LEVERAGING MRD FOR TREATMENT ESCALATION VS DE-ESCALATION IN MYELOMA

Jonathan L. Kaufman, MD

Hematology and Medical Oncology

Winship Cancer Institute

Emory University

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

NCI
Designated Comprehensive Cancer Center

COI

- Grant/Research Support:
  - Janssen; BMS; GlaxoSmithKline; Pfizer; Beigene; Kite Pharma, Inc.; Amgen; Abbvie; Novartis; Genentech; Fortis Therabeutics, Inc; Takeda; Genmab; Heidelberg Pharma AB; Nexcella, Inc; Poseida
- Consultant:
  - Sanofi; Sebia; BMS; Ascentage

MRD at a tool for decision making

Discontinuation/De-escalation

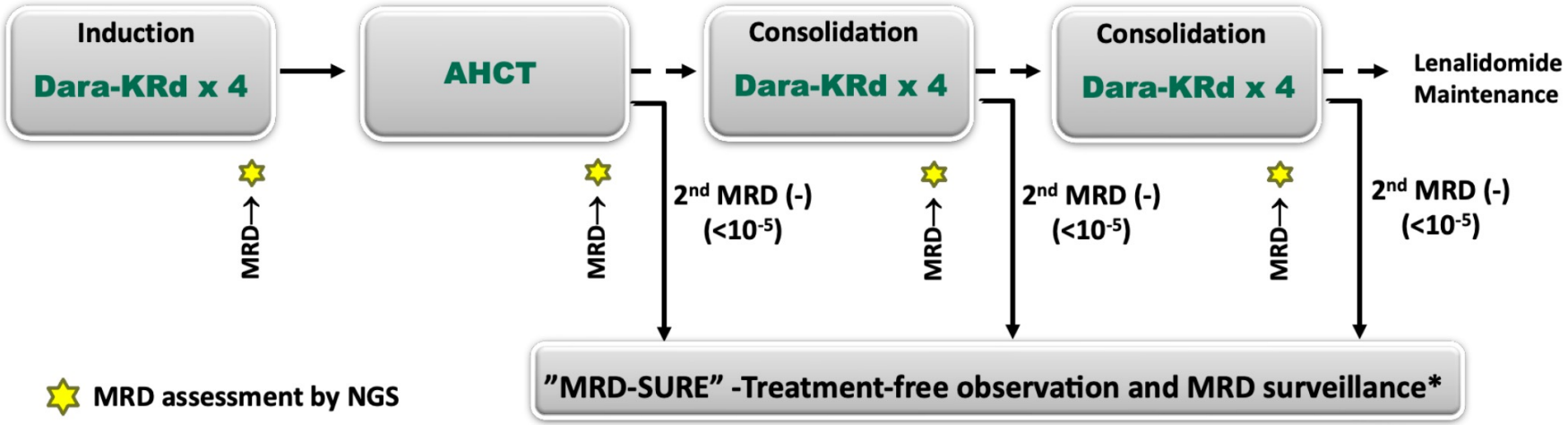
Resumption

Escalation

Change

Methods

- Patients treated in the MASTER trial (N=116)
  - Daratumumab, **carfilzomib**, lenalidomide, dexamethasone
  - Treatment cessation determined by 2 consecutive MRD $<10^{-5}$
  - At least yearly MRD testing



*24 and 72 weeks after completion of therapy

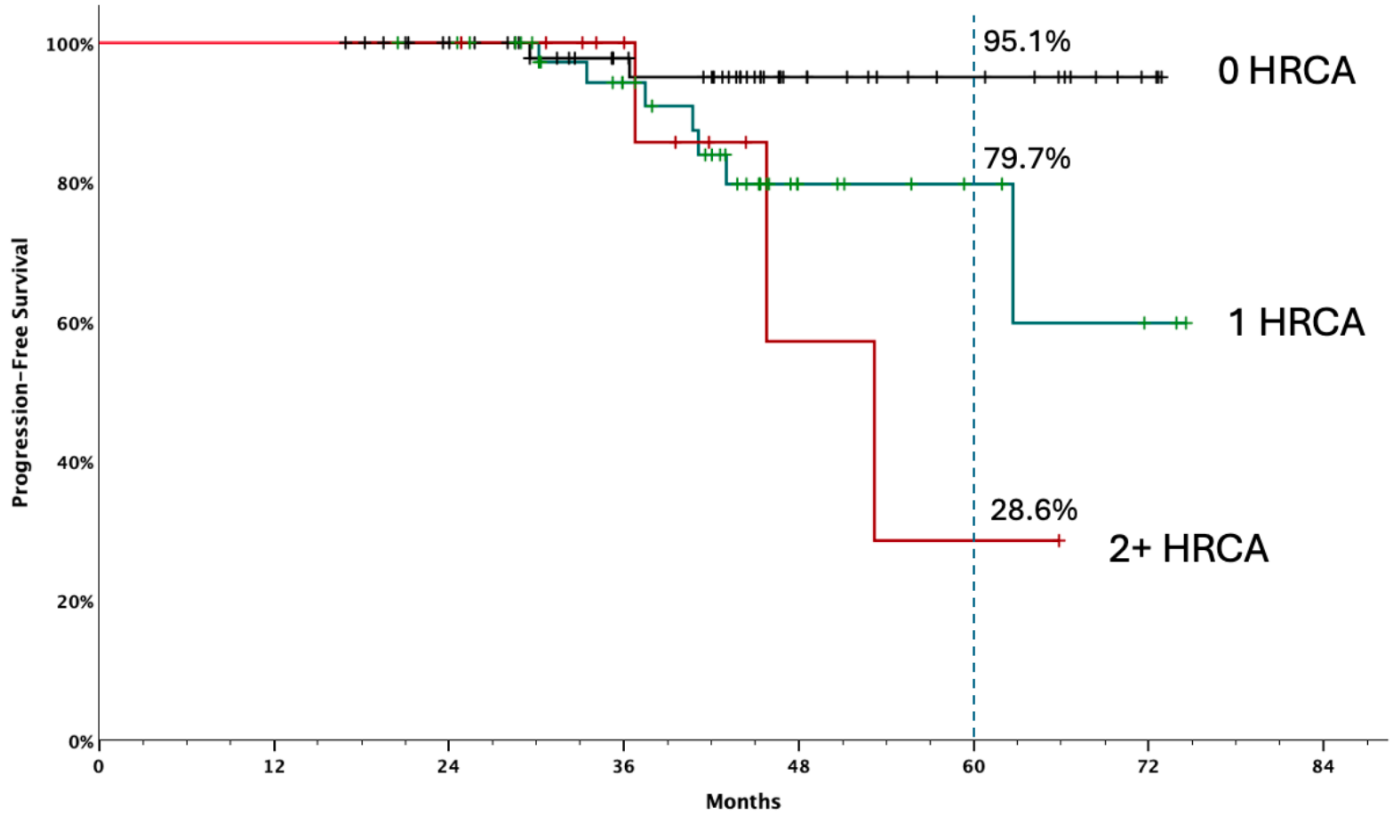
- Institutional SOC database (N=105)
  - Daratumumab, **bortezomib**, lenalidomide, dexamethasone
  - Treatment cessation suggested after 2 consecutive MRD $<10^{-5}$
  - At least yearly MRD testing

