Highlights from IMW 2021

1-2 febbraio 2022
Bologna
Royal Hotel Carlton

Paola Tacchetti
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Istituto di Ematologia "Seràgnoli"

Dalle terapie one-size-fits-all alle terapie guidate dalla valutazione MRD

Coordinatore Scientifico
Michele CAVO

Comitato Scientifico
Michele CAVO
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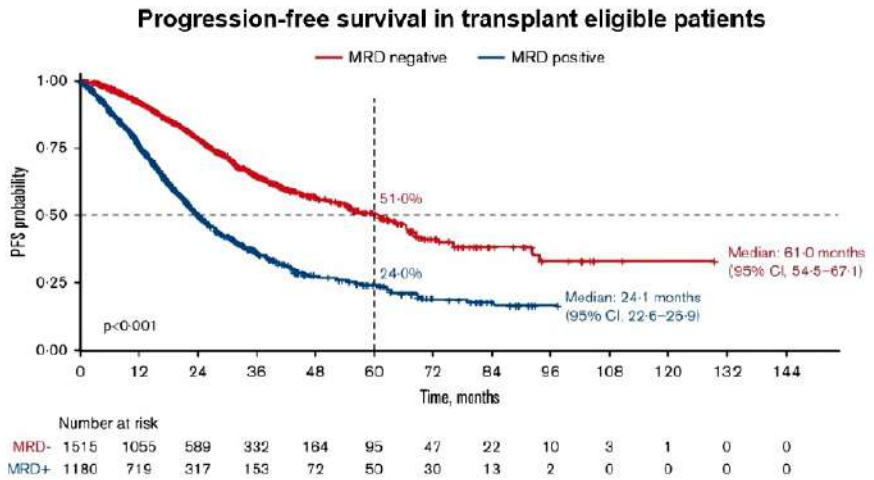
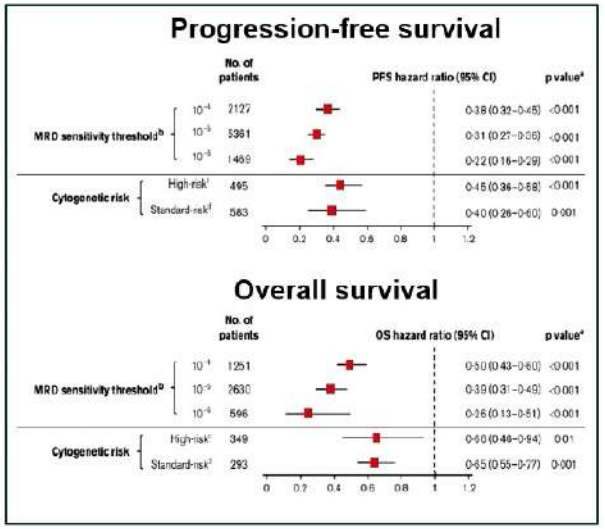
Treatment paradigm for transplant-eligible patients

Sequential blocks of therapy

Continued cytoreduction
Sustained suppression of disease burden

Role of MRD-negativity in NDMM





Cavo M et al. Blood 2011;117(23):6063-73; Kumar S, et al. Lancet Oncology 2016;17:e328-46; Gay F et al. Haematologica 2018;103(2): 197-211;
Munshi et al. Blood Adv. 2020 Dec 8;4(23):5988-5999

Selected phase 2-3 studies including MRD negativity as treatment endpoint

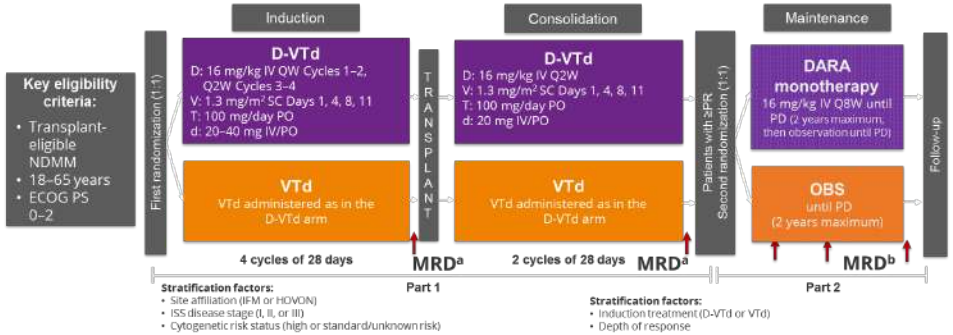
	PETHEMA / GEM2012	VRD x 6	ASCT	VRD x 2
CR		33.4	44.1	50.2
MFC (2.9 X 10^{-6})		28.9	42.1	45.2
	CASSIOPEIA	VTD x 4	ASCT	VTD x 2
≥ CR		8.9	14.6	26
MFC (10^{-5}) / NGS (10^{-5})		23		44 / 37
	CASSIOPEIA	D-VTD x 4	ASCT	D-VTD x 2
≥ CR		14.4	22.6	38.8
MFC (10^{-5}) / NGS (10^{-5})		35		64 / 57
	GRIFFIN	VRD x 4	ASCT	VRD x 2
≥ CR		13.4	19.6	42.3
NGS (10^{-5})		8		20
	GRIFFIN	D-VRD x 4	ASCT	D-VRD x 2
≥ CR		19.2	27.3	51.5
NGS (10^{-5})		22		50

