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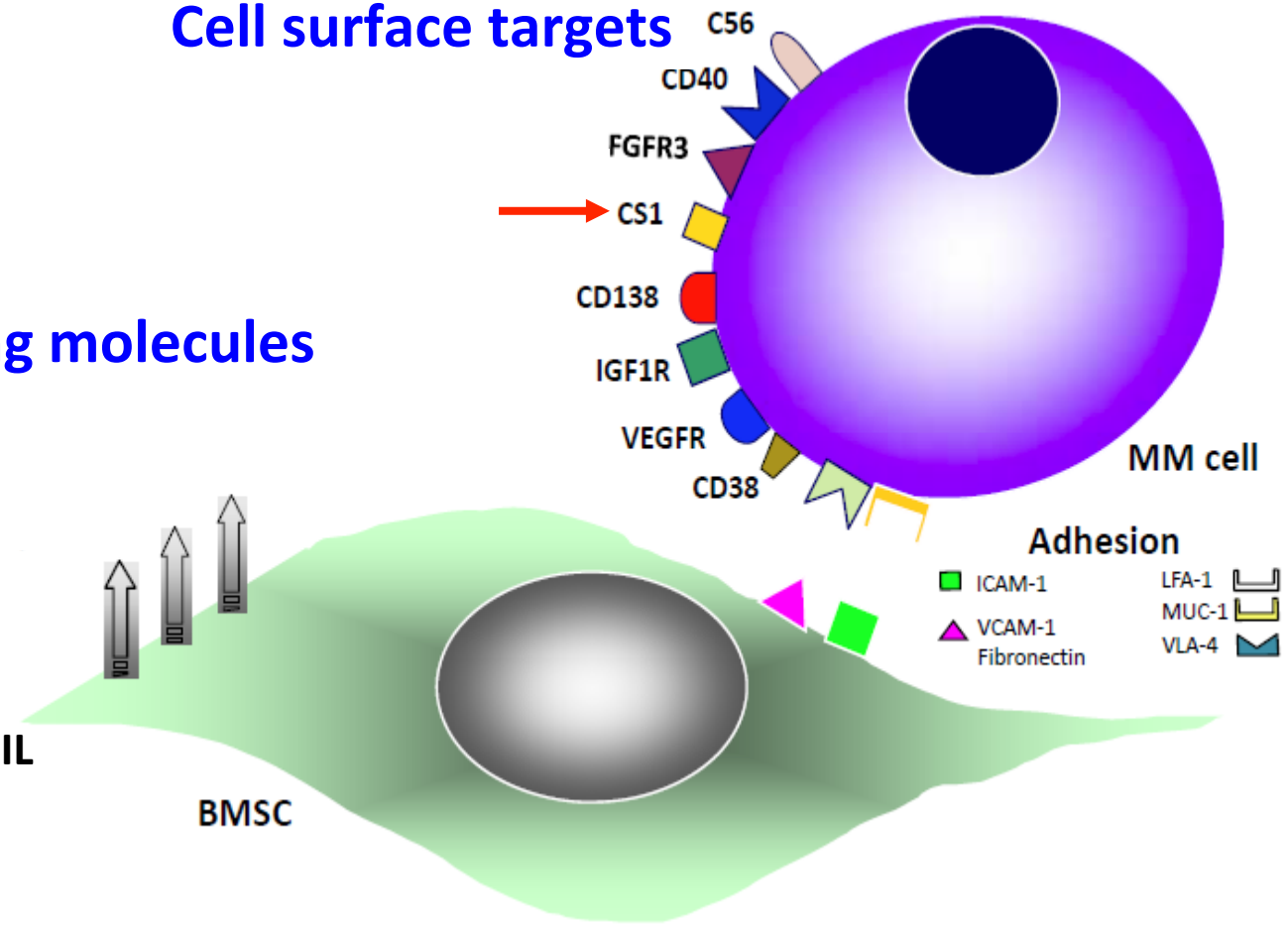
Targets for monoclonal antibody therapy in multiple myeloma (MM)

Cell surface targets

Signaling molecules

IL-6
RANKL
DKK1
VEGF
IGF-1
SDF-1α
BAFF, APRIL



Adapted from: Anderson KC, *J Clin Oncol 2012.*

SLAMF7/CS1: expression profile on hemopoietic cells

- Cell surface glycoprotein receptor
- SLAM (Signaling Lymphocyte Activating Molecule) family:

  SLAM/CD150

  2B4

  CD84

  NTB-A

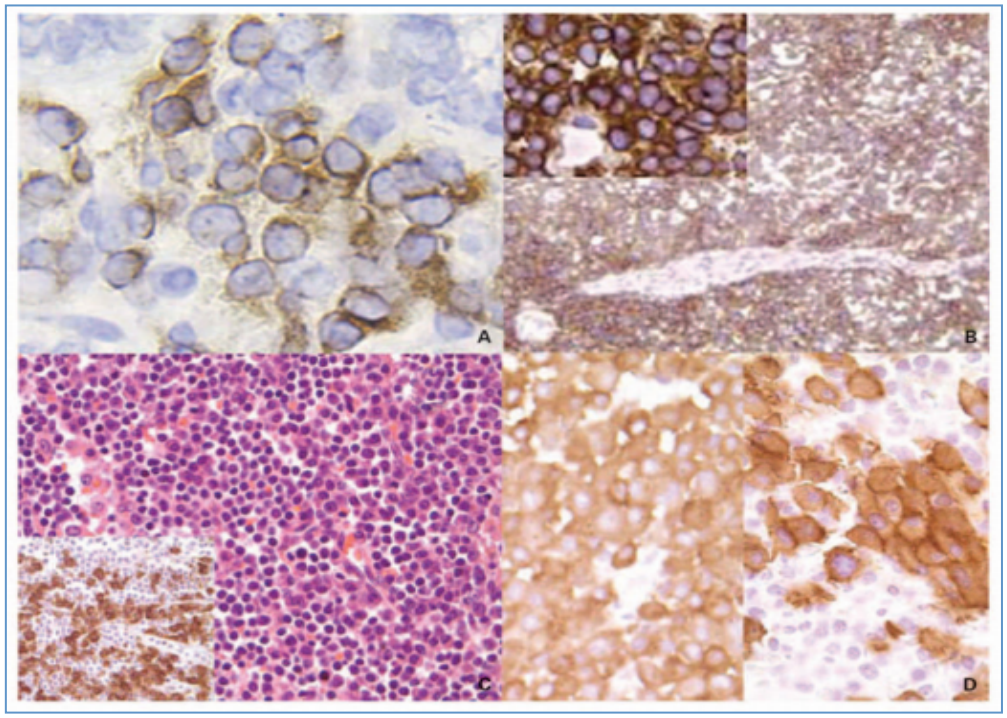
  Ly-9

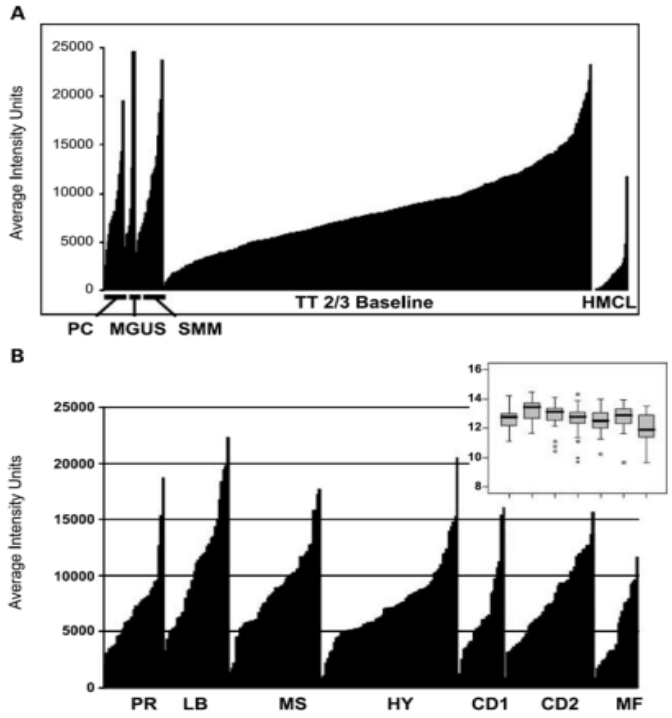
Cell type	CS-1 expression
Non-hematopoietic cell	-
Activated monocytes	+
Immature dendritic cells	-
Mature dendritic cells	+
NK cells, NK-T cells	+
$CD8^+$ T lymphocytes	+
Activated B lymphocytes	+
Normal plasma cells	+
MM plasma cells	**++**

Veillette A et al., *Crit Rev Oncol Hematol 2013.*

SLAMF7/CS1: expression levels in MM patients

- **CS1 is highly expressed on >95% of MM cells:**
  - ❑ Lower expression on NK cells
  - ❑ Little to no expression on normal tissues and HSCs





Hsi ED et al. Clin Cancer Res. 2008;Tai YT et al. Blood. 2008;
Van Rhee F et al. Mol Cancer Ther. 2009; Ionial S et al. ASH 2009 Abstract# 432

SLAMF7/CS1: an atypical SLAM family member

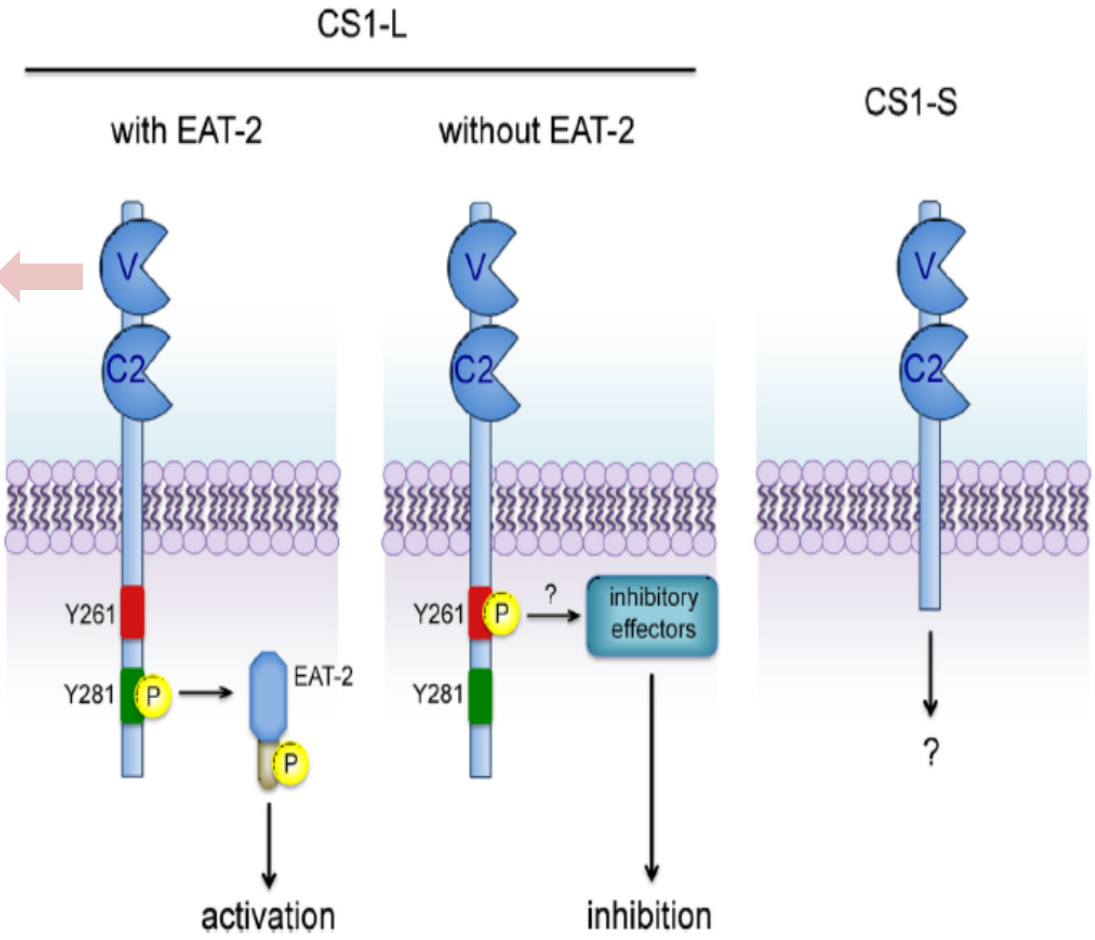
SLAM family receptors.

