Progetto Ematologia-Romagna

2018

Gli anticorpi monoclonali nel Mieloma Multiplo

Dr. Vittorio Montefusco

FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI

DISCLOSURES

Lecture fees: Janssen, Bristol Myers Squibb

- General considerations

- Elotuzumab

- Daratumumab

- Future developments

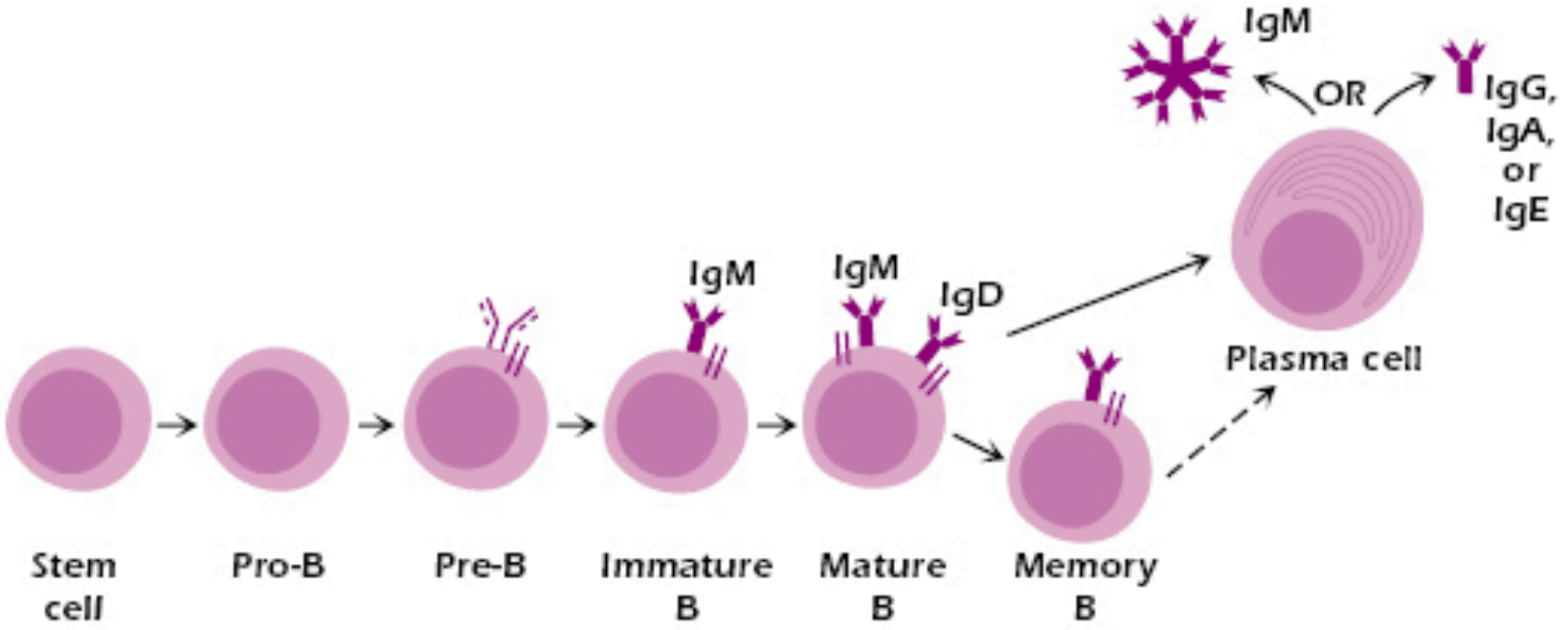
- General considerations

- Elotuzumab

- Daratumumab

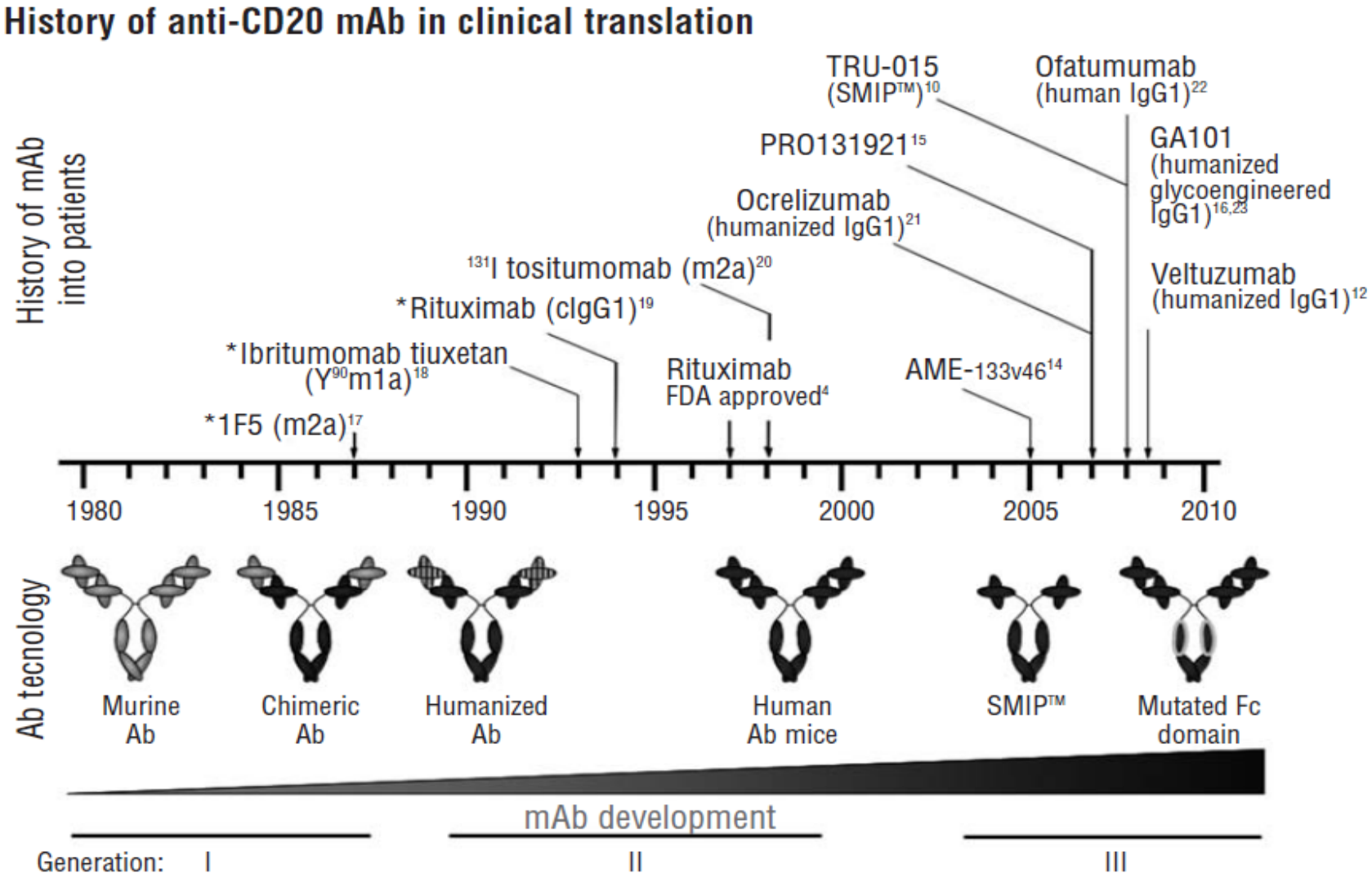
- Future developments

Stages in B-cell differentiation



Plasma cells belong to the B-cell lineage, however they do not appear to be easily killed by monoclonal antibodies.

MoAbs have a pivotal role in the B cell lymphoma treatment since the 1990s



From S.H. Lim et al. Haematologica 2010

Rituximab in CD20+ MM

bjh review

Anti-CD20 monoclonal antibody therapy in multiple myeloma

Prashant Kapoor,[1] Patricia T. Greipp,[2] William G. Morice,[3] S. Vincent Rajkumar,[1] Thomas E. Witzig[1] and Philip R. Greipp[1]

[1]Division of Hematology, Mayo Clinic, Rochester, MN, [2]Department of Molecular Medicine, Mayo Clinic, Rochester, MN, and [3]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA

haematologica | 2010; 95(1)

Several small series have been reported on the use of Rituximab in MM.

Only few responses, mainly SD and MR have been observed.

It has been hypotesized that the high expression of complement regulatory proteins, CD55 and CD59, may protect plasma cells from killing.

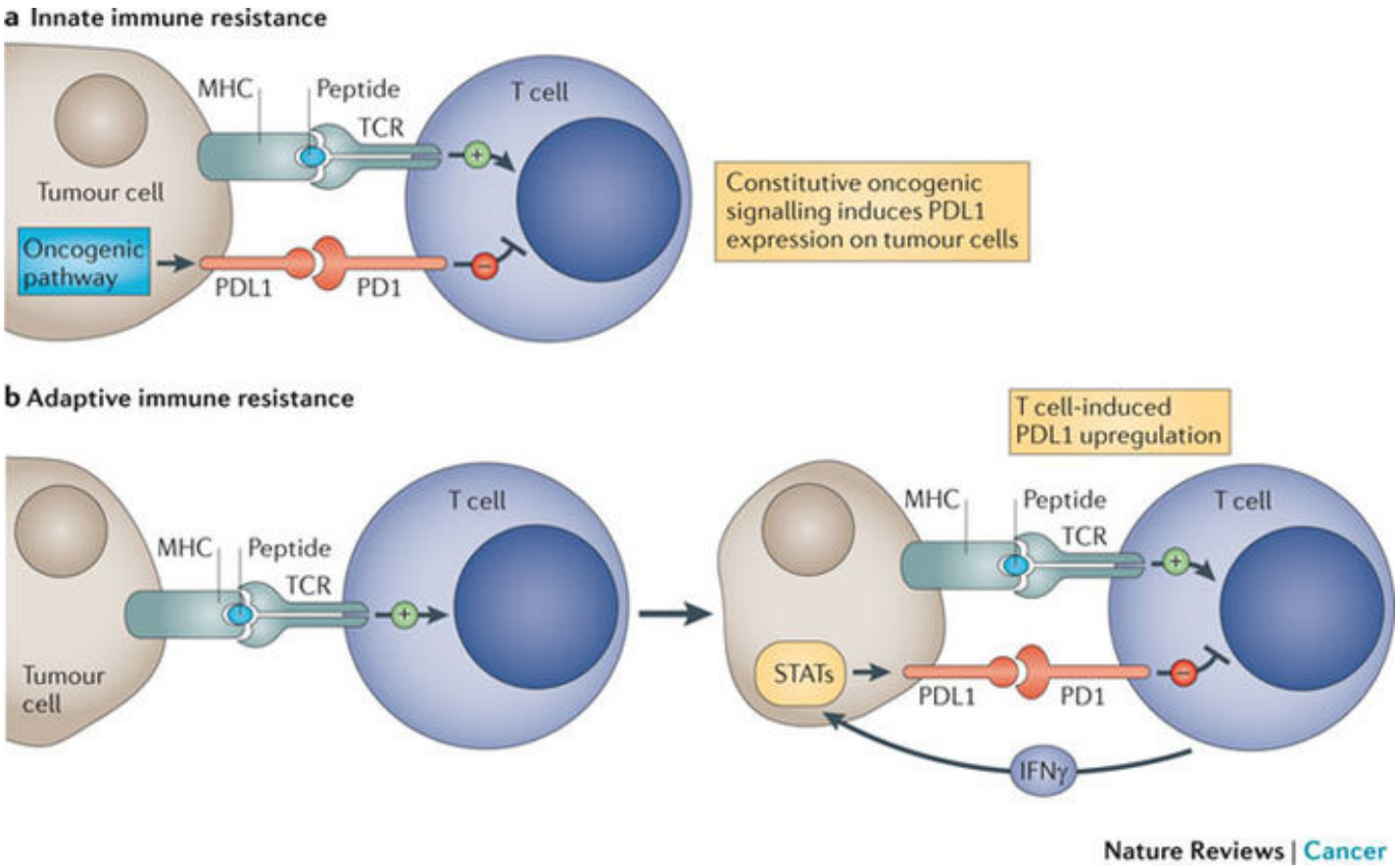
Several antigens have been targeted

CD40 → H.M. Horton et al. *Blood,* 2010. **FAILED**
CD138 → K.M. Dhodapkar et al. *J Exp Med,* 2002. **FAILED**
CD74 → R. Stein et al. *Blood,* 2004. **FAILED**
CD162 → C. Tripodo et al. *Curr Cancer Drug Targets,* 2009. **FAILED**
CD66 → M. Ringhoffer et al. *BJH,* 2005. **FAILED**
IL6 → M. Trikha et al. *Clin Canc Research,* 2003. **FAILED**
VEGF → M. Raschko et al. *Blood,* 2007. **FAILED**
GM2 → T. Ishii et al. *Blood,* 2008. **FAILED**
CD200 → **FAILED**
BCMA → T. Ishii

More promising antigens

SLAMF7 (CS1)
CD38
PD1 (??)

PD1



From D.M. Pardoll. Nature Reviews Cancer 2012

PD1

The first results on PD1 block with nivolumab were obtained in a hematological basket trial, which included 27 heavily pretreated MM patients.

ORR

MM → 4%
DLBCL → 36%
FL → 40%
PTCL → 40%

Toxicity

Grade 3/4 → 19%

Lesokhin et al. JCO 2016

PD1 + IMiDs

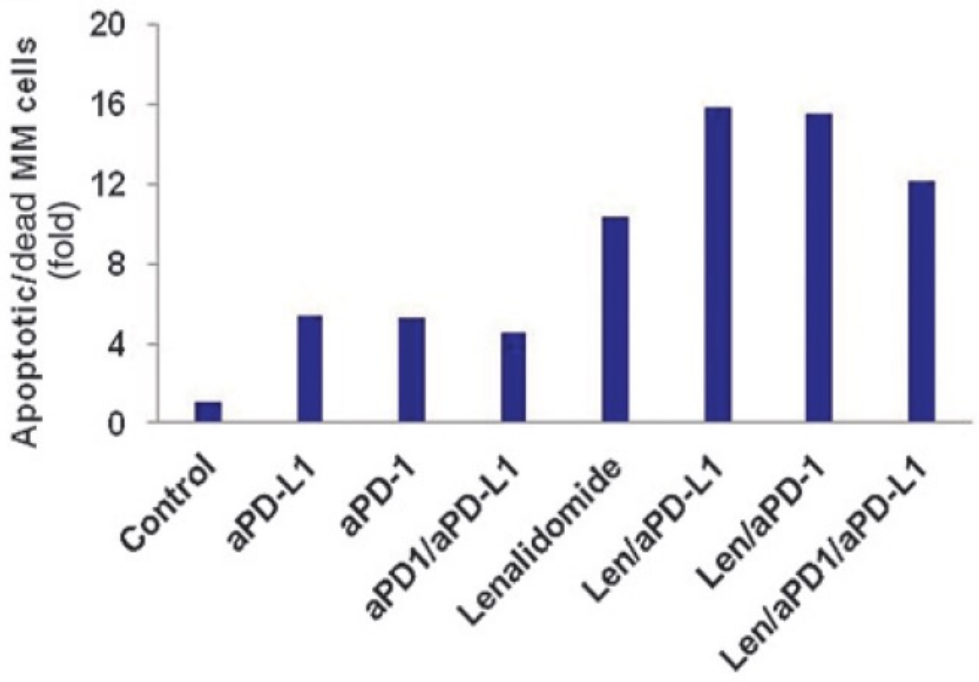
Cancer Therapy: Preclinical

Clinical Cancer Research

Lenalidomide Enhances Immune Checkpoint Blockade-Induced Immune Response in Multiple Myeloma

Güllü Görgün[1], Mehmet K. Samur[1,2], Kristen B. Cowens[1], Steven Paula[1], Giada Bianchi[1], Julie E. Anderson[1], Randie E. White[1], Ahaana Singh[1], Hiroto Ohguchi[1], Rikio Suzuki[1], Shohei Kikuchi[1], Takeshi Harada[1], Teru Hideshima[1], Yu-Tzu Tai[1], Jacob P. Laubach[1], Noopur Raje[3], Florence Magrangeas[4,5], Stephane Minvielle[4,5], Herve Avet-Loiseau[6], Nikhil C. Munshi[1,7], David M. Dorfman[8], Paul G. Richardson[1], and Kenneth C. Anderson[1]

Apoptotic death in MM plasma cells



PD1 + IMiDs

KEYNOTE-023 phase I trial evaluated Pembrolizumab + Rd in RR MM patients.

62 patients enrolled, median of 4 previous lines of therapy, 76% Len refractory.

ORR 50% (36% in Len-refractory).

No excess of toxicity observed (no pneumonia, no colytis).

