Highlights from IMW 2019

19-20 novembre 2019
Bologna
Royal Hotel Carlton

La terapia di seconda e terza linea del paziente non refrattario a lenalidomide

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Nessun conflitto d’interesse da dichiarare

Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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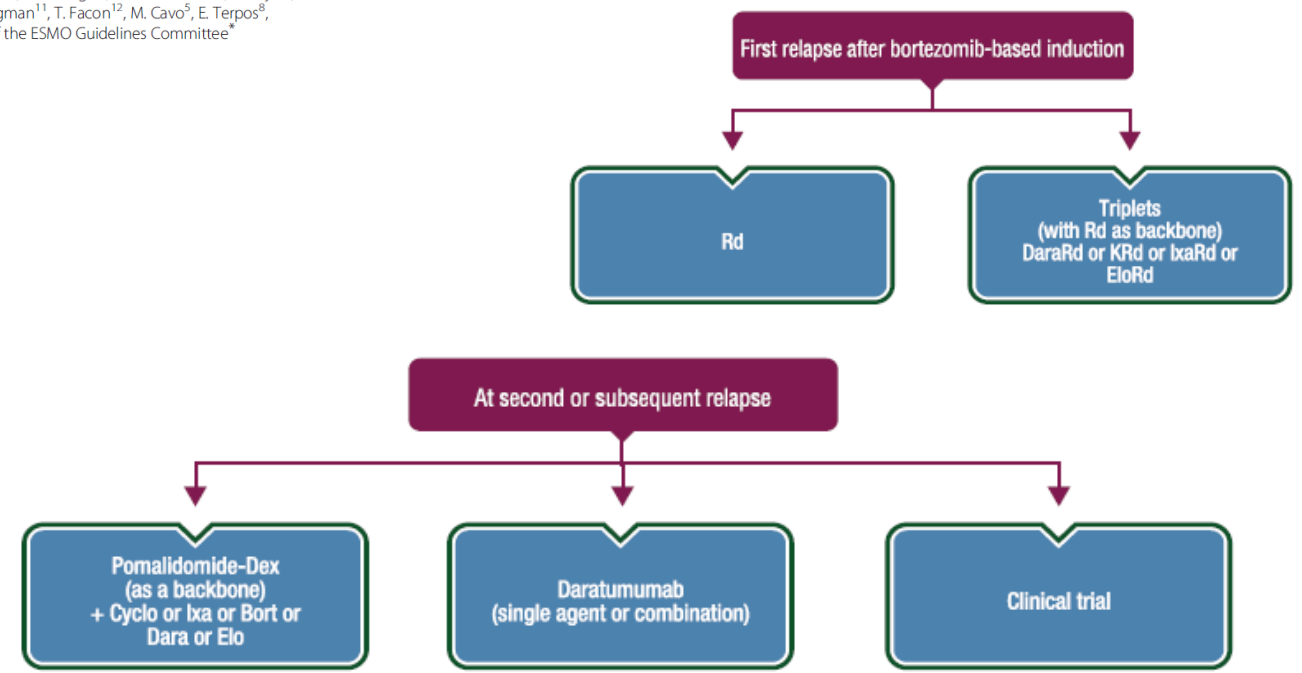


Choice based upon:

- Patient characteristics
- Disease characteristics
- Frontline therapy
  - response duration
  - progression on therapy
- Drug access
- Patient choice

PD While Not on Lenalidomide Maintenance

Triplets (with Rd as backbone)

Daratumumab + Rd

Carfilzomib + Rd

Ixazomib + Rd

Elotuzumab + Rd

POLLUX trial

Multicenter, randomized (1:1), open-label, active-controlled, phase 3 study

Key eligibility criteria

- RRMM
- ≥1 prior line of therapy
- Prior lenalidomide exposure, but not refractory
- Patients with creatinine clearance ≥30 mL/min

Stratification factors

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

RANDOMIZE

1:1

DRd (n = 286)

Daratumumab 16 mg/kg IV
- qw in Cycles 1-2, q2w in Cycles 3-6, then q4w until PD

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

d 40 mg PO
- 40 mg weekly until PD

Rd (n = 283)

