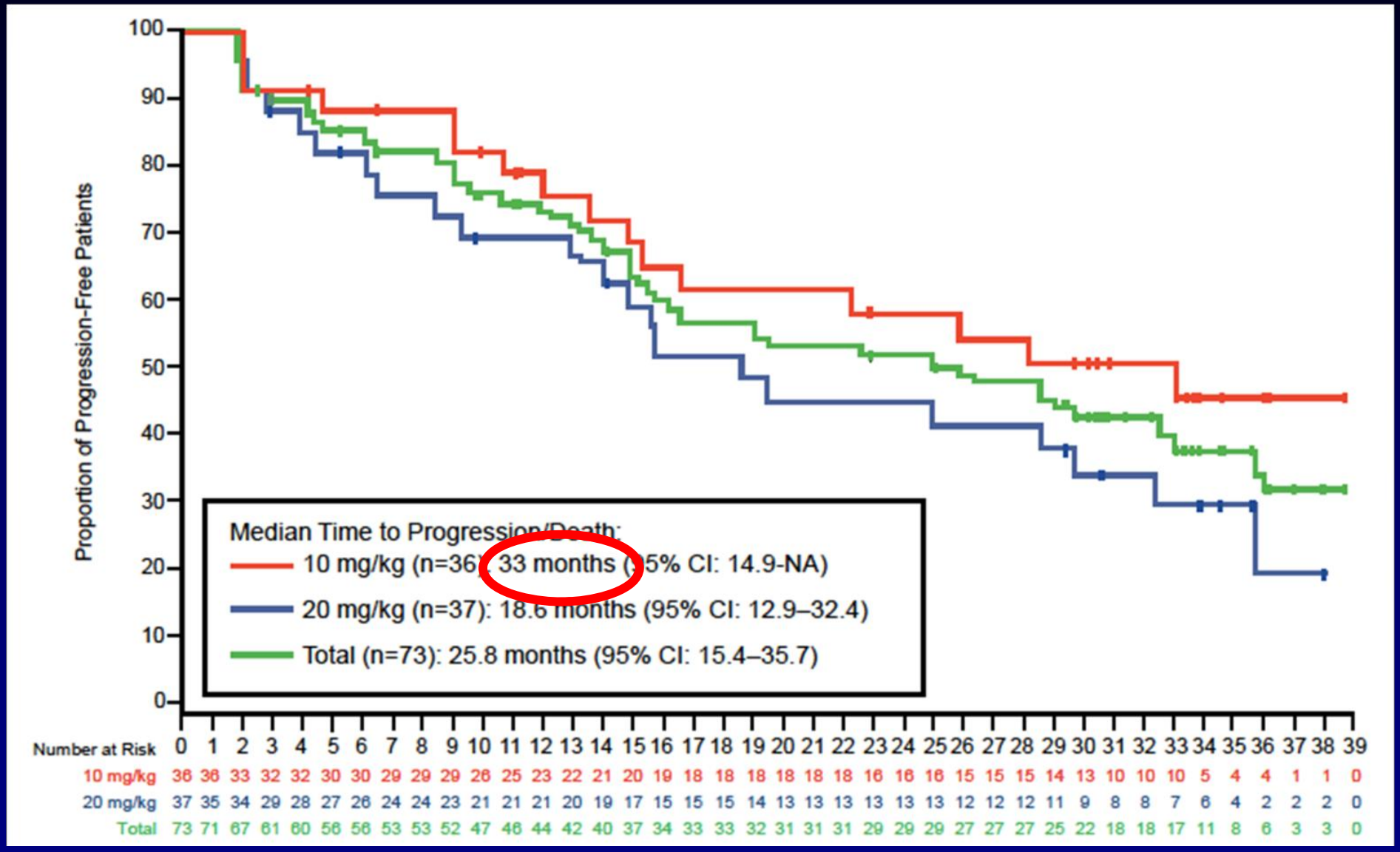


* Maximum percentage decrease from baseline to 60 d after permanent discontinuation of elotuzumab or start of new line of MM therapy.

† Eight pts without measurable disease (baseline and all on-study serum M-protein levels <0.5 g/dL) were not included.