Mateos et al. ASCO 2016

PD1 + IMiDs

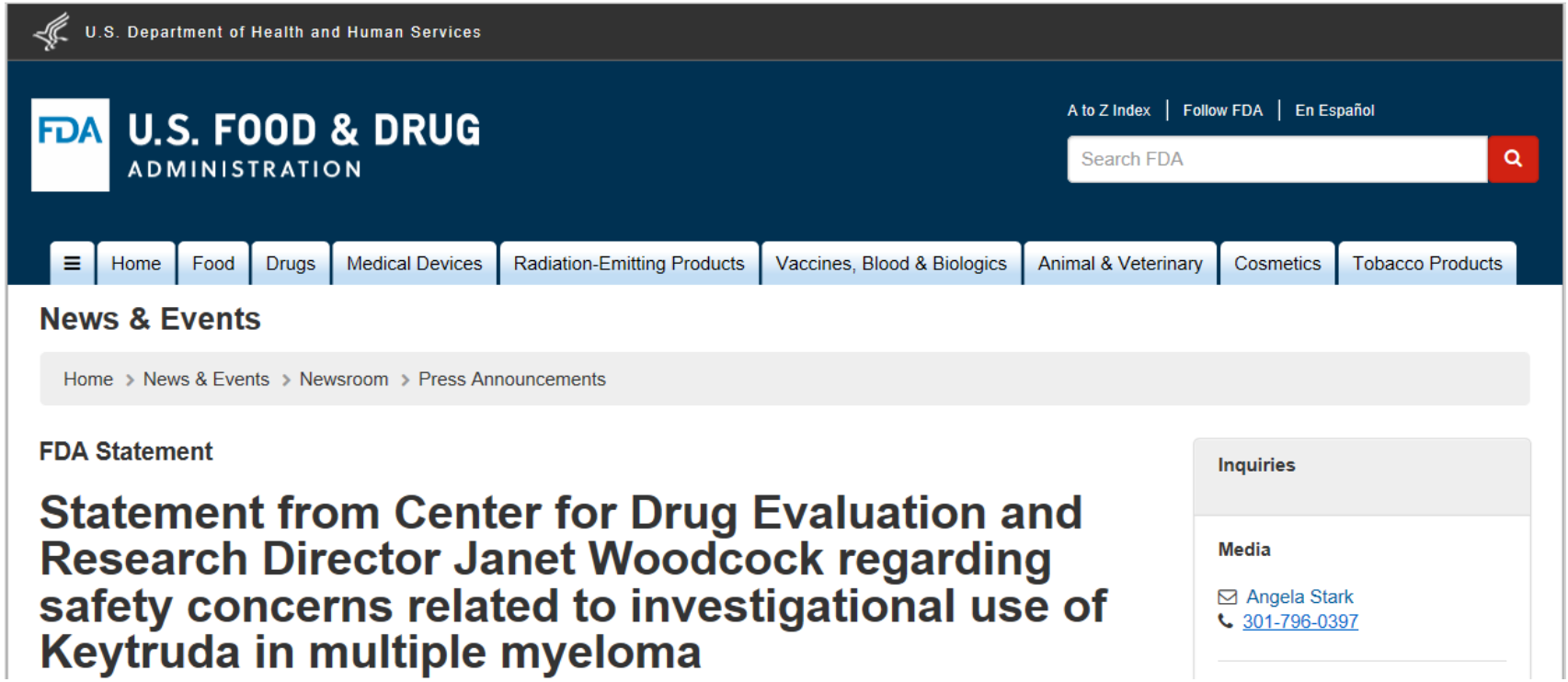
KEYNOTE-183 phase III trial with Poma-Dex with or without Pembrolizumab in R o RR MM patients.

KEYNOTE-185 phase III trial with Rd with or without Pembrolizumab in newly diagnosed MM

PD1 + IMiDs

KEYNOTE-183 phase III trial with Poma-Dex with or without Pembrolizumab in R o RR MM patients.

KEYNOTE-185 phase III trial with Rd with or without



- General considerations

- **Elotuzumab**

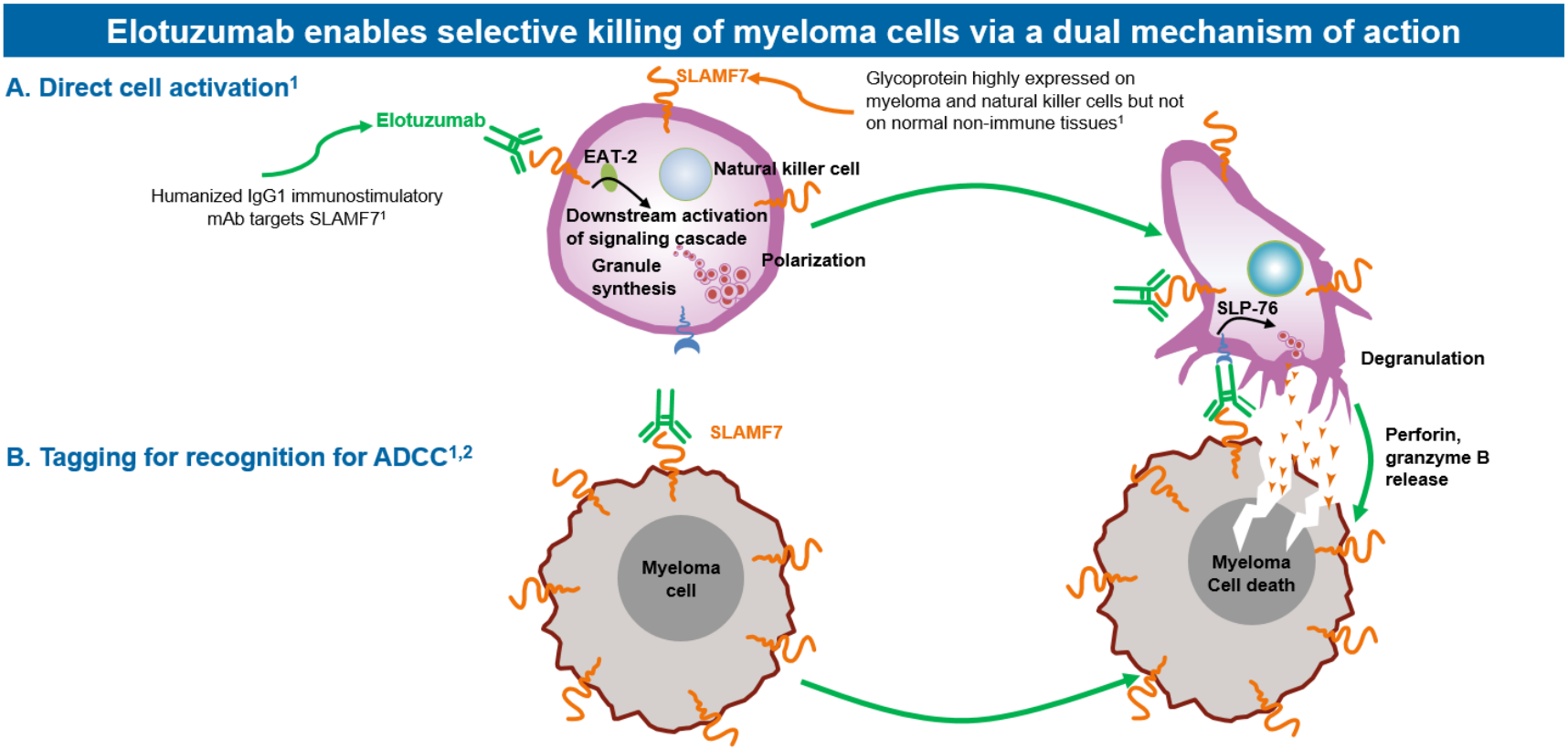
-Daratumumab

- Future developments

SLAMF7

Elotuzumab is an IgG/k anti-SLAMF7 MoAb

SLAMF7 is expressed on plasma cells and NK cells



Adapted from Einsele et al. *Ther Adv Hematol* 2016

SLAMF7

Elotuzumab is an IgG/k anti-SLAMF7 MoAb

In a phase I trial 35 patients were treated with Elotuzumab from 0,5 to 20 mg/Kg.

Patients had an advenced disease (4.5 median number of previous line of therapy, 82% previously exposed to lenalidomide and bortezomib.

ORR → 0%

NcCusswn et al. *ASCOl* 2015

Eloquent 2 study

Patients

- RRMM
- 1–3 prior lines of therapy
- Prior lenalidomide permitted in 10% of patients (if sensitive)

ELd: n=321

Elo (10 mg/kg IV): Cycles 1 and 2 weekly, Cycle 3+ every other week
Len (25 mg PO): Days 1–21
Dex (40 mg): Weekly equivalent

Ld: n=325

Len (25 mg PO): Days 1–21
Dex (40 mg PO): Weekly

Repeat every 28 days

Co-primary endpoints: PFS and ORR

Secondary endpoints: OS

Exploratory endpoints: safety and DOR

Start	Primary analysis	-------- Extended analyses ----------	
Jun 2011	2-y PFS (minFU: 24 mo)	3-y PFS (minFU: 33 mo) Interim OS (minFU: 36 mo)	**4-y PFS[a] (FU: 48 mo)** Data cut-off: Oct 18, 2016

Dimopoulos et al. *EHA* 2017

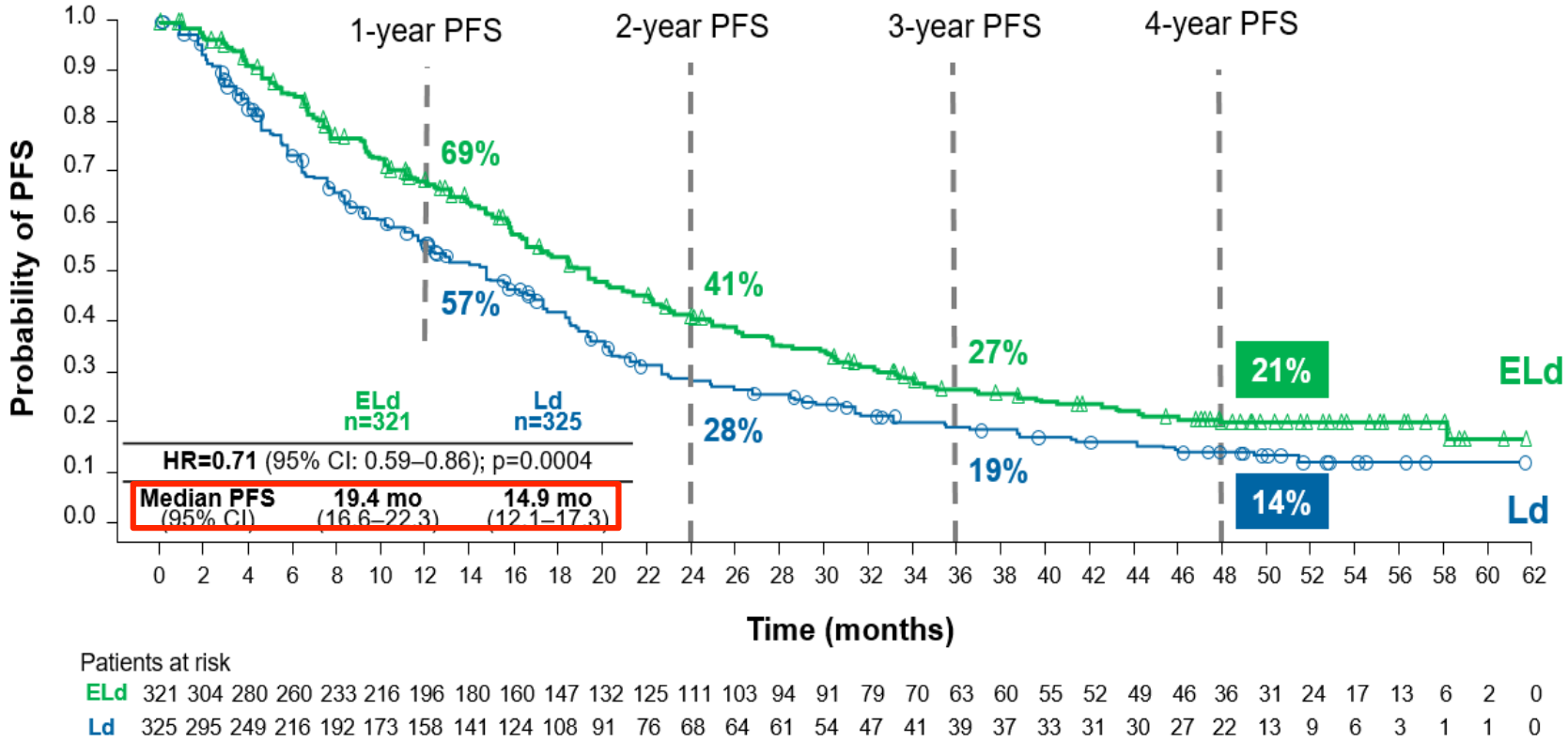
Eloquent 2 study

Characteristic	ELd (n=321)	Ld (n=325)
Age, median (range), years	67 (37–88)	66 (38–91)
ISS stage at diagnosis,[a] n (%)		
I	141 (44)	138 (42)
II	102 (32)	105 (32)
III	66 (21)	68 (21)
Cytogenetic profile, n (%)[a]		
del(17p) ≥ 1 cell	102 (32)	104 (32)
del(17p) ≥ 60% of cells	62 (19)	61 (19)
t(4;14)	30 (9)	31 (10)
Previous regimens, median (range)	2 (1–4)	2 (1–4)
Previous therapies, n (%)		
Bortezomib	219 (68)	231 (71)
Melphalan (PO or IV)	220 (69)	197 (61)
Thalidomide	153 (48)	157 (48)
Lenalidomide	16 (5)	21 (6)
Response to most recent line of therapy,[c] n (%)		
Refractory	113 (35)	114 (35)
Relapsed	207 (65)	211 (65)
Risk category,[a] n (%)		
High[d]	60 (19)	66 (20)
Low[e]	14 (4)	22 (7)
Standard[f]	231 (72)	221 (68)
Time from diagnosis, median (range), years	3.5 (0.3–17.3)	3.5 (0.1–16.2)

Dimopoulos et al. *EHA* 2017

Eloquent 2 study

PFS



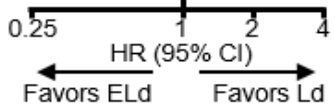
- At 4 years, ELOQUENT-2 has the longest follow-up for PFS in RRMM
- 29% reduction in the risk of progression or death (sustained over time)
- 50% relative improvement in the PFS rate at 4 years (21% vs 14%) in favor of ELd

Dimopoulos et al. *EHA* 2017

Eloquent 2 study

Subgroup analysis for PFS

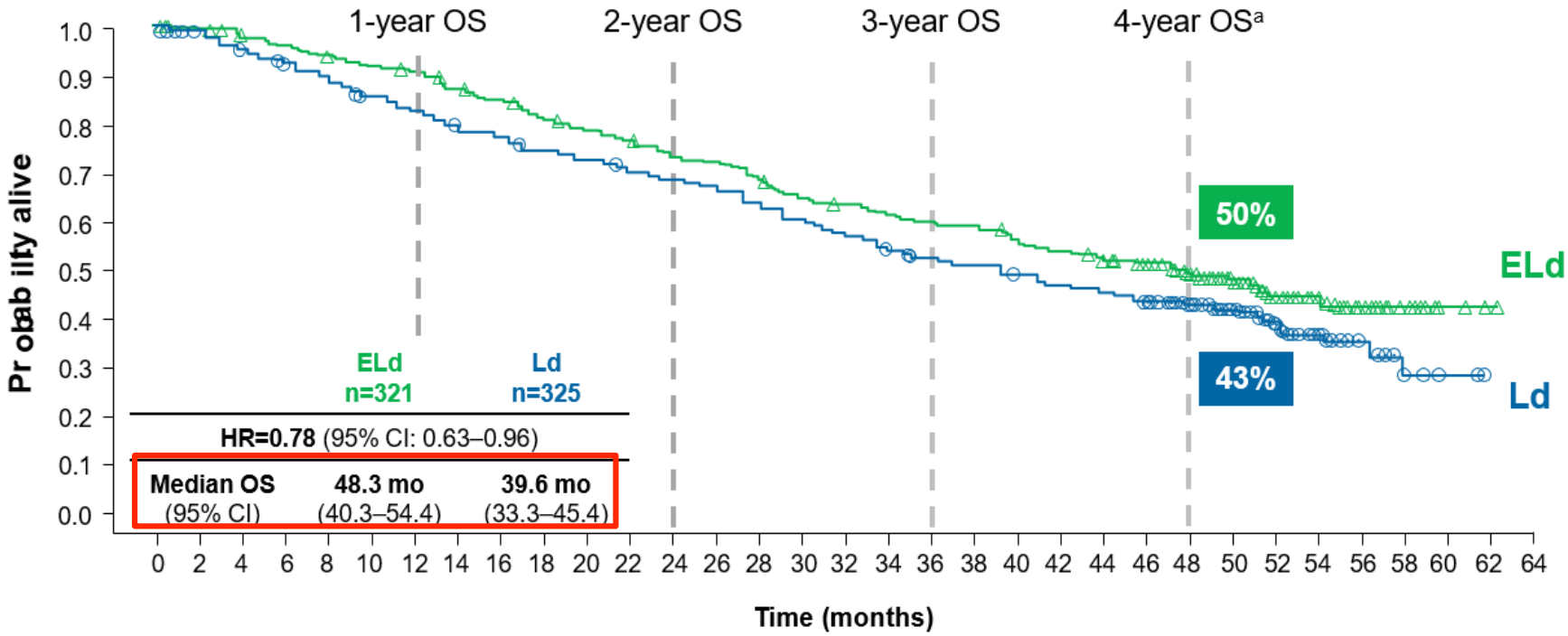
Subgroup	Events, n (total patients) ELd	Events, n (total patients) Ld	HR (95% CI)
All patients	221 (321)	233 (325)	0.71 (0.59–0.86)
Age <75 years	178 (253)	189 (264)	0.74 (0.60–0.91)
Age ≥75 years	43 (68)	44 (61)	0.63 (0.41–0.96)
Age <65 years	90 (134)	102 (142)	0.69 (0.52–0.92)
Age ≥65 years	131 (187)	131 (183)	0.75 (0.59–0.95)
ISS stage I	92 (142)	90 (138)	0.73 (0.54–0.97)
ISS stage II	72 (102)	80 (105)	0.82 (0.60–1.13)
ISS stage III	52 (66)	52 (68)	0.69 (0.47–1.01)
del(17p) present[c]	68 (102)	71 (104)	0.72 (0.52–1.01)
t(4;14) present	24 (30)	26 (31)	0.56 (0.32–0.98)
Refractory	84 (113)	85 (114)	0.60 (0.44–0.81)
Relapsed	137 (207)	148 (211)	0.79 (0.62–0.99)
1 prior therapy	103 (151)	113 (159)	0.77 (0.59–1.01)
2 or 3 prior therapies	118 (170)	120 (166)	0.68 (0.53–0.87)
Prior bortezomib	158 (219)	170 (231)	0.66 (0.53–0.83)
No prior bortezomib	63 (102)	63 (94)	0.85 (0.60–1.21)
≥Median time from diagnosis	97 (160)	114 (163)	0.59 (0.45–0.78)
<Median time from diagnosis	124 (161)	119 (162)	0.86 (0.67–1.11)



Dimopoulos et al. *EHA* 2017

Eloquent 2 study

OS



Toxicity

Elotuzumab did not add significant toxicity to that observed with Rd, including infusion reactions.