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

d 40 mg PO
- 40 mg weekly until PD

Cycles: 28 days

Primary endpoint

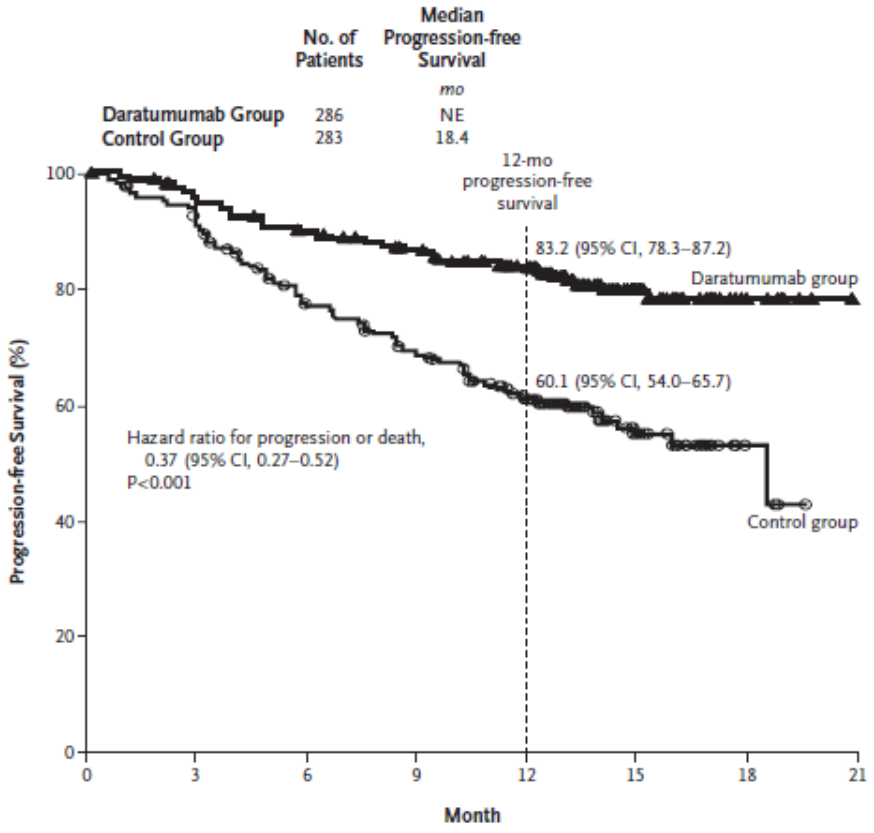
- PFS

Secondary endpoints

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

POLLUX trial

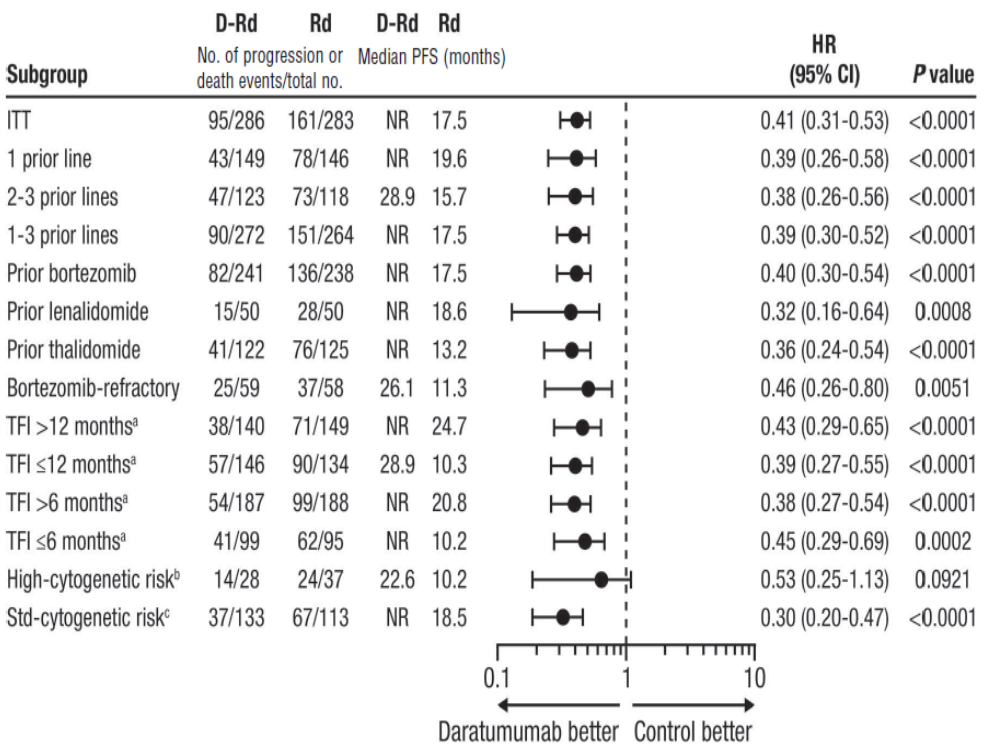
Characteristic	Daratumumab Group (N=286)	Control Group (N=283)
Age		
Median (range) — yr	65 (34–89)	65 (42–87)
Distribution — no. (%)		
<65 yr	133 (46.5)	140 (49.5)
65 to 74 yr	124 (43.4)	108 (38.2)
≥75 yr	29 (10.1)	35 (12.4)
Race — no. (%)†		
White	207 (72.4)	186 (65.7)
Black	5 (1.7)	11 (3.9)
Asian	54 (18.9)	46 (16.3)
Other or unreported	20 (7.0)	40 (14.1)
ECOG performance-status score — no. (%)‡		
0	139 (48.6)	150 (53.0)
1 or 2	147 (51.4)	133 (47.0)
ISS disease stage — no. (%)§		
I	137 (47.9)	140 (49.5)
II	93 (32.5)	86 (30.4)
III	56 (19.6)	57 (20.1)
Cytogenetic profile — no./total no. (%)¶		
Standard risk	193/228 (84.6)	176/211 (83.4)
High risk	35/228 (15.4)	35/211 (16.6)
Median time since diagnosis (range) — yr	3.5 (0.4–27.0)	4.0 (0.4–21.7)
Median no. of previous lines of therapy (range)	1 (1–11)	1 (1–8)
Previous therapy — no. (%)		
Autologous stem-cell transplant	180 (62.9)	180 (63.6)
Proteasome inhibitor	245 (85.7)	242 (85.5)
Immunomodulatory drug	158 (55.2)	156 (55.1)
Glucocorticoid	280 (97.9)	281 (99.3)
Alkylating agent	268 (93.7)	270 (95.4)
Proteasome inhibitor and immunomodulatory drug	125 (43.7)	125 (44.2)
Proteasome inhibitor, immunomodulatory drug, and alkylating agent	118 (41.3)	121 (42.8)
Bortezomib and lenalidomide	44 (15.4)	43 (15.2)
Refractory disease — no. (%)		
To last line of therapy	80 (28.0)	76 (26.9)
To proteasome inhibitor only	57 (19.9)	46 (16.3)
To immunomodulatory drug only	10 (3.5)	11 (3.9)
To proteasome inhibitor and immunomodulatory drug	7 (2.4)	14 (4.9)



NEJM 2016

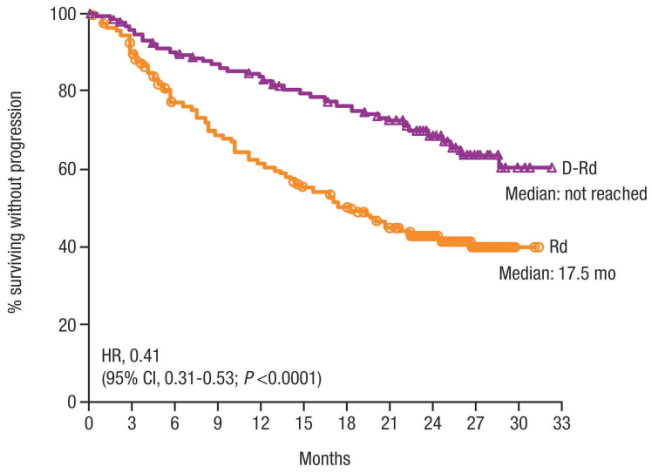
Update POLLUX trial

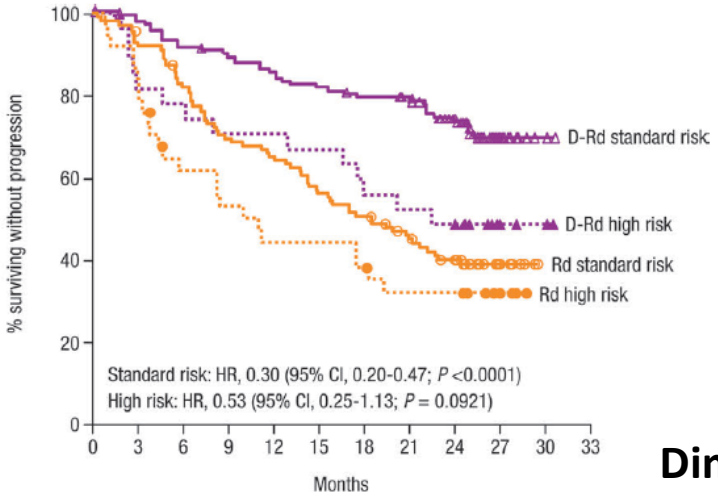
Subgroup	# of patients in group D-Rd	# of patients in group Rd	ORR, n (%)[a] D-Rd	ORR, n (%)[a] Rd	*P*[c]
ITT	281	276	261 (92.9)	211 (76.4)	<0.0001
Prior lines of therapy					
1	147	142	137 (93.2)	114 (80.3)	0.0003
2-3	120	115	114 (95.0)	85 (73.9)	<0.0001
1-3	267	257	251 (94.0)	199 (77.4)	<0.0001
Prior therapy					
Bortezomib	237	232	218 (92.0)	175 (75.4)	<0.0001
Lenalidomide	50	47	42 (84.0)	32 (64.0)	0.0233
Thalidomide	119	123	109 (91.6)	87 (70.7)	<0.0001
Refractory to bortezomib	57	56	50 (87.7)	38 (67.9)	0.0113
Treatment-free interval					
≤12 months	143	131	129 (90.2)	87 (66.4)	<0.0001
>12 months	138	145	132 (95.7)	124 (85.5)	0.0038
≤6 months	98	92	87 (88.8)	57 (62.0)	<0.0001
>6 months	183	184	174 (95.1)	154 (83.7)	0.0004
Cytogenetic risk[e]					
High[f]	27	36	23 (85.2)	24 (66.7)	0.0435
Standard	132	111	125 (94.7)	91 (82.0)	0.0004

