Maintenance Therapy in Multiple Myeloma, for everyone? Until when? with what?

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INTERNATIONAL MYELOMA FOUNDATION

HOSPITAL MILITAR CENTRAL BOGOTÁ

Conflict of interest

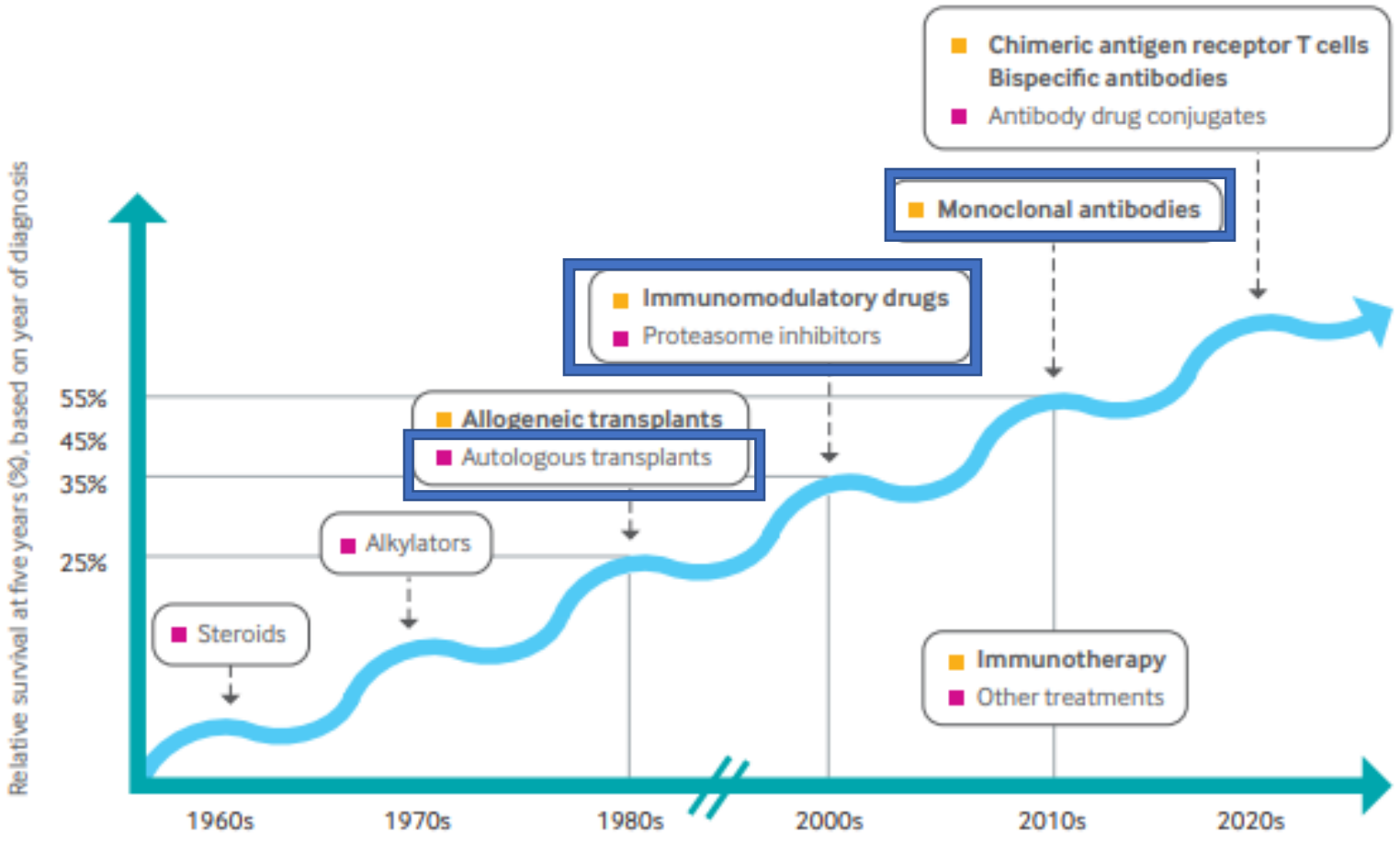
Support research	Janssen – Sanofi - BMS - Pfizer
Employee	Instituto Nacional de Cancerología de Colombia E.S.E. Hospital Militar Central de Colombia
Honoraria	Pfizer, Takeda, Amgen, Janssen, Sanofi, Roche, BMS
Stakeholder	Accionista en Hemocure SAS y SHOT SAS
Staff of speaker	No
Scientific Advisory Board	Pfizer, Takeda, Amgen, Janssen, Sanofi, Roche

Agenda

- Timeline of drug discovery in multiple myeloma
- Definition of maintenance therapy MT and continuous therapy CT
- Requirements for MT and CT
- Drugs used for MT and CT
- Evidence on MT or CT
- Future directions
- Take-home messages

Timeline of drug discovery in multiple myeloma

Timeline of drug discovery and year of multiple myeloma diagnosis (by decade)



- Hope for the cure
- "Fixed duration of therapy and the disease (MM) never returns after stopping therapy"

Shah UA, Mailankody S. Emerging immunotherapies in multiple myeloma. BMJ. 2020 Sep 21;370:m3176.

Definition of maintenance therapy MT and continuous therapy CT

Multiple myeloma is an incurable disease

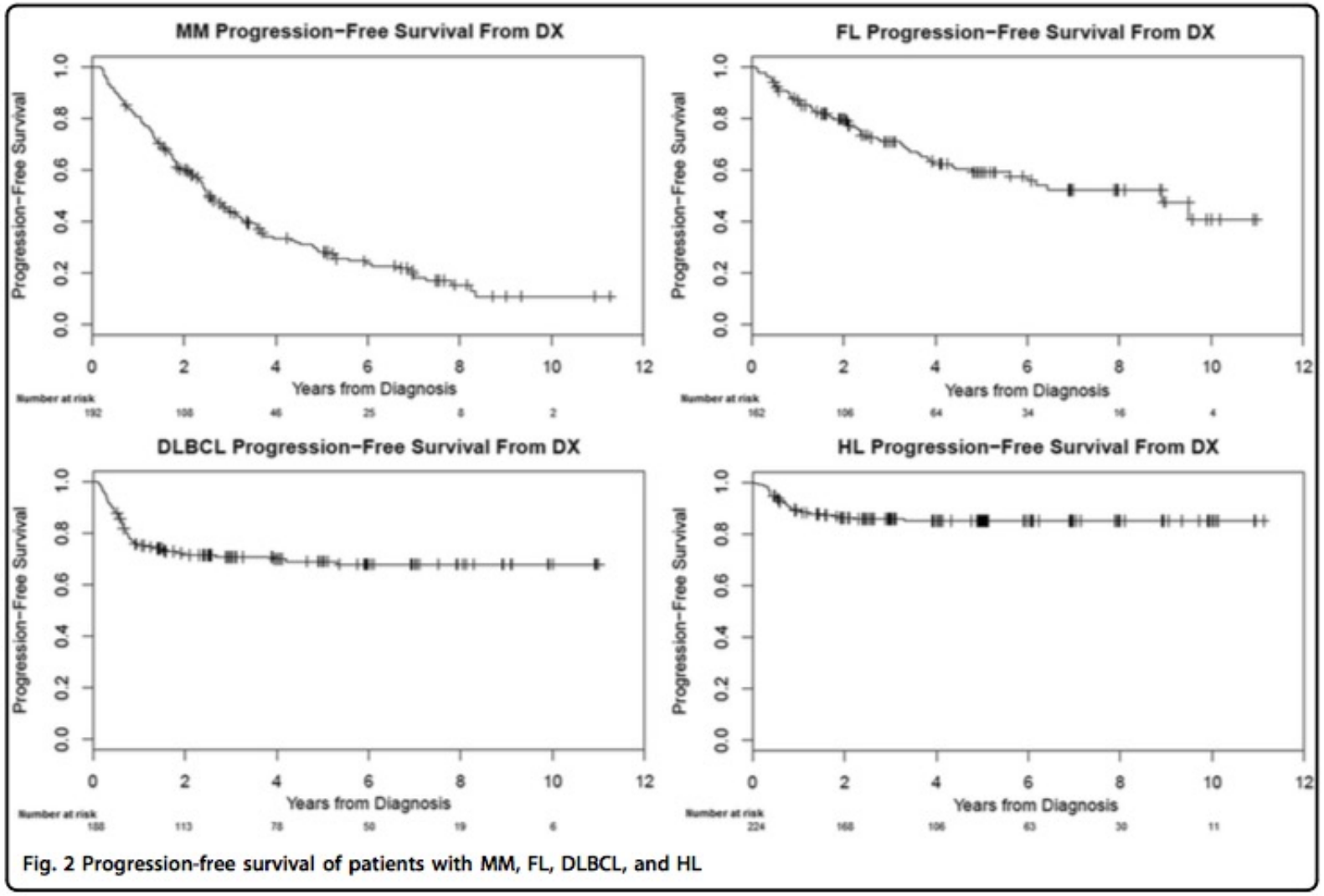
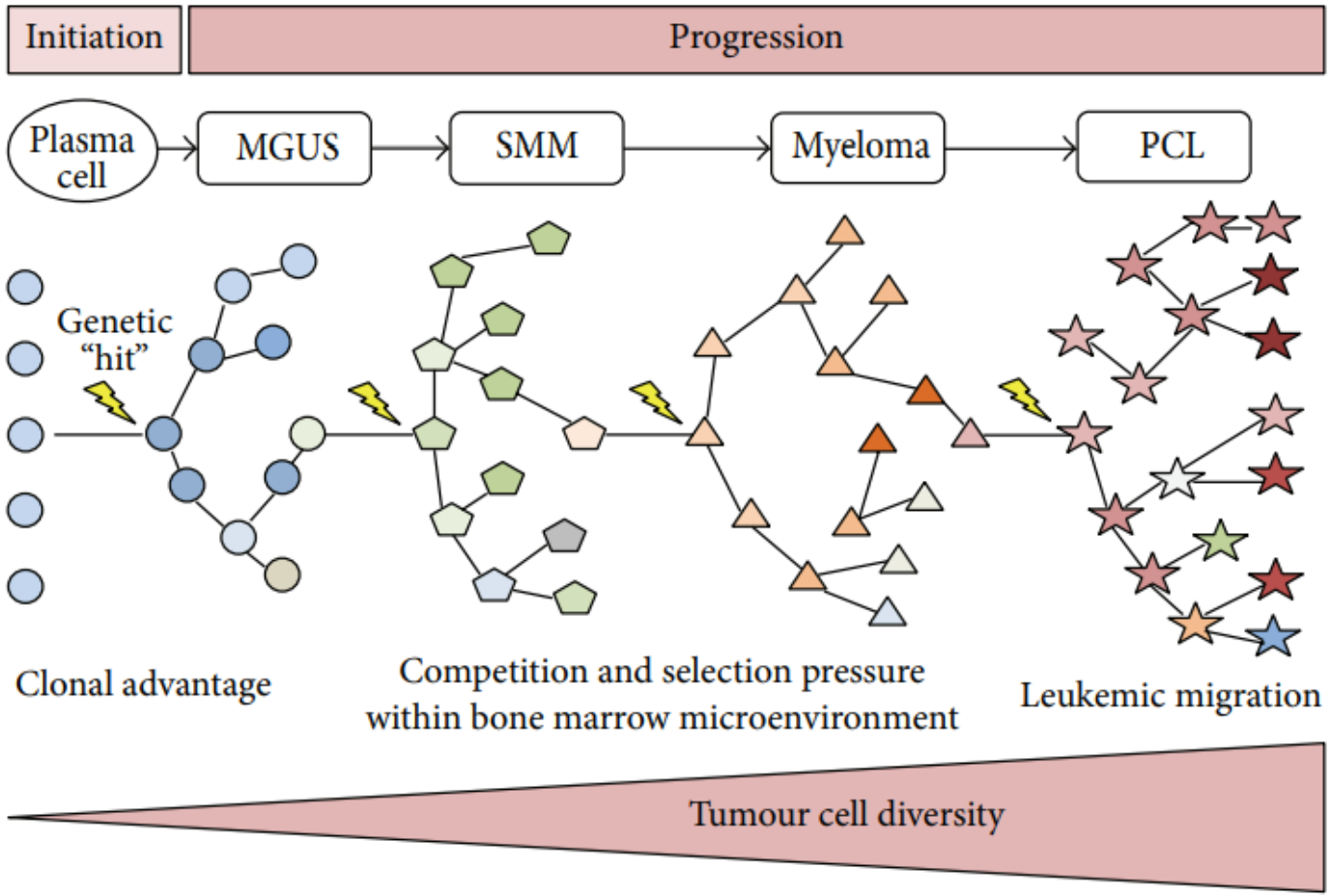


Fig. 2 Progression-free survival of patients with MM, FL, DLBCL, and HL

Ravi P, Kumar SK, Cerhan JR, Maurer MJ, Dingli D, Ansell SM, Rajkumar SV. Defining cure in multiple myeloma: a comparative study of outcomes of young individuals with myeloma and curable hematologic malignancies. Blood Cancer J. 2018 Feb 28;8(3):26.



Prideaux SM, Conway O'Brien E, Chevassut TJ. The genetic architecture of multiple myeloma. Adv Hematol. 2014;2014:864058. doi: 10.1155/2014/864058. Epub 2014 Apr 3.

Definition of maintenance and continuous therapy

Maintenance therapy MT

- Patients undergoing to transplant
- One or two drugs after transplant

Continuous therapy CT

- Non-transplant eligible patients
- The same regimen used in the induction

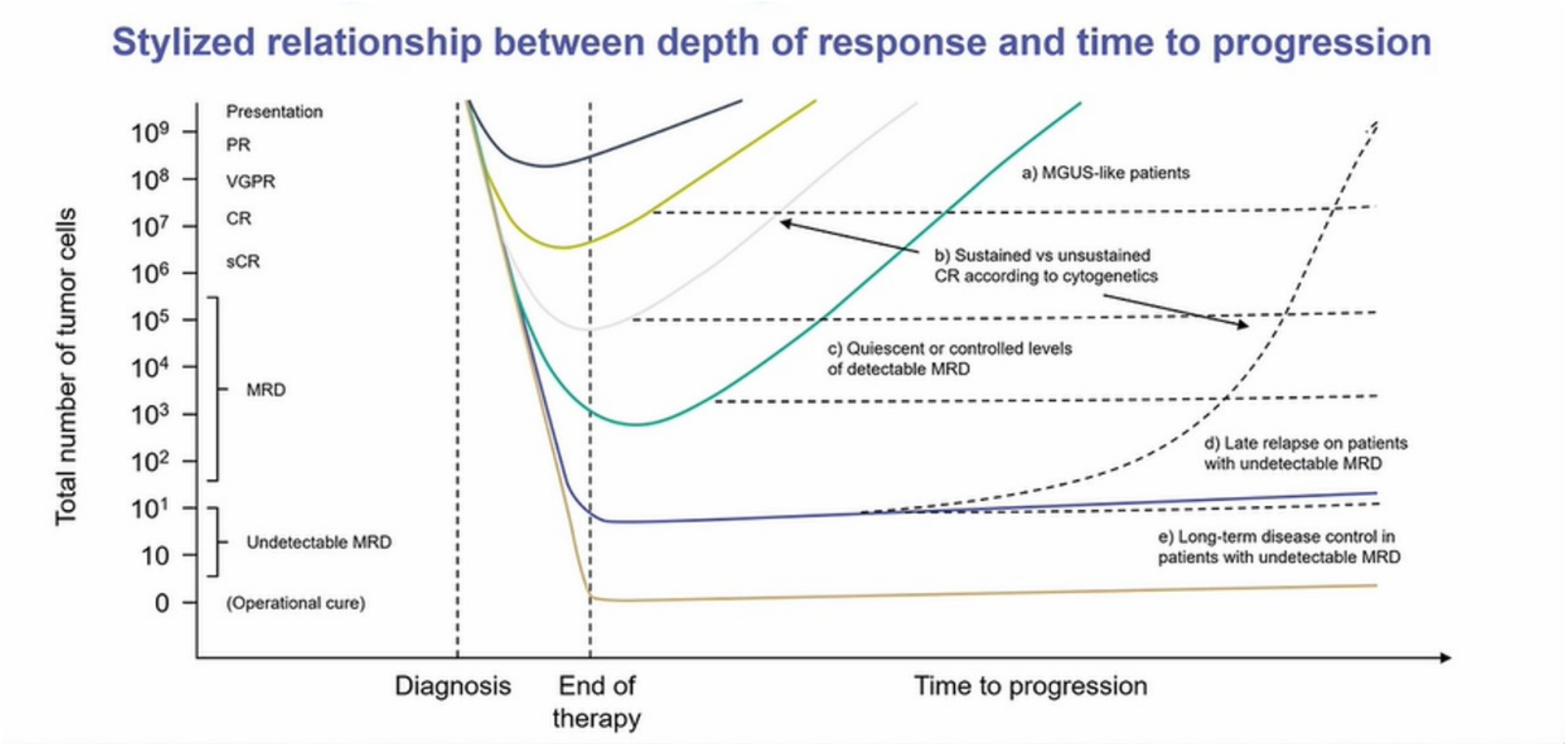
PFS

The goal of both MT or CT is to control minimal residual disease (MRD) minimizing the toxicity

OS

Richardson PG, Laubach J, Gandolfi S, Facon T, Weisel K, O'Gorman P. Maintenance and continuous therapy for multiple myeloma. Expert Rev Anticancer Ther. 2018 Aug;18(8):751-764.

