KEY UPDATES AND EXPERT DISCUSSION FROM MYELOMA ROUNDS

This activity is provided by The Leukemia & Lymphoma Society and Medical Learning Institute, Inc., in collaboration with the Association of Cancer Care Centers™ (ACCC).

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WELCOME AND INTRODUCTIONS

Amanda O'Neill, LMSW
Senior Manager, Professional Education
The Leukemia & Lymphoma Society
Rye Brook, NY

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TARGET AUDIENCE

This CE activity is intended for hematologists-oncologists, medical oncologists, nurse practitioners, nurses and pharmacists involved in the care of patients with myeloma.

EDUCATIONAL OBJECTIVES

After completing this CE activity, the participant should be better able to:

- Describe the latest developments in myeloma, including current and emerging treatments
- Engage patients and caregivers in discussions on clinical trials, newly approved therapies and emerging therapies for myeloma, including combination therapies, CAR T-cell therapy and bispecific antibodies
- Identify disparities and challenges in diagnosis and treatment of myeloma
- Apply evidence-based treatment strategies for optimal patient care
- Access patient support resources

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SPEAKERS

Edward A. Stadtmauer, MD (Chair, Myeloma Rounds, Philadelphia)

Section Chief, Hematologic Malignancies

Roseman, Tarte, Harrow, and Shaffer Families'

President's Distinguished Professor

University of Pennsylvania Abramson Cancer Center

Philadelphia, PA

Cindy Varga, MD (Chair, Myeloma Rounds, Durham)

Associate Professor

Atrium Health Levine Cancer Institute

Plasma Cell Dyscrasia Division

Department of Hematology and Oncology

Charlotte, NC

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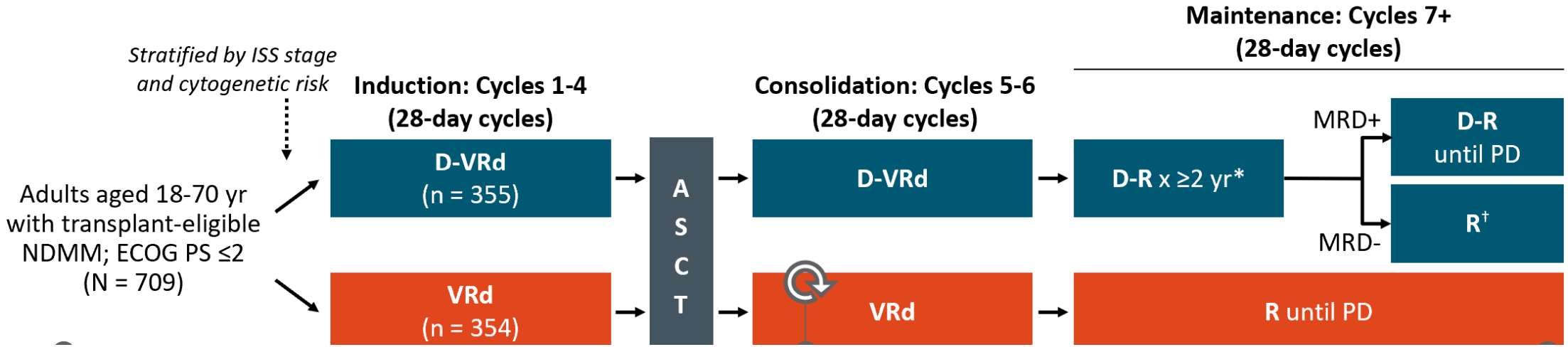
Update on Clinical Trials of Early Use of Immunotherapy for Myeloma

Edward A. Stadtmauer, MD
Section Chief, Hematologic Malignancies
Roseman, Tarte, Harrow, and Shaffer Families'
President's Distinguished Professor
University of Pennsylvania Abramson Cancer Center
Philadelphia, PA

PERSEUS: DARA + VRD IN TRANSPLANT ELIGIBLE MM

Multicenter, open-label, **randomized phase III trial**; current analysis median f/u: 47.5 months



Dosing: D 1800 mg SC QW (induction cycles 1-2)/Q2W (induction cycles 3-4 and consolidation)/Q4W (maintenance); V 1.3 mg/m^2 SC on Days 1, 4, 8, 11; R 25 mg PO on D1-21 (induction and consolidation)/10 mg PO on Days 1-28 (maintenance); d 40 mg PO/IV on Days 1-4, 9-12. *D stopped after 2 yr in those with ≥CR and sustained MRD negativity (10^{-5}) for 12 mo. †Restart D if confirmed loss of CR without PD or MRD recurrence.

- **Primary endpoint:** PFS
- **Key secondary endpoints:** ≥CR rate, MRD negativity rate, OS

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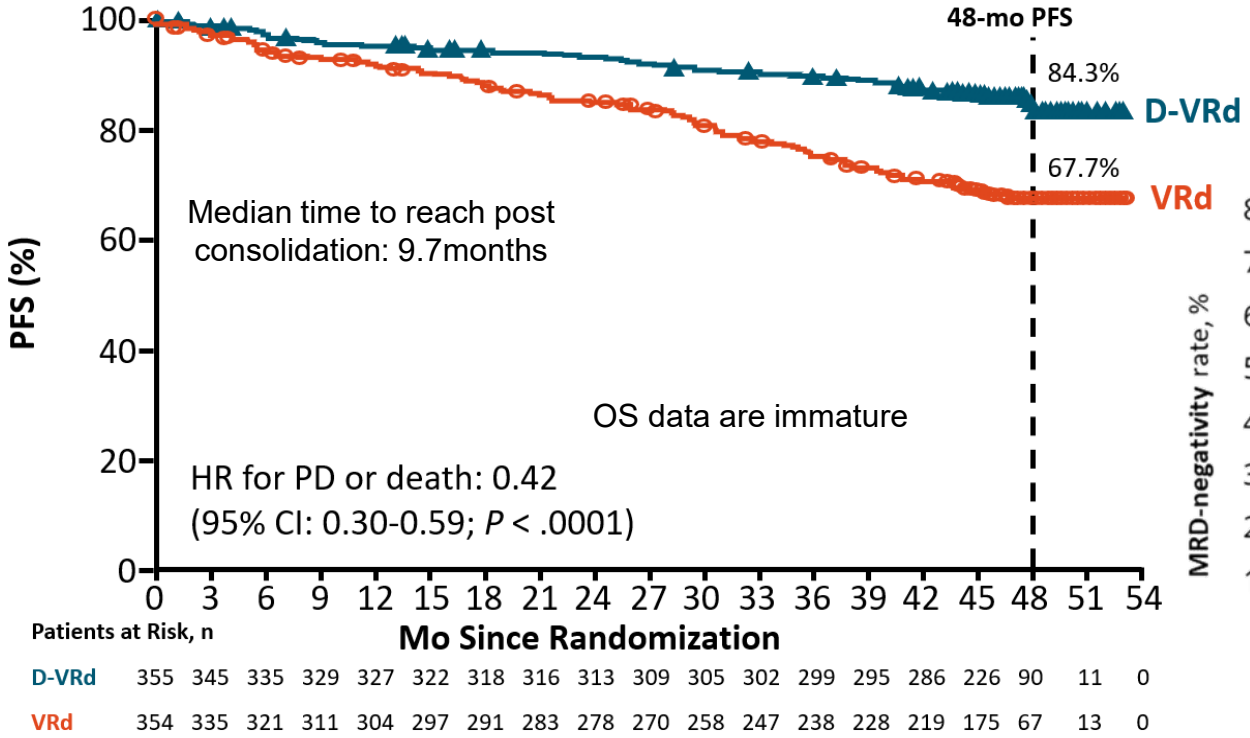
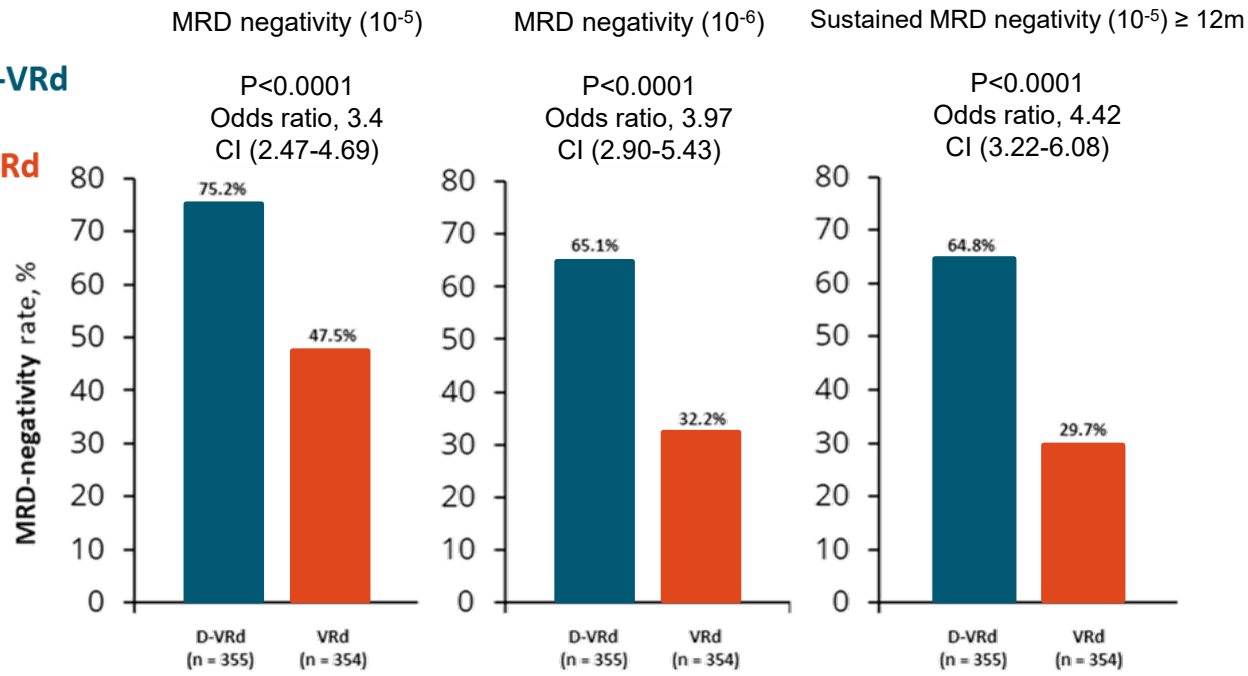
Sonneveld. NEJM. 2023.

PERSEUS: IMPROVED PFS, ACHIEVED DURABLE MRD



Overall and sustained MRD-negativity rates



MRD-negativity: Patients who achieved both MRD negativity and ≥CR.
Patients who were non evaluable/indeterminate results were considered MRD positive

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Sonneveld. NEJM. 2023.

PERSEUS UPDATE: SUMMARY

1. Adds support for quadruplet therapy with anti-CD38 in newly diagnosed MM.
2. Dara-R maintenance associated with higher rates of MRD negativity and conversion to sustained MRD negativity.
3. Only 30% in high-risk population could sustain MRD negativity – unmet need.
4. Need long term Overall Survival data.

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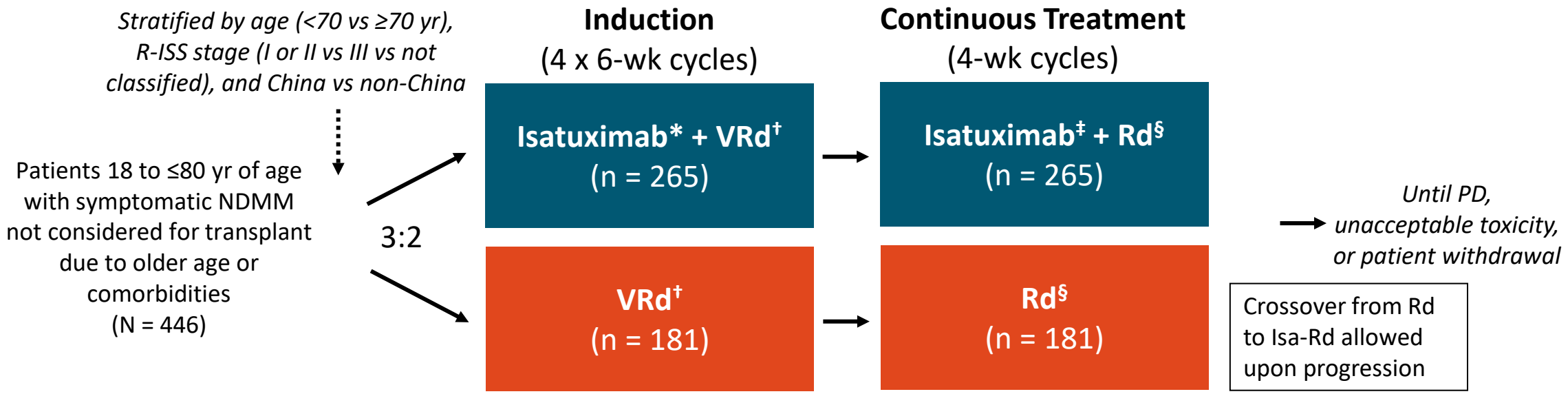
Rodriguez-Otero. ASCO 2024. Abstr 7502. NCT03710603.

IMROZ: ISA+VRD VS VRD IN TRANSPLANT INELIGIBLE MM

International, randomized, open-label phase III trial



*Isa IV (C1 only) 10 mg/kg Q1W; Isa IV (C2-4) 10 mg/kg Q2W. †V: SC 1.3 mg/m^2 on D1,4,8,11,22,25,29,32; R: PO 25 mg on D1-14 and 22-35; d: IV/PO 20 mg on D1,2,4,5,8,9,11,12,15,22,23,25,26,29,30,32,33. ‡Isa IV (C5-17) 10 mg/kg Q2W; Isa IV (C18+) 10 mg/kg monthly. §R: PO 25 mg on D1-21; d: IV/PO 20 mg on Q1W.

- **Primary endpoints:** PFS
- **Secondary endpoints:** CR rate, MRD− CR (NGS 10-5) rate, ≥ VGPR rate, OS

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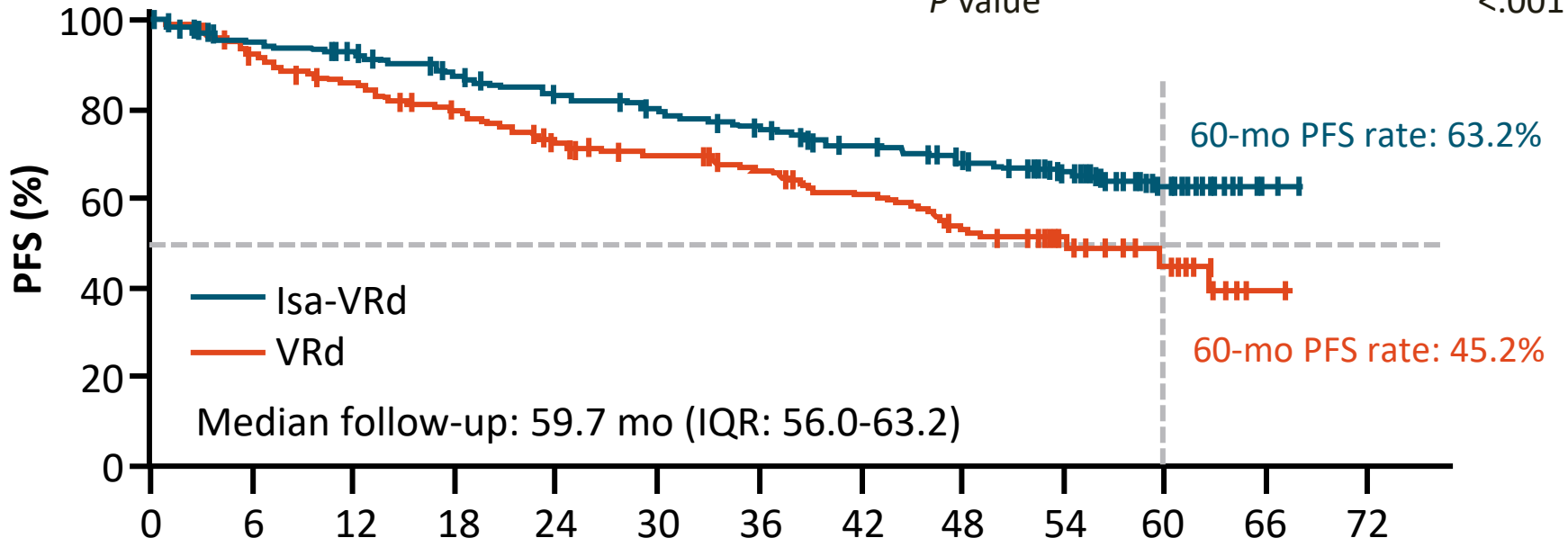
Facon. ASCO 2024. Abstr 7500. Facon. NEJM. 2024.

IMROZ: PFS IN ITT POPULATION

Parameter, n (%)	Isa + VRd (n = 265)	VRd (n = 181)
Median PFS, mo	NR	54.34
HR (98.5% CI)	0.60 (0.41-0.88)	
P value	<.001	



Patients at Risk, n													
Isa-VRd	265	243	234	217	201	190	177	164	153	104	43	2	0
VRd	181	155	141	121	104	96	89	81	70	51	20	2	0

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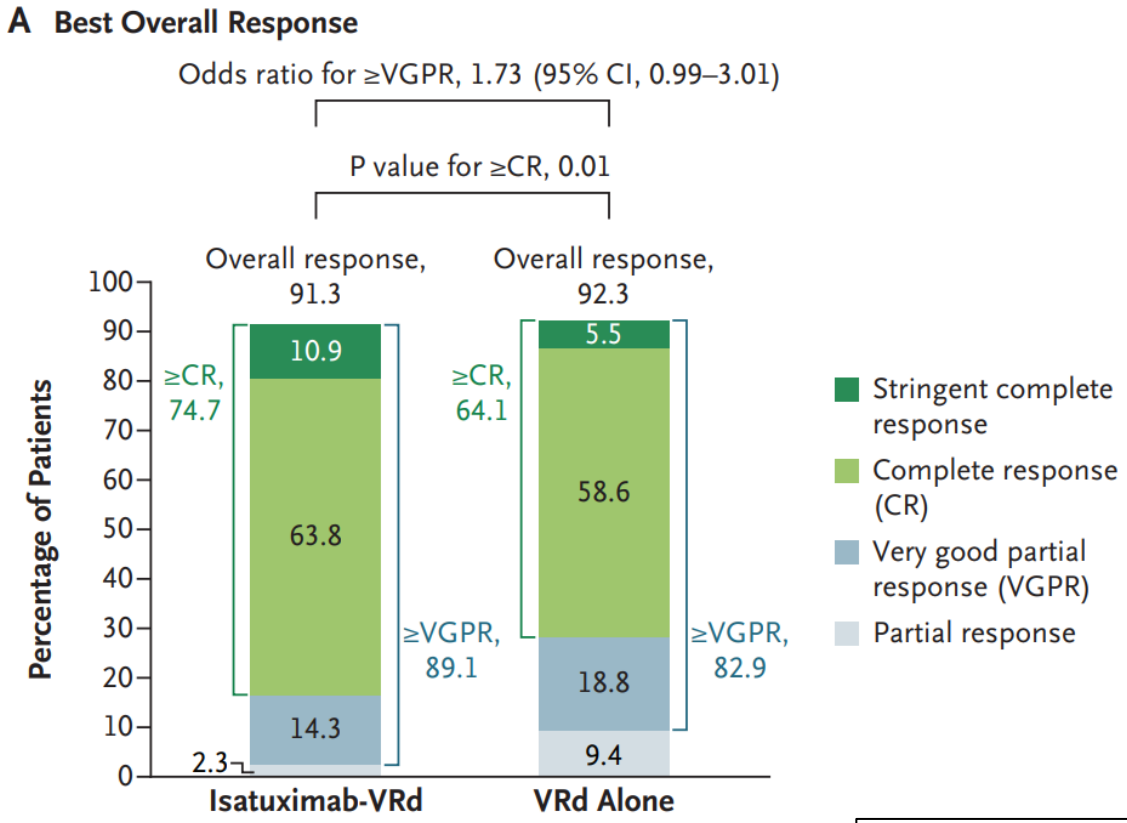
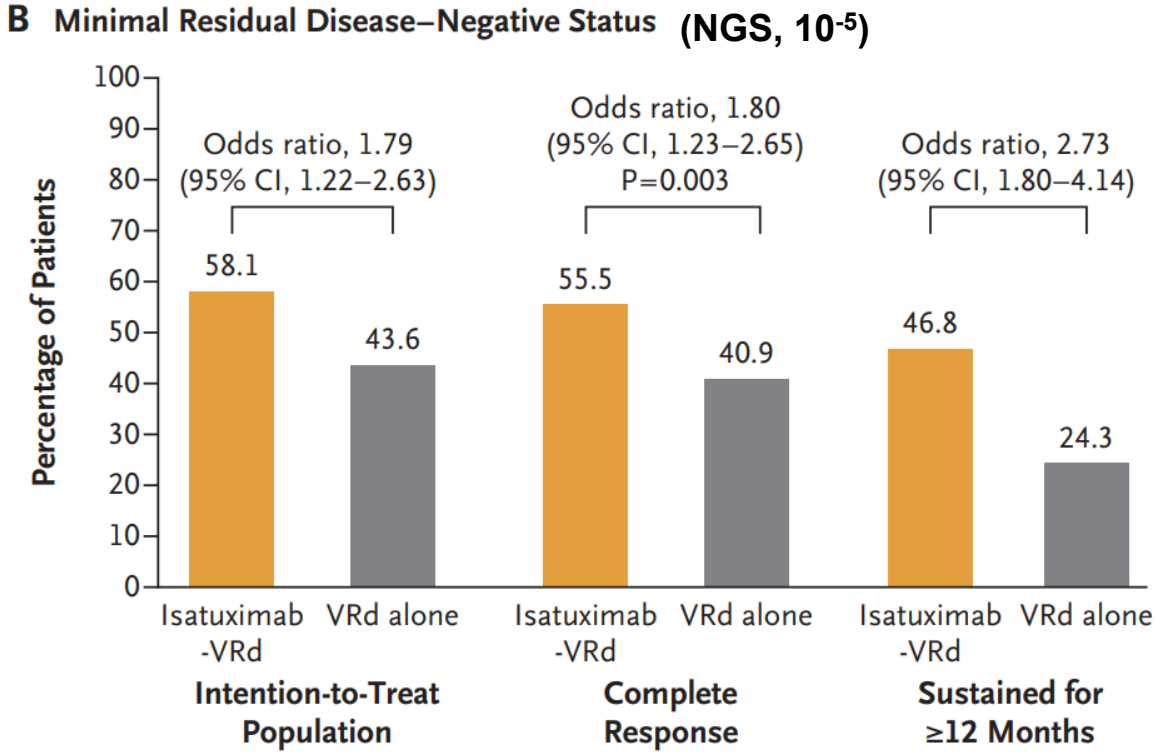
Facon. ASCO 2024. Abstr 7500. Facon. NEJM. 2024.

IMROZ: DEPTH OF RESPONSE





Time to MRD -, median
Isa-VRD: 14.72 (11.53-24.08mo)
VRd: 32.79 (17.51-45.11 mo)

Isa-VRd followed by Isa-Rd resulted in deep response rates with significant improvement in MRD- CR rate as well as higher rates of MRD- for ≥12mo

Facon. ASCO 2024. Abstr 7500. Facon. NEJM. 2024.

IMROZ: SAFETY SUMMARY

TEAE	Isatuximab + VRd (n = 263)	VRd (n = 181)
Any TEAE, n (%)	262 (99.6)	178 (98.3)
▪ Grade ≥3	241 (91.6)	152 (84.0)
▪ Grade 5*	29 (11.0)	10 (5.5)
▪ Serious	186 (70.7)	122 (67.4)
▪ Leading to treatment discontinuation	60 (22.8)	47 (26.0)
Invasive second primary malignancies		
▪ Solid tumors	22 (8.4)	14 (5.3)
▪ Hematologic	3 (1.1)	1 (0.4)

Deaths were caused mainly by infection, Isa-VRd (17,6.5%) vs VRd (7,3.9%)

Quality of life measurements by EORTC QLQ-C30 GHS, remained stable over time in both groups

*Grade 5 AEs mostly due to infection. In Isa-VRd arm: infections (n = 16); sudden death (n = 4); n = 1 each renal tubular acidosis, septic shock, hepatic cirrhosis, neuroendocrine carcinoma of the skin, febrile neutropenia, respiratory failure, dyspnea, pulmonary embolism, undetermined. In VRd arm: infections (n = 7); n = 1 each pulmonary embolism, pleural effusion, undetermined.

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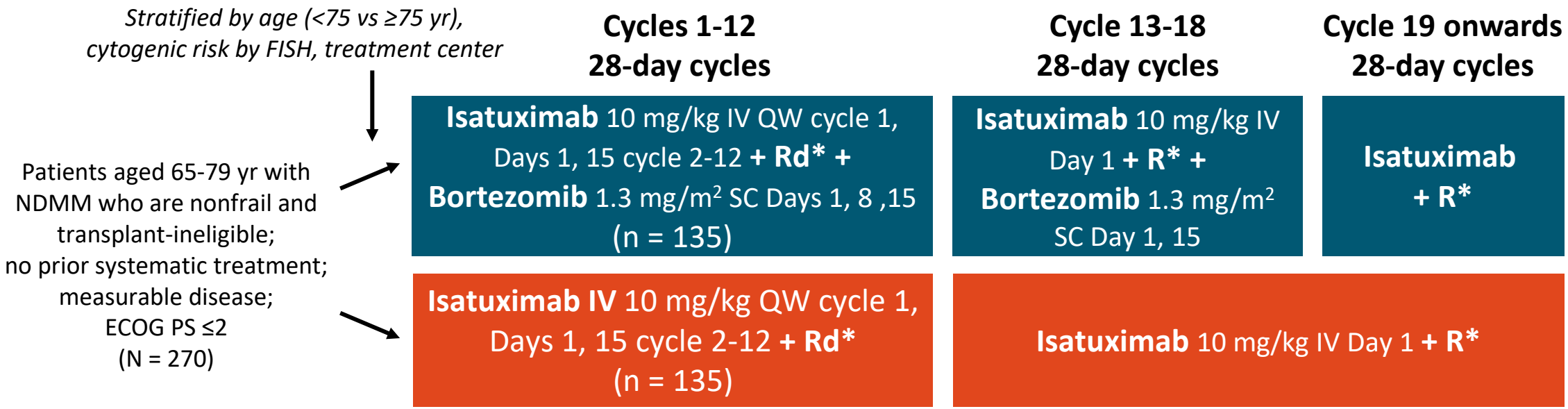
Facon. ASCO 2024. Abstr 7500. Facon. NEJM. 2024.