Receptor	Alternative name	Physiological ligand	Number of ITSMs	Expression pattern	Interaction with		Phenotypes knock-out mice
					SAP	EAT-2	
SLAM	CD150 SLAMF1	SLAM	2	T, B, DC, Mϕ, plat	+	+	T, Mϕ, plat, NK-T
Ly-9	CD229 SLAMF3	Ly-9	1	T, B, NK, DC, Mϕ	+	+	$CD4^+$ T, innate-like $CD8^+$ T, NK-T
2B4	CD244 SLAMF4	CD48	3	NK, $CD8^+$ T, DC, Mϕ, eos	+	+	NK
CD84	SLAMF5	CD84	2	T, B, NK, DC, Mϕ, gran, plat, mast, eos	+	+	T, B (GC)
NTB-A	Ly108 CD352 SLAMF6	NTB-A	2	T, B, NK, DC, neutro	+	+	T, B, neutro, NK-T
CS1	CRACC CD319 SLAMF7	CS1	1	Human: NK, NK-T, DC, B, PC, T Mouse: NK, NK-T, DC, Mϕ, B, T	−	+	NK

Veillette A et al., *Crit Rev Oncol Hematol 2013.*

SLAMF7/CS1: structure and function interplay

mediates self-adhesion



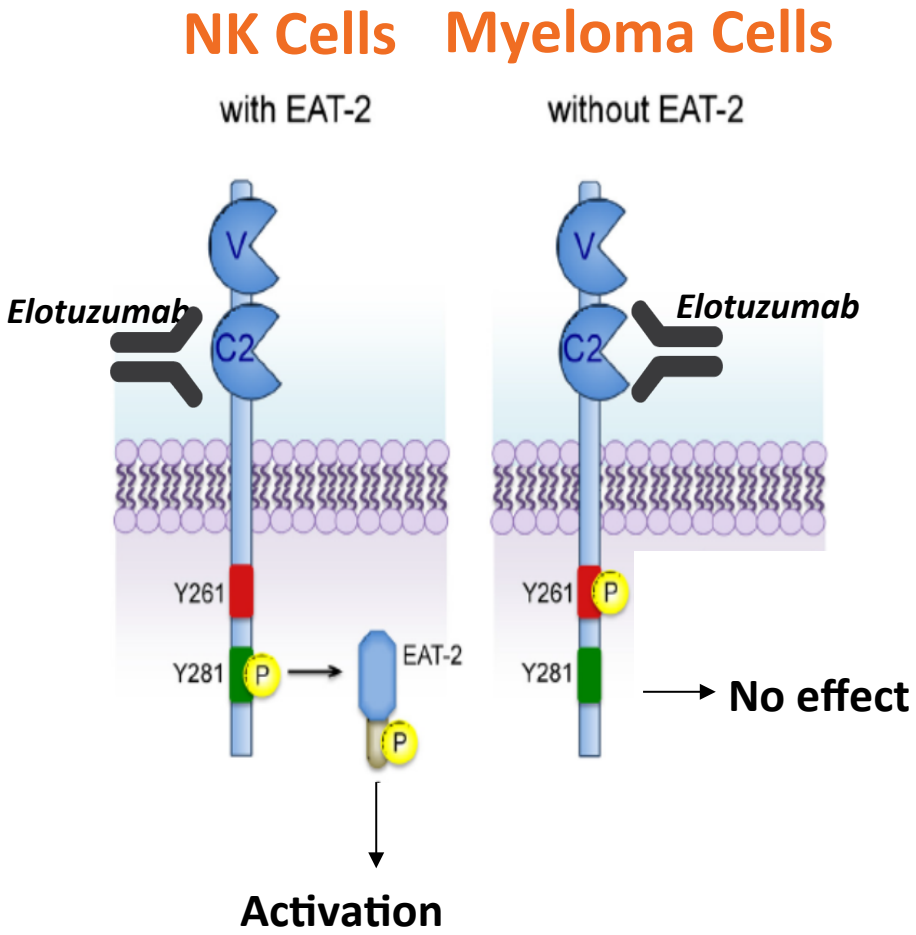
Adapted from: Veillette A et al., *Crit Rev Oncol Hematol 2013.*

SLAMF7/CS1: functions

Cell type	EAT-2 expression	SLAMF7 function
Activated Monocytes	-	Decrease of proinflammatory cytokine secretion
NK cells	+	Increase of IFNγ production, cytotoxic activity
B cells	-	Proliferation and cytokine production
T cells	-	Inhibition of antigen-induced T cell proliferation and cytokine production
NK-T cells		unknown
Dendritic cells	+	unknown
MM plasma cells	-	Adhesion to BMSC

Veillette A et al., *Crit Rev Oncol Hematol 2013*; Cruz-Munoz ME et al., *Nat Immunol 2009.*

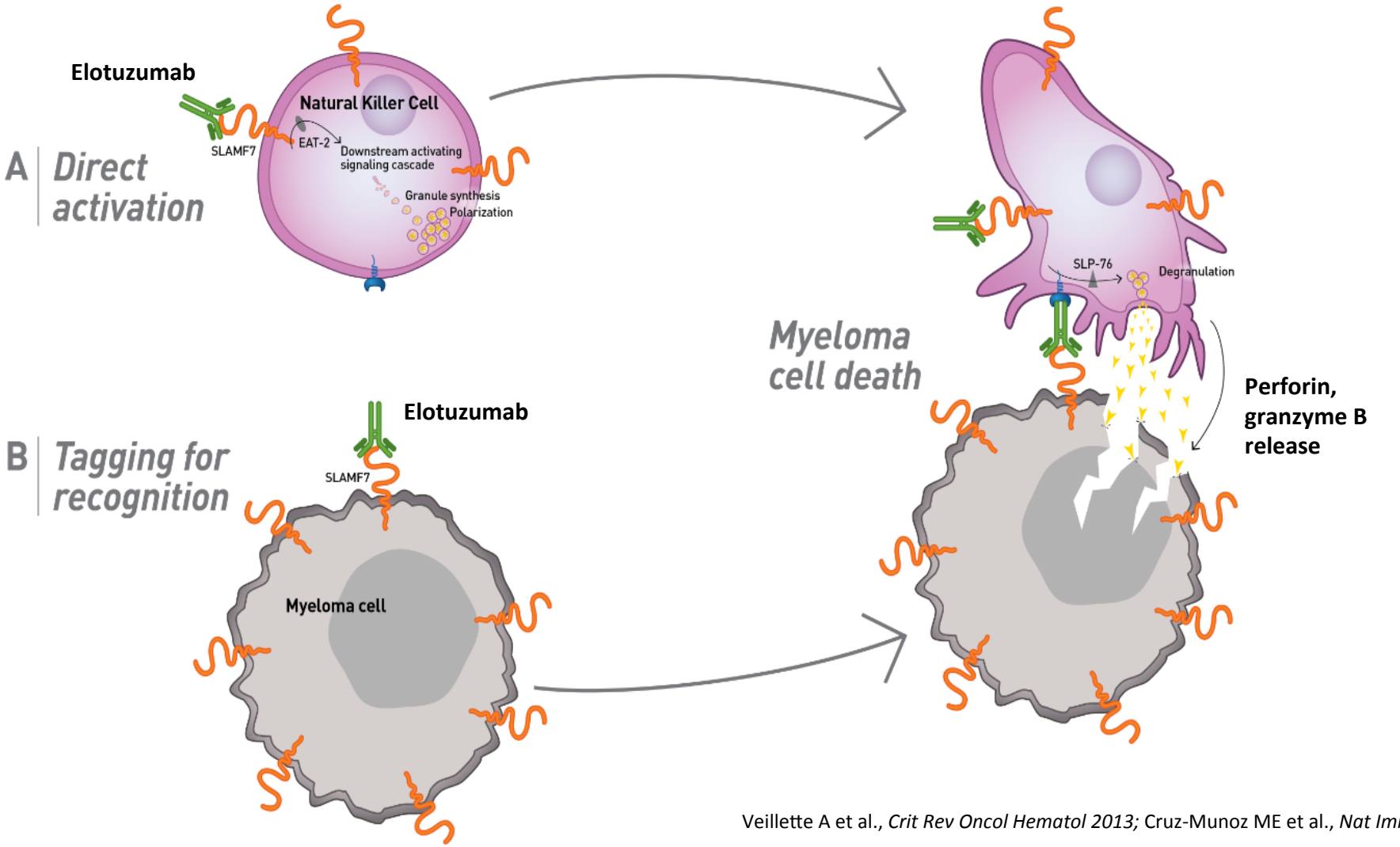
Elotuzumab (Elo): a monoclonal antibody targeting SLAMF7/CS1



- 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*)

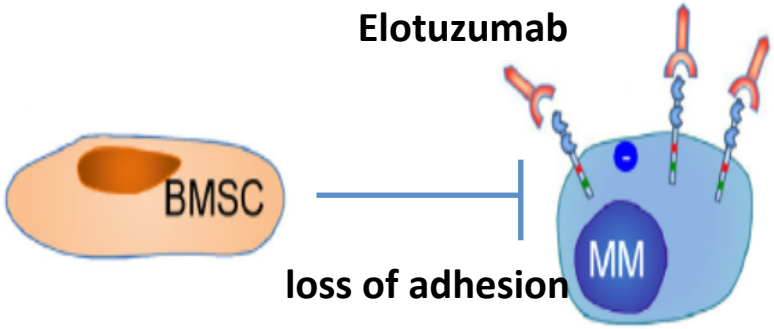
Veillette A et al., *Crit Rev Oncol Hematol 2013;* Cruz-Munoz ME et al., *Nat Immunol 2009;* Guo H et al., *Mol Cell Bio 2015*.

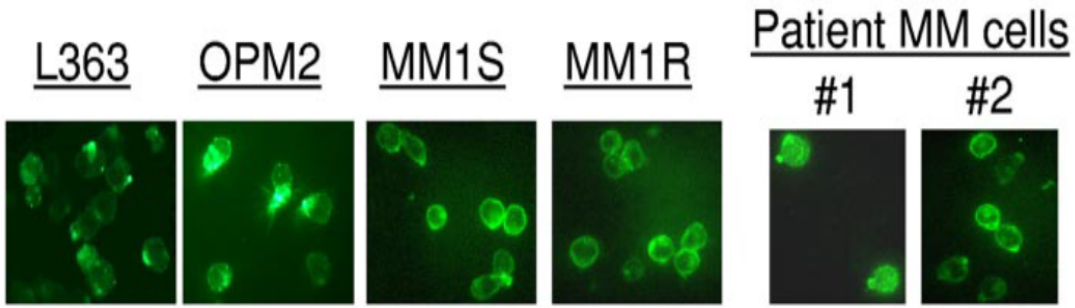
Elo mechanisms of action in MM (I)

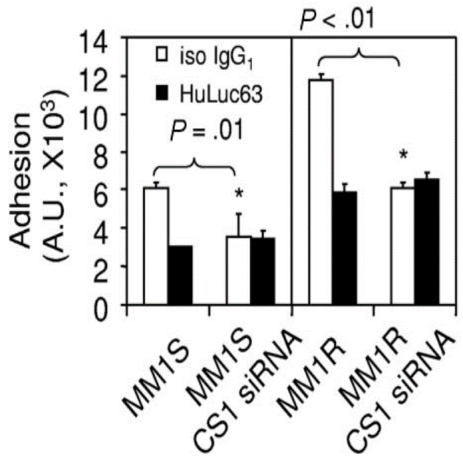


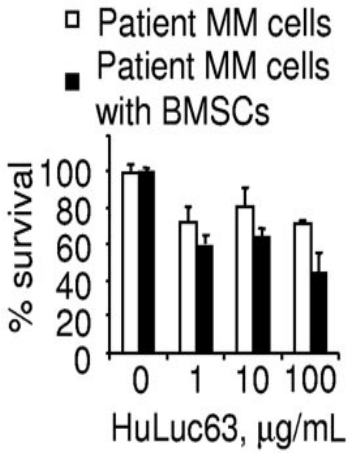
Veillette A et al., *Crit Rev Oncol Hematol 2013;* Cruz-Munoz ME et al., *Nat Immunol 2009.*

Elo mechanisms of action in MM (II)





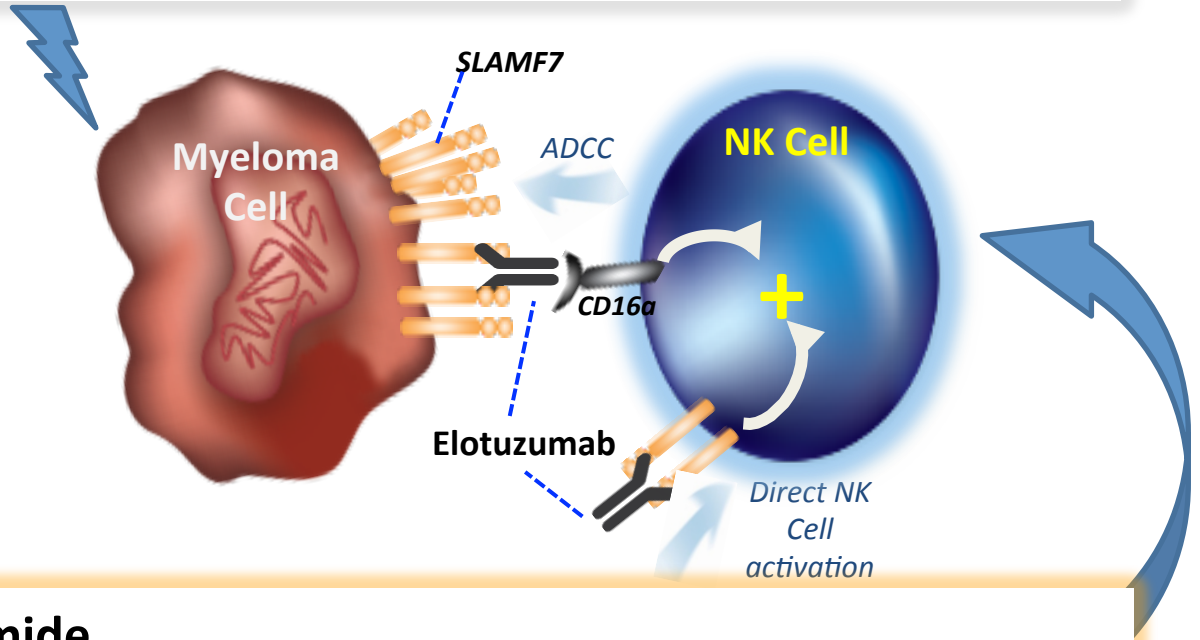




Veillette A et al., *Crit Rev Oncol Hematol 2013;* Tai YT et al., *Blood 2008 ;* Guo H et al., *Mol Cell Biol 2015.*