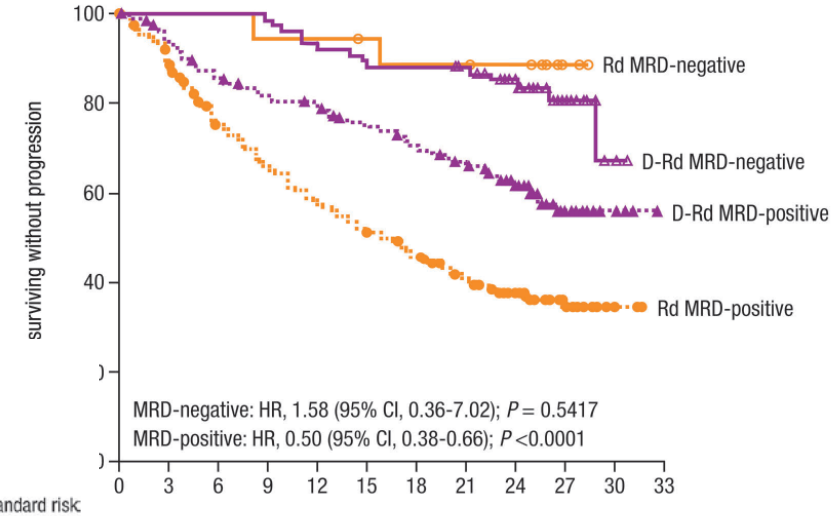


Dimopoulos et al Haematologica 2018

Update POLLUX trial

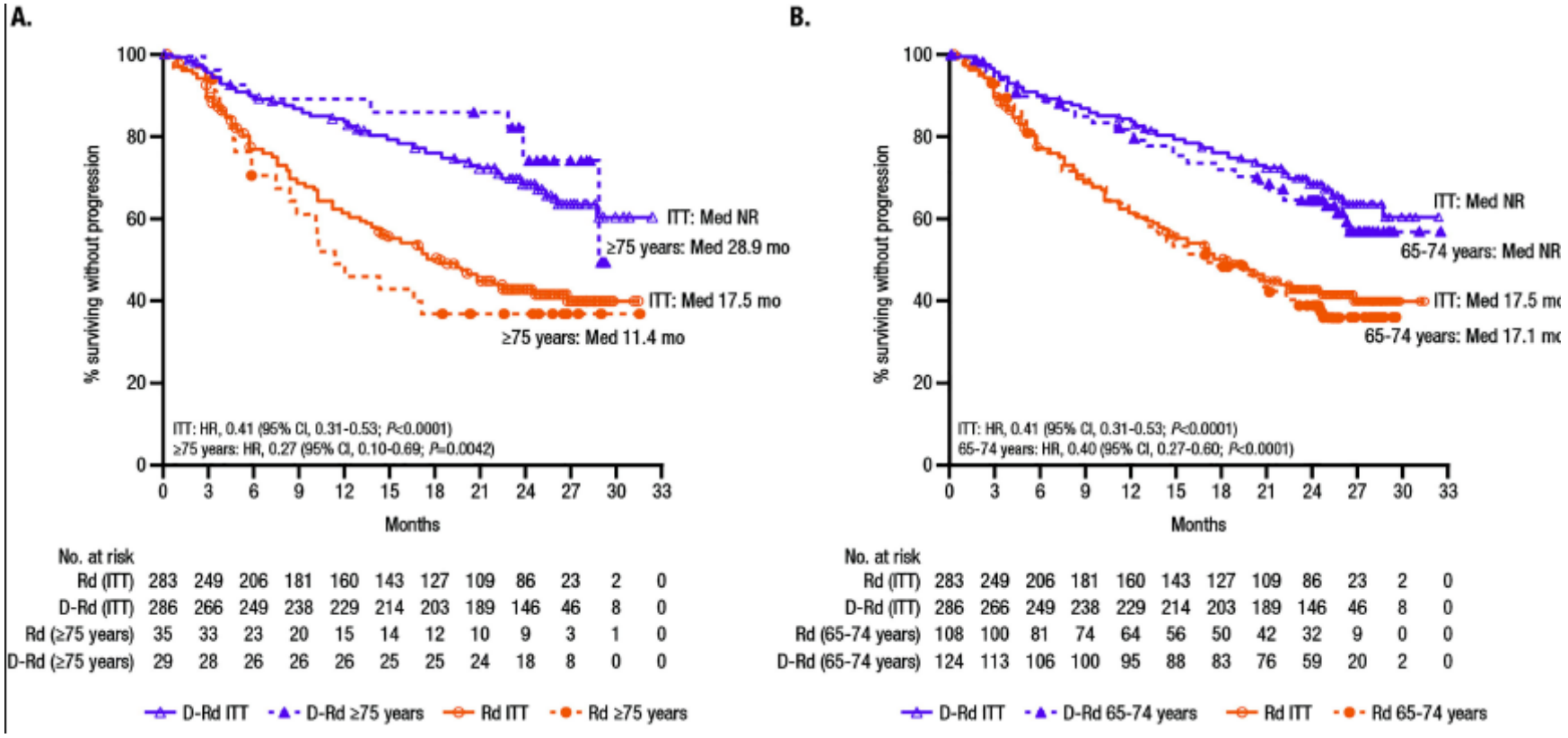






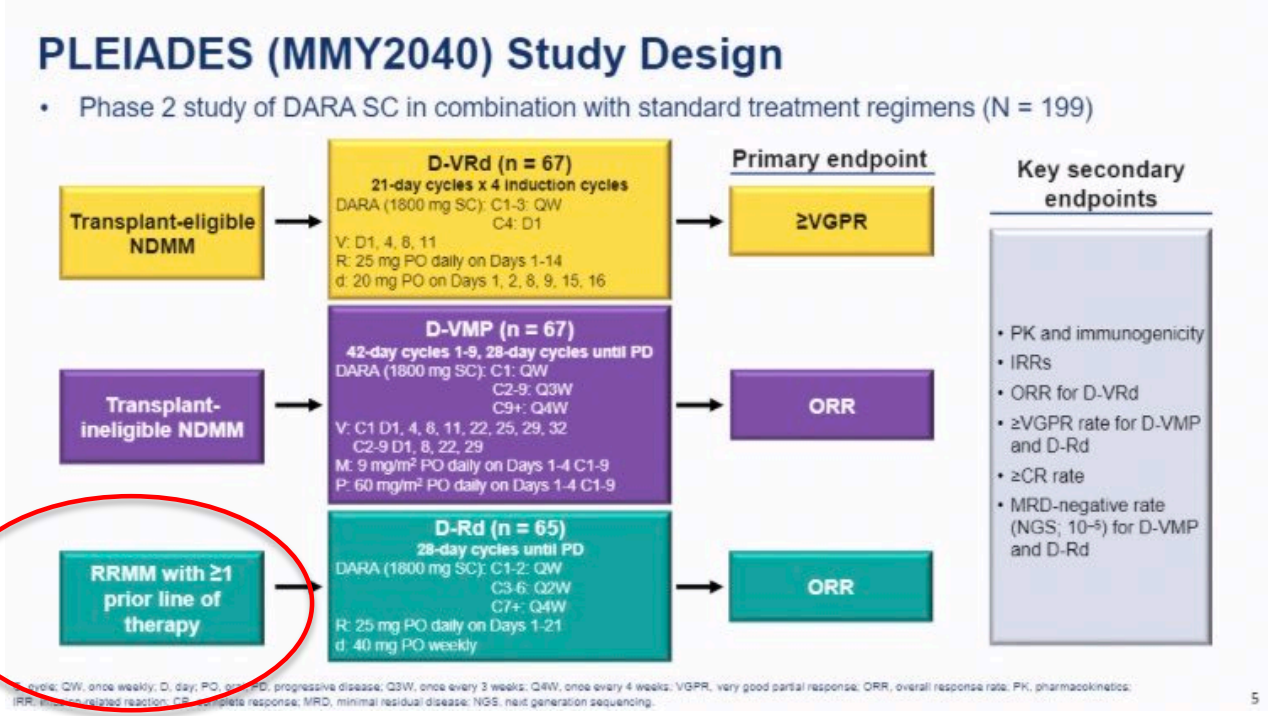
Dimopoulos et al Haematologica 2018

Update POLLUX trial



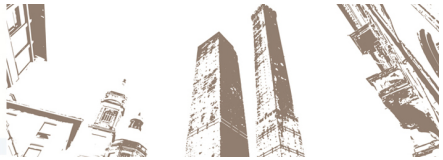
Mateos et al Haematologica 2019

65 patients
ORR 90.8%
>= VGPR 64.6%



Chari et al, IMW 2019

ASPIRE trial



- Randomized, open-label, multicenter phase III trial

Stratified by β_2-microglobulin, prior bortezomib, and prior lenalidomide

Pts with symptomatic R/R MM after 1-3 prior treatments with ≥ PR to ≥ 1 prior regimen (N = 792)

KRd* (n = 396)
Carfilzomib 27 mg/m² IV
Days 1, 2, 8, 9, 15, 16 (20 mg/m² days 1, 2, cycle 1 only)
Lenalidomide 25 mg Days 1-21
Dexamethasone 40 mg Days 1, 8, 15, 22

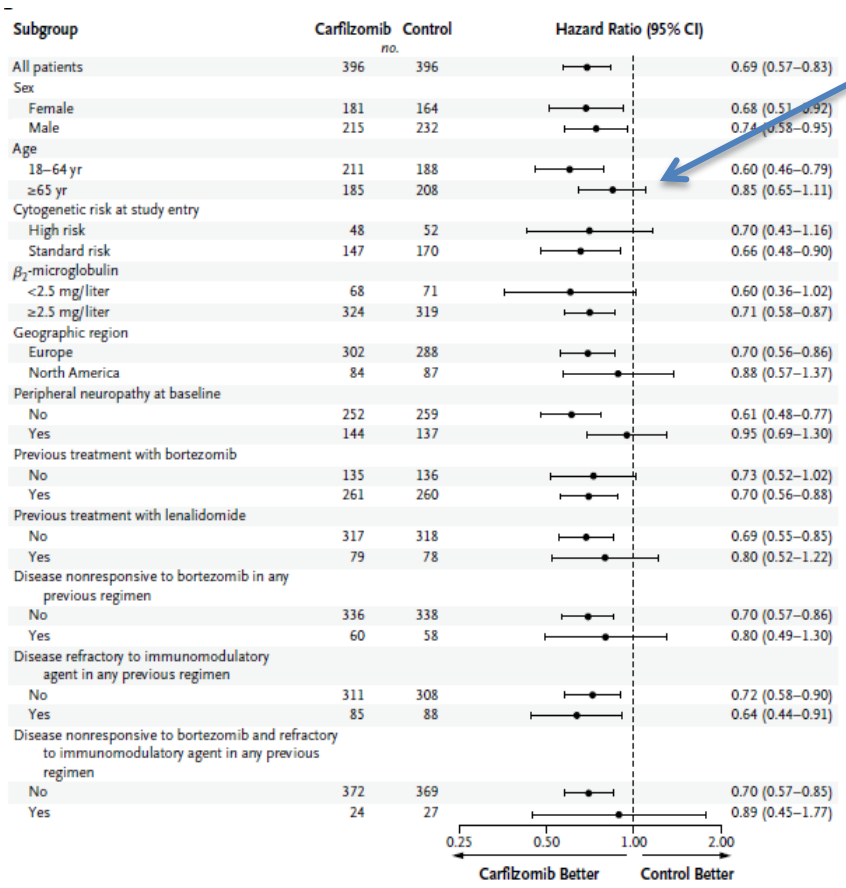
28 day cycles

Rd (n = 396)
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.