BENEFIT: ISA-VRD VS ISA-RD

- Multicenter, open-label, randomized, phase III trial

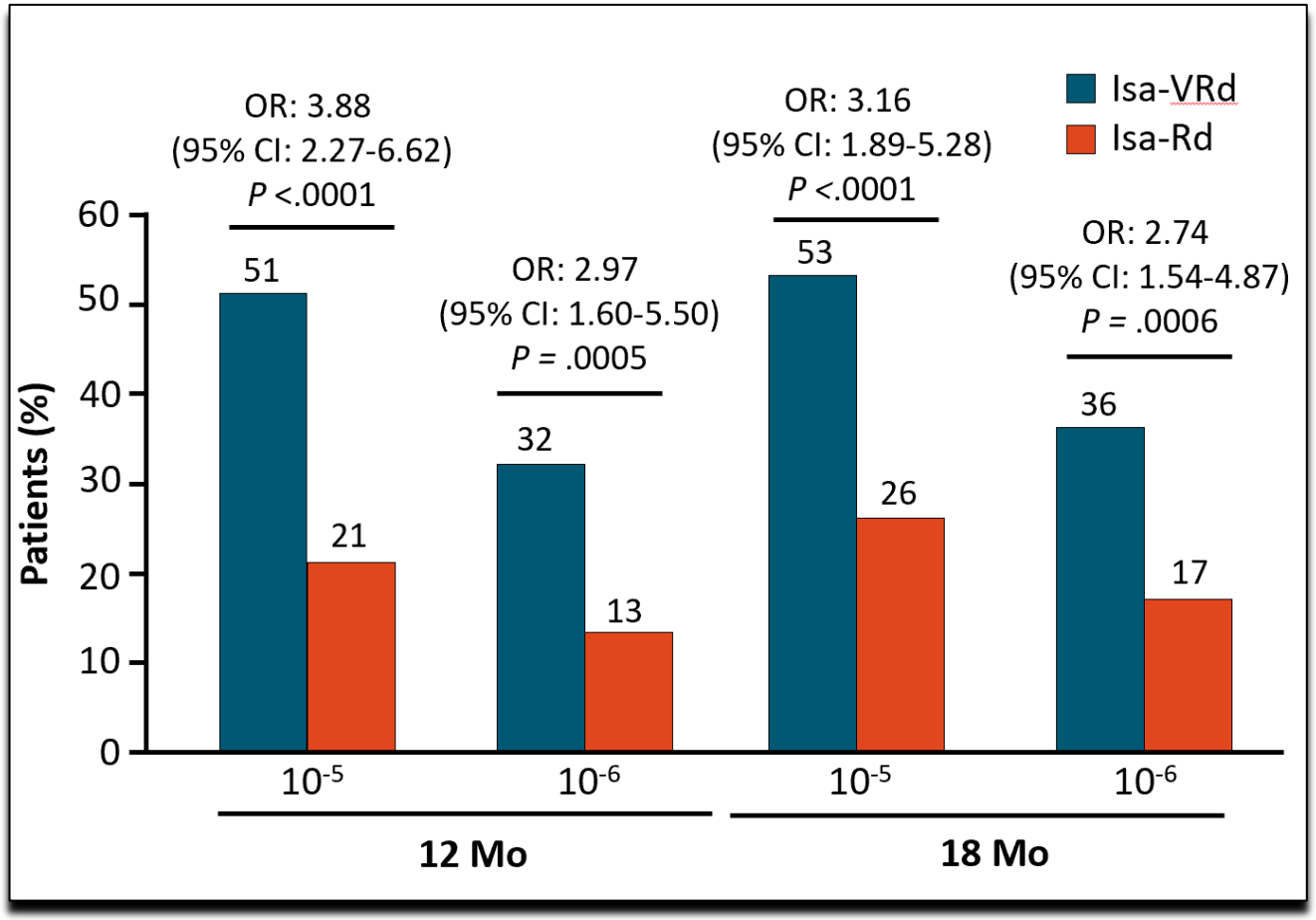


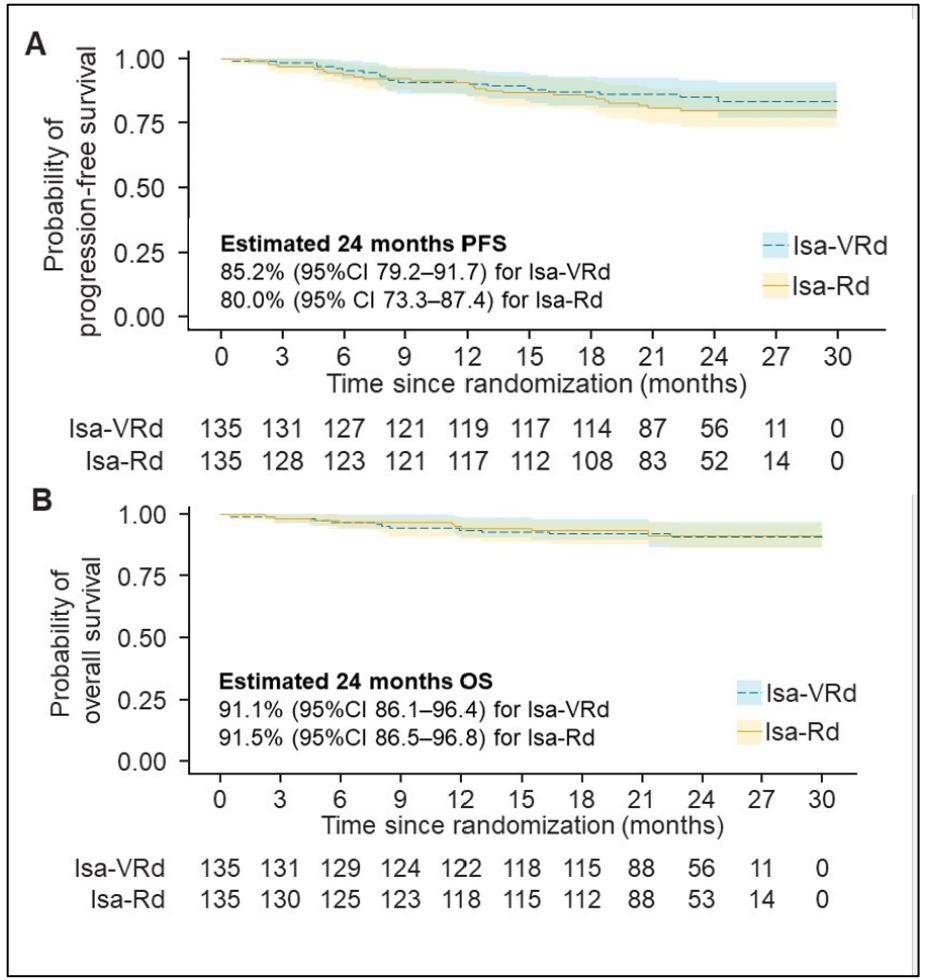
*R: lenalidomide 25 mg PO Days 1-21, d: dexamethasone 20 mg IV QW.

- **Primary endpoint:** MRD (10^{-5}) at 18 mo
- **Key secondary endpoints:** ORR (CR, ≥ VGPR), MRD– CR (10^{-5}), PFS, OS, safety

Leleu. Nature Medicine. 2024, Leleu ASCO 2024 Abstr 7501.

BENEFIT: IMPROVED MRD, BUT NO PFS/OS BENEFIT





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Leleu. Nature Medicine. 2024, Leleu ASCO 2024 Abstr 7501;.

BENEFIT: HIGHER RATES OF NEUROPATHY

AEs, n (%)	Isa-VRd (n = 135)		Isa-Rd (n = 135)	
	Any Gr	Gr ≥3	Any Gr	Gr ≥3
Hematologic				
▪ Neutropenia	77 (57)	53 (40)	82 (61)	61 (45)
▪ Lymphopenia	53 (39)	44 (33)	38 (28)	33 (24)
▪ Anemia	30 (22)	13 (10)	27 (20)	7 (5)
▪ Thrombocytopenia	37 (27)	16 (12)	19 (14)	8 (5)
	Any Gr	**Gr ≥2**	**Any Gr**	**Gr ≥2**
Infections/Infestation				
▪ Respiratory system	65 (48)	47 (35)	64 (47)	54 (40)
▪ Other	61 (45)	48 (36)	48 (36)	35 (28)
Nervous system disorder				
▪ **Peripheral neuropathy**	70 (52)	**37 (27)**	38 (28)	**13 (10)**
▪ Other	38 (28)	19 (14)	41 (30)	17 (13)

12% (16) discontinued therapy due to nervous system disorders ≥2

Leleu. Nature Medicine. 2024, Leleu ASCO 2024 Abstr 7501.

QUADRUPLET IN TRANSPLANT DEFERRED: SUMMARY

1. **IMROZ:**
   - Improved PFS and higher rates of MRD negativity with Isa-VRd
   - Higher rates of infection; but QOL maintained
   - Overall Survival data immature

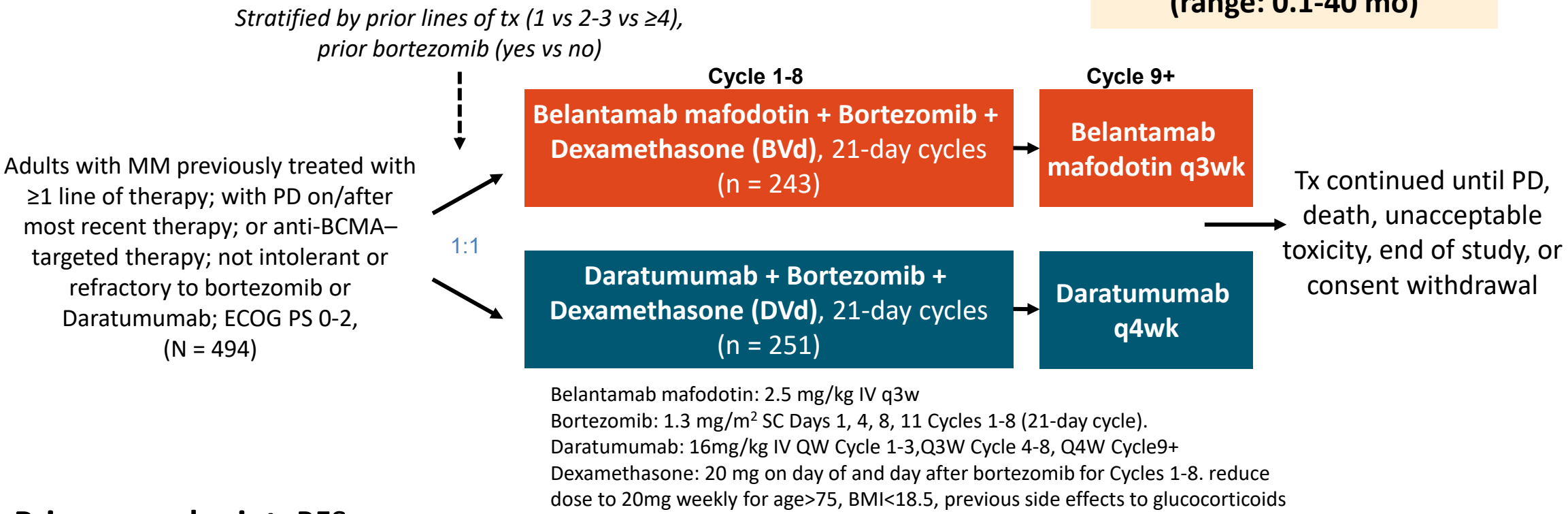
2. **BENEFIT:**
   - Addition of bortezomib showed improvement in MRD negativity rates but with tradeoffs – higher rates of grade ≥2 neuropathy with Isa-VRd vs Isa-Rd
   - No PFS/OS benefit: Long term follow-up needed

Facon. ASCO 2024. Abstr 7500. Facon. NEJM. 2024.
Leleu. Nature Medicine. 2024, Leleu ASCO 2024 Abstr 7501.

DREAMM-7: BVD VS DVD

- Multicenter, randomized, open-label phase III trial

Median follow-up: 28.2 mo (range: 0.1-40 mo)



Belantamab mafodotin: 2.5 mg/kg IV q3w
Bortezomib: 1.3 mg/m^2 SC Days 1, 4, 8, 11 Cycles 1-8 (21-day cycle).
Daratumumab: 16mg/kg IV QW Cycle 1-3,Q3W Cycle 4-8, Q4W Cycle9+
Dexamethasone: 20 mg on day of and day after bortezomib for Cycles 1-8. reduce dose to 20mg weekly for age>75, BMI<18.5, previous side effects to glucocorticoids

- **Primary endpoint:** PFS
- **Key secondary endpoints:** OS, DoR, MRD negativity, ORR, PFS2, safety, QoL

Hungria NEJM 2024, Mateos ASCO 2024 Abstract 7503.

DREAMM-7: BASELINE CHARACTERISTICS

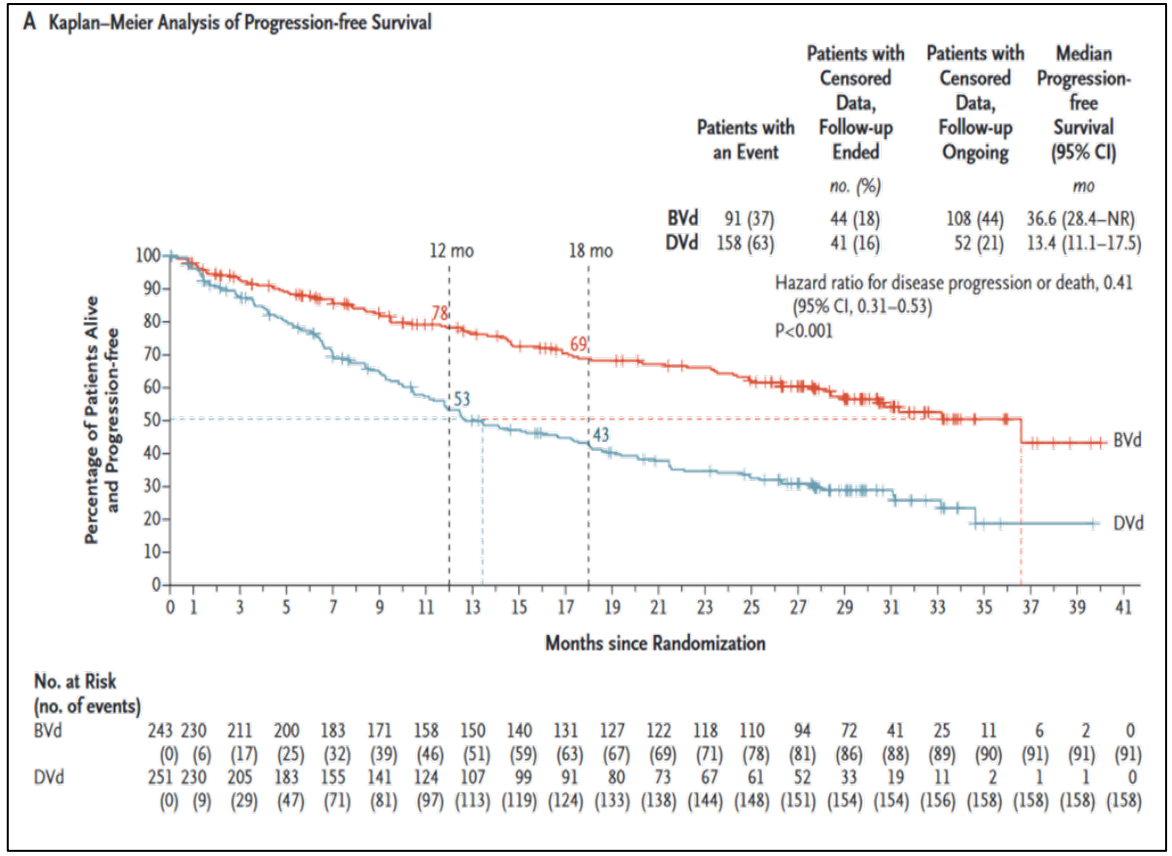
Baseline characteristics	ITT population	
	BVd (N=243)	DVd (N=251)
Age, median (range), years	65.0 (34-86)	64.0 (32-89)
<65, n (%)	121 (50)	126 (50)
65 to <75, n (%)	85 (35)	95 (38)
≥75, n (%)	37 (15)	30 (12)
Male/female, n (%)	128 (53)/115 (47)	144 (57)/107 (43)
White/Black or African American/other, n (%)[a]	206 (85)/8 (3)/ 28 (12)	203 (81)/12 (5)/34 (14)
ECOG PS ≤1, n (%)	232/242 (96)	235/246 (96)
R-ISS stage at screening, n (%)		
I	102 (42)	103 (41)
II	130 (53)	132 (53)
III	9 (4)	14 (6)
Unknown	2 (<1)	2 (<1)
Years since diagnosis, median (range)	4.28 (0.2-26.0)	3.94 (0.1-23.4)
Cytogenetic abnormalities, n (%)		
High risk[b]	67 (28)	69 (27)
Standard risk[c]	175 (72)	175 (70)
Missing or non-evaluable	1 (<1)	7 (3)
Extramedullary disease, n (%)		
Yes	13 (5)	25 (10)
No	230 (95)	226 (90)

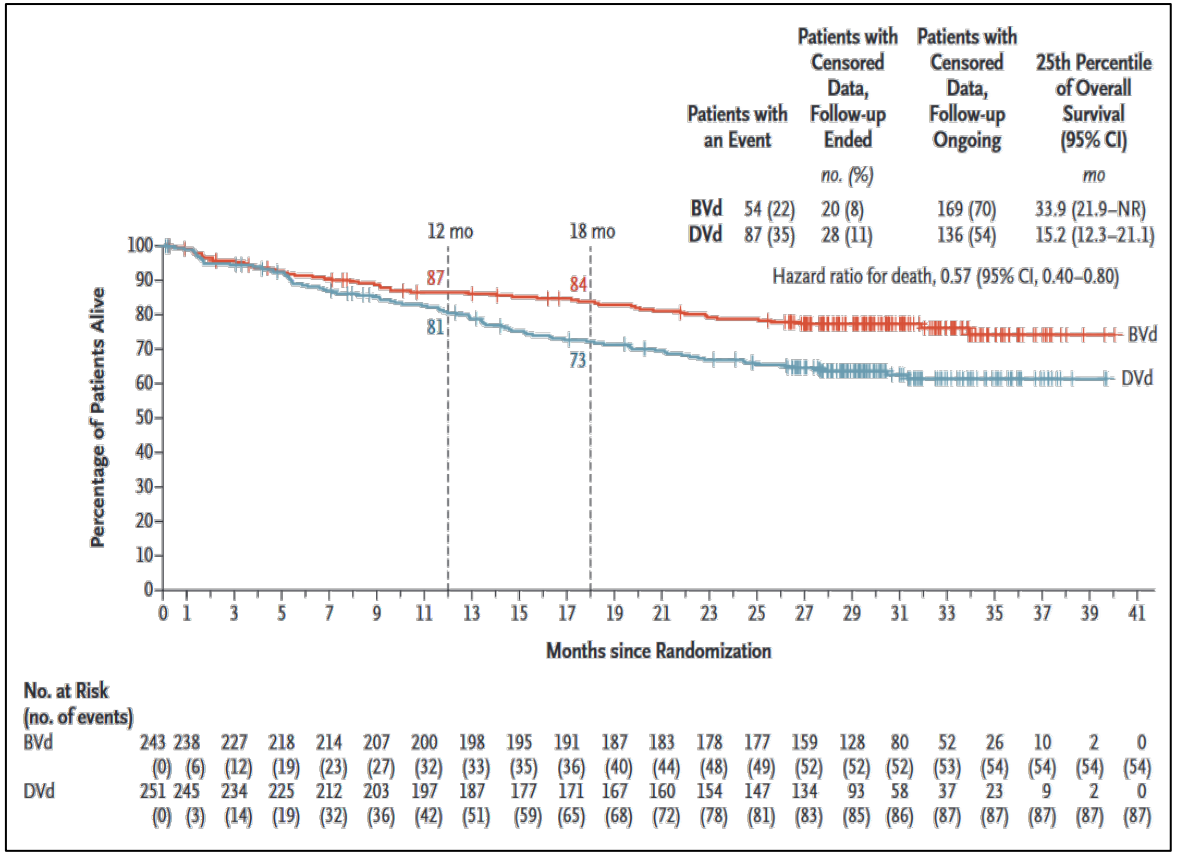
Prior Bortezomib 80%
Prior Lenalidomide 50%
Failed lenalidomide 30%

b High risk cytogenetics: presence of ≥ 1 of the following: t(4;14), t(14;16), or del(17p13)

Hungria NEJM 2024, Mateos ASCO 2024 Abstract 7503.

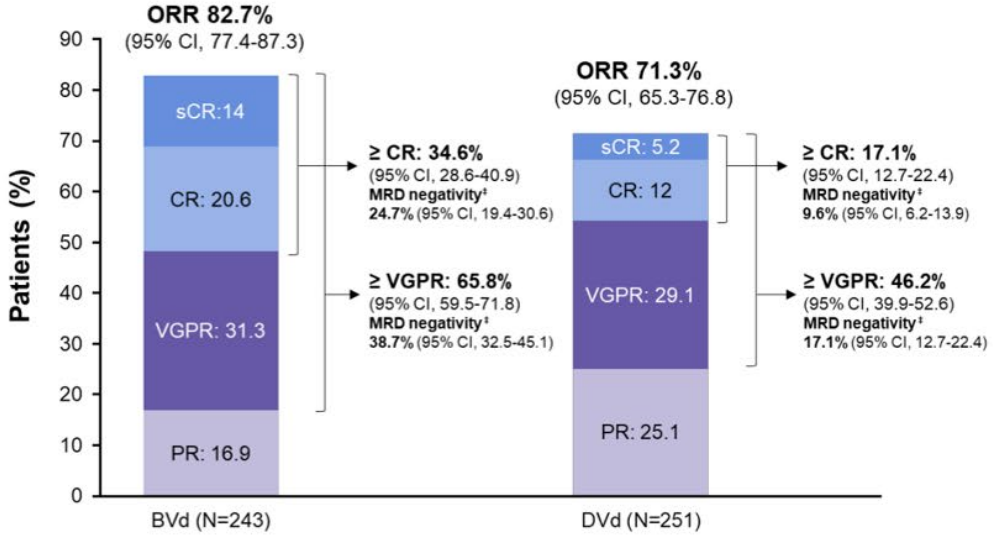
DREAMM-7: IMPROVED PFS AND POSITIVE TREND IN OS





Hungria NEJM 2024, Mateos ASCO 2024 Abstract 7503.

DREAMM-7: HIGHER RESPONSE WITH BVD



Categories	BVd n/N	DVd n/N	HR (95% CI)	HR (95% CI)†
All patients (stratified)	91/243	158/251		0.41 (0.31-0.53)
No. of prior LOT (1 vs 2 or 3 vs ≥4)				
1	46/125	76/125		0.52 (0.36-0.76)
2 or 3	30/88	62/99		0.34 (0.22-0.53)
≥4	15/30	20/27		0.38 (0.19-0.75)
No. of prior LOT (1 vs >1)				
1	46/125	76/125		0.52 (0.36-0.76)
>1	45/118	82/126		0.36 (0.25-0.52)
Prior bortezomib				
Yes	79/210	132/211		0.45 (0.34-0.59)
No	12/33	26/40		0.42 (0.21-0.84)
Prior lenalidomide				
Yes	44/127	88/130		0.33 (0.23-0.48)
No	47/116	70/121		0.57 (0.39-0.83)
Disease refractory to lenalidomide				
Yes	33/79	64/87		0.37 (0.24-0.56)
No	58/164	94/164		0.48 (0.34-0.67)
R-ISS staging at screening				
I	37/102	64/103		0.42 (0.28-0.64)
II/III	53/139	94/146		0.45 (0.32-0.64)
Age				
<65 years	42/121	84/126		0.39 (0.27-0.56)
65 to <75 years	37/85	61/95		0.48 (0.32-0.73)
≥75 years	12/37	13/30		0.62 (0.28-1.38)
Sex				
Female	48/115	59/107		0.59 (0.40-0.87)
Male	43/128	99/144		0.35 (0.25-0.50)
Time to relapse after completion of 1L treatment				
≤12 months	23/49	31/50		0.46 (0.26-0.79)
>12 months	68/194	127/201		0.43 (0.32-0.58)
Cytogenetics risk‡				
High risk	26/67	48/69		0.36 (0.22-0.58)
Standard risk	65/175	106/175		0.48 (0.35-0.65)
Missing or not evaluable	0/1	4/7		NE
Extramedullary disease at baseline				
Yes	8/13	18/25		0.57 (0.24-1.34)
No	83/230	140/226		0.44 (0.34-0.58)

Hungria NEJM 2024, Mateos ASCO 2024 Abstract 7503.

DREAMM-7: OCULAR SIDE EFFECTS

Table 3. Adverse Events Reported in at Least 15% of Patients in Either Group (Safety Population).*

Event	BVd (N=242)		DVd (N=246)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	no. of patients (%)			
Any adverse event	242 (100)	230 (95)	246 (100)	192 (78)
Blood and lymphatic system disorders				
Thrombocytopenia†	167 (69)	134 (55)	122 (50)	87 (35)
Infections and infestations				
Ocular events				
Any	191 (79)	82 (34)	72 (29)	7 (3)
Blurred vision	160 (66)	53 (22)	26 (11)	2 (1)
Dry eye	123 (51)	17 (7)	17 (7)	0
Photophobia	114 (47)	5 (2)	6 (2)	0
Eye irritation	103 (43)	12 (5)	13 (5)	0
Foreign-body sensation in eye	106 (44)	8 (3)	10 (4)	0
Eye pain	77 (32)	2 (1)	8 (3)	1 (<1)
Cataract	49 (20)	17 (7)	25 (10)	6 (2)

Dose reductions (44%), delays (78%), discontinuation (9%)

> 90% patients had resolution in symptoms

No Difference in global QOL despite AE between BVd vs DVd over time

Hungria NEJM 2024, Mateos ASCO 2024 Abstract 7503.

