The Most Relevant News in Multiple Myeloma in 2022

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Induction for Transplant-eligible Myeloma Patients

Preferred Regimens
- Bortezomib/lenalidomide/dexamethasone (category 1)
- Carfilzomib/lenalidomide/dexamethasone

Other Recommended Regimens
- Daratumumab/lenalidomide/bortezomib/dexamethasone

Useful In Certain Circumstances
- Bortezomib/thalidomide/dexamethasone (category 1)
- Bortezomib/cyclophosphamide/dexamethasone[e]
- Bortezomib/doxorubicin/dexamethasone
- Carfilzomib/cyclophosphamide/dexamethasone[f]
- Cyclophosphamide/lenalidomide/dexamethasone
- Daratumumab/bortezomib/thalidomide/dexamethasone
- Daratumumab/carfilzomib/lenalidomide/dexamethasone
- Daratumumab/cyclophosphamide/bortezomib/dexamethasone
- Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide/bortezomib[g] (VTD-PACE)
- Ixazomib/cyclophosphamide/dexamethasone[f]
- Ixazomib/lenalidomide/dexamethasone (category 2B)

https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf ; Version 1.2023

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GRIFFIN Trial

Clinical Trial > Blood. 2020 Aug 20;136(8):936-945. doi: 10.1182/blood.2020005288.

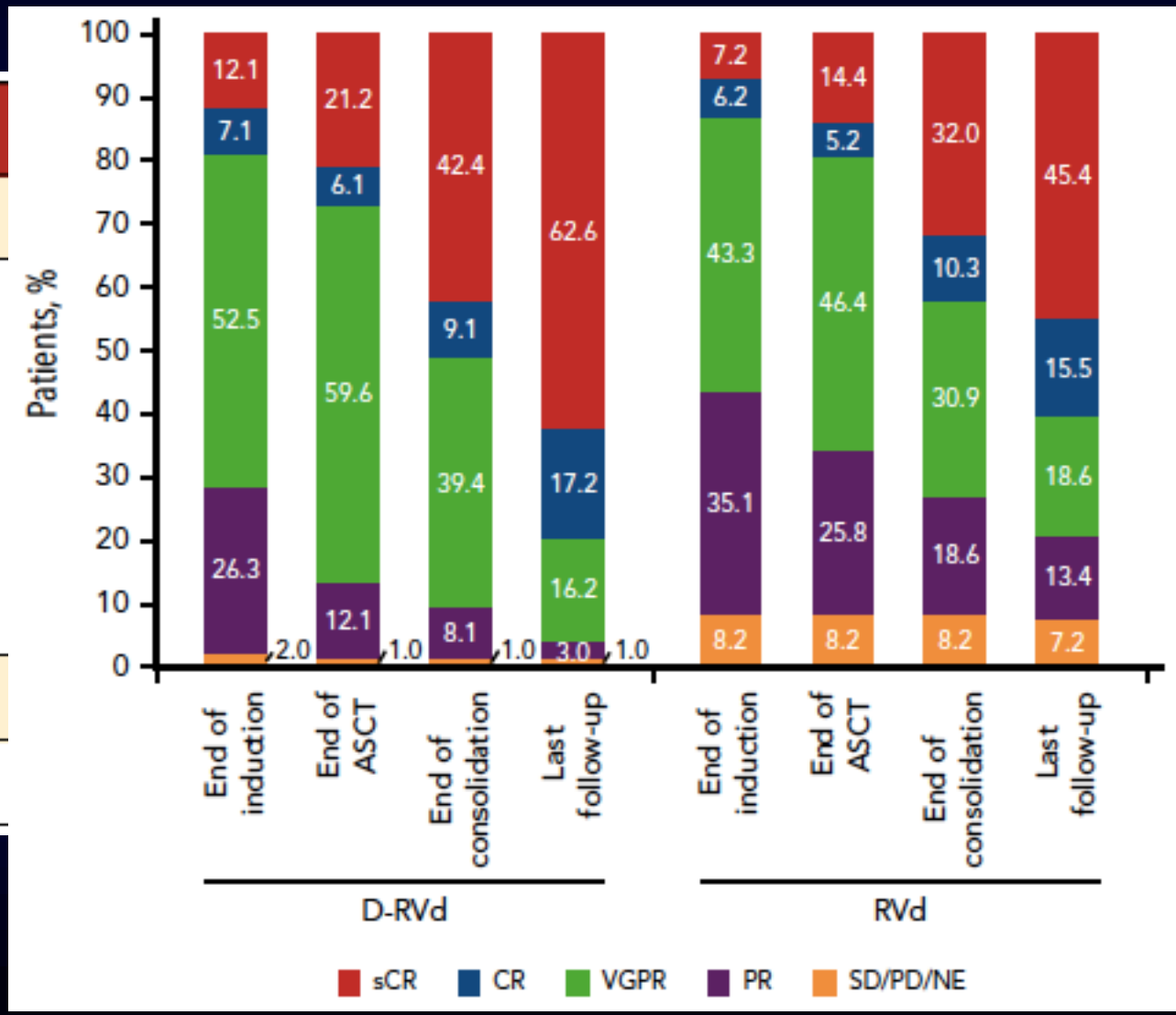
Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial

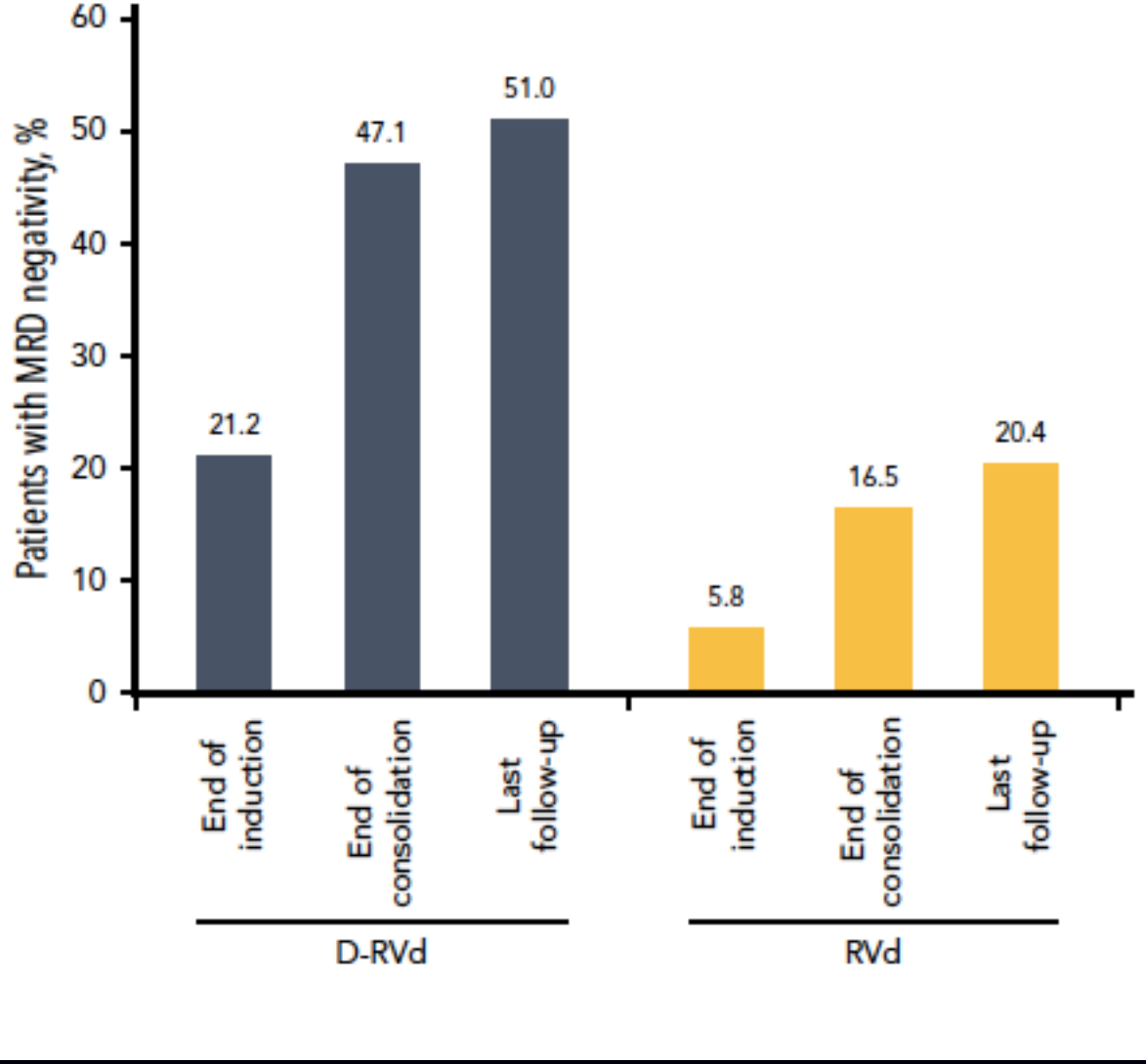
Peter M Voorhees [1], Jonathan L Kaufman [2], Jacob Laubach [3], Douglas W Sborov [4], Brandi Reeves [5], Cesar Rodriguez [6], Ajai Chari [7], Rebecca Silbermann [8], Luciano J Costa [9], Larry D Anderson Jr [10], Nitya Nathwani [11], Nina Shah [12], Yvonne A Efebera [13], Sarah A Holstein [14], Caitlin Costello [15], Andrzej Jakubowiak [16], Tanya M Wildes [17], Robert Z Orlowski [18], Kenneth H Shain [19], Andrew J Cowan [20], Sean Murphy [21], Yana Lutska [21], Huiling Pei [22], Jon Ukropec [23], Jessica Vermeulen [24], Carla de Boer [24], Daniela Hoehn [21], Thomas S Lin [21], Paul G Richardson [3]

Affiliations + expand

PMID: 32325490 PMCID: PMC7441167 DOI: 10.1182/blood.2020005288

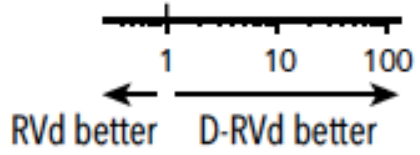
Response Data



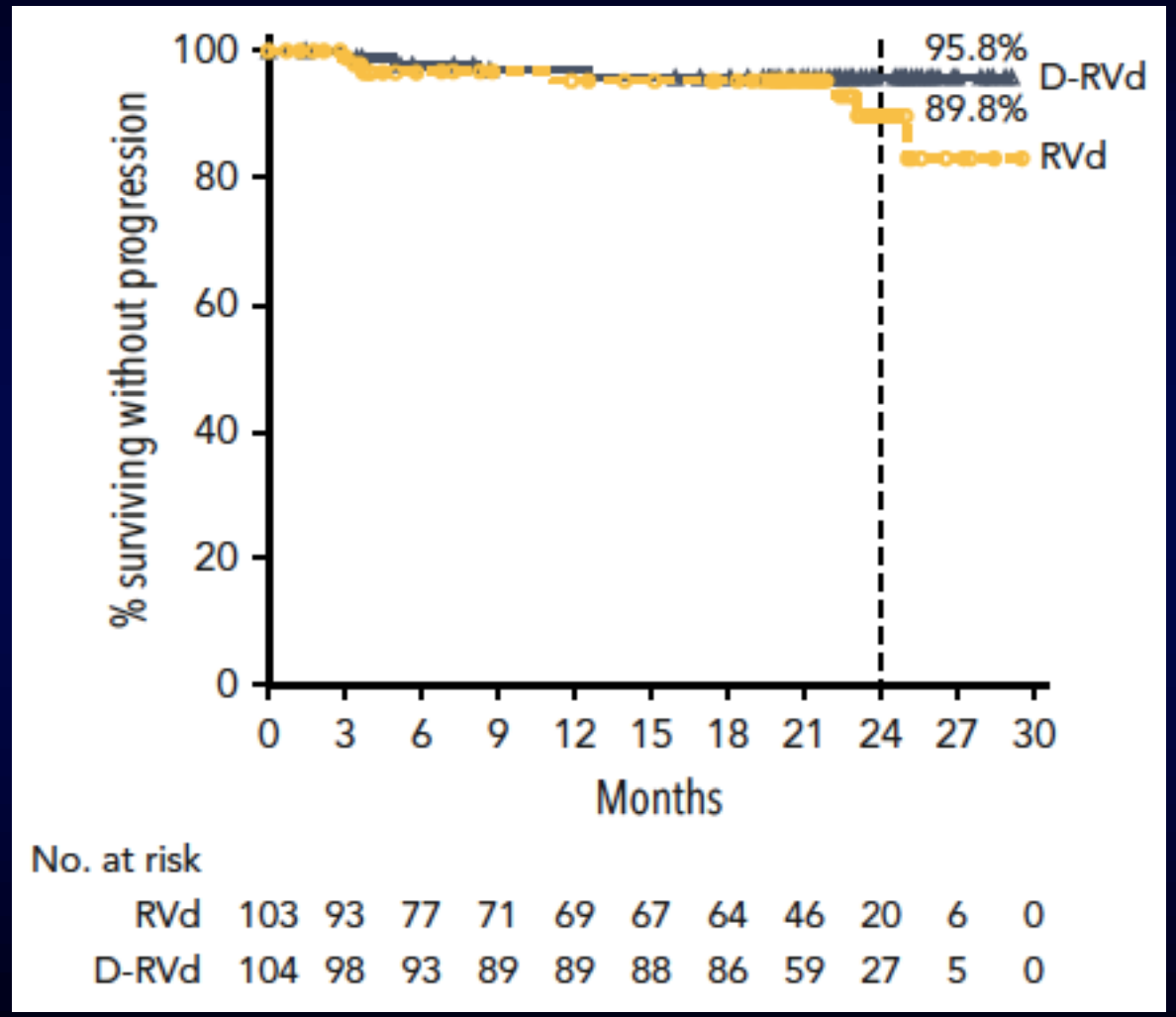


Subgroups & PFS

Subgroup	RVd minimal residual disease negative, n (%)	D-RVd minimal residual disease negative, n (%)	Odds Ratio (95% CI)
Sex			
Male	10/60 (16.7)	26/58 (44.8)	4.06 (1.73-9.54)
Female	11/43 (25.6)	27/46 (58.7)	4.13 (1.68-10.19)
Age			
<65 yr	16/75 (21.3)	38/76 (50.0)	3.69 (1.81-7.52)
≥65 yr	5/28 (17.9)	15/28 (53.6)	5.31 (1.57-17.97)
ISS disease stage			
I	6/50 (12.0)	25/49 (51.0)	7.64 (2.75-21.19)
II	10/37 (27.0)	20/40 (50.0)	2.70 (1.04-7.01)
III	5/14 (35.7)	8/14 (57.1)	2.40 (0.52-10.99)
Type of multiple myeloma			
IgG	11/52 (21.2)	29/55 (52.7)	4.16 (1.78-9.73)
Non-IgG	10/51 (19.6)	22/46 (47.8)	3.76 (1.53-9.26)
Cytogenetic risk			
High risk	4/14 (28.6)	6/16 (37.5)	1.50 (0.32-6.99)
Standard risk	17/83 (20.5)	45/82 (54.9)	4.72 (2.37-9.40)
ECOG PS score			
0	5/40 (12.5)	21/39 (53.8)	8.17 (2.64-25.25)
1 or 2	16/62 (25.8)	32/62 (51.6)	3.07 (1.44-6.53)



22.1 months f/u



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Toxicity

Adverse event, n (%)	D-RVd, n = 99		RVd, n = 102	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Hematologic				
Neutropenia	57 (57.6)	41 (41.4)	36 (35.3)	22 (21.6)
Thrombocytopenia	43 (43.4)	16 (16.2)	36 (35.3)	9 (8.8)
Leukopenia	36 (36.4)	16 (16.2)	29 (28.4)	7 (6.9)
Anemia	35 (35.4)	9 (9.1)	33 (32.4)	6 (5.9)
Lymphopenia	30 (30.3)	23 (23.2)	28 (27.5)	22 (21.6)
Nonhematologic				
Fatigue	68 (68.7)	6 (6.1)	62 (60.8)	6 (5.9)
Upper respiratory tract infection	62 (62.6)	1 (1.0)	45 (44.1)	2 (2.0)
Peripheral neuropathy*	59 (59.6)	7 (7.1)	74 (72.5)	8 (7.8)
Diarrhea	59 (59.6)	7 (7.1)	51 (50.0)	4 (3.9)
Constipation	51 (51.5)	2 (2.0)	40 (39.2)	1 (1.0)
Cough	50 (50.5)	0	27 (26.5)	0
Nausea	49 (49.5)	2 (2.0)	50 (49.0)	1 (1.0)
Pyrexia	45 (45.5)	2 (2.0)	28 (27.5)	3 (2.9)
Insomnia	42 (42.4)	2 (2.0)	31 (30.4)	1 (1.0)
Back pain	36 (36.4)	1 (1.0)	34 (33.3)	4 (3.9)
Peripheral edema	34 (34.3)	2 (2.0)	35 (34.3)	3 (2.9)
Arthralgia	33 (33.3)	0	33 (32.4)	2 (2.0)
Infusion-related reaction	42 (42.4)	6 (6.1)†	NA	NA

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Induction for Transplant-ineligible Myeloma Patients

Preferred Regimens
- Bortezomib/lenalidomide/dexamethasone (category 1)
- Daratumumab/lenalidomide/dexamethasone (category 1)

Other Recommended Regimens
- Daratumumab/bortezomib/melphalan/prednisone (category 1)
- Carfilzomib/lenalidomide/dexamethasone
- Daratumumab/cyclophosphamide/bortezomib/dexamethasone
- Ixazomib/lenalidomide/dexamethasone

Useful In Certain Circumstances
- Lenalidomide/low-dose dexamethasone (category 1)[k]
- Bortezomib/dexamethasone
- Bortezomib/cyclophosphamide/dexamethasone[e]
- Bortezomib/lenalidomide/dexamethasone (VRD-lite) for frail patients
- Carfilzomib/cyclophosphamide/dexamethasone[f]
- Cyclophosphamide/lenalidomide/dexamethasone

https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf ; Version 1.2023

VRd : SWOG0777

Clinical Trial > Blood Cancer J. 2020 May 11;10(5):53. doi: 10.1038/s41408-020-0311-8.

