Nuevas Dianas Terapéuticas en Pacientes con Mieloma Múltiple

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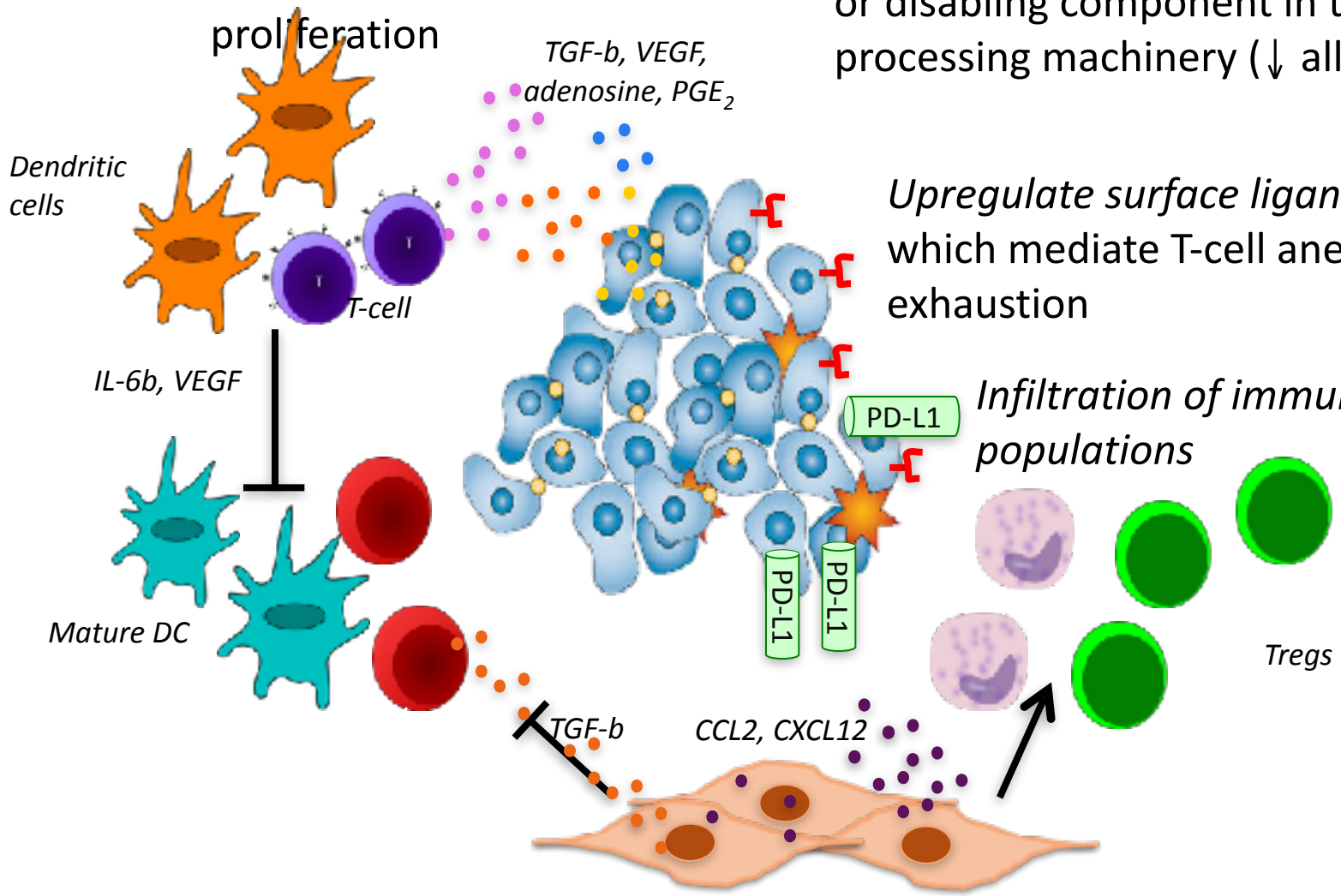
Myeloma Escape from Immunity

Suppression of dendritic cell and T-cell activation and proliferation

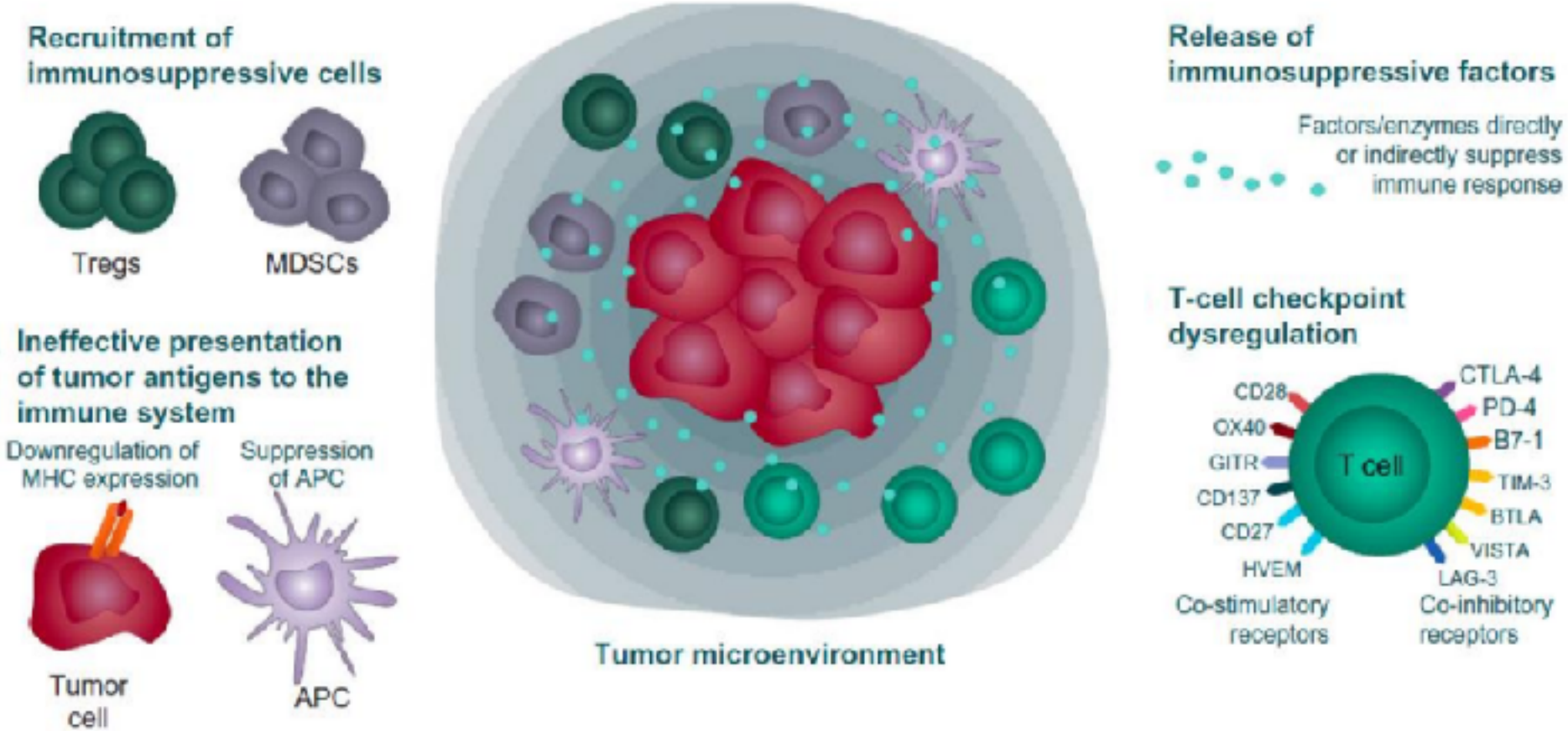
Downregulation of MHC class I or disabling component in the Ag processing machinery (↓ alloreactivity)