DREAMM-8: BPD VS PVD

- Multicenter, randomized, open-label phase III trial

Stratified by prior lines of tx (1 vs 2-3 vs ≥4), prior bortezomib (yes vs no), prior anti-CD38 mAb (yes vs no)

Median follow-up: 21.8 mo (range: 0.03-39.23 mo)

Adults with MM previously treated with ≥1 line of therapy (including lenalidomide); with PD on/after most recent therapy; no prior treatment with pomalidomide or anti-BCMA–targeted therapy; not intolerant or refractory to bortezomib; ECOG PS 0-2
(N = 302)

Belantamab mafodotin + Pomalidomide + Dexamethasone (BPd), 28-day cycles
(n = 155)

Bortezomib + Pomalidomide + Dexamethasone (PVd), 21-day cycles
(n = 147)

Tx continued until PD, unacceptable toxicity, end of study, or consent withdrawal

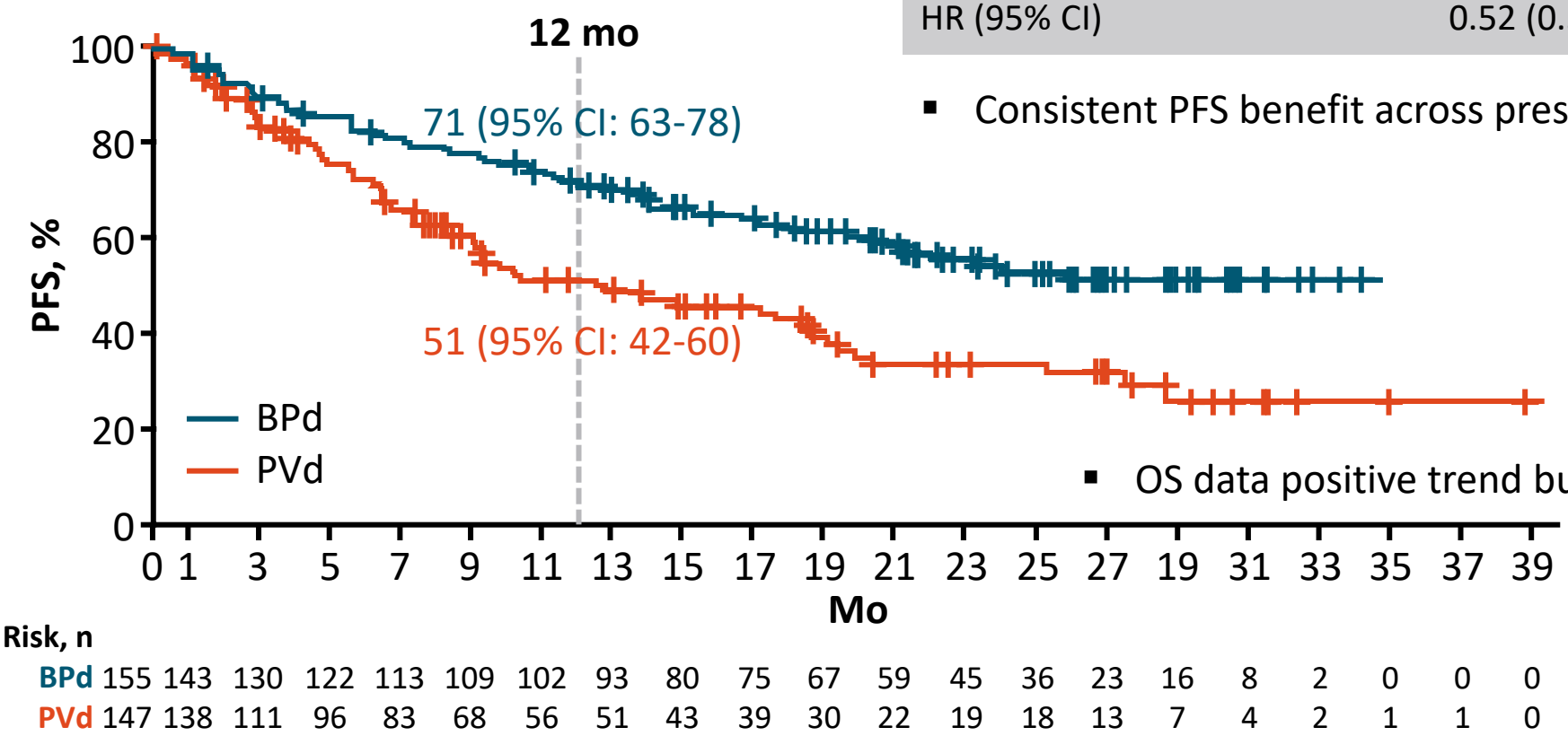
Belantamab mafodotin: 2.5 mg/kg IV Cycle 1, 1.9 mg/kg IV Cycle 2 onward.
Bortezomib: 1.3 mg/m^2 SC Days 1, 4, 8, 11 Cycles 1-8, then Days 1, 8 (21-day cycle).
Pomalidomide: 4 mg PO; in BPd regimen: Days 1-21 28-day cycle; in PVd regimen: Days 1-14 (21-day cycle).
Dexamethasone: 40 mg on Days 1, 8, 15, 22 in BPd regimen; 20 mg on day of and day after bortezomib in PVd regimen.

- **Primary endpoint:** PFS
- **Key secondary endpoints:** OS, DoR, MRD negativity, ORR, PFS2, safety, QoL

Dimpoulos. NEJM. 2024.

DREAMM-8: PFS (PRIMARY ENDPOINT)

	BPd (n = 155)	PVd (n = 147)
Patients with an event	62 (40)	80 (54)
mPFS, mo	NR	12.7
HR (95% CI)	0.52 (0.37-0.73) *P* <.001	



- Consistent PFS benefit across prespecified subgroups
- OS data positive trend but not significant

Patients at Risk, n

BPd	155	143	130	122	113	109	102	93	80	75	67	59	45	36	23	16	8	2	0	0	0
PVd	147	138	111	96	83	68	56	51	43	39	30	22	19	18	13	7	4	2	1	1	0

Dimpoulos. NEJM. 2024.

BELANTAMAB FOR RRMM: SUMMARY

1. Belantamab + bortezomib /dex showing excellent clinical efficacy with improved PFS and MRD negativity in RRMM, even in poor prognostic risk groups (DREAMM-7)
2. Unique ocular side effects although manageable with reduced frequency dosing
3. Unclear role in the early relapsed setting, still only available by EAP
   - April 2024: FDA approval for CAR-T cell therapy in early lines of therapy

Dimpoulos. NEJM. 2024, Hungria NEJM 2024, Mateos ASCO 2024 Abstract 7503

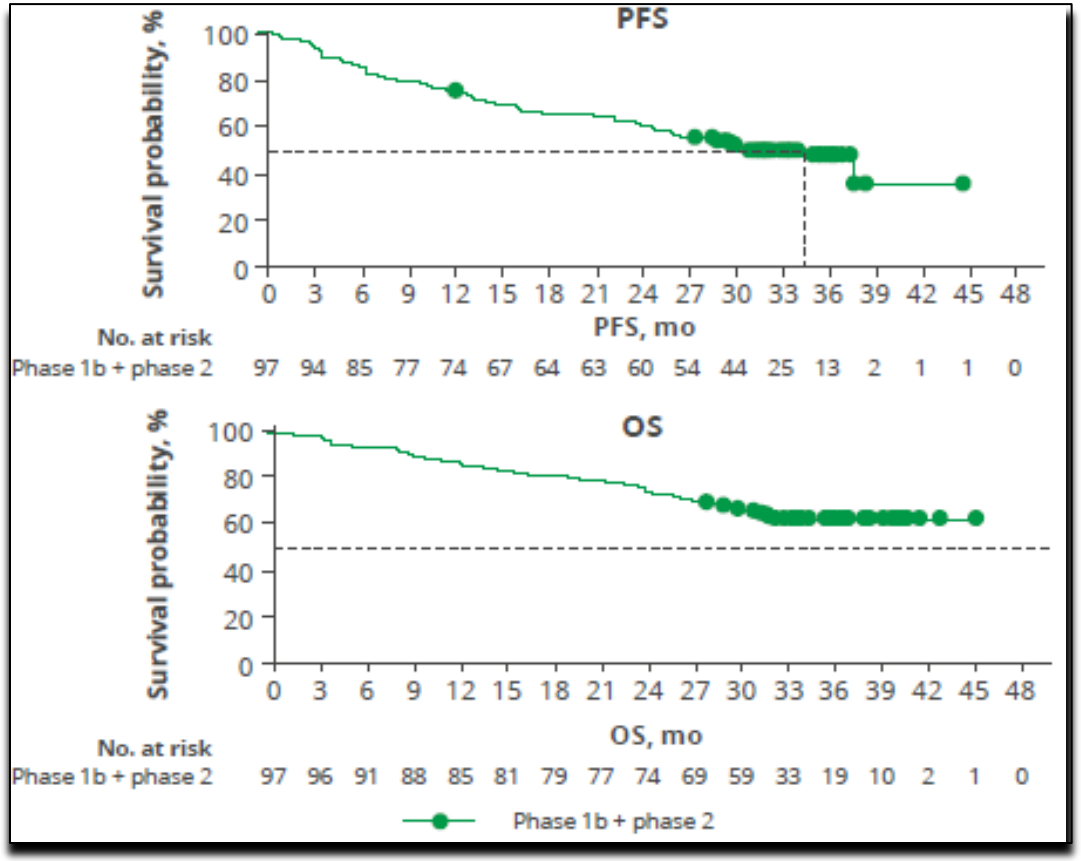
CARTITUDE-1: LONG-TERM FOLLOW-UP (MED 33 MOS.) WITH CILTA-CEL

Median 6 prior lines,
88% triple-refractory

- **ORR = 98%**
  - CR/sCR = 83%

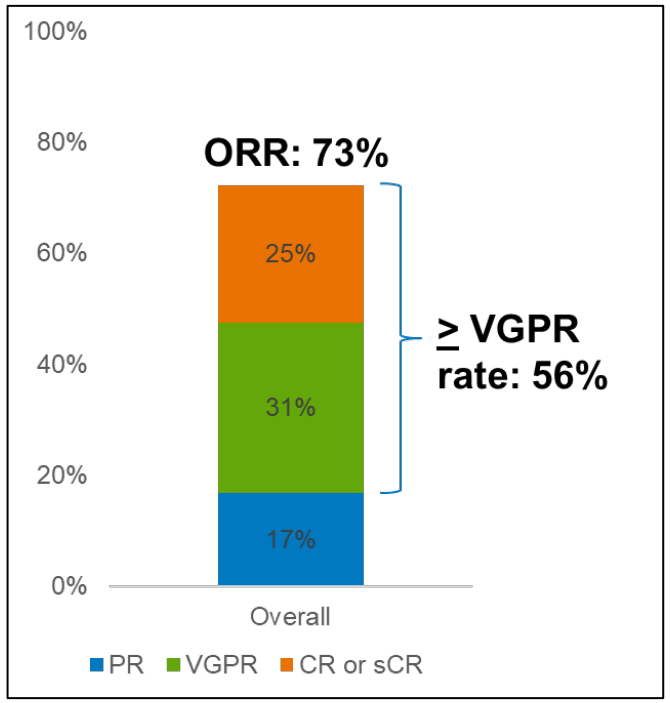
- **Median PFS = 34.9 mos.**
- **Median DOR = 33.9 mos.**
- **Median OS = not reached**

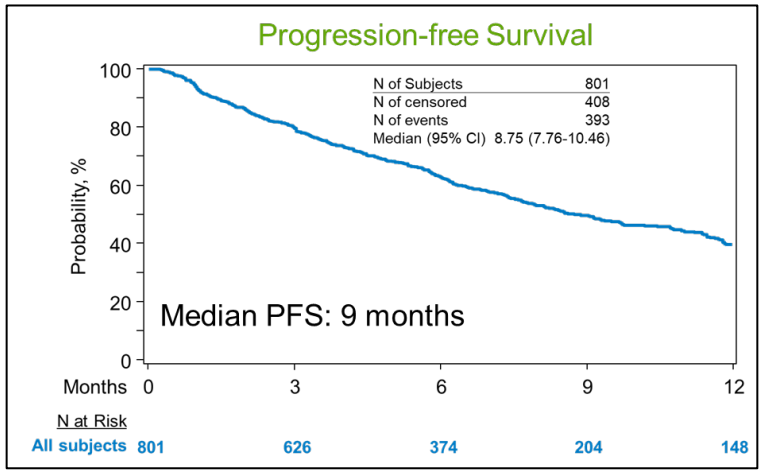
Subgroups	mPFS (95% CI), mo	30-mo PFS rate	36-mo PFS rate
All patients	34.9 (25.2–NE)	54.2%	47.5%
≥CR[a]	38.2 (34.9–NE)	66.8%	59.8%
12-mo sustained MRD negativity[b]	NR (NE–NE)	74.9%	NE
12-mo sustained MRD-negative ≥CR[b]	NR (NE–NE)	78.5%	NE

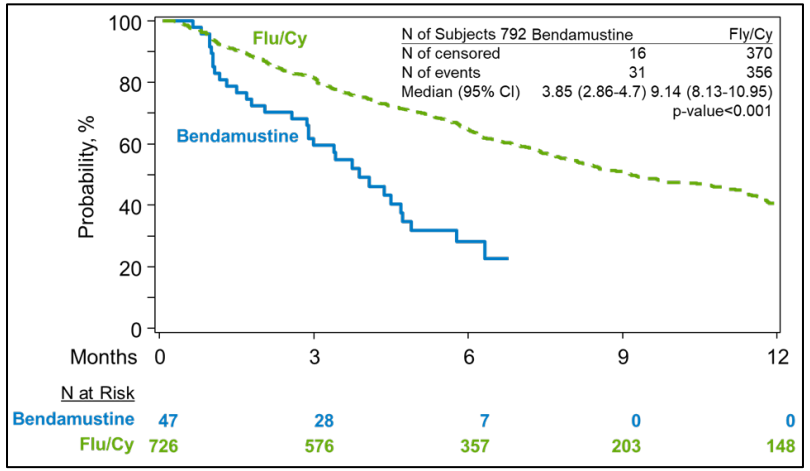


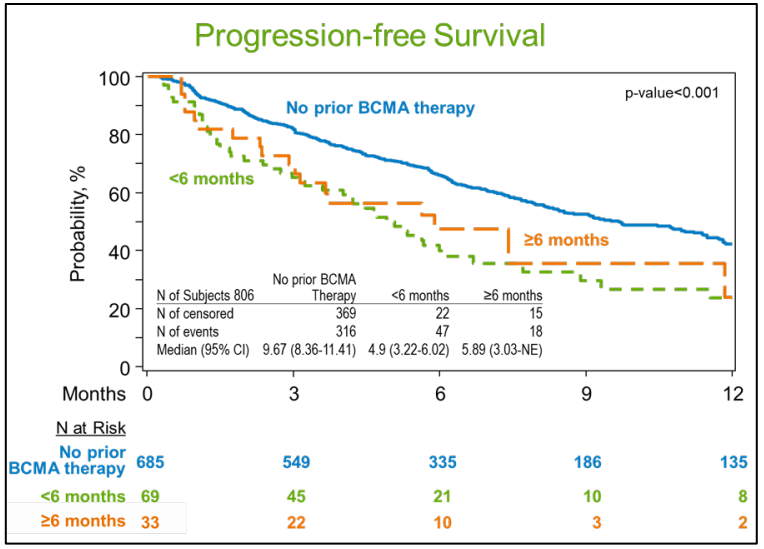
Lin et al, ASCO 2023, #8009.

IDE-CEL IN RRMM: CIBMTR REAL-WORLD COHORT (N=821)







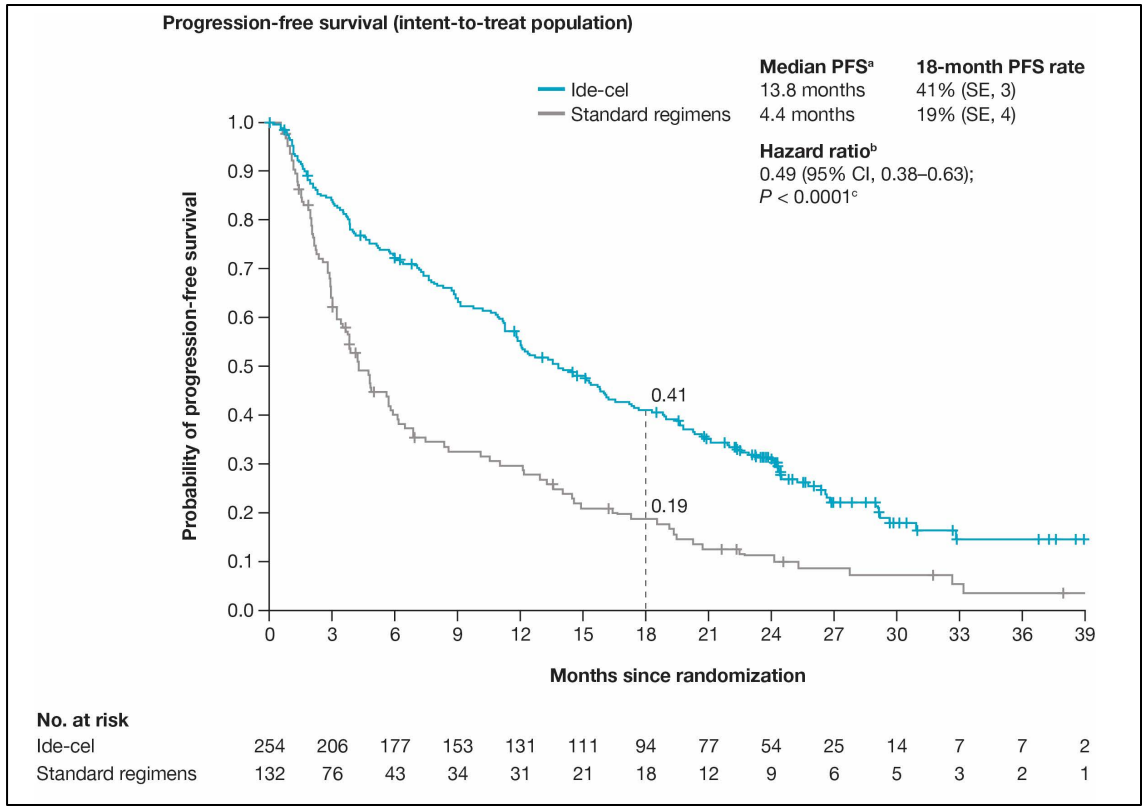


SPM (N=33)	N(%)
Basal cell/Squamous cell skin cancer	20 (61)
AML/MDS	8 (24)
Malignant Melanoma	2 (6)
Breast Cancer	1 (3)
CNS malignancy	1 (3)
Genitourinary malignancy	1 (3)

No T cell malignancies reported

Sidana et al, ASH 2023, #1027.

UPDATED KARMMA-3: IDE-CEL VS SOC IN 2-4 PRIOR LINES

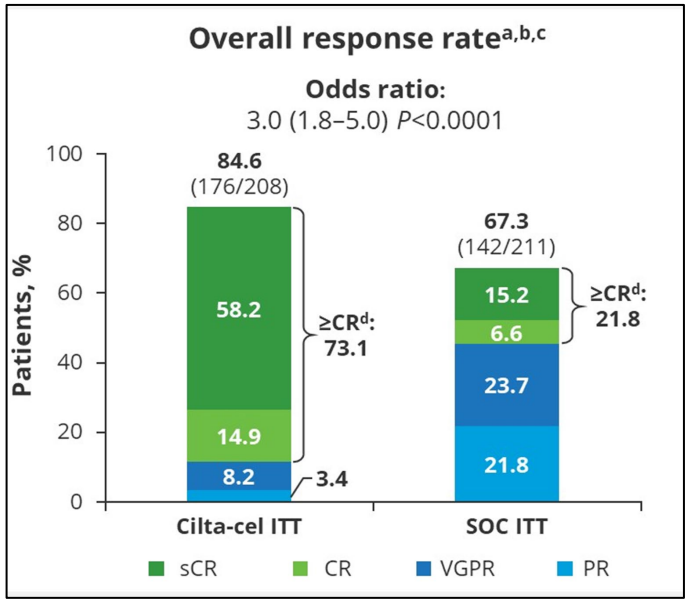


	Ide-cel (n = 254)	Standard regimens (n = 132)
ORR,[a] % (95% CI)	71.3 (65.7–76.8)	42.4 (34.0–50.9)
OR (95% CI)[b]	3.4 (2.2–5.2)	
CR rate,[c] % (95% CI)	43.7 (37.6–49.8)	5.3 (1.5–9.1)
Median DOR, months (95% CI)[d,e]	16.6 (12.1–19.6)	9.7 (5.5–16.1)
DOR rate at 18 months, % (SE)[f]	46.1 (3.8)	27.6 (6.4)
MRD negativity in patients with ≥ CR, n/N (%)[g]	57/254 (22.4)	1/132 (0.8)
95% CI	(17.3–27.6)	(0.0–2.2)
Median TTNT, months (range)[d,h]	20.9 (16.6-24.2)	7.0 (5.3-8.5)
Median EFS, months (95% CI)[d]	13.3 (11.3–15.7)	3.9 (3.0–5.3)
Median PFS2, months (95% CI)[d]	23.5 (18.4–27.9)	16.7 (12.2–20.3)[i]

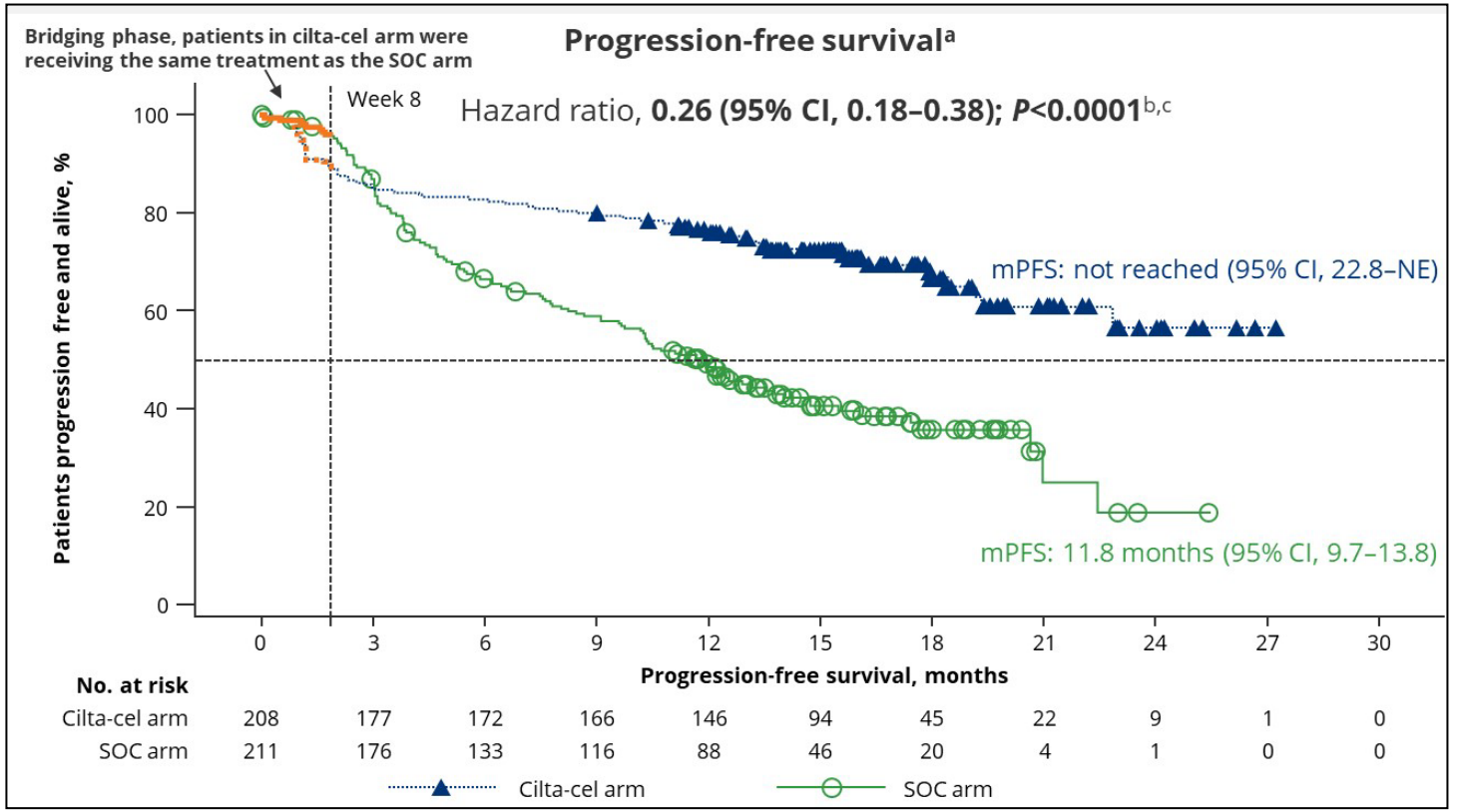
Crossover allowed to ide-cel in SOC arm (53%)

Rodriguez-Otero et al, ASH 2023, #1028.

CARTITUDE-4: CILTA-CEL VS DPD OR VPD IN 1-3 PRIOR LINES

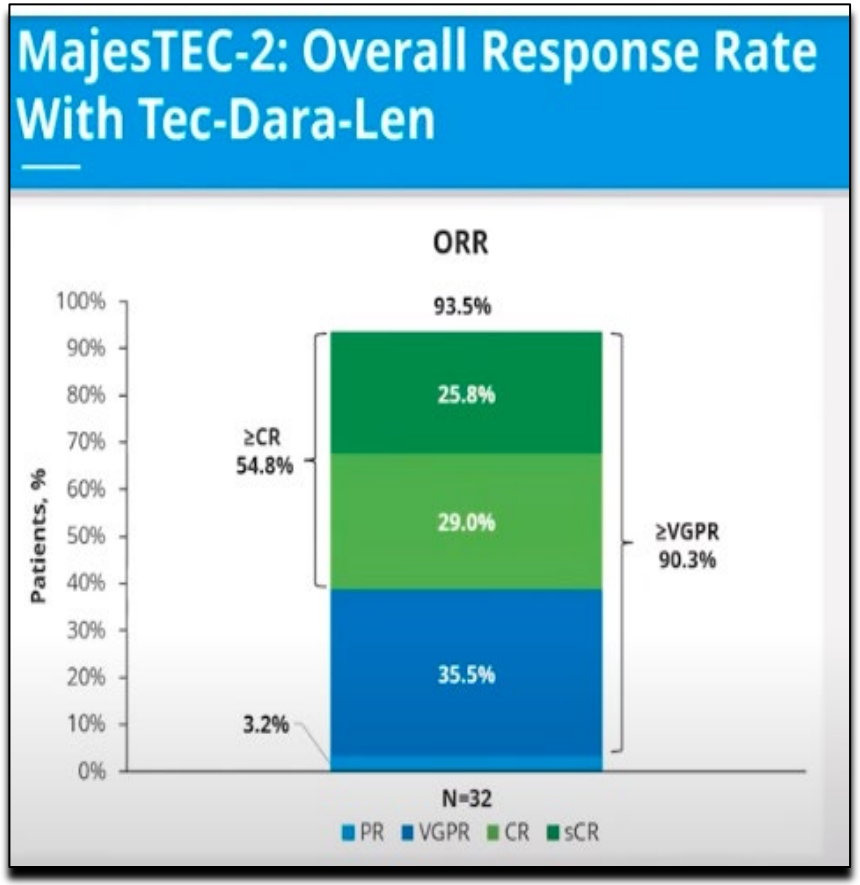


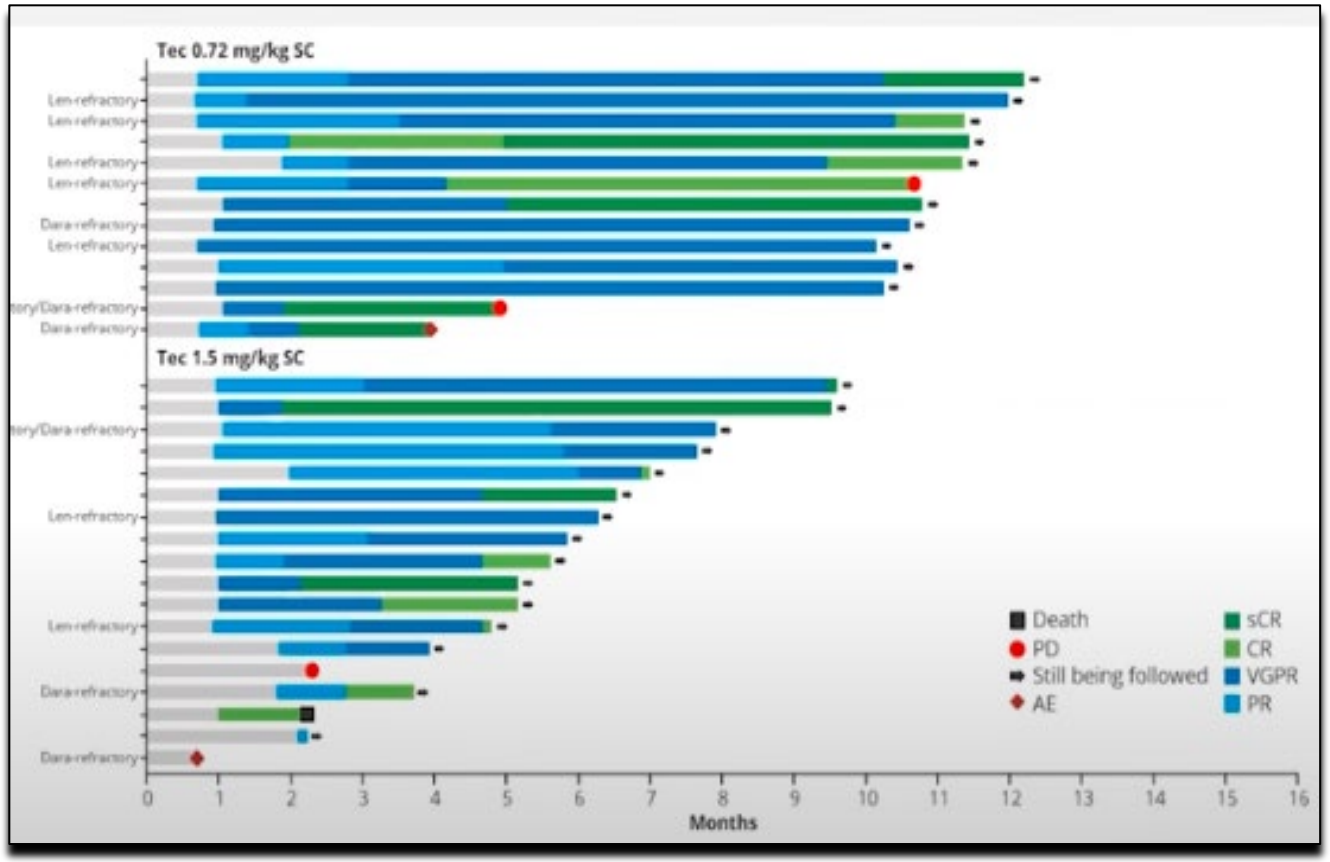
Outcome	Cilta-cel (N=208)	SOC (N=211)
12-month DOR rate, % (95% CI)	84.7 (78.1–89.4)	63.0 (54.2–70.6)
Duration of response, months median (95% CI)	NR	16.6 (12.9–NE)



Dhakal et al, ASCO 2023, #LBA106.