Elo synergizes with Lenalidomide to enhance MM cell death

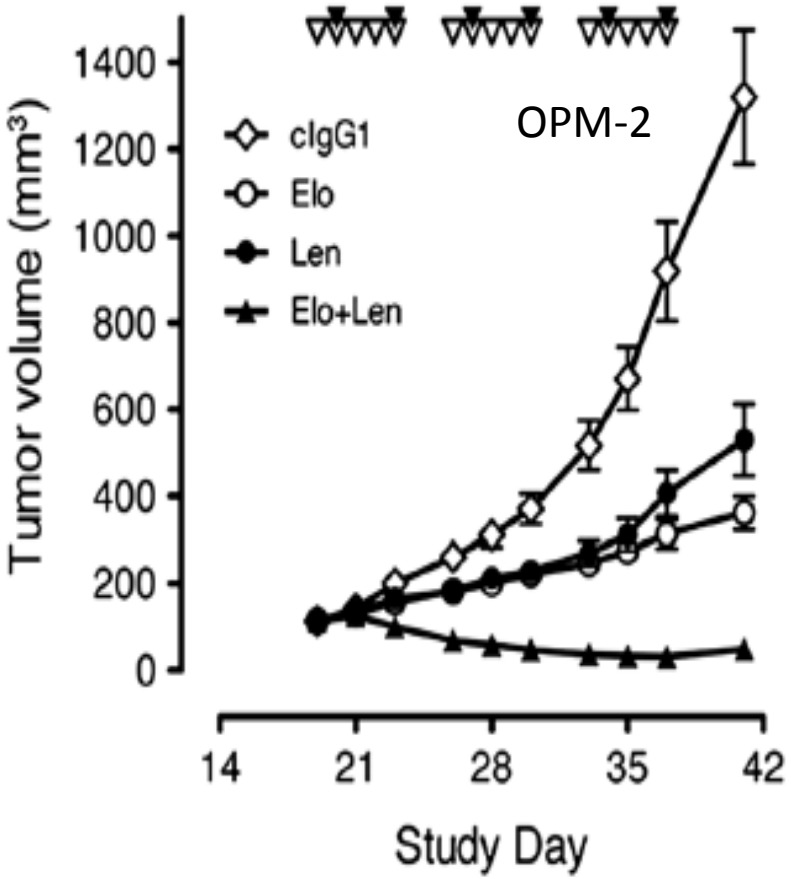
Lenalidomide
Induces myeloma cell injury and lowers threshold for NK cell-mediated killing of myeloma cells by Elotuzumab

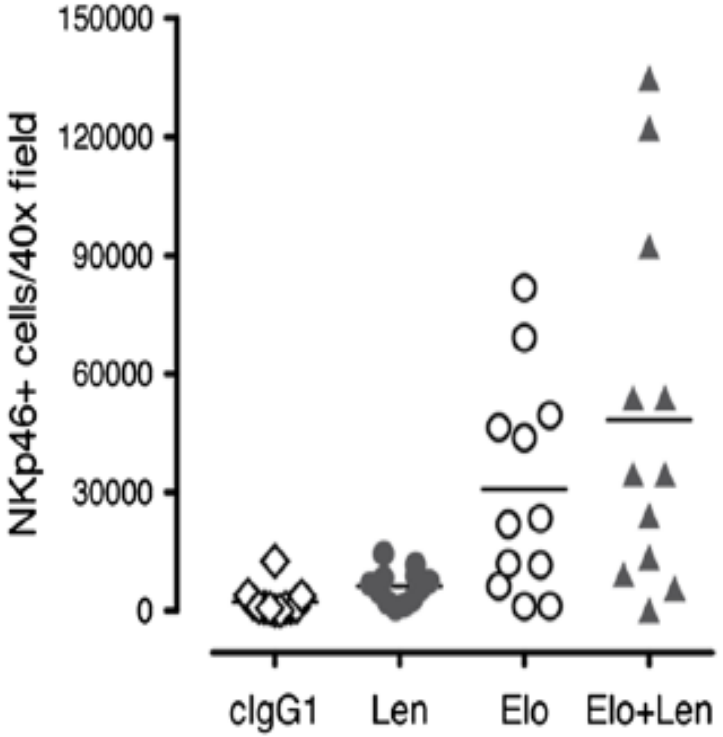


Lenalidomide
Enhances adaptive and innate immune system including production of IL2 to increase NK cell activity

Balasa B et al., *Cancer Immunol Immunother 2015*.

Elo plus Lenalidomide: *in vivo* effects



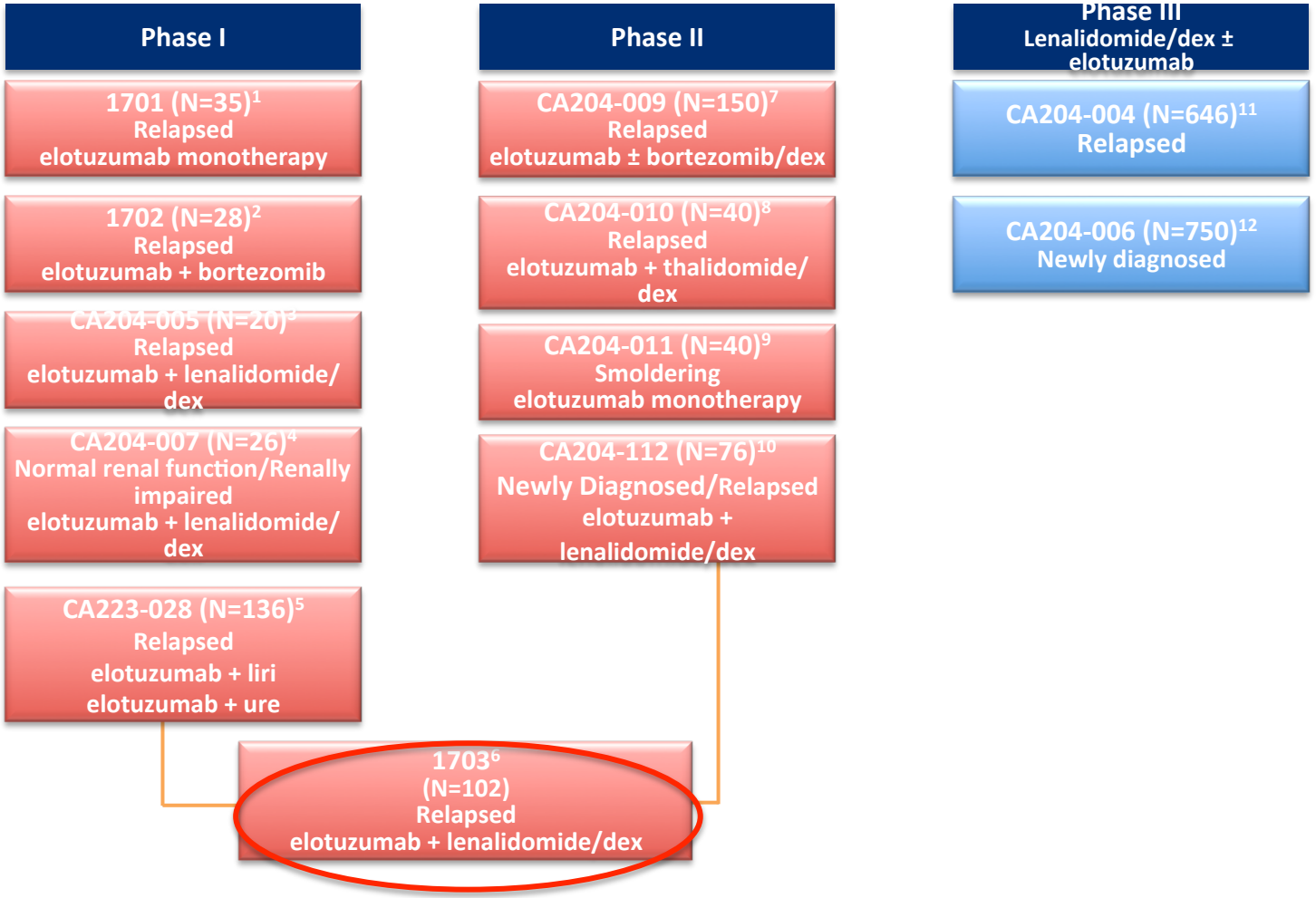


Elo= Elotuzumab, Len= Lenalidomide

Xenograft Mouse model: IcrTac:ICR-Prkdc^{scid}: lacks of T/B cells due to a defect in V(D)J recombination

Balasa B et al., *Cancer Immunol Immunother 2015*.

Elo: Clinical Development Program



Dex= dexamethasone; liri= lirilumab; ure= urelumab.

1. Clinicaltrials.gov. NCT00425347. 2. Clinicaltrials.gov. NCT00726869. 3. Clinicaltrials.gov. NCT01241292. 4. Clinicaltrials.gov. NCT01393964. 5. Clinicaltrials.gov. NCT02252263. 6. Clinicaltrials.gov. NCT00742560. 7. Clinicaltrials.gov. NCT01478048. 8. Clinicaltrials.gov. NCT01632150. 9. Clinicaltrials.gov. NCT01441973. 10. Clinicaltrials.gov. NCT02159365. 11. Clinicaltrials.gov. NCT01239797. 12. Clinicaltrials.gov. NCT01335399.

Phase 1 and 2 Elo Trials: Summary

Trial	Phase	Treatment	Sample Size	Efficacy (%)	Median PFS
1701	1	Elotuzumab monotherapy	35	SD=26.5	—
1702	1	Elotuzumab + Bortezomib	28	ORR=48	9.46 mo
1703	1	Elotuzumab + Lenalidomide/ Dexamethasone	28	ORR=82	33 months
1703	2	Elotuzumab + Lenalidomide/ Dexamethasone	73	ORR=84	29 months
009	2	Elotuzumab + Bortezomib/ Dexamethasone	152	ORR=65	9.7 months

1701: Tolerability

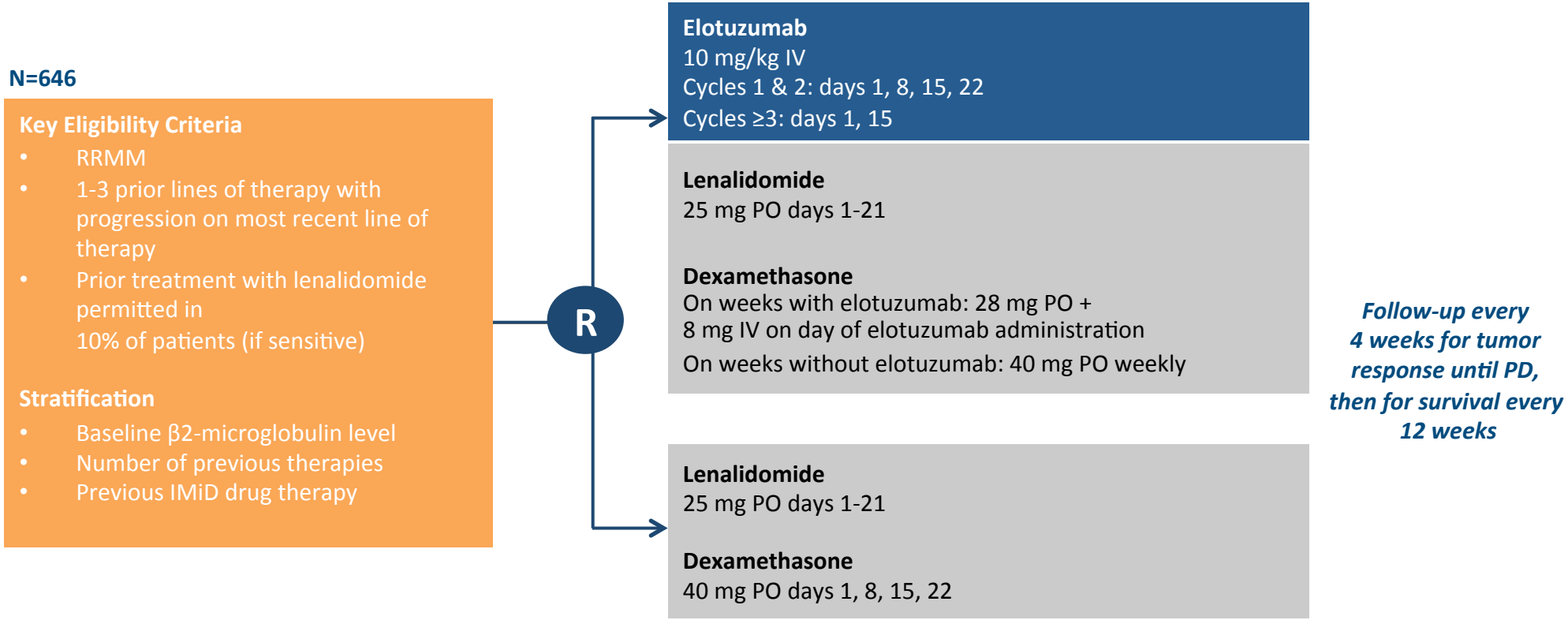
- MTD was not reached up to the highest dose level of 20 mg/kg
- Key SAEs were first dose infusion reactions (IR)
  - Grade 3 allergic reaction, Grade 2 rigors, fever, chest pressure, bradycardia
  - No dose correlation seen for infusion reactions
  - No serious infusion reactions following IV corticosteroid premedication
- No neutropenia or thrombocytopenia
- Transient reduction in lymphocytes seen within hours following first dose

AEs	No. (%)
No. with any treatment-related AEs	18 (52.9)
Chills	11 (32.4)
Pyrexia	6 (17.6)
Flushing	4 (11.8)
Chest discomfort	3 (8.8)
Fatigue	3 (8.8)
Headache	3 (8.8)
Sinus tachycardia	3 (8.8)
Vomiting	3 (8.8)
Anorexia	2 (5.9)
Dyspnea	2 (5.9)
Serum creatinine increased	2 (5.9)

AEs were generally mild to moderate in severity, and AEs attributed to study medication were **primarily infusion-related**

Zonder JA et al., *Blood 2012*.

