Mieloma Multiplo:

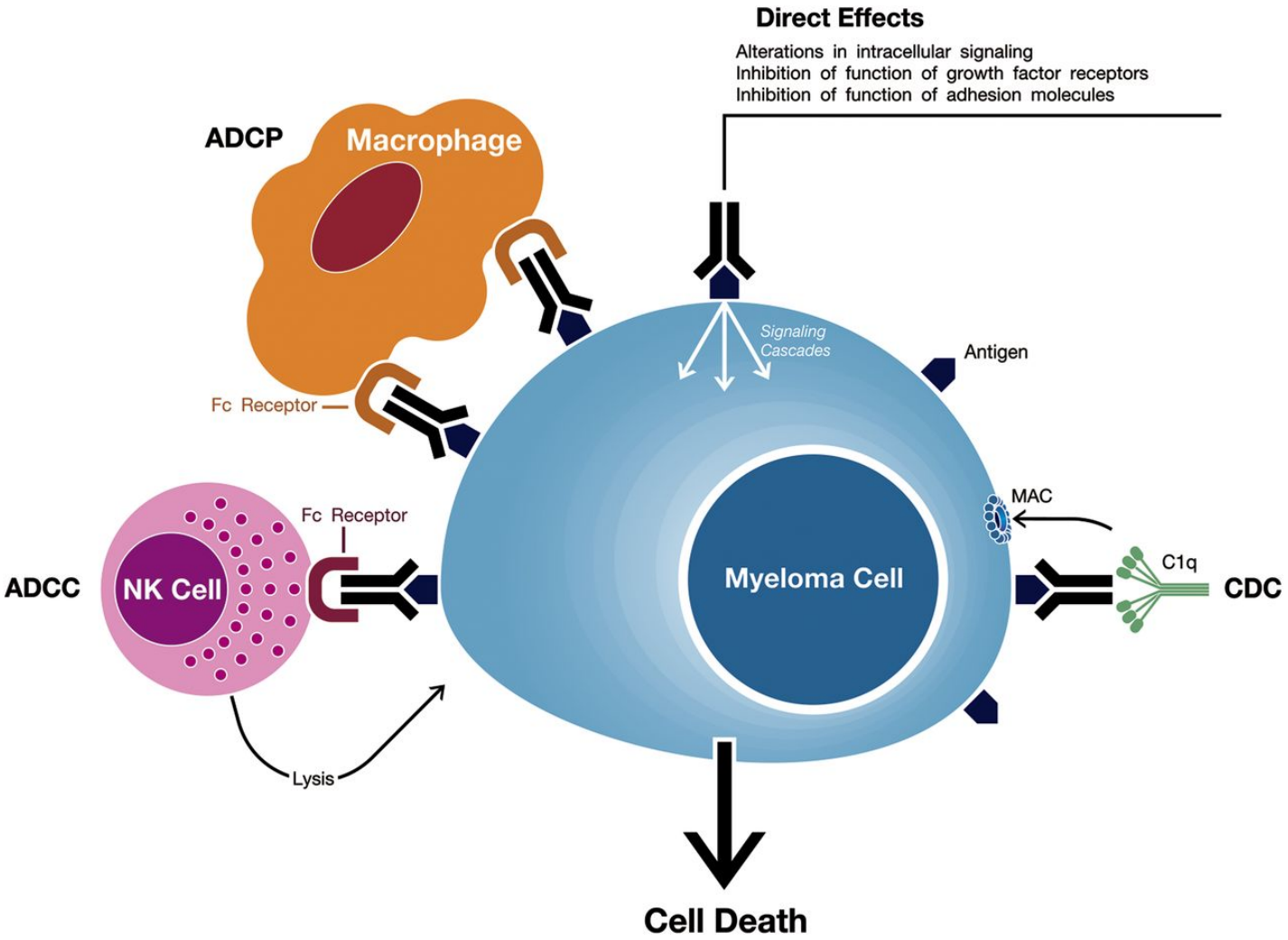
gli anticorpi monoclonali nel management terapeutico

Paola Tacchetti

"Seràgnoli" Institute of Hematology
Bologna University School of Medicine

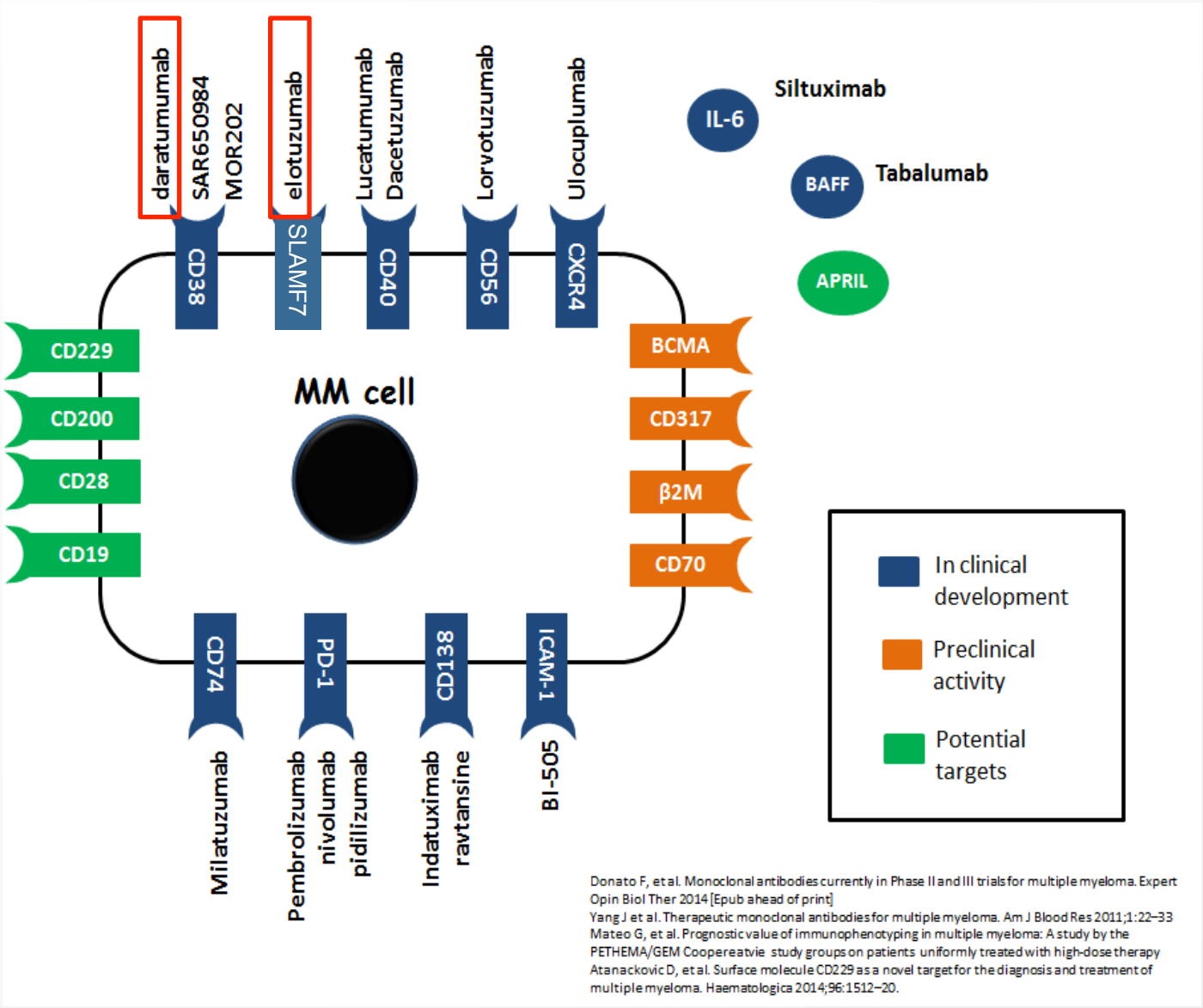
ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

Mechanisms of action of monoclonal antibodies targeting surface antigens on MM cells



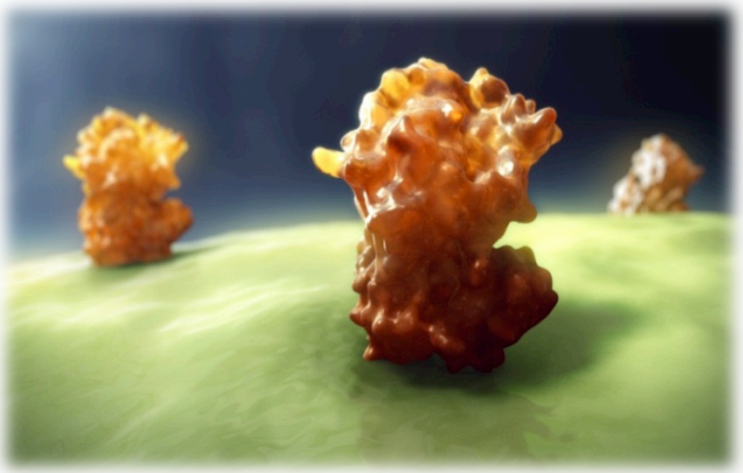
Niels W. C. J. van de Donk et al. Blood 2016;127:681-695

Targets for mAbs



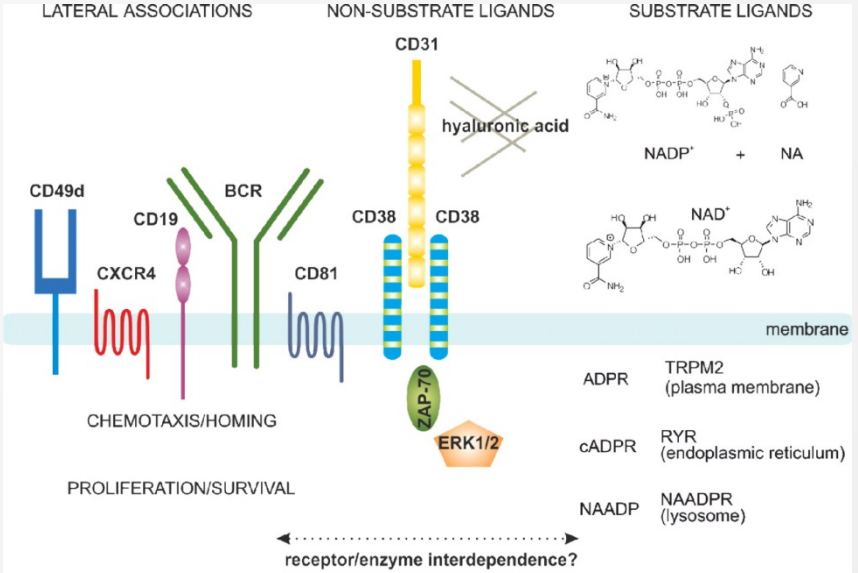
Lonial S et al, Leukemia 2015

CD38, cell surface receptor and an ectoenzyme, is a rational therapeutic target for treatment of myeloma



- Type II **transmembrane protein** (m.w. ≈45 kDa)
- **Highly and uniformly expressed on myeloma cells**
  - CD38 present on CD4, CD8, NK cells and B lymphocytes at a relatively low level
  - Also some CD38 expression on tissues of non-hematopoietic origin

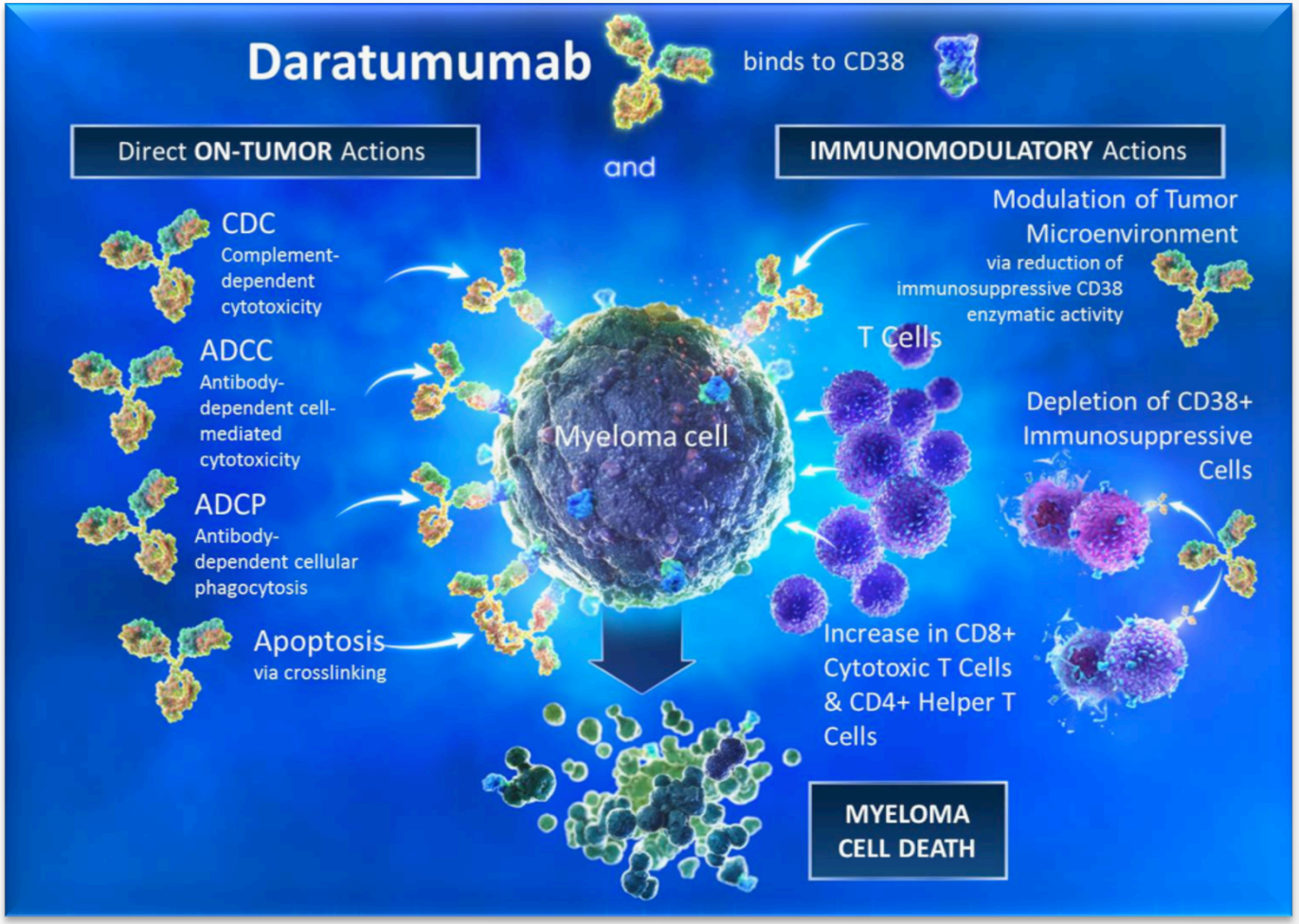
- CD38 has several intracellular functions
  1. Regulates **signaling, homing and adhesion** in close contact with BCR complex and CXCR4
  2. Regulates **activation and proliferation of human T lymphocytes**
  3. As an ectoenzyme, CD38 interacts with NAD+ and NADP+, which are converted to cADPR, ADPR, and NAADP in **intracellular Ca2+-mobilization**



Malavasi F, et al. Blood 2011;118:3470-3478.

