Novità terapeutiche nel mieloma multiplo

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07/6/18

Novità Terapeutiche

1) TERAPIA DI MANTENIMENTO DOPO TRAPINATO AUTOLOGO CON

LENALIDOMIDE

2) NUOVI REGIMI TERAPEUTICI PER IL MM RIC/REFRATTARIO

EloRd

KRd

Kd

DaraRd

DaraVd

TERAPIA DI I LINEA PAZIENTE FIT PER TRAPIANTO

INDUZIONE
(4 CICLI VTD, BORTEZOMIB-TALIDOMDIE-DESAMETASONE)

MOBILIZZAZIONE
(CICLOFOSFAMIDE 2-3 G/MQ + G-CSF E RACCOLTA PBSC)

1-2 TRAPIANTI
(MELPHALAN AD ALTE DOSI E TRAPIANTO AUTOLOGO PBSC)

CONSOLIDAMENTO
(2 VTD)

MANTENIMENTO
(LENALIDOMIDE FINO A PROGRESSIONE)

Indication, clinical trials and posology

«Revlimid» come monoterapia e' indicato per la terapia di mantenimento di pazienti adulti con mieloma multiplo di nuova diagnosi sottoposti a trapianto autologo di cellule staminali.

CALGB 100104

A phase III randomized, double-blind study of maintenance therapy with lenalidomide or placebo following autologous stem cell transplantation for multiple myeloma

460 US patients
81.6 months follow-up
REVLIMID monotherapy improved PFS and OS

IFM 2005-02

Benefit of a maintenance treatment with lenalidomide following autologous stem cell transplantation in patients with myeloma and aged less than 65 years

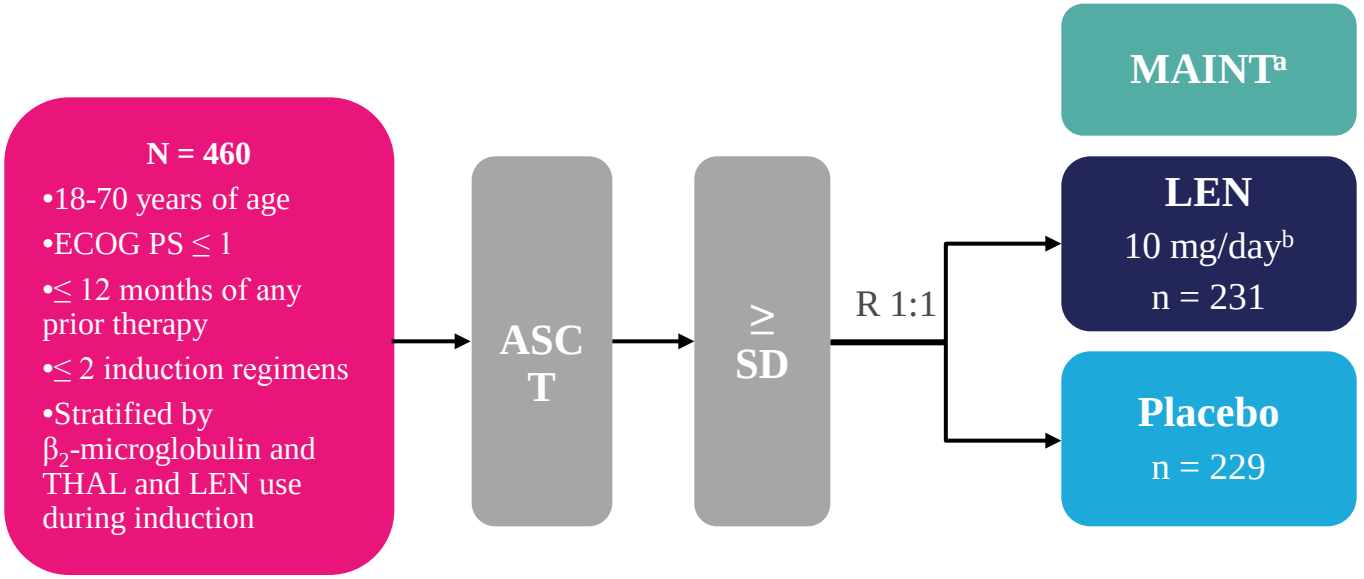
614 EU patients (Fr, BE, CH)
96.7 months follow-up
REVLIMID monotherapy improved PFS

Dose raccomandata

- **10 mg** per via orale una volta al giorno, somministrata continuativamente (**nei giorni 1-28 di cicli ripetuti di 28 giorni**)
- Dopo 3 cicli di terapia di mantenimento con lenalidomide, la dose può essere aumentata a 15 mg per via orale una volta al giorno, se tollerata.
- **fino a progressione della malattia o a comparsa di intolleranza.**

CALGB update: LEN maint after ASCT for MM

study design

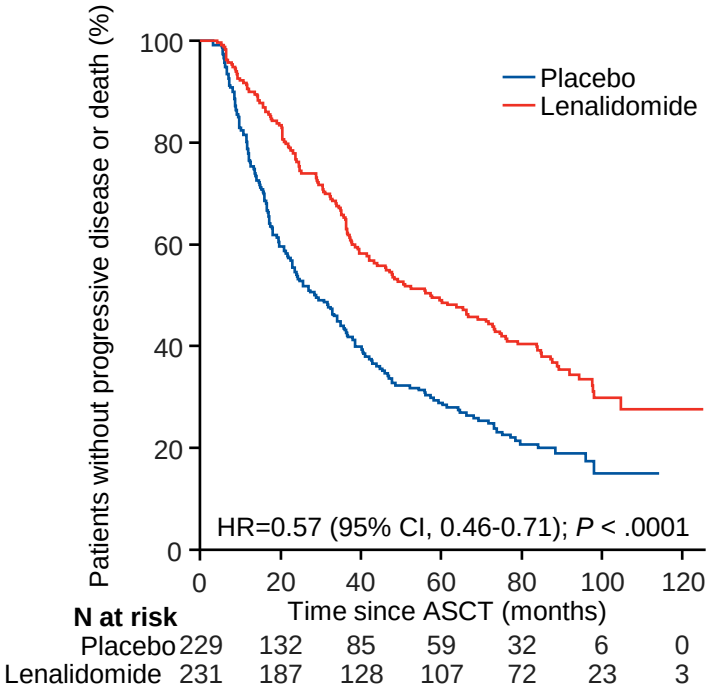


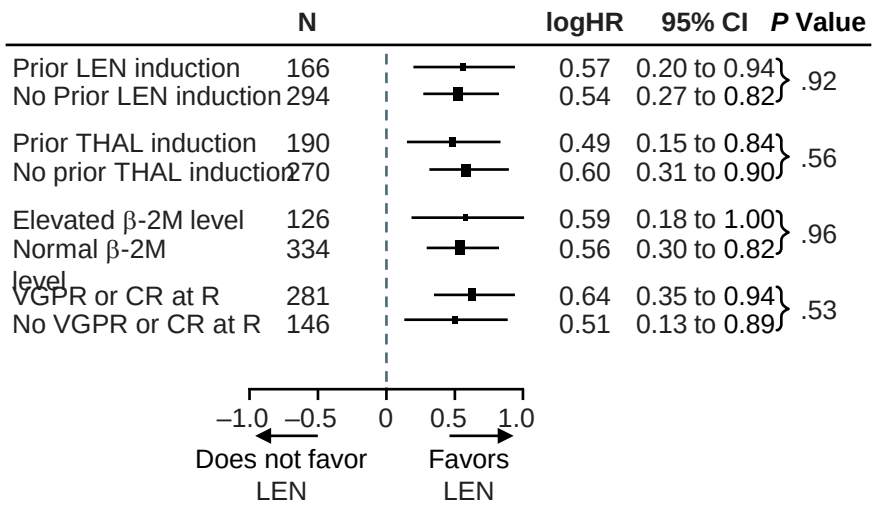
- **Primary endpoint: TTP (time to PD or death)**
- Secondary endpoint: OS, CR, feasibility of long-term LEN administration
- Exploratory endpoint: SPMs
- Data cutoff: October 19, 2016 (91-month median follow-up)

Of the 128 eligible **pts without PD** in the placebo group, **86 (67%) crossed over and received LEN therapy**

[a] Holstein SA, et al. Lancet Haematol 2017;4(9):e431-e442.

CALGB update: LEN maint after ASCT for MM *TTP*[a]

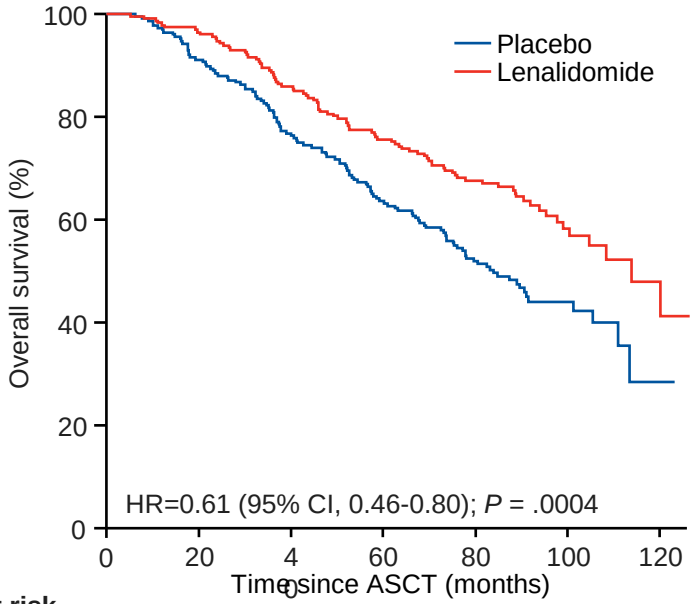




- The median TTP was **57.3 mos** in the LEN group and **28.9 mos** in the placebo group (*P* < .0001)
- There was a benefit of LEN MAINT for TTP across all stratification groups

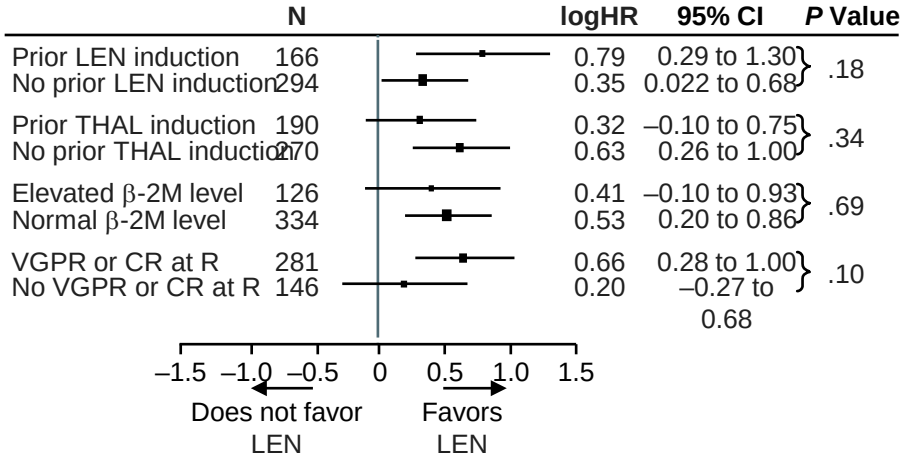
CALGB update: LEN maint after ASCT for MM

OS



N at risk

Placebo	229	205	169	137	96	26	1
Lenalidomide	231	220	193	167	128	44	7



- The median OS was **113.8 mos** and **84.1** mos with LEN and placebo, respectively (*P* = .0004)

CALGB update: LEN maint after ASCT for MM

most common grade ≥ 3 adverse events

AEs, n (%)[a]	LEN (n = 231)	Placebo n = 229	
		No Crossover (n = 143)	Crossover (n = 86)
Hematologic			
Hemoglobin	11 (5)	0	1 (1)
Leukopenia	31 (13)	2 (1)	10 (12)
Lymphopenia	21 (9)	2 (1)	5 (6)
Neutropenia	116 (50)	11 (8)	30 (35)
Thrombocytopenia	34 (15)	7 (5)	5 (6)
Nonhematologic			
Conduction abnormality	1 (< 1)	1 (1)[b]	1 (1)
Fatigue	0	0	0
Rash	9 (4)	1 (1)	1 (1)
Diarrhea	12 (5)	2 (1)	3 (3)
Febrile neutropenia	15 (6)	3 (2)	1 (1)
Infection[c]	15 (6)	3 (2)	4 (5)
Infection with normal ANC or grade 1 or 2 neutrophils	14 (6)[b]	3 (2)	1 (1)
Pain	6 (3)	6 (4)	2 (2)
Vascular	1 (< 1)[b]	0	0

- The most common grade 3/4 AEs were **neutropenia** (50% with LEN and 18% with placebo) and **thrombocytopenia** (15% with LEN and 5% with placebo)
- **Rate of grade 3-4 peripheral neuropathy was 2%** for both LEN and placebo arms

[a]olstein SA, et al. Lancet Haematol 2017;4(9):e431-e442.

CALGB update: LEN maint after ASCT for MM *spms* (EXPLORATORY OBJECTIVE)

SPMs, n		LEN (n = 231)	Placebo (n = 229)	
			No Crossover (n = 143)	Crossover (n = 86)
Hematologic	MDS/AML	10	—	—
	MDS	—	—	1
	B-cell ALL	6	—	2
	Hodgkin lymphoma	1	—	—
	Waldenstrom macroglobulinemia	1	—	—
Solid tumor	Breast	3	1	—
	Colon	3	—	—
	Prostate	2	—	—
	Endometrial	2	—	1
	Ovarian and endometrial	—	1	—
	Glioblastoma multiforme	1	—	—
	Melanoma	1	1	2
	Papillary thyroid	1	—	—
	Salivary gland carcinoma	1	—	—
	Renal cell	—	—	1
	Invasive SCC	—	—	1
	Lung carcinoid	—	1	—
Noninvasive	SCC	5	1	—
	BCC + SCC	3	—	2
	DCIS	2	—	—
	BCC	1	—	3

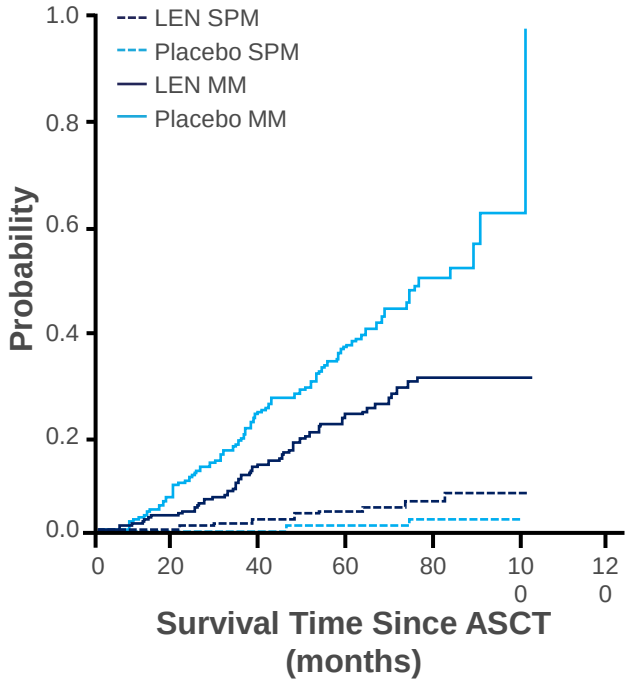
- 18 hematologic (8%), 14 solid tumor (6%), and 11 (5%) noninvasive SPMs were diagnosed following randomization in the LEN arm vs 3 hematologic (1%), 9 solid tumor (4%), and 6 (3%) noninvasive SPMs in the placebo arm

Holstein SA, et al. Lancet Haematol 2017;4(9):e431-e442.