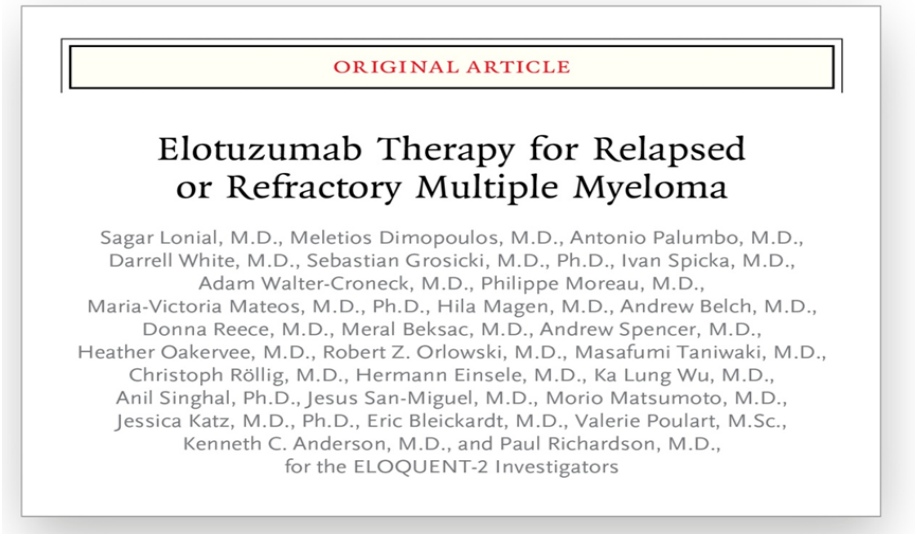
Study CA204-004 (ELOQUENT-2): Phase 3 Study of EloRd vs Rd in RRMM[1-4]



ERd, elotuzumab, lenalidomide/dexamethasone; IMiD, immunomodulatory drug; IV, intravenous; PD, progressive disease; PO, orally; R, randomization; Rd, lenalidomide/dexamethasone; RRMM, relapsed/refractory multiple myeloma.

1. Clinicaltrials.gov. NCT01239797. 2. Lonial S et al. *N Engl J Med*. 2015;373:621-631. 3. Supplement to Lonial S et al. *N Engl J Med*. 2015;373:621-631.
4. Supplement to Dimopoulos MA et al. *Br J Hematol.* 2017 [Epub ahead of print].

ELOQUENT-2: primary analysis

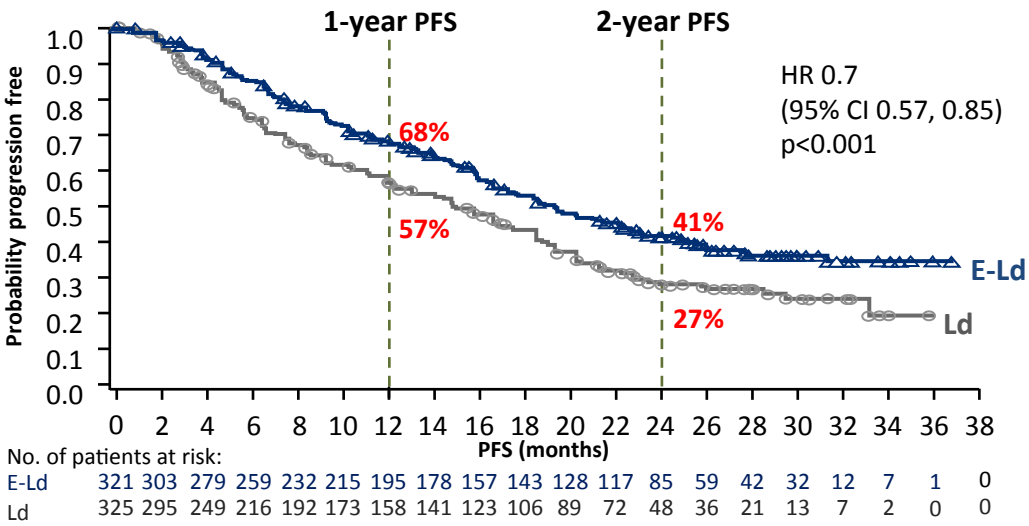


ORIGINAL ARTICLE

Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma

Sagar Lonial, M.D., Meletios Dimopoulos, M.D., Antonio Palumbo, M.D., Darrell White, M.D., Sebastian Grosicki, M.D., Ph.D., Ivan Spicka, M.D., Adam Walter-Croneck, M.D., Philippe Moreau, M.D., Maria-Victoria Mateos, M.D., Ph.D., Hila Magen, M.D., Andrew Belch, M.D., Donna Reece, M.D., Meral Beksac, M.D., Andrew Spencer, M.D., Heather Oakervee, M.D., Robert Z. Orlowski, M.D., Masafumi Taniwaki, M.D., Christoph Röllig, M.D., Hermann Einsele, M.D., Ka Lung Wu, M.D., Anil Singhal, Ph.D., Jesus San-Miguel, M.D., Morio Matsumoto, M.D., Jessica Katz, M.D., Ph.D., Eric Bleickardt, M.D., Valerie Poulart, M.Sc., Kenneth C. Anderson, M.D., and Paul Richardson, M.D., for the ELOQUENT-2 Investigators

Co-primary endpoint: PFS



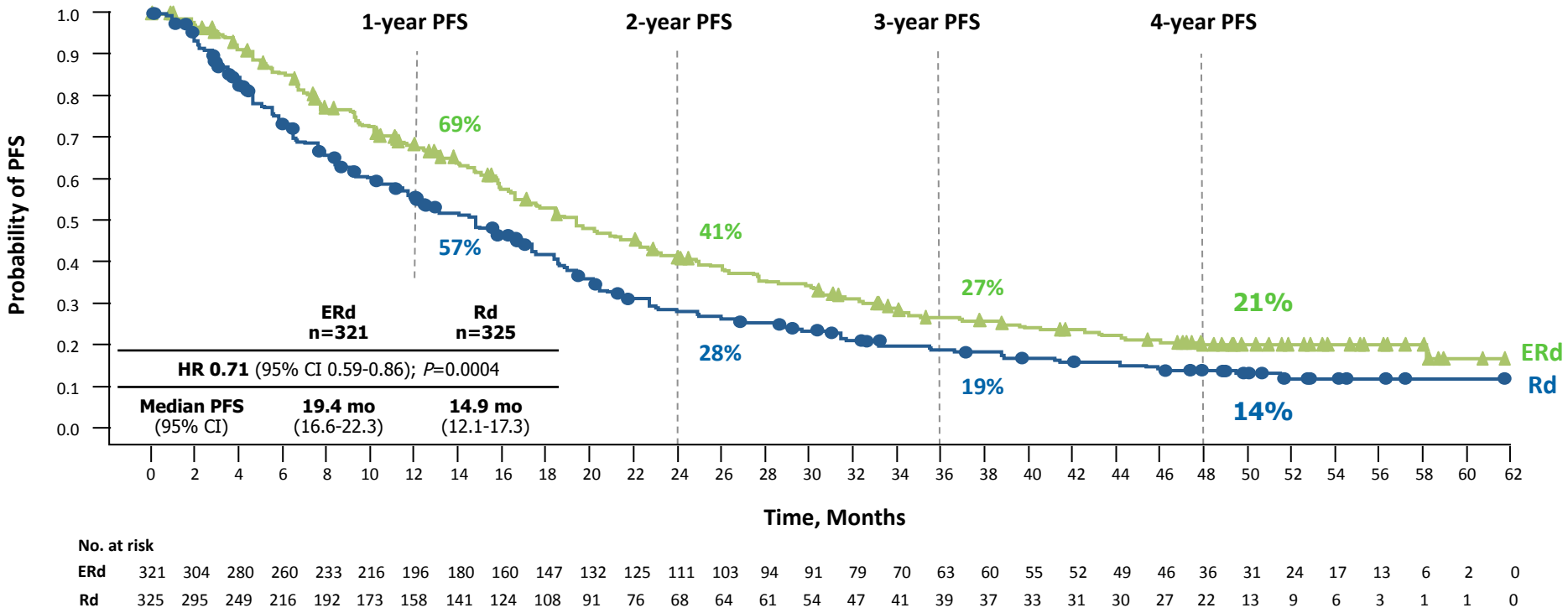
From *N Engl J Med*, Lonial S et al, Elotuzumab therapy for relapsed or refractory multiple myeloma, 373, 621–31.

Co-primary endpoint: ORR	E-Ld	Ld
%	79	66
95% CI	74, 83	60, 71

ELOQUENT-2 demonstrated clinical benefits of E-Ld compared with lenalidomide and dexamethasone (Ld) alone[1]

1. Lonial S. et al. *N Engl J Med,* 2015

4-Year Follow-Up: Durable PFS Benefit Demonstrated with ERd Versus Rd (Primary PFS Definition)[1]*

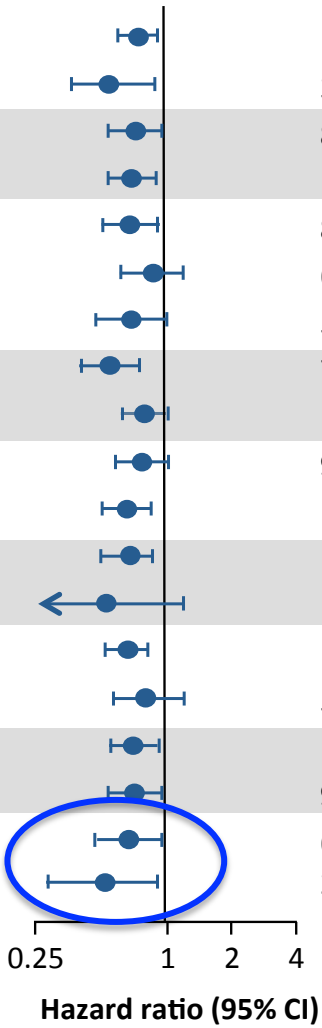


- At 4 years, ELOQUENT-2 has the longest follow-up for PFS in RRMM
- 29% reduction in the risk of progression or death (sustained over time)
- 50% relative improvement in the PFS rate at 4 years (21% vs 14%) in favor of ERd

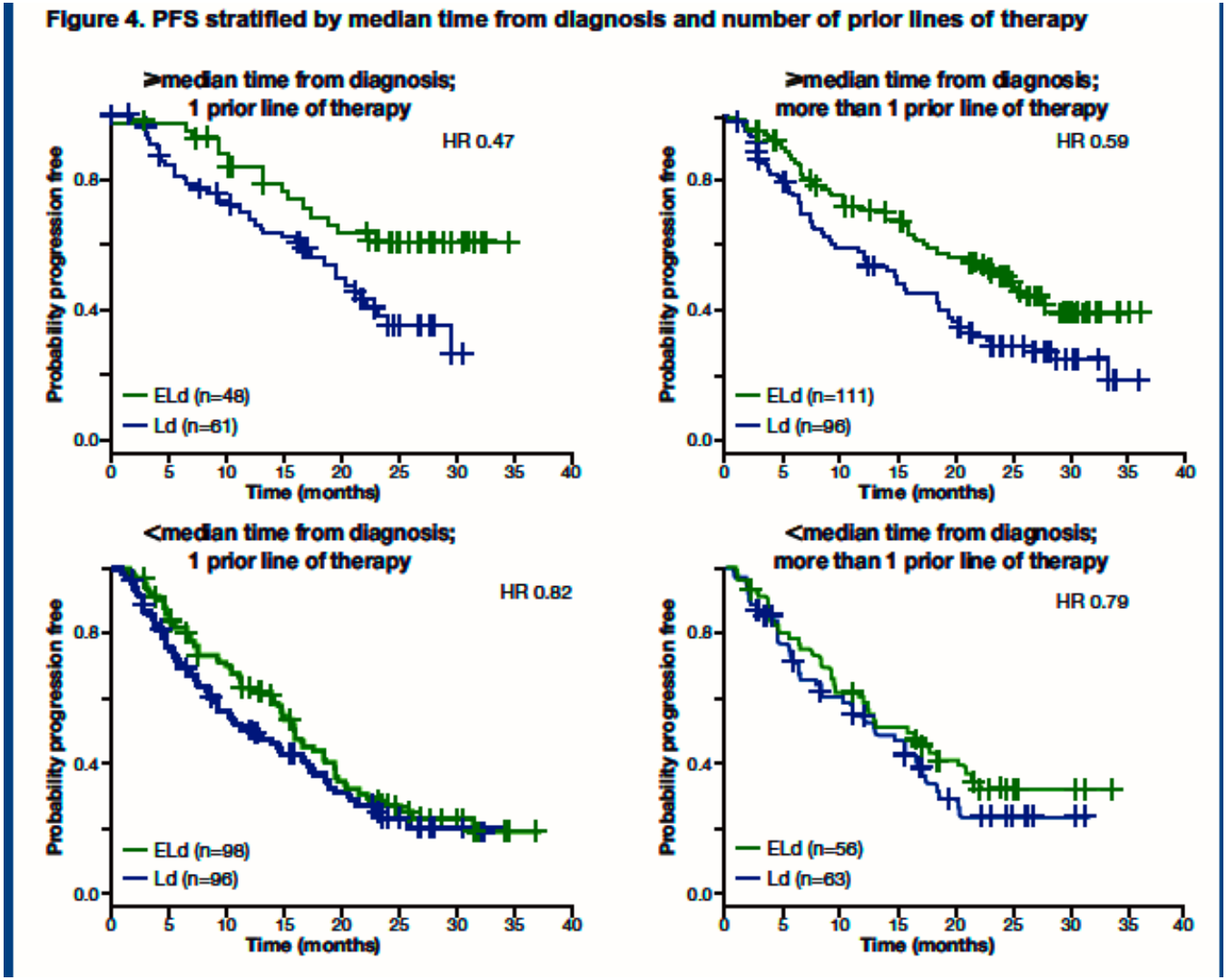
*Minimum follow-up 48 months.
CI, confidence interval; ERd, elotuzumab, lenalidomide/dexamethasone; HR, hazard ratio; PFS, progression-free survival; Rd, lenalidomide/dexamethasone.
1. Dimopoulos MA et al. Oral presentation at EHA 2017. Abstract S456.