Dimopoulos et al. *EHA* 2017

Eloquent 2 study

Essential informations to remember:

EloRd median PFS 19 months
EloRd median OS 48 months

Benefit across all subgroups

Very well tolerated

- General considerations

- Elotuzumab

-Daratumumab

- Future developments

CD38

CD38 is:

- **highly expressed on MM plasma cells**
- **has a low expression on erythrocytes, lymphoid and myeloid cells.**

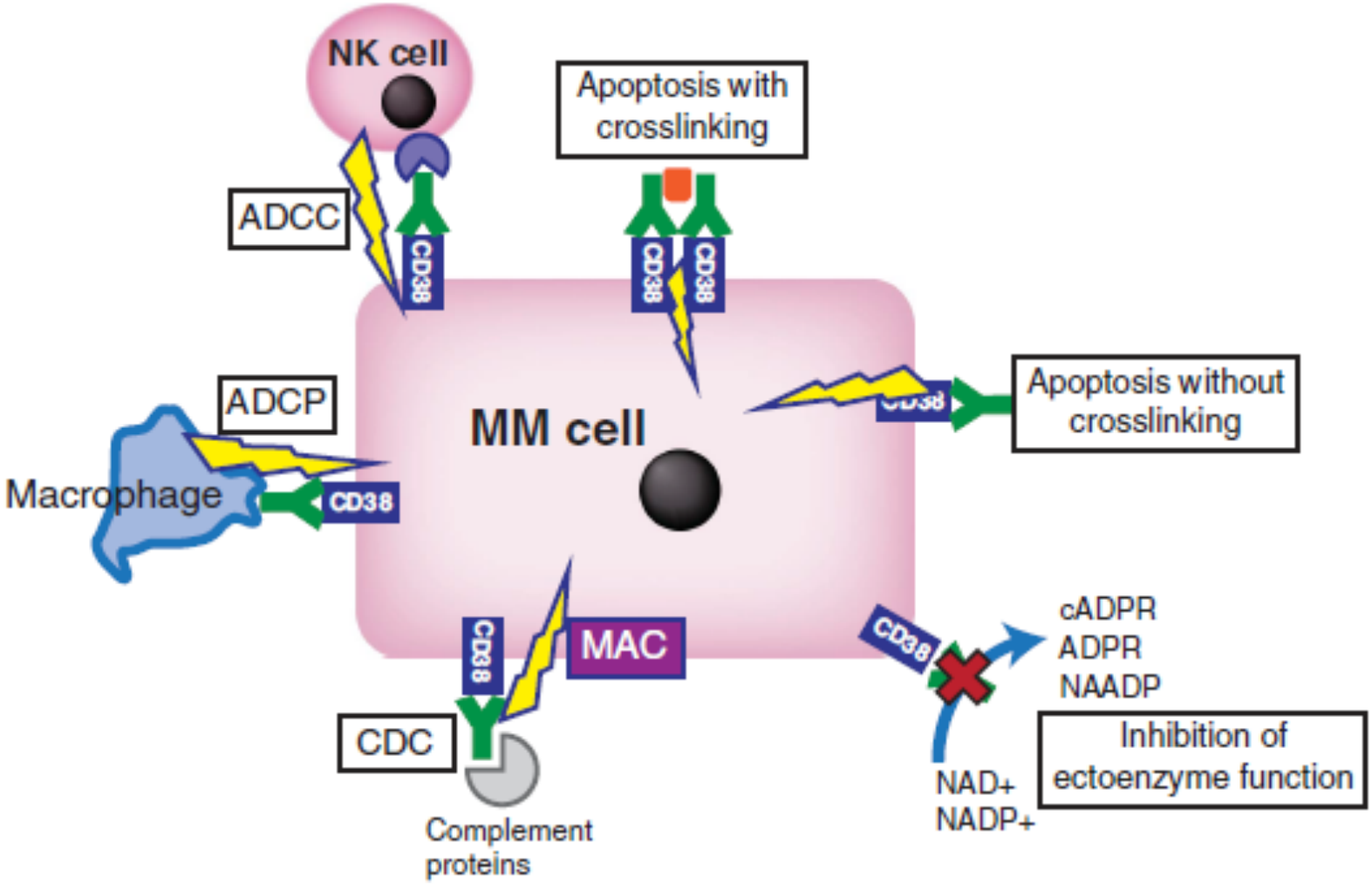
CD38 has:

- **adhesion functions**
- **signaling functions, since contribute to intracellular calcium mobilization and adenosine production, and adenosine favours local immunological tolerance**
- **costimulatory functions in T-lymphocytes**

Malavasi et al. *Physiol Rev* 2008
Van De Donk et al. *Blood* 2015
Chen et al. ASCO 2018

CD38

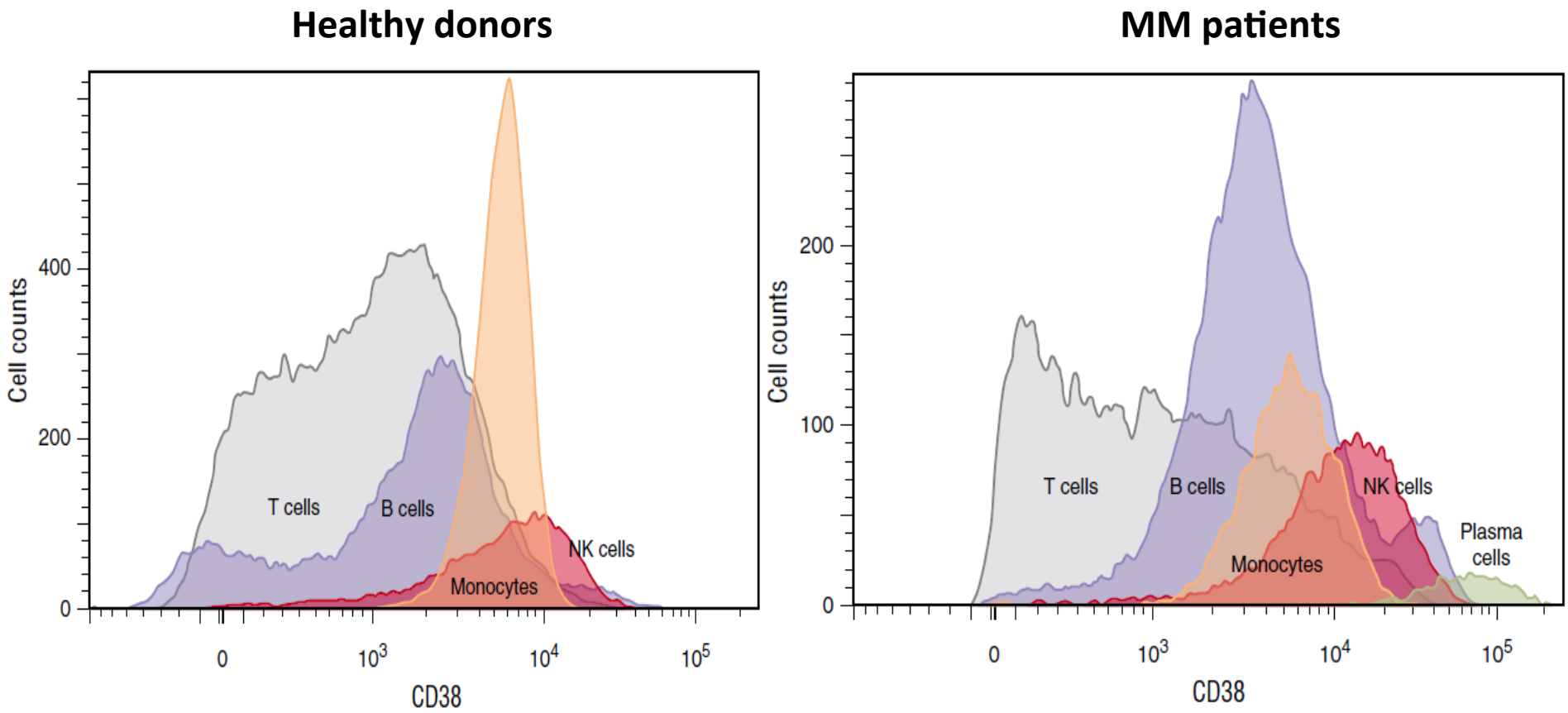
Anti-CD38 MoAbs have several mechanisms of action



From Lonial et al. *Blood* 2016

CD38

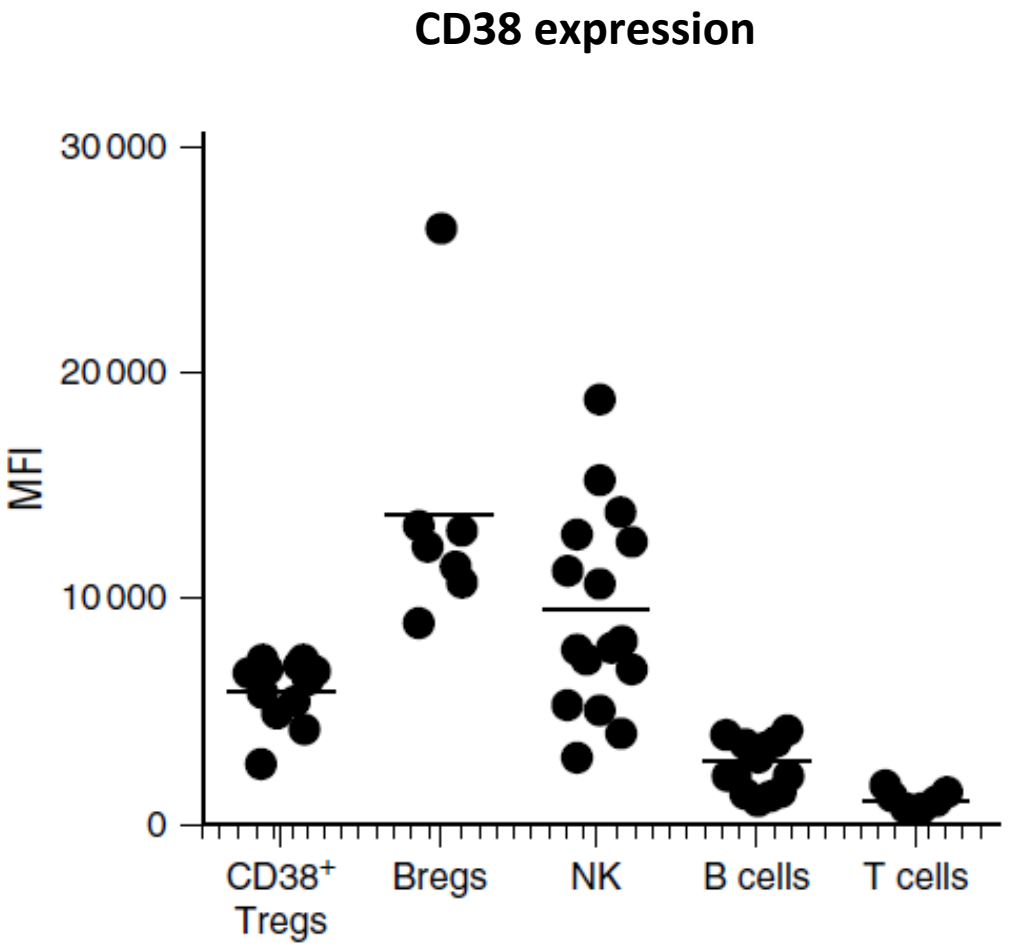
CD38 expression



Krejcik et al. *Blood* 2016

CD38

CD38+ B-regulatory cells on lymphocytes

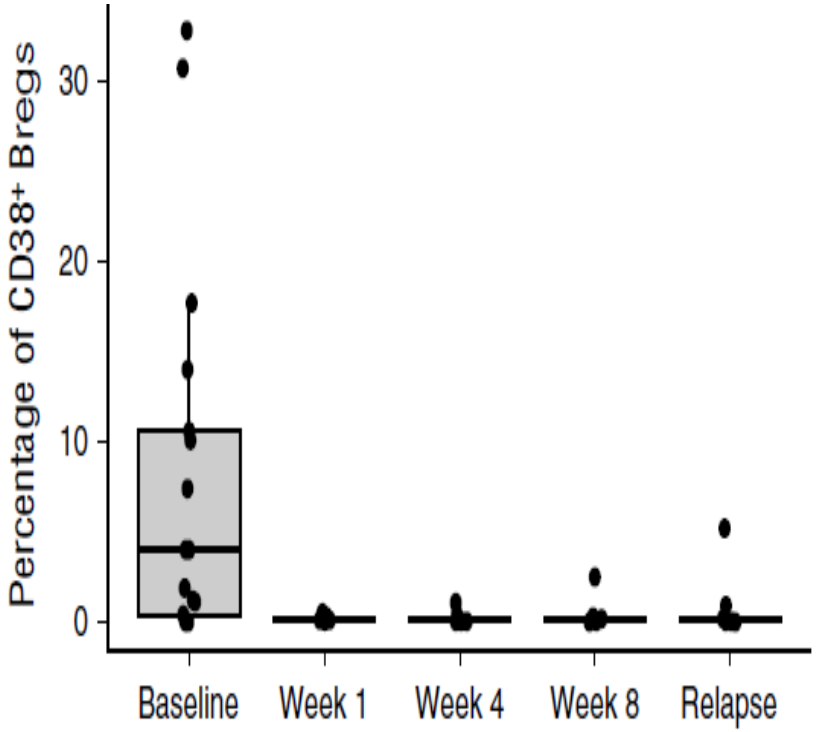


Krejcik et al. *Blood* 2016

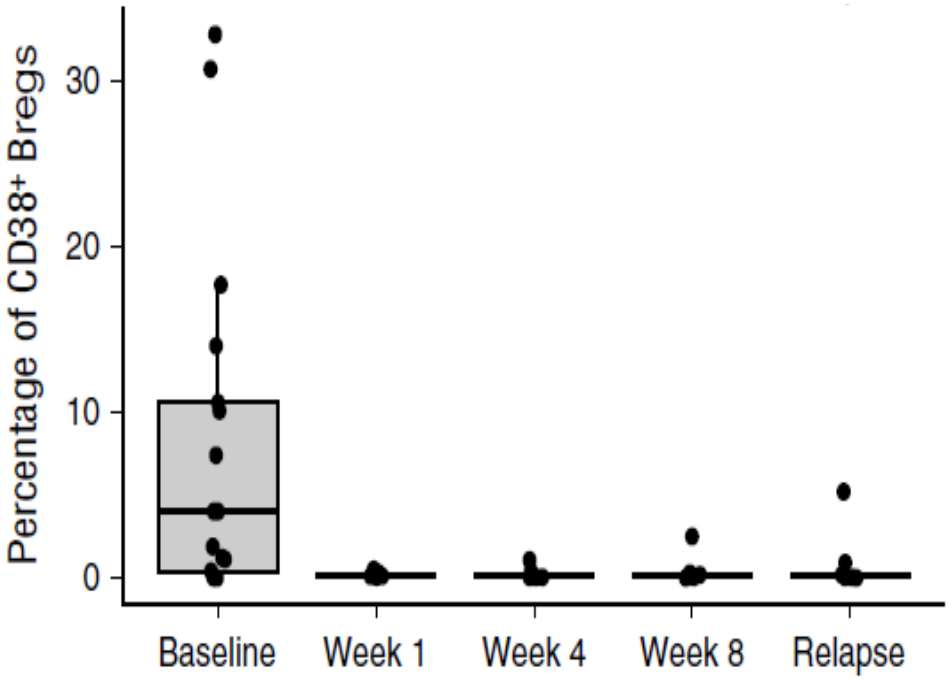
CD38

CD38+ B-regulatory cells and Dara therapy

B-regulatory cells during Dara therapy



T-regulatory cells during Dara therapy



Krejcik et al. *Blood* 2016

Daratumumab

1st line	2nd – 3rd line	≥3rd line
Transplant eligible **Dara – VRd + AutoSCT** *Transplant ineligible* **Dara - Rd** **Dara - VMP**	**Dara - Vd** **Dara - Rd**	**Dara mono** **Dara - PD**

