

Up-Front Management of Newly Diagnosed Multiple Myeloma



Research To Practice®

AN INTEGRATED APPROACH TO ONCOLOGY EDUCATION

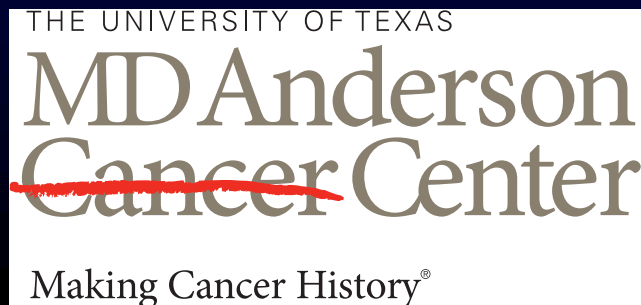
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Transplant Eligible Patients

PRIMARY THERAPY FOR TRANSPLANT CANDIDATES ^{a-d}
Preferred Regimens • Bortezomib/lenalidomide/dexamethasone (category 1) • Bortezomib/cyclophosphamide/dexamethasone^g
Other Recommended Regimens • Carfilzomib/lenalidomide/dexamethasone • Daratumumab^f/lenalidomide/bortezomib/dexamethasone • Ixazomib/lenalidomide/dexamethasone (category 2B)
Useful In Certain Circumstances • Bortezomib/doxorubicin/dexamethasone • Carfilzomib/cyclophosphamide/dexamethasone^g • Ixazomib/cyclophosphamide/dexamethasone^g • Bortezomib/thalidomide/dexamethasone (category 1) • Cyclophosphamide/lenalidomide/dexamethasone • Daratumumab^f/cyclophosphamide/bortezomib/dexamethasone • Daratumumab^f/bortezomib/thalidomide/dexamethasone • Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide/bortezomib^h (VTD-PACE)



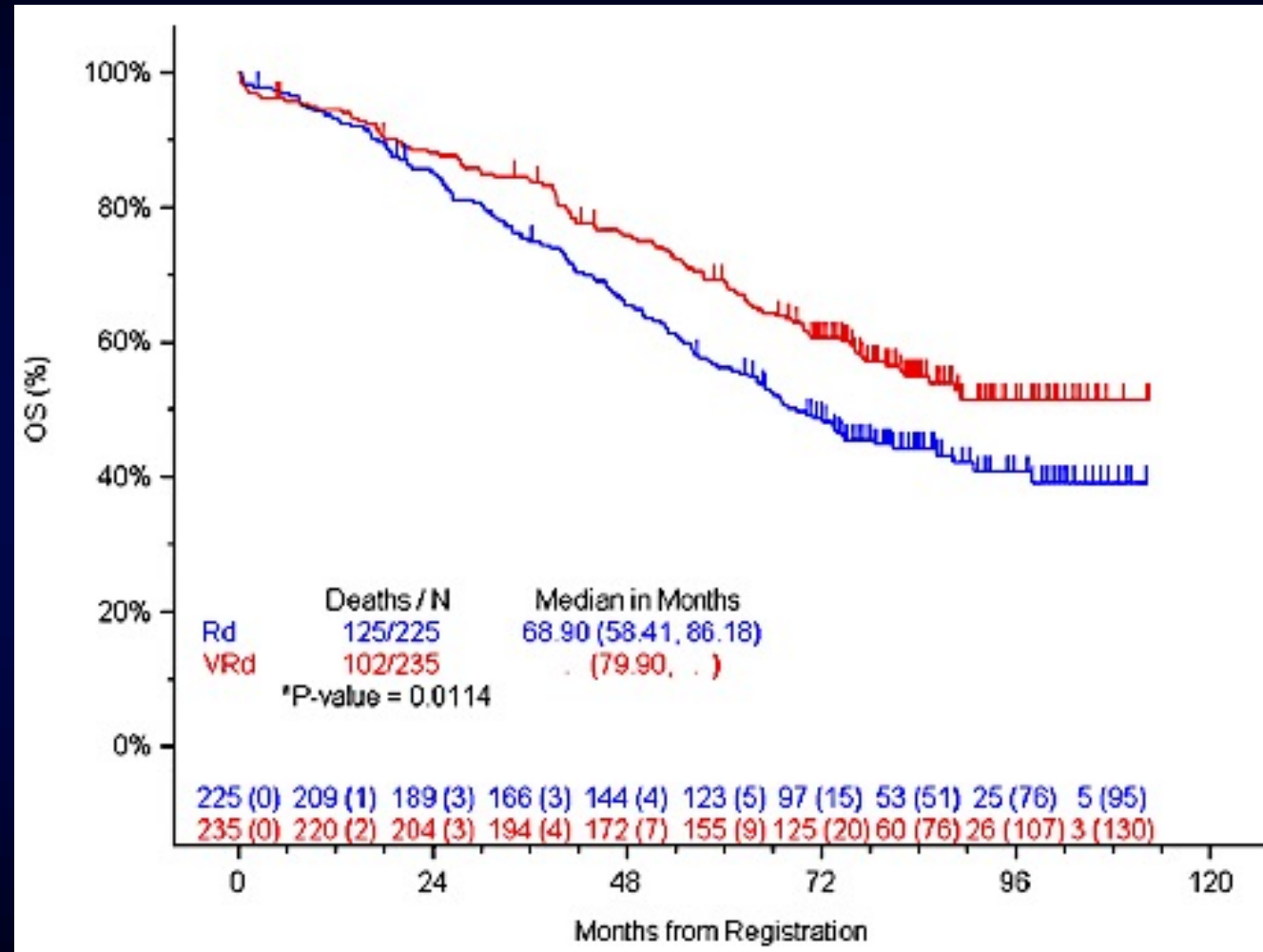
VRd: Updated SWOG-S0777 Data

	VRd ^a (n = 215)	Rd ^a (n = 207)
Complete response (CR)	24.2% (52)	12.1% (25)
Very good partial response (VGPR)	50.7% (109)	41.1% (85)
VGPR or better	74.9% (161)	53.2% (110)
Partial response (PR)	15.3% (33)	25.6% (53)
Overall response rate (ORR)	90.2% (194)	78.8% (163)
Stable disease (SD)	7.0% (15)	16.4% (34)
PD or Death	2.8% (6)	4.8% (10)