ELOQUENT: Predefined Subgroups

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



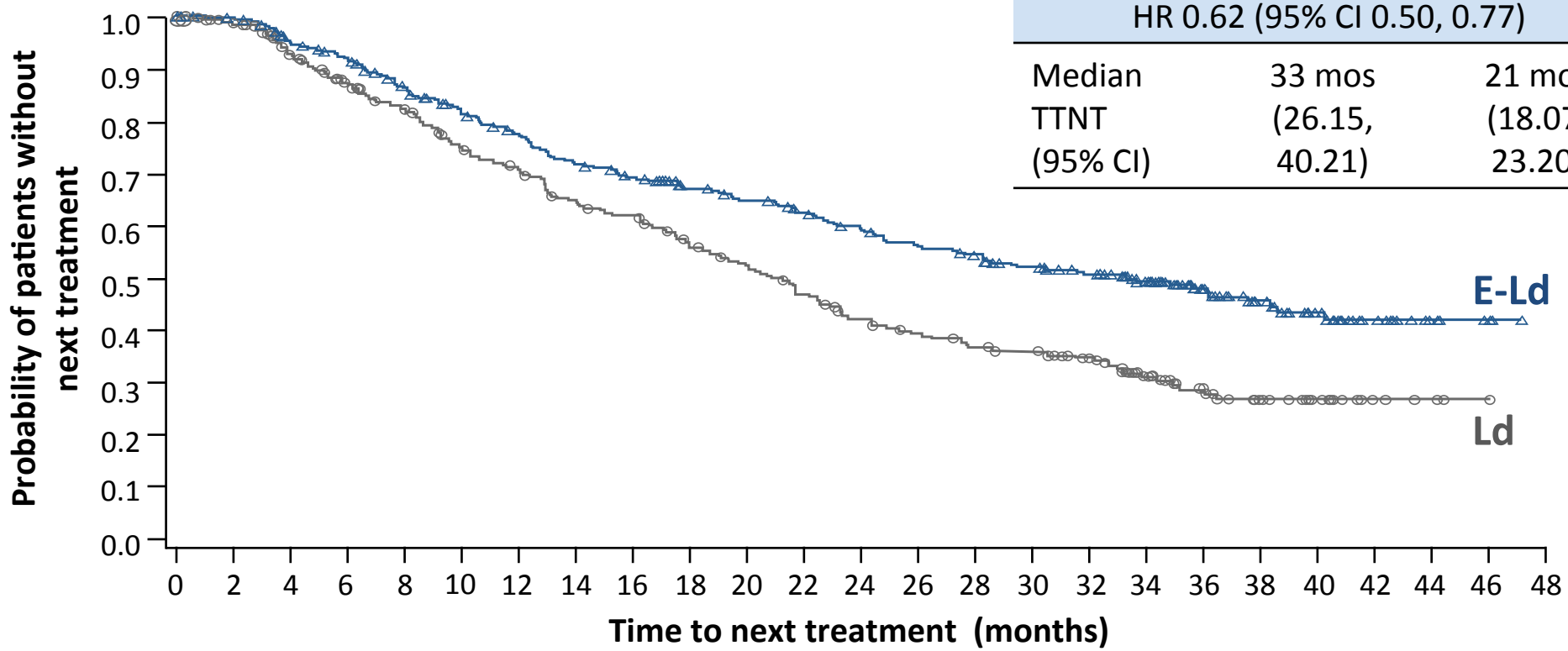
PFS stratified by median time from diagnosis and > 1 prior line of therapy



Dimopoulos MA et al, *Br J Haematol*, 2017

Eloquent-2: Time to next treatment

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



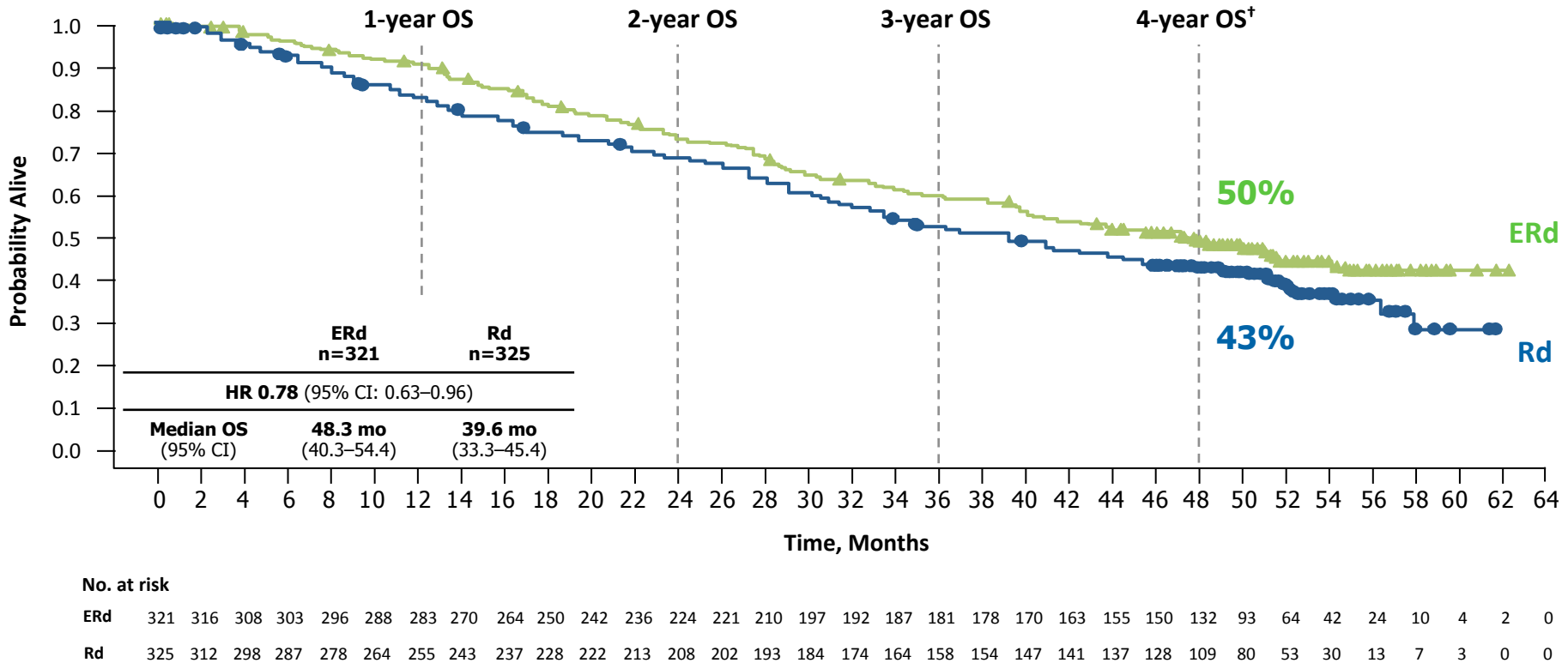
No. of patients at risk

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

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

Dimopoulos MA et al, *Br J Haematol*, 2017

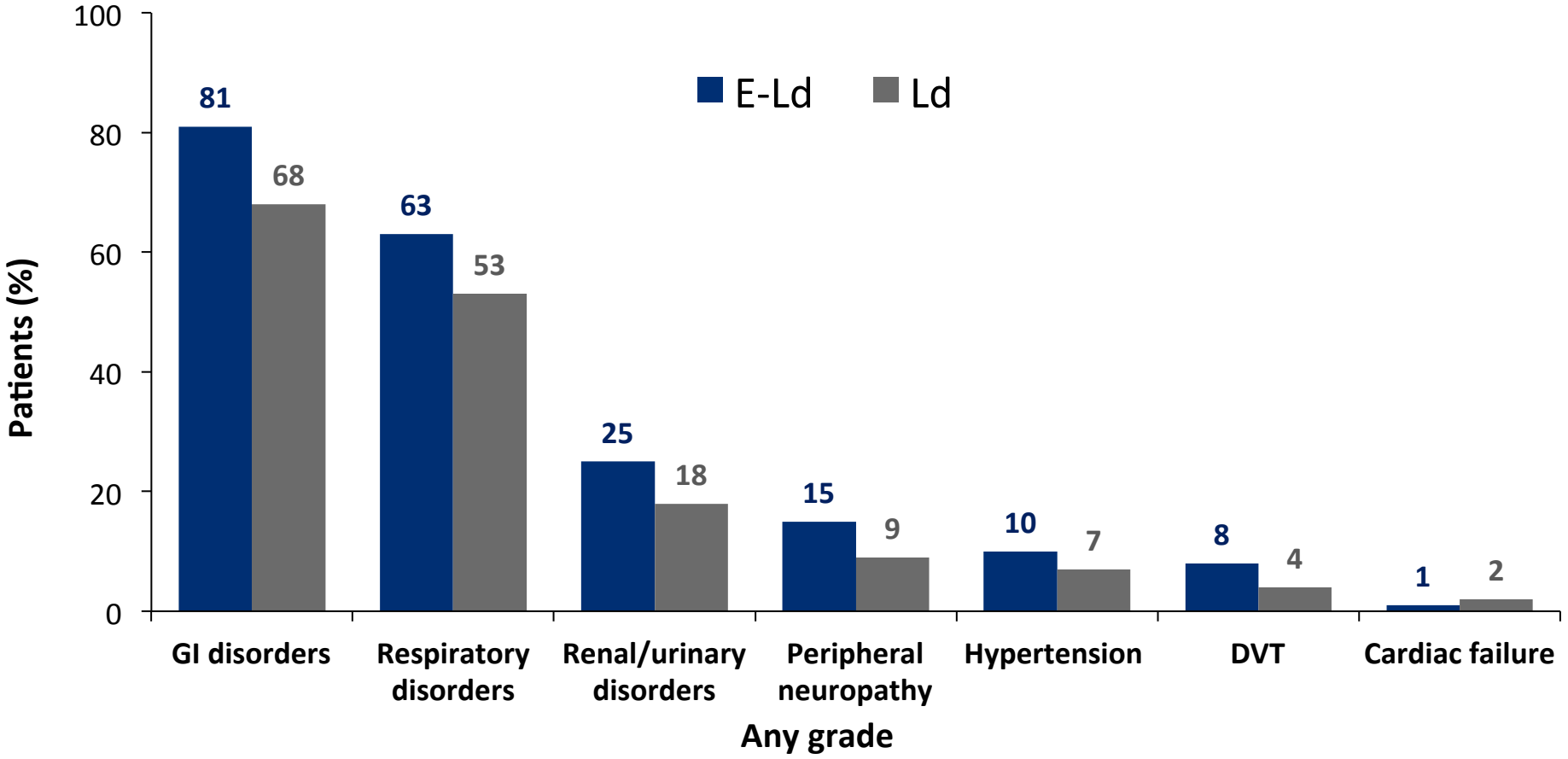
4-Year Follow-Up: OS Trend in Favor of EloRd Versus Rd Maintained[1]*



Early separation of OS curves was maintained over time in favor of ERd vs Rd

*Minimum follow-up 48 months. †OS analysis was not prespecified at 4-year follow-up; final analysis planned after 427 events.
CI, confidence interval; ERd, elotuzumab, lenalidomide/dexamethasone; HR, hazard ratio; OS, overall survival; Rd, lenalidomide/dexamethasone.
1. Dimopoulos MA et al. Oral presentation at EHA 2017. Abstract S456.