	FORTE	KCD x 4	ASCT	KRD x 4
≥ CR		8*	24*	47*
MFC (10^{-5})				42
	FORTE	KRD x 4	ASCT	KRD x 4
≥ CR		16	34*	60*
NGS (10^{-5})				58
	FORTE	KRD	KRD	KRD x 12
≥ CR				61*
NGS (10^{-5})				54
	NCT02405364	KRD x 4	ASCT	KRD x 4
≥ CR				64
MFC ($2.5x10^{-5}$) / NGS (10^{-6})				92.6 / 63
	NCT01816791	KRD x 4	ASCT	KRD x 4
≥ CR		16	25	65
NGS (10^{-5})				60

* Confirmed and unconfirmed

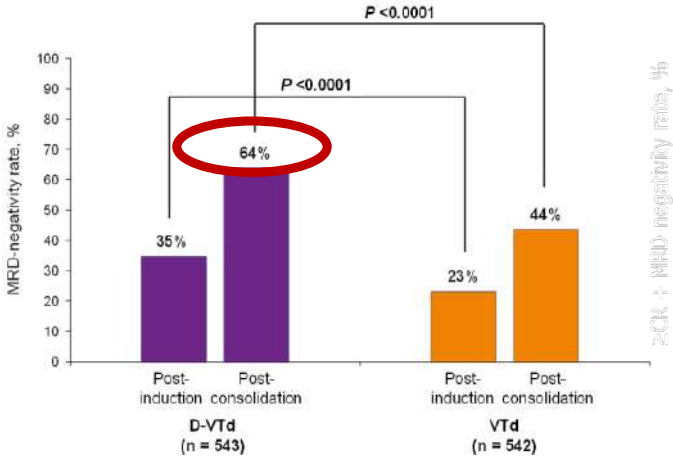
Rosinol L et al, Blood 2019; 134: 1337-1345; Paiva B et al, JCO 2019; 38: 784-792; Moreau P et al, Lancet 2019; 394: 29-38; Voorhes PM et al, Blood 2020; 136: 936-945; Gay F et al, ASH 2020, Oral Abstract; Roussel M et al, Blood 2021; 138:113-121; Jasielec JK et al, Blood 2020; 136: 2513-2523

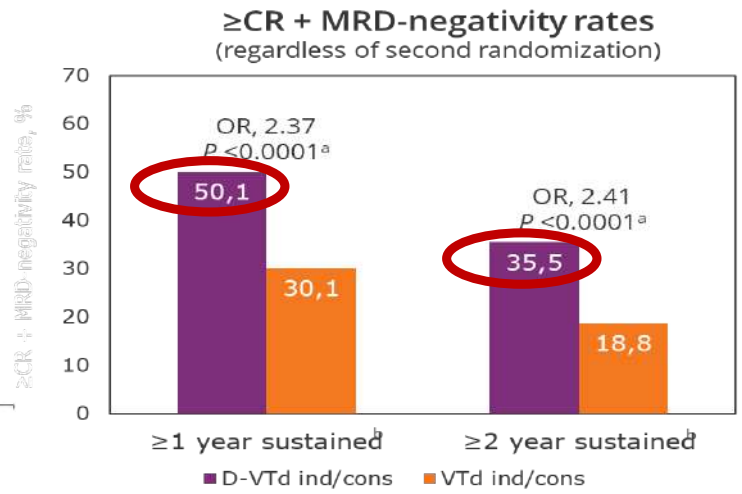
DARA-VTd in TE-NDMM: CASSIOPEIA phase 3 trial

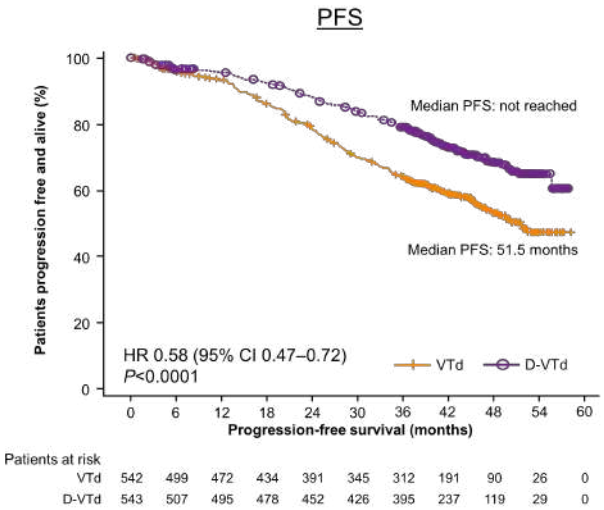


DaraVTd has been approved by FDA and EMA for the treatment of transplant eligible newly diagnosed MM patients