Daratumumab

1st line	2nd – 3rd line	≥3rd line
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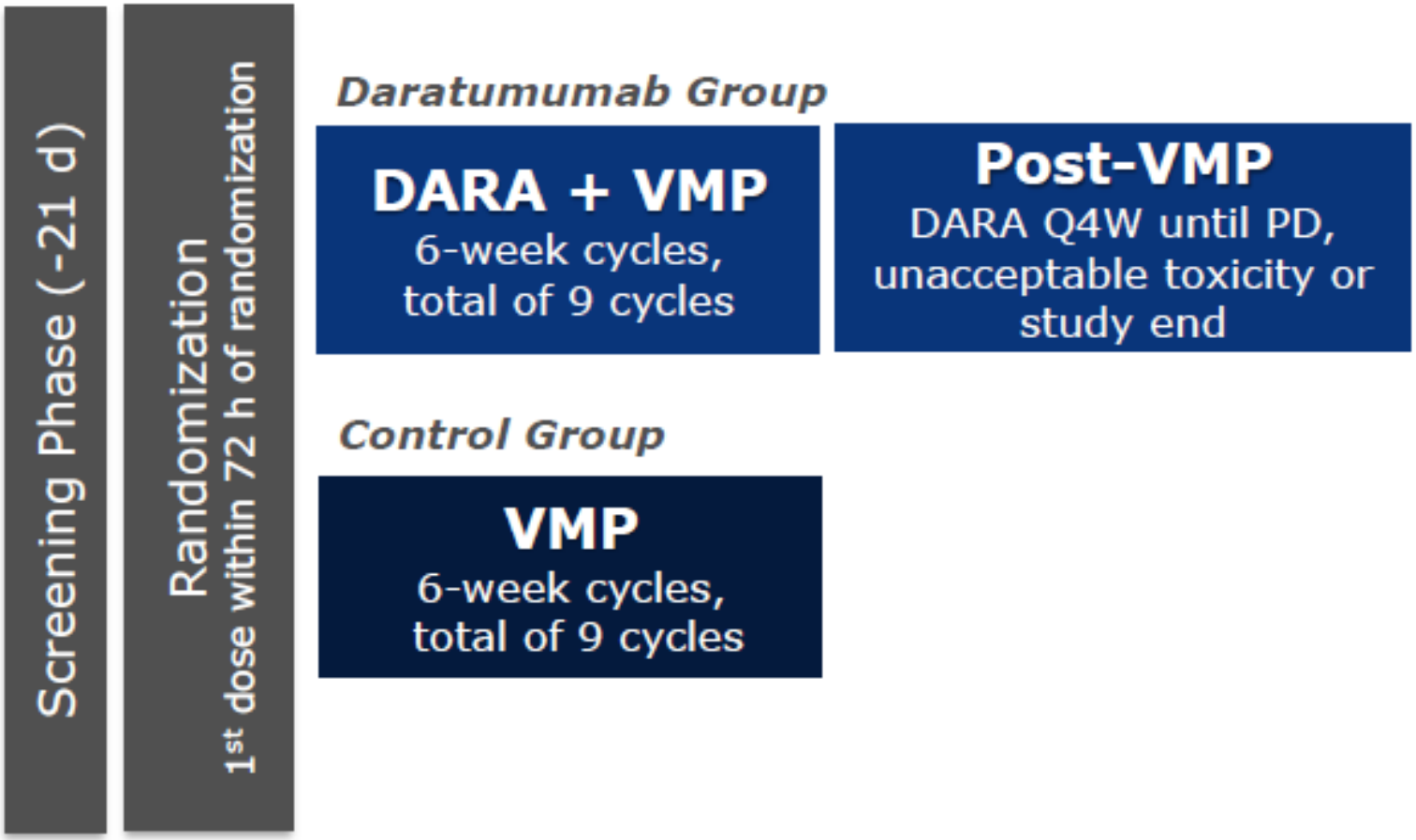
Daratumumab –VMP (Alcyone)



Primary Endpoint	Progression-free survival (PFS)
Secondary Endpoints	• ORR • ≥VGPR rate • ≥CR rate • MRD (Negative status; 10^{-5}) • OS • Safety

Mateos et al. *NEJM* 2018

Daratumumab –VMP (Alcyone)

Baseline characteristics

	Dara-VMP (N=350)	VMP (N=356)
Age, median (range)	71 (40-93)	71 (50-91)
age ≥75 yr	104 (30%)	107 (30%)
ISS		
I	78 (22%)	99 (28%)
II	182 (52%)	173 (49%)
III	90 (26%)	84 (24%)
Cytogenetics		
Standard risk	261/314 (83%)	257/302 (85%)
High risk [17p-, t(4;14), t(14;16)]	53/314 (17%)	45/302 (15%)

Mateos et al. *NEJM* 2018

Daratumumab –VMP (Alcyone)

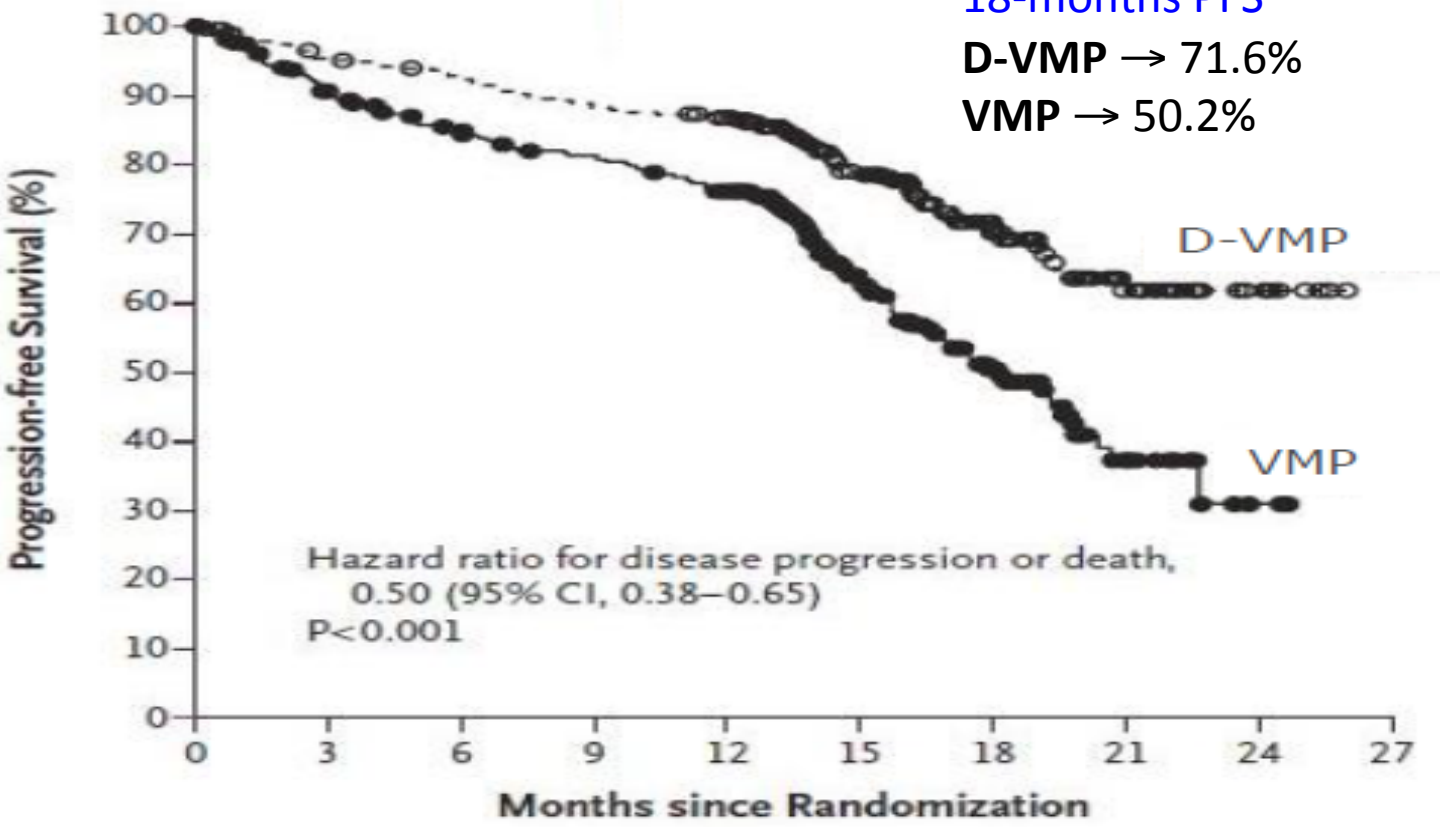
PFS

Median follow-up: 16.5 months

18-months PFS

D-VMP → 71.6%

VMP → 50.2%



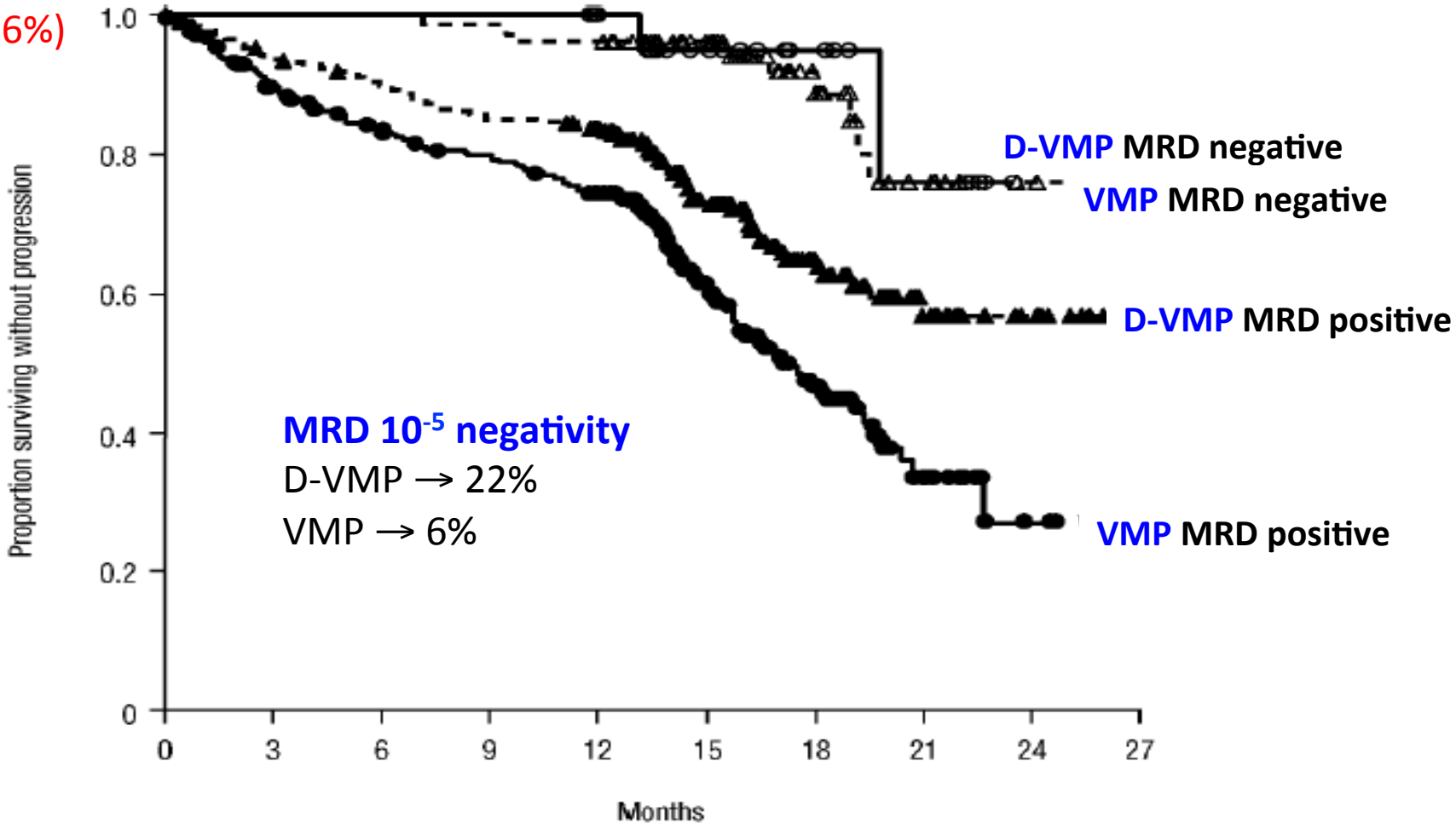
Mateos et al. *NEJM* 2018

Daratumumab –VMP (Alcyone)

PFS according to MRD 10^{-5}

D-VMP 78 (18%)

VMP 22 (6%)

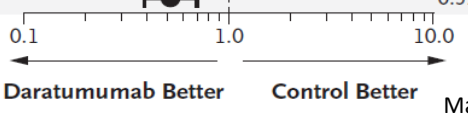


Mateos et al. *NEJM* 2018

Daratumumab –VMP (Alcyone)

Subgroups analysis for PFS

Subgroup	Daratumumab Group	Control Group	Daratumumab Group	Control Group	Hazard Ratio (95% CI)
	no. of progression events or deaths/total no.		*median progression-free survival (mo)*		
Sex					
Male	50/160	68/167	NE	18.1	0.60 (0.42–0.87)
Female	38/190	75/189	NE	17.9	0.41 (0.28–0.61)
Age					
<75 yr	60/246	101/249	NE	17.9	0.49 (0.36–0.68)
≥75 yr	28/104	42/107	NE	20.4	0.53 (0.32–0.85)
Race					
White	79/297	121/304	NE	18.1	0.56 (0.42–0.74)
Other	9/53	22/52	NE	16.8	0.26 (0.12–0.57)
Geographic region					
Europe	80/289	121/295	NE	18.1	0.57 (0.43–0.76)
Other	8/61	22/61	NE	17.5	0.22 (0.10–0.50)
Baseline creatinine clearance					
≤60 ml/min	32/150	63/145	NE	16.9	0.36 (0.24–0.56)
>60 ml/min	56/200	80/211	NE	18.3	0.63 (0.45–0.88)
Baseline hepatic function					
Normal	73/301	115/303	NE	19.1	0.53 (0.40–0.71)
Impaired	15/46	28/52	NE	13.5	0.42 (0.22–0.80)
ISS disease stage					
I	12/69	18/67	NE	19.4	0.50 (0.24–1.05)
II	35/139	70/160	NE	17.5	0.49 (0.32–0.73)
III	41/142	55/129	NE	16.8	0.53 (0.35–0.79)
Type of multiple myeloma					
IgG	51/207	93/218	NE	17.4	0.45 (0.32–0.64)
Non-IgG	26/82	29/83	NE	NE	0.81 (0.48–1.37)
Cytogenetic profile at trial entry					
High risk	24/53	19/45	18.0	18.1	0.78 (0.43–1.43)
Standard risk	54/261	108/257	NE	17.4	0.39 (0.28–0.55)
ECOG performance status					
0	14/78	35/99	NE	19.4	0.40 (0.21–0.74)
1 or 2	74/272	108/257	NE	17.6	0.52 (0.39–0.70)



Mateos et al. *NEJM* 2018

Daratumumab –VMP (Alcyone)

Toxicity

Event, n (%)	D-VMP (N=346)		VMP (N=354)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Hematologic AEs				
Neutropenia	172 (49.7)	138 (39.9)	186 (52.5)	137 (38.7)
Thrombocytopenia	169 (48.8)	119 (34.4)	190 (53.7)	133 (37.6)
Anemia	97 (28.0)	55 (15.9)	133 (37.6)	70 (19.8)
Nonhematologic AEs				
Peripheral sensory neuropathy	98 (28.3)	5 (1.4)	121 (34.2)	14 (4.0)
Diarrhea	82 (23.7)	9 (2.6)	87 (24.6)	11 (3.1)
Pyrexia	80 (23.1)	2 (0.6)	74 (20.9)	2 (0.6)
Nausea	72 (20.8)	3 (0.9)	76 (21.5)	4 (1.1)
Infections	231 (66.8)	80 (23.1)	170 (48.0)	52 (14.7)
Upper respiratory tract infection	91 (26.3)	7 (2.0)	49 (13.8)	5 (1.4)
Pneumonia	53 (15.3)	39 (11.3)	17 (4.8)	14 (4.0)
Second primary cancer	8 (2.3)	NA	9 (2.5)	NA
Any infusion-related reaction	96 (27.7)	15 (4.3)	NA	NA