Eloquent-2: Adverse events of special interest



Infusion reactions of any grade were experienced by 10% of patients

- **Most infusion reactions were Grade 1 or 2 and occurred during the first treatment cycle**
- **There were no Grade 4 or 5 infusion reactions**

Biomarker Study: Effects of Elo on Soluble SLAMF7 Levels in MM[1]*

- Soluble SLAMF7 has been detected in the serum of patients with MM, but is not detected in healthy individuals
  - sSLAMF7 levels may be associated with MM disease stage
- This study was performed to determine if sSLAMF7 could be a biomarker of MM and to see the effects of sSLAMF7 levels on elotuzumab treatment

Study Design

- Two ELISAs were developed to detect sSLAMF7 in the presence of elotuzumab
  - Total assay detected unbound and elotuzumab-bound sSLAMF7
  - Free assay detected unbound sSLAMF7
- Before initial elotuzumab infusion and during treatment, serum samples from patients treated with elotuzumab were collected from the following clinical trials*
  - CA204-011 (elotuzumab monotherapy in SMM)
  - HuLuc63-1703 (ERd in RRMM)
  - CA204-009 (EVd in RRMM)

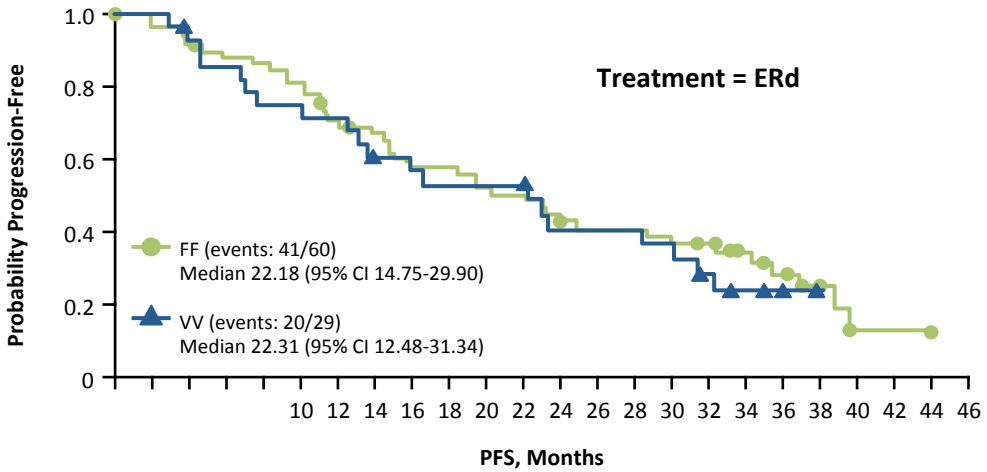
Conclusions

- Serum concentration of elotuzumab in patients is in vast excess compared with levels of sSLAMF7, suggesting that sSLAMF7 is unlikely to impair the activity of elotuzumab
- While baseline sSLAMF7 level was not an independent predictor of clinical outcome, early changes in sSLAMF7 may provide an indication of the likelihood of response to elotuzumab-containing regimens
- Decreases in free sSLAMF7 levels occur regardless of treatment regimen, but the greater decrease seen with elotuzumab may reflect not only enhanced reduction of tumor burden, but also targeted elimination of SLAMF7+ myeloma cells

*Patient samples from 3 clinical trials were used in this study; CA2014-011, HuLuc63-1703, and CA204-009.
ELISA, enzyme-linked immunosorbent assay; ERd, elotuzumab, lenalidomide/dexamethasone; EVd, elotuzumab, bortezomib/dexamethasone; MM, multiple myeloma;
SLAMF7, signaling lymphocyte activation molecule F7; SMM, smoldering multiple myeloma; sSLAMF7, soluble SLAMF7. 1. Postelnek J et al. Poster presentation at ASH 2015. Abstract 2964.

Fcγ Receptor Polymorphisms and PFS in MM: PFS by Genotype in Patients Treated with EloRd[1]

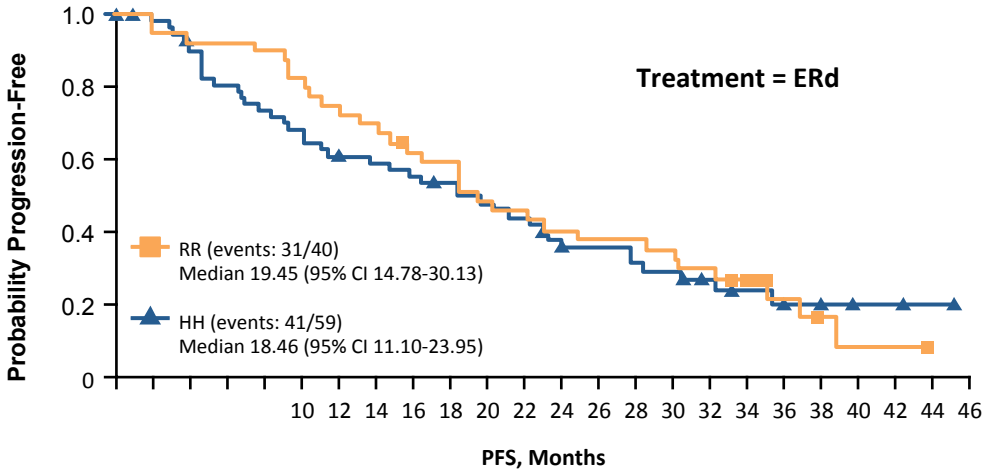
PFS by CD16a Genotype



No. at risk

VV	29	29	26	24	21	21	20	16	15	14	14	14	10	10	10	9	6	4	2	0	0	0	0
FF	60	57	54	51	50	47	40	37	31	31	28	27	22	20	20	18	17	12	9	6	1	1	0	0

PFS by CD32a Genotype



No. at risk

HH	59	56	50	45	41	38	33	32	30	28	25	23	17	16	14	13	9	6	4	4	2	2	1	0
RR	40	38	37	37	36	33	30	27	23	22	18	17	15	14	14	13	11	8	4	2	1	1	0	0

Adapted from Poulart V et al. 2016.[1]
CI, confidence interval; ERd, elotuzumab, lenalidomide/dexamethasone; MM, multiple myeloma; PFS, progression-free survival.
1. Poulart V et al. Poster presentation at EHA 2016. Abstract E1281.

Study CA204-125 (ELOQUENT-3): Phase 2 Study of EloPd vs Pd in RRMM[1,2]

N=121

Key Eligibility Criteria

- Refractory MM or RRMM
- ≥2 prior lines of therapy with at least 2 consecutive cycles of lenalidomide and PI alone or in combination
- Refractory to lenalidomide and PI, and to last treatment
- Measurable disease
- Prior treatment with pomalidomide not permitted
- Prior ASCT within 12 weeks not permitted

R

Elotuzumab
10 mg/kg IV
Cycles 1 & 2: days 1, 8, 15, 22
20 mg/kg IV
Cycles 3+: day 1

Pomalidomide
4 mg PO days 1-21 of each cycle

Dexamethasone
Cycles 1 and 2: 28 mg + 8 mg IV* or
8 mg PO + 8 mg IV†; days 1, 8, 15, 22
Cycles 3+: Same as prior cycles on weeks with elotuzumab; 40 mg PO* or 20 mg PO†
on weeks without elotuzumab

Pomalidomide
4 mg PO days 1-21 of each cycle

Dexamethasone
40 mg* or 20 mg† PO days 1, 8, 15, 22

Start Date: March 2016
Estimated Study Completion Date: March 2019
Estimated Primary Completion Date: September 2017
Status: Ongoing, not recruiting participants

- **Primary Endpoint:** PFS
- **Secondary Endpoints:** ORR, OS

*For patients aged ≤75 years. †For patients aged >75 years. Cycles are 28 days.
ASCT, autologous stem cell transplant; EPd, elotuzumab + pomalidomide/dexamethasone; IV, intravenous; MM, multiple myeloma; PI, proteasome inhibitor; ORR, overall response rate; OS, overall survival; Pd, pomalidomide/dexamethasone; PFS, progression-free survival; PO, orally; R, randomization; RRMM, relapsed/refractory multiple myeloma.
1. Clinicaltrials.gov. NCT02654132. 2. San Miguel J et al. Poster presentation at ASCO 2016. Abstract TPS8066.

Study CA204-006 (ELOQUENT-1): Phase 3 Study of EloRd vs Rd in NDMM[1]

N=750

Key Eligibility Criteria

- Newly diagnosed MM with no prior systemic anti-myeloma therapy
- Measurable disease
- Subjects who are not candidates for high-dose therapy plus stem-cell transplant because of age or coexisting conditions
- Subjects with active plasma cell leukemia, HIV, or active hepatitis A, B, or C not permitted
- Smoldering MM, defined as asymptomatic MM with absence of lytic bone lesions, not permitted
- MGUS not permitted

R

Elotuzumab
10 mg/kg IV
Cycles 1 & 2: days 1, 8, 15, 22
Cycles 3-18: days 1, 15
Cycles ≥19: 20 mg/kg monthly

Lenalidomide
25 mg PO days 1-21

Dexamethasone
Weeks without Elo: 40 mg PO
Weeks with Elo: 8 mg IV + 28 mg PO

Lenalidomide
25 mg PO days 1-21

Dexamethasone
40 mg PO weekly

Follow-up every 4 weeks for tumor assessment until progression and every 16 weeks for survival

Start Date: May 2011
Estimated Study Completion Date: January 2019
Estimated Primary Completion Date: April 2018
Status: Ongoing, not recruiting participants

- **Primary Endpoint:** PFS
- **Secondary Endpoints:** ORR, OS

Elo, elotuzumab; ERd, elotuzumab, lenalidomide/dexamethasone; HIV, human immunodeficiency virus; IV, intravenous; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; NDMM, newly diagnosed multiple myeloma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, orally;
R, randomization; Rd, lenalidomide/dexamethasone. 1. Clinicaltrials.gov. NCT01335399.

Study CA204-011: Phase 2 Biomarker Study of Elo Monotherapy to Assess the Association Between NK Cell Status and Efficacy in High-Risk SMM[1,2]

N=41

Key Eligibility Criteria

- Confirmed diagnosis of SMM according to IMWG and that is considered high-risk according to the following:
  - Serum M-protein ≥3 gm/dL and BMPCs ≥10% or
  - Serum M-protein 1-3 g/dL and BMPC ≥10% and abnormal FLC ratio of <0.125 or >8.0
  - Urine M-protein >200 mg/24 hours, ≥10% BMPCs, and serum FLC ratio ≤0.125 or ≥8.0

Elotuzumab
20 mg/kg IV
Cycle 1: day 1, 8
Cycle ≥2: once monthly

Elotuzumab
10 mg/kg IV
Cycles 1 and 2: days 1, 8, 15, 22
Cycle ≥3: day 1, 15

Repeat every 28 days until progression, unacceptable toxicity, withdrawal of consent, or end of study

Start Date: December 2011
Study Completion Date: January 2017
Primary Completion Date: May 2014
Status: Completed

- **Primary Endpoints:** Association between elotuzumab-induced change in M-protein and baseline percentage of $CD56^{dim}/CD16^{+}/CD3^{-}/CD45^{+}$ NK cells in bone marrow
- **Secondary Endpoints:** ORR (IMWG criteria), change from baseline in QTc interval, 2-year PFS, safety

CD, cluster of differentiation; BMPC, bone marrow plasma cell; FLC, free light chain; IMWG, International Myeloma Working Group; IV, intravenous; NK, natural killer; ORR, overall response rate; PFS, progression-free survival; QTc, corrected QC interval; SMM, smoldering multiple myeloma.

1. Clinicaltrials.gov. NCT01441973. 2. Richardson P et al. Oral presentation at EHA 2016. Abstract S815.

Rationale for targeting SLAMF7/CS1 with CAR T cells in MM

- Recent studies with autologous chimeric antigen receptor (CAR)-T cells targeting BCMA have shown promise in the treatment of patients with relapsed/refractory.

- SLAMF7/CS1 is highly expressed on MM tumor cells and is present in only a subset of T cells, B cells and NK cells among normal tissues.

- Elo, a monoclonal antibod targeting SLAMF7 has been found to be safe and effective in patients with MM.

- Preclinical work has demonstrated that anti-SLAMF7 CAR-T therapy can efficiently eradicate MM cells *in vitro* and *in vivo (Chu J et al, Clin Cancer Res 2014; Danhof S et al, Blood. 2015)*.