Results

Characteristics		MASTER (N=116)	Institutional Database (N=105)	All (N=221)	MRD-SURE subset (N=121)
Median follow up in mo. (95% C.I.)		45.3 (44.0-46.5)	29.3 (27.5-31.1)	40.6 (36.9-44.3)	44.0 (41.6-46.3)
Median age in years (IQR)		61 (55-68)	62 (56-68)	61 (55.5-68)	61 (54-67)
Female		51 (44%)	42 (40%)	93 (42%)	58 (48%)
Race/ethnicity					
	Non-Hispanic White	88 (76%)	63 (60%)	151 (68%)	86 (71%)
	Non-Hispanic Black	25 (22%)	40 (38%)	65 (30%)	31 (26%)
	Other/unavailable	3. (3%)	2 (2%)	5 (2%)	4 (3%)
ECOG Performance Status					
	0	40 (35%)	26 (25%)	66 (30%)	32 (26%)
	1	53 (46%)	66 (63%)	119 (54%)	67 (55%)
	2	23 (20%)	13 (12%)	36 (16%)	22 (18%)
International Staging System (ISS)					
	I	43 (37%)	40 (38%)	83 (38%)	46 (38%)
	II	46 (40%)	33 (31%)	79 (36%)	47 (39%)
	III	27 (23%)	20 (19%)	47 (21%)	25 (21%)
	unavailable	0 (0%)	12 (11%)	12 (5%)	3 (3%)
High LDH		25 (22%)	14 (13%)	39 (18%)	17 (14%)
Number of HRCA					
	0	49 (42%)	54 (51%)	103 (47%)	55 (46%)
	1	43 (37%)	39 (37%)	82 (37%)	50 (41%)
	2+	24 (21%)	11 (11%)	35 (16%)	16 (13%)
	unavailable	0 (0%)	1 (1%)	1 (1%)	0 (0%)
Quadruplet regimen					
	Dara-KRd	116 (100%)	0 (0%)	116 (52%)	83 (69%)
	Dara-VRd	0 (0%)	105 (100%)	105 (48%)	38 (31%)
Median N of cycles of quadruplet therapy (IQR)		8 (4-12)	8 (4-8)	8 (4-8)	4 (4-8)

Blood. 2025 Apr 7:blood.2024027674. doi: 10.1182/blood.2024027674. Online ahead of print.