Mateos et al. *NEJM* 2018

Daratumumab –VMP (Alcyone)

Essential informations to remember:

D-VMP 18-months PFS → 72%

Benefit across all subgroups

MRD negativity in 18%

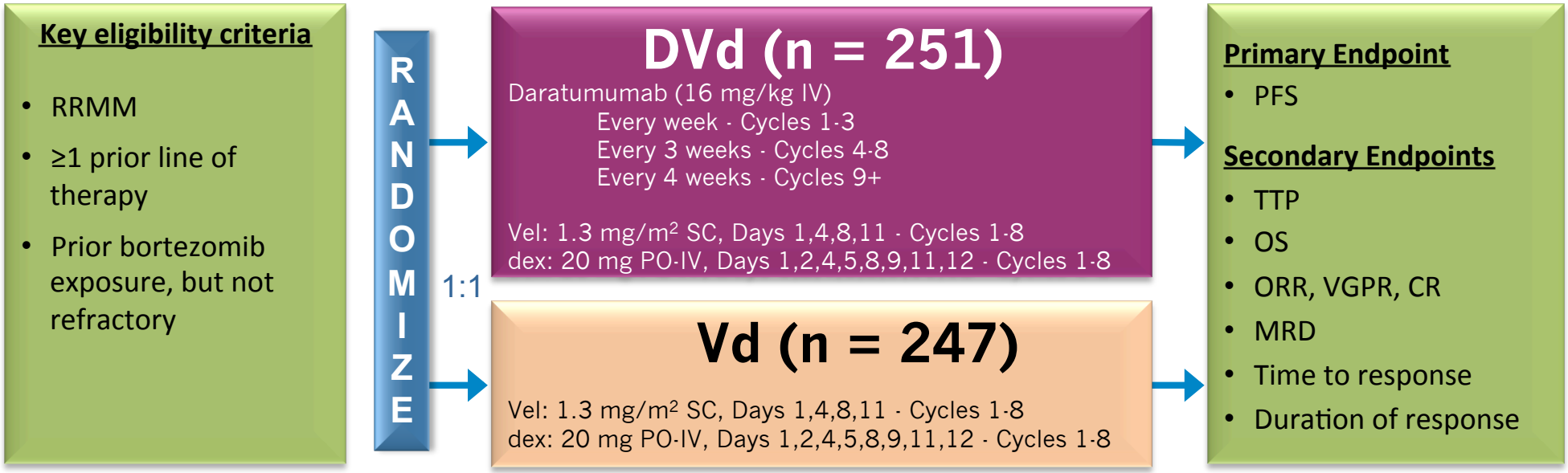
Minimal additional toxicity

Daratumumab

1st line	2nd – 3rd line	≥3rd line
Transplant eligible		
Dara – VRd + AutoSCT	**Dara - Vd**	Dara mono
	Dara - Rd	Dara - PD
Transplant ineligible		
Dara - Rd		
Dara - VMP		

Daratumumab – Vd (Castor)

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



498 patients enrolled

Palumbo et al. *NEJM* 2016

Daratumumab – Vd (Castor)

Baseline characteristics

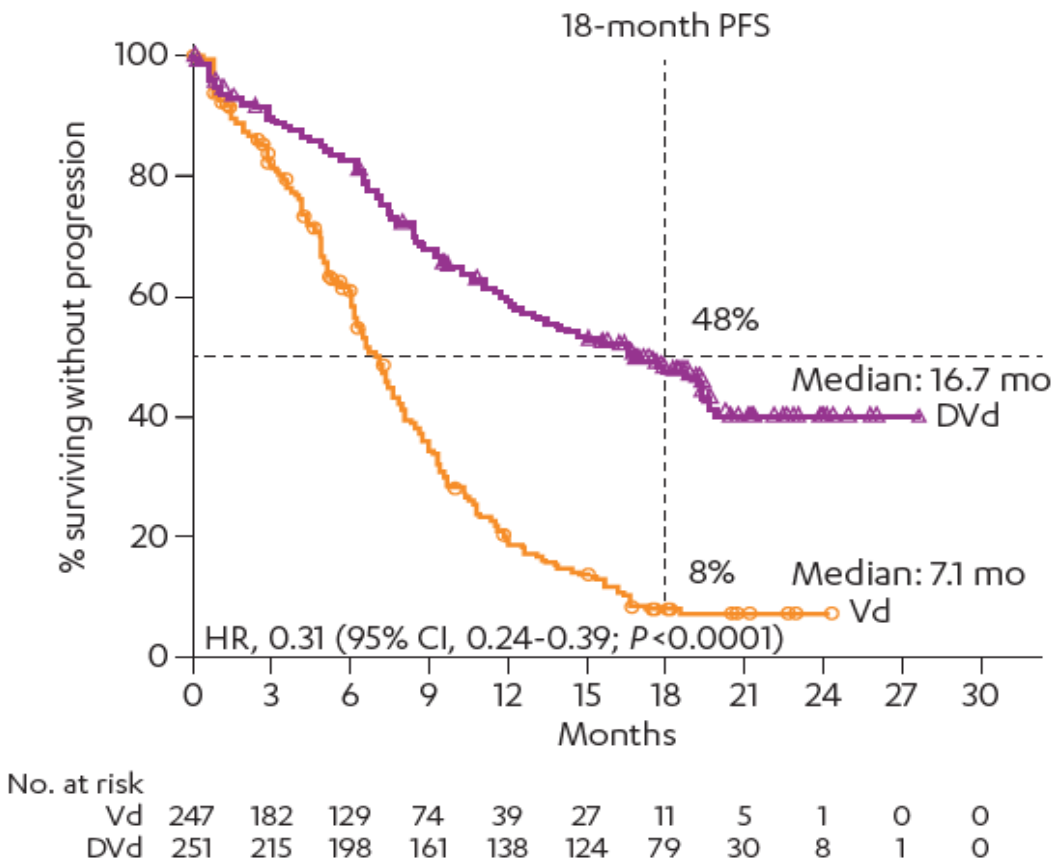
	DVd	Vd
Age, median (range)	64 yrs (30-88)	64 yrs (33-85)
17p-	16%	12%
t(4;14)	8%	9%
Median time from diagnosis	3,8 yrs (0,7 - 20)	3,7 yrs (0,6 - 18)
Prior auto-SCT	62%	60%
Prior PI	67%	70%
Prior IMiD	71%	80%
Refractory to IMiD	30%	36%

Palumbo et al. *NEJM* 2016

Daratumumab – Vd (Castor)

CASTOR UPDATED RESULTS

PFS



	DVd	Vd
Median follow-up (range)	26.9	
Median duration of treatment, mo	13.4	5.2
Median PFS ITT, mo	16.7	7.1
HR (95% CI) *P* value	0.32 (0.25-0.40) *P* <0.0001	
Median PFS 1PL, mo 24 mo – PFS rate	26.2 55%	7.9 8%
HR (95% CI) *P* value	0.23 (0.16-0.33) *P* <0.0001	
ORR[b], %	85	63
≥CR, %	30	10
MRD-negative (10^{-5})[a], %	12	2

Responses continue to deepen in the DVd group with longer follow-up

Spencer et al. *ASH* 2017

Daratumumab – Vd (Castor)

Toxicities G3-G4

	DaraVd	Vd
Neutropenia	12.8%	4.2%
Thrombocytopenia	45.0%	32.9%
Anemia	14.4%	16.0%
Pneumonia	10.3%	10.1%
Peripheral sensory neuropathy	4.5%	6.8%
Hypertension	6.6%	0.8%
Diarrhea	3.7%	1.3%

Palumbo et al. *NEJM* 2016

Daratumumab – Vd (Castor)

Essential informations to remember:

D-Vd median PFS → 17 months

Benefit across all subgroups

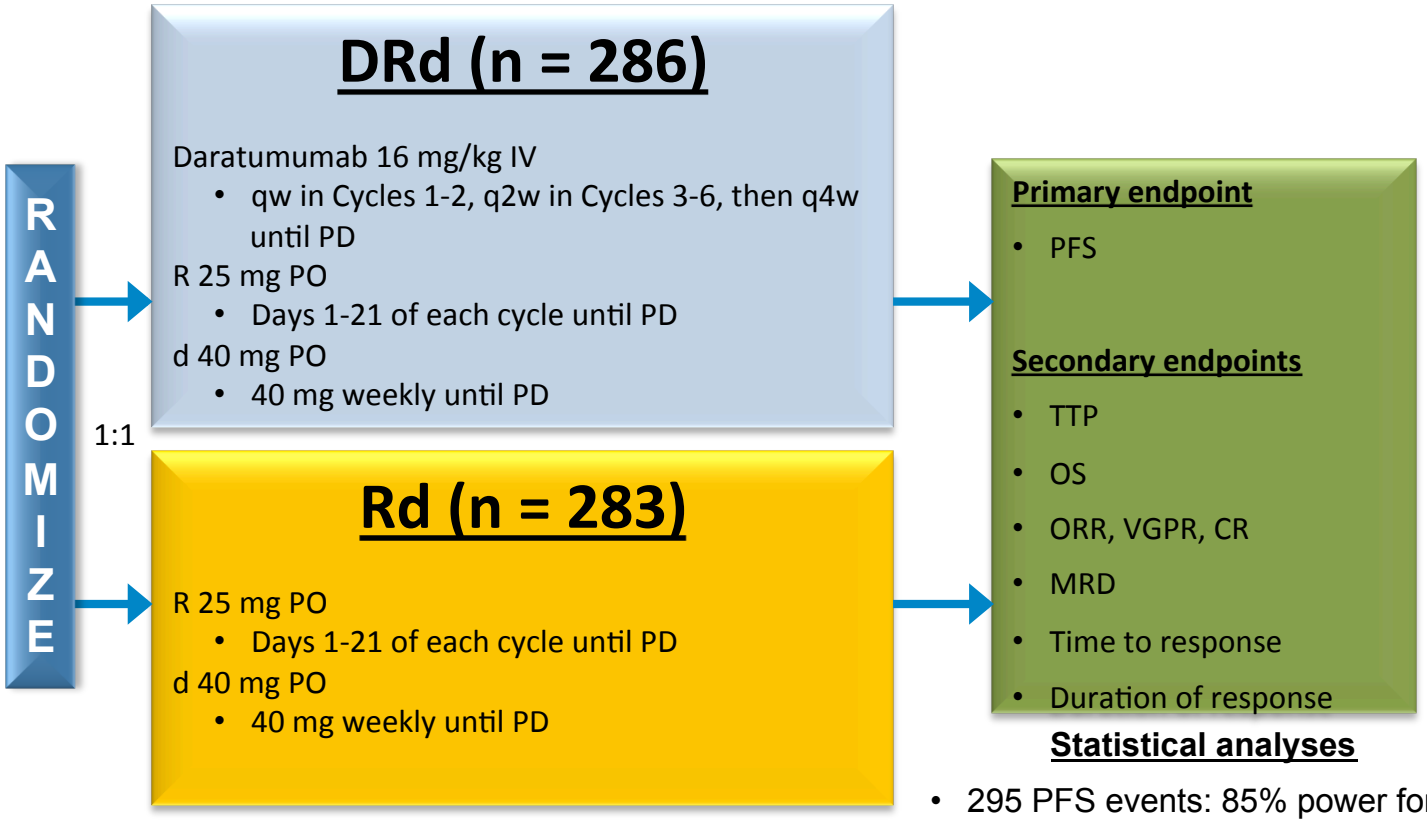
Minimal additional toxicity

Daratumumab

1st line	2nd – 3rd line	≥3rd line
Transplant eligible Dara – VRd + AutoSCT *Transplant ineligible* Dara - Rd Dara - VMP	Dara - Vd **Dara - Rd**	Dara mono Dara - PD

Daratumumab – Rd (Pollux)

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



Stratification factors

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

Statistical analyses

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

569 patients enrolled

Dimopoulos et al. *NEJM* 2016

Daratumumab – Rd (Pollux)

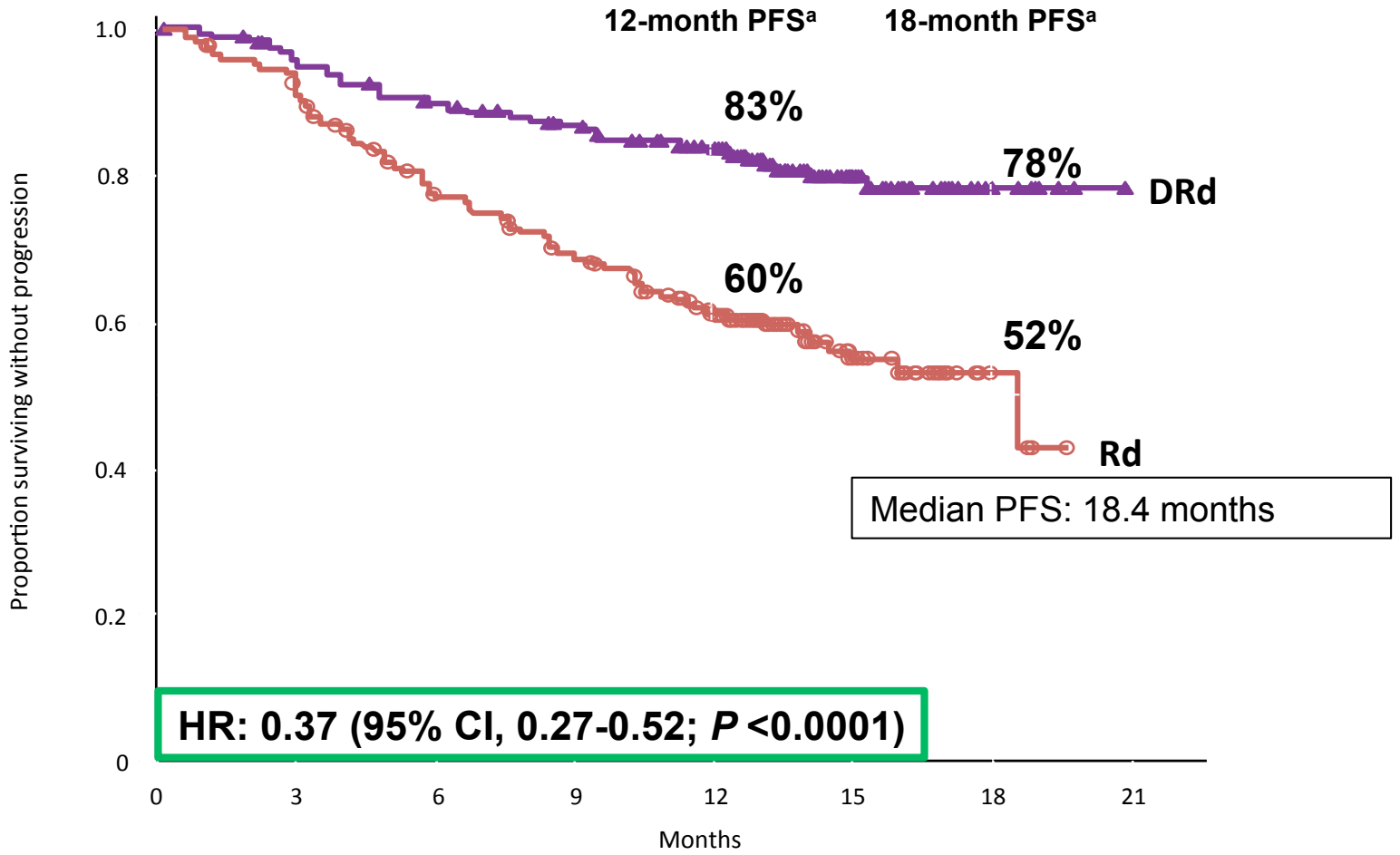
Baseline characteristics

	DRd	Rd
Age, median (range)	65 yrs (34-89)	65 yrs (42-87)
High risk cytogenetic	15%	17%
ISS 3	20%	20%
Median time from diagnosis	3,5 yrs (0,4 - 27)	4,0 yrs (0,4 - 22)
Prior auto-SCT	63%	64%
Prior PI	86%	86%
Prior IMiD	55%	55%
Refractory to PI	20%	16%

Dimopoulos et al. *NEJM* 2016

Daratumumab – Rd (Pollux)

