IMMUNOTERAPIA NEL MIELOMA MULTIPLO E NEL LINFOMA DI HODGKIN:
Ruolo nel paziente con MM ricaduto

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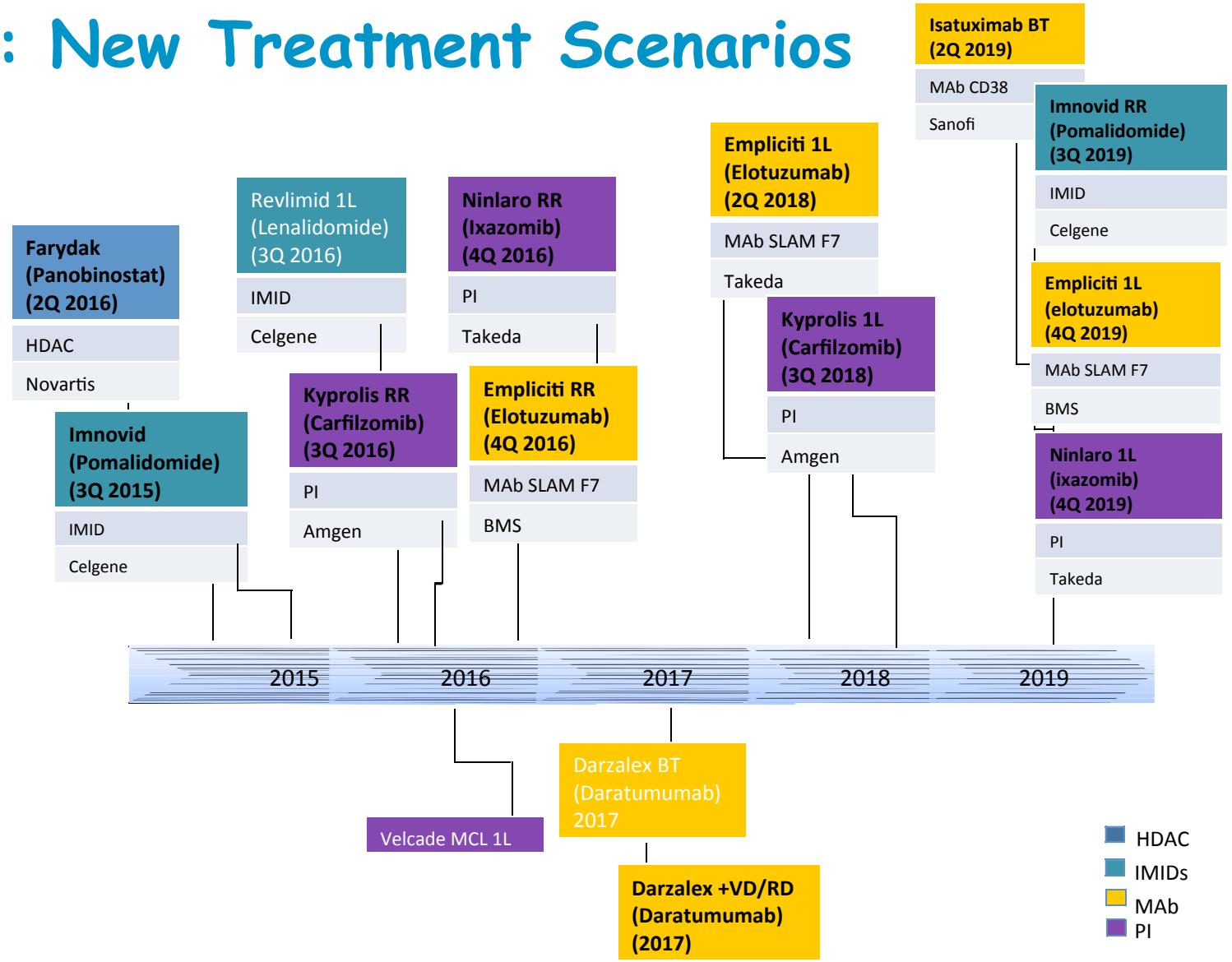
Bergamo

Milano, 9 Novembre 2017

MM: New Treatment Scenarios



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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., Paul Richardson, M.D., for the ELOQUENT-2 Investigators

N Engl J Med
Volume 373(7):621-631
August 13, 2015

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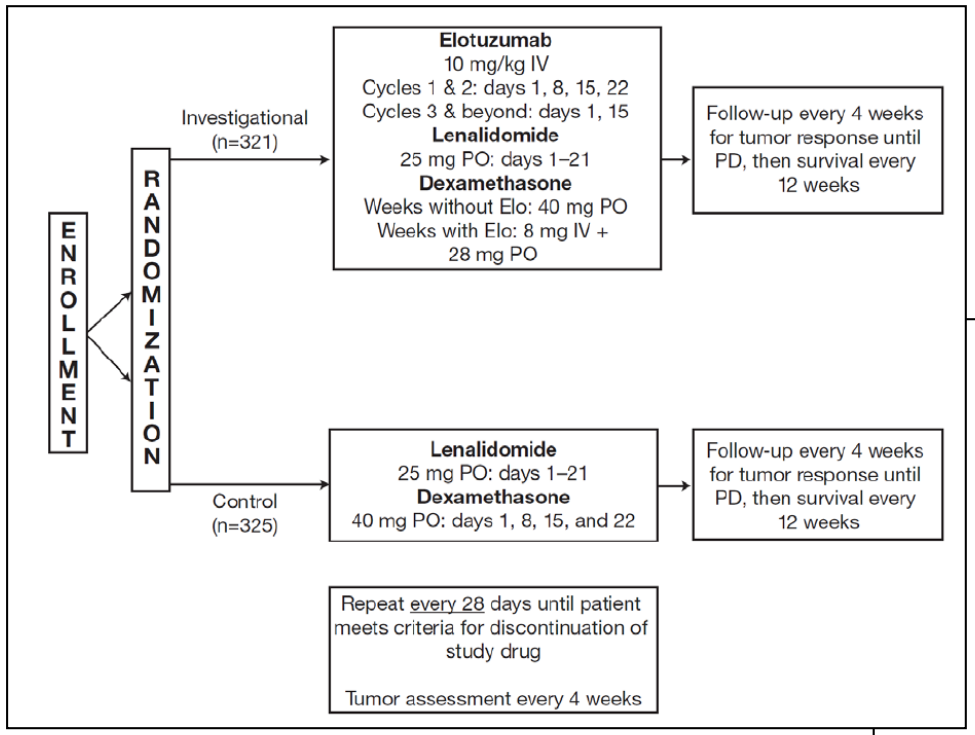
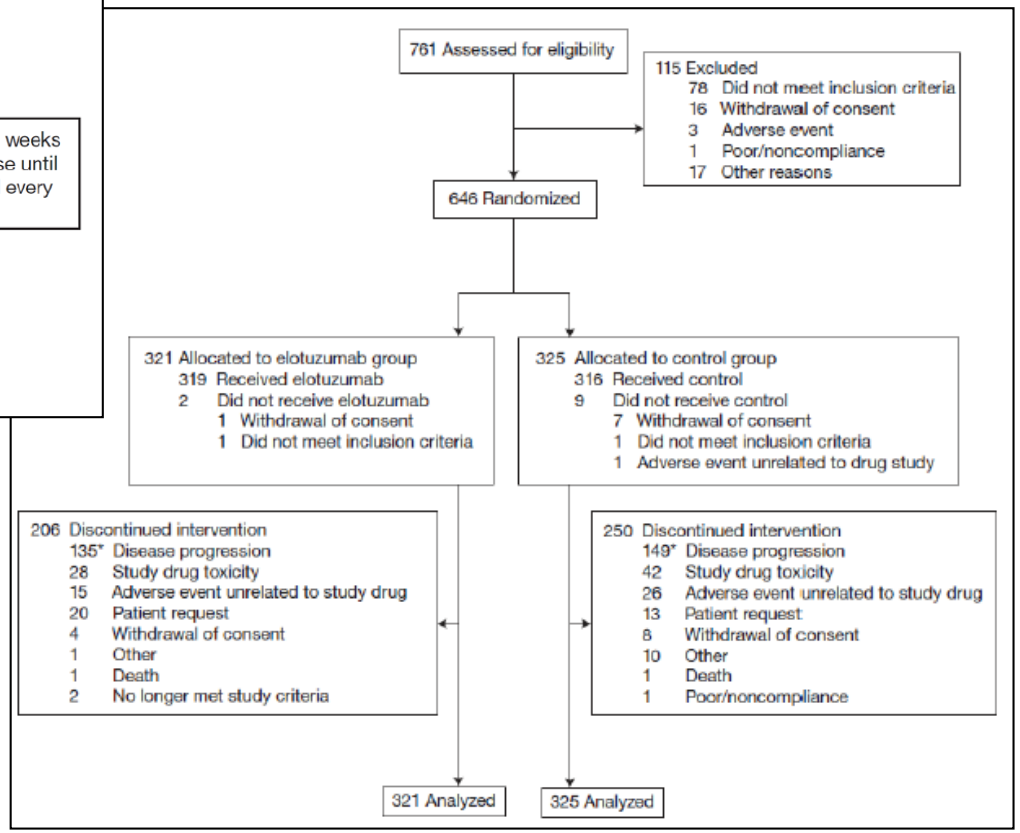
The NEW ENGLAND JOURNAL of MEDICINE

ELOQUENT-2: A Phase III Trial





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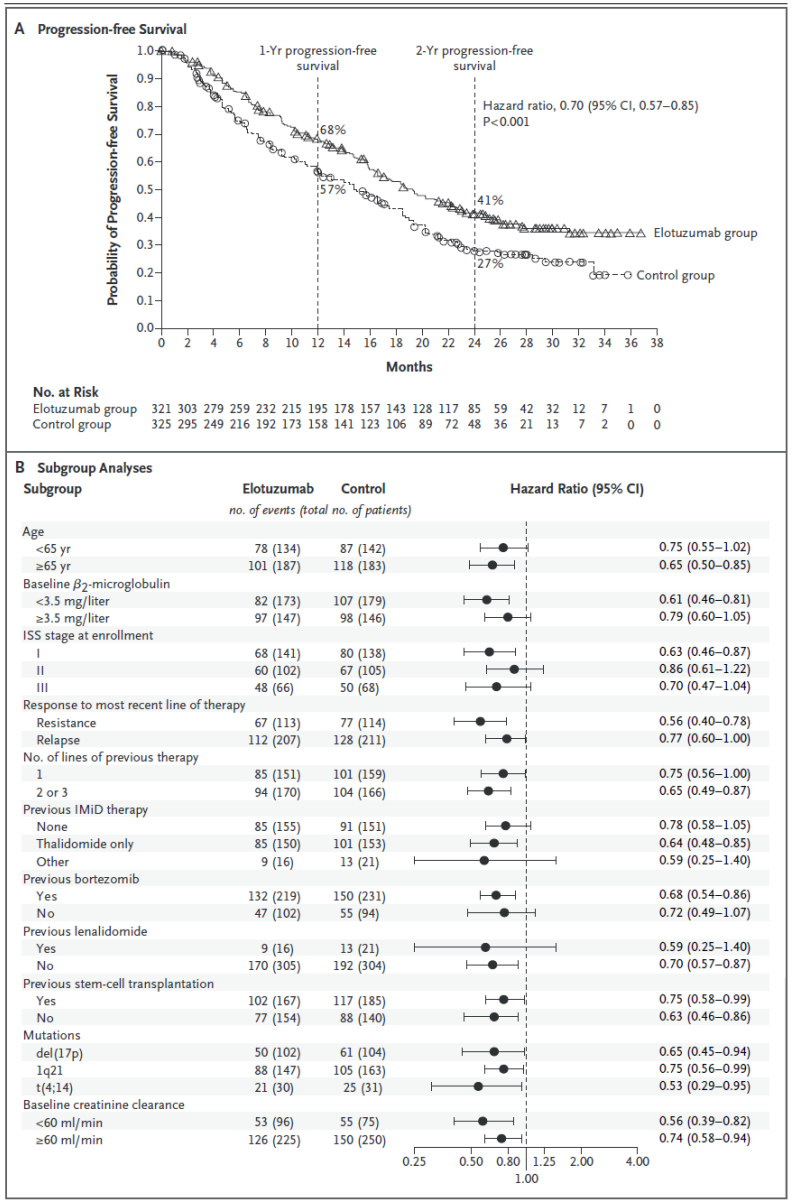
Lonial et al. NEJM 2015;373:621

ELOQUENT-2: A Phase III Trial

Table 1. Characteristics of the Patients at Baseline (Intention-to-Treat Population).