ASPIRE trial

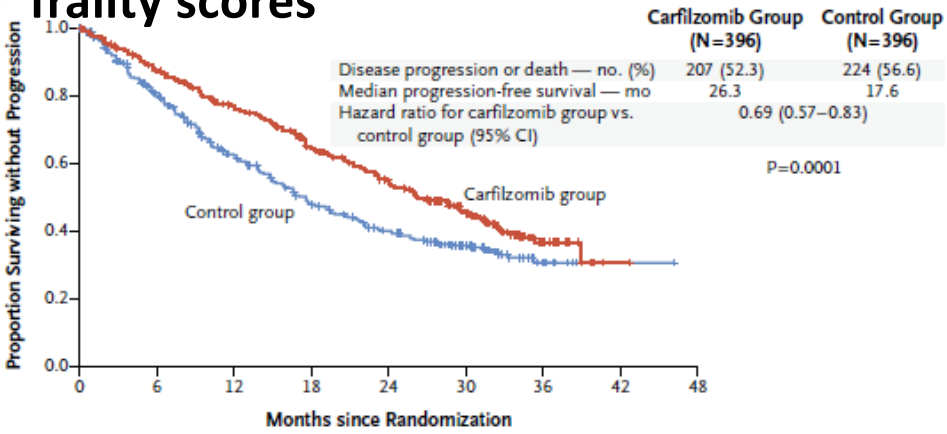
Confirmed across various frailty scores

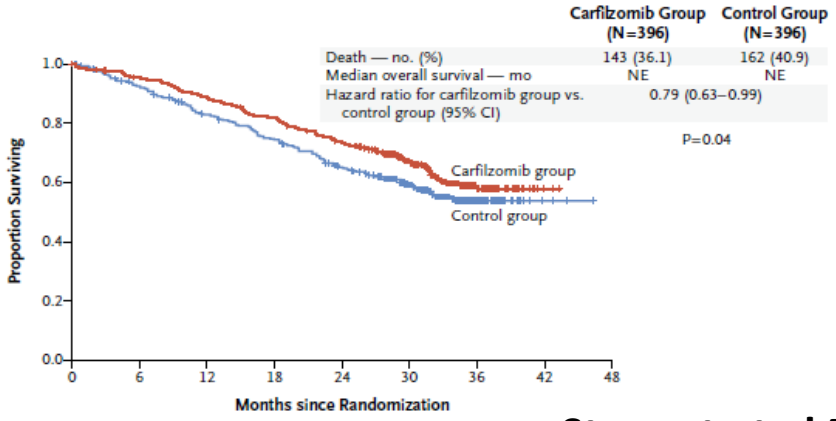


Subgroup	Carfilzomib (no.)	Control (no.)	Hazard Ratio (95% CI)
All patients	396	396	0.69 (0.57–0.83)
Sex			
Female	181	164	0.68 (0.51–0.92)
Male	215	232	0.74 (0.58–0.95)
Age			
18–64 yr	211	188	0.60 (0.46–0.79)
≥65 yr	185	208	0.85 (0.65–1.11)
Cytogenetic risk at study entry			
High risk	48	52	0.70 (0.43–1.16)
Standard risk	147	170	0.66 (0.48–0.90)
β_2-microglobulin			
<2.5 mg/liter	68	71	0.60 (0.36–1.02)
≥2.5 mg/liter	324	319	0.71 (0.58–0.87)
Geographic region			
Europe	302	288	0.70 (0.56–0.86)
North America	84	87	0.88 (0.57–1.37)
Peripheral neuropathy at baseline			
No	252	259	0.61 (0.48–0.77)
Yes	144	137	0.95 (0.69–1.30)
Previous treatment with bortezomib			
No	135	136	0.73 (0.52–1.02)
Yes	261	260	0.70 (0.56–0.88)
Previous treatment with lenalidomide			
No	317	318	0.69 (0.55–0.85)
Yes	79	78	0.80 (0.52–1.22)
Disease nonresponsive to bortezomib in any previous regimen			
No	336	338	0.70 (0.57–0.86)
Yes	60	58	0.80 (0.49–1.30)
Disease refractory to immunomodulatory agent in any previous regimen			
No	311	308	0.72 (0.58–0.90)
Yes	85	88	0.64 (0.44–0.91)
Disease nonresponsive to bortezomib and refractory to immunomodulatory agent in any previous regimen			
No	372	369	0.70 (0.57–0.85)
Yes	24	27	0.89 (0.45–1.77)