There is a clear link between MRD and long-term outcomes



Paiva B, van Dongen JJ, Orfao A. New criteria for response assessment: role of minimal residual disease in multiple myeloma. Blood. 2015 May 14;125(20):3059-68.

Overall survival has improved in Multiple Myeloma

- Use of at least triplets in the first line and in relapses
- Achieve deeper remissions – MRD
- Continuous therapy CT or maintenance therapy MT

Harousseau JL, Attal M. How I treat first relapse of myeloma. Blood. 2017 Aug 24;130(8):963-973

Requirements for MT and CT

- Treatments must be tolerable for a prolonged period of time
- Should not be associated with cumulative or chronic toxicity
- Should not adversely affect patients' quality of life
- Should ideally be convenient with a minimal treatment burden for patients
- Should not impact the feasibility or efficacy of subsequent treatment at relapse

Dimopoulos MA, Jakubowiak AJ, McCarthy PL, Orlowski RZ, Attal M, et al. Developments in continuous therapy and maintenance treatment approaches for patients with newly diagnosed multiple myeloma. Blood Cancer J. 2020 Feb 13;10(2):17.

Drugs used for maintenance therapy and continuous therapy

Latin America

Table 1. Baseline Characteristics of the Patients in the retrospective analysis

Characteristic		
Country – no. (%) (CI95%)	**86(100)**	
Argentina	25 (29)	(20.2-39.3)
Chile	21 (24)	(16.2-34.3)
Colombia	19 (22)	(14.2-31.7)
México	12 (14)	(7.78-22.5)
Uruguay	6 (7)	(2.87-13.94)
Ecuador	3 (4)	(0.89-9.19)
Age – yr		
Mean	35.4	(35.4-37.3)
SD	(4.3)	
Male Sex – no. (%)	52(60)	(49.86-70.37)
Type of myeloma		
IgG	41(48)	(37.28-58.22)
IgA	12(14)	(7.78-22.52)
Light chain	18(21)	(13.31-30.48)
Non-secretory	10(12)	(6.06-19.75)
Other	5 (5)	(2.16-12.41)
Involved Light chain		
Kappa	37(43)	(32.87-53.63)
Lambda	24(28)	(19.21-38.07)
Missing data	25(29)	(20.22-39.31)
ISS		
I	21(24)	(16.22-34.31)
II	26(30)	(21.24-40.54)
III	24(28)	(19.21-38.07)
Unknown	15(18)	(10.49-26.55)
Cytogenetic abnormalities – no./total no. of patients who could be evaluated *		
FISH t (4;14) +	4/25	(5.29-34.22)
FISH t (14;16) +	1/25	(0.19-18.19)
FISH del 17p +	1/28	(0.17-16.38)

* Missing data correspond to 71% for t (4;14) and t (14;16), and 67% for del 17p

Overall Survival

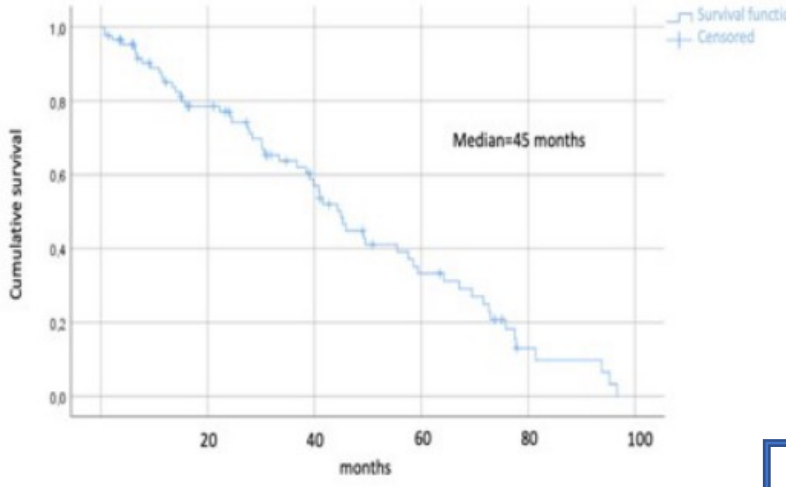


Table 2. Clinical features, chemotherapeutic regimen and response to treatment

Feature - no. (%)		
Hypercalcemia	15(17)	(10.49-26.55)
Renal Failure	23(27)	(18.21-36.83)
Anemia	36(42)	(31.79-52.47)
Bone disease	44(51)	(40.65-61.60)
Fractures	20(23)	(15.24-33.04)
Plasmocytoma	20(23)	(15.24-33.04)
Chemotherapeutic regimen – no (%)		
VCD/CyBorD	32(37)	(27.49-47.77)
VTD	16(19)	(11.42-27.87)
CTD	12(14)	(7.78-22.52)
Tal/Dex	8(9)	(4.41-16.90)
VRD	4(5)	(1.49-10.84)
Other	14(16)	(9.57-25.22)
Outcome		
Best response attained (frontline) – no (%)		
Stringent complete response	3(4)	(0.89-9.19)
Complete response	13(15)	(8.67-23.87)
Very good partial response	14(16)	(9.57-25.22)
Partial response	24(28)	(19.21-38.07)
Stable disease	9(11)	(5.22-18.33)
Progressive disease	5(6)	(2.16-12.41)
Missing data	18(21)	(13.31-30.48)
Transplant features – no (%)		
Finally transplanted population	53(62)	(51.04-71.44)
Post-transplant consolidation	7(8)	(3.62-15.44)
Maintenance †	39(45)	(35.07-55.94)

† Thalidomide based (13%), lenalidomide (26%), Bortezomib (6%), other (1%), missing data (55%)

Martínez-Cordero H, Peña C, Schutz N, Bove V, Villano F, Osorio R, et al. Real-World Outcomes in Latin-American Patients with Multiple Myeloma Under 40 Years Old. *Blood* (2019) 134 (Supplement_1): 5508.

Thalidomide → Rarely used nowadays
Median duration only 18 months
Toxicity

Pomalidomide

Lenalidomide

Standard of care
Cytopenia, rash, diarrhea and SPM

Bortezomib

Ixazomib

Carfilzomib

Monoclonal AB

Combinations

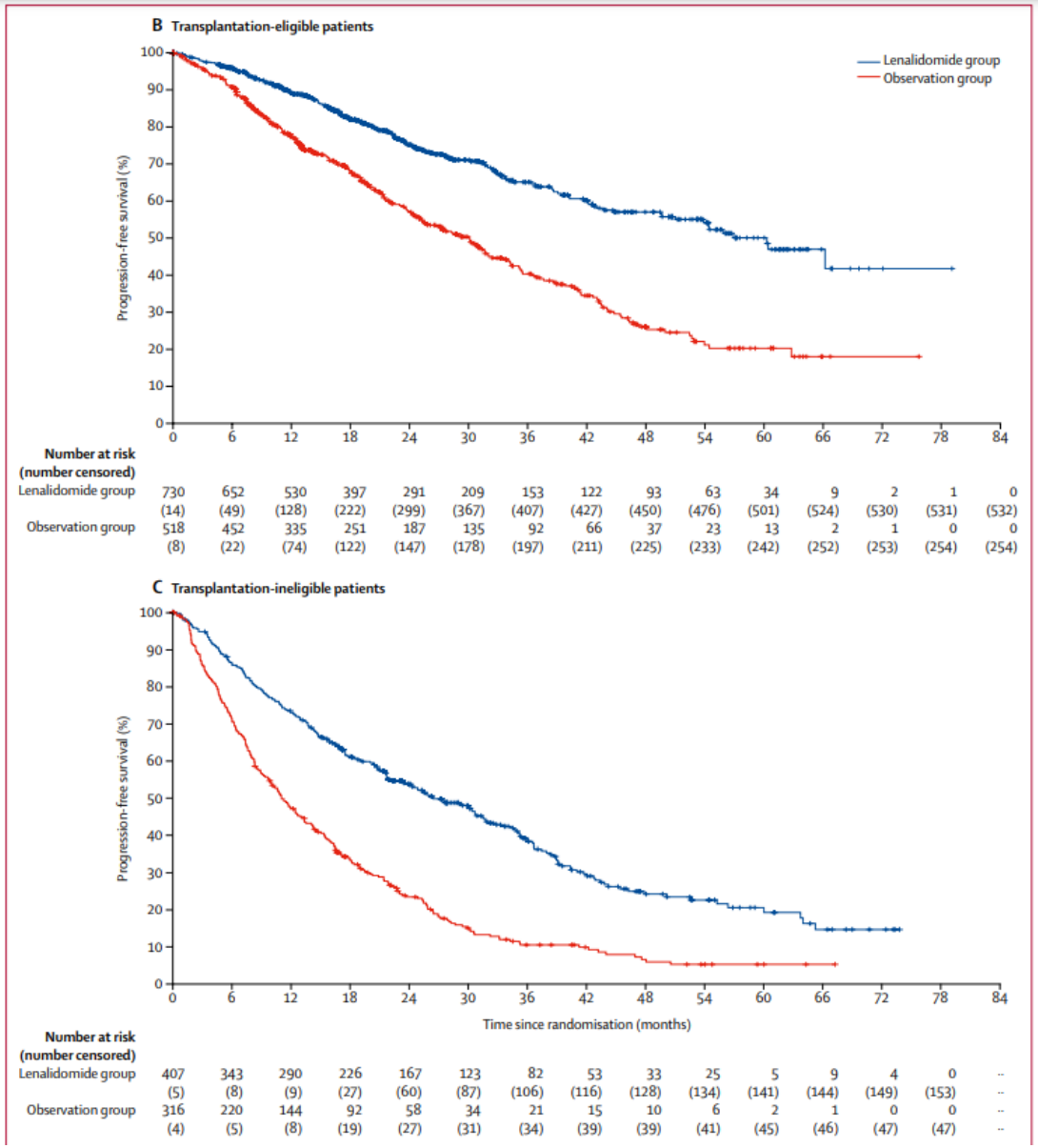
Holstein SA, Suman VJ, Hillengass J, McCarthy PL. Future Directions in Maintenance Therapy in Multiple Myeloma. J Clin Med. 2021 May 24;10(11):2261.

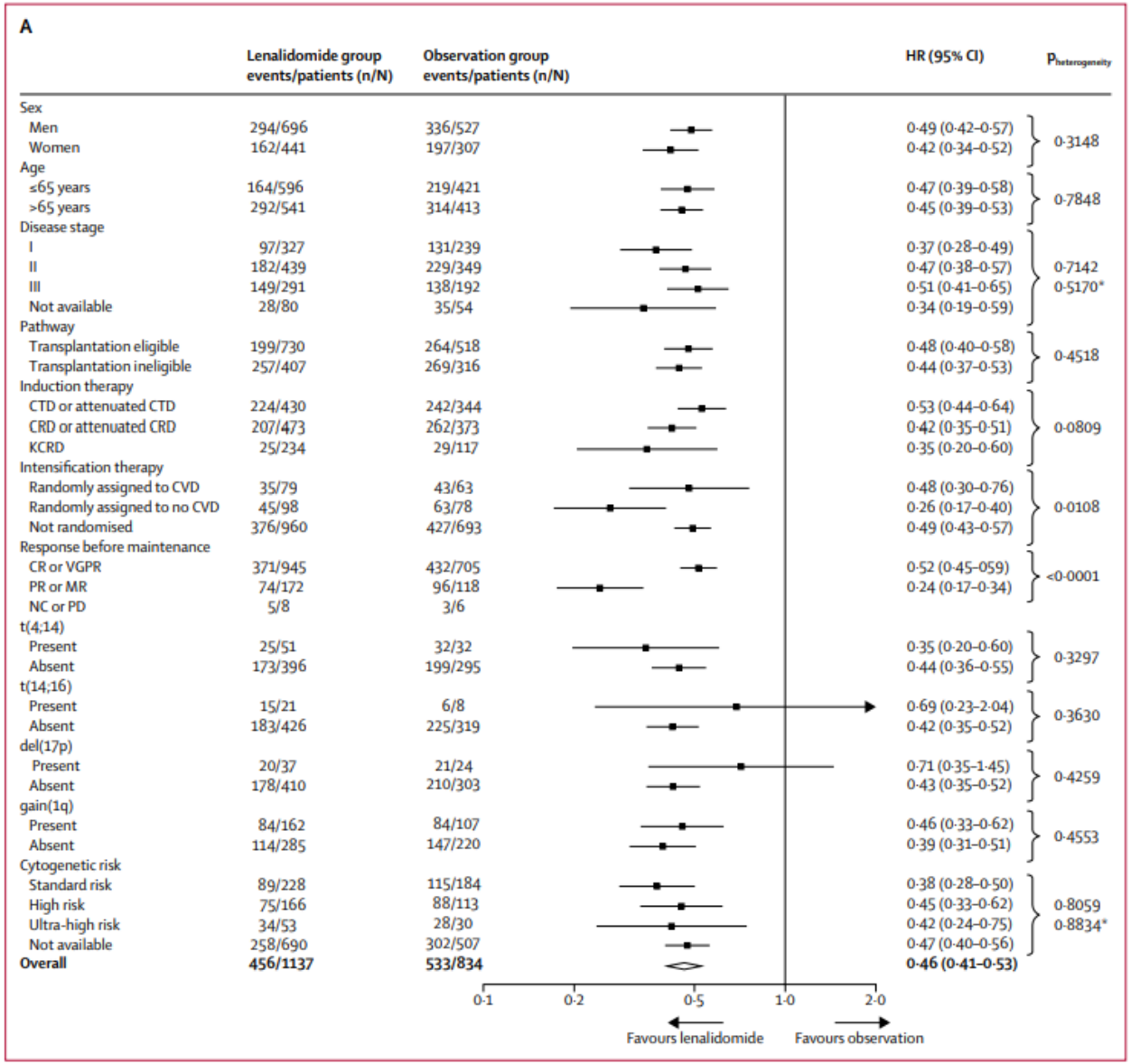
Lenalidomide

Table 1. Summary of randomized phase III trials evaluating lenalidomide maintenance after ASCT.