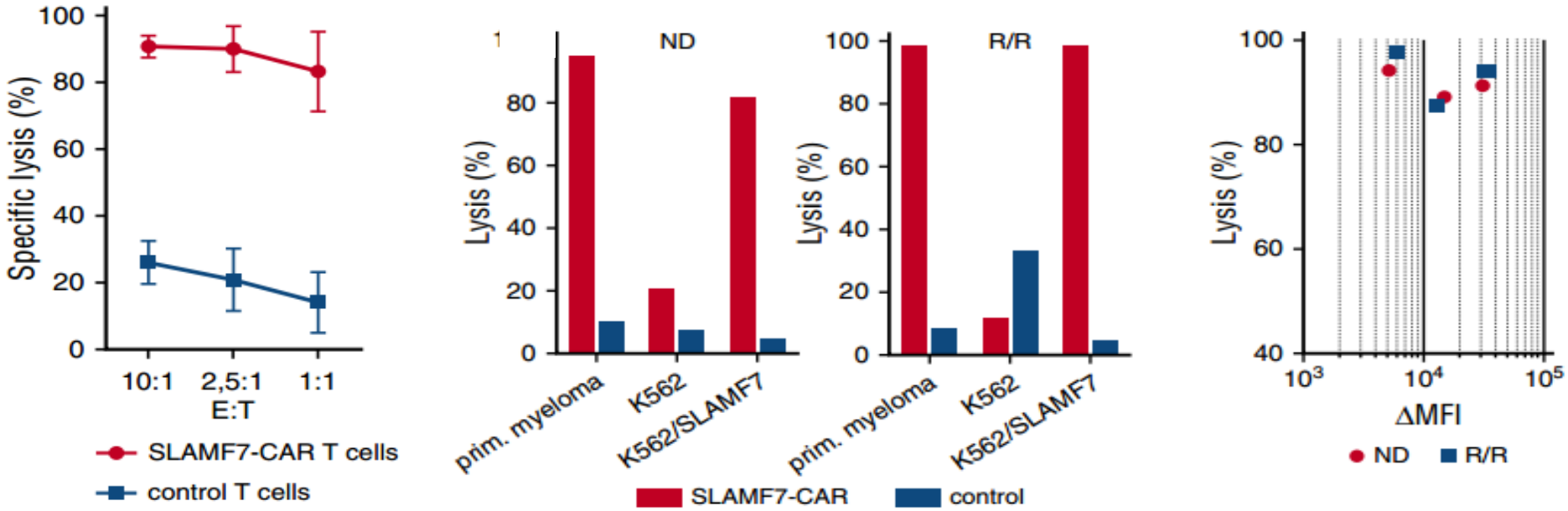
Adapted from Mathur R, ASH 2017

SLAMF7-CAR T cells eliminate myeloma and confer selective fratricide of SLAMF7^{+} normal lymphocytes

Tea Gogishvili,* Sophia Danhof,* Sabrina Prommersberger, Julian Rydzek, Martin Schreder, Christian Brede, Hermann Einsele, and Michael Hudecek

blood

SLAMF7-CAR T cells exert rapid and complete cytolysis of primary myeloma cells

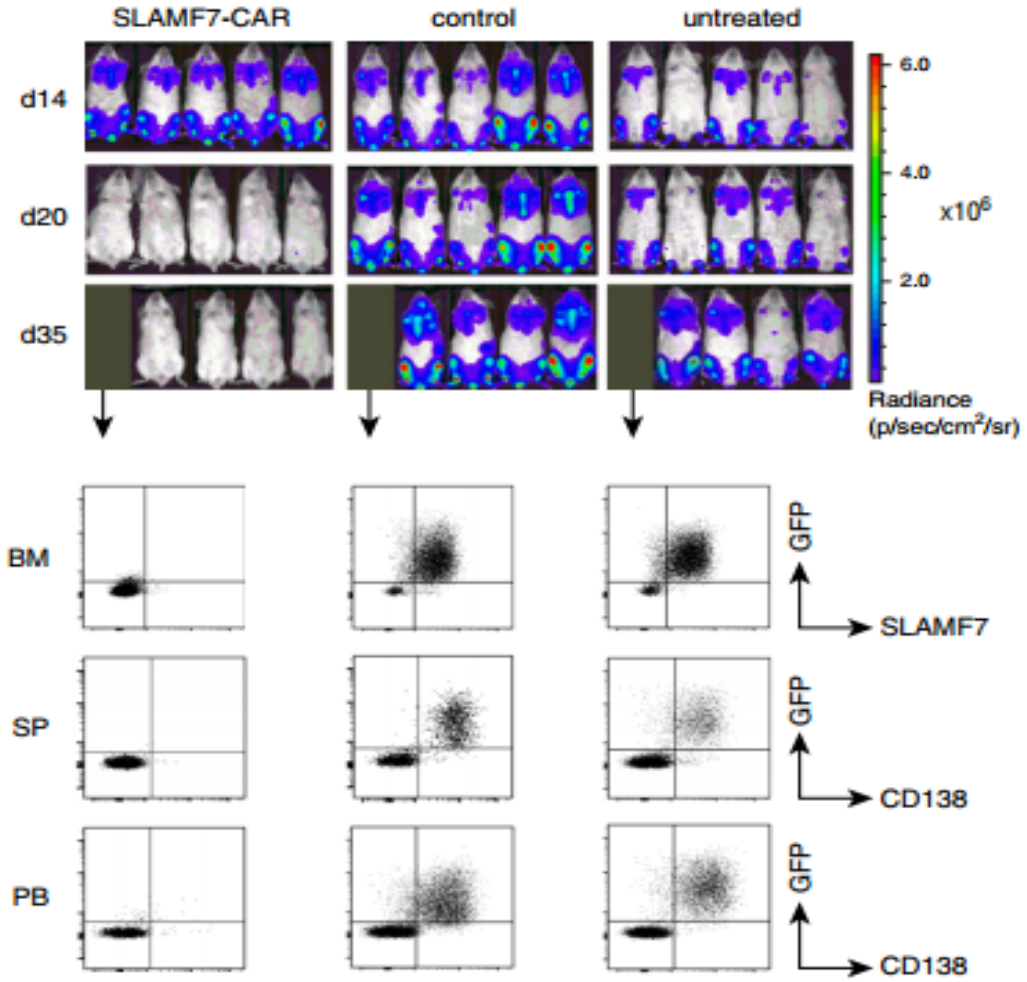


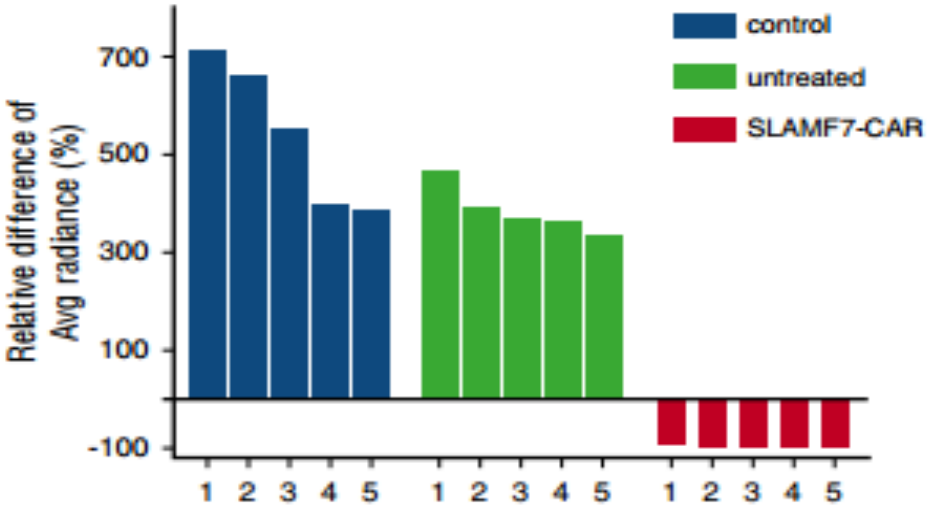
❑ SLAMF7-CAR T cells conferred near-complete cytolysis of primary myeloma cells in all 7 patients (percent specific lysis range, 87.5%-97.9%; mean, 92.5%), irrespective of the SLAMF7 expression level in a given patient.

❑*NO* difference in cytolytic activity against myeloma cells from **ND** and **R/R** patients.

Gogishvili et l, Blood. 2017

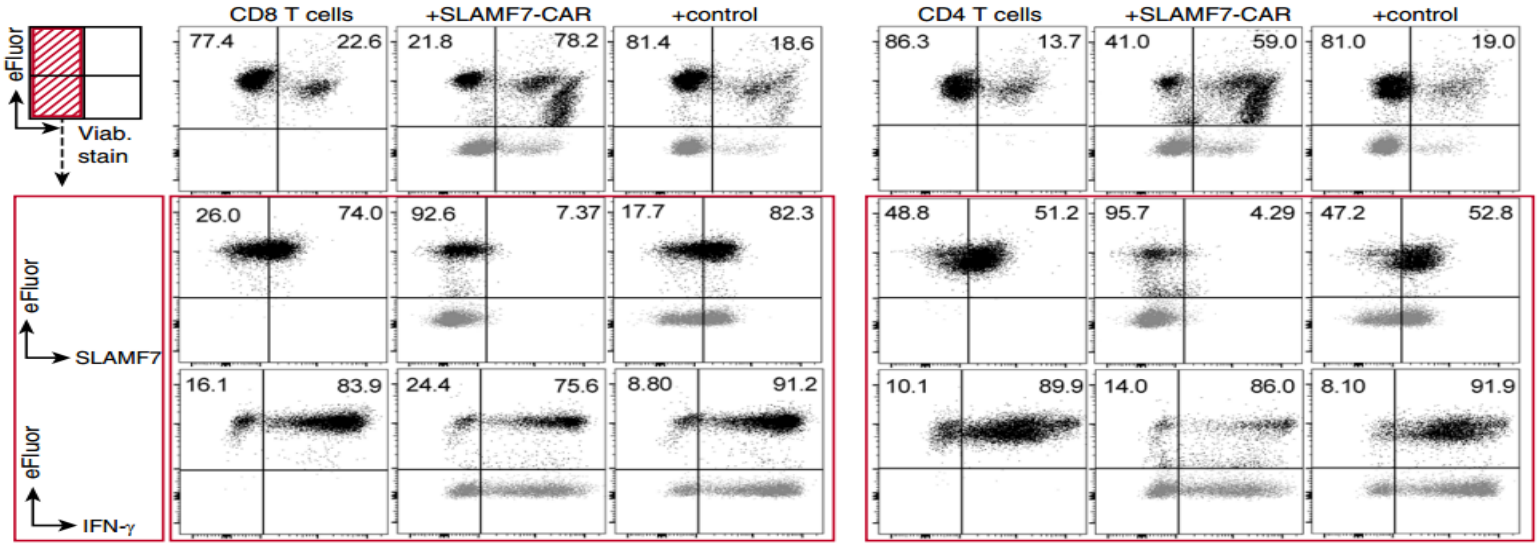
SLAMF7-CAR T cells eradicate systemic myeloma in a xenograft model

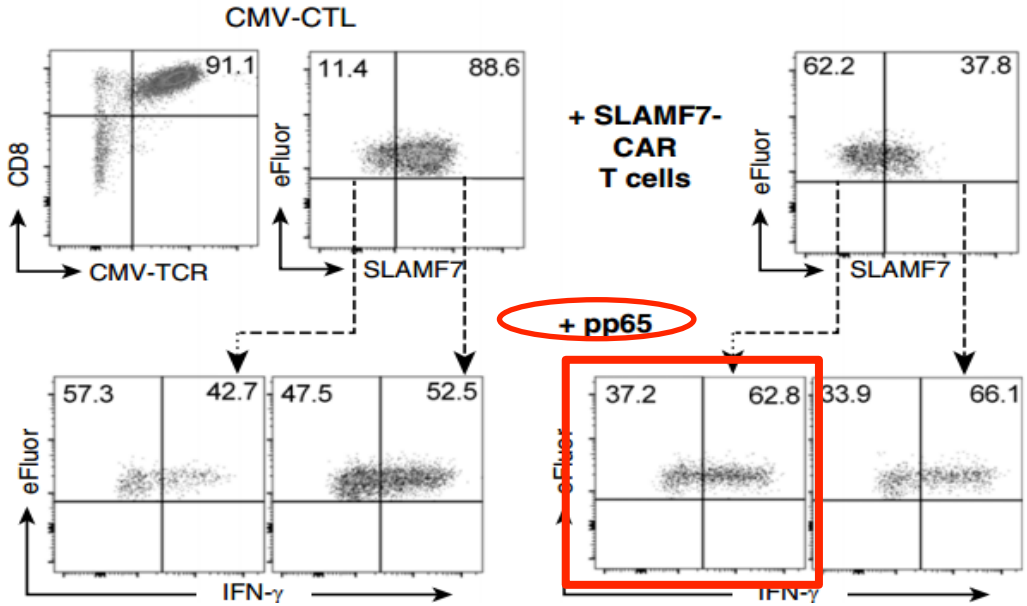




Gogishvili et l, Blood. 2017

SLAMF7-CAR T cells confer selective fratricide of SLAMF7^{+} normal lymphocytes





- CD8+ SLAMF7-CAR T cells induced specific fratricide of SLAMF7$^{+/high}$ target cells in each of the lymphocyte subsets.
- SLAMF7$^{-/low}$ fraction, including **virus-specific T cells** was spared from fratricide and remained viable and functional.