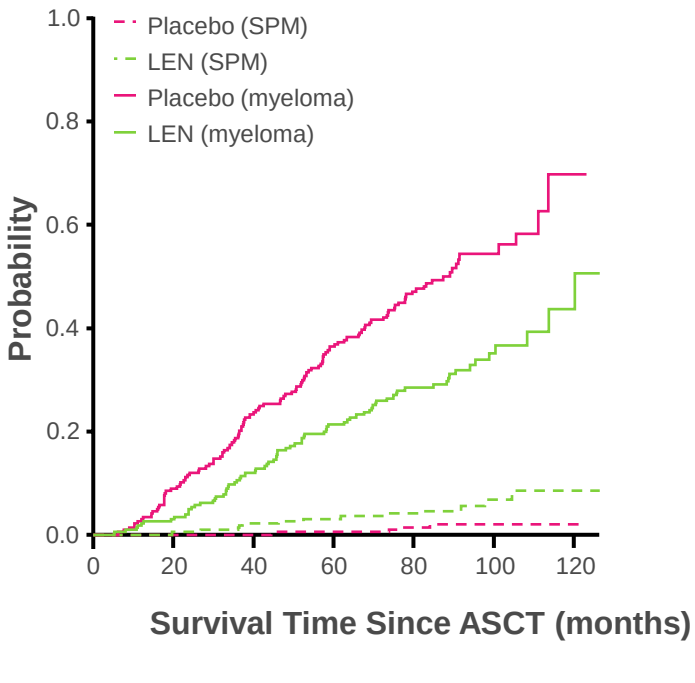
CALGB 100104: death by spm vs death by mm

- Results from an updated analysis using an October 2016 cutoff were consistent with an earlier analysis[1,2]
- The CIR of death from MM was higher with placebo ($P < .0001$), whereas the CIR of death from SPM was higher with LEN ($P = .031$)[2]

Cutoff: Nov 2014[1]



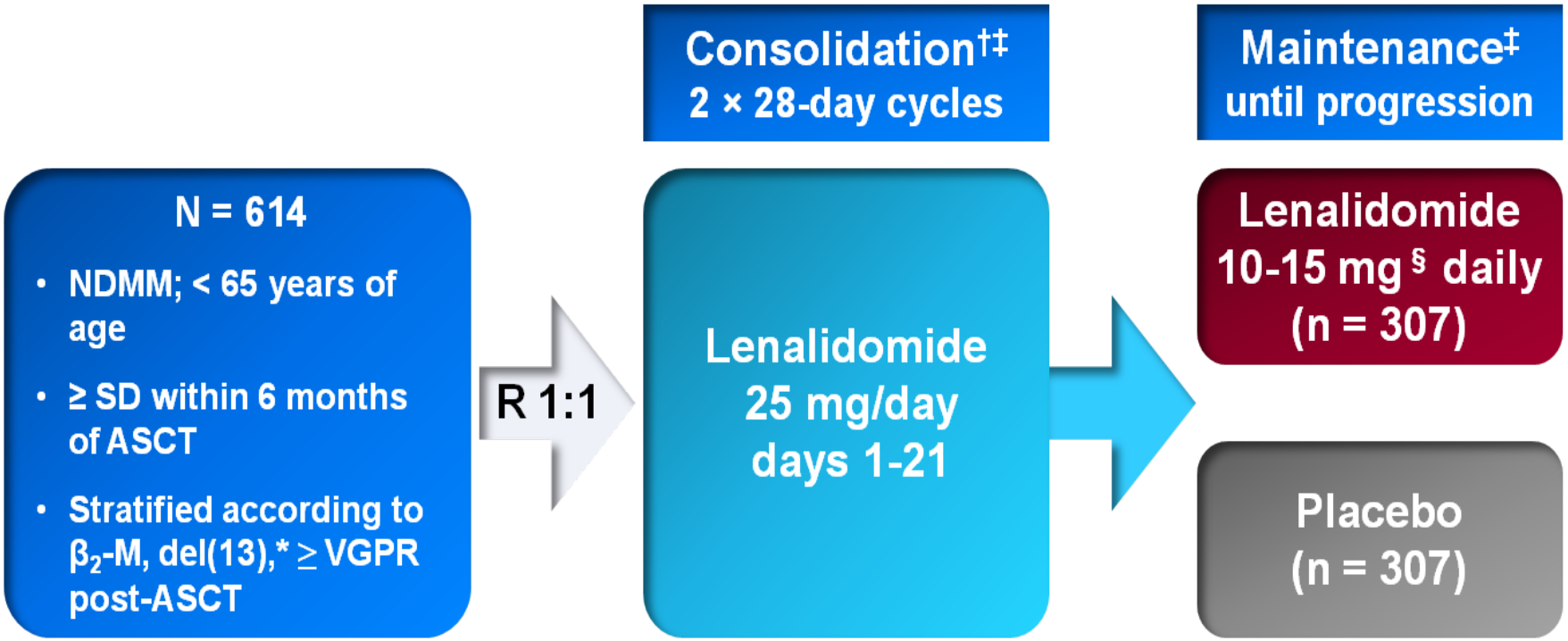
Cutoff: Oct 2016[2]



ASCT, autologous stem cell transplant; CALGB, Cancer and Leukemia Group B; CIR, cumulative incidence risk; LEN, lenalidomide; MM, multiple myeloma; SPM, second primary malignancy.

1. Holstein SA. *J Clin Oncol.* 2015;33(suppl):8523. 2. Reprinted from Holstein SA, et al. *Lancet Haematol*. 2017;4(9):e431-e442, Copyright 2017, with permission from Elsevier.

IFM 2005-02: study design and endpoints



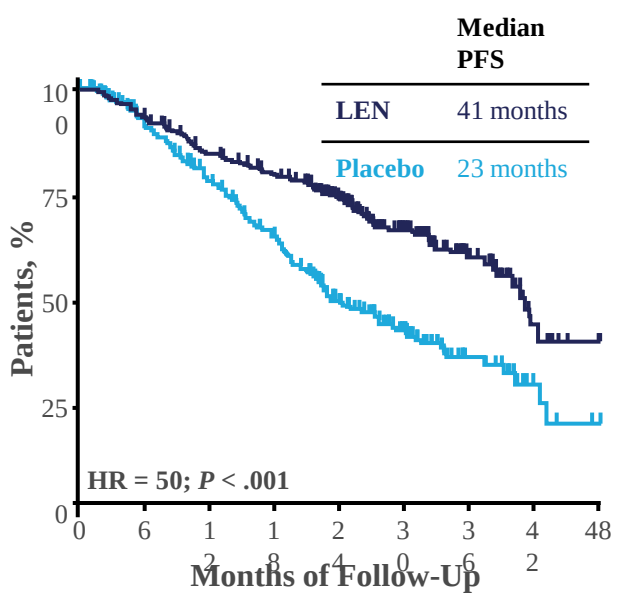
Primary endpoint: PFS
Secondary endpoints: ORR, EFS, OS

[a] As measured by FISH; [b] Consolidation phase added at first protocol amendment (Sept 2006).
ASCT, autologous stem cell transplant; β_2-M, β_2-microglobulin; EFS, event-free survival; FISH, fluorescence in situ hybridization; IFM, Intergroupe Francophone du Myélome; LEN, lenalidomide; NDMM, newly diagnosed multiple myeloma; OS, overall survival; PFS, progression-free survival; R, randomization; SD, stable disease; VGPR, very good partial response.
Attal M. *N Engl J Med.* 2012;366:1782-1791.

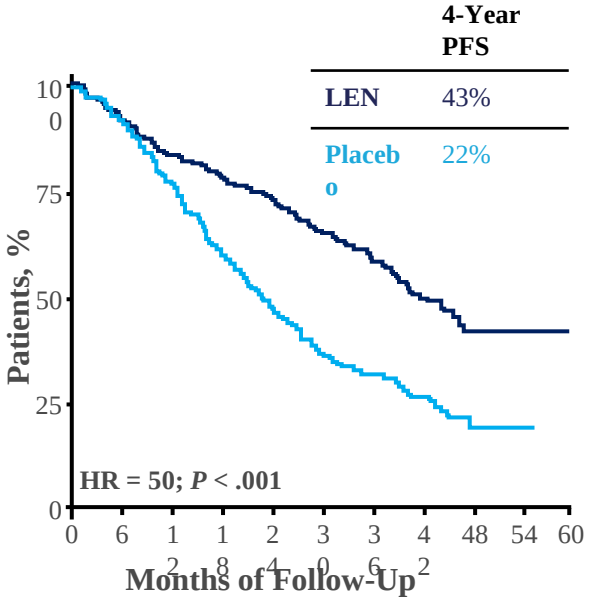
IFM 2005-02: Progression-Free Survival

- **LEN maintenance significantly prolonged median PFS vs placebo**
  - PFS improvement observed across all stratified patient subgroups (β_2-M, del(13q), ≥ VGPR post-ASCT)

Cutoff: July 2010



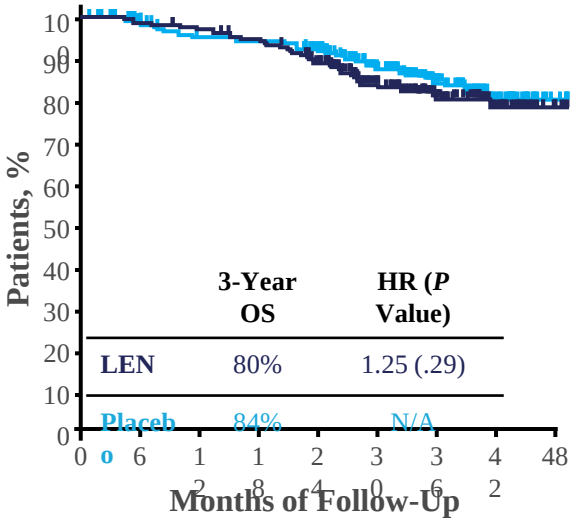
Cutoff: Oct 2011



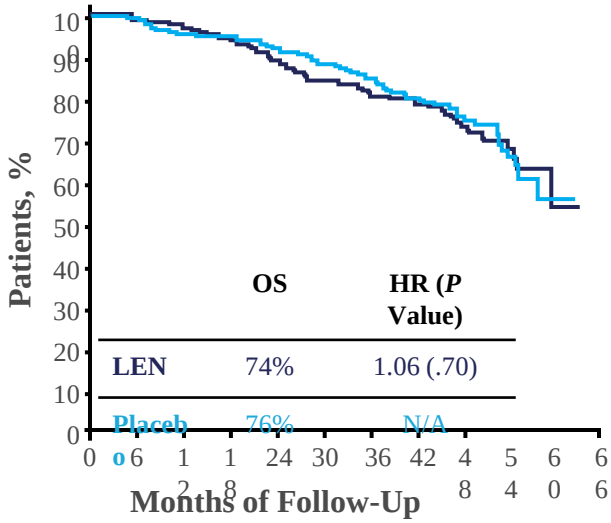
ASCT, autologous stem cell transplant; β_2-M, β_2-microglobulin; HR, hazard ratio; IFM, Intergroupe Francophone du Myélome; LEN, lenalidomide;
PFS, progression-free survival; VGPR, very good partial response.
Attal M. *N Engl J Med.* 2012;366:1782-1791.

IFM 2005-02: overall Survival

- With a median follow-up of 45 months, no differences in OS have been observed across treatment arms
  - 4 year OS (post-randomization): 73% (LEN) vs 75% (placebo)



Cutoff: July 2010



Cutoff: Oct 2011

HR, hazard ratio; IFM, Intergroupe Francophone du Myélome; LEN, lenalidomide; N/A, not applicable; OS, overall survival; PBO, placebo.

Attal M. *N Engl J Med.* 2012;366:1782-1791.

IFM 2005-02: Post-Randomization* AEs

- Only **1%** of patients in the Lenalidomide arm reported **grade 3/4 febrile neutropenia**
- Incidence of grade 3/4 DVT was 2% with Lenalidomide vs. 1% with placebo
- The rate of **grade 3/4 peripheral neuropathy was 1%** for both Lenalidomide and placebo arms
- Discontinuation due to AEs: 27% with Lenalidomide vs. 15% with placebo

Grade 3/4 AEs occurring in ≥ 5%, n (%)	Lenalidomide (n = 306)	Placebo (n = 302)
Haematological	179 (58)	68 (22)
Neutropenia	157 (51)	53 (18)
Thrombocytopenia	44 (14)	20 (7)
Non-haematological	NR	NR
Infection	41 (13)	15 (5)
Fatigue	15 (5)	6 (2)

* Data as of study unblinding (July 2010); includes AEs reported as a result of both consolidation and maintenance.

AE: adverse event; DVT: deep-vein thrombosis; IFM: Intergroupe Francophone du Myélome; NR: not reported.

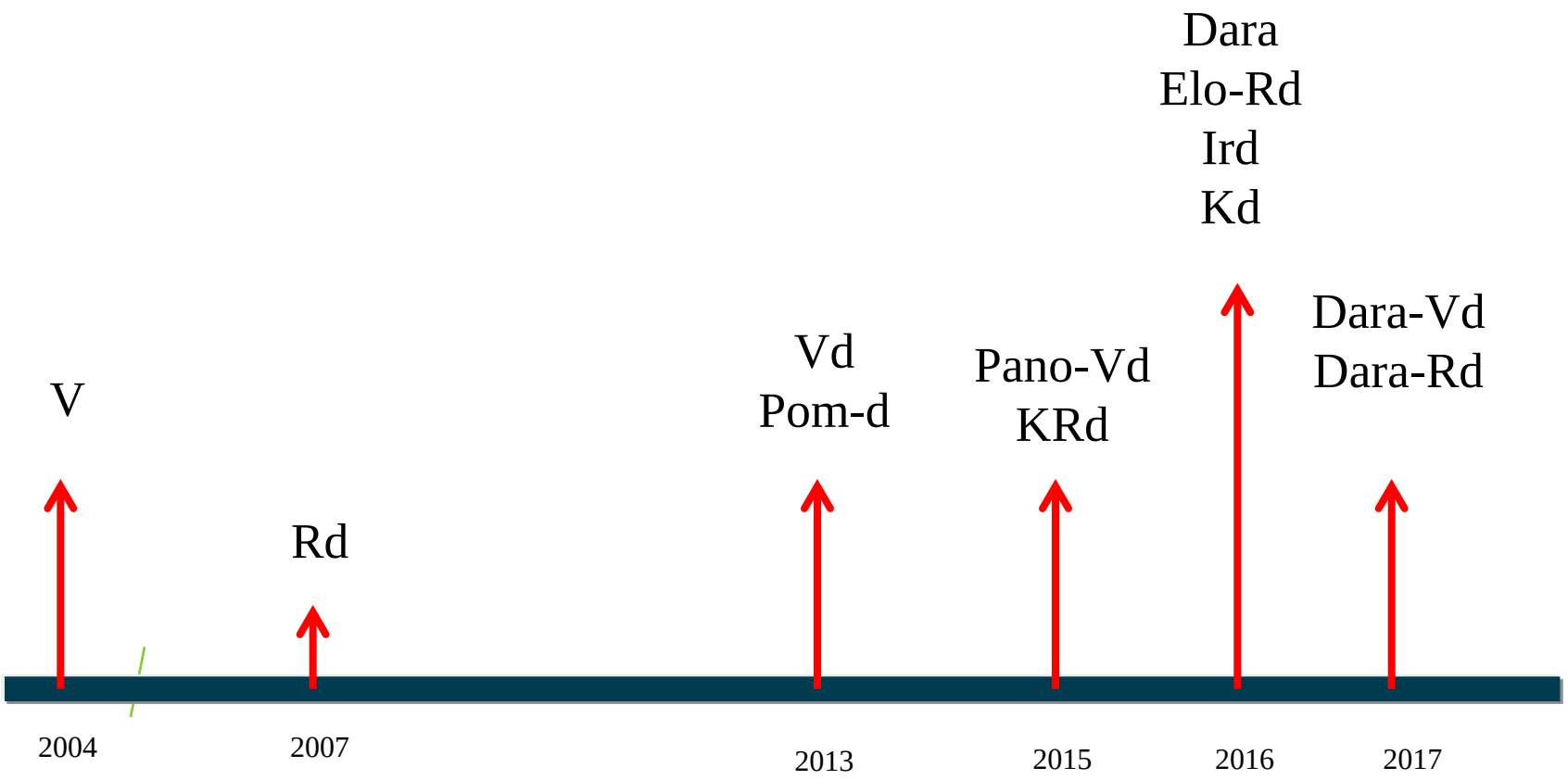
Attal M. *N Engl J Med*. 2012;366:1782-91.