Upregulate surface ligands which mediate T-cell anergy / exhaustion

Infiltration of immunosupresive cell populations

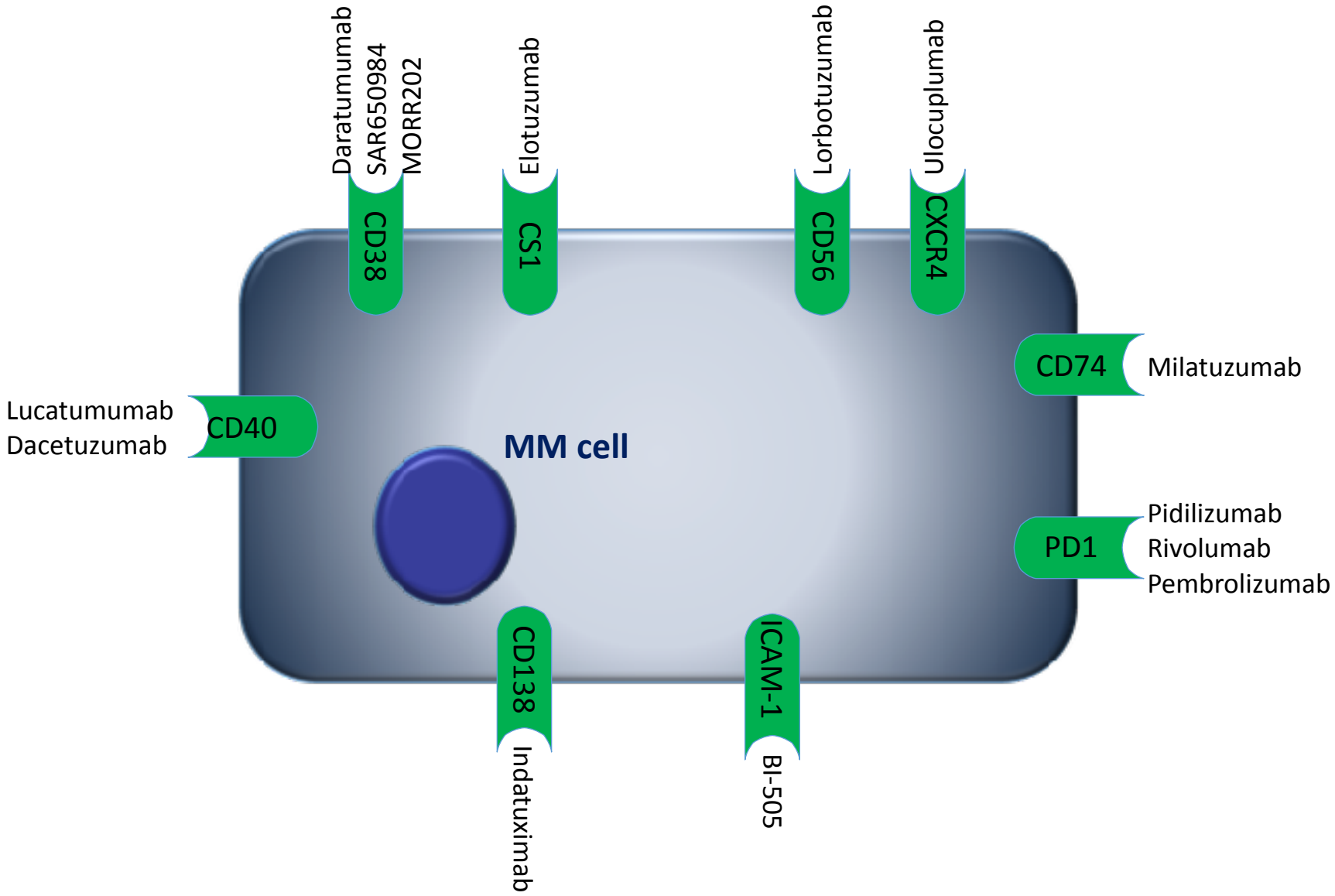


Immune Dysregulation, T cell Inactivation, and Tumor Escape



Davies M. Cancer Mgmt and Research. 2014

Monoclonal Antibody (MoAb) Therapy in MM



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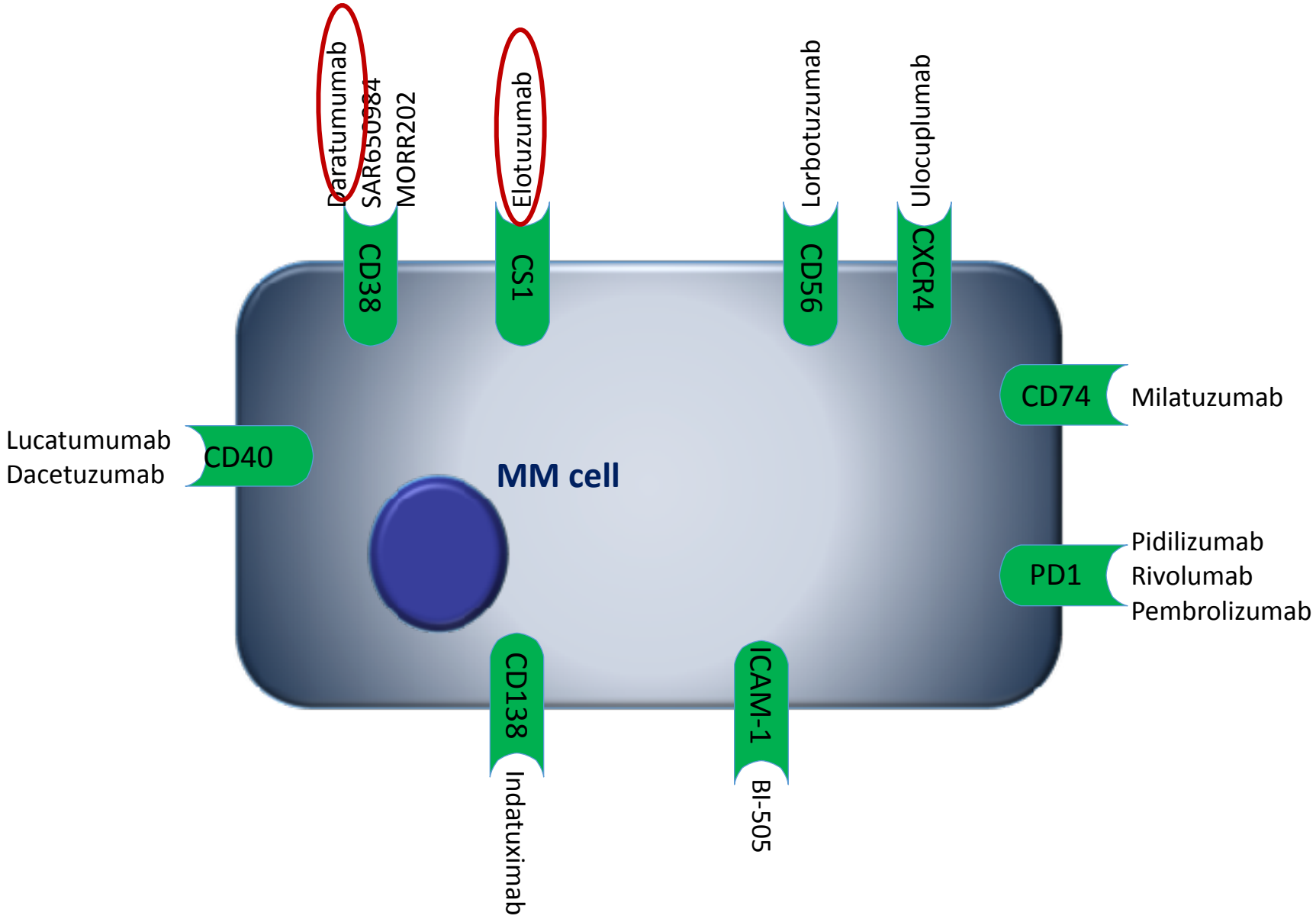
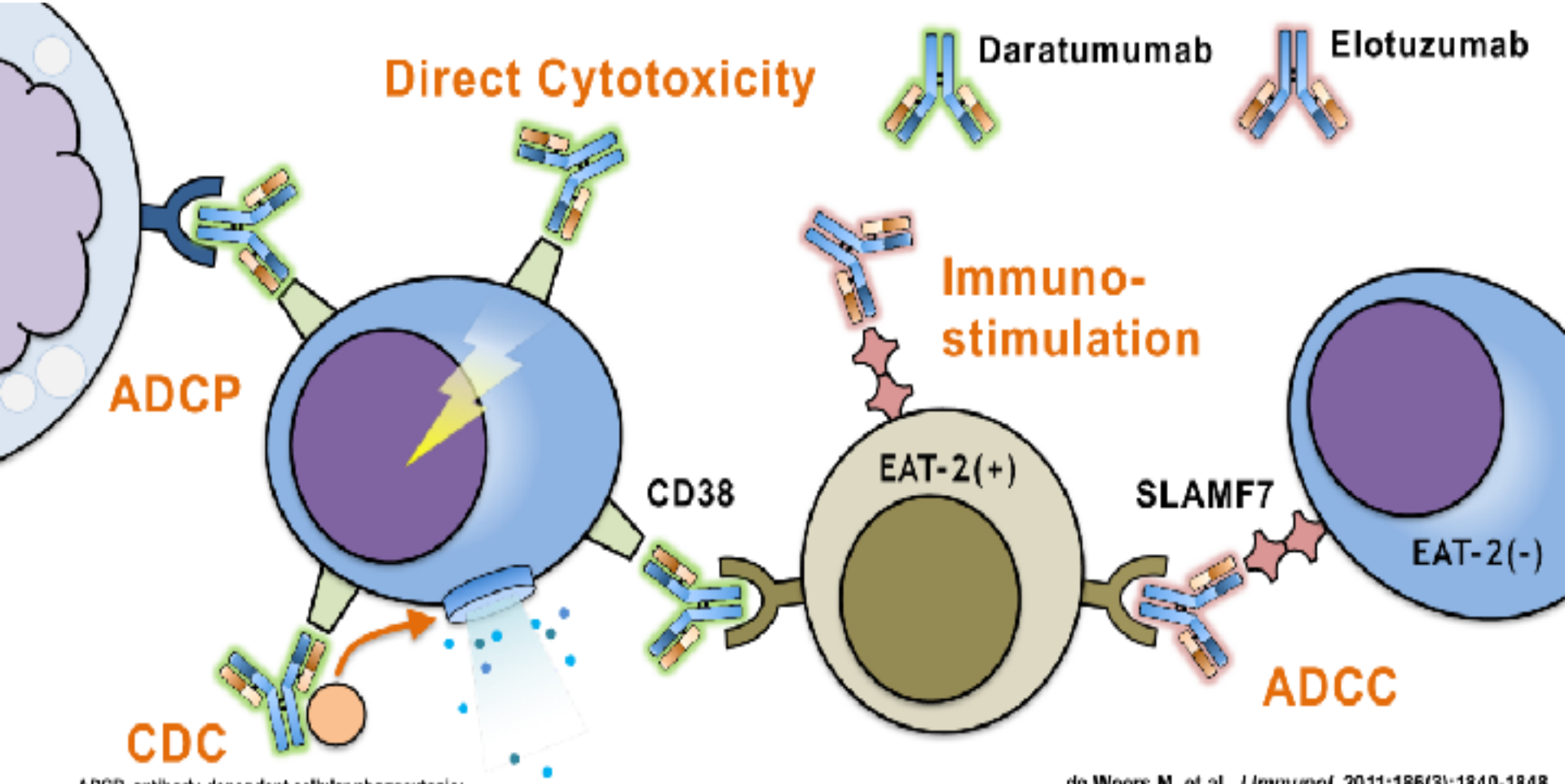


MoAbs in MM: Mechanism of Action



ADCP, antibody-dependent cellular phagocytosis;
CDC, complement-dependent cytotoxicity; ADCC, antibody-dependent cellular cytotoxicity

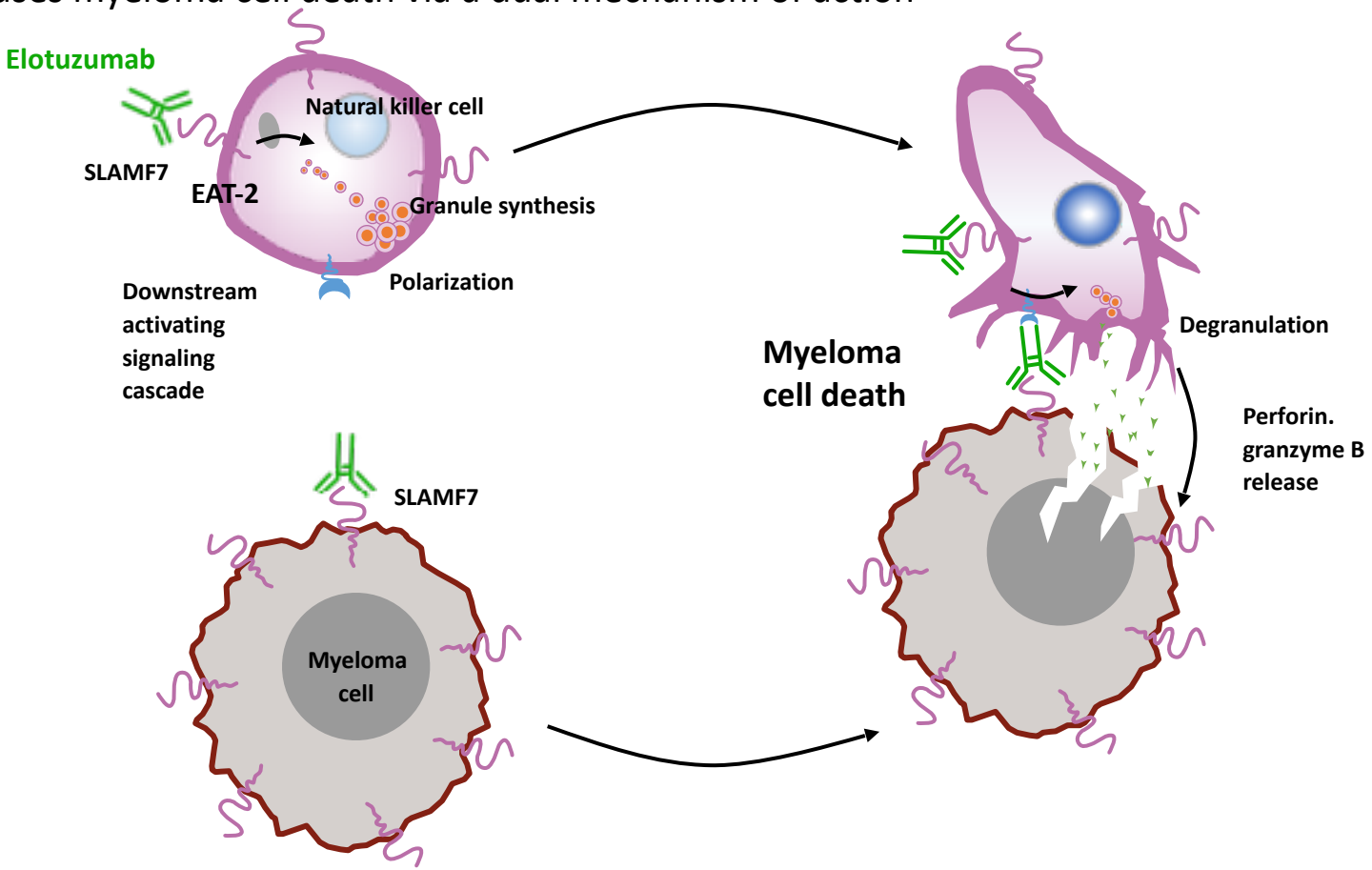
de Weers M, et al. *J Immunol*. 2011;186(3):1840-1848.
Collins SM, et al. *Cancer Immunol Immunother*. 2013;62(12):1841-1849.

