Targettare il microambiente Nel mieloma multiplo

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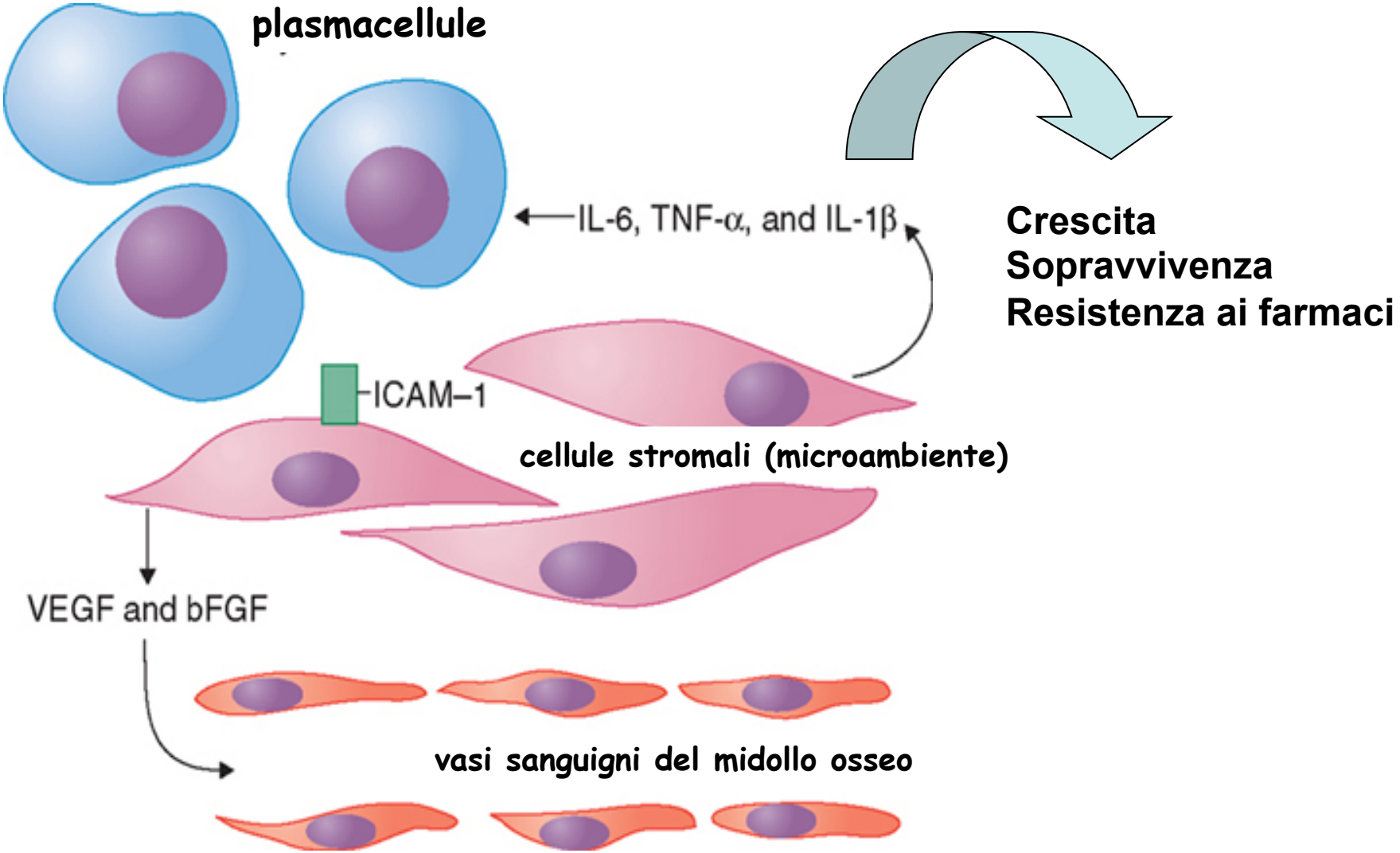
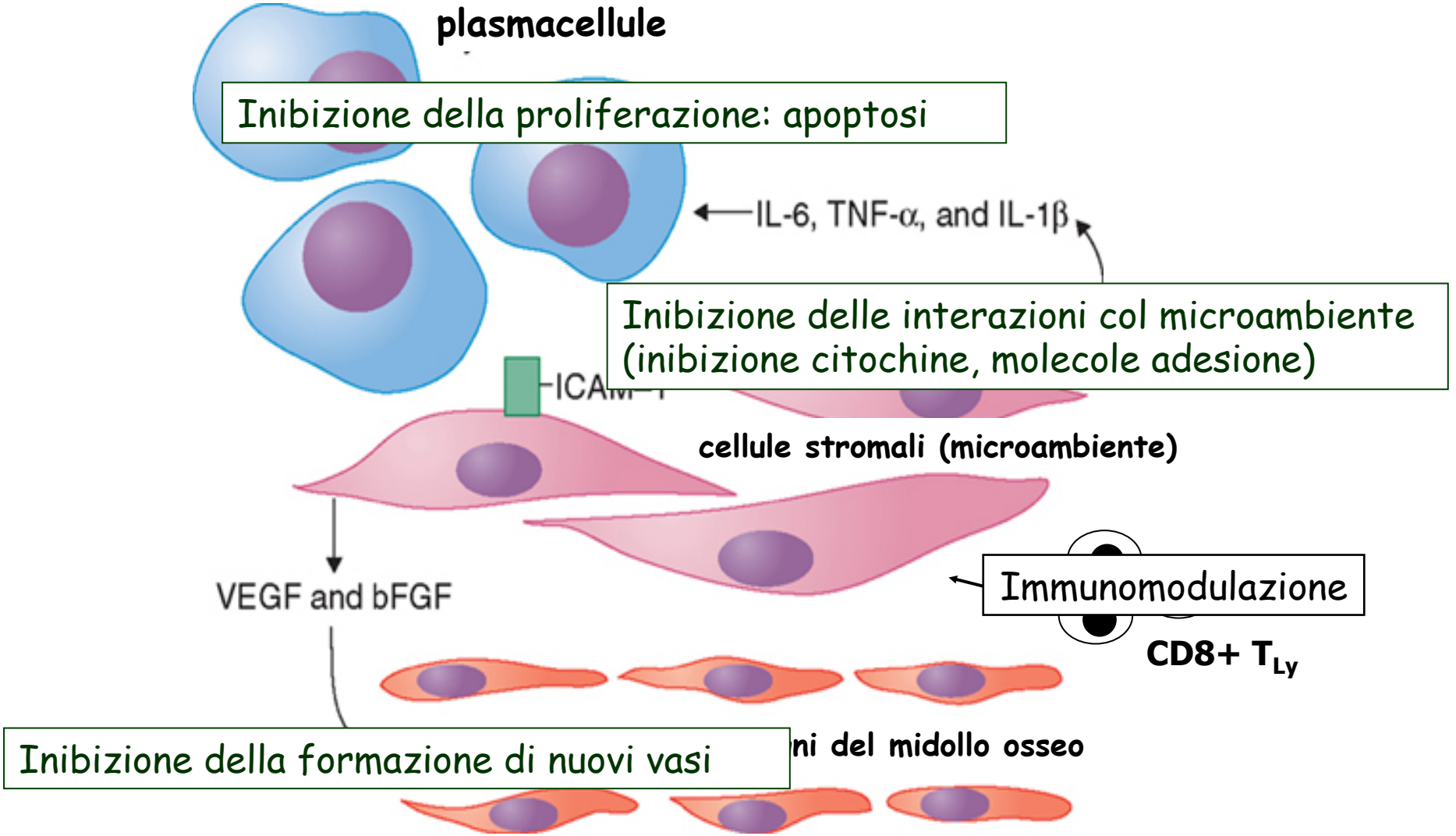
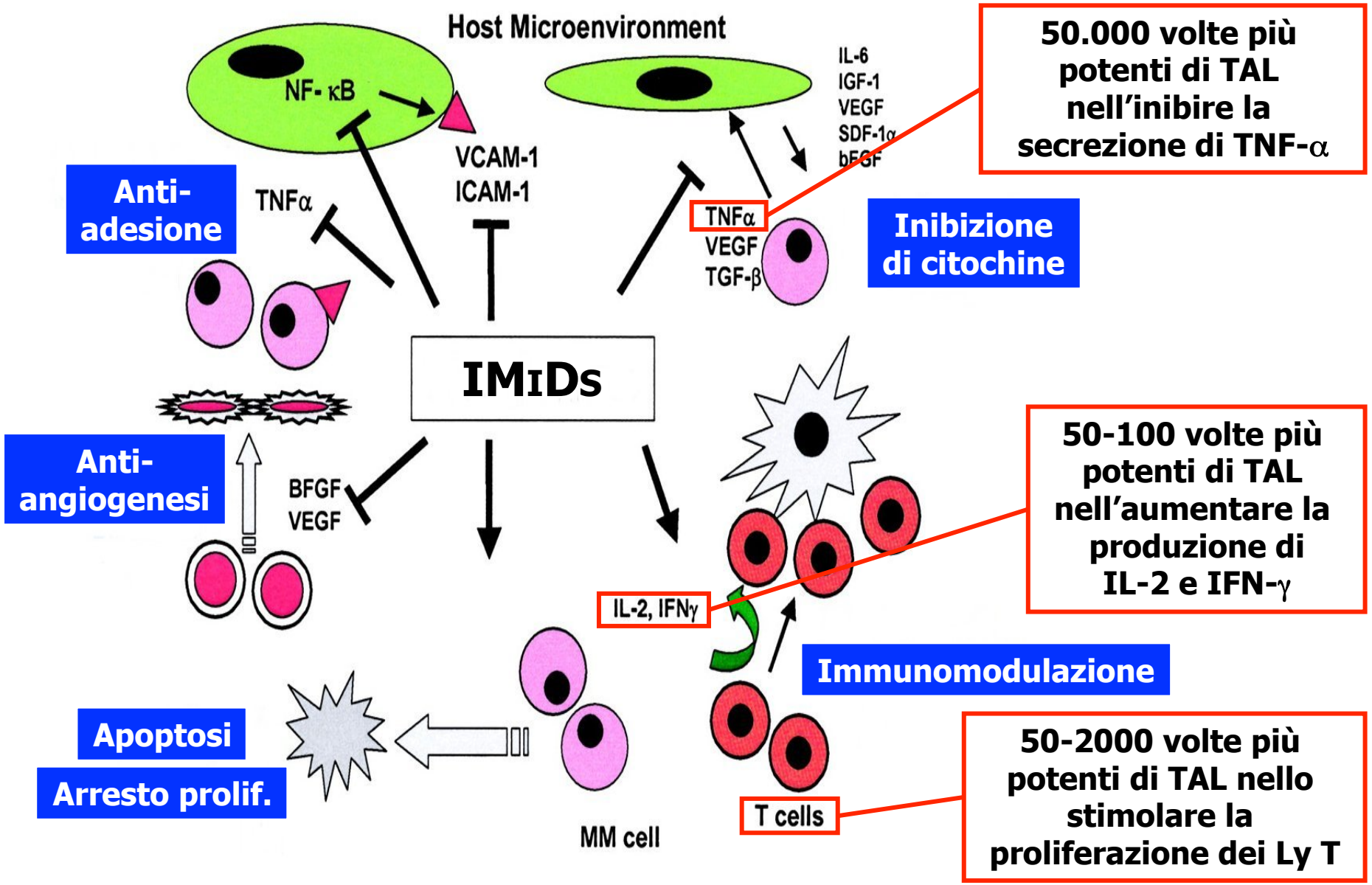
Il mieloma multiplo: un modello di interazione tra cellule neoplastiche e microambiente midollare



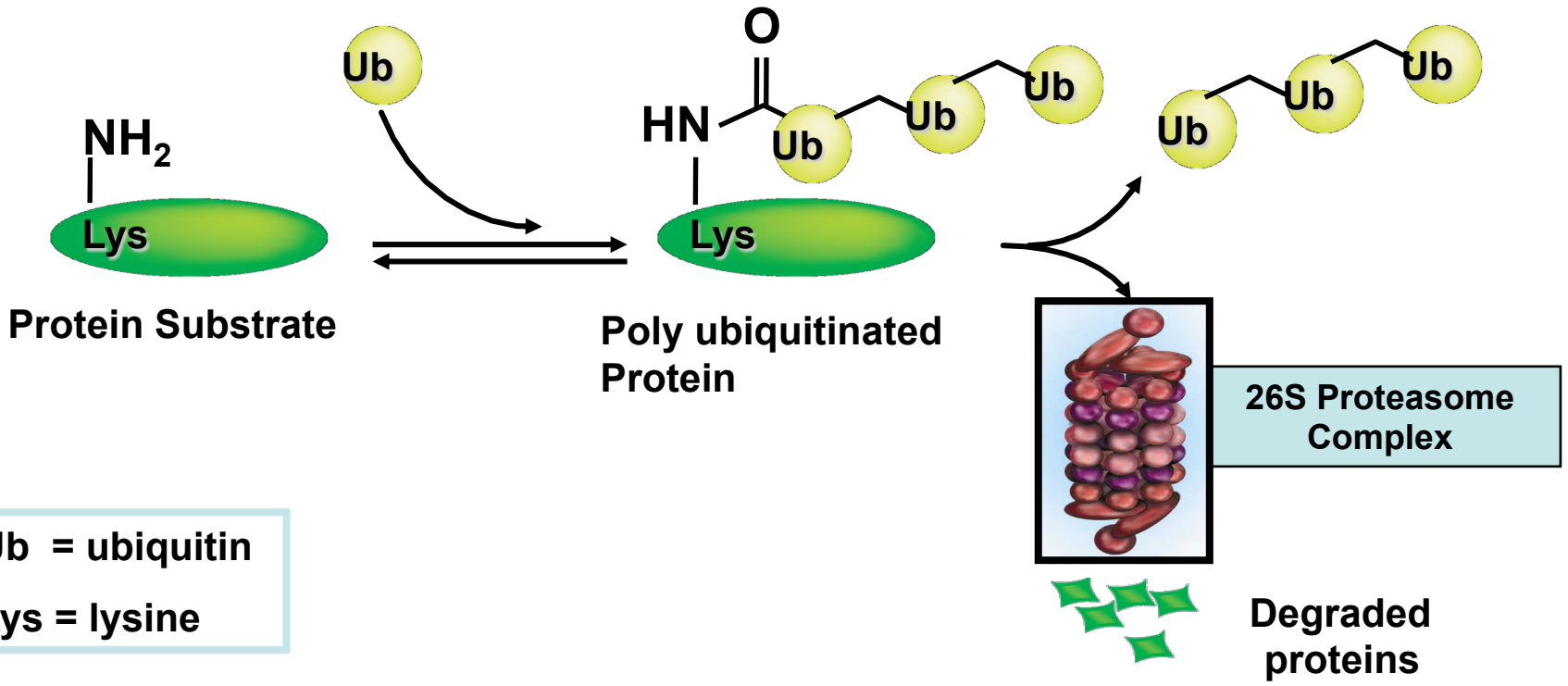
MECCANISMI DI AZIONE DEI FARMACI DIRETTI CONTRO IL MICROAMBIENTE MIDOLLARE



MECCANISMI DI AZIONE DEGLI IMiDs



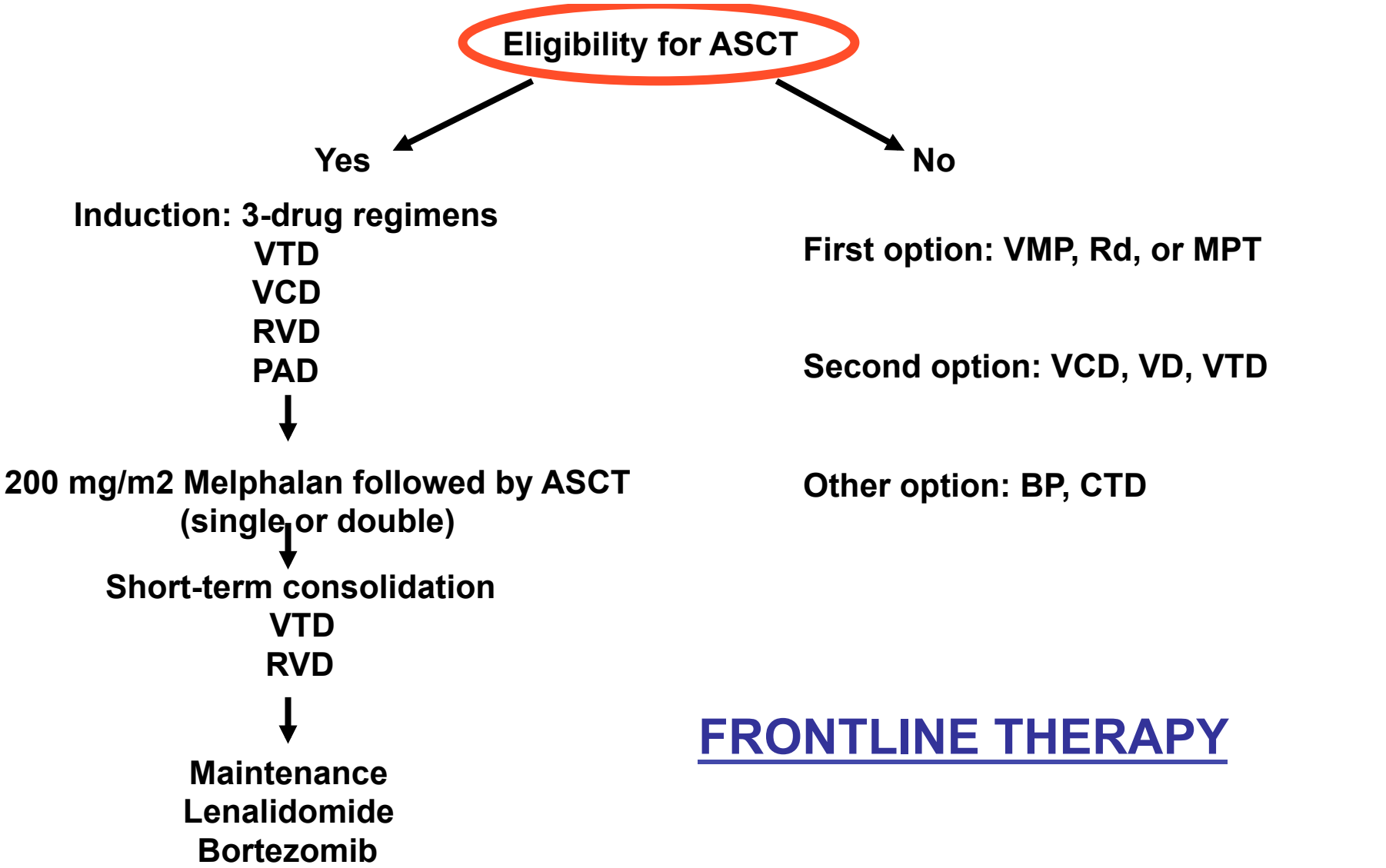
Ubiquitin-Proteasome Pathway



Ub = ubiquitin

Lys = lysine

Myung J. Med Res Rev. 2001
De Martino GN. J Biol Chem. 1999



FRONTLINE THERAPY

Frontline therapy of multiple myeloma.
Moreau P, Attal M, Facon T.
Blood. 2015 May 14;125(20):3076-3084. Epub 2015 Apr 2. Review

Main randomized trials in R/R MM

Regimen	ORR, %	CR, %	TTP/PFS, mo	OS
Bortezomib vs Dexamethasone[1]	38 vs 18	6 vs 1	6.2 vs 3.5	80% vs 66% @ 1 year
Bortezomib+Doxil vs Bortezomib[2]	44 vs 41	4 vs 2	9.3 vs 6.5	76% vs 65% @ 15 mo
Lenalidomide-dexamethasone vs Dexamethasone[3,4]	61/60.2 vs 19./24	14.1/15.9 vs 0.6/3.4	11.1/11.3 vs 4.7/4.7	29.6/NR vs 20.2/20.6 mo
Pomalidomide – dexamethasone vs Dexamethasone[5]	31 vs 10	1 vs 0	4 vs 1.9	12.7 vs 8.1 mo