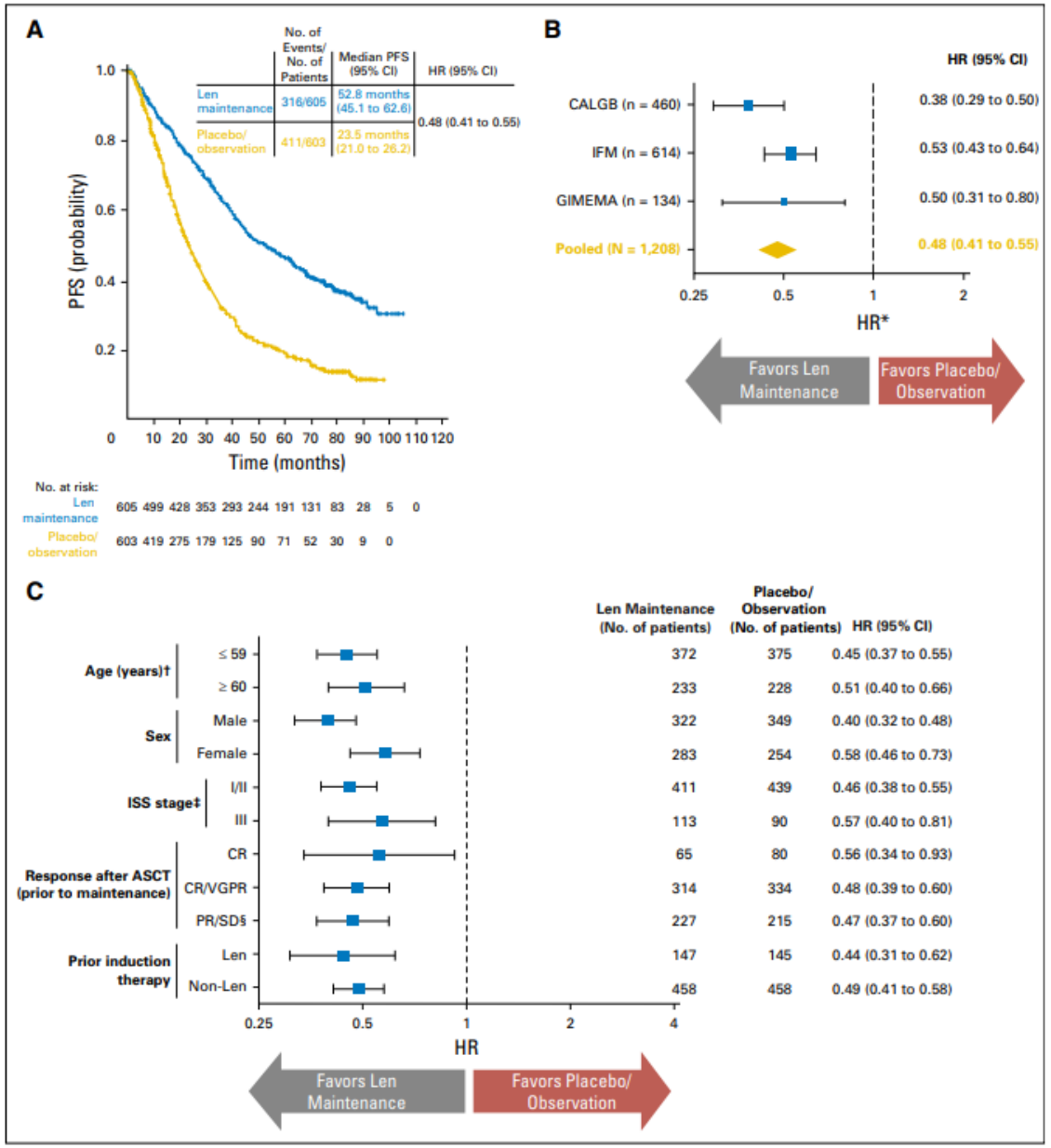
Study	N	Induction Therapy	Dosing Schedule	Intended Duration of Maintenance	Reported Duration of Lenalidomide Maintenance	TTP or PFS (Maintenance vs. No)	OS (Maintenance vs. No)	SPMs
CALGB 100104 [7,8]	460	≤2 regimens; 94% received a regimen containing Thal, Len, and/or Bor	10 mg continuous, increase up to 15 mg	Until progression	31 months (median)	Median TTP *: 57 vs. 29 months (HR, 0.57; $p < 0.0001$)	Median OS *: 114 vs. 84 months ($p = 0.0004$)	Len: 8% hematologic, 6% solid tumor, 5% noninvasive Pbo: 1% hematologic, 4% solid tumor, 3% noninvasive
IFM 2005-02 [6,11]	614	46% received vincristine, doxorubicin, Dex and 46% received Bor and Dex 21% received tandem transplant	All patients received 2 cycles of consolidation (25 mg/d, 21 out of 28 days) Maintenance: 10 mg continuous, increase up to 15 mg	Stopped due to concerns regarding second primary malignancies at a median time of 2 years (range 1–3 years)	25 months (mean)	Median PFS: 41 vs. 23 months (HR, 0.50; $p < 0.001$) 4-year PFS: 43 vs. 22% ($p < 0.001$)	Median follow-up 45 months: 74 vs. 76% ($p = 0.7$) 4-year OS: 73% vs. 75% ($p = 0.7$)	Len: 4% hematologic, 3% solid tumor, 2% nonmelanoma skin cancer Pbo: 2% hematologic, 1% solid tumor, 1% nonmelanoma skin cancers
RV-MM-209 [9,11]	402	4 cycles Len/Dex followed by either transplant or MPR	10 mg (21 out of 28 days)	Until progression	35 months (mean) (TE population)	Median PFS **: 42 vs. 22 months (HR, 0.47; $p < 0.001$)	3-year OS **: 88% vs. 79% ($p = 0.14$)	4.3% (Len) vs. 4.3% (Obs)
Myeloma XI [10]	1247 ***	CTD vs. RCD followed by CVD if suboptimal response	10 mg (21 out of 28 days)	Until progression	NR for TE population	Median PFS: 57 vs. 30 months (HR, 0.48; $p < 0.0001$)	3-year OS: 88 vs. 80% (HR, 0.69; $p = 0.014$)	3-year cumulative incidence: 5.3% (Len) vs. 3.1% (Obs) ****

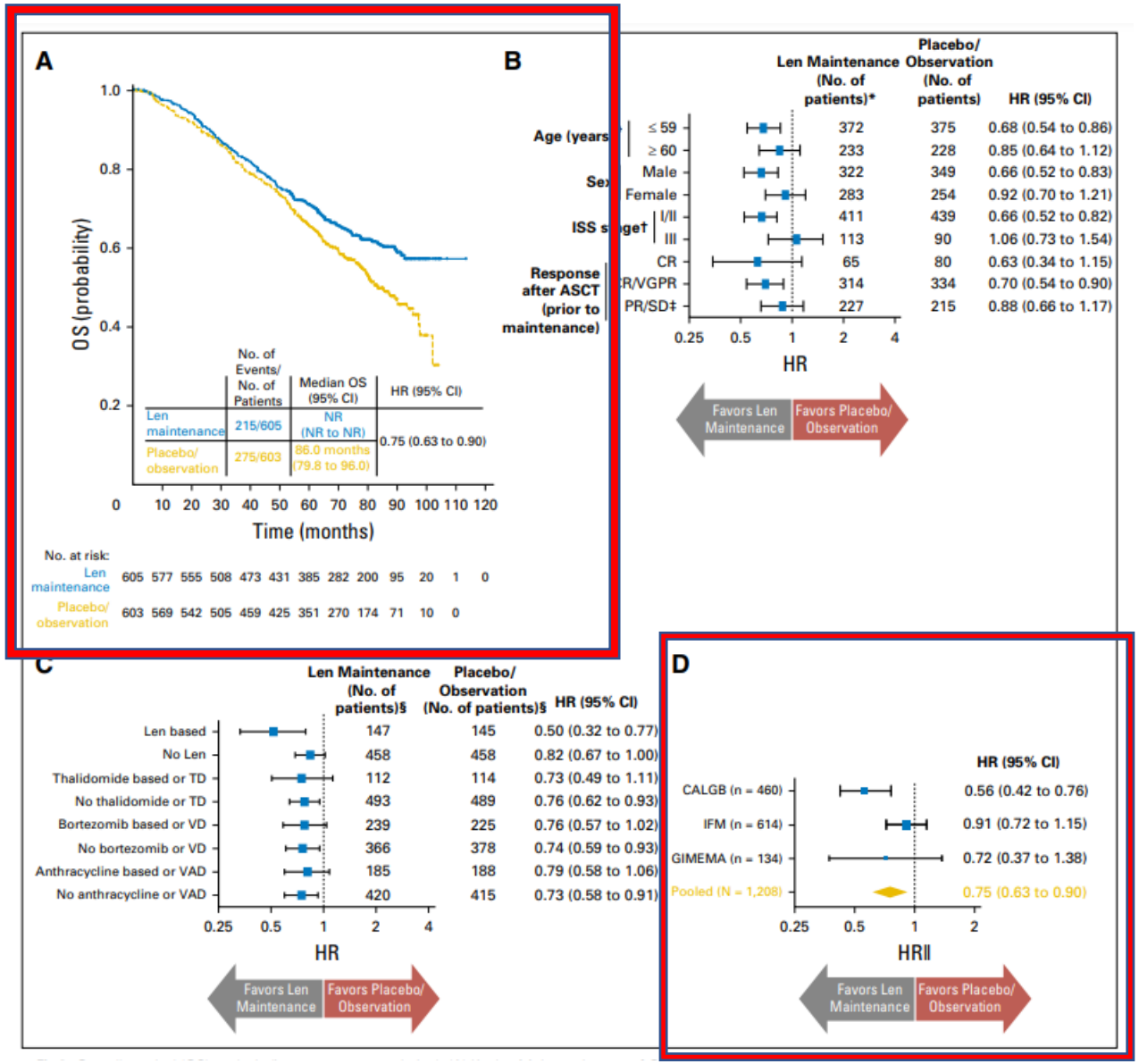
Holstein SA, Suman VJ, Hillengass J, McCarthy PL. Future Directions in Maintenance Therapy in Multiple Myeloma. J Clin Med. 2021 May 24;10(11):2261.





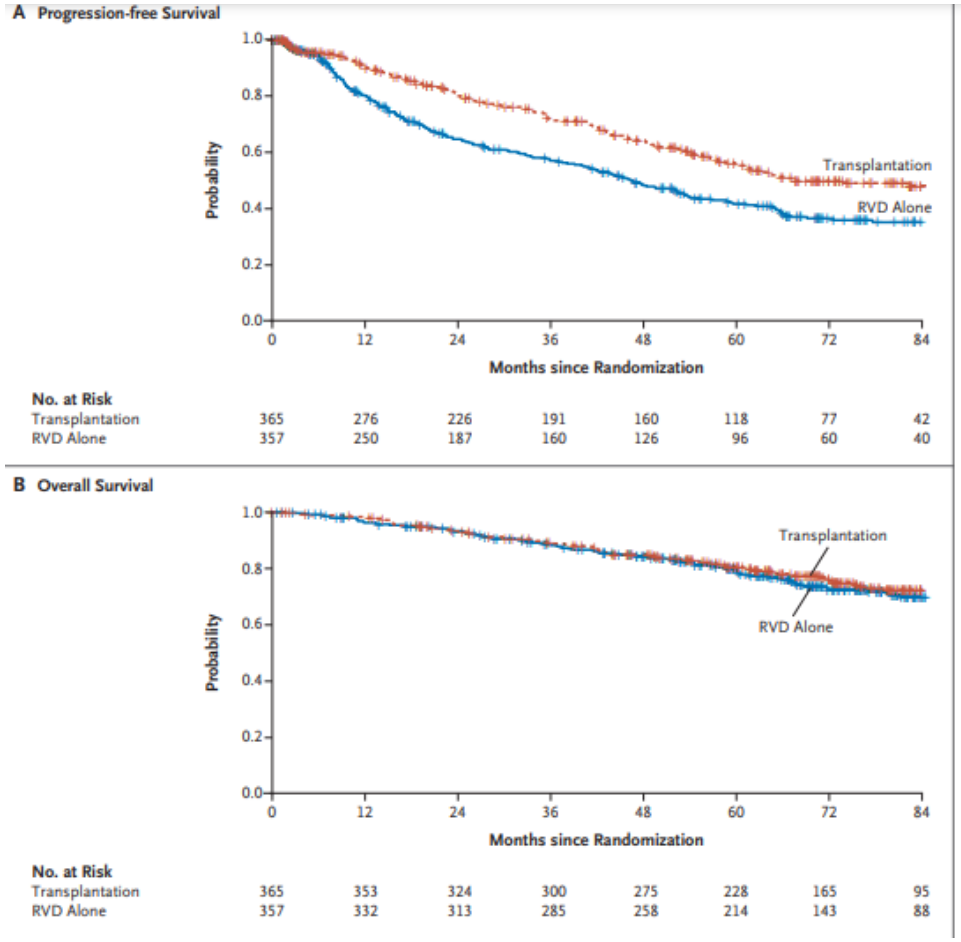
Jackson GH, Davies FE, Pawlyn C, Cairns DA, Striha A, Collett C, et al. Lenalidomide maintenance versus observation for patients with newly diagnosed multiple myeloma (Myeloma XI): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2019 Jan;20(1):57-73.





McCarthy PL, Holstein SA, Petrucci MT, Richardson PG, Hulin C, Tosi P, et al . Lenalidomide Maintenance After Autologous Stem-Cell Transplantation in Newly Diagnosed Multiple Myeloma: A Meta-Analysis. J Clin Oncol. 2017 Oct 10;35(29):3279-3289.