Elotuzumab: Immunostimulatory Mechanism of Action

- Elotuzumab is an immunostimulatory monoclonal antibody that recognizes SLAMF7, a protein highly expressed by myeloma and natural killer cells[1]
- Elotuzumab causes myeloma cell death via a dual mechanism of action[2]

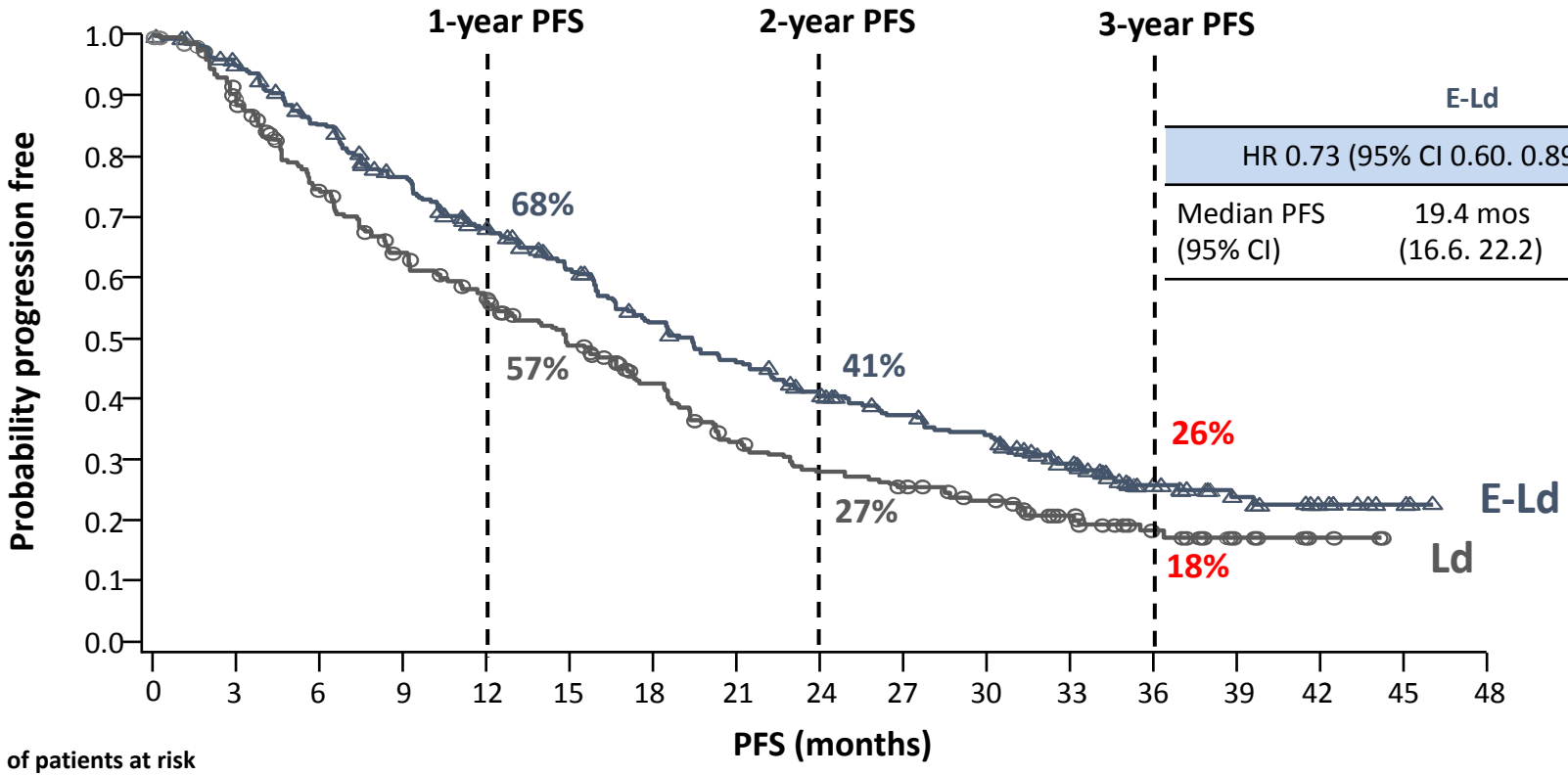
A Directly activating natural killer cells

B Tagging for recognition (ADCC)



1. Hsi ED et al. *Clin Cancer Res* 2008;14:2775–84; 2. Collins SM et al. *Cancer Immunol Immunother* 2013;62:1841–9.
ADCC=antibody-dependent cell-mediated cytotoxicity; SLAMF7=signaling lymphocytic activation molecule F7

Eloquent-2: PFS



	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)

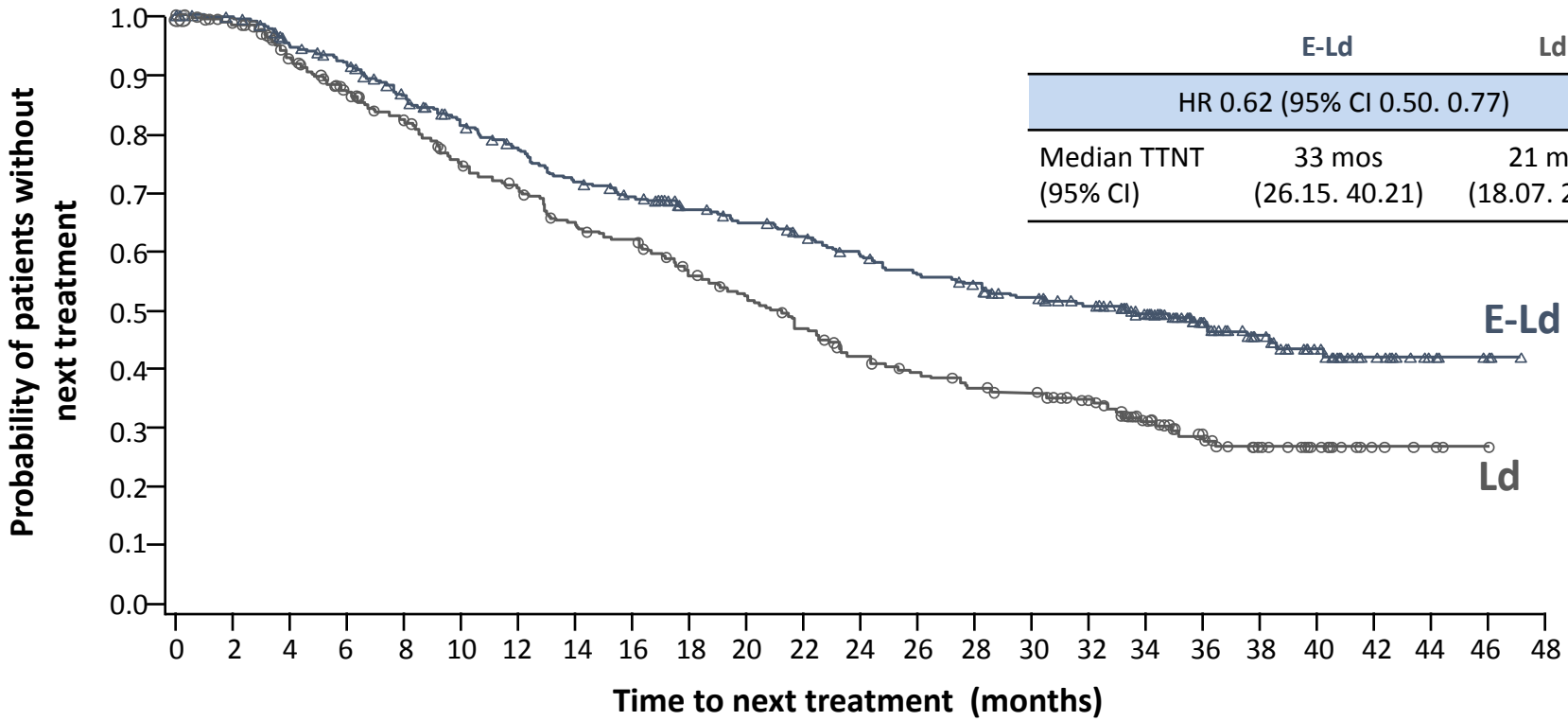
No. of patients at risk

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**

Eloquent-2: TTNT



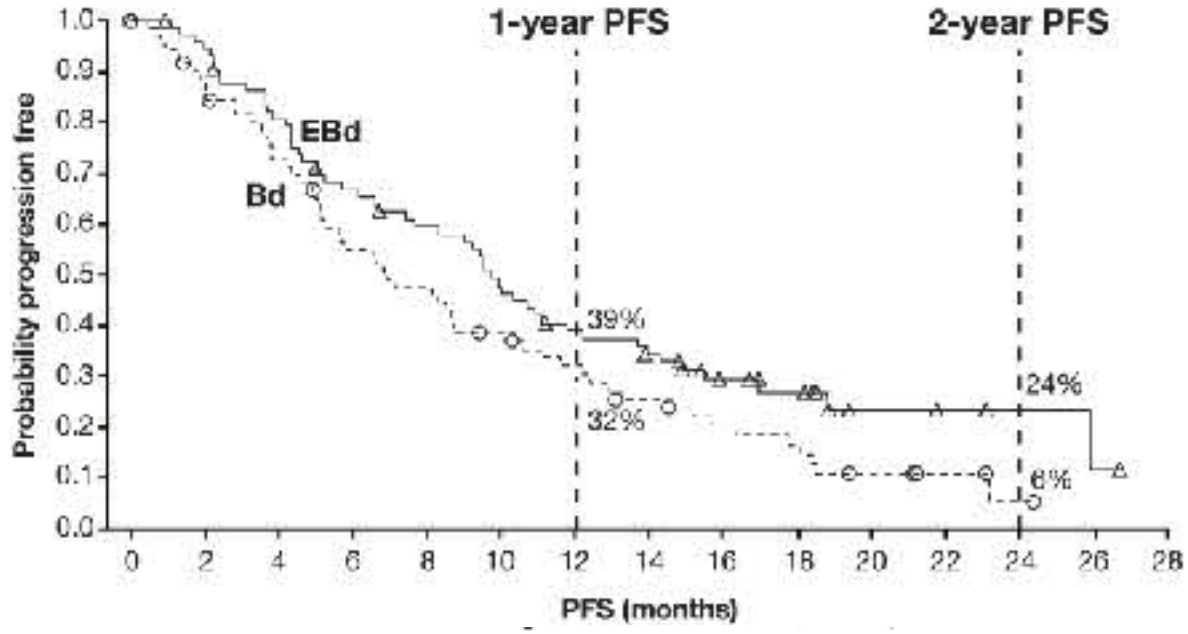
	E-Ld	Ld
HR 0.62 (95% CI 0.50. 0.77)		
Median TTNT (95% CI)	33 mos (26.15. 40.21)	21 mos (18.07. 23.20)