PFS

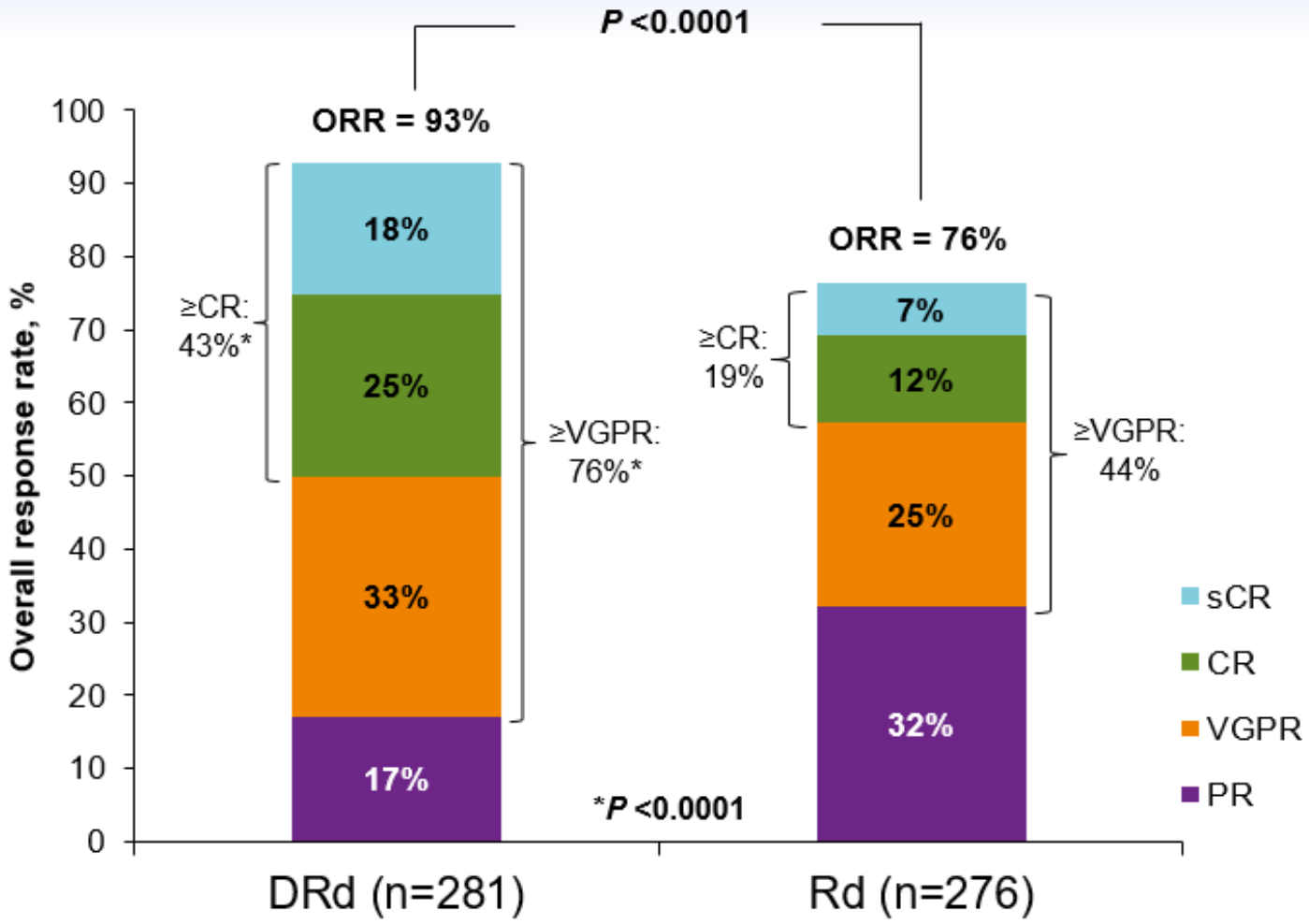


Median duration of response: not reached for DRd vs 17.4 months for Rd

Dimopoulos et al. *NEJM* 2016

Daratumumab – Rd (Pollux)

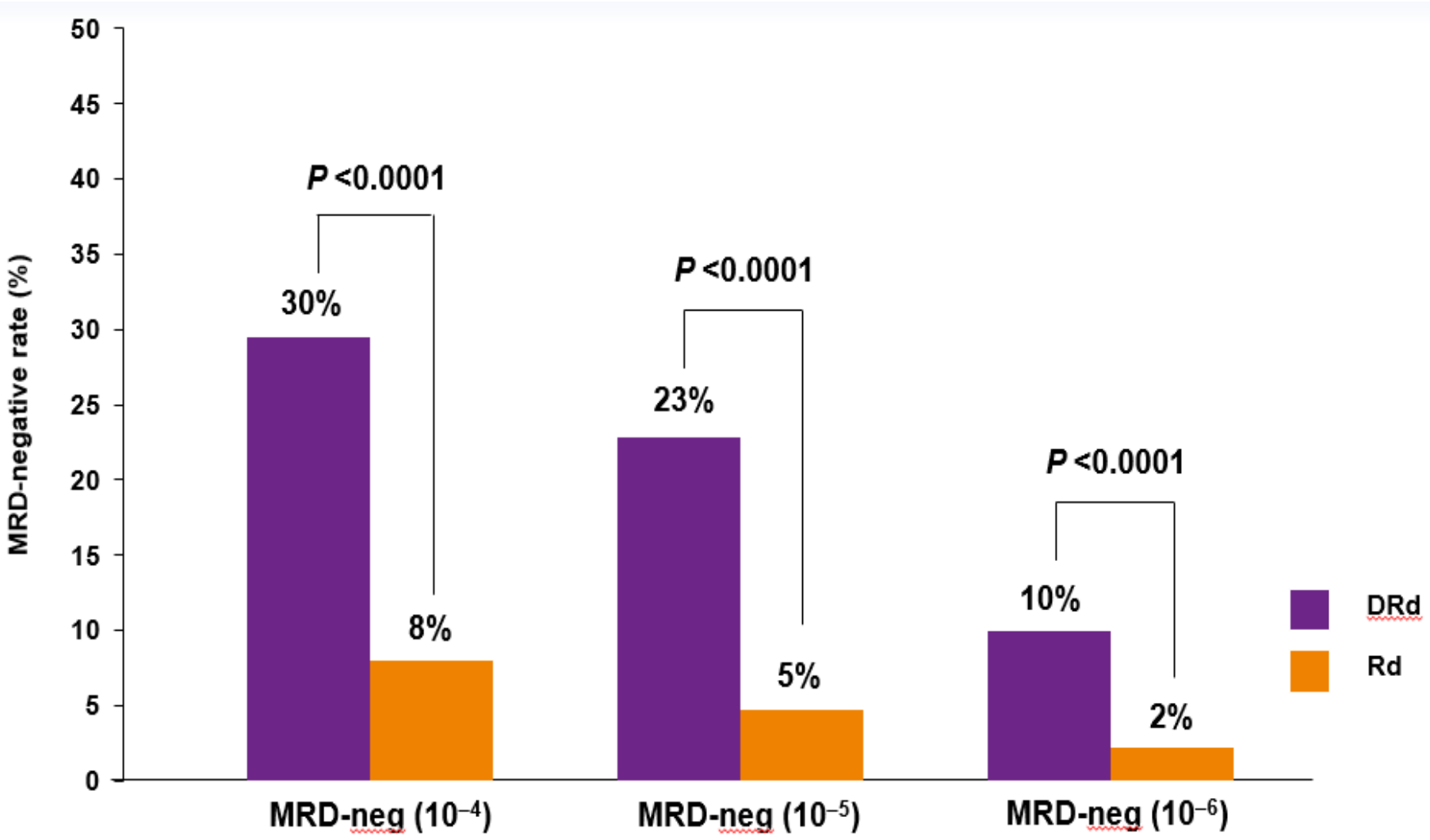
ORR



Dimopoulos et al. *NEJM* 2016

Daratumumab – Rd (Pollux)

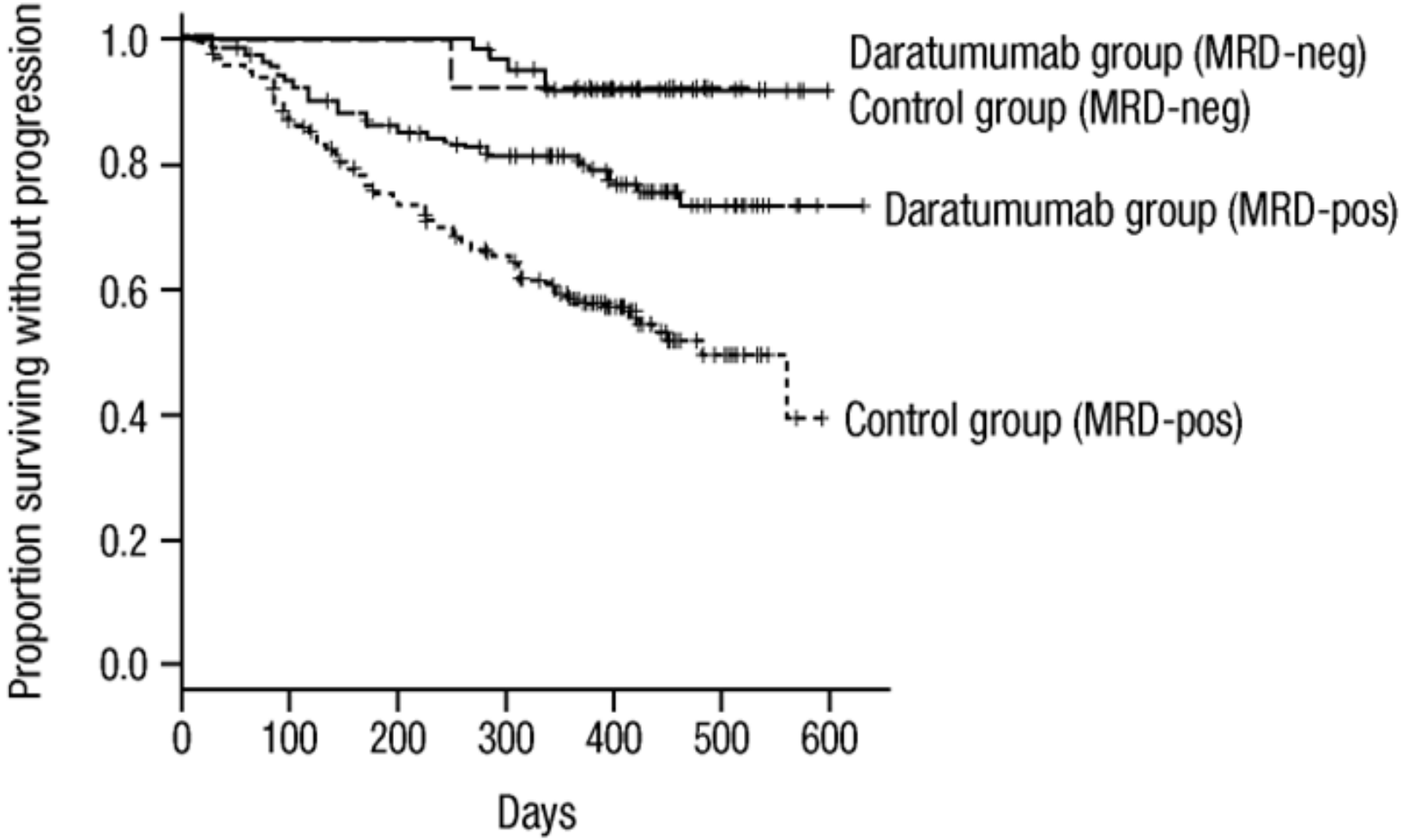
MRD negativity rate



Dimopoulos et al. *NEJM* 2016

Daratumumab – Rd (Pollux)

PFS according to MRD 10^{-5}

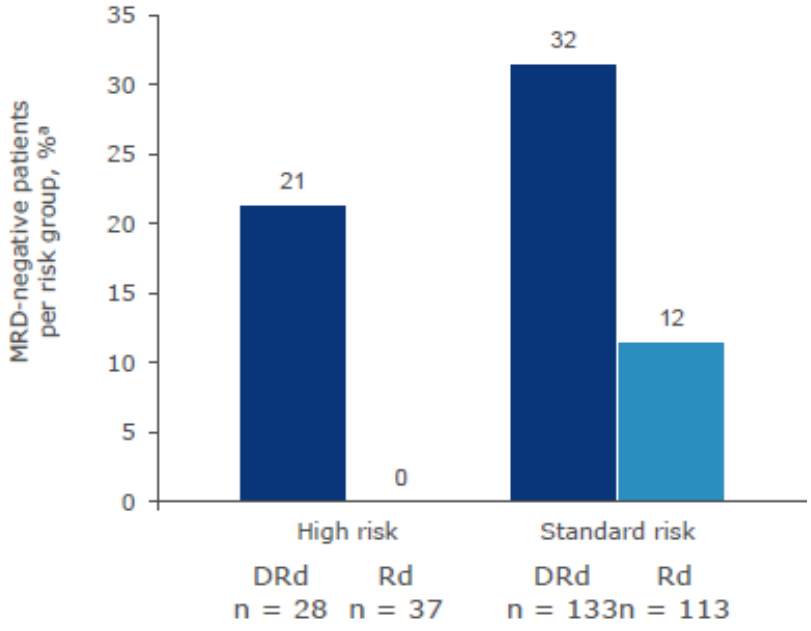


Dimopoulos et al. *NEJM* 2016

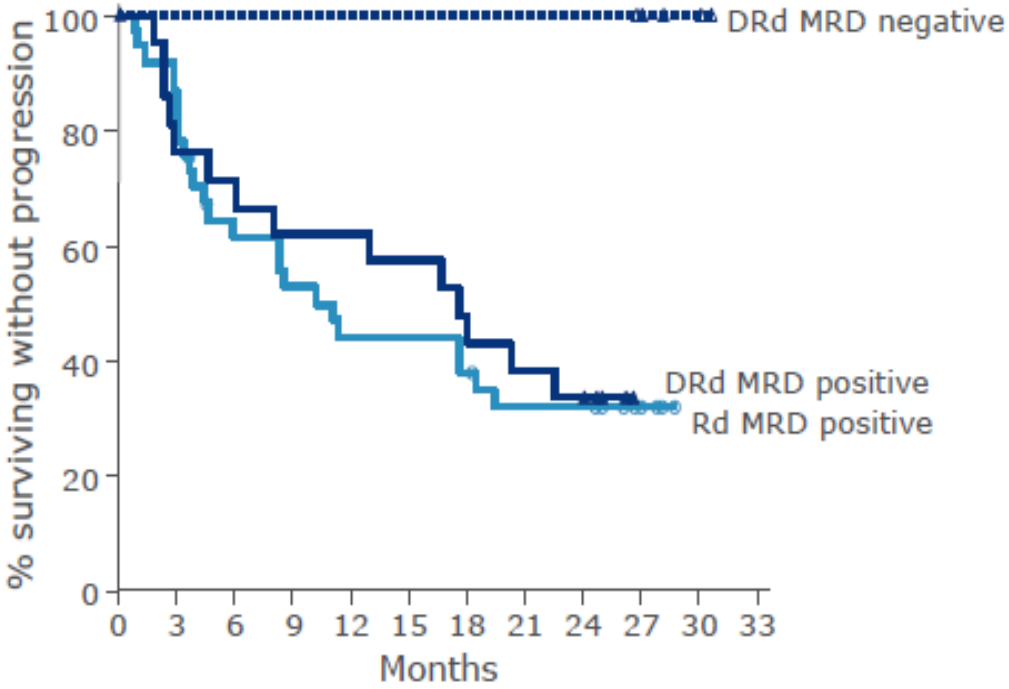
Daratumumab – Rd (Pollux)

MRD 10^{-5} by cytogenetic status

MRD 10^{-5} negativity rates



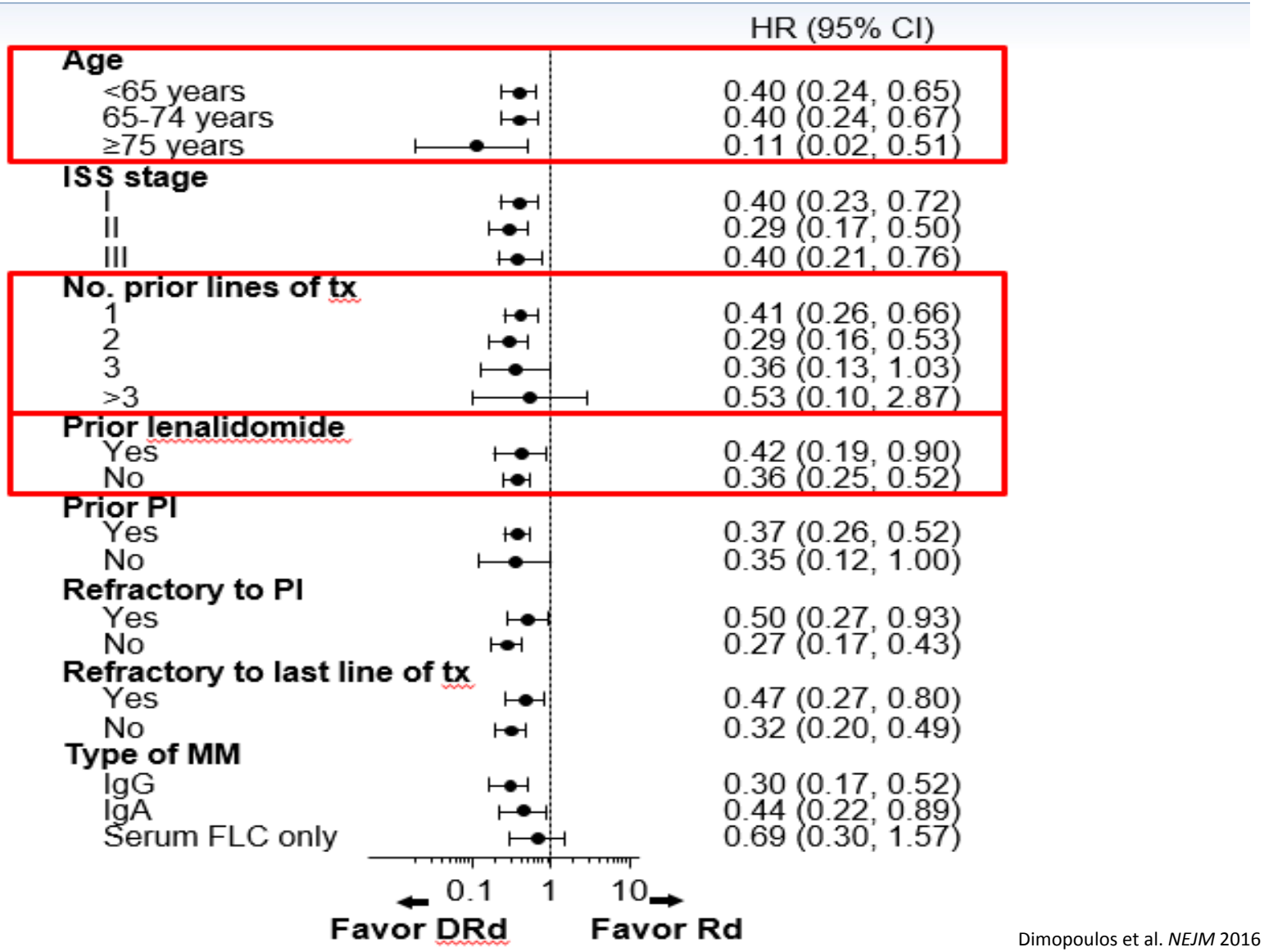
PFS in high risk patients



Weisel et al. *ASCO* 2017

Daratumumab – Rd (Pollux)