MRD rates (10^{-5}), MFC

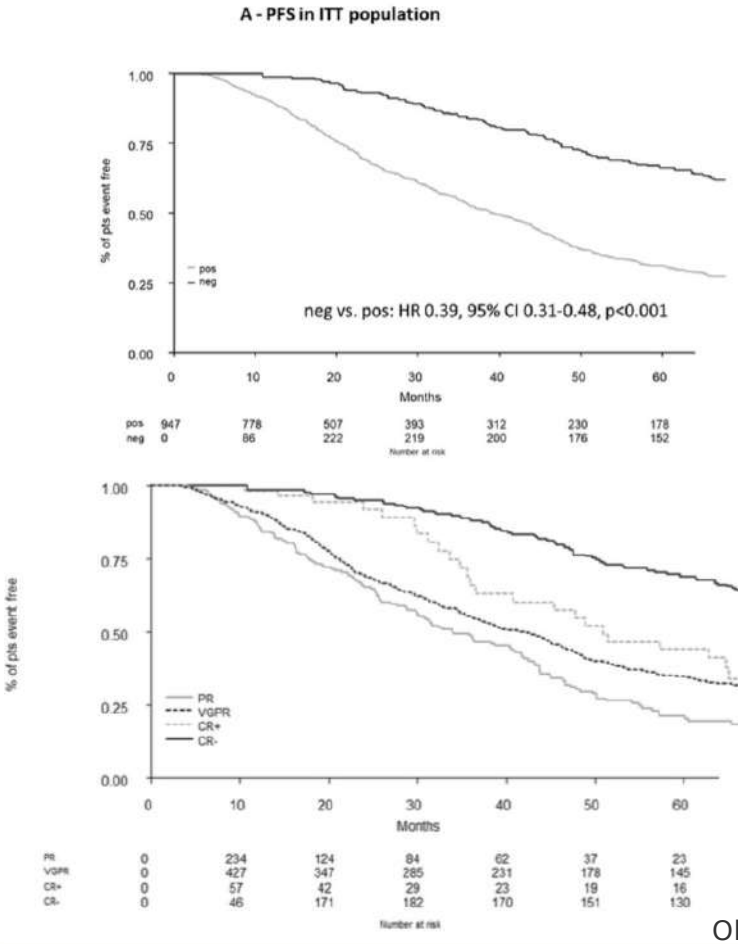


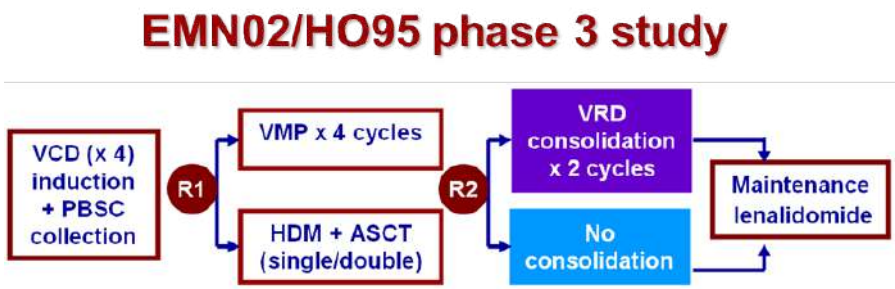


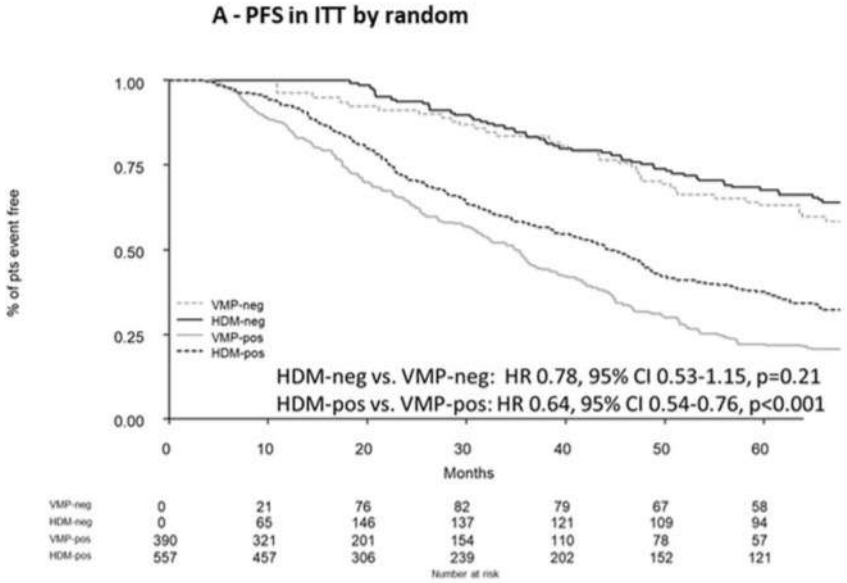


Moreau P, et al. Lancet. 2019; Moreau P, et al. Lancet Oncol. 2021; Avet-Loiseau H. et al. ASH 2021 oral 82