Richardson. ASH 2012. Abs 202 & IMW 2013 (P-214)

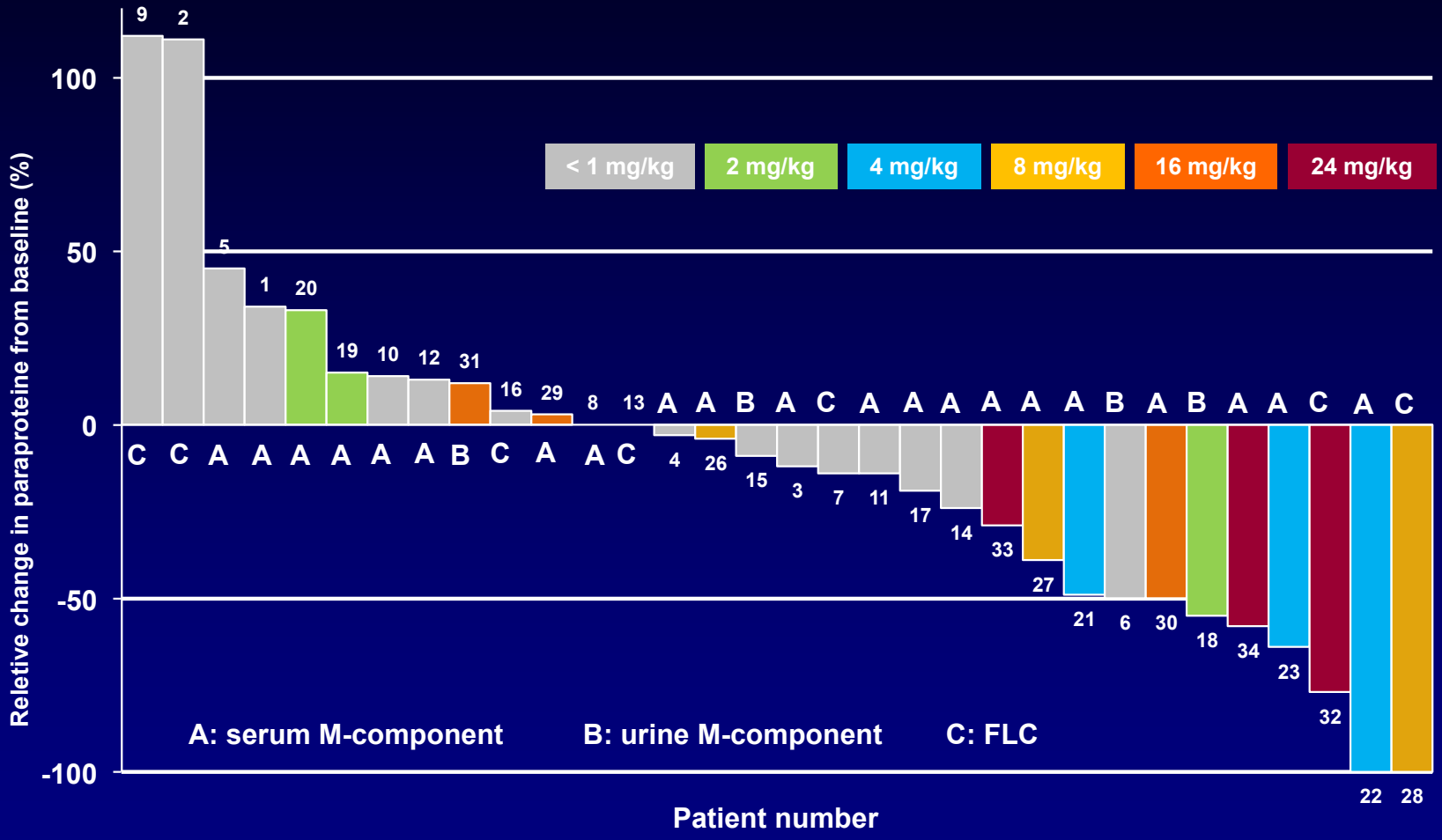
PFS of Elotuzumab (Anti-CS1 MoAb)