Characteristic	Elotuzumab Group (N=321)	Control Group (N=325)	All Patients (N=646)
Median age (range) — yr	67 (37–88)	66 (38–91)	66 (37–91)
Cytogenetic profile — no. (%)*			
del(17p)			
Yes	102 (32)	104 (32)	206 (32)
No	213 (66)	218 (67)	431 (67)
Not reported	6 (2)	3 (1)	9 (1)
t(4;14)			
Yes	30 (9)	31 (10)	61 (9)
No	285 (89)	290 (89)	575 (89)
Not reported	6 (2)	4 (1)	10 (2)
Disease stage according to International Staging System — no. (%)†			
I	141 (44)	138 (42)	279 (43)
II	102 (32)	105 (32)	207 (32)
III	66 (21)	68 (21)	134 (21)
Not reported	12 (4)	14 (4)	26 (4)
Previous therapy regimens‡			
Median no. (range)	2 (1–4)	2 (1–4)	2 (1–4)
Regimens — no. (%)			
1	151 (47)	159 (49)	310 (48)
2	118 (37)	114 (35)	232 (36)
3 or more	52 (16)	52 (16)	104 (16)
Previous stem-cell transplantation — no. (%)	167 (52)	185 (57)	352 (54)
Previous therapies — no. (%)			
Bortezomib	219 (68)	231 (71)	450 (70)
Melphalan	220 (69)	197 (61)	417 (65)
Thalidomide	153 (48)	157 (48)	310 (48)
Lenalidomide	16 (5)	21 (6)	37 (6)



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Lonial et al. NEJM 2015;373:621

ELOQUENT-2: A Phase III Trial

Table 2. Treatment Response (Intention-to-Treat Population).*

Response	Elotuzumab Group (N=321)	Control Group (N=325)
Overall response rate		
Patients with response — no. (%)†	252 (79)	213 (66)
95% CI — %	74–83	60–71
Best overall response — no. (%)		
Complete response (sCR + CR)	14 (4)‡	24 (7)
Very good partial response	91 (28)	67 (21)
Combined response (sCR + CR + VGPR)	105 (33)	91 (28)
Partial response	147 (46)	122 (38)
Minimal response	22 (7)	33 (10)
Stable disease	30 (9)	54 (17)
Progressive disease	8 (2)	8 (2)
Could not be evaluated	9 (3)	17 (5)

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ELOQUENT-2: A Phase III Trial

Table 3. Adverse Events.*

Event	Elotuzumab Group (N=318)		Control Group (N=317)	
	Any Grade	Grade 3 to 4	Any Grade	Grade 3 to 4
Common hematologic toxic effect — no. (%)†				
Lymphocytopenia	316 (99)	244 (77)	311 (98)	154 (49)
Anemia	306 (96)	60 (19)	301 (95)	67 (21)
Thrombocytopenia	266 (84)	61 (19)	246 (78)	64 (20)
Neutropenia	260 (82)	107 (34)	281 (89)	138 (44)
Common nonhematologic adverse event — no. (%)				
General disorder				
Fatigue	149 (47)	27 (8)	123 (39)	26 (8)
Pyrexia	119 (37)	8 (3)	78 (25)	9 (3)
Peripheral edema	82 (26)	4 (1)	70 (22)	1 (<1)
Nasopharyngitis	78 (25)	0	61 (19)	0
Gastrointestinal disorder				
Diarrhea	149 (47)	16 (5)	114 (36)	13 (4)
Constipation	113 (36)	4 (1)	86 (27)	1 (<1)
Musculoskeletal or connective-tissue disorder				
Muscle spasms	95 (30)	1 (<1)	84 (26)	3 (1)
Back pain	90 (28)	16 (5)	89 (28)	14 (4)
Other disorder				
Cough	100 (31)	1 (<1)	57 (18)	0
Insomnia	73 (23)	6 (2)	82 (26)	8 (3)

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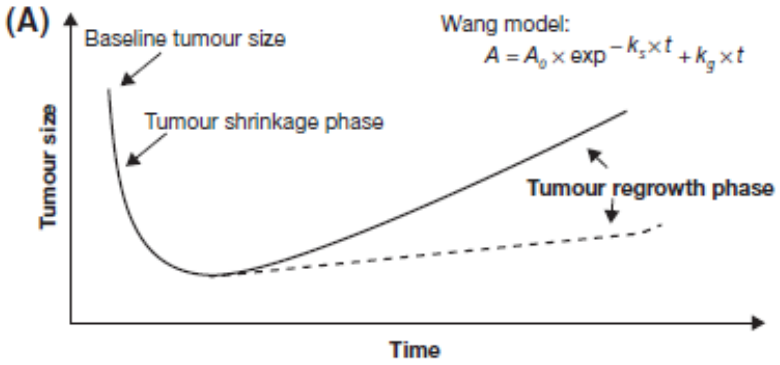
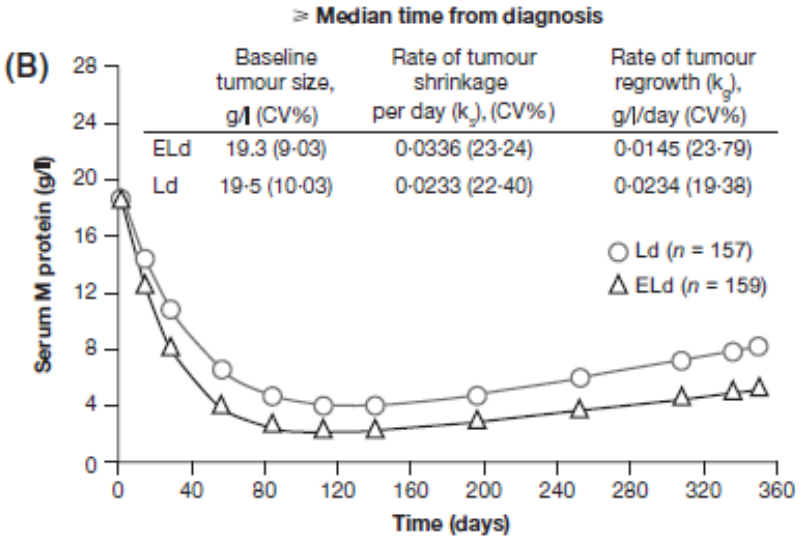
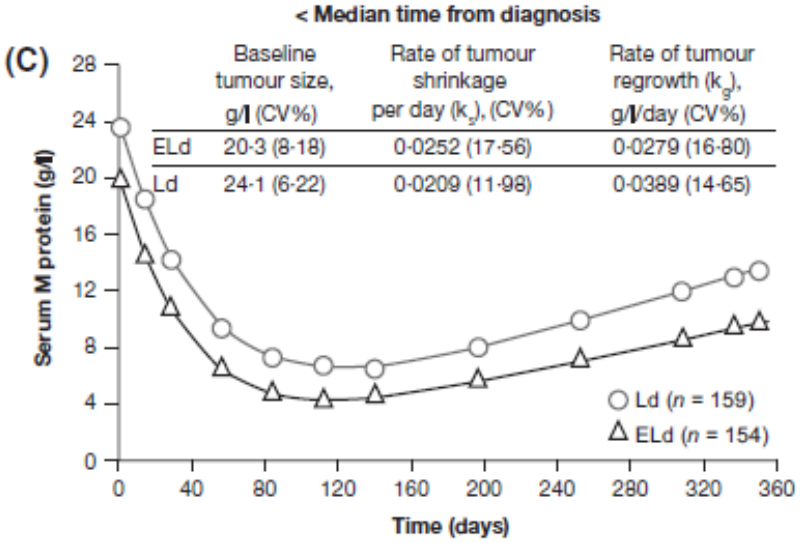
Lonial et al. NEJM 2015;373:621

ELOQUENT-2: Up-Date & *Post-Hoc* Analyses

Fig 1. Serum M-protein dynamic modelling.







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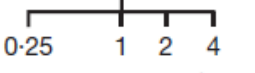
Dimopoulos et al. BJH 2017;178:896-905

ELOQUENT-2: Up-Date & *Post-Hoc* Analyses

(A)

	Events, *n* (Patients, *n*) ELd	Events, *n* (Patients, *n*) Ld	Hazard ratio (95% CI)	Interaction *P*-value
Age (<75 years)	169 (253)	178 (264)	0·76 (0·62–0·94)	0·3875
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)	0·9315
Age (≥65 years)	122 (187)	124 (183)	0·72 (0·56–0·92)	
ISS stage at enrolment (I)	83 (141)	86 (138)	0·70 (0·52–0·95)	0·5401
ISS stage at enrolment (II)	69 (102)	72 (105)	0·90 (0·64–1·25)	
ISS stage at enrolment (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)	0·0463
Response to most recent line of therapy (relapsed)	131 (206)	137 (211)	0·82 (0·65–1·05)	
Number of lines of prior therapy (1)	98 (151)	107 (159)	0·79 (0·60–1·05)	0·4189
Number 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)	0·4507
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)	0·3754
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)	0·9258
Prior stem cell transplant (no)	96 (154)	91 (140)	0·74 (0·55–0·98)	
del(17p) (yes)[a]	61 (102)	67 (104)	0·70 (0·49–0·99)	0·9091*
t(4;14) (yes)	24 (30)	26 (31)	0·52 (0·29–0·93)	0·2793†
⩾ median time from diagnosis	89 (160)	108 (163)	0·60 (0·45–0·79)	0·0623
< median time from diagnosis	119 (161)	112 (162)	0·87 (0·67–1·13)	



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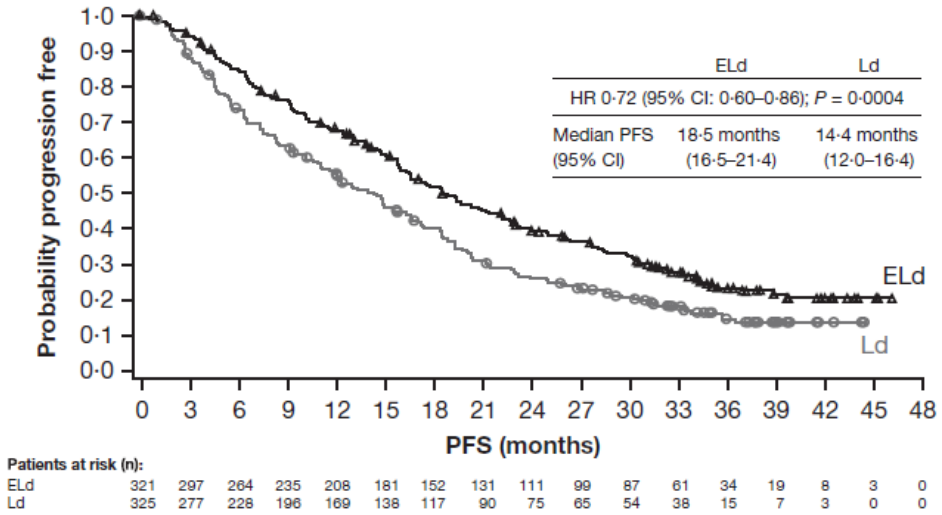
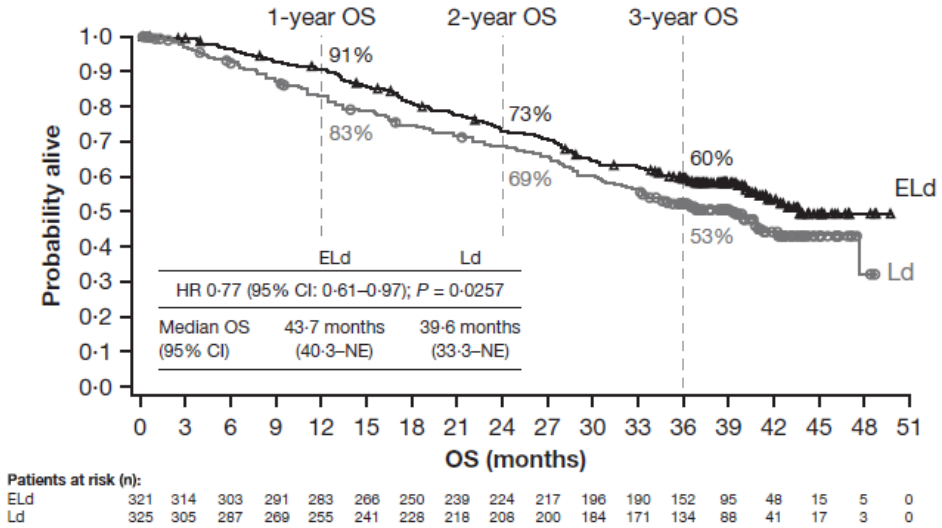
Dimopoulos et al. BJH 2017;178:896-905

ELOQUENT-2: Up-Date & *Post-Hoc* Analyses





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AIFA

Aprile 2017:
Elo-Rd è indicato in pazienti adulti che abbiano ricevuto almeno una linea di terapia precedente

Median time to next treatment
33 vs 21 months (HR 0.62)

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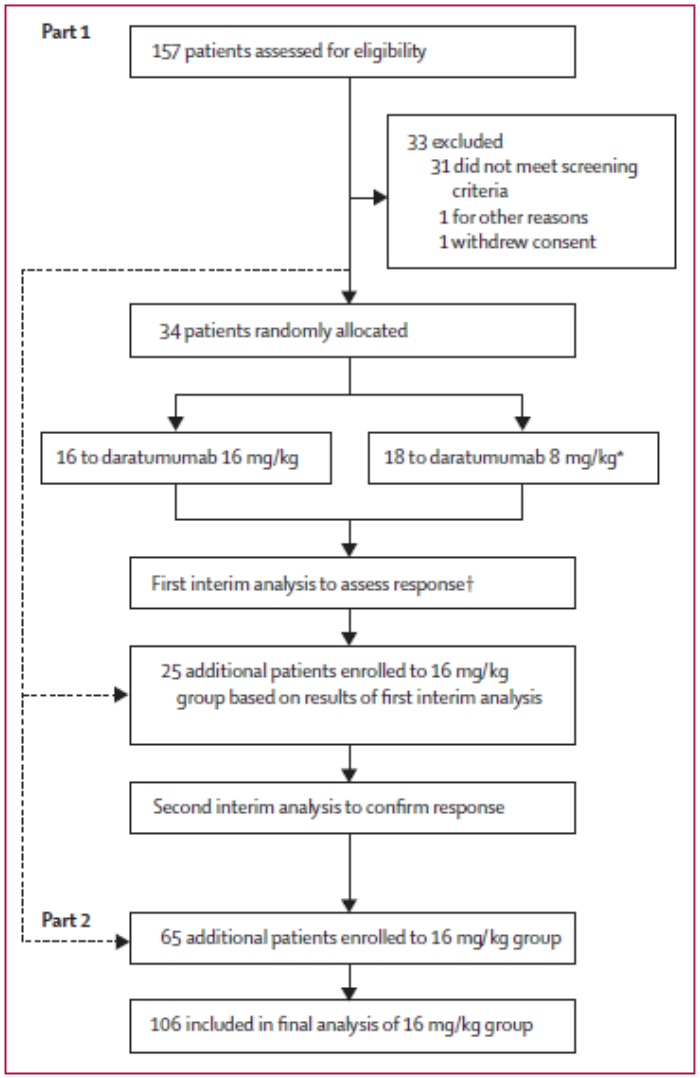
Dimopoulos et al. BJH 2017;178:896-905