- Confirmed best responses



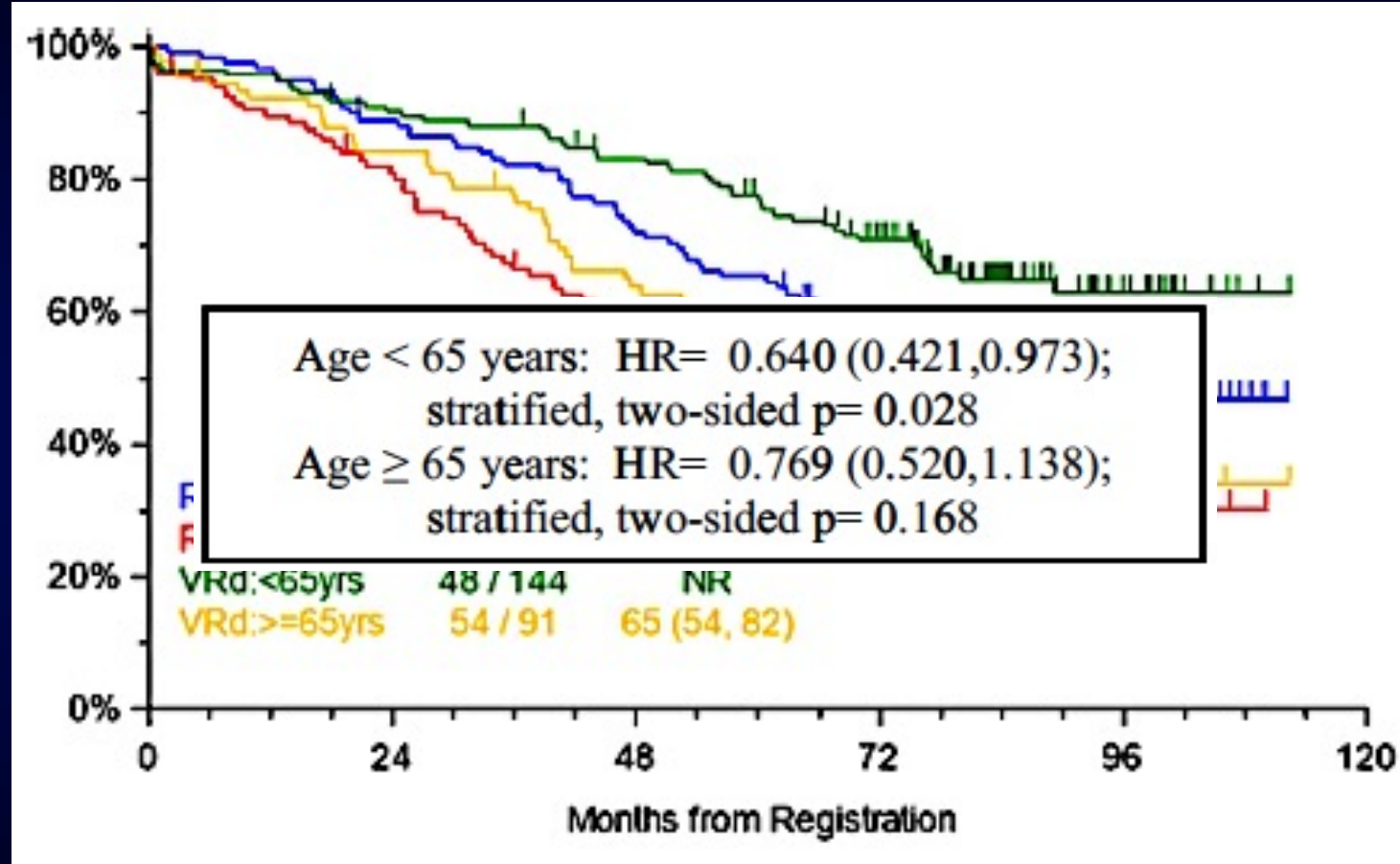
SWOG-S0777: PFS & OS Data



Durie, BGM et al. Blood Cancer J. 10: 53. doi: 10.1038/s41408-020-0311-8.

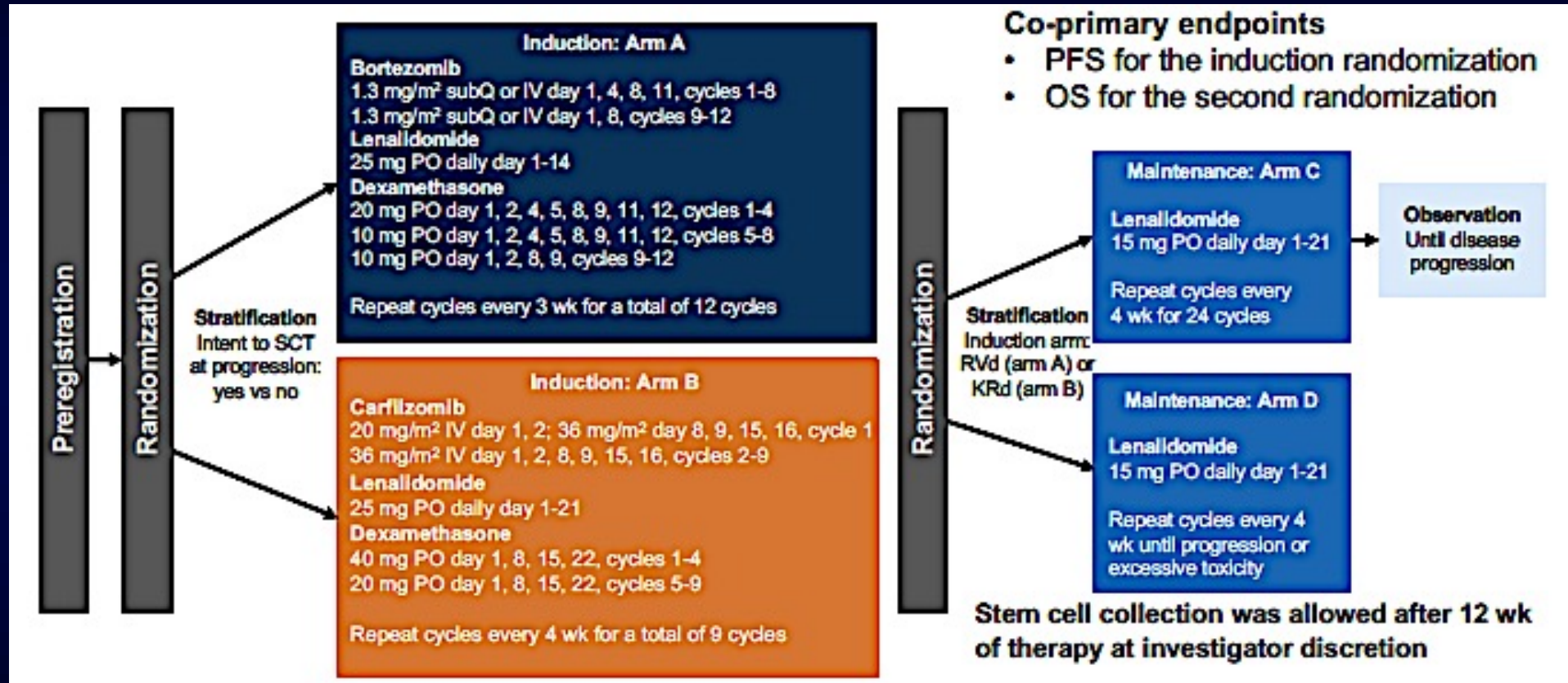


SWOG-S0777: Other Notable Findings





ENDURANCE Trial: VRd or KRd?





ENDURANCE: Response Data

	Bortezomib, lenalidomide, and dexamethasone group (n=527)	Carfilzomib, lenalidomide, and dexamethasone group (n=526)	p value
Stringent complete response	21 (4%)	31 (6%)	--
Complete response	57 (11%)	65 (12%)	--
Very good partial response	263 (50%)	292 (56%)	--
Partial response	103 (20%)	68 (13%)	--
Stable disease	40 (8%)	34 (6%)	--
Progressive disease	1 (<1%)	0 (0%)	--
Unevaluable disease or insufficient data	42 (8%)	36 (7%)	--
Negative for minimal residual disease	38 (7%; 5-10)	54 (10%; 8-13)	0.079
Complete response or better	78 (15%; 12-18)	96 (18%; 15-22)	0.13
Very good partial response or better	341 (65%; 61-69)	388 (74%; 70-77)	0.0015
Partial response or better	444 (84%; 81-87)	456 (87%; 84-90)	0.26