Longer term follow-up of the randomized phase III trial SWOG S0777: bortezomib, lenalidomide and dexamethasone vs. lenalidomide and dexamethasone in patients (Pts) with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant (ASCT)

Brian G M Durie [1], Antje Hoering [2], Rachael Sexton [2], Muneer H Abidi [3], Joshua Epstein [4], S Vincent Rajkumar [5], Angela Dispenzieri [5], Stephen P Kahanic [6], Mohan C Thakuri [7], Frederic J Reu [8], Christopher M Reynolds [9], Robert Z Orlowski [# 10], Bart Barlogie [#]

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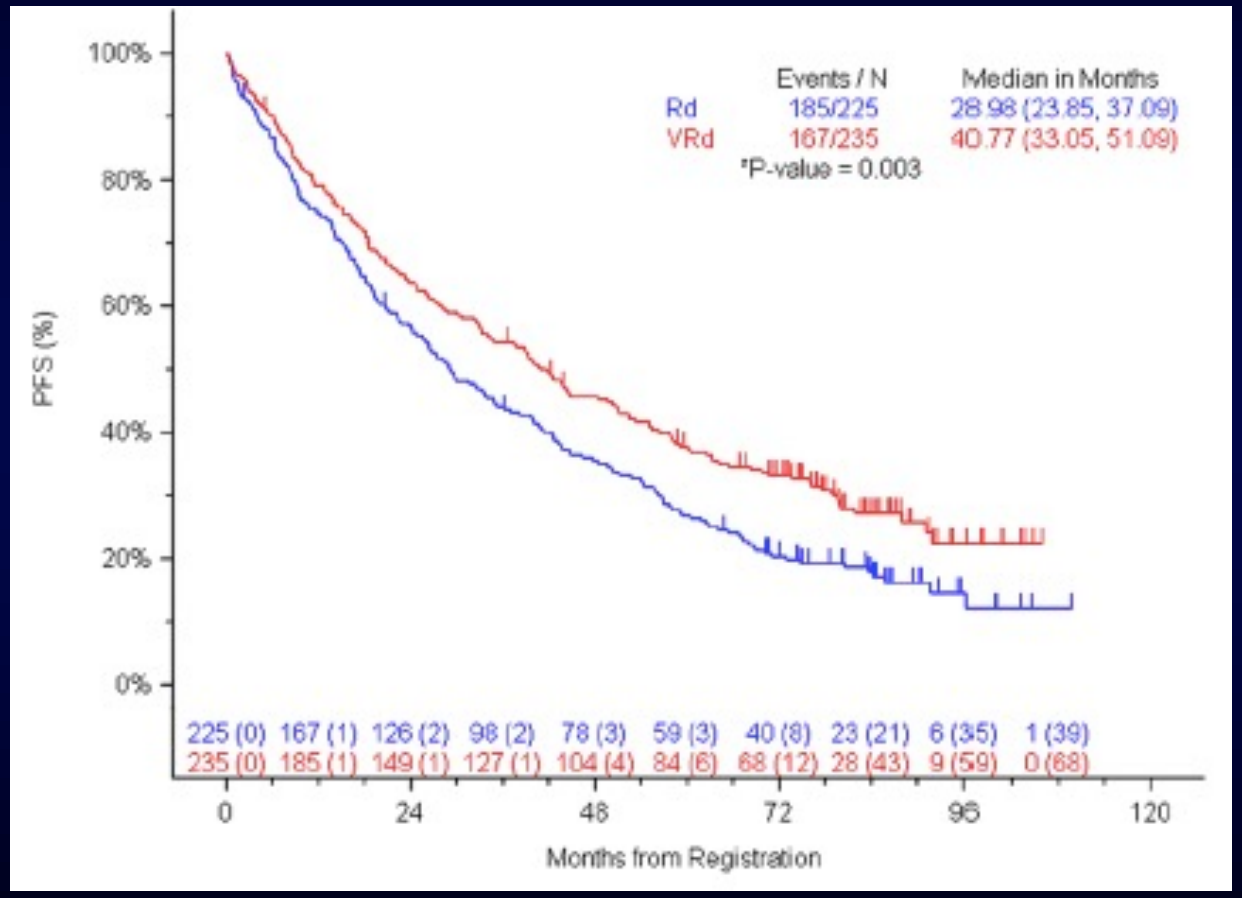
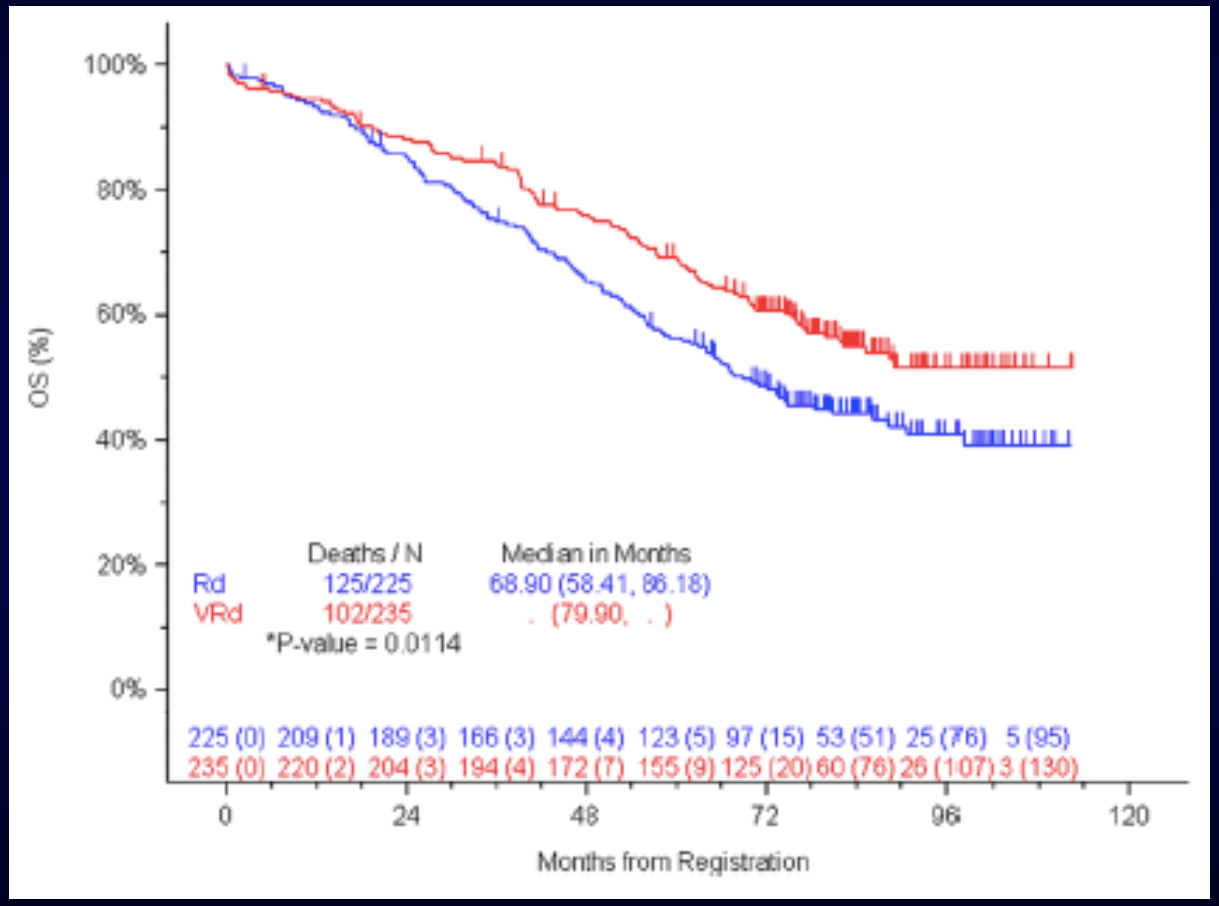
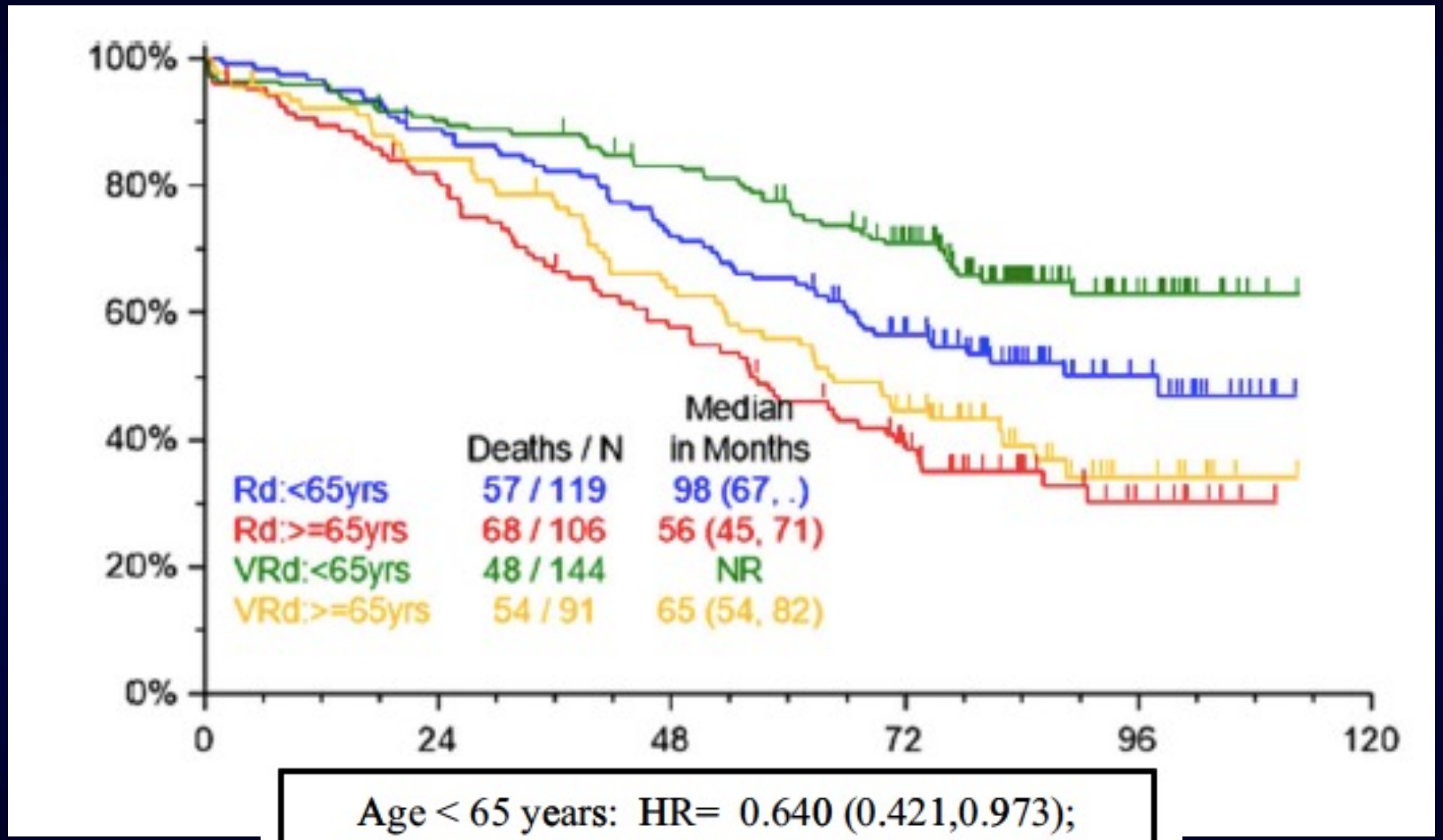
Updated PFS & OS





OS by Age



Age < 65 years: HR= 0.640 (0.421,0.973);
stratified, two-sided p= 0.028

Age ≥ 65 years: HR= 0.769 (0.520,1.138);
stratified, two-sided p= 0.168

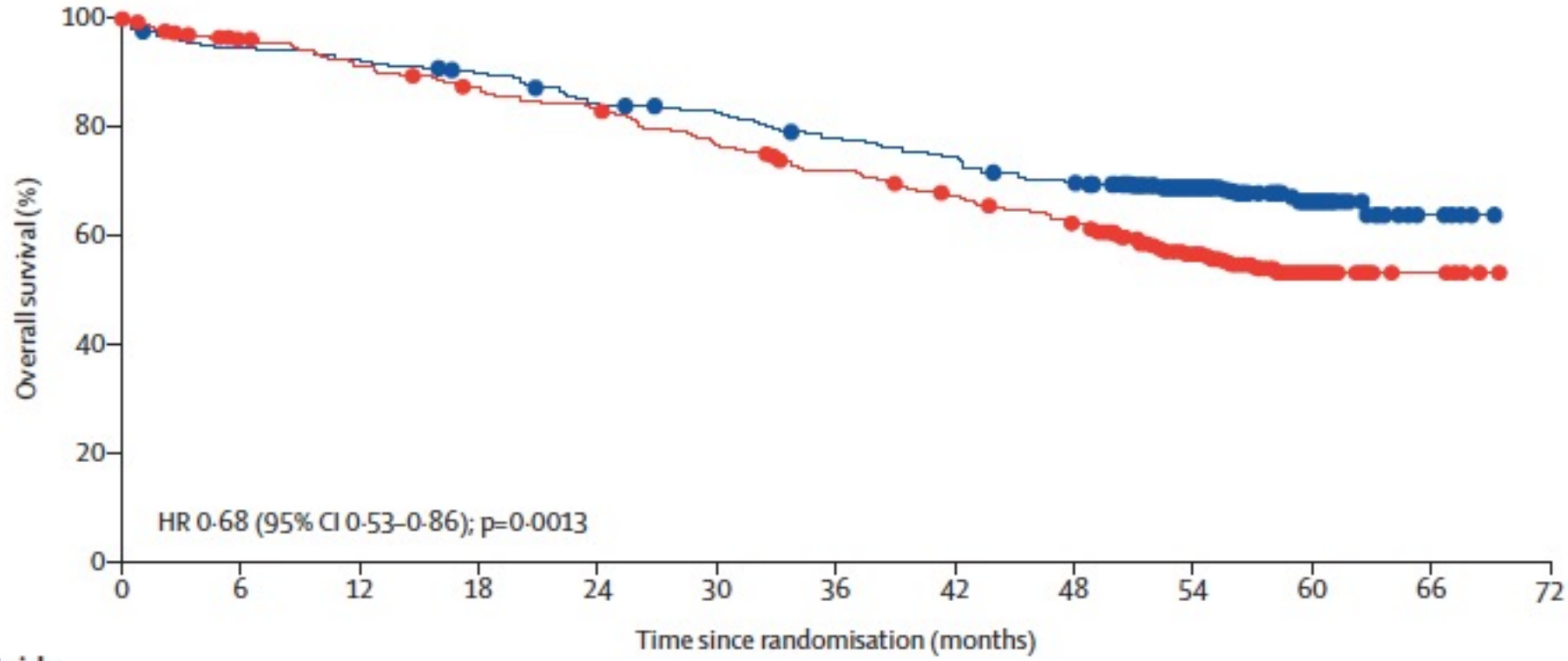
DRd : MAIA

Clinical Trial > Lancet Oncol. 2021 Nov;22(11):1582-1596.
doi: 10.1016/S1470-2045(21)00466-6. Epub 2021 Oct 13.

Daratumumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone alone in newly diagnosed multiple myeloma (MAIA): overall survival results from a randomised, open-label, phase 3 trial

Thierry Facon [1], Shaji K Kumar [2], Torben Plesner [3], Robert Z Orlowski [4], Philippe Moreau [5], Nizar Bahlis [6], Supratik Basu [7], Hareth Nahi [8], Cyrille Hulin [9], Hang Quach [10], Hartmut Goldschmidt [11], Michael O'Dwyer [12], Aurore Perrot [13], Christopher P Venner [14], Katja Weisel [15], Joseph R Mace [16], Noopur Raje [17], Mourad Tiab [18], Margaret Macro [19], Laurent Frenzel [20], Xavier Leleu [21], Tahamtan Ahmadi [22], Jianping Wang [23], Rian Van Rampelbergh [24], Clarissa M Uhlar [25], Brenda Tromp [26], Maria Delioukina [25], Jessica Vermeulen [26], Saad Z Usmani [27]

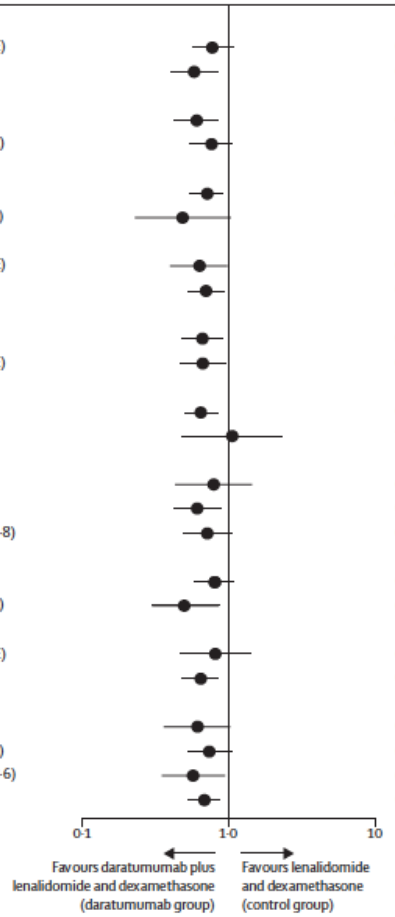
Updated PFS & OS



Number at risk (number censored)													
Lenalidomide and dexamethasone	369 (0)	343 (13)	324 (14)	308 (16)	294 (16)	270 (17)	251 (20)	232 (22)	213 (24)	134 (85)	42 (171)	5 (208)	0 (213)
Daratumumab plus lenalidomide and dexamethasone	368 (0)	346 (3)	338 (3)	328 (5)	305 (6)	297 (8)	280 (9)	266 (9)	249 (10)	170 (86)	63 (189)	6 (245)	0 (251)

Subgroups & Response Data

	Daratumumab plus lenalidomide and dexamethasone group		Lenalidomide and dexamethasone group		Hazard ratio (95% CI)
	Deaths (n)/ patients (N)	Median overall survival, months (95% CI)	Deaths (n)/ patients (N)	Median overall survival, months (95% CI)	
Sex					
Male	71/189	NE (NE–NE)	88/195	57·2 (49·1–NE)	0·78 (0·57–1·06)
Female	46/179	NE (NE–NE)	68/174	NE (58·3–NE)	0·58 (0·40–0·84)
Age					
<75 years	52/208	NE (NE–NE)	80/208	NE (NE–NE)	0·60 (0·42–0·85)
≥75 years	65/160	NE (58·8–NE)	76/161	55·7 (47·3–NE)	0·76 (0·55–1·06)
Race					
White	106/336	NE (NE–NE)	138/339	NE (56·0–NE)	0·71 (0·55–0·91)
Other	11/32	NE (43·4–NE)	18/30	49·1 (32·1–NE)	0·48 (0·23–1·03)
Region					
North America	33/101	NE (NE–NE)	46/102	55·7 (46·5–NE)	0·63 (0·40–0·98)
Other	84/267	NE (NE–NE)	110/267	NE (57·2–NE)	0·70 (0·53–0·93)
Baseline renal function (creatine clearance)					
>60 mL/min	59/206	NE (NE–NE)	89/227	NE (57·2–NE)	0·66 (0·48–0·92)
≤60 mL/min	58/162	NE (62·8–NE)	67/142	54·8 (47·3–NE)	0·67 (0·47–0·96)
Baseline hepatic function*					
Normal	104/335	NE (NE–NE)	144/340	NE (55·1–NE)	0·65 (0·51–0·84)
Impaired	13/31	NE (23·6–NE)	12/29	NE (38·6–NE)	1·05 (0·48–2·30)
International Staging System disease stage†					
I	19/98	NE (NE–NE)	24/103	NE (NE–NE)	0·79 (0·43–1·44)
II	50/163	NE (NE–NE)	69/156	NE (48·9–NE)	0·61 (0·42–0·88)
III	48/107	62·8 (42·4–NE)	63/110	47·3 (33·9–54·8)	0·72 (0·49–1·04)
Type of multiple myeloma‡					
IgG	74/225	NE (NE–NE)	90/231	NE (58·3–NE)	0·80 (0·59–1·09)
Non-IgG	22/74	NE (NE–NE)	37/76	53·7 (41·7–NE)	0·50 (0·30–0·86)
Cytogenetic risk at study entry					
High risk	25/48	55·6 (33·2–NE)	26/44	42·5 (29·8–NE)	0·80 (0·46–1·39)
Standard risk	80/271	NE (NE–NE)	116/279	NE (55·7–NE)	0·64 (0·48–0·85)
ECOG performance status					
0	24/127	NE (NE–NE)	36/123	NE (NE–NE)	0·61 (0·36–1·02)
1	64/178	NE (NE–NE)	82/187	58·3 (51·3–NE)	0·74 (0·53–1·03)
≥2	29/63	62·8 (43·4–NE)	38/59	39·0 (27·3–48·6)	0·57 (0·35–0·94)
All patients	**117/368**	**NE (NE–NE)**	**156/369**	**NE (55·7–NE)**	**0·68 (0·53–0·86)**



	Daratumumab plus lenalidomide and dexamethasone group (n=368)	Lenalidomide and dexamethasone group (n=369)	Odds ratio (95% CI)	p value
Overall response	342 (92·9%; 89·8–95·3)	301 (81·6%; 77·2–85·4)	3·00 (1·85–4·86)	<0·0001
Complete response or better	188 (51%)	111 (30%)	2·44 (1·80–3·30)	<0·0001
Stringent complete response	130 (35%)	56 (15%)	3·06 (2·14–4·38)	<0·0001
Complete response	58 (16%)	55 (15%)	..	..
Very good partial response or better	298 (81%)	210 (57%)	3·28 (2·34–4·59)	<0·0001
Very good partial response	110 (30%)	99 (27%)	..	..
Partial response	44 (12%)	91 (25%)	..	..
Stable disease	11 (3%)	55 (15%)	..	..
Progressive disease	1 (<1%)	0	..	..
Response could not be measured	14 (4%)	13 (4%)	..	..
Negative status for minimal residual disease*[13]	114 (31%)	38 (10%)	3·91 (2·62–5·84)	<0·0001

Data presented as n (%; 95% CI), n (%), or odds ratio (95% CI). Odds ratios and p values were provided for the the key secondary endpoints that were part of the hierarchical testing procedure; the odds ratio, 95% CI, and p value for stringent complete response were also generated. *These values are from a median follow-up of 47·9 months (IQR 44·2–51·3).

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Induction Therapy Summary

- Transplant-eligible patients
  - Dara-VRd when possible
  - Phase III data coming (PERSEUS)
- Transplant-ineligible patients
  - Dara-Rd for standard risk
  - VRd-lite for molecularly high risk
  - Data coming for quadruplets (CEPHEUS (Dara) & IMROZ (Isa))

Maintenance Therapy

Transplant eligible

Preferred Regimens
- Lenalidomide[h] (category 1)

Other Recommended Regimens
- Bortezomib
- Daratumumab
- Ixazomib (category 2B)[i]

Useful In Certain Circumstances
- Bortezomib/lenalidomide ± dexamethasone[j]
- Carfilzomib/lenalidomide[j]

Transplant ineligible

Preferred Regimens
- Lenalidomide (category 1)

Other Recommended Regimens
- Bortezomib
- Ixazomib (category 2B)[i]

Useful In Certain Circumstances
- Bortezomib/lenalidomide[j]

https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf ; Version 1.2023

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FORTE Study

Clinical Trial > Lancet Oncol. 2021 Dec;22(12):1705-1720.
doi: 10.1016/S1470-2045(21)00535-0. Epub 2021 Nov 11.

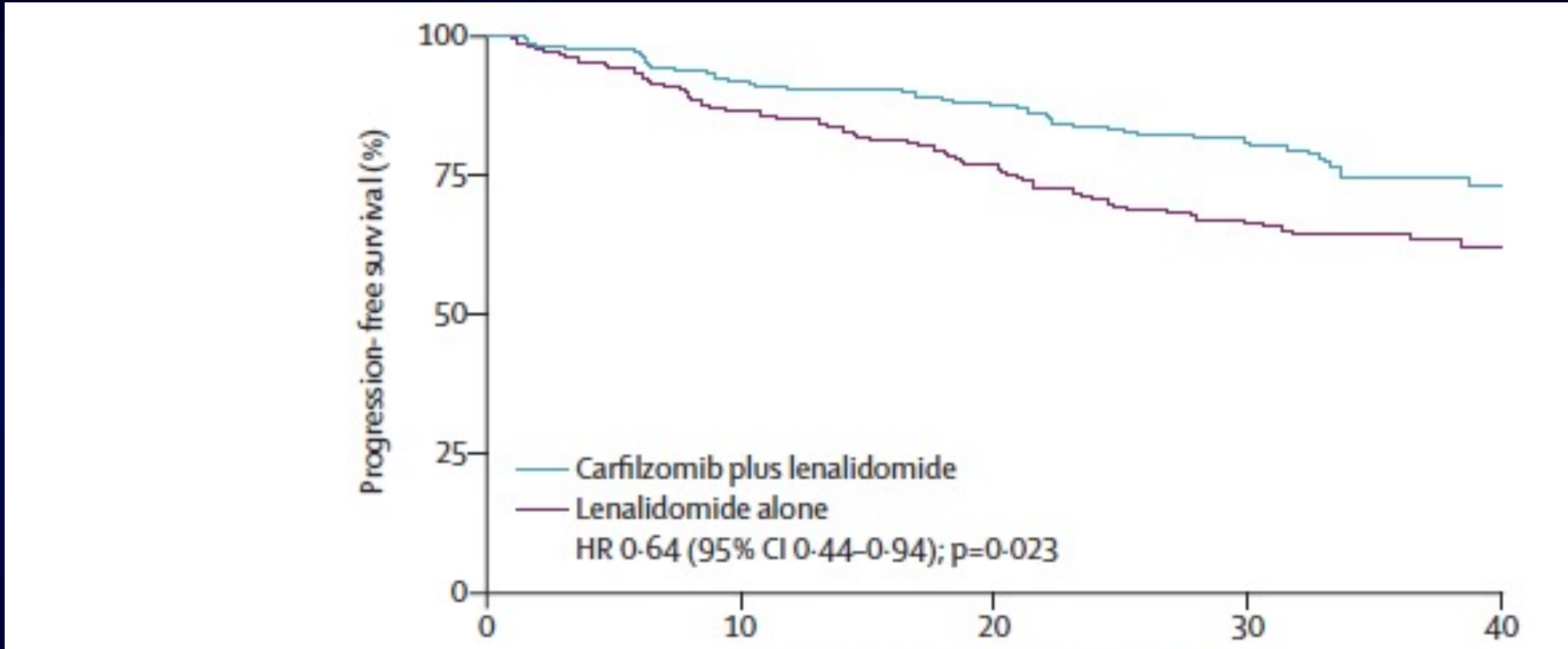
Carfilzomib with cyclophosphamide and dexamethasone or lenalidomide and dexamethasone plus autologous transplantation or carfilzomib plus lenalidomide and dexamethasone, followed by maintenance with carfilzomib plus lenalidomide or lenalidomide alone for patients with newly diagnosed multiple myeloma (FORTE): a randomised, open-label, phase 2 trial

Francesca Gay [1], Pellegrino Musto [2], Delia Rota-Scalabrini [3], Luca Bertamini [4], Angelo Belotti [5], Monica Galli [6], Massimo Offidani [7], Elena Zamagni [8], Antonio Ledda [9], Mariella Grasso [10], Stelvio Ballanti [11], Antonio Spadano [12], Michele Cea [13], Francesca Patriarca [14], Mattia D'Agostino [4], Andrea Capra [4], Nicola Giuliani [15], Paolo de Fabritiis [16], Sara Aquino [17], Angelo Palmas [18], Barbara Gamberi [19], Renato Zambello [20], Maria Teresa Petrucci [21], Paolo Corradini [22], Michele Cavo [8], Mario Boccadoro [4]

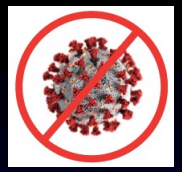
Affiliations + expand

PMID: 34774221 DOI: 10.1016/S1470-2045(21)00535-0

PFS for Second Randomization



Number at risk (number censored)					
Carfilzomib plus lenalidomide	178 (1)	162 (2)	151 (5)	123 (22)	41 (95)
Lenalidomide alone	178 (0)	154 (0)	135 (2)	108 (11)	39 (75)



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Toxicities

	Carfilzomib plus lenalidomide (n=173)			Lenalidomide alone (n=177)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Overall	109 (63%)	64 (37%)	20 (12%)	85 (48%)	56 (32%)	12 (7%)
Haematological*	17 (10%)	29 (17%)	15 (9%)	18 (10%)	35 (20%)	11 (6%)
Anaemia	4 (2%)	4 (2%)	1 (1%)	4 (2%)	1 (1%)	--
Neutropenia	10 (6%)	26 (15%)	9 (5%)	7 (4%)	32 (18%)	9 (5%)
Thrombocytopenia	6 (3%)	2 (1%)	5 (3%)	9 (5%)	2 (1%)	3 (2%)
Non-haematological†	108 (62%)	42 (24%)	6 (3%)	78 (44%)	24 (14%)	1 (1%)
Cardiac	3 (2%)	5 (3%)	--	1 (1%)	--	1 (1%)
Coronary heart disease	--	2 (1%)	--	--	--	1 (1%)
Heart failure	--	3 (2%)	--	--	--	--
Tachyarrhythmia	1 (1%)	3 (2%)	--	--	--	--
Dermatological	14 (8%)	2 (1%)	--	12 (7%)	3 (2%)	--
Rash	9 (5%)	2 (1%)	--	8 (5%)	3 (2%)	--
Gastroenterological	55 (32%)	9 (5%)	--	38 (21%)	4 (2%)	--
Diarrhoea	28 (16%)	7 (4%)	--	35 (20%)	2 (1%)	--
Nausea and vomiting	37 (21%)	2 (1%)	--	1 (1%)	--	--
Hepatic	3 (2%)	2 (1%)	--	4 (2%)	--	--
Cholestasis	1 (1%)	--	--	--	--	--
Hepatic failure	--	1 (1%)	--	--	--	--
Aminotransferases increased	2 (1%)	1 (1%)	--	4 (2%)	--	--
Infection	28 (16%)	8 (5%)	--	30 (17%)	13 (7%)	--
Febrile neutropenia	--	--	--	--	2 (1%)	--
Sepsis	--	--	--	--	--	--
Pneumonia	3 (2%)	5 (3%)	--	6 (3%)	4 (2%)	--
Lower respiratory tract	10 (6%)	1 (1%)	--	10 (6%)	2 (1%)	--
Upper respiratory tract	10 (6%)	1 (1%)	--	17 (10%)	--	--
Gastroenteritis	1 (1%)	--	--	1 (1%)	--	--
Genitourinary tract	3 (2%)	--	--	3 (2%)	1 (1%)	--
Neurological	14 (8%)	2 (1%)	1 (1%)	11 (6%)	1 (1%)	--
Cerebrovascular disease	--	--	--	1 (1%)	1 (1%)	--
Renal‡	3 (2%)	--	2 (1%)	3 (2%)	1 (1%)	--
Creatinine increase	--	--	--	1 (1%)	--	--
Renal failure	1 (1%)	--	2 (1%)	1 (1%)	1 (1%)	--
Respiratory	12 (7%)	2 (1%)	--	2 (1%)	--	--
Respiratory failure	1 (1%)	--	--	--	--	--
Vascular						
Hypertension	28 (16%)	8 (5%)	4 (2%)	3 (2%)	1 (1%)	--
Venous thromboembolism§	18 (10%)	6 (3%)	--	--	--	--
Other thrombosis	--	1 (1%)	--	--	1 (1%)	--
Thrombotic microangiopathy	4 (2%)	--	--	1 (1%)	--	--
	--	1 (1%)	4 (2%)	--	--	--
Other	63 (36%)	2 (1%)	--	21 (12%)	5 (3%)	--
Fatigue	13 (8%)	1 (1%)	--	6 (3%)	5 (3%)	--
Fever of unknown origin	36 (21%)	1 (1%)	--	7 (4%)	--	--

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TOURMALINE-MM4 Study

Clinical Trial > J Clin Oncol. 2020 Dec 1;38(34):4030-4041. doi: 10.1200/JCO.20.02060. Epub 2020 Oct 6.