1.Richardson PG, et al. N Engl J Med. 2005; 352:2487-2498 2.Orlowski RZ, et al J Clin Oncol. 2007: 3892-3901. 3.Weber DM, et al N Engl J Med. 2007; 357: 2133-2142 4. Dimopoulous M, et al. N Engl J med,. 2007; 357: 2123-2132, 5. San Miguel et al, Lancet Oncol 2013; 14(11): 1055-66

Treatment options for R/R MM

Transplant Eligible Patients

Bortezomib-based Induction

↓

ASCT

Transplant Inelegible Patients

VMP/MPT
Ld

FIRST RELAPSE

Second Transplant

- **Lenalidomide-dexamethasone**
- **Bortezomib-dexamethasone/ Doxil**

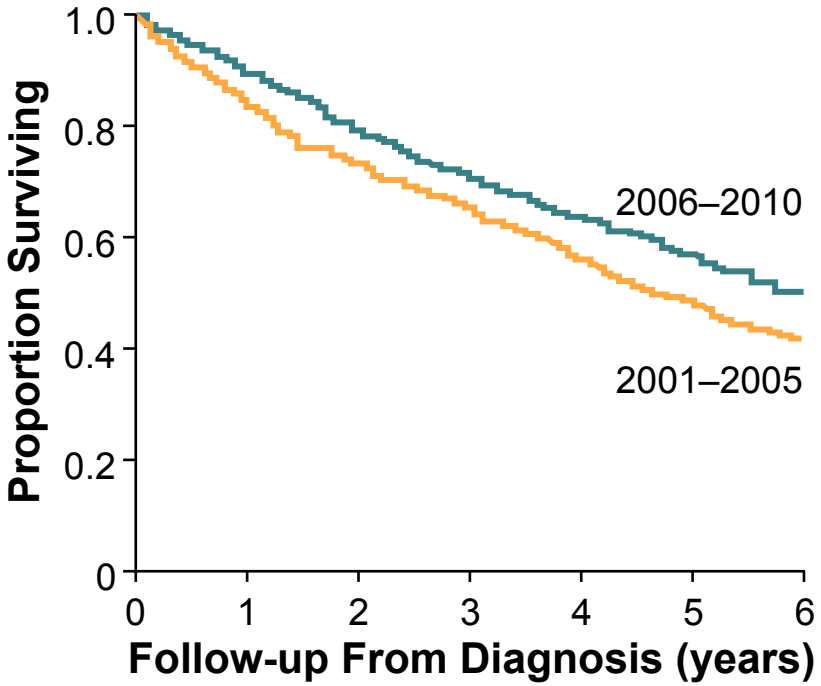
SECOND RELAPSE

- **Lenalidomide-dexamethasone**
- **Bortezomib-dexamethasone/Doxil**
- **Pomalidomide-Dexamethasone***

*at second or subsequent relapse in pts previously treated with both lenalidomide and bortezomib

OS Improvement in the Traditional Treatment Landscape

- There are 1038 patients grouped into 2001–2005 and 2006–2010 cohorts
- Survival improved over time, particularly in patients aged >65 years (*P*=0.001)

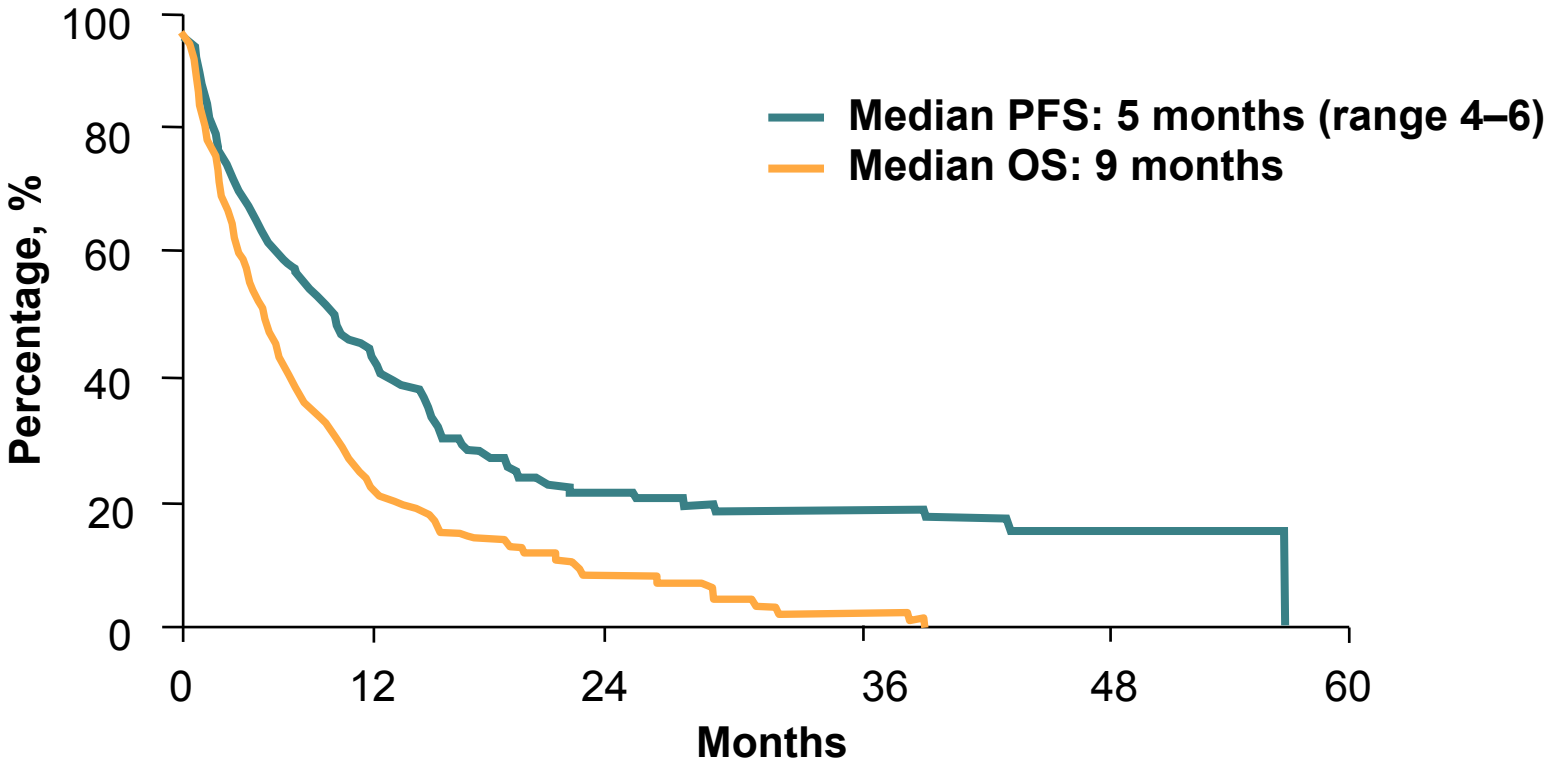


Survival	2001–2005	2006–2010	*P*
Median OS, years	4.6	6.1	0.002
6-year estimated OS, %	40	51	< 0.001

Kumar SK et al. *Leukemia*. 2013. doi:10.1038/lev.2013.313..

Prognosis for Patients Refractory to Novel Agents Remains Poor

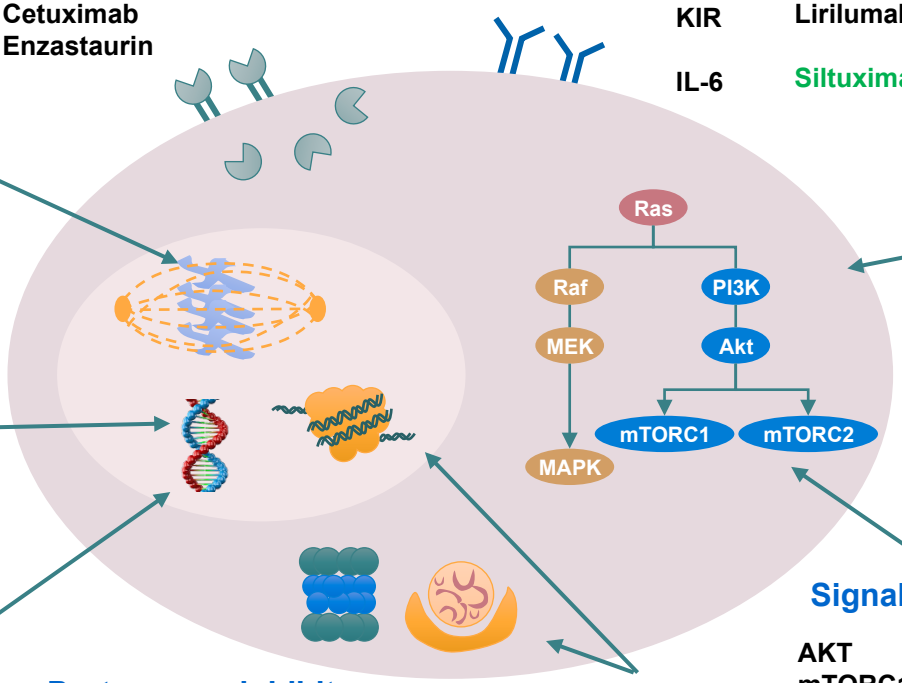
Patients refractory to bortezomib and relapsed or refractory to or ineligible for immunomodulatory drugs



- Despite the benefit observed with novel agents in the last few years, new drugs are still needed for relapsed/refractory patients

Kumar SK et al. *Leukemia*. 2012;26:149-157.

Main Targets in Multiple Myeloma and Drugs Tested Against Them



Kinase inh

CDK 1, 2, 5, 9	Dinaciclib
FGFR3	Dovitinib/AB1010/MFGR 1877S
cKit/PDGFR	Imatinib/Dasatinib
VEGF-R	Bevacizumab
IGF-1R	AVE1642 / CP-751, 851
EGF-R	Cetuximab
PKC	Enzastaurin

Monoclonal antibodies

SLAMF7	Elotuzumab
CD38	Daratumumab/SAR650984
CD138	nBT062-DM4
CD56	Lorvotuzumab
CD40	Dacetuzumab/Lucatumumab
KIR	Lirilumab
IL-6	Siltuximab

Cell cycle inhibitors

KSP inh	Arry-520
Aurora K	Inh MLN8237
CDK 4/6 inh	Seliciclib

IMIDs

Thalidomide
Lenalidomide
Pomalidomide

Alkylators

Melphalan
Cyclophosphamide
Bendamustine
Melflufen

Other DNA damaging

DNA damaging	Zalypsis
PARP inhibitor	Veliparib
Hypoxia act alkylator	TH-302

Proteasome inhibitors

Bortezomib
Carfilzomib
Ixazomib
Oprozomib
Marizomib

Hsp-90 inhibitors

Tanespimycin
AUY922

HDAC inh

Panobinostat
Vorinostat
Romidepsin
Givinostat
Rocilinostat

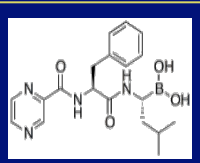
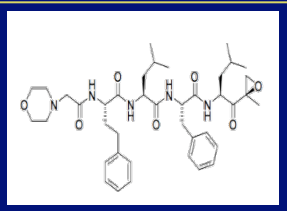
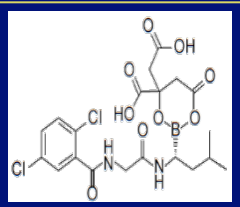
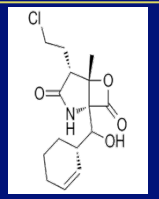
Signaling Pathways

AKT	Perifosine/GSK2110183
mTORC1s	Everolimus/Temsirolimus
mTOR C1/C2	MLN0128/INK128
Farn transf	Tipifarnib
p38/MAPK inh	Aplidin
p38/JNK act	SCIO-469
MEK	Selumetinib

Adapted from Ocio EM et al. *Leukemia*. 2014;28:525 -542.

Red: approved; **Green**: in phase III

Proteasome inhibitors

	Bortezomib	Carfilzomib	Ixazomib	Marizomib
Structure & chemical class				
	Boronate[3]	Epoxyketone	Boronate[3]	Lactam/β-lactone[3]
Type of Inhibition	Reversible[4]	**Irreversible**[4]	Reversible[4]	**Irreversible**[4]
Mechanism of Action	•Inhibits preferentially **β5**, but also **β1** and **β2**[2] •Formation of tetrahedral intermediate with side-chain hydroxyl groups (with proteasome and other classes of proteases)[6]	•Inhibits preferentially **β5**, but also **β1** and **β2**[2] •Formation of covalent adduct with N-terminal threonine active site (exclusively within the proteasome)[6]	•Inhibits preferentially **β5**, but also **β1** and **β2**[2]	•Inhibits **all three** proteolytic activities, with **IC50 values** in the **nM range**[5]
Route of Administration	Intravenous, subcutaneous[4]	Intravenous[3]	Oral[4]	Intravenous[4]

Proteasome inhibitors vary by chemical class, mechanism of action, type of inhibition[1-6]

[1] Mujtaba and Dou. Discov Med 2011;12(67):471-80; [2] Muz et al., Drug Des Devel Ther 2016;10:217-26; [3] Wang. Oncology (Williston Park) 2011; 25 Suppl 2:19-24; [4] Kurtin and Bilotti. J Adv Pract Oncol 2013;4(5): 307-21; [5] Potts et al., Curr Cancer Drug Targets 2011;11(3):254-84; [6] Arastu-Kapur et al. Clin Cancer Res 2011;17:2734-43.

Monoclonal antibodies

Target	Antibody	Mechanism of action	Activity as single agent	Activity/under evaluation in combo
CS1 (SLAM F7)	**Elotuzumab (Humanized IgG1k)**	ADCC Enhance NK activity Interference with cell interaction	-	+ VD + Rd
CD38	**Daratumumab (Fully human IgG1k)**	ADCC CDC ADCP	+	+ V-based + Rd + Pd
	Isatuximab (SAR650984; chimeric IgG1k)	Direct induction of apopotosis Modulation CD38 function	+	+ VCD + Rd
	MOR202 (fully human IgG1λ)		+	

MM: multiple myeloma; ADCC: antibody depandent cell-mediated cytotoxicity; ADCP: antibody depedent cell-mediated phagocytosis; CDC; complement dependent cytotoxicity; VD: bortezomib-dexamethasone; Rd: lenalidomide;dexamethasone; Pd: pomalidomide-dexamethasone; VCD: bortezomib-cyclophosphamide-dexamethasone; V: bortezomib

Nuovi trattamenti nel MM R/R:

- Len-dex come back-bone (PIs, Ab monoclonali, check-point inhibitors)
- PIs come back-bone

ASPIRE: Carfilzomib, Lenalidomide, and Dexamethasone (KRd) vs Lenalidomide and Dexamethasone (Rd)

Randomization

N=792

Stratification:

- β_2-microglobulin
- Prior bortezomib
- Prior lenalidomide

28-day cycles

KRd

Carfilzomib 27 mg/m^2 IV (10 min)

Days 1, 2, 8, 9, 15, 16 (20 mg/m^2 days 1, 2, cycle 1 only)

Lenalidomide 25 mg *Days 1–21*

Dexamethasone 40 mg *Days 1, 8, 15, 22*

After cycle 12, carfilzomib given on days 1, 2, 15, 16

After cycle 18, carfilzomib discontinued

Rd

Lenalidomide 25 mg *Days 1–21*

Dexamethasone 40 mg *Days 1, 8, 15, 22*

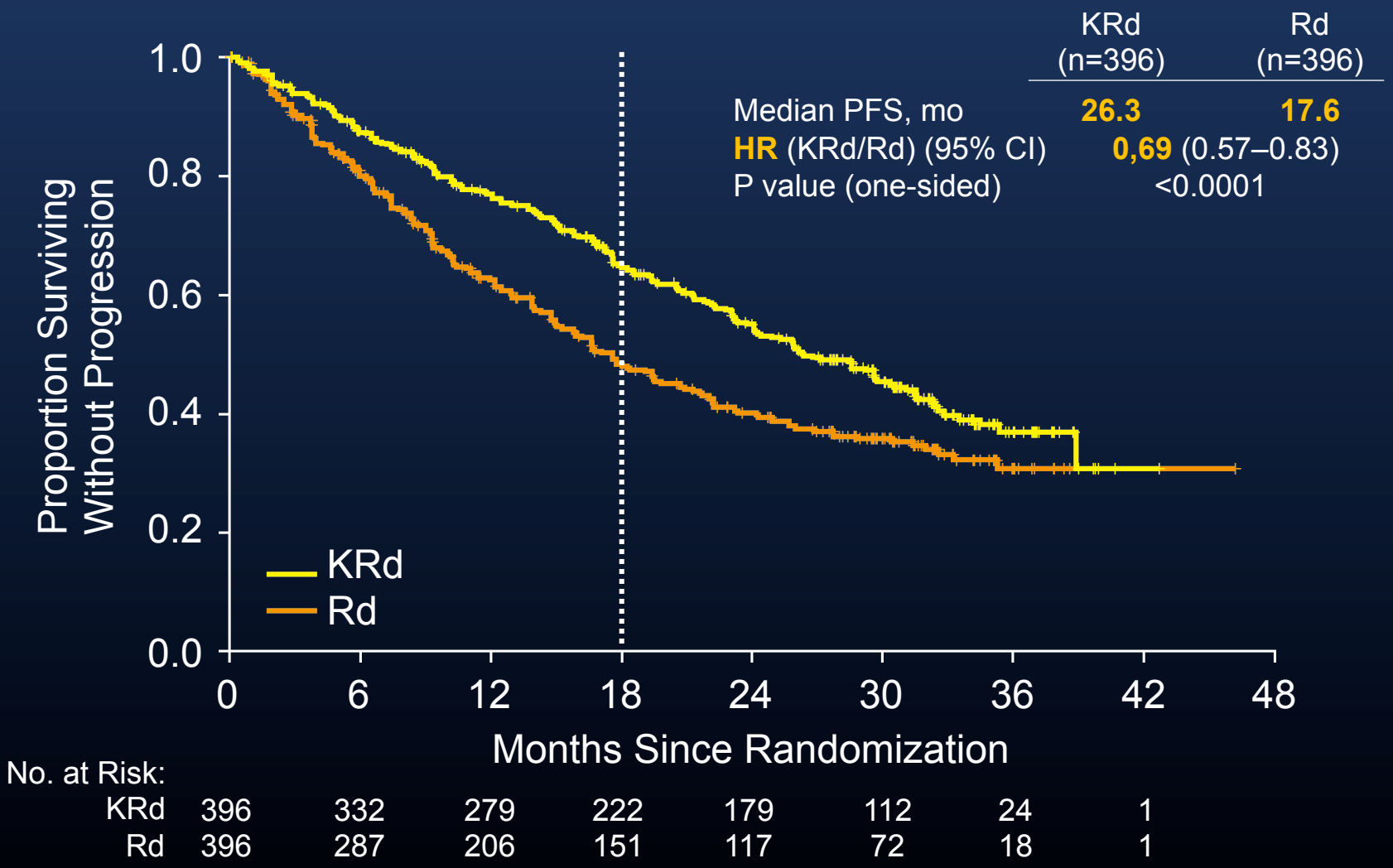
Primary endpoint: PFS

Stewart K et al, NEJM 2015

- **1–3 prior treatments, not lena refractory, no PD on bort**

(20% lena exposed, 15% bort refractory)