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

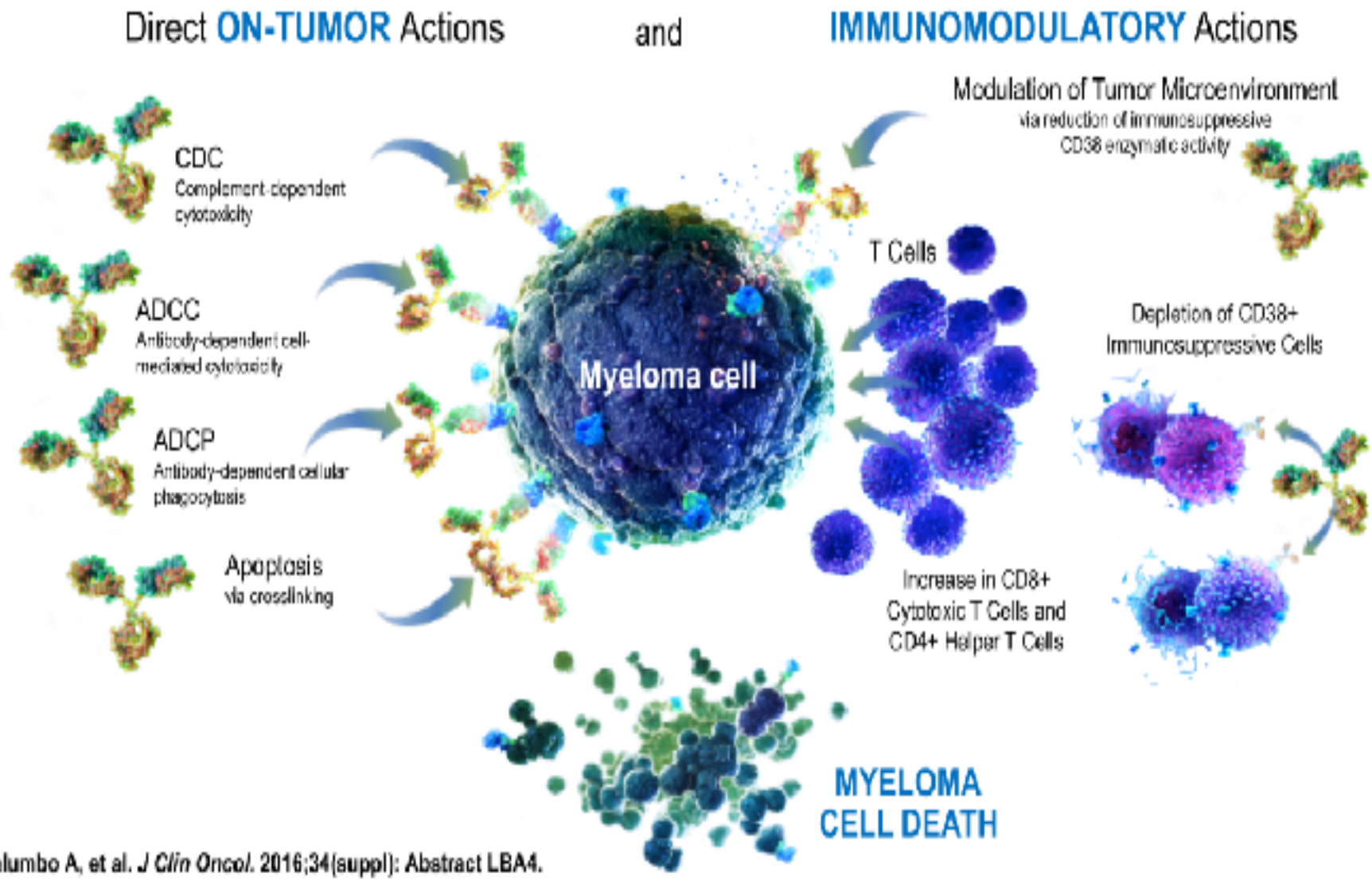
Bortezomib/Dexamethasone w/wo Elotuzumab: PFS



Efficacy endpoints	EVd (n=321)	Vd (n=325)
Median PFS, mo	14.9	9.7
HR (95% CI)	0.72 (0.59-0.88)	
Median OS, mo	NR	NR
HR (95% CI)	0.61 (0.32-1.15)	
ORR, %	66	63

Bd, bortezomib/dexamethasone; EBd, elotuzumab +bortezomib/dexamethasone.

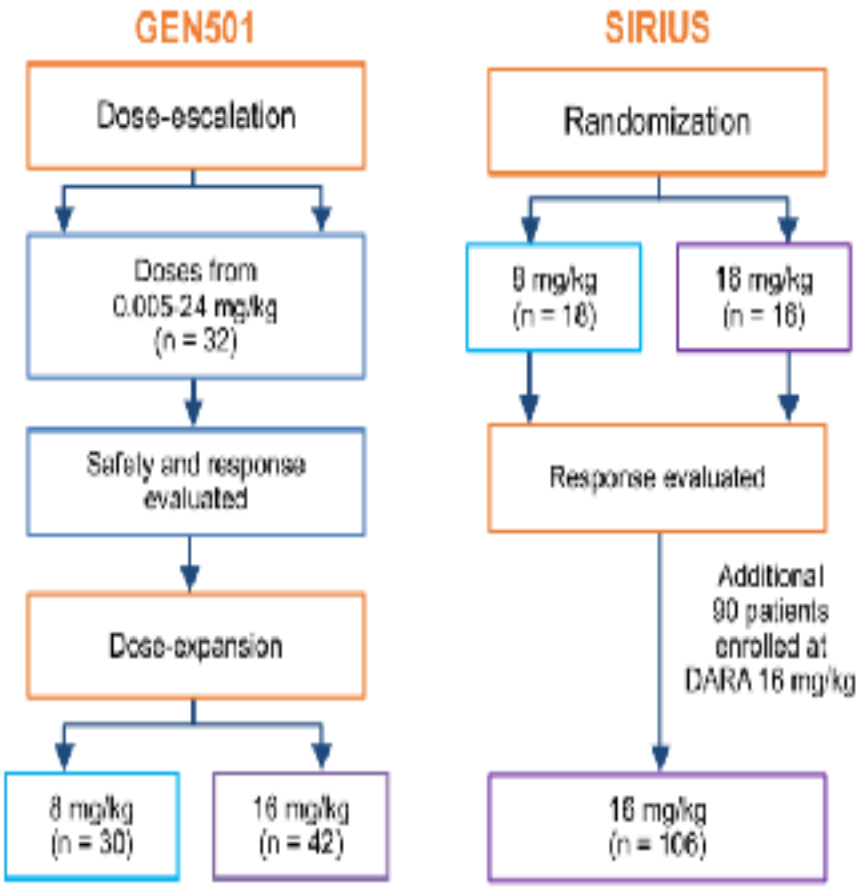
Daratumumab: Mechanism of Action



Palumbo A, et al. *J Clin Oncol.* 2016;34(suppl): Abstract LBA4.

GEN501 & Sirius: Dara Monotherapy

- GEN501[2]
  - Open-label, multicenter, phase I/II, dose-escalation and dose-expansion study
  - RRMM ≥2 prior lines of therapy including PI and IMiD, ECOG 0-2
- SIRIUS[3]
  - Open-label, multicenter, phase II study
  - RRMM ≥3 prior lines of therapy, including PI and IMiD, or double refractory, ECOG 0-2

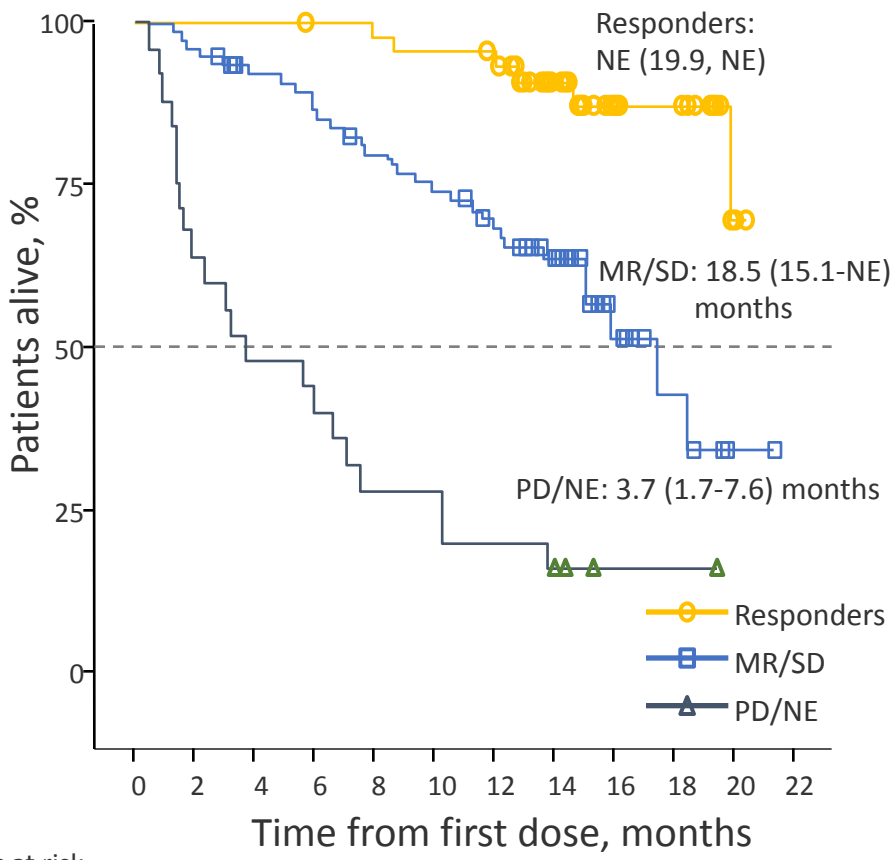


16 mg/kg; N = 148

IMiD, immunomodulatory imide drug; PI, proteasome inhibitor

1. Usmani SZ, et al. *Blood*. 2016;128(1):37-44. 2. Lokhorst HM, et al. *N Engl J Med*. 2015;373(13):1207-1219. 3. Lonial S, et al. *Lancet*. 2016;387(10027):1551-1560.