Daratumumab: Mechanism of Action

- Human CD38 IgGκ monoclonal antibody
- Direct and indirect anti-myeloma activity[1-5]
- Depletes CD38+ immunosuppressive regulatory cells[5]
- Promotes T-cell expansion and activation[5]



1. Lammerts van Bueren J, et al. Blood. 2014;124:Abstract 3474
2. Jansen JMH, et al. Blood. 2012;120:Abstract 2974
3. de Weers M, et al. J Immunol. 2011;186:1840-8
4. Overdijk MB, et al. MAbs. 2015;7:311-21
5. Krejcik J, et al. Blood. 2016. 128(3):384-94

DARATUMUMAB SINGLE AGENT

Daratumumab as a single agent[1,2]

Approved by FDA and conditionally approved by EMA in relapsed/refractory multiple myeloma

Patients received a median of 5 prior lines of therapy

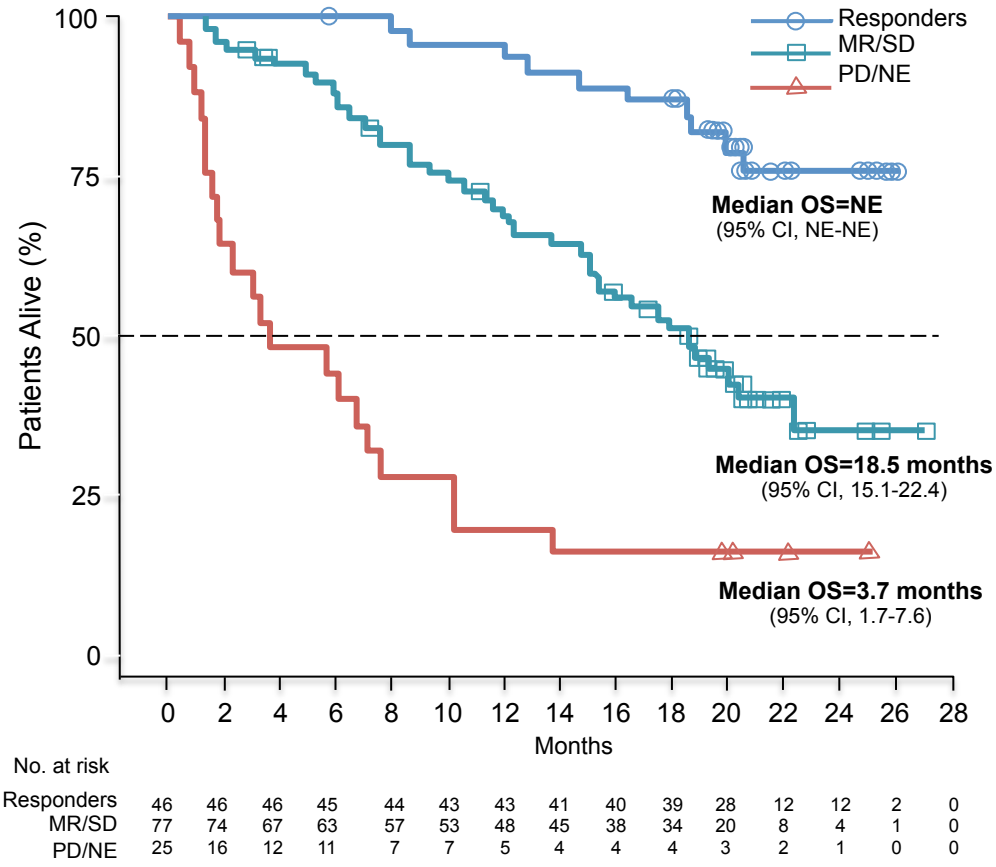
86.5% of patients were double refractory to a proteasome inhibitor (PI) and immunomodulatory drug (IMiD)[3]

Combined overall response rate (ORR): 31%[3]

Median overall survival (OS) of 20.1 months[3]

2-year OS was ~75% in responders

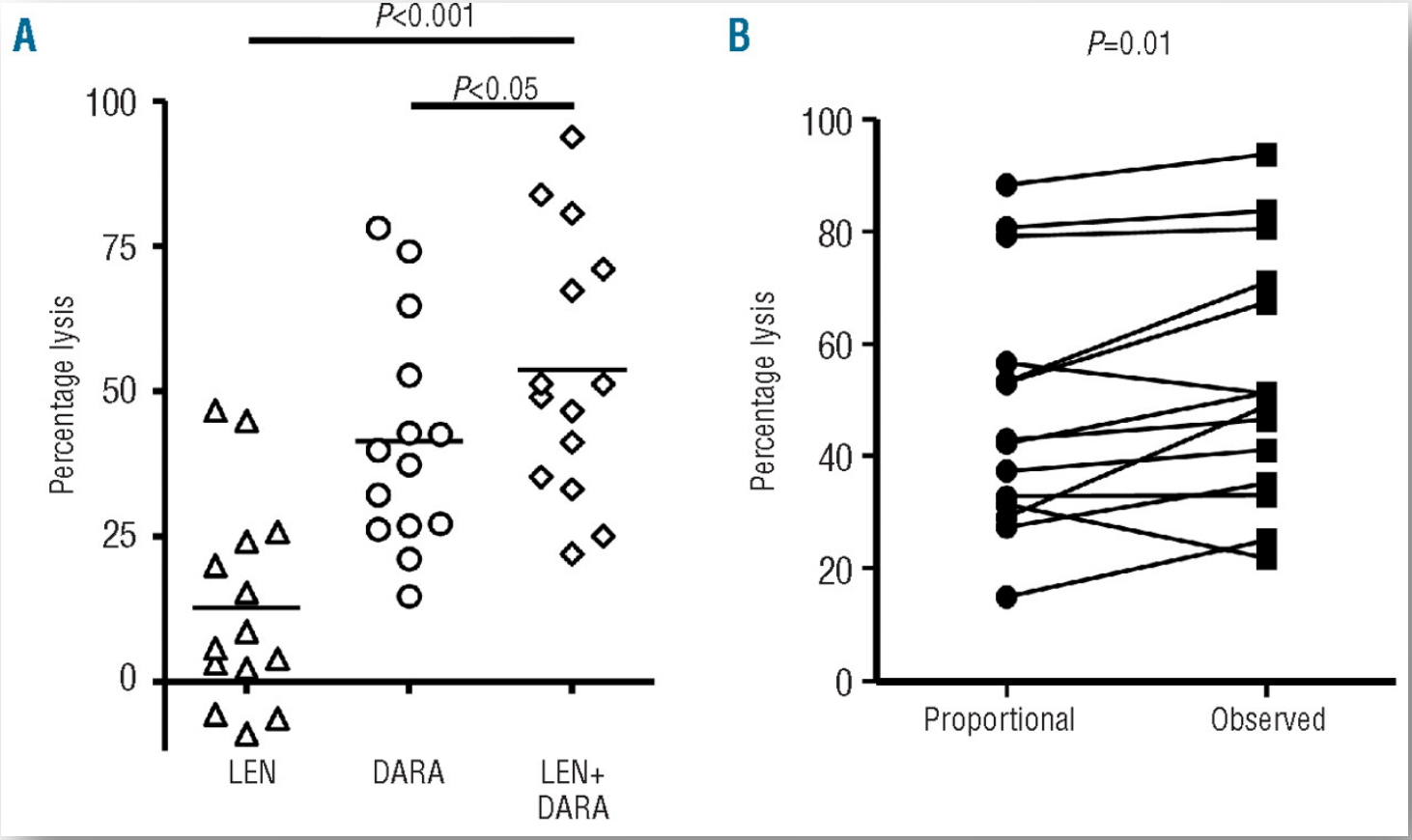
Median OS was 18.5 months in MR/SD patients



MR, minimal response; SD, stable disease; PD, progressive disease; OS, overall survival; CI, confidence interval; NE, not evaluable.

1. Lokhorst HM, et al. *N Engl J Med*. 2015;373:1207-19.
2. Lonial S, et al. *Lancet*. 2016;387:1551-60.
3. Usmani SZ, et al. *Blood*. 2016;128:37-44.

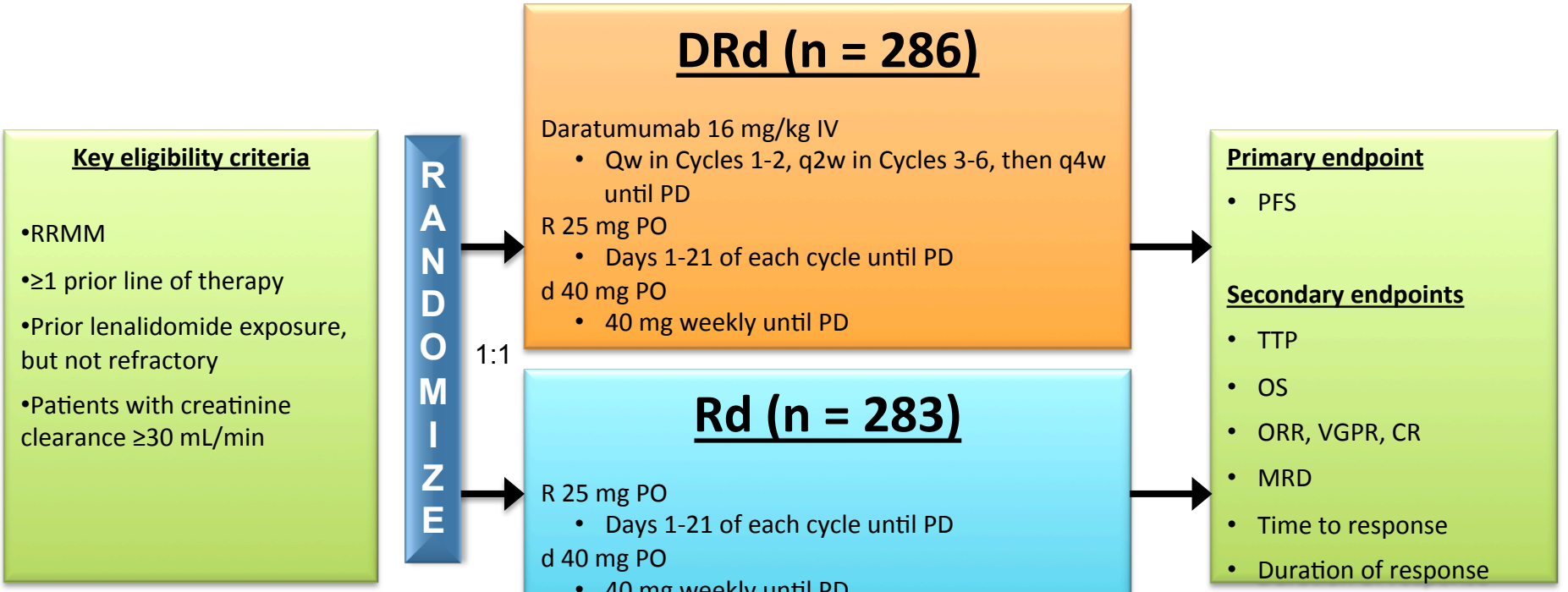
Improvement of DARA-induced ADCC by LEN in BM-MNC of MM patients