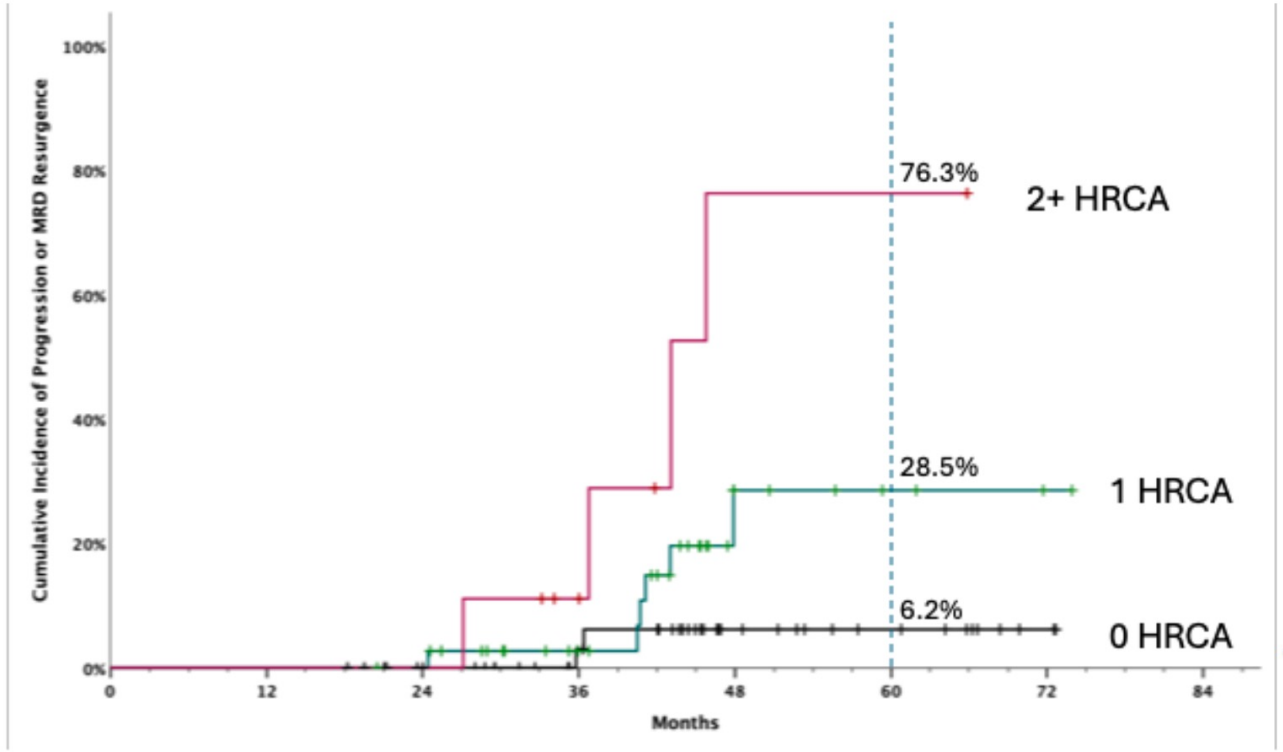
PFS in patients who achieved S-MRD<10^{-5}



Number at risk (number censored)								
0 HRCA	56 (0)	56 (0)	50 (6)	37 (18)	18 (36)	11 (43)	3 (51)	0 (54)
1 HRCA	42 (0)	42 (0)	41 (1)	29 (11)	9 (27)	5 (31)	2 (33)	0 (35)
2 HRCA	12 (0)	12 (0)	12 (0)	8(4)	2(8)	1 (8)	0 (9)	0 (9)

Blood. 2025 Apr 7:blood.2024027674. doi: 10.1182/blood.2024027674. Online ahead of print.

PMRS in MRD-SURE for patients who achieved S-MRD<10^{-5}



Number at risk (number censored)								
0 HRCA	48 (0)	48 (0)	43 (5)	32 (15)	15 (31)	9 (37)	2 (44)	0 (46)
1 HRCA	38 (0)	38 (0)	37 (1)	25 (12)	6 (26)	3 (29)	1 (31)	0 (32)
2 HRCA	9 (0)	9 (0)	9 (0)	6(2)	1(4)	1(4)	0 (5)	0 (5)

Very low risk of progression or MRD resurgence despite no ongoing therapy

Blood. 2025 Apr 7:blood.2024027674. doi: 10.1182/blood.2024027674. Online ahead of print.

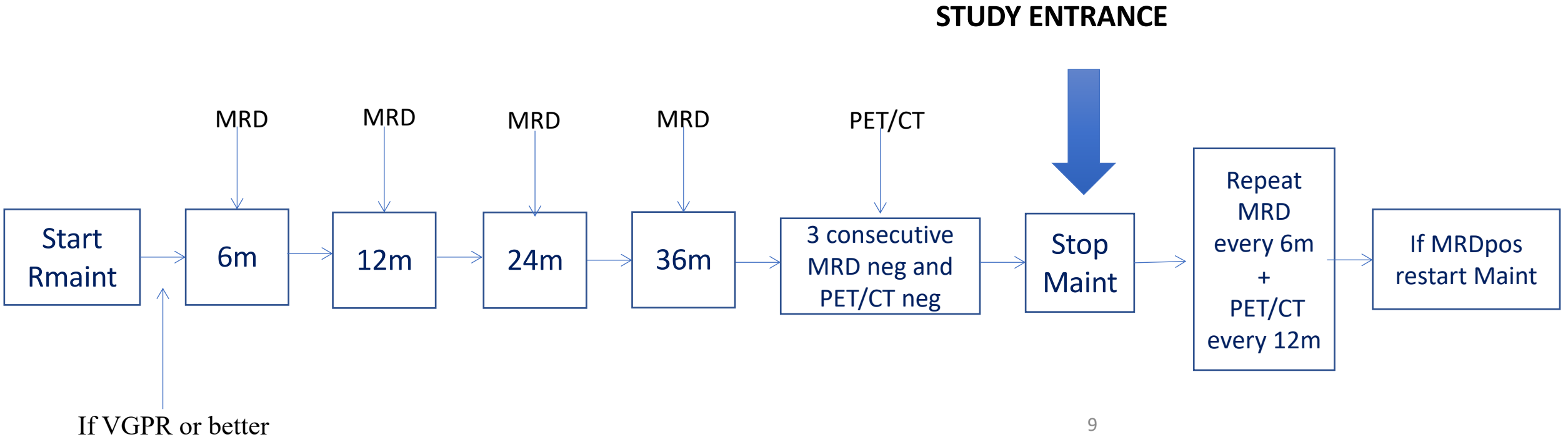
Sustained MRD Negativity for Three Years Can Guide Discontinuation of Lenalidomide Maintenance after ASCT in Multiple Myeloma: Results from a Prospective Cohort Study