OS: Combined Analysis of GEN501/ MMY2002



Patients at risk												
Responders	46	46	46	45	44	43	42	29	15	13	3	0
MR/SD	77	74	67	63	57	53	47	37	10	5	1	0
PD/NE	25	16	12	11	7	7	5	4	1	1	0	0

20.1 mo	Median OS Combined 2002/501
83%	Of patients benefited (SD or better / DCR)
31%	31% with PR or better, DoR 7.6 mo
sCR	Deep Responses 3 sCR

POLLUX & CASTOR: Dara-based RCT in Relapsed MM

POLLUX

RANDOMIZE

DRd (n = 286)

D 16 mg/kg IV
Every week: Cycles 1-2
Every 2 weeks: Cycles 3-6
Every 4 weeks until PD
R 25 mg PO (similar to Rd alone)
d 40 mg

Rd (n = 283)

R 25 mg PO
Days 1-21 of each cycle until PD
d 40 mg weekly until PD

MRD assessments

- At suspected CR
- 3 & 6 months after CR

Patient characteristics

- Median (range) prior lines: 1 (1-11)
- Prior V: 84%
- Prior R: 18%

CASTOR

RANDOMIZE

DVd (n = 251)

D 16 mg/kg IV
Every week: Cycles 1-3
Every 3 weeks: Cycles 4-8
Every 4 weeks: Cycles 9+
V 1.3 mg/m^2 SC (similar to Vd alone)
d 20 mg

Vd (n = 247)

V 1.3 mg/m^2 SC on Days 1, 4, 8, and 11 for 8 cycles
d 20 mg on Days 1, 2, 4, 5, 8, 9, 11, and 12 for 8 cycles

MRD assessments

- At suspected CR
- 6 & 12 months after first study dose

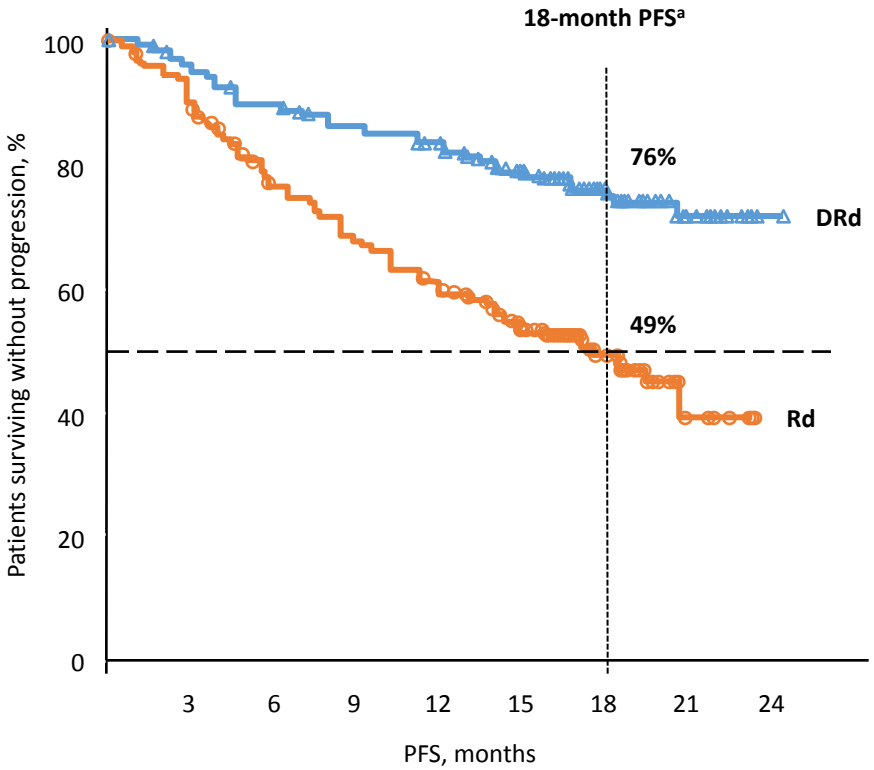
Patient characteristics

- Median (range) prior lines: 2 (1-10)
- Prior V: 66%
- Prior R: 42%

DRd, daratumumab, lenalidomide, and dexamethasone; D, daratumumab; IV, intravenous; PD, progressive disease; R, lenalidomide; PO, orally; Rd, lenalidomide and dexamethasone; d, dexamethasone; CR, complete response; DVd, daratumumab, bortezomib, and dexamethasone; V, bortezomib; SC, subcutaneously; Vd, bortezomib and dexamethasone.

POLLUX & CASTOR: Updated PFS

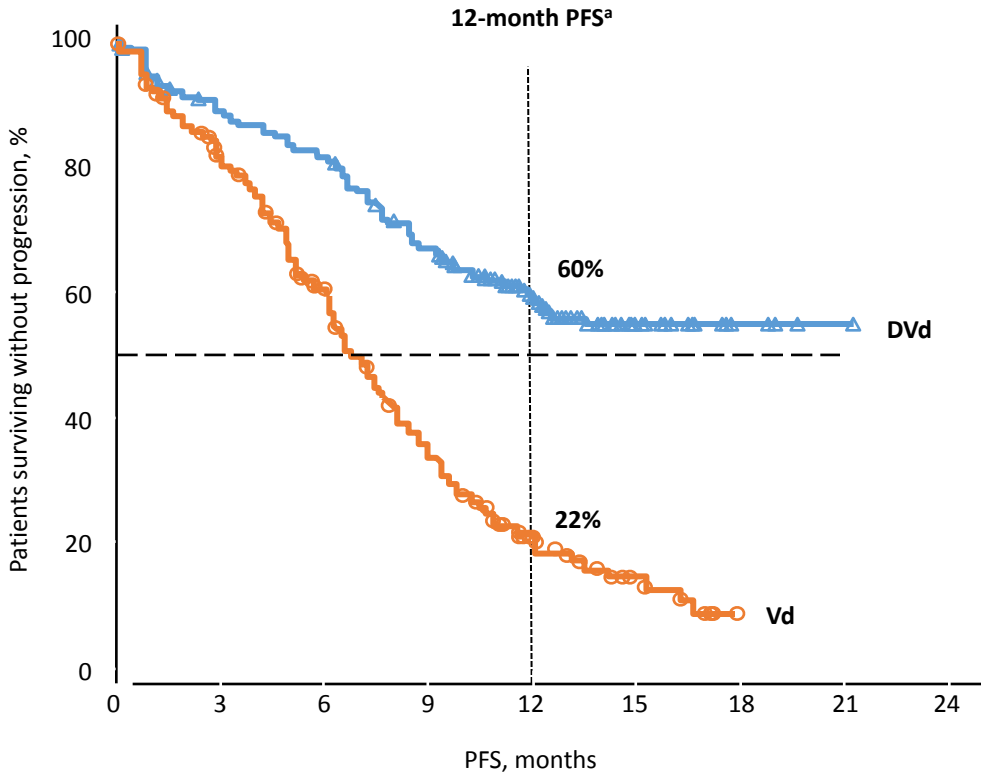
POLLUX



Median (range) follow-up:
17.3 (0-24.5) months

- **Median PFS**
  - DRd: not reached; Rd: 17.5 months
  - HR: 0.37 (95% CI, 0.28-0.50; *P* <0.0001)

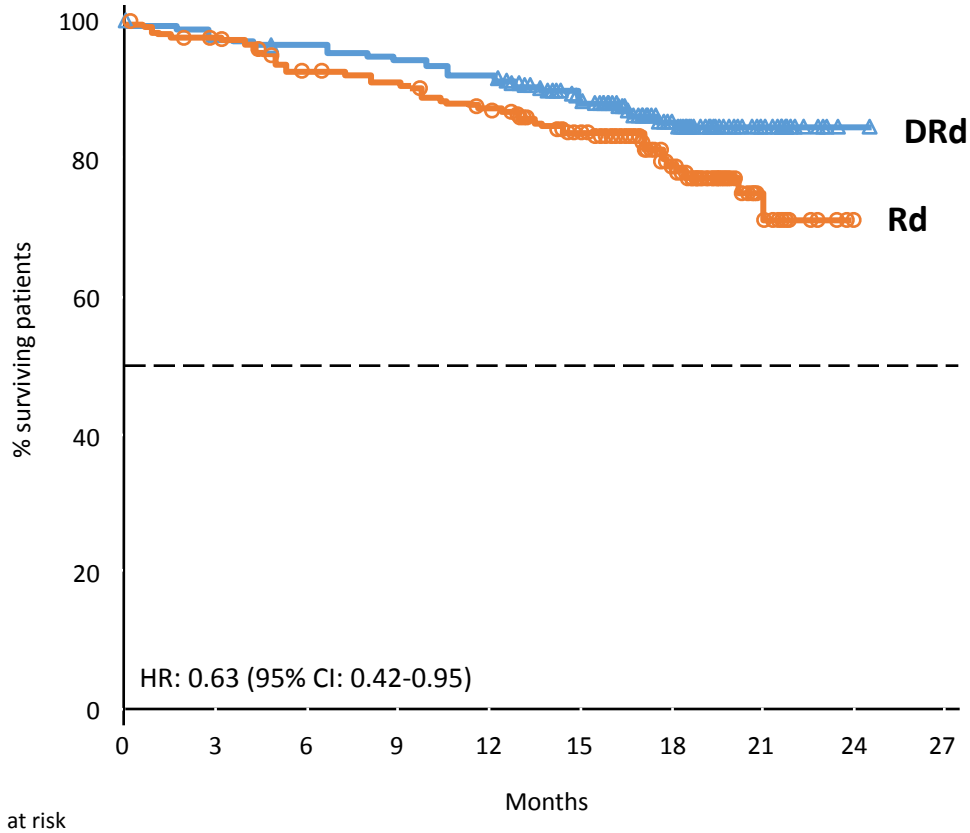
CASTOR



Median (range) follow-up:
13.0 (0-21.3) months

- **Median PFS**
  - DVd: not reached; Vd: 7.1 months
  - HR: 0.33 (95% CI, 0.26-0.43; *P* <0.0001)