Maintenance therapy - DETERMINATION

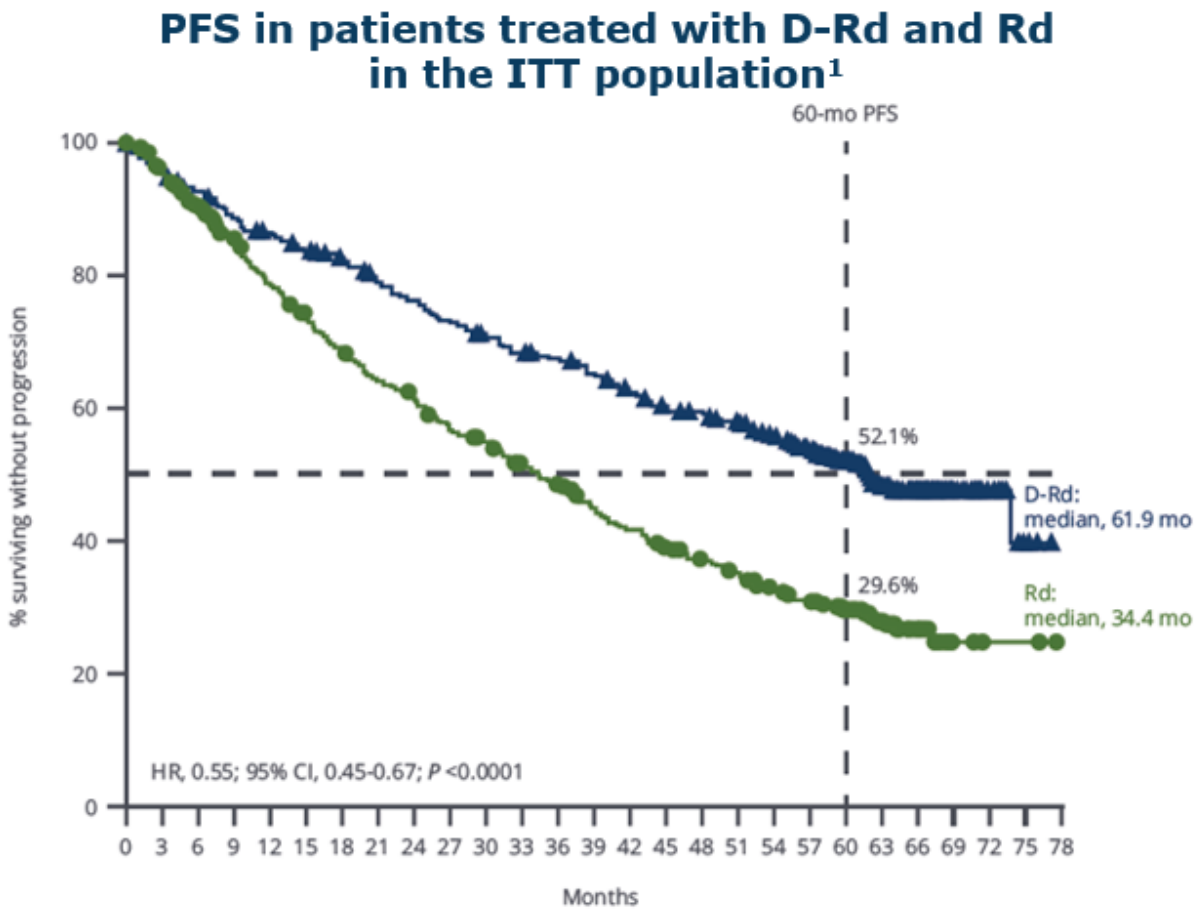


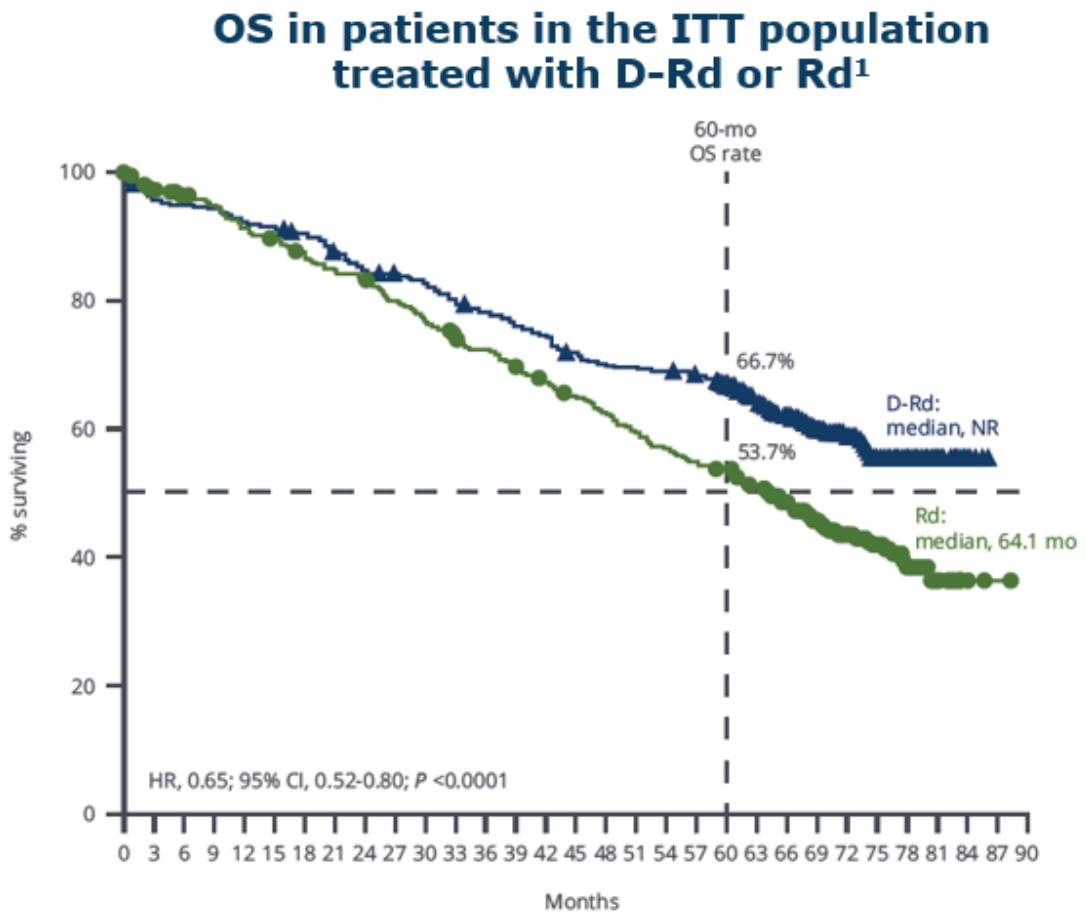
Median progression-free survival was 46.2 months (95% CI, 38.1 to 53.7) in the RVD-alone group and 67.5 months (95% CI, 58.6 to not reached) in the transplant group.

Estimated overall survival was 79.2% and 80.7%, respectively (hazard ratio for death, 1.10; 95% CI, 0.73 to 1.65; P>0.99).

Richardson PG, Jacobus SJ, Weller EA, Hassoun H, Lonial S, Raje NS, et al. Triplet Therapy, Transplantation, and Maintenance until Progression in Myeloma. N Engl J Med. 2022 Jul 14;387(2):132-147.

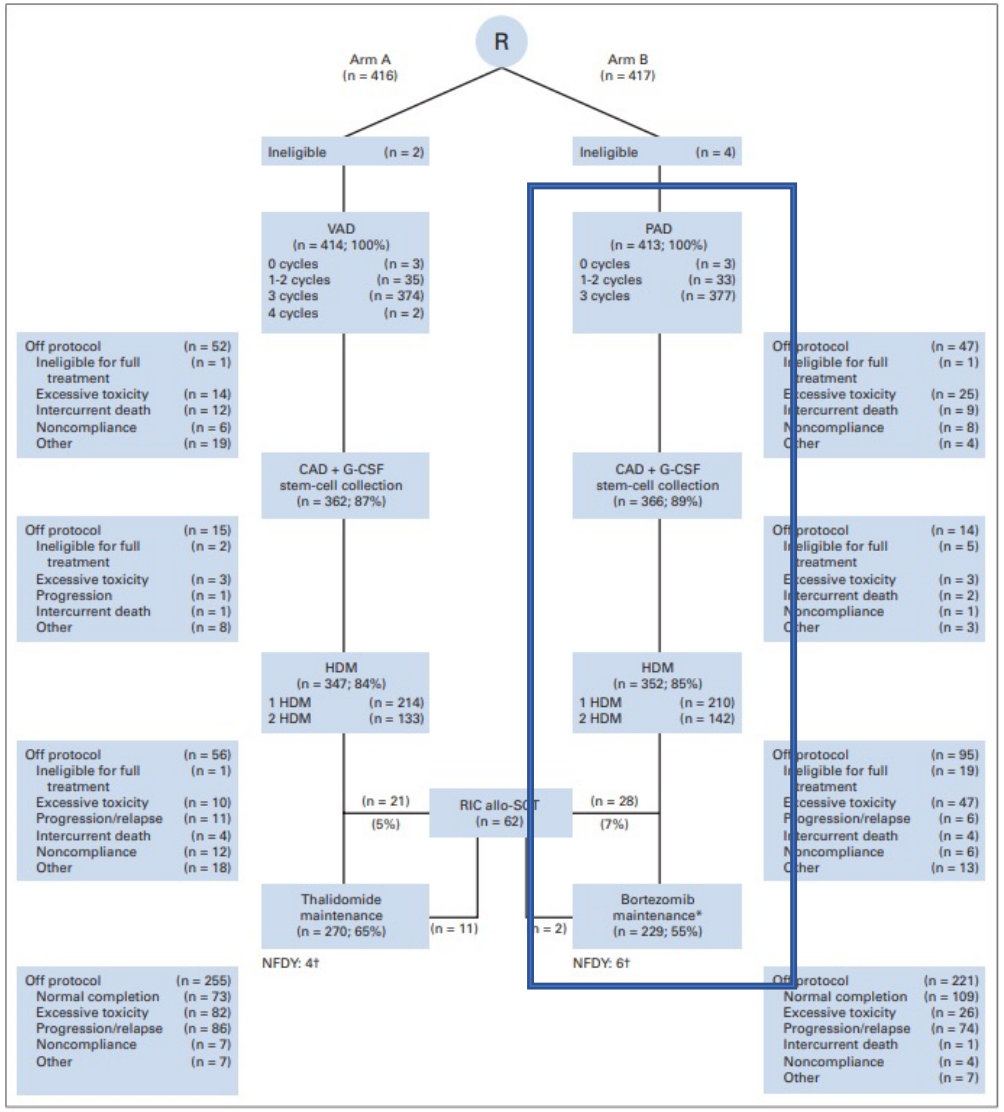
Continuous therapy - MAIA

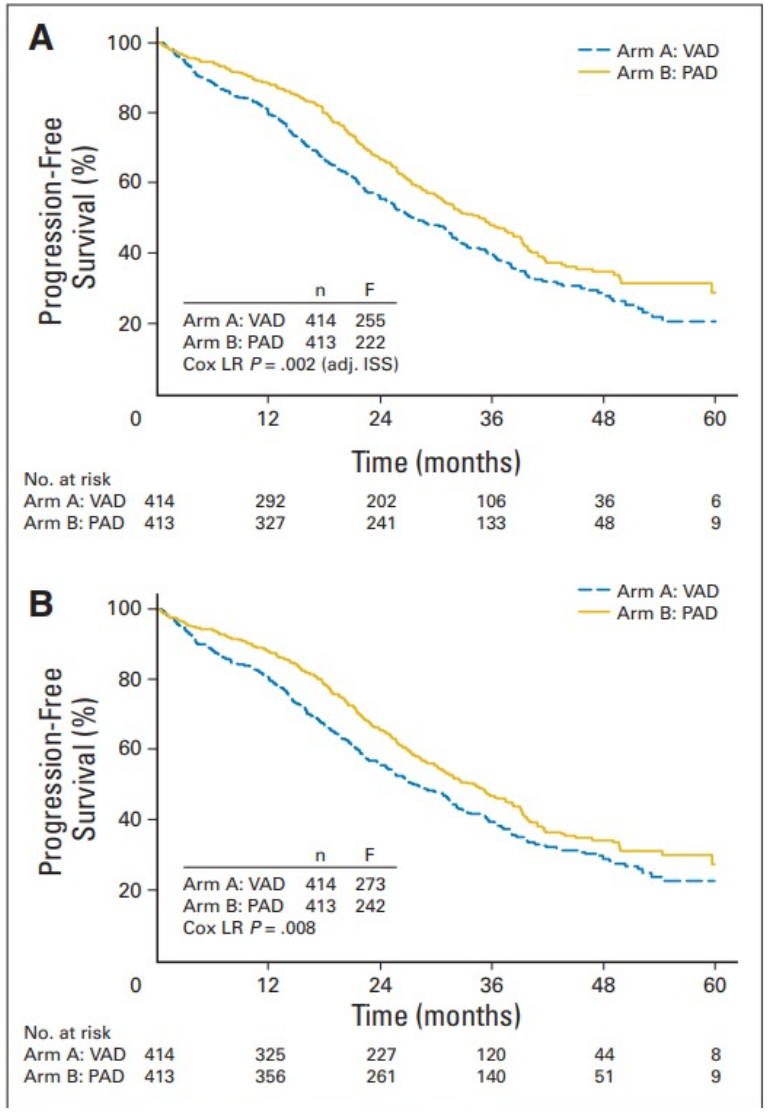




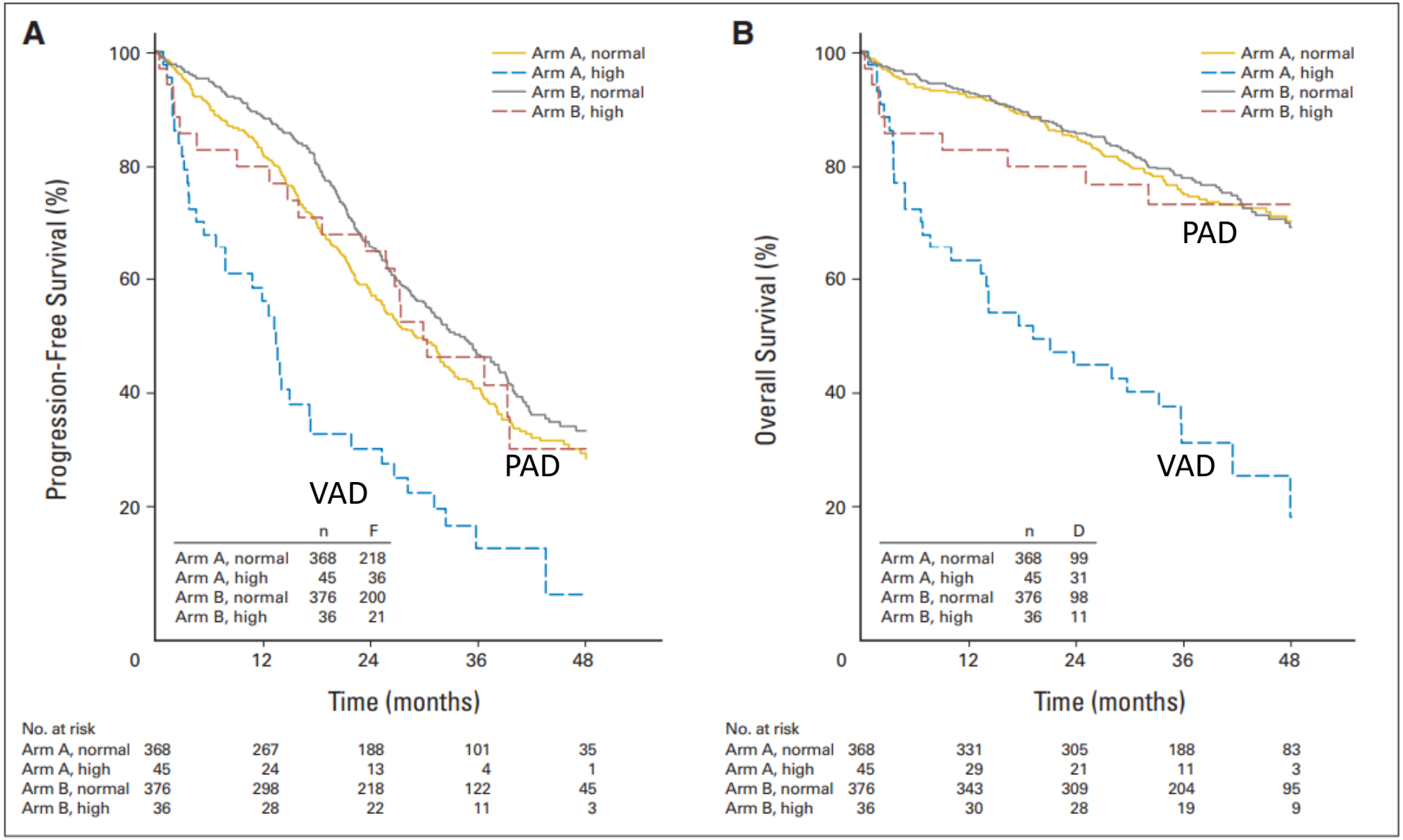
Kumar S, et al. Presented at ASH, Virtual, 5–8 December 2022. Abstract 4559

Bortezomib





Sonneveld P, Schmidt-Wolf IG, van der Holt B, El Jarari L, Bertsch U, Salwender H, et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/ GMMG-HD4 trial. J Clin Oncol. 2012 Aug 20;30(24):2946-55.