0.25 0.50 1.00 2.00

Carfilzomib Better | Control Better

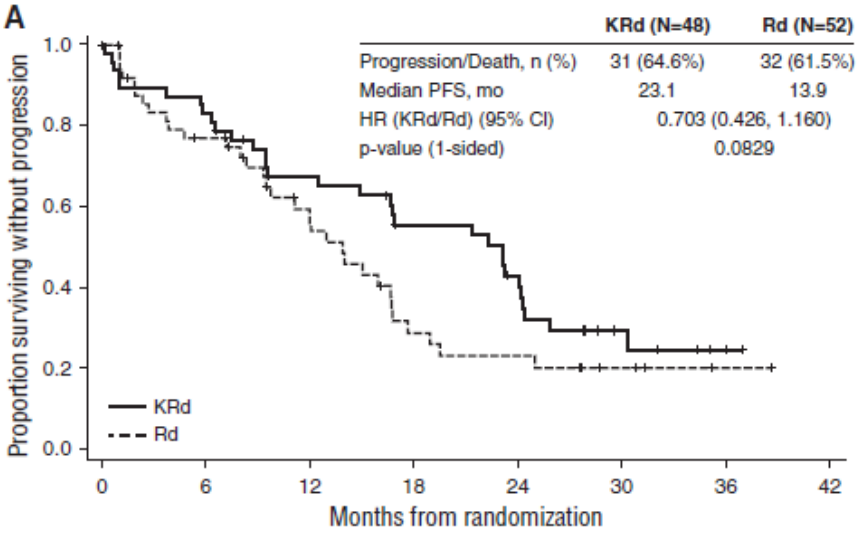




Stewart et al NEJM 2015

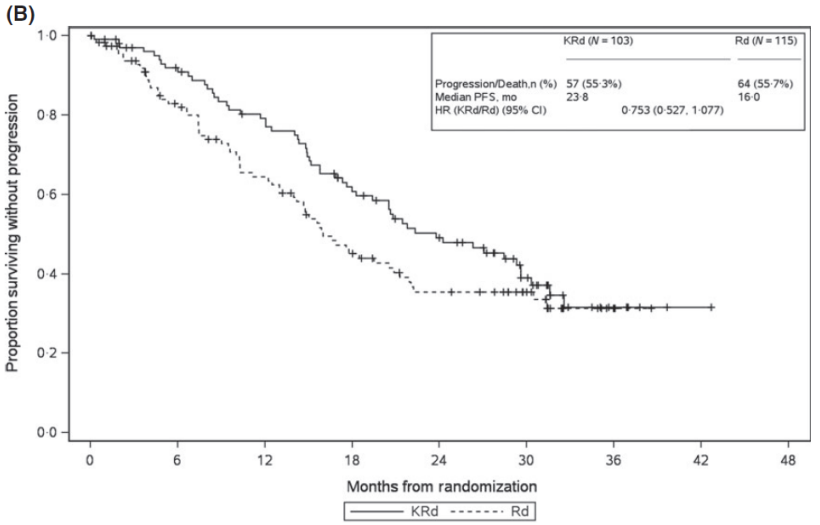
Update ASPIRE trial

Increased PFS in high-risk



Avet Loiseau et al, Blood 2016

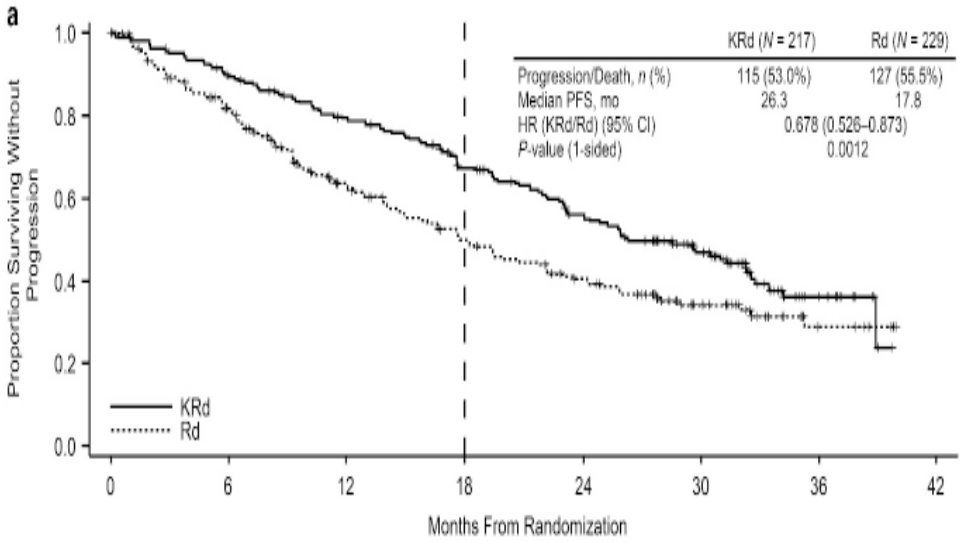
PFS advantage even in patients > 70yrs



Dimopoulos et al, Br J Haematol 2017

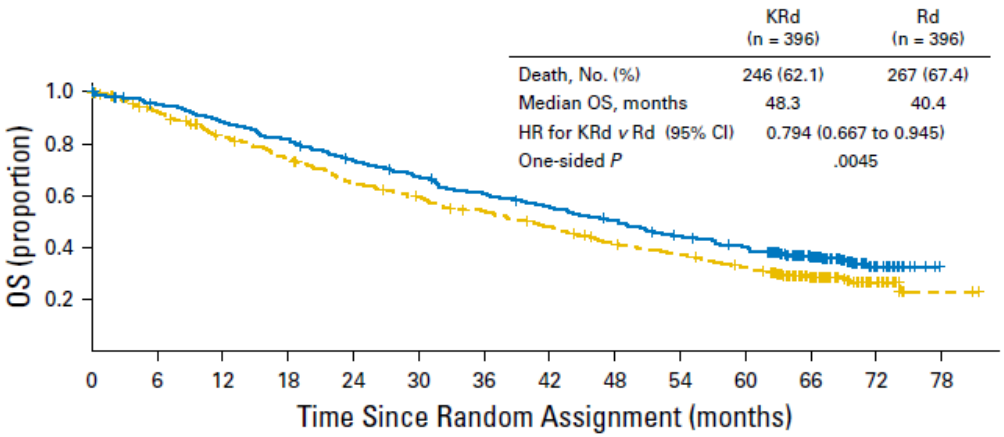
Update ASPIRE trial

Increased PFS after ASCT



Hari et al, Leukemia 2017

Increase in OS

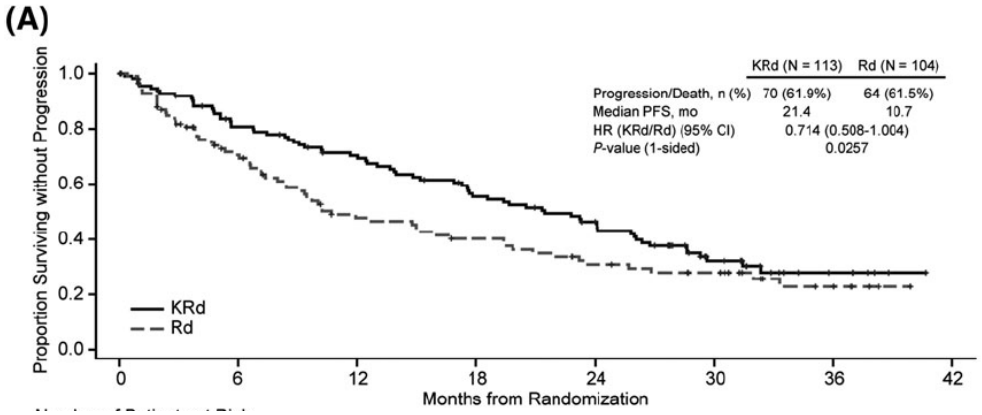


Siegel et al JCO 2018

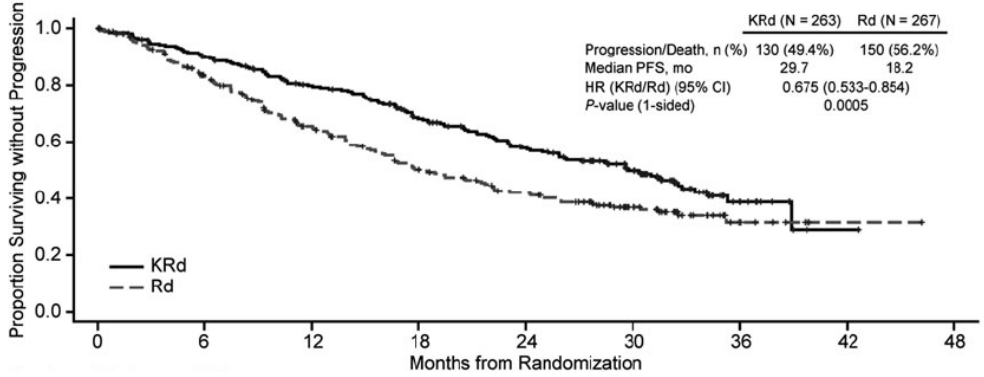
Update ASPIRE trial

Early vs late relapse

(A)



(B)



Mateos et al Hematol Oncol 2018

TOURMALINE 1 trial

- Randomized, double-blind, placebo-controlled phase III trial[1]

Stratified by prior therapy (1 vs 2-3), ISS stage (I-II vs III), and prior PI exposure (yes vs no)

R/R MM pts with measurable disease; 1-3 prior treatments; CrCl ≥ 30 mL/min; not refractory to PIs or lenalidomide (N = 722)

Ixazomib 4 mg PO D1,8,15 + Lenalidomide 25 mg* D1-21 + Dexamethasone 40 mg D1,8,15,22 (n = 360)

Placebo D1,8,15 + Lenalidomide 25 mg* D1-21 + Dexamethasone 40 mg D1,8,15,22 (n = 362)

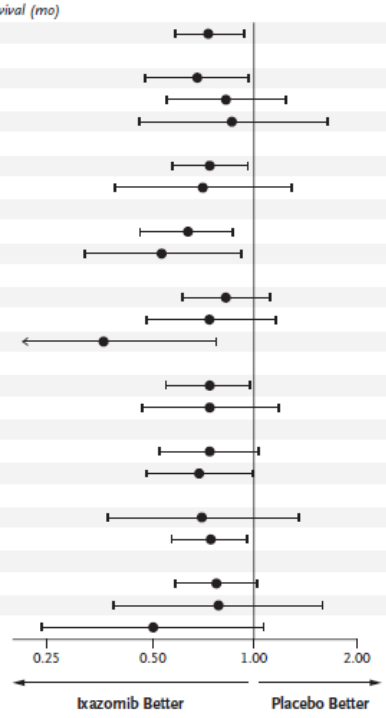
28-day cycles until PD or unacceptable toxicity

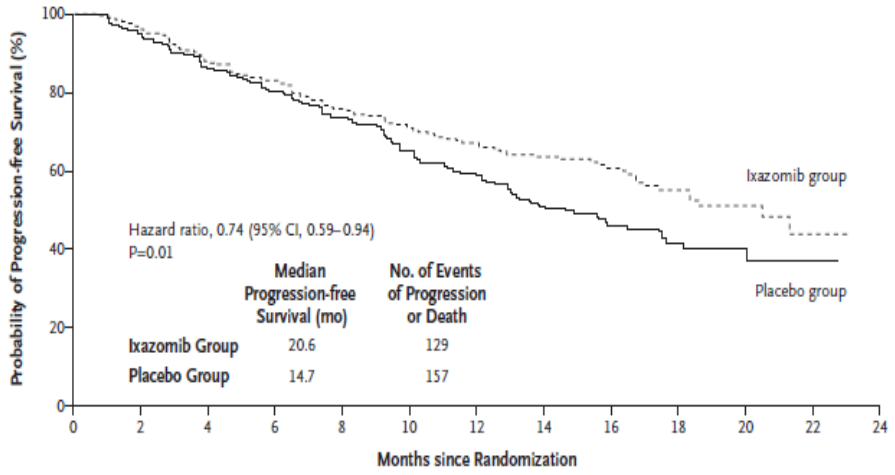
- Primary endpoint: PFS by IRC per IMWG criteria[2]

*10 mg for pts with CrCl ≤ 60 or ≤ 50 mL/min.