Van der Veer et al. Haematologica 2011;96:284-290

POLLUX: Study Design

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



Stratification factors

- No. prior lines of therapy
- ISS stage at study entry
- Prior lenalidomide

Cycles: 28 days

Statistical analyses

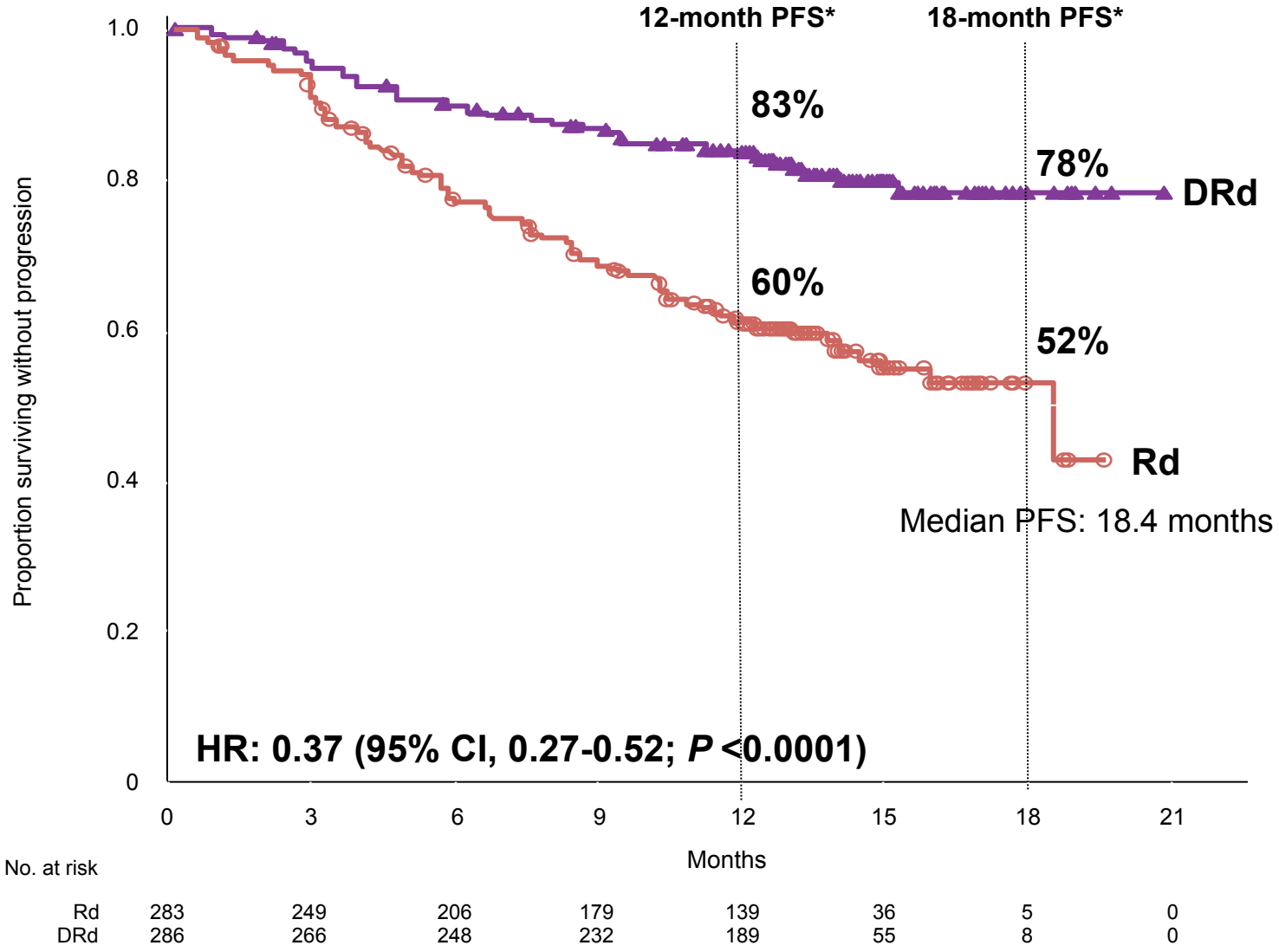
- 295 PFS events: 85% power for 7.7 month PFS improvement
- Interim analysis: ~177 PFS events

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.

Dimopoulos MA et al. EHA 2016

POLLUX: Progression-free Survival

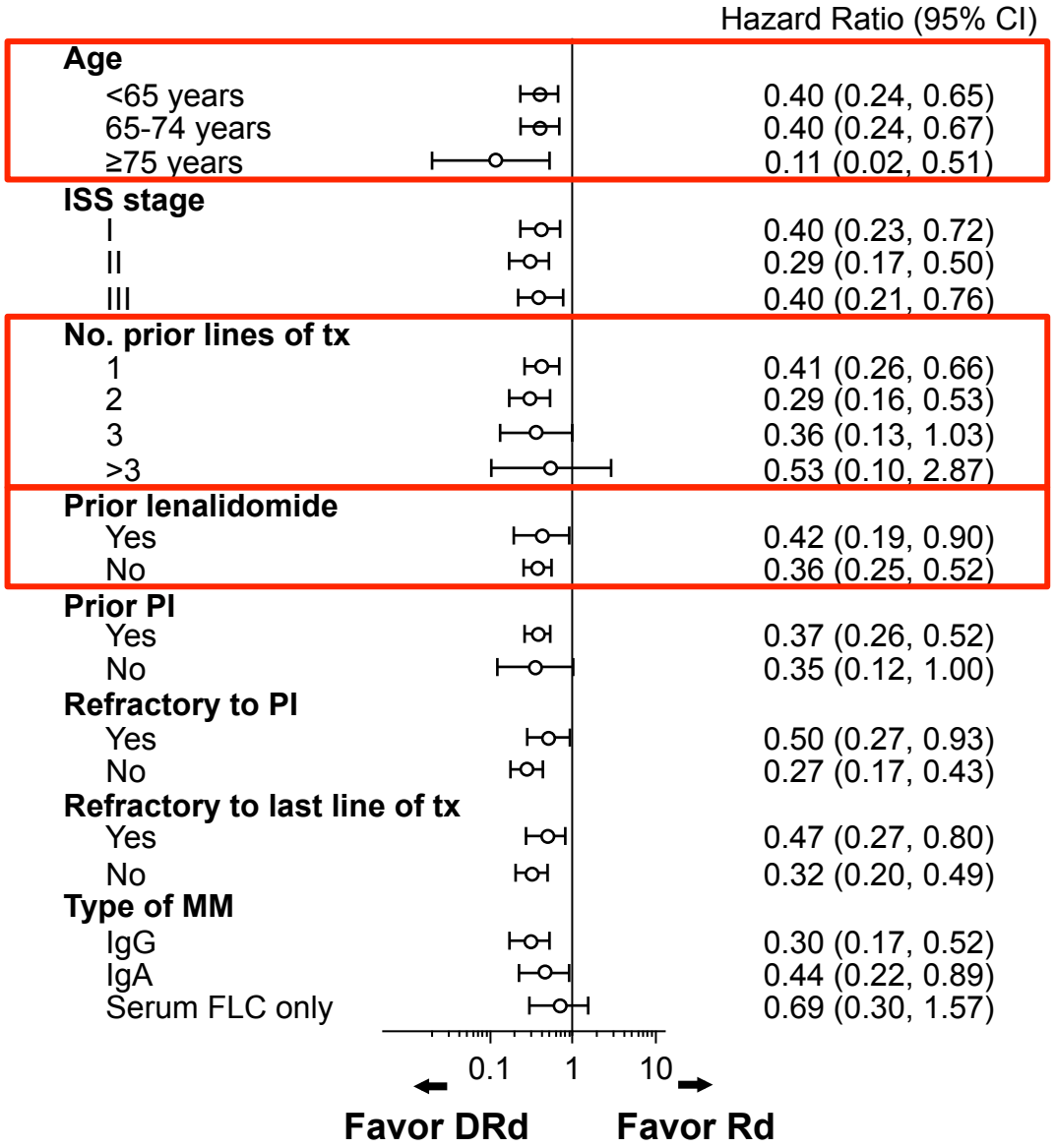


63% reduction in the risk of disease progression or death for DRd vs Rd

*KM estimate; HR, hazard ratio.

Dimopoulos MA et al. EHA 2016

POLLUX: PFS, Subgroup Analysis

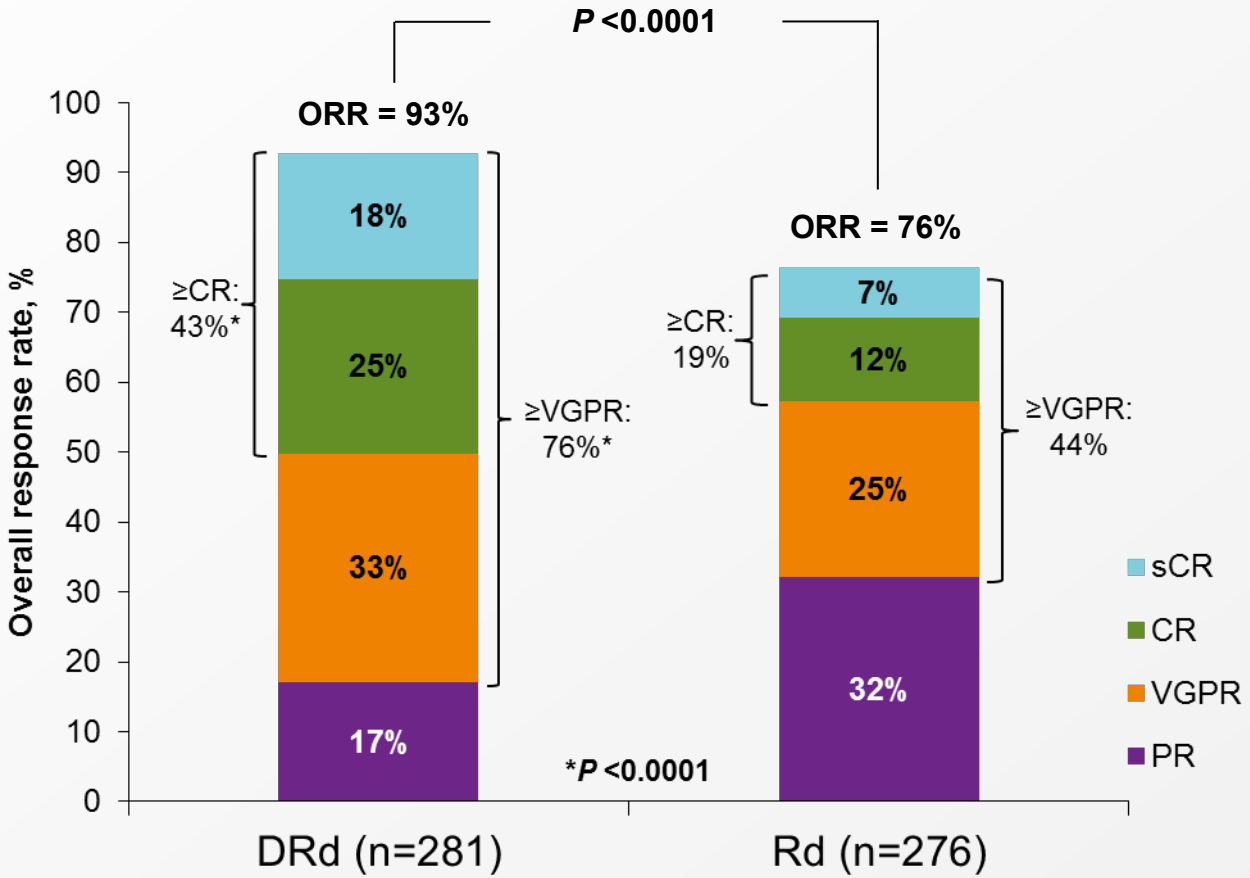


Higher efficacy was observed for DRd versus Rd across all subgroups

Tx, treatment; MM, multiple myeloma; IgG, immunoglobulin G; IgA, immunoglobulin A; FLC, free light chain.

Dimopoulos MA et al. EHA 2016

POLLUX: Overall Response Rate[a]

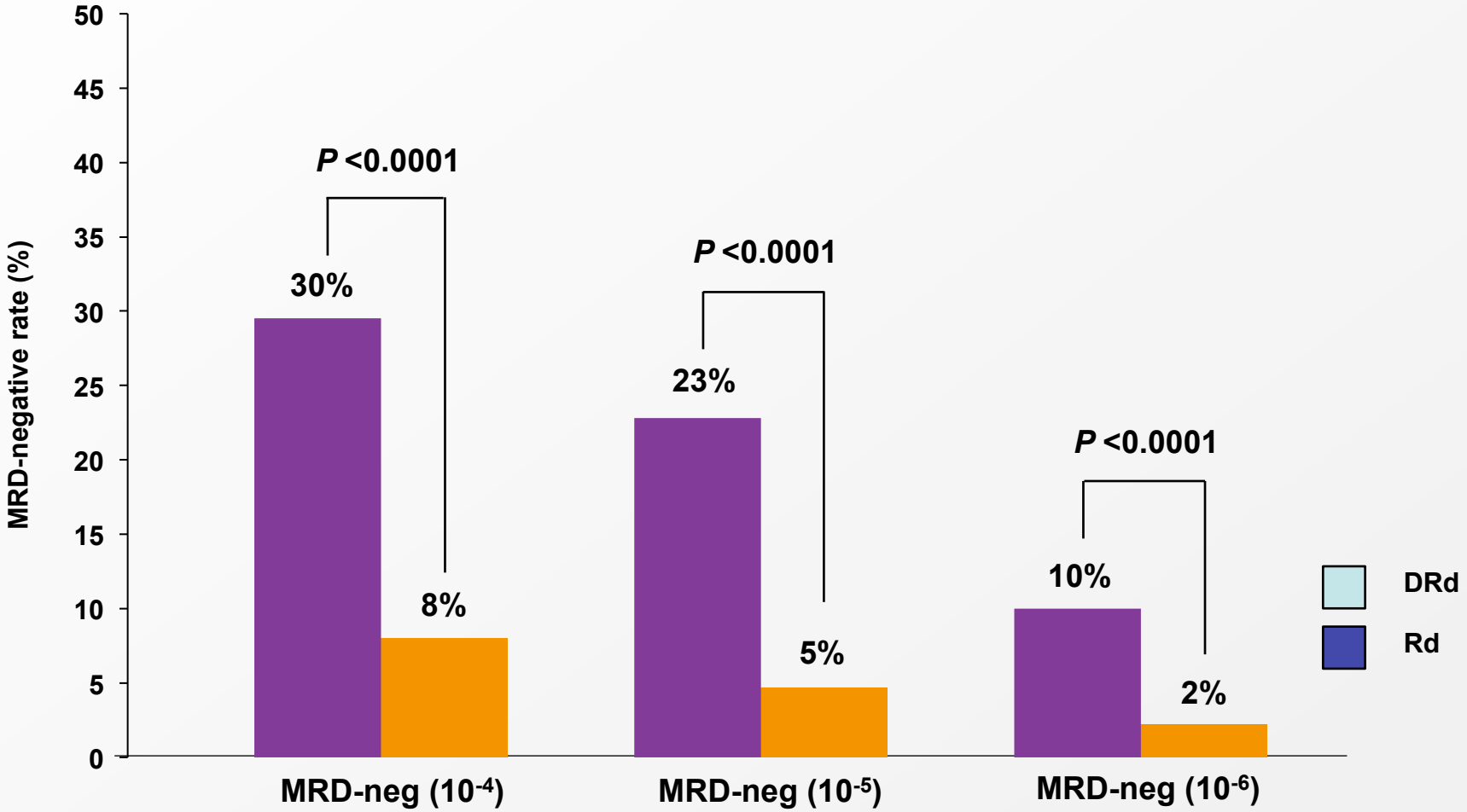


- Median duration of response: Not reached for DRd vs 17.4 months for Rd
- Median time to response: 1.0 month for DRd vs 1.3 months for Rd

[a]When serum interference was suspected, CR was confirmed using the daratumumab interference reflex assay.