MRD (MFC, cut-off 10^{-5}) in the EMN02/HOVON 95 MM trial







Oliva S, et al. Blood Cancer Journal 2021

MANHATTAN trial: wKRd-Dara

Safety and Effectiveness of Weekly Carfilzomib, Lenalidomide, Dexamethasone, and Daratumumab Combination Therapy for Patients With Newly Diagnosed Multiple Myeloma
The MANHATTAN Nonrandomized Clinical Trial

MRD neg. rate (MFC) after 8 cycles: 71% (29/41)

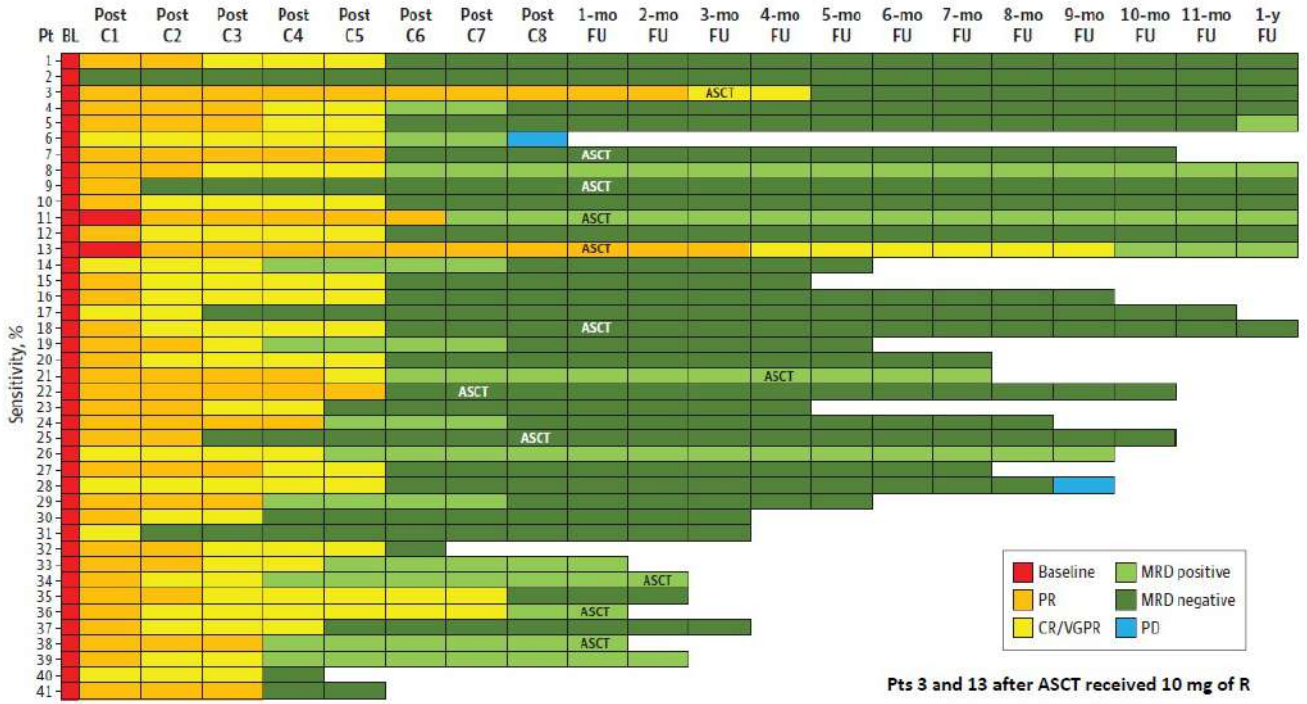
(MRD-CR rate: 59%)

Median time to MRD neg.: 6 cycles.

ORR: 100%

MRD negativity was not significantly different for pts with HR vs SR disease (odds ratio, 1.7; 95% CI, 0.36-8.6; *P* = .50), and the same was true for the association between MRD status and age (<60 y vs ≥60 y) (odds ratio, 0.48; 95%CI, 0.08-2.3; *P* = .32).

8 patients have been assessed for MRD at 1-year follow-up, and 7 of these 8 patients (88%) showed 1-year sustained MRD negativity.



