Anticorpi monoclonali nel mieloma

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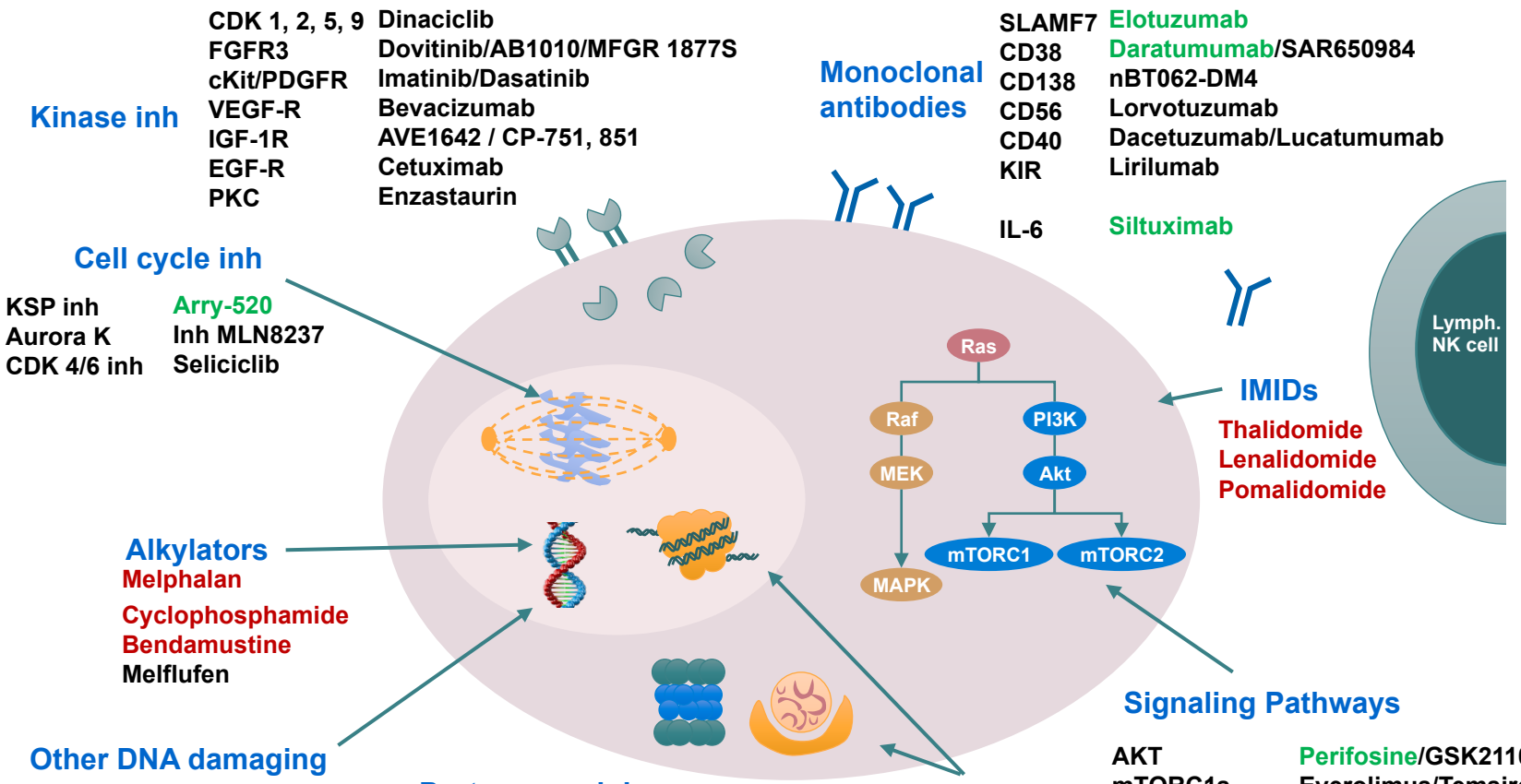
Main Targets in Multiple Myeloma Plasma Cells and Drugs Tested Against Them



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

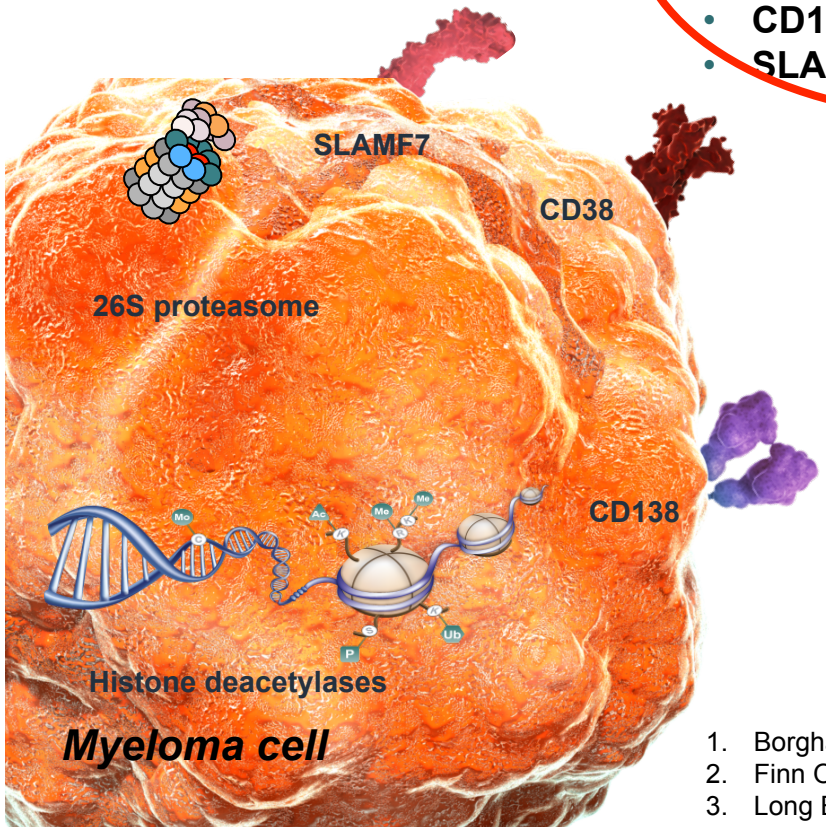
Red: approved; **Green**: in phase III

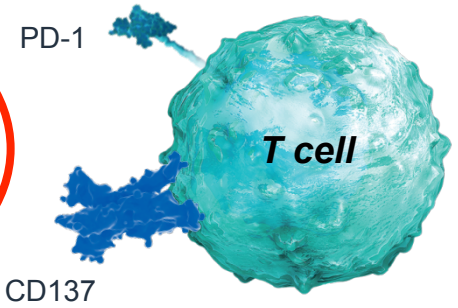
Ongoing Research in Multiple Myeloma

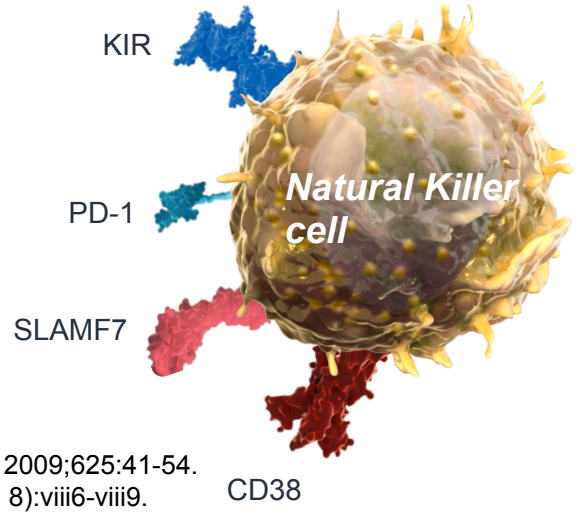
1. *Targeting biochemical processes within the myeloma cell*
   - *Proteasome inhibitors*
   - *HDAC inhibitors*

2. *Monoclonal antibodies that target an antigen expressed by myeloma cells*
   - **CD38**
   - **CD138**
   - **SLAMF7**

3. *Immuno-oncology therapies to activate the immune system*
   - **PD-1**
   - **KIR**
   - **SLAMF7**

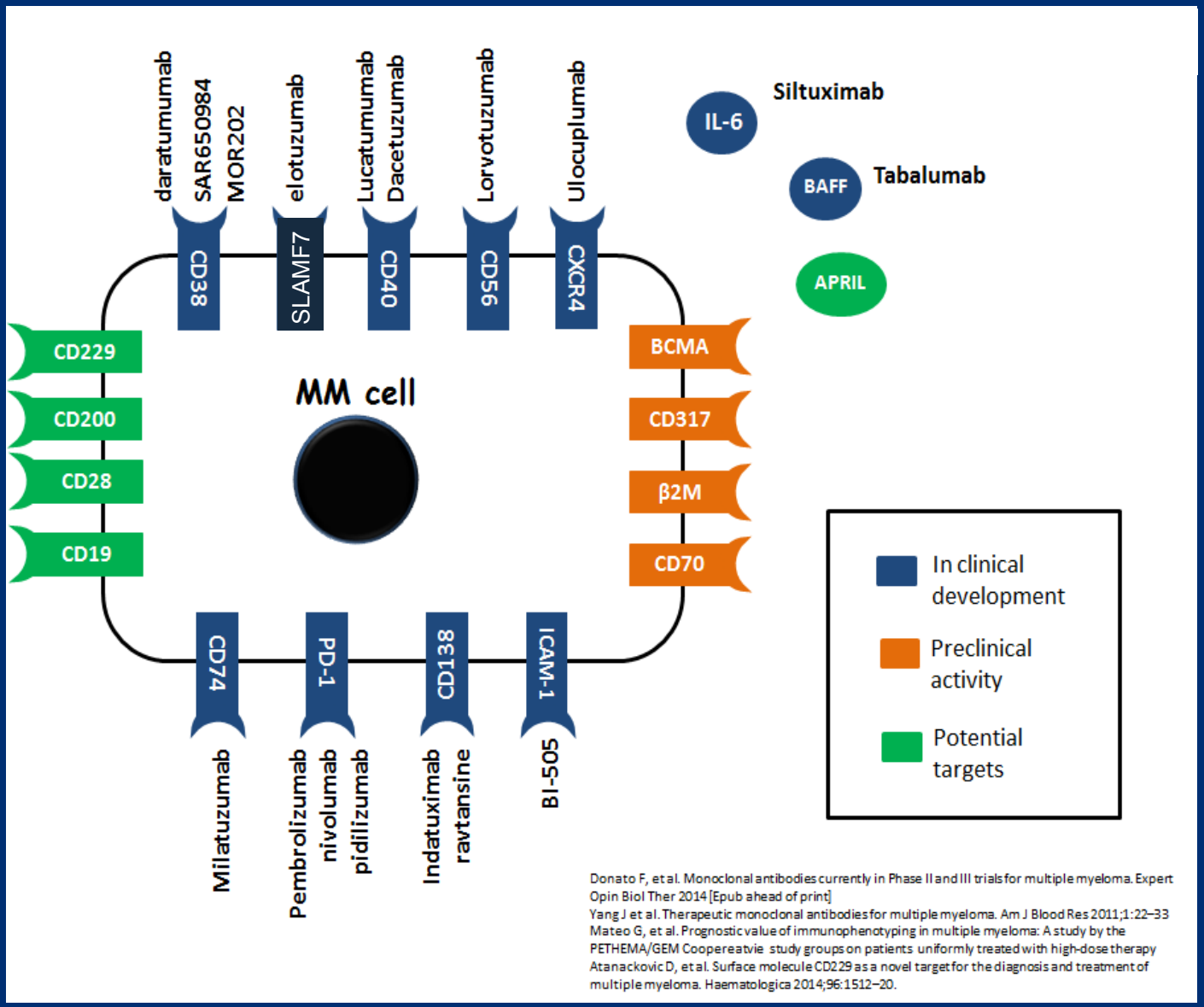






1. Borghaei H et al. *Eur J Pharmacol*. 2009;625:41-54.
2. Finn OJ. *Ann Oncol*. 2012;23(suppl 8):viii6-viii9.
3. Long EO et al. *Annu Rev Immunol*. 2013;13:227–258