Richardson. ASH 2012. Abs 202 & IMW 2013 (P-214)

Daratumumab: Maximal change in M-Component

n=32 with median of 6 prior lines (2-12)



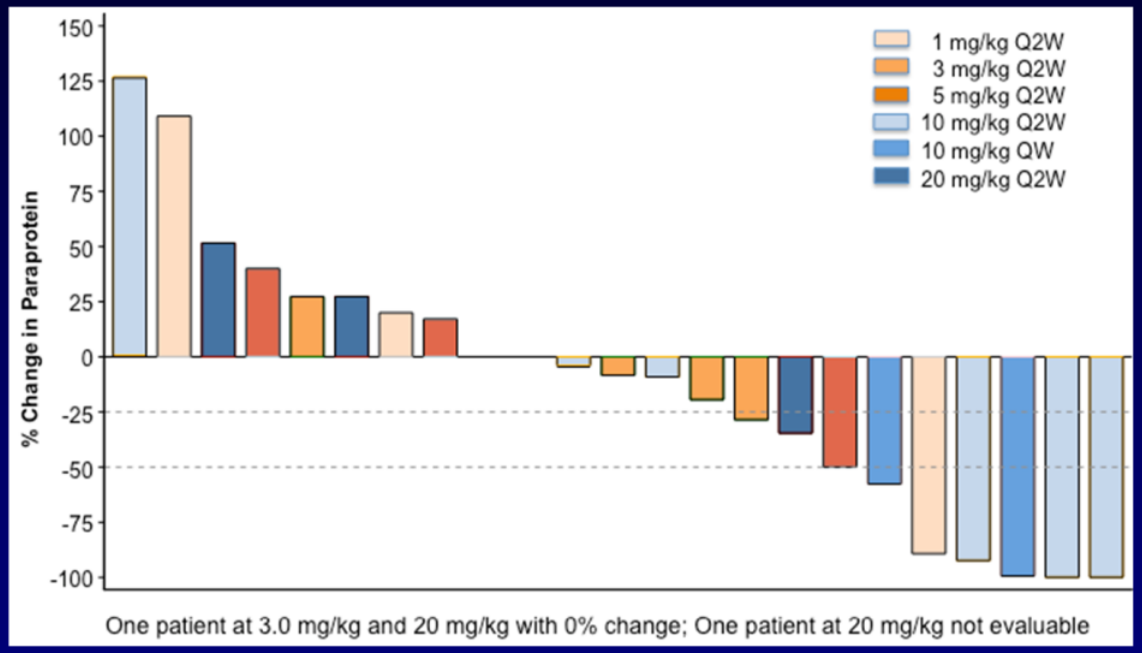
Expansion phase @ 16 mg/Kg → 46% ≥ PR *(3 VGPR + 3 PR)*

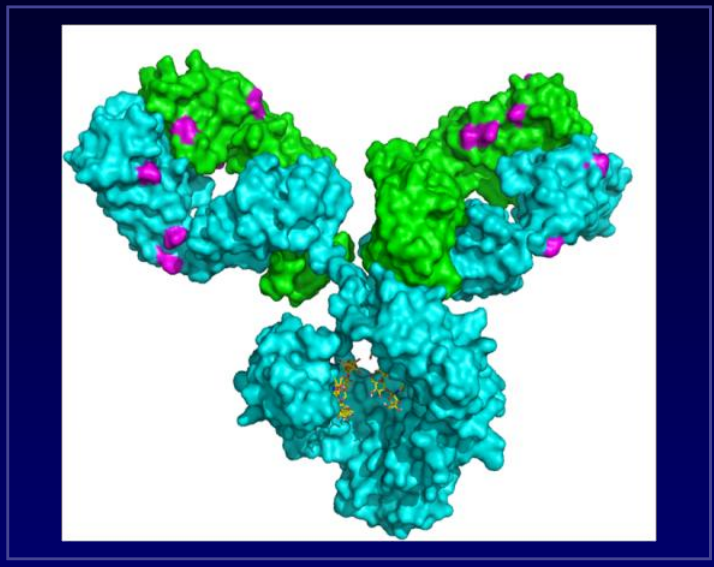
Plesner. ASH 2012 & Lokhorst EHA 2013 & ASCO 2014