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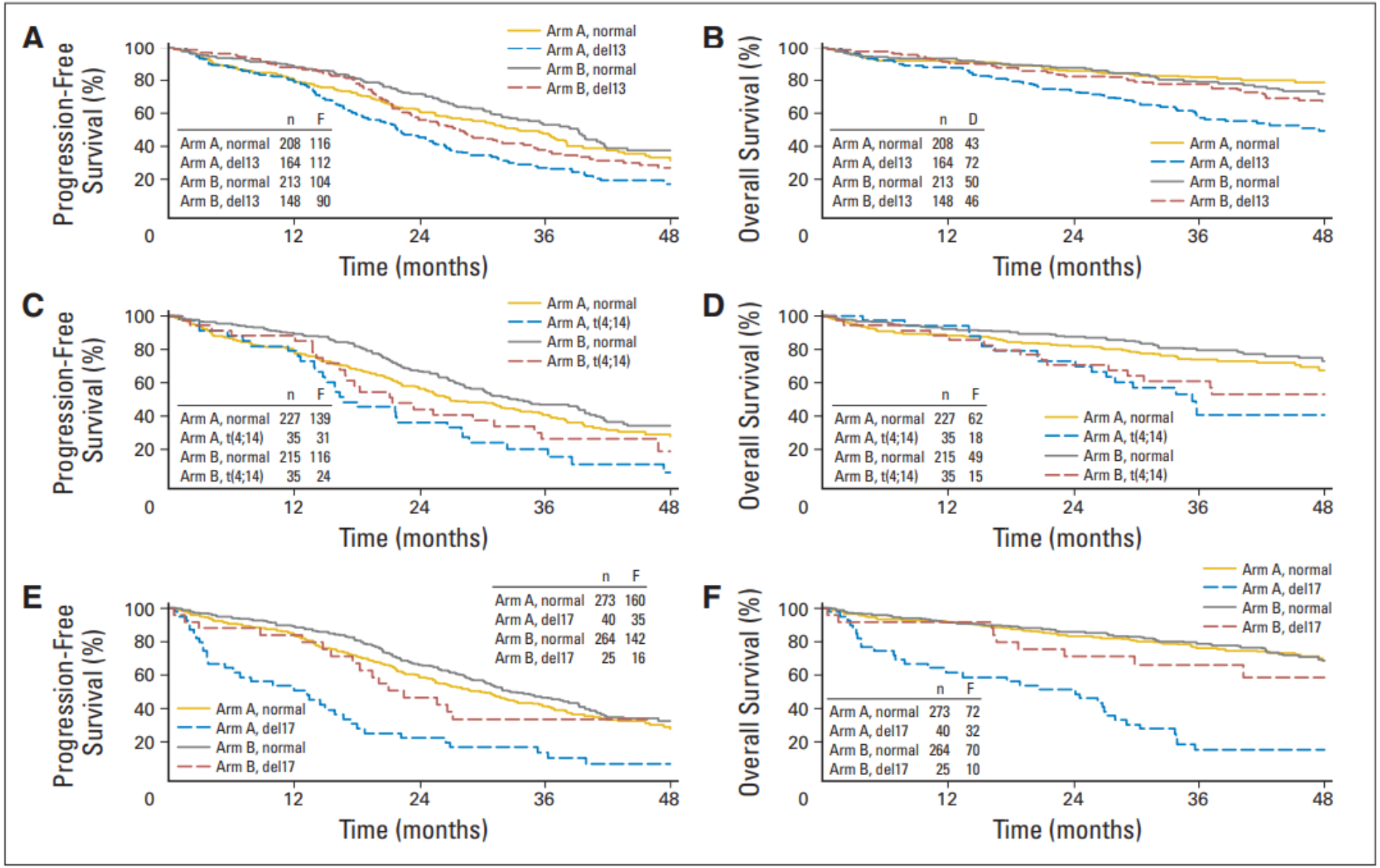

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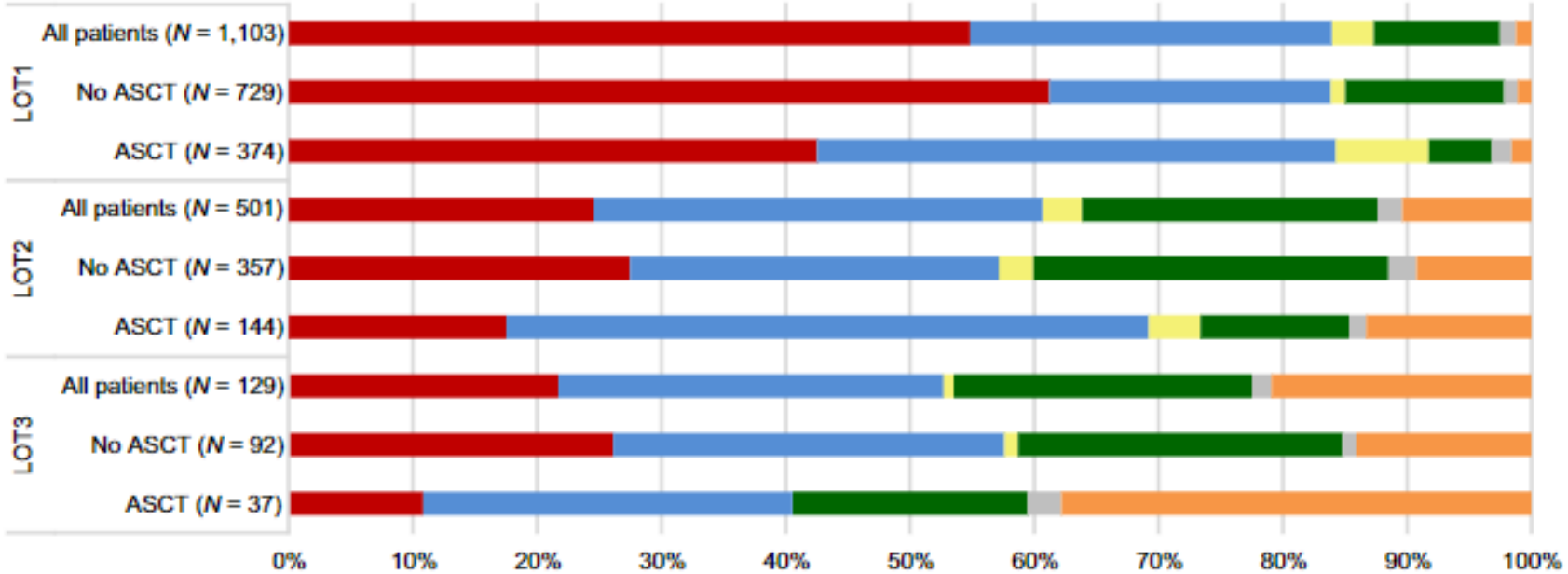
Latin America

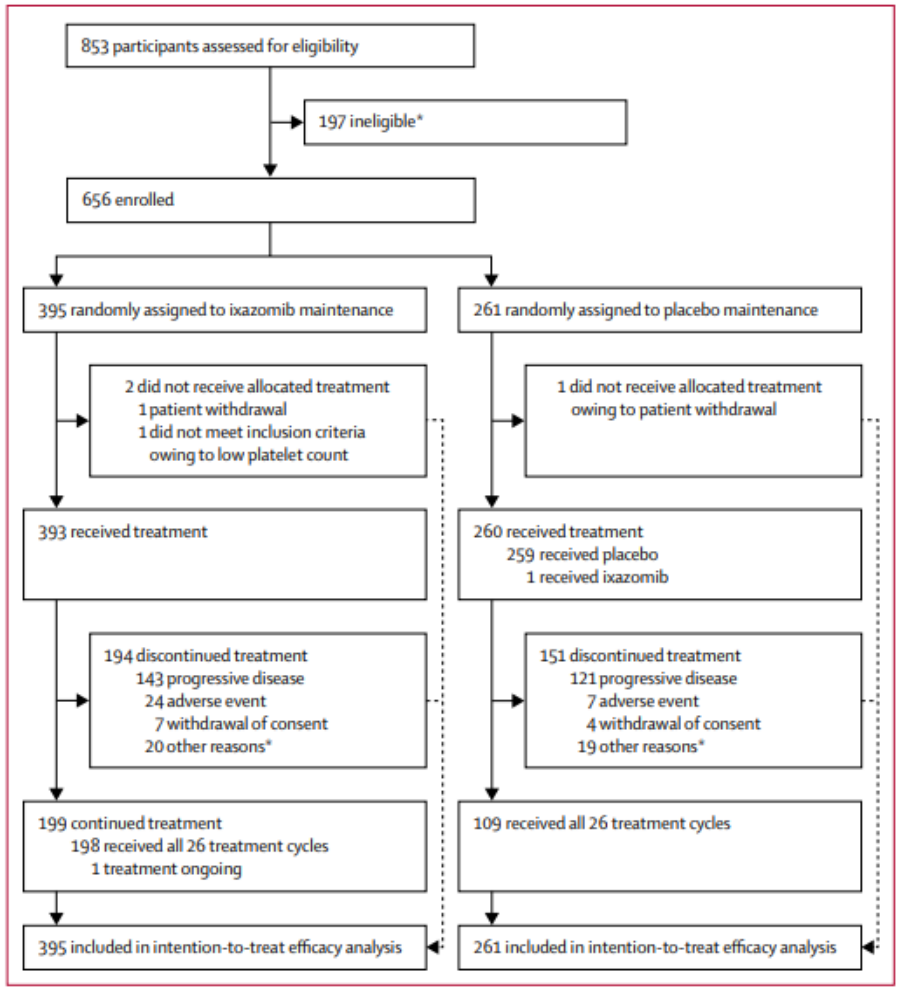


	LOT1			LOT2			LOT3		
	All patients (N=1,103)	No ASCT (N=729)	ASCT (N=374)	All patients (N=501)	No ASCT (N=357)	ASCT (N=144)	All patients (N=129)	No ASCT (N=92)	ASCT (N=37)
Thalidomide-based	54·9%	61·2%	42·5%	24·6%	27·5%	17·4%	21·7%	26·1%	10·8%
Bortezomib-based	29·1%	22·6%	41·7%	36·1%	29·7%	51·2%	31·0%	31·5%	29·7%
Bortezomib+thalidomide	3·4%	1·2%	7·5%	3·2%	2·8%	4·2%	0·8%	1·1%	0·0%
Chemotherapy	10·2%	12·8%	5·1%	23·8%	28·6%	11·8%	24·0%	26·1%	18·9%
Corticosteroids only	1·3%	1·1%	1·6%	2·0%	2·2%	1·4%	1·6%	1·1%	2·7%
Newer agents	1·3%	1·1%	1·6%	10·4%	9·2%	13·2%	20·9%	14·1%	37·8%

de Moraes Hungria VT, Martínez-Baños DM, Peñafiel CR, Miguel CE, Vela-Ojeda J, et al . Multiple myeloma treatment patterns and clinical outcomes in the Latin America Haemato-Oncology (HOLA) Observational Study, 2008-2016. Br J Haematol. 2020 Feb;188(3):383-393.

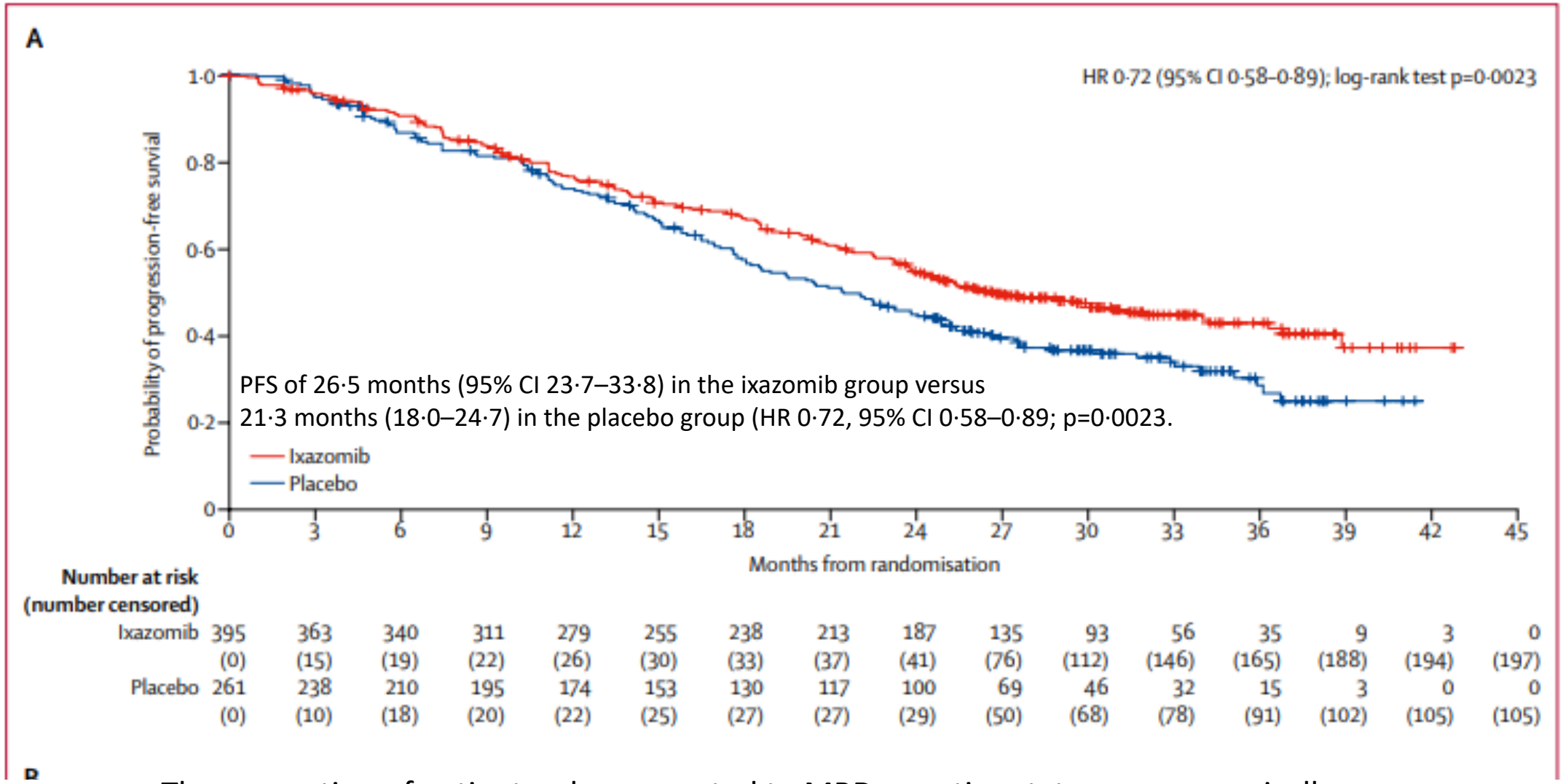
Ixazomib

Maintenance post ASCT Tourmaline MM3



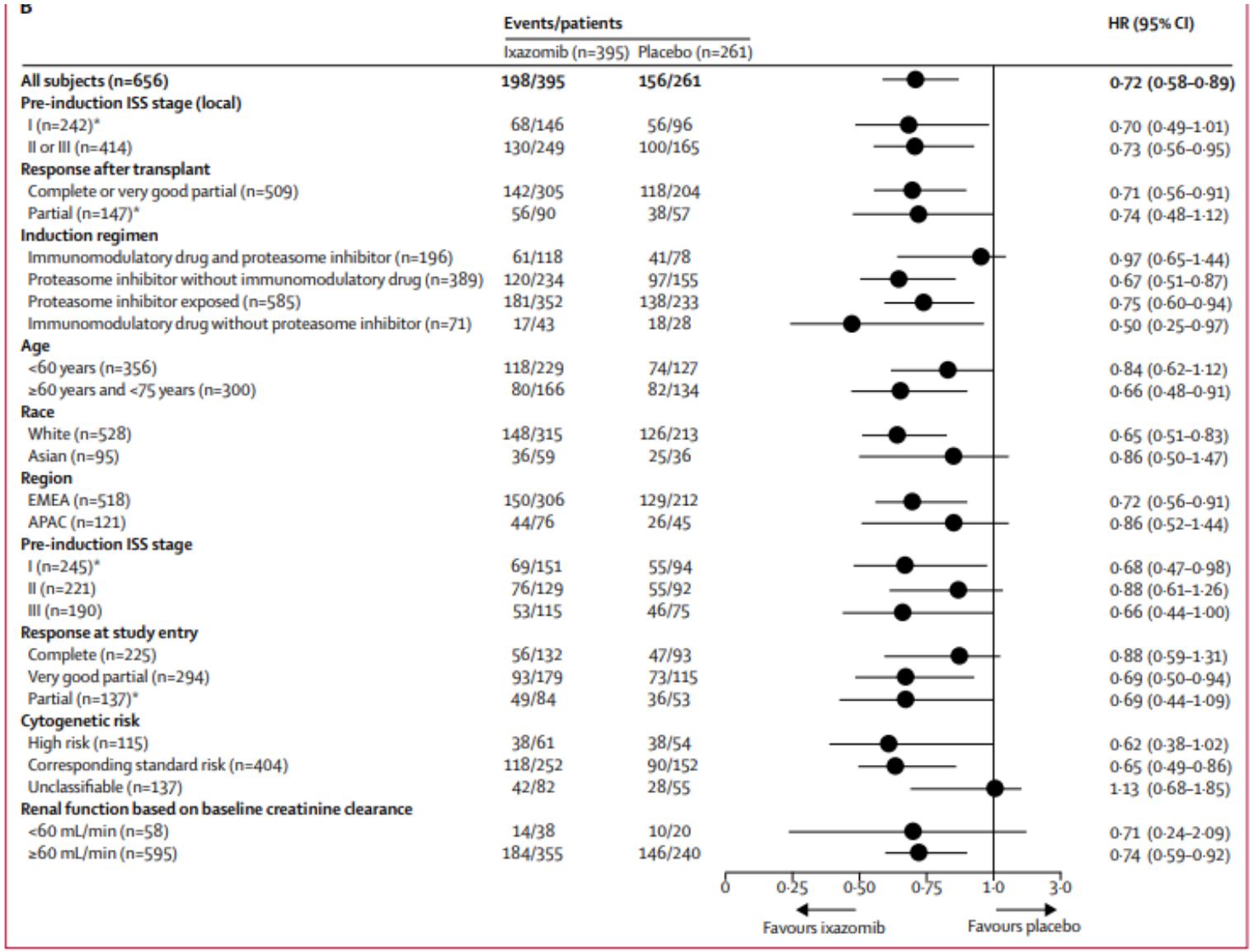
- Double - blind randomized trial
- 656 patients
- 30 countries in Europe, the Middle East, Africa, Asia, and North and South America
- PI and IMID induction
- Ixazomib fixed duration
- Patients must not have received post-ASCT consolidation therapy or a double (tandem) ASCT.