SIRIUS: A Phase II trial with Daratumumab



	Daratumumab 16 mg/kg (n=106)
Age (years)	
Median (range)	63·5 (31·0–84·0)
18 to <65	58 (55%)
65 to <75	36 (34%)
≥75	12 (11%)
Men	52 (49%)
Ethnic origin	
White	84 (79%)
Black or African American	15 (14%)
Asian	4 (4%)
Not reported, other, unknown	3 (3%)
Eastern Cooperative Oncology Group score	
0	29 (27%)
1	69 (65%)
2	8 (8%)
International Staging System staging	
I	26 (25%)
II	40 (38%)
III	40 (38%)
Cytogenetics profile*	
t (4; 14)	9 (10%)
del17p	16 (17%)
del13q	30 (32%)
amp1q21	23 (24%)
Other	43 (45%)
Renal function (baseline creatinine clearance)	
≥1·0 mL/s (≥60 mL/min)	60 (57%)
0·5 to <1·0 mL/s (30 to <60 mL/min)	42 (40%)
<0·5 mL/s (<30 mL/min)	4 (4%)
Extramedullary plasmacytomas	
≥1	14 (13%)

(Table 1 continues in next column)

	Daratumumab 16 mg/kg (n=106)
(Continued from previous column)	
Time since initial diagnosis (years; median, range)	4·8 (1·1–23·8)
Lines of previous therapy	
>3	87 (82%)
Median (range)	5 (2–14)
Previous proteasome inhibitor	106 (100%)
Bortezomib	105 (99%)
Carfilzomib	53 (50%)
Previous immunomodulatory drug	106 (100%)
Lenalidomide	105 (99%)
Pomalidomide	67 (63%)
Thalidomide	47 (44%)
Previous steroids	106 (100%)
Dexamethasone	106 (100%)
Previous autologous stem cell transplantation	85 (80%)
Refractory to	
Both proteasome inhibitor and immunomodulatory drug	101 (95%)
Last line of previous therapy	103 (97%)
Bortezomib	95 (90%)
Carfilzomib	51 (48%)
Lenalidomide	93 (88%)
Pomalidomide	67 (63%)
Thalidomide	29 (27%)
Alkylating agent	82 (77%)
Bortezomib + lenalidomide	87 (82%)
Bortezomib + lenalidomide + carfilzomib	42 (40%)
Bortezomib + lenalidomide + pomalidomide	57 (54%)
Bortezomib + lenalidomide + carfilzomib + pomalidomide	33 (31%)

Data are number (%), unless otherwise indicated. *Cytogenetic abnormalities were detected by fluorescence in-situ hybridisation or karyotyping, or both at baseline (n=95).

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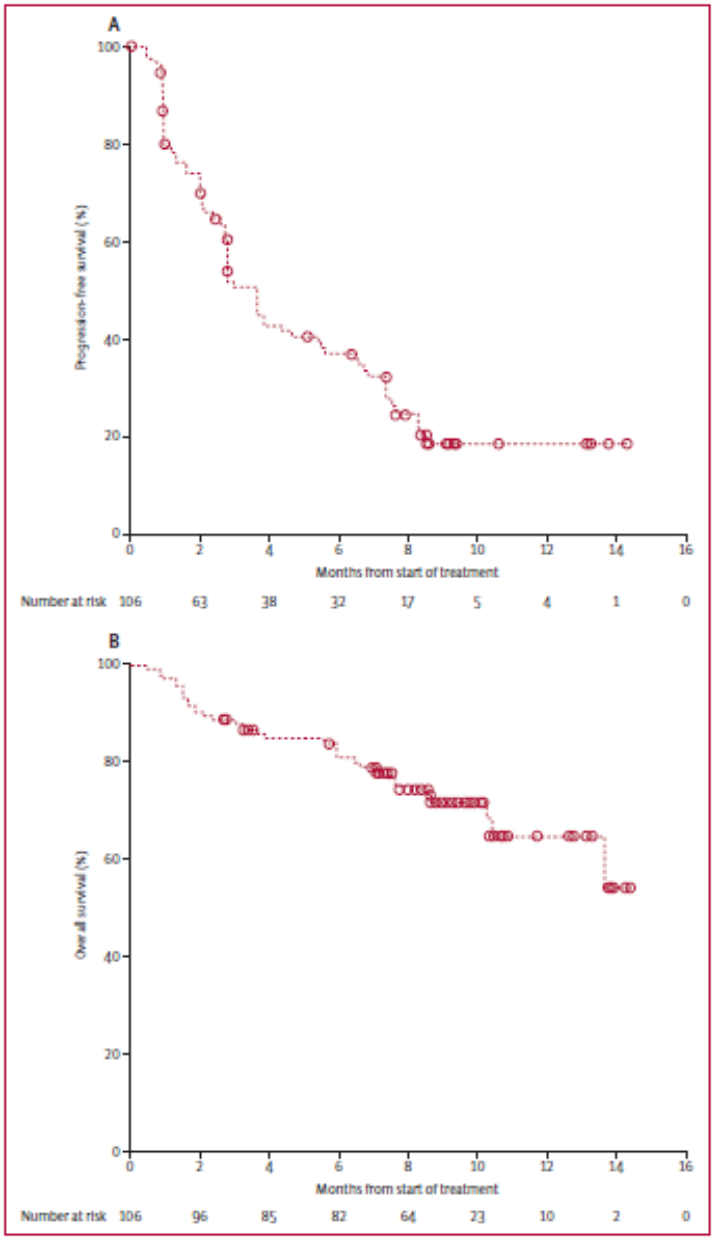
Lonial et al. Lancet 2016; 387:1551

SIRIUS: A Phase II trial with Daratumumab

	Daratumumab 16 mg/kg group (n=106)
Stringent complete response	3 (2·8%, 0·6–8·0)
Complete response	0
Very good partial response	10 (9·4%, 4·6–16·7)
Partial response	18 (17·0%, 10·4–25·5)
Minimal response	5 (4·7%, 1·5–10·7)
Stable disease	46 (43·4%, 33·8–53·4)
Progressive disease	18 (17·0%, 10·4–25·5)
Not evaluable	6 (5·7%, 2·1–11·9)
Overall response rate*	31 (29·2%, 20·8–38·9)
Clinical benefit rate†	36 (34·0%, 25·0–43·8)
Very good partial response or better‡	13 (12·3%, 6·7–20·1)

Data are number (%, 95% CI). *Defined as stringent complete response, complete response, very good partial response, plus partial response. †Defined as overall response rate plus minimal response. ‡Defined as stringent complete response, complete response, plus very good partial response.

Table 2: **Overall best responses**



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Lonial et al. Lancet 2016; 387:1551

SIRIUS: A Phase II trial with Daratumumab

Median time to first response: 1.0 month
Median duration of response: 7.4 months
Median PFR: 3.7 months
Median OS: 17.5 months

	Daratumumab 16 mg/kg (n=106)	
	Any grade	Grade 3 or 4
Fatigue	42 (40%)	3 (3%)
Anaemia	35 (33%)	25 (24%)
Nausea	31 (29%)	0
Thrombocytopenia	27 (25%)	20 (19%)
Neutropenia	24 (23%)	13 (12%)
Back pain	23 (22%)	3 (3%)
Cough	22 (21%)	0 (0%)

Data are number (%).

Table 3: Most common (≥20%) treatment-emergent adverse events

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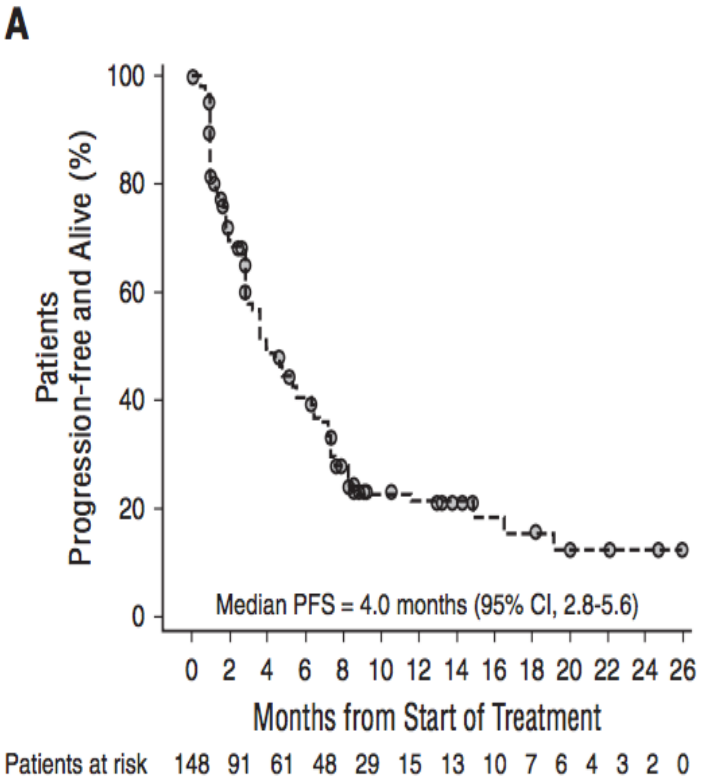
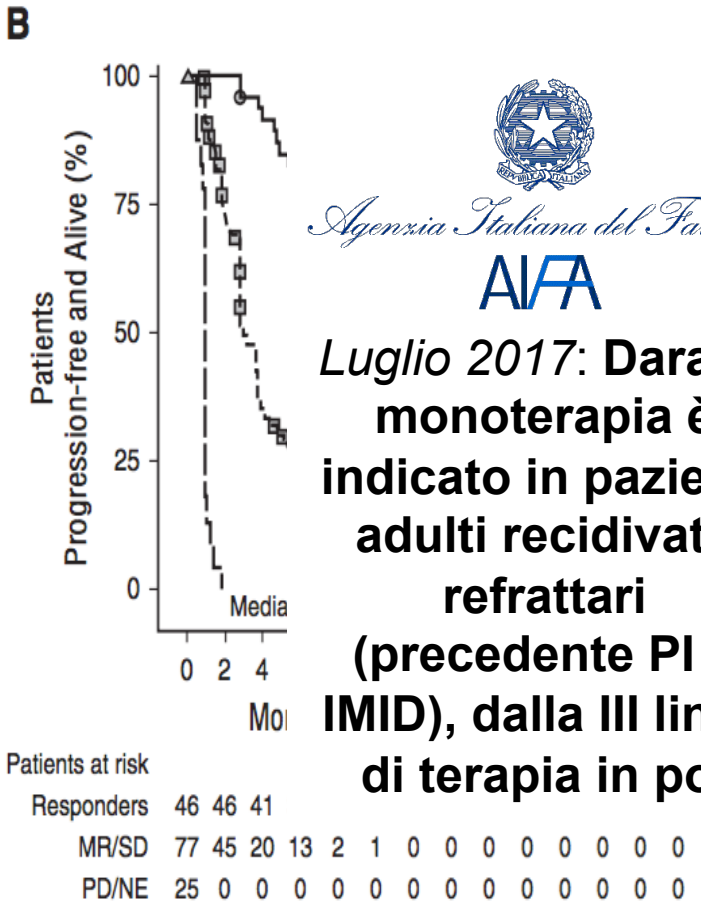
SIRIUS: A Phase II trial with Daratumumab





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Luglio 2017: **Dara in monoterapia è indicato in pazienti adulti recidivati/ refrattari (precedente PI e IMID), dalla III linea di terapia in poi**

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Lonial et al. Lancet 2016; 387:1551

CASTOR Trial on Dara-Vd

Figure S1. Study design.

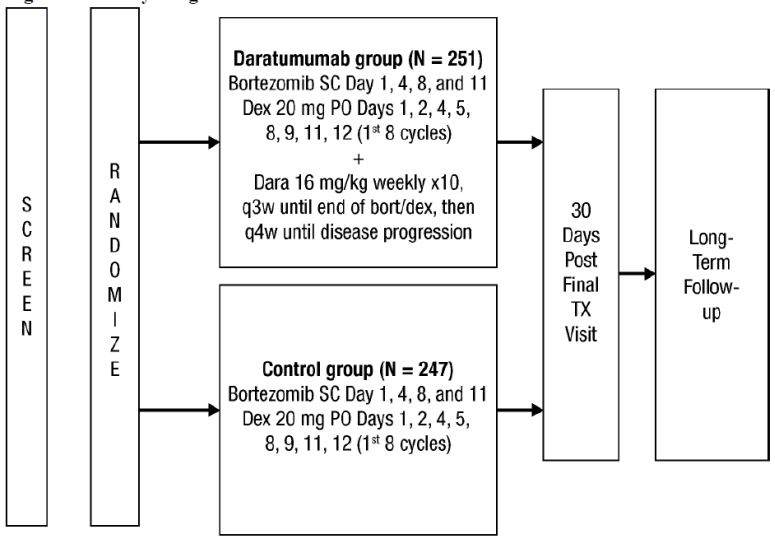

Table 1. Demographic, Baseline Disease, and Clinical Characteristics in the Intention-to-Treat Population.*

Characteristic	Daratumumab Group (N=251)	Control Group (N=247)
Age		
Median (range) — yr	64 (30–88)	64 (33–85)
Distribution — no. (%)		
<65 yr	132 (52.6)	125 (50.6)
65–74 yr	96 (38.2)	87 (35.2)
≥75 yr	23 (9.2)	35 (14.2)
Type of measurable disease — no. (%)		
IgG	125 (49.8)	138 (55.9)
IgA	56 (22.3)	54 (21.9)
Other	5 (2.0)	4 (1.6)
Detected in urine only	40 (15.9)	36 (14.6)
Detected in serum free light-chains only	25 (10.0)	14 (5.7)
Not evaluated	0	1 (0.4)
ISS disease staging — no. (%)†		
I	98 (39.0)	96 (38.9)
II	94 (37.5)	100 (40.5)
III	59 (23.5)	51 (20.6)
Cytogenetic profile — no. (%)‡		
Standard-risk cytogenetic abnormality	140/181 (77.3)	137/174 (78.7)
High-risk cytogenetic abnormality	41/181 (22.7)	37/174 (21.3)
Del17p	28/181 (15.5)	21/174 (12.1)
t(4;14)	14/181 (7.7)	15/174 (8.6)
t(14;16)	4/181 (2.2)	5/174 (2.9)
Median time since initial diagnosis of multiple myeloma (range) — yr	3.87 (0.7–20.7)	3.72 (0.6–18.6)
Number of previous lines of therapy — no. (%)		
1	122 (48.6)	113 (45.7)
2	70 (27.9)	74 (30.0)
3	37 (14.7)	32 (13.0)
>3	22 (8.8)	28 (11.3)
Median no. of previous lines of therapy (range)	2 (1–9)	2 (1–10)
Previous autologous stem-cell transplantation — no. (%)	156 (62.2)	149 (60.3)
Previous alkylating agent therapy — no. (%)	240 (95.6)	224 (90.7)
Previous proteasome inhibitor therapy — no. (%)	169 (67.3)	172 (69.6)
Previous immunomodulatory drug therapy — no. (%)	179 (71.3)	198 (80.2)
Previous proteasome inhibitor + immunomodulatory drug therapy — no. (%)	112 (44.6)	129 (52.2)
Disease refractory to last line of therapy — no. (%)	76 (30.3)	85 (34.4)