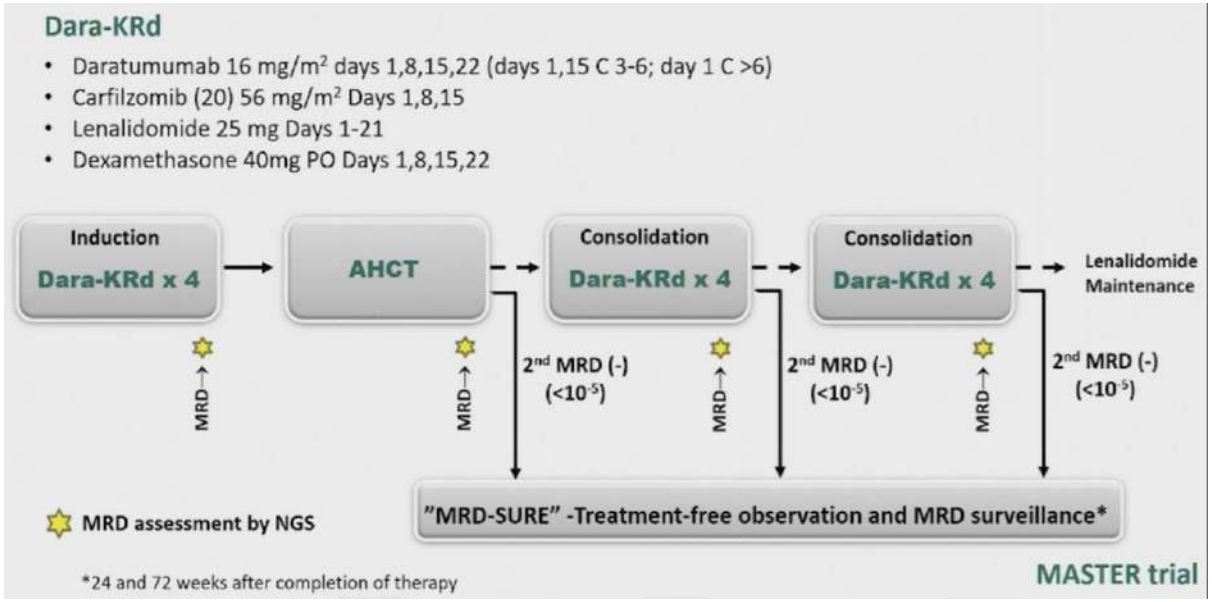
Landgren O et al. JAMA 2021

MASTER trial: DaraKRd, ASCT, and MRD response-adapted consolidation and treatment cessation

Patients[1,2]

Key inclusion criteria
- NDMM with measurable disease
- ECOG PS 0–2
- CrCl ≥ 40 mL/min

Key exclusion criteria
- Clinically significant cardiopulmonary disease, concomitant or recent malignancy



Endpoints[1]

Primary endpoints: rate of MRD-negative responses ($< 10^{-5}$) by NGS
Key secondary endpoints: Response rates, frequency of imaging plus MRD-negative CR, post-AHCT MRD, safety
Exploratory endpoints: MRD-negative rates with threshold of 10^{-6} by NGS

Costa L et al. IMW 2021; ASH 2021; JCO 2021

MASTER trial: Patients

- 123 patients enrolled across 5 sites
- 118 (96%) with MRD trackable by ClonoSEQ®
- Median follow-up of 23.8 months