Dimopoulos MA, Gay F, Schjesvold F, Beksac M, Hajek R, Weisel KC, et al, Oral ixazomib maintenance following autologous stem cell transplantation (TOURMALINE-MM3): a double-blind, randomised, placebo-controlled phase 3 trial. Lancet. 2019 Jan 19;393(10168):253-264.



The proportion of patients who converted to MRD-negative status was numerically higher with ixazomib (12%) than placebo (7%)

Dimopoulos MA, Gay F, Schjesvold F, Beksac M, Hajek R, Weisel KC, et al, Oral ixazomib maintenance following autologous stem cell transplantation (TOURMALINE-MM3): a double-blind, randomised, placebo-controlled phase 3 trial. Lancet. 2019 Jan 19;393(10168):253-264.



Dimopoulos MA, Gay F, Schjesvold F, Beksac M, Hajek R, Weisel KC, et al, Oral ixazomib maintenance following autologous stem cell transplantation (TOURMALINE-MM3): a double-blind, randomised, placebo-controlled phase 3 trial. Lancet. 2019 Jan 19;393(10168):253-264.

	Ixazomib group (n=394)			Placebo group (n=259)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Common haematological adverse events of any cause						
Neutropenia*	36 (9%)	17 (4%)	3 (1%)	20 (8%)	9 (3%)	0
Thrombocytopenia*	53 (13%)	14 (4%)	5 (1%)	8 (3%)	0	2 (1%)
Anaemia	29 (7%)	4 (1%)	0	10 (4%)	2 (1%)	0
Common non-haematological adverse events of any cause						
Infections and infestations (MedDRA SOC)†	292 (74%)	55 (14%)	3 (1%)	166 (64%)	21 (8%)	0
Upper respiratory tract infection	101 (26%)	2 (1%)	0	54 (21%)	1 (<1%)	0
Viral upper respiratory tract infection	94 (24%)	0	0	69 (27%)	0	0
Pneumonia†	40 (10%)	23 (6%)	1 (<1%)	21 (8%)	11 (4%)	0
Gastrointestinal disorders (MedDRA SOC)	270 (69%)	25 (6%)	0	124 (48%)	3 (1%)	0
Nausea	154 (39%)	1 (<1%)	0	40 (15%)	0	0
Diarrhoea	137 (35%)	10 (3%)	0	61 (24%)	2 (1%)	0
Vomiting	106 (27%)	6 (2%)	0	28 (11%)	0	0
Rash*	120 (30%)	7 (2%)	0	57 (22%)	0	0
Cough	87 (22%)	0	0	55 (21%)	1 (<1%)	0
Arthralgia	86 (22%)	3 (1%)	0	30 (12%)	1 (<1%)	0
Pyrexia	84 (21%)	1 (<1%)	0	38 (15%)	0	0
Fatigue	79 (20%)	5 (1%)	0	43 (17%)	1 (<1%)	0
Back pain	77 (20%)	5 (1%)	0	49 (19%)	1 (<1%)	0
Peripheral neuropathy*	73 (19%)	1 (<1%)	0	39 (15%)	0	0
Headache	43 (11%)	0	0	23 (9%)	0	0
Influenza	42 (11%)	3 (1%)	0	30 (12%)	1 (<1%)	0
Other adverse events of clinical interest						
Acute renal failure	11 (3%)	1 (<1%)	0	8 (3%)	1 (<1%)	0
Cardiac arrhythmias	19 (5%)	7 (2%)	0	7 (3%)	2 (1%)	0
Liver impairment	24 (6%)	9 (2%)	0	11 (4%)	3 (1%)	1 (<1%)
Hypotension or orthostatic hypotension	4 (1%)	1 (<1%)	0	1 (<1%)	0	0
New primary malignant tumour‡	12 (3%)	..	..	8 (3%)	..	..

Dimopoulos MA, Gay F, Schjesvold F, Beksac M, Hajek R, Weisel KC, et al, Oral ixazomib maintenance following autologous stem cell transplantation (TOURMALINE-MM3): a double-blind, randomised, placebo-controlled phase 3 trial. Lancet. 2019 Jan 19;393(10168):253-264.

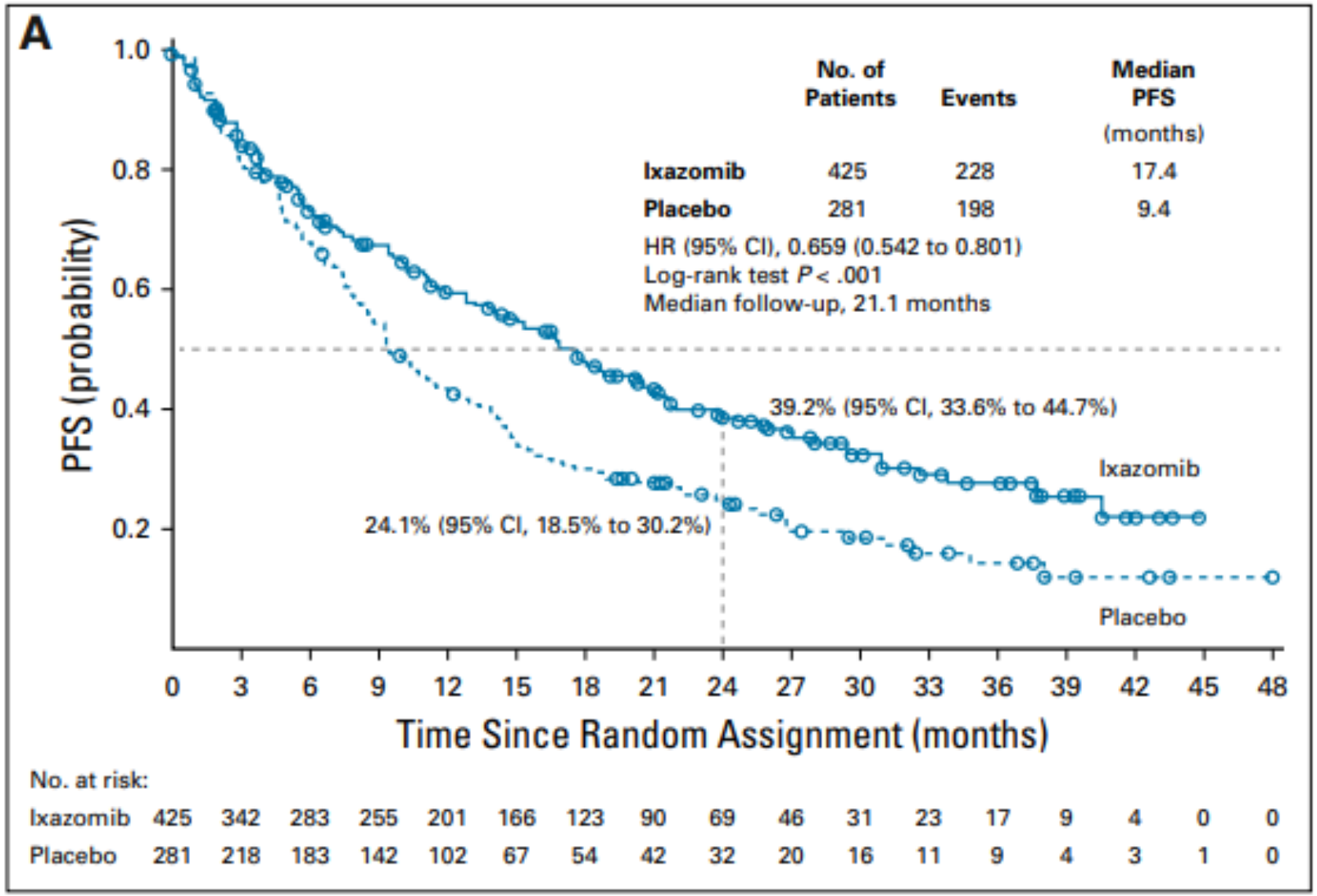
Continuous therapy Tourmaline MM4

TABLE 1. Baseline Characteristics of Patients in the Intention-to-Treat Population (continued)

Characteristic	Ixazomib (n = 425)	Placebo (n = 281)
Induction regimen containing[i]		
PI	351 (82.6)	230 (81.9)
Bortezomib	346 (81.4)	228 (81.1)
Immunomodulatory drug	137 (32.2)	94 (33.5)
Thalidomide	92 (21.6)	63 (22.4)
Lenalidomide	47 (11.1)	32 (11.4)
PI plus immunomodulatory drug	66 (15.5)	44 (15.7)
Common regimens (≥ 5% overall)		
VMP	117 (27.5)	88 (31.3)
VCd	112 (26.4)	75 (26.7)
VTd	27 (6.4)	14 (5.0)
Rd	20 (4.7)	16 (5.7)
CTd	21 (4.9)	14 (5.0)
Response at study entry[i]		
CR	96 (22.6)	62 (22.1)
VGPR	168 (39.5)	112 (39.9)
PR	161 (37.9)	107 (38.1)
Median time from start of induction to first maintenance dose (range), months	9.5 (5.6-15.0)	9.4 (6.3-14.8)

- Double - blind placebo-controlled
- 706 patients (3:2)
- 187 sites in 34 countries
- 3 mg or matching placebo on days 1, 8, and 15 of 28-day cycles increased to 4 mg after 5 cycles

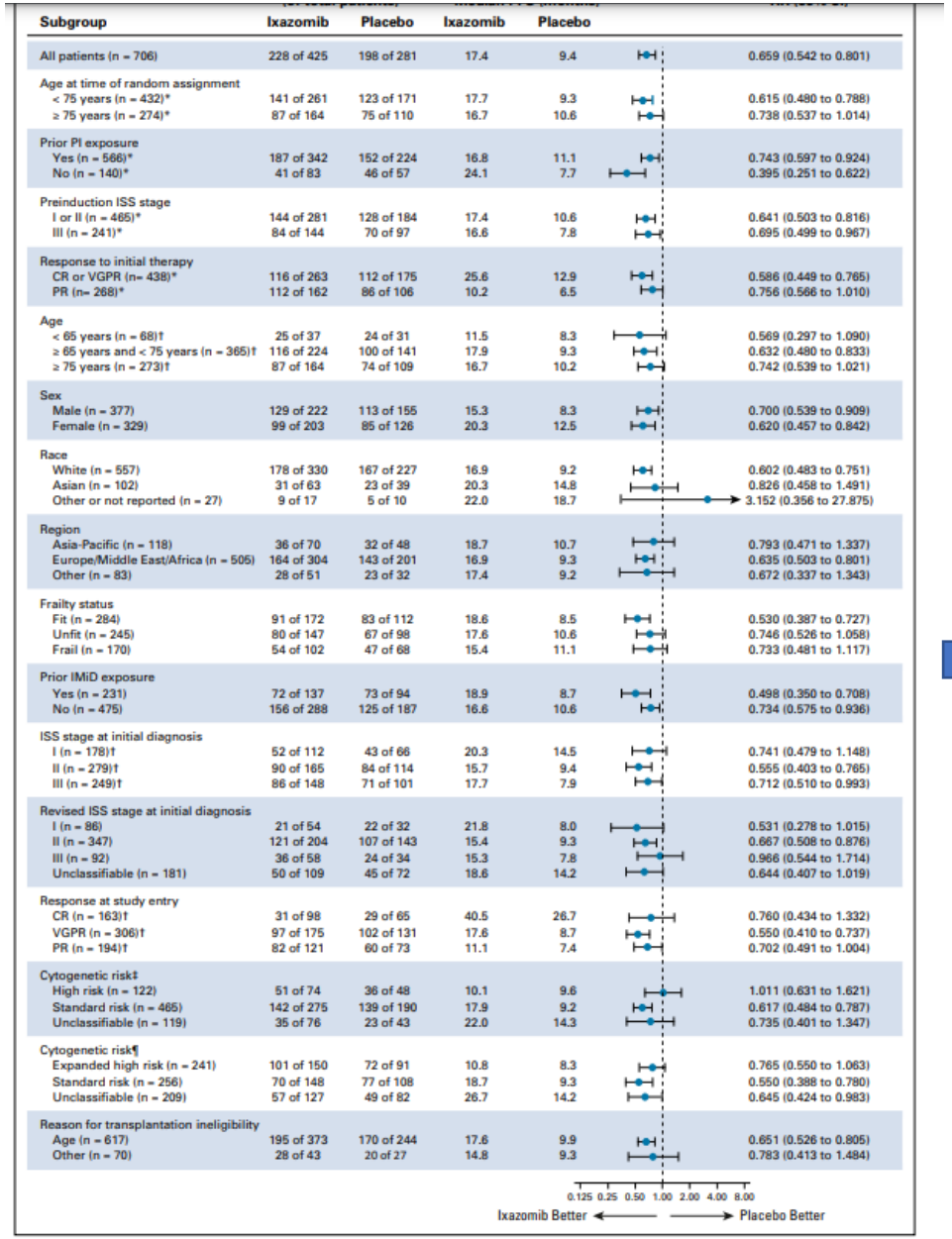
Dimopoulos MA, Špička I, Quach H, Oriol A, Hájek R, Garg M, et al; Ixazomib as Postinduction Maintenance for Patients With Newly Diagnosed Multiple Myeloma Not Undergoing Autologous Stem Cell Transplantation: The Phase III TOURMALINE-MM4 Trial. J Clin Oncol. 2020 Dec 1;38(34):4030-4041. PMC7768338.



PFS since randomization was 17.4 months (95% CI, 14.8 to 20.3 months) versus 9.4 months (95% CI, 8.5 to 11.5 months.

34.1% reduction in risk of progression.

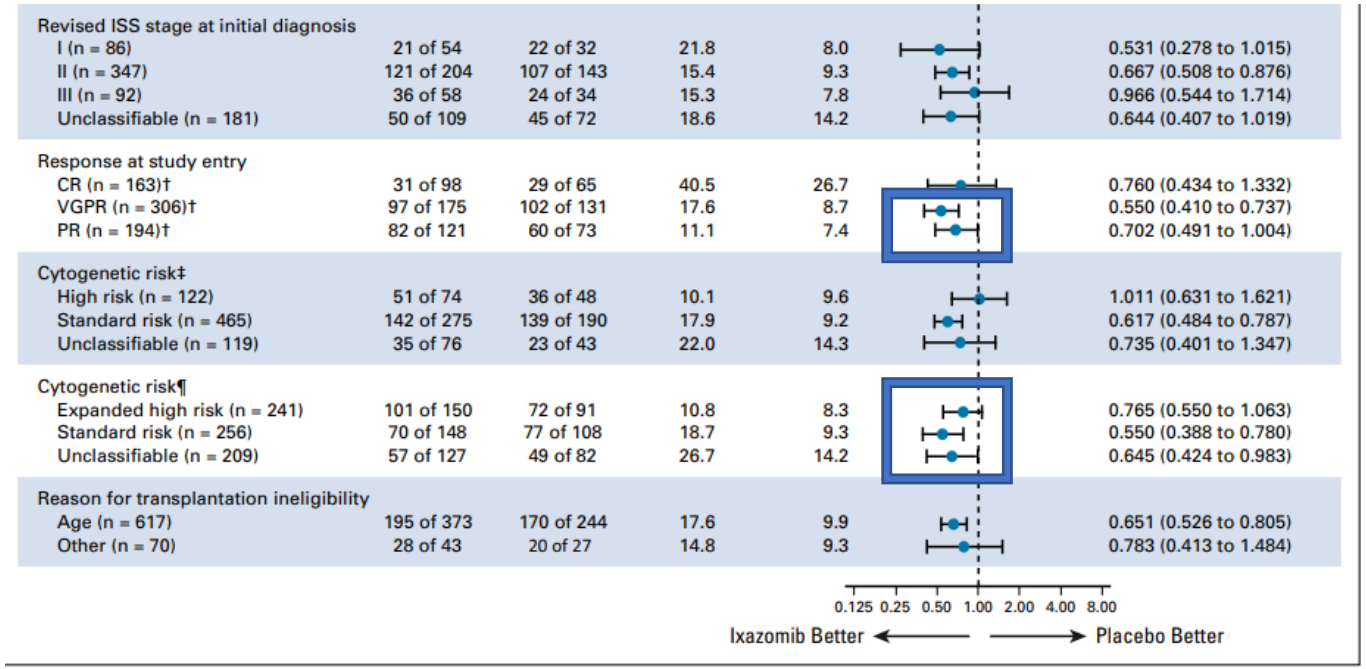
Dimopoulos MA, Špička I, Quach H, Oriol A, Hájek R, Garg M, et al; Ixazomib as Postinduction Maintenance for Patients With Newly Diagnosed Multiple Myeloma Not Undergoing Autologous Stem Cell Transplantation: The Phase III TOURMALINE-MM4 Trial. J Clin Oncol. 2020 Dec 1;38(34):4030-4041. PMC7768338.