Palumbo et al. NEJM 2016;375:754

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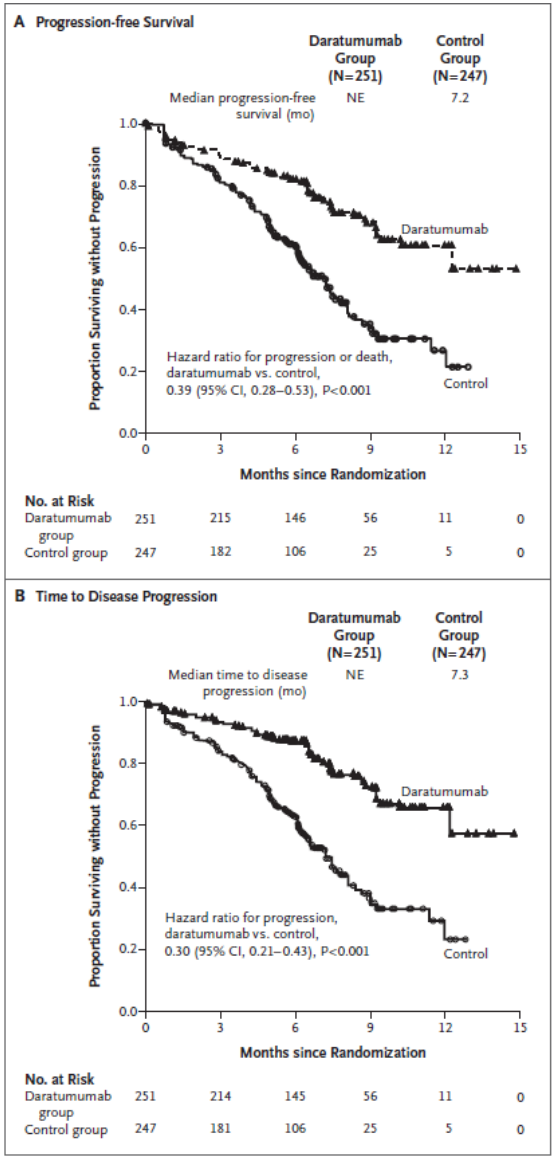
CASTOR Trial on Dara-Vd

Table 2. Summary of Responses among Patients Who Could Be Evaluated for Response.*

Response Category	Daratumumab Group (N=240)	Control Group (N=234)	P Value†
Overall response			
No. with response	199	148	
Rate — % (95% CI)	82.9 (77.5–87.5)	63.2 (56.7–69.4)	<0.001
Best overall response — no. (%)			
Complete response or better	46 (19.2)	21 (9.0)	0.001
Complete response	35 (14.6)	16 (6.8)	
Stringent complete response‡	11 (4.6)	5 (2.1)	
Very good partial response or better	142 (59.2)	68 (29.1)	<0.001
Very good partial response	96 (40.0)	47 (20.1)	
Partial response	57 (23.8)	80 (34.2)	
Minimal response	10 (4.2)	20 (8.5)	
Stable disease	24 (10.0)	47 (20.1)	
Progressive disease	5 (2.1)	16 (6.8)	
Response could not be evaluated	2 (0.8)	3 (1.3)	



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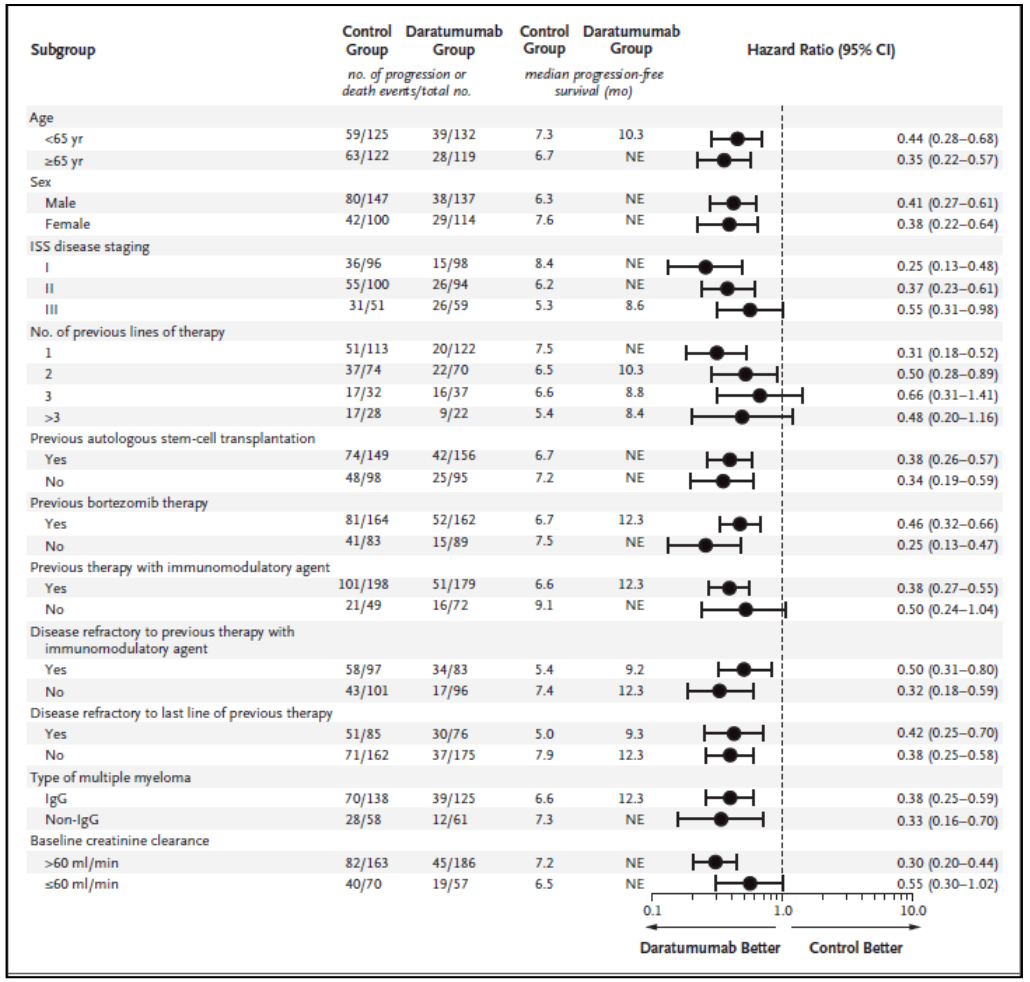
Progressive disease	5 (2.1)	16 (6.8)	
Response could not be evaluated	2 (0.8)	3 (1.3)	



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Palumbo et al. NEJM 2016;375:754

CASTOR Trial on Dara-Vd

Table 3. Most Common Adverse Events in the Safety Population.*

Event	Daratumumab Group (N=243)		Control Group (N=237)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Common hematologic adverse event				
Thrombocytopenia	143 (58.8)	110 (45.3)	104 (43.9)	78 (32.9)
Anemia	64 (26.3)	35 (14.4)	74 (31.2)	38 (16.0)
Neutropenia	43 (17.7)	31 (12.8)	22 (9.3)	10 (4.2)
Lymphopenia	32 (13.2)	23 (9.5)	9 (3.8)	6 (2.5)
Common nonhematologic adverse events				
Peripheral sensory neuropathy	115 (47.3)	11 (4.5)	89 (37.6)	16 (6.8)
Diarrhea	77 (31.7)	9 (3.7)	53 (22.4)	3 (1.3)
Upper respiratory tract infection	60 (24.7)	4 (1.6)	43 (18.1)	2 (0.8)
Fatigue	52 (21.4)	11 (4.5)	58 (24.5)	8 (3.4)
Cough	58 (23.9)	0	30 (12.7)	0
Constipation	48 (19.8)	0	37 (15.6)	2 (0.8)
Dyspnea	45 (18.5)	9 (3.7)	21 (8.9)	2 (0.8)
Insomnia	41 (16.9)	0	35 (14.8)	3 (1.3)
Peripheral edema	40 (16.5)	1 (0.4)	19 (8.0)	0
Asthenia	21 (8.6)	2 (0.8)	37 (15.6)	5 (2.1)
Pyrexia	38 (15.6)	3 (1.2)	27 (11.4)	3 (1.3)
Pneumonia	29 (11.9)	20 (8.2)	28 (11.8)	23 (9.7)
Hypertension	21 (8.6)	16 (6.6)	8 (3.4)	2 (0.8)
Secondary primary cancer†	6 (2.5)	NA	1 (0.4)	NA

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Figure S1. Study design.

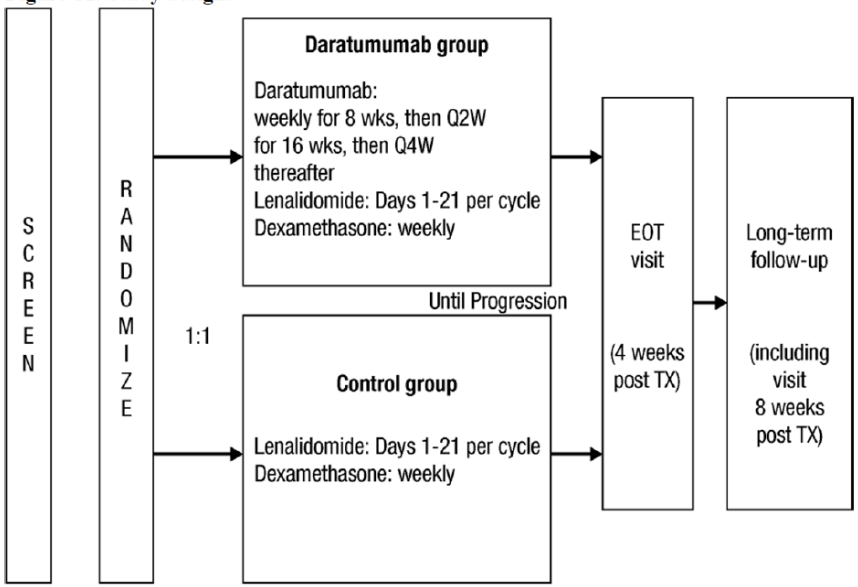

Table 1. Demographic, Baseline Disease, and Clinical Characteristics in the Intention-to-Treat Population.*

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)

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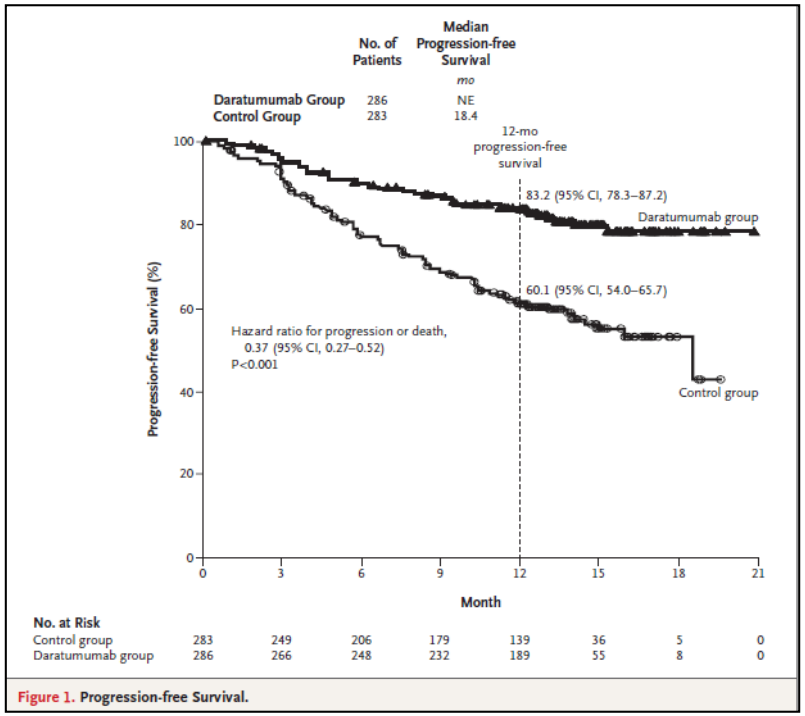

Figure 1. **Progression-free Survival.**

Subgroup	Daratumumab Group (no. of progression events or deaths/total no.)	Control Group (no. of progression events or deaths/total no.)	Daratumumab Group (median progression-free survival (mo))	Control Group (median progression-free survival (mo))	Hazard Ratio (95% CI)
Age					
<65 yr	24/133	55/140	NE	18.4	0.40 (0.24–0.65)
65–74 yr	26/124	43/108	NE	NE	0.40 (0.24–0.67)
≥75 yr	3/29	18/35	NE	11.4	0.11 (0.02–0.51)
ISS disease stage					
I	18/137	40/140	NE	18.4	0.40 (0.23–0.72)
II	21/93	45/86	NE	11.7	0.29 (0.17–0.50)
III	14/56	31/57	NE	8.8	0.40 (0.21–0.76)
No. of previous lines of therapy					
1	27/149	55/146	NE	18.4	0.41 (0.26–0.66)
2	16/85	39/80	NE	11.9	0.29 (0.16–0.53)
3	7/38	14/38	NE	NE	0.36 (0.13–1.03)
>3	3/14	8/19	NE	NE	0.53 (0.10–2.87)
Previous lenalidomide					
Yes	10/50	20/50	NE	NE	0.42 (0.19–0.90)
No	43/236	96/233	NE	18.4	0.36 (0.25–0.52)
Previous proteasome inhibitor					
Yes	48/245	103/242	NE	18.4	0.37 (0.26–0.52)
No	5/41	13/41	NE	NE	0.35 (0.12–1.00)
Refractory to proteasome inhibitor					
Yes	19/64	28/60	NE	12.2	0.50 (0.27–0.93)
No	29/181	75/182	NE	18.4	0.27 (0.17–0.43)
Refractory to last line of therapy					
Yes	23/80	40/76	NE	10.3	0.47 (0.27–0.80)
No	30/206	76/207	NE	18.4	0.32 (0.20–0.49)
Type of multiple myeloma					
IgG	16/151	50/158	NE	18.4	0.30 (0.17–0.52)
IgA	13/49	26/51	NE	11.8	0.44 (0.22–0.89)
Serum free light chain only	13/39	15/33	NE	13.8	0.69 (0.30–1.57)