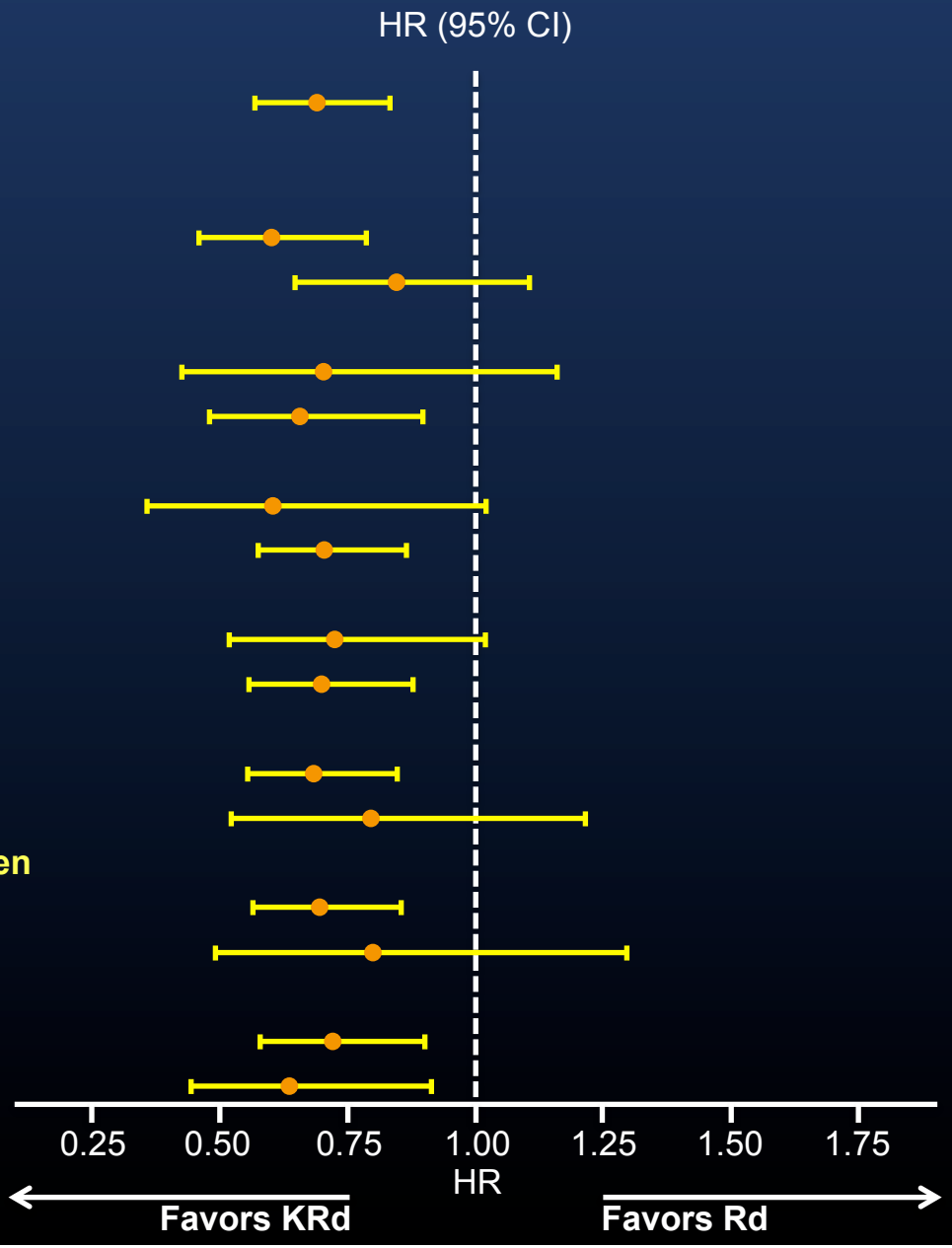
Primary Endpoint: Progression-Free Survival
ITT Population (N=792)



Stewart K et al, NEJM 2015

Primary Endpoint: Progression-Free Survival by Subgroup

Intent-to-treat group	KRd (n)	Rd (n)
Overall	396	396
Subgroup		
Age, years		
18–64	211	188
≥65	185	208
Risk group by FISH		
High-risk (12%)	48	52
Standard-risk	147	170
$ß_2$-microglobulin, mg/L		
<2.5	68	71
≥2.5	324	319
Prior treatment with bortezomib		
No	135	136
Yes	261	260
Prior treatment with lenalidomide		
No	317	318
Yes	79	78
Non-responsive to bortezomib in any prior regimen		
No	336	338
Yes	60	58
Refractory to IMiD in any prior regimen		
No	311	308
Yes	85	88



Stewart K et al, NEJM 2015

Safety: KRd vs Rd

Category	KRd (n=392)	Rd (n=389)
Median treatment duration, weeks	88.0	57.0
Any AE, % Grade ≥3 treatment-emergent AE	96.9 83.7	97.2 80.7
Treatment discontinuations, % PD AE	69.9 39.8 15.3	77.9 50.1 17.7
Serious AE, %	59.7	53.7
Deaths within 30 days of last dose, % PD Aes	7.7 0.5 6.9	8.5 1.3 6.9

Adverse event of interest, %	KRd (n=392)		Rd (n=389)	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Dyspnoea	19.4	2.8	14.9	1.8
Peripheral neuropathy†	17.1	2.6	17.0	3.1
Hypertension	14.3	4.3	6.9	1.8
Acute renal failure†	8.4	3.3	7.2	3.1
Cardiac failure†	6.4	3.8	4.1	1.8
Deep vein thrombosis	6.6	1.8	3.9	1.0
Ischaemic heart disease†	5.9	3.3	4.6	2.1
Pulmonary embolism	3.6	3.1	2.3	2.3
Second primary malignancy†	2.8	2.3	3.3	2.8

AE, adverse event; KRd, carfilzomib with lenalidomide and weekly dexamethasone; Rd, lenalidomide and weekly dexamethasone.

Stewart AK, et al. N Engl J Med 2015;372:142–52.

ENDEAVOR: Carfilzomib and Dexamethasone (Kd) vs Bortezomib and Dexamethasone (Vd)

Randomization 1:1

N=929

Stratification:

- Prior proteasome inhibitor therapy
- Prior lines of treatment
- ISS stage
- Route of V administration

Kd

Carfilzomib 56 mg/m^2 IV

Days 1, 2, 8, 9, 15, 16 (20 mg/m^2 days 1, 2, cycle 1 only)

Infusion duration: 30 minutes for all doses

Dexamethasone 20 mg

Days 1, 2, 8, 9, 15, 16, 22, 23

28-day cycles until PD or unacceptable toxicity

Vd

Bortezomib 1.3 mg/m^2 (IV bolus or subcutaneous injection)

Days 1, 4, 8, 11

Dexamethasone 20 mg

Days 1, 2, 4, 5, 8, 9, 11, 12

21-day cycles until PD or unacceptable toxicity

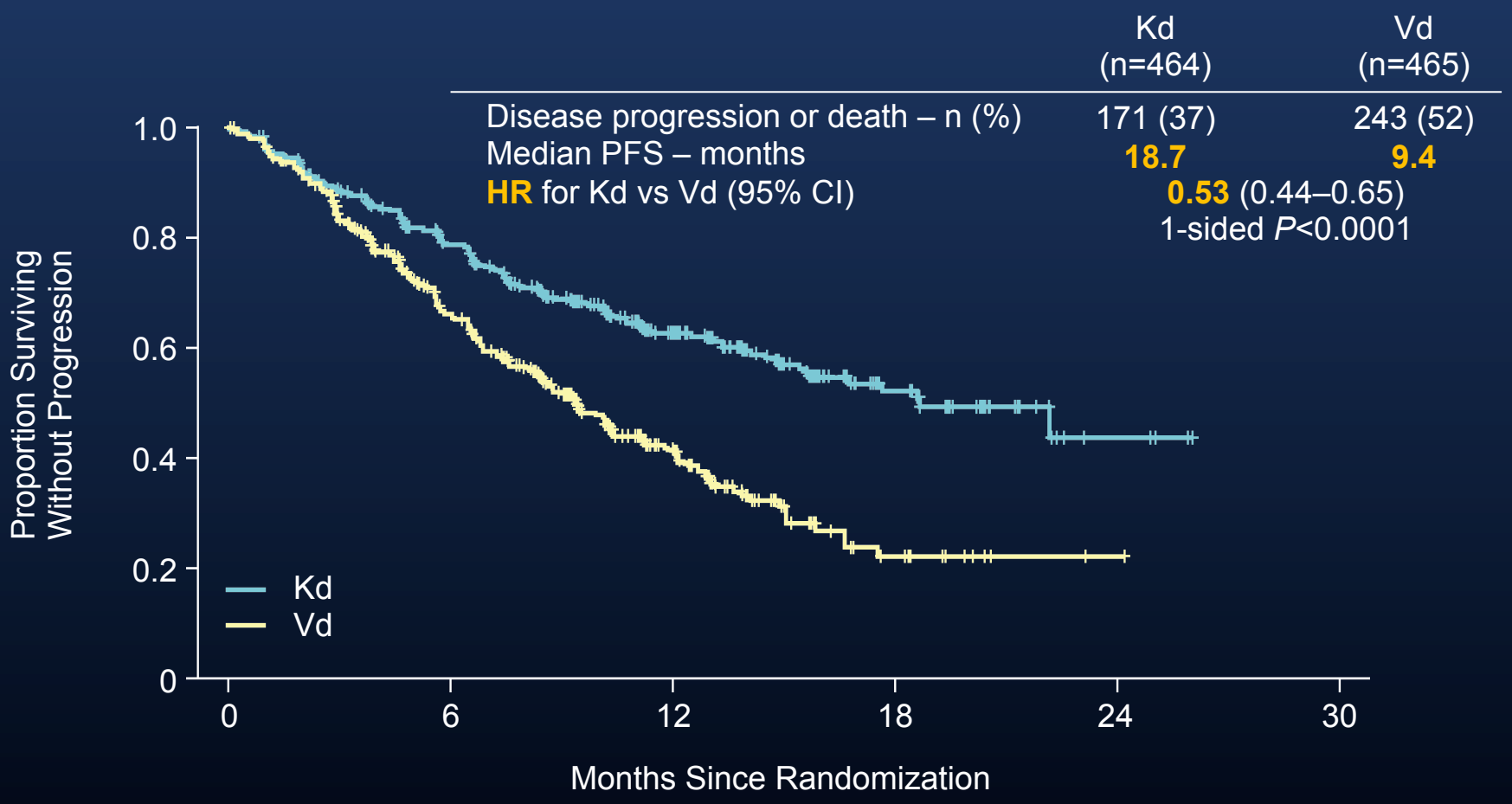
Primary endpoint: PFS

- **1–3 prior treatments, not Carf or Bort refractory**

(54% bort exposed, 38% lena exposed)

Dimopoulos D et al, Lancet Oncology 2016

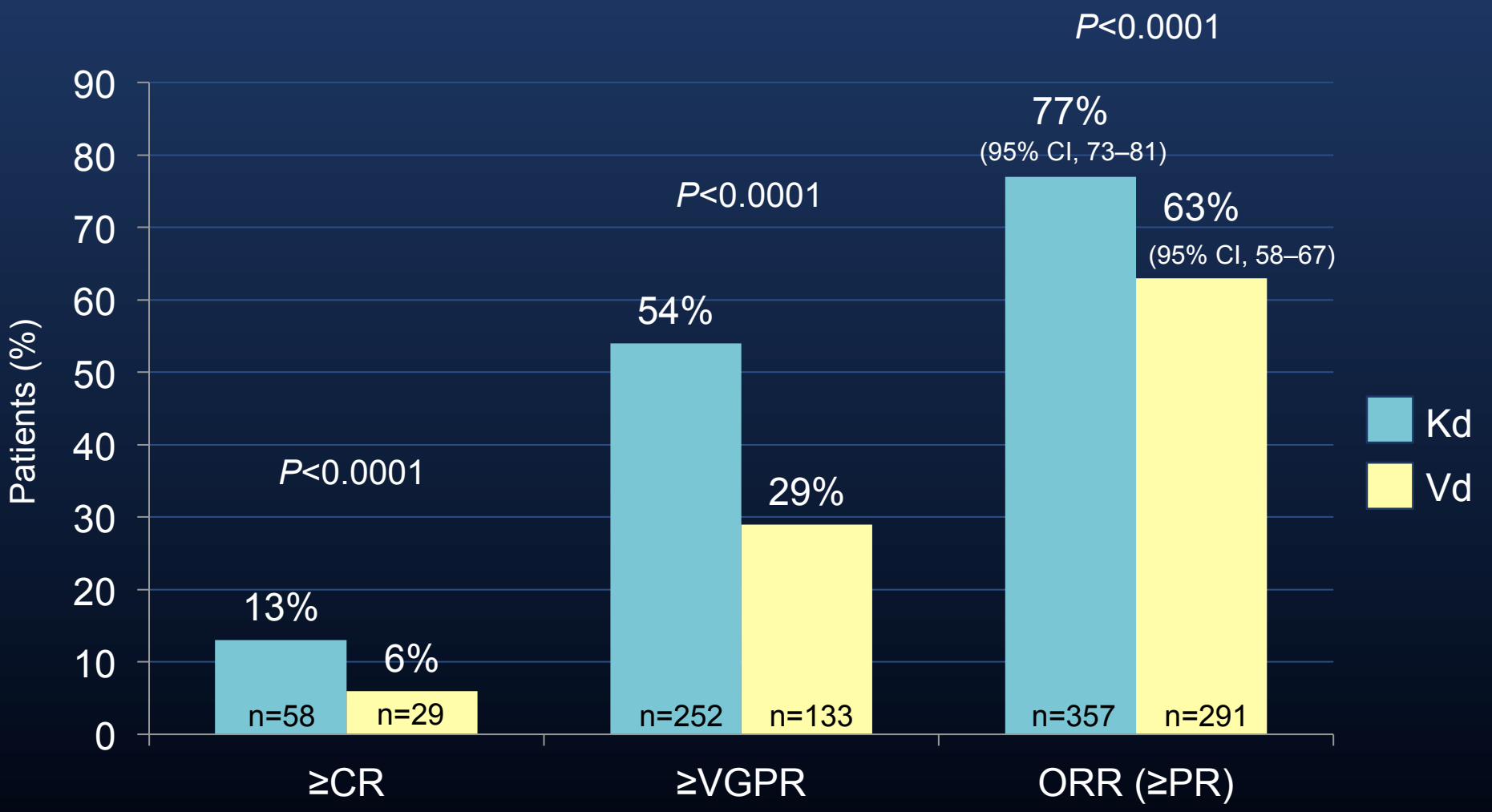
Primary End Point: Progression-Free Survival
Intent-to-Treat Population (N=929)



- **Median follow-up: 11.2 months**

Dimopoulos D et al, Lancet Oncology 2016

Secondary End Point: Response Rates

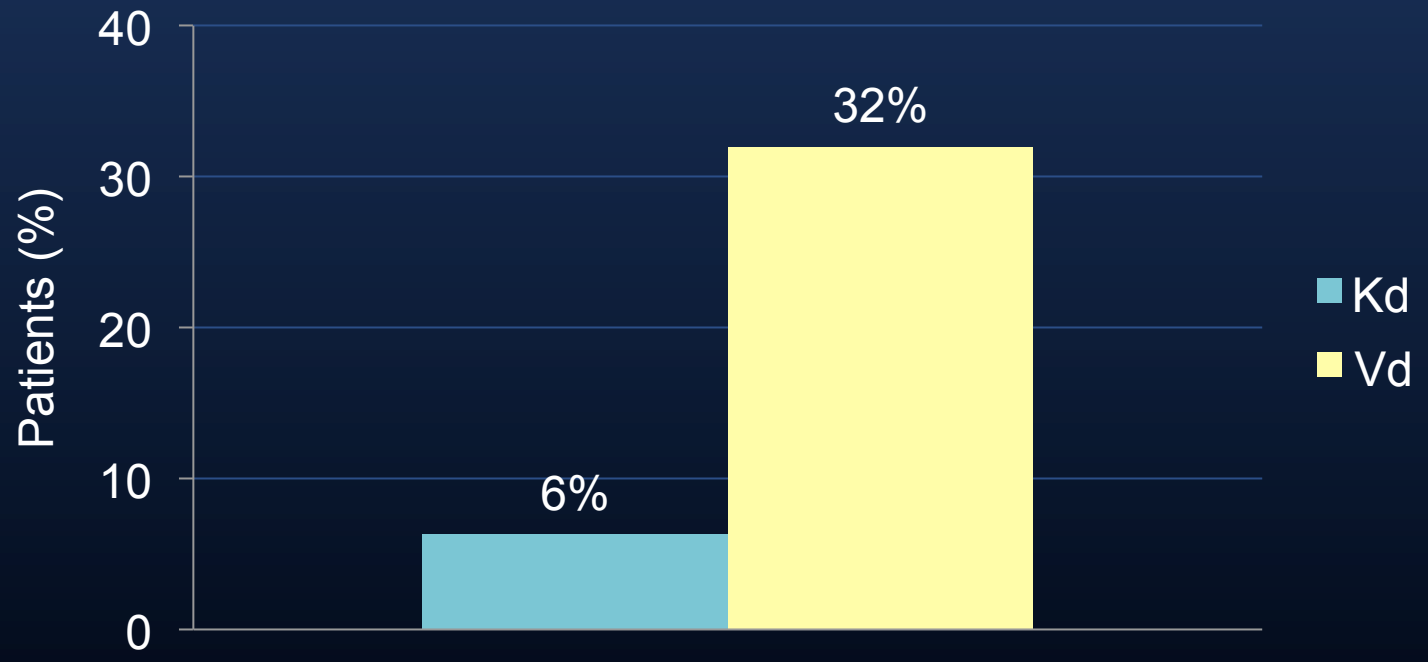


- **Median DOR: 21.3 months (95% CI, 21.3–NE) for Kd vs 10.4 months (95% CI, 9.3–13.8) for Vd**

Dimopoulos D et al, Lancet Oncology 2016

Secondary End Point: Grade ≥2 Peripheral Neuropathy*

1-sided *P*<0.0001
Odds ratio (95% CI): 0.14 (0.09–0.21)

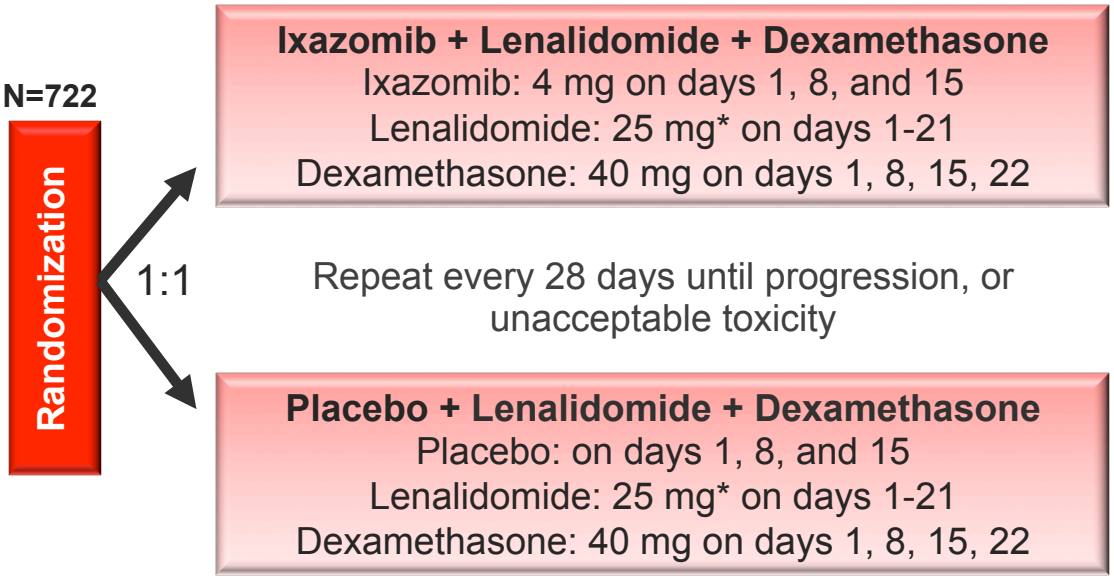


- **Among patients in the Vd group, 79% received subcutaneous bortezomib throughout their treatment**

Dimopoulos D et al, Lancet Oncology 2016

TOURMALINE-MM1: Phase 3 study of weekly oral ixazomib plus lenalidomide-dexamethasone

Global, double-blind, randomized, placebo-controlled study design



Stratification:
- Prior therapy: 1 vs 2 or 3
- ISS: I or II vs III
- PI exposure: yes vs no