CONCLUSIONS:

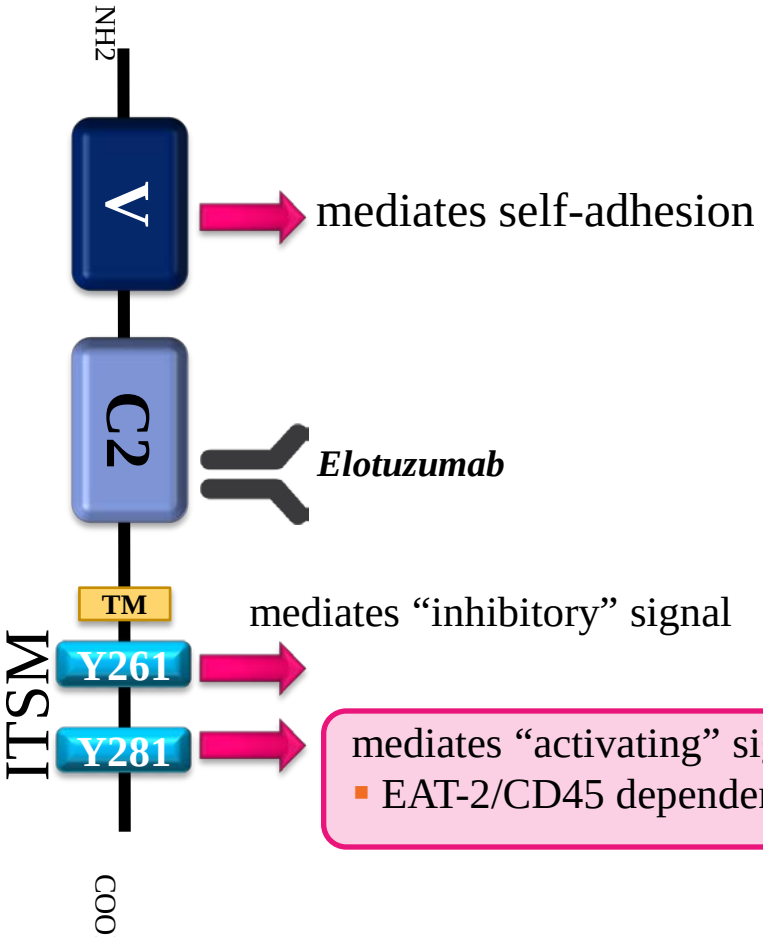
	CALGB		IFM 2005-02	
	LENA	**PLACEBO**	**LENA**	**PLACEBO**
Patients	231	229	307	307
TTP	57m	28m		
PFS			41m	23m
OS	113m	84m	nr	nr

TERAPIA DI SALVATAGGIO

COMBINAZIONI APPROVATE DA EMA



Elotuzumab: A Monoclonal Antibody Targeting SLAMF7



Elotuzumab

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

SLAMF7

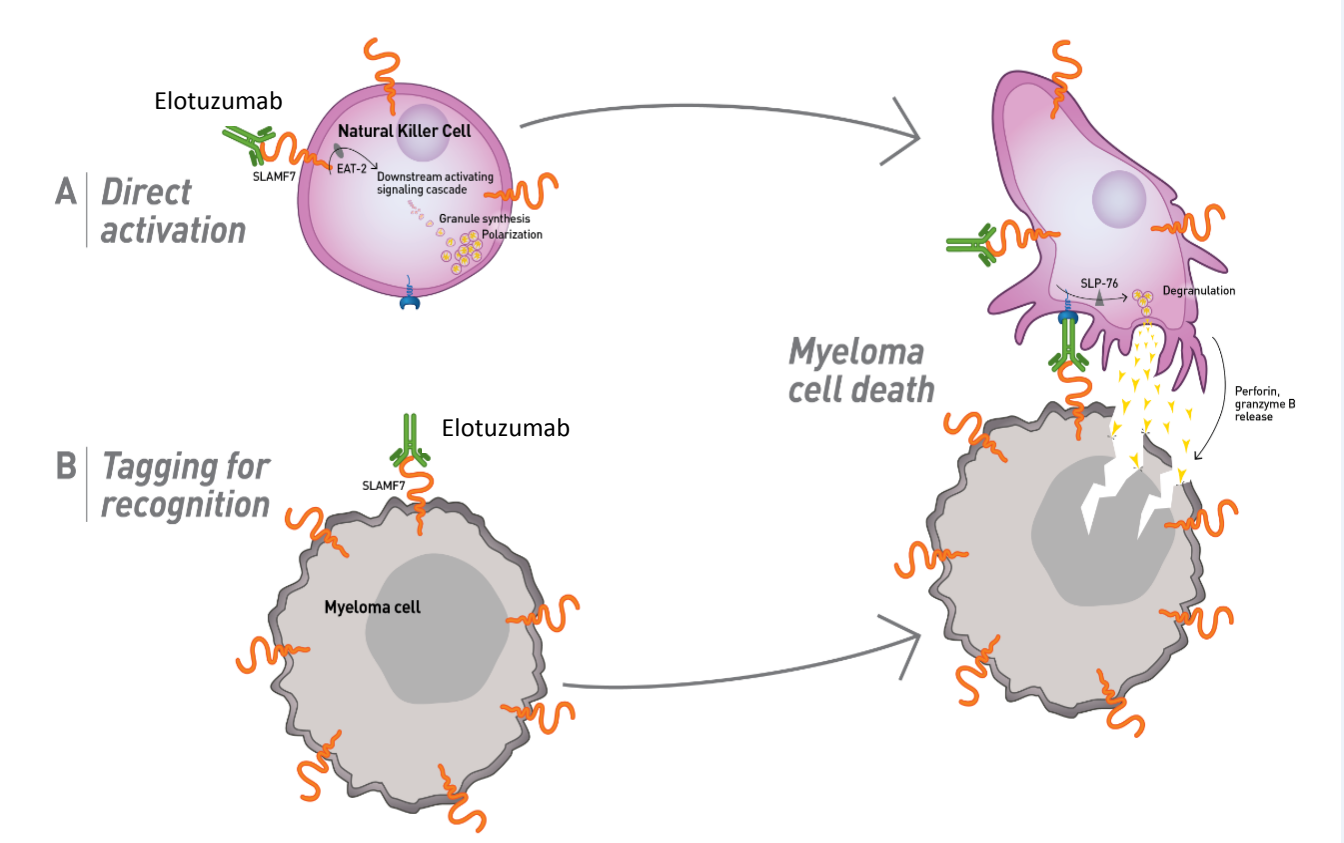
- Expression highest on Plasma Cells
- Varied expression across hematopoietic cells (NK, NK-T, DC, B, TCD8+, PC)
- Not express on non-hematopoietic cells
- SLAMF7 K/O Phenotype: compromised NK function

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

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

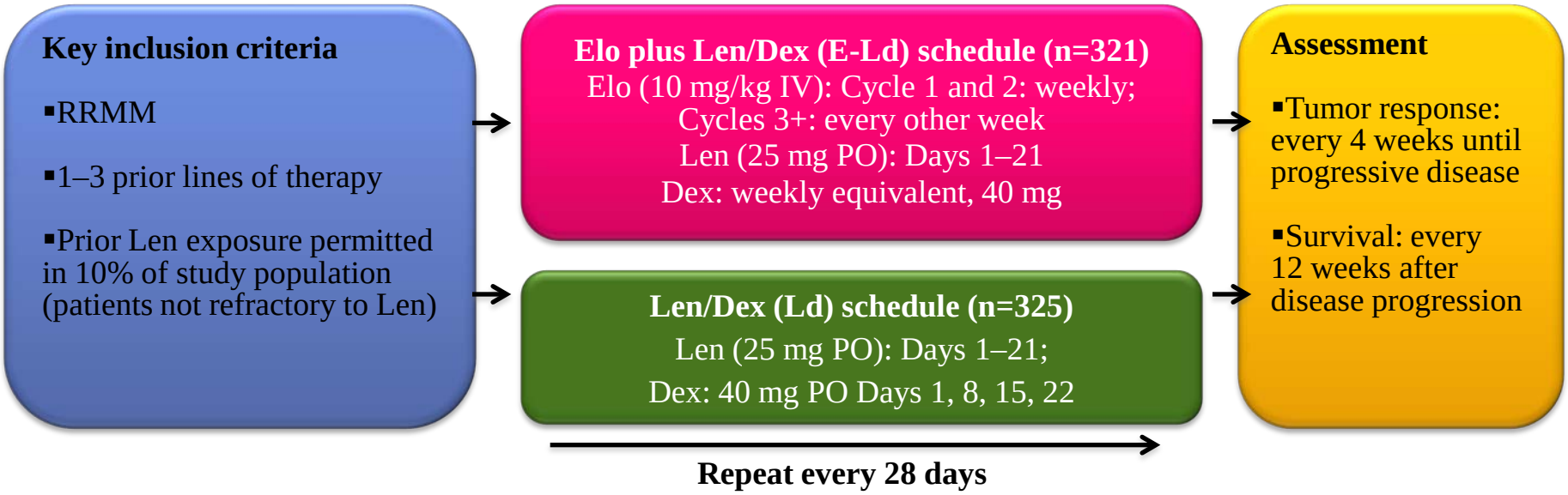
Elotuzumab works via a dual mechanism of action by both directly activating Natural Killer Cells and through antibody-dependent cell-mediated cytotoxicity (ADCC) to cause targeted Myeloma cell death

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



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

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

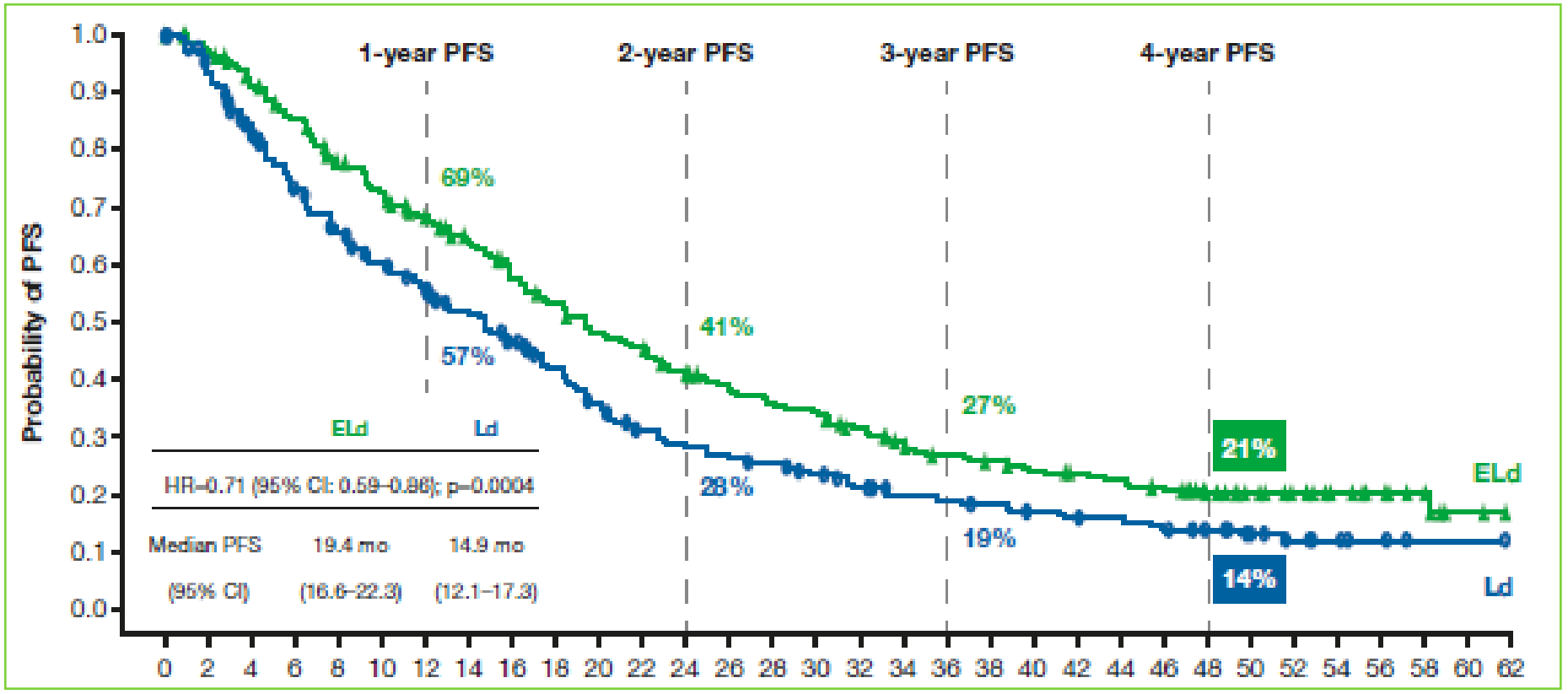


- Open-label, international, randomized, multicenter, **phase 3 trial** (168 global sites)
- **646 pts**
- Median n° treatment cycles Elo Ld: 19 (1-42)
- 83% pts received more than 90% dose intensity

Approved by FDA for use in MM pts with ≥ 1 prior therapies (Nov 2015)

Lonial S et al, NEJM 2015

PFS

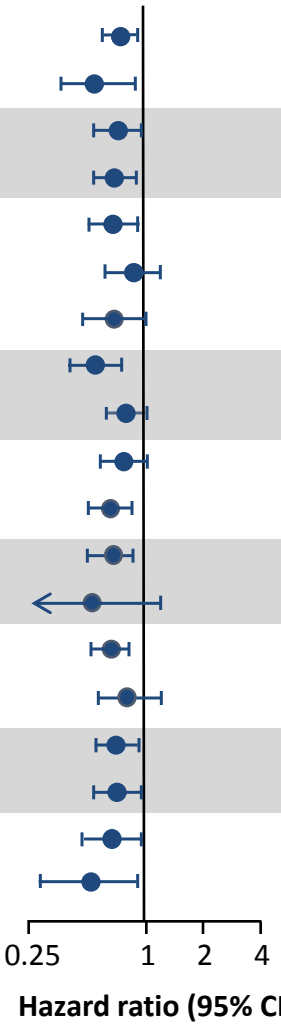


	E-Ld	Ld
HR 0.73 (95% CI 0.60, 0.89); p=0.0014		
Median PFS (95% CI)	19.4 mos (16.6, 22.2)	14.9 mos (12.1, 17.2)