Dimopoulos MA et al. EHA 2016

POLLUX: MRD-negative Rate



Significantly higher MRD-negative rates for DRd vs Rd

Response-evaluable set. Assessed by next generation sequencing in bone marrow.

Dimopoulos MA et al. EHA 2016

POLLUX: Infusion-related Reactions (IRRs)

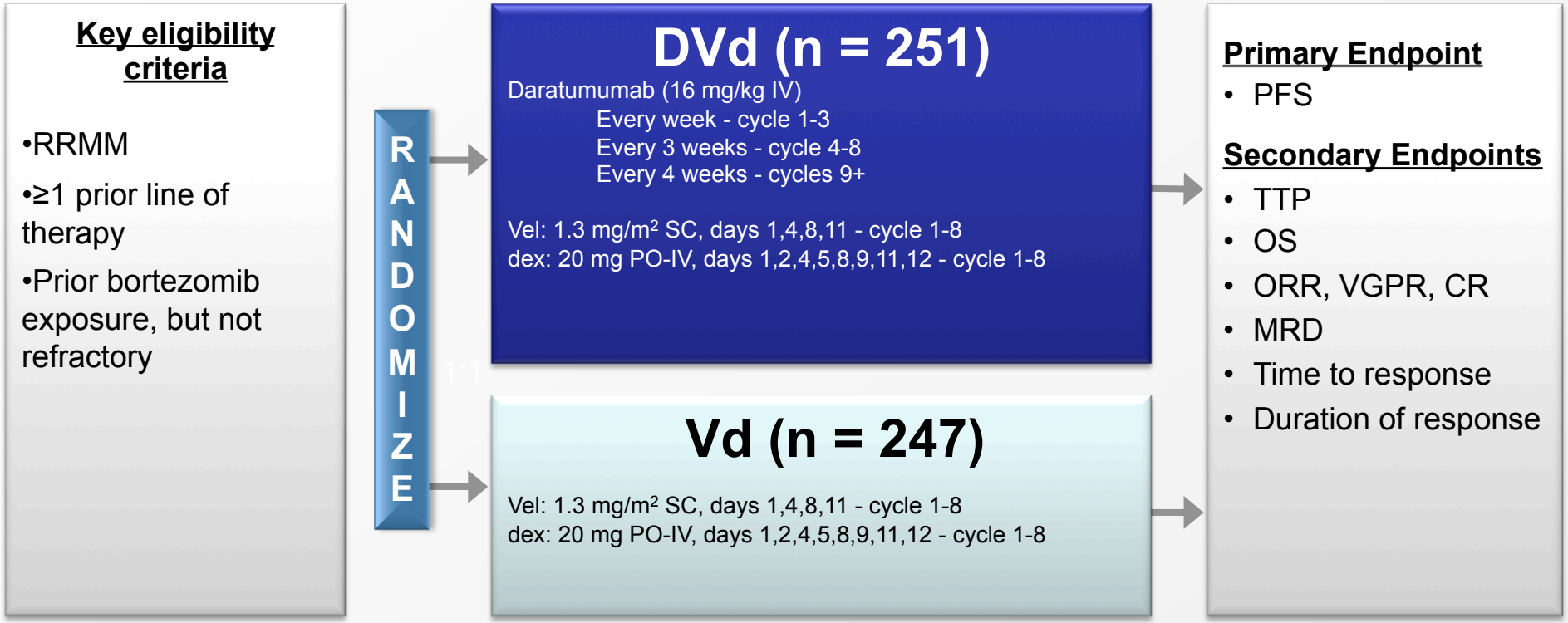
IRRs ≥2%	Safety Analysis Set (n = 283)	
	All grades (%)	Grade 3 (%)
Patients with IRRs	48	5
Cough	9	0
Dyspnea	9	0.7
Vomiting	6	0.4
Nausea	5	0
Chills	5	0.4
Bronchospasm	5	0.4
Pruritus	3	0.4
Throat irritation	3	0
Headache	3	0
Nasal congestion	3	0
Wheezing	2	0.7
Laryngeal edema	2	0.4
Rhinorrhea	2	0
Pyrexia	2	0

- No grade 4 or 5 IRRs were reported
- 92% of all IRRs occurred during the first infusion
- 1 patient discontinued daratumumab due to an IRR

Dimopoulos MA et al. EHA 2016

CASTOR: Study Design

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



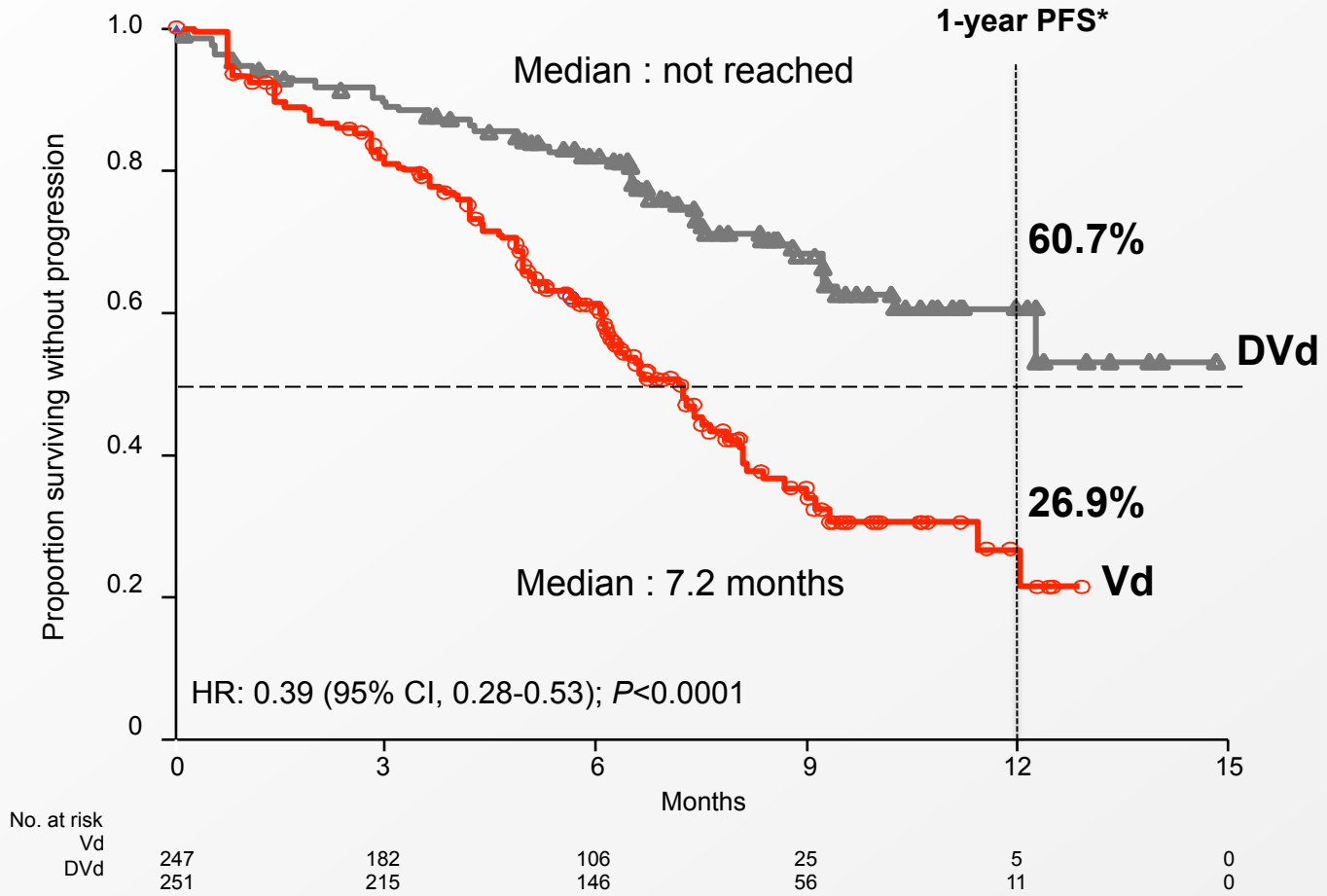
- Cycles 1-8: repeat every 21 days
- Cycles 9+: repeat every 28 days

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

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. N Engl J Med 2016;375:754-66

CASTOR: Progression-free Survival

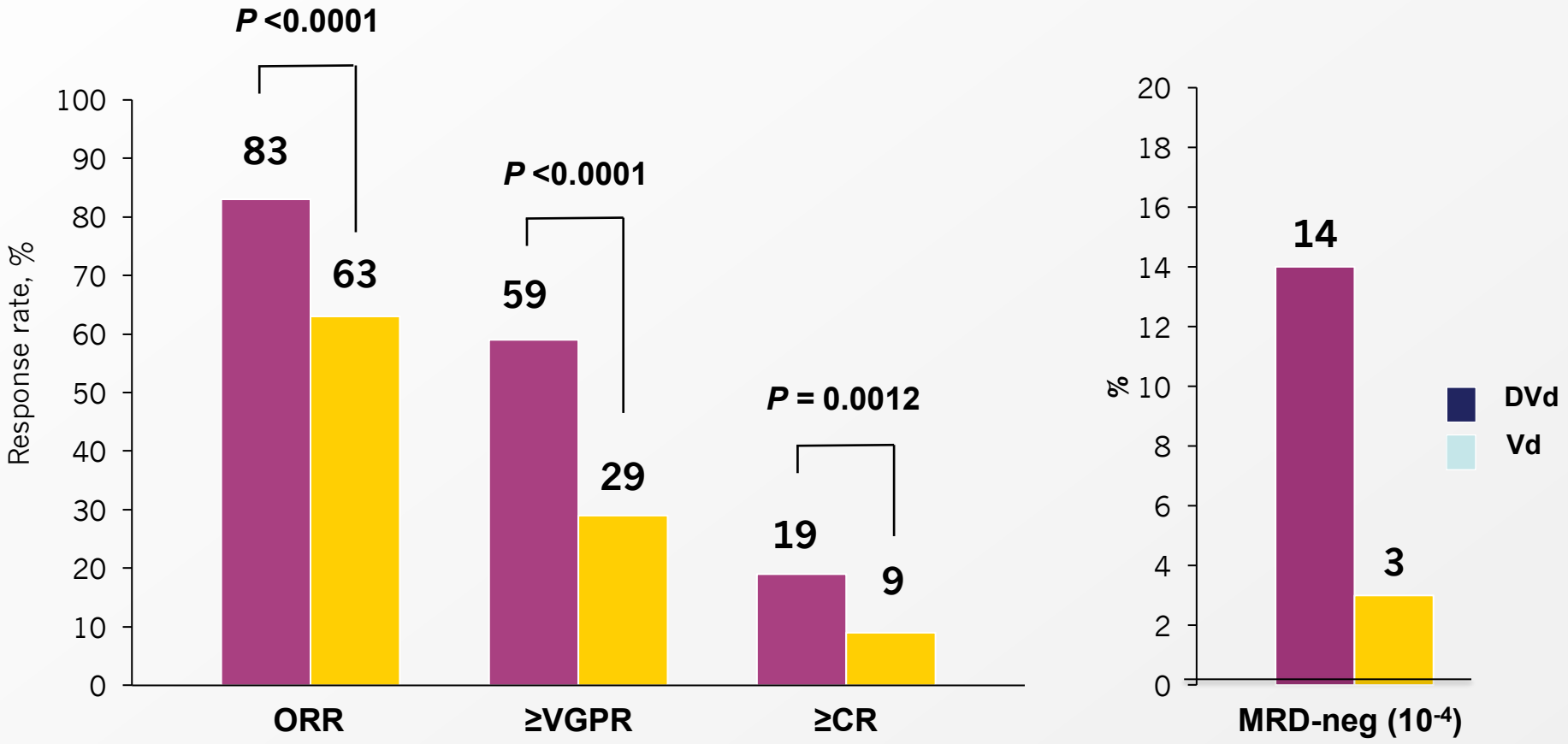


61% reduction in the risk of disease progression or death for DVd vs Vd

*KM estimate; HR, hazard ratio.