Primary endpoint:
- PFS

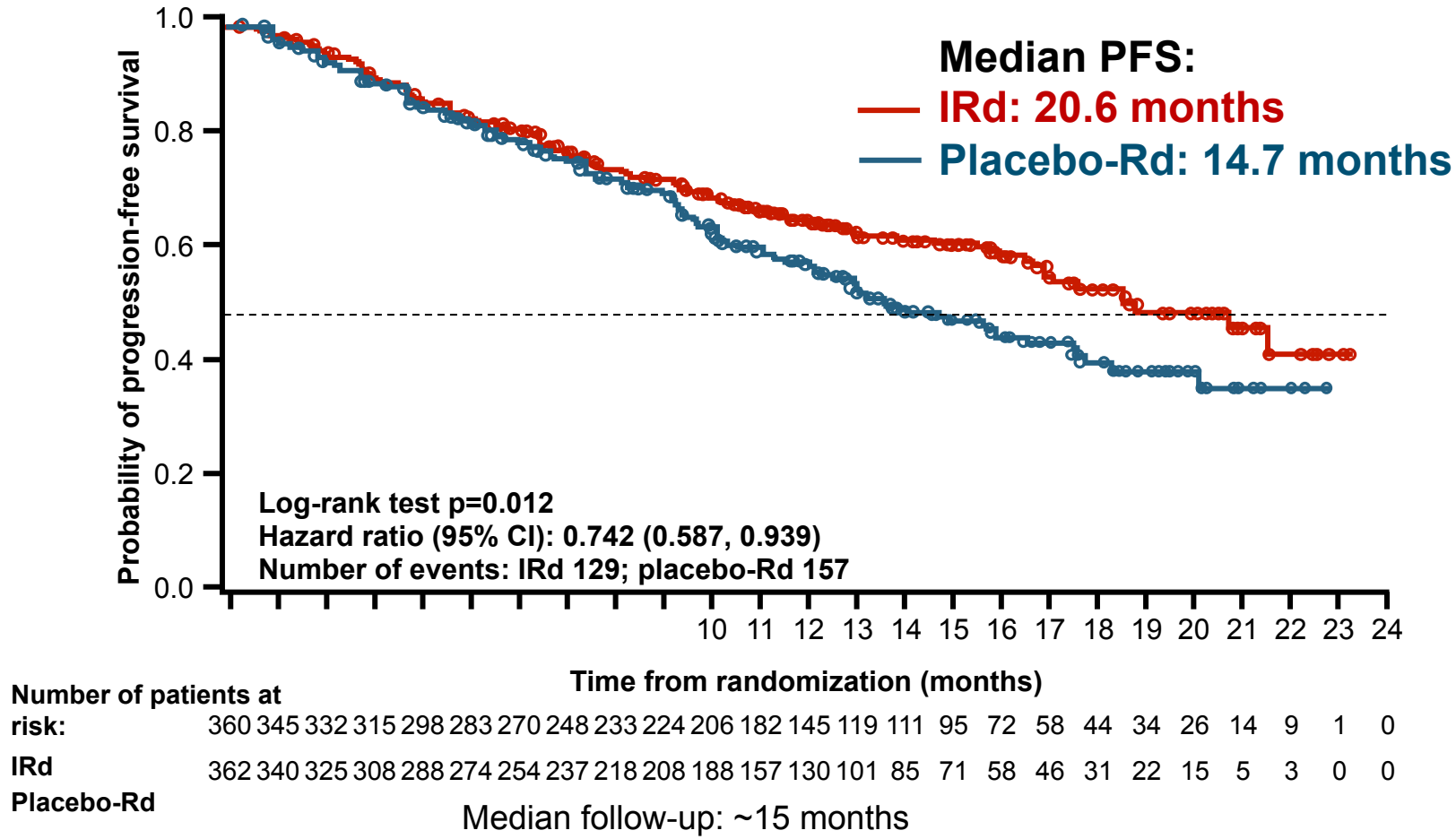
Key secondary endpoints:
- OS
- OS in patients with del(17p)

- Received 1–3 prior treatments
- Not refractory to len or bort
- 70% bort exposed, 12% lena exposed

*10 mg for patients with creatinine clearance ≤60 or ≤50 mL/min, depending on local label/practice

1. Rajkumar S, et al. Blood 2011;117:4691–5.

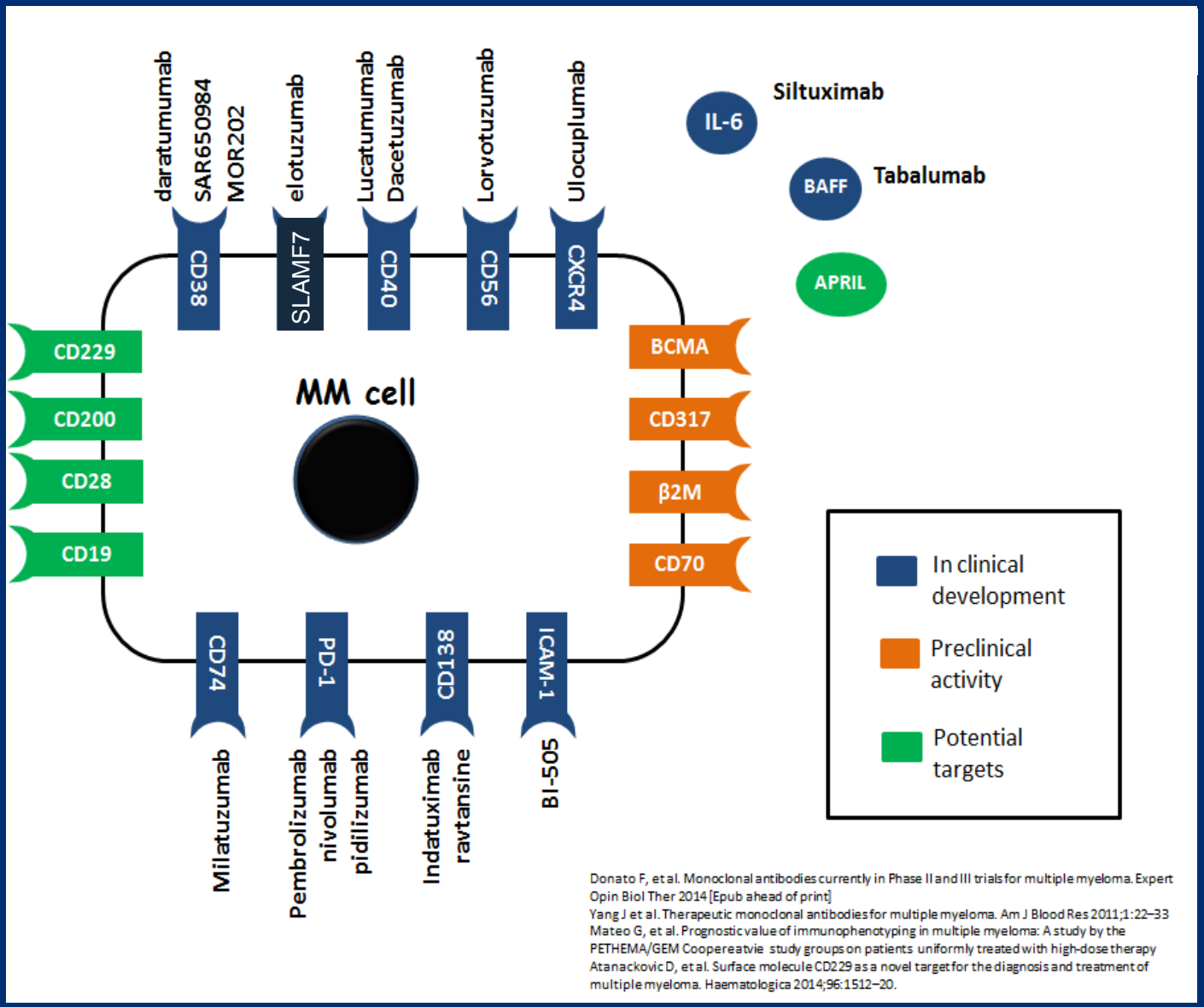
Final PFS analysis(median fup: 23 mos): A significant, 35% improvement in PFS with IRd vs placebo-Rd



Median follow-up: ~15 months

Moreau P et al, NEJM 2016

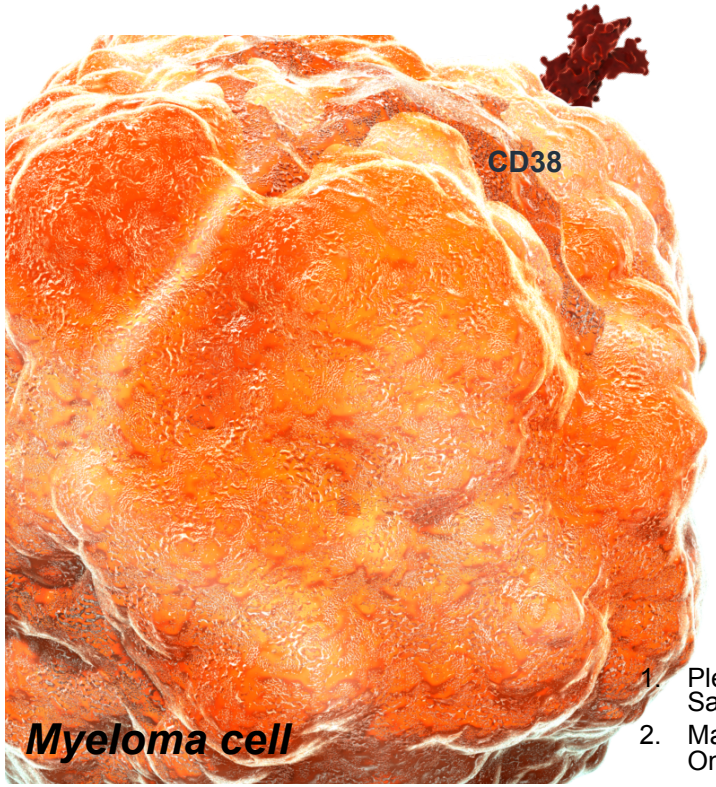
Targets for mAbs



Lonial S et al, Leukemia 2015

Ongoing Research Into Tumor-Directed Antibody Therapy in Multiple Myeloma

Monoclonal antibodies that target an antigen expressed by myeloma cells



These antibodies bind to the surface of the myeloma cell to induce:

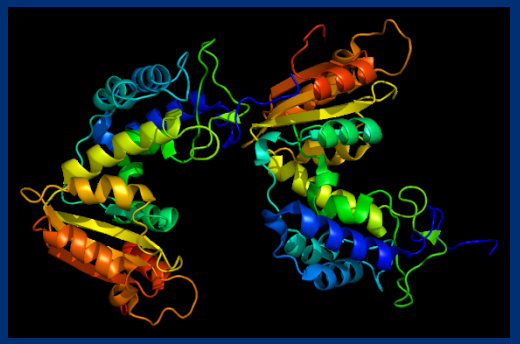
- Antibody-dependent cellular cytotoxicity (ADCC)
- Antibody-dependent cellular phagocytosis (ADCP)
- Complement-dependent cytotoxicity (CDC)
- Direct apoptosis

Tumor-Directed Antibodies	Target
Daratumumab	CD38
SAR650984 (Izatuximab)	CD38

1. Plesner et al. Abstract presented at: 56th ASH Annual Meeting and Exposition; December 6-9: San Francisco, CA. Abstract 84.
2. Martin et al. Abstract presented at: 50th Annual Meeting of the American Society of Clinical Oncology, May 30–June 3, 2014. Abstract 8512.

CD38 as a Target

- Type II transmembrane glycoprotein which is highly expressed in MM
- Enzymatic activities include cADPR and NAADP production that are needed for calcium signaling and regulation
- As an antigen, responsible for regulation of adhesion, proliferation, and differentiation



Malavasi et al. *Physiol Rev* 2008
Lonial S et al, Leukemia 2015

Distribution of human CD38

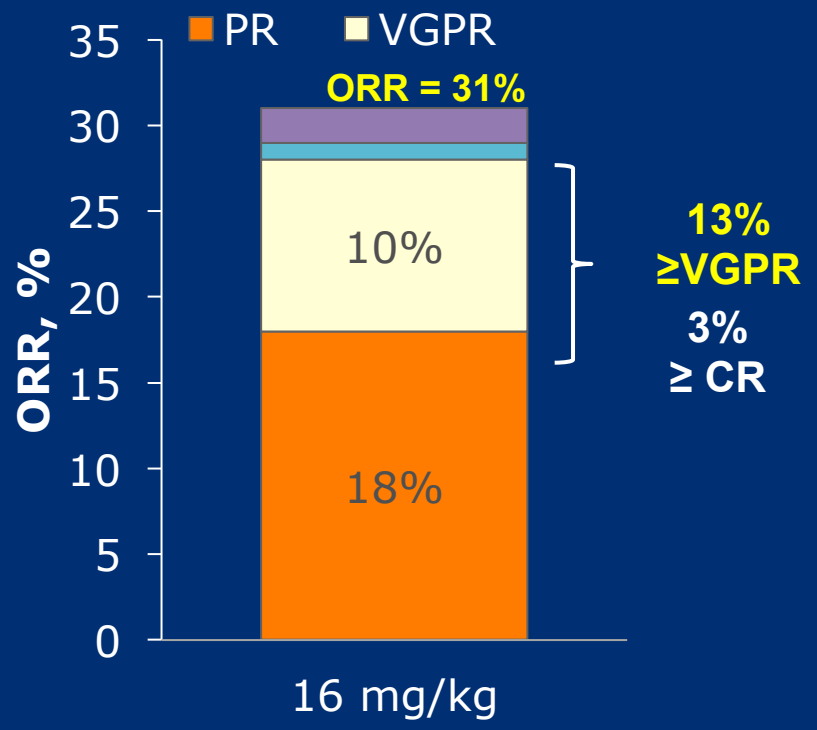
Tissue	Cell population
Lymphoid	
Blood	T-cells (precursors, activated) B-cells (precursors, activated) Myeloid cells (monocytes, macrophages, dendritic cells) NK cells Erythrocytes Platelets
Bone marrow	Precursors (very early CD34+ cells are CD38-) Plasma cells
Cord blood	T and B lymphocytes, monocytes
Thymus	Cortical thymocytes
Lymph nodes	Germinal center B cells
Non-lymphoid	
Bone	Osteoclasts
Brain	Purkinje cells Neurofibrillary tangles
Eye	Cornea Retinal ganglia cells
Gut	Intraepithelial lymphocytes *Lamina propria* lymphocytes
Pancreas	β-cells
Muscle	Sarcolemma (smooth and striated muscle)
Prostate	Epithelial cells
Kidney	Glomeruli

- CD38 expression is low on most mature lymphoid and myeloid cells[1]
- CD38 is not expressed on pluripotent hematopoietic precursor cells, which are crucial to long-term bone marrow recovery[2-3]

1. Malavasi F, et al. *Physiol Rev* 2008; 88: 841–886; 2. Theilgaard-Monck, et al. *Bone Marrow Transplant* 2003; 32: 1125–1133; 3. Terstappen, et al. *Blood* 1991; 77: 1218–1227

DARATUMUMAB in heavily pre-treated patients: Combined Analysis of GEN501 and SIRIUS trials

	16 mg/kg (N = 148)	
	n (%)	95% CI
ORR (sCR+CR+VGPR +PR)	46 (31)	23.7-39 .2
Best response		
sCR	3 (2)	0.4-5.8
CR	2 (1)	0.2-4.8
VGPR	14 (10)	5.3-15. 4
PR	27 (18)	12.4-25 .4
MR	9 (6)	2.8-11. 2
SD	68 (46)	37.7-54 .3
PD	18 (12)	7.4-18. 5
NE	7 (5)	1.9-9.5
VGPR or better (sCR +CR+VGPR)	19 (13)	7.9-19. 3
CR or better (sCR +CR)	5 (3)	1.1-7.7

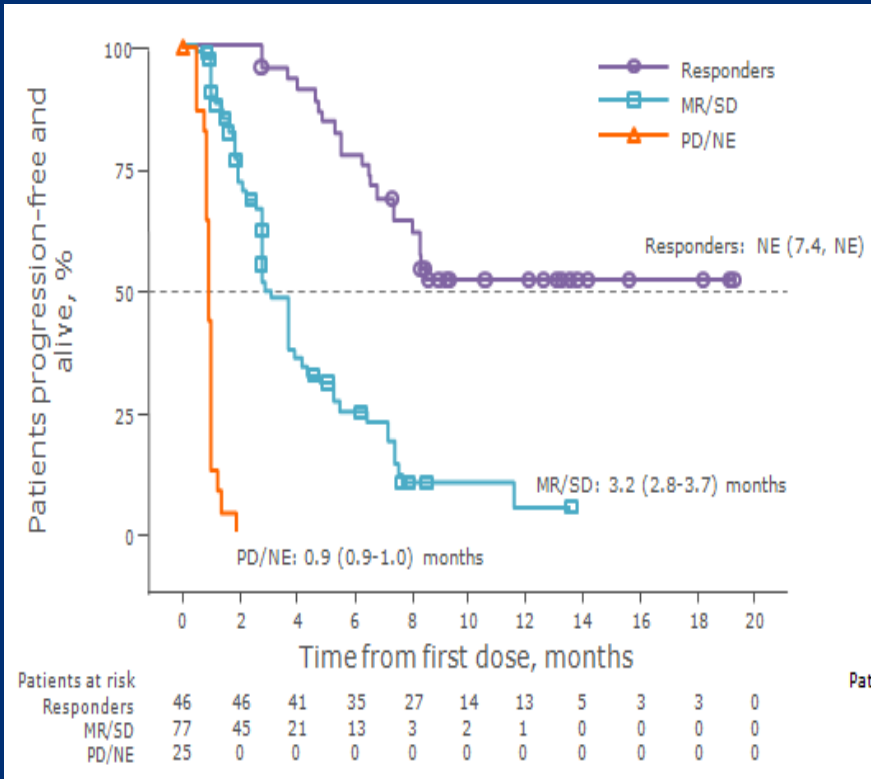


- ORR = 31%
- ORR was consistent in subgroups including age, number of prior lines of therapy, refractory status, c renal function

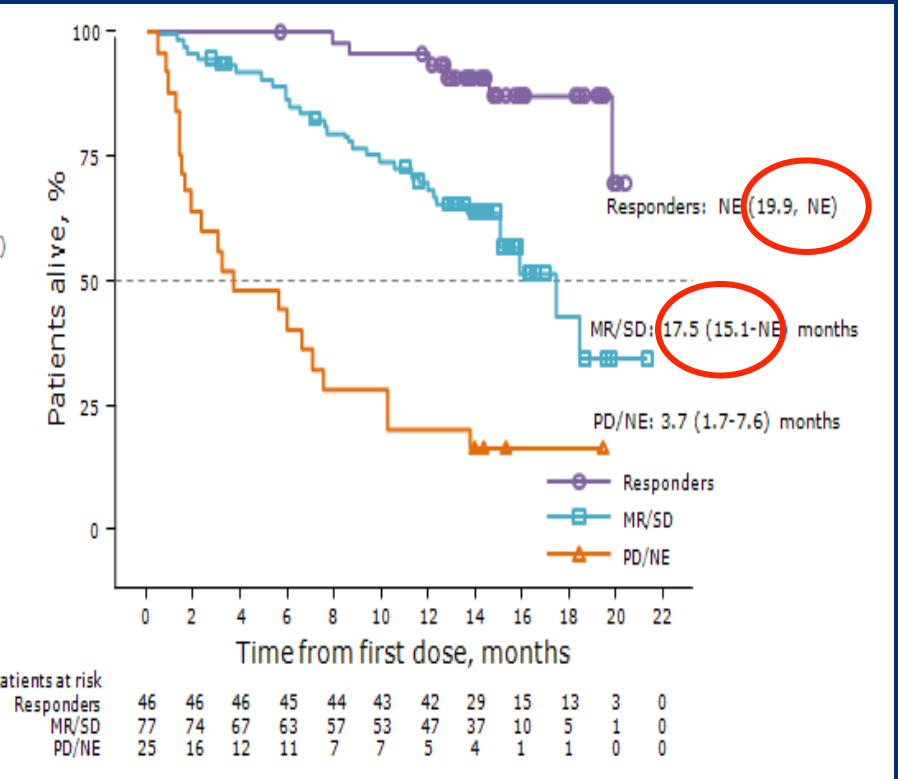
Usmani S et al, Blood 2016

GEN501 and SIRIUS (MMY2002) Combined Analysis

Progression-free Survival



Overall Survival



- **For the combined analysis, median OS = 19.9 (95% CI, 15.1-NE) months**
- **1-year overall survival rate = 69% (95% CI, 60.4-75.6)**