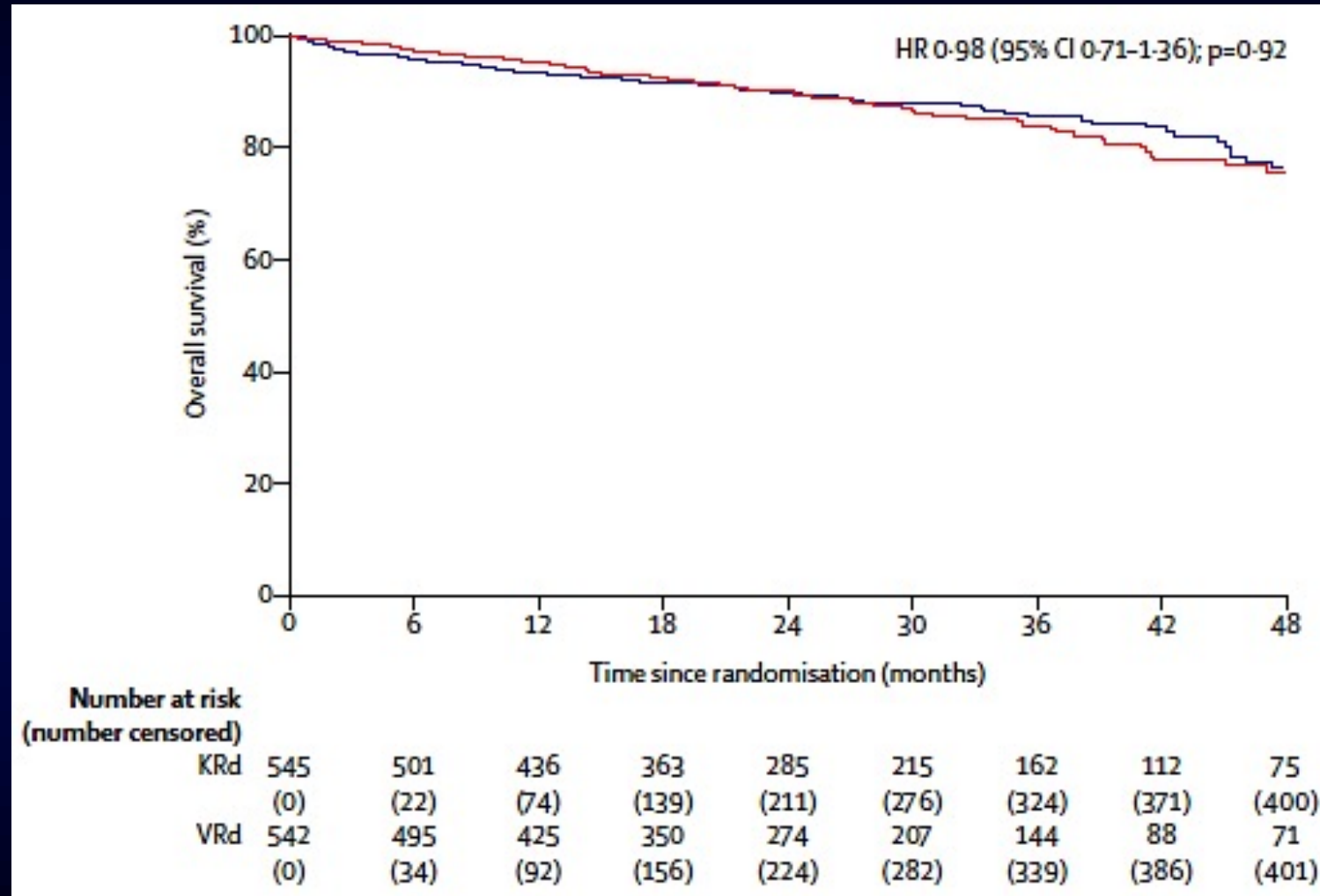
Data are n (%), or n (%; 95% CI). We calculated p values using the χ^2 test.

Kumar, S et al. Lancet Oncol. 21: 1317, 2020.



ENDURANCE: PFS & OS Data

KRd —————
VRd —————



Kumar, S et al. Lancet Oncol. 21: 1317, 2020.



ENDURANCE: Subgroups

	VRd group (events, n/ patients, N)	KRd group (events, n/ patients, N)	Hazard ratio (95% CI)
Age, years			
<70	101/375	98/368	0.93 (0.71-1.23)
≥70	40/167	59/177	1.29 (0.86-1.94)
Cytogenetics			
Normal	69/326	97/331	1.35 (0.99-1.84)
Abnormal	50/128	43/127	0.75 (0.50-1.15)
t(4;14) status			
Absent	91/379	112/391	1.07 (0.81-1.42)
Present	14/44	14/36	1.16 (0.54-2.47)
t(11;14) status			
Absent	76/336	100/347	1.14 (0.85-1.54)
Present	29/87	26/80	0.84 (0.49-1.43)
Creatinine concentration, mg/dL			
<2	132/506	151/520	1.04 (0.82-1.31)
≥2	6/25	9/36	0.75 (0.23-2.42)

Kumar, S et al. Lancet Oncol. 21: 1317, 2020.



ENDURANCE: Adverse Events

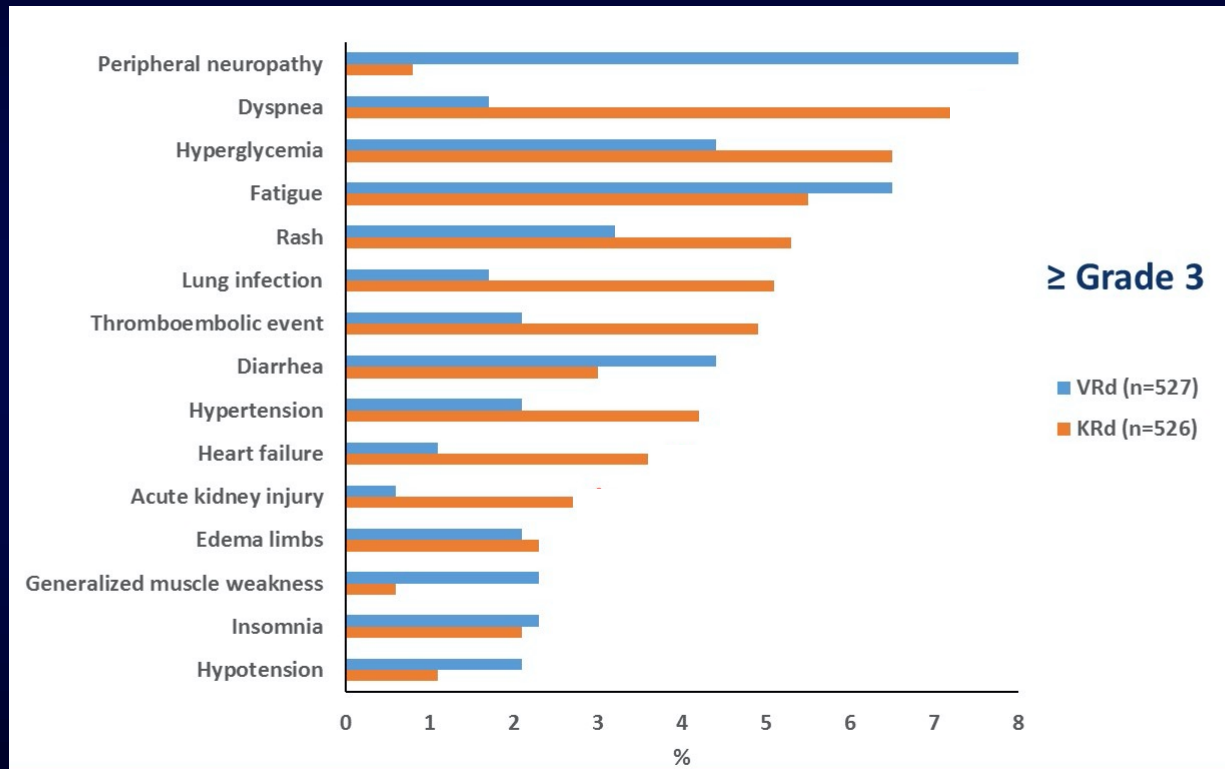
Treatment-Related AE, %	VRd (n = 527)	KRd (n = 526)	P Value
Grade 3-5	59.4	65.6	.038
Grade 4-5	11.6	13.3	.394
Grade 3	47.8	52.3	--
Grade 4	11.4	12.0	--
Grade 5	0.2	1.3	--

Treatment-Related Nonhematologic AE, %	VRd (n = 527)	KRd (n = 526)	P Value
Grade 3-5	41.4	48.3	.024
Grade 4-5	4.0	8.2	.004
Grade 3	37.4	40.1	--
Grade 4	3.8	6.8	--
Grade 5	0.2	1.3	--