Subgroup analysis for PFS



Dimopoulos et al. *NEJM* 2016

Daratumumab – Rd (Pollux)

Most relevant toxicities

	DRd		Rd	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Thrombocytopenia	27%	13%	27%	13%
Neutropenia	59%	12%	35%	20%
Diarrhea	43%	5%	25%	3%
Anemia	31%	12%	35%	20%
Upper respiratory tract infect.	32%	1%	20%	1%
Cough	29%	0%	12%	0%
Pneumonia	14%	8%	13%	1%
Fatigue	35%	6%	28%	2%

Dimopoulos et al. *NEJM* 2016

Daratumumab – Vd (Pollux)

Essential informations to remember:

D-Rd 18-months PFS → 78%

Benefit across all subgroups

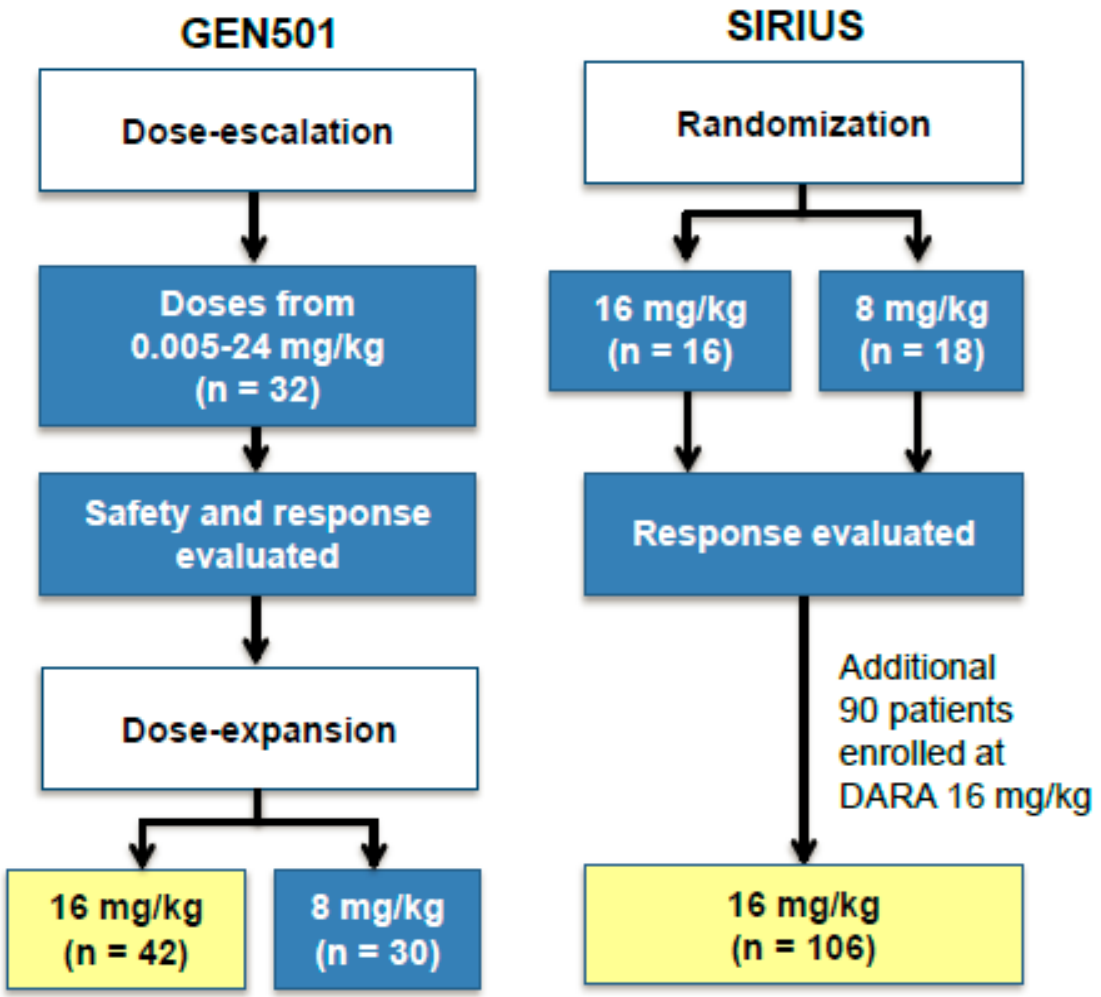
MRD 10-5 negativity in 23%

Minimal additional toxicity

Daratumumab

1st line	2nd – 3rd line	≥3rd line
Transplant eligible Dara – VRd + AutoSCT *Transplant ineligible* Dara - Rd Dara - VMP	Dara - Vd Dara - Rd	**Dara mono** Dara - PD

Daratumumab monotherapy



16 mg/kg
N = 148

Usmani et al. *Blood* 20016

Daratumumab monotherapy

Baseline characteristics

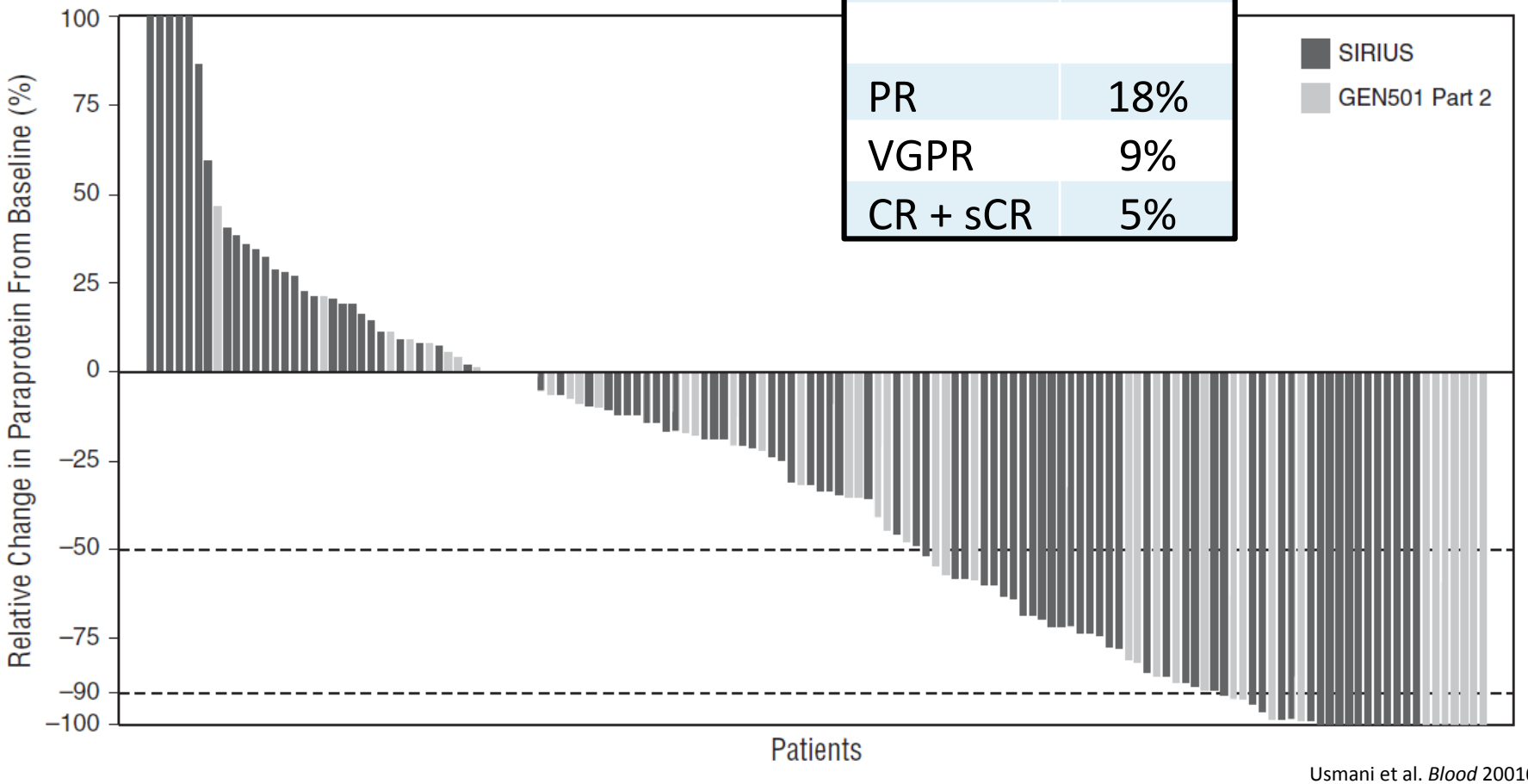
	GEN501 42 pts	Sirius 106 pts	Combined studies 148 pts
Age, median (range)	64 (44-76)	63 (31-784	64 (31-84)
Extramedullary plasmocytomas	10%	13%	12%
t(4;14)		10%	
del17p		17%	
amp1q		24%	
Previous lines, median (range)	4 (2-12)	5 (2-14)	5 (2-14)
Prior ASCT	74%	80%	78%
Prior bortezomib	100%	99%	99%
Prior carfilzomib	19%	50%	41%
Prior lenalidomide	95%	99%	99%
Prior pomalidomide	36%	63%	55%
Refractory to a PI + an IMiD	64%	95%	87%

Usmani et al. *Blood* 20016

Daratumumab monotherapy

ORR

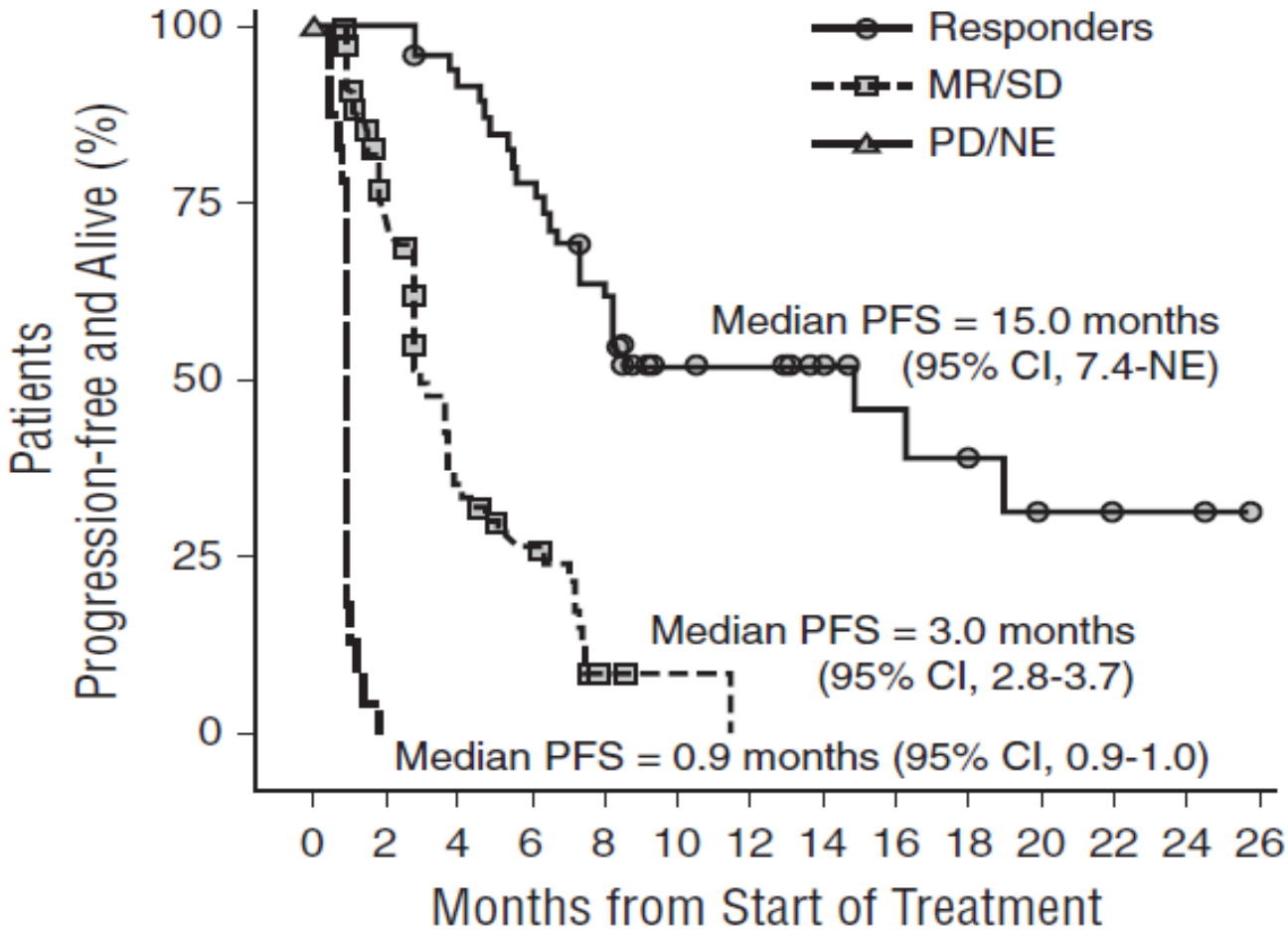
ORR	31%
PR	18%
VGPR	9%
CR + sCR	5%



Usmani et al. *Blood* 20016

Daratumumab monotherapy

PFS



Usmani et al. *Blood* 20016

Daratumumab – Vd (Pollux)

Essential informations to remember:

ORR 31%

Median PFS in ≥ PR → 15 months

Daratumumab

1st line	2nd – 3rd line	≥3rd line
Transplant eligible		
Dara – VRd + AutoSCT	Dara - Vd	Dara mono
	Dara - Rd	**Dara - PD**
Transplant ineligible		
Dara - Rd		
Dara - VMP		

Daratumumab – Poma - Dex

Phase 1b trial

Daratumumab 16 mg/kg weekly in cycle 1 + 2, every 2 weeks in cycles 3-6, then every 4 weeks

Pomalidomide 4 mg on days 1 to 21, every 4 weeks

Dexamethasone 40 mg (20 mg in >75 yrs) weekly

Chari et al. *Blood* 2017

Daratumumab – Poma - Dex

Baseline characteristics

103 pts with refractory MM

Median age: **64 yrs** (range 35-86)

Prior therapy	
PI + IMiD	102 (99)
PI	102 (99)
BORT	101 (98)
CARF	34 (33)
IXA	2 (2)
LEN	103 (100)
THAL	29 (28)
BORT + LEN	101 (98)
BORT + LEN + CARF	34 (33)
Steroids	103 (100)
Chemotherapy	103 (100)