POLLUX: Overall Survival



No. at risk

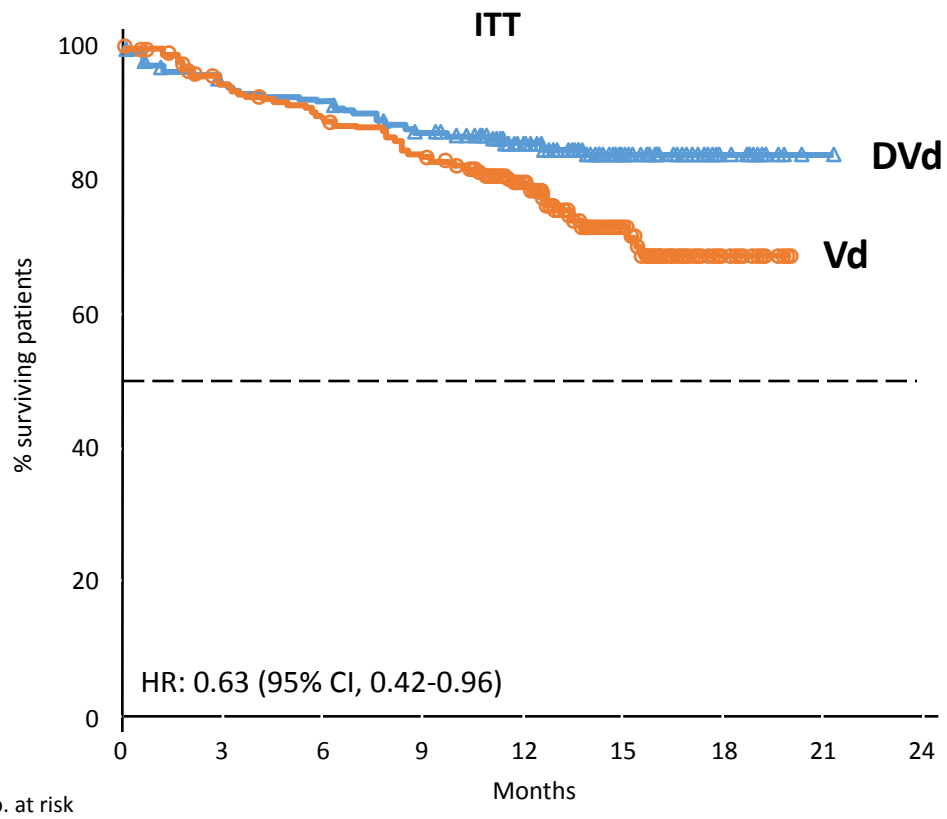
Rd	283	272	255	249	236	215	94	18	0	0
DRd	286	277	271	266	260	232	102	21	1	0

- **OS events**
  - 40 (14%) in DRd
  - 56 (20%) in Rd

Curves are beginning to separate, but OS data are immature

ITT population.
Median OS was not reached; results did not cross the prespecified stopping boundary.

CASTOR: Overall Survival



No. at risk

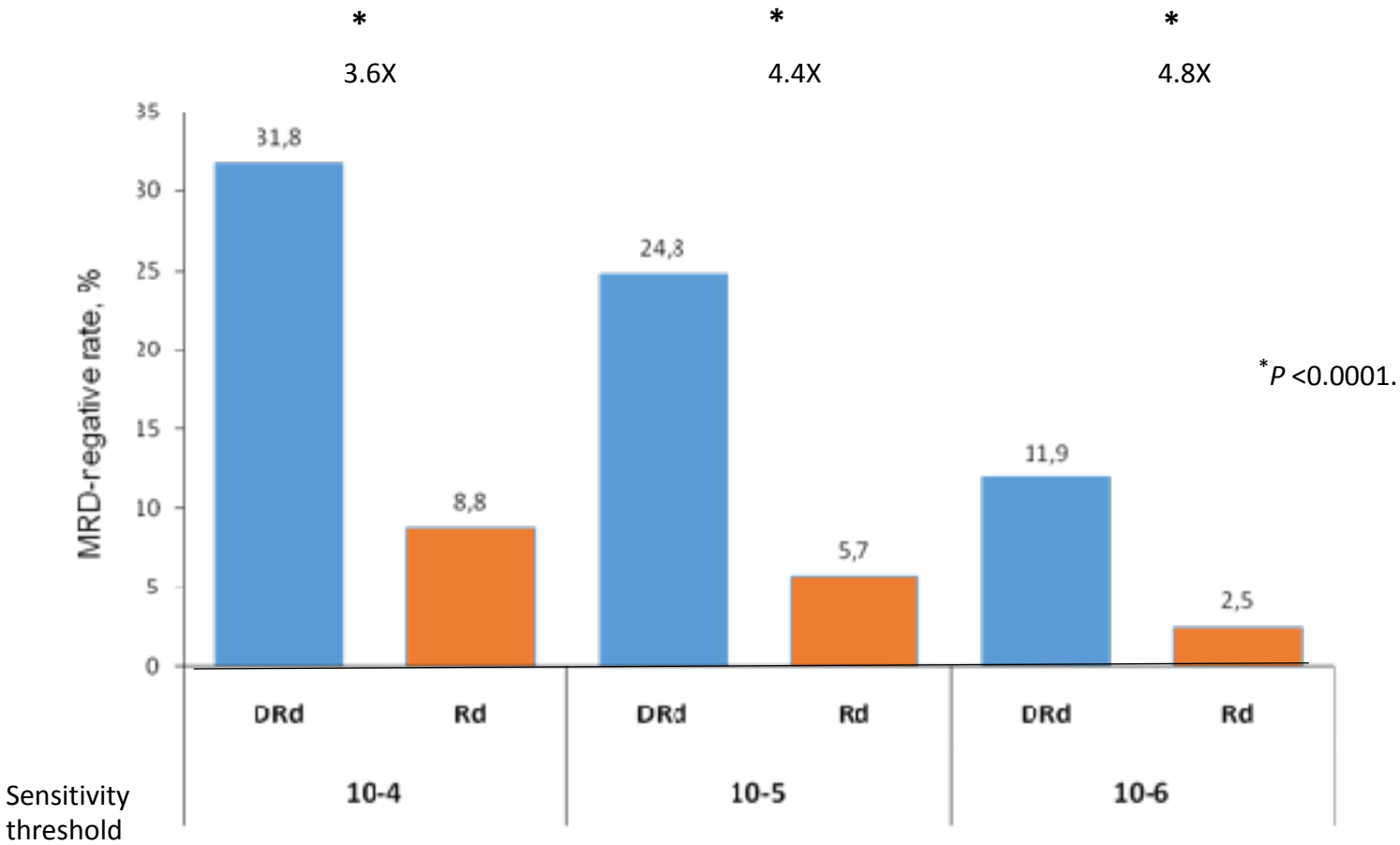
Vd	247	219	206	192	134	57	13	0	0
DVd	251	231	225	211	152	64	13	1	0

- **OS events**
  - 37 (15%) in DVd
  - 58 (24%) in Vd
- **OS HR for DVd versus Vd by prior lines:**
  - 1 prior line = HR: 0.42 (95% CI, 0.19-0.93)
  - 1 to 3 prior lines = HR: 0.54 (95% CI, 0.34-0.84)

Curves are beginning to separate, but OS data are immature

Median OS was NR; results did not cross the prespecified stopping boundary.

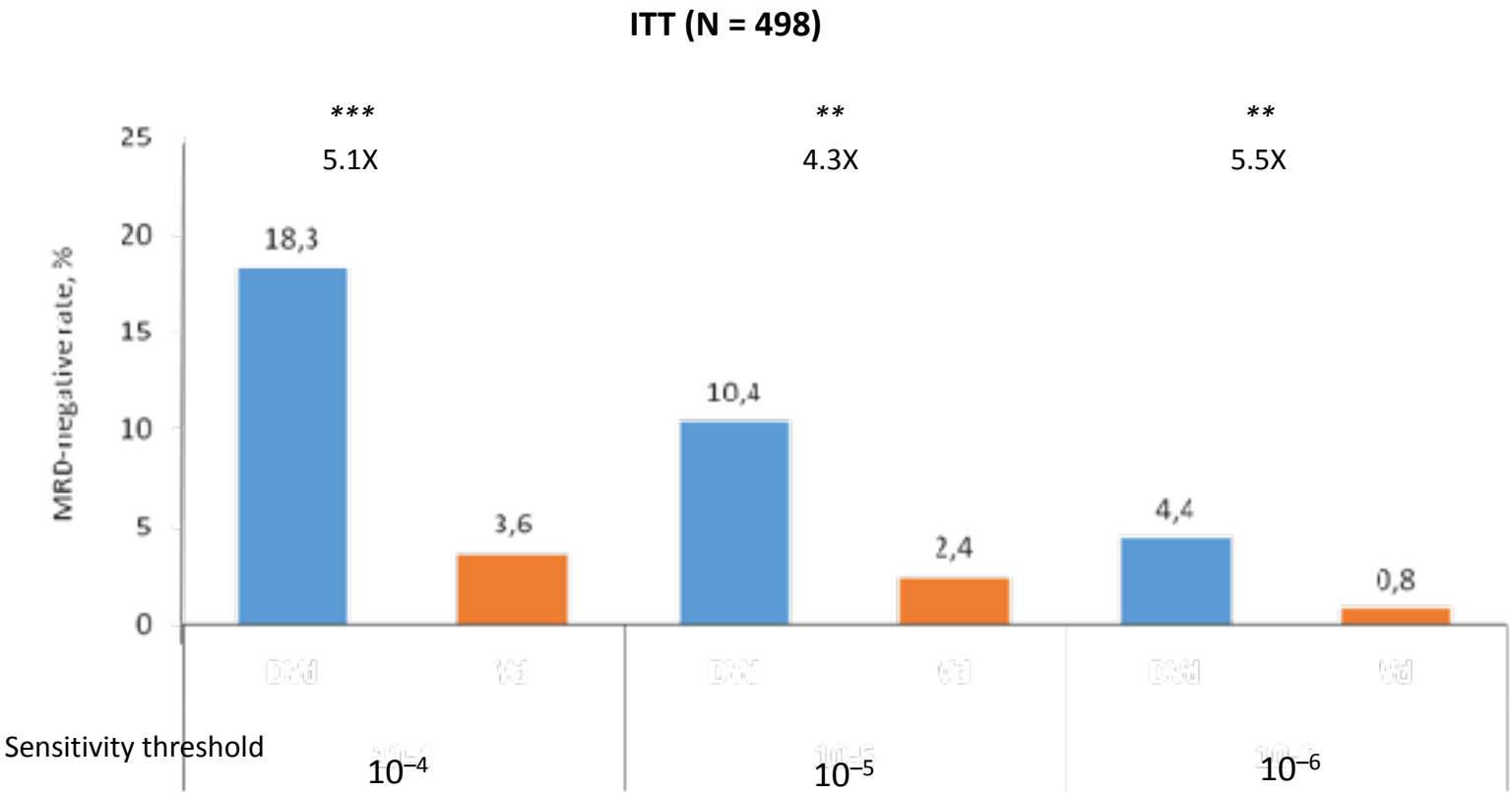
POLLUX: MRD-Negativity Rate



MRD-negative rates were >3-fold higher at all thresholds

ITT population.
P values are calculated using likelihood-ratio chi-square test.