TOURMALINE 1 trial

Subgroup	Ixazomib Group	Placebo Group	Ixazomib Group	Placebo Group	Hazard Ratio (95% CI)
	no. of patients		*median progression-free survival (mo)*		
All patients	360	362	20.6	14.7	0.74
Age					
≤65 yr	168	176	20.6	14.1	0.68
>65–75 yr	145	125	17.5	17.6	0.83
>75 yr	47	61	18.5	13.1	0.87
ISS stage (stratification factor)					
I or II	314	318	21.4	15.7	0.75
III	46	44	18.4	10.1	0.72
Cytogenetic risk					
Standard risk	199	216	20.6	15.6	0.64
High risk	75	62	21.4	9.7	0.54
No. of prior therapies					
1	224	217	20.6	15.9	0.83
2	97	111	17.5	14.1	0.75
3	39	34	NE	10.2	0.37
Proteasome inhibitor					
Exposed	250	253	18.4	13.6	0.74
Not exposed	110	109	NE	15.7	0.75
Prior immunomodulatory drug therapy					
Exposed	193	204	NE	17.5	0.74
Not exposed	167	158	20.6	13.6	0.70
Refractory to last prior therapy					
Yes	59	55	NE	NE	0.71
No	301	307	20.6	14.1	0.74
Relapsed or refractory					
Relapsed	276	280	18.7	15.6	0.77
Refractory	42	40	NE	13.0	0.78
Relapsed and refractory	41	42	NE	13.1	0.51

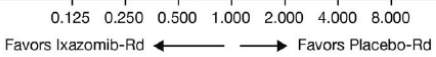




Moreau et al NEJM 2016

Update TOURMALINE 1 trial

Variable	Subgroup	Median PFS, months (events/n) Ixazomib-Rd	Placebo-Rd	HR	95% CI
Overall population	All (N=722)	20.6 (129/360)	14.7 (157/362)	0.742	(0.587, 0.939)
Prior PI	Exposed (n=503)	18.4 (93/250)	13.6 (114/253)	0.739	(0.561, 0.974)
	Naïve (n=219)	NE (36/110)	15.7 (43/109)	0.749	(0.479, 1.171)
Prior bortezomib	Exposed (n=498)	18.5 (93/248)	13.6 (112/250)	0.746	(0.564, 0.985)
	Naïve (n=224)	NE (36/112)	15.9 (45/112)	0.747	(0.474, 1.178)
Prior immunomodulatory drug	Exposed (n=397)	NE (69/193)	17.5 (86/204)	0.744	(0.537, 1.031)
	Naïve (n=325)	20.6 (60/167)	13.6 (71/158)	0.700	(0.491, 0.998)
Prior thalidomide	Exposed (n=327)	NE (57/157)	15.7 (69/170)	0.750	(0.523, 1.077)
	Naïve (n=395)	20.6 (72/203)	13.6 (88/192)	0.695	(0.505, 0.956)
Prior lenalidomide	Exposed (n=88)	NE (13/44)	17.5 (21/44)	0.582	(0.275, 1.234)
	Naïve (n=634)	20.6 (116/316)	13.9 (136/318)	0.766	(0.596, 0.985)
Thalidomide refractory	Yes (n=89)	16.6 (14/40)	13.0 (23/49)	0.726	(0.366, 1.441)
	No (n=633)	20.6 (115/320)	15.6 (134/313)	0.754	(0.586, 1.970)
Prior therapies	1 (n=425)	20.6 (80/212)	16.6 (88/213)	0.882	(0.650, 1.197)
	2 or 3 (n=297)	NE (49/148)	12.9 (69/149)	0.580	(0.401, 0.838)



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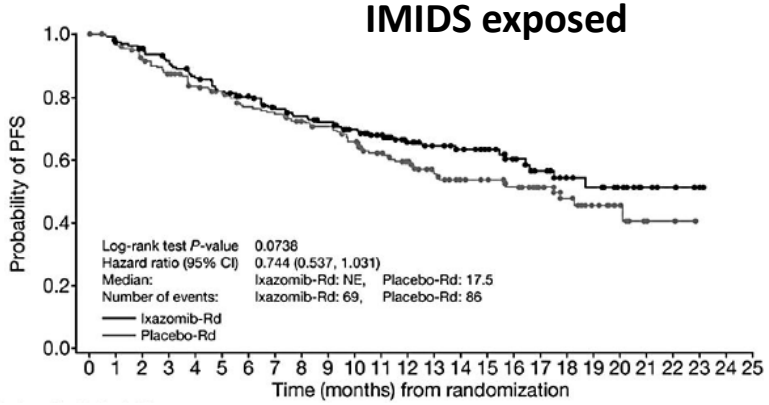
IMIDS exposed



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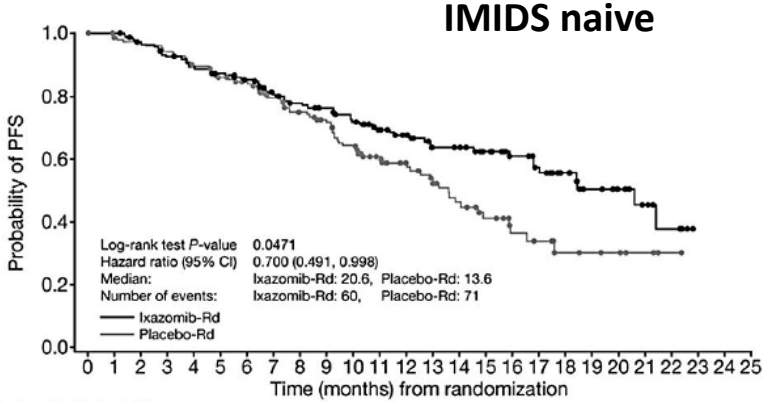
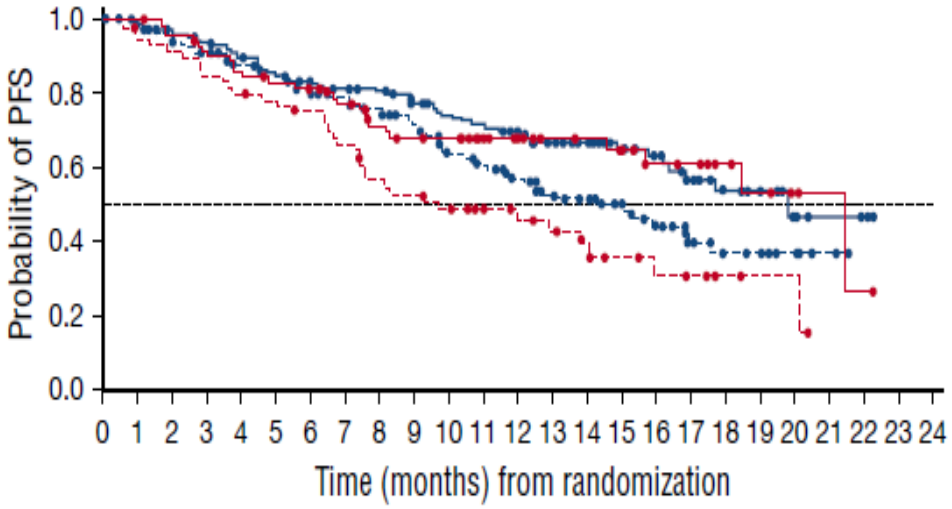
IMIDS naive