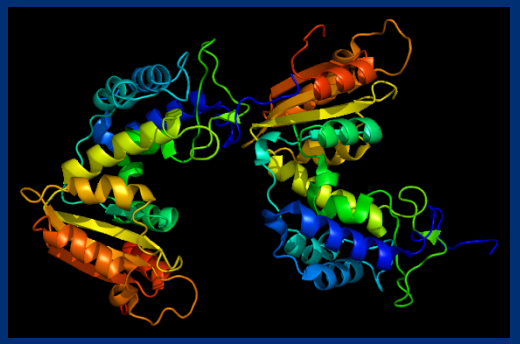
Targets for mAbs



Lonial S et al, Leukemia 2015

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

Three monoclonal antibodies targeting anti-CD38

Fully human anti-CD38 mAb:

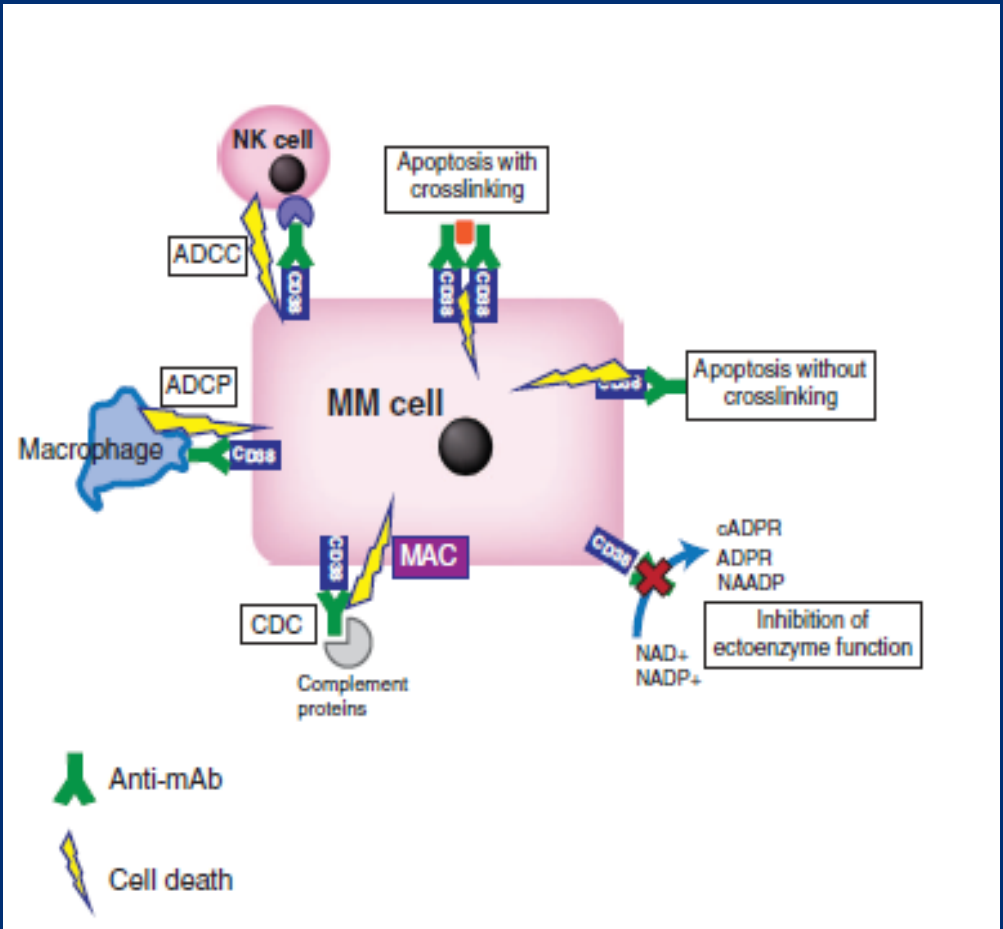
- Daratumumab (DARA)
- MOR202 (MOR)

Chimeric anti-CD38 mAb:

- Isatuximab (SAR650984, SAR, Sanofi)

https://download.ama-assn.org/resources/doc/usan/x-pub/isatuximab.pdf
de Weers et al. J Immunol 2011;186: 1840–1848
http://www.morphosys.com/pipeline/proprietary-product-portfolio/mor202

Therapeutic impact of targeting CD38

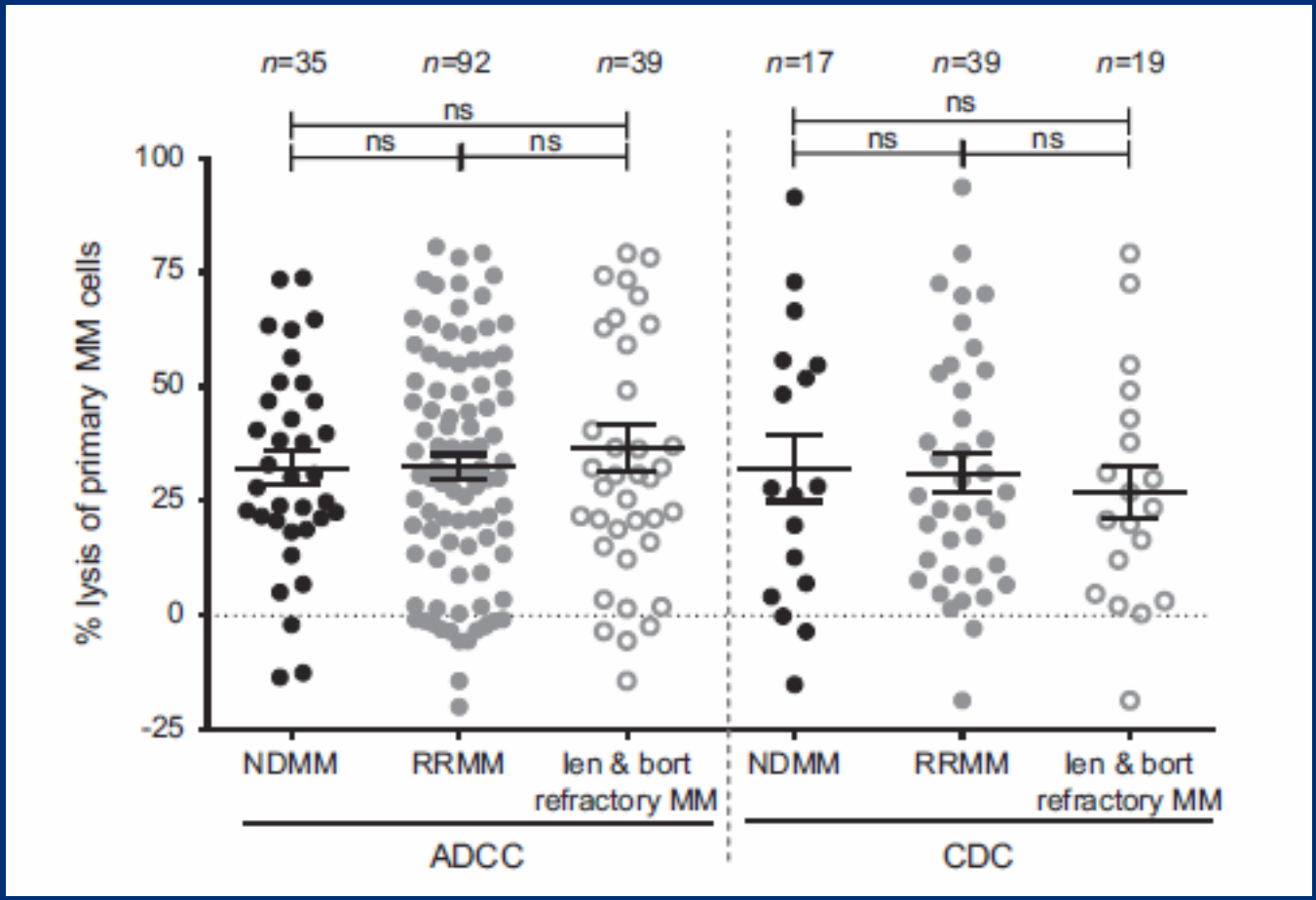


The binding CD38-antibody induces:

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

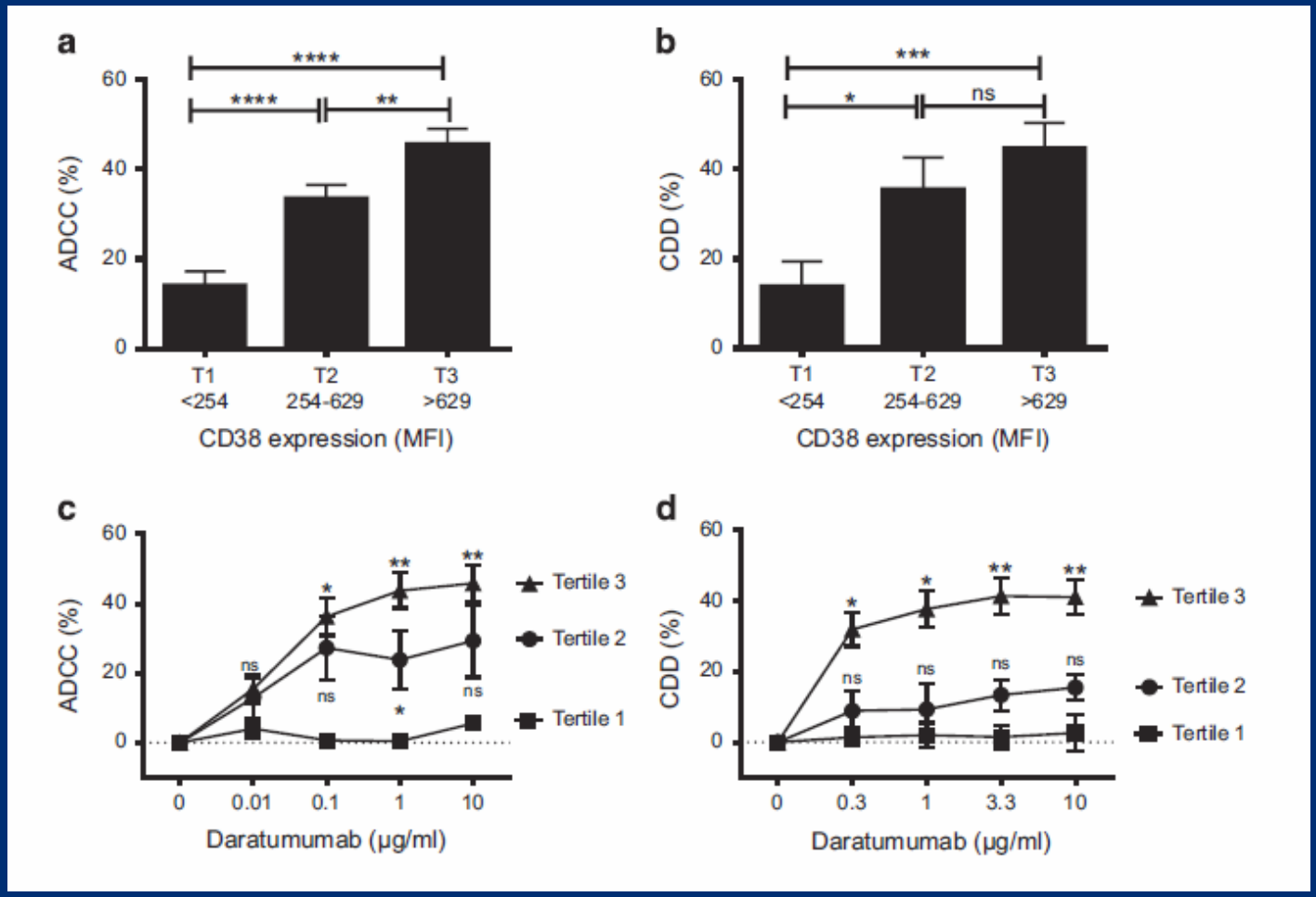
Lonial S et al, Leukemia 2015

ADCC and CDC is not dependent upon when a patient is treated



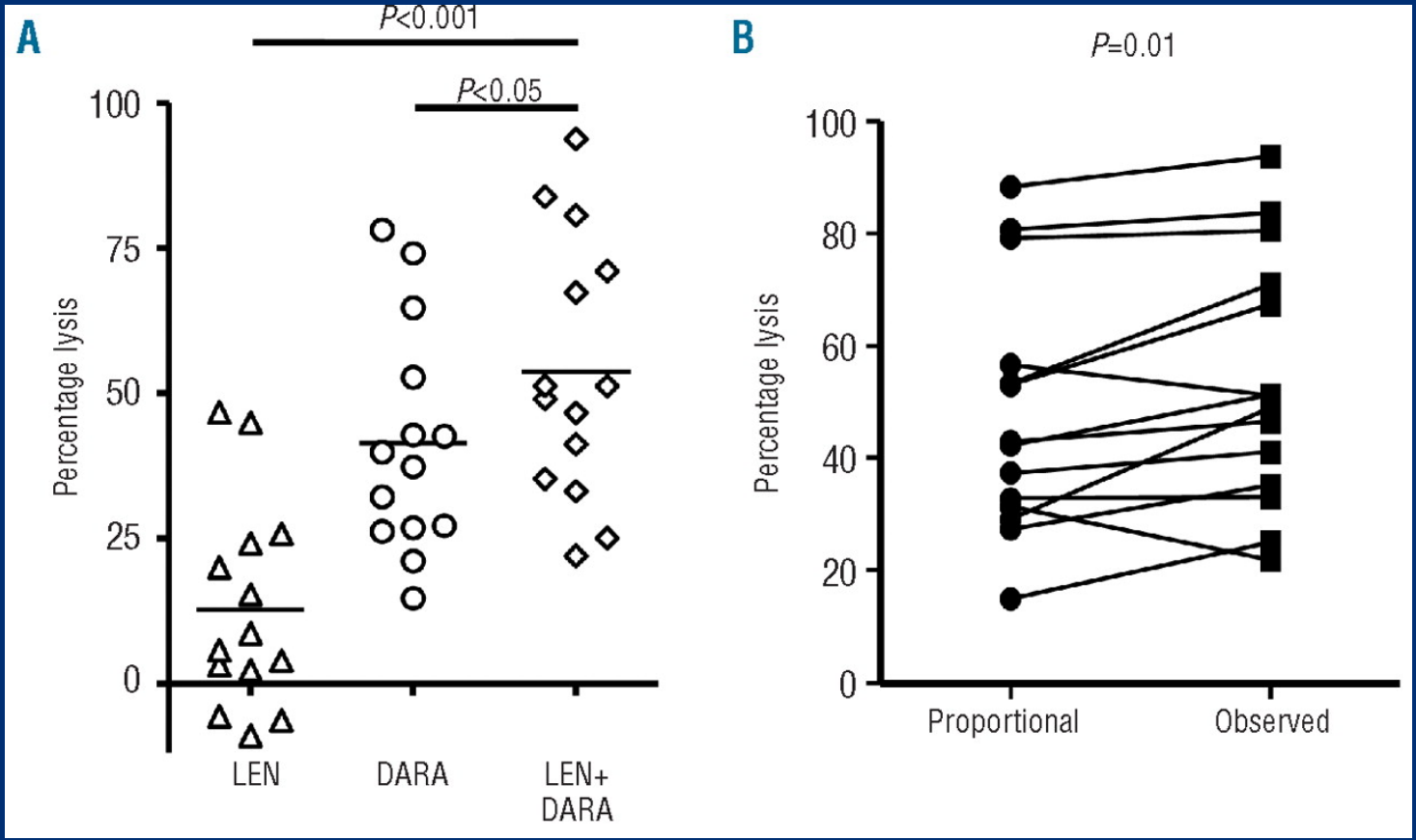
Nijhof et al, *Leukemia* 2015 (epub)

CD38 Expression Correlated With Cell Death (Patient Samples)



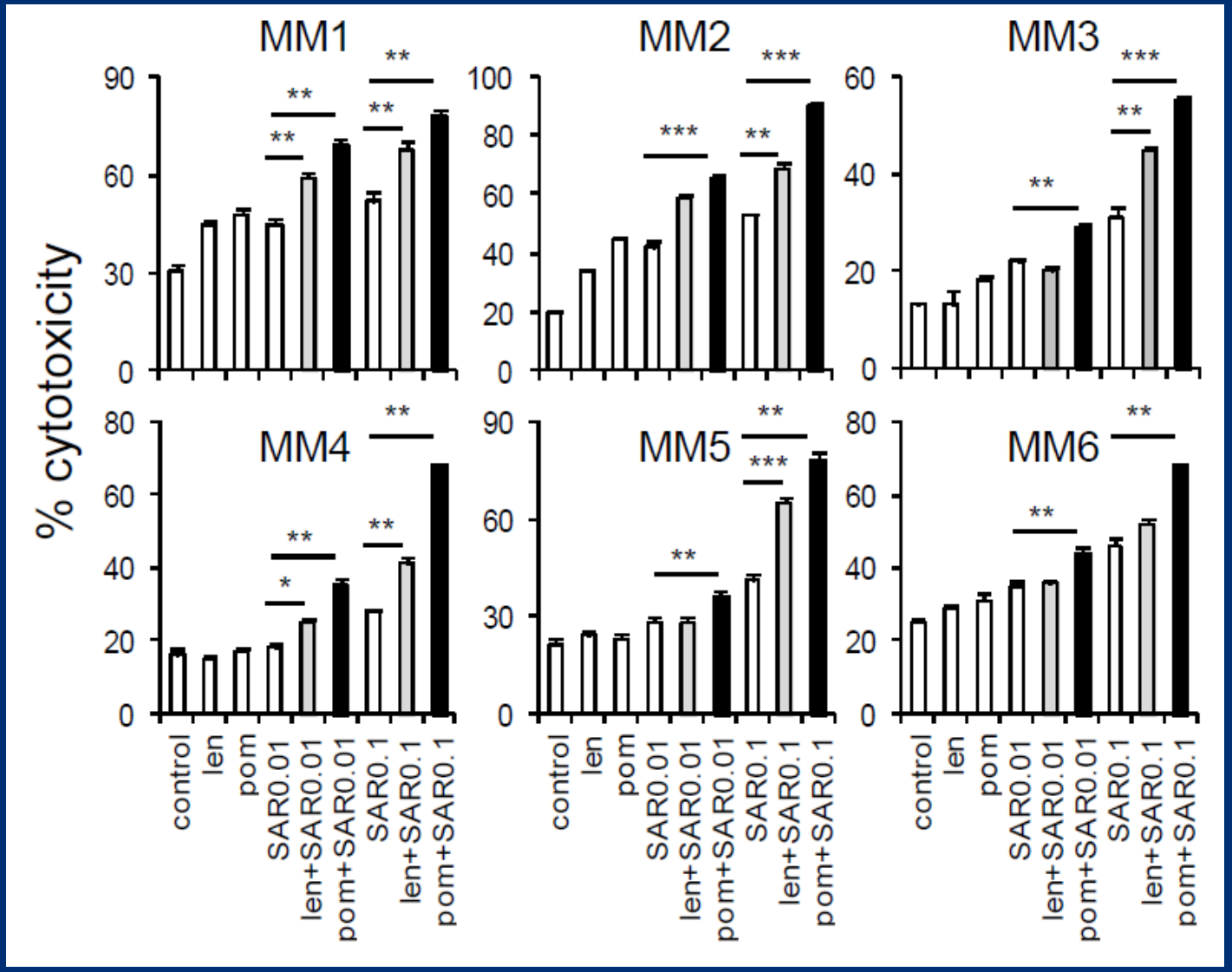
Nijhof et al, *Leukemia* 2015 (epub)

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



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

IMiD effect with SAR



Jiang et al. *Leukemia* 2015 (epub)

Daratumumab in R/R MM: SINGLE AGENT ACTIVITY

Dose-escalation cohorts

Part 1: 32 pts

Open label, weekly iv infusion, 8 weeks

Dose-escalation: 3+3 scheme*

0.005→0.05→0.1→0.5→1.0 →2.0→4.0→8.0→16.0 →24.0 mg/kg

* - start with pre-dose at 10% of full dose, max 10 mg
- 3 weeks' delay after first full dose
- governed by independent data monitoring committee

Expansion cohort: Extended treatment for close to 2 years

Part 2: 72 pts

Open label, single arm, 8 and 16 mg/kg

8 weekly infusions followed by

8 biweekly infusions followed by up to

72 monthly infusions

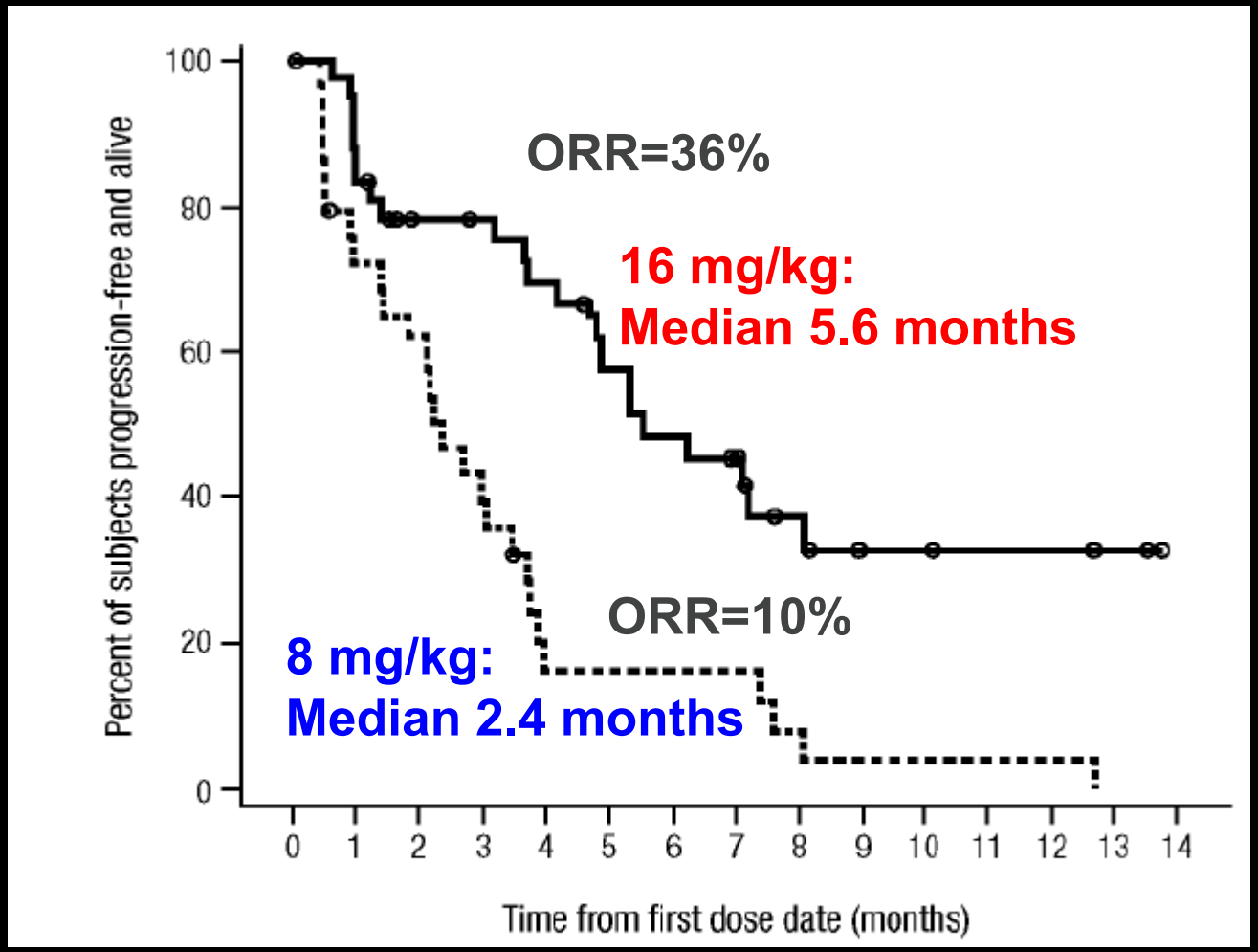
Different combinations of premedications, predose infusions, infusion volumes, and infusion rates (3 – 4 hours)