Panagiotis Malandrakis, MD[1*], *Ioannis Ntanasis-Stathopoulos, MD, PhD, MSc*[1*], *Ioannis V Kostopoulos, PhD*[2*], *Vasiliki Spiliopoulou, MD*[1*], *Despina Fotiou, MD*[1*], *Foteini Theodorakakou, MD*[1*], *Magdalini Migkou, MD*[1*], *Nikolaos Kanellias*[1*], *Evangelos Eleutherakis-Papaiakovou, MD*[1*], *Efstathios Kastritis, MD*[1*], *Maria Gavriatopoulou*[1*], *Ourania Tsitsilonis, MD, PhD*[2*], *Meletios Dimopoulos, MD*[1] *and Evangelos Terpos, MD, PhD*[1]

[1]*Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece*
[2]*Department of Biology, School of Science, National and Kapodistrian University of Athens (NKUA), Athens, Greece*

ASH 2024; *Blood* (2025) 145 (20): 2353–2360.

Protocol Design



ASH 2024; *Blood* (2025) 145 (20): 2353–2360.

Results: Conversion from MRD (-) to MRD (+)

52 pts discontinued lenalidomide maintenance, after 3-year sustained MRD negativity

median follow-up: 3 years (range 0.58-4.70 years)

12 (23%) pts converted to MRD pos, and restarted lenalidomide (6 high risk cytogenetics)

4 (7.6%) pts progressed (2 high risk cytogenetics) and

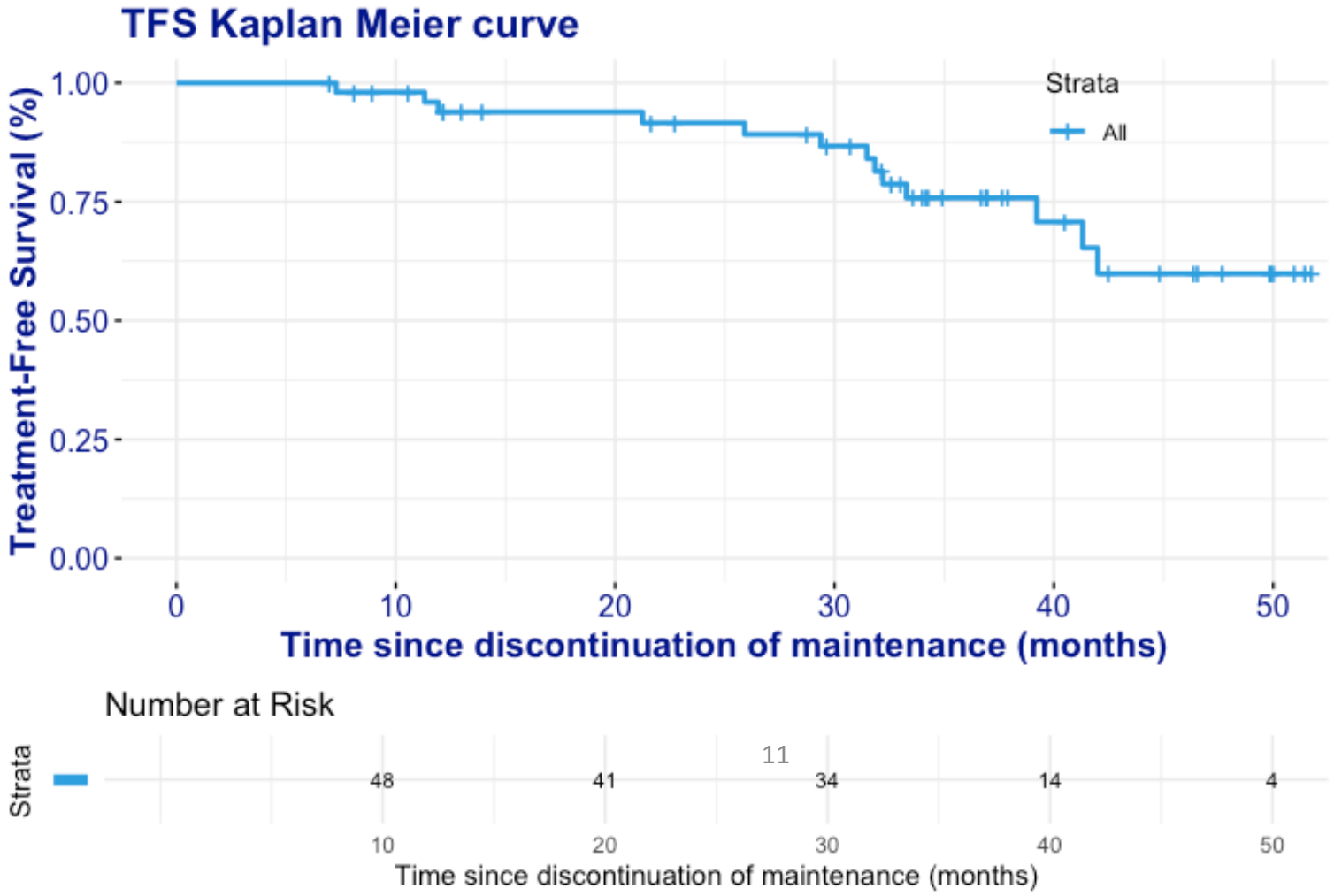
one died (not MM related/second primary malignancy)

Time from Discontinuation (months)	0	6	12	18	24	30	36	42	48
At risk	52	51	45	39	36	33	21	11	7
MRD neg	52	49	43	38	34	30	19	11	7

ASH 2024; *Blood* (2025) 145 (20): 2353–2360.