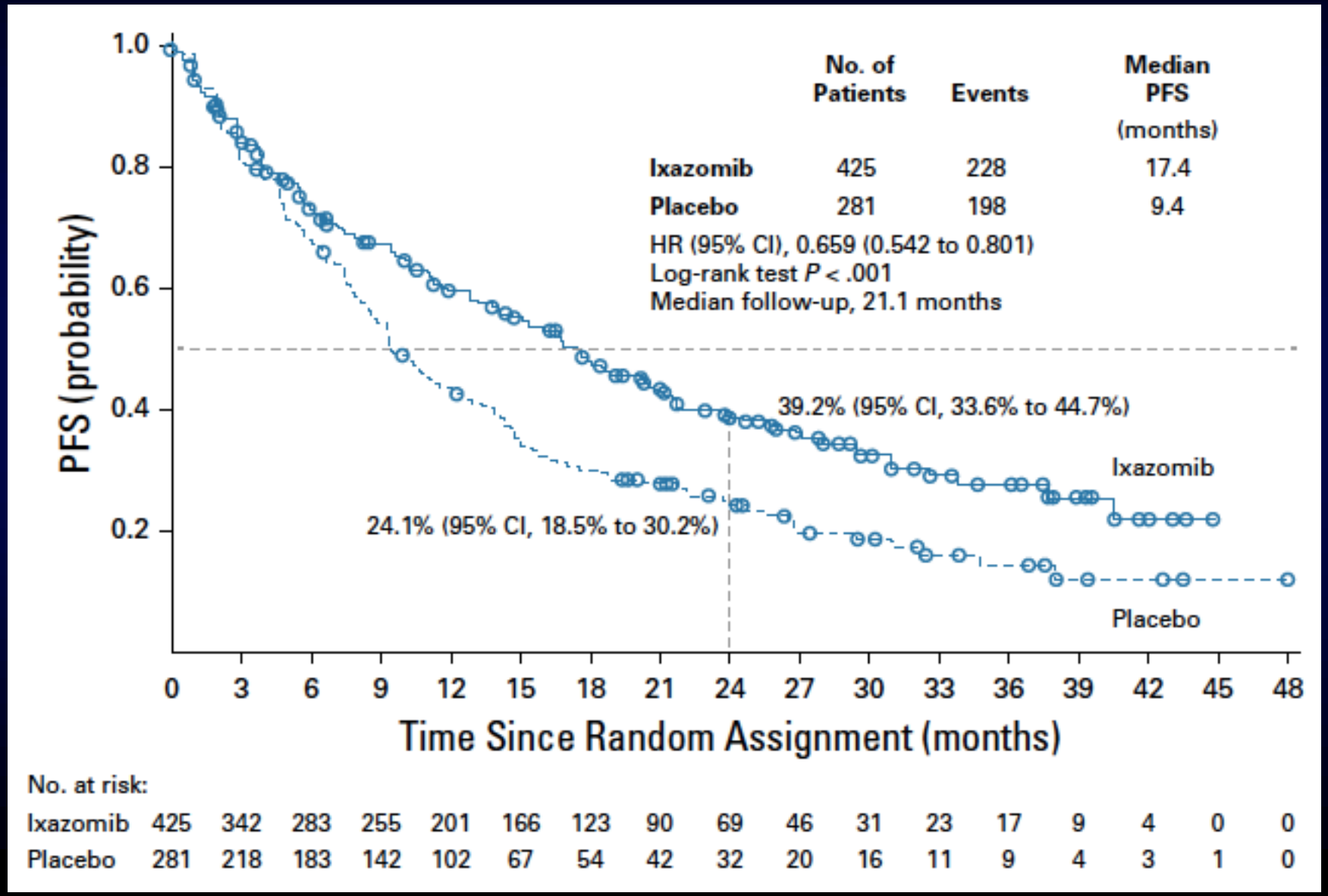
Ixazomib as Postinduction Maintenance for Patients With Newly Diagnosed Multiple Myeloma Not Undergoing Autologous Stem Cell Transplantation: The Phase III TOURMALINE-MM4 Trial

Meletios A Dimopoulos [1], Ivan Špička [2], Hang Quach [3], Albert Oriol [4], Roman Hájek [5], Mamta Garg [6], Meral Beksac [7], Sara Bringhen [8], Eirini Katodritou [9], Wee-Joo Chng [10], Xavier Leleu [11], Shinsuke Iida [12], María-Victoria Mateos [13], Gareth Morgan [14], Alexander Vorog [15], Richard Labotka [15], Bingxia Wang [15], Antonio Palumbo [15], Sagar Lonial [16], TOURMALINE-MM4 study group

Affiliations + expand

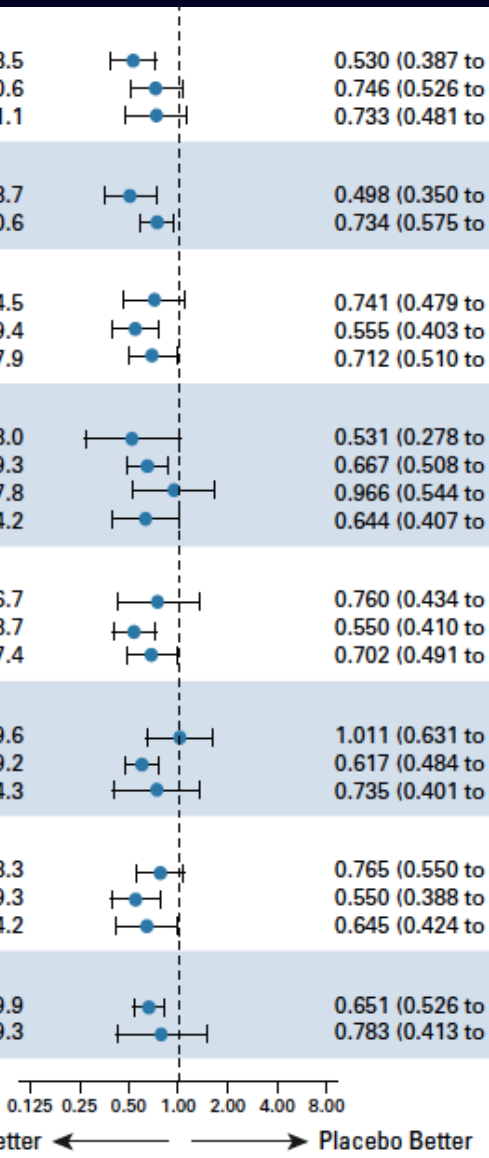
PMID: 33021870 PMCID: PMC7768338 DOI: 10.1200/JCO.20.02060

PFS Data


No. of Patients
Events
Median PFS (months)
Ixazomib 425 228 17.4
Placebo 281 198 9.4
HR (95% CI), 0.659 (0.542 to 0.801)
Log-rank test P < .001
Median follow-up, 21.1 months
39.2% (95% CI, 33.6% to 44.7%)
24.1% (95% CI, 18.5% to 30.2%)
Ixazomib
Placebo
PFS (probability)
1.0
0.8
0.6
0.4
0.2
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48
Time Since Random Assignment (months)
No. at risk:
Ixazomib 425 342 283 255 201 166 123 90 69 46 31 23 17 9 4 0 0
Placebo 281 218 183 142 102 67 54 42 32 20 16 11 9 4 3 1 0

Subgroup Data

Frailty status					
Fit (n = 284)	91 of 172	83 of 112	18.6	8.5	0.530 (0.387 to 0.727)
Unfit (n = 245)	80 of 147	67 of 98	17.6	10.6	0.746 (0.526 to 1.058)
Frail (n = 170)	54 of 102	47 of 68	15.4	11.1	0.733 (0.481 to 1.117)
Prior IMiD exposure					
Yes (n = 231)	72 of 137	73 of 94	18.9	8.7	0.498 (0.350 to 0.708)
No (n = 475)	156 of 288	125 of 187	16.6	10.6	0.734 (0.575 to 0.936)
ISS stage at initial diagnosis					
I (n = 178)†	52 of 112	43 of 66	20.3	14.5	0.741 (0.479 to 1.148)
II (n = 279)†	90 of 165	84 of 114	15.7	9.4	0.555 (0.403 to 0.765)
III (n = 249)†	86 of 148	71 of 101	17.7	7.9	0.712 (0.510 to 0.993)
Revised ISS stage at initial diagnosis					
I (n = 86)	21 of 54	22 of 32	21.8	8.0	0.531 (0.278 to 1.015)
II (n = 347)	121 of 204	107 of 143	15.4	9.3	0.667 (0.508 to 0.876)
III (n = 92)	36 of 58	24 of 34	15.3	7.8	0.966 (0.544 to 1.714)
Unclassifiable (n = 181)	50 of 109	45 of 72	18.6	14.2	0.644 (0.407 to 1.019)
Response at study entry					
CR (n = 163)†	31 of 98	29 of 65	40.5	26.7	0.760 (0.434 to 1.332)
VGPR (n = 306)†	97 of 175	102 of 131	17.6	8.7	0.550 (0.410 to 0.737)
PR (n = 194)†	82 of 121	60 of 73	11.1	7.4	0.702 (0.491 to 1.004)
Cytogenetic risk‡					
High risk (n = 122)	51 of 74	36 of 48	10.1	9.6	1.011 (0.631 to 1.621)
Standard risk (n = 465)	142 of 275	139 of 190	17.9	9.2	0.617 (0.484 to 0.787)
Unclassifiable (n = 119)	35 of 76	23 of 43	22.0	14.3	0.735 (0.401 to 1.347)
Cytogenetic risk¶					
Expanded high risk (n = 241)	101 of 150	72 of 91	10.8	8.3	0.765 (0.550 to 1.063)
Standard risk (n = 256)	70 of 148	77 of 108	18.7	9.3	0.550 (0.388 to 0.780)
Unclassifiable (n = 209)	57 of 127	49 of 82	26.7	14.2	0.645 (0.424 to 0.983)
Reason for transplantation ineligibility					
Age (n = 617)	195 of 373	170 of 244	17.6	9.9	0.651 (0.526 to 0.805)
Other (n = 70)	28 of 43	20 of 27	14.8	9.3	0.783 (0.413 to 1.484)



Toxicity Data

Adverse Event	Ixazomib Group (n = 426)			Placebo Group (n = 276)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Other TEAEs of clinical interest						
Cardiac arrhythmias[a,c]	18 (4.2)	6 (1.4)	0 (0.0)	13 (4.7)	2 (0.7)	0 (0.0)
Heart failure[a,d]	5 (1.2)	2 (0.5)	0 (0.0)	4 (1.4)	1 (0.4)	1 (0.4)
Hypotension[a]	10 (2.3)	0 (0.0)	0 (0.0)	3 (1.1)	0 (0.0)	0 (0.0)
Liver impairment[a]	19 (4.5)	6 (1.4)	0 (0.0)	7 (2.5)	3 (1.1)	0 (0.0)
Myocardial infarction[a,e]	1 (0.2)	0 (0.0)	1 (0.2)	4 (1.4)	1 (0.4)	0 (0.0)
Renal impairment[a,f]	16 (3.8)	4 (0.9)	4 (0.9)	5 (1.8)	0 (0.0)	0 (0.0)
Herpes zoster	13 (3.1)	1 (0.2)	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)
In patients receiving antiviral prophylaxis	1/274 (0.4)	0 (0.0)	0 (0.0)	0/167 (0.0)	0 (0.0)	0 (0.0)
In patients not receiving prophylaxis	12/152 (7.9)	1/152 (0.7)	0 (0.0)	2/109 (1.8)	0 (0.0)	0 (0.0)
New primary malignant tumor	22 (5.2)	—		17 (6.2)	—	
Back pain	61 (14.3)	1 (0.2)	0 (0.0)	31 (11.2)	1 (0.4)	0 (0.0)
Arthralgia	49 (11.5)	2 (0.5)	0 (0.0)	20 (7.2)	2 (0.7)	0 (0.0)
Pyrexia	48 (11.3)	1 (0.2)	0 (0.0)	14 (5.1)	0 (0.0)	1 (0.4)
Fatigue	46 (10.8)	6 (1.4)	0 (0.0)	28 (10.1)	1 (0.4)	0 (0.0)

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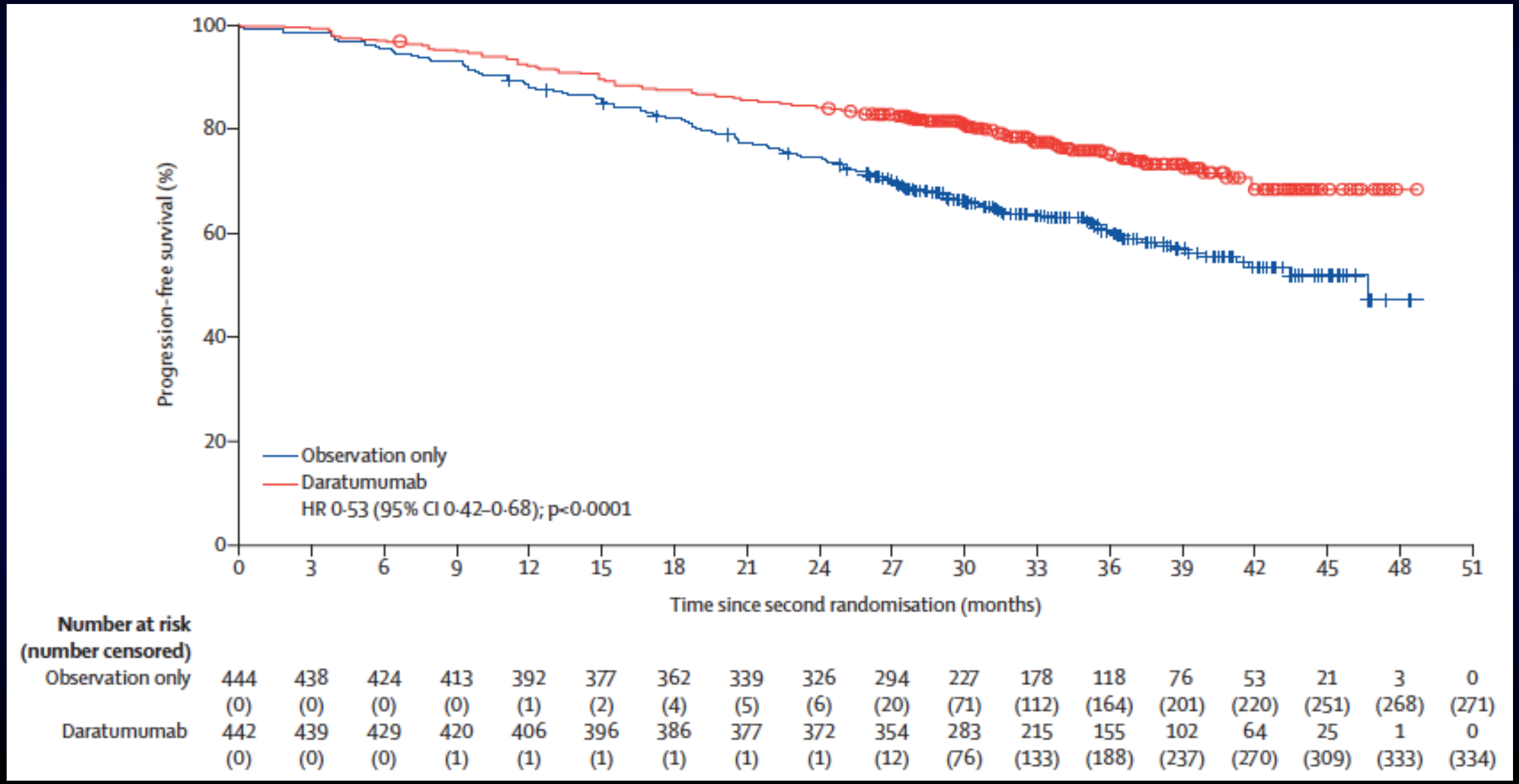
Dara for Maintenance ?

Clinical Trial > Lancet Oncol. 2021 Oct;22(10):1378-1390.
doi: 10.1016/S1470-2045(21)00428-9. Epub 2021 Sep 13.

Maintenance with daratumumab or observation following treatment with bortezomib, thalidomide, and dexamethasone with or without daratumumab and autologous stem-cell transplant in patients with newly diagnosed multiple myeloma (CASSIOPEIA): an open-label, randomised, phase 3 trial

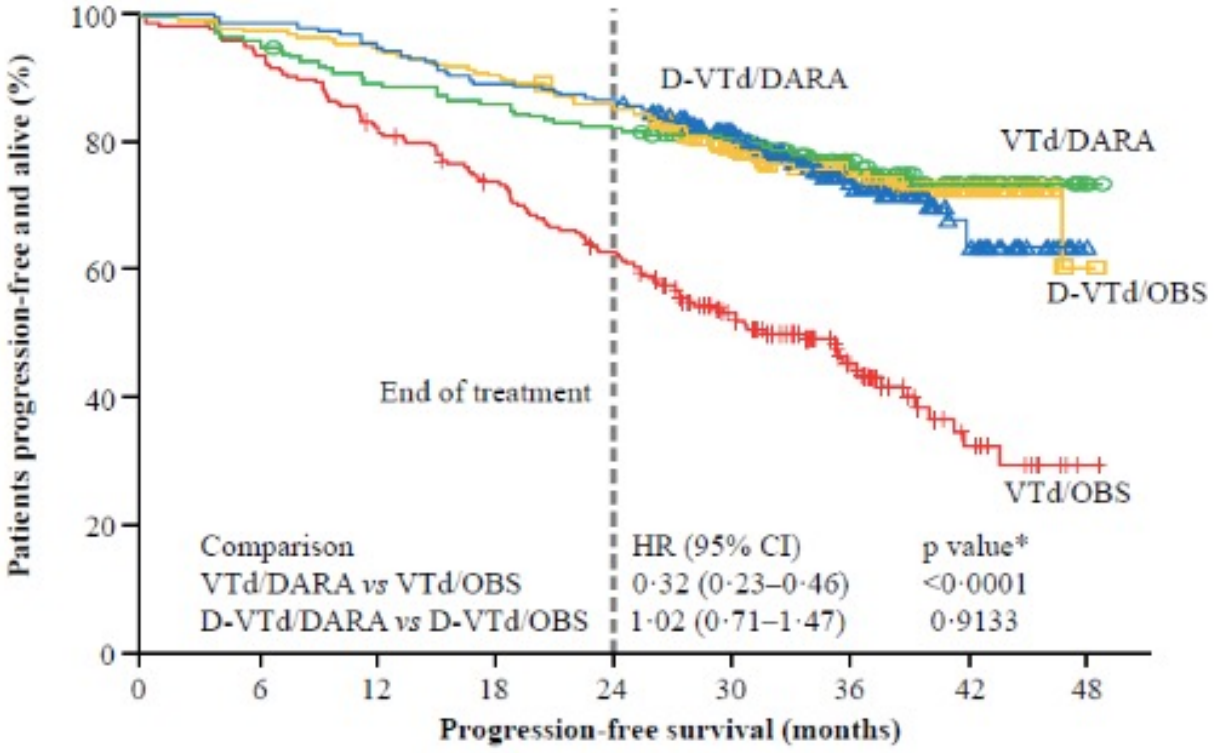
Philippe Moreau [1], Cyrille Hulin [2], Aurore Perrot [3], Bertrand Arnulf [4], Karim Belhadj [5], Lotfi Benboubker [6], Marie C Béné [7], Sonja Zweegman [8], Hélène Caillon [9], Denis Caillot [10], Jill Corre [11], Michel Delforge [12], Thomas Dejoie [9], Chantal Doyen [13], Thierry Facon [14], Cécile Sonntag [15], Jean Fontan [16], Mohamad Mohty [17], Kon-Siong Jie [18], Lionel Karlin [19], Frédérique Kuhnowski [20], Jérôme Lambert [21], Xavier Leleu [22], Margaret Macro [23], Frédérique Orsini-Piocelle [24], Murielle Roussel [25], Anne-Marie Stoppa [26], Niels W C J van de Donk [8], Soraya Wuillème [7], Annemiek Broijl [27], Cyrille Touzeau [28], Mourad Tiab [29], Jean-Pierre Marolleau [30], Nathalie Meuleman [31], Marie-Christiane Vekemans [32], Matthijs Westerman [33], Saskia K Klein [34], Mark-David Levin [35], Fritz Offner [36], Martine Escoffre-Barbe [37], Jean-Richard Eveillard [38], Réda Garidi [39], Tahamtan Ahmadi [40], Maria Krevvata [41], Ke Zhang [42], Carla de Boer [43], Sanjay Vara [44], Tobias Kampfenkel [43], Veronique Vanquickelberghe [45], Jessica Vermeulen [43], Hervé Avet-Loiseau [11], Pieter Sonneveld [27]

PFS Data



Number at risk (number censored)																		
Observation only	444 (0)	438 (0)	424 (0)	413 (0)	392 (1)	377 (2)	362 (4)	339 (5)	326 (6)	294 (20)	227 (71)	178 (112)	118 (164)	76 (201)	53 (220)	21 (251)	3 (268)	0 (271)
Daratumumab	442 (0)	439 (0)	429 (0)	420 (1)	406 (1)	396 (1)	386 (1)	377 (1)	372 (1)	354 (12)	283 (76)	215 (133)	155 (188)	102 (237)	64 (270)	25 (309)	1 (333)	0 (334)

However …



Patients at risk (censored)

VTd/OBS	215 (0)	201 (0)	176 (1)	155 (4)	131 (5)	83 (33)	43 (63)	15 (84)	1 (97)
VTd/DARA	213 (0)	203 (0)	189 (1)	182 (1)	174 (1)	138 (34)	79 (88)	34 (130)	1 163)
D-VTd/OBS	229 (0)	223 (0)	216 (0)	207 (0)	195 (1)	144 (38)	75 (101)	38 (136)	2 (171)
D-VTd/DARA	229 (0)	226 (0)	217 (0)	204 (0)	198 (0)	145 (42)	76 (100)	30 (140)	0 (170)

- Is Dara maintenance beneficial if it was given during induction?
- Should we give Dara as maintenance if it was not given with induction?