Median 4 lines prior treatment

Lokhorst et al. N Engl J Med 2015

Progression-free survival

Median follow-up: 16.9 months (8 mg/kg), 10.2 months (16 mg/kg)



- DOR: 6.9m & NR
- 65% of the patients who had responded to 16 mg did not have progression @ 12 months

OS @ 12 months: 77% in both groups

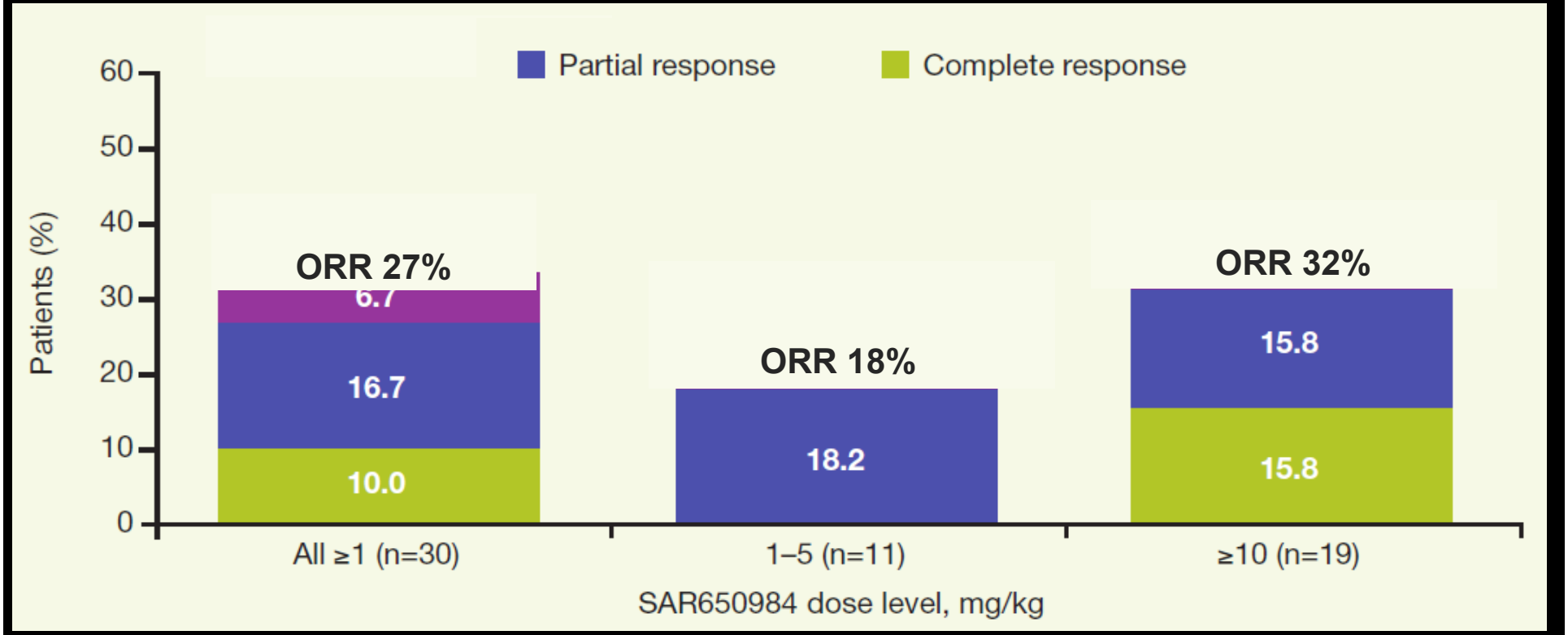
Lokhorst et al. N Engl J Med 2015

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

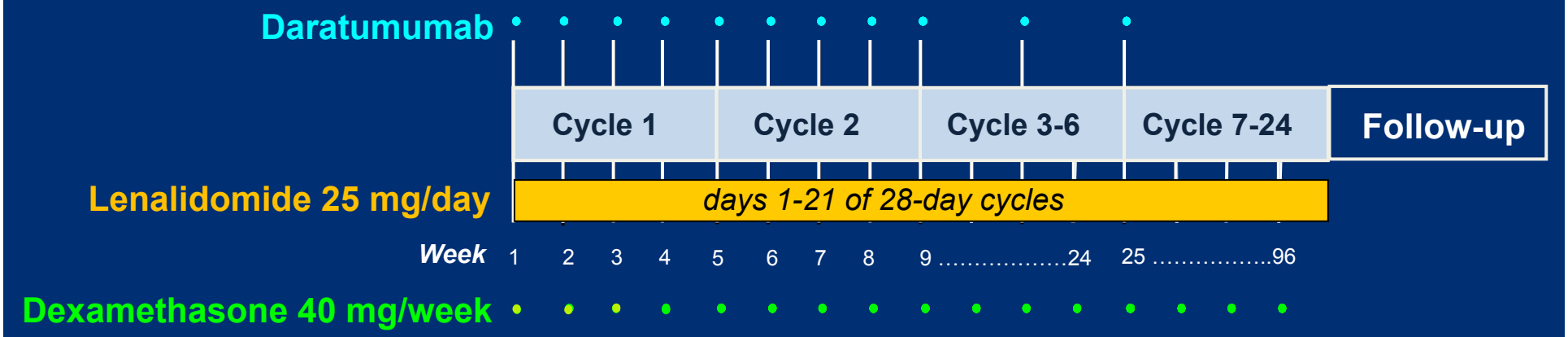
Isatuximab (SAR) in R/R MM (Phase I): SINGLE AGENT ACTIVITY



- 40 pts, median 6 lines prior therapy
- Minor responses or better : 33.7% (38.3% at >10 mg)
- Time to response 4.6 weeks
- Escalating doses 1-20 mg/kg q2W: MTD not reached

Martin et al. ASCO 2014

Daratumumab with LD in R/R MM



Daratumumab dosing

- **Part 1 (n=13):**
  Dose escalation study: 2-16 mg/kg
- **Part 2 (n=32):**
  Expansion cohort: 16 mg/kg

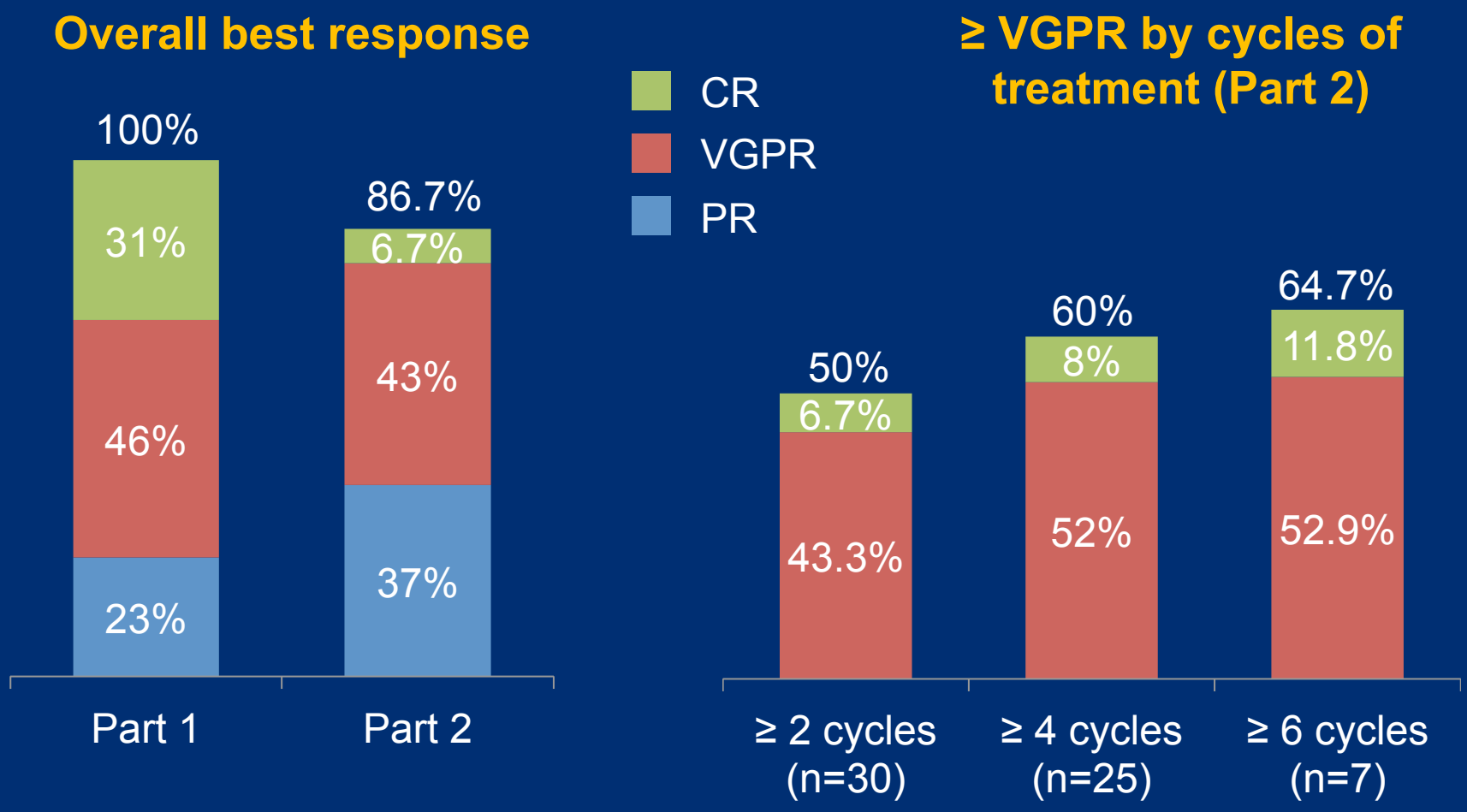
Key inclusion criteria:

- Part 1: relapsed and refractory MM following 2-4 prior lines
- Part 2: relapsed and refractory MM following ≥ 1 prior lines (no upper limit)
- Patients refractory or intolerant to LEN excluded

Plesner et al. ASH 2014

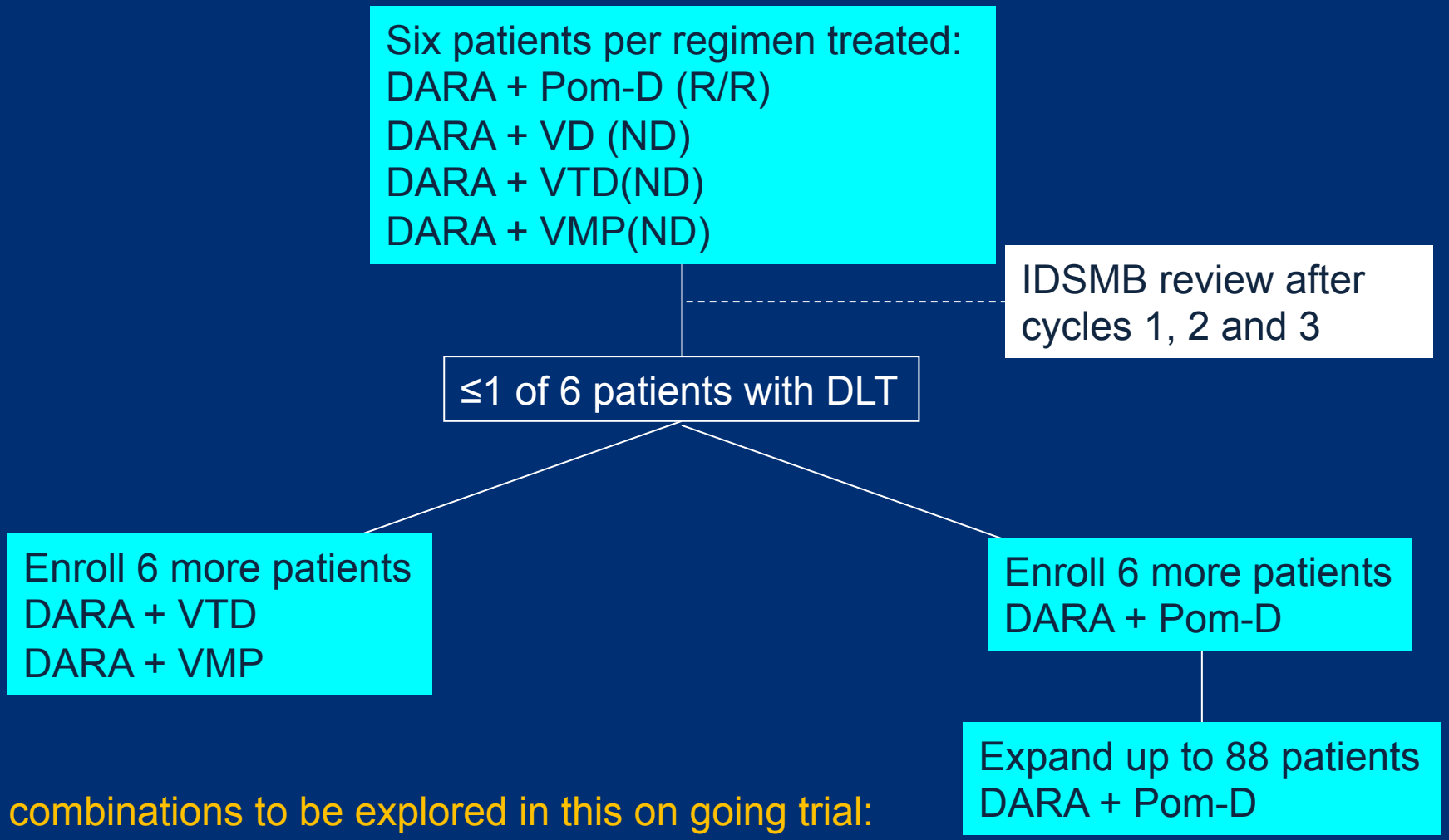
Overall best response

Mean duration of follow-up: 12.9 months (Part 1), 5.6 months (Part 2)