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

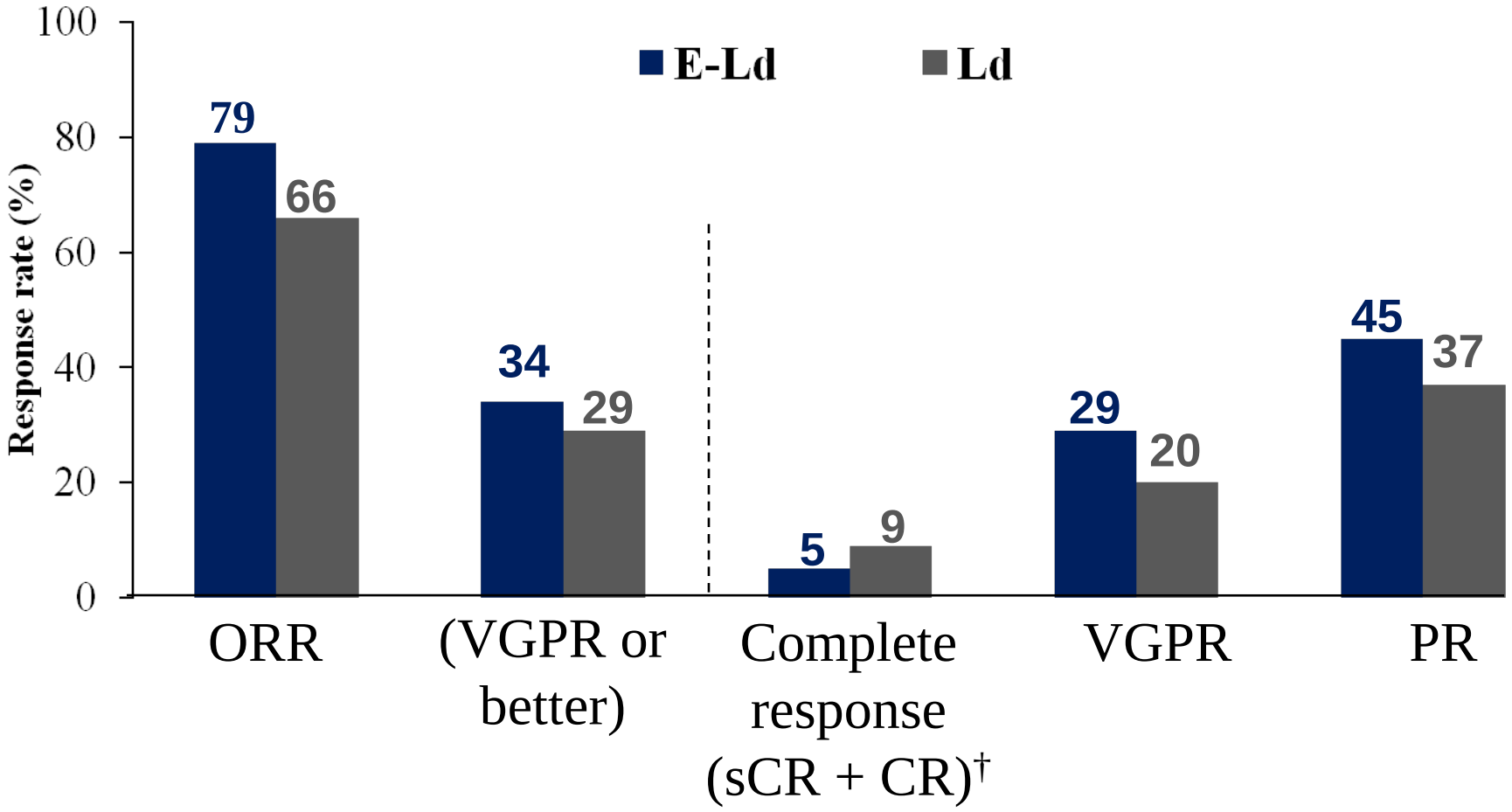
- **Overall 27% reduction in the risk of disease progression or death**
- **Relative improvement in PFS of 44% at 3 years**

PFS: 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)

ORR



*Defined as partial response or better

†Complete response rates in the E-Ld group may be underestimated due to interference from therapeutic antibody in immunofixation and serum protein electrophoresis assay

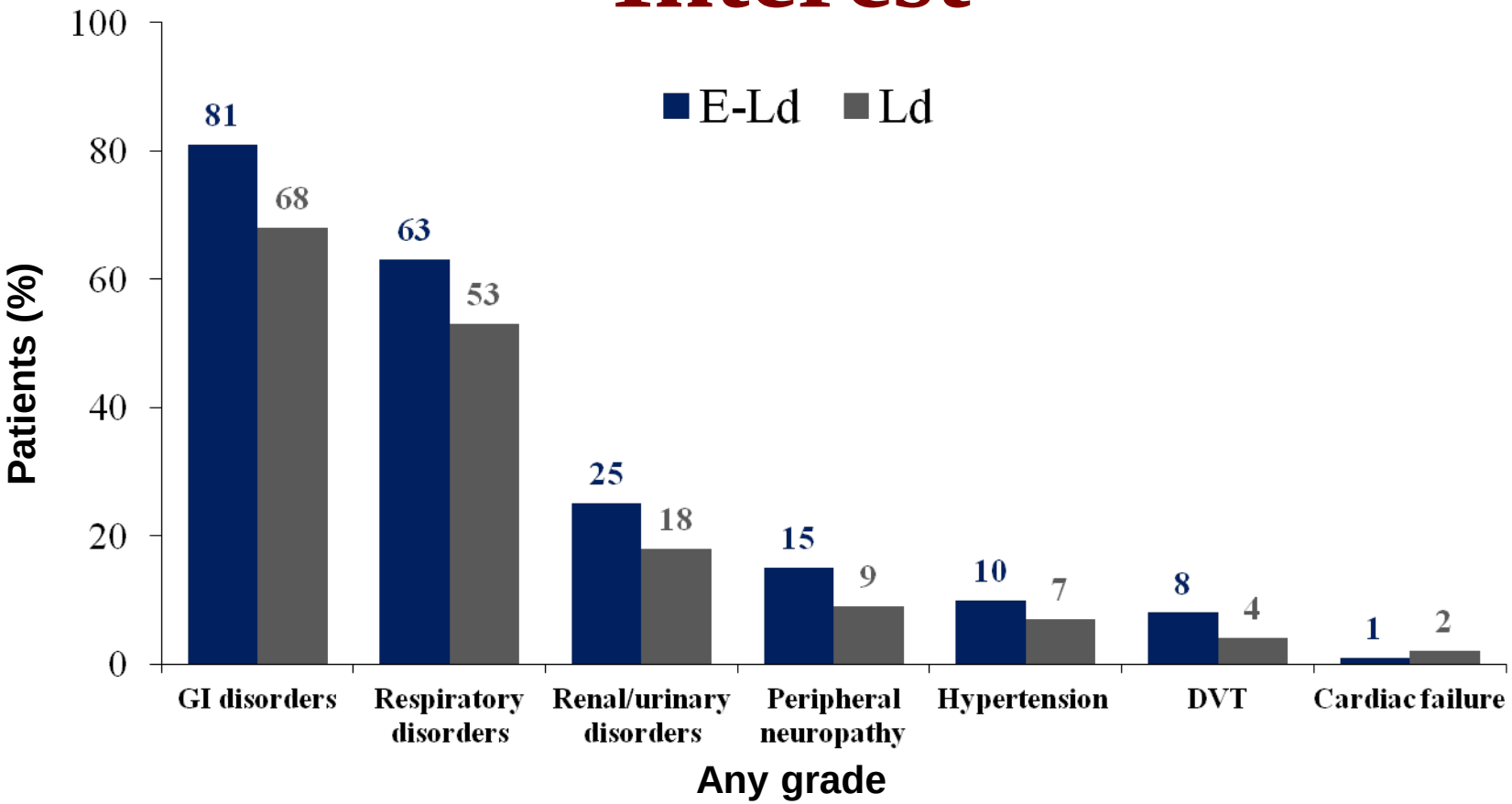
Adverse Events

Adverse events reported in ≥30% of patients, n (%)	E-Ld (n=318)		Ld (n=317)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
All AEs regardless of relationship	**316 (99)**	**248 (78)**	**314 (99)**	**212 (67)**
Non-Hematologic Adverse Events				
Fatigue	154 (48)	29 (9)	128 (40)	26 (8)
Diarrhea	152 (48)	17 (5)	118 (37)	15 (5)
Pyrexia	122 (38)	9 (3)	79 (25)	9 (3)
Constipation	114 (36)	4 (1)	88 (28)	1 (<1)
Cough	105 (33)	1 (<1)	60 (19)	0
Muscle spasms	96 (30)	2 (<1)	84 (27)	3 (<1)
Hematologic Adverse Events				
Anemia	130 (41)	49 (15)	118 (37)	52 (16)
Neutropenia	108 (34)	81 (26)	137 (43)	105 (33)

- **The exposure-adjusted* infection rate was 198 in the E-Ld arm and 192 in the Ld arm**
- **Exposure-adjusted* second primary malignancy rate was 5 and 3 in the E-Ld and Ld arms, respectively**

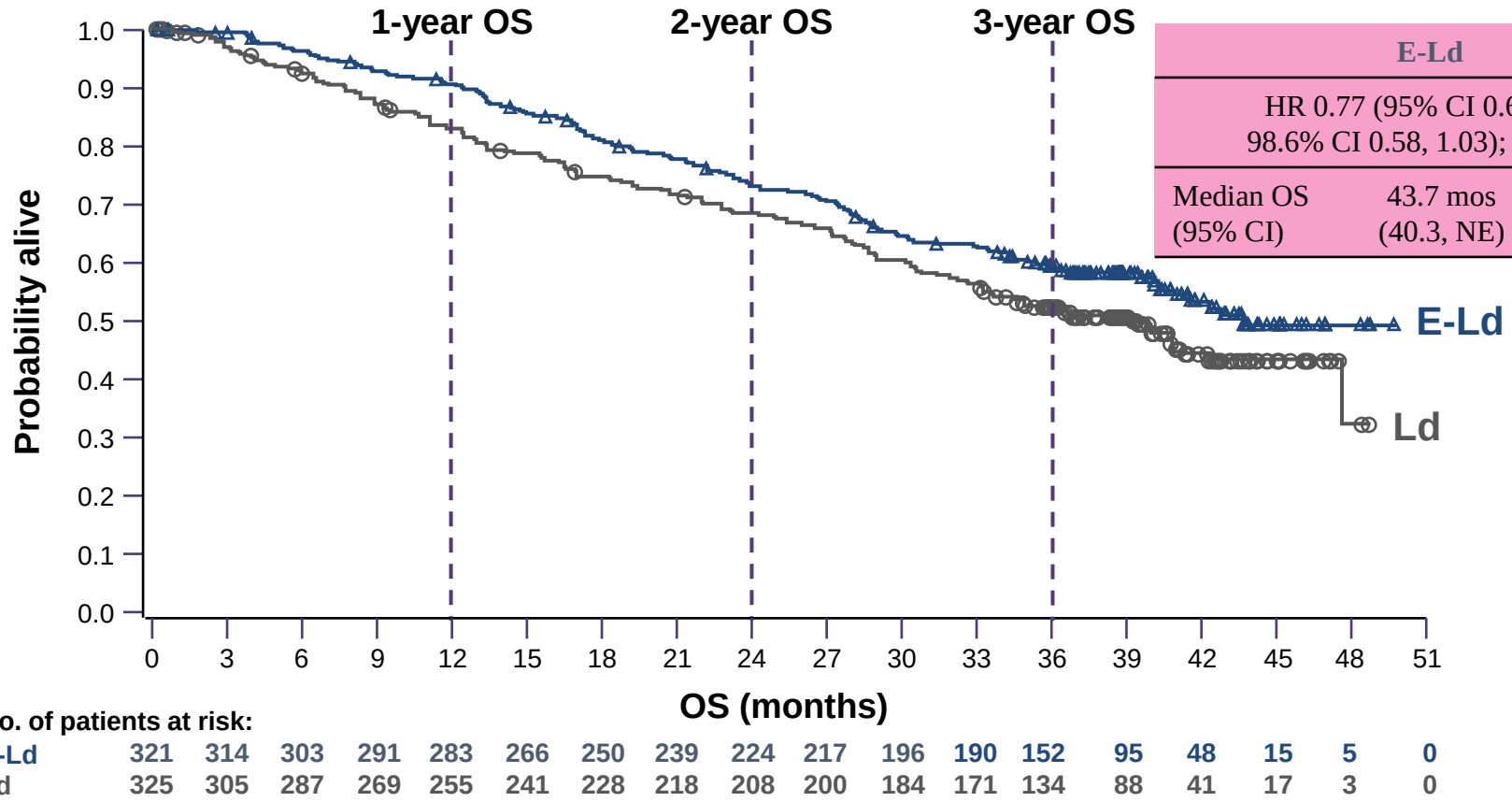
*Incidence rate/100 person-years of exposure

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

Interim Overall Survival



	E-Ld	Ld
HR 0.77 (95% CI 0.61, 0.97; 98.6% CI 0.58, 1.03); p=0.0257		
Median OS (95% CI)	43.7 mos (40.3, NE)	39.6 mos (33.3, NE)

No. of patients at risk:

E-Ld	321	314	303	291	283	266	250	239	224	217	196	190	152	95	48	15	5	0
Ld	325	305	287	269	255	241	228	218	208	200	184	171	134	88	41	17	3	0

Prespecified interim analysis for overall survival indicates a strong trend (p=0.0257) with early separation sustained over time for E-Ld vs Ld

CARFILZOMIB

- E’ un potente, irriversibile inibitore selettivo del proteosoma
- Infuso ev
- Rispetto a Bortezomib determina una minor neurotossicità

ASPIRE: Phase 3 Study Design

28-day cycles

Patient with relapsed multiple myeloma

Randomization 1:1

N = 792

Stratification:

- **β_2-microglobulin**
- **Prior bortezomib**
- **Prior lenalidomide**

KRd

Carfilzomib 27 mg/m^2 IV (10 minutes)
Days 1, 2, 8, 9, 15, 16 (20 mg/m^2 days 1, 2, cycle 1 only)
Lenalidomide 25 mg *days 1–21*
Dexamethasone 40 mg *days 1, 8, 15, 22*

After cycle 12, carfilzomib given on days 1, 2, 15, 16

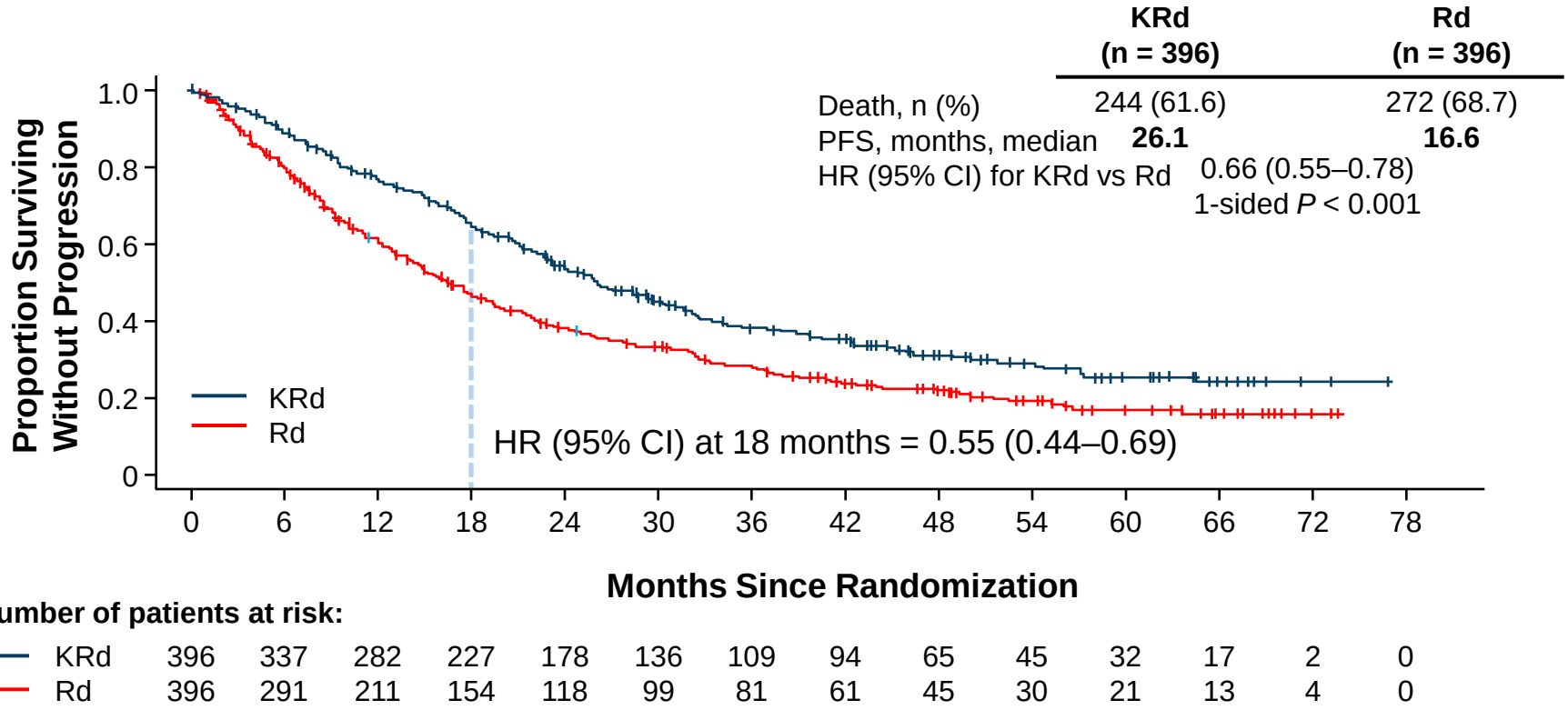
***After cycle 18, carfilzomib discontinued**[*]**