CASTOR: MRD-Negativity Rate

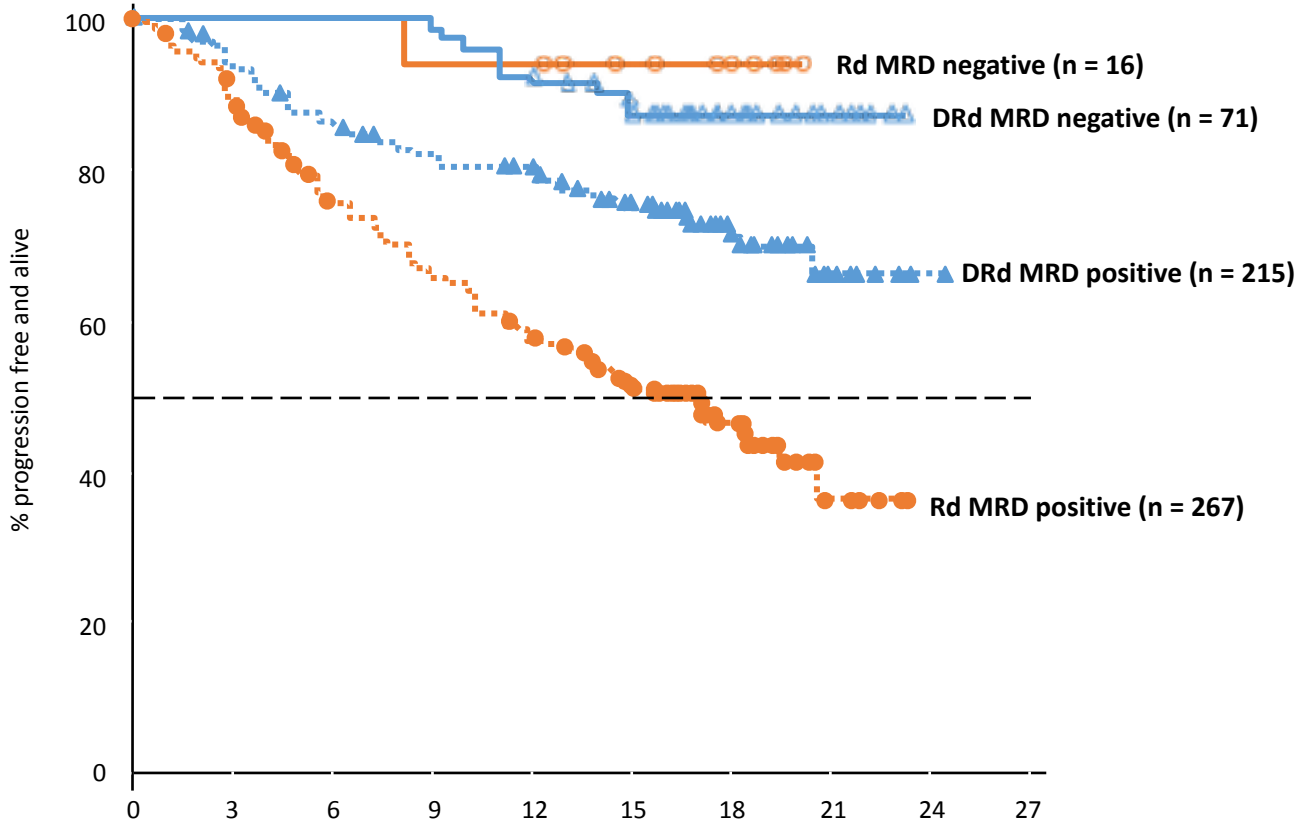


- MRD was evaluated by ClonoSEQ-NGS–based assay in a central laboratory at 3 sensitivity thresholds, for patients with suspected CR and also for patients who maintain CR at Cycle 9 and Cycle 15

MRD-negative rates for DVd were ≥3-fold higher across all thresholds

***P <0.0001. **P <0.01. NS, not significant; NGS, next-generation sequencing.
P values calculated using likelihood-ratio chi-square test.
MRD-negativity rate = proportion of patients with negative MRD test results at any time during treatment.

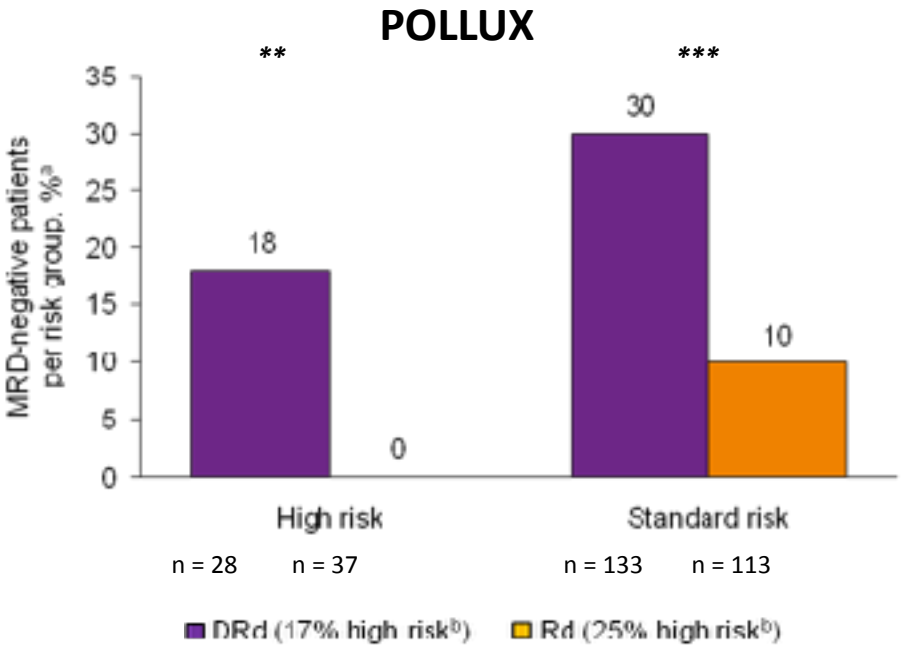
PFS: MRD Status (10^{-5})

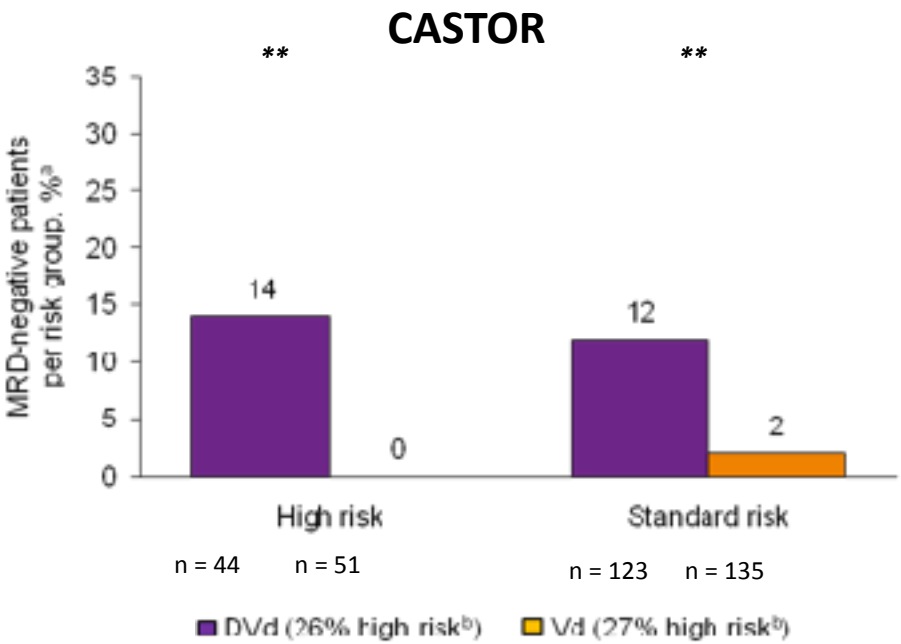


No. at risk										
Rd MRD negative	16	16	16	15	15	12	10	0	0	0
DRd MRD negative	71	71	71	70	66	57	28	6	0	0
Rd MRD positive	267	233	190	166	144	120	38	5	0	0
DRd MRD positive	215	195	178	167	161	137	54	9	1	0

MRD negativity is associated with better outcomes

POLLUX & CASTOR: MRD- by Citogenetic Risk





- No high-risk MRD-negative patients have progressed or converted to MRD positive
  - High risk = any of t(4;14), t(14;16), del17p
  - Standard risk = conclusive absence of all 3 markers

In high-risk patients, MRD-negative status was achieved only in those treated with daratumumab-containing regimens

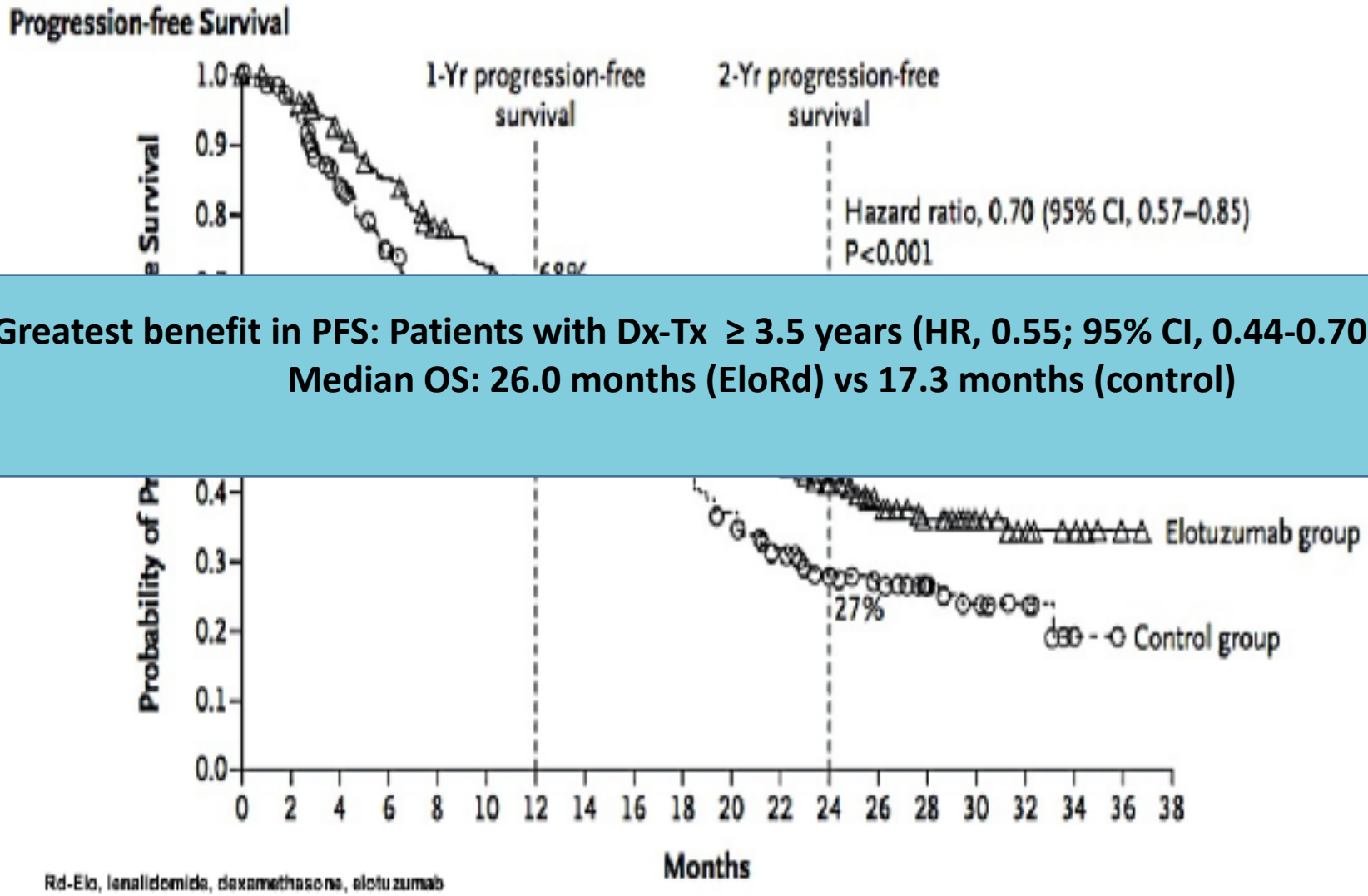
*** *P* <0.0001.