ENDURANCE: Specific AEs of Interest

Nonhematologic Treatment-Related AEs $\geq 2\%$

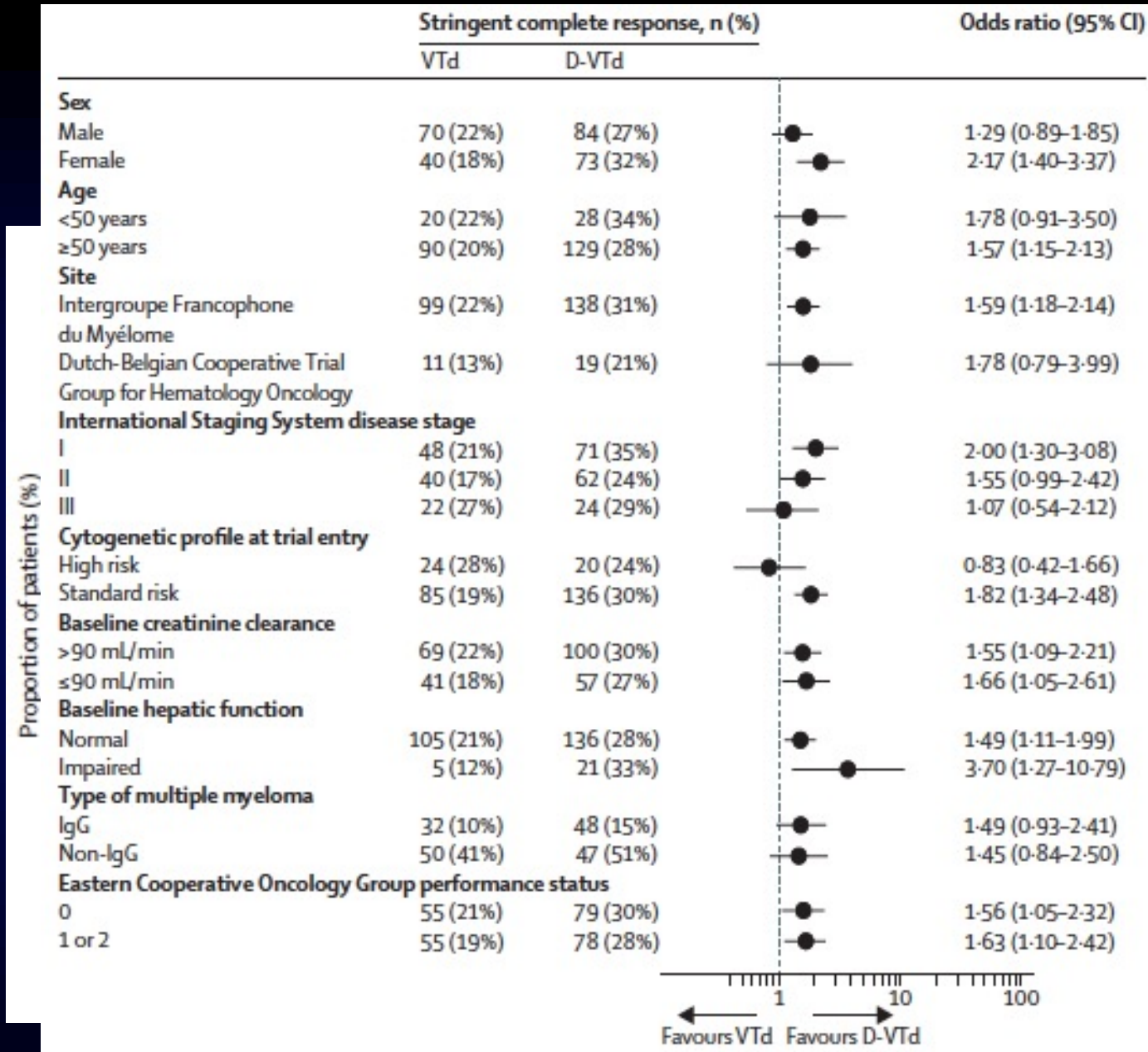


Treatment-Related AE of Interest, %	VRd (n = 527)	KRd (n = 526)	P Value
Cardiac, pulmonary, and renal			
▪ Total	4.8	16.1	< .001
▪ Grade 3	4.6	12.6	
▪ Grade 4	0	2.5	
▪ Grade 5	0.2	1	
Peripheral neuropathy			
▪ Total	53.4	24.4	< .001
▪ Grade 1/2*	45.4	23.6	
▪ Grade 3	8	0.8	

*Not required reporting.