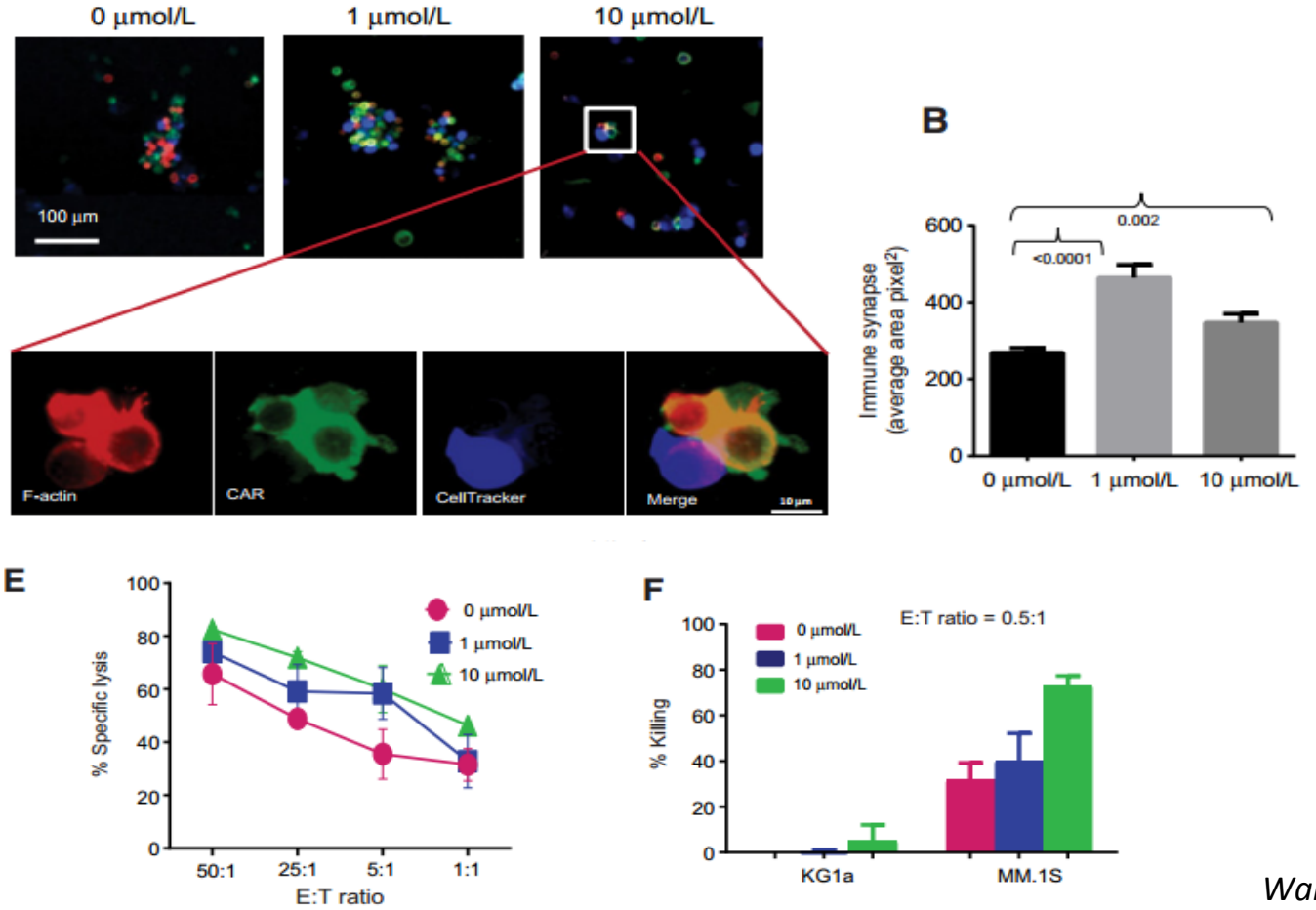
Gogishvili et l, Blood. 2017

Lenalidomide Enhances the Function of CS1 Chimeric Antigen Receptor–Redirected T Cells Against Multiple Myeloma

Xiuli Wang[1], Miriam Walter[1], Ryan Urak[1], Lihong Weng[1], Christian Huynh[1], Laura Lim[1], ChingLam W. Wong[1], Wen-Chung Chang[1], Sandra H. Thomas[1], James F. Sanchez[1,2], Lu Yang[3], Christine E. Brown[1], Flavia Pichiorri[1,2], Myo Htut[1,2], Amrita Y. Krishnan[1,2], and Stephen J. Forman[1]

Clinical Cancer Research

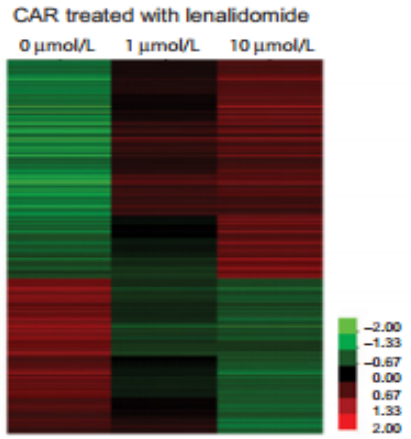
Lenalidomide improves immune synapse formation between CAR T cells and tumor cells

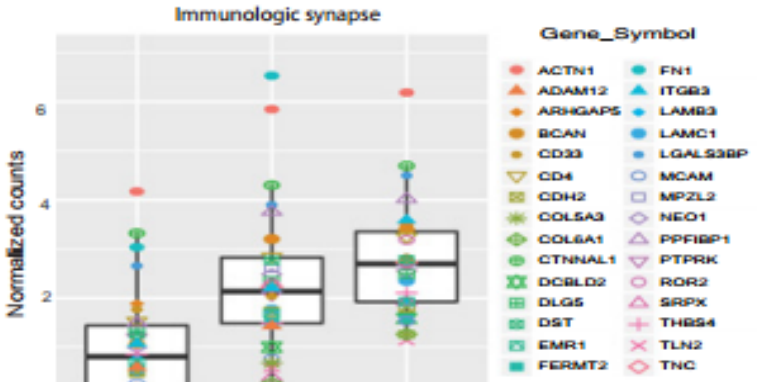


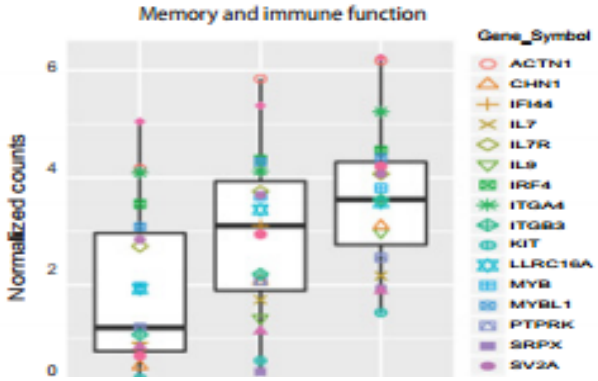
Wang X et al, Clin Canc Res 2018

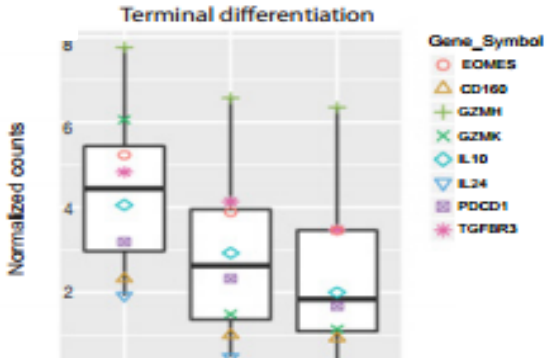
Lenalidomide enhances transcriptional signatures of immune synapse and T-cell function

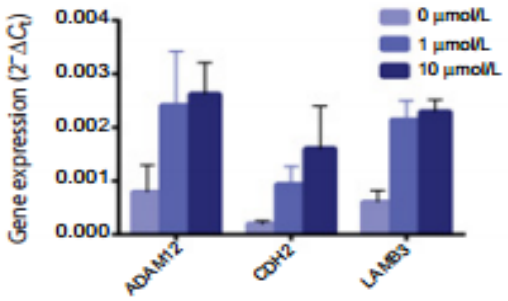
- *IL7, ACTIN1, KIT, WNT5B, IL9,* and *MYB*, together with genes associated with enhanced effector function, such as *IRF4* and IFI44, or related to better homing capacity such as integrins *ITGA4* and *ITGB3* are upregulated .
- Lenalidomide suppresses genes in CAR T cells associated with exhaustion (e.g. *PDCD1, CD160*), terminal differentiation (*GZMK, GZMH* and *EOMES*), and immune suppression signals (*TGFBR3* and *IL10*).

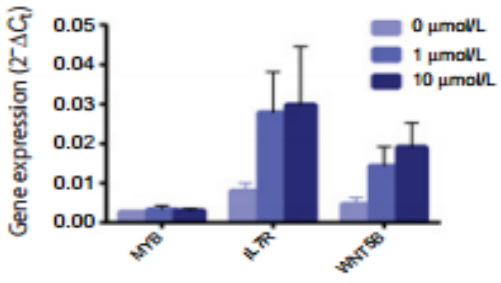


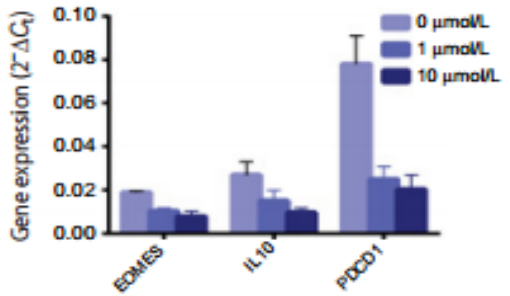








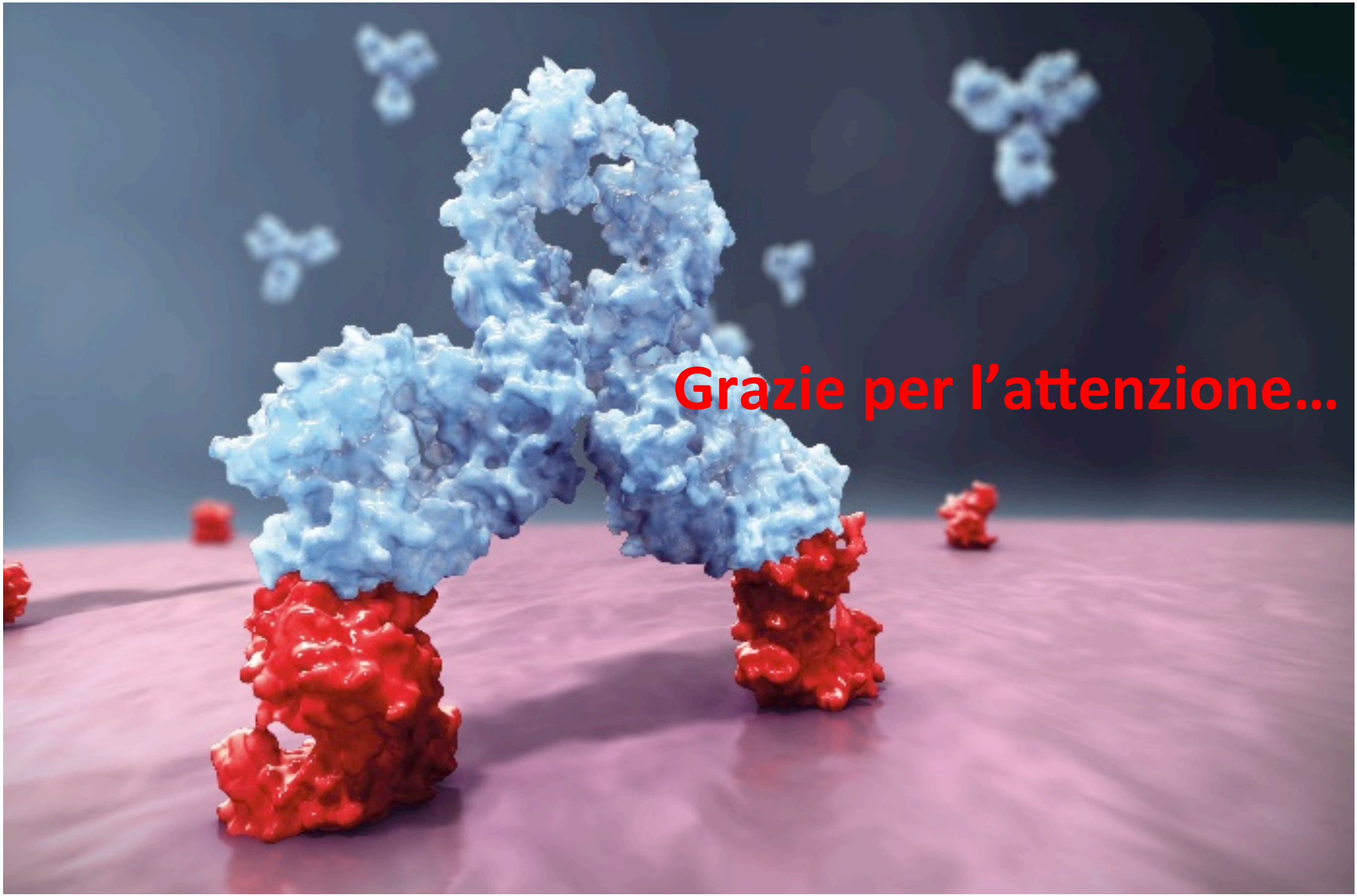




Wang X et al, Clin Canc Res 2018

SLAMF7-CAR T: Key Points

- SLAMF7-CAR T cells are effective against refractory MM cells.
- SLAMF7-CAR T cells led to resolution of medullary and extramedullary myeloma in a murine xenograft model *in vivo.*
- SLAMF7-CAR T cells confer fratricide of SLAMF7$^{+/high}$ normal lymphocytes.
- Importantly, however, the fratricide conferred by SLAMF7-CAR T cells spares the **SLAMF7$^{-/low}$ fraction** in each cell subset and preserves functional lymphocytes, including virus-specific T cells.
- Lenalidomide potentiates SLAMF7-CAR T cells anti-myeloma effect modulating their transcriptional profiles.


Grazie per l’attenzione…