Subgroup	Ixazomib	Placebo	Ixazomib	Placebo	
All patients (n = 706)	228 of 425	198 of 281	17.4	9.4	0.659 (0.542 to 0.801)
Age at time of random assignment					
< 75 years (n = 432)*	141 of 261	123 of 171	17.7	9.3	0.615 (0.480 to 0.788)
≥ 75 years (n = 274)*	87 of 164	75 of 110	16.7	10.6	0.738 (0.537 to 1.014)
Prior PI exposure					
Yes (n = 566)*	187 of 342	152 of 224	16.8	11.1	0.743 (0.597 to 0.924)
No (n = 140)*	41 of 83	46 of 57	24.1	7.7	0.395 (0.251 to 0.622)
Preinduction ISS stage					
I or II (n = 465)*	144 of 281	128 of 184	17.4	10.6	0.641 (0.503 to 0.816)
III (n = 241)*	84 of 144	70 of 97	16.6	7.8	0.695 (0.499 to 0.967)
Response to initial therapy					
CR or VGPR (n= 438)*	116 of 263	112 of 175	25.6	12.9	0.586 (0.449 to 0.765)
PR (n= 268)*	112 of 162	86 of 106	10.2	6.5	0.756 (0.566 to 1.010)
Age					
< 65 years (n = 68)†	25 of 37	24 of 31	11.5	8.3	0.569 (0.297 to 1.090)
≥ 65 years and < 75 years (n = 365)†	116 of 224	100 of 141	17.9	9.3	0.632 (0.480 to 0.833)
≥ 75 years (n = 273)†	87 of 164	74 of 109	16.7	10.2	0.742 (0.539 to 1.021)
Sex					
Male (n = 377)	129 of 222	113 of 155	15.3	8.3	0.700 (0.539 to 0.909)
Female (n = 329)	99 of 203	85 of 126	20.3	12.5	0.620 (0.457 to 0.842)
Race					
White (n = 557)	178 of 330	167 of 227	16.9	9.2	0.602 (0.483 to 0.751)
Asian (n = 102)	31 of 63	23 of 39	20.3	14.8	0.826 (0.458 to 1.491)
Other or not reported (n = 27)	9 of 17	5 of 10	22.0	18.7	3.152 (0.356 to 27.875)
Region					
Asia-Pacific (n = 118)	36 of 70	32 of 48	18.7	10.7	0.793 (0.471 to 1.337)
Europe/Middle East/Africa (n = 505)	164 of 304	143 of 201	16.9	9.3	0.635 (0.503 to 0.801)
Other (n = 83)	28 of 51	23 of 32	17.4	9.2	0.672 (0.337 to 1.343)
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)

0.125 0.25 0.50 1.00 2.00 4.00 8.00

Ixazomib Better ← → Placebo Better



Dimopoulos MA, Špička I, Quach H, Oriol A, Hájek R, Garg M, et al; Ixazomib as Postinduction Maintenance for Patients With Newly Diagnosed Multiple Myeloma Not Undergoing Autologous Stem Cell Transplantation: The Phase III TOURMALINE-MM4 Trial. J Clin Oncol. 2020 Dec 1;38(34):4030-4041. PMC7768338.

	Ixazomib Group (n = 426)			Placebo Group (n = 276)		
Adverse Event	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Common hematologic TEAEs of any cause						
Thrombocytopenia[a]	20 (4.7)	9 (2.1)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Neutropenia[a]	10 (2.3)	8 (1.9)	1 (0.2)	9 (3.3)	4 (1.4)	0 (0.0)
Common nonhematologic TEAEs of any cause						
GI disorders (MedDRA SOC)	222 (52.1)	22 (5.2)	0 (0.0)	93 (33.7)	7 (2.5)	0 (0.0)
Nausea	114 (26.8)	2 (0.5)	0 (0.0)	22 (8.0)	0 (0.0)	0 (0.0)
Vomiting	103 (24.2)	7 (1.6)	0 (0.0)	12 (4.3)	2 (0.7)	0 (0.0)
Diarrhea	99 (23.2)	8 (1.9)	0 (0.0)	34 (12.3)	2 (0.7)	0 (0.0)
Infections and infestations (MedDRA SOC)[b]	206 (48.4)	28 (6.6)	0 (0.0)	104 (37.7)	12 (4.3)	0 (0.0)
Upper respiratory tract infection	67 (15.7)	2 (0.5)	0 (0.0)	30 (10.9)	1 (0.4)	0 (0.0)
Rash[a]	109 (25.6)	12 (2.8)	0 (0.0)	29 (10.5)	0 (0.0)	0 (0.0)
Peripheral neuropathy[a]	83 (19.5)	7 (1.6)	0 (0.0)	30 (10.9)	0 (0.0)	0 (0.0)
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)
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)	—	

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Monoclonal antibodies - Daratumumab

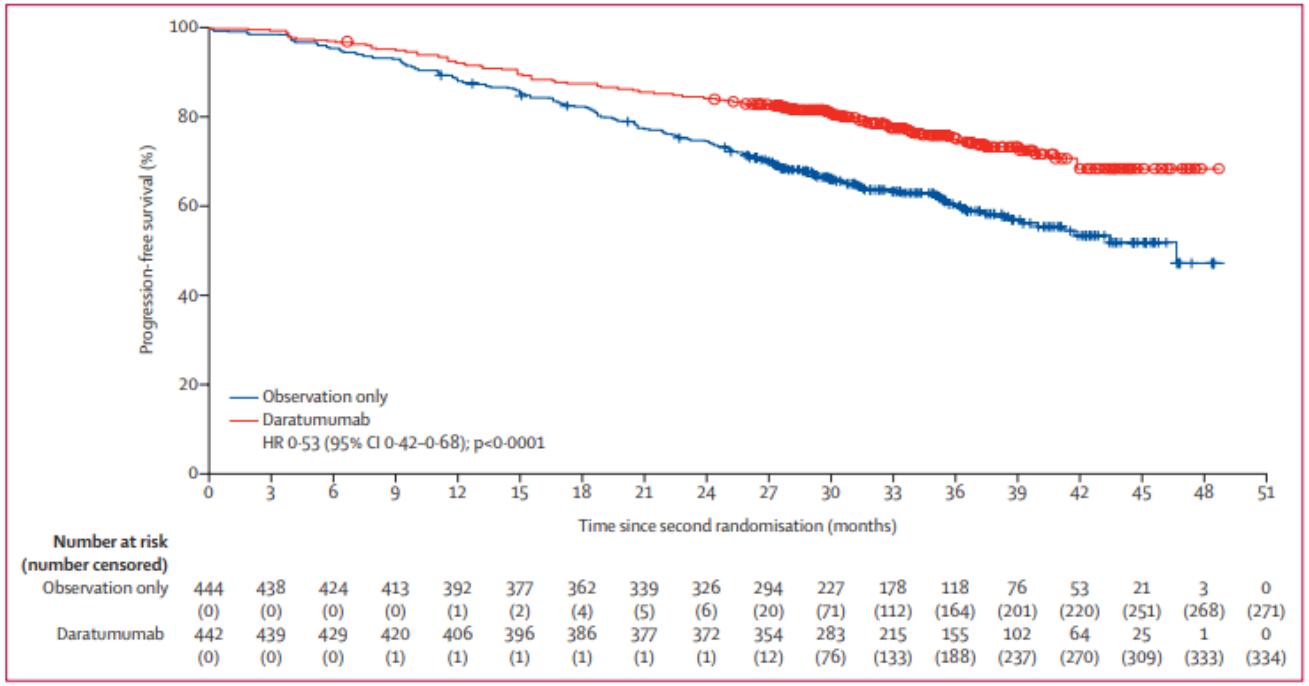
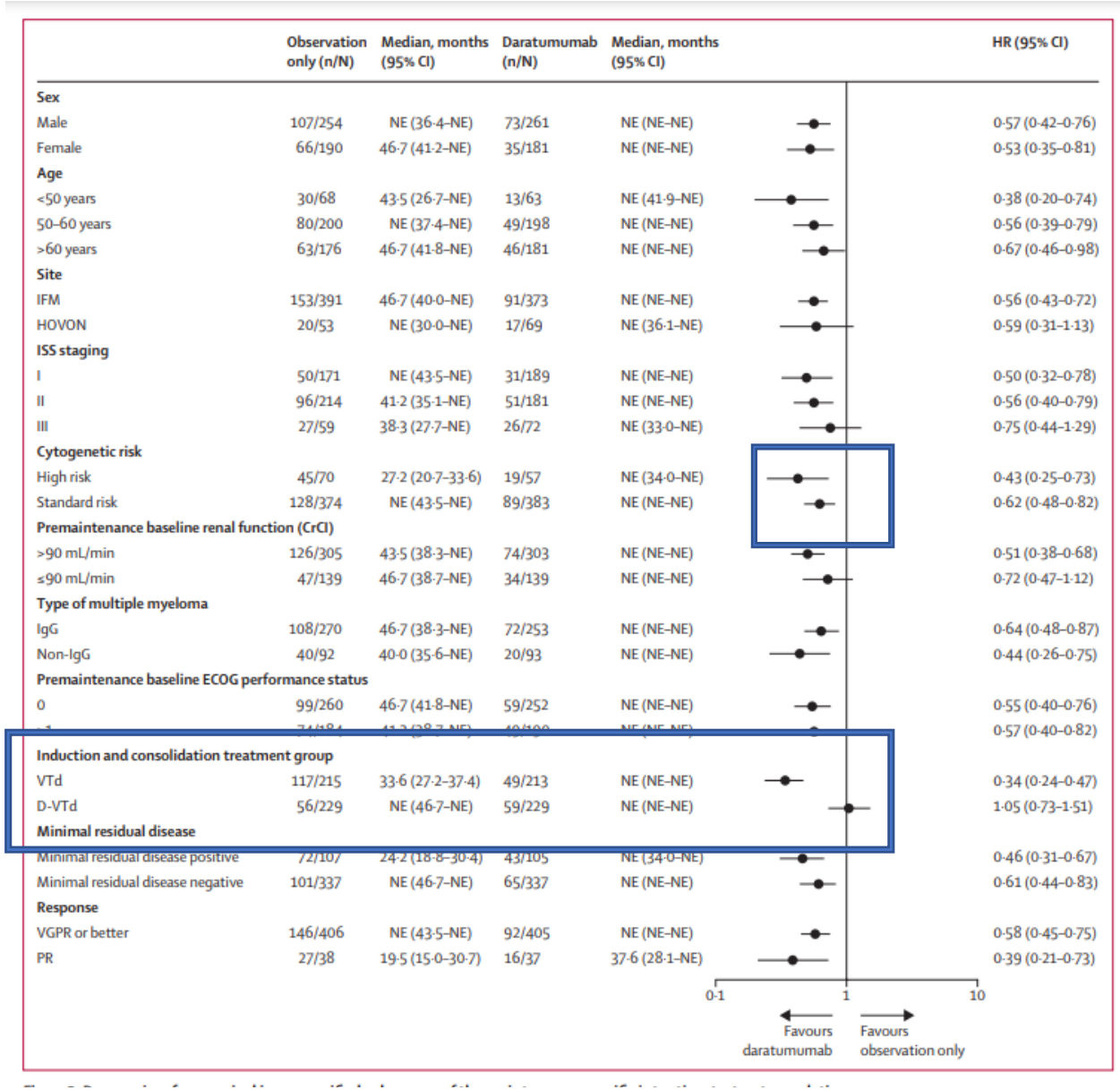


Figure 2: **Kaplan-Meier estimates of progression-free survival in patients in the maintenance-specific intention-to-treat population**
HR=hazard ratio.

- Phase III trial CASSIOPEIA
- 11 academic and community practice centers in Europe
- Patients who achieved partial response (PR) or better were randomised 1:1 to DARA 16 mg/kg IV every 8 weeks or OBS for up to 2 years.
- Interaction with Daratumumab used at induction

Moreau P, Hulin C, Perrot A, Arnulf B, Belhadj K, Benboubker L, et al. 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. Lancet Oncol. 2021 Oct;22(10):1378-1390.



	Observation only (n/N)	Median, months (95% CI)	Daratumumab (n/N)	Median, months (95% CI)	HR (95% CI)
Sex					
Male	107/254	NE (36·4–NE)	73/261	NE (NE–NE)	0·57 (0·42–0·76)
Female	66/190	46·7 (41·2–NE)	35/181	NE (NE–NE)	0·53 (0·35–0·81)
Age					
<50 years	30/68	43·5 (26·7–NE)	13/63	NE (41·9–NE)	0·38 (0·20–0·74)
50–60 years	80/200	NE (37·4–NE)	49/198	NE (NE–NE)	0·56 (0·39–0·79)
>60 years	63/176	46·7 (41·8–NE)	46/181	NE (NE–NE)	0·67 (0·46–0·98)
Site					
IFM	153/391	46·7 (40·0–NE)	91/373	NE (NE–NE)	0·56 (0·43–0·72)
HOVON	20/53	NE (30·0–NE)	17/69	NE (36·1–NE)	0·59 (0·31–1·13)
ISS staging					
I	50/171	NE (43·5–NE)	31/189	NE (NE–NE)	0·50 (0·32–0·78)
II	96/214	41·2 (35·1–NE)	51/181	NE (NE–NE)	0·56 (0·40–0·79)
III	27/59	38·3 (27·7–NE)	26/72	NE (33·0–NE)	0·75 (0·44–1·29)
Cytogenetic risk					
High risk	45/70	27·2 (20·7–33·6)	19/57	NE (34·0–NE)	0·43 (0·25–0·73)
Standard risk	128/374	NE (43·5–NE)	89/383	NE (NE–NE)	0·62 (0·48–0·82)
Premaintenance baseline renal function (CrCl)					
>90 mL/min	126/305	43·5 (38·3–NE)	74/303	NE (NE–NE)	0·51 (0·38–0·68)
≤90 mL/min	47/139	46·7 (38·7–NE)	34/139	NE (NE–NE)	0·72 (0·47–1·12)
Type of multiple myeloma					
IgG	108/270	46·7 (38·3–NE)	72/253	NE (NE–NE)	0·64 (0·48–0·87)
Non-IgG	40/92	40·0 (35·6–NE)	20/93	NE (NE–NE)	0·44 (0·26–0·75)
Premaintenance baseline ECOG performance status					
0	99/260	46·7 (41·8–NE)	59/252	NE (NE–NE)	0·55 (0·40–0·76)
					0·57 (0·40–0·82)
Induction and consolidation treatment group					
VTd	117/215	33·6 (27·2–37·4)	49/213	NE (NE–NE)	0·34 (0·24–0·47)
D-VTd	56/229	NE (46·7–NE)	59/229	NE (NE–NE)	1·05 (0·73–1·51)
Minimal residual disease					
Minimal residual disease positive	72/107	24·2 (18·8–30·4)	43/105	NE (34·0–NE)	0·46 (0·31–0·67)
Minimal residual disease negative	101/337	NE (46·7–NE)	65/337	NE (NE–NE)	0·61 (0·44–0·83)
Response					
VGPR or better	146/406	NE (43·5–NE)	92/405	NE (NE–NE)	0·58 (0·45–0·75)
PR	27/38	19·5 (15·0–30·7)	16/37	37·6 (28·1–NE)	0·39 (0·21–0·73)

Moreau P, Hulin C, Perrot A, Arnulf B, Belhadj K, Benboubker L, et al. 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. Lancet Oncol. 2021 Oct;22(10):1378-1390.