Rd[*]

Lenalidomide 25 mg *days 1–21*
Dexamethasone 40 mg *days 1, 8, 15, 22*

[*]All patients received Rd until disease progression, withdrawal of consent, or toxicity.
IV = intravenous; KRd = carfilzomib, lenalidomide, and dexamethasone; Rd = lenalidomide and dexamethasone.
Siegel DS, et al; [published online ahead of print January 17, 2018]. ***J Clin Oncol*****. doi: 10.1200/JCO.2017.76.5032.**

PFS ASPIRE

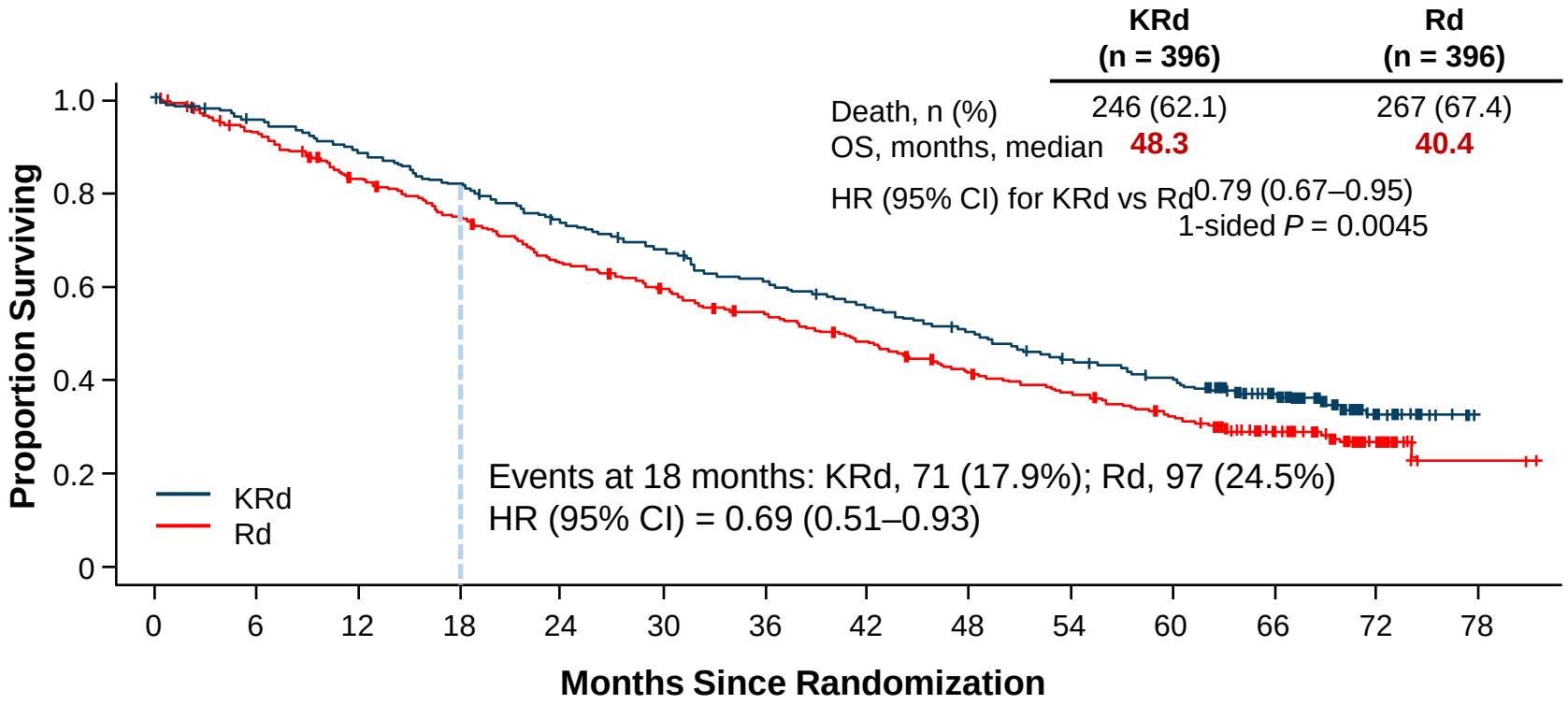


- Data cutoff date: April 28, 2017; median follow-up: 48.8 (KRd) and 48.0 (Rd) months
- Carfilzomib discontinued after 18 cycles

CI = confidence interval; HR = hazard ratio; KRd = carfilzomib, lenalidomide, and dexamethasone; PFS = progression-free survival; Rd = lenalidomide and dexamethasone.

Siegel DS, et al; [published online ahead of print January 17, 2018]. *J Clin Oncol.* doi: 10.1200/JCO.2017.76.5032.

ASPIRE OS



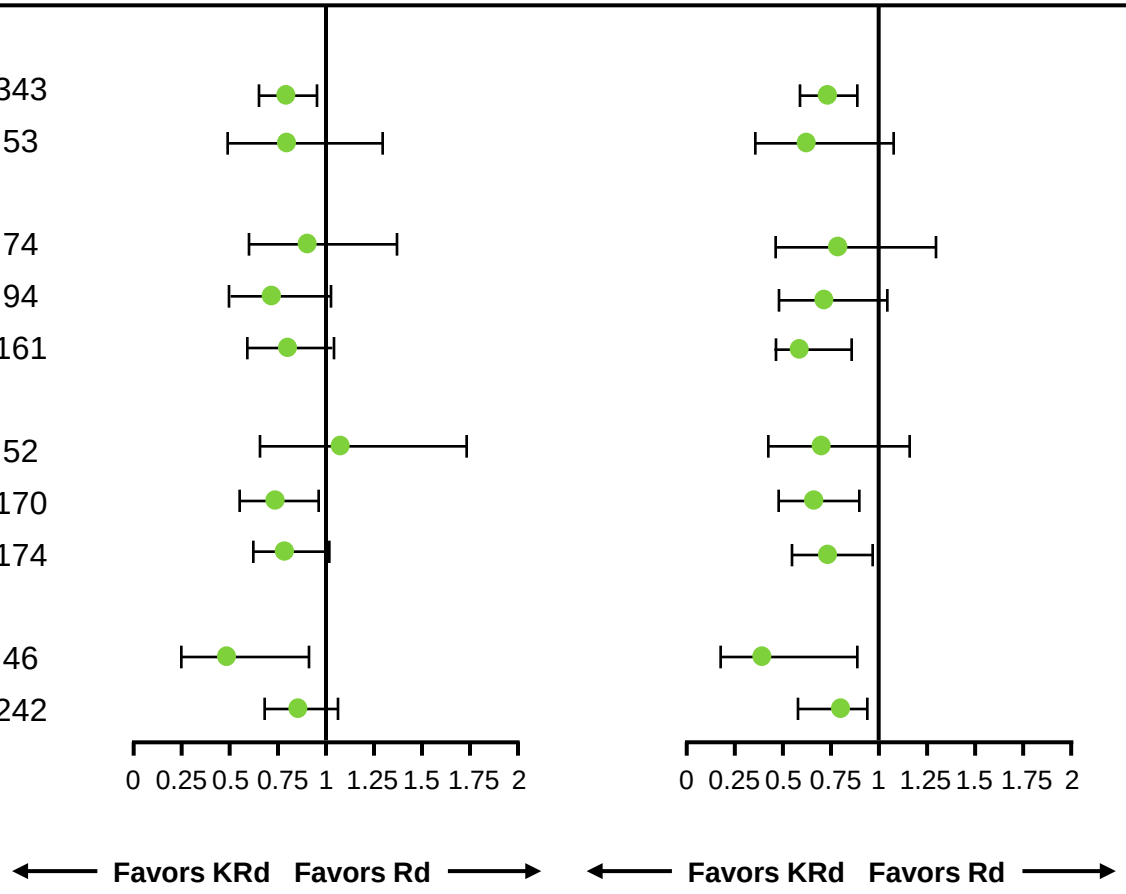
Number of patients at risk:

KRd	396	369	343	316	282	259	232	211	190	166	149	88	22	0
Rd	396	356	313	281	243	220	199	176	149	133	113	69	20	3

Siegel DS, et al; [published online ahead of print January 17, 2018]. *J Clin Oncol*. doi: 10.1200/JCO.2017.76.5032.
Stewart AK, et al. Slides presented at: Annual Meeting of the American Society of Hematology; December 9-12, 2017; Atlanta, GA.

Subgroup Analyses: OS and PFS

Subgroup	KRd Number of Patients	Rd Number of Patients
Age, years		
18–74	353	343
≥ 75	43	53
Stage at initial diagnosis		
I	64	74
II	99	94
III	185	161
Risk group by FISH		
High*	48	52
Standard	147	170
Unknown	201	174
R-ISS stage		
I	42	46
II or III	231	242



1. Siegel DS, et al; [published online ahead of print January 17, 2018]. *J Clin Oncol*. doi: 10.1200/JCO.2017.76.5032.
2. Stewart AK, et al. Slides presented at: Annual Meeting of the American Society of Hematology; December 9-12, 2017; Atlanta, GA.

ORR (KRD vs Rd)

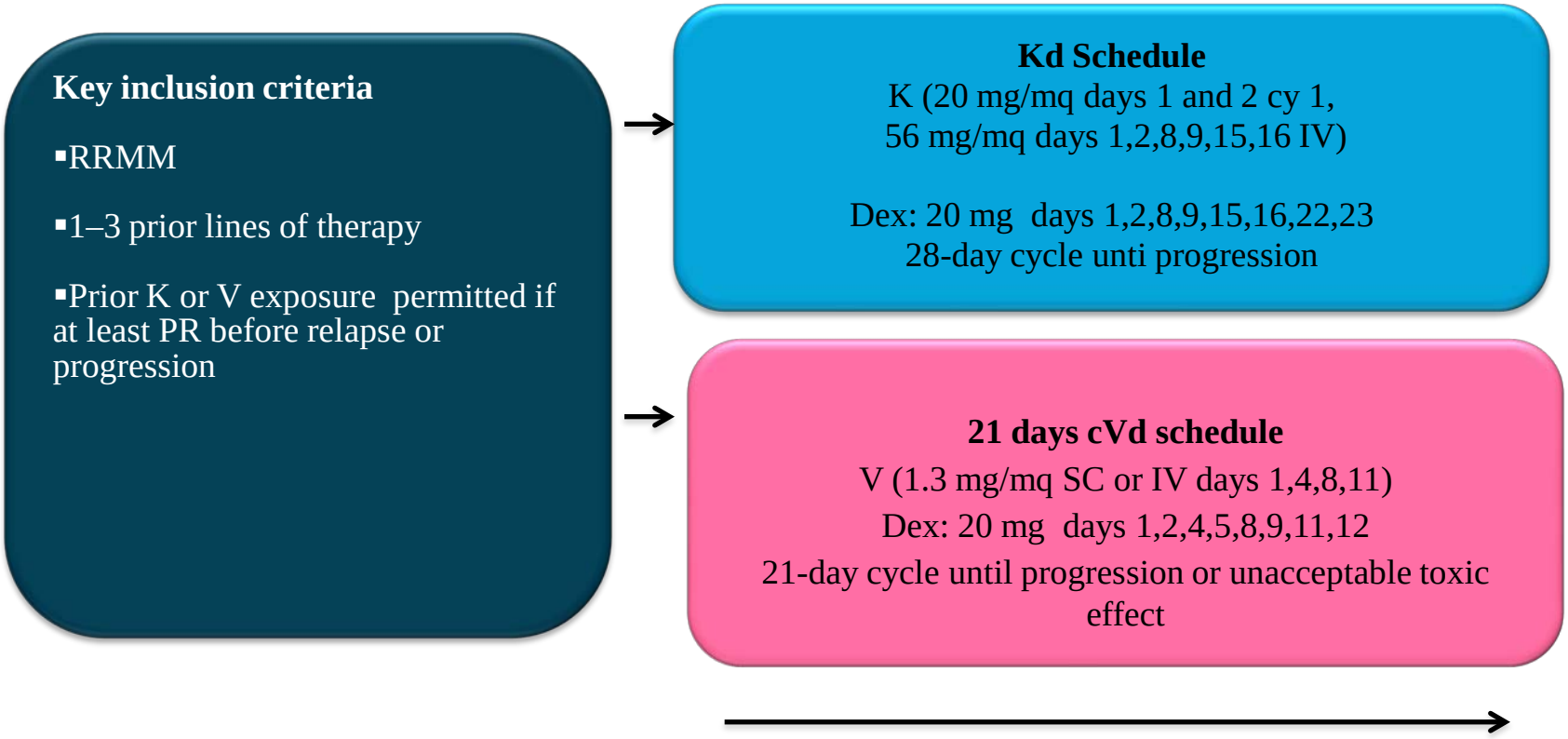
ORR :	**87%**	**vs**	**66%**
> = VGPR	**69%**	**vs**	**40%**
CR	**31%**	**vs**	**9%**
sCR	**14%**	**vs**	**4%**

Adverse Events of Interest

AE (SMQN), %	KRd (n = 392)		Rd (n = 389)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Acute renal failure	9.2	3.8	7.7	3.3
Cardiac failure	7.1	**4.3**	4.1	2.1
Ischemic heart disease	6.9	**3.8**	4.6	2.3
Hypertension	17.1	**6.4**	8.7	2.3
Hematopoietic thrombocytopenia*	32.7	**20.2**	26.2	14.9
Peripheral neuropathy	18.9	2.8	17.2	3.1

1. Siegel DS, et al; [published online ahead of print January 17, 2018]. *J Clin Oncol*. doi: 10.1200/JCO.2017.76.5032.
2. Medical Dictionary for Regulatory Activities (MedDRA), version 14.0. MedDRA®. MedDRA® trademark is owned by IFPMA on behalf of ICH.