Daratumumab + LD 11 pts … 4 prior lines → *5 VGPR; 3 PR; 2 MR* *Plesner. ASCO 2014*

SAR-650984
Naked humanized anti-CD38 mAb from Sanofi

- n=39 MM. *Prior lines 6 (2-14)*





1. ADCC: Antibody dep cytotox.
2. CDC: Complement dep. Cytotox.
3. Direct apoptosis

>1 mg/Kg n=34 …….... ≥ PR 24% (2 CR, 6 PR)

>10 mg/Kg n=18 …….. ≥ PR 33%

(2 CR, 4 PR)

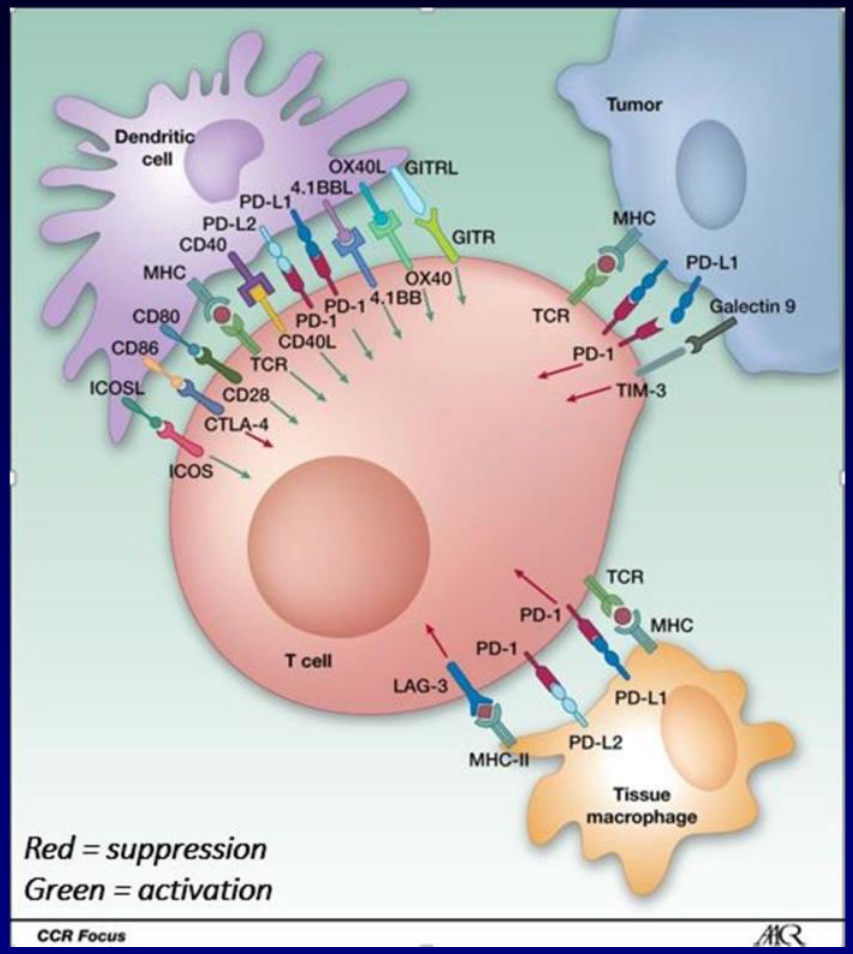
Safety: Infusion reactions with the 1st dose