	Daratumumab (n=440)				Observation only (n=444)			
	Grade 1/2	Grade 3	Grade 4	Grade 5	Grade 1/2	Grade 3	Grade 4	Grade 5
Infections and infestations								
Bronchitis	166 (38%)	2 (<1%)	1 (<1%)	0	130 (29%)	4 (1%)	0	0
Nasopharyngitis	76 (17%)	0	0	0	49 (11%)	0	0	0
Upper respiratory tract infection	64 (15%)	0	0	0	35 (8%)	1 (<1%)	0	0
Herpes zoster	30 (7%)	1 (<1%)	0	0	63 (14%)	2 (<1%)	0	0
Pneumonia	18 (4%)	10 (2%)	1 (<1%)	0	13 (3%)	6 (1%)	0	0
Blood and lymphatic system disorders								
Lymphopenia	15 (3%)	14 (3%)	2 (<1%)	0	9 (2%)	3 (1%)	5 (1%)	0
Neutropenia	3 (1%)	9 (2%)	0	0	0	10 (2%)	0	0
Gastrointestinal disorders								
Diarrhoea	56 (13%)	1 (<1%)	0	0	25 (6%)	1 (<1%)	0	0
General disorders and administration site conditions								
Asthenia	60 (14%)	0	0	0	51 (11%)	2 (<1%)	0	0
Influenza-like illness	54 (12%)	0	0	0	49 (11%)	0	0	0
Immune system disorders								
Hypogammaglobulinaemia	53 (12%)	3 (1%)	0	0	13 (3%)	3 (1%)	0	0
Musculoskeletal and connective tissue disorders								
Arthralgia	50 (11%)	1 (<1%)	0	0	50 (11%)	2 (<1%)	0	0
Back pain	45 (10%)	2 (<1%)	0	0	59 (13%)	2 (<1%)	0	0
Nervous system disorders								
Peripheral sensory neuropathy	65 (15%)	4 (1%)	0	0	46 (10%)	5 (1%)	0	0
Respiratory, thoracic, and mediastinal disorders								
Cough	78 (18%)	1 (<1%)	0	0	40 (9%)	0	0	0
Vascular disorders								
Hypertension	15 (3%)	13 (3%)	0	0	10 (2%)	7 (2%)	0	0

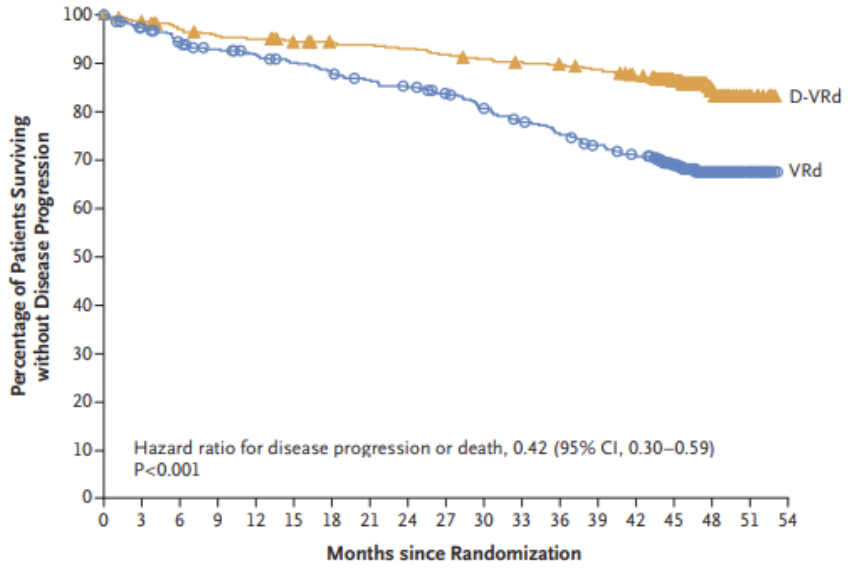
Data are n (%). Adverse events of grade 1 or 2 that were reported in at least 10% of patients in either treatment group and grade 3–5 adverse events that were reported in at least 2% of patients in either treatment group are listed.

Table 2: **Most common adverse events during treatment or observation in the maintenance-specific safety population**

Moreau P, Hulin C, Perrot A, Arnulf B, Belhadj K, Benboubker L, et al. 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. Lancet Oncol. 2021 Oct;22(10):1378-1390.

PERSEUS

A Kaplan–Meier Estimates



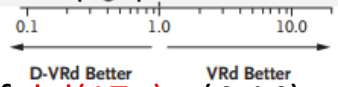
No. at Risk

D-VRd	355	345	335	329	327	322	318	316	313	309	305	302	299	295	286	226	90	11	0
VRd	354	335	321	311	304	297	291	283	278	270	258	247	238	228	219	175	67	13	0

HR for disease progression or death, 0.42; 95% confidence interval, 0.30 to 0.59; P<0.001); the P value crossed the prespecified stopping boundary (P=0.0126)

B Subgroup Analyses

Subgroup	Disease Progression or Death		Median Progression-free Survival		Hazard Ratio for Disease Progression or Death (95% CI)
	D-VRd	VRd	D-VRd	VRd	
	no. of events/total no. of patients		*mo*		
Sex					
Male	36/211	61/205	NE	NE	0.51 (0.34–0.77)
Female	14/144	42/149	NE	NE	0.29 (0.16–0.53)
Age					
<65 yr	30/261	84/267	NE	NE	0.30 (0.20–0.46)
≥65 yr	20/94	19/87	NE	NE	0.97 (0.52–1.81)
Race					
White	47/330	95/323	NE	NE	0.42 (0.30–0.60)
Other	3/25	8/31	NE	NE	0.40 (0.11–1.50)
ISS disease stage					
I	18/186	35/178	NE	NE	0.46 (0.26–0.81)
II	19/114	43/125	NE	NE	0.37 (0.22–0.64)
III	13/55	25/50	NE	41.9	0.42 (0.22–0.83)
Type of multiple myeloma					
IgG	28/204	58/185	NE	NE	0.36 (0.23–0.57)
Non-IgG	13/78	31/96	NE	NE	0.46 (0.24–0.88)
Cytogenetic risk					
Standard	25/264	62/266	NE	NE	0.35 (0.22–0.56)
High	24/76	38/78	NE	44.1	0.59 (0.36–0.99)
Indeterminate	1/15	3/10	NE	NE	0.16 (0.02–1.56)
ECOG performance-status score					
0	28/221	60/230	NE	NE	0.42 (0.27–0.66)
≥1	22/134	43/124	NE	NE	0.41 (0.25–0.69)

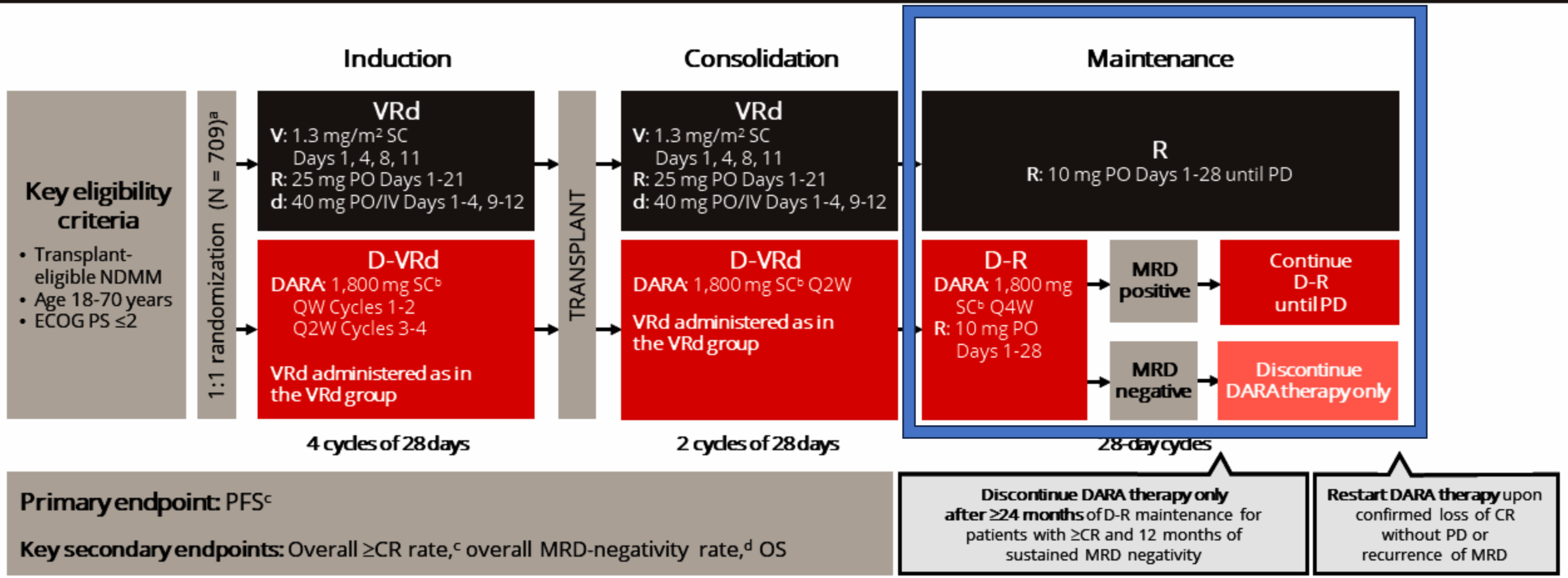


MRD status‡			
MRD-negative status — no. (%)			
10^{-5} sensitivity threshold	267 (75.2)	168 (47.5)	<0.001
10^{-6} sensitivity threshold	231 (65.1)	114 (32.2)	—
Sustained MRD-negative status, assessed at 10^{-5} sensitivity threshold, for ≥12 mo — no. (%)	230 (64.8)	105 (29.7)	—

high risk was defined as the presence of del(17p), t(4;14), or t(14;16).

Sonneveld P, Dimopoulos MA, Boccadoro M, Quach H, Ho PJ, Beksac M, Daratumumab, Bortezomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2024 Jan 25;390(4):301-313.

PERSEUS: Study Design



Primary endpoint: PFS[c]

Key secondary endpoints: Overall ≥CR rate,[c] overall MRD-negativity rate,[d] OS

Discontinue DARA therapy only after ≥24 months of D-R maintenance for patients with ≥CR and 12 months of sustained MRD negativity

Restart DARA therapy upon confirmed loss of CR without PD or recurrence of MRD

ECOG PS, Eastern Cooperative Oncology Group performance status; V, bortezomib; SC, subcutaneous; PO, oral; d, dexamethasone; IV, intravenous; QW, weekly; Q2W, every 2 weeks; PD, progressive disease; Q4W, every 4 weeks; MRD, minimal residual disease; OS, overall survival; ISS, International Staging System; rHuPH20, recombinant human hyaluronidase PH20; IMWG, International Myeloma Working Group; VGPR, very good partial response. [a]Stratified by ISS stage and cytogenetic risk. [b]DARA 1,800 mg co-formulated with rHuPH20 (2,000 U/mL; ENHANZE® drug delivery technology, Halozyme, Inc., San Diego, CA, USA). [c]Response and disease progression were assessed using a computerized algorithm based on IMWG response criteria. [d]MRD was assessed using the clonoSEQ assay (v.2.0; Adaptive Biotechnologies, Seattle, WA, USA) in patients with ≥VGPR post-consolidation and at the time of suspected ≥CR. Overall, the MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity (10^{-5} threshold) and ≥CR at any time.

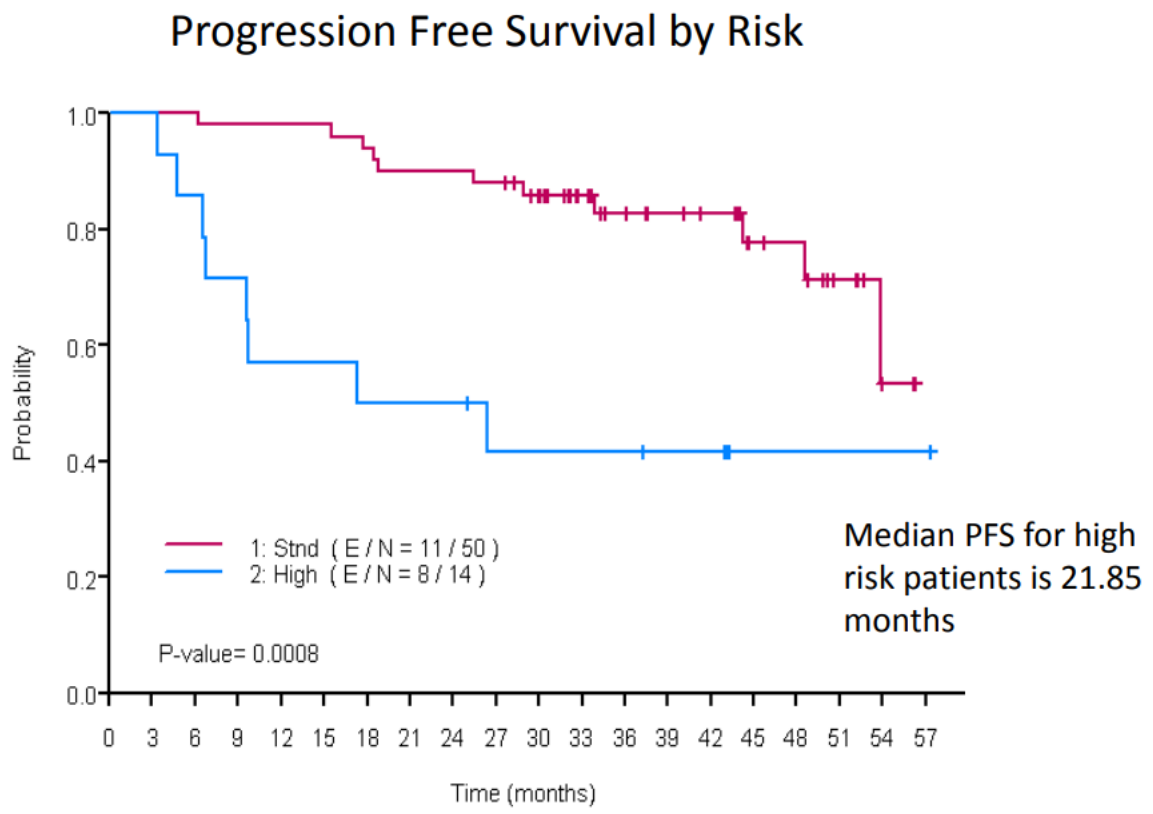
Presented by P Sonneveld at the 65th American Society of Hematology (ASH) Annual Meeting; December 9-12, 2023; San Diego, CA, USA

Combinations

- The downsides of combination therapy include the potential for increased burden to the patients, in terms of toxicities, time away from work/family, and finances.

- Lenalidomide plus Bortezomib
- Lenalidomide plus Carfilzomib FORTE
- Lenalidomide plus Daratumumab
- Lenalidomide plus elotuzumab
- Lenalidomide plus Ixazomib

Lenalidomide plus Ixazomib in HRD



8/16 pts with PD had high risk disease

- Lenalidomide plus Ixazomib: With a median follow-up of 37.8 months, the median PFS was not yet reached and the estimated 2-year PFS was 81%
- The incidence of peripheral neuropathy was limited to grade 1/2 and 6 grade 3 events
- Hematological adverse events were manageable with dose reductions

Patel, K.K.; Shah, J.J.; Feng, L.; Lee, H.C.; Manasanch, E.E.; Thomas, S.K.; Weber, D.M.; Munoz, S.C.; Morphey, A.; Bashir, Q.; et al. Update on a Phase II Study of Ixazomib with Lenalidomide As Maintenance Therapy Following Autologous Stem Cell Transplant in Patients with Multiple Myeloma. Blood 2017, 130, 437

Future directions

- MRD Directed therapy
  - MIDAS
  - RADAR
  - DRAMMATIC
  - MASTER
  - REMNANT
  - PREDATOR
- BiTES in MT and CT
- Maintenance after CAR T cell therapy

Take-home massages

- Maintenance therapy and continuous therapy are the SOC
- MT and CT should fulfill some requirements regarding the efficacy, safety, tolerability, quality of life.
- Oral treatments are preferable.
- Lenalidomide is so far the SOC in several countries either in MT and CT
- From the group of PIs, Ixazomib offers an excellent profile for MT or CT in patients with a contraindication to lenalidomide or in combination therapy.
- Combination therapy is an attractive option for patients specially for high-risk patients although the evidence is somehow limited

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