Usmani S et al, Blood 2016

GEN501 and SIRIUS (MMY2002) Combined Analysis: Summary of Clinical Safety

TEAE, n (%)	Any grade N = 148	Grade ≥3 N = 148
Fatigue	61 (41)	3 (2)
Nausea	42 (28)	0
Anemia	41 (28)	26 (18)
Back pain	36 (24)	3 (2)
Cough	33 (22)	0
Neutropenia	30 (20)	15 (10)
Thrombocytopenia	30 (20)	21 (14)
Upper respiratory tract infection	30 (20)	1 (<1)

- AEs were consistent with the individual GEN501 and SIRIUS studies; no new safety signals were identified
- 48% of patients had IRRs
  - 46%, 4%, and 3% occurred during the first, second, and subsequent infusions, respectively

Usmani S et al, Blood 2016

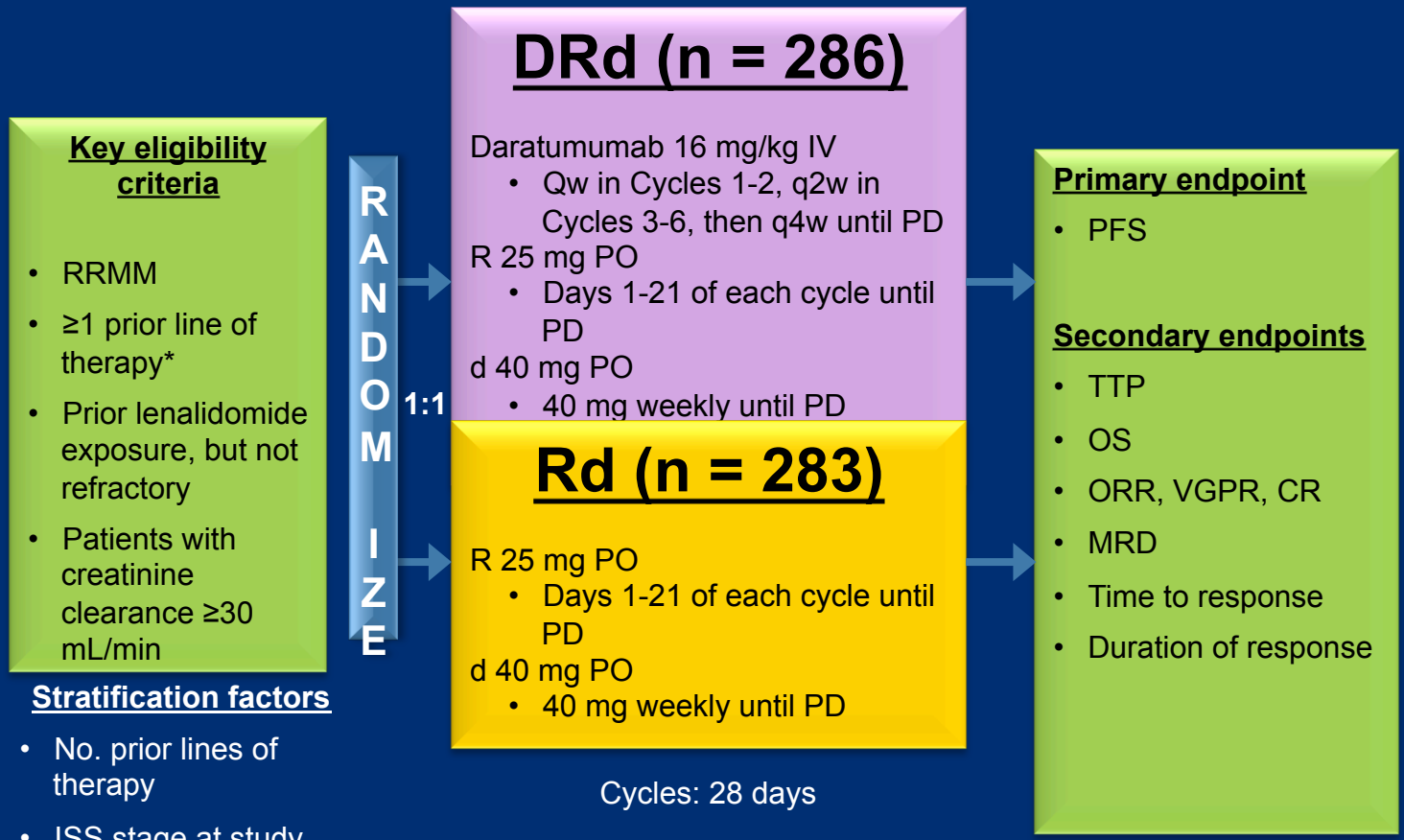
Tolerability

- **Most AEs grade 1 or 2**
  - Most common (≥ 25% of pts): **fatigue, allergic rhinitis, pyrexia**
  - Nasopharyngitis 24%, cough 21%
- **Grade 3 or 4 AEs:**
  - 53% in 8mg/kg group and **26% in 16 mg/kg group**
  - In ≥ 2 patients: pneumonia (5 pts), thrombocytopenia (4 pts), neutropenia, leukopenia, anemia, hyperglycemia (2 each)
- **Infusion-related reactions:**
  - **71% (all grade 1/2, except 1 grade 3)**
  - Mostly during **first infusion** (only 8% in subsequent infusions)
  - No discontinuation

Lokhorst et al. N Engl J Med 2015

POLLUX: Study Design

Multicenter, randomized (1:1), open-label, active-controlled phase 3 study



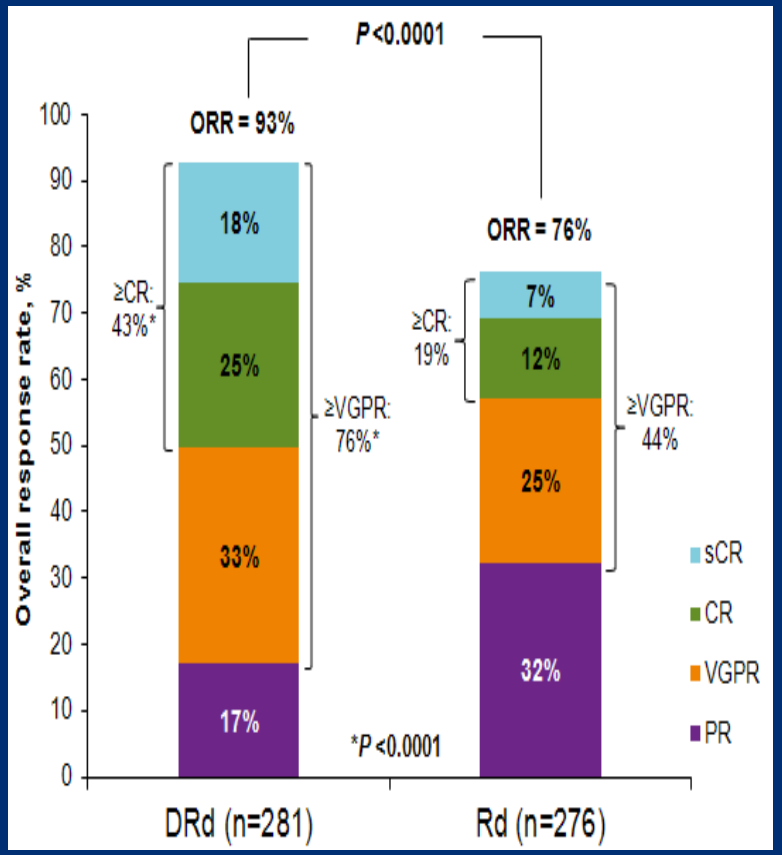
Pre-medication for the DRd treatment group consisted of dexamethasone 20 mg[a], paracetamol, and an antihistamine

[a]On daratumumab dosing days, dexamethasone was administered 20 mg premed on Day 1 and 20 mg on Day 2; RRMM, relapsed or refractory multiple myeloma; ISS, international staging system; R, lenalidomide; DRd, daratumumab/lenalidomide/dexamethasone; IV, intravenous; qw, once weekly; q2w, every 2 weeks; q4w, every 4 weeks; PD, progressive disease; PO, oral; d, dexamethasone; Rd, lenalidomide/dexamethasone; TTP, time to progression; MRD, minimal-residual disease.* around 90% of pts 1-3 prior lines

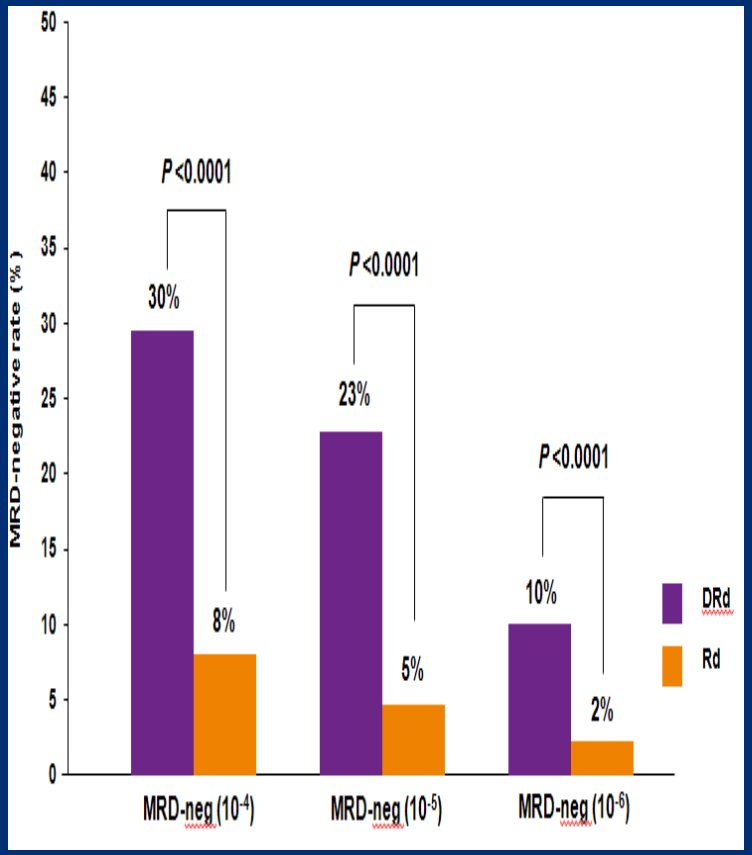
Dimopoulus MA et al. NEJM 2016

POLLUX: Study Design

Overall response rate



MRD negative rate



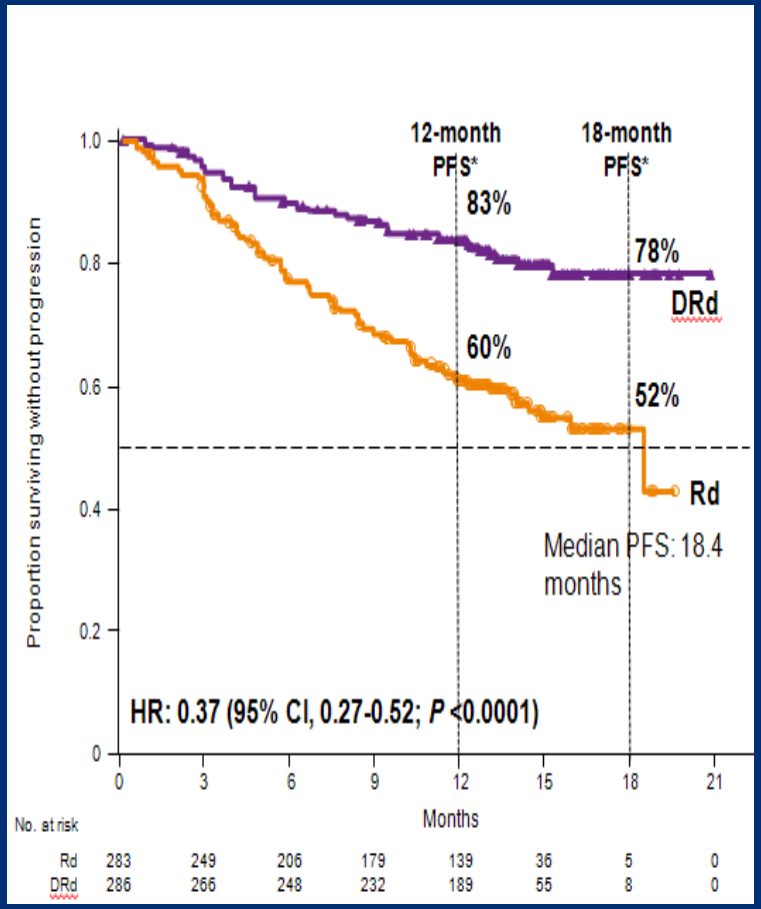
- Median duration of response: Not reached for DRd vs 17.4 months for Rd
- Median time to response: 1.0 month for DRd vs 1.3 months for Rd

Significantly higher MRD-negative rates for DRd vs Rd

Dimopoulus MA et al. NEJM 2016

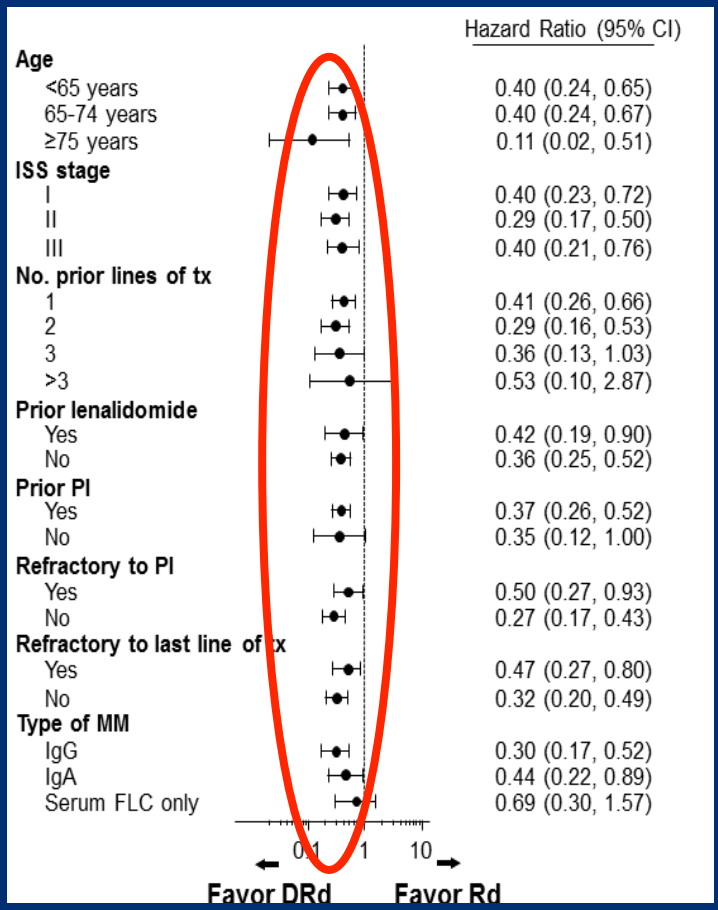
POLLUX: Study Design

Progression-free Survival (PFS)