Plesner et al. ASH 2014

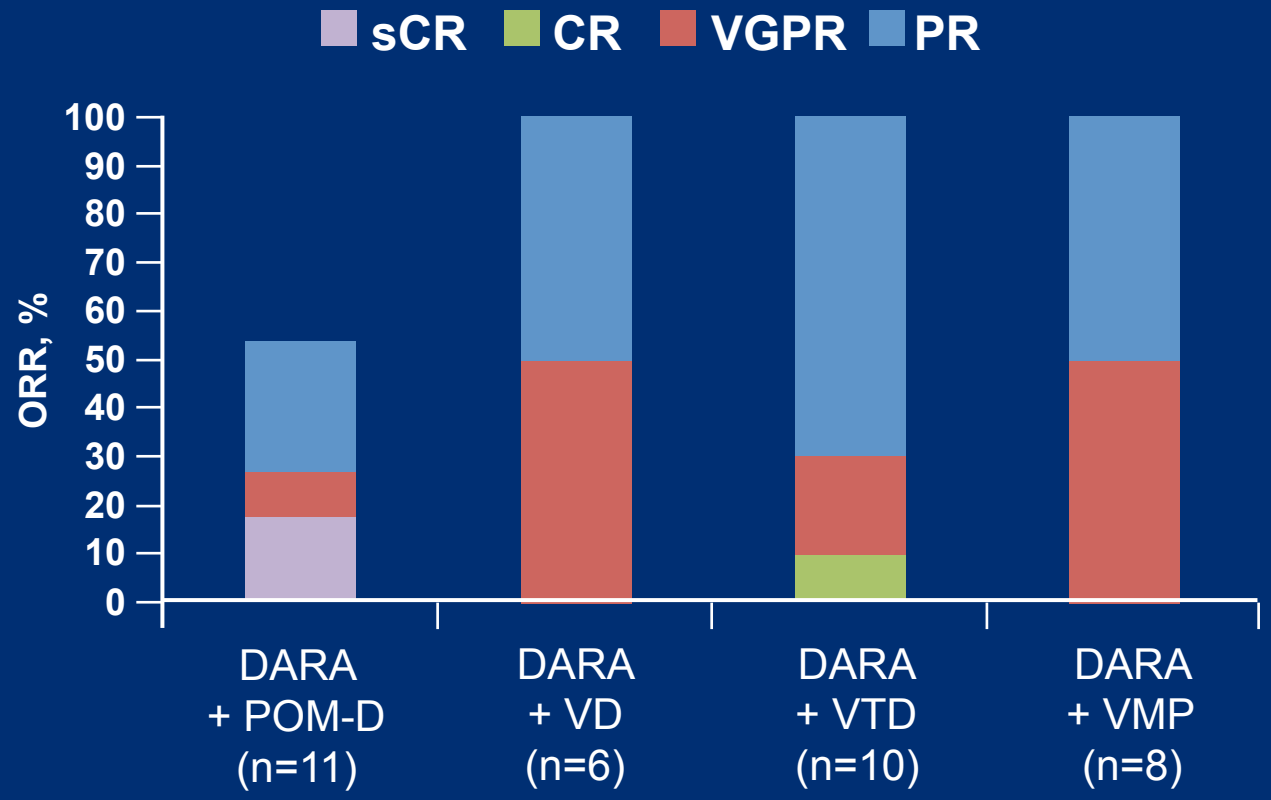
An Open-label, Multicenter, Phase 1b Study of Daratumumab in Combination with Backbone Regimens in Patients with MM (MMY1001; NCT01998971)



Other combinations to be explored in this on going trial:
DARA + Carfilzomib-dex
DARA + KRd
(www.clinicaltrials.gov)

Mateos et al. EHA 2015

Response rate



- ORR 54.5% in rel/ref patients receiving DARA+POM-D
- ORR 100% in newly diagnosed patients receiving DARA+VD, DARA +VTD or DARA+VMP

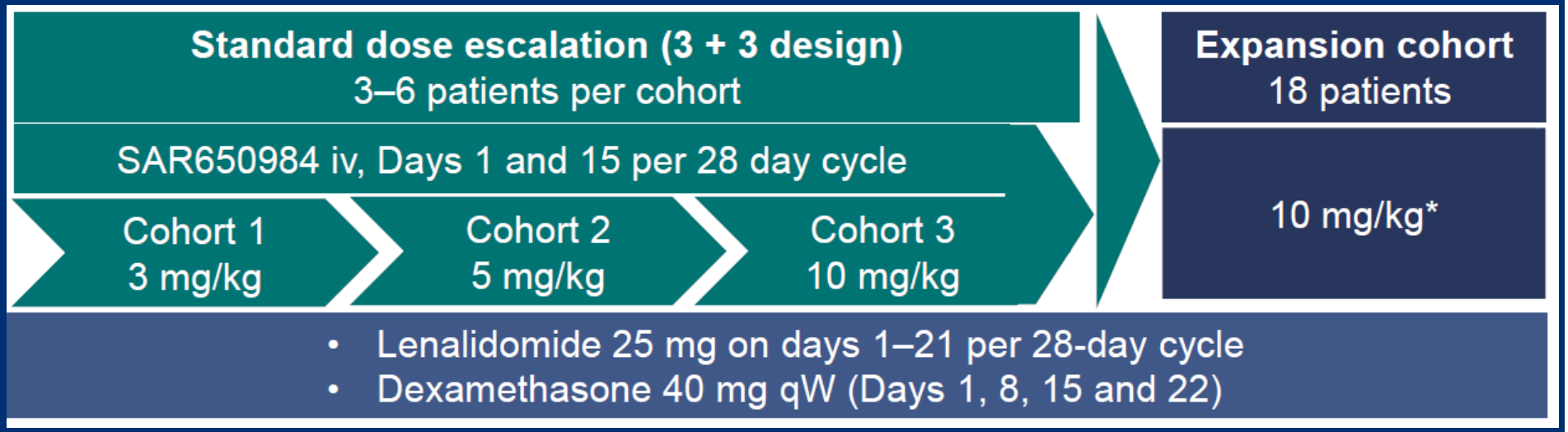
Mateos et al. EHA 2015

Ongoing studies with DARA in MM

- Relapsed/Refractory:
  - Dara **Vd** vs Vd
  - Dara **Rd** vs Rd
- Newly diagnosed:
  - Dara **VMP** vs VMP
  - Dara **Rd** vs Rd
  - Dara **VTD** vs VTD + **ASCT** + consolidation + Dara maintenence vs observ

Phase 1b: Isatuximab + Len/dex in rel/ref MM

- 3 + 3 dose escalation + expansion study

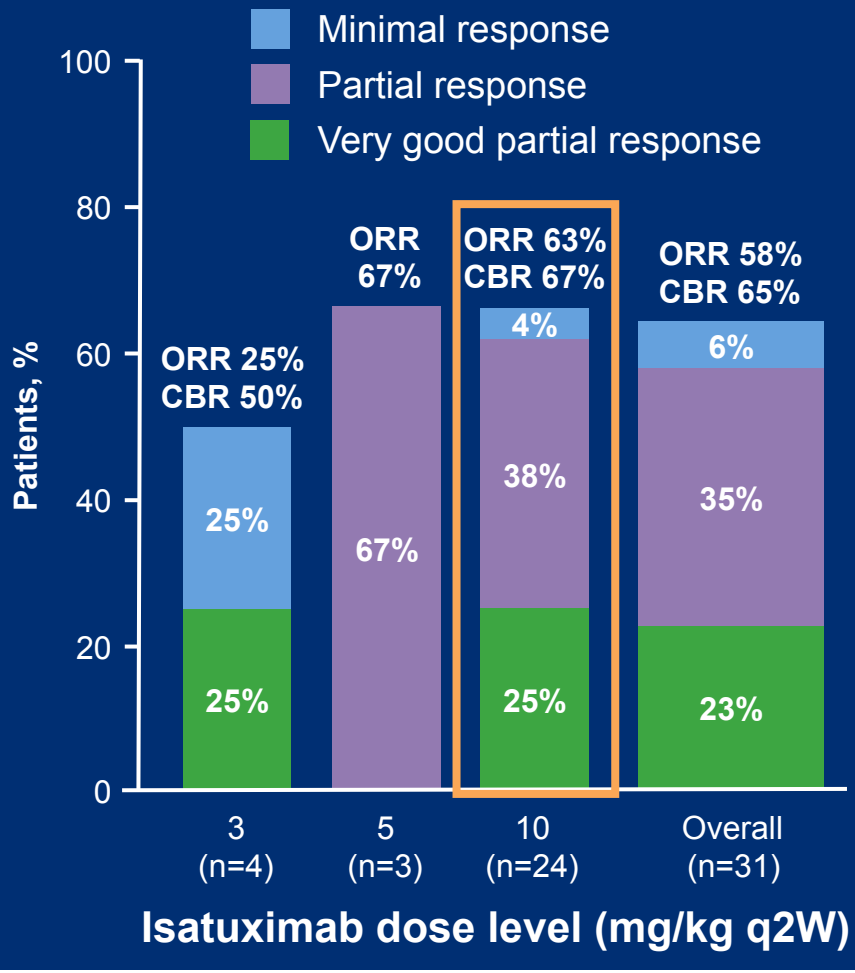


- Patients: n=31
  - Median 6 prior lines
  - 94% prior Len
  - Refractory to IMiD: 81%