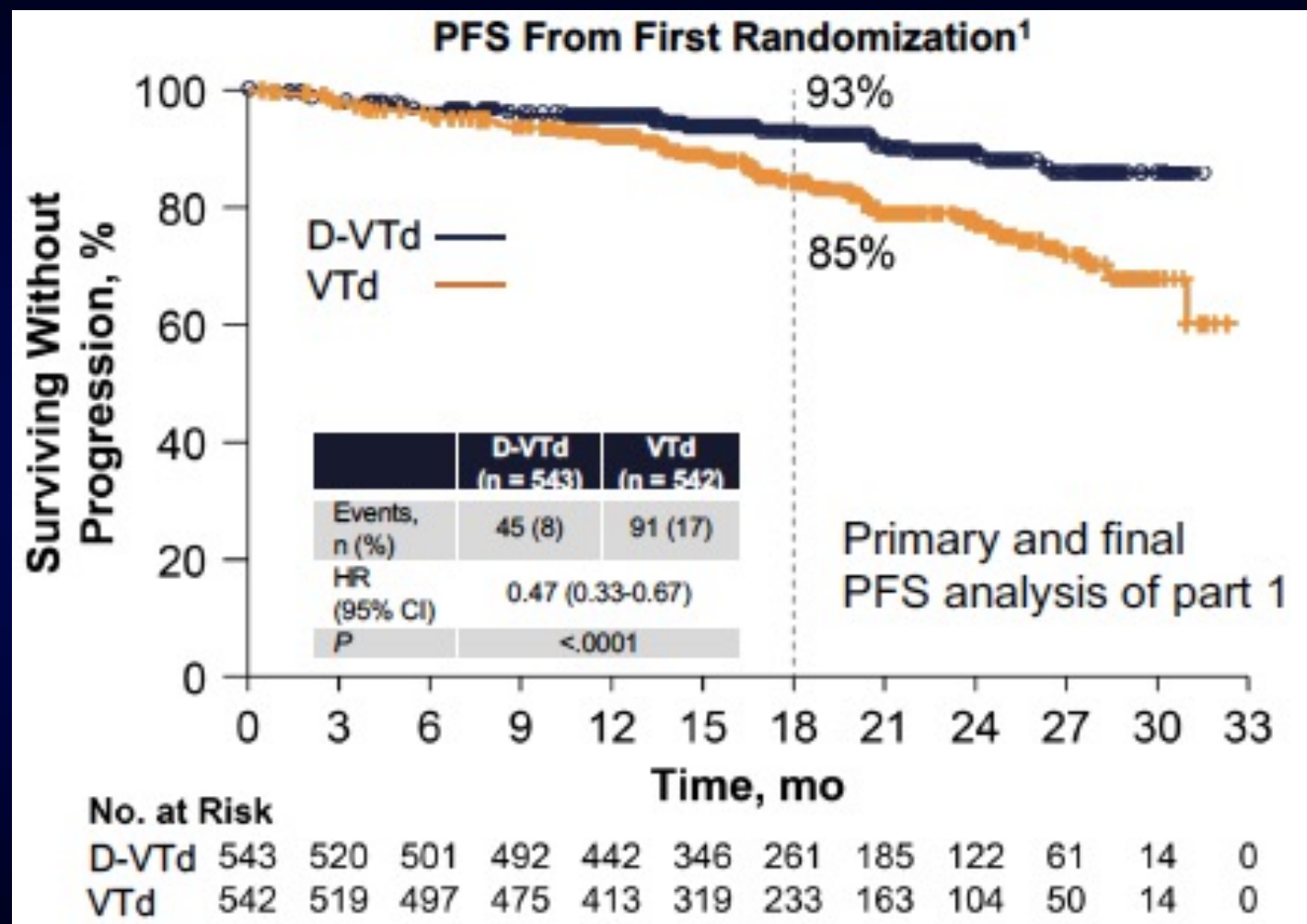


Phase III
CASSIOPEIA Trial of
VTd vs D-VTd in
NDMM





CASSIOPEIA: PFS Data



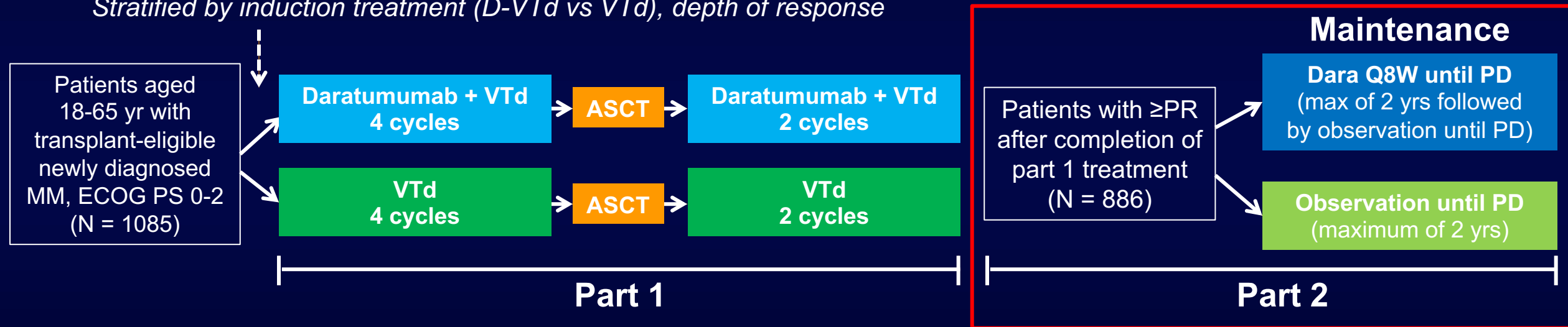
Moreau, P et al. Lancet 394: 29, 2019.



CASSIOPEIA Part 2

- Open-label, global, multicenter, randomized phase III trial

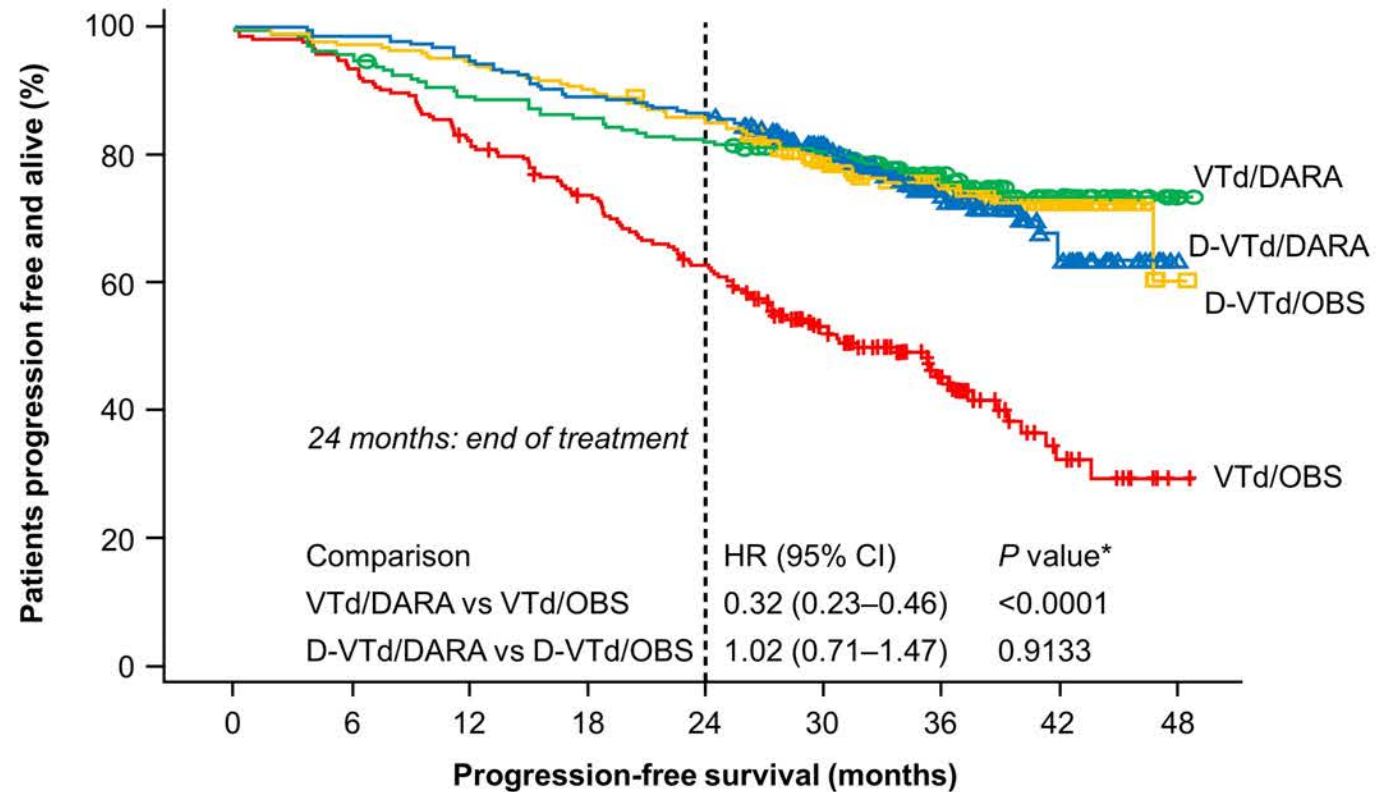
Stratified by induction treatment (D-VTd vs VTd), depth of response



- Primary endpoint (part 2): PFS (after second randomization)