63% reduction in the risk of disease progression or death for DRd vs Rd

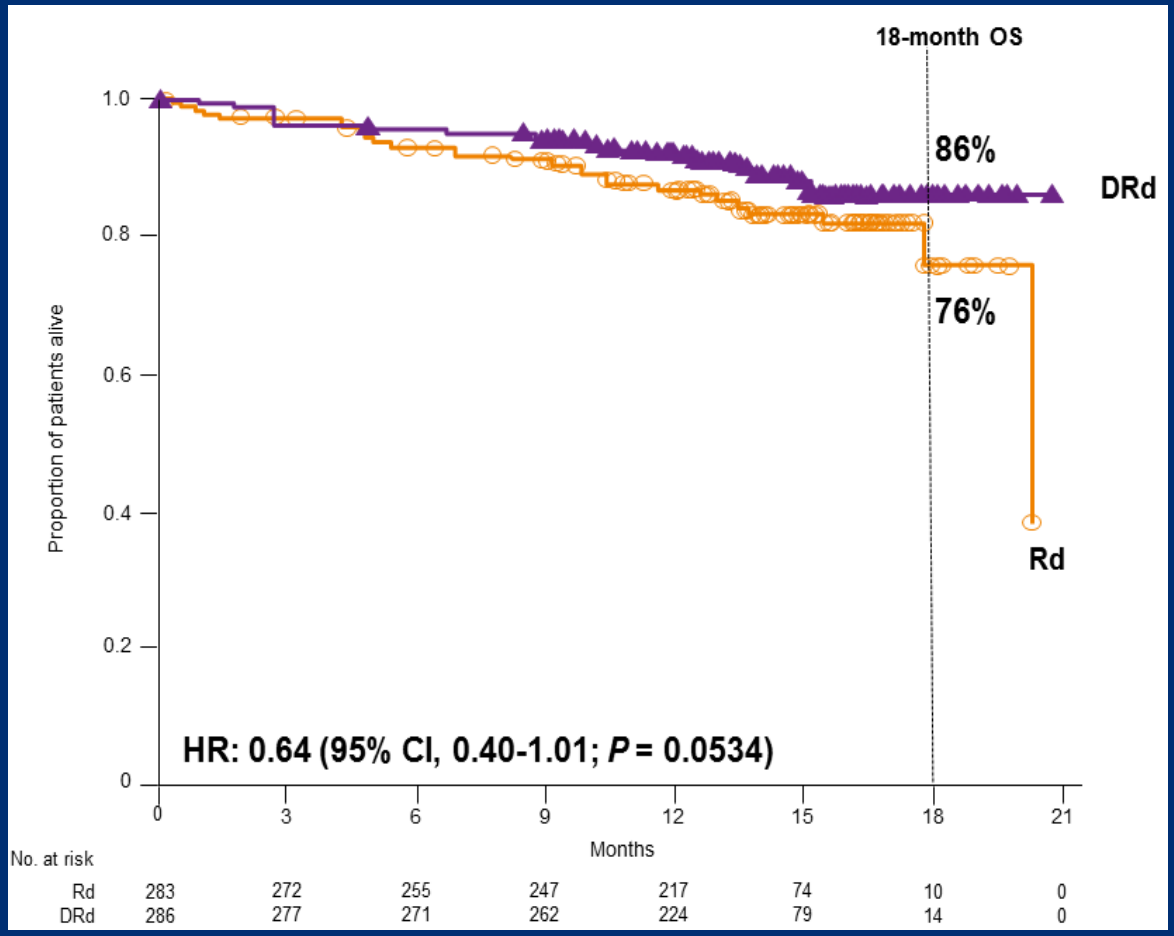
PFS: Subgroup analysis



Higher efficacy was observed for DRd versus Rd across all subgroups

Dimopoulus MA et al. NEJM 2016

Overall Survival

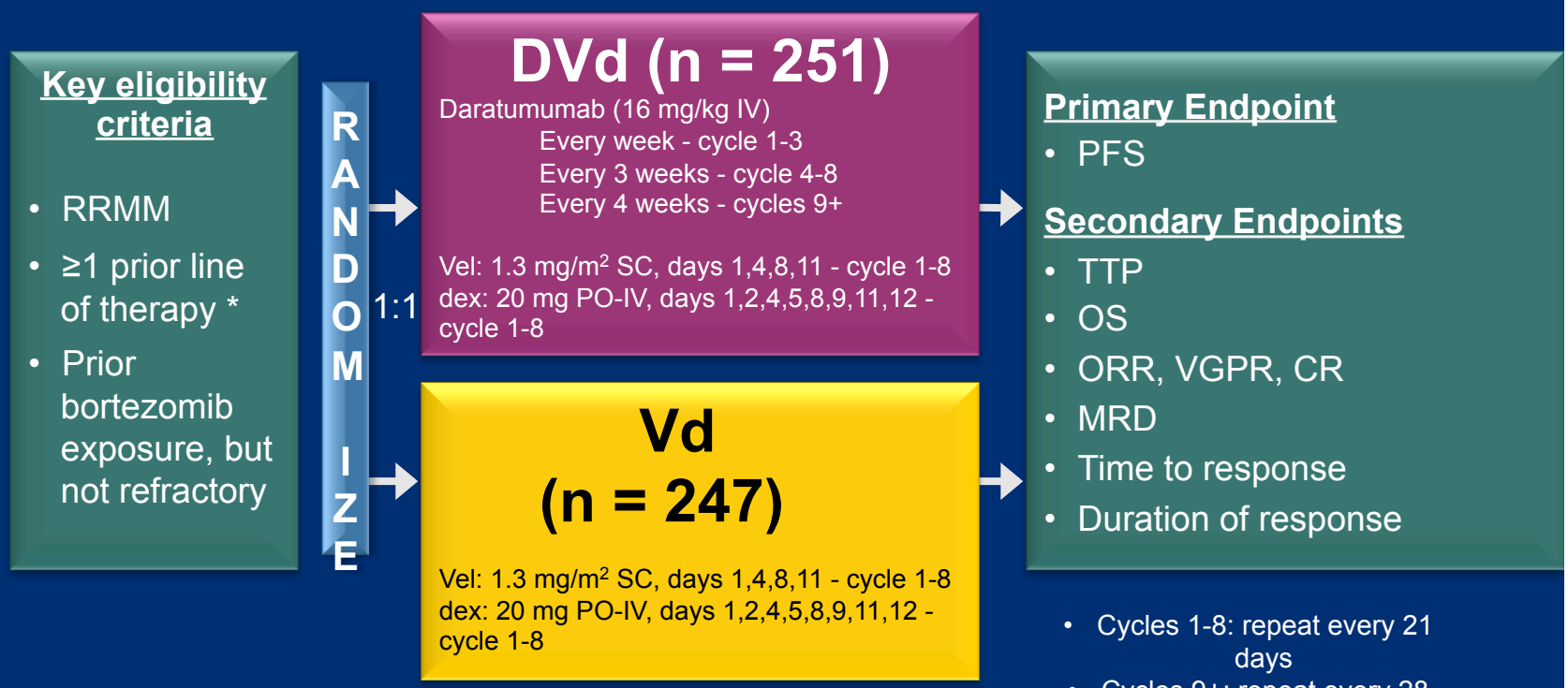


18-month overall survival: 86% in DRd versus 76% in Rd

Dimopoulus MA et al. NEJM 2016

CASTOR: Study Design

Multicenter, randomized, open-label, active-controlled phase 3 study



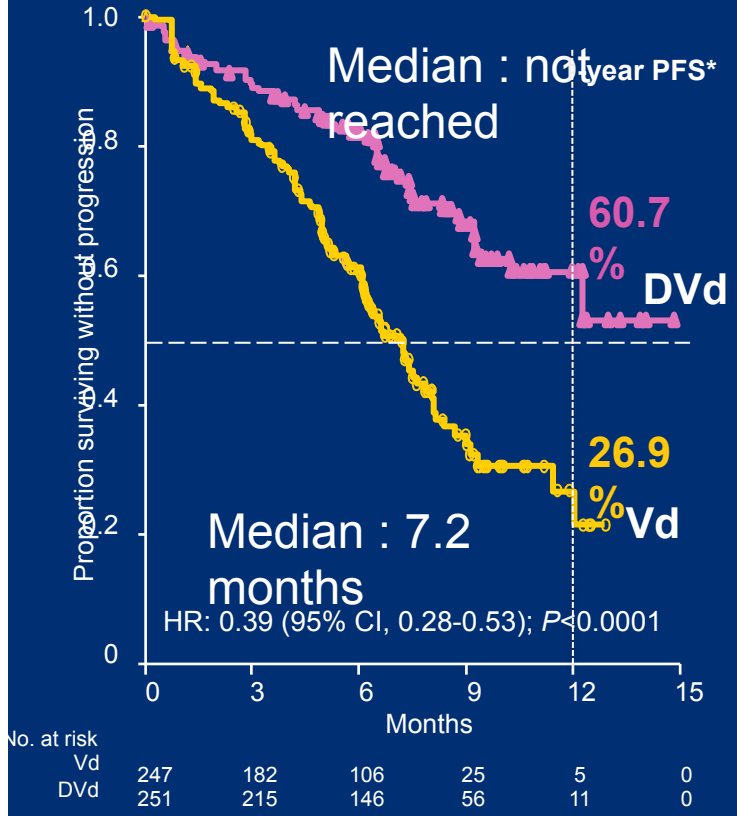
Daratumumab IV administered in 1000 mL to 500 mL; gradual escalation from 50 mL to 200 mL/min permitted

*90% 1-3 prior line of therapy; RRMM, relapsed or refractory multiple myeloma; DVd, daratumumab/bortezomib/dexamethasone; IV, intravenous; Vel, bortezomib; SC, subcutaneous; dex, dexamethasone; PO, oral; Vd, bortezomib/dexamethasone; PFS, progression-free survival; TTP, time to progression; ORR, overall response rate; VGPR, very good partial response; CR, complete response; MRD, minimal residual disease.

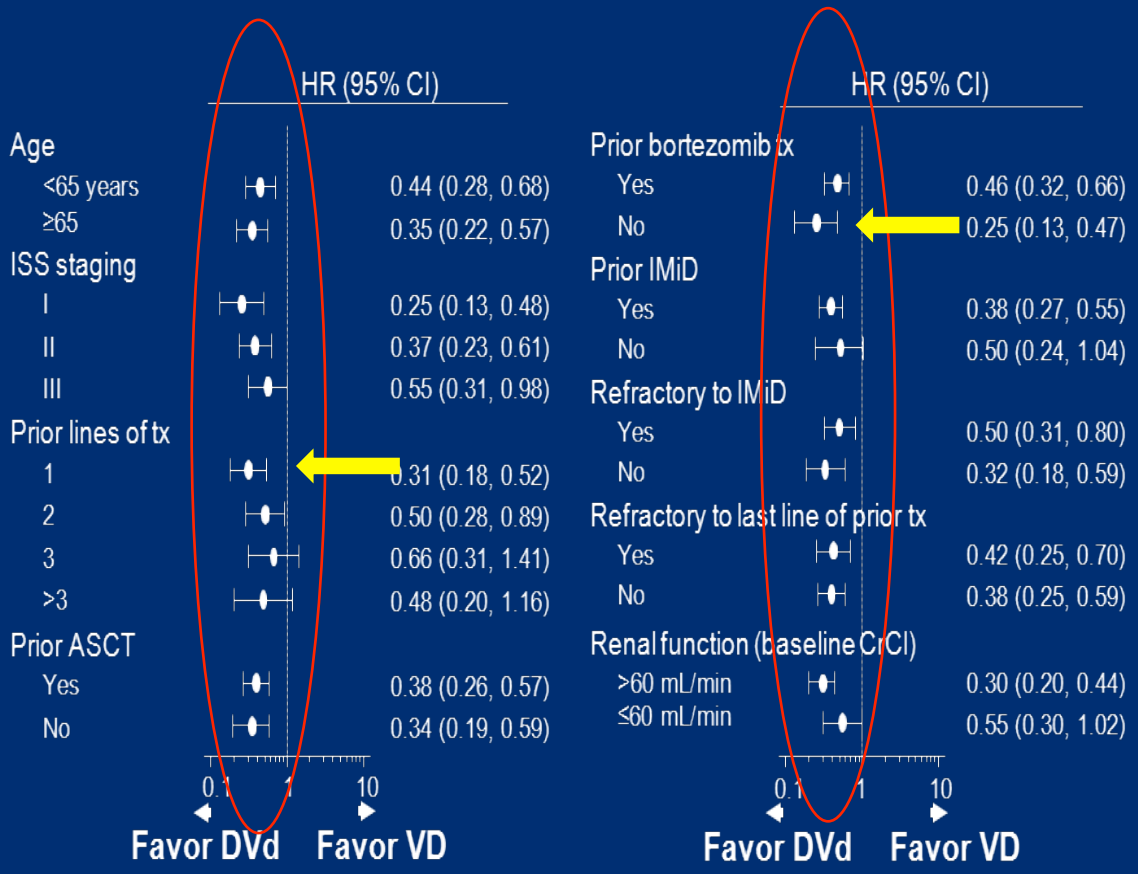
Palumbo A et al. NEJM 2016

CASTOR: Study Design

Progression-free Survival (PFS)



PFS: subgroup analysis

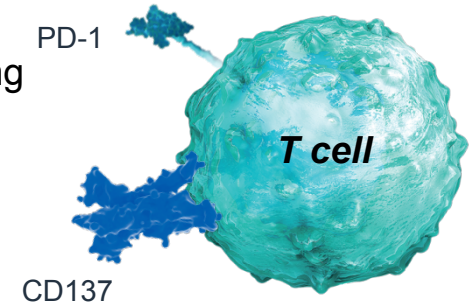


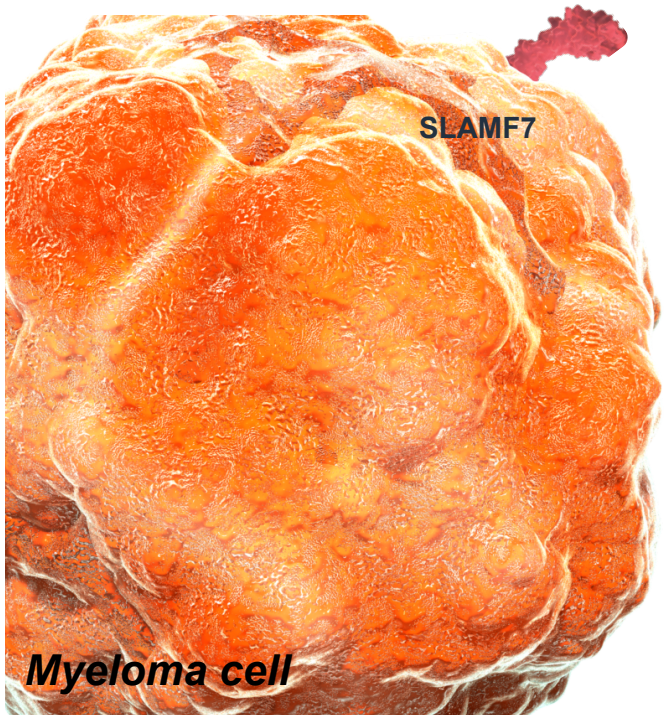
61% reduction in the risk of disease progression or death for DVd vs Vd

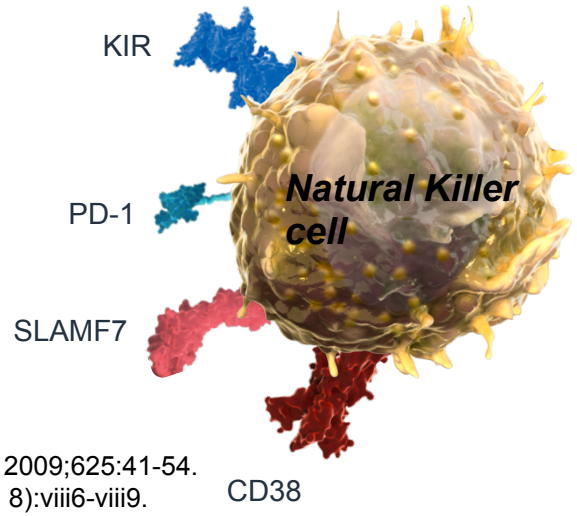
Palumbo A et al. NEJM 2016

Ongoing Immuno-Oncology Research in Multiple Myeloma

- Immuno-oncology (I-O) is a modality under investigation for its potential to harness the body's own immune system to help fight cancer
  - I-O therapies can activate immune effector cells to induce myeloma cell death by engaging activation pathways or blocking inhibitory pathways
  - Additionally, if the target is also expressed on myeloma cells, I-O therapies can recruit immune effector cells via ADCC
  - Pathways under investigation include SLAMF7, CD137, KIR, and PD-1

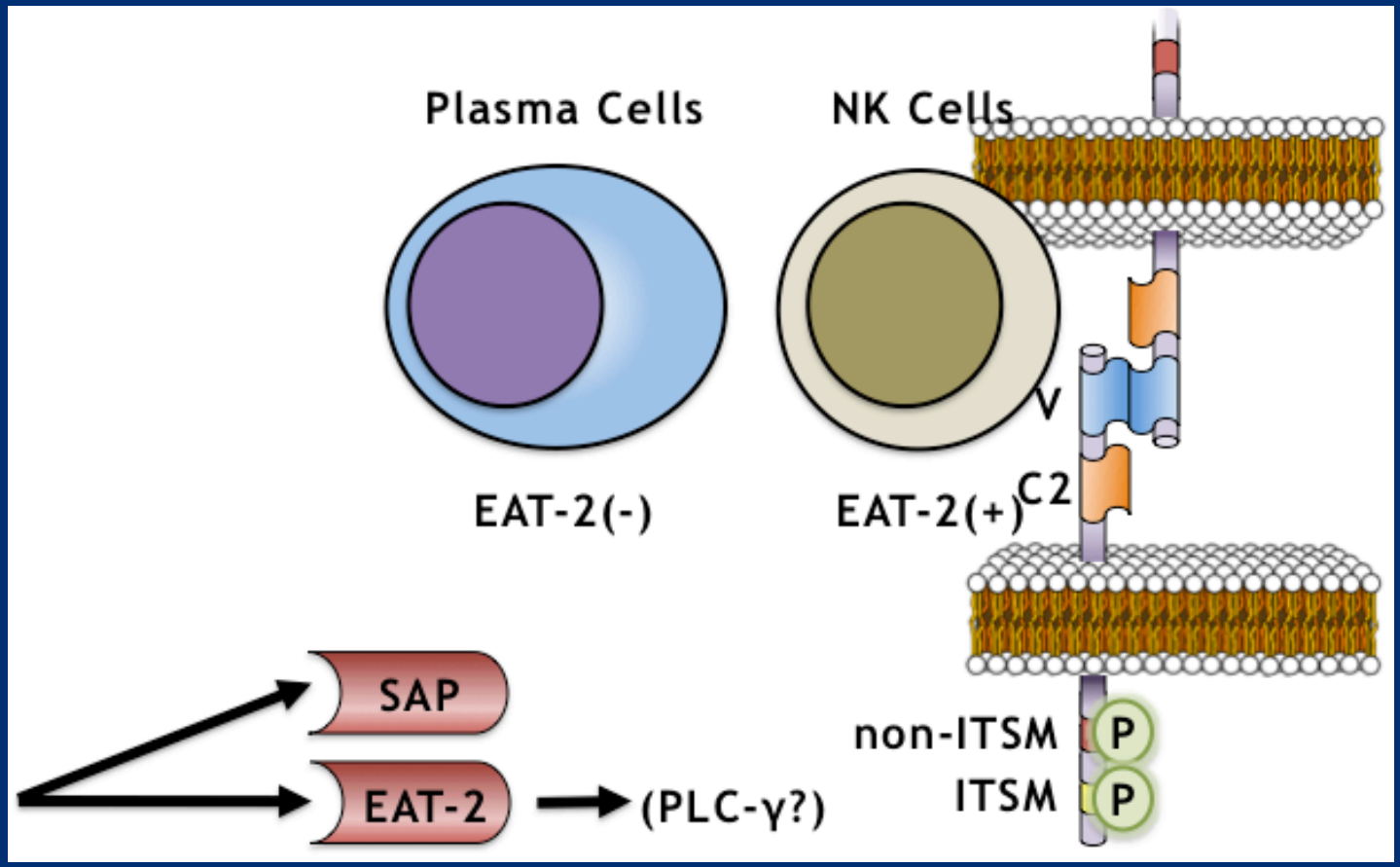






1. Borghaei H et al. *Eur J Pharmacol*. 2009;625:41-54.
2. Finn OJ. *Ann Oncol*. 2012;23(suppl 8):viii6-viii9.
3. Long EO et al. *Annu Rev Immunol*. 2013;13:227–258

SLAMF7 as a target: dual mechanism of action



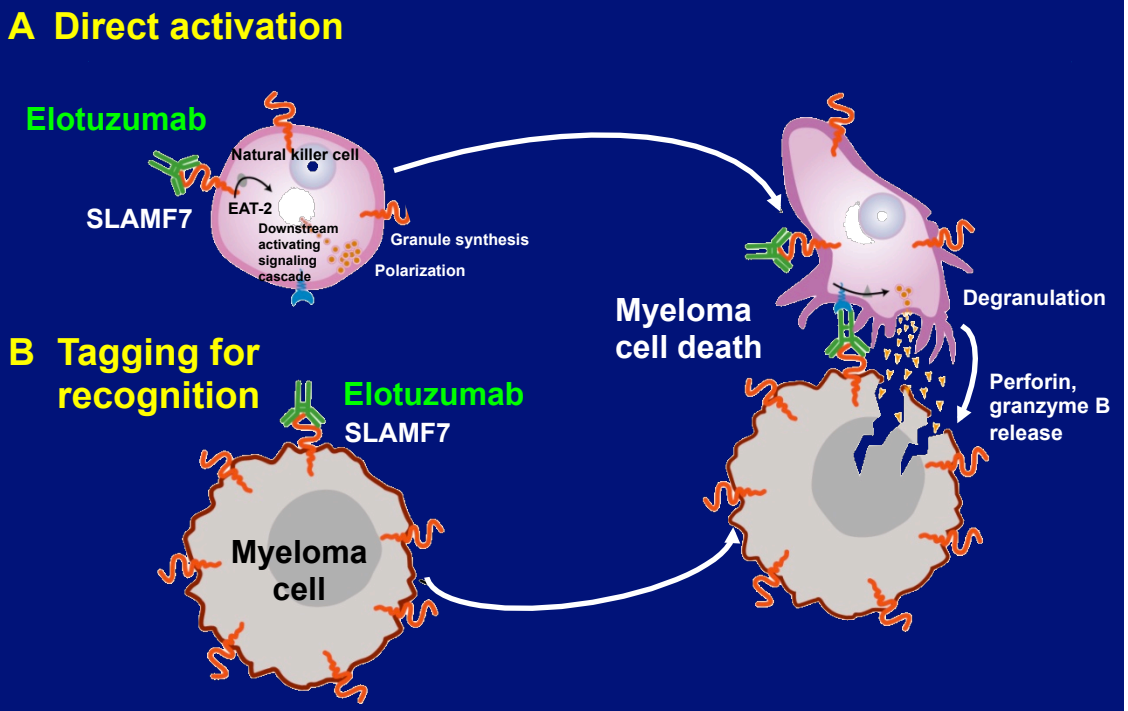
- **SLAMF7** is a glycoprotein highly expressed on >95% of **myeloma cells**
- It shows lower expression on **NK cells (activatory action)** and little to no expression on normal tissues or hematopoietic stem cells