Palumbo A et al. N Engl J Med 2016;375:754-66

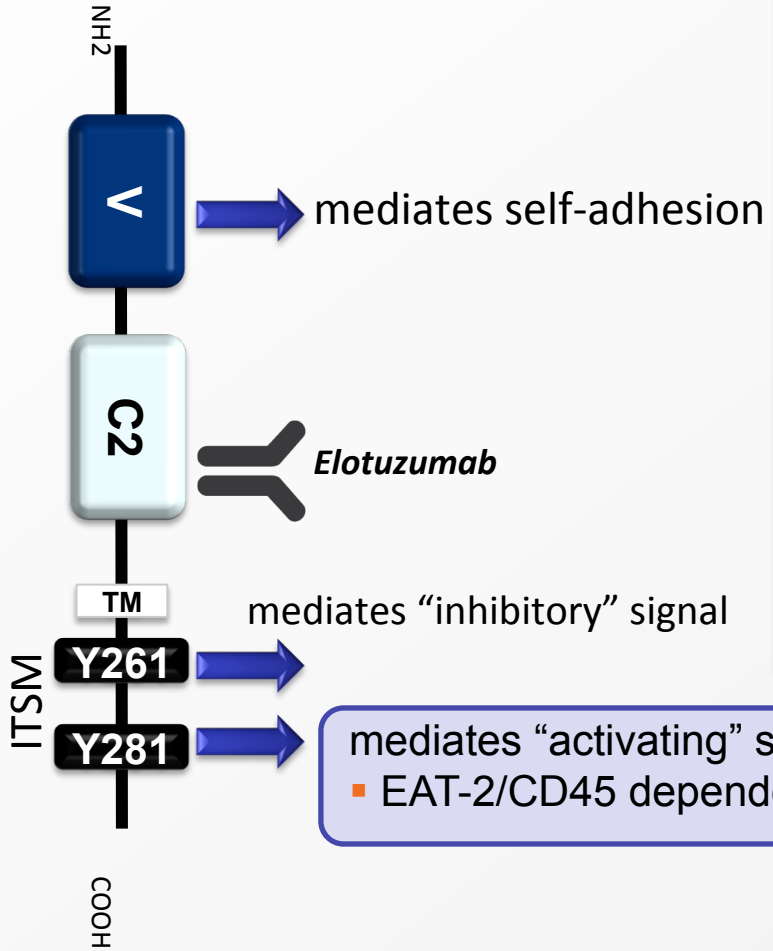
CASTOR: Overall Response Rate[a]



[a]Response-evaluable population.

Palumbo A et al. N Engl J Med 2016;375:754-66

Elotuzumab:
A Monoclonal Antibody Targeting SLAMF7



Elotuzumab

- Humanized, IgG1 mab specific for human SLAMF7
  - No cross-reactivity with non-human homologues or other SLAM family members
- Binds to a membrane-proximal motif of SLAMF7
  - Critical for mediating killing of target cells (in vitro)

SLAMF7

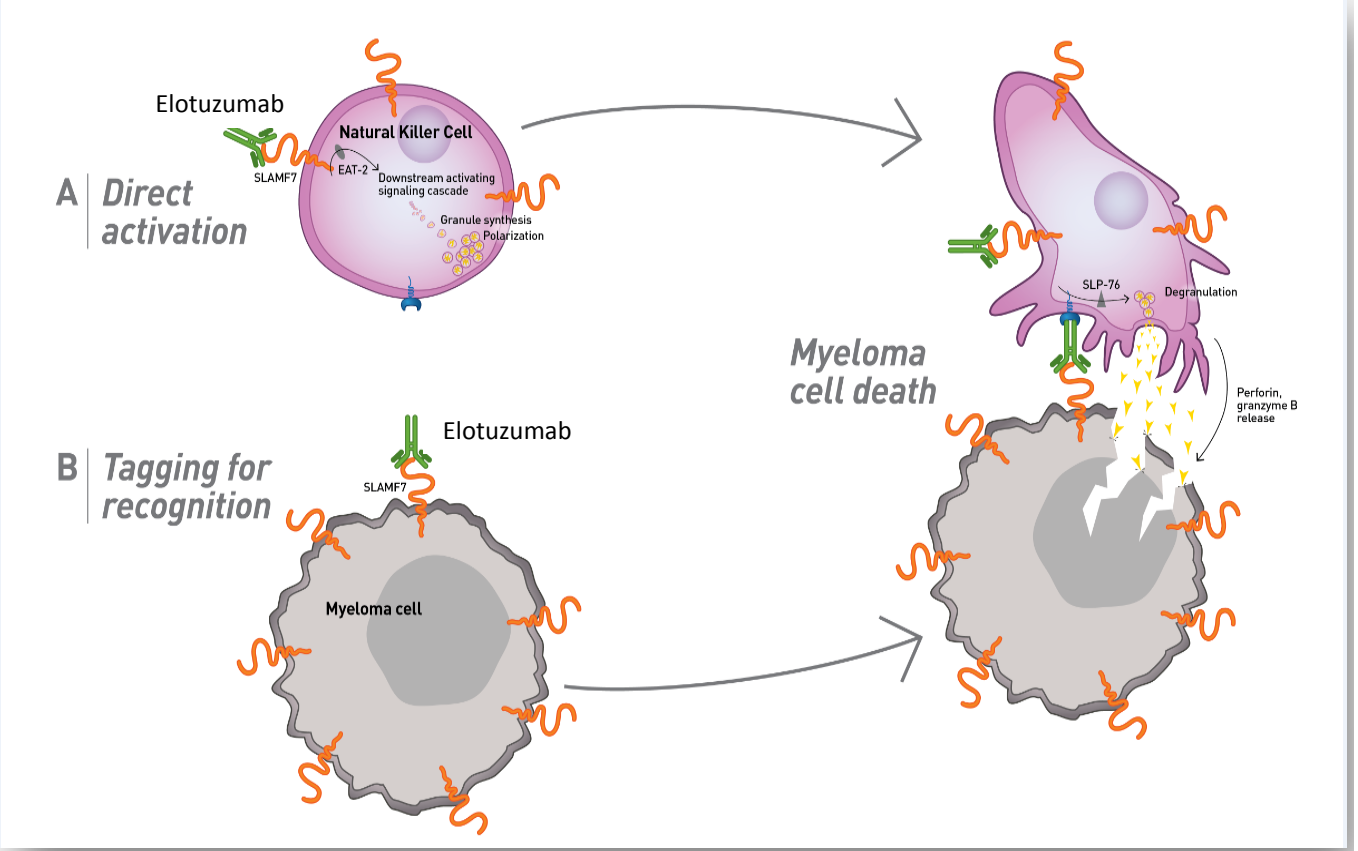
- Expression highest on Plasma Cells
- Varied expression across hematopoietic cells (NK, NK-T, DC, B, TCD8+, PC)
- Not express on non-hematopoietic cells
- SLAMF7 K/O Phenotype: compromised NK function

SLAMF7 = Signalling Lymphocyte Activation Molecule Family 7; ADCC=Antibody-dependent cellular cytotoxicity
ITSM = Intracellular Tyrosine Switch Motif
EAT-2 = Ewing's Sarcoma associated transcript 2

Veillette and Guo, Critical Reviews in Onc and Heme, 2013.
Cruz-Munoz et al, Nature Immunology, 2009.

Elotuzumab works via a dual mechanism of action by both directly activating Natural Killer Cells and through antibody-dependent cell-mediated cytotoxicity (ADCC) to cause targeted Myeloma cell death

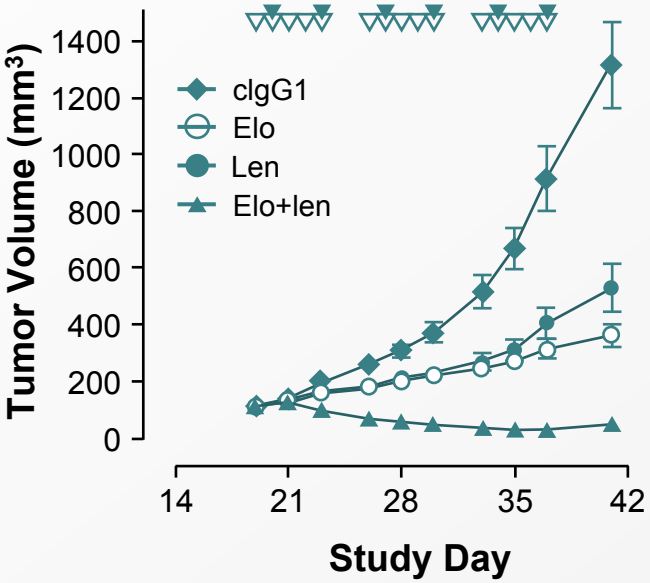
- **A: Direct activation**
  Binding to SLAMF7 directly activates natural killer cells,[2] but not myeloma cells[3]
- **B: Tagging for recognition**
  Elotuzumab activates natural killer cells via CD16, enabling selective killing of myeloma cells via antibody-dependent cellular cytotoxicity (ADCC) with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

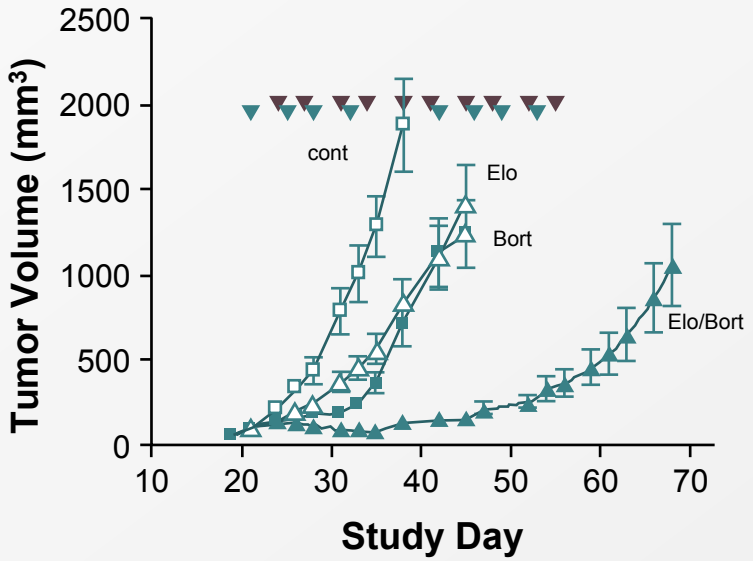
Elotuzumab Exhibits Synergy With Both Lenalidomide and Bortezomib

- No single agent activity
- Lenalidomide and bortezomib enhance the NKC-Mediated anti-myeloma activity of elotuzumab



Elotuzumab/lenalidomide[2]

- Lenalidomide enhances T-cell activation and cytokine production leading to **Natural Killer cell stimulation**
- Lenalidomide also exhibits **direct antimyeloma activity**, which enhances the cells' sensitivity to Natural Killer cell-mediated killing



Elotuzumab/bortezomib[1]

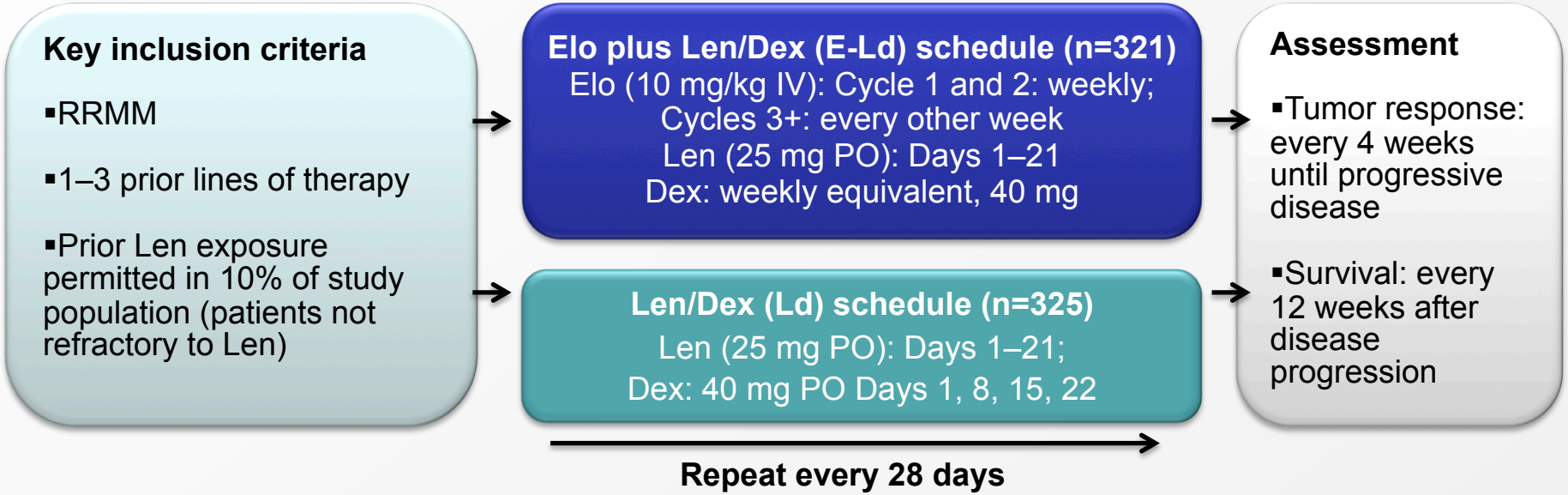
- Bortezomib exhibits direct **antimyeloma activity**, which augments the cells' sensitivity to Natural Killer cell-mediated killing by enhancing activating ligands and reducing inhibitory ligands on myeloma cells

A, B – *in vivo* tumor growth inhibition of OPM2 xenograft in SCID mice.