ENDEAVOR: Kd vs Vd in R/R MM (phase 3)

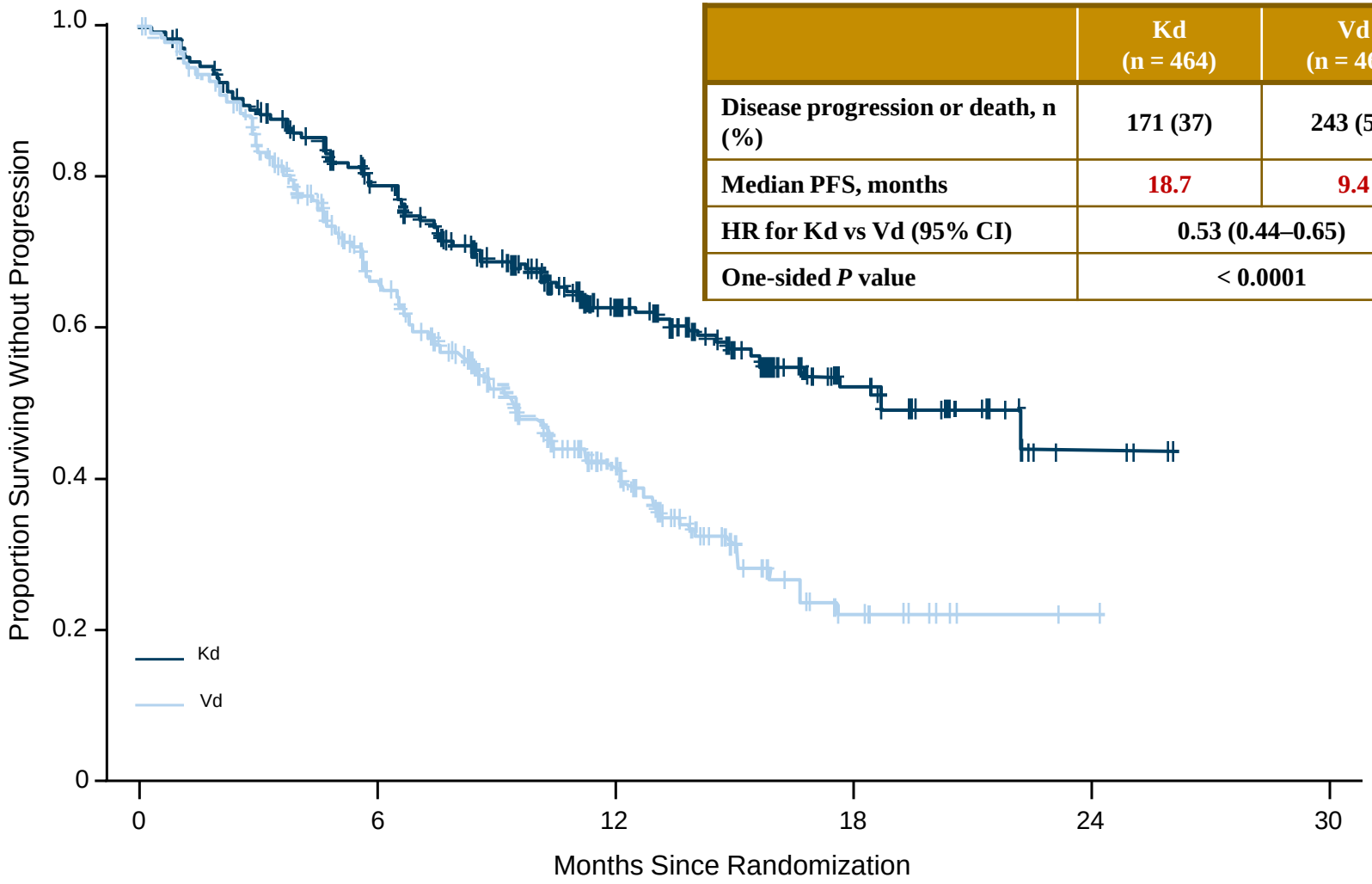


- Open-label, international, randomized, multicenter, **phase 3 trial**
- **929 pts**

Lonial S et al, NEJM 2015

ENDEAVOR PFS

	Kd (n = 464)	Vd (n = 465)
Disease progression or death, n (%)	171 (37)	243 (52)
Median PFS, months	18.7	9.4
HR for Kd vs Vd (95% CI)	0.53 (0.44–0.65)	
One-sided *P* value	< 0.0001	



Median follow-up: 11.9 months (carfilzomib), 11.1 months (bortezomib)

CI = confidence interval; HR = hazard ratio; Kd = carfilzomib and dexamethasone; PFS = progression-free survival; Vd = bortezomib and dexamethasone

Dimopoulos et al., *Lancet Oncol*. 2016;17(1):27-38.

ENDEAVOR

AE

	Kd (n = 463)	Vd (n = 456)
Median duration of treatment	48.0	27.0
Relative dose intensity of PI, %	92.0	85.4
Any grade AE, n (%)	456 (98.5)	451 (98.9)
Grade ≥3 AE, n (%)	365 (78.8)	316 (69.3)
AE leading to discontinuation of all study drugs, n (%)	73 (15.8)	68 (14.9)
AE leading to death, n (%)	29 (6.3)	21 (4.6)
Grade ≥3 AE, reported in ≥5% of patients in any subgroup, n (%)		
Anemia	72 (15.6)	45 (9.9)
Thrombocytopenia	40 (8.6)	42 (9.2)
Pneumonia	39 (8.4)	36 (7.9)
Lymphocyte count decreased	29 (6.3)	8 (1.8)
Dyspnea	29 (6.3)	10 (2.2)
Fatigue	27 (5.8)	34 (7.5)
Platelet count decreased	17 (3.7)	24 (5.3)
Diarrhea	15 (3.2)	38 (8.3)
Grade ≥3 AE of interest, n (%)		
Hypertension	64 (13.8)	15 (3.3)
Cardiac Failure	24 (5.2)	9 (2.0)
Peripheral neuropathy	11 (2.4)	39 (8.6)

ENDEAVOR: Conclusions

- In this randomized head-to-head trial, Kd provided a statistically significant and clinically meaningful benefit compared to Vd
  - PFS (18.7 months Kd vs 9.4 months Vd; $P < 0.0001$)*
  - ORR (77% vs 63%; $P < 0.0001$)*
  - Increased CR rate (13% Kd vs 6% Vd; $P = 0.0010$)*
- Kd provided 7.6 months median OS benefit (47.6 months Kd vs 40.0 months Vd; HR 0.791, $P = 0.010$)
- Safety is consistent with previous findings
- **Patients in ENDEAVOR lived longer with carfilzomib than bortezomib**

*Dimopoulos MA, et al. *Lancet Oncol.* 2016;17:27-38

CR = complete response; HR = hazard ratio; Kd = carfilzomib and dexamethasone; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; Vd = bortezomib and dexamethasone

Dimopoulos MA, et al. *Lancet Oncol.* Published Online August 23, 2017 as http://dx.doi.org/10.1016/S1470-2045(17)30578-8.

Monoclonal antibodies targeting CD38

- **Fully human**:

DARATUMUMAB

MOR202

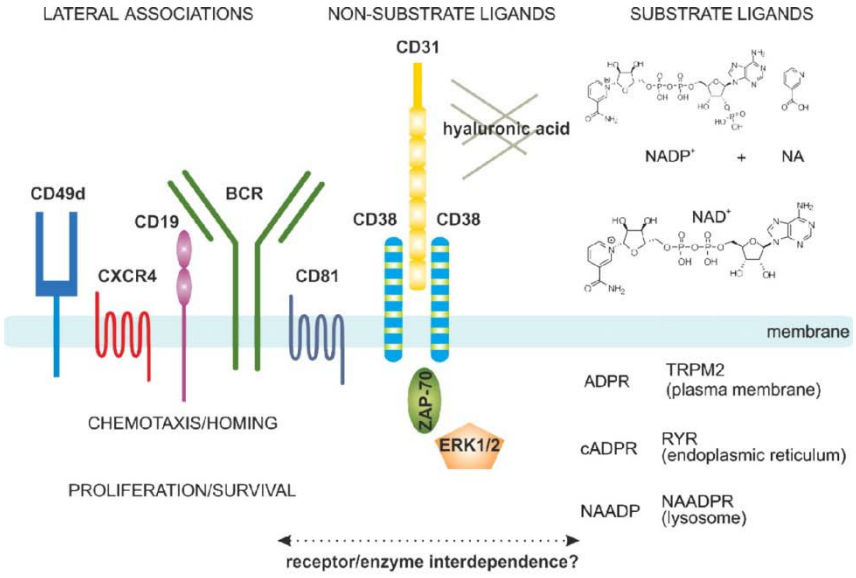
- **Chimeric:**

ISATUXIMAB

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

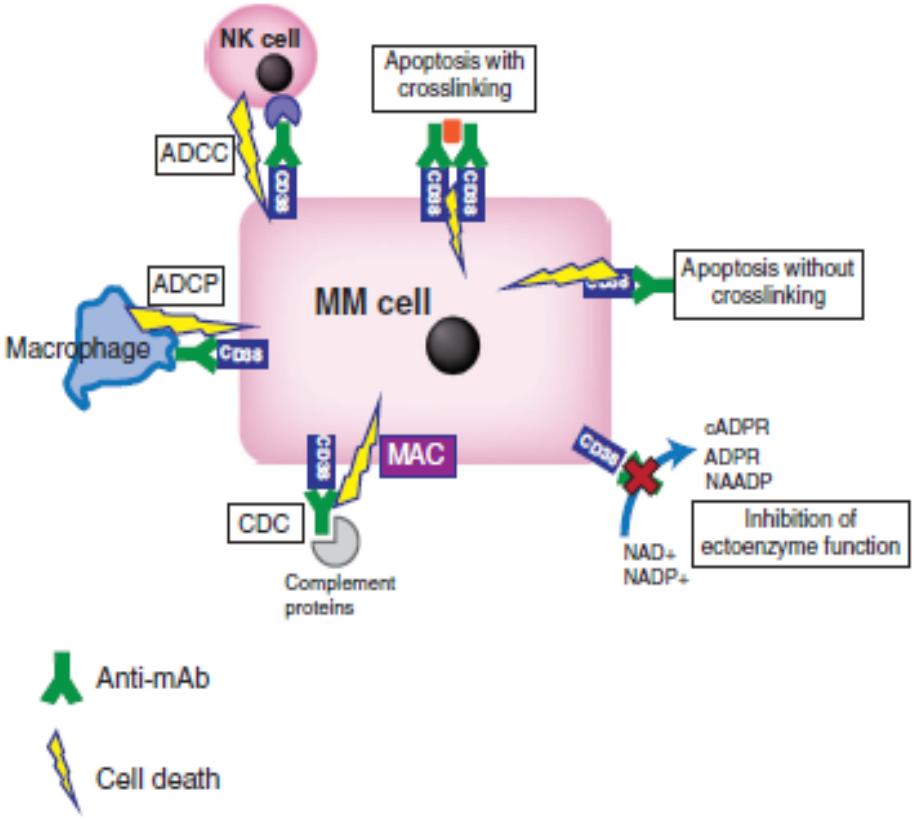
- CD38 has several intracellular functions
  1. Regulates **signaling, homing and adhesion** in close contact with BCR complex and CXCR4
  2. Regulates **activation and proliferation of human T lymphocytes**
  3. As an ectoenzyme, CD38 interacts with NAD+ and NADP+, which are converted to cADPR, ADPR,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

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



DARATUMUMAB

- **Fully human mAb**



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

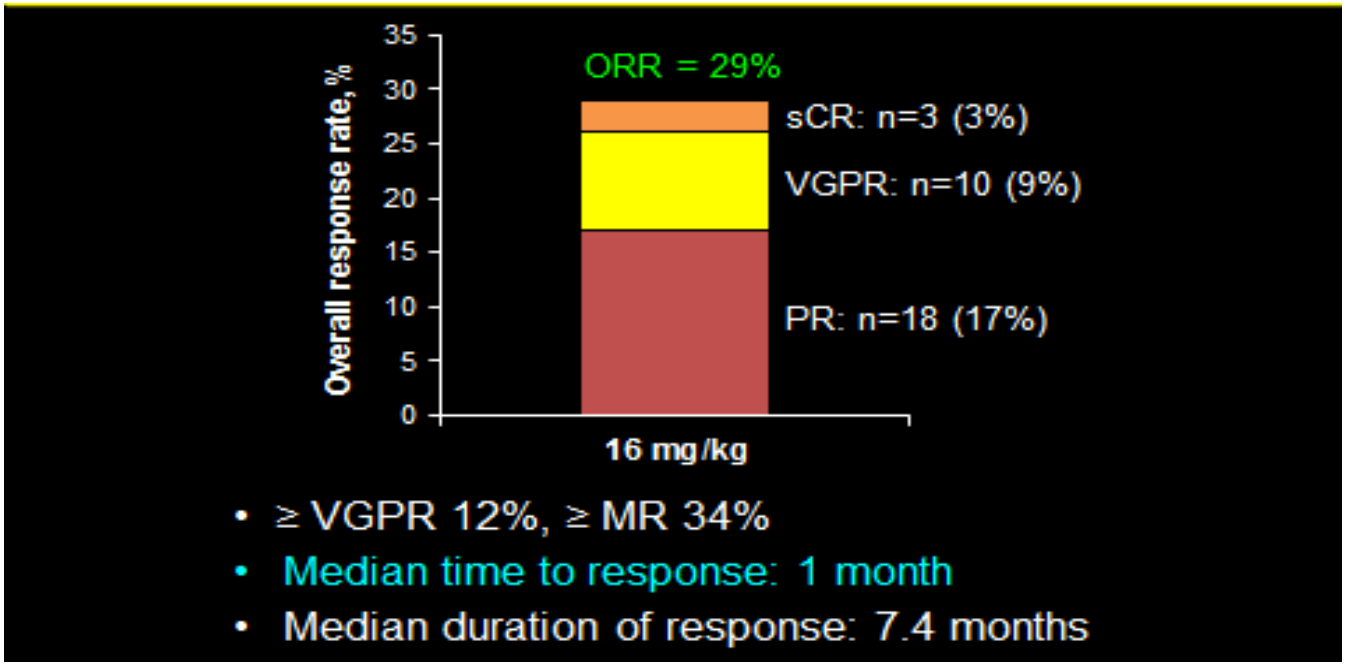
DARATUMUMAB SINGLE AGENT
Phase II SIRIUS shows Activity in Heavily Pretreated

Mediana: 5 linee precedenti

95% double refractory

48% Carfilz

63% POMA



- Median PFS: 3.7 mos (95% CI: 2.8-4.6); 1-yr OS: 65% (95% CI: 51.2-75.%)
- Most common grade 3/4 AEs: thrombocytopenia (25%), anemia (24%), neutropenia (14%); infusion-related reactions occurred in 43% (most grade 1/2)

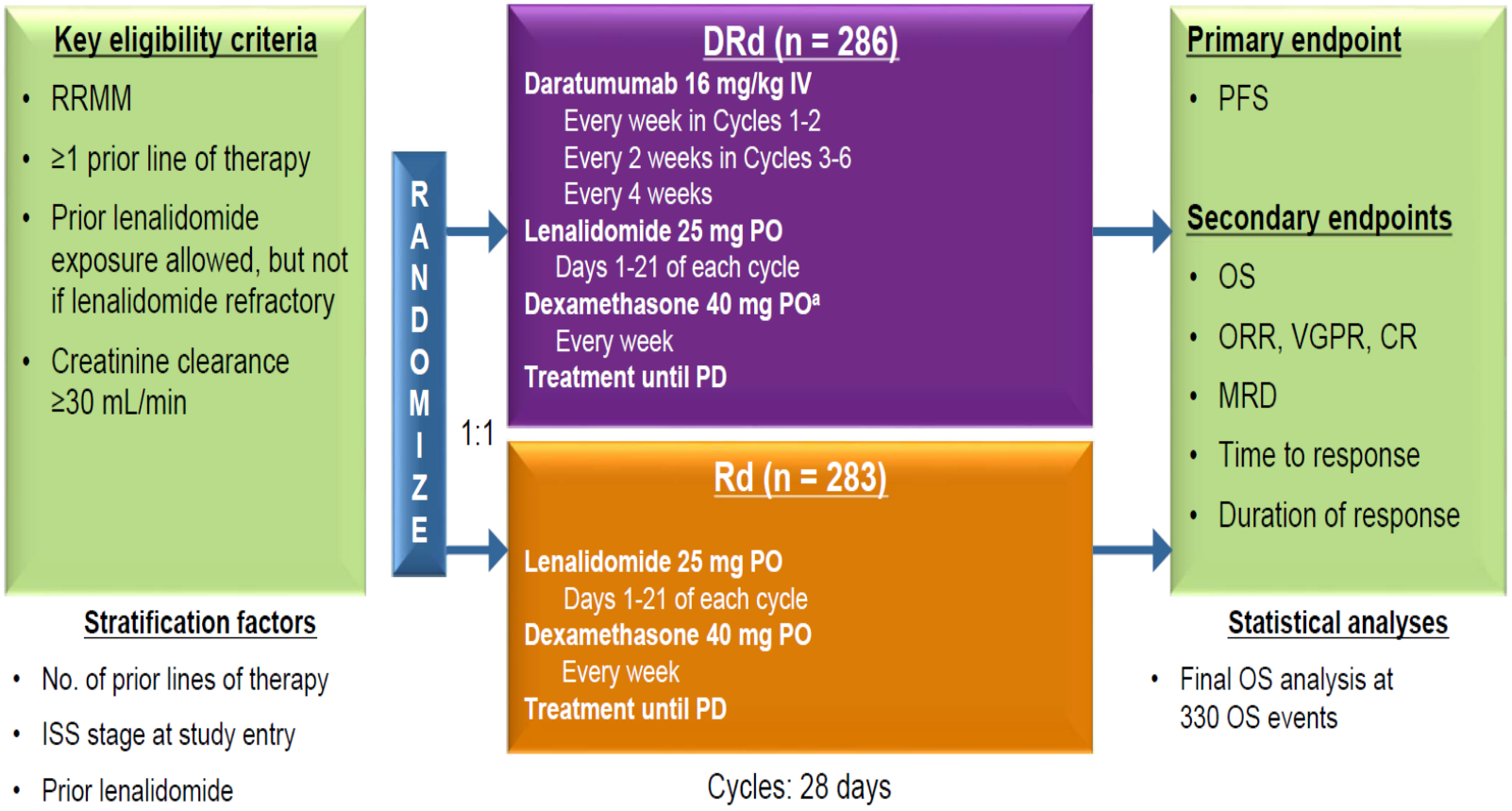
Approved by FDA for use in MM pts who had received ≥ 3 prior lines of therapy or were refractory to a PI and an IMiD (Nov 2015)