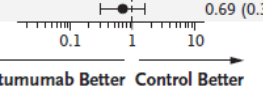

Figure 2. **Prespecified Subgroup Analyses.**

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Table 2. Summary of Responses among Patients with a Response That Could Be Evaluated.*

Response Category	Daratumumab Group (N=281)	Control Group (N=276)	P Value†
Overall response			
No. with response	261	211	—
Rate — % (95% CI)	92.9 (89.2–95.6)	76.4 (71.0–81.3)	<0.001
Clinical benefit — no. (%)‡	266 (94.7)	237 (85.9)	—
Best overall response — no. (%)			
Complete response or better	121 (43.1)	53 (19.2)	<0.001
Stringent complete response§	51 (18.1)	20 (7.2)	—
Complete response	70 (24.9)	33 (12.0)	—
Very good partial response or better	213 (75.8)	122 (44.2)	<0.001
Very good partial response	92 (32.7)	69 (25.0)	—
Partial response	48 (17.1)	89 (32.2)	—
Minimal response	5 (1.8)	26 (9.4)	—
Stable disease	13 (4.6)	33 (12.0)	—
Progressive disease	0	4 (1.4)	—
Response could not be evaluated	2 (0.7)	2 (0.7)	—

Table 3. Most Common Adverse Events during Treatment in the Safety Population.*

Event	Daratumumab Group (N=283)		Control Group (N=281)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Hematologic adverse event				
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)
Nonhematologic adverse event				
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)
Nasopharyngitis	68 (24.0)	0	43 (15.3)	0
Nausea	68 (24.0)	4 (1.4)	40 (14.2)	0
Pyrexia	57 (20.1)	5 (1.8)	31 (11.0)	4 (1.4)
Insomnia	55 (19.4)	1 (0.4)	55 (19.6)	2 (0.7)
Dyspnea	52 (18.4)	9 (3.2)	32 (11.4)	2 (0.7)
Back pain	50 (17.7)	4 (1.4)	48 (17.1)	4 (1.4)
Vomiting	47 (16.6)	3 (1.1)	15 (5.3)	2 (0.7)
Asthenia	45 (15.9)	8 (2.8)	36 (12.8)	7 (2.5)
Peripheral edema	43 (15.2)	2 (0.7)	37 (13.2)	3 (1.1)
Pneumonia	40 (14.1)	22 (7.8)	37 (13.2)	23 (8.2)

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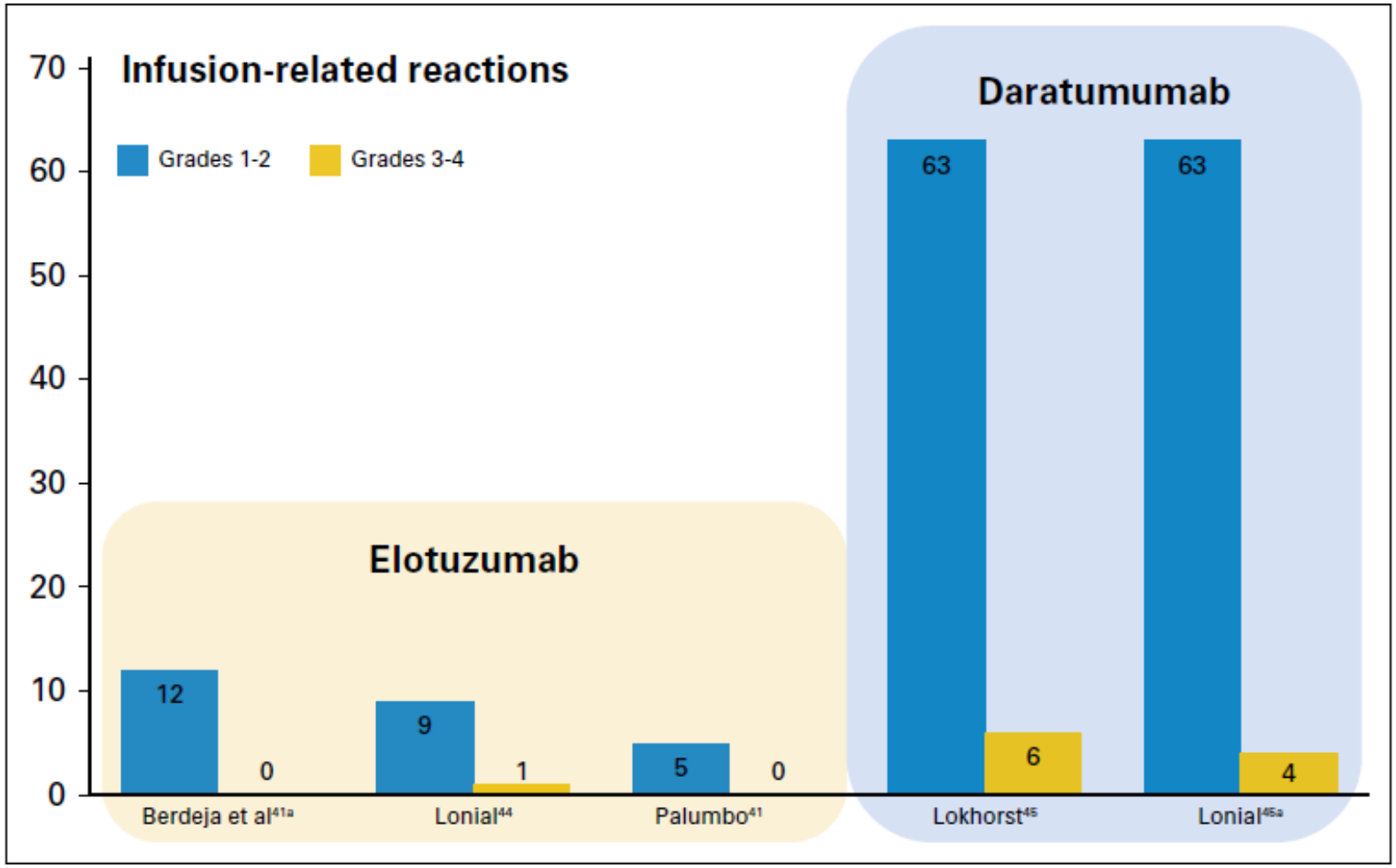
Infusion-Related Reactions



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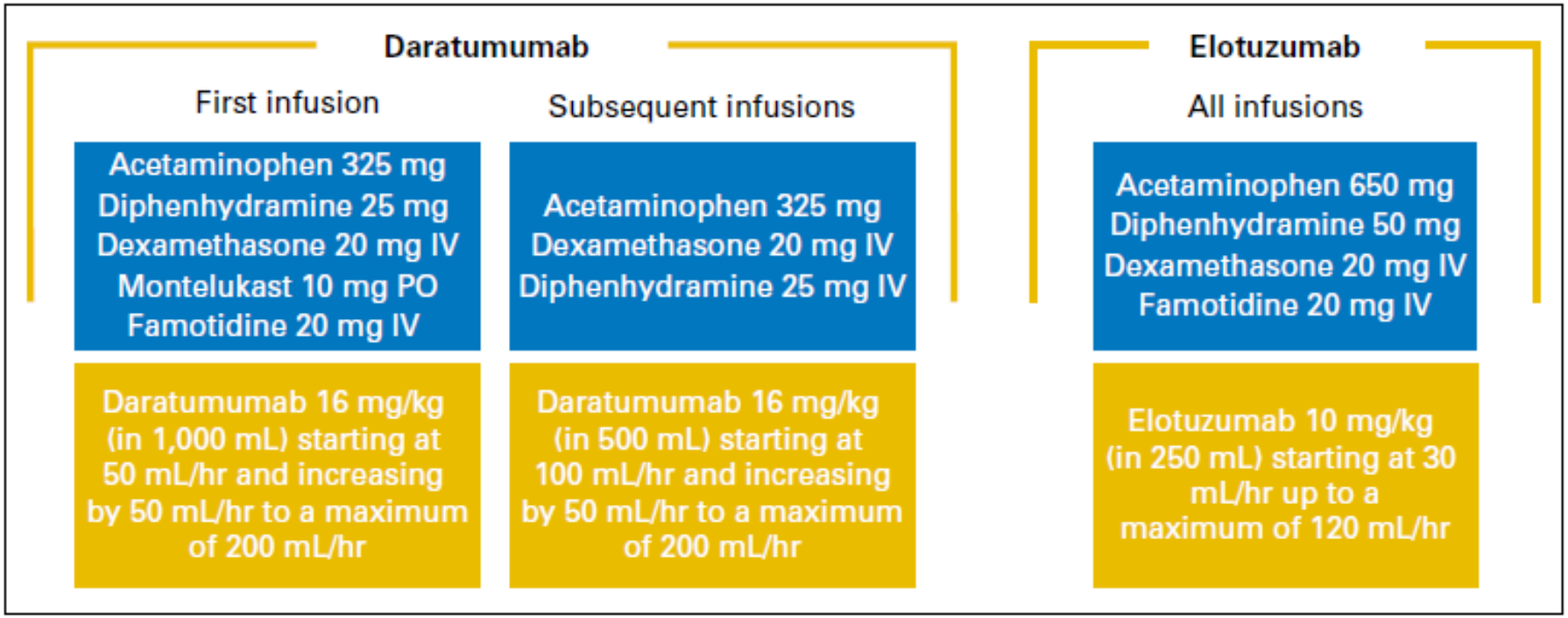
Infusion-Related Reactions



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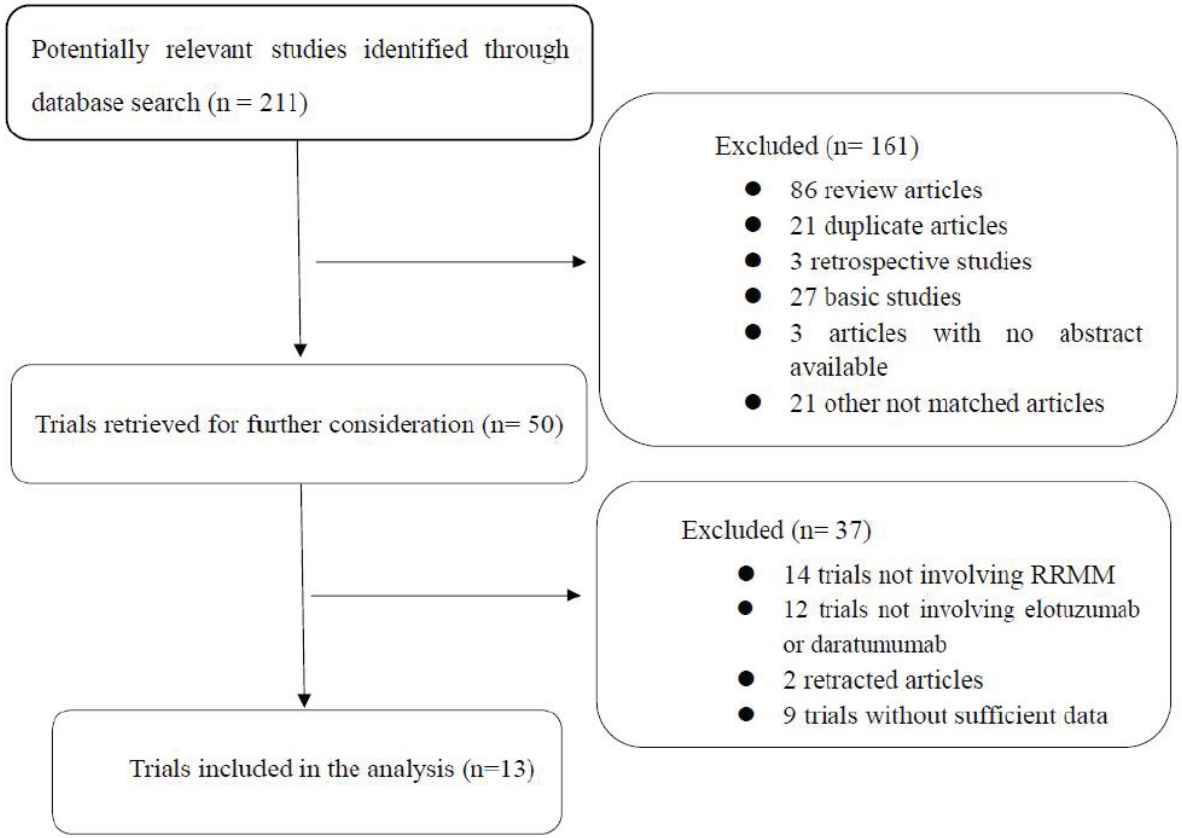

Figure 1: Identification and selection of the studies included in the meta-analysis

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Table 2: Clinical trials information