1. Van Rhee F et al. *Mol CanTher*. 2009;8:2616-2624.
2. Balasa et al. *Cancer Imm and Immunothe*. 2015; 64 (1):61-73.

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

Elotuzumab is approved by FDA and EMA in combination with len-dex for patients who have received at least 1 prior lines of therapy

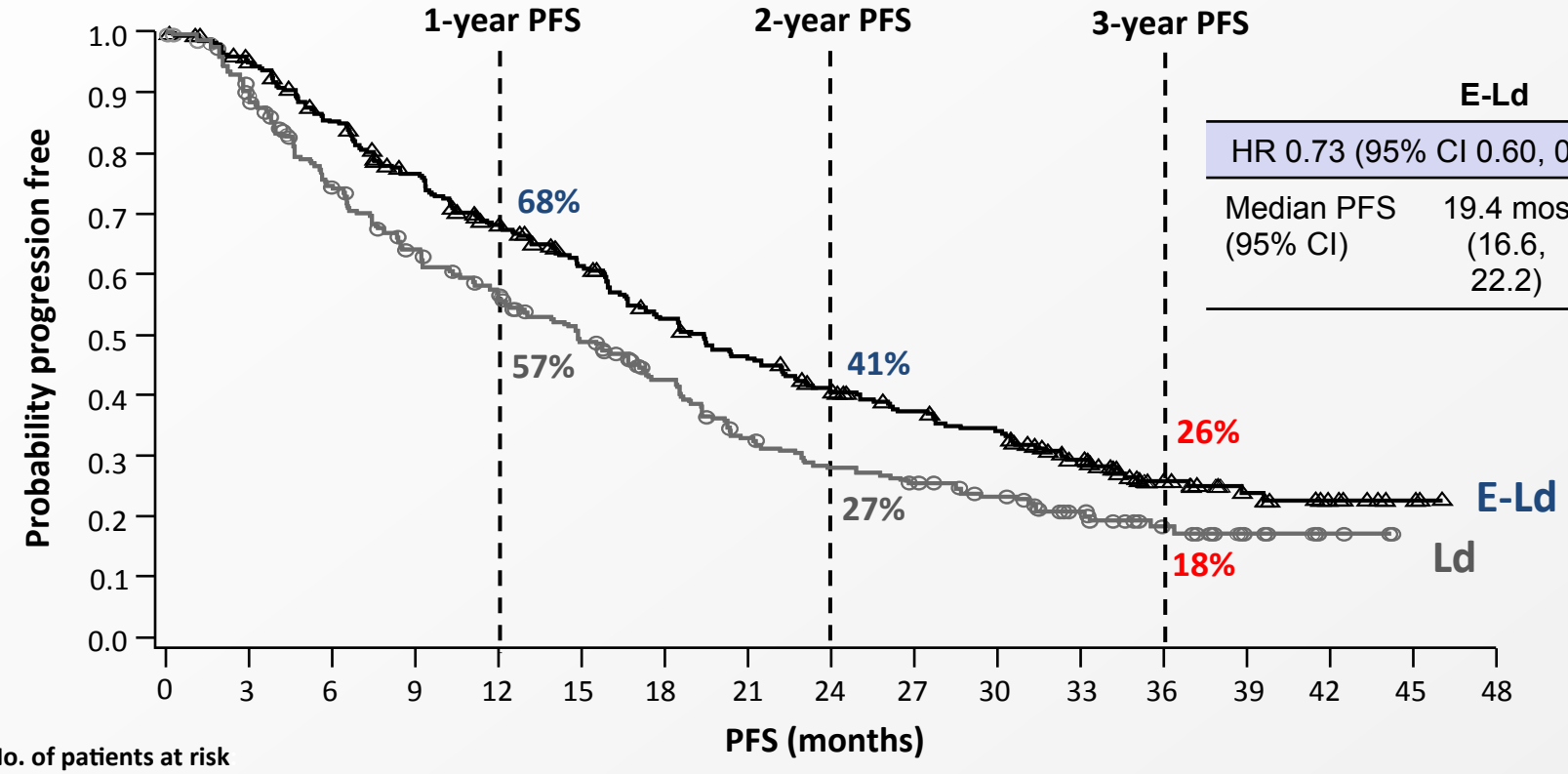


- Open-label, international, randomized, multicenter, **phase 3 trial** (168 global sites)
- **646 pts**
- Median n° treatment cycles Elo Ld: 19 (1-42)
- 83% pts received more than 90% dose intensity

Lonial S et al, NEJM 2015

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

Extended Progression-Free Survival



	E-Ld	Ld
HR 0.73 (95% CI 0.60, 0.89); p=0.0014		
Median PFS (95% CI)	19.4 mos (16.6, 22.2)	14.9 mos (12.1, 17.2)

No. of patients at risk

E-Ld	321	293	259	227	195	171	144	125	107	94	85	59	34	19	8	3	0
Ld	325	266	215	181	157	130	106	80	67	60	51	36	15	7	3	0	0

PFS benefit with E-Ld was maintained over time (vs Ld):

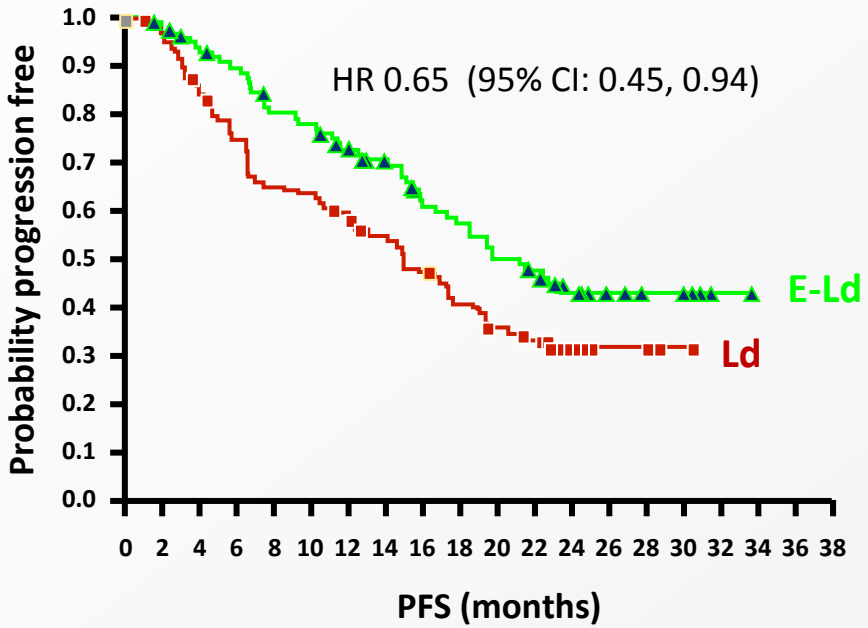
- **Overall 27% reduction in the risk of disease progression or death**
- **Relative improvement in PFS of 44% at 3 years**

Lonial S et al, NEJM 2015
Dimopoulos MA, et al ASH 2015

ELOQUENT-2: EloRd vs Rd

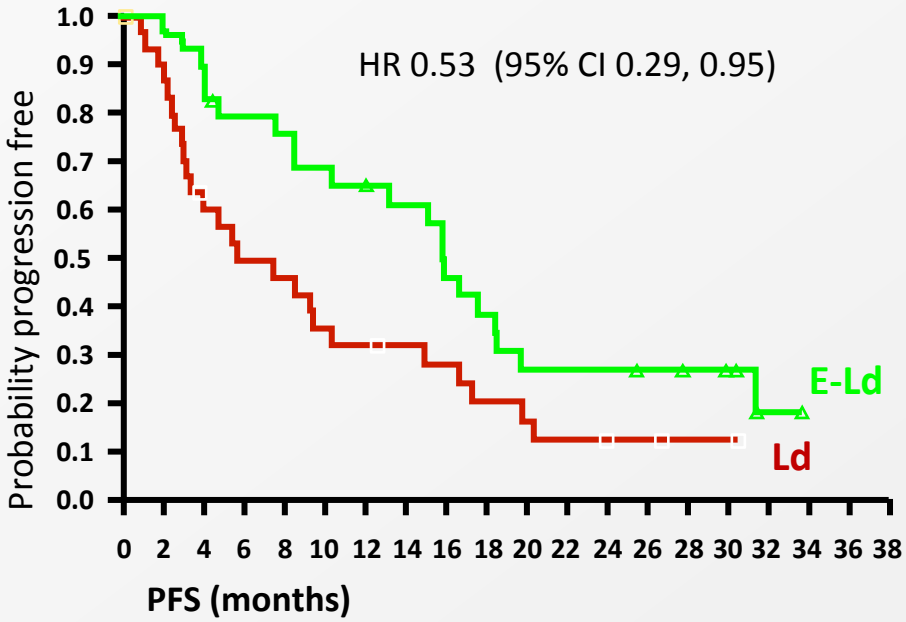
PFS according to del(17p) and t(4;14)

del(17p)+



E-Ld: median (95% CI): 21.19 (16.62, NE)
Ld: median (95% CI): 14.92 (10.61, 18.50)

t(4;14)+



E-Ld: median (95% CI): 15.84 (8.41, 18.46)
Ld: median (95% CI): 5.55 (3.09, 10.25)

Elo-Rd del(17p) negativity: median (95% CI): 18.46 (15.84, 22.77)

Dimopoulos M et al, ASH 2015
Lonial S et al, NEJM 2015

ELOQUENT-2: EloRd vs Rd
INFUSION REACTIONS

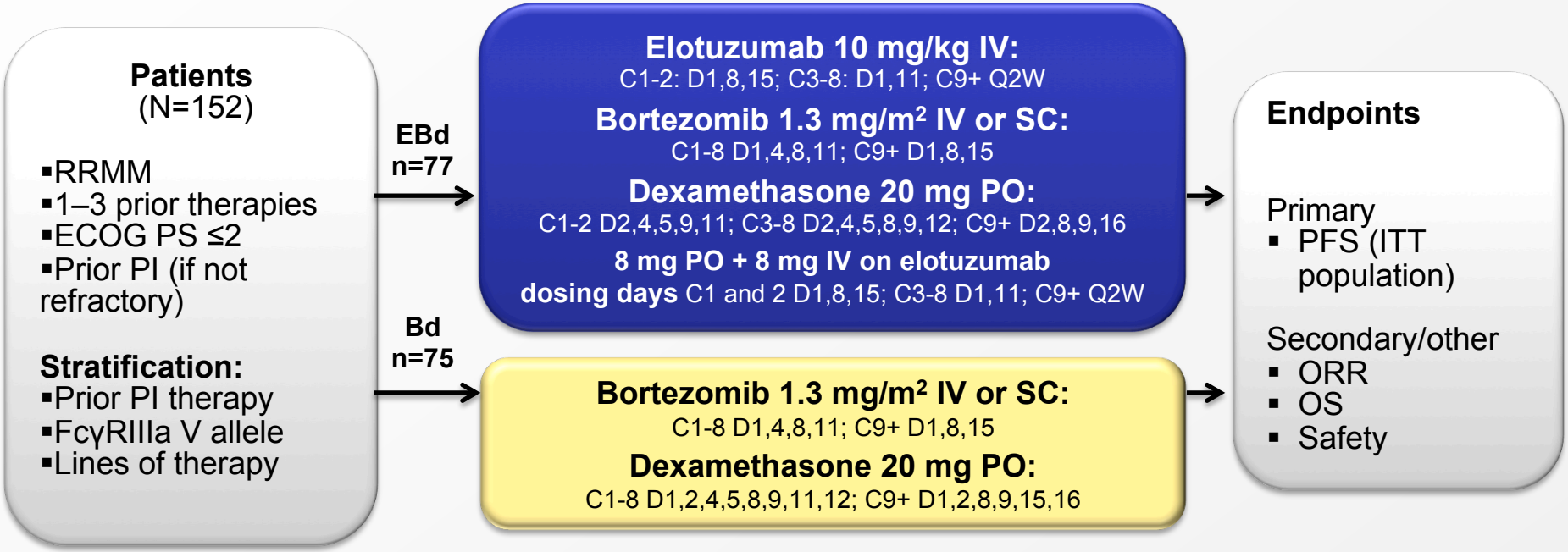
Events, n (%)	E-Ld (n=318)		
	Grade 1/2	Grade 3	Grade 4/5
Infusion reaction	29 (9)	4 (1)	0
Pyrexia	10 (3)	0	0
Chills	4 (1)	0	0
Hypertension	3 (1)	1 (<1)	0