Maintenance Therapy Summary

- Transplant-eligible patients
  - Len for standard risk
  - Bor/Len (or Car/Len) for high-risk
  - More data needed to routinely recommend Dara (S1803 (R ± Dara))
- Transplant-ineligible patients
  - Len for standard risk
  - Bor/Len for molecularly high-risk
  - Consider Ixa if no plan to continue a component of baseline induction

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Treatment of Early Relapse (1-3 Lines)

THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA[a-d,l-m]

Preferred Regimens for Early Relapses (1–3 prior therapies)

Order of regimens does not indicate comparative efficacy

- If relapse is >6 months, the regimen used for primary therapy may be repeated.
- For patients still sensitive to bortezomib and/or lenalidomide, any of the regimens listed on this page may be appropriate.
- Ixazomib/lenalidomide/dexamethasone (category 1)
- Bortezomib/lenalidomide/dexamethasone

Bortezomib-Refractory	Lenalidomide-Refractory
• Daratumumab/lenalidomide/dexamethasone (category 1) • Daratumumab/carfilzomib/dexamethasone (category 1) • Carfilzomib/lenalidomide/dexamethasone (category 1) • Isatuximab-irfc/carfilzomib/dexamethasone (category 1) • Carfilzomib/pomalidomide/dexamethasone	• Daratumumab/carfilzomib/dexamethasone (category 1) • Daratumumab/bortezomib/dexamethasone (category 1) • Isatuximab-irfc/carfilzomib/dexamethasone (category 1) • Carfilzomib/pomalidomide/dexamethasone
After one prior therapy including lenalidomide and a PI ▸ Daratumumab/pomalidomide/dexamethasone (category 1)	*After one prior therapy including lenalidomide and a PI* ▸ Daratumumab/pomalidomide/dexamethasone (category 1)
After two prior therapies including lenalidomide and a PI ▸ Isatuximab-irfc/pomalidomide/dexamethasone (category 1)	*After two prior therapies including lenalidomide and a PI* ▸ Isatuximab-irfc/pomalidomide/dexamethasone (category 1)
After two prior therapies including an IMiD and a PI and with disease progression on/within 60 days of completion of last therapy ▸ Ixazomib/pomalidomide/dexamethasone	*After two prior therapies including an IMiD and a PI and with disease progression on/within 60 days of completion of last therapy* ▸ Pomalidomide/bortezomib/dexamethasone (category 1) ▸ Ixazomib/pomalidomide/dexamethasone

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Other Options

THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA[a-d,l-o]	
• If relapse is >6 months, the regimen used for primary therapy may be repeated. • For patients still sensitive to bortezomib and/or lenalidomide, any of the regimens listed on this page may be appropriate.	
Other Recommended Regimens for Early Relapses (1–3 prior therapies)	
• Bortezomib/liposomal doxorubicin/dexamethasone (category 1) • Carfilzomib (twice weekly)/dexamethasone (category 1) • Elotuzumab/lenalidomide/dexamethasone (category 1) • Selinexor/bortezomib/dexamethasone (once weekly) (category 1) • Bortezomib/cyclophosphamide/dexamethasone • Carfilzomib/cyclophosphamide/dexamethasone • Cyclophosphamide/lenalidomide/dexamethasone • Daratumumab/cyclophosphamide/bortezomib/dexamethasone • Elotuzumab/bortezomib/dexamethasone • Ixazomib/cyclophosphamide/dexamethasone	*After two prior therapies including an IMiD and a PI and disease progression on/within 60 days of completion of last therapy* ▸ Pomalidomide/cyclophosphamide/dexamethasone *After two prior therapies including lenalidomide and a PI* ▸ Elotuzumab/pomalidomide/dexamethasone
Useful in Certain Circumstances for Early Relapses (1–3 prior therapies)	
• Bortezomib/dexamethasone (category 1) • Lenalidomide/dexamethasone (category 1) • Carfilzomib/cyclophosphamide/thalidomide/dexamethasone • Carfilzomib (weekly)/dexamethasone • Selinexor/daratumumab/dexamethasone • Selinexor/carfilzomib/dexamethasone • Venetoclax/dexamethasone only for t(11;14) patients	*After two prior therapies including IMiD and a PI and with disease progression on/within 60 days of completion of last therapy* ▸ Pomalidomide/dexamethasone (category 1) ▸ Selinexor/pomalidomide/dexamethasone *For treatment of aggressive MM* ▸ Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP) ▸ Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE) ± bortezomib (VTD-PACE) *After at least three prior therapies including a PI and an IMiD or are double-refractory to a PI and an IMiD* ▸ Daratumumab

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Overview

Review > Annu Rev Med. 2019 Jan 27;70:521-547.
doi: 10.1146/annurev-med-112017-091045.

New Drugs in Multiple Myeloma

Chutima Kunacheewa [1 2], Robert Z Orlowski [1 3]

Affiliations – collapse

Affiliations

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2 Division of Hematology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.
3 Department of Experimental Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, Texas 77030, USA.

PMID: 30691369 DOI: 10.1146/annurev-med-112017-091045

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Relapsed Disease

		1–3 prior lines of therapy	≥ 4 prior lines of therapy
Relapsed disease	Frail	• Bortezomib ±dex, • Lenalidomide/dex, • Pomalidomide ±dex, • Ixazomib/lenalidomide/dex	• Bortezomib ±dex • Carfilzomib • Daratumumab • Ixazomib/lenalidomide/dex • Lenalidomide/dex • Pomalidomide ±dex • BCMA-ADC
	Fit	• Carfilzomib/dex • Carfilzomib/lenalidomide/dex • Daratumumab/bortezomib/dex • Daratumumab/lenalidomide/dex • Elotuzumab/lenalidomide/dex • Ixazomib/lenalidomide/dex • Panobinostat/bortezomib/dex • Daratumumab/pomalidomide/dex • Bortezomib/pomalidomide/dex • Bortezomib/pegylated liposomal doxorubicin ±dex	• Carfilzomib/dex • Daratumumab/bortezomib/dex • Daratumumab/lenalidomide/dex • Ixazomib/lenalidomide/dex • Panobinostat/bortezomib/dex • Daratumumab/pomalidomide/dex • Selinexor/dex • BCMA CAR-T cell vs. BCMA BiTE vs. BCMA-ADC • Bortezomib/pegylated liposomal doxorubicin ±dex

- Focus is on regimens with FDA approvals in USA

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Refractory Disease

		1–3 prior lines of therapy	≥ 4 prior lines of therapy
Recently dual bortezomib and lenalidomide refractory	Frail	• Pomalidomide ±dex	• Carfilzomib • Daratumumab • Pomalidomide ±dex • BCMA-ADC
	Fit	• Carfilzomib/dex • Panobinostat/bortezomib/dex • Daratumumab/pomalidomide/dex • Elotuzumab/pomalidomide/dex	• Carfilzomib/dex • Daratumumab • Panobinostat/bortezomib/dex • Daratumumab/pomalidomide/dex • Elotuzumab/pomalidomide/dex • Selinexor/dex • BCMA CAR-T cell vs. BCMA BiTE vs. BCMA-ADC

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Early Relapse Summary

- Early line relapsed/refractory myeloma (1-3 prior lines)
  - Multiple triplet regimens available
  - Consider tweaking maintenance if indolent relapse
  - Repeat a prior therapy if disease was not refractory (2nd ASCT)
  - Otherwise, an α-CD38 + a drug from a new class in 1st relapse
  - In 2nd and 3rd relapse, use as many new drugs/MoAs as is feasible
    - Selinexor + PI, venetoclax + PI
    - Soon, hopefully belantamab +PI or IMiD

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Treatment of Late Relapse

THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA[a-d,l-n]
Therapies for Patients with Late Relapses (>3 prior therapies)
• **Bendamustine** • **Bendamustine/bortezomib/dexamethasone** • **Bendamustine/carfilzomib/dexamethasone** • **Bendamustine/lenalidomide/dexamethasone** • **High-dose or fractionated cyclophosphamide** *After at least four prior therapies, including an anti-CD38 monoclonal antibody, a PI, and an IMiD* ▸ **Belantamab mafodotin-blmf** ▸ **Idecabtagene vicleucel** ▸ **Ciltacabtagene autoleucel** *After at least four prior therapies and whose disease is refractory to at least two PIs, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody* ▸ **Selinexor/dexamethasone**

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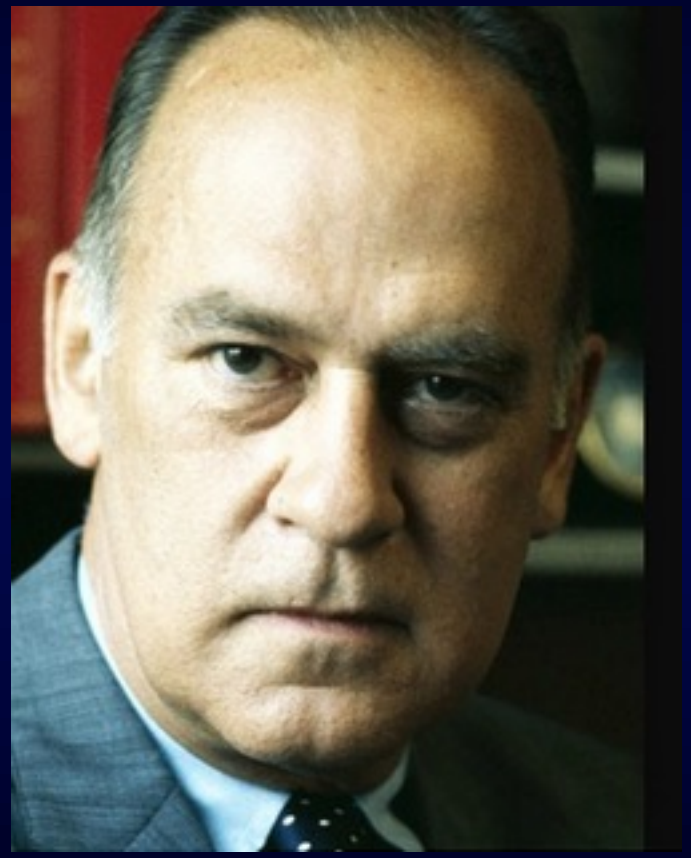
Key Considerations

- Frailty
- Myeloma-related and other co-morbidities
- Molecular risk & disease burden/pace of progression
- Previous treatments and their prior efficacy & tolerability
- Patient & family preferences for treatment route & location
- Ability of the patient to access new drugs and/or clinical trials

What is Frailty?



- Supreme Court justice when asked to define obscenity

> I shall not today attempt further to define the kinds of material but I know it when I see it.
>
> — Potter Stewart —

- Applies equally to frailty

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Simplified Scale

Clinical Trial

Epub 2019 Aug

A simpli… transpla… multiple… trial

Thierry Facon [1], Mohamad Moht…, Paula Rodriguez…, Eileen Boyle [2], …, Xavier Leleu [16], …, Antoine Tinel [21], Jean Yves Mary…

…0539-0.

…n …gnosed …020)

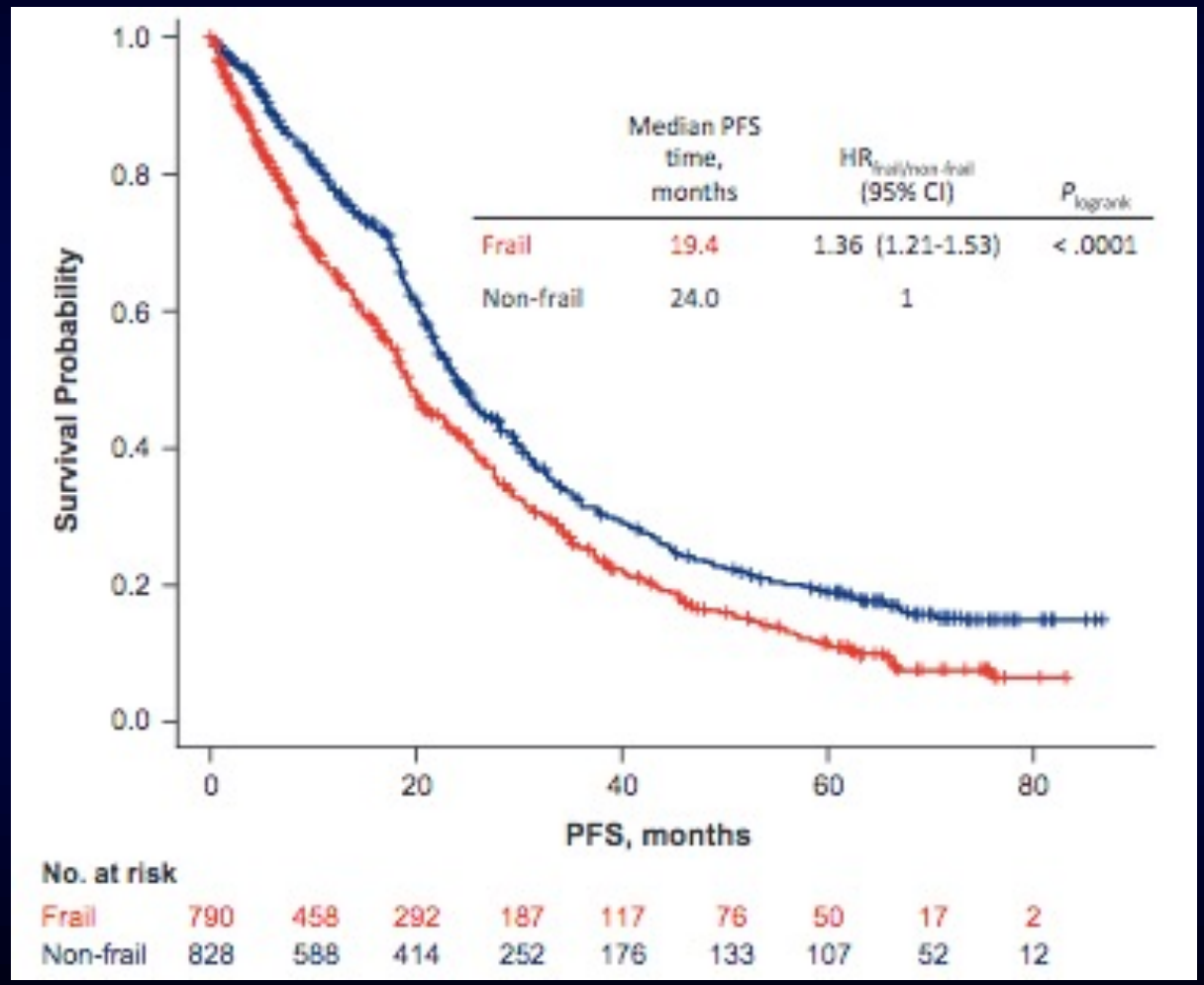
…[12], …lacro [15], …el Sturniolo [20], …e Hulin [22],