Lonial S, et al. ASCO 2015. Abstract LBA8512
Lonial S et al Lancet 2016

DARA-Rd

POLLUX Study Design

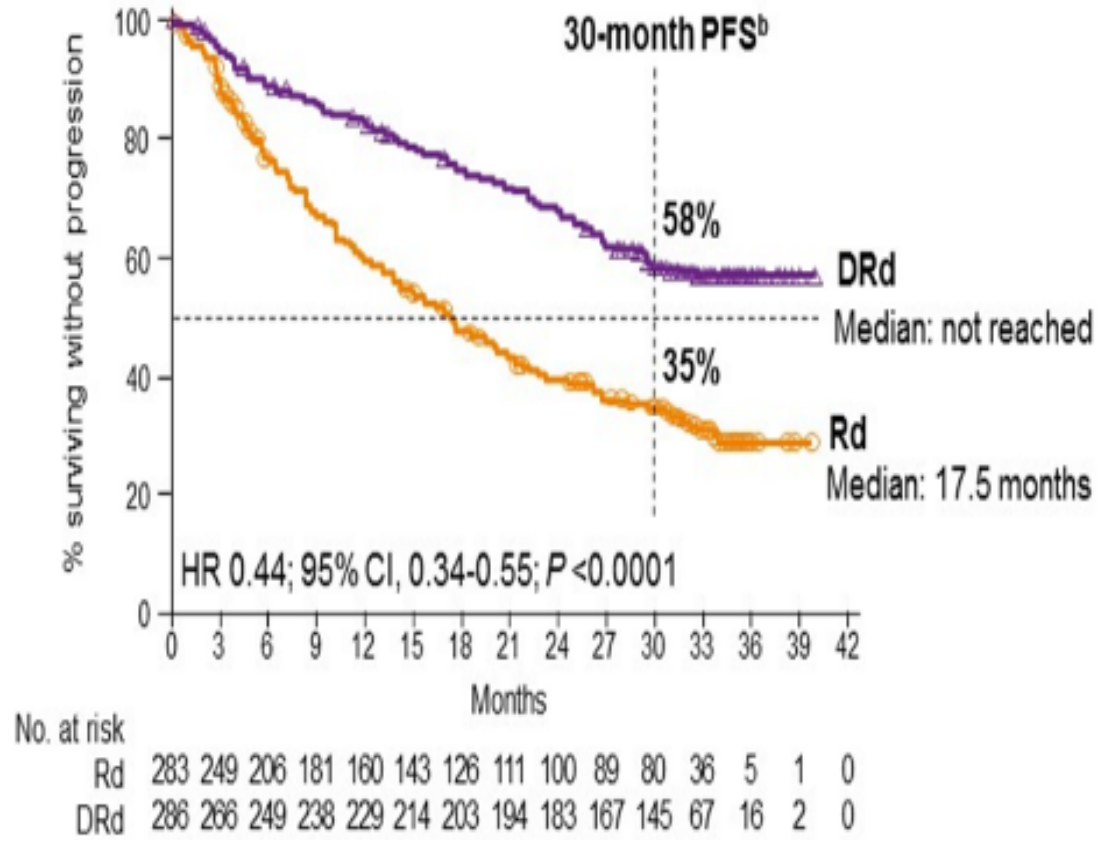
Open-label, multicenter, randomized (1:1), active-controlled, phase 3 study



Moreau et al. Poster 1883 ASH 2017

DARA-Rd
PFS

Median follow-up: 32.9 months



mPFS: NR vs 17,5 m

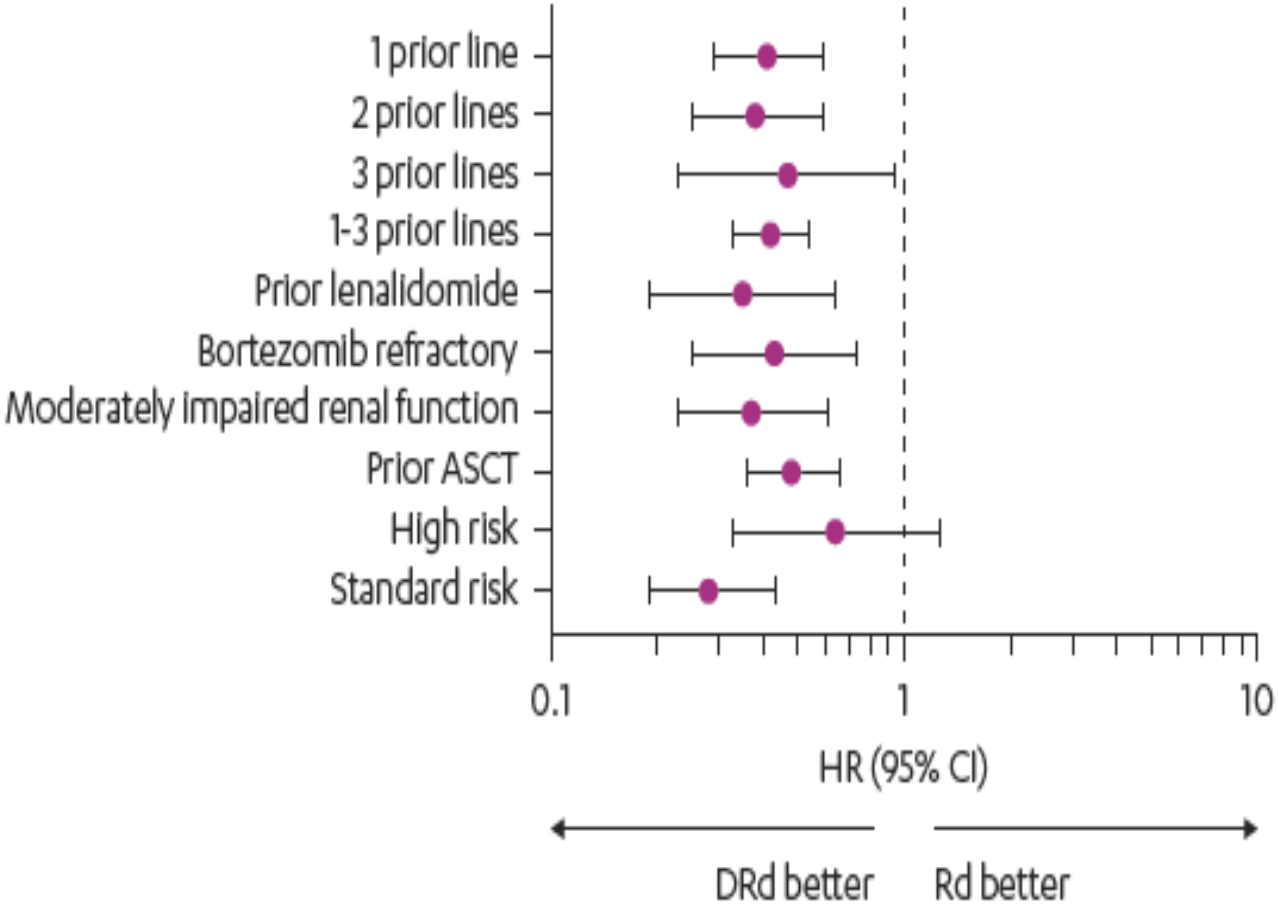
PFS DRd @30m: 58%

HR: 0.44;

P<0,0001→riduzione del rischio di progressione o morte del 56% nel gruppo daratumumab rispetto al gruppo di controllo

Dimopoulos et al. ASH 2017 Oral communication, abstract 739

Forest plot summarizing the PFS subgroup analyses of DRd versus Rd

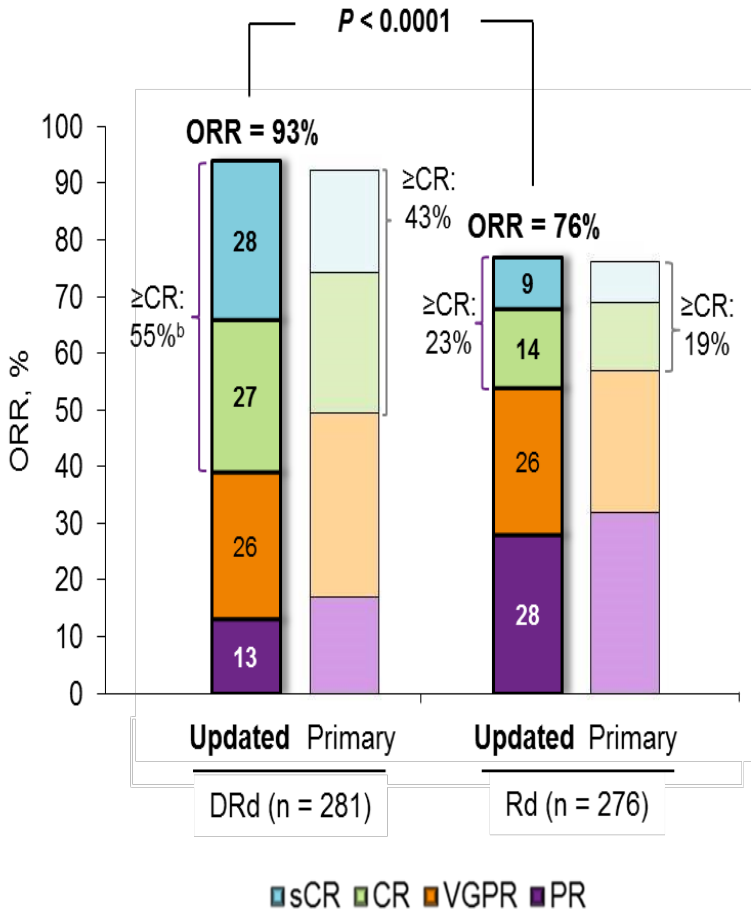


Moreau et al. Poster 1883 ASH 2017

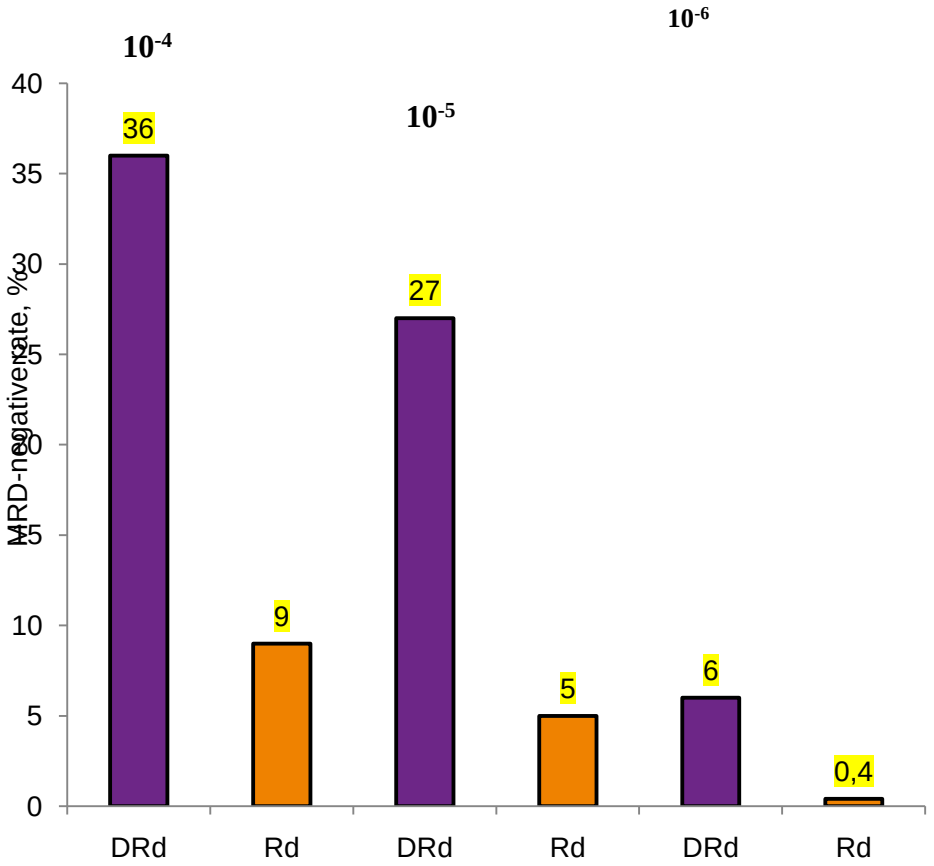
ORR and MRD

ORR: 93% vs 76%
≥CR: 55% vs 23%

Overall Response Rate[a]



MRD-negative Rate



[a]Response evaluable population. [b]*P* <0.0001 for DRd versus Rd.

Meletios A. Dimopoulos et al. – Poster 3145 ASH 2017

AE ematologici

	DRd n = 283		Rd n = 281	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Neutropenia	168 (59.4)	147 (51.9)	121 (43.1)	104 (37.0)
Anemia	88 (31.1)	35 (12.4)	98 (34.9)	55 (19.6)
Thrombocytopenia	76 (26.9)	36 (12.7)	77 (27.4)	38 (13.5)
Febrile neutropenia	16 (5.7)	16 (5.7)	7 (2.5)	7 (2.5)
Lymphopenia	17 (6.0)	15 (5.3)	15 (5.3)	10 (3.6)

- Gradi 3 or 4 di neutropenia sono stati più comuni con DRd
- **Nonostante ciò, I tassi di infezioni o infestazioni di grado 3/4 sono stati solo leggermente superiori per DRd vs Rd (28.3% vs 22.8%)**

Dimopoulos et al. N Engl J Med 2016;375:1319-31.

AE non ematologici

	DRd n = 283		Rd n = 281	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Diarrhea	121 (42.8)	15 (5.3)	69 (24.6)	9 (3.2)
Fatigue	100 (35.3)	18 (6.4)	78 (27.8)	7 (2.5)
Upper respiratory tract infection	90 (31.8)	3 (1.1)	58 (20.6)	3 (1.1)
Constipation	83 (29.3)	3 (1.1)	71 (25.3)	2 (0.7)
Cough	82 (29.0)	0	35 (12.5)	0
Muscle spasms	73 (25.8)	2 (0.7)	52 (18.5)	5 (1.8)
Pneumonia	40 (14.1)	22 (7.8)	37 (13.2)	23 (8.2)

- La Diarrea è stato l'AE non ematologico più comune nel gruppo DRd

Dimopoulos et al. N Engl J Med 2016;375:1319-31.