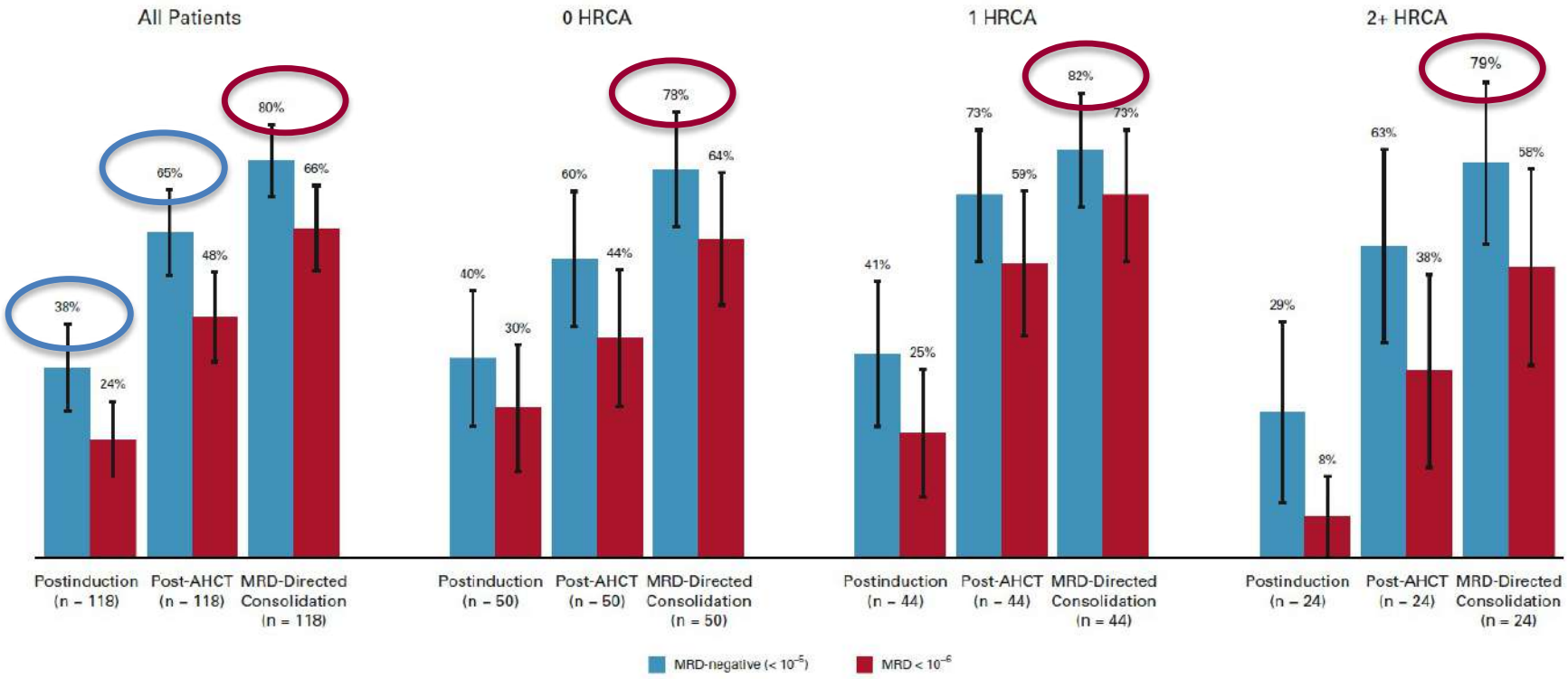
Characteristic		Standard-risk 0 HRCA N=53 (43%)	High-risk 1 HRCA N=46 (37%)	Ultra high-risk 2+ HRCA N=24 (20%)	Total N=123
Gender					
	Male	33 (62%)	24 (52%)	13 (54%)	70 (57%)
	Female	20 (38%)	22 (48%)	11 (46%)	53 (43%)
Age					
	Median (range)	60 (36-79)	61 (35-77)	60 (41-72)	60 (35-79)
	Age ≥ 70	12 (23%)	10 (22%)	2 (8%)	24 (20%)
Race/ethnicity					
	Whites	42 (79%)	33 (72%)	19 (79%)	94 (76%)
	Racial/ethnic minorities	11 (21%)	13 (28%)	5(21%)	29 (23%)
ECOG					
	0-1	42 (79%)	40 (87%)	17 (71%)	99 (80%)
	2	11 (21%)	6 (13%)	7 (29%)	24 (20%)

Characteristic		Standard-risk 0 HRCA N=53 (43%)	High-risk 1 HRCA N=46 (37%)	Ultra high-risk 2+ HRCA N=24 (20%)	Total N=123
LDH					
	<ULN	45 (85%)	34 (74%)	18 (75%)	97 (79%)
	≥ ULN	8 (15%)	12 (26%)	6 (25%)	26 (21%)
Cytogenetic abnormality					
	hyperdiploidy	27 (51%)	20 (44%)	4 (17%)	51 (41%)
	del(13q)	19 (36%)	20 (44%)	18 (75%)	57 (46%)
	gain/amplification 1q	0 (0%)	24(52%)	20 (83%)	44 (36%)
	del(1p)	3 (6%)	4 (9%)	5 (21%)	12 (10%)
	t(11;14)	14 (26%)	7 (15%)	0 (0%)	21 (17%)
	t(4;14)	0 (0%)	8 (17%)	13 (54%)	21 (17%)
	t(14;16)	0 (0%)	2 (4%)	4 (17%)	6 (5%)
	del(17p)	0 (0%)	12 (26%)	14 (58%)	26 (21%)
R-ISS					
	1	25 (47%)	11 (24%)	0 (0%)	35 (28%)
	2	27 (51%)	23 (50%)	13 (54%)	63 (51%)
	3	1 (2%)	12 (26%)	11 (46%)	25 (20%)

HRCA: gain/amp 1q; t(4;14), t(14;20), t(14;16) or del (17p)