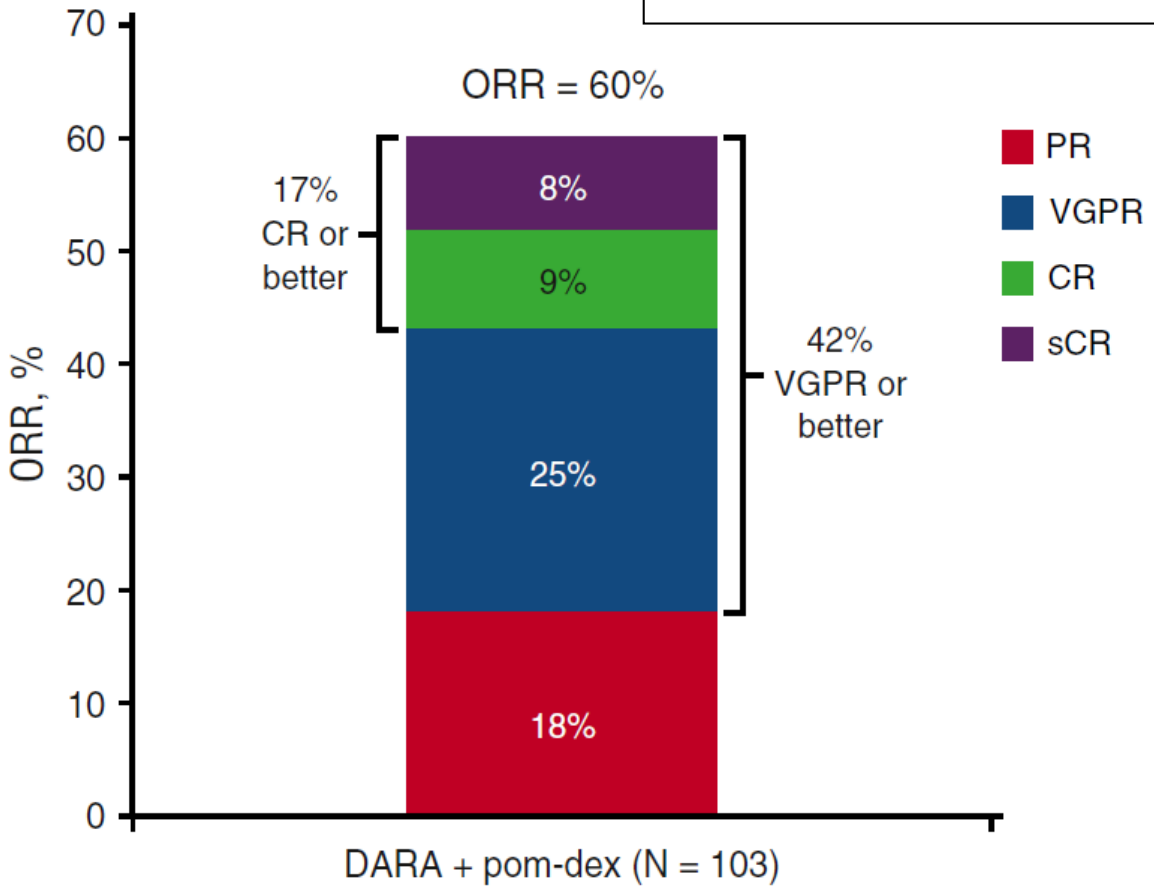
Refractory to	
PI only	9 (9)
IMiD only	21 (20)
PI + IMiD	73 (71)
Cytogenetic abnormality	
Standard risk	65 (75)
High risk‡	22 (25)
del17p	16 (18)
t(4;14)	6 (7)
t(14;16)	1 (1)

Chari et al. *Blood* 2017

Daratumumab – Poma - Dex

ORR

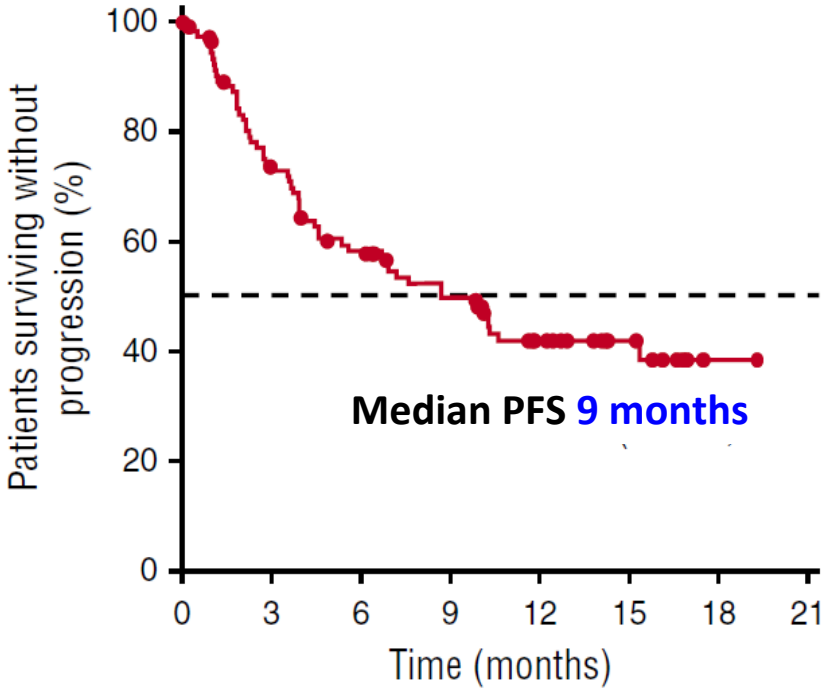
29% of CR pts were MRD 10^{-5} negative



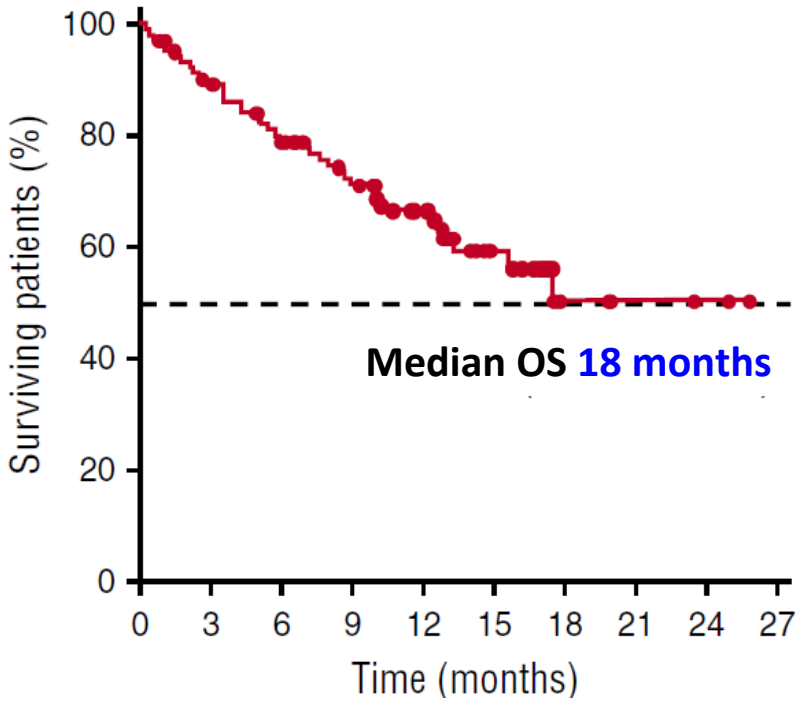
Chari et al. *Blood* 2017

Daratumumab – Poma - Dex

PFS



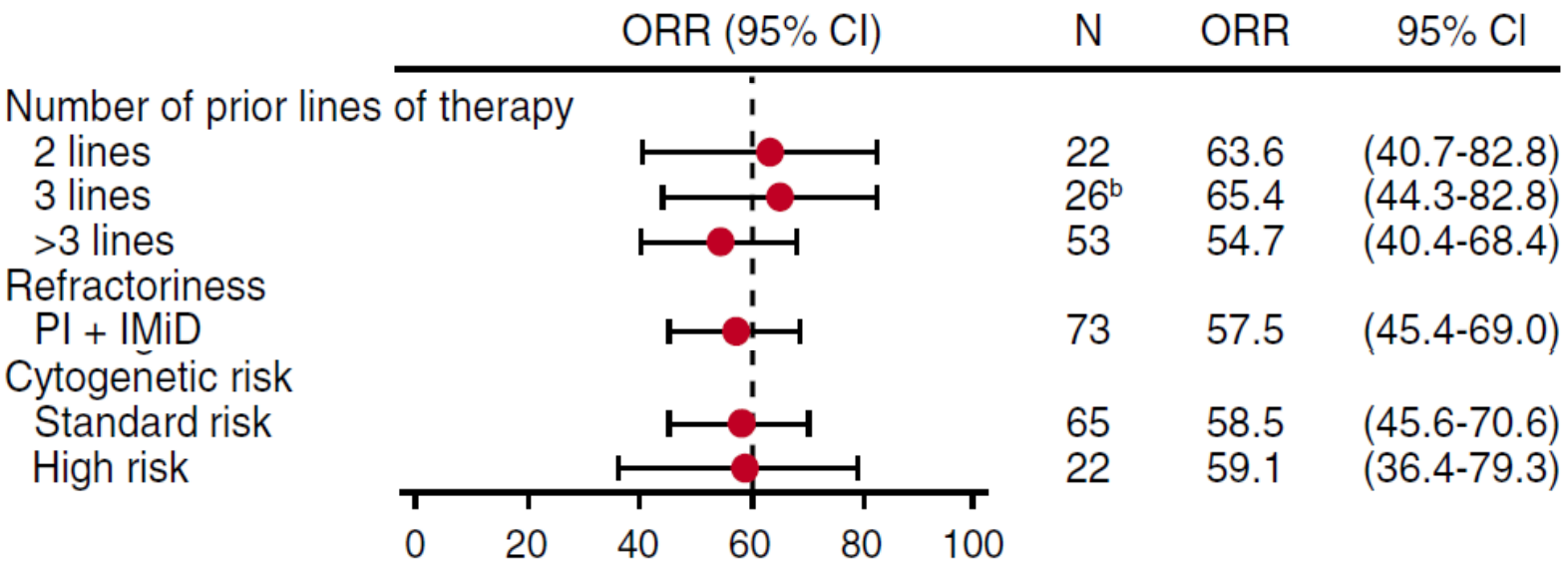
OS



Chari et al. *Blood* 2017

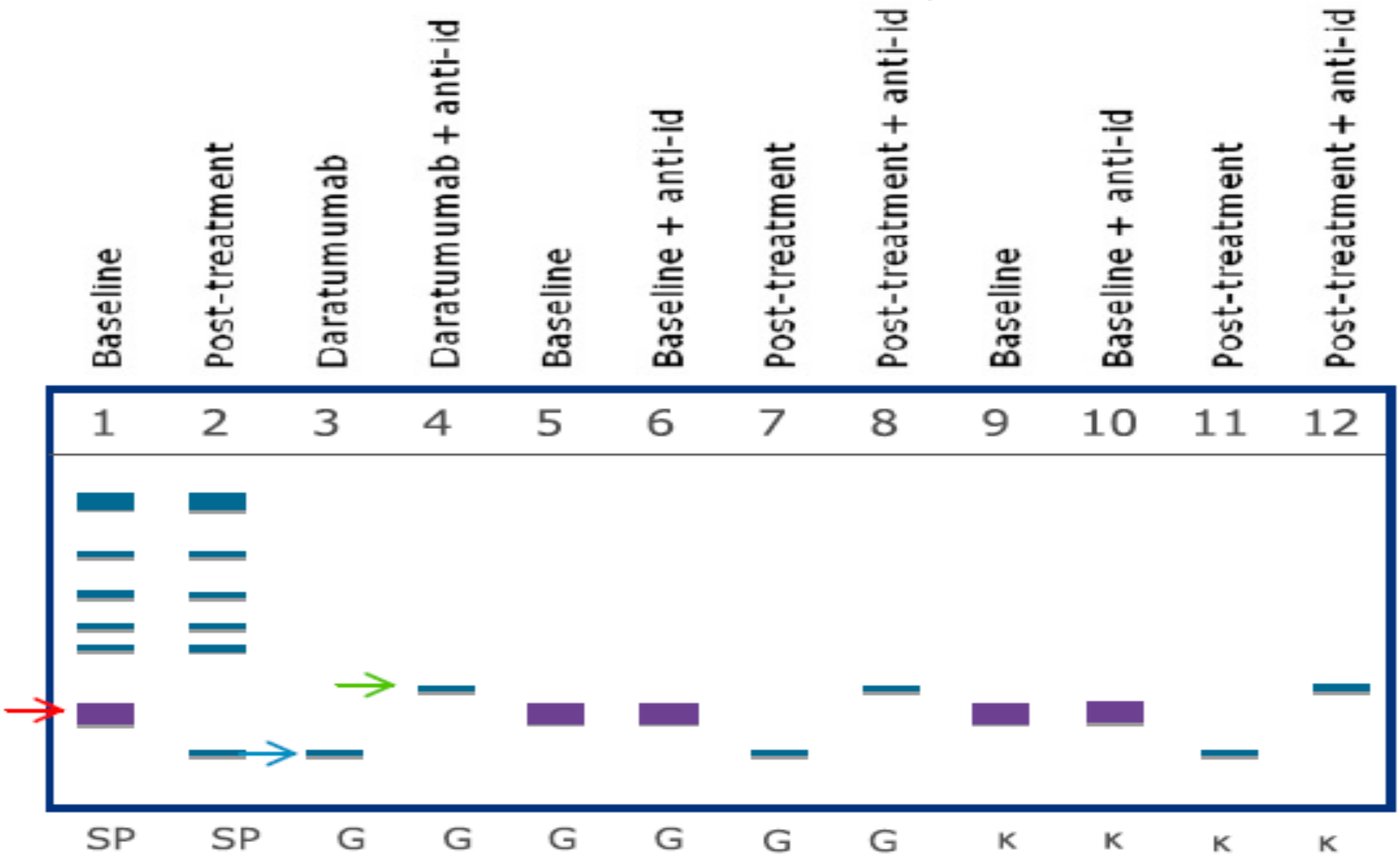
Daratumumab – Poma - Dex

Subgroup analysis for ORR



Chari et al. *Blood* 2017

Daratumumab and serological response

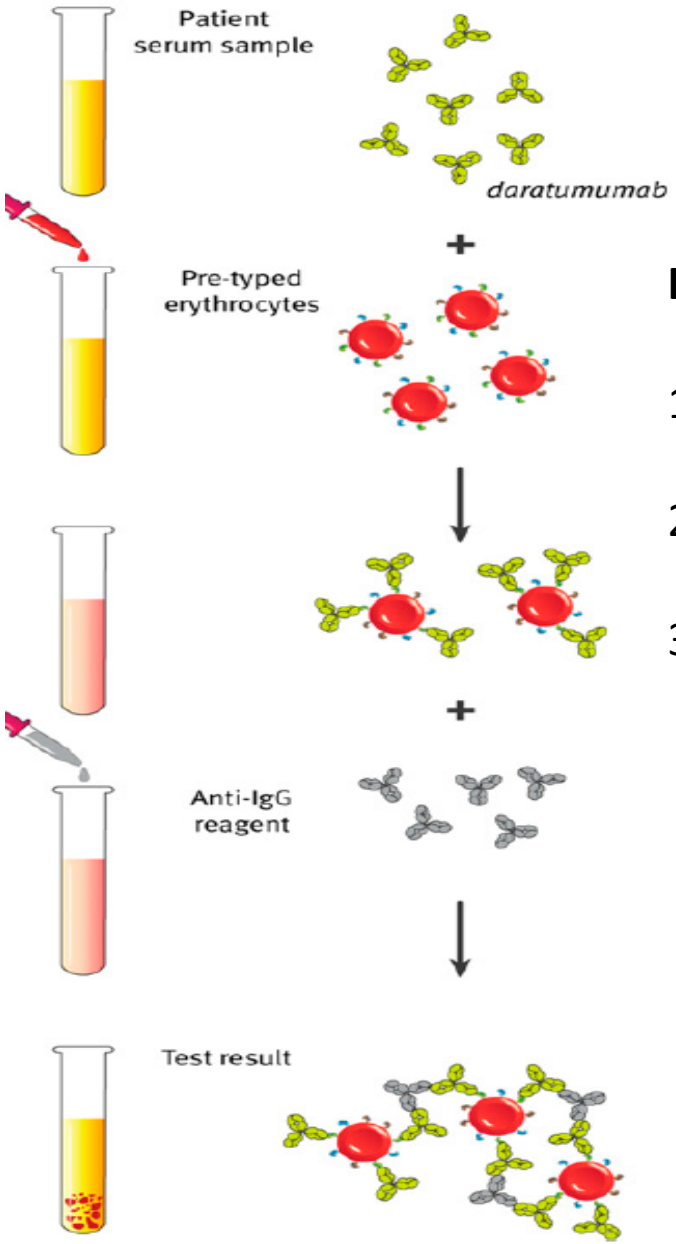


DIRA negative

→no M-protein

From van de Donk et al. *Blood* 2016

Daratumumab and blood compatibility testing



How to manage this situation

1) Extensive red cell phenotyping before Dara start
2) RBC group genotyping (alternative: expensive!)
3) CD38 denaturation with dithiothreitol (DTT) before blood compatibility testing (KELL will be denaturated)

From van de Donk et al. *Blood* 2016

- General considerations

- Elotuzumab

- Daratumumab

- **Future developments**

New monoclonal antibodies for MM

Agent	Target	Company	Features	Clinical Study
Antibody–drug conjugates				
GSK2857916	BCMA	GSK	J6M0-mcMMAF	Phase I
Indatuximab ravtansine	CD138	Biotest	nBT062-SPDB-DM4	Phase I-IIa
Bispecific antibodies				
BCMA bispecific	BCMA	Pfizer	CD3, IgG-like	Preclinical
EM801	BCMA	Celgene	CD3, IgG-like	Preclinical
AMG420	BCMA	Amgen	CD3, BiTE	Preclinical
FcRH5/CD3 TDB	FcRH5	Genentech	CD3, IgG-like	Preclinical
BiTE-hIgFc (STL001)	CD138	Unknown	BiTE-Fc fusion	Preclinical

From Sherbenou et al. *Clin Lymph, Myel, Leuk* 2017