SAFETY

- **Tassi di Discontinuazione per AE simili (6.7% vs 7.8%)**
- AE fatali: 3.9% vs 5.3%
- DVT : 1,8% daratumumab *vs* 3,9% RD
- SAE: 48,8% daratumumab vs 42,0% RD.
- SPMs: 2.8% vs 3.6%
- **Nessun caso di emolisi osservato**

Dimopoulos et al. N Engl J Med 2016;375:1319-31.

	DRd n = 283	
	Any grade	Grade 3/4
Total number of patients with IRRs	135 (47.7)	15 (5.3)
Cough	24 (8.5)	0
Dyspnea	24 (8.5)	2 (0.7)
Vomiting	16 (5.7)	1 (0.4)
Nausea	14 (4.9)	0
Bronchospasm	13 (4.6)	1 (0.4)
Chills	13 (4.6)	1 (0.4)
Pruritus	8 (2.8)	1 (0.4)
Throat irritation	8 (2.8)	0
Headache	7 (2.5)	0
Nasal congestion	7 (2.5)	0
Wheezing	6 (2.1)	2 (0.7)
Laryngeal edema	6 (2.1)	1 (0.4)
Rhinorrhea	6 (2.1)	0
Pyrexia	6 (2.1)	0

- IRR di qualsiasi grado 47,7% dei pazienti
- 92% delle IRRs si è manifestato alla prima infusione
- **5,3% di grado 3**
- No grado 4 o 5
- 1 paziente ha discontinuato per una IRR di Grado 3 (ha continuato a ricevere Rd)

Dimopoulos et al. N Engl J Med 2016;375:1319-31.Supplement

CASTOR: Study Design

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

Key eligibility criteria

- RRMM
- ≥1 prior line of therapy
- Prior bortezomib exposure, bu t not refractory

RANDOMIZE 1:1

DVd (n = 251)

Daratumumab (16 mg/kg IV)
Every week - cycles 1-3
Every 3 weeks - cycles 4-8
Every 4 weeks - cycles 9+

Vel: 1.3 mg/m^2 SC, days 1,4,8,11 - cycles 1-8
dex: 20 mg PO-IV, days 1,2,4,5,8,9,11,12 - cycles 1-8

- Cycles 4-8: repeat every 21 days
- Cycles 9+: repeat every 28 days

Vd (n = 247)

Vel: 1.3 mg/m^2 SC, days 1,4,8,11 - cycles 1-8
dex: 20 mg PO-IV, days 1,2,4,5,8,9,11,12 - cycles 1-8

Primary Endpoint

- PFS

Secondary Endpoints

- TTP
- OS
- ORR, VGPR, CR
- MRD
- Time to response
- Duration of response

Statistical analyses

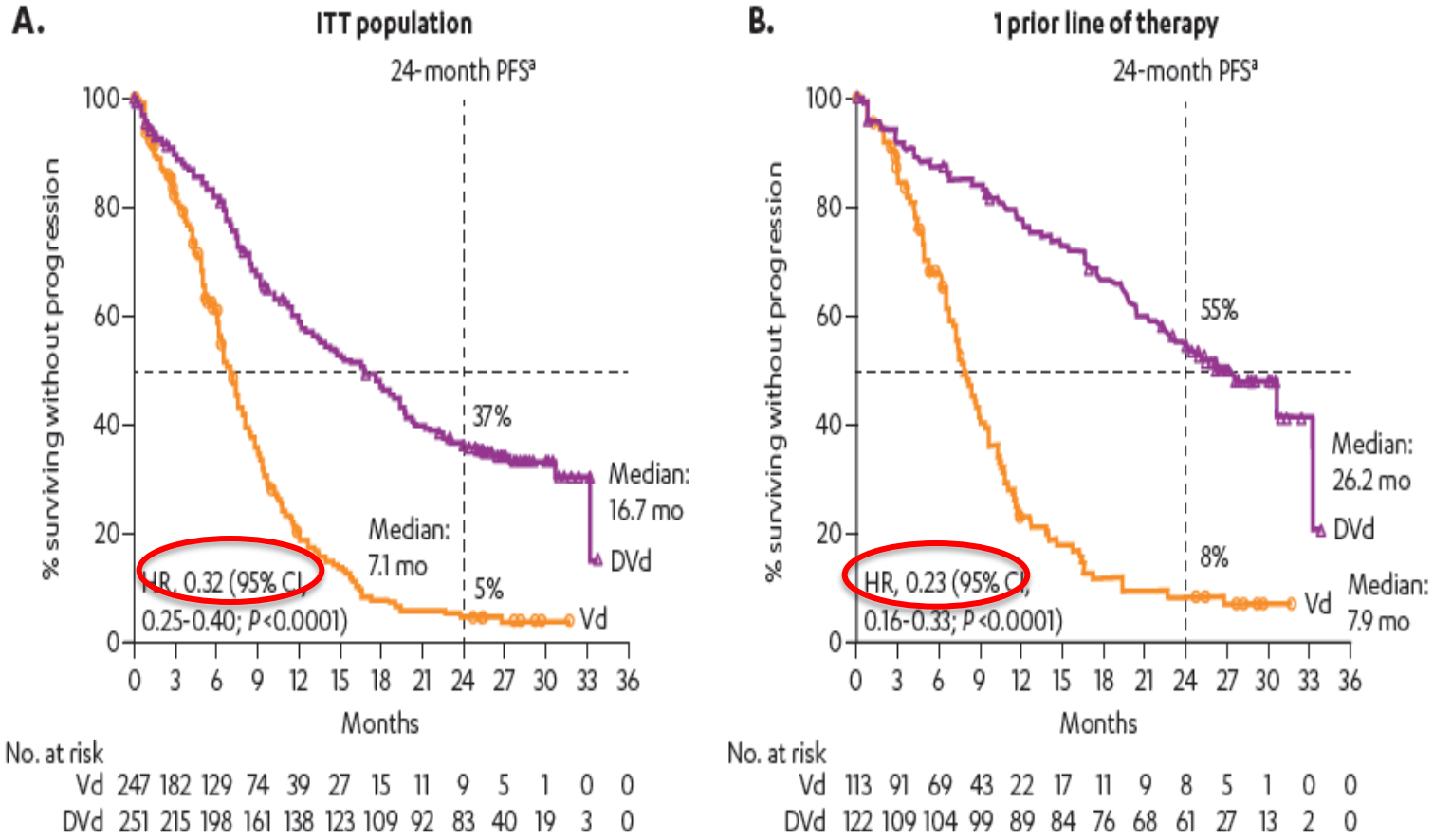
- 295 PFS events: 85% power for 4.3 month PFS improvement
- Interim analysis: ~177 PFS events

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

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

CASTOR-PFS

Median follow-up: 26.9 months



mPFS: 16,7 vs 7,1 mesi

mPFS: 26,2 vs 7,9 mesi

Spencer et al. Poster 3145 ASH 2017

ORR and MRD

	ITT Population		1 prior LOT		2 prior LOT		3 prior LOT		1-3 prior LOT	
	DVd	Vd	DVd	Vd	DVd	Vd	DVd	Vd	DVd	Rd
ORR[a]										
N	240	234	119	109	64	71	35	29	218	209
%	85	63	92	74	84	65	69	41	86	67
P value	<0.0001		0.0007		0.0563		0.0487		<0.0001	
≥VGPR, %	63	29	77	42	61	18	34	28	65	32
P value	<0.0001		<0.0001		<0.0001		0.6999		<0.0001	
≥CR, %	30	10	43	15	25	9	11	3	33	11
P value	<0.0001		<0.0001		0.0118		0.3009		<0.0001	
sCR, %	10	3	14	5	6	1	6	0	11	3
MRD-negative rate (10^{-5})[b]										
N	251	247	122	113	70	74	37	32	229	219
%	12	2	16	3	11	0	5	3	13	2
P value	<0.0001		0.0002		0.0005		0.64		<0.0001	

Spencer et al. Poster 3145 ASH 2017

AE

	All grades ≥25%		Grade 3 and 4 ≥5%	
TEAE	DVd	Vd	DVd	Vd
Hematologic (%)				
Thrombocytopenia	59.7	44.3	45.7	32.9
Anemia	28.4	31.6	15.2	16.0
Neutropenia	18.9	9.7	13.6	4.6
Lymphopenia	13.2	3.8	9.9	2.5
Nonhematologic (%)				
Pneumonia	15.6	13.1	10.3	10.1
Peripheral sensory neuropathy	49.8	38.0	4.5	6.8
Hypertension	9.9	3.4	6.6	0.8
Upper respiratory tract infection	32.9	18.1	2.5	0.4
Diarrhea	35.4	22.4	3.7	1.3
Cough	28.0	12.7	0	0

TEAE, treatment-emergent adverse event; DVd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone.

- **Discontinuazioni del trattamento dovute a TEAEs: 9.5% vs 9.3%**
- **SPM: 4.1% vs 1.3%**

Spencer et al. Poster 3145 ASH 2017

	RD MM009-MM010	EloRd Eloquent-2	KRd Aspire	DRd POLLUX	VD up to 8 cycle(EV)	Kd Endeavor	DVd CASTOR
Previous lines	≥2 (82%)	Median 2	Median 2	median1 >1 48%	1	Median 2	median2
% pts alto rischi citogenetico	-	32% del(17p) 9% t(4;14)	12.1%	Del17p 11.0% t(4;14) 4.4%	-	21%	15,5 % Del17p 7,7% t(4;14) 2,2% t(14;16)
%pts ≥75	-	21%	10.9%	10,1%	50% > 65 Y	17%	9,5%
Stato di refrattarietà	-	35% resistente al trattamento più recente, inclusi BTZ (22%) e TAL (10%)	NR to BTZ 15,2% LEN 7,3% ANY IMiDS 21,5% NR to BTZ and IMiDS REF 6,1%	28 % Last line 19,9 % ONLY PI 3,5 % ONLY IMiDS 2,4% BOTH PI & IMIDS	-	3% BTZ 24% LEN	30,3% LAST LINE 18% LEN as LAST LINE 30% IMIDS
Esposizione	36% THAL 7,6% BTZ	5% LEN 68% BTZ 48% THAL 69% MELPH	65.9% BTZ 19,9% LEN 58,8 ANY IMiDS 36,9% BTZ&IMiDS	84,3% BTZ 2,1% K 0,7% IXA 17,5% LEN 0,7% POM 42,7% THAL 15,4 % BTZ+LEN	41% PRIOR IMID 70% PRIOR DEX	54% BTZ <1% K 38%LEN 45 % THAL	67% PI 65% BTZ 71 % IMiDS 45% PI+IMiDS
ORR%	60	79	87	93	75	77	85
>CR%	16	4	32	55	10	13	30
Median PFS	11.1 m	19.4 m	26.1 m	NR 58% at 30 m	13.6 mTTP	17.6	16.7
Median OS	38.0 m	48.3 m	48.3 mo	NR	70% @2yrs	47.6	NR
MRD rates 10^{-5}	-	-	-	27%	-	-	12%

TERAPIA ALLA I RECIDIVA

FIT per Tx se PSF dopo Tx > 3 anni

Trapianto di salvataggio

NON REFRATTARI A LENALIDOMIDE

1° scelta:
DaraRd
(PFS @30m 65%)

2° scelta:
KRd
(PFS 26 m)

3° scelta:
EloRd (PSF 19m)
IxaRd
Rd (PFS 11 m)

REFRATTARI A LENALIDOMIDE

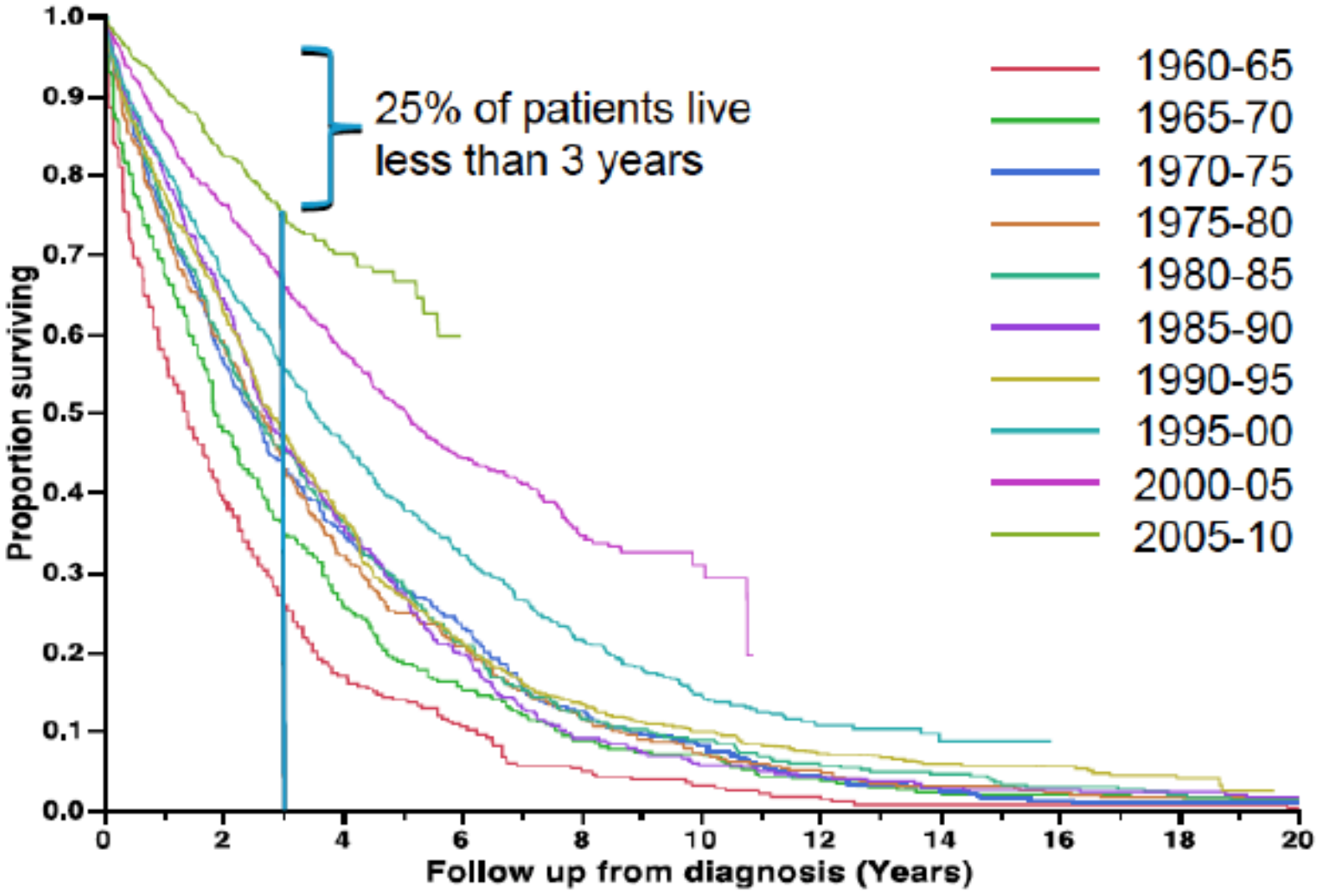
1° scelta:
DaraVd
(PFS 26 m)

2° scelta:
Kd
(PFS 22.2 m)

Moreau P- EMN 2018, Turin

Il mieloma è una malattia curabile?

Improving Survival in MM



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Dott.ssa Alessandra D'Addio
Dott.ssa Giulia Daghia
Dott.ssa Michela Rondoni
Dott. Francesco Saraceni
Dott.ssa Arbana Dizdari

A tutti i pazienti e familiari

A
infermieri, OSS, amministr
ativi , data managers

A Ravenna AIL