Martin et al. ASH 2014

Response and PFS

Response by dose level and overall



PFS at 9 months follow-up

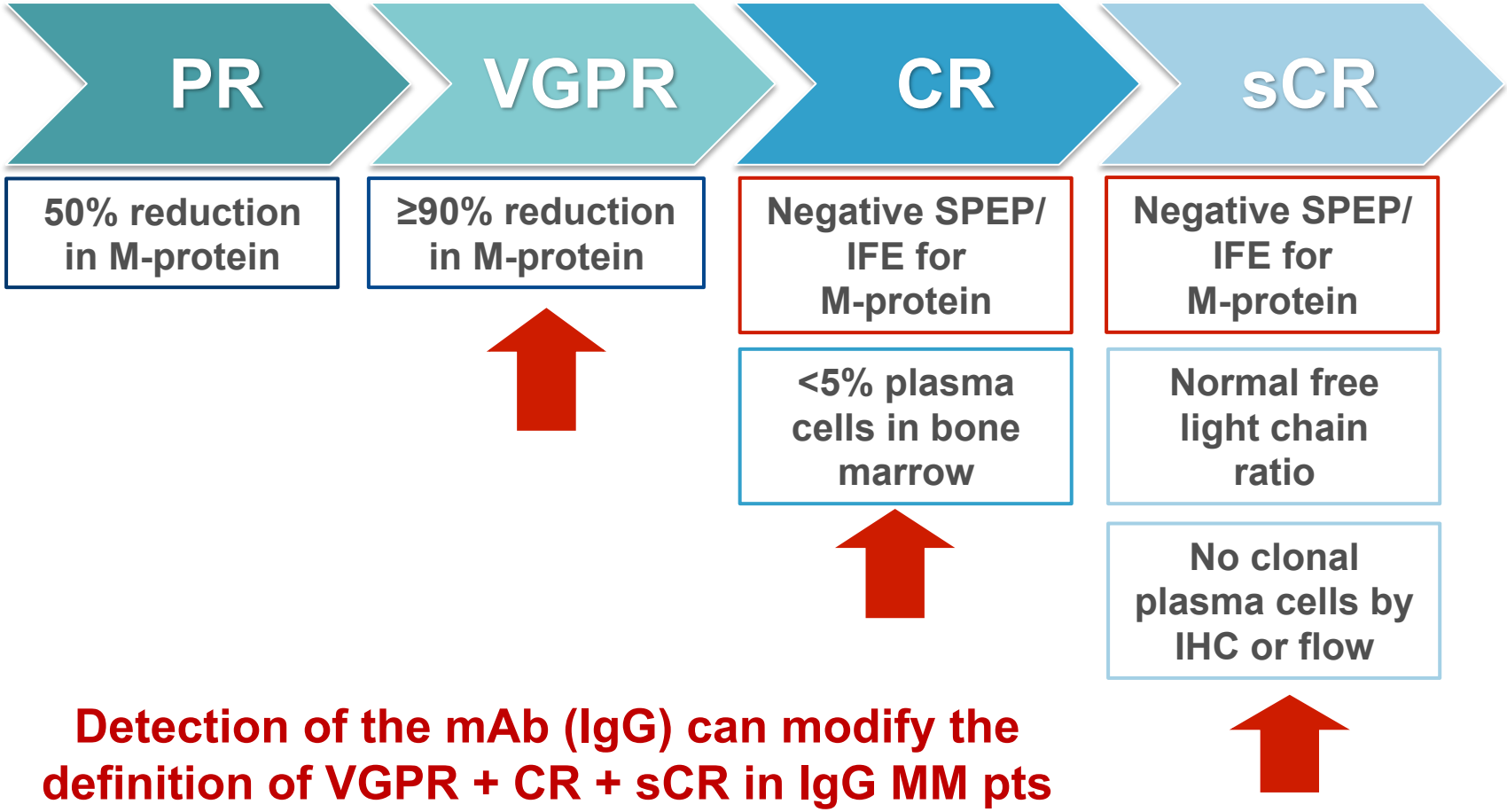
- Overall (n=31): 6.2 mos
- 1-2 prior lines (n=7): not reached
- ≥ 3 prior lines (n=24): 5.8 mos

Martin et al. ASH 2014

Managing mAb therapy in the clinic

- Special considerations with anti-CD38 mAb therapy
  - Infusion-related reactions (IRRs)
  - Assessment of response
  - Blood typing

Clinical assessment of M-protein response in MM and interference through mAbs



Detection of the mAb (IgG) can modify the definition of VGPR + CR + sCR in IgG MM pts

The daratumumab concentration used clinically is equivalent to 1g/L

McCudden C, et al. ASCO 2015

Development of an assay to distinguish M-protein from therapeutic antibody

- Daratumumab IFE reflex assay (DIRA):
  - Incubation of serum samples of baseline and daratumumab-treated patients with or without an anti-idiotype mAb
  - IFE: Daratumumab migration is shifted from the gamma region by the anti-idiotype mAb

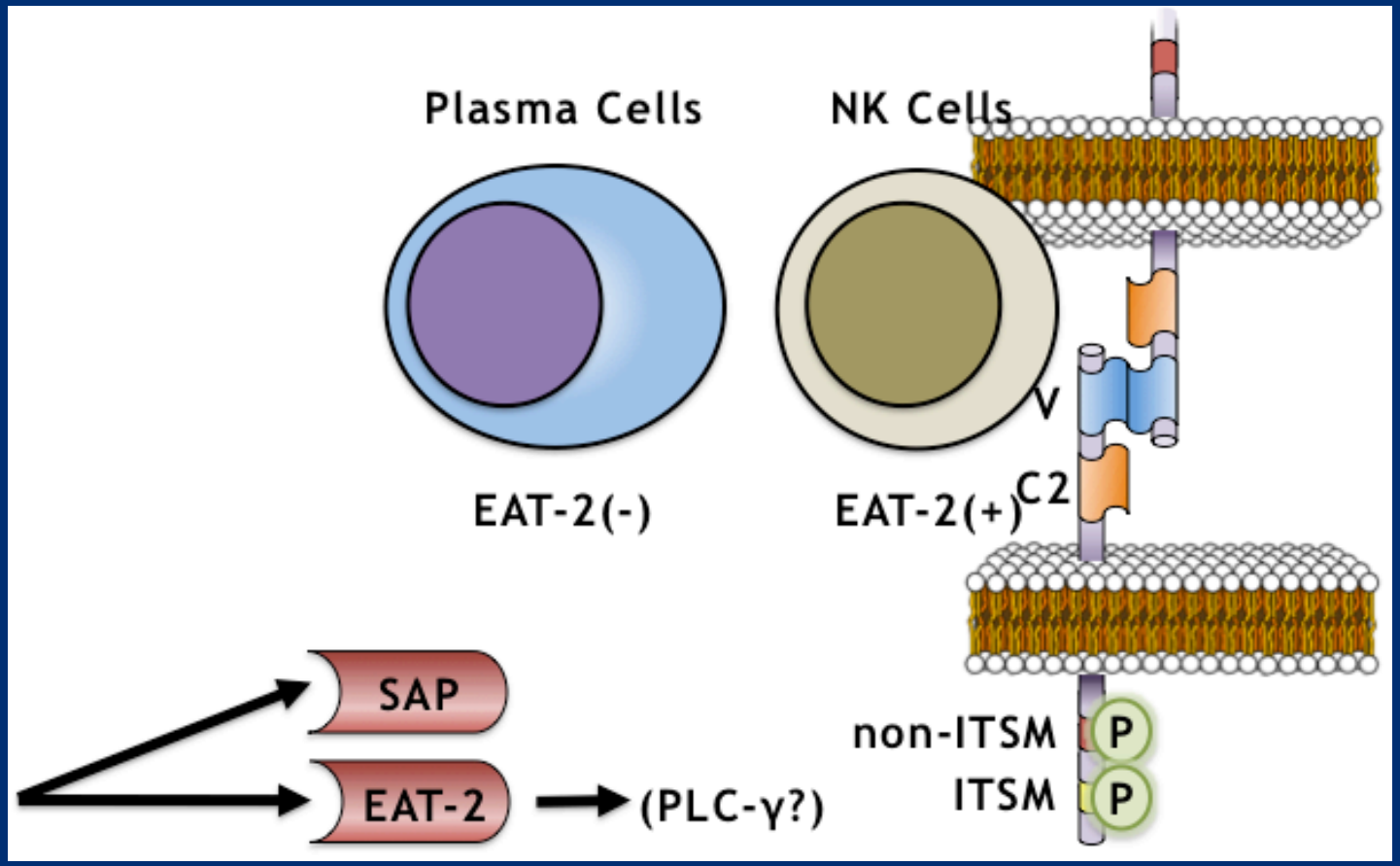
McCudden C, et al. ASCO 2015

Blood compatibility testing for patients receiving anti-CD38 mAbs

- CD38 is weakly expressed on human red blood cells (RBCs)
- Daratumumab binds to CD38 on RBCs → false positive results in the Indirect Antiglobulin Test (indirect Coombs test)
- Daratumumab does not interfere with the major antigens of ABO/RhD typing, but with the minor ones
- Options to circumvent the in vitro effect:
  - Dithiothreitol (DTT): denaturation of RBC CD38 epitopes → prevention of Dara binding to RBCs
  - Anti-idiotype mAb and soluble CD38 → prevention of Dara binding to RBCs

Chapuy et al. Transfusion. 2015;55(6 Pt 2):1545-54
Oostendorp et al. Transfusion. 2015;55(6 Pt 2):1555-62

SLAMF7 as a target



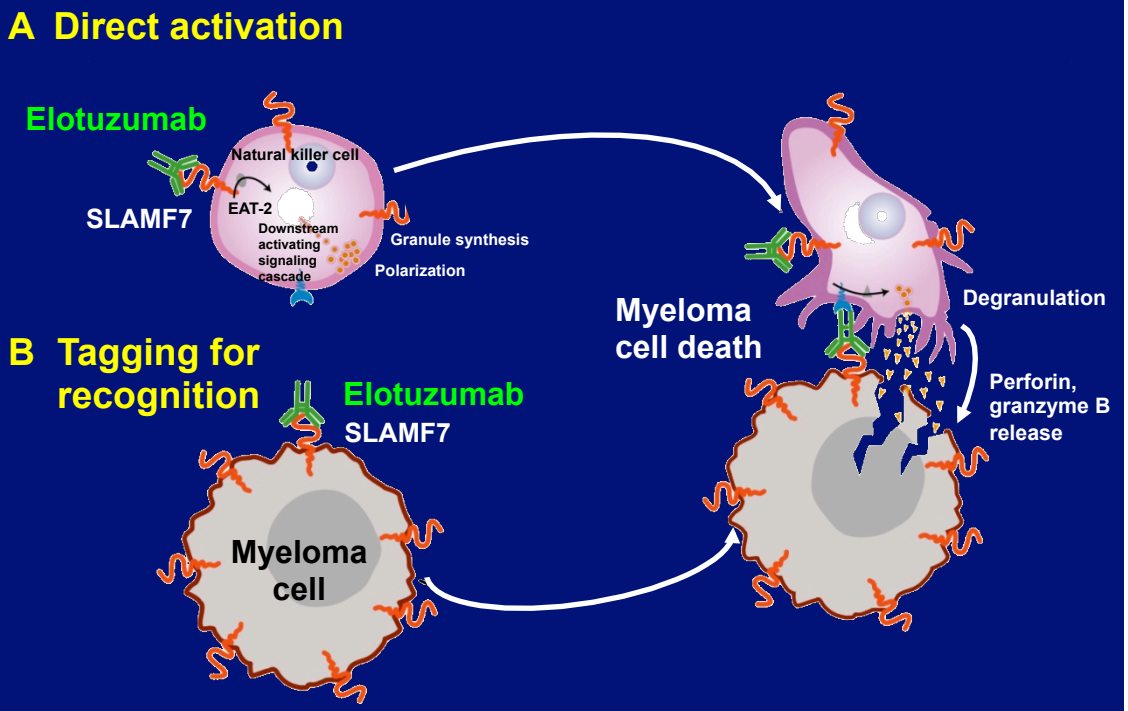
- SLAMF7 is a glycoprotein highly expressed on >95% of **myeloma cells**
- It shows lower expression on **NK cells** and little to no expression on normal tissues or hematopoietic stem cells

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]

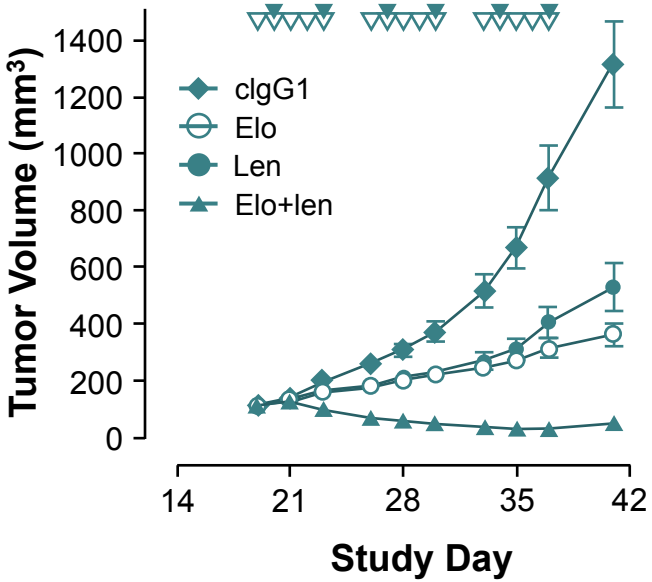


1. Hsi ED et al. *Clin Cancer Res* 2008;14:2775–84
2. Collins SM et al. *Cancer Immunol Immunother* 2013;62:1841–9
3. Guo H et al. *Mol Cell Biol* 2015;35:41–51