BCMA BISPECIFICS IN EARLIER RELAPSED MM (1-3 PRIOR LINES)





81% of responders (n=31) progression free at med f/up 8 months

Searle et al, ASH 2022, #160.

CONCLUSIONS

- Unprecedented activity of CAR T cells and Bispecific Abs in relapsed/refractory MM
  - Ide-cel and Cilta-cel (BCMA CAR T)
  - Teclistamab and Elranantamab (BCMA BsAbs)
  - Talquetamab (GPRC5D BsAb)
  - Multiple additional agents in development
- Moving to early relapse (1-3 prior lines)
  - Eventually upfront and maintenance
- Toxicities remain an issue
  - CRS and neurotox (early), Cytopenias and infections (late)
  - Watch for GPRC5D-related toxicities (skin, nails, tastebuds/tongue)
- Sequential T cell-directed therapies feasible and active
  - Optimal sequence remains unknown
  - Dual-targeted therapy approaches showing promise
- Resurrection of Balantamab mafadotin but where to put it?

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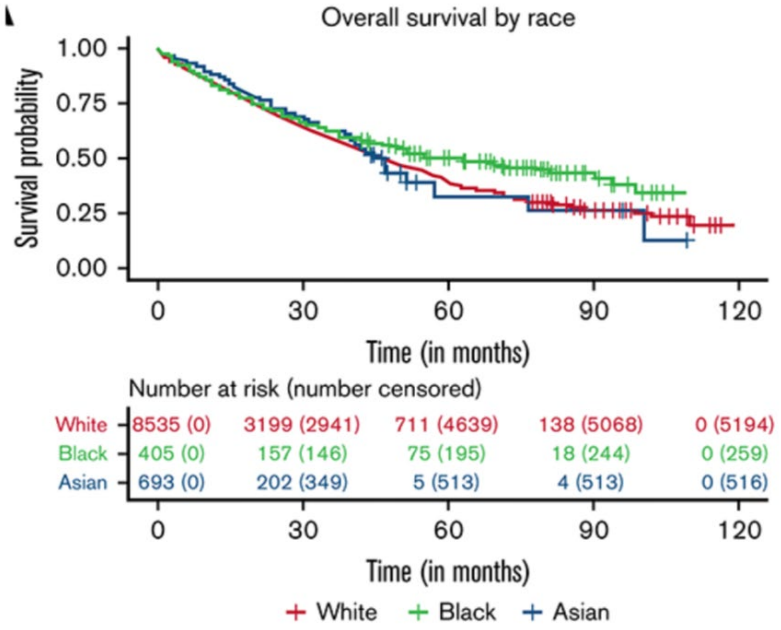
DISPARITIES IN ACCESS TO CLINICAL TRIALS

- 19 Registration Trials MM (2006-2019) - 10,157 patients

- 84% White, 7% Asian, 4% Black
- 4% Hispanic



- **Contributing Factors**
  - Financial burdens
  - Lack of caregiver support/transportation
  - Referral bias
  - Physician bias
  - Cultural beliefs/mistrust
  - Language barriers

- **Potential Solutions:**
- April 2022 FDA Industry Draft Guidance
  - Diversity Action Plans
- Expense Reimbursement
  - Industry, Lazarex iMPACT Program
- Unconscious Bias Training
- Non-Profit Advocacy and Research Efforts
  - LLS Office of Public Policy, Equity in Access Research Program
  - IMF M-Power Program

Kanapuru et al. Blood Adv. 2022.

How Do We Treat AL Amyloidsis ?

Cindy Varga, MD
Associate Professor
Department of Hematologic Oncology and Blood Disorders
Plasma Cell Disorders Division
Charlotte, NC

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BACKGROUND

- AL amyloidosis is a systemic disorder associated with a **low burden plasma cell or B cell lymphoproliferative disorder**
    - Monoclonal immunoglobulins or light chains that misfold
- Treatment is to focus on the rapid reduction/elimination of plasma cells (CR or VGPR) to achieve an organ response
- High dose melphalan/SCT was developed for AL in the 1990's and has historically been associated with the best outcomes

MEL/SCT

- ORR 80-85%
- 30-50% CR rate and 66% organ response
- Fixed number of cycles of bortezomib-based induction prior to ASCT has led to superior outcomes compared to ASCT alone
- 2/3 of patients who undergo ASCT are alive 10 years following transplant
- Transplant-related mortality is higher in patients with AL amyloidosis
  - Up to 20-30%
  - 5-10% in later years due to more meticulous selection of candidates

Gustine JN et al. Am J Hematol. (2022).

BACKGROUND

- Dose adjustments to account for organ dysfunction and to address the higher rate of toxicity in this fragile population
- **Two-thirds** of newly diagnosed patients are not eligible for ASCT
- For transplant ineligible patients, **cytoxan-bortezomib-dexamethasone**
- There is a critical need to develop **targeted agents** that more rapidly promote organ response with favorable tolerability profiles.

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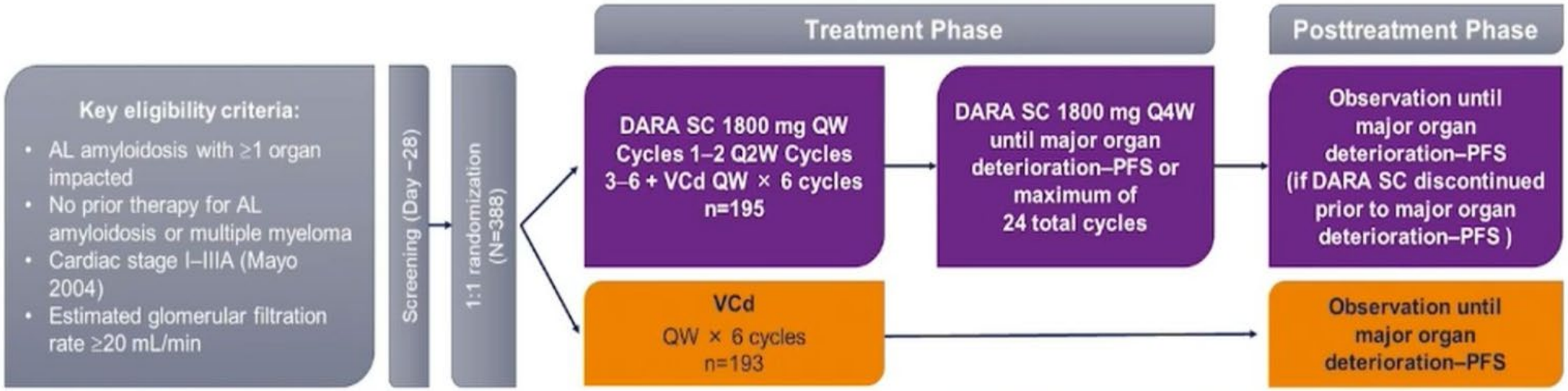
ANDROMEDA STUDY DESIGN

- **ANDROMEDA is a randomized, open-label, active-controlled, phase 3 study of D-VCd vs VCd alone in patients with newly diagnosed AL amyloidosis**



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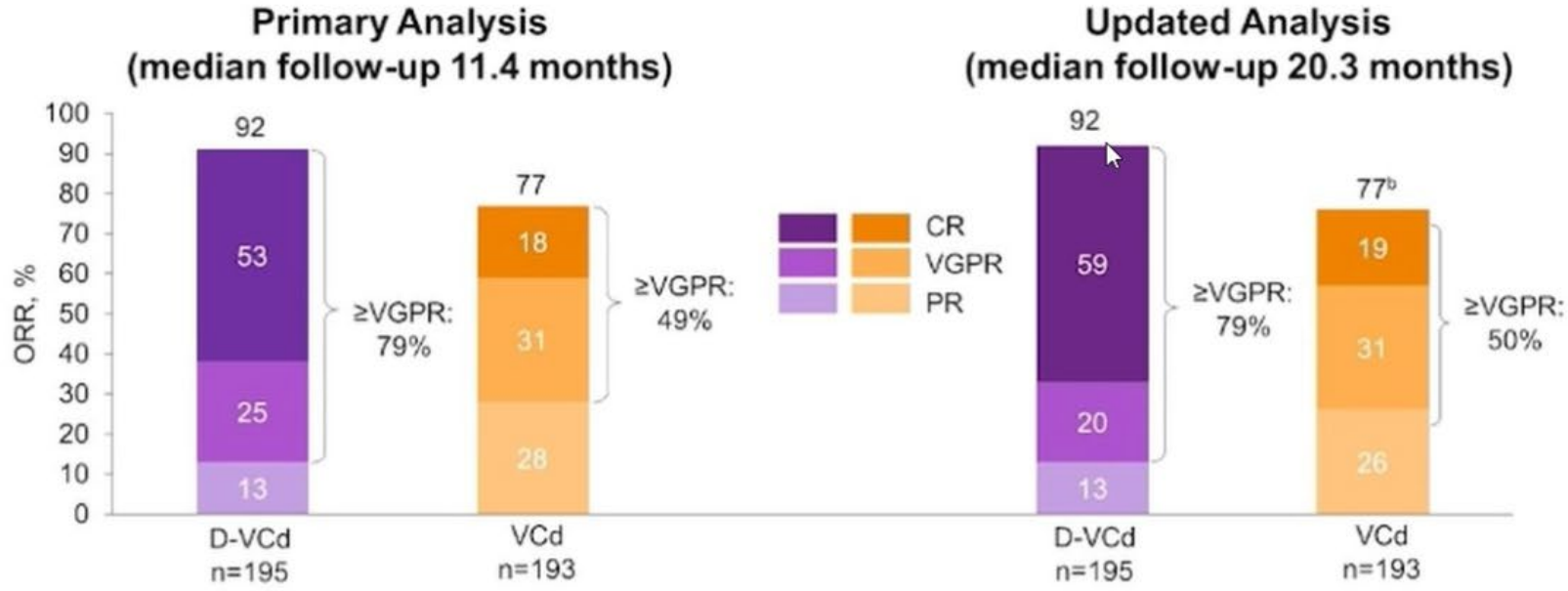
Kastritis et al. NEJM 2021.

RESULTS

Longer follow-up confirmed the significantly higher rate of hematologic overall response (92% vs 77%) and ≥VGPR (79% vs 50%) with D-VCd vs VCd

- ≥VGPR: odds ratio 3.7, 95% CI 2.4–5.9, *P*<0.0001
- Median time to ≥VGPR[a] was 0.56 months for D-VCd and 0.82 months for VCd



mong ≥VGPR responders (D-VCd, n=154; VCd, n=97); [b]Numbers have been rounded.
, confidence interval; CR, complete response; D-VCd, daratumumab/bortezomib/cyclophosphamide/dexamethasone; ORR, overall response rate; PR, partial response; VGPR, very good partial response.

CR rate in the Dara arm is 59% = nearly the same as CR rate with ASCT

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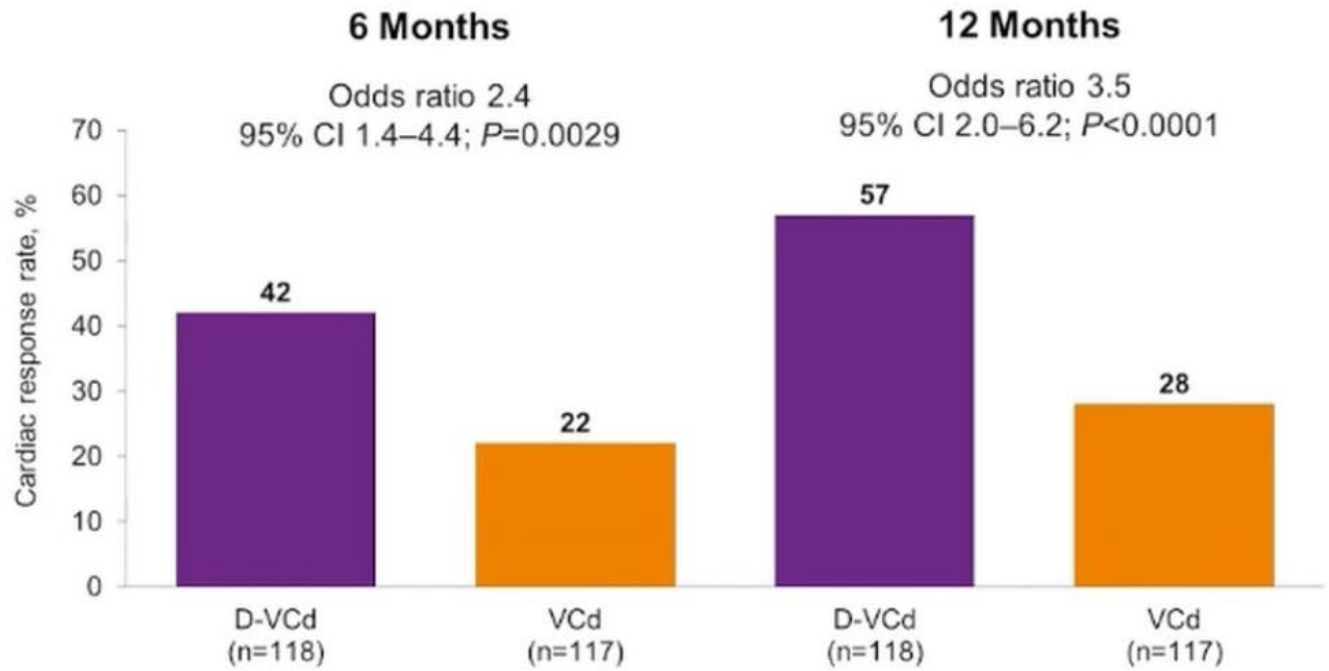
Kastritis et al. NEJM 2021.

ORGAN RESPONSES

Cardiac Response Rate at 6 and 12 Months

- Cardiac response rates improved with longer follow-up, with a doubling of response when adding DARA to VCd at 12 months



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Kastritis et al. NEJM 2021.

CONCLUSIONS

- The addition of daratumumab to VCd resulted in:
  - Deeper hematologic responses
  - Increased organ responses
  - Better outcomes compared
- CRs were achieved in >50% of patients who received Dara-VCd
  - Median time to CR was **60 days**
- Dara-VCd became the first (and only) **FDA-approved induction** regimen and is now **widely accepted as a standard of care**.

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MODERN ROLE OF ASCT?

Dara-CVd may increase # of patients eligible for ASCT

Dara-CVd may limit the role of ASCT for pts in a VGPR or better

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SWOG S2213

Comparing Dara-VCd + ASCT to Dara-VCd for People Who Have Newly Diagnosed AL Amyloidosis

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WHEN TO USE ASCT IN THE ERA OF D-CVD?

- Achieving a VGPR after 4 cycles of Dara-CVd with an organ response
  - Continue Dara-CVd vs ASCT?
- Achieving a VGPR after 4 cycles of Dara-CVd **without** an organ response
  - Continue Dara-CVd vs ASCT?
  - dFLC>20? iFLC>10?
- Not achieving a PR < 2 cycles of Dara-CVd?
  - Continue Dara-CVd vs ASCT?
- Relapse <1 year of completing Dara-CVd?
  - Restart Dara-CVd vs. ASCT?

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TREATMENT OPTIONS FOR RELAPSED/REFRACTORY AL AMYLOIDOSIS

Proteasome inhibitors	IMIDs	Alkylating agents	Antibodies → plasma cells
• *Bortezomib (Velcade)* • Ixazomib (Ninlaro) • Carfilzomib (Kyprolis)	• Lenalidomide (Revlimid) • Pomalidomide (Pomalyst) • Thalidomide (Thalomid)	• Bendamustine (Bendeka) • Melphalan (Alkeran) • Propylene glycol-free melphalan (Evomela) • *Cyclophosphamide (Cytoxan)* • ~~Melflufen (Pepaxto)~~	• *Daratumumab (Darzalex)* • Isatuximab (Sarclisa) • Elotuzumab (Empliciti)

Novel targeted therapy	Novel immunotherapy	T cell redirecting therapy	Amyloid-directed therapy
• Venetoclax (Venclexta) BCL-2 inhibitor • Selinexor (Xpovio) Blocks XPO-1, nuclear export protein	• ~~Belantamab (Belamaf)~~ Anti-BCMA antibody drug conjugate • STI 6129 Anti-CD38 antibody drug conjugate	• Teclistimab Bispecific anti-BCMA antibodies • Taquestamab anti-GPRC5D • Idecabtagene vicleucel (Abecma) anti-BCMA CAR T cell • Citacabtagene autoleucel (Carvykti) anti-BCMA CAR T cell	• NEOD001 (birtamimab) anti-LC antibody • CAEL-101 (anselamimab) anti-LC antibody

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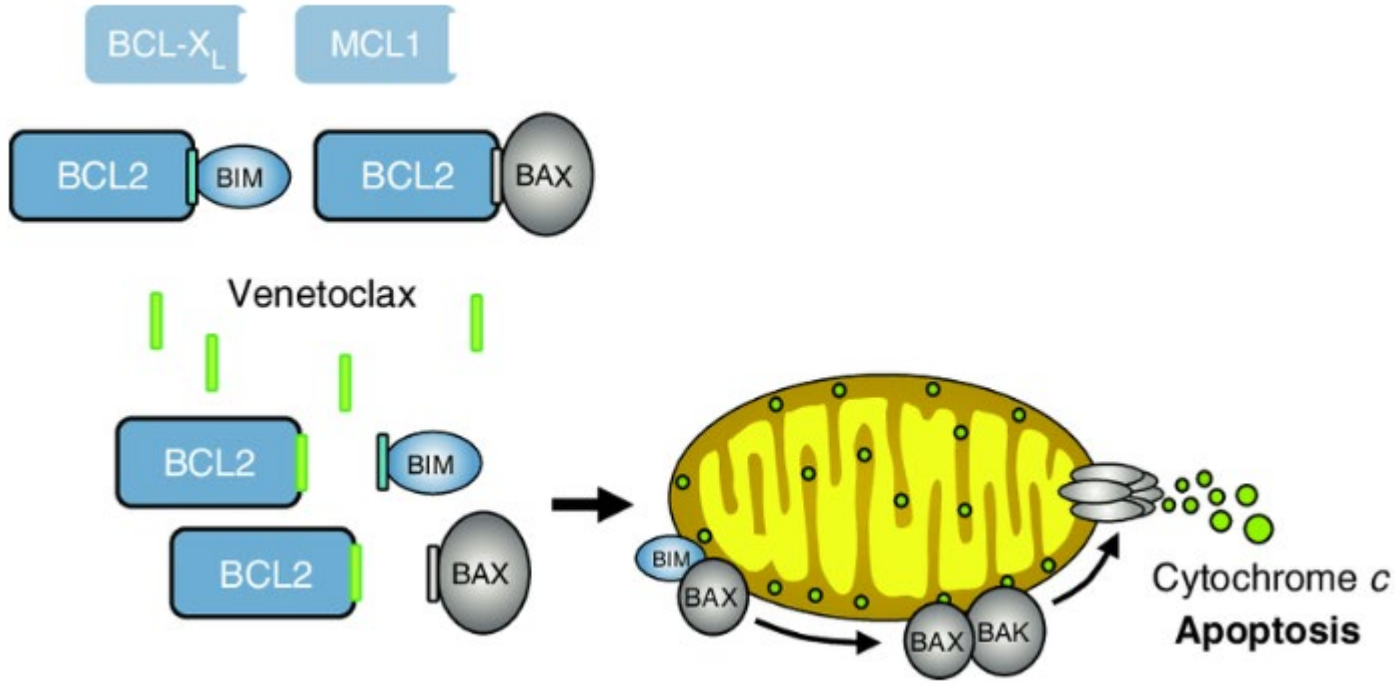
TARGETED THERAPY

40-50% of patients with AL have t (11;14) which may render patients responsive to bcl2 inhibitor (ie. venetoclax)



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VENETOCLAX

Table 4. Studies reporting on venetoclax in AL amyloidosis.

	Sidiqi 2020 BCJ [11]	Pasquer 2021 BJH [12]	Nahi * 2021 AJH [13]	Premkumar 2021 BCJ [14]	Current Cohort
Number of patients	12	10	8	43	26
% t(11;14)	92%	70%	100%	72%	88%
Median prior lines	2 (range 1–4)	Not reported (70% 3 + pervious lines)	Not reported	3	3.5 (range 1–7)
Daily doses	7–800 mg; 5–400 mg	5–400 mg; 4–200 mg; 1–100 mg	400 mg	100–800 mg	Median 400 mg, range 200–800
ORR %	88%	66.6%	71%	68%	88%
Infections	in 2 patients	Not reported	Not reported	7% grade 3+	11% G3-5
TLS	0	0	0	0	0
G3+ cytopenias	Not reported	1 patient (10%) with anemia and grade 3 thrombocytopenia	Not reported	9%	11% G3-4
Treatment discontinuation due to toxicity	16%	30%	Not reported	19%	8%
Death on therapy	0	5 patients (50%) died: 3 from heart failure not attributed to venetoclax, 1 from infection and 1 from an unknown cause	0	1 patient died due to sepsis and 1 due to heart failure not attributed to venetoclax	1 patient died due to infection
mDOR	Not reported	241 days	Not reported	Not reported	25 months
mPFS	Not reported	Not reported	Not reported	31 months ‡	25 months ‡
mOS	Not reported	10.5 months	Not reported	Not reached	33 months

Abbreviations: ORR—overall response rate; G—grade; TLS—tumor lysis syndrome; mDOR—median duration of response; mPFS—median progression-free survival; mOS—median overall survival. * This study reported on t(11:14) MM and AL patients. Some of the data in the table are missing, as the study did not report on all variables in AL patients separately. ‡ In Premkumar et al. [14], progression-free survival was reported; in the current study, event-free survival is reported (capturing hematological progression/change in therapy for inadequate response/death as events).

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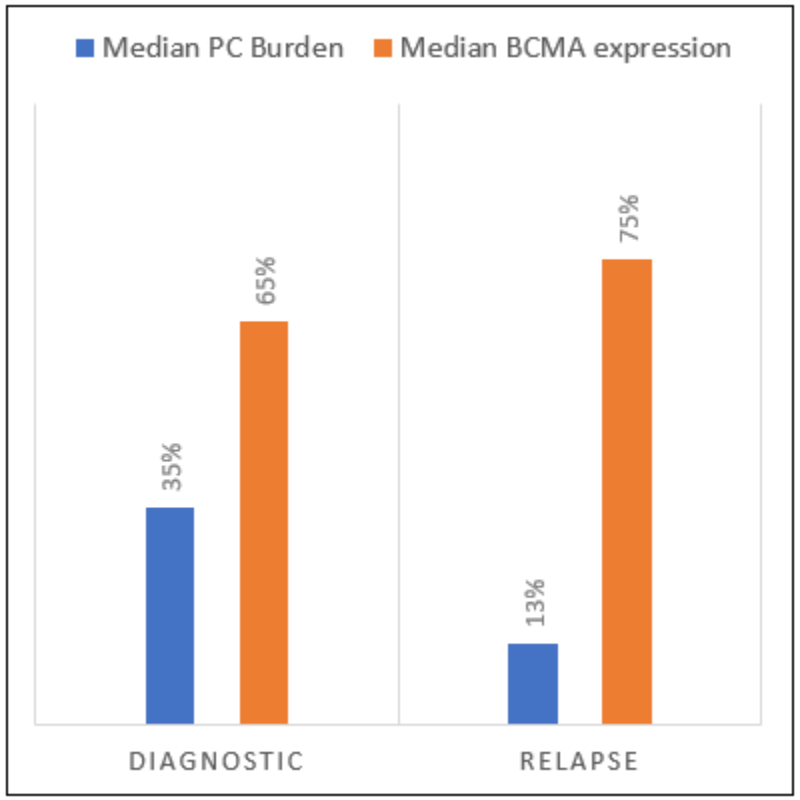
Lebel et al. Cancers 2023

BCMA

- BCMA is expressed on the surface of amyloidogenic plasma cells
- Present at diagnosis AND retained at relapse



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Bal et al. ASH 2019.