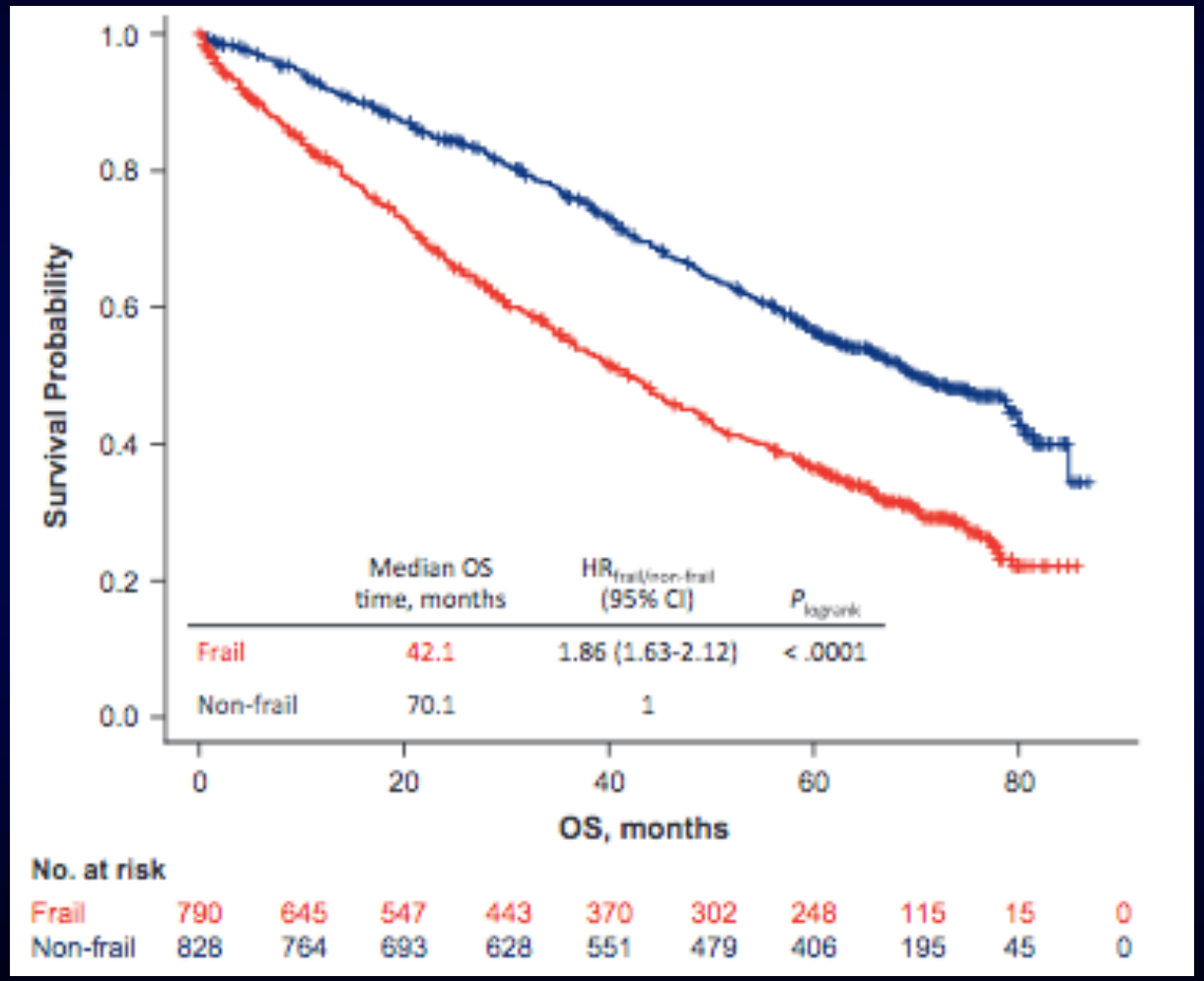
Table 1 ECOG proxy of IMWG algorithm of frailty

Category	Score
Age	
≤75 years	0
76–80 years	1
>80 years	2
Charlson Comorbidity Index	
≤1	0
>1	1
ECOG performance status	
0	0
1	1
≥2	2
Sum of scores	
Nonfrail	0–1
Frail	≥2

ECOG Eastern Cooperative Oncology Group, *IMWG* International Myeloma Working Group

Outcomes


Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
Median PFS time, months
HR frail/non-frail (95% CI)
P logrank
Frail 19.4 1.36 (1.21-1.53) < .0001
Non-frail 24.0 1
0 20 40 60 80
PFS, months
No. at risk
Frail 790 458 292 187 117 76 50 17 2
Non-frail 828 588 414 252 176 133 107 52 12


Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
Median OS time, months
HR frail/non-frail (95% CI)
P logrank
Frail 42.1 1.86 (1.63-2.12) < .0001
Non-frail 70.1 1
0 20 40 60 80
OS, months
No. at risk
Frail 790 645 547 443 370 302 248 115 15 0
Non-frail 828 764 693 628 551 479 406 195 45 0

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Ide-cel : The Right KarMMa?

Clinical Trial > N Engl J Med. 2021 Feb 25;384(8):705-716. doi: 10.1056/NEJMoa2024850.

Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma

Nikhil C Munshi [1], Larry D Anderson Jr [1], Nina Shah [1], Deepu Madduri [1], Jesús Berdeja [1], Sagar Lonial [1], Noopur Raje [1], Yi Lin [1], David Siegel [1], Albert Oriol [1], Philippe Moreau [1], Ibrahim Yakoub-Agha [1], Michel Delforge [1], Michele Cavo [1], Hermann Einsele [1], Hartmut Goldschmidt [1], Katja Weisel [1], Alessandro Rambaldi [1], Donna Reece [1], Fabio Petrocca [1], Monica Massaro [1], Jamie N Connarn [1], Shari Kaiser [1], Payal Patel [1], Liping Huang [1], Timothy B Campbell [1], Kristen Hege [1], Jesús San-Miguel [1]

Affiliations + expand

PMID: 33626253 DOI: 10.1056/NEJMoa2024850

Subgroup	No. of Patients	Overall Response (95% CI) *percent*
Age		
<65 yr	83	
≥65 yr	45	
Sex		

Response (%)

Probability of Survival

1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0

Median, 19.4 mo (95% CI, 18.2–NE)

0 2 4 6 8 10 12 14 16 18 20 22

Months

No. at Risk	128	122	114	108	104	97	82	55	38	27	12	0

0 10 20 30 40 50 60 70 80 90 100

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Adverse Events

Variable	Any Grade	Grade 3 or 4
	no. of patients (%)	
Adverse event*		
Any	128 (100)	127 (99)
Hematologic		
Neutropenia	117 (91)	114 (89)
Anemia	89 (70)	77 (60)
Thrombocytopenia	81 (63)	67 (52)
Leukopenia	54 (42)	50 (39)
Lymphopenia	35 (27)	34 (27)
Febrile neutropenia	21 (16)	20 (16)
Gastrointestinal		
Diarrhea	45 (35)	2 (2)
Nausea	37 (29)	0
Constipation	20 (16)	0
Other		
Hypokalemia	45 (35)	3 (2)
Fatigue	43 (34)	2 (2)
Hypophosphatemia	38 (30)	20 (16)
Hypocalcemia	34 (27)	10 (8)
Pyrexia	32 (25)	3 (2)
Hypomagnesemia	30 (23)	0
Decreased appetite	27 (21)	1 (<1)
Headache	27 (21)	1 (<1)
Hypogammaglobulinemia	27 (21)	1 (<1)
Cough	26 (20)	0
Hyponatremia	24 (19)	7 (5)
Hypoalbuminemia	22 (17)	4 (3)
Aspartate aminotransferase level increased	21 (16)	2 (2)
Hypotension	21 (16)	1 (<1)
Cytokine release syndrome†	107 (84)	7 (5)
Neurotoxic effect‡	23 (18)	4 (3)

Cilta cel

J Clin Oncol. 2022 Jun 4;JCO2200842. doi: 10.1200/JCO.22.00842. Online ahead of print.

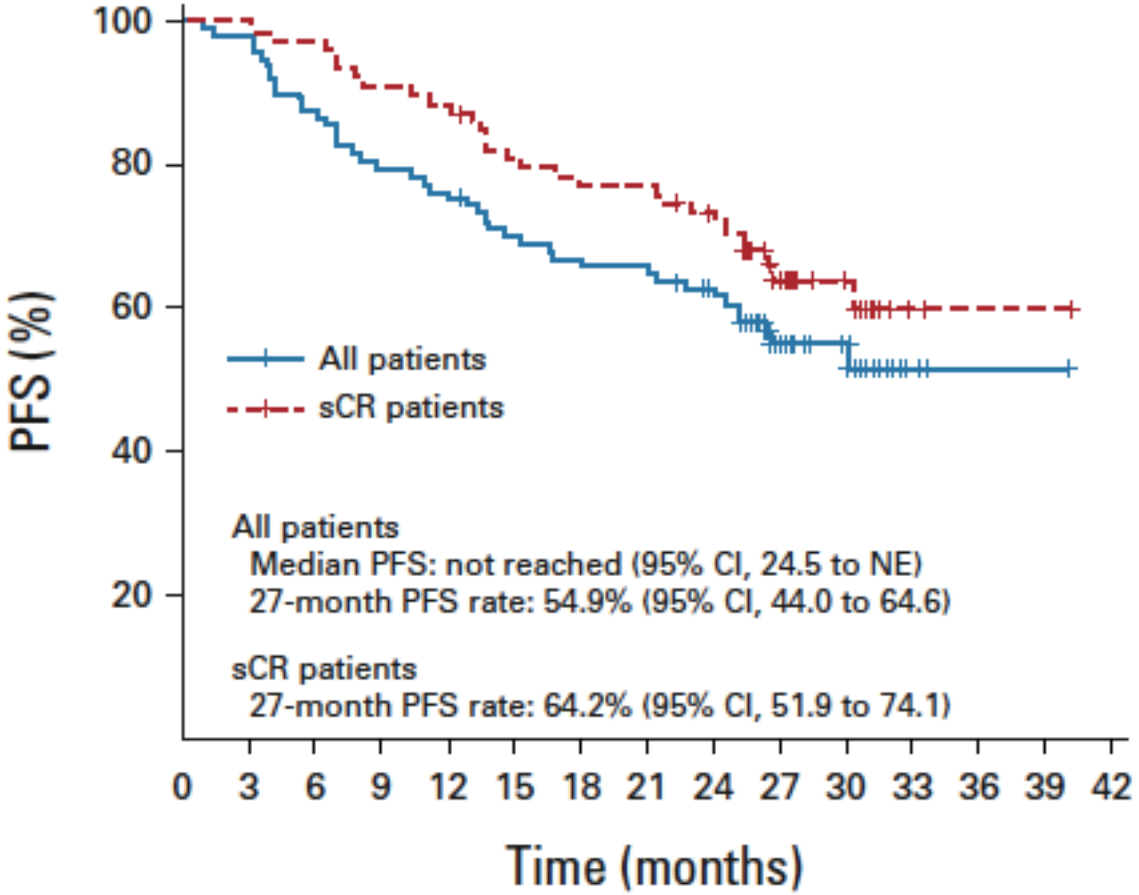
Ciltacabtagene Autoleucel, an Anti-B-cell Maturation Antigen Chimeric Antigen Receptor T-Cell Therapy, for Relapsed/Refractory Multiple Myeloma: CARTITUDE-1 2-Year Follow-Up

Thomas Martin [1], Saad Z Usmani [2], Jesus G Berdeja [3], Mounzer Agha [4], Adam D Cohen [5], Parameswaran Hari [6], David Avigan [7], Abhinav Deol [8], Myo Htut [9], Alexander Lesokhin [2], Nikhil C Munshi [10] [11], Elizabeth O'Donnell [12], A Keith Stewart [13], Jordan M Schecter [14], Jenna D Goldberg [14], Carolyn C Jackson [14], Tzu-Min Yeh [14], Arnob Banerjee [15], Alicia Allred [15], Enrique Zudaire [15], William Deraedt [16], Yunsi Olyslager [16], Changwei Zhou [17], Lida Pacaud [17], Deepu Madduri [14], Andrzej Jakubowiak [18], Yi Lin [19], Sundar Jagannath [20]

Affiliations + expand

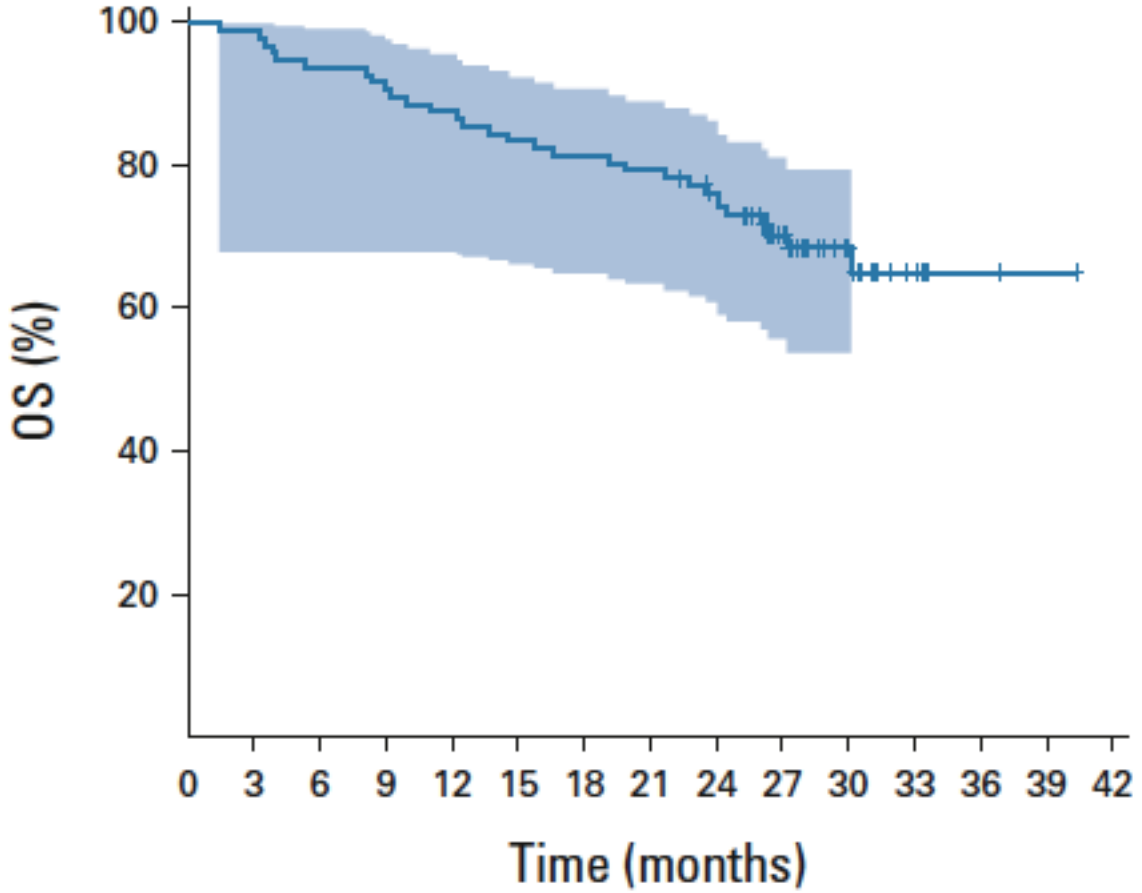
PMID: 35658469 DOI: 10.1200/JCO.22.00842

PFS & OS Data



No. at risk:

All patients	97	95	85	77	74	67	64	63	57	27	17	3	1	1	0
sCR patients	80	80	78	73	71	64	62	61	55	27	17	3	1	1	0



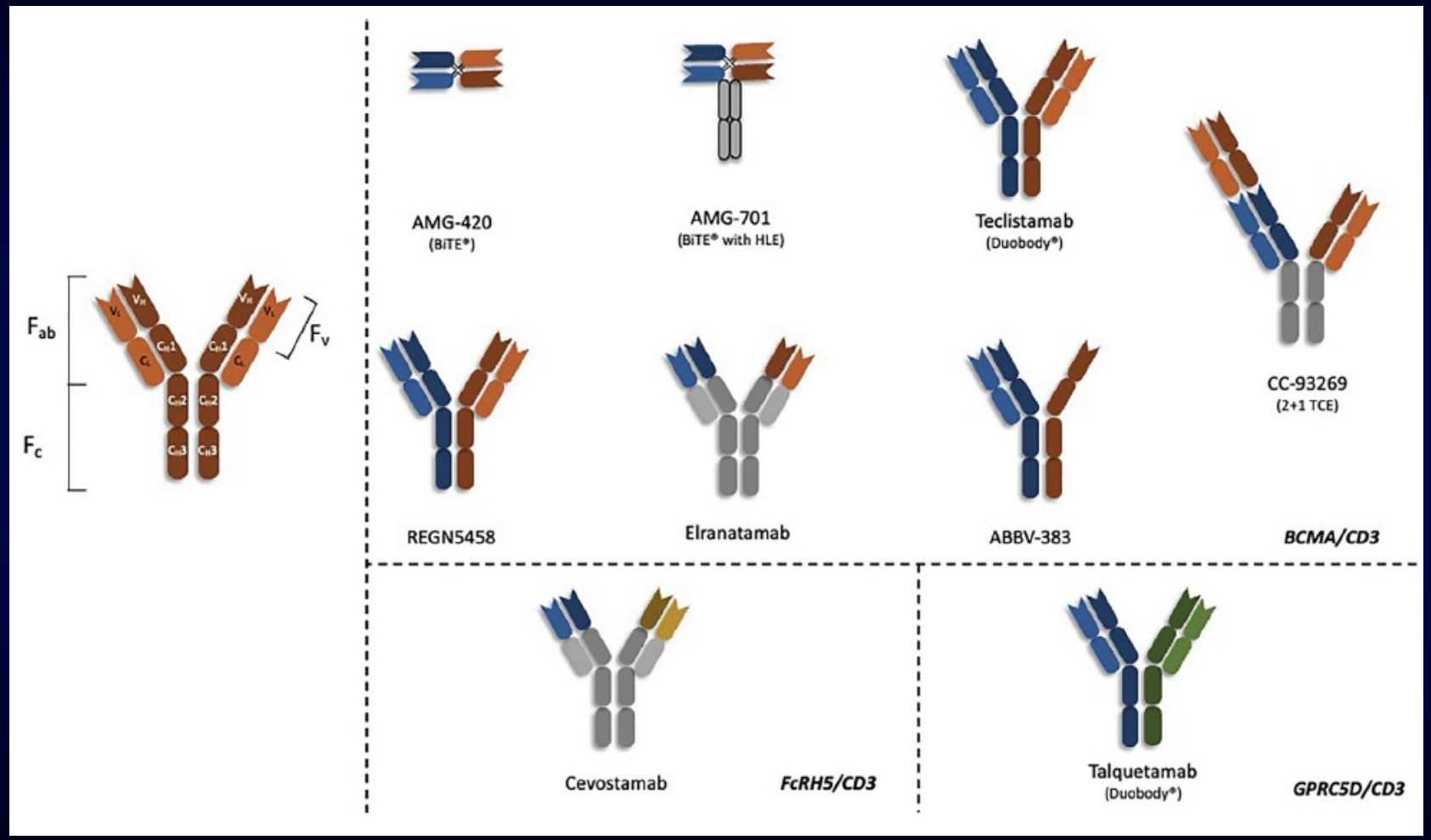
No. at risk:

	97	96	91	88	85	81	79	77	71	42	22	6	2	1	0

Adverse Event Data

AE	Total (N = 97), No. (%)		
	Any Grade	Grade 3/4	Grade 5
Any AE	97 (100)	91 (94)	6 (6.2)
Hematologic			
Neutropenia	93 (95.9)	92 (94.8)	0
Anemia	79 (81.4)	66 (68.0)	0
Thrombocytopenia	77 (79.4)	58 (59.8)	0
Leukopenia	60 (61.9)	59 (60.8)	0
Lymphopenia	52 (53.6)	49 (50.5)	0
Metabolism and nutrition disorders			
Hypocalcemia	31 (32.0)	3 (3.1)	0
Hypophosphatemia	30 (30.9)	7 (7.2)	0
Decreased appetite	28 (28.9)	1 (1.0)	0
Hypoalbuminemia	27 (27.8)	1 (1.0)	0
Hyponatremia	22 (22.7)	4 (4.1)	0
Hypokalemia	20 (20.6)	2 (2.1)	0
GI			
Diarrhea	29 (29.9)	1 (1.0)	0
Nausea	27 (27.8)	1 (1.0)	0
Constipation	22 (22.7)	0	0
Others			
Fatigue	36 (37.1)	5 (5.2)	0
Cough	34 (35.1)	0	0
AST increased	28 (28.9)	5 (5.2)	0
ALT increased	24 (24.7)	3 (3.1)	0
Pyrexia	20 (20.6)	0	0
Chills	20 (20.6)	0	0
Cytokine release syndrome	92 (94.8)	4 (4.1)	1 (1.0)
Neurotoxicity[a]	21 (21.6)	11 (11.3)	1 (1.0)

Approaches to T Cell Engagement



Lancman, G et al. Hematology Am Soc Hematol Educ Program 2020: 264-271.