Mateos et al Haematologica 2017

Update TOURMALINE 1 trial

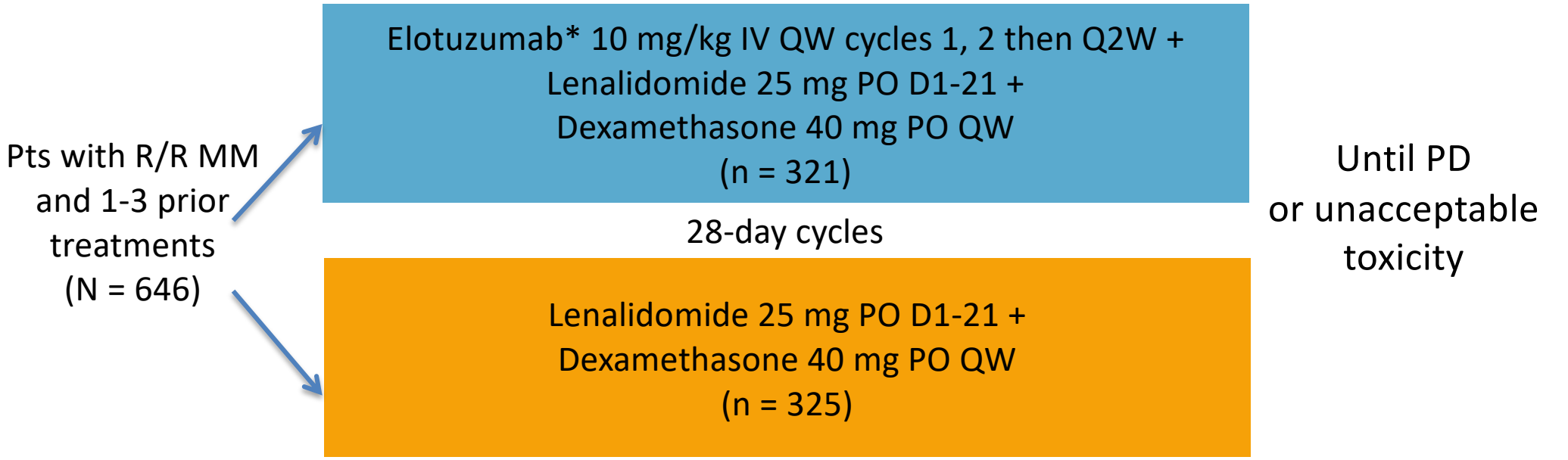


Variable	Subgroup	n/N (events/pts) Ixazomib-Rd	n/N (events/pts) Placebo-Rd	Median PFS (months) Ixazomib-Rd	Median PFS (months) Placebo Rd	HR (95% CI)
All patients	ALL	129/360	157/362	20.6	14.7	0.742 (0.587–0.939)
Cytogenetic risk	High-risk	26/75	35/62	21.4	9.7	0.543 (0.321–0.918)
	Expanded high-risk	62/155	83/154	17.5	11.1	0.664 (0.474–0.928)
	Standard-risk	61/199	91/216	20.6	15.6	0.640 (0.462–0.888)
del(17p)*	Positive (5%)	14/36	20/33	21.4	9.7	0.596 (0.286–1.243)
	Positive (20%)	13/29	19/30	21.4	6.7	0.611 (0.286–1.308)
	Positive (60%)	10/19	8/14	15.7	5.1	0.490 (0.146–1.644)
t(4;14)*	Positive (3%)	11/36	11/25	18.5	12.0	0.645 (0.250–1.663)
	Positive (20%)	11/36	10/22	18.5	12.0	0.685 (0.259–1.811)
	Positive (60%)	8/25	8/15	18.5	9.3	0.518 (0.166–1.615)
Amp 1q21*	Positive (3%)	36/80	48/92	15.4	11.3	0.781 (0.492–1.240)
	Positive (20%)	31/73	41/79	16.4	11.3	0.682 (0.413–1.123)
	Positive (60%)	25/50	31/55	11.9	11.1	0.683 (0.381–1.224)

Avet Loiseau Blood 2017

ELOQUENT – 2 trial

- Randomized, open-label, multicenter phase III trial



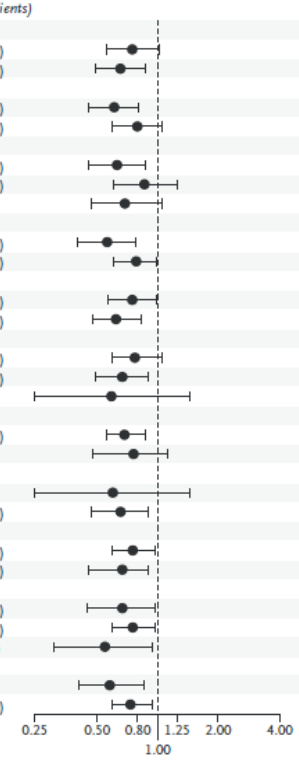
**Prophylactic medication administered prior to elotuzumab to mitigate infusion -related reactions.*

- Primary endpoints: PFS, ORR

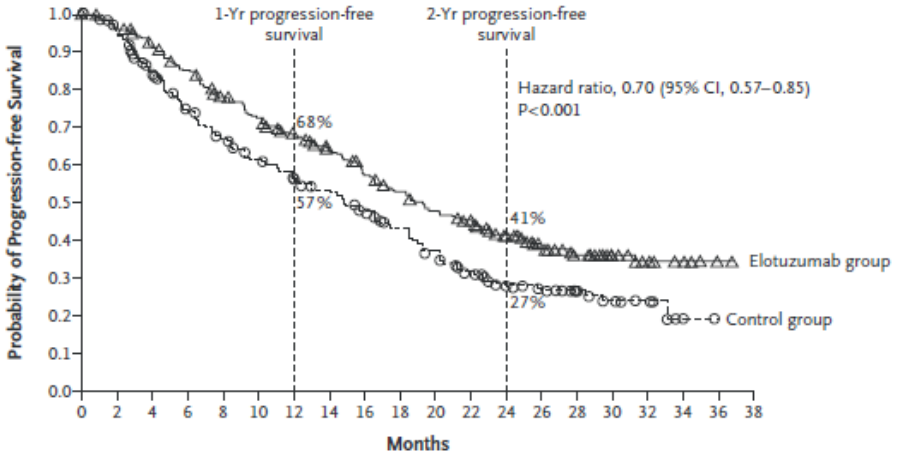
ELOQUENT – 2 trial

B Subgroup Analyses

Subgroup	Elotuzumab (no. of events / total no. of patients)	Control (no. of events / total no. of patients)	Hazard Ratio (95% CI)
Age			
<65 yr	78 (134)	87 (142)	0.75 (0.55–1.02)
≥65 yr	101 (187)	118 (183)	0.65 (0.50–0.85)
Baseline β_2-microglobulin			
<3.5 mg/liter	82 (173)	107 (179)	0.61 (0.46–0.81)
≥3.5 mg/liter	97 (147)	98 (146)	0.79 (0.60–1.05)
ISS stage at enrollment			
I	68 (141)	80 (138)	0.63 (0.46–0.87)
II	60 (102)	67 (105)	0.86 (0.61–1.22)
III	48 (66)	50 (68)	0.70 (0.47–1.04)
Response to most recent line of therapy			
Resistance	67 (113)	77 (114)	0.56 (0.40–0.78)
Relapse	112 (207)	128 (211)	0.77 (0.60–1.00)
No. of lines of previous therapy			
1	85 (151)	101 (159)	0.75 (0.56–1.00)
2 or 3	94 (170)	104 (166)	0.65 (0.49–0.87)
Previous IMiD therapy			
None	85 (155)	91 (151)	0.78 (0.58–1.05)
Thalidomide only	85 (150)	101 (153)	0.64 (0.48–0.85)
Other	9 (16)	13 (21)	0.59 (0.25–1.40)
Previous bortezomib			
Yes	132 (219)	150 (231)	0.68 (0.54–0.86)
No	47 (102)	55 (94)	0.72 (0.49–1.07)
Previous lenalidomide			
Yes	9 (16)	13 (21)	0.59 (0.25–1.40)
No	170 (305)	192 (304)	0.70 (0.57–0.87)
Previous stem-cell transplantation			
Yes	102 (167)	117 (185)	0.75 (0.58–0.99)
No	77 (154)	88 (140)	0.63 (0.46–0.86)
Mutations			
del(17p)	50 (102)	61 (104)	0.65 (0.45–0.94)
1q21	88 (147)	105 (163)	0.75 (0.56–0.99)
t(4;14)	21 (30)	25 (31)	0.53 (0.29–0.95)
Baseline creatinine clearance			
<60 ml/min	53 (96)	55 (75)	0.56 (0.39–0.82)
≥60 ml/min	126 (225)	150 (250)	0.74 (0.58–0.94)