Treatment-Free Survival (TFS)

- ✓ The 1-, 2- and 3-year TFS rates were 93.9%, 91.6% and 75.8%, respectively,



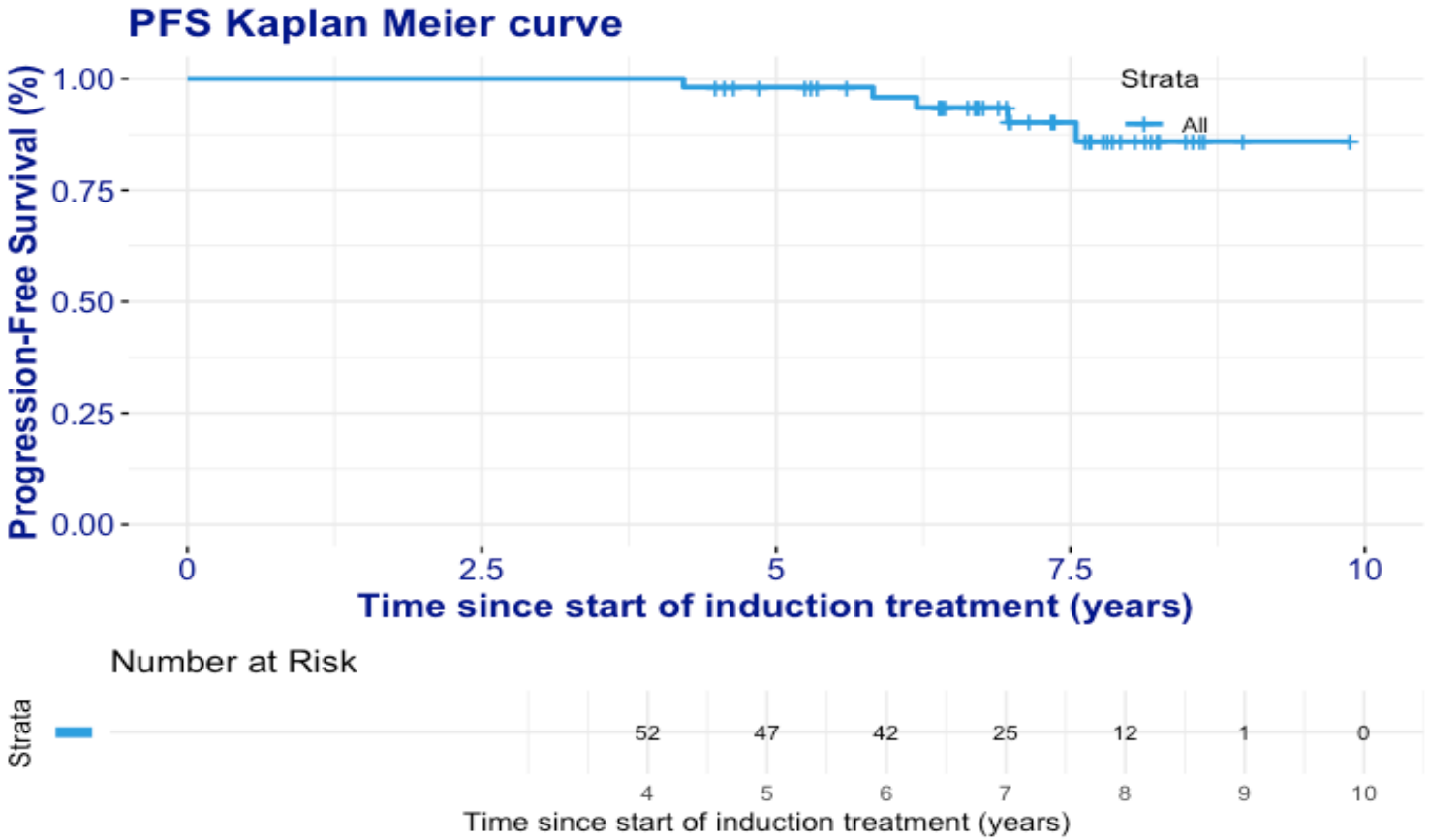
TFS was defined as the time from maintenance discontinuation to treatment re-initiation, progression, death from any cause or last follow-up.

ASH 2024; *Blood* (2025) 145 (20): 2353–2360.

PFS

- ✓ **The overall median PFS was not reached, while the 7-year PFS was 90.2% (95% CI: 81.2%-100.0%)**