Adapted from Guo et al, *Mol Cell Biol* 2015

Dual Mechanism of Action of Elotuzumab

- Humanized IgG1 immunostimulatory monoclonal antibody targeted against SLAMF7

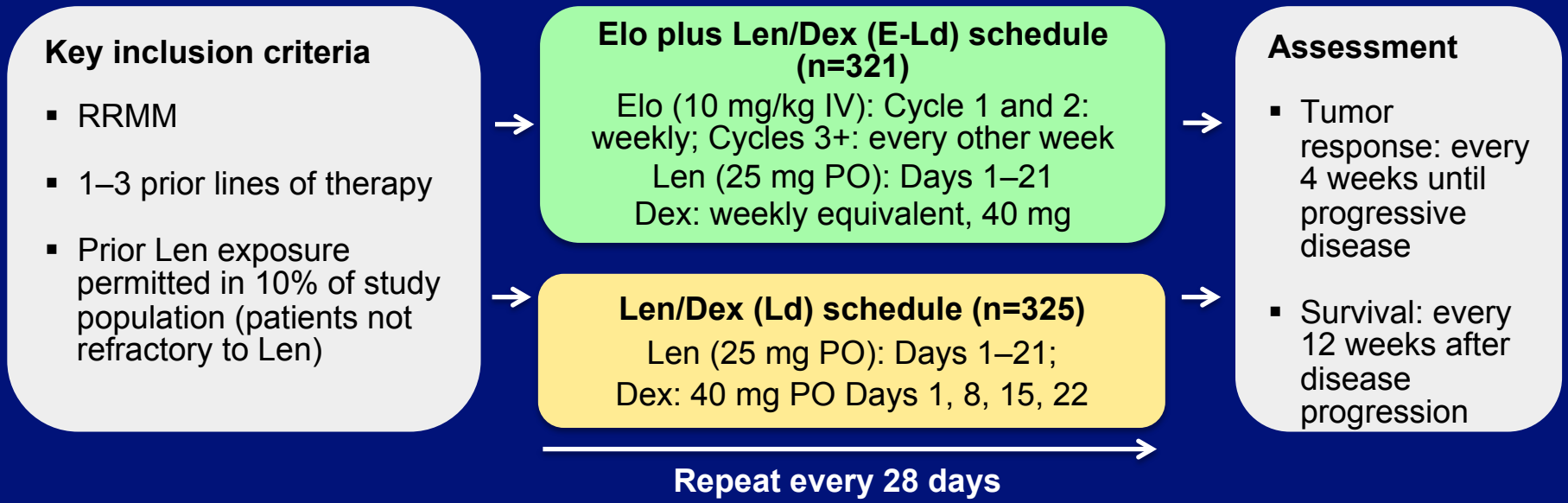
- **A: Direct activation**
  Binding to SLAMF7 directly activates natural killer cells,[2] but not myeloma cells[3]
- **B: Tagging for recognition**
  Elotuzumab activates natural killer cells via CD16, enabling selective killing of myeloma cells via antibody-dependent cellular cytotoxicity (ADCC) with minimal effects on normal tissue[2]



1. Hsi ED et al. *Clin Cancer Res* 2008;14:2775–84
2. Collins SM et al. *Cancer Immunol Immunother* 2013;62:1841–9
3. Guo H et al. *Mol Cell Biol* 2015;35:41–51

SLAMF7 = Signaling Lymphocyte Activation Molecule-F7

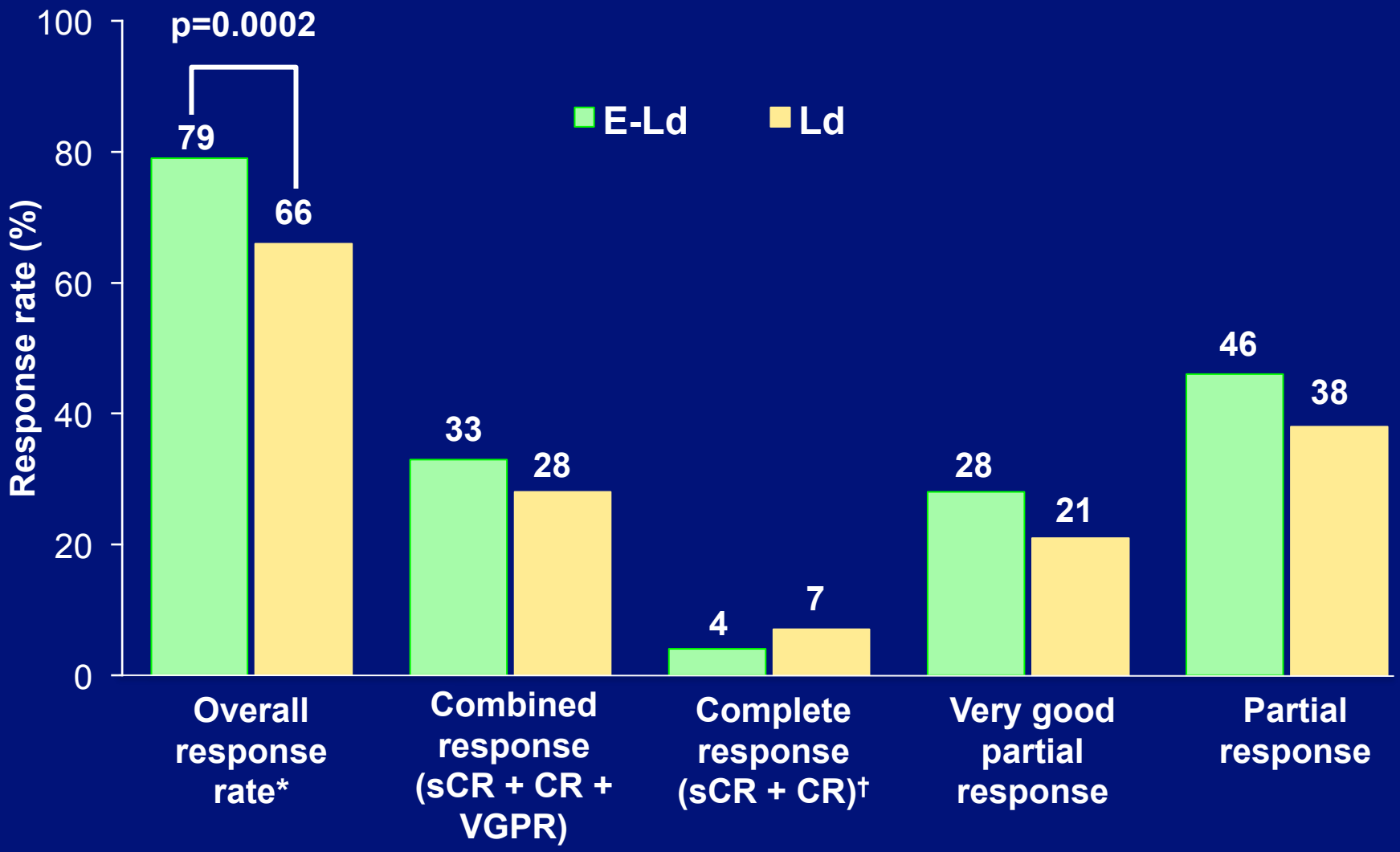
ELOQUENT-2: Elo-Ld vs Ld in R/R MM



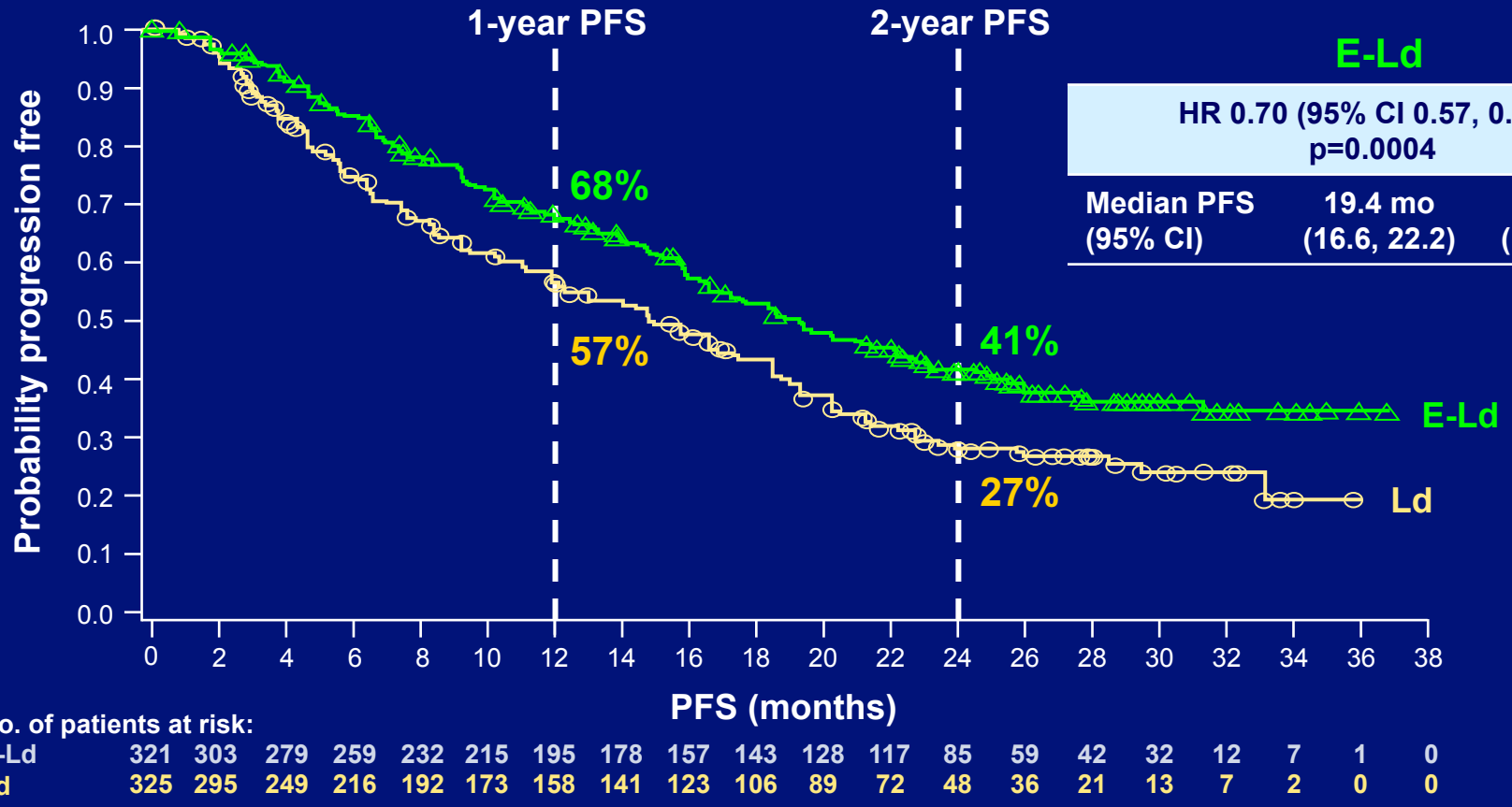
- **Open-label, international, randomized, multicenter, phase 3 trial (168 global sites)**
- **Median n° treatment cycles Elo Ld: 19 (1-42)**
- **83% pts received more than 90% dose intensity**

Lonial S et al, NEJM 2015

Co-primary Endpoint: Overall Response Rate



Co-primary Endpoint: Progression-Free Survival



	E-Ld	Ld
HR 0.70 (95% CI 0.57, 0.85); p=0.0004		
Median PFS (95% CI)	19.4 mo (16.6, 22.2)	14.9 mo (12.1, 17.2)

No. of patients at risk:

E-Ld	321	303	279	259	232	215	195	178	157	143	128	117	85	59	42	32	12	7	1	0
Ld	325	295	249	216	192	173	158	141	123	106	89	72	48	36	21	13	7	2	0	0

E-Ld–treated patients had a 30% reduction in the risk of disease progression or death; treatment difference at 1 and 2 years was 11% and 14%, respectively

PFS analysis used the primary definition of PFS

Extended Progression-Free Survival

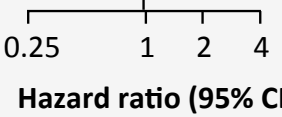
Parameter	Progression-free survival		
	E-Ld	Ld	Relative difference (%)
Median PFS (months)	**19.4**	**14.9**	
1-year PFS (%)	**68**	**57**	19
2-year PFS (%)	**41**	**28**	52
3-year PFS (%)	**26**	**18**	44
Primary analysis Hazard ratio (95% CI)	0.70 (0.57, 0.85) p=0.0004		
3-year follow-up Hazard ratio (95% CI)	0.73 (0.60, 0.89)		

Dimopoulos M et al, ASH 2015

ELOQUENT-2

Progression-Free Survival: Predefined Subgroups

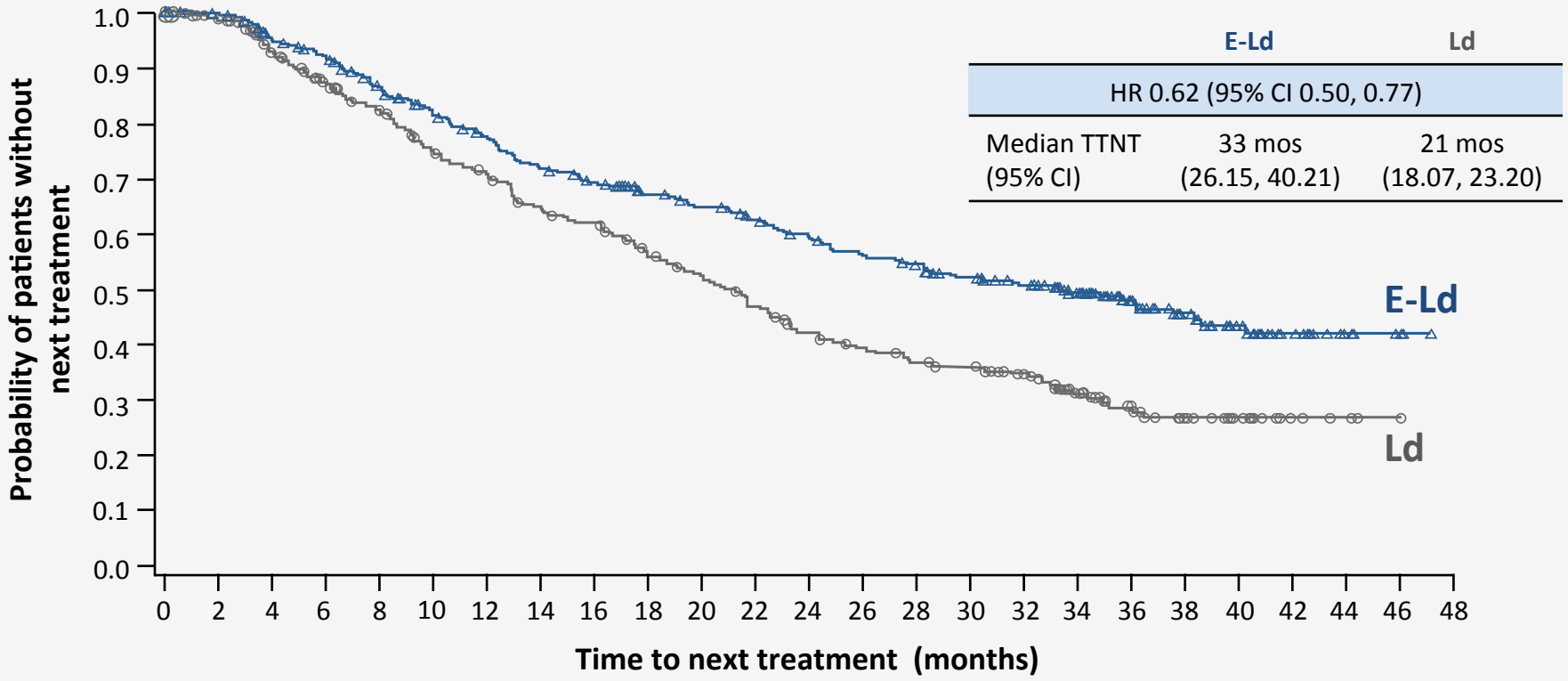
	No. of events (no. of patients)		Hazard ratio
	E-Ld	Ld	(95% CI)
Age (<75 years)	169 (253)	178 (264)	0.76 (0.62–0.94)
Age (≥75 years)	39 (68)	42 (61)	0.59 (0.38–0.91)
Age (<65 years)	86 (134)	96 (142)	0.74 (0.55–0.99)
Age (≥65 years)	122 (187)	124 (183)	0.72 (0.56–0.92)
ISS stage at enrollment (I)	83 (141)	86 (138)	0.70 (0.52–0.95)
ISS stage at enrollment (II)	69 (102)	72 (105)	0.90 (0.64–1.25)
ISS stage at enrollment (III)	52 (66)	51 (68)	0.72 (0.49–1.06)
Response to most recent line of therapy (refractory)	76 (113)	83 (114)	0.57 (0.41–0.78)
Response to most recent line of therapy (relapsed)	131 (206)	137 (211)	0.82 (0.65–1.05)
No. of lines of prior therapy (1)	98 (151)	107 (159)	0.79 (0.60–1.05)
No. of lines of prior therapy (2 or 3)	110 (170)	113 (166)	0.68 (0.52–0.88)
Prior IMiD therapy (prior thalidomide only)	100 (150)	108 (153)	0.68 (0.52–0.90)
Prior IMiD therapy (other)	10 (16)	14 (21)	0.55 (0.24–1.25)
Prior bortezomib (yes)	151 (219)	163 (231)	0.68 (0.55–0.85)
Prior bortezomib (no)	57 (102)	57 (94)	0.83 (0.58–1.21)
Prior stem cell transplant (yes)	112 (167)	129 (185)	0.73 (0.57–0.94)
Prior stem cell transplant (no)	96 (154)	91 (140)	0.74 (0.55–0.98)
del(17p) (yes)	61 (102)	67 (104)	0.70 (0.49–0.99)
t(4;14) (yes)	24 (30)	26 (31)	0.52 (0.29–0.93)



Dimopoulos M et al, ASH 2015

ELOQUENT-2

Time to Next Treatment



	E-Ld	Ld
HR 0.62 (95% CI 0.50, 0.77)		
Median TTNT (95% CI)	33 mos (26.15, 40.21)	21 mos (18.07, 23.20)

No. of patients at risk

E-Ld	321	315	294	282	259	239	225	208	198	182	174	165	153	144	138	126	118	94	65	46	32	14	6	3	0
Ld	325	305	276	251	232	206	193	174	166	148	135	120	105	96	89	85	76	46	30	20	13	5	3	1	0

E-Ld-treated patients had a median delay of 1 year in the time to next treatment vs Ld-treated patients

Dimopoulos M et al, ASH 2015

Infusion Reactions

Events, n (%)	E-Ld (n=318)		
	Grade 1/2	Grade 3	Grade 4/5
Infusion reaction	**29 (9)**	**4 (1)**	**0**
Pyrexia	10 (3)	0	0
Chills	4 (1)	0	0
Hypertension	3 (1)	1 (<1)	0

- **Infusion reactions occurred in 10% of patients**
- **70% of infusion reactions occurred with the first dose**
- **No Grade 4 or 5 infusion reactions**
- **Elotuzumab infusion was interrupted in 15 (5%) patients due to an infusion reaction (median interruption duration 25 minutes)**
- **2 (1%) patients discontinued the study due to an infusion reaction**

Cancer Cells: Evasion of Immune Response

Suppression of dendritic cell & T-cell activation and proliferation
(by cytokine production)

Downregulation of MHC class I on the surface of cancer cells to prevent Ag presentation

Upregulation of surface inhibitory ligands which mediate T-cell anergy / exhaustion
(PD-1/PD-L1 pathway)

Recruitment of counterregulatory/ immunosuppressive cells
(such as T-regs and MDSCs)