CASSIOPEIA Part 2: PFS Data

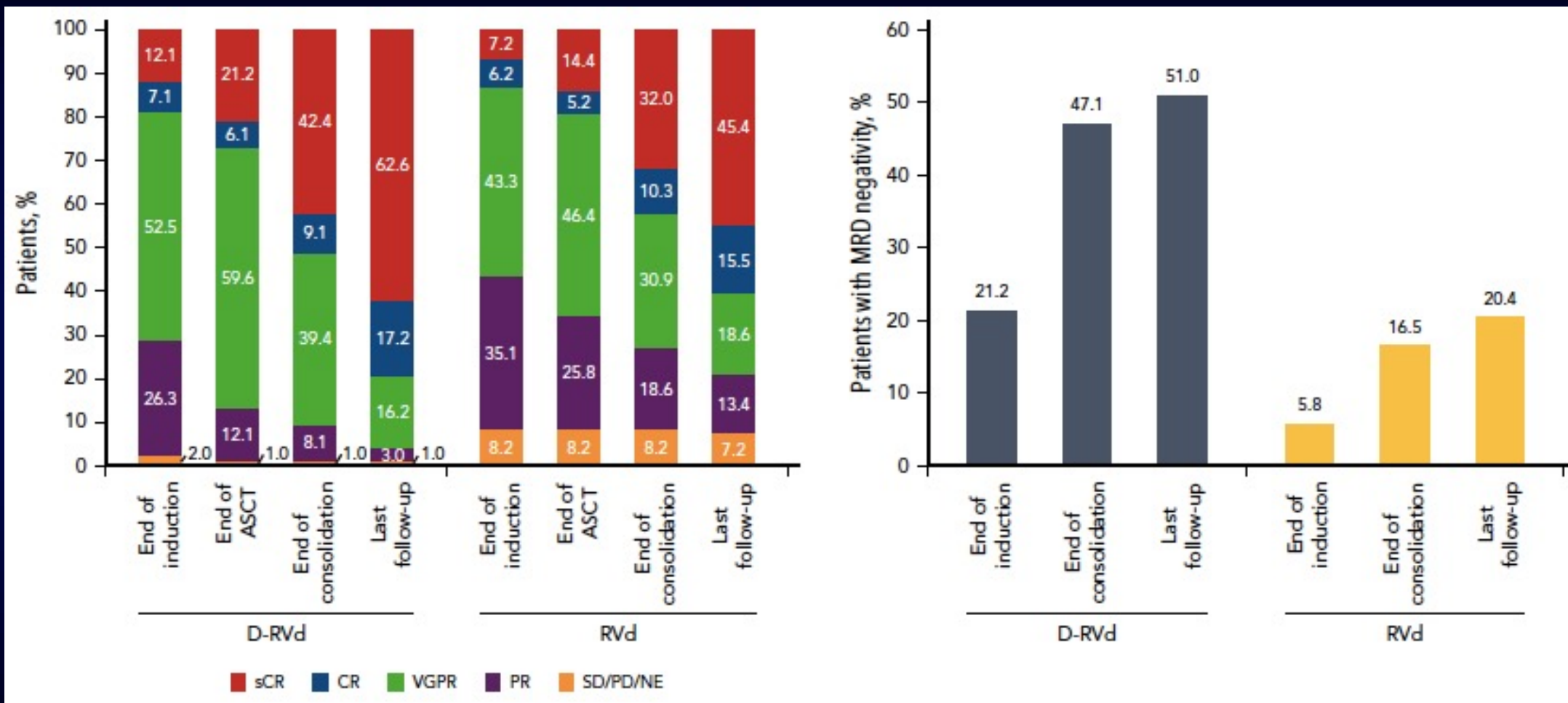


Patients at risk

VTd/OBS	215	201	176	155	131	83	43	15	1
VTd/DARA	213	203	189	182	174	138	79	34	1
D-VTd/OBS	229	223	216	207	195	144	75	38	2
D-VTd/DARA	229	226	217	204	198	145	76	30	0



GRIFFIN Trial of D-RVd in Transplant-Eligible NDMM



Voorhees, P et al. Blood 136: 936, 2020.



GRIFFIN: Updated Response Depth & MRD

MRD Status at 12-Mo-Maintenance Cutoff*	D-VRd	VRd	P Value [‡]
ITT population [†]	(n = 104)	(n = 103)	
▪ MRD negative, %	62.5	27.2	< .0001
▪ MRD negative and ≥ CR, %	59.6	24.3	< .0001
Patients with ≥ CR	(n = 81)	(n = 59)	
▪ MRD negative, %	76.5	42.4	< .0001
MRD evaluable in ITT patients [§]	(n = 83)	(n = 71)	
▪ MRD negative, %	78.3	39.4	< .0001
Durable MRD Negativity*	(n = 104)	(n = 103)	P Value [‡]
Sustained MRD negativity lasting ≥ 6 mos	37.5	7.8	< .0001
Sustained MRD negativity lasting ≥ 12 mos	28.8	2.9	< .0001

*MRD negativity threshold: 1 tumor cell/10⁵ white cells using BM aspirates by NGS. [†]Patients with missing/inconclusive MRD assessment considered MRD positive. [‡]Fisher's exact test. [§]Includes patients with baseline and post-baseline MRD samples.

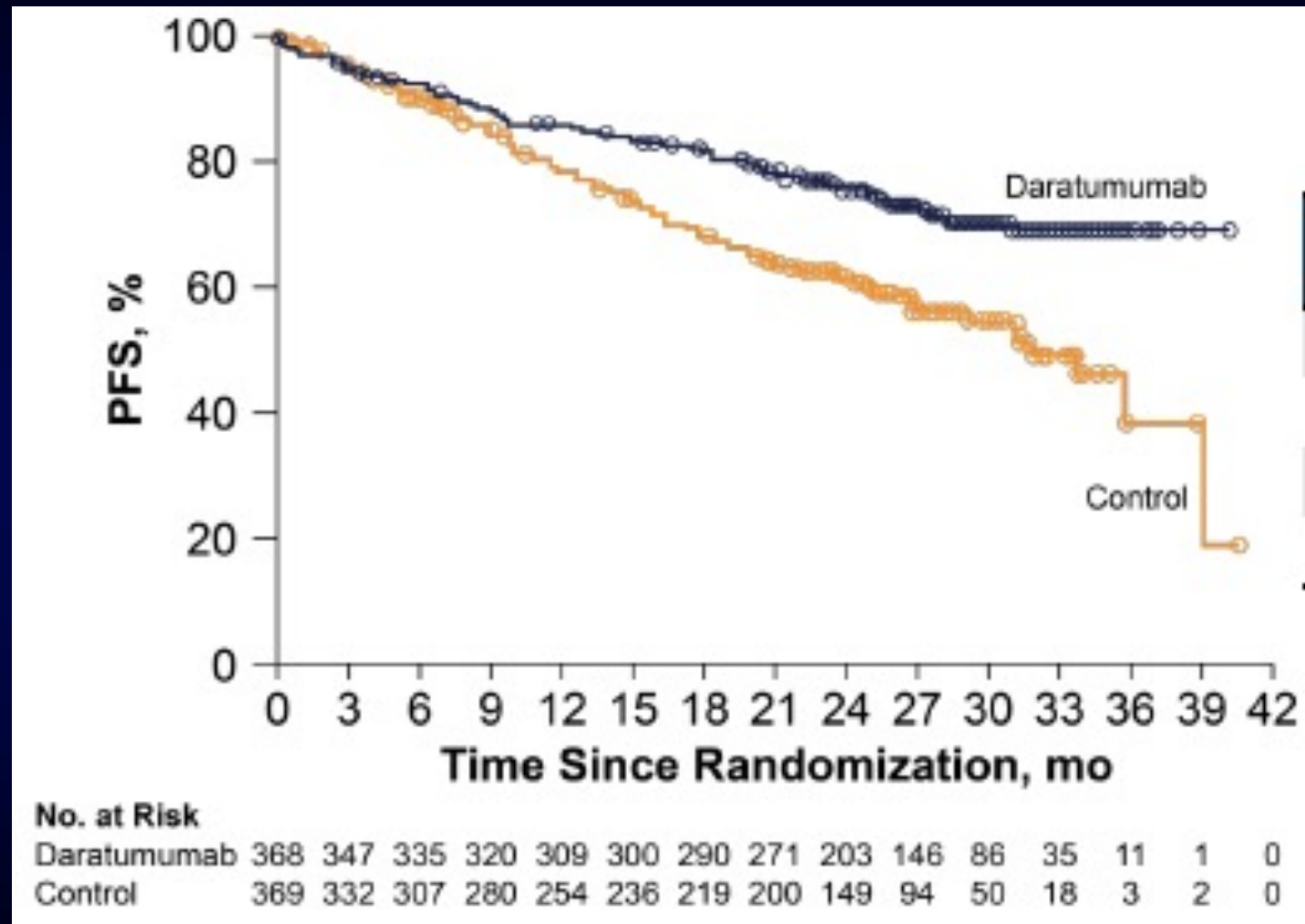


Transplant Ineligible Patients

PRIMARY THERAPY FOR NON-TRANSPLANT CANDIDATES ^{a-d}
Preferred Regimens • Bortezomib/lenalidomide/dexamethasone (category 1)^j • Daratumumab^f/lenalidomide/dexamethasone (category 1) • Lenalidomide/low-dose dexamethasone (category 1)^k • Bortezomib/cyclophosphamide/dexamethasone⁶
Other Recommended Regimens • Carfilzomib/lenalidomide/dexamethasone • Ixazomib/lenalidomide/dexamethasone • Daratumumab^f/bortezomib/melphalan/prednisone (category 1) • Daratumumab^f/cyclophosphamide/bortezomib/dexamethasone
Useful In Certain Circumstances • Bortezomib/dexamethasone • Cyclophosphamide/lenalidomide/dexamethasone • Carfilzomib/cyclophosphamide/dexamethasone^g
MAINTENANCE THERAPY
Preferred Regimens • Lenalidomide (category 1)
Other Recommended Regimens • Bortezomib
Useful In Certain Circumstances • Bortezomib/lenalidomide