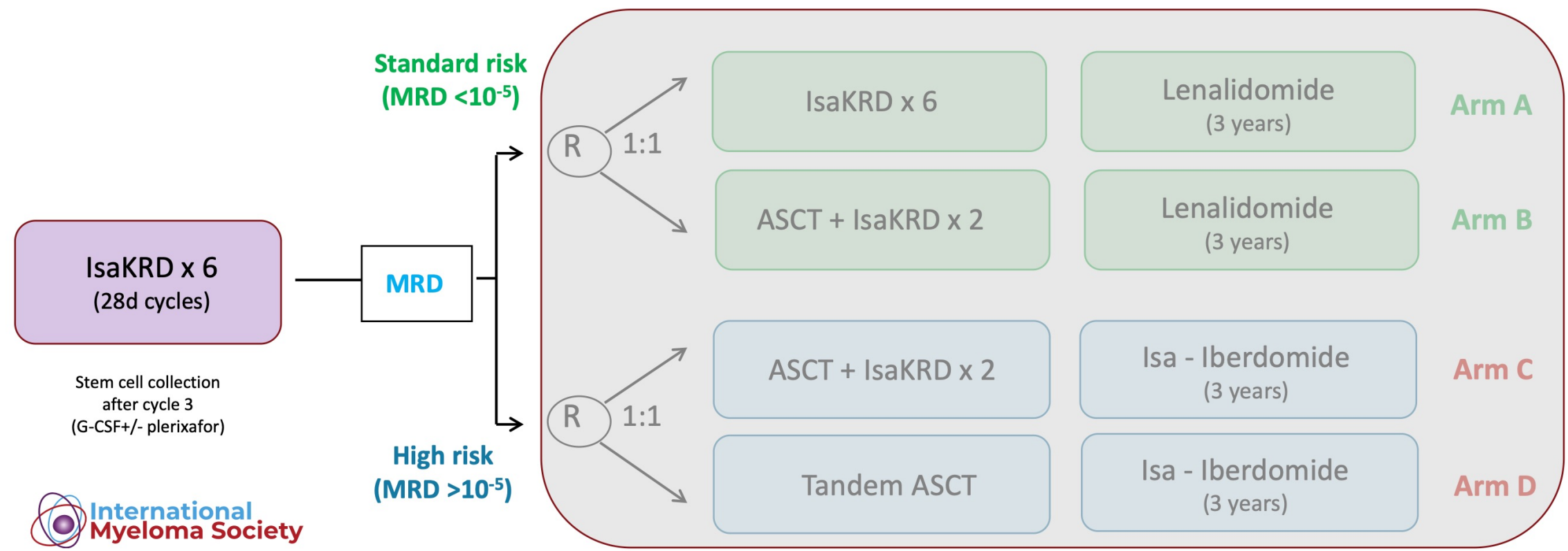
- ✓ The 1-, 2- and 3-year landmark PFS rates were 96.0%, 96.0% and 92.9%, respectively.



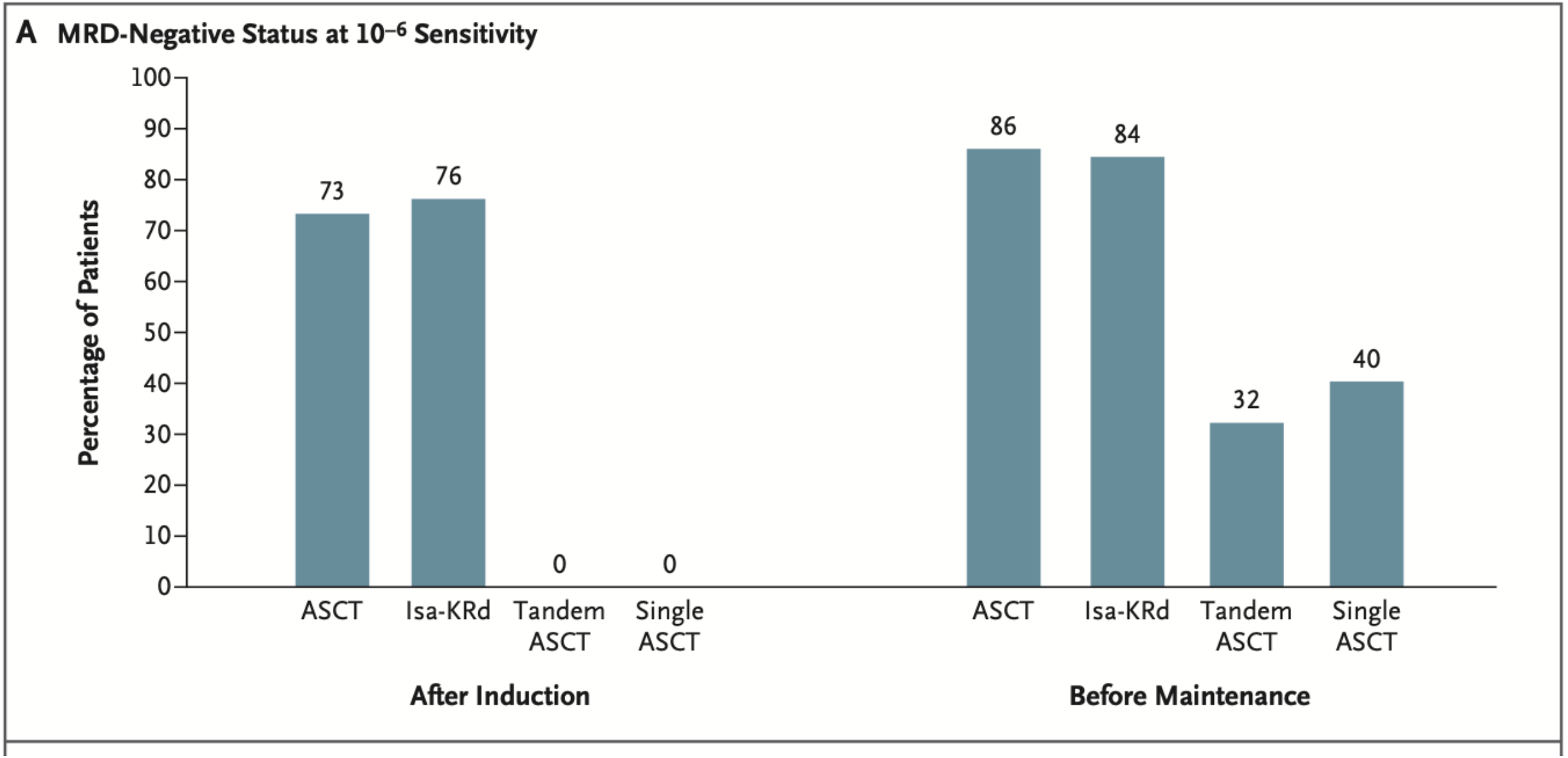
ASH 2024; *Blood* (2025) 145 (20): 2353–2360.