Costa L et al. IMW 2021; ASH 2021; JCO 2021

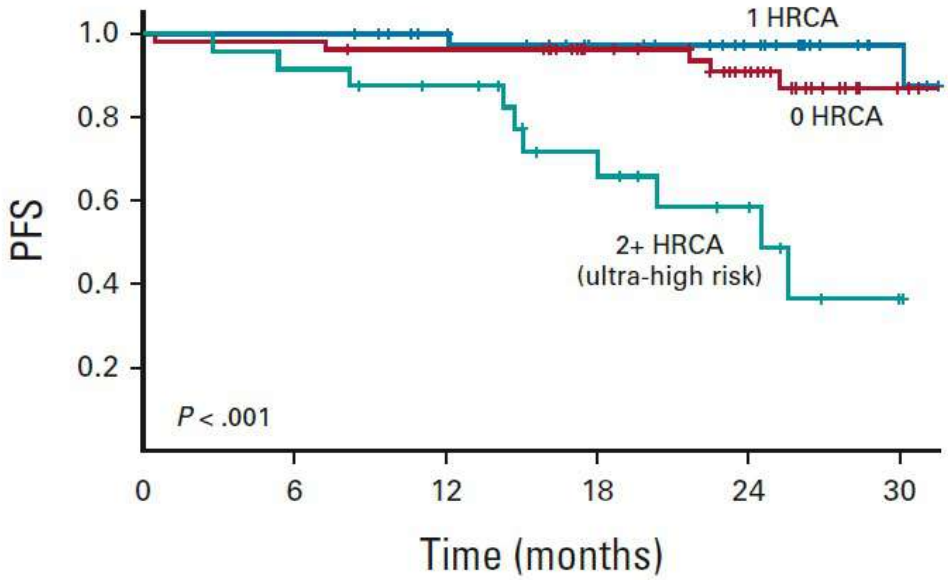
MASTER trial: Achievement of MRD negativity according to phase of therapy and number of HRC



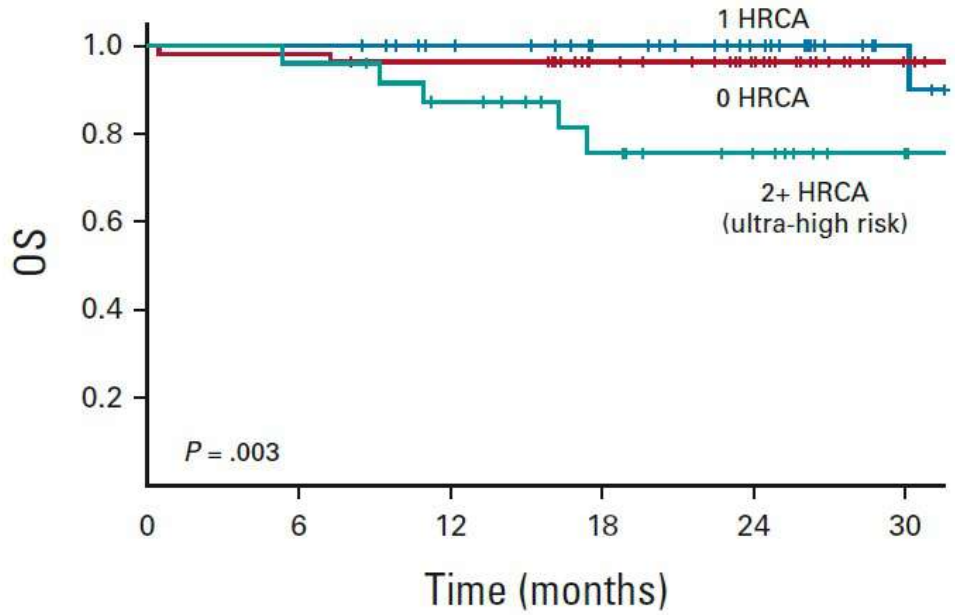
HRCA: gain/amp 1q; t(4;14), t(14;20), t(14;16) or del (17p)

Costa L et al. IMW 2021; ASH 2021; JCO 2021

MASTER trial: Progression-Free and Overall Survival



No. at risk:						
0 HRCA	50	49	46	36	27	10
1 HRCA	44	44	36	30	23	9
2+ HRCA	24	22	19	12	7	2



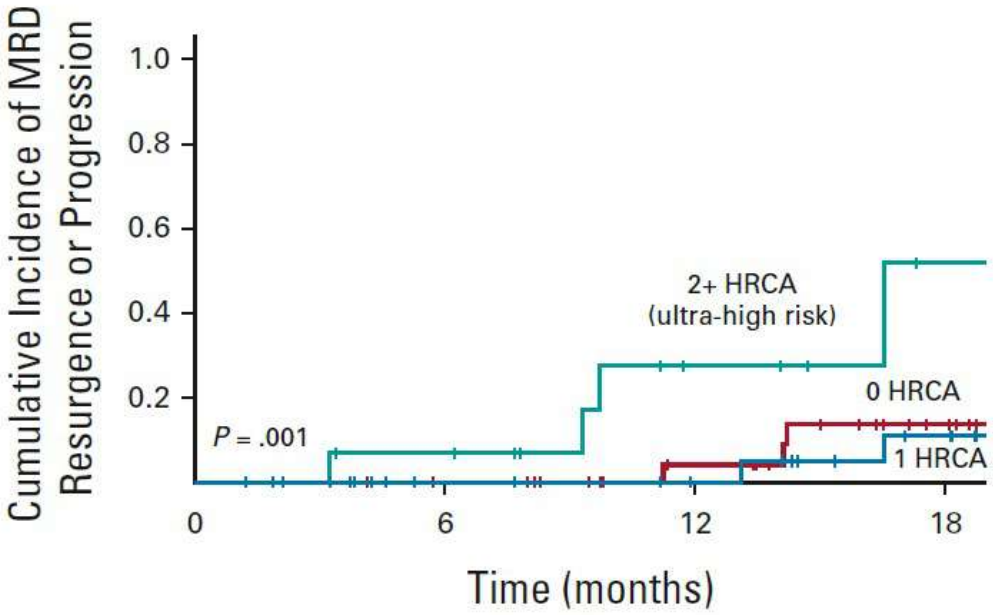
No. at risk:						
0 HRCA	50	49	46	36	29	11
1 HRCA	44	44	36	30	23	9
2+ HRCA	24	23	19	13	9	3