FIRST REPORT OF CAR T TREATMENT IN AL AMYLOIDOSIS AND RRMM

- 60F IgA lambda MM (R-ISS 2) w anemia + bone dz

First line (9/2014)

VRd x 6 → Bu/MEL ASCT → VRd x 2 → sCR
Len/Ixa/dex maintenance x 19 months

↓

serologic progression + anemia

Second line (10/2017)

Dara-carfilzomib/dex x 14 → VGPR
Dara maintenance x 10 months

↓

serologic progression w/o MM end organ damage
Low albumin+ non-specific proteinuria (2.6g/24hrs)

Fat pad biopsy → Congo red +
Renal biopsy → Amyloid deposits, Congo red +
Bone marrow with 23% lambda-restricted PCs

Oliver-Caldes et al. 2021.

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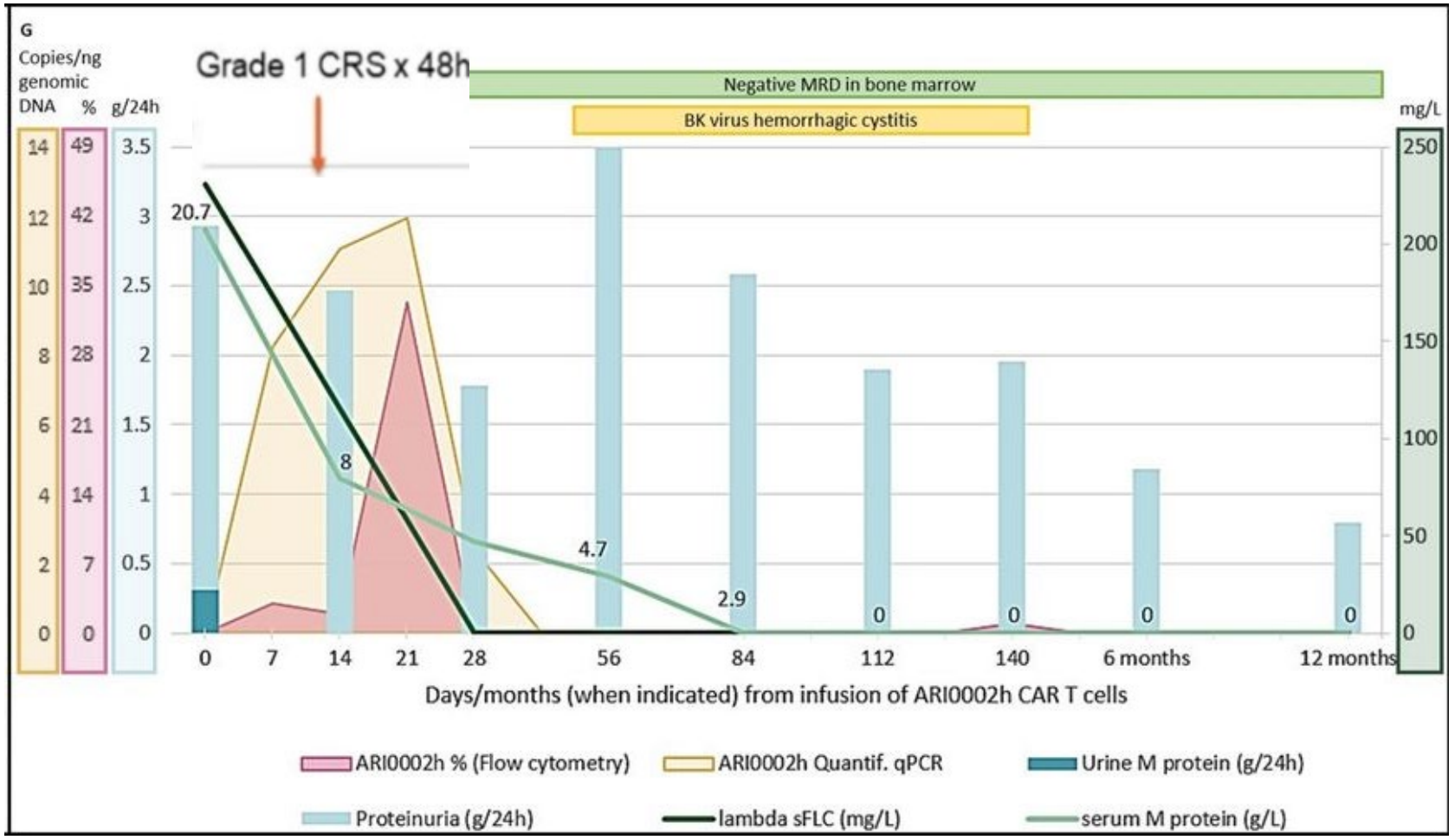
CLINICAL + LABORATORY DATA FOLLOWING INFUSION OF ARI0002H*

*ARI0002h- academic 2nd gen humanized 41BB lentiviral CART targeting BCMA



- **3y post CART, remains in MRD neg CR**
- **<500mg/24h proteinuria**

Oliver-Caldes et al. J Immunother Cancer 2021.

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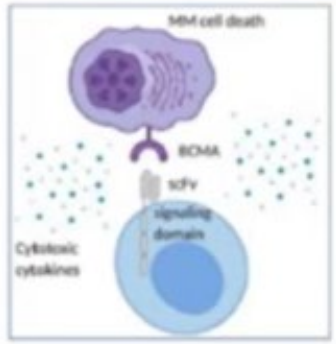
Feasibility of a novel academic BCMA-CART (HBI0101) for the treatment of relapsed and refractory amyloidosis



Dr. Moshe Gatt

ISA meeting, Sept. 2022

Moshe E. Gatt, Shlomit Kfir-Erenfeld, Nathalie Asherie, Sigal Grisariu, Batia Avni, Eran Zimran, Miri Assayag, Tatyana Dubnikov Sharon, Marjorie Pick, Eyal Lebel, Adir Shaulov, Yael C. Cohen, Irit Avivi, Cyrille J. Cohen, Polina Stepensky

Department of Hematology, and Department of Bone Marrow Transplantation and Cancer Immunotherapy

Hadassah Medical Center, Faculty of Medicine, Hebrew University of Jerusalem.

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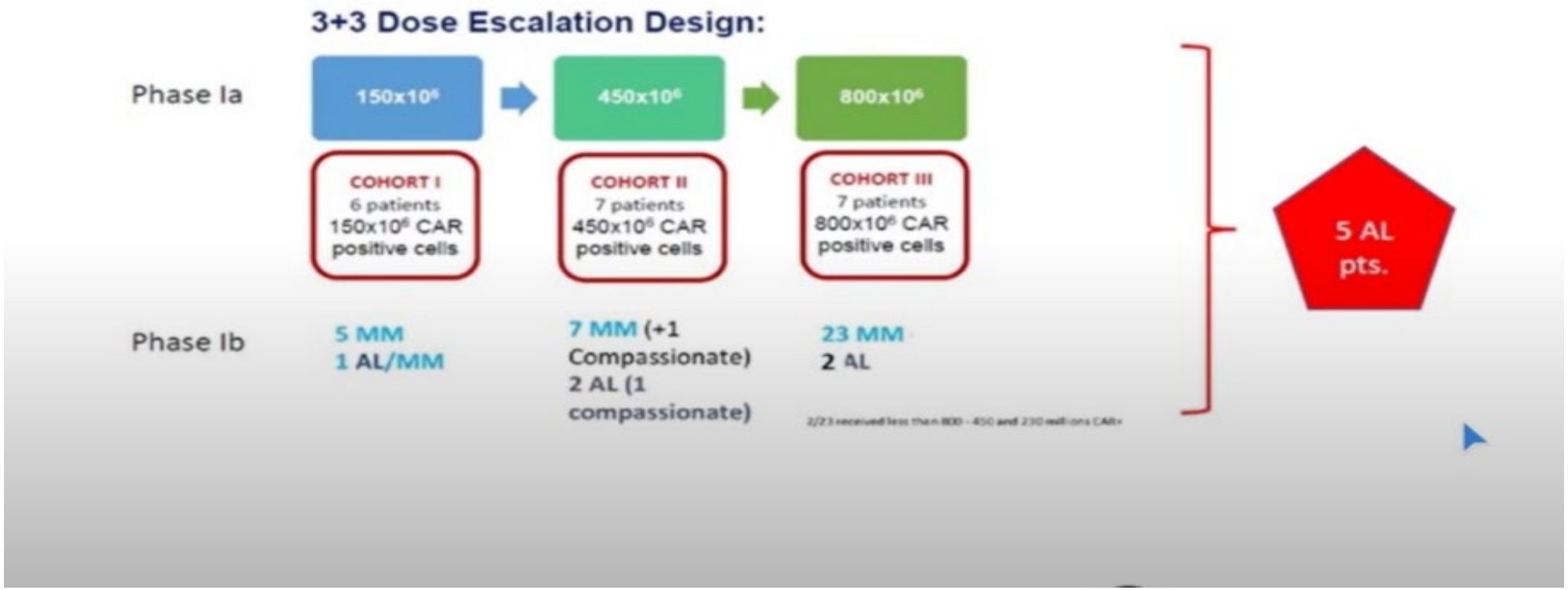
PHASE 1 CLINICAL TRIAL OF HBI0101

- ✓ A Phase Ia\Ib Dose Escalation and Safety Study of HBI0101 BCMA.CART in Relapsed Refractory Multiple Myeloma and AL amyloidosis Patients
- ✓ The Ph-Ia was designed as a dose-escalation 3X3 protocol. 20 pts.
- ✓ The Ph-Ib is ongoing at 800 $X10^6$ cells



Kfir-Erenfeld et al. Clin Cancer Res 2022.

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PATIENTS' BASELINE CHARACTERSITCS

	Patient 1*	Patient 2	Patient 3	Patient 4** (compassionate)	Patient 5
Age	64	58	**82**	63	64
Gender	Male	Female	Male	Male	Male
Involved FLC (mg/L)	155	183	87	560	71
dFLC (mg/L)	143	177	50	550	51
BMPCs (%)	3	15	1	15	1
FISH cytogenetics	T11:14	T14:16 1Q+	14Q- NOS	T11:14	T11:14
Organ involvement	**Cardiac**, Renal, Autonomic	**Cardiac**, Renal, **Hepatic**	Renal, GI	**Cardiac**, Hepatic, Lung, Soft tissue, Autonomic	**Cardiac**, Soft tissue, PNS
NYHA stage	**3**	**4**	1	**3**	2
ProBNP (pg/ml)	**7500**	2008	119	2773	731
Trop T (ng/L)	60	60	8	78	18.3
Creatinine (mmol\L)	80	72	110	100	82
Albuminuria (g/24h)	0.3	0.3	**2.4**	0.1	0.1
ALKP (u/L)	45	218	84	140	84
MAYO stage	3a	3a	1	3a	2
ECOG PS	0	2	0	0	1

*MM
** MDS

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RESULTS –SAFETY

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
CAR+ cells infused (x10^6)	150	450	800	450	800
Adverse events of interest					
CRS	No	Yes	Yes	Yes	Yes
CRS grade		2	**3**	**3**	1
Time to onset (days)		2	3	1	2
CRS duration (days)		2	**4**	1	1
Tocilizumab use (number of doses)	0	1	**3**	1	1
Steroids use	No	No	Yes	No	No
Vasopressor use	No	No	Yes	No	No
High flow oxygen use	No	No	**Yes**	**Yes**	No
ICANs	No	No	No	No	No

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RESULTS - EFFICACY

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
CAR+ cells infused ($x10^6$)	150	450	800	450	800
Best hematologic response	CR	CR	CR	CR	CR
iFLC at best response (mg/L)	0.6	0.9	1	7	0.4
dFLC at best response (mg/L)	0	0	0	1.4	0.2
MRD (10^{-5}) negativity at Day 30 , Day 180	Yes, Yes	Yes, Yes	Yes	Yes	Yes
Time to best confirmed response (days)	27	57	17	17	30
Follow up (months)	10.5	12	10	8	1.5
DOR	9.5 (died in CR)	10	9 (ongoing)	4	NA
Organ response	Yes	Yes	Yes	Yes	NA
Delta response (% reduction) proBNP (pg/ml)/ Albuminuria (g/d)	-4800 (-64%) / NA	-1295 (-64%) / NA	NA / -3.03 (-100%)	-1872 (-68%) / NA	NA / NA
NYHA change	III to II	IV to II	NA	III to II	NA
Additional organ responses Alk Phos (u/l)	NA	Hepatic: 280 to 150 / No ascites	No edema	NA	NA

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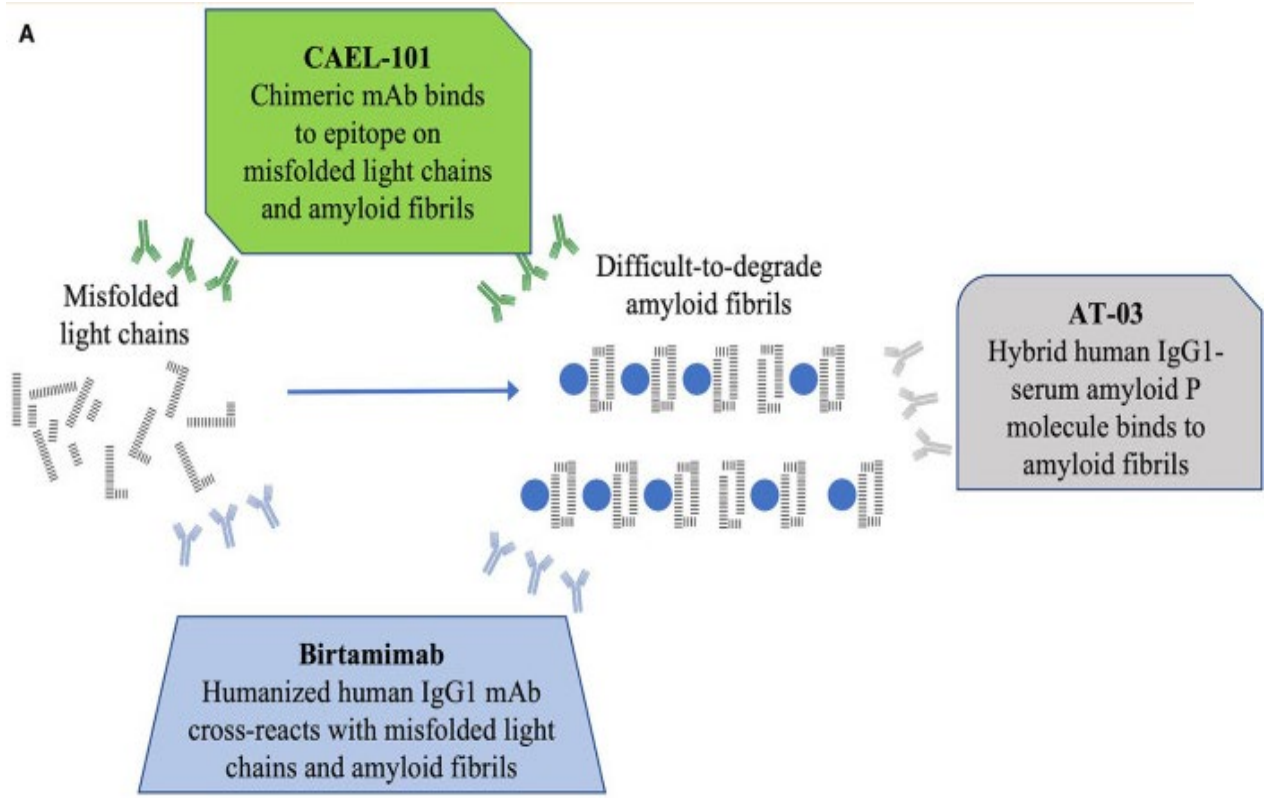
BISPECIFIC ANTIBODIES

Trials using Teclistamab, Elranatanamb, ABBV 383 are in development in AL amyloidosis

FIBRIL-DIRECTED THERAPIES

- **NEOD001(Birtamimab):** humanized IgG1 mAb that cross reacts with misfolded LCs and amyloid fibrils
- **CAEL101 (Anselamimab):** chimeric mAb binds to epitope on misfolded LCs and fibrils
- **AT-03:** Fusion protein comprising serum amyloid protein (SAP) linked to a single-chain human IgG1 Fc domain



Dima et al. Clinical Reviews 2023.

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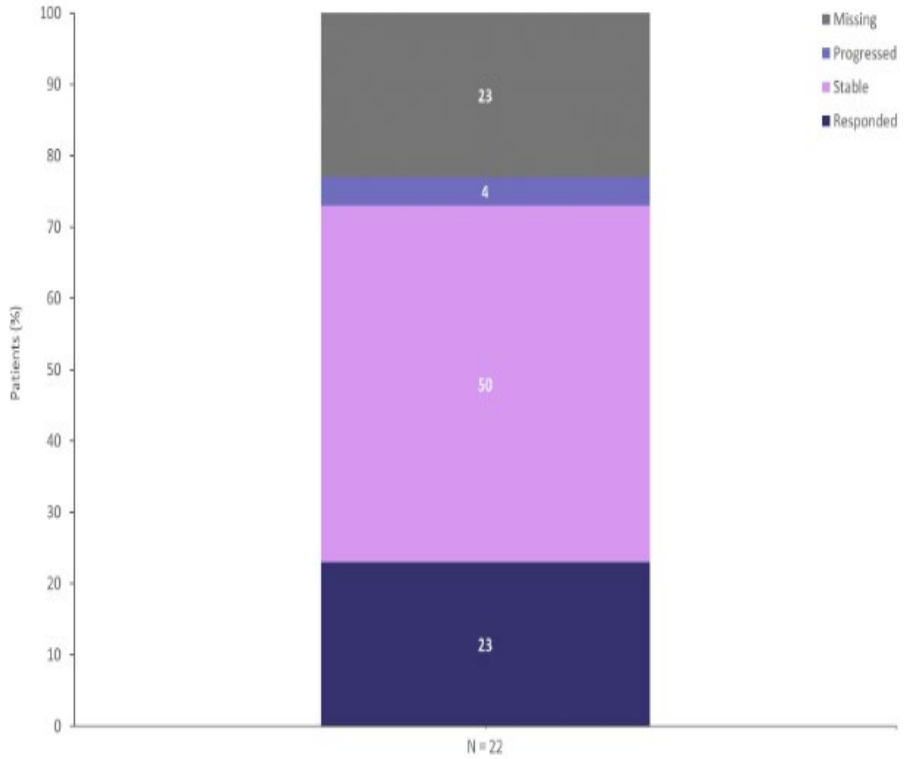
ANTI-AMYLOID FIBRILS

- **CAEL101**
  - Phase I/II trial evaluating the safety and tolerability of CAEL-101 in 25 patients with AL amyloidosis.
    - PART A: CAEL 101 + CYBORD
    - PART B: CAEL 101 + Dara CYBORD
  - Cardiac response 23%
  - Well tolerated, no evidence of organ toxicity. Most TEAEs were mild or moderate in severity

Figure 1. Response rates in patients receiving CAEL-101 therapy after 18 months*



*Adapted from Liedtke.[1]

Liedtke et al. EHA 2023.

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ANTI-AMYLOID FIBRILS

CAEL101

- Phase III trial in Stage IIIA/Stage IIIB cardiac AL amyloidosis
  - Ongoing trial

CONCLUSIONS

- The addition of Daratumumab to frontline setting has completely changed the treatment algorithm in AL amyloidosis
    - May decrease or increase the use of ASCT which is currently being studied
- Immunotherapies such as CART and BsAbs look very promising
    - These have unique toxicities
- Anti-fibrillar therapies may complement immunotherapies/chemotherapy

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Secondary Malignancies and CAR T

Cindy Varga, MD
Associate Professor
Department of Hematologic Oncology and Blood Disorders
Plasma Cell Disorders Division
Charlotte, NC

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FOOD AND DRUG ASSOCIATION

- **October 31, 2023**
  - FDA aware of 22 cases of T cell cancers after tx with 5 of 6 CAR T products
  - In 3/22 cases for which genetic sequencing has been performed, **the CAR transgene has been detected in the malignant clone**
  - May present as soon as weeks following infusion
- **November 2023**
  - FDA issued a warning about a risk of secondary cancers **— particularly T cell malignancies including chimeric antigen receptor CAR-positive lymphoma—** that may be associated with BCMA- or CD19-directed autologous CAR T cell immunotherapies

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FOOD AND DRUG ASSOCIATION

- **January 2024**
  - The agency formed label changes for each of the **6 approved CAR T-cell** products
  - **Boxed warning** revisions were made to indicate the risk of developing secondary T-cell malignancies following treatment

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BLOOD JOURNAL- MARCH 2024

- FDA Adverse Event Reporting System (FEARS) reported on secondary primary malignancies (SPMs) in an issue of **Blood Journal**
- The study authors analyzed ***12,394*** unique CAR T AE reports
  - 536 (**4.3%**) secondary primary malignancies (SPMs) were identified
- **Leukemias** made up **61.2%** (n = 333/536) of the SPMs and **2.7%** of all CART AE reports (n = 333/12,394)
  - Myelodysplastic syndromes made up 38.8%, and acute myeloid leukemia made up 19.8%

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Elsallab M et al. *Blood*. 2024. doi.10.1182/blood.2024024166.

BLOOD JOURNAL- MARCH 2024

- **Skin neoplasms** were the second most common
  - 10.1% of patients and 0.4% of all CAR T reports
    - non-melanoma skin neoplasms (7.8%), and skin melanomas (2.2%)

- In 3.2% of reports, **T-cell NHLs** were identified:
  - 12 large T-cell lymphomas, 3 peripheral T-cell lymphoma, 1 angioimmunoblastic T-cell lymphoma, 1 enteropathy-associated T-cell lymphoma

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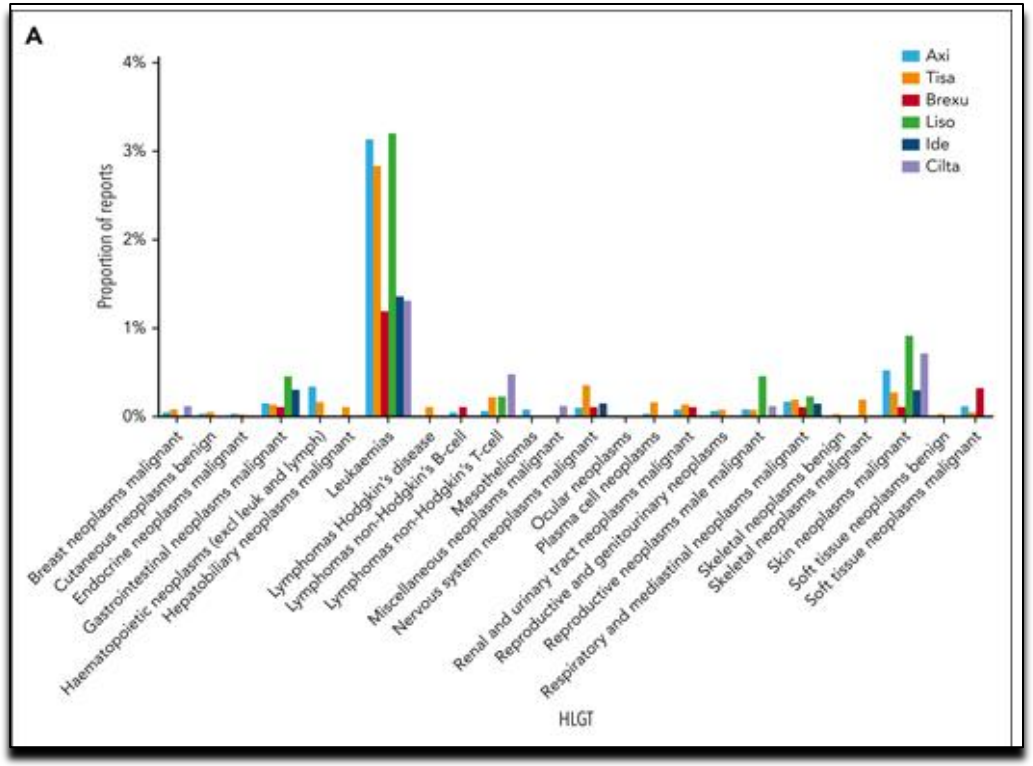
Elsallab M et al. *Blood*. 2024. doi.10.1182/blood.2024024166.

MDS/AML

- Reporting odds ratio (ROR) **MDS:**
  - Axi-cel (ROR, 3.5; 95% CI, 2.9-4.2)
  - Tisa-cel (ROR, 1.3; 95% CI, 1.0-1.8)
  - Liso-cel (ROR, 4.6; 95% CI, 2.4-8.5)
  - **Ide-cel (ROR, 2,8; 95% CI, 1.2-6.7)**
  - **Cilta-cel (ROR, 6.7; 95% CI, 3.3-13.5)**
- Reporting odds ratio (ROR) **AML**
  - Tisa-cel (ROR, 1.5; 95% CI, 1.2-2.0)
  - **Cilta-cel (ROR, 4.1; 95% CI, 1.3-2.8)**



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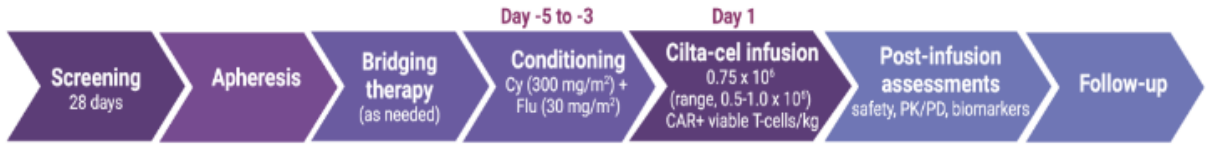
Elsallab M et al. *Blood*. 2024. doi.10.1182/blood.2024024166.

CARTITUDE-1: LATE RELAPSE

- After median follow-up of 33.4 months, a total of **26 Secondary Primary Malignancies (SPMs) (26%)** were reported out of 98 study participants
  - **Hematologic (n=10)**
    - 7 MDS, 3 AML, 1 B cell lymphoma
  - **Skin cancers (n=8)**
    - 4 BCC, 3 SCC, 2 invasive melanoma
  - Other (n=8)

Figure 1. CARTITUDE-1 study design[1]



CAR, chimeric antigen receptor; Cy, cyclophosphamide; Flu, fludarabine; PD, pharmacodynamics; PK, pharmacokinetics.