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Teclistamab

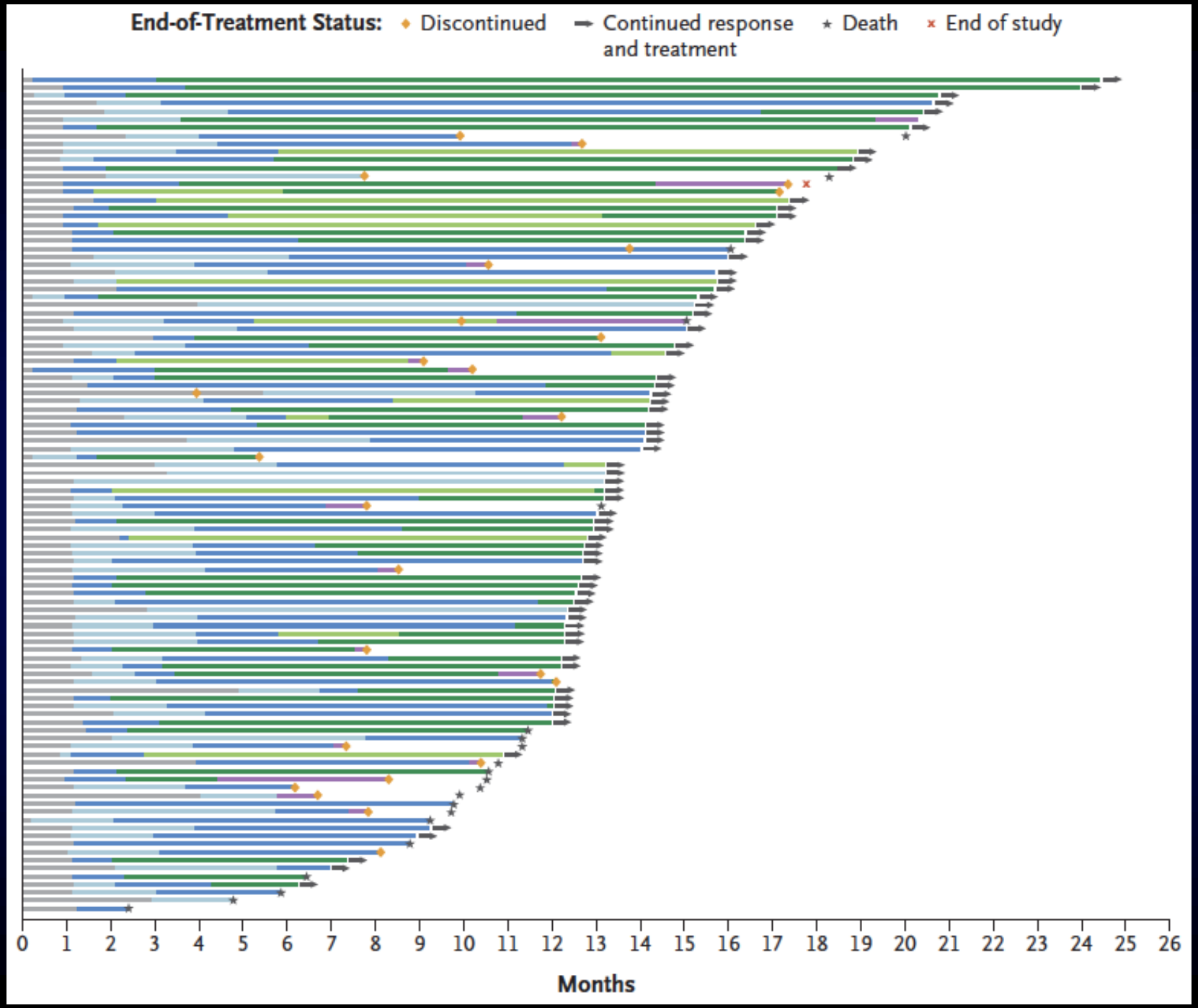
Clinical Trial > N Engl J Med. 2022 Aug 11;387(6):495-505. doi: 10.1056/NEJMoa2203478. Epub 2022 Jun 5.

Teclistamab in Relapsed or Refractory Multiple Myeloma

Philippe Moreau [1], Alfred L Garfall [1], Niels W C J van de Donk [1], Hareth Nahi [1], Jesús F San-Miguel [1], Albert Oriol [1], Ajay K Nooka [1], Thomas Martin [1], Laura Rosinol [1], Ajai Chari [1], Lionel Karlin [1], Lotfi Benboubker [1], Maria-Victoria Mateos [1], Nizar Bahlis [1], Rakesh Popat [1], Britta Besemer [1], Joaquín Martínez-López [1], Surbhi Sidana [1], Michel Delforge [1], Lixia Pei [1], Danielle Trancucci [1], Raluca Verona [1], Suzette Girgis [1], Shun X W Lin [1], Yunsi Olyslager [1], Mindy Jaffe [1], Clarissa Uhlar [1], Tara Stephenson [1], Rian Van Rampelbergh [1], Arnob Banerjee [1], Jenna D Goldberg [1], Rachel Kobos [1], Amrita Krishnan [1], Saad Z Usmani [1]

Affiliations + expand

PMID: 35661166 DOI: 10.1056/NEJMoa2203478



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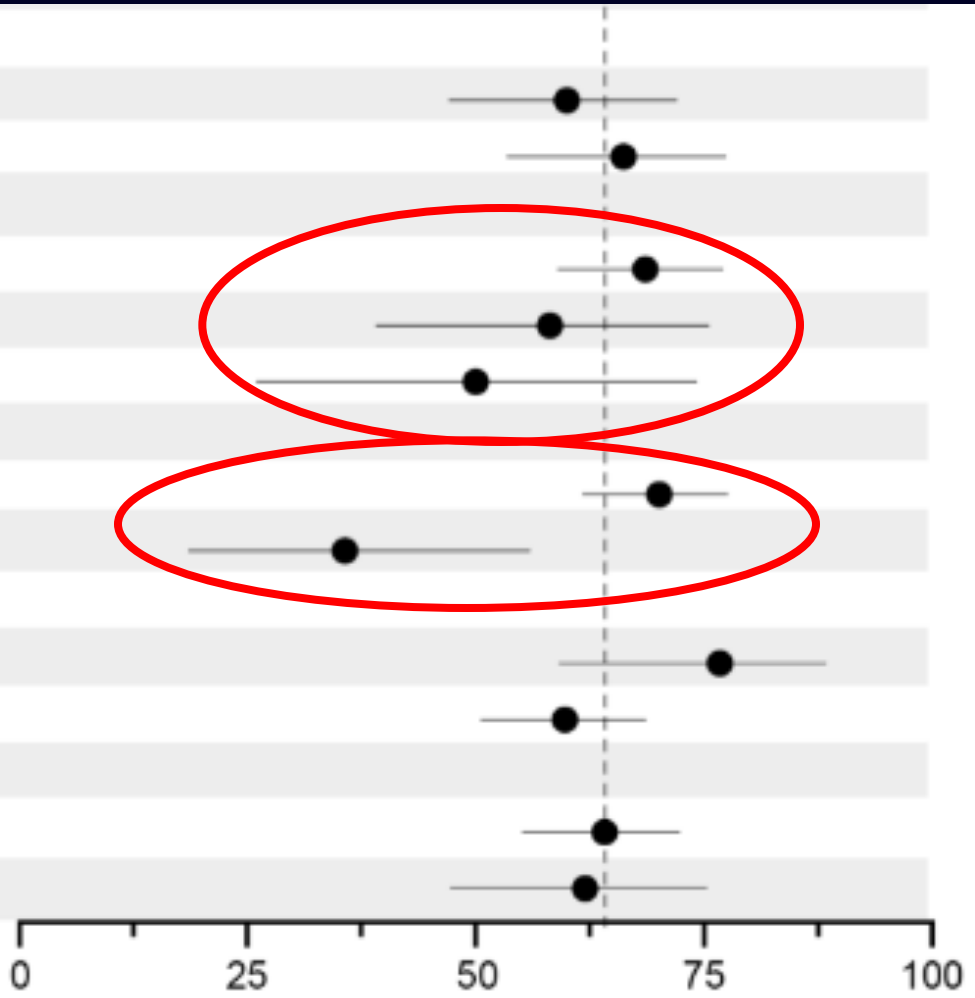
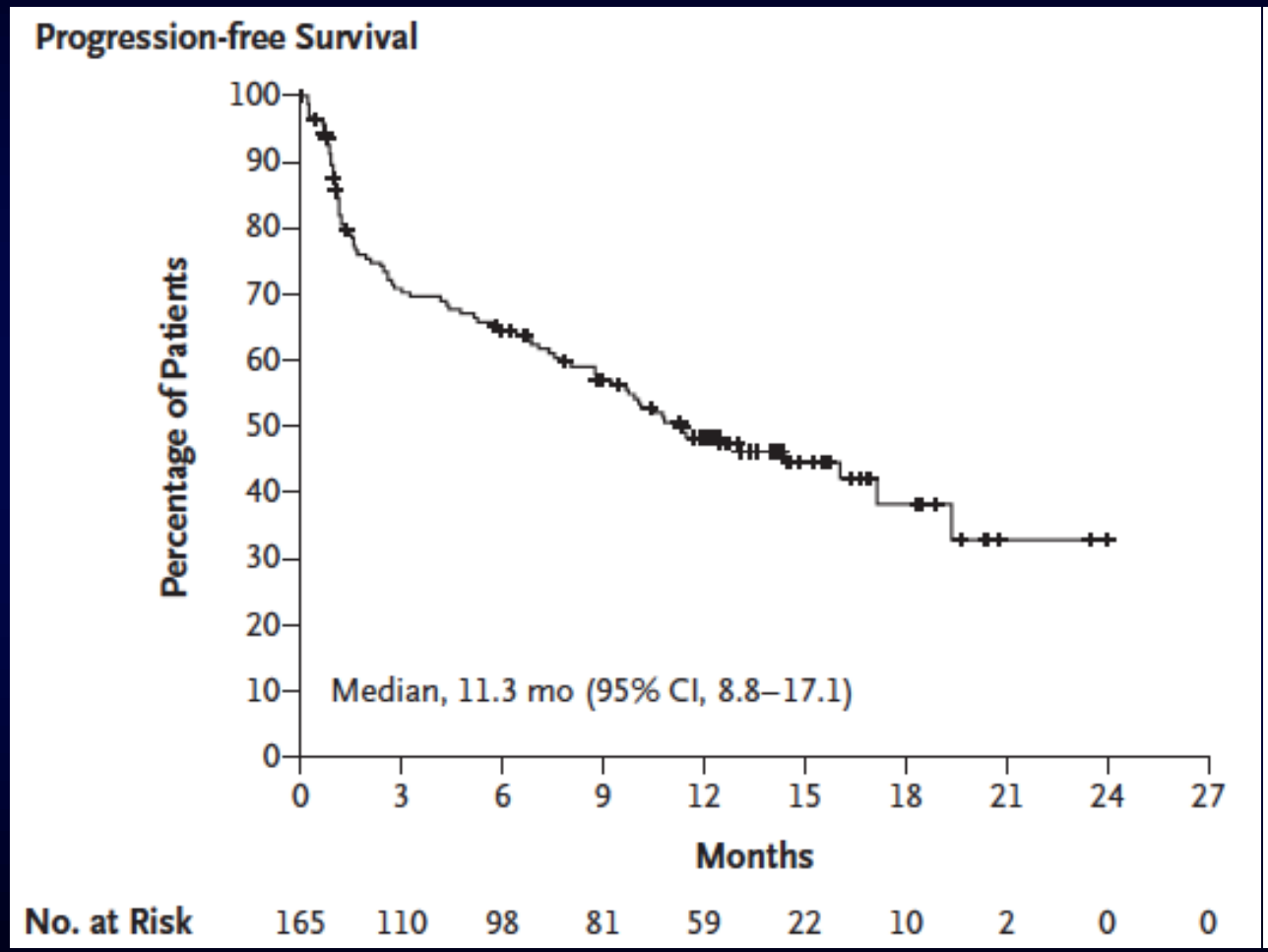
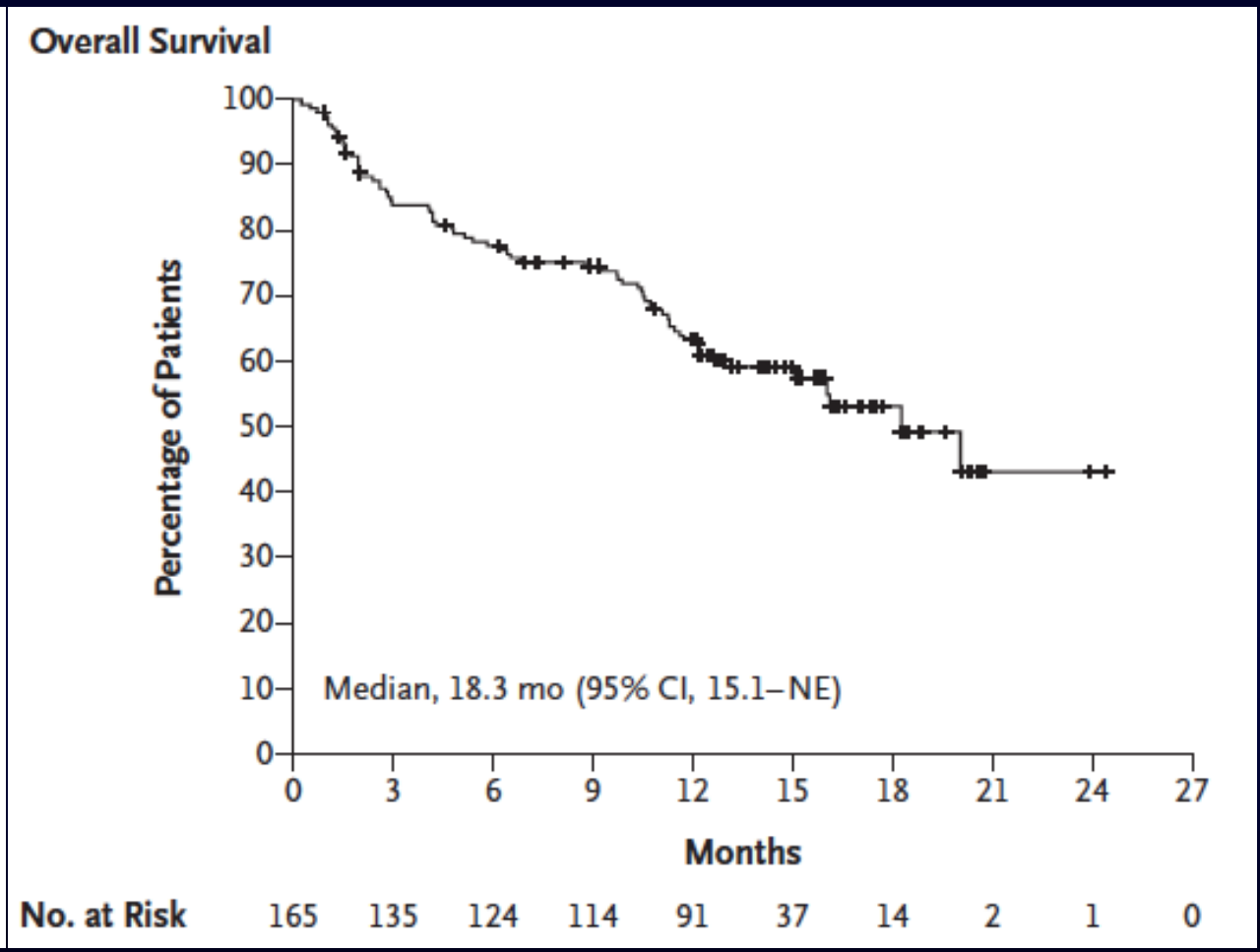
Subgroup Analyses