** *P* <0.005.

Earlier use of MoAbs in MM

- Less toxic than traditional cytotoxic agents
- Good partners for IMiDs
- Immune system less impaired (key for ADCC)
- Improved ORR, CR rate, and PFS
- Increasing likelihood of reaching MRD(-) status
- MRD(-) patients may enjoy longer PFS

ELOQUENT-2: PFS According to Previous Lines of Therapy

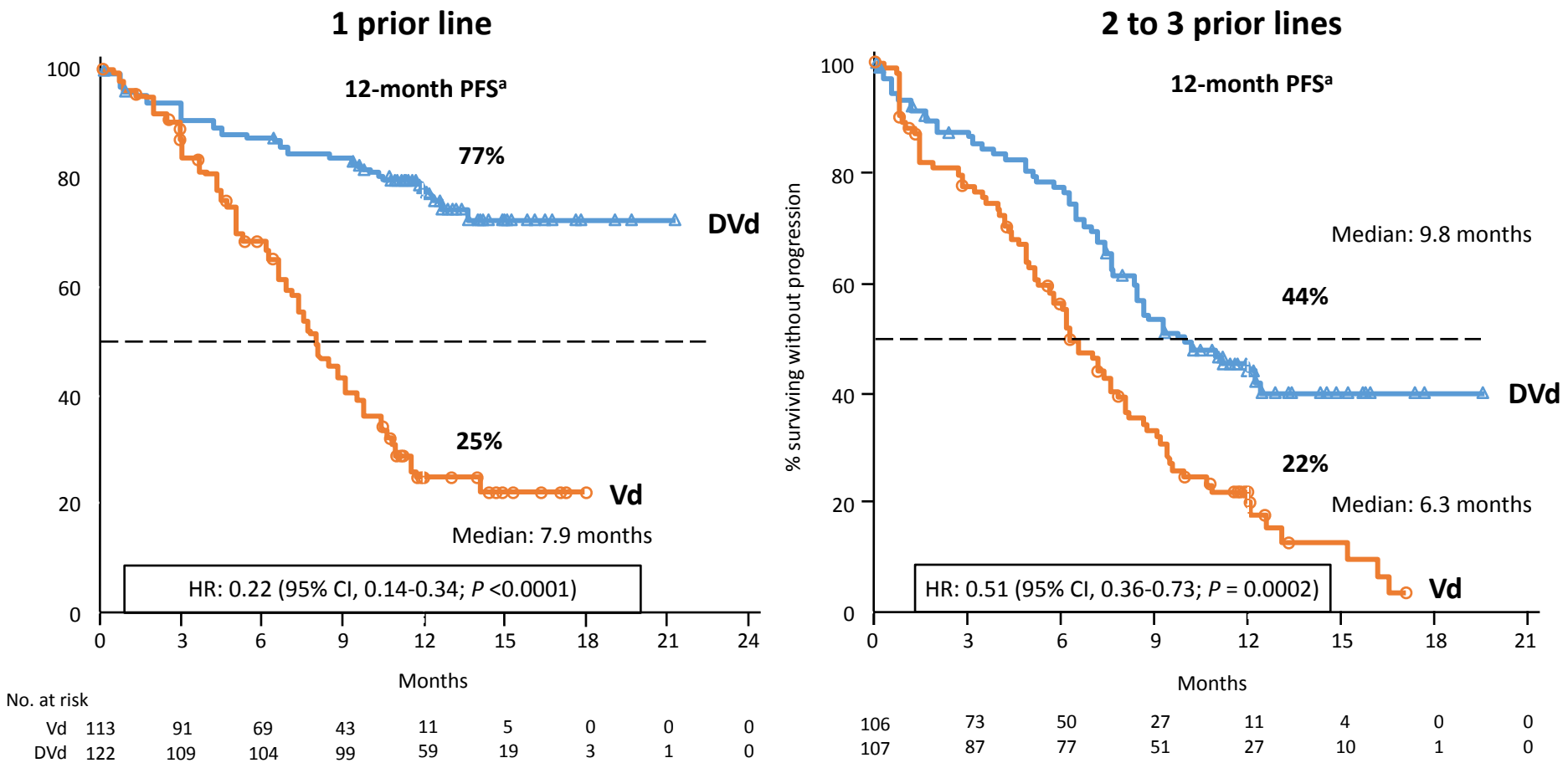


Greatest benefit in PFS: Patients with Dx-Tx ≥ 3.5 years (HR, 0.55; 95% CI, 0.44-0.70; P<0.001)
Median OS: 26.0 months (EloRd) vs 17.3 months (control)

Rd-Elo, lenalidomide, dexamethasone, elotuzumab

Lonial S, et al. *N Engl J Med*. 2015;373(7):621-631.

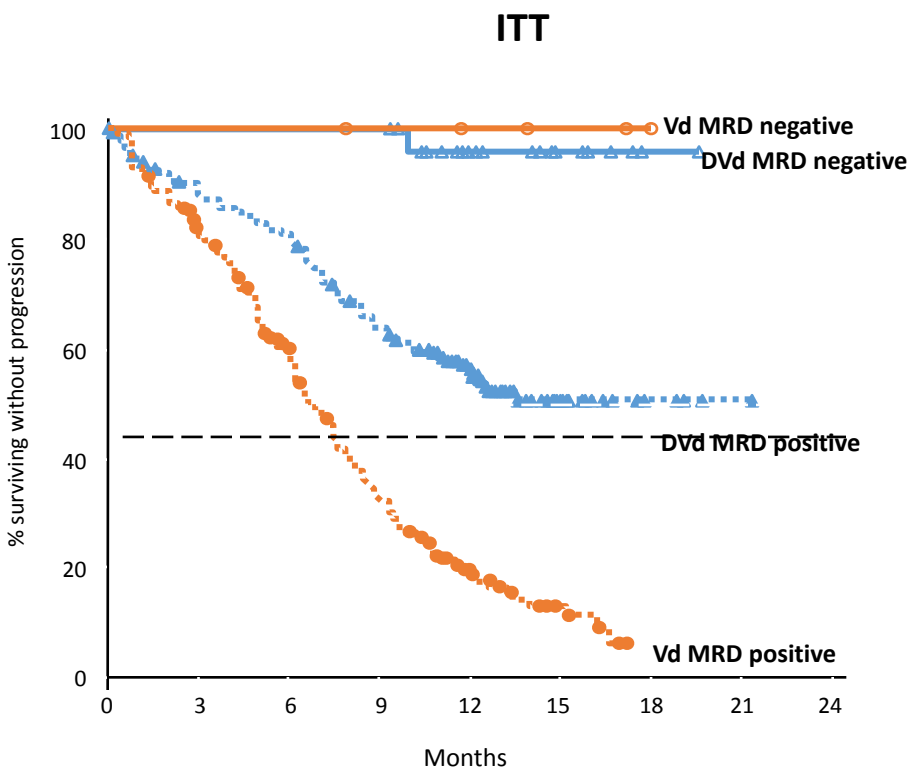
More Pronounced Benefit from Dara Early (CASTOR)

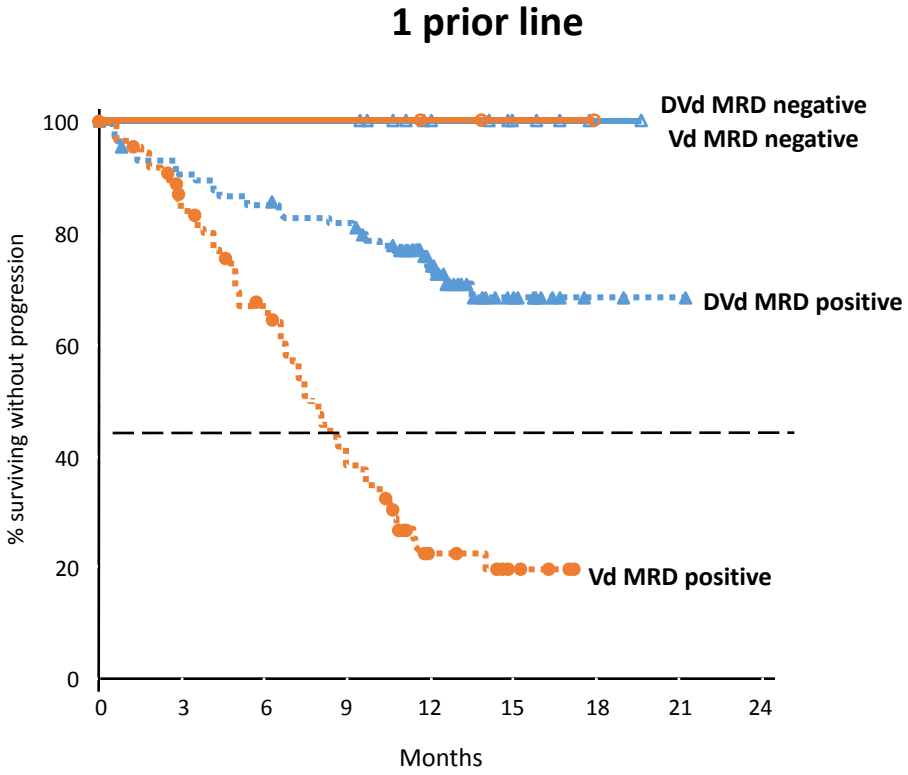


DVd is superior to Vd regardless of prior lines of therapy, with greatest benefit observed in 1 prior line

[a]Kaplan-Meier estimate.

PFS: MRD Status (10^{-5})





MRD negativity is associated with better outcomes

Conclusions

- The addition of daratumumab and elotuzumab to treatment regimens for myeloma represents a major milestone
- Elotuzumab is synergistic with lenalidomide/dex and associated with an improved PFS
- Daratumumab has demonstrated significant single-agent activity in heavily pretreated patients, as well as unprecedented improvements in PFS when combined with lenalidomide/dex and bortezomib/dex

Conclusions

- DRd is superior to Rd regardless of number of prior lines of therapy or the cytogenetic risk
- The largest magnitude of benefit with DVd is observed in patients with one prior line of therapy
- Particularly relevant finding in the dara-based trials is the magnitude of MRD negativity observed in patients with RRMM
- The safety profile in daratumumab-based therapies was not different to that observed in patients not receiving daratumumab


Thank You