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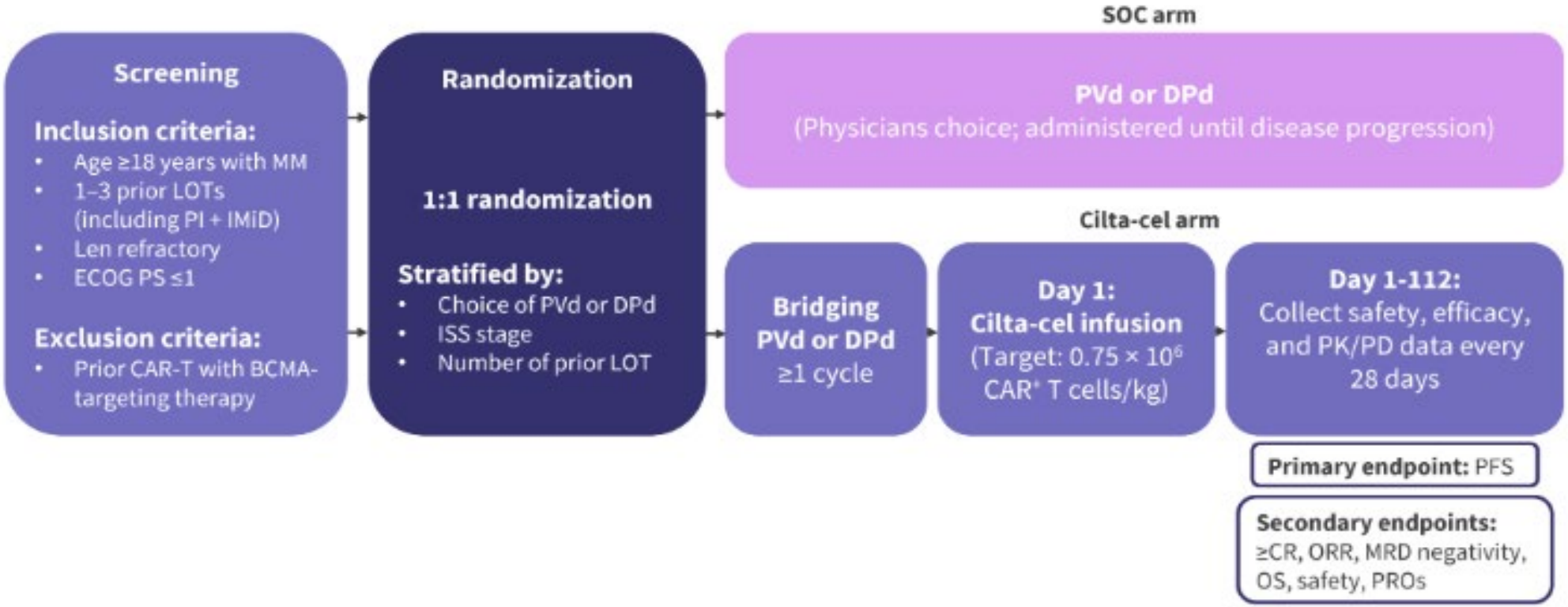
Berdeja et al. Lancet. 2021.

CARTITUDE-4 – EARLY RELAPSE

Figure 1. Study design*



San Miguel et al. *NEJM* 2023.

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CARTITUDE-4: SPMS

After a F/U of 15.9 months…

Supplemental Table 6. Second primary malignancies after treatment with cilta-cel or standard care (safety population)

	Cilta-cel (n=208)	Standard care (n=208)
Patients with second primary malignancies	9 (4.3)	14 (6.7)
Cutaneous/noninvasive malignancies	5 (2.4)	10 (4.8)
Basal cell carcinoma	2 (1.0)	7 (3.4)
Bowen disease	0	2 (1.0)
Lip squamous cell carcinoma	0	1 (0.5)
Malignant melanoma	1 (0.5)	0
Malignant melanoma in situ	1 (0.5)	0
Squamous cell carcinoma of skin	2 (1.0)	4 (1.9)
Hematologic malignancies	3 (1.4)	0
Acute myeloid leukemia	1 (0.5)	0
Myelodysplastic syndrome	1 (0.5)[a]	0
Peripheral T-cell lymphoma	1 (0.5)	0
Noncutaneous/invasive malignancies	1 (0.5)	4 (1.9)
Angiosarcoma	1 (0.5)	0
Invasive lobular breast carcinoma	0	1 (0.5)
Pleomorphic malignant fibrous histiocytoma	0	1 (0.5)
Renal cell carcinoma	0	1 (0.5)
Tonsil cancer	0	1 (0.5)

[a]At study entry, patient had essential thrombocythemia.

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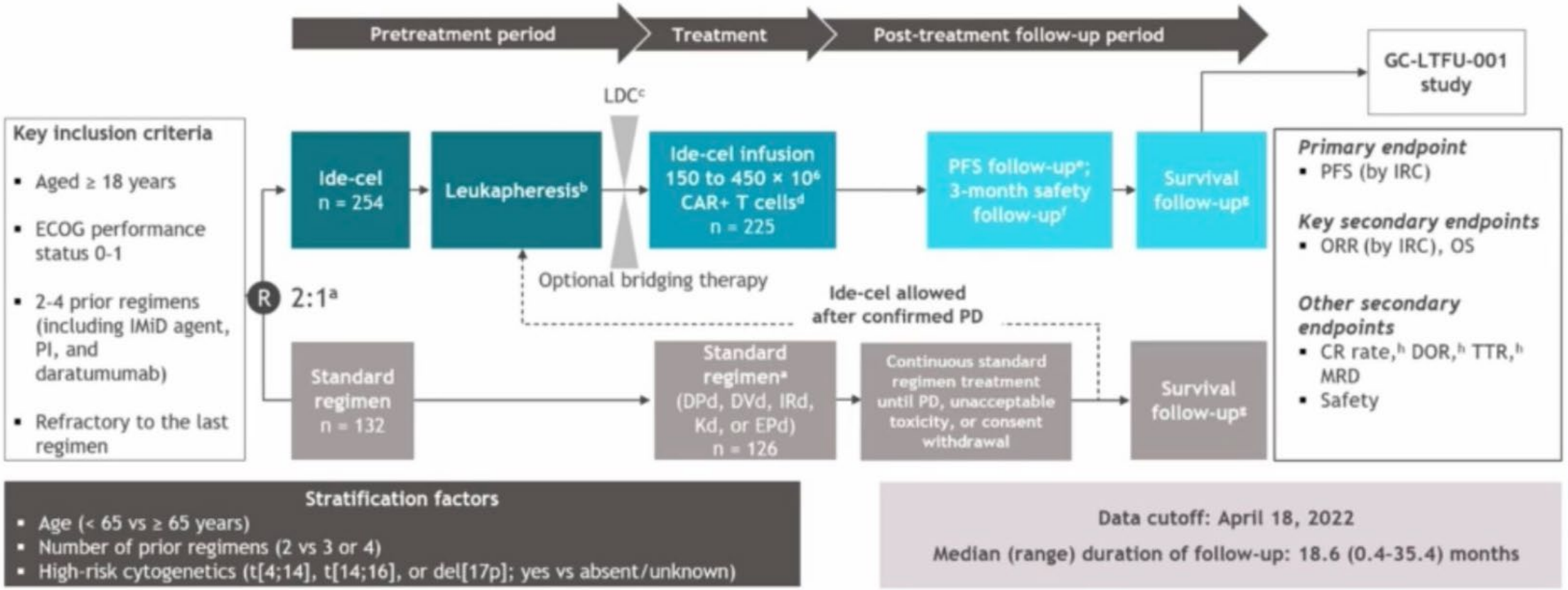
San Miguel et al. *NEJM* 2023

KARMMA-3



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Rodriguez-Otero et al. *NEJM* 2023

KARMMA-3

Table S11. Second Primary Malignancy (Safety Population).

Second primary malignancy category Second primary malignancy subcategory Preferred term	Ide-cel (n=225)	Standard regimens* (n=126)
	Patients — no. (%)	
Any second primary malignancy	13 (6)	5 (4)
Invasive second primary malignancy	9 (4)	3 (2)
Hematological malignancy	3 (1)	0
Myelodysplastic syndrome	2 (1)	0
Acute myeloid leukemia	1 (<1)	0
Solid tumor	6 (3)	3 (2)
Malignant melanoma	2 (1)	0
Breast cancer (of bilateral origin)	1 (<1)	0
Breast cancer	1 (<1)	0
Rectal adenocarcinoma	1 (<1)	0
Small intestine adenocarcinoma	1 (<1)	0
Gastrointestinal stromal tumor	0	1 (1)
Lentigo maligna	0	1 (1)
Bronchial carcinoma	0	1 (1)

The median time to onset of myeloid neoplasm from ide-cel infusion 338 days (range 277 to 794).

San Miguel et al. *NEJM* 2023.

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PATHOPHYSIOLOGY FOR SPMS?

- Is it the CAR-T itself or the immunosuppressive microenvironment that participates in the **malignant clonal evolution?**

- Insertional oncogenesis due to insertion of a viral vector near an oncogene?

STANFORD STUDY

- Study looked at over 700 patients treated with CAR T at Stanford Health Care
  - SPMs around 6.5% in the three years after therapy
  - In the case of a fatal secondary T-cell cancer, researchers attributed it to the **immunosuppression** caused by CAR-T cell therapy, rather than the CAR-T therapy itself
    - Researches looked at **protein levels, RNA sequences and DNA from single cells** across multiple tissues and time points
      - Lymphoma was already **brewing** in their body at very low levels

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CLONAL HEMATOPOIESIS OF INDETERMINATE POTENTIAL (CHIP)

- Expansion of subclonal populations of hematopoietic cells with mutations in genes associated with myeloid malignancies in otherwise healthy people with **normal** hematologic parameters
- Affecting at least 10% of people >70 years old
- Most common mutations occur in the epigenetic modifiers ***DNMT3A*, *TET2*, and *ASXL1***
  - frequently seen in **older people and in cancer patients** who underwent chemotherapy or radiotherapy
- Risk of transformation to malignancy is approximately 0.5% to 1% per year *(=MGUS to MM)*

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CLONAL CYTOPENIA OF UNDETERMINED SIGNIFICANCE (CCUS)

- Persistent cytopenias with genetic aberrations, which do not meet the diagnostic criteria for MDS
- 75% chance of developing myelodysplastic syndromes (MDS) or a related condition within **four to five years**
- Number and size of mutations is the strongest predictor for progression to a myeloid malignancy

PREVALENCE OF CHIP IN MULTIPLE MYELOMA

Retrospective study:

- 101 MM patients, the majority exposed to > 2 years of Len
- Stored mononuclear blood samples were sent for NGS using a panel encompassing 42 gene mutations
- **Thirty patients were found to have CHIP**
  - DNMT3A (12%), TET2 (5%), and TP53 (4%)
  - 33% had > 1 mutation
- At 68 months median follow up, 13% developed subsequent malignancy/premalignant condition including MDS (3%)
- No significant difference in age, gender, duration of Len or survival in those with versus without a CHIP mutation

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Padmos et al. ASCO Conference 2020; Abstract 8542.

CHIP AT THE TIME OF ASCT IN MM

Retrospective Study:

- Sequencing of the **stem cell product** from 629 MM patients at DFCI (2003–2011) detected CHIP in 136/629 patients (21.6%).
- 3.3% of patients who received **IMiD maintenance** developed a therapy-related myeloid neoplasm (TMN).
- However, regardless of CHIP status, the use of IMiD maintenance was associated with improved PFS and OS.
- In those not receiving IMiD maintenance, CHIP is associated with decreased OS (HR:1.34, $p = 0.02$) and PFS (HR:1.45, $p < 0.001$) due to an increase in MM progression rather than from SPM.
- Hyperinflammatory phenotype induced by CHIP might contribute to MM progression?

CHIP AT TIME OF CAR T

- Two recent studies have found that the incidence of CHIP in adult patients enrolled on **CAR T trials** was 34% - 48%
  - Incidence is 5% to 10% in a similarly aged healthy population

- Three recent studies have investigated the impact of preexisting CHIP on the safety and efficacy of CAR T-cell therapy

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Uslu et al. Blood Cancer Discov 2022;3:382–4; Miller et al. Blood Advances 2021; Teipel et al Blood Advances 2022.

CHIP AT TIME OF CAR T

- Saini et al. Blood Cancer Discov 2022
  - A total of 114 large B-cell lymphoma patients treated with CD19 CAR T-cell were analyzed
  - Median age was 63
    - Somatic mutations were detected in pretreatment **peripheral blood samples** of **36.8%** of the patient population.
    - The rate of grade ≥3 ICANS was **significantly higher** in patients with CHIP.
    - **Higher toxicities** with somatic mutations in the genes **DNMT3A and TET2**
    - No differences in CAR T-cell response rates or overall survival were observed between cohorts

CHIP AT TIME OF CAR T

- Miller et al. Blood Advances 2022
  - Reported on 154 CAR T cell–treated NHL and MM patients
  - CHIP-associated genes were detected **in 48%** of the study population
  - CHIP was associated with increased rates of CRS severity AND a higher rate of complete responses.
    - Only seen in patients younger than 60 years
  - No differences in overall survival

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CHIP AT TIME OF CAR T

- Teipel et al. Blood Advances 2022
  - 34% of the study population had mutations in CHIP-associated genes, mainly in DNMT3A and TP53
  - No significant differences were observed in the occurrence and severity of CRS or ICANS
  - No difference in outcome and overall survival

UNANSWERED QUESTIONS

- Affect therapy response through CHIP-harboring engineered immune cells itself?
- Interplay with the host immune system and tumor microenvironment?
- Does the size of the CHIP clone matter?

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SUMMARY

- CHIP appears to be associated with increased severity of CRS and ICANS
- CHIP might affect T- cell programming/expansion and enhance CAR-T cell activity
- New strategies involving targeting insertion of the CAR construct to specific loci might help reduce the risk of cancers
- Benefits of CAR T cell therapies continue to outweigh the risks for the approved indications
- Patients should be monitored life-long for new malignancies

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Clinical Use of MRD Testing in Myeloma

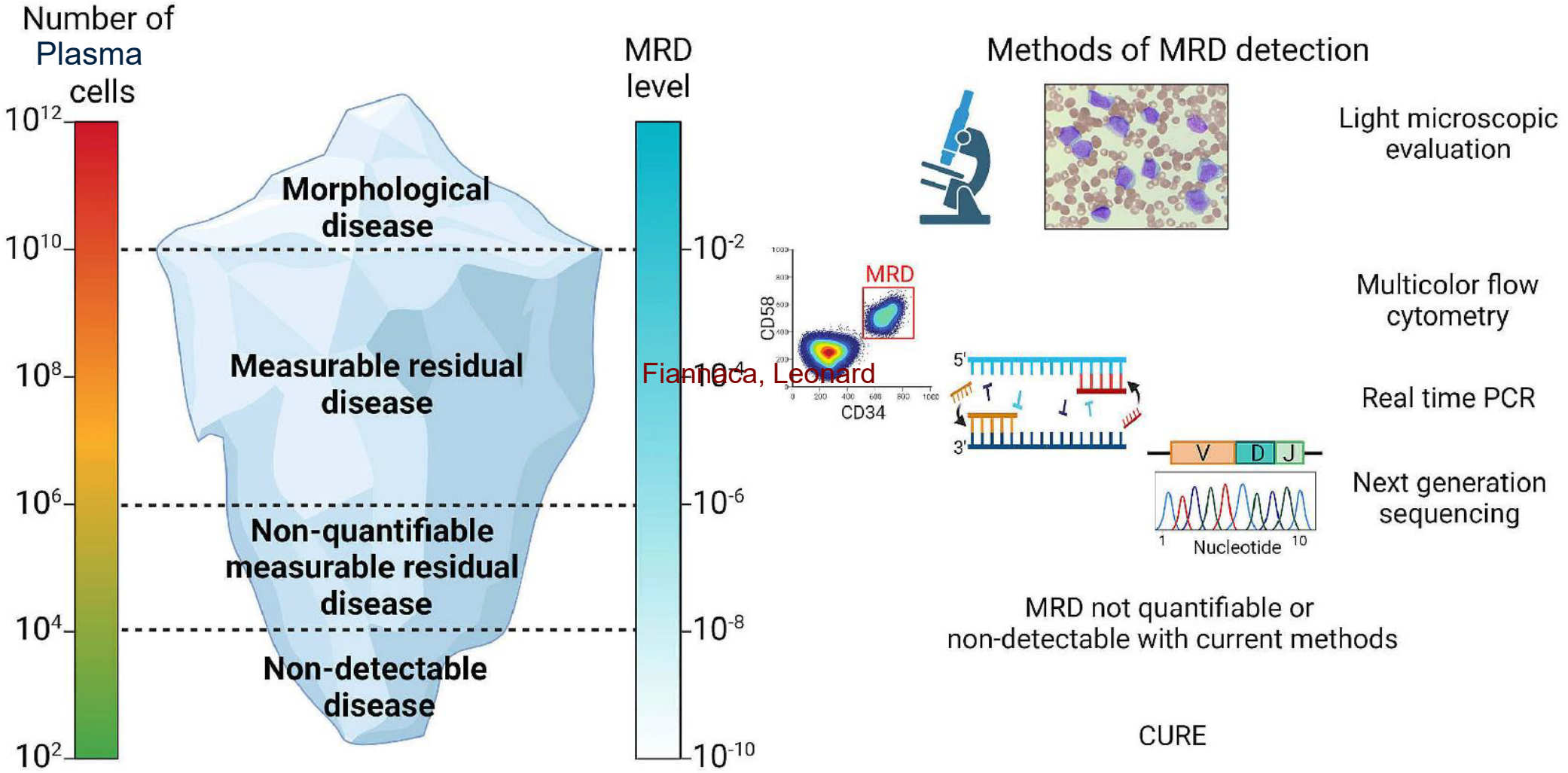
Edward A. Stadtmauer, MD
Section Chief, Hematologic Malignancies
Roseman, Tarte, Harrow, and Shaffer Families'
President's Distinguished Professor
University of Pennsylvania Abramson Cancer Center
Philadelphia, PA

CASE PRESENTATION

- 45-year-old female with history of IgG kappa MM, R-ISS 1, with no high-risk cytogenetic abnormalities. She initially presented with anemia and moderate hypercalcemia.

- The patient received induction therapy with dara-VRd, followed by melphalan 200 mg/m2 ASCT, then lenalidomide maintenance therapy. Best response was sCR, MRD-negative (10-6), PET/CT-negative.

- Repeat BM biopsy at 2 years post-ASCT shows sustained MRD-negativity (10-6). She has remained on lenalidomide maintenance, which she is tolerating relatively well except for mild insomnia.



Fiannaca, Leonard

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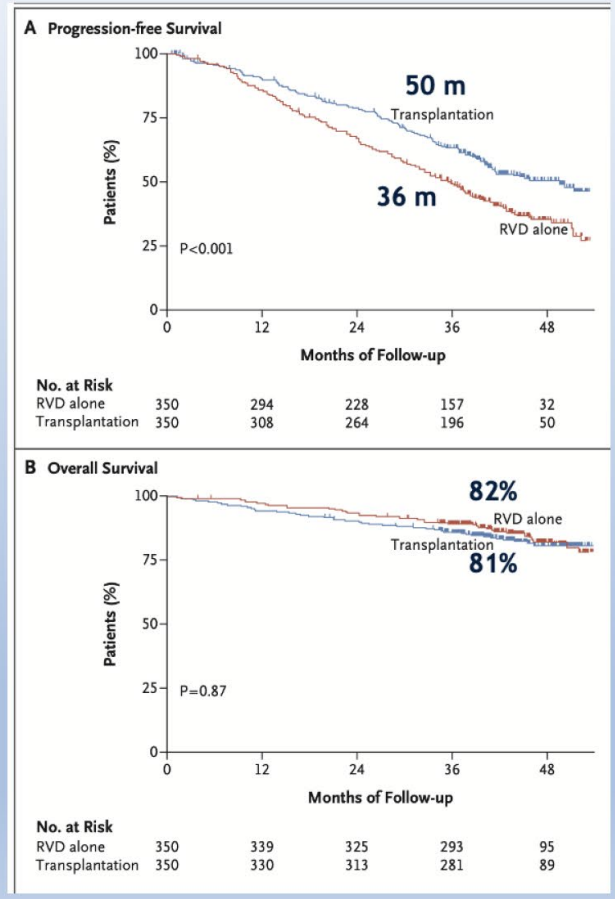
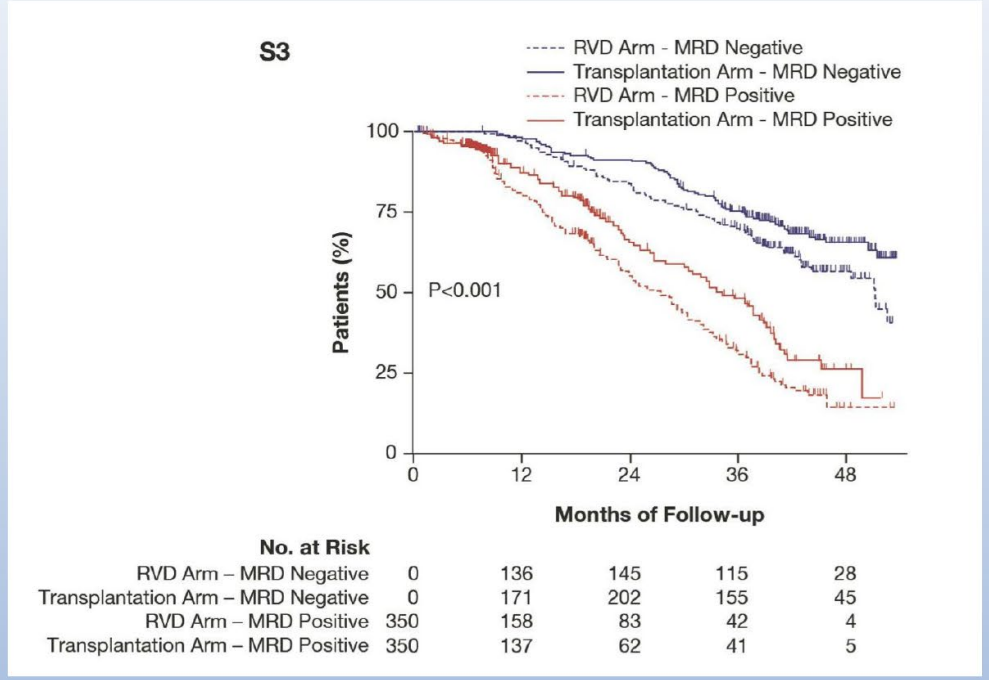
IFM 2009 Study: MRD as a Predictor of Progression Free Survival





The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 APRIL 6, 2017 VOL. 376 NO. 14

Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma

DOI: 10.1056/NEJMoa1611750

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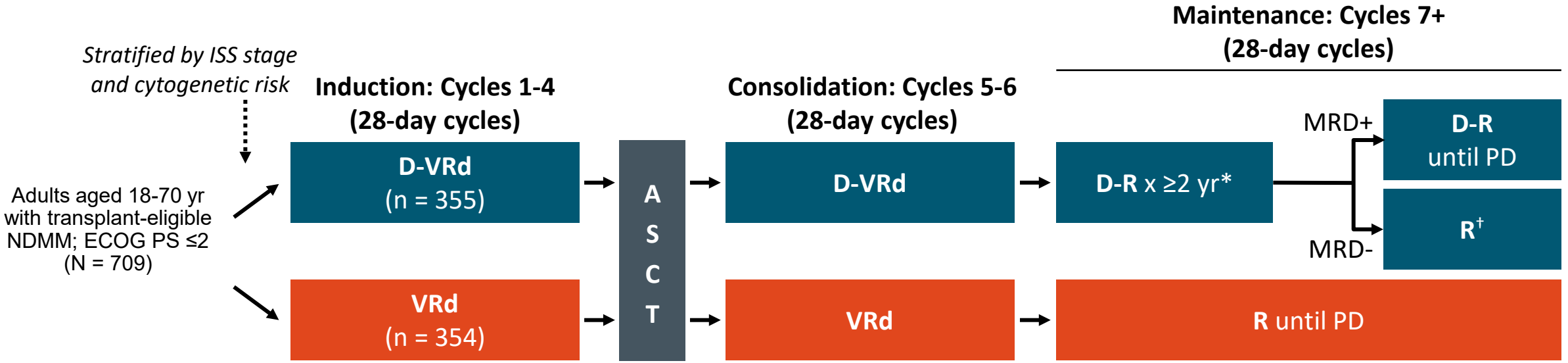
PERSEUS: DARA + VRD IN TRANSPLANT ELIGIBLE MM

Multicenter, open-label, **randomized phase III trial**; current analysis median f/u: 47.5 months



Dosing: D 1800 mg SC QW (induction cycles 1-2)/Q2W (induction cycles 3-4 and consolidation)/Q4W (maintenance); V 1.3 mg/m^2 SC on Days 1, 4, 8, 11; R 25 mg PO on D1-21 (induction and consolidation)/10 mg PO on Days 1-28 (maintenance); d 40 mg PO/IV on Days 1-4, 9-12. *D stopped after 2 yr in those with ≥CR and sustained MRD negativity (10^{-5}) for 12 mo. †Restart D if confirmed loss of CR without PD or MRD recurrence.