BCMA tumor expression†	
≥67.2%	38/65
<67.2%	42/65
Bone marrow plasma cells‡	
≤30%	75/111
>30% to <60%	18/31
≥60%	8/18
Extramedullary plasmacytomas‡	
0	94/137
≥1	10/28
No. of prior lines of therapy	
≤3	32/43
>3	72/122
Refractory status	
Triple-class§	80/128
Penta-drug‖	30/50



Response Durability





Adverse Events

Event	Any Grade	Grade 3 or 4
	no. of patients (%)	
Any adverse event	165 (100)	156 (94.5)
Hematologic		
Neutropenia	117 (70.9)	106 (64.2)
Anemia	86 (52.1)	61 (37.0)
Thrombocytopenia	66 (40.0)	35 (21.2)
Lymphopenia	57 (34.5)	54 (32.7)
Leukopenia	29 (17.6)	12 (7.3)
Nonhematologic		
Diarrhea	47 (28.5)	6 (3.6)
Fatigue	46 (27.9)	4 (2.4)
Nausea	45 (27.3)	1 (0.6)
Injection-site erythema	43 (26.1)	0
Pyrexia	45 (27.3)	1 (0.6)
Headache	39 (23.6)	1 (0.6)
Arthralgia	36 (21.8)	1 (0.6)
Constipation	34 (20.6)	0
Cough	33 (20.0)	0
Pneumonia	30 (18.2)	21 (12.7)
Covid-19	29 (17.6)	20 (12.1)
Bone pain	29 (17.6)	6 (3.6)
Back pain	27 (16.4)	4 (2.4)
Cytokine release syndrome†	119 (72.1)	1 (0.6)
Neurotoxic event	24 (14.5)	1 (0.6)

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Neurotoxicity

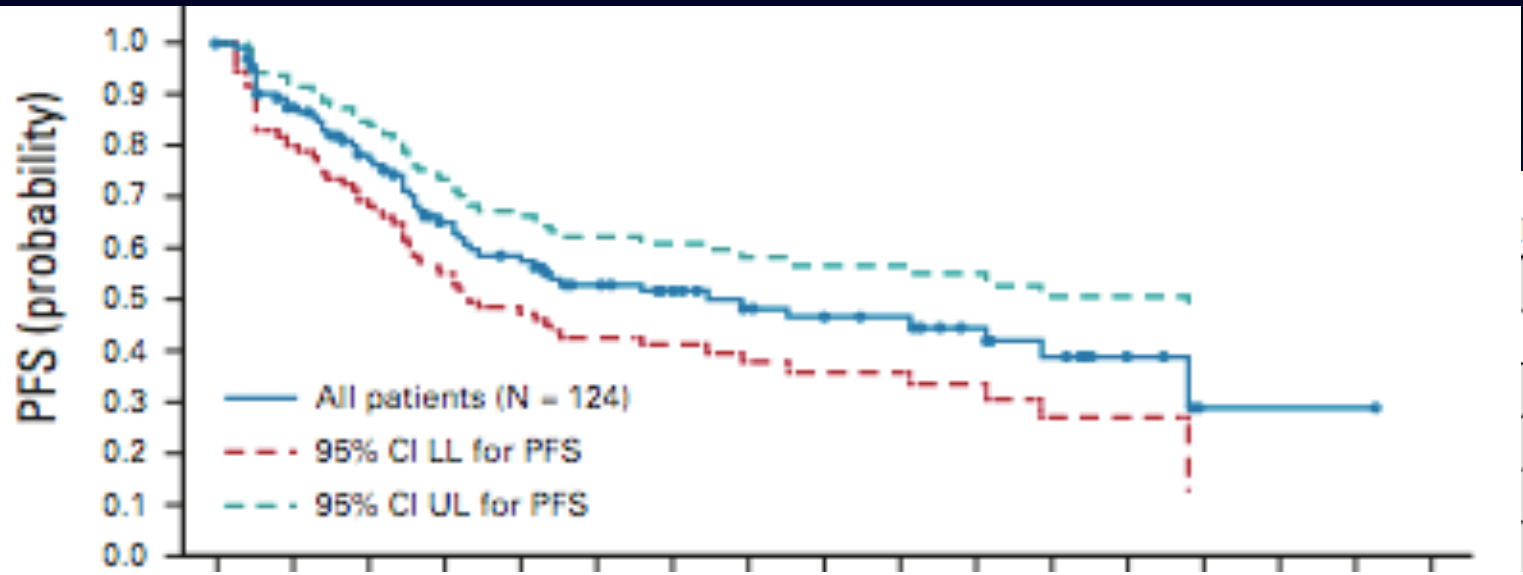
Maximum toxicity grade — no. (%)	
Grade 1	14 (8.5)
Grade 2	9 (5.5)
Grade 3	0 (0)
Grade 4	1 (0.6)
Median time to onset relative to most recent dose (range), days	3.0 (1–13)
Duration, median (range), days	7.0 (1–291)
Patients requiring supportive measures for neurotoxic events — no. (%)§	14 (8.5)
Tocilizumab	3 (1.8)
Dexamethasone	3 (1.8)
Levetiracetam	2 (1.2)
Gabapentin	1 (0.6)

Elranatamab BCMA x CD3

TEAE, %	Grade 1	Grade 2	Grade 3	Grade 4	Total (n = 30)
Hematological					
▪ Lymphopenia	0	0	6 (20.0)	19 (63.3)	25 (83.3)
▪ Anemia	0	3 (10.0)	15 (50.0)	0	18 (60.0)
▪ Neutropenia	0	0	7 (23.3)	9 (30.0)	16 (53.3)
▪ Thrombocytopenia	3 (10.0)	2 (6.7)	5 (16.7)	6 (20.0)	16 (53.3)
▪ Leukopenia	1 (3.3)	3 (10.0)	7 (23.3)	1 (3.3)	12 (40.0)
Non-hematological					
▪ CRS	17 (56.7)	5 (16.7)	0	0	22 (73.3)
▪ Injection site reaction	13 (43.3)	2 (6.7)	0	0	15 (50.0)
▪ Nausea	5 (16.7)	5 (16.7)	1 (3.3)	0	11 (36.7)
▪ Increased AST	5 (16.7)	2 (6.7)	3 (10.0)	0	10 (33.3)
▪ Increased ALT	5 (16.7)	1 (3.3)	3 (10.0)	0	9 (30.0)
▪ Diarrhea	6 (20.0)	2 (6.7)	1 (3.3)	0	9 (30.0)
▪ Vomiting	7 (23.3)	1 (3.3)	0	0	8 (26.7)
▪ Decreased appetite	5 (16.7)	2 (6.7)	0	0	7 (23.3)
▪ Dry skin	5 (16.7)	2 (6.7)	0	0	7 (23.3)
▪ Hypokalemia	1 (3.3)	5 (16.7)	1 (3.3)	0	7 (23.3)
▪ Arthralgia	3 (10.0)	2 (6.7)	1 (3.3)	0	6 (20.0)
▪ ICANS	3 (10.0)	3 (10.0)	0	0	6 (20.0)
▪ Pyrexia	5 (16.7)	1 (3.3)	0	0	6 (20.0)

Bahlis, N et al. ASCO Annual Meeting & Exposition, Abstract 8006, 2021.

ABBV-383 BCMA x CD3

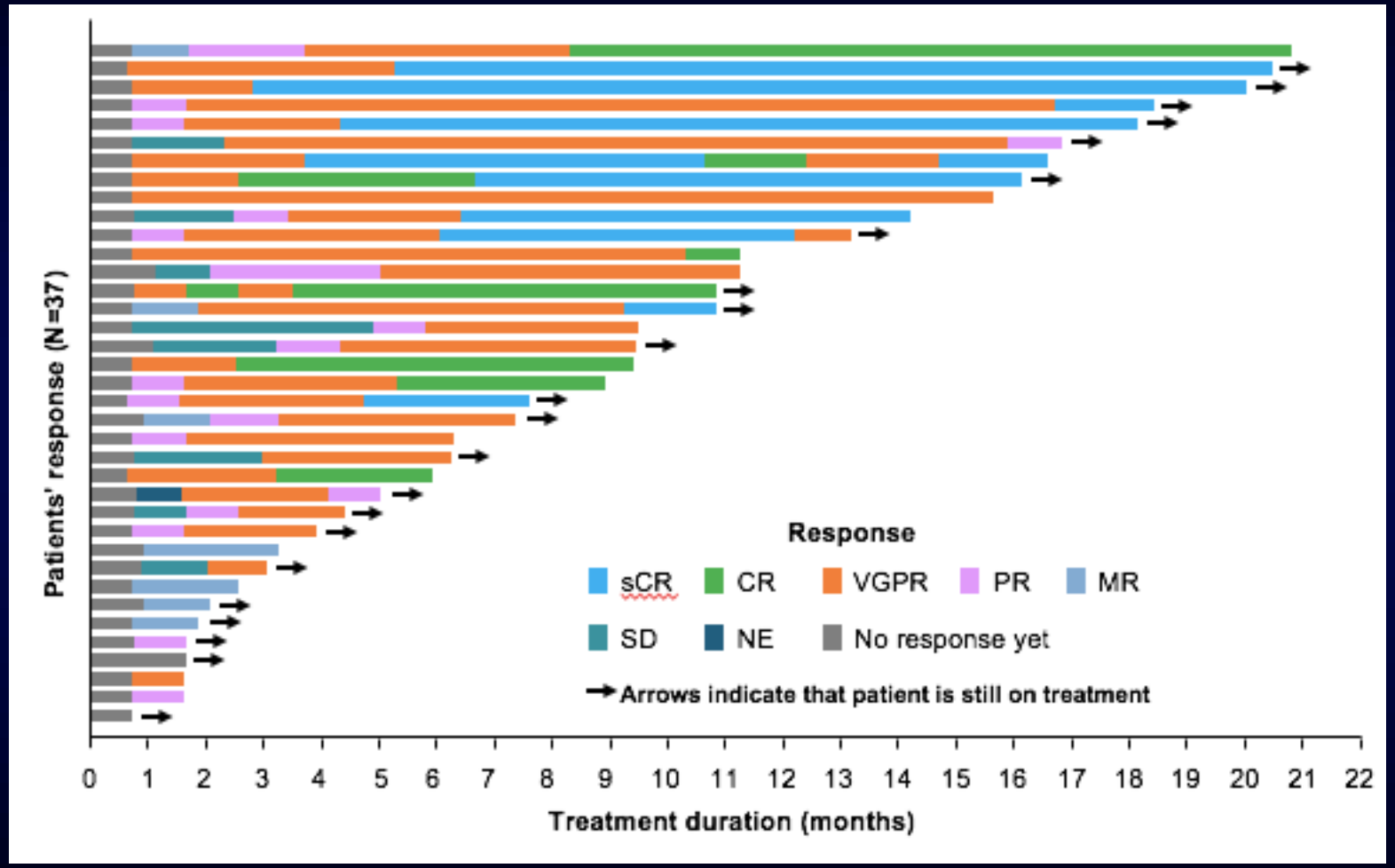


Overview	Total (N = 122)
ORR, No.	69 (57)
≥ VGPR,	52 (43)
Best over	
sCR	21 (17)
CR	14 (11)
VGPR	17 (14)
PR	(14)
MR	(2)
SD	(30)
PD	(12)

PFS	60 mg (EXP) (n = 51)	≥ 40 mg (ESC + EXP) (n = 81)	All Patients (N = 124)
Median, months (range)	NR (4.7-NR)	NR (6.3-NR)	10.4 (5.0-19.2)
KM estimate, % (95% CI)			
6 months	60.8 (43.6 to 74.2)	63.5 (50.4 to 74.0)	57.5 (47.3 to 66.4)
12 months	57.0 (39.4 to 71.3)	57.9 (44.6 to 69.1)	46.6 (35.9 to 56.6)

D'Souza, A et al. J Clin Oncol. https://doi.org/10.1200/JCO.22.01504.

REGN 5458 BCMA x CD3



Zonder, JA et al. IMS Annual Meeting & Exposition, OAB-056, 2022.

Talquetamab : GPRC5D

Nonhematologic AEs in ≥20% of Total SC Population, n (%)	405 µg/kg SC QW* (n = 30)		800 µg/kg SC Q2W* (n = 25)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
CRS	23 (77)	1 (3)	18 (72)	0 (0)
Dysgeusia	18 (60)	NA	9 (36)	NA
Dysphagia	11 (37)	0 (0)	4 (16)	0 (0)
Skin exfoliation	11 (37)	0 (0)	9 (36)	0 (0)
Fatigue	9 (30)	1 (3)	7 (28)	0 (0)
Weight decreased	9 (30)	0 (0)	6 (24)	0 (0)
Nail disorder	9 (30)	NA	5 (20)	NA
Pyrexia	6 (20)	0 (0)	4 (16)	0 (0)
Dry mouth	8 (27)	0 (0)	10 (40)	0 (0)
Diarrhea	8 (27)	0 (0)	3 (12)	0 (0)
Nausea	7 (23)	0 (0)	3 (12)	0 (0)
ALT increased	6 (20)	1 (3)	8 (32)	1 (4)

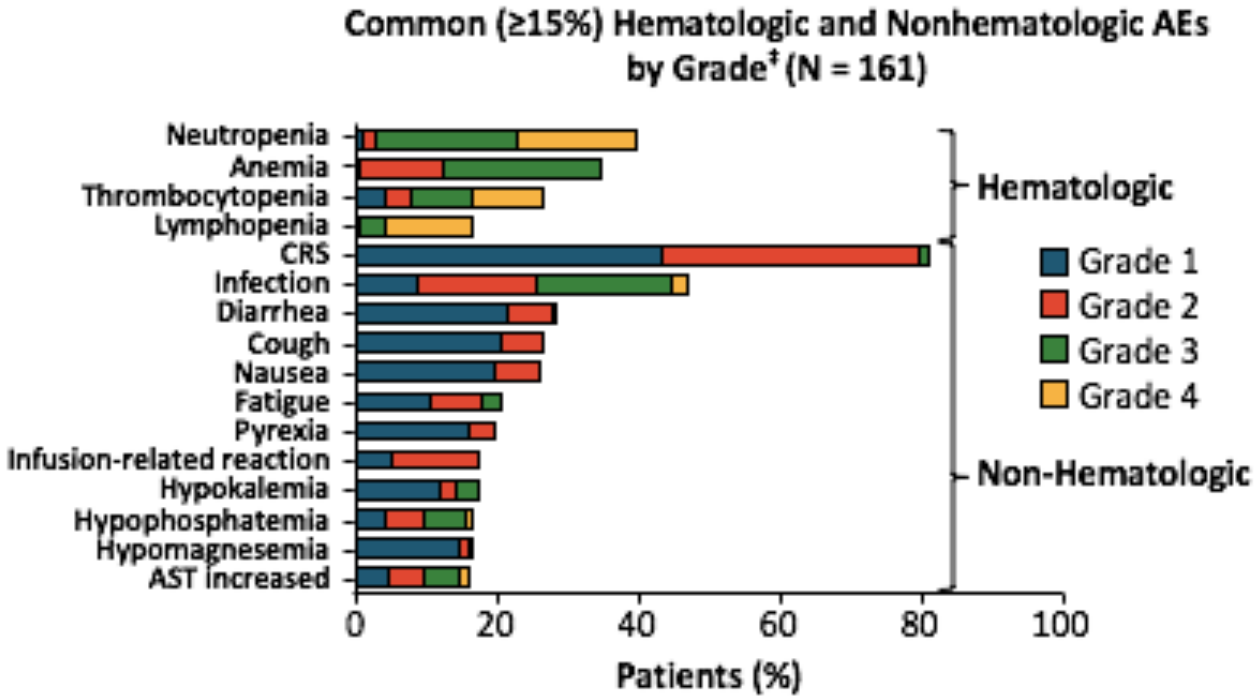
*With 2-3 step-up doses.

Krishnan, A et al. ASH Annual Meeting & Exposition, Abstract 158, 2021.

Cevostamab : FcRH5

Best Response in Evaluable Patients by Dose Level

AE, n (%)	All Grade (N = 161)
Any grade	160 (99.4)
▪ Grade 3	53 (32.9)
▪ Grade 4	46 (28.6)
▪ Grade 5*†	6 (3.7)
▪ Cevostamab related†	1 (0.6)
SAE (any grade)	96 (59.6)
AE leading to discontinuation	21 (13.0)
▪ Cevostamab related	7 (4.3)



Dose Level (n = 83)

Dose Level (n = 60)

Trudel, S et al. ASH Annual Meeting & Exposition, Abstract 157, 2021.

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Late Relapse Summary

- Later line relapsed/refractory myeloma (>3 prior lines)
  - Venetoclax-based combos for t(11;14)
  - Alkylating agent-based combos can work well
    - Beware of bendamustine's effects on T-cells for later CAR T or TCE
  - BCMA-targeted CAR T cell products when/where available
  - T-cell engagers to multiple targets, especially BCMA, GPRC5D, FcRH5
  - All of these agents will be moving earlier (KarMMA-3!)
  - Other drugs coming also, including iberdomide & mezigdomide, as well as other α-CD38s (modakafusp alfa)

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Remaining Challenges in Late Relapse

- Infectious toxicities & prophylactic approaches
- Debulk in high tumor burden/extramedullary disease/PCL, and how?
- How to differentiate those who benefit from a CAR T vs. TCE (?T-cell exhaustion)
- Is sequential therapy (CAR ➜ TCE or TCE ➜ CAR) against the same target rational?
- Can TCE therapy against target 1 be followed by TCE therapy against target 2, or will T-cell exhaustion preclude this?