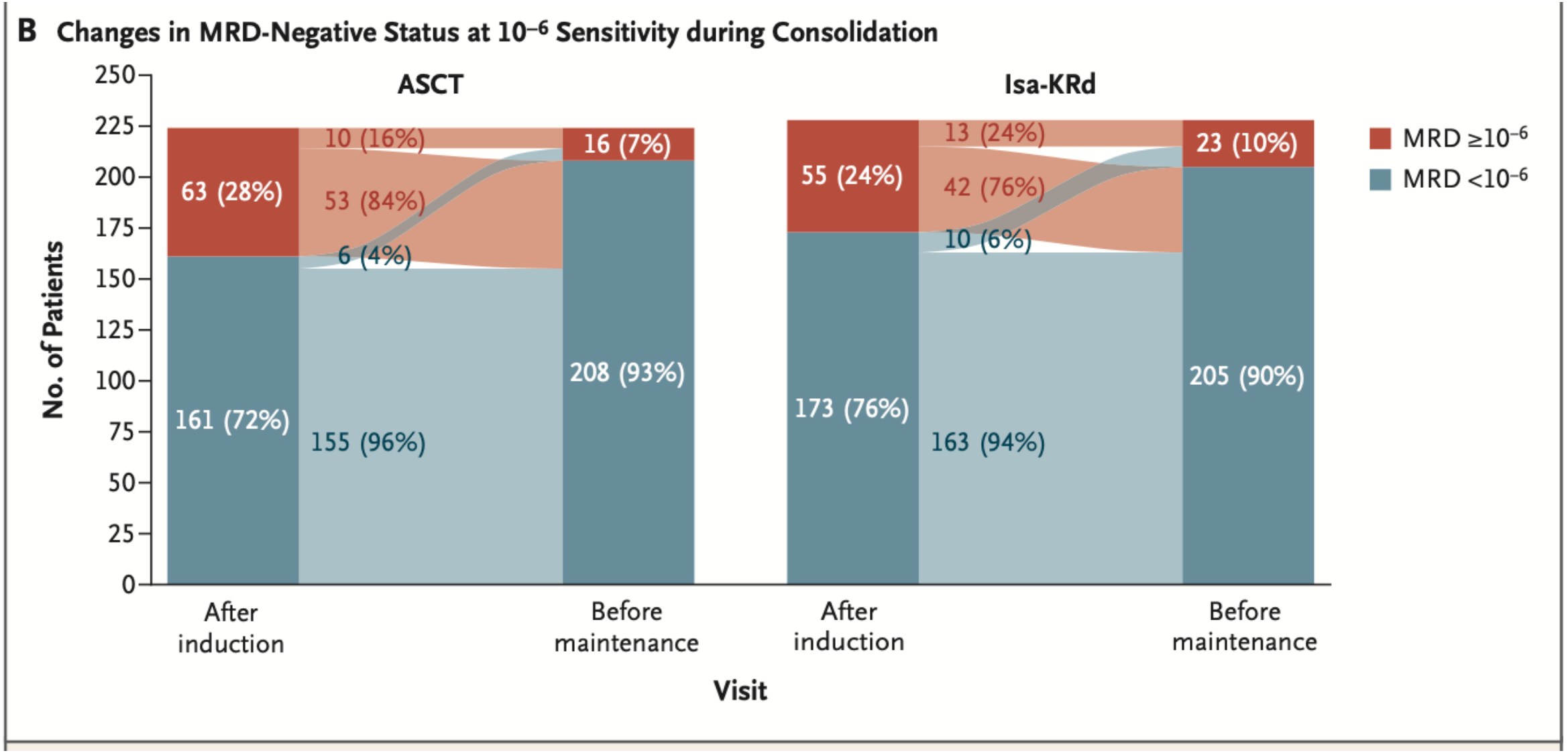
Study design

MIDAS = MInimal residual Disease Adapted Strategy

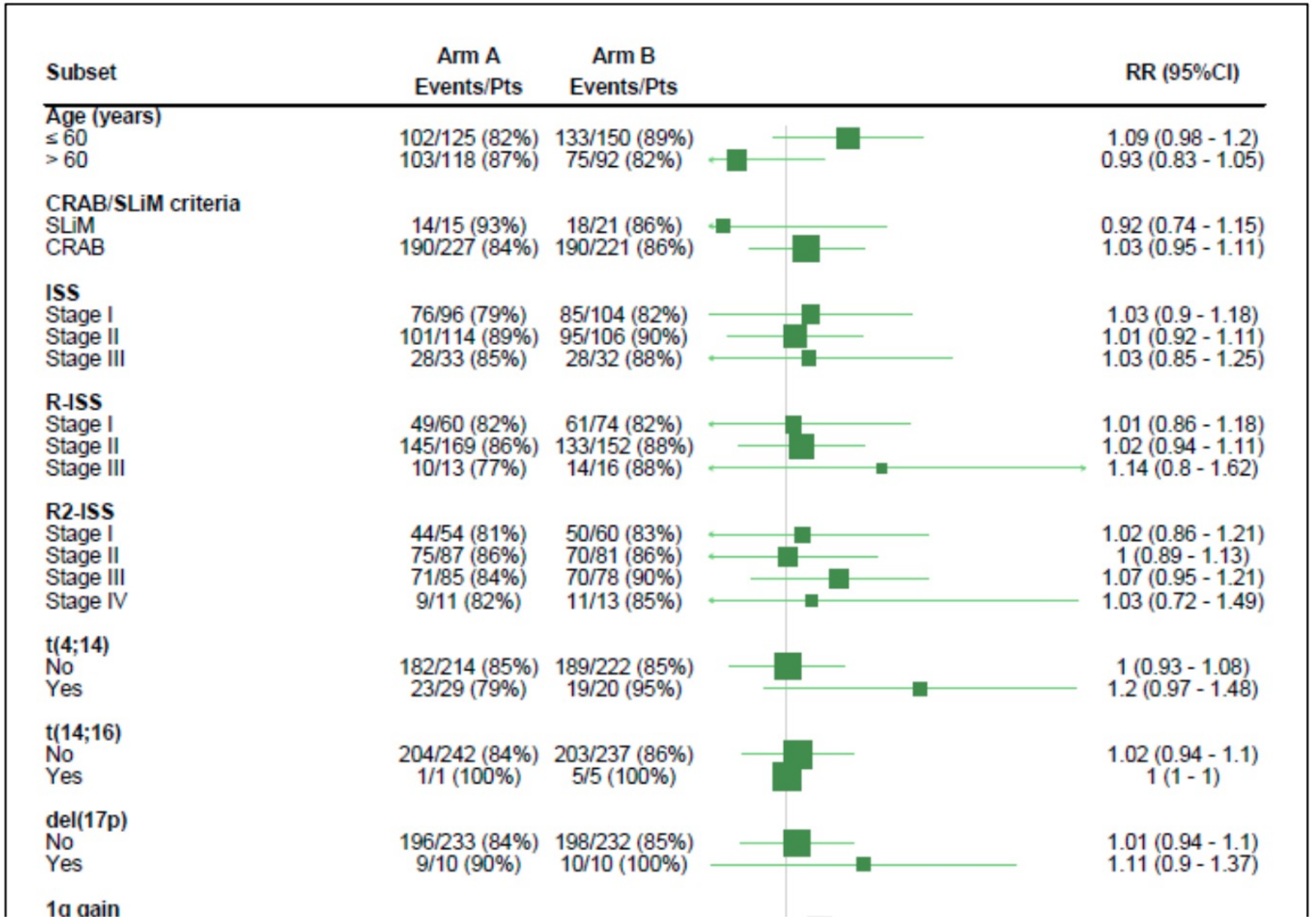


N Engl J Med . 2025 Jun 3.doi: 10.1056/NEJMoa2505133. Online ahead of print.


A MRD-Negative Status at 10⁻⁶ Sensitivity
Percentage of Patients
100
90
80
70
60
50
40
30
20
10
0
73
76
0
0
86
84
32
40
ASCT
Isa-KRd
Tandem ASCT
Single ASCT
ASCT
Isa-KRd
Tandem ASCT
Single ASCT
After Induction
Before Maintenance



N Engl J Med . 2025 Jun 3.doi: 10.1056/NEJMoa2505133. Online ahead of print.


Subset
Arm A Events/Pts
Arm B Events/Pts
RR (95%CI)
Age (years)
≤ 60 102/125 (82%) 133/150 (89%) 1.09 (0.98 - 1.2)
> 60 103/118 (87%) 75/92 (82%) 0.93 (0.83 - 1.05)
CRAB/SLiM criteria
SLiM 14/15 (93%) 18/21 (86%) 0.92 (0.74 - 1.15)
CRAB 190/227 (84%) 190/221 (86%) 1.03 (0.95 - 1.11)
ISS
Stage I 76/96 (79%) 85/104 (82%) 1.03 (0.9 - 1.18)
Stage II 101/114 (89%) 95/106 (90%) 1.01 (0.92 - 1.11)
Stage III 28/33 (85%) 28/32 (88%) 1.03 (0.85 - 1.25)
R-ISS
Stage I 49/60 (82%) 61/74 (82%) 1.01 (0.86 - 1.18)
Stage II 145/169 (86%) 133/152 (88%) 1.02 (0.94 - 1.11)