- **Primary endpoint:** PFS
- **Key secondary endpoints:** ≥CR rate, MRD negativity rate, OS

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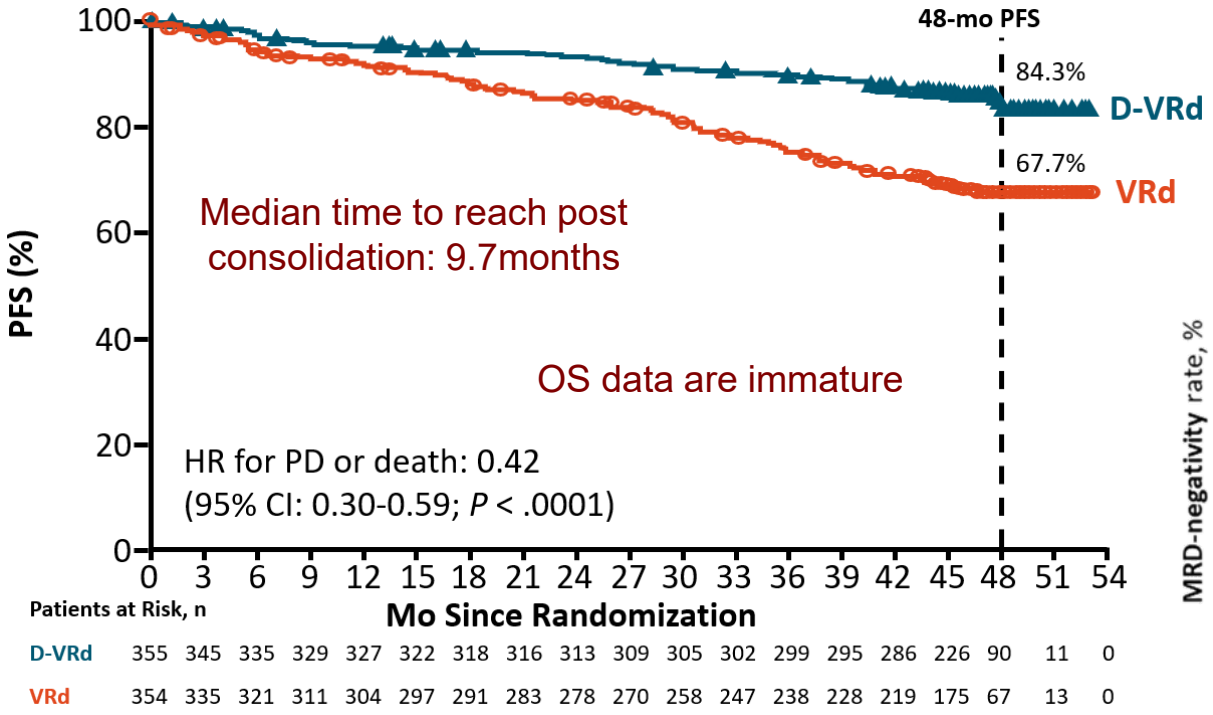
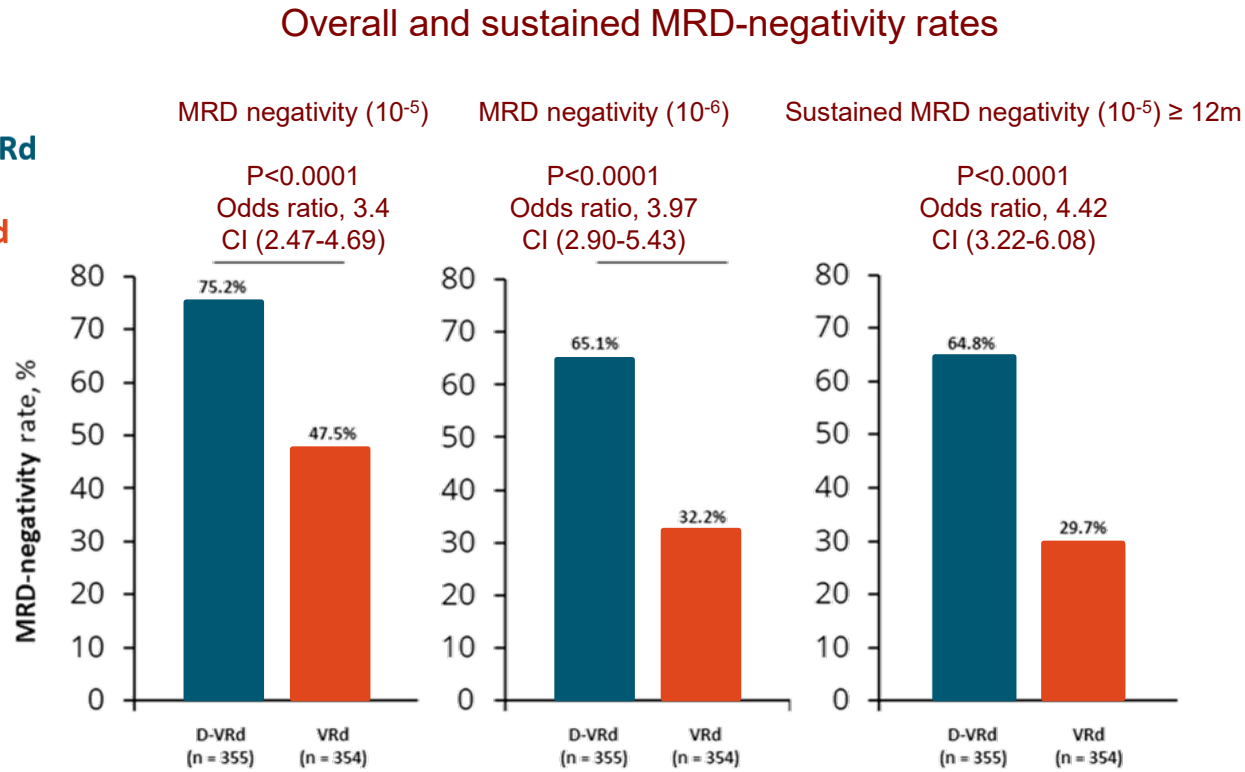
Sonneveld. NEJM. 2023.

PERSEUS: IMPROVED PFS, ACHIEVED DURABLE MRD





MRD-negativity: Patients who achieved both MRD negativity and ≥CR.
Patients who were non evaluable/indeterminate results were considered MRD positive

Sonneveld. NEJM. 2023.

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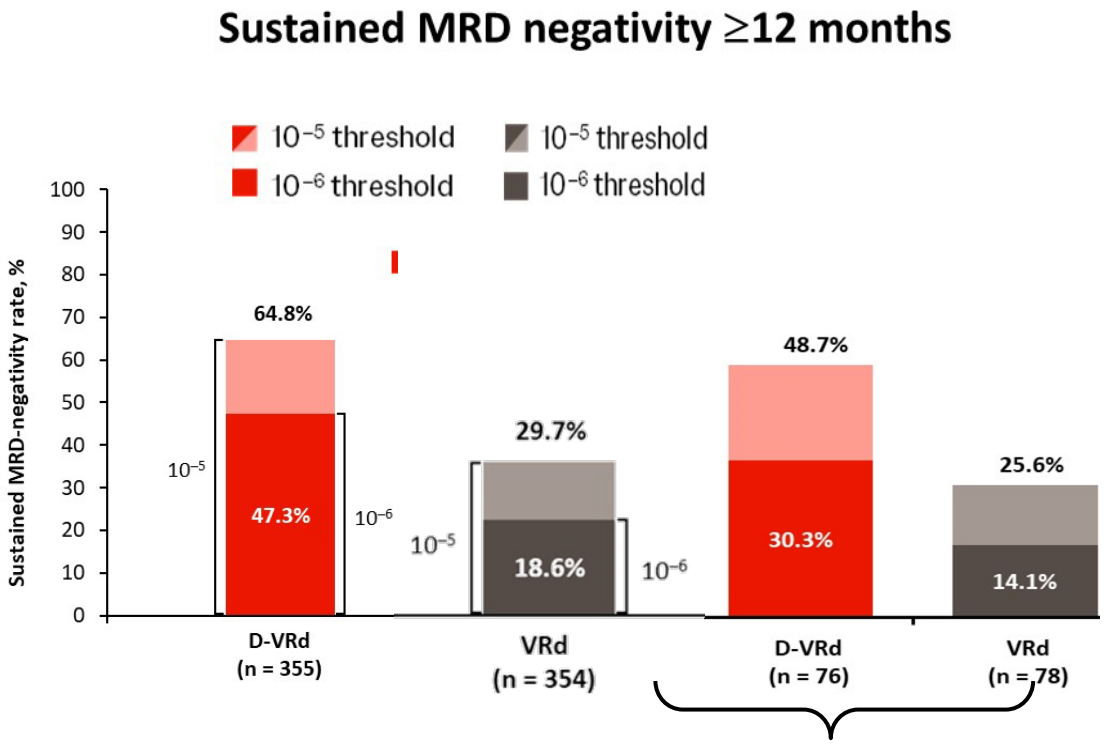
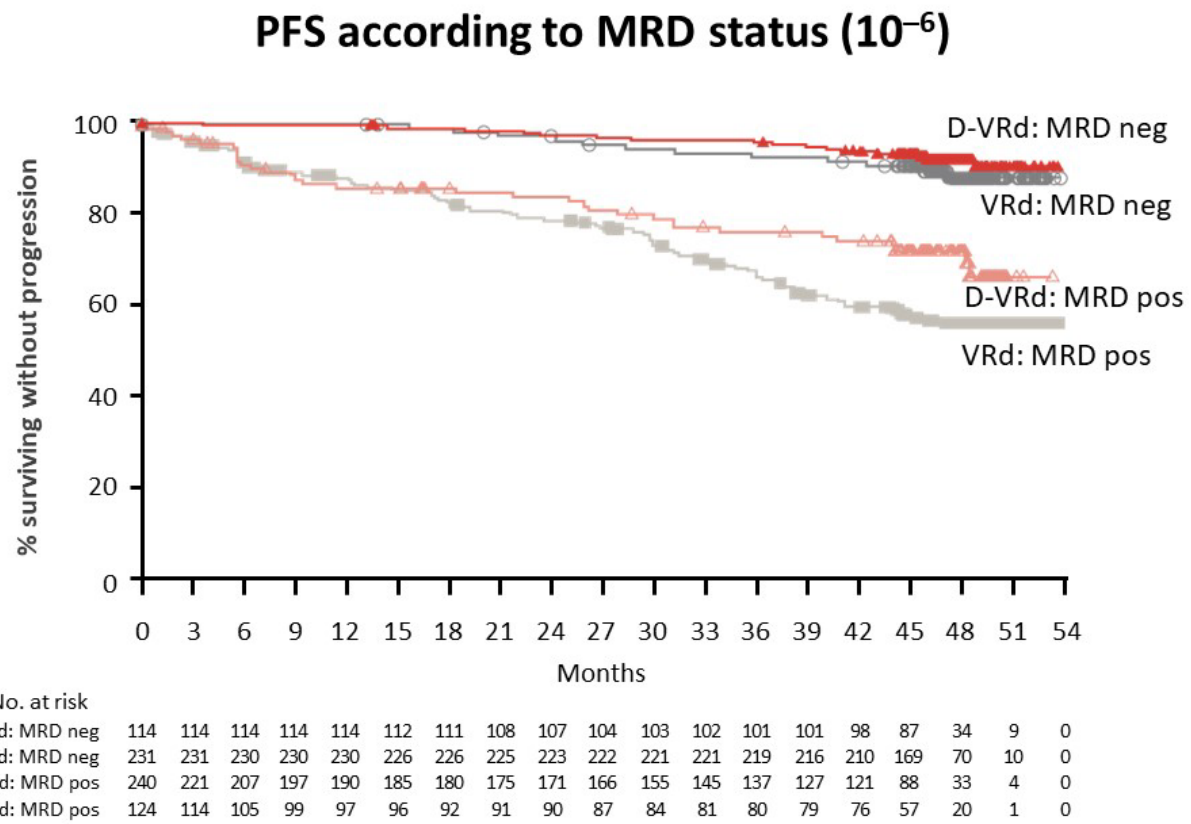
PERSEUS: SUSTAINED MRD NEGATIVITY AT 12 MONTHS



High risk
defined as del(17p),
t(4;14) and/or t(14;16)



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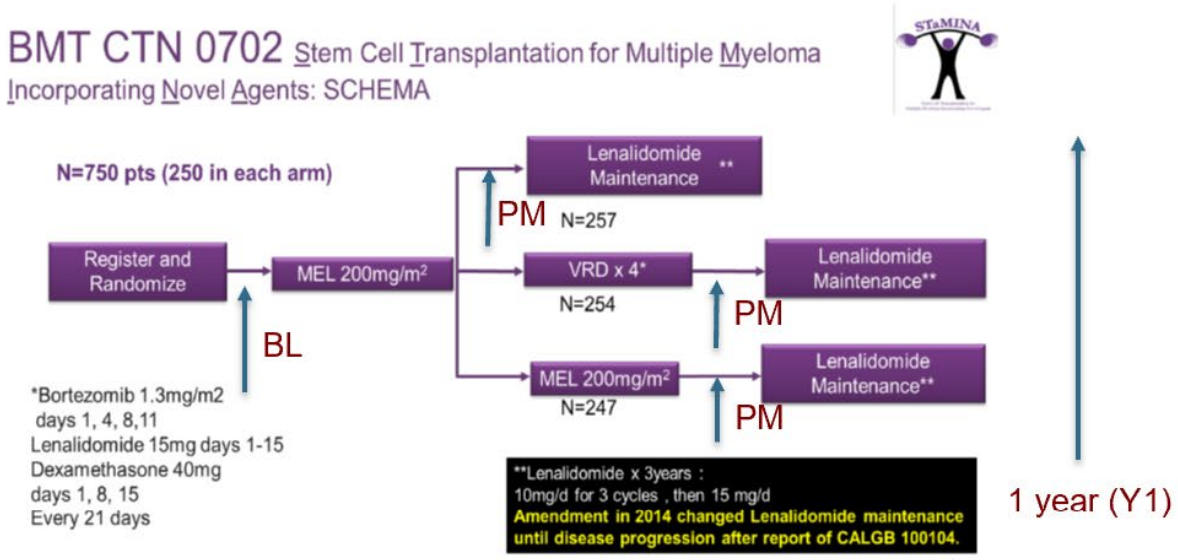
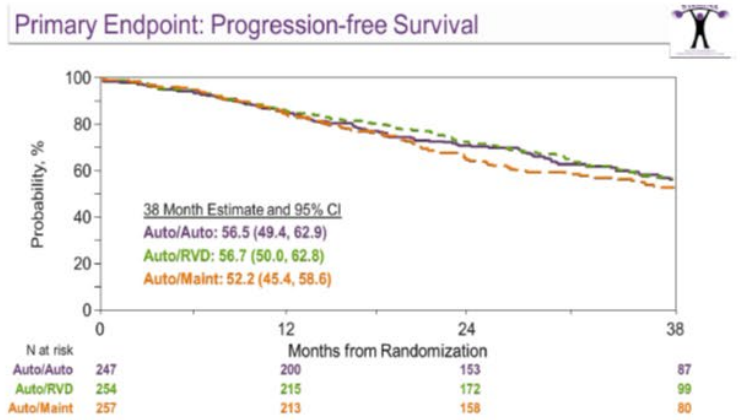
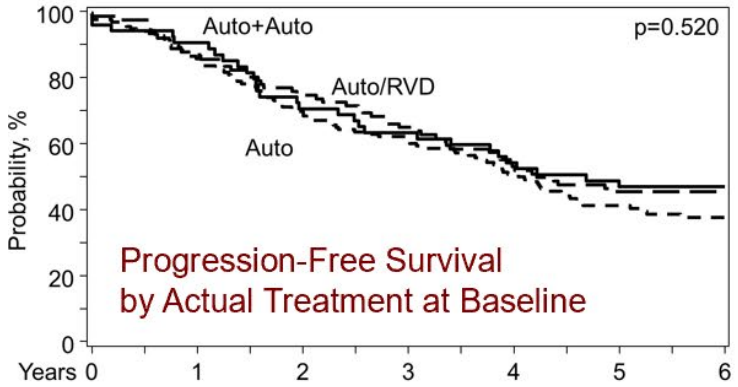
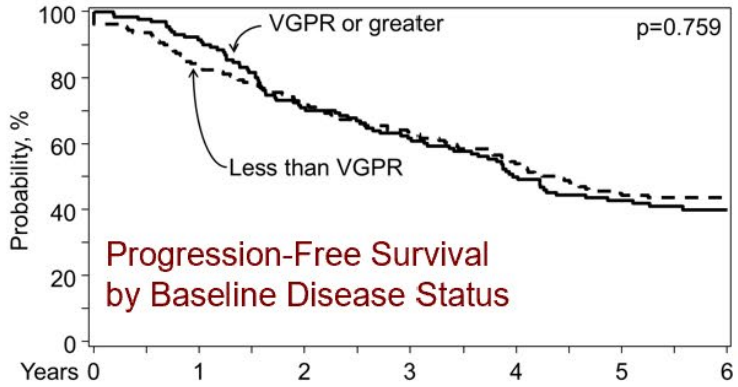
Rodriguez-Otero. ASCO 2024. Abstr 7502. NCT03710603.

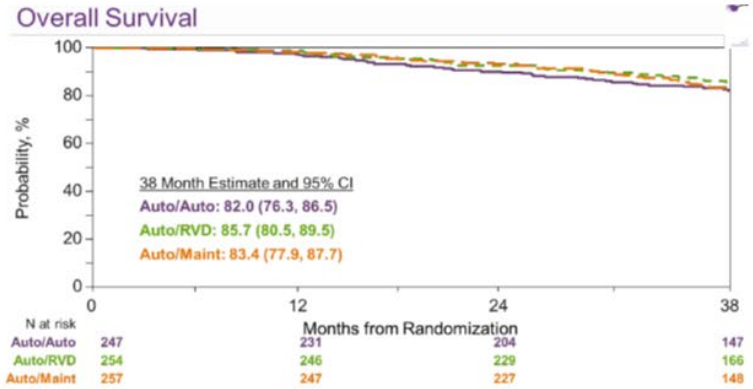
STAMINA (BMT CTN 0702) and the PRIMER Study











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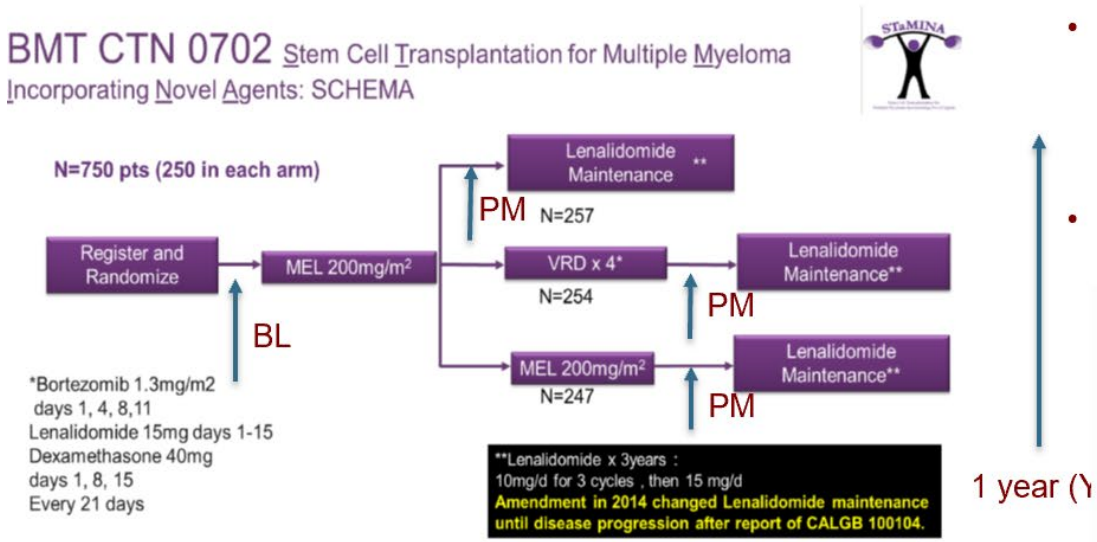
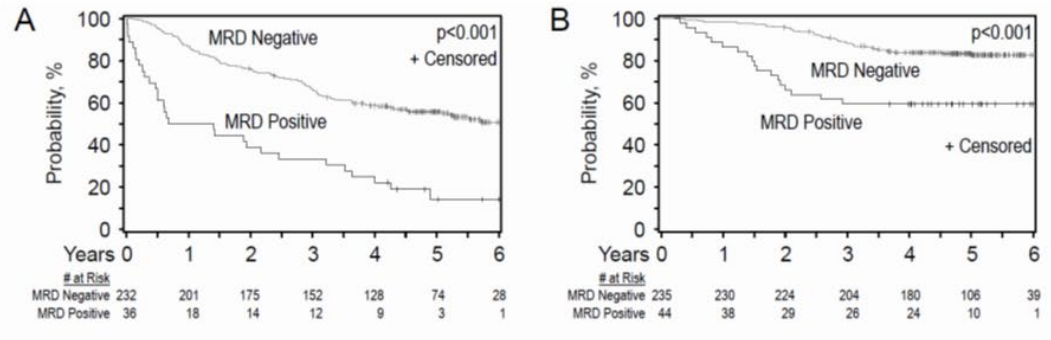
J Clin Oncol 2019, 37:589-597.

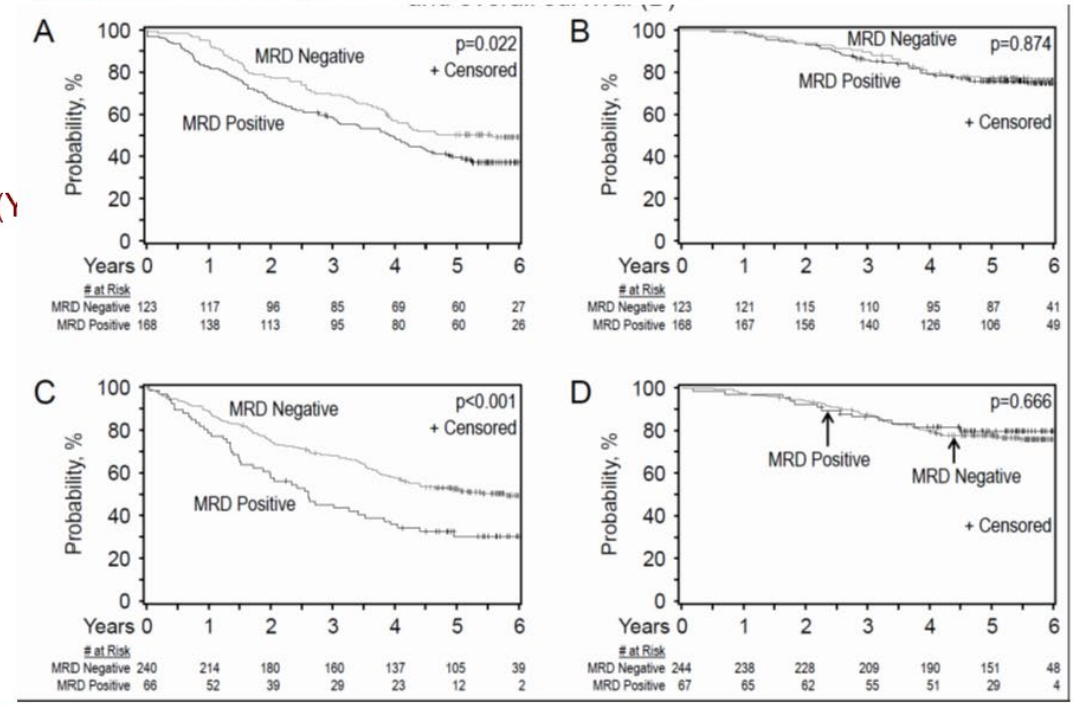
STAMINA (BMT CTN 0702) and the PRIMER Study





Y1 MRD Status and PFS (A), and OS (B)

- Primer Sub Study: 435 patients consented to the MRD panel which included 10 monoclonal antibodies measured via 6-color MFC. MRD was measured at Baseline/preAutoHCT (BL), Pre-maintenance (PM), and 1 year (Y1) post AutoHCT with a sensitivity of 10-5 to 10-6.
- **MRDneg at 1 year post AutoHCT with lenalidomide maintenance was prognostic for improved 6-year PFS and OS.**



BL MRD Status and PFS (A), and OS (B) PM MRD Status and PFS (C) and OS (D)

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J Clin Oncol 2019, 37:589-597. J Clin Oncol. 2024 Aug 10;42(23):2757-2768.

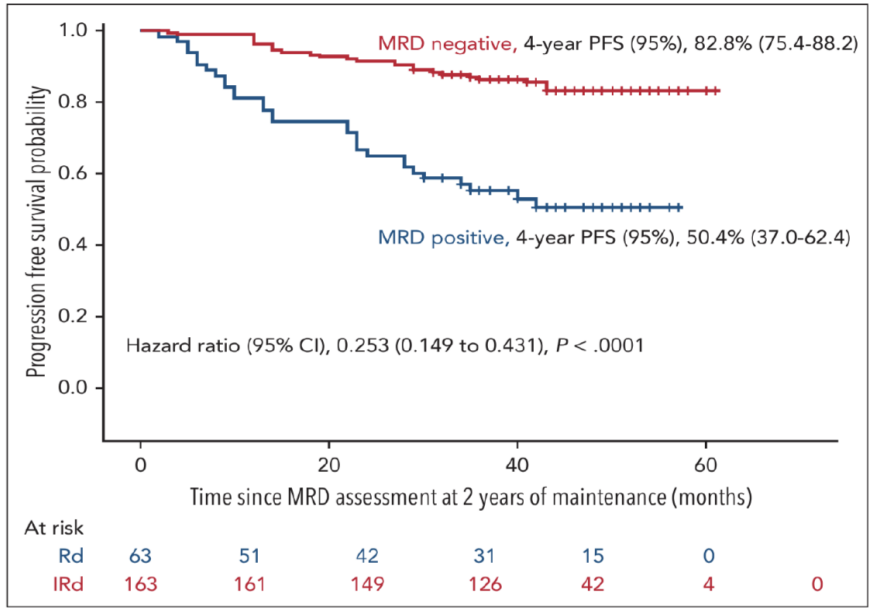
FDA ODAC VOTED 12-0 TO RECOMMEND MRD AS A MM ENDPOINT

On April 12, 2024, FDA ODAC voted 12-0 in favor of using minimal residual disease (MRD) as an accelerated approval endpoint in multiple myeloma clinical trials

Conclusion: The Applicants have worked with the broader MM community to develop a novel endpoint of MRD that has the potential to expedite drug development in MM. While there are still outstanding questions on how to best use MRD, the meta-analyses conducted **(University of Miami and IMF led i2TEAMM**) represent robust assessments of MRD that support its prognostic value, provide information regarding the appropriate timing of MRD assessment, and suggest that MRD may be appropriate to use as an intermediate clinical endpoint to support accelerated approval.

ROSIÑOL STUDY: MAINTENANCE THEARPY DISCONTNUTION IN PTS WITH SUSTAINED MRD NEGATIVITY

- Prior **VRd induction → ASCT → VRd consolidation**
- Randomization:
  - **Rd** (len-dex) maintenance x2 years
  - **IRd** (ixa-len-dex) maintenance x2 years
- MRD assessment after 2-years:
  - **MRD positive → Rd** x3 years
  - **MRD negative** → DISCONTINUE therapy (EuroFlow, 2 x 10^{-6})
- RESULTS
  - 332 patients enrolled
  - (similar PFS in Rd and IRd arms)
  - 163 patients MRD negative → **DISCONTINUED** therapy → **4-year PFS 83%**
  - 63 patients MRD positive → CONTINUED Rd → **4-year PFS 50.4%**



Rosiñol et al., *Blood* (2023) 142 (18): 1518–1528.