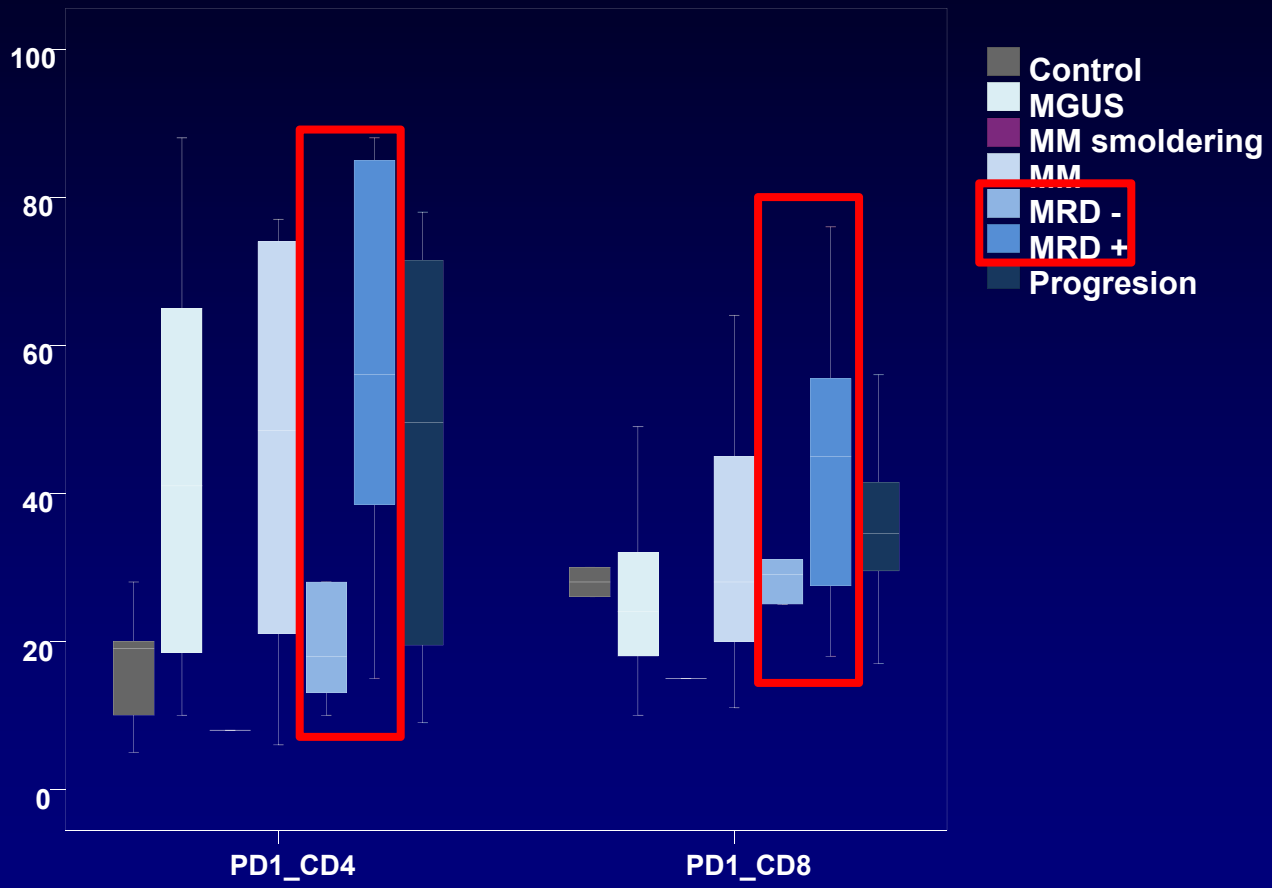
Martin, ASH 2013 & ASCO 2014

SAR-650984 + LD 12 pts … 6 prior lines → *4 VGPR; 3 PR, 1 MR*

Martin. ASCO 2014

Immunotherapy: Check Point inhibitors





T lymphocytes (both CD4 & CD8) of patients in CR with persistent MRD display display the highest expression of PD1

MK-3475 (MSD Anti-PD1) + Lenalidomide + Dexamethasone in RR MM

Siegel. ASCO 2014

Summary

- IMiDs are a “new class” of agents with a pleiotropic mechanism of action: tumoricidal and immunomodulatory.
- They have a common binding molecule: Cereblon, but it alone does not explain the whole activity of these agents.
- Thalidomide / Lenalidomide / Pomalidomide display different profile of toxicity and efficacy.
- They are approved for the treatment of R/R MM, MDS 5q-, and Relapsed MCL.
- Combinations with MoAb targeting immune mechanisms seem specially attractive.

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IMiDs

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