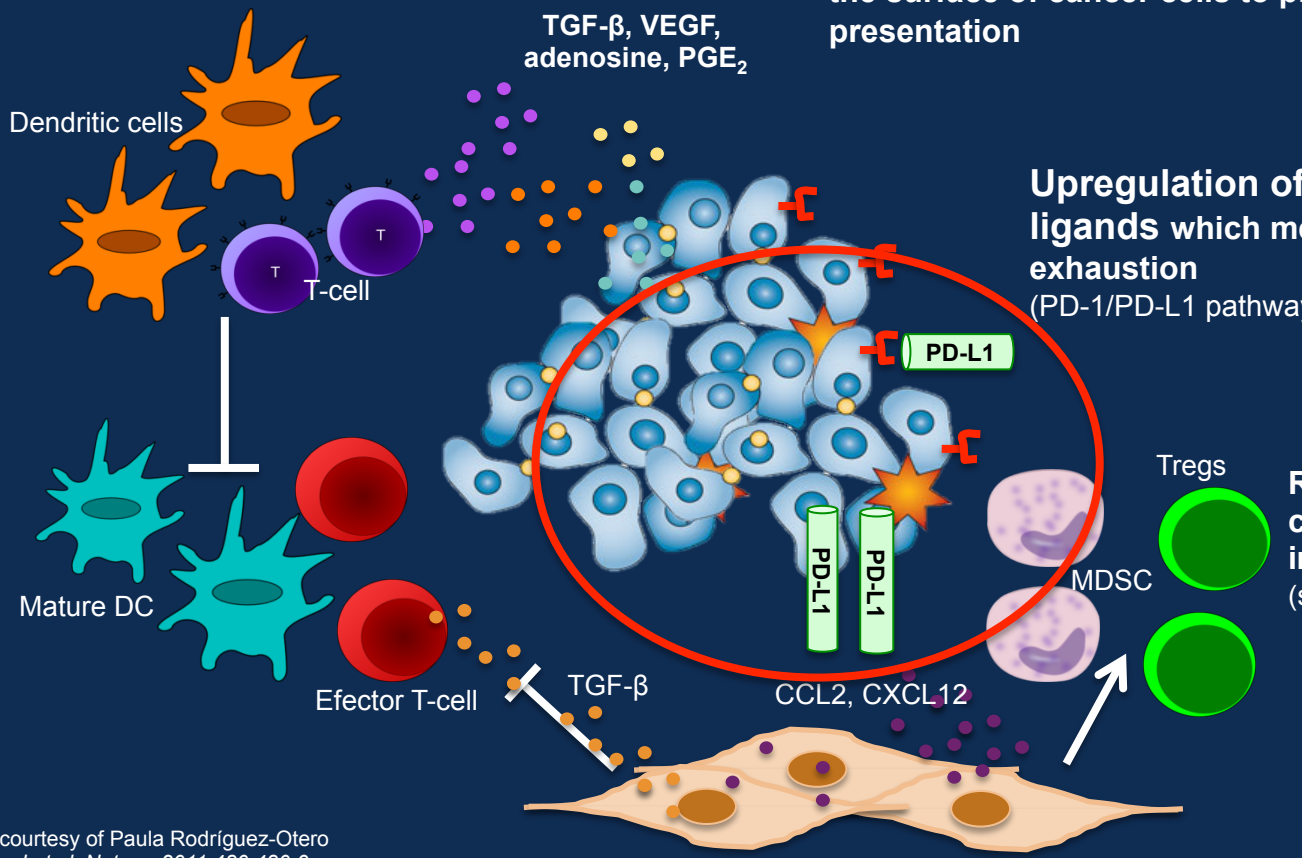
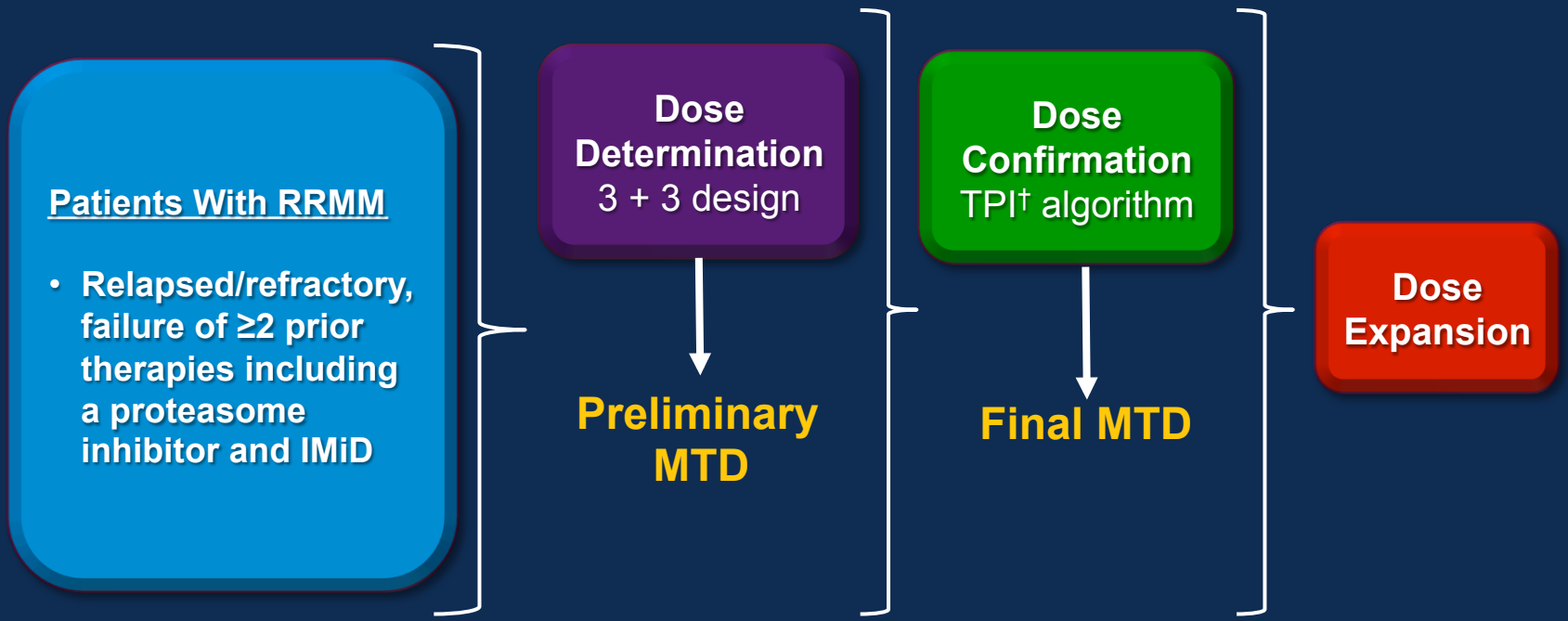


Image courtesy of Paula Rodríguez-Otero
Mellman *I et al. Nature, 2011;480:480-9.*

KEYNOTE-023: Phase 1 Trial of Pembrolizumab + Lenalidomide and Low-Dose Dexamethasone in RRMM



- Primary end points: Safety and tolerability
- Secondary end points: ORR, DOR, PFS, OS

†TPI = Toxicity Probability Interval
(Ji Y et al. *Clin Trials.* 2007;4:235-244)

Antitumor Activity
Central Review (IMWG 2006)

Best Overall Response n (%)	Efficacy Population† (n = 40)	Len-Refractory (n = 29)
Overall response rate	**20 (50)**	**11 (38)**
Stringent complete response (sCR)	1 (3)	1 (3)
Very good partial response (VGPR)	5 (13)	3 (10)
Partial response (PR)	14 (35)	7 (24)
Stable disease (SD)	19 (48)	17 (59)
Disease control rate (CR+PR+SD)	39 (98)	28 (97)
Progressive disease (PD)	1 (3)	1 (3)

†11 patients NE by central review
3 discontinued within cycle 1 for reasons other than PD (2 no treatment assessments and 1 SD by investigator)
8 inadequate myeloma data for response assessment (5 PD and 3 SD by investigator)

Treatment options for R/R MM

Transplant Eligible Patients

Bortezomib-based Induction

↓

Autologous Transplant

Transplant Inelegible Patients

VMP/MPT
Ld

FIRST RELAPSE

Second Transplant

Rd, KRd, ERd,IRd

Vd, EVd; Kd

SECOND RELAPSE

Rd,KRd,Erd,IRd

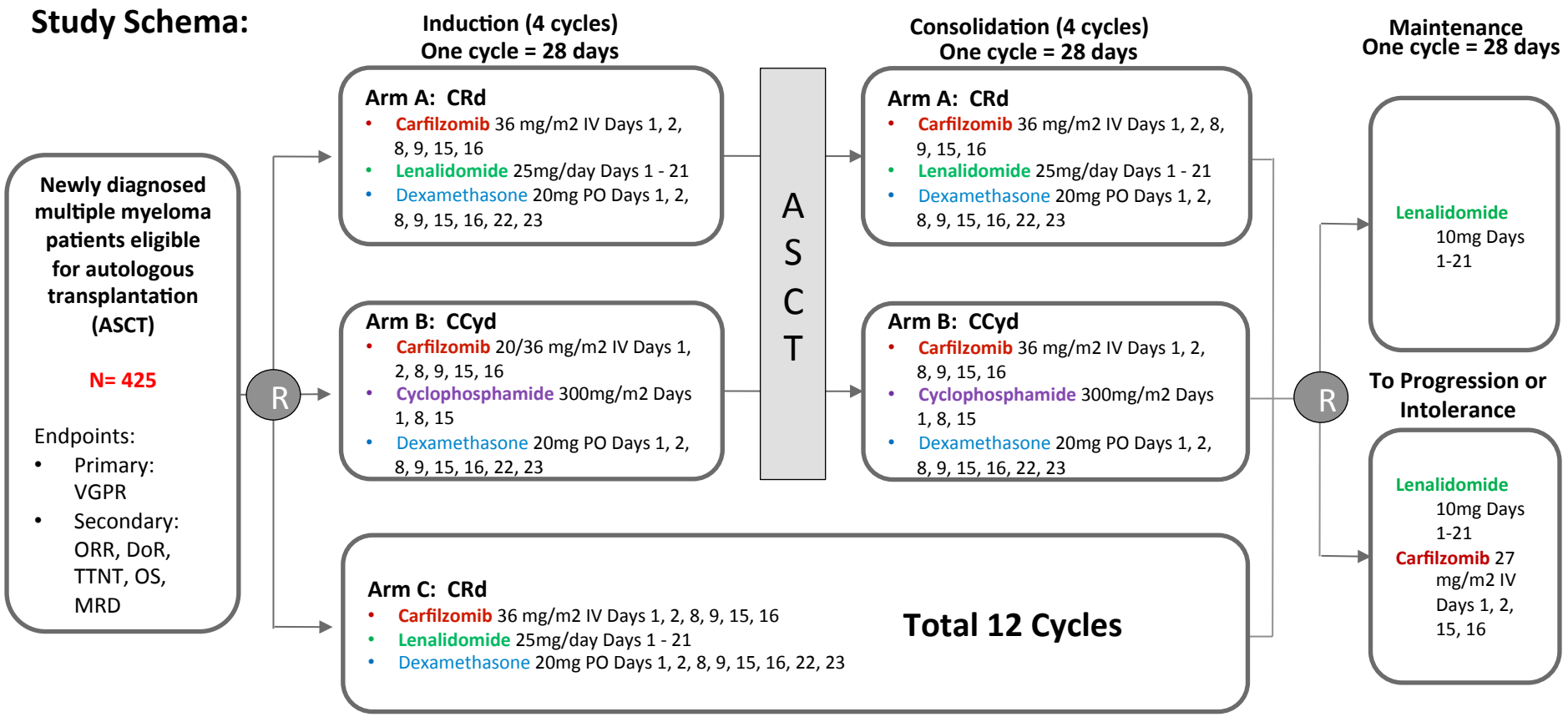
Kd

Vd,EVd,Kd

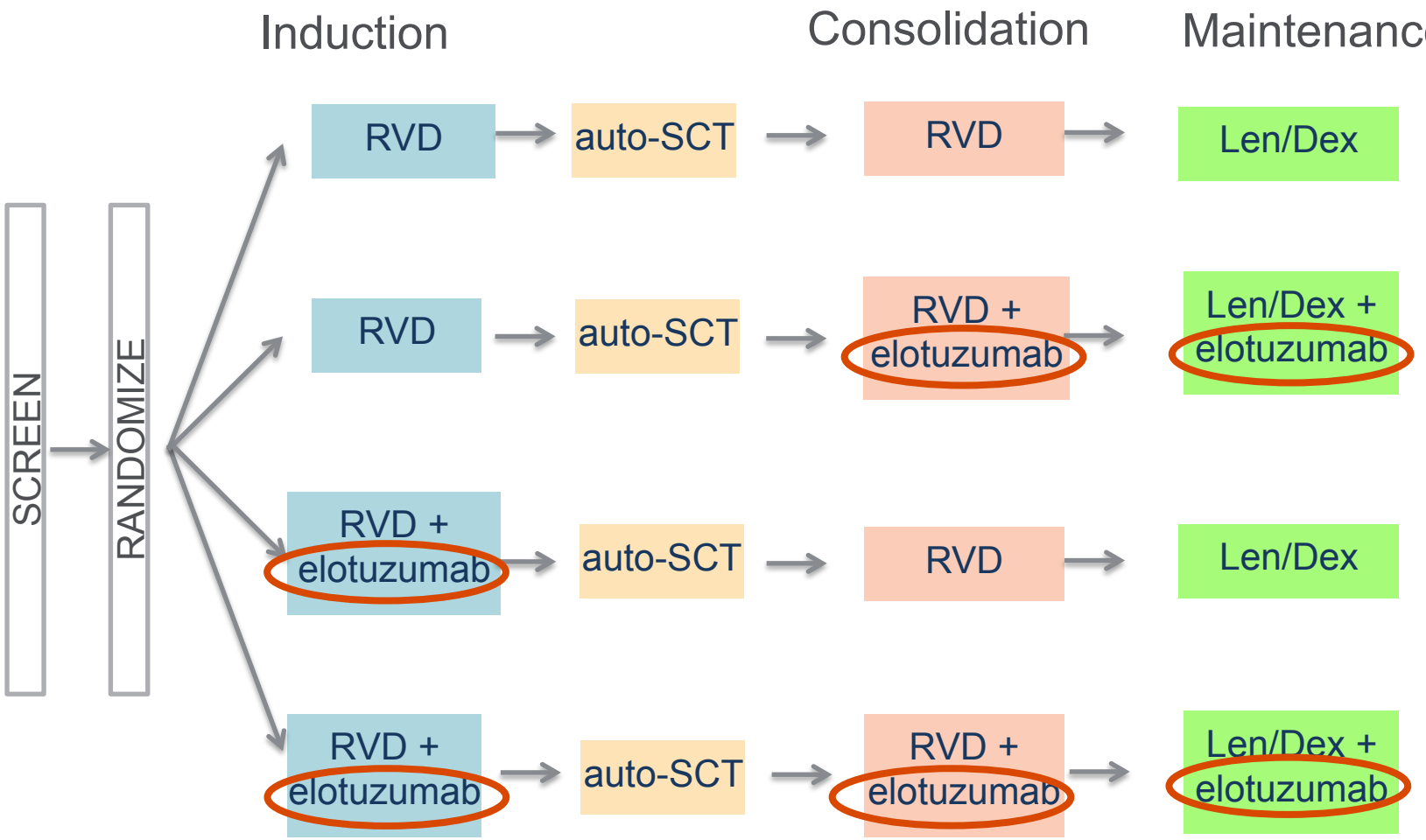
Pomalidomide-Dexamethasone

Daratumumab Single Agent

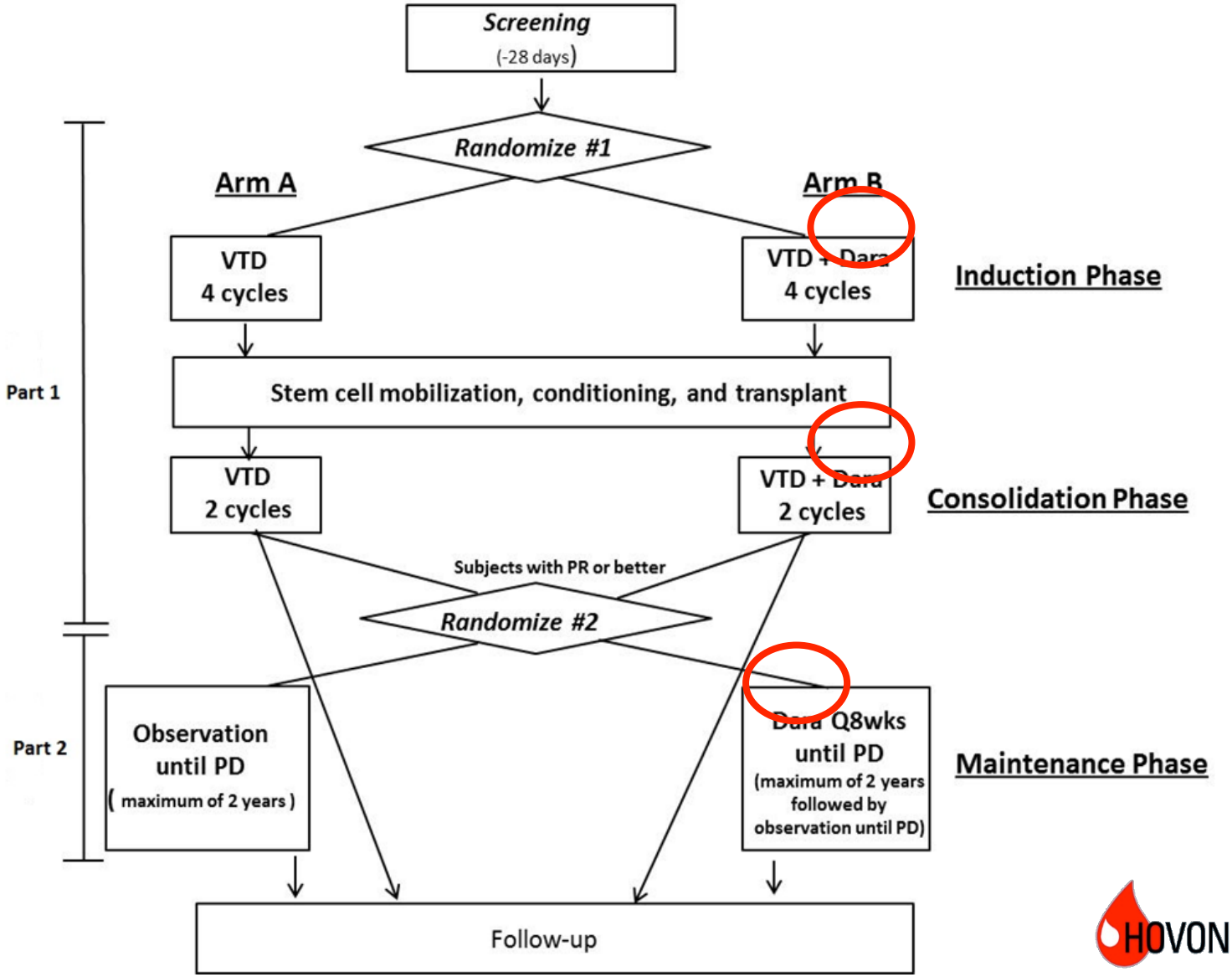
FORTE study design



Phase 3: Elotuzumab + VRD induction/consolidation + maintenance in newly diagnosed MM (GMMG-HD6)



Phase 3: Daratumumab + VTD induction/consolidation + maintenance in newly diagnosed MM (CASSIOPEA)



Novel agent–based therapies for patients eligible for a transplant (induction-consolidation-maintenance): present-future

	Bortezomib-based	Thalidomide-based	Lenalidomide-based	PI + IMiD-based
2-drug combinations	VD	TD	Rd RD*	
3-drug combinations	PAD VCD	TAD CTD	RAD CRD	VTD VRD **KRD**/KTD **Ixa-RD**
4-drug combinations				(VTDC) (RVCD) **VTD-Dara** **VRD-Elo**

*Trial was performed in SCT-eligible and –ineligible patients

IMiD, immunomodulatory drug

Adapted from Cavo M et al. Blood. 2011;117:6063;
Rosinol L et al. Expert Rev Hematol. 2014;7:43; Ludwig H et al. Leukemia. 2014;28:981.;
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000539/human_med_001130.jsp&mid=WC0b01ac058001d124

Treatment of elderly patients present-future

MP based :

Carfilzomib-MP vs VMP: Clarion

Daratumumab- VMP vs VMP: Alcyone

RD based :

Ixazomib-RD vs RD: Tourmaline 2

Elotuzumab-RD vs RD: Eloquent 1

Daratumumab-RD vs RD: Maia

Conclusions

- Availability of newer combos in newly diagnosed and R/R MM and of newer class of agents
- High response rates, extended TTP, PFS and TTNT
- Favorable safety profile
- Warning for cardiac toxicity of Carfilzomib
- Infusion reactions for MoAbs
- Similarity but also differences in between studies (previous drugs exposure/refractoriness, drugs duration, cytogenetic high-risk cut off)
- **Need to identify sub-groups of patients mostly benefiting from each combo**
- **Need to identify from the very beginning a long-term treatment strategy**