- 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

Lonial S et al, NEJM 2015

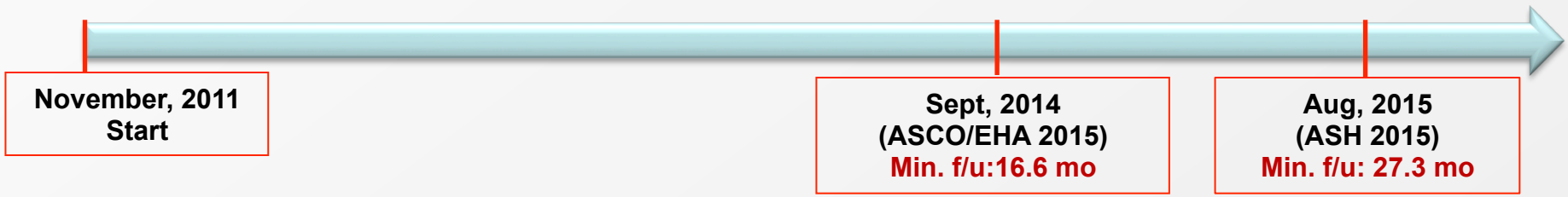
Elo-Bd vs Bd in R/R MM

- Phase 2, open-label, randomized, multicenter trial



Premedication regimen given to mitigate infusion reactions

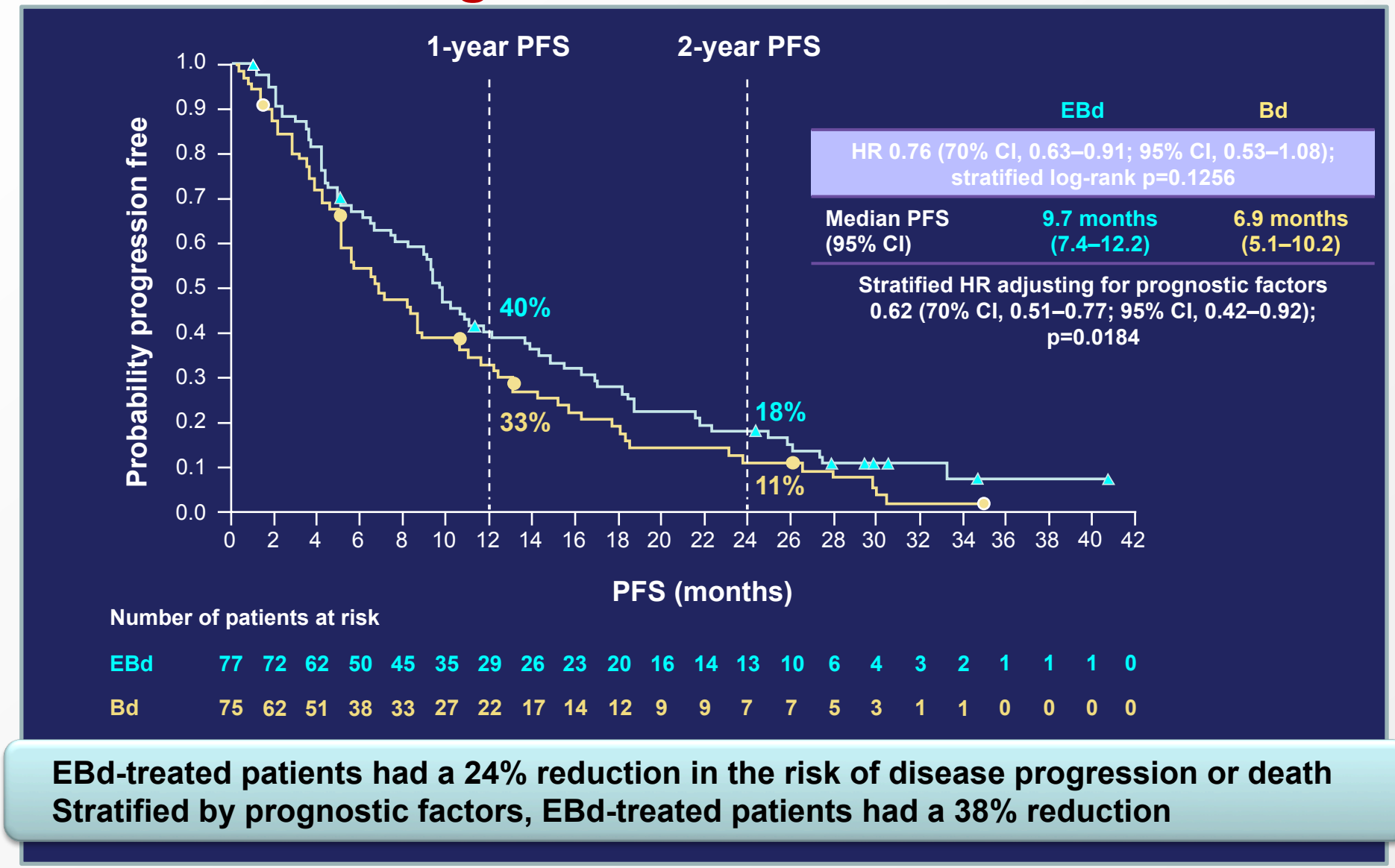
Elotuzumab IV administered over ~2–3 hours; gradual escalation to 5 mL/min permitted



- **2-sided 0.30 significance level specified to test for PFS difference between arms**
- **Study had 80% power to detect a hazard ratio of 0.69 with 103 events**

Jakuboviak A et al. Blood 2016

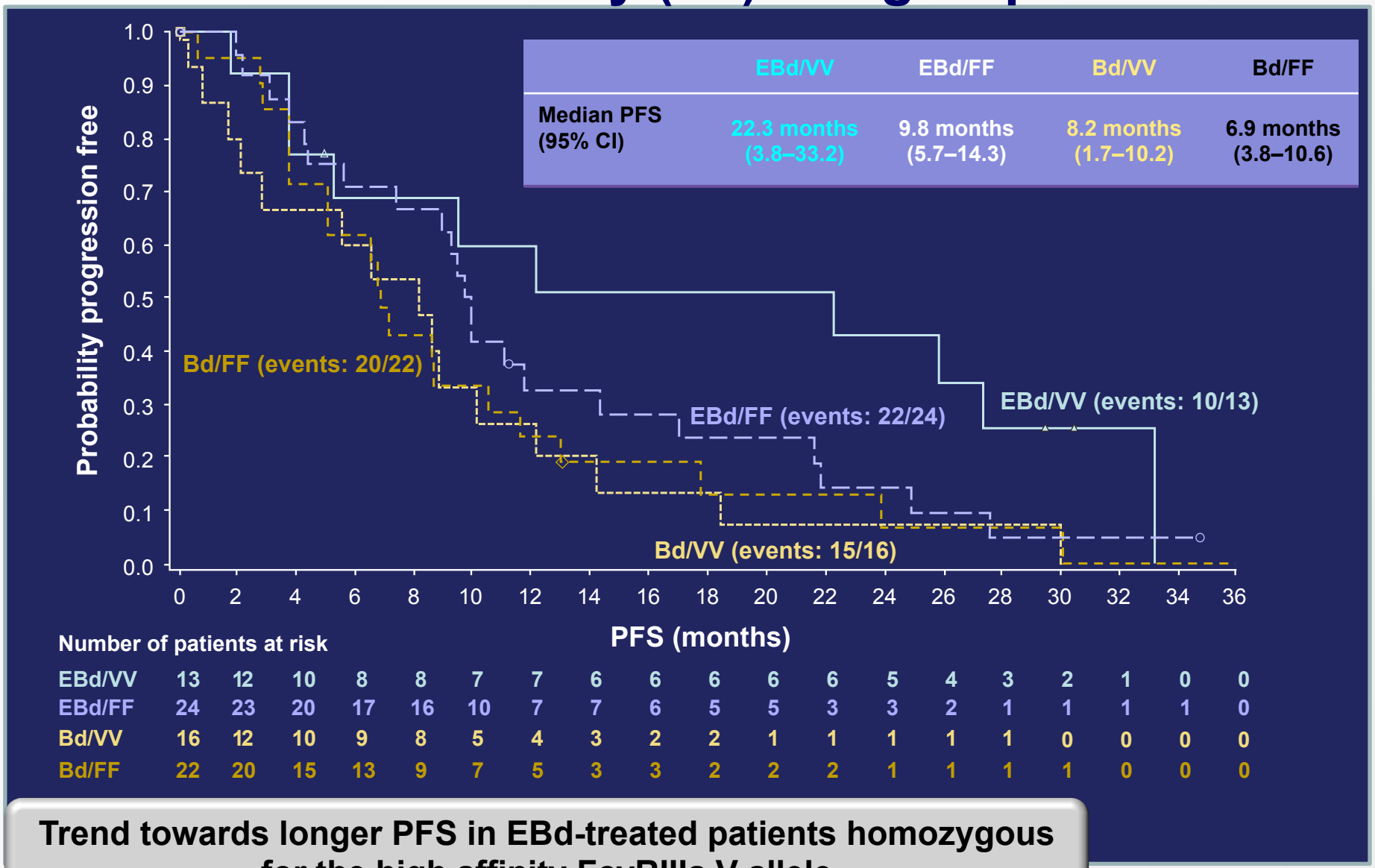
Elo-VD vs VD in R/R MM:
Progression Free Survival



EBd-treated patients had a 24% reduction in the risk of disease progression or death
Stratified by prognostic factors, EBd-treated patients had a 38% reduction

Jakuboviak A et al. Blood 2016

PFS: FcγRIIIa High-Affinity (VV) and Low-Affinity (FF) Subgroups



	EBd/VV	EBd/FF	Bd/VV	Bd/FF
Median PFS (95% CI)	22.3 months (3.8–33.2)	9.8 months (5.7–14.3)	8.2 months (1.7–10.2)	6.9 months (3.8–10.6)

Number of patients at risk

EBd/VV	13	12	10	8	8	7	7	6	6	6	6	6	5	4	3	2	1	0	0
EBd/FF	24	23	20	17	16	10	7	7	6	5	5	3	3	2	1	1	1	1	0
Bd/VV	16	12	10	9	8	5	4	3	2	2	1	1	1	1	1	0	0	0	0
Bd/FF	22	20	15	13	9	7	5	3	3	2	2	2	1	1	1	1	0	0	0

Trend towards longer PFS in EBd-treated patients homozygous for the high affinity FcγRIIIa V allele

Jakuboviak A et al. Blood 2016

Dara-based Studies

	POLLUX DRd vs Rd
PFS HR (95% CI)	0.37 (0.27-0.52)
ORR	93%
≥VGPR	76%
≥CR	43%
Duration of response, mo	NE
OS HR (95% CI)	0.64 (0.40-1.01)

Dimopoulos MA et al. EHA 2016

	CASTOR DVd vs Vd
PFS HR (95% CI)	0.39 (0.28-0.53)
ORR	83%
≥VGPR	59%
≥CR	19%
Duration of response, mo	NE
OS HR (95% CI)	0.77 (0.47-1.26)

Palumbo A et al. N Engl J Med 2016;375:754-66

Elo-based Studies

	ELOQUENT-2 EloRd vs Rd
PFS HR (95% CI)	0.73 (0.60-0.89)
ORR	79%
≥VGPR	33%
≥CR	4%
Duration of response, mo	20.7
OS HR (95% CI)	0.77 (0.61-0.97)

Lonial S et al, NEJM 2015

	EloVd vs Vd
PFS HR (95% CI)	0.76 (0.59-0.88)
ORR	66%
≥VGPR	36%
≥CR	4%
Duration of response, mo	11.4
OS HR (95% CI)	0.61 (0.32-1.15)

Jakuboviak A et al. Blood 2016

Table 5. Management and prevention of adverse events associated with elotuzumab and CD38-targeting antibodies

Adverse event	Antibody	Prevention and management
General management of adverse events	CD38-targeting antibodies and elotuzumab	In general, dose-delay is the primary method for the management of side effects (and not dose-reductions)
Infections	CD38-targeting antibodies and elotuzumab	No formal recommendations can be made at the present time. Herpes zoster prophyaxis should be considered. It is recommended to screen patients for HIV, HBV, and HCV before start of therapy.
Infusion-related reactions	Infusion-related reactions occur more frequently with CD38-targeting antibodies than with elotuzumumab Daratumumab/Isatuximab: 40-50% Elotuzumab: 10%	Prevention Premedication consisting of steroids, antihistamines and acetaminophen, 30-60 minutes prior to infusion.* For patients treated with CD38-targeting antibodies with higher risk of respiratory complications (eg, FEV1 <80%), postinfusion medication should be considered (eg, antihistamines, β-2 adrenergic receptor agonist by inhalation, or control medication for patients with asthma and COPD such as inhalation corticosteroids) For daratumumab: patients with known COPD with a FEV1 <50% of the predicted normal value, with moderate or severe persistent asthma within the past two years, or with uncontrolled asthma, were excluded from trials with daratumumab. Therefore, we recommend to perform FEV1 testing for patients with suspicion of having COPD, and it should be considered to exclude patients from daratumumab treatment if FEV1 <50% of predicted. Given similar pattern and frequency of infusion-related reactions, we also recommend FEV1 testing for patients planned to be treated with isatuximab. Treatment: Interrupt infusion, consider administration of corticosteroids, antihistamines, IV fluid, or β-2 adrenergic receptor agonist by inhalation; after infusion reaction is resolved, restart infusion at lower rate (e.g. half of that used before the interruption) Patients experiencing respiratory events, which occur more frequently with CD38-targeting antibodies, may benefit from pre- and postinfusion prophylaxis with a bronchodilator or in case patients have concomitant asthma or COPD additional medication such as inhalation corticosteroids to control lung disease

Van de Donk NWCJ et al, Blood 2016

Table 6. Management of laboratory interference associated with elotuzumab and CD38-targeting antibodies