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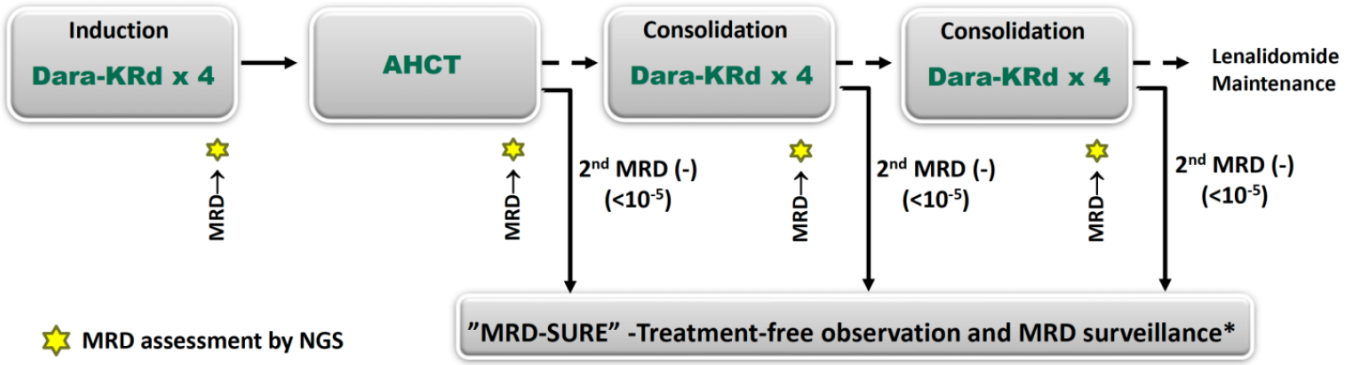
MASTER TRIAL

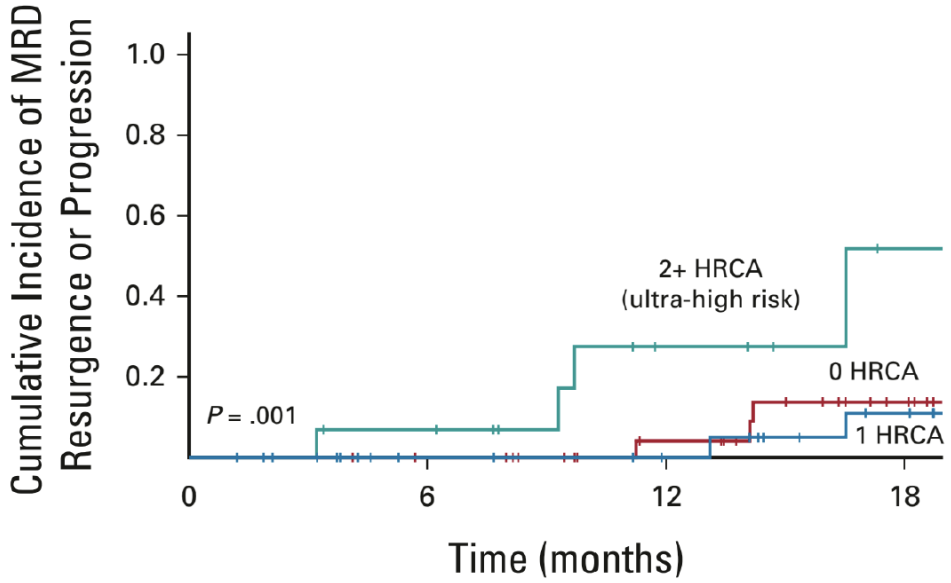
Dara-KRd

- Daratumumab 16 mg/m^2 days 1,8,15,22 (days 1,15 C 3-6; day 1 C >6)
- Carfilzomib (20) 56 mg/m^2 Days 1,8,15
- Lenalidomide 25 mg Days 1-21
- Dexamethasone 40mg PO Days 1,8,15,22



*24 and 72 weeks after completion of therapy

MASTER trial



No. at risk:				
0 HRCA	33	31	23	12
1 HRCA	36	24	21	14
2+ HRCA	15	23	5	0

Cumulative incidence of MRD resurgence or progression 12 months after cessation of therapy: 4%, 0%, and 27% for patients with 0, 1, or 21 HRCA, respectively.

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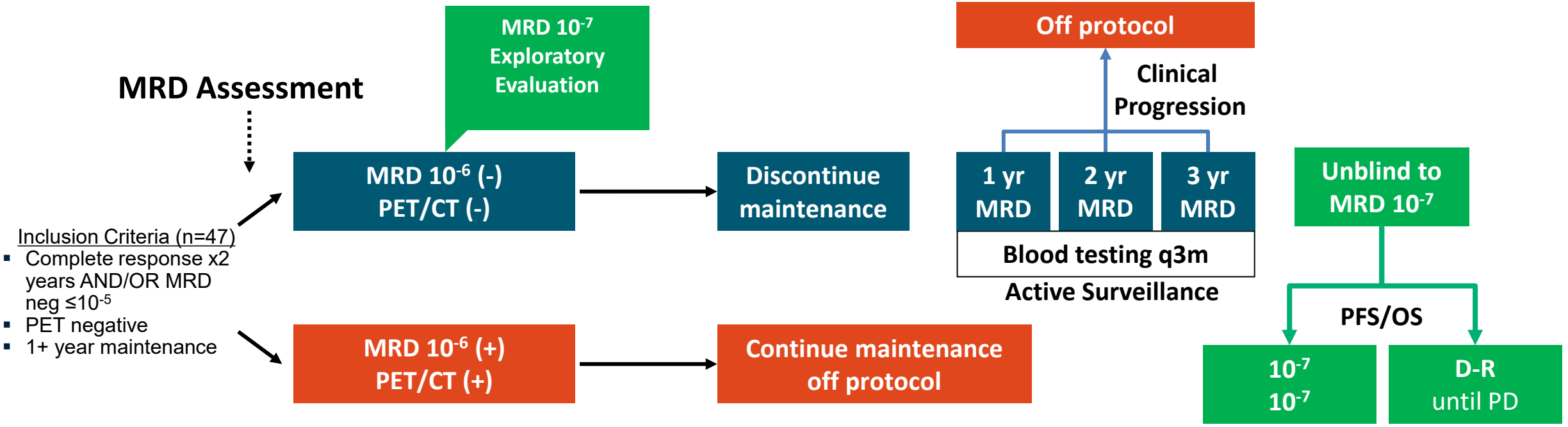
Costa J Clin Onc 2021.

MRD2STOP (47 PTS)



- **Primary endpoint:** MRD resurgence and PFS
- MRD assessment performed with PET, flow cytometry (10^{-5}), NGS (clonoSEQ 10^{-6}), and CD138-selected NGS (clonoSEQ 10^{-7})

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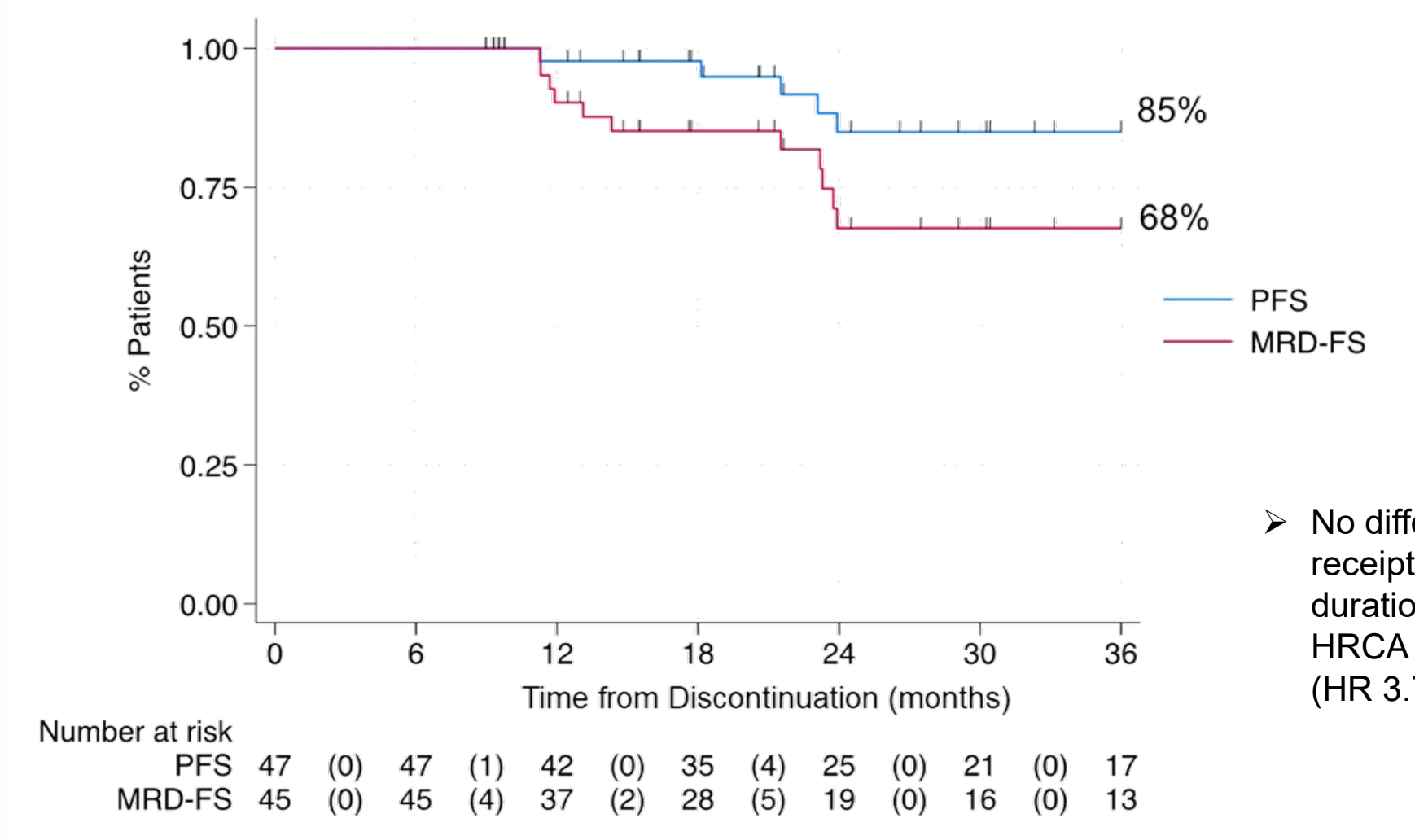
Derman ASCO 2024.

MRD2STOP: HIGH 3-YEAR PFS AND MRD-FS (10^{-6})



- No differences in PFS by high risk cyto, receipt of quad, consolidation, or ASCT or duration of consolidation/maintenance HRCA associated with inferior MRD-FS (HR 3.7 CI 1.2-11.7, p=0.02)

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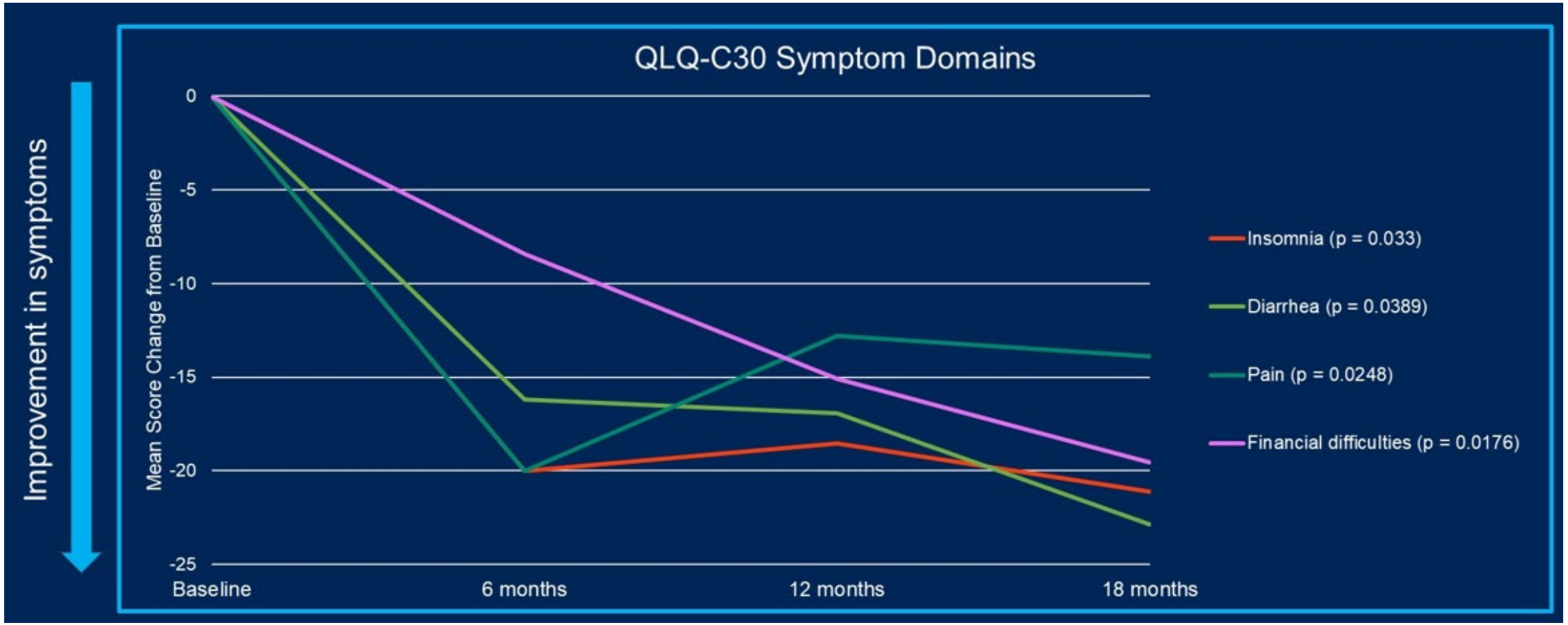
Derman ASCO 2024.

MRD2STOP: QOL IMPROVEMENT, COST BENEFIT



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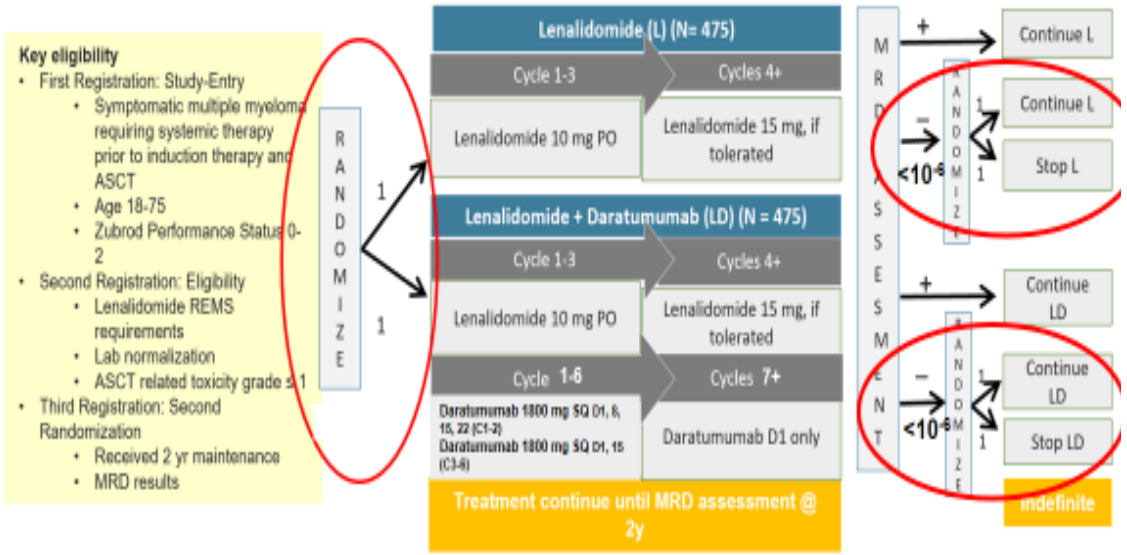
The DRAMMATIC (S1803/BMT CTN 1706) TRIAL

NCT04071457

DRAMMATIC Trial Schema



- Registration Step 1: *baseline specimen for ID (B-cell clonality) mandatory as of Feb 2024 1174/1420 enrolled
- Registration Step 2: within 180 days after ASCT (***1st randomization***) as of Feb 2024 1071/1214
- Registration Step 3: completed 24 months of maintenance and MRD-neg + ≥VGPR (*$<10^{-5}$) (***2nd randomization***) as of Feb 2024 551

PERSEUS and DRAMMATIC asked different questions?

Questions PERSEUS asked:

- Does adding Dara to VRD-AHCT- R_{main} platform improve PFS?
- Does adding Dara to VRD-AHCT-R_{main} platform improve MRD-neg rates/durability?

PERSEUS was not designed to answer the question whether single agent vs. Dara-based doublet maintenance treatment is superior after AHCT, and if *all* maintenance can be discontinued after achieving deep MRD-negativity.

Questions DRAMMATIC is asking:

- Does Dara added to R_{main} improve OS?
- Does Dara added to R_{main} improve MRD-neg rates?
- Can deep MRD-neg (10^{-6} threshold) determine duration of maintenance therapy?

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WHAT IS BEST MRD TEST?

- **MRD assessment using BM based methods remains the gold standard**
  Comparison between flow cytometry and NGS methods have been performed and suggest they are comparable
  The availability, cost, prognostic power, and consistency are important factors to consider.

- Imaging methods provide additional information particularly regarding extramedullary disease and high risk MM.
  Combining both MRD methods seems optimal for patients care.

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Blood. 2020;136(Supplement 1):44-45 Blood. 2021;138(Supplement 1):82. Blood Cancer J. 2020;10(10):108.. Br J Haematol. 2022;198(3)515-522.

SUMMARY

- MRD assessment methods allow identification of patients with deep hematologic response and should be incorporated into all MM clinical trials.
- Bone marrow-based methods using NGF and NGS are the most available, standardized, and sensitive methods.
- Whole body imaging should be combined with BM MRD assessment provide better evaluation especially in the setting of high risk cytogenetic and extramedullary disease.
- Achievement of MRD negativity is a very strong prognosis factor that is now an established endpoint in myeloma clinical trials
- Persistent or sustained MRD negativity portends better outcome in newly diagnosed and relapsed refractory disease, including after CAR T cell therapy in myeloma
- **As of now, there is insufficient data to utilize results of MRD testing to make individual MM patient treatment decisions. Several clinical trials are currently ongoing to establish if MRD can be used to guide therapy and to monitor disease activity.**

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Haematologica. 2024 Feb 8. doi: 10.3324/haematol.2023.284662 [Epub ahead of print].

CASE PRESENTATION

- 45-year-old female with history of IgG kappa MM, R-ISS 1, with no high-risk cytogenetic abnormalities. She initially presented with anemia and moderate hypercalcemia.

- The patient received induction therapy with dara-RVd, followed by melphalan 200 mg/m2 ASCT, then lenalidomide maintenance therapy. Best response was sCR, MRD-negative (10-6), PET/CT-negative.

- Repeat BM biopsy at 3 years post-ASCT shows sustained MRD-negativity (10-6). She has remained on lenalidomide maintenance, which she is tolerating relatively well except for mild insomnia.

Penn Myeloma Program

- Edward Stadtmauer, MD
- Dan Vogl, MD
- Adam Cohen, MD
- Alfred Garfall, MD
- Adam Waxman, MD
- Sandra Susanibar Adaniya, MD
- Shivani Kapur, MD
- Patricia Mangan, CRNP
- Mcinerney, Jillian CRNP
- Michelle Biala, CRNP
- Leah Power, CRNP
- Beggache, Meriem, CRNP
- Bree Vaotogo, RN
- Theresa Sabato, RN
- Amy Baldwin, RN
- Danielle Pollack, RN
- Gabrielle Digrazio, RN
- Sara Whittington, RN
- Samantha Le, RN
- Oksana de Mesa, RN
- Danielle Zubka, RN
- Justice Steed, RN
- Maria Raguza-Lopez
- Gulgule, Zachary V
- Cynthia Diaczynsky
- Anjana Nair
- Karin Vislocka
- Abbie Etzweiler
- Christine Nocera
- Girgis, Sarah M
- Fiannaca, Leonard

Center for Cellular Immunotherapies

- Carl June, MD
- Michael Milone, MD, PhD
- Bruce Levine, MD
- Don Siegel, MD, PhD
- Simon Lacey, PhD
- Jos Melenhorst, PhD
- Regina Young, PhD
- Gabriela Plesa, PhD

NIH P01 CA214278-01

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- CME & CE courses: www.LLS.org/CE
- Fact Sheets for HCPs: www.LLS.org/HCPbooklets
- Videos for HCPs: www.LLS.org/HCPvideos
- Podcast series for HCPs: www.LLS.org/HCPpodcast

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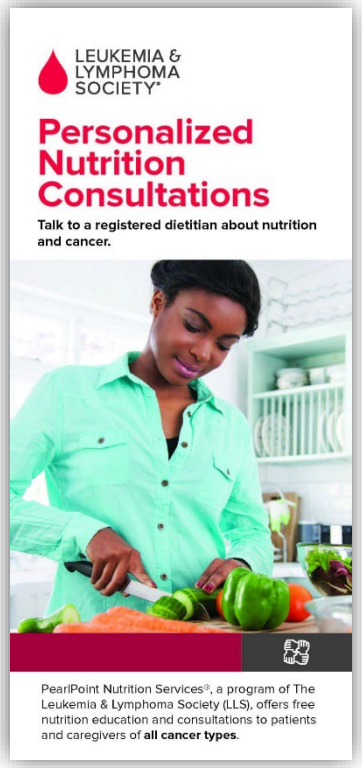
FREE LLS RESOURCES FOR PATIENTS

- **Information Specialists** – Personalized assistance for managing treatment decisions, side effects, and dealing with financial and psychosocial challenges (IRC).
  - www.LLS.org/IRC
- **Clinical Trial Nurse Navigators** – RNs and NPs provide a personalized service for patients seeking treatment in a clinical trial, sift through the information and provide information to bring back to their HC team (CTSC).
  - www.LLS.org/CTSC
- **Nutrition Education Services Center** – one-on-one consultation with a registered dietician for patients/caregivers of all cancer types (NESC).
  - www.LLS.org/Nutrition
- **Reach out** **Monday–Friday, 9 am to 9 pm ET**
  - Phone: (800) 955-4572
  - Live chat: www.LLS.org/IRC
  - Email: www.LLS.org/ContactUs
  - HCP Patient Referral Form: www.LLS.org/HCPreferral



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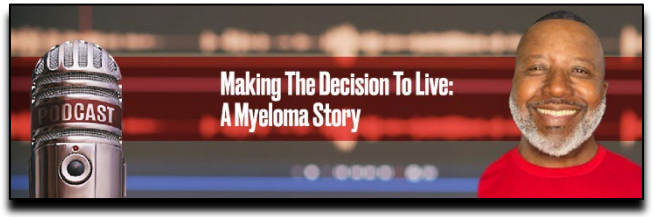
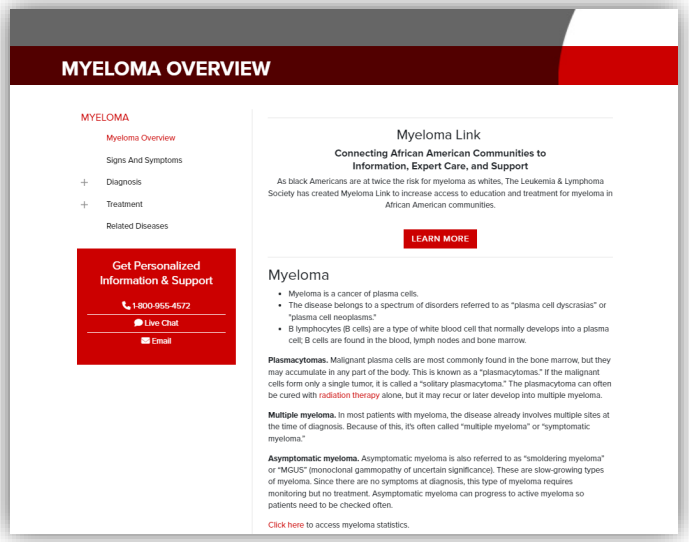
FREE LLS RESOURCES FOR PATIENTS AND CAREGIVERS

❑ Webcasts, Videos, Podcasts, Booklets:

- ➢ www.LLS.org/Webcasts
- ➢ www.LLS.org/EducationVideos
- ➢ www.LLS.org/Podcast
- ➢ www.LLS.org/Booklets





❑ www.LLS.org/Myeloma

❑ Support Resources

- ❑ Financial Assistance: www.LLS.org/Finances
  - Urgent Need
  - Patient Aid
  - Travel Assistance
- ❑ Other Support: www.LLS.org/Support
  - LLS Regions
  - Online Weekly Chats Facilitated by Oncology SW
  - LLS Community Social Media Platform
  - First Connection Peer to Peer Program

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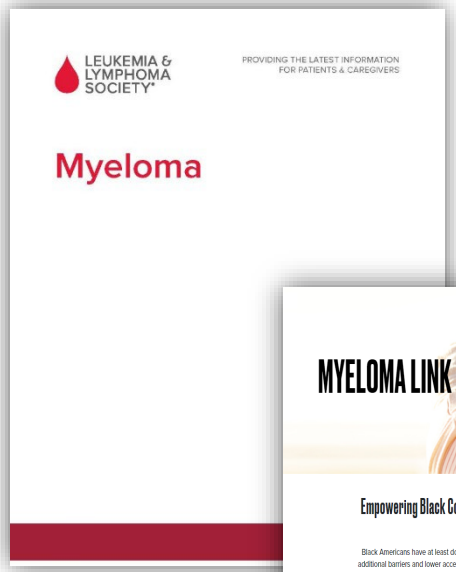
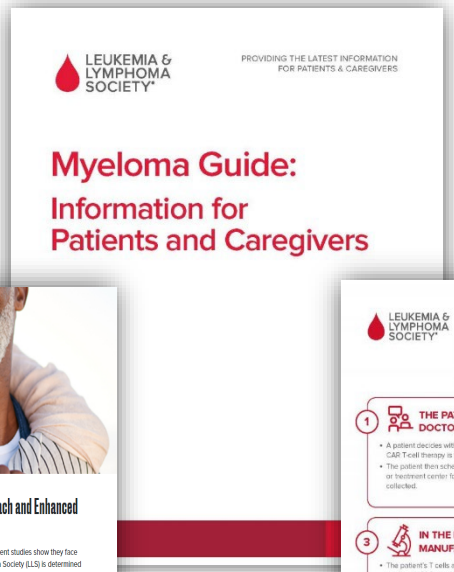
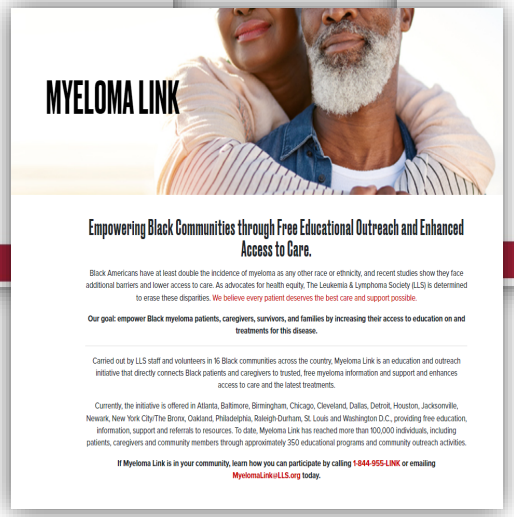
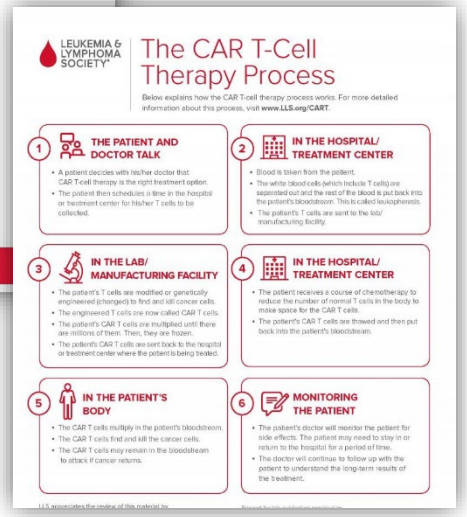
FREE LLS RESOURCES FOR YOUR PATIENTS









- ❑ www.LLS.org/Myelomalink

BOOKLETS AND FACT SHEETS

English – www.LLS.org/Booklets
Spanish – www.LLS.org/Materiales

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THANK YOU

To speak with an Information Specialist or to refer a patient:
Phone: (800) 955-4572 Email: www.LLS.org/ContactUs

For questions about this program, concerns, or assistance for people with disabilities or grievances, please contact us at Profeducation@LLS.org

We have one goal: A world without blood cancers

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