Study	Trial name	Phase	Median age (range)	Median prior therapy (range)	No. of patients	Regimen	Dose(mg/kg)	Follow-up (months)	Median PFS time (months)	OS rate -year
Elotuzumab										
Jakubowiak A(2016) [32]	NCT01478048	II	65(25-82)	1(1-3)	77	EVd	10	15.9	9.7	73%-2
			65(25-85)	1(1-3)	75	Vd		11.7	6.9	66%-2
Lonial S (2015) [11]	ELOQUENT-2	III	67(37-88)	2(1-4)	321	ERd	10	24.5	19.4	-
			66(38-91)	2(1-4)	325	Rd		24.5	14.9	-
RichardsonP G(2015) [27]	1703	II	60.6(39-77)	2(1-3)	36	ERd	10	21.2	32.49	-
			63.3(41-82)	2(1-3)	37	ERd	20	16.8	25	-
Mateos(2016) [31]	NCT01632150	II	64(49-82)	3(1-8)	40	ETd	10	-	3.9	63%-1
Jakubowiak A J(2012) [30]	NCT00726869	I	63(41-77)	2(1-3)	28	EV	2.5-20	-	9.46(TTP)	-
Lonial S(2012) [28]	NCT00742560	Ib	60(41-83)	3(1-10)	29	ERd	5,10,20	16.4	NR(TTP)	-
Zonder J A(2012) [29]	NCT00425347	I	64.5(46-87)	4.5(2-10)	35	E	0.5-20	-	-	-
Daratumumab										
Palumbo A(2016) [5]	CASTOR	III	64(30-88)	2(1-9)	240	DVd	16	7.4	NR	-
			64(33-85)	2(1-10)	234	Vd		7.4	7.2	-
Dimopoulos M A(2016) [13]	POLLUX	III	65(34-89)	1(1-11)	286	DRd	16	13.5	NR	92%-1
			65(42-87)	1(1-8)	283	Rd		13.5	18.4	87%-1
Lokhorst H M(2015) [35]	GEN501	II	59(38-76)	4(3-10)	30	D	8	16.9	2.4	77%-1
		II	64(44-76)	4(2-12)	42	D	16	10.2	5.6	77%-1
		I	61.5(42-76)	6.3(2-12)	32	D	0.005-24	-	-	-
Lonial S(2016) [12]	SIRIUS	II	63.5(31-84)	5(2-14)	106	D	16	9.3	3.7	65%-1
Plesner T(2016) [34]	GEN503	II	59.5(41-76)	2(1-3)	32	DRd	16	15.6	NE	90%-1.5
		I	62(48-76)	3(2-4)	13	DRd	2-16	23.5	-	-
Chari A(2015) [33]	NCT01998971	Ib	64(35-86)	3.5(2-10)	77	DPd	16	2.4	-	-

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Table 3 : Summary of response and survival outcomes from mAbs

Regimen	No. of trials	ORR (95% CI)	*P* for ORR	At least VGPR(95% CI)	*P* for at least VGPR	OR of ORR (95% CI)	OR of at least VGPR (95% CI)	HR of PFS (95% CI)
mAb	13	57(38-76)		32(19-46)				
Triplet	10	76(69-84)	P_{23}<0.000	48(34-61)	P_{23}<0.000	2.3(1.48-3.56)	2.33(1.25-4.33)	0.52(0.36-0.75)
Doublet	1	48(29-67)	P_{12}=0.002	7(-2-17)	P_{12}=1			
Single	2	17(4-31)	P_{13}<0.000	4(0-8)	P_{13}<0.000			
Elotuzumab	7	60(29-91)		29(15-44)				
Triplet	5	73(61-84)	P_{23}<0.000	38(27-48)	P_{23}=0.002	1.63(1.03-2.58)	1.33(0.97-1.77)	0.70(0.59-0.84)
Doublet	1	48(29-67)	P_{12}<0.000	7(-2-17)	P_{12}=0.192			
Single	1	1(-3-6)	P_{13}<0.000	1(-3-6)	P_{13}<0.000			
Daratumumab	6	54(33-76)		35(13-57)				
Triplet	4	81(71-91)	Pd<0.000	59(44-75)	Pd<0.000	3.25(2.31-4.56)	3.75(2.88-4.88)	0.38(0.30-0.48)
Single(16mg/kg)	2	31(24-38)		11(6-16)				

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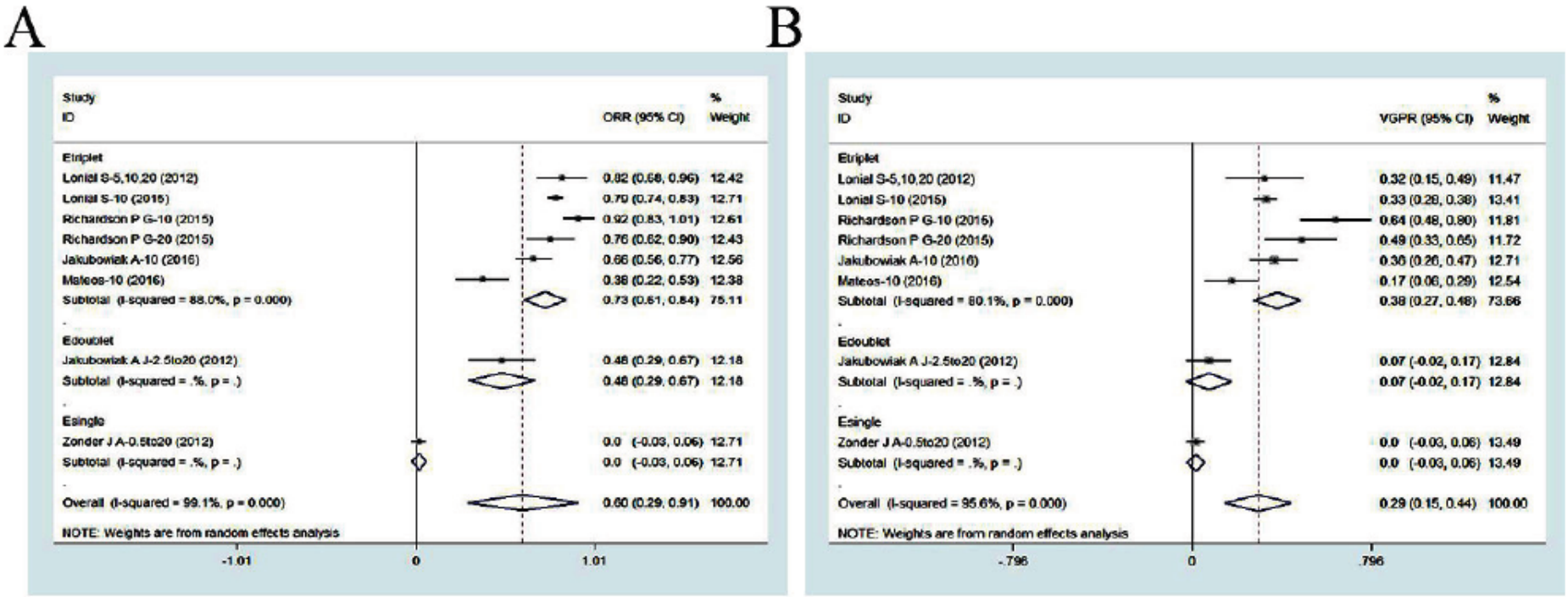

Figure 3: Meta-analysis of the efficacy of elotuzumab-based regimens in patients with RRMM: (A) overall response rate of elotuzuamb-based single, doublet and triplet regimens; (B) at least very good partial response of elotuzumab-based single, doublet and triplet regimens. ORR, overall response rate; VGPR, very good partial response; CI, confidence interval. Etriplet, elotuzumab-based triplet regimen; Edoublet, elotuzumab-based doublet regimen; Esingle, elotuzumab-based single regimen

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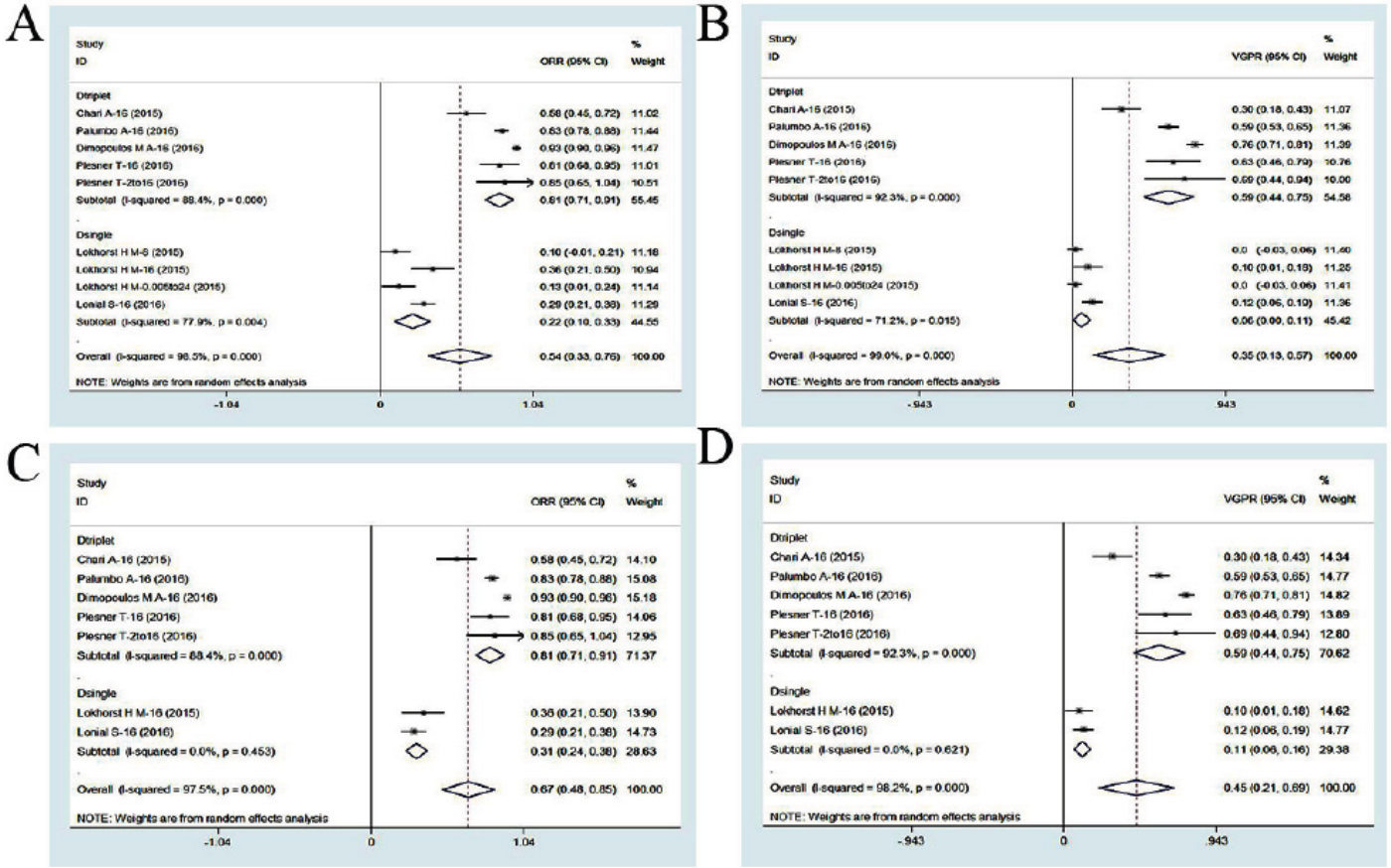

Figure 4: Meta-analysis of the efficacy of daratumumab-based regimens in patients with RRMM:(A) overall response rate of daratumumab-based single and triplet regimens;(B) at least very good partial response of daratumumab-based single and triplet regimens;(C) overall response rate of daratumumab-based monotherapy (16mg/kg);(D) at least very good partial response of daratumumab-based monotherapy (16mg/kg). ORR, overall response rate; VGPR, very good partial response;CI, confidence interval.Dtriplet, daratumumab-based triplet regimen; Dsingle, daratumumab-based single regimen.

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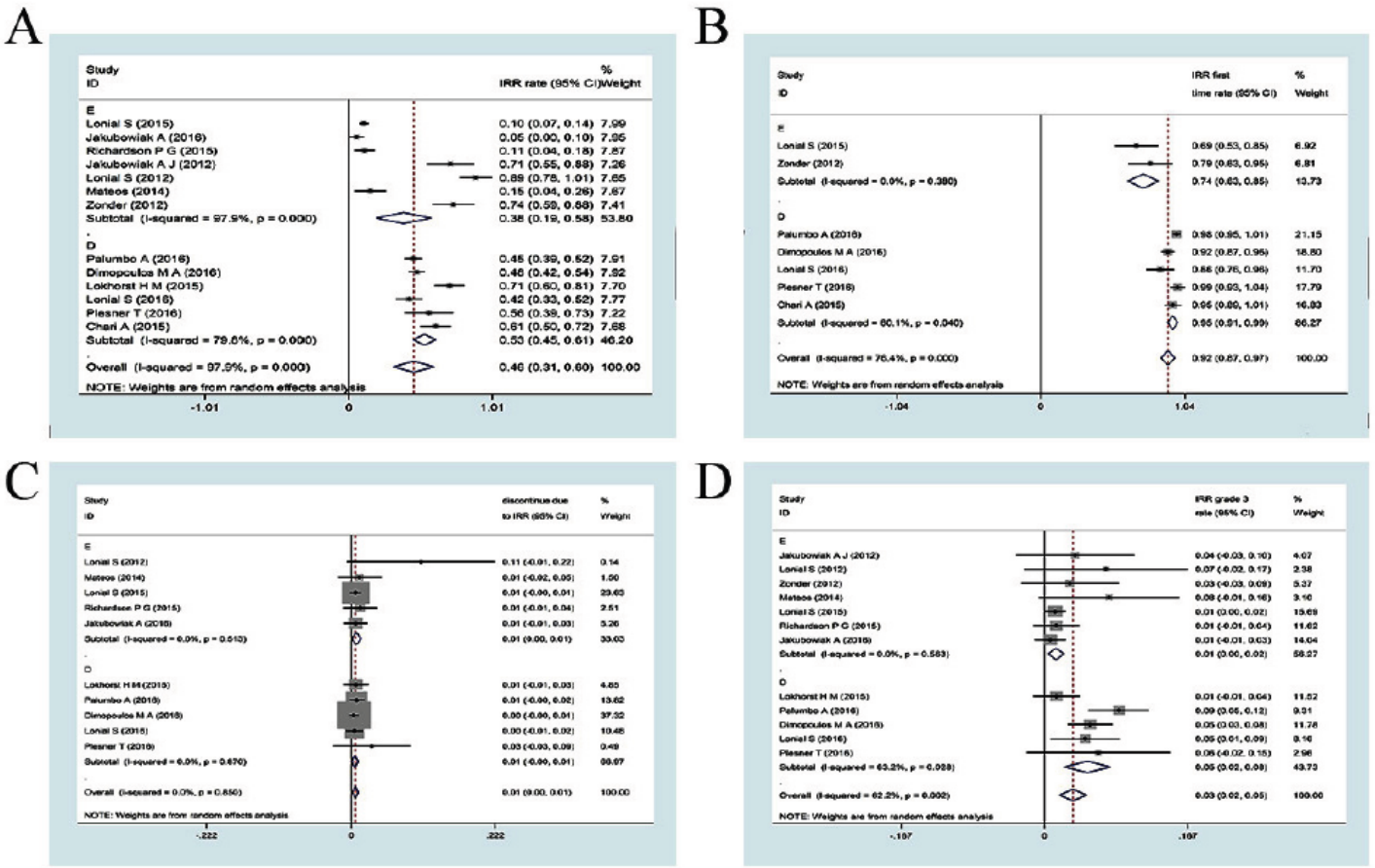