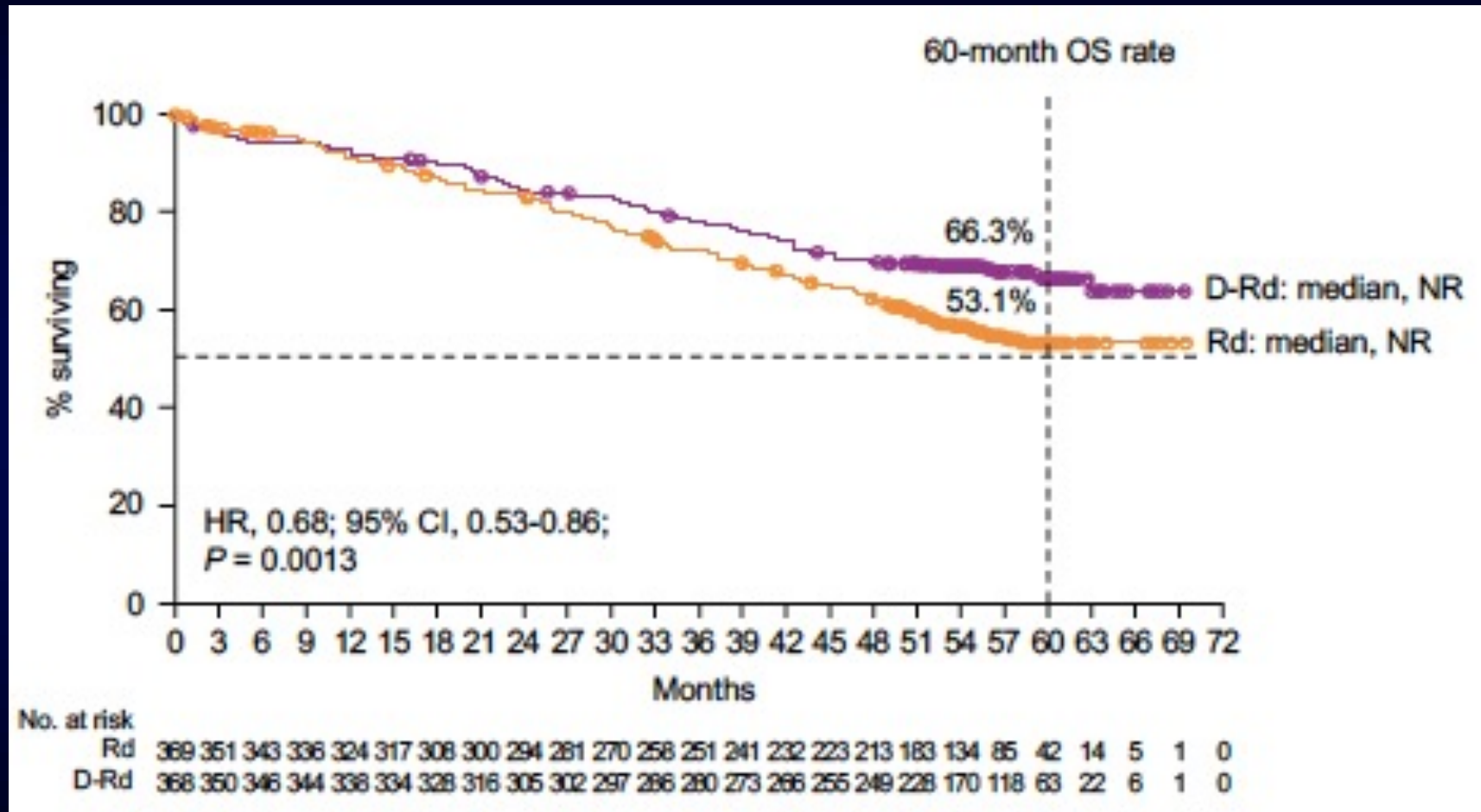
MAIA Trial of D-Rd vs Rd: PFS Curves



Facon, T et al. N Engl J Med. 380: 2104, 2019.



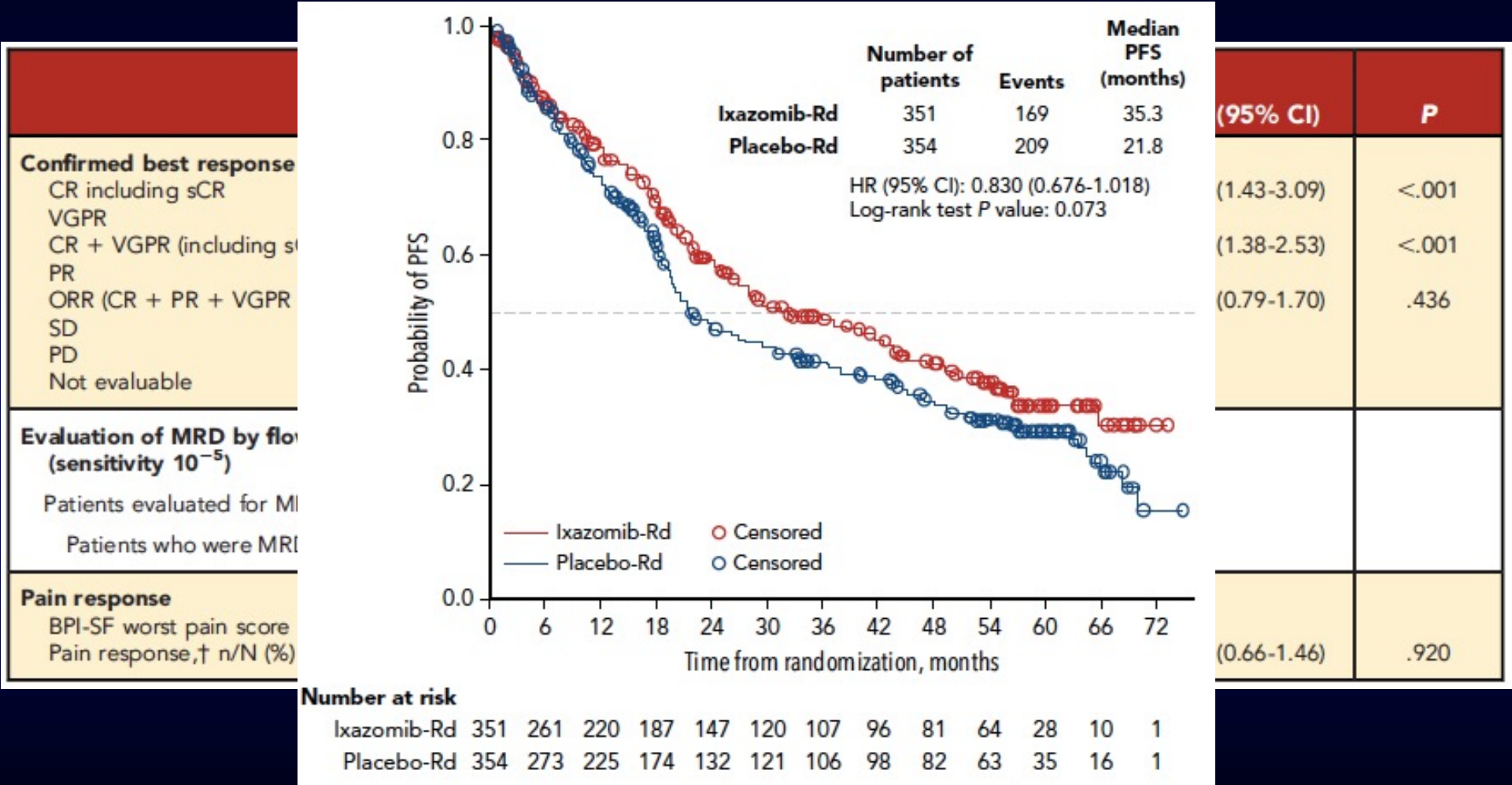
Updated MAIA Data



Facon, T et al. EHA Abstract LB1901, 2021.