Stage III 10/13 (77%) 14/16 (88%) 1.14 (0.8 - 1.62)
R2-ISS
Stage I 44/54 (81%) 50/60 (83%) 1.02 (0.86 - 1.21)
Stage II 75/87 (86%) 70/81 (86%) 1 (0.89 - 1.13)
Stage III 71/85 (84%) 70/78 (90%) 1.07 (0.95 - 1.21)
Stage IV 9/11 (82%) 11/13 (85%) 1.03 (0.72 - 1.49)
t(4;14)
No 182/214 (85%) 189/222 (85%) 1 (0.93 - 1.08)
Yes 23/29 (79%) 19/20 (95%) 1.2 (0.97 - 1.48)
t(14;16)
No 204/242 (84%) 203/237 (86%) 1.02 (0.94 - 1.1)
Yes 1/1 (100%) 5/5 (100%) 1 (1 - 1)
del(17p)
No 196/233 (84%) 198/232 (85%) 1.01 (0.94 - 1.1)
Yes 9/10 (90%) 10/10 (100%) 1.11 (0.9 - 1.37)
1q gain

Conclusion

- Assessment for MRD is here to stay in myeloma
- Current technology requires bone marrow biopsy
- Future will include blood based assays
- Emerging data support discontinuation in specific patient scenarios
  - Long term PFS/OS data is not available
  - Optimal MRD cutpoint and timing not known
- Emerging data suggest the ability to use MRD as a tool in decision making for optimal consolidation after induction
  - PFS data pending
  - Subset analysis for individualized care will be critical