SLAMF7 = Signaling Lymphocyte Activation Molecule-F7

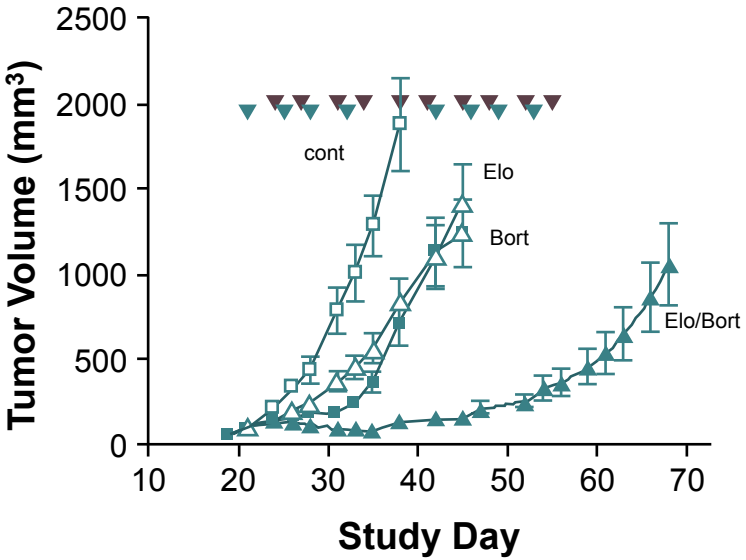
Elotuzumab Exhibits Synergy With Both Lenalidomide and Bortezomib

- 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]

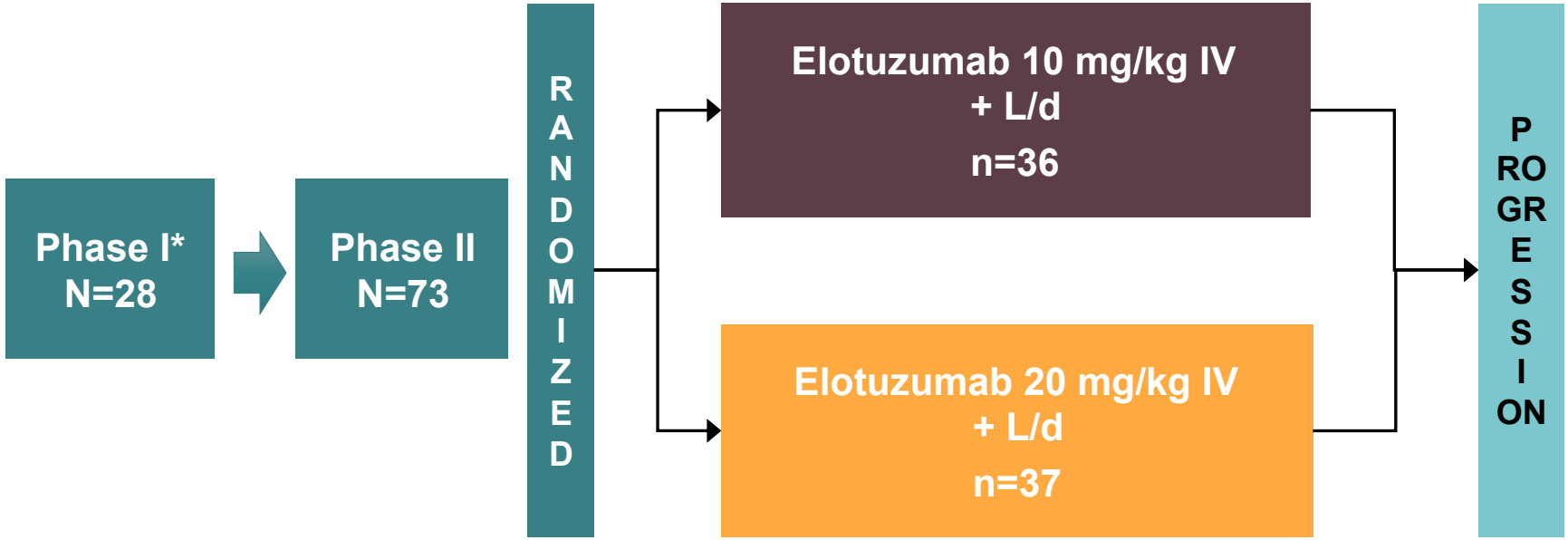
- Bortezomib exhibits direct antimyeloma activity, which augments the cells' sensitivity to Natural Killer cell-mediated killing by enhancing activating ligands and reducing inhibitory ligands on myeloma cells

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.

No single agent activity of Elotuzumab

Phase Ib/II study of Elo-Len-Dex in R/R MM



- Phase II: patients (N=73) with R/R MM with 1–3 prior therapies were randomized to elotuzumab 10 or 20 mg/kg IV combined with
  - Lenalidomide 25 mg po
  - Low-dose dexamethasone 40 mg po

  Until PD

* *Lonial S et al. *J Clin Oncol.* 2012;30:1953-1959.

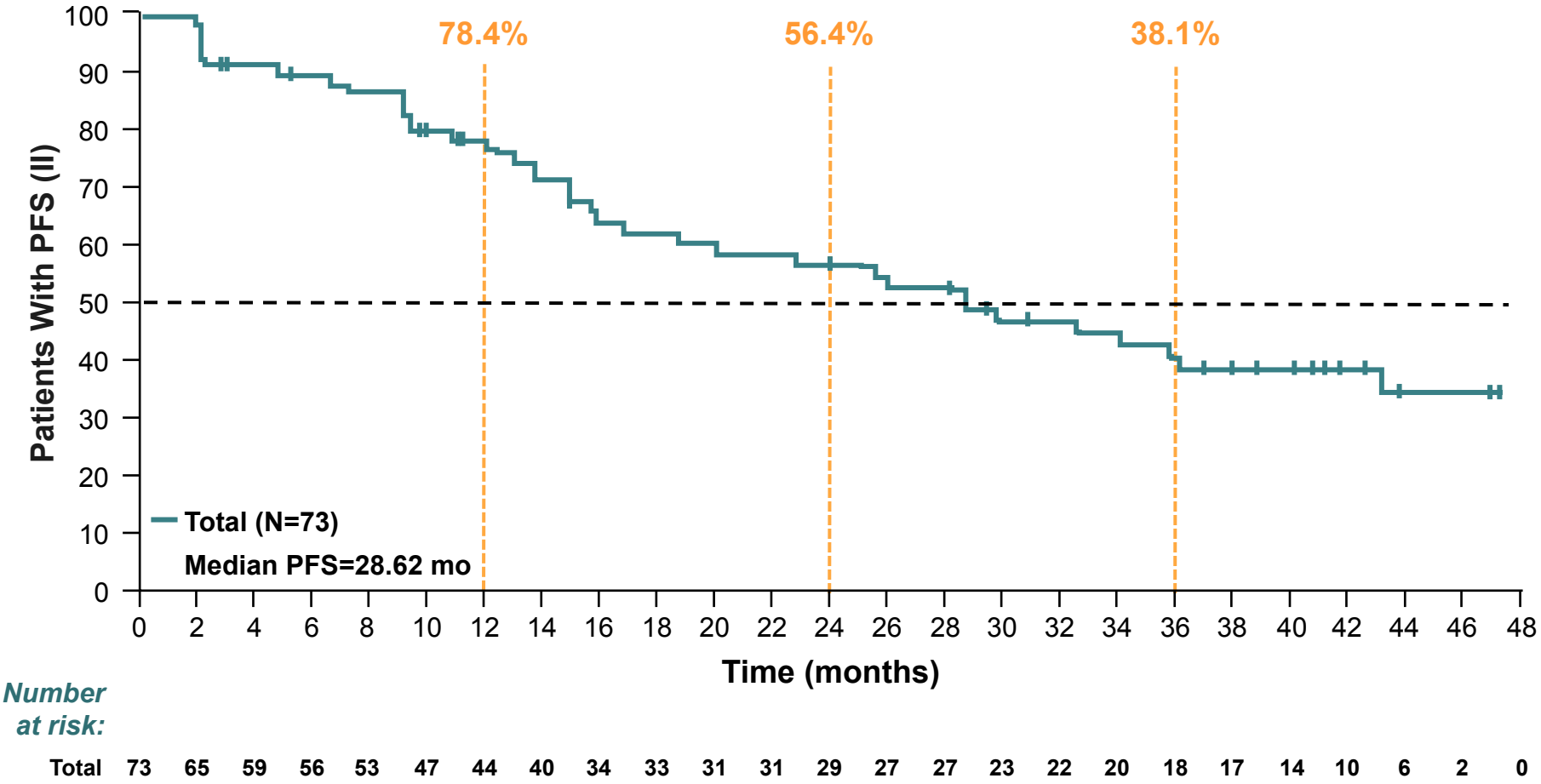
Richardson P et al, ASH 2014

Phase II Efficacy: Overall Response Rate (ORR)

Assessment	Elotuzumab dose group		
	10 mg/kg (n=36)	20 mg/kg (n=37)	Total (n=73)
Overall response*, n (%)	**33 (92)**	**28 (76)**	**61 (84)**
Best confirmed response, n (%)			
Stringent complete response (sCR)	2 (6)	1 (3)	3 (4)
Complete response (CR)	4 (11)	3 (8)	7 (10)
Very good partial response (VGPR)	**17 (47)**	**14 (38)**	**31 (43)**
Partial response (PR)	10 (28)	10 (27)	20 (27)
Stable disease (SD)	3 (8)	7 (19)	10 (14)
Missing	0	2 (5)	2 (3)
Median time to first response, (mo)	1.0	1.7	1.0
Median duration of response (mo)	23.0	18.0	20.8