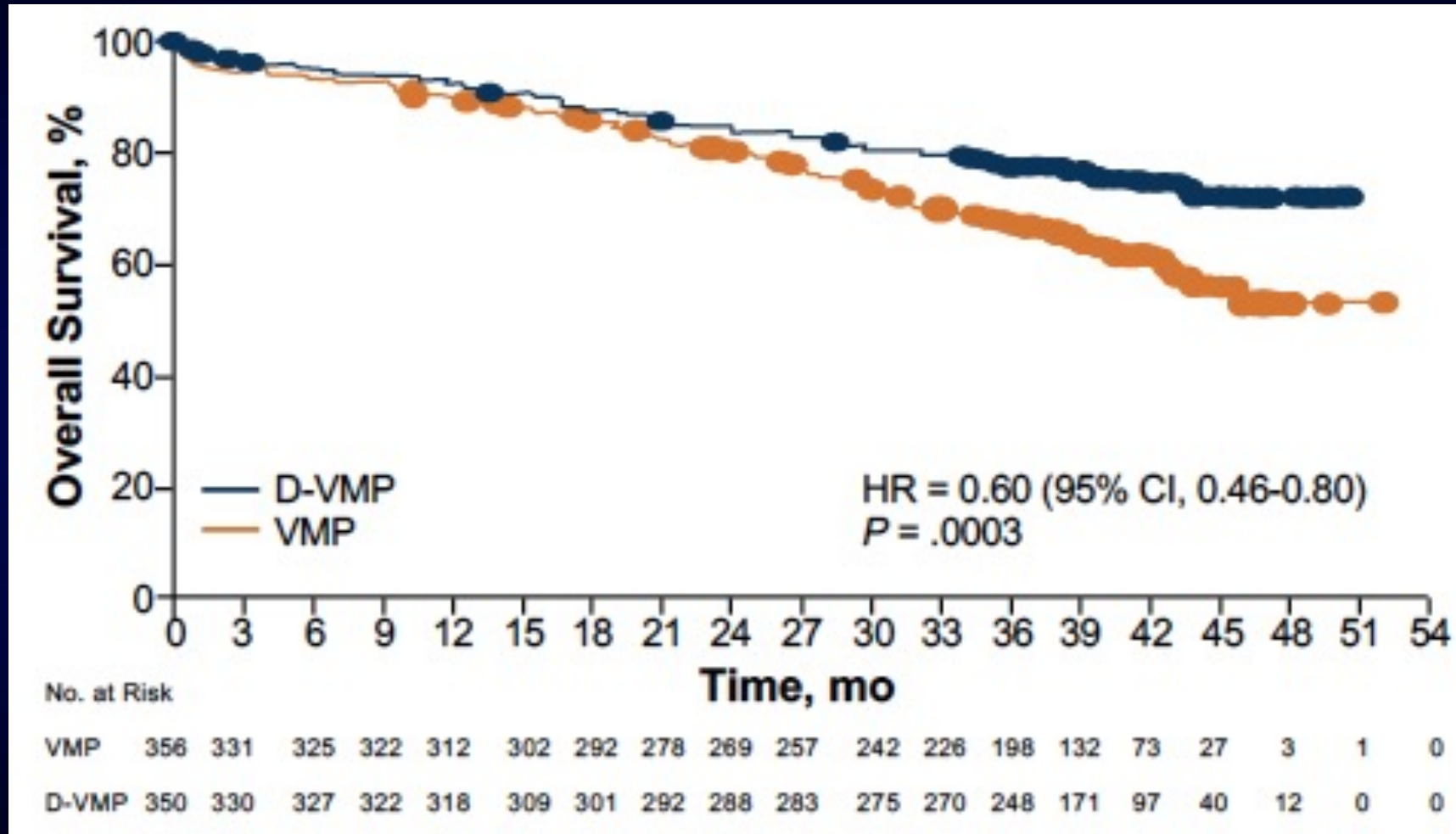
TOURMALINE-MM2 Trial of Ixa-Rd vs Rd in Transplant-Ineligible NDMM



Facon, T et al. Blood 137: 3616, 2021.



ALCYONE Trial of D-VMP vs VMP: Updated OS Data



Mateos, M-V et al. Lancet 395: 132, 2020.



Maintenance Options

- Transplant eligible

MAINTENANCE THERAPY
<u>Preferred Regimens</u> • Lenalidomide¹ (category 1)
<u>Other Recommended Regimens</u> • Ixazomib (category 1) • Bortezomib
<u>Useful In Certain Circumstances</u> • Bortezomib/lenalidomide

- Transplant ineligible

MAINTENANCE THERAPY
<u>Preferred Regimens</u> • Lenalidomide (category 1)
<u>Other Recommended Regimens</u> • Bortezomib
<u>Useful In Certain Circumstances</u> • Bortezomib/lenalidomide



Ixazomib as Post-Induction Maintenance: TOURMALINE-MM4



Endpoint	No. of Patients		Events	Median PFS (months)	Hazard Ratio (95% CI)	P
	Ixazomib (n = 425)	Placebo (n = 281)				
Median PFS in prespecified subgroups, months ^{a,b}						
Patients with a CR or VGPR with initial therapy (n = 263 v n = 175)	25.6	12.9		0.586 (0.449 to 0.765)		< .001
Patients with preinduction ISS stage III disease (n = 144 v n = 97)	16.6	7.8		0.695 (0.499 to 0.967)		.030
Patients aged ≥ 75 years (n = 164 v n = 110)	16.7	10.6		0.738 (0.537 to 1.014)		.060
Median total PFS landmarked from start of induction, months ^b	26.3	20.3		0.650 (0.534 to 0.791)		< .001
Median time to progression, months ^b	17.8	9.6		0.655 (0.537 to 0.799)		< .001
Response improvements during maintenance						
VGPR/PR patients with deepening response during treatment, No. (%)	62 (14.6)	23 (8.2)		—		.004 ^c
VGPR patients converting to CR during study, No. (%)	41 (9.6)	16 (5.7)		—		—
PR patients converting to VGPR or better during study, No. (%)	21 (4.9)	7 (2.5)		—		—

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

Dimopoulos, MA et al. J Clin Oncol. 38: 4030, 2020.



Conclusions: Induction

- Category 1 recommendations
 - VRd for transplant-eligible (TE)
 - VRd-lite or DRd for transplant-ineligible (TIE)
- Quadruplets are gaining traction
 - VTd-Dara, VRd-Dara in TE
 - ? VMP-Dara in TIE
 - ? IRd-Dara in TIE



Conclusions: Maintenance

- Category 1 recommendations
 - Len or Ixa for TE
 - Len or Ixa for TIE
- Outcomes in high-risk disease still suboptimal
 - May need to consider adding V or I to R for both TE and TIE
- Ongoing studies will change this landscape
 - Len $\pm$ Dara : Ongoing SWOG study



Challenges

- Outcomes in high-risk still suboptimal
 - May need to consider adding Dara to VRd (for TE) or V/Ixa to DRd (for TIE)
- Frail patients an area of unmet medical need
- Ongoing studies will change the landscape further
 - Adding CD38- or BCMA-targeted mAbs
 - Potential use of bispecifics and even CAR Ts