Figure 5: Meta-analysis of the IRRs of mAbs-based regimens in patients with RRMM: (A) any grade infusion-related reactions rate of mAbs;(B) the rate of IRR occurs in first time infusion; (C) grade 3 infusion-related reactions rate of mAbs;(D) the rate of discontinue due to IRRs. IRR, infusion related reactions; CI, confidence interval; E: elotuzumab; D: daratumumab

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Table 5: Summary of response and survival outcomes from novel agent-based regimens

Novel agent	Regimen	Median prior therapy (range)	ORR (%)	At least VGPR (%)	HR of PFS	Median PFS (months)
Triplet						
Daratumumab [13]	D+R+d/R+d	1(1-11)/1(1-8)	92.9/76.4	75.8/44.2	0.37	NR/18.4
Daratumumab [5]	D+V+d/V+d	2(1-9)/2(1-10)	82.9/63.2	59.2/29	0.39	NR/7.2
Carfilzomib [8]	C+R+d/R+d	2(1-3)	87.1/66.7	69.9/40.4	0.69	26.3/17.6
Elotuzumab [11]	E+R+d/R+d	2(1-4)	78.5/65.5	32.7/28	0.70	19.4/14.9
Elotuzumab [32]	E+V+d/V+d	1(1-3)	66.2/62.6	36.3/26.7	0.72	9.7/6.9
Ixazomib [10]	I+R+d/R+d	1(1-3)	78.3/71.5	48.1/39	0.74	20.6/14.7
Panobinostat [9]	P+V+d/V+d	1(1-3)	60.7/54.6	27.6/15.7	0.63	12/8.1
Doublet						
Carfilzomib [39]	C+d/V+d	2(1-3)	76.7/62.4	54/29	0.53	18.7/9.4
Elotuzumab [30]	E+V	2(1-3)	48.1	7.4	NE	9.46
Pomalidomide [7]	Po+d/d	5(2-14)/5(2-17)	31/10	4.6/0.6	0.48	4/1.9
Single						
Daratumumab-16	D	5(2-14)	31	1	NE	4
Carfilzomib [40]	C	5(1-20)	28	10	NE	NE
Pomalidomide [40]	Po	5(1-17)	19	2	NE	NE
Elotuzuamb [29]	E	4.5(2-10)	0	0	NE	NE

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Table 6: Monoclonal antibodies being evaluated in multiple myeloma

Antibody	Target	Phase
Isatuximab (SAR650984)	CD38	III
MOR202	CD38	I/IIa
Milatuzumab	CD74	I/II
Indatuximab ravtansine (drug conjugate)	CD138	I/II
Tabalumab	B-cell activating factor	II
Siltuximab	IL6	II
Lucatumumab	CD40	I
Dacetumumab	CD40	I
BHQ880	DKK1	II
Sotatercept (RAP-011)	Activin receptor ligand trap	IIa
huN901-DM1 (drug conjugate)	CD56	I
Pembrolizumab	PD1	II/III
Nivolumab	PD1	II/III
Atezolizumab	CD274 (PD-L1)	I

IL6, interleukin 6; PD1, programmed cell death 1; PD-L1, programmed cell death ligand 1.

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Tiantian Zhang et al. Oncotarget 2017, advanced publication

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Table 1. Patient demographics, baseline characteristics, and disposition

	Isatuximab dose, mg/kg Q2W			Isatuximab dose, mg/kg QW/Q2W		
Characteristic	**3 (n = 4)**	**5 (n = 3)**	**10 (n = 24)**	**10 (n = 12)**	**20 (n = 14)**	**Overall (n = 57)**
Median age (range), y	60 (48-69)	65 (58-67)	58 (45-74)	60 (45-76)	65 (42-74)	61 (42-76)
Female/male, n (%)	3/1 (75/25)	1/2 (33/67)	10/14 (42/58)	7/5 (58/42)	4/10 (29/71)	25/32 (44/56)
Race, n (%)						
White	4 (100)	3 (100)	19 (79)	8 (67)	12 (86)	46 (81)
Black	0	0	3 (13)	2 (17)	2 (14)	7 (12)
Other	0	0	2 (8)	2 (17)	0	4 (7)
Median time since diagnosis (range), y	7 (3-11)	4 (3-4)	5 (1-12)	6 (2-12)	4 (3-17)	4 (1-17)
Type of myeloma at diagnosis, n (%)						
IgG	3 (75)	3 (100)	11 (46)	7 (58)	8 (57)	32 (51)
IgA	1 (25)	0	3 (13)	3 (25)	3 (21)	10 (18)
IgE	0	0	1 (4)	0	0	1 (2)
Light chain	0	0	8 (33)	2 (17)	3 (21)	13 (23)
Staging at diagnosis, n (%)						
Stage I	0	1 (33)	4 (17)	6 (50)	5 (36)	16 (28)
Stage II	2 (50)	1 (33)	4 (17)	1 (8)	3 (21)	11 (19)
Stage III	1 (25)	1 (33)	11 (46)	5 (42)	4 (29)	22 (39)
Missing	1 (25)	0	5 (21)	0	2 (14)	8 (14)
Bone marrow plasma cells, %						
Mean (SD)	43.3 (24.7)	33.3 (28.9)	39.0 (31.9)*	37.9 (21.7)†	47.7 (34.3)‡	40.9 (29.4)
Median (range)	32.5 (28-50)	50.0 (0-50)	31.0 (0-91)	35 (6-75)‡	40 (2-95)	35 (0-95)
Plasmacytoma present at baseline, n (%)	1 (25)	0	3 (13)	0	0	4 (7)
High-risk MM,§ n (%)	1 (25)	1 (33)	8 (33)	1 (8)	4 (29)	15 (26)
Median number of prior regimens (range)	9.5 (3-14)	7 (6-8)	6.5 (2-12)	6.5 (3-15)	8 (5-12)	7 (2-15)
Median number of prior lines (range)	7 (3-12)	6 (5-7)	4 (1-10)	5 (1-8)	6.5 (3-10)	5 (1-12)
Patients with prior stem cell transplant (%)	4 (100)	2 (67)	23 (96)	12 (100)	13 (93)	54 (95)
Patients with prior therapy						
LEN, n (%)	4 (100)	3 (100)	22 (92)	11 (92)	14 (100)	54 (95)
Refractory to LEN, n/N (%)	4/4 (100)	1/3 (33)	21/22 (95)	8/11 (73)	13/14 (93)	47/54 (87)
POM, n (%)	1 (25)	1 (33)	8 (33)	6 (50)	11 (79)	27 (47)
Refractory to POM, n/N (%)	1/1 (100)	1/1 (100)	8/8 (100)	6/6 (100)	11/11 (100)	27/27 (100)
BORT, n (%)	4 (100)	3 (100)	22 (92)	11 (92)	14 (100)	54 (95)
Refractory to BORT, n/N (%)	1/4 (25)	3/3 (100)	15/22 (68)	6/11 (55)	10/14 (71)	35/54 (65)
CAR, n (%)	1 (25)	2 (67)	13 (54)	9 (75)	12 (86)	37 (65)
Refractory to CAR, n/N (%)	1/1 (100)	2/2 (100)	13/13 (100)	6/9 (67)	12/12 (100)	34/37 (92)
Refractory to IMiD-containing regimen	4 (100)	2 (67)	21 (88)	9 (75)	14 (100)	50 (88)

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Table 2. TEAEs and laboratory abnormalities occurring in >20% of patients (all grades) or ≥5% (grade 3/4)

	All-grade/grade 3/4 events, no. of patients					All patients (n =57), n (%)	
	3 mg/kg Q2W (n = 4)	5 mg/kg Q2W (n = 3)	10 mg/kg Q2W (n = 24)	10 mg/kg QW/Q2W (n = 12)	20 mg/kg QW/Q2W (n = 14)	All grades	Grade 3/4
TEAE							
Any event	4/3	3/3	24/21	12/10	14/13	57 (100)	50 (88)
Diarrhea	3/0	2/0	15/0	4/0	6/0	30 (53)	0
Fatigue	3/1	2/0	12/1	5/2	6/0	28 (49)	4 (7)
URTI	2/0	2/0	10/0	6/0	3/0	23 (40)	0
Nausea	2/0	2/0	11/0	1/0	4/0	20 (35)	0
Insomnia	2/0	2/0	9/1	2/0	3/0	18 (32)	1 (2)
Pyrexia	1/0	0/0	8/0	5/0	4/0	18 (32)	0
Dyspnea	0/0	0/0	9/0	2/0	5/2	16 (28)	2 (4)
Cough	3/0	1/0	6/0	2/0	3/0	15 (26)	0
Headache	1/0	0/0	5/0	4/0	3/0	13 (23)	0
Muscle spasms	2/0	2/0	6/0	2/0	1/0	13 (23)	0
Vomiting	1/0	1/0	8/0	1/0	2/0	13 (23)	0
Hypokalemia	0/0	0/0	5/1	3/1	4/1	12 (21)	3 (5)
Nasal congestion	1/0	0/0	4/0	3/0	4/0	12 (21)	0
Pneumonia	0/0	1/1	1/1	1/1	2/2	5 (9)	5 (9)
Lung infection	0/0	0/0	3/2	0/0	1/1	4 (7)	3 (5)
Anaphylactic reaction	1/1	0/0	0/0	0/0	2/2	3 (5)	3 (5)
Febrile neutropenia	0/0	0/0	3/3	0/0	0/0	3 (5)	3 (5)
Laboratory abnormalities*							
Anemia	4/0	3/0	23/9	12/2	12/3	54 (98)	14 (25)
Lymphopenia	2/0	3/1	23/16	11/6	12/9	52 (95)	32 (58)
Neutropenia	3/3	3/2	22/12	11/8	10/8	49 (89)	33 (60)
Leukopenia	3/1	3/1	23/13	11/7	10/7	50 (91)	29 (53)
Thrombocytopenia	3/2	3/1	23/13	12/0	9/5	50 (91)	21 (38)

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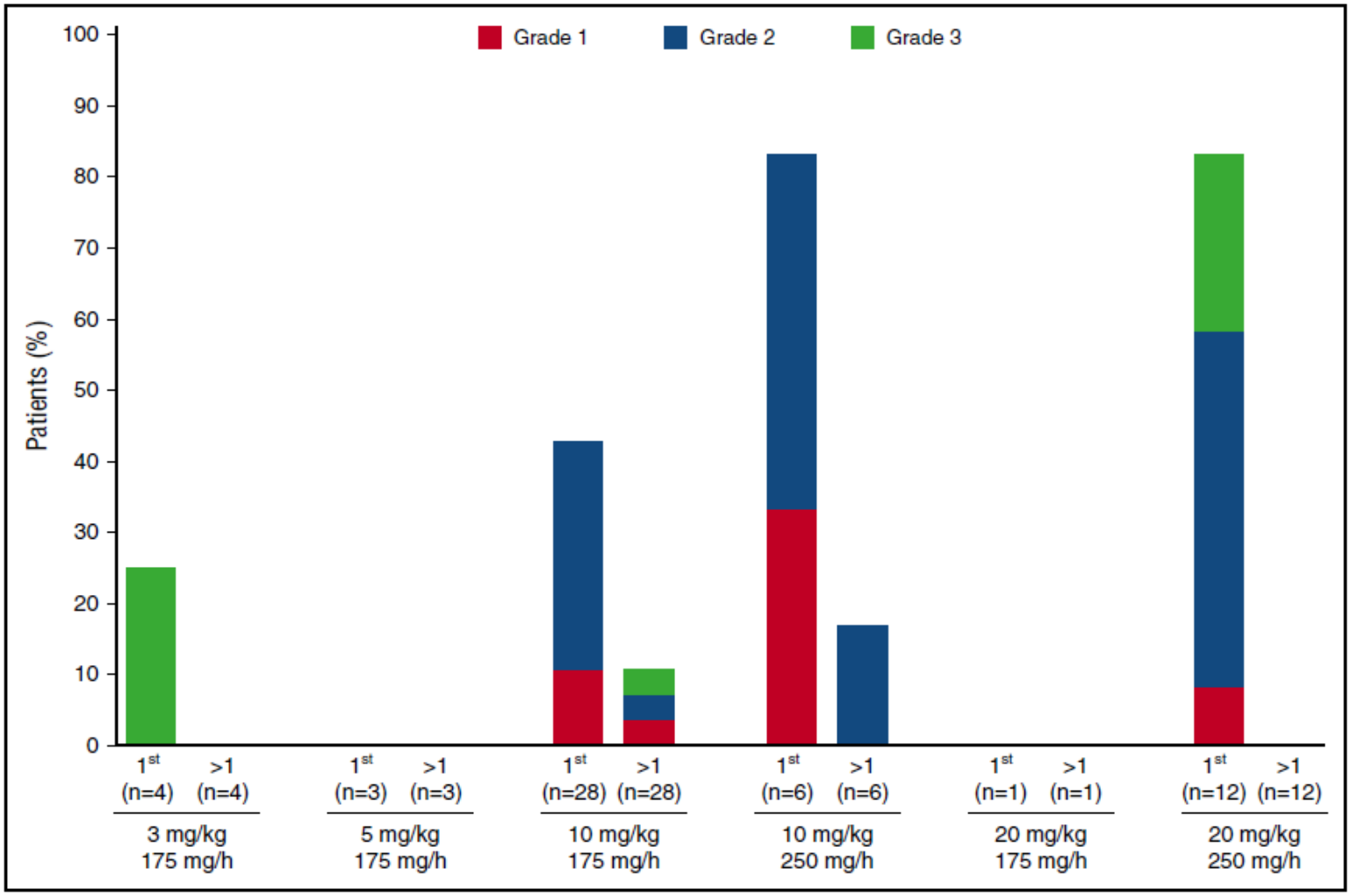

Figure 1. IARs by grade and infusion number. IARs during first infusion or after first infusion are displayed for each dose, according to initial infusion rate. No IARs were observed after the fourth infusion.