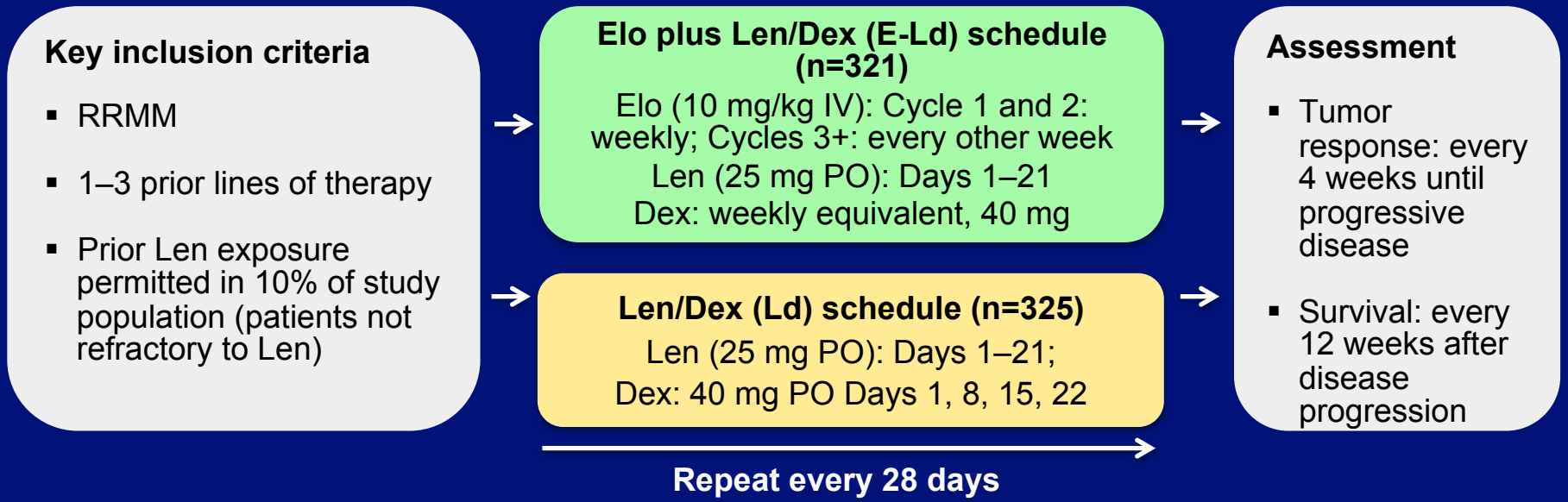
Richardson P et al, ASH 2014

Phase II Efficacy: Progression-Free Survival



Richardson P et al, ASH 2014

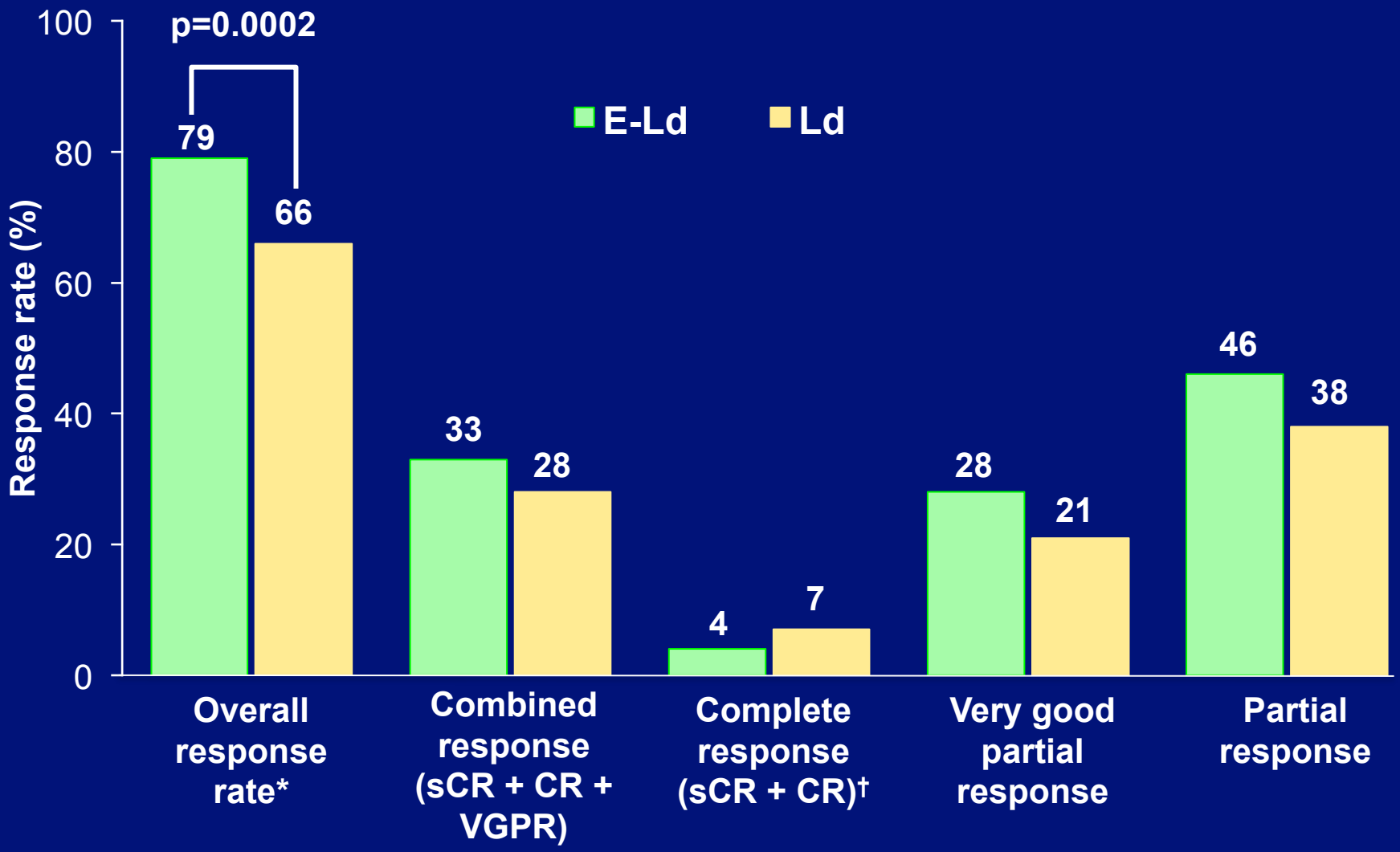
ELOQUENT-2: Elo-Ld vs Ld in R/R MM



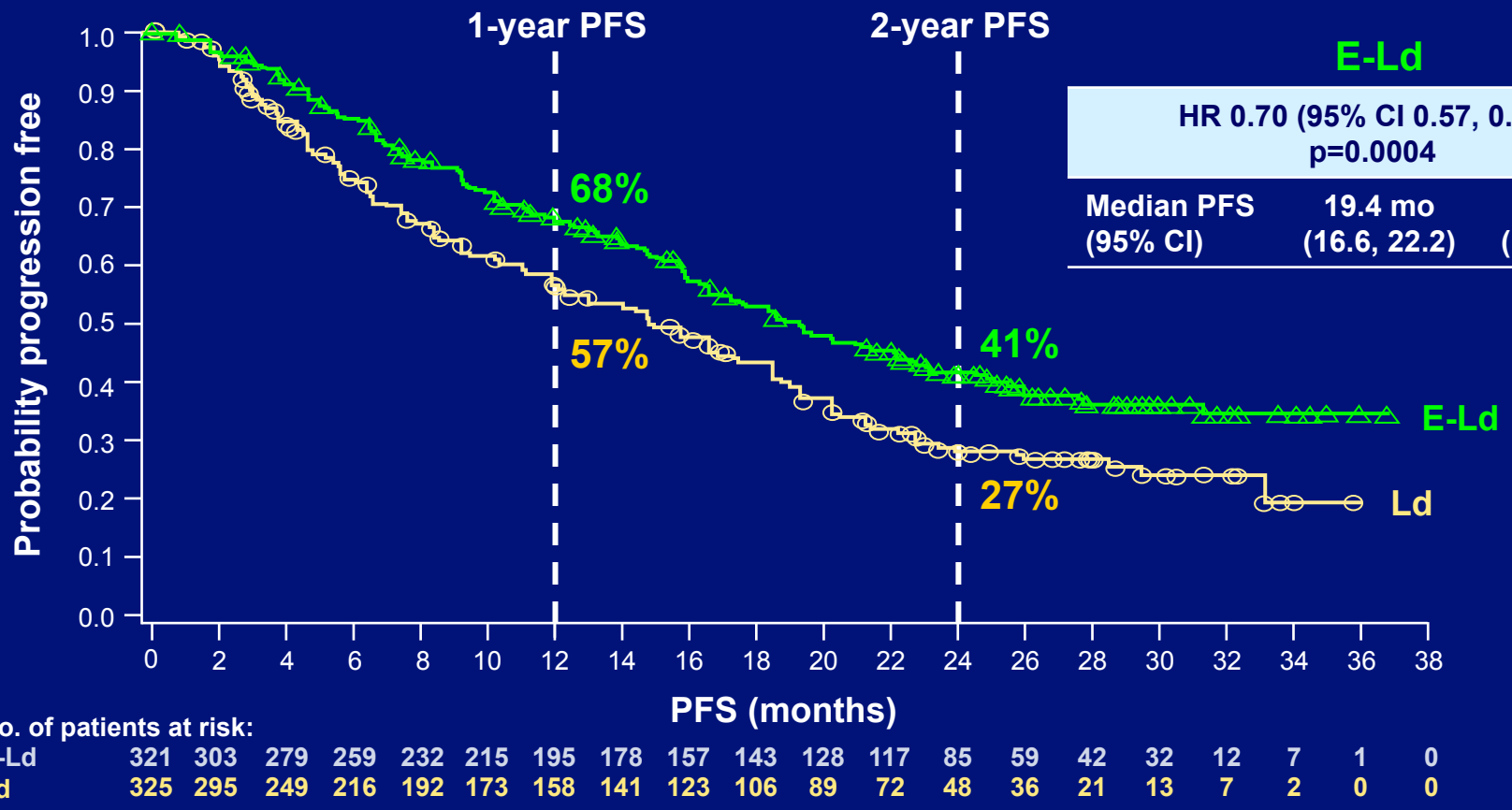
- **Open-label, international, randomized, multicenter, phase 3 trial (168 global sites)**
- **Median n° treatment cycles Elo Ld: 19 (1-42)**
- **83% pts received more than 90% dose intensity**

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:

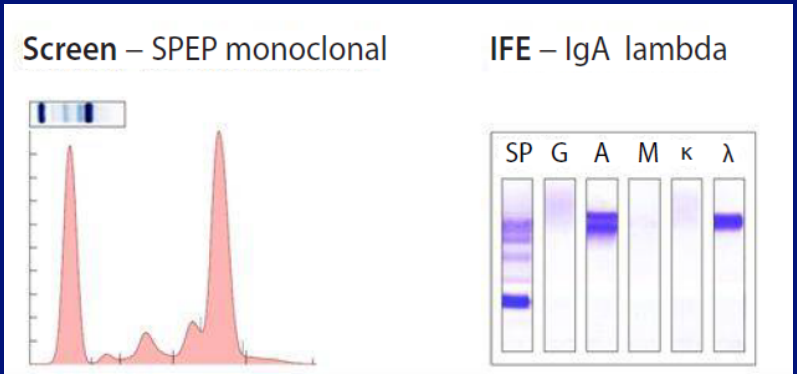
E-Ld	321	303	279	259	232	215	195	178	157	143	128	117	85	59	42	32	12	7	1	0
Ld	325	295	249	216	192	173	158	141	123	106	89	72	48	36	21	13	7	2	0	0

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

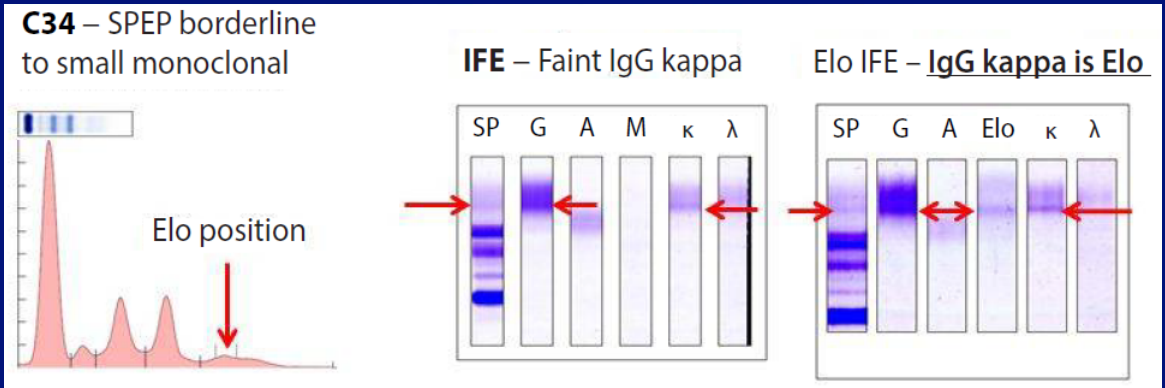
PFS analysis used the primary definition of PFS

Detection of Elotuzumab by SPEP and SIFE

- **Baseline:**



- **Cycle 34 (2.6 years of treatment):**



Elotuzumab can be detected in the SPEP/SIFE with good specificity and sensitivity, indicating that complete response rate could be underestimated

SIFE = serum immunofixation electrophoresis; SPEP = serum protein electrophoresis

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**

Conclusions and future directions

- Remarkable single-agent activity of anti CD-38 moAbs
- Very positive and solid results of DARA in heavily pre-treated MM patients
- Combination therapies based upon rational preclinical models
- High response rates of moAbs with Ld and Vd, encouraging activity with current backbone agents
- Favorable safety profile, with no additional toxiticies a part from infusion reactions: ideal partners for combination regimens, across all lines and for all patients

- Extensive ongoing clinical development
- Further define methods to enhance CD38 expression and to optimize combos