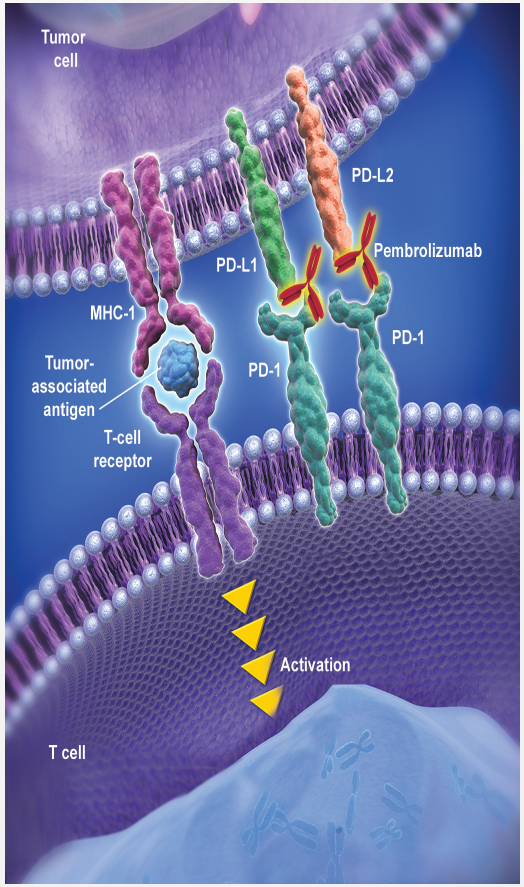
Laboratory test	Antibody	Management
Interference with serum protein electrophoresis and immunofixation assays	Several therapeutic antibodies	DIRA should be performed when daratumumab-treated patients with IgG-κ M-protein have achieved deep response (M-protein <2 g/L) New assays are in development for elotuzumab, isatuximab and MOR202
Interference with multiparametric flow cytometry	Daratumumab, isatuximab, MOR202, and possibly other therapeutic antibodies	Use of newly developed antibodies for flow cytometry, which bind to different epitopes compared with the therapeutic antibody Application of alternative plasma cell identification markers
Interference with blood compatibility testing	CD38-targeting antibodies (also observed with anti-CD44 antibodies)	Denaturation of CD38 from reagent RBCs by dithiothreitol Neutralization of therapeutic antibody with neutralizing antibodies or recombinant soluble CD38 Extensive RBC antigen phenotyping before the patient receives the first infusion of the CD38-targeting antibody or RBC antigen genotyping when the patient has already received treatment with an anti-CD38 antibody or a recent blood transfusion (<3 mo) A wallet card that informs physicians and blood banks of the interference with blood compatibility testing should be provided to all patients treated with CD38-binding antibodies

DIRA, daratumumab interference reflex assay.

Van de Donk NWCJ et al, Blood 2016

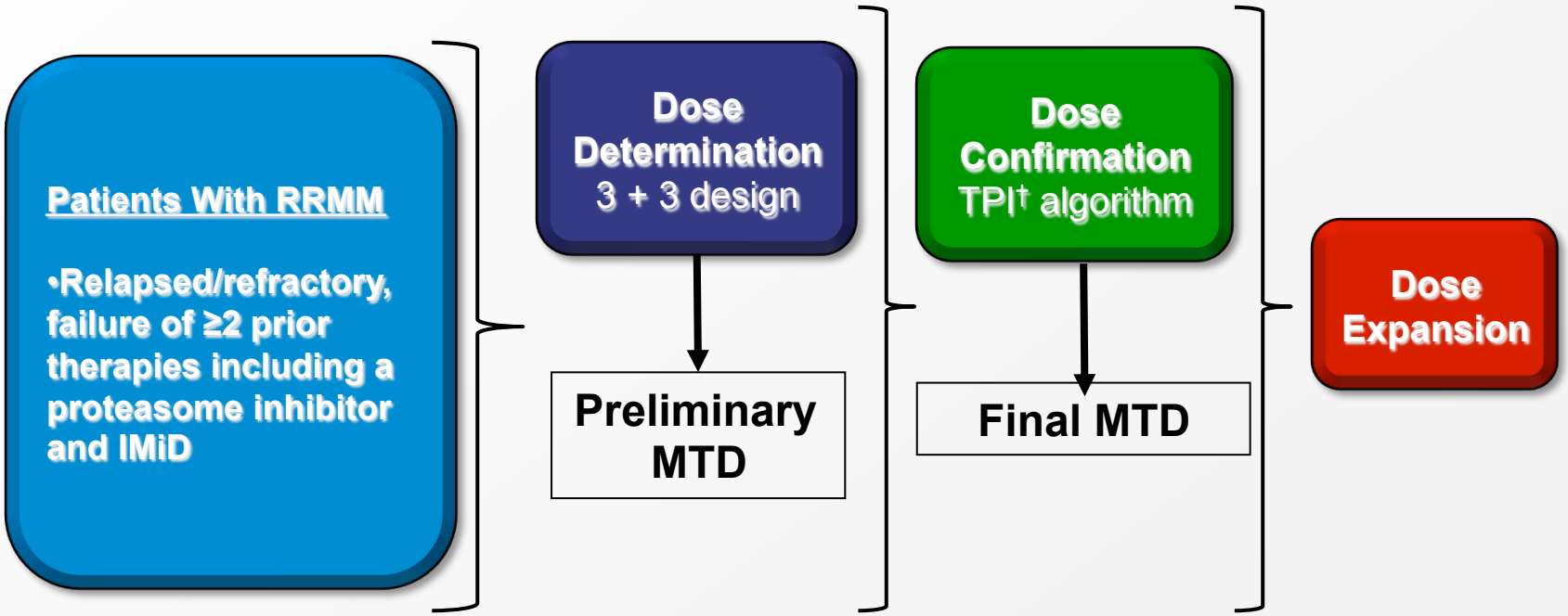
Pembrolizumab
Immuno-oncology

- The PD-1 pathway is often exploited by tumors to evade immune surveillance:[1-3]
  - PD1 is upregulated on activated T-cells
  - *Binding* of the PD-1 receptor to its ligands, PD-L1 and PD-L2 (expressed on the surface of APC & Tumor cells) *inhibits T-cell activation*
- Role of PD-1 inhibitors in multiple myeloma[1-2]
  - PD-1 is increased among T-cells of patients with MRD/RR disease
  - PD-1 blockade prolonged survival mice with 5TGM-1 PD-L1–positive MM cells
- Pembrolizumab blocks interaction between PD-1 and PD-L1/PD-L2[4-6]
  - Robust antitumor activity and manageable safety in multiple cancers
- Rationale for the combination of IMiDs and PD-L1 blockade[7]
  - Lenalidomide reduces PD-L1 and PD-1 expression on MM cells and T and myeloid derived suppressor cells
  - Lenalidomide enhances checkpoint blockade–induced effector cytokine production in MM bone marrow and induced cytotoxicity against MM cells



1. Liu J et al, *Blood*. 2007;110:296-304; 2. Tamura H, et al. *Leukemia*. 2013;27:464-72; 3. Paiva B, et al. *Leukemia*. 2015. 2015;29:2110-3;
4. Keir ME et al. *Annu Rev Immunol*. 2008;26:677-704; 5. Hallett WH et al. *Biol Blood Marrow Transplant*. 2011;17:1133-1145; 6. Homet Moreno B, Ribas A. *Br J Cancer*. 2015;112:1421-1427; 7. Görgün G. et al. *Clin Cancer Res*. 2015;21:4607-18.

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

- **MTD pembro 200 mg iv Q2W + Len 25 mg + Dex with**
- **Safety analysis: all patients enrolled in the study (N = 51)**
- **Efficacy analysis: patients who completed 3 cycle of treatment or discontinued for PD (N = 40)**

Mateos MV et al, ASCO 2016

KEYNOTE-023: Treatment-Related Adverse Events

n (%)	All AEs	Grade 3-5
All AEs (N = 51)	48 (94)	33 (65)
AEs in ≥6 Patients		
Neutropenia	19 (37)	17 (33)
Thrombocytopenia	21 (41)	9 (18)
Diarrhea	14 (28)	0
Fatigue	13 (26)	1 (2)
Anemia	11 (22)	6 (12)
Pruritus	6 (12)	0
Hyperglycemia	9 (18)	4 (8)
Muscle spasms	7 (14)	0
Myalgia	8 (16)	0
Blurred vision	7 (14)	0
Dizziness	6 (12)	0
Dyspnea	6 (12)	0

n (%)	Pembro + Len + Dex (N = 51)
Hyperthyroidism Grade 1	1 (2)
Hypothyroidism Grade 1	2 (4)
Thyroiditis Grade 1	1 (2)
Increased transaminases Grade 3	1 (2)
Renal failure Grade 3	1 (2)

Immune-Mediated Adverse Events

Mateos MV et al, ASCO 2016

KEYNOTE-023: Antitumor Activity
Central Review (IMWG 2006)

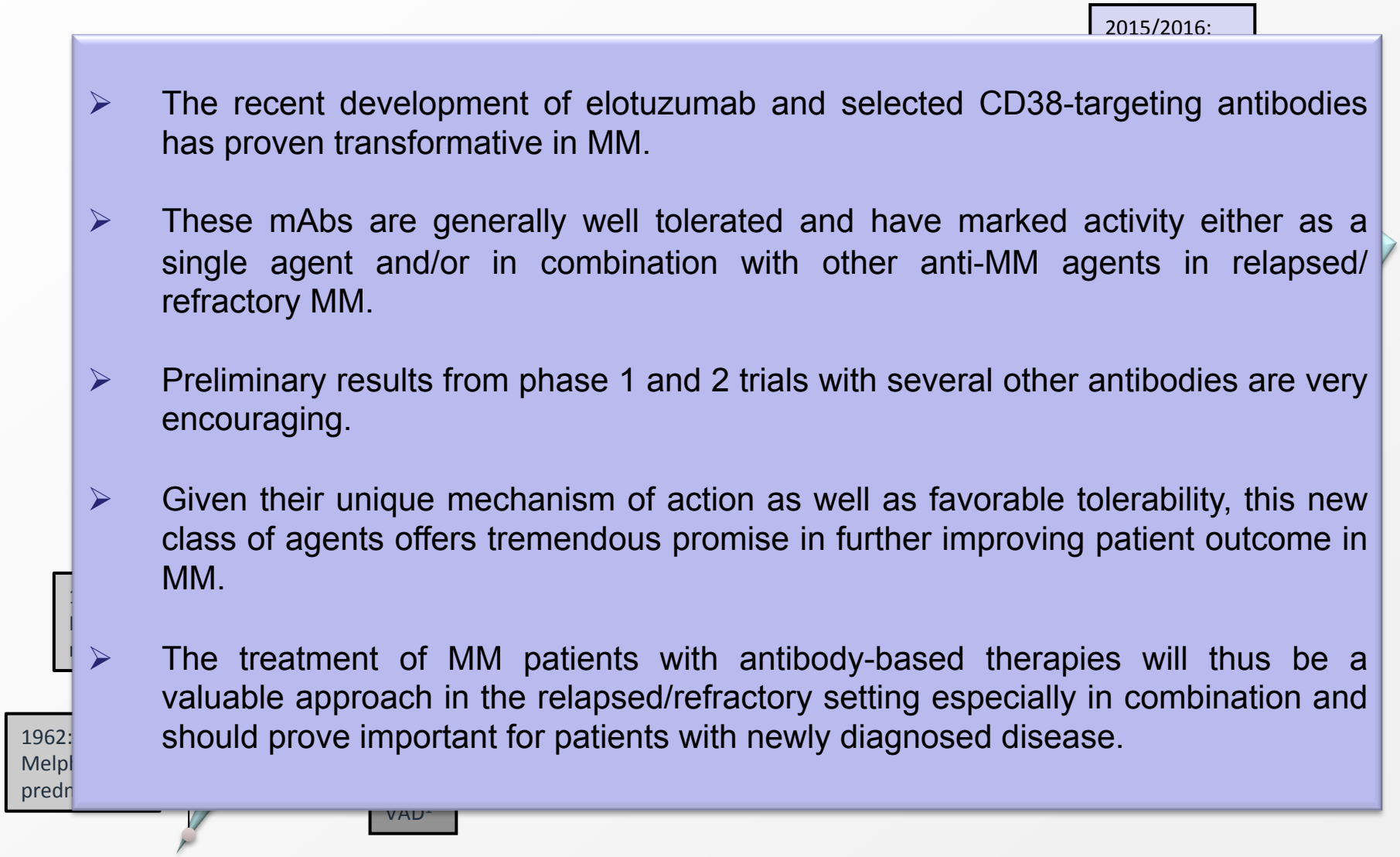
Best Overall Response n (%)	Efficacy Population† (n = 40)	Len-Refractory (n = 29)
Overall response rate	20 (50)	11 (38)
Stringent complete response (sCR)	1 (3)	1 (3)
Very good partial response (VGPR)	5 (13)	3 (10)
Partial response (PR)	14 (35)	7 (24)
Stable disease (SD)	19 (48)	17 (59)
Disease control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

Mateos MV et al, ASCO 2016

Conclusions and future directions

- The recent development of elotuzumab and selected CD38-targeting antibodies has proven transformative in MM.
- These mAbs are generally well tolerated and have marked activity either as a single agent and/or in combination with other anti-MM agents in relapsed/ refractory MM.
- Preliminary results from phase 1 and 2 trials with several other antibodies are very encouraging.
- Given their unique mechanism of action as well as favorable tolerability, this new class of agents offers tremendous promise in further improving patient outcome in MM.
- The treatment of MM patients with antibody-based therapies will thus be a valuable approach in the relapsed/refractory setting especially in combination and should prove important for patients with newly diagnosed disease.



ABMT=autologous bone marrow transplant; VAD=vincristine/doxorubicin/dexamethasone.

1. Latif T et al. *Exp Hematol Oncol*. 2012;1:27. 2. Kyprolis [prescribing information]. Onyx Pharmaceuticals, Inc; South San Francisco, CA.
3. Pomalyst [prescribing information]. Celgene Corporation; Summit, NJ.