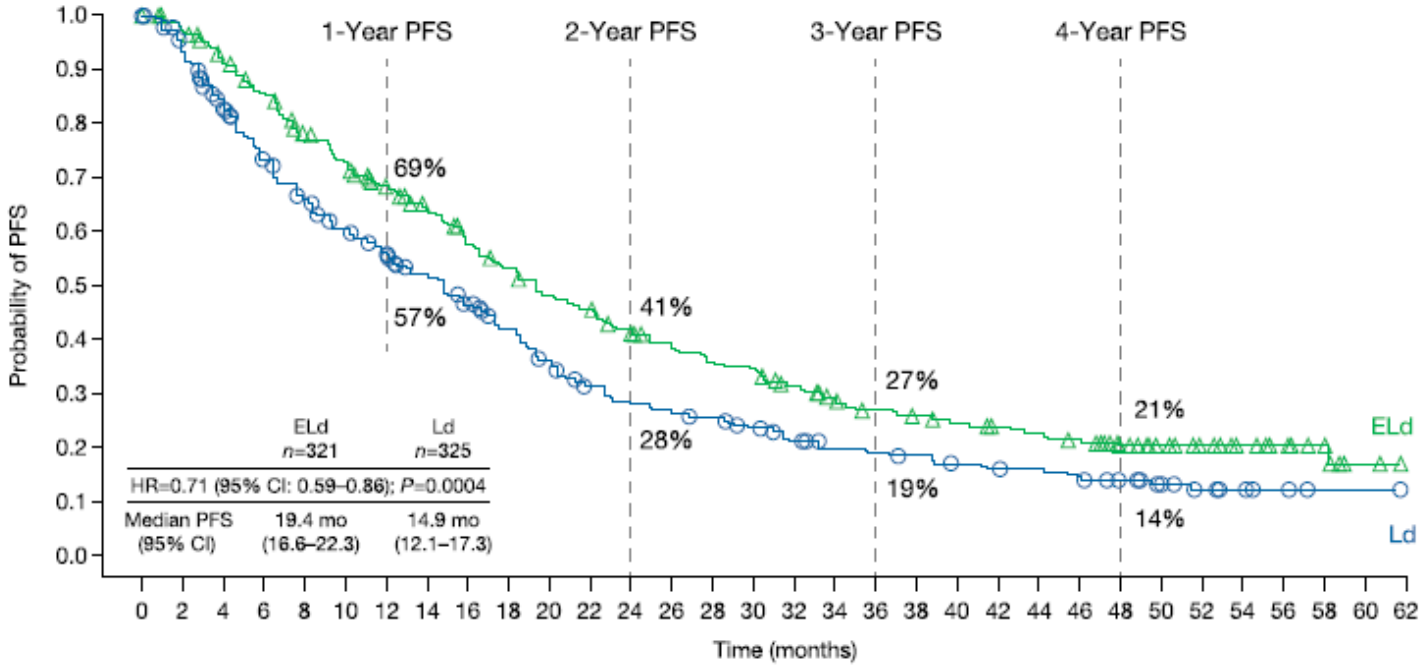


A Progression-free Survival



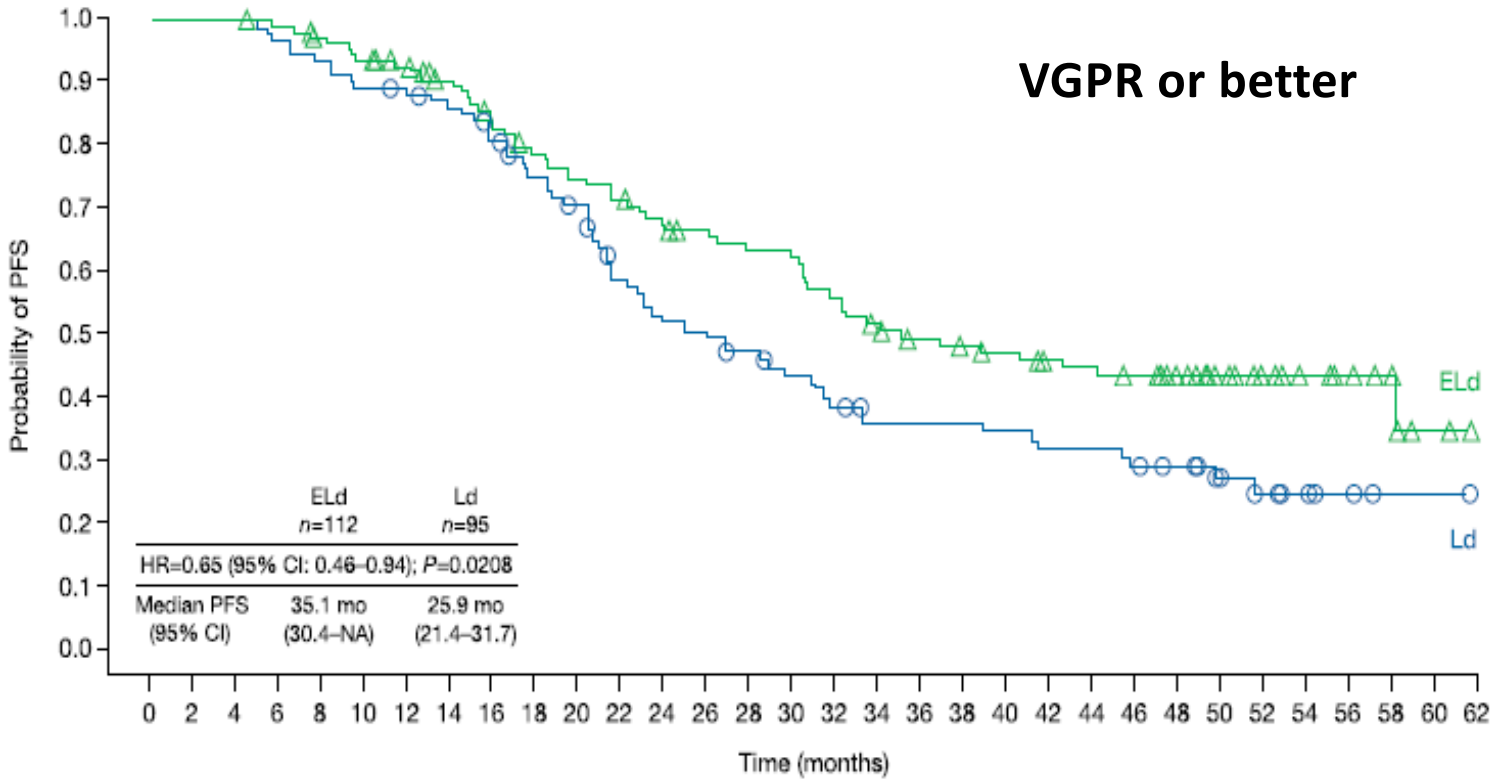
Lonial al NEJM 2015

Update ELOQUENT – 2 trial



Dimopoulos et al, Cancer 2018

Update ELOQUENT – 2 trial



Dimopoulos et al, Cancer 2018

ELOQUENT-2 final survival analysis

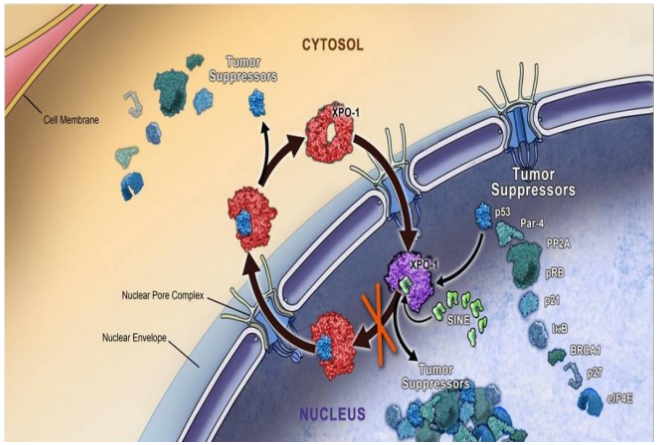
	ERd (n= 321, %)	Rd (n= 325, %)
Median OS (months, 95% CI)	48.3 (40.3-51.9)	39.6 (33.3-45.3)
1-year OS	91%	83%
2-year OS	73%	69%
3-year OS	60%	53%
4-year OS	50%	43%
5-year OS	40%	33%

Dimopoulos et al IMW 2019

SUMMARY of trial results

Trial	ORR, %	≥ CR, %	≥ VGPR, %	Median PFS, Mos	Median OS, Mos
ASPIRE: KRd vs Rd[1]	87 vs 67	32 vs 9	70 vs 40	26.3 vs 16.6 HR: 0.69	48.3 vs 40.4 HR: 0.79
TOURMALINE-MM1: IxaRd vs Rd[2]	78 vs 72	14 vs 7	48 vs 39	20.6 vs 14.7 HR: 0.74	NR
POLLUX: DRd vs Rd[3-5]	93 vs 76	57 vs 23	80 vs 49	44.5 vs 17.5 HR: 0.44	NR vs NR HR: 0.63
ELOQUENT-2: ERd vs Rd[6,7]	79 vs 66	5 vs 9	36 vs 30	19.4 vs 14.9 HR: 0.73	48.3 vs 39.6 HR: 0.78

Safety and Efficacy of the Combination of Selinexor, Lenalidomide and Dexamethasone (SRd) in Patients with Relapsed/Refractory Multiple Myeloma (RRMM)



Multicenter dose escalation study
20 evaluable patients

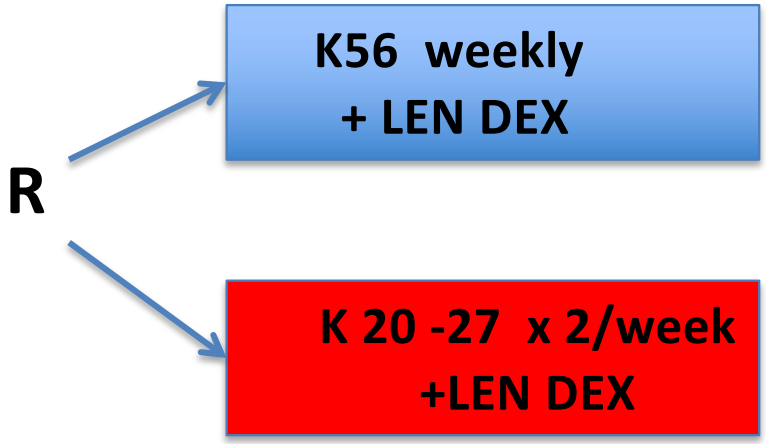
LEN untreated
ORR 92%
PFS not reached (> 1 yr)

White et al, IMW 2019

ARROW 2 trial

460 patients
1-3 prior line therapy
Non Lena non PI refractory

Primary endpoint
ORR



Leleu IMW 2019

CONFIRM trial (IFM)

430 patients
One prior line therapy
Non Lena non Dara refractory

Primary endpoint OS at 4 years
Hypothesis: non inferior