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Figure 2. IMWG response overall and by dose: efficacy evaluable population. sCR, stringent complete response.

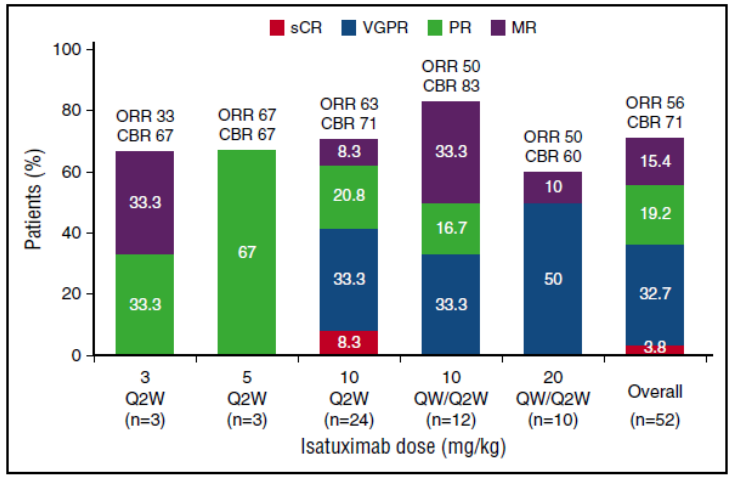
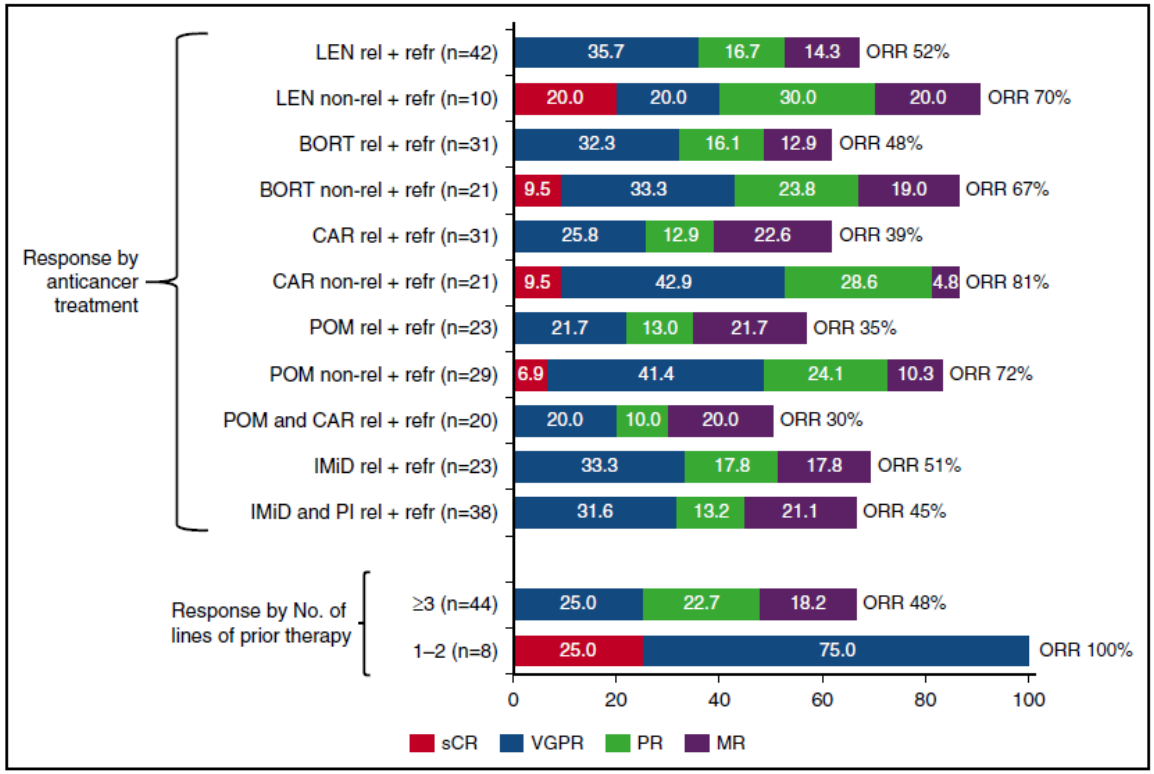


Figure 3. Response rate by previous anticancer therapy



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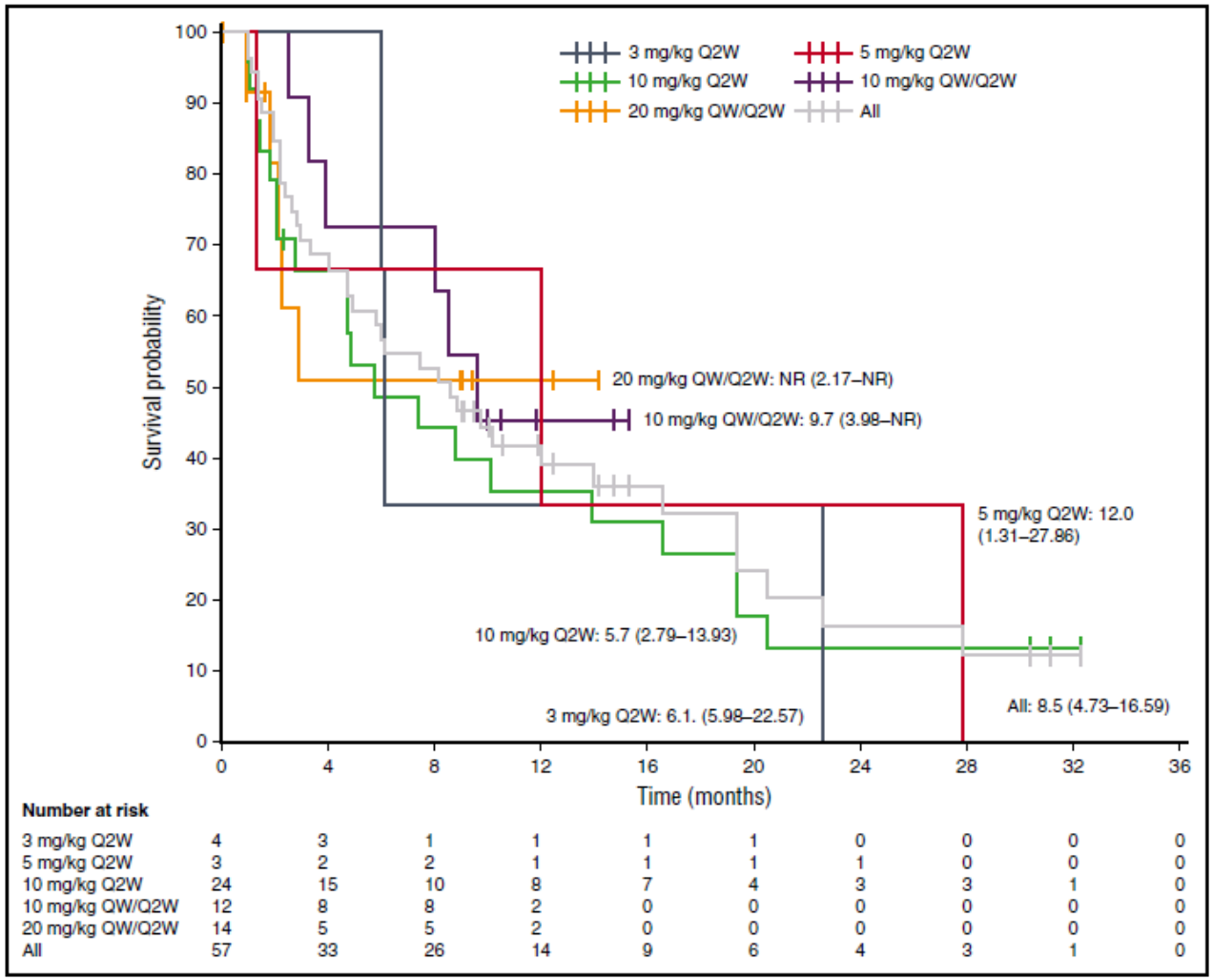

Number at risk

3 mg/kg Q2W	4	3	1	1	1	1	0	0	0	0
5 mg/kg Q2W	3	2	2	1	1	1	1	0	0	0
10 mg/kg Q2W	24	15	10	8	7	4	3	3	1	0
10 mg/kg QW/Q2W	12	8	8	2	0	0	0	0	0	0
20 mg/kg QW/Q2W	14	5	5	2	0	0	0	0	0	0
All	57	33	26	14	9	6	4	3	1	0

Figure 4. Kaplan-Meier analysis of PFS. Median PFS (95% CI) (months) is plotted for each dose cohort and the total population. NR, not reached.

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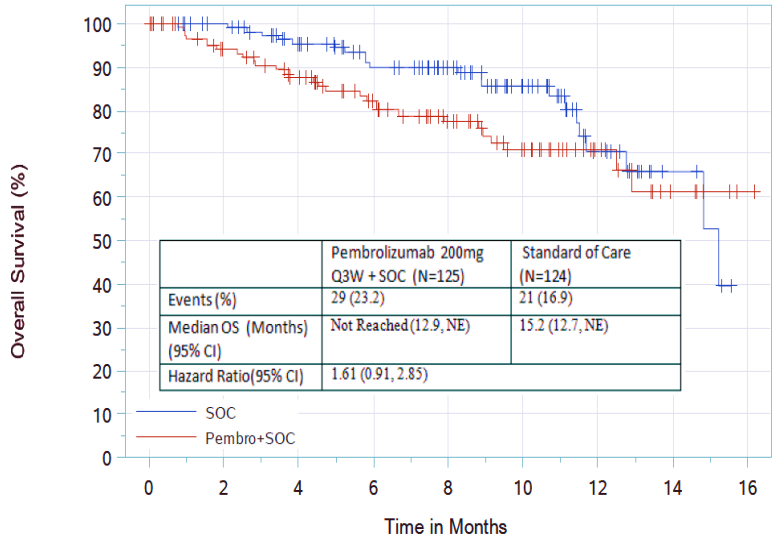
Protocolli sperimentali sospesi nel nostro centro:

- CA209-602:

  An Open-Label, Randomized Phase 3 Trial of Combinations of Nivolumab, Elotuzumab, Pomalidomide and Dexamethasone in Relapsed and Refractory Multiple Myeloma

FROM 01/SEP/17 PARTIAL CLINICAL HOLD, EFFECTIVE IMMEDIATELY.

KEYNOTE-103: Pom-Dex+/-Pembro

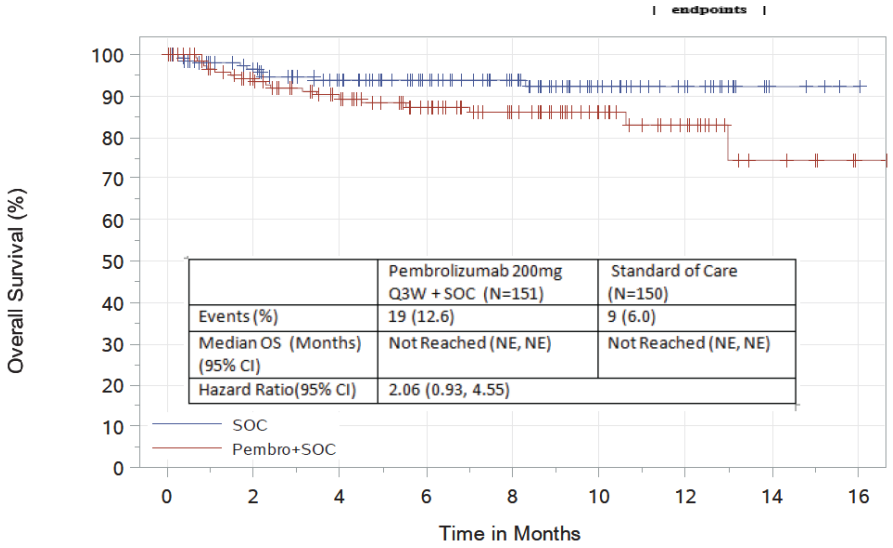


	Pembrolizumab 200mg Q3W + SOC (N=125)	Standard of Care (N=124)
Events (%)	29 (23.2)	21 (16.9)
Median OS (Months) (95% CI)	Not Reached (12.9, NE)	15.2 (12.7, NE)
Hazard Ratio(95% CI)	1.61 (0.91, 2.85)	

Number of Subjects at Risk

SOC	124	115	99	83	67	42	18	6	0
Pembro+SOC	125	105	91	73	53	37	18	7	1

KEYNOTE-185: Len-Dex+/-Pembro



	Pembrolizumab 200mg Q3W + SOC (N=151)	Standard of Care (N=150)
Events (%)	19 (12.6)	9 (6.0)
Median OS (Months) (95% CI)	Not Reached (NE, NE)	Not Reached (NE, NE)
Hazard Ratio(95% CI)	2.06 (0.93, 4.55)	

Number of Subjects at Risk

SOC	150	124	102	82	56	31	19	5	1
Pembro+SOC	151	122	100	79	58	32	20	7	2

Protocolli sperimentali in attivazione:

- MMY2040:

  A Multicenter Phase 2 Study to Evaluate Subcutaneous Daratumumab in Combination with Standard Multiple Myeloma Treatment Regimens

- Dara-SC + VTd in newly diagnosed transplant eligible MM;
- Dara-SC + VMP in newly diagnosed transplant ineligible MM;
- Dara-SC + Rd in relapsed / refractory MM with 1 prior line of therapy

Grazie per l’attenzione

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