Costa L et al. IMW 2021; ASH 2021; JCO 2021

MASTER trial: MRD-SURE

- 84 patients achieved MRD-SURE
  - 0 HRCA – 62%
  - 1 HRCA- 78%
  - 2+ HRCA – 63%
- Median follow up in MRD-SURE: 14.2 mo.
- Risk of MRD resurgence or progression 12 months after treatment cessation
  - 0 HRCA – 4%
  - 1 HRCA- 0%
  - 2+ HRCA – 27%
- **None** of patients entering MRD-SURE died from MM progression

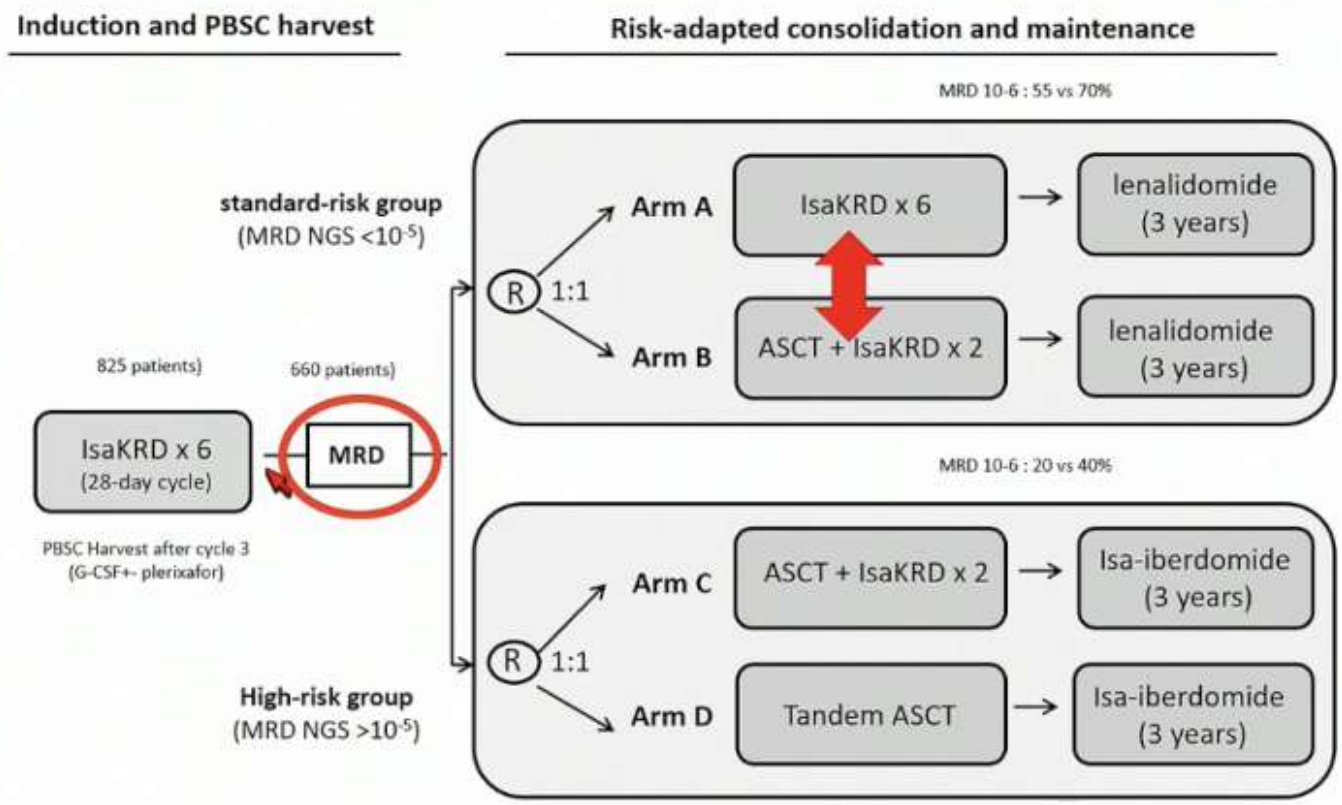
HRCA = gain/amp 1q, t(4;14), t(14;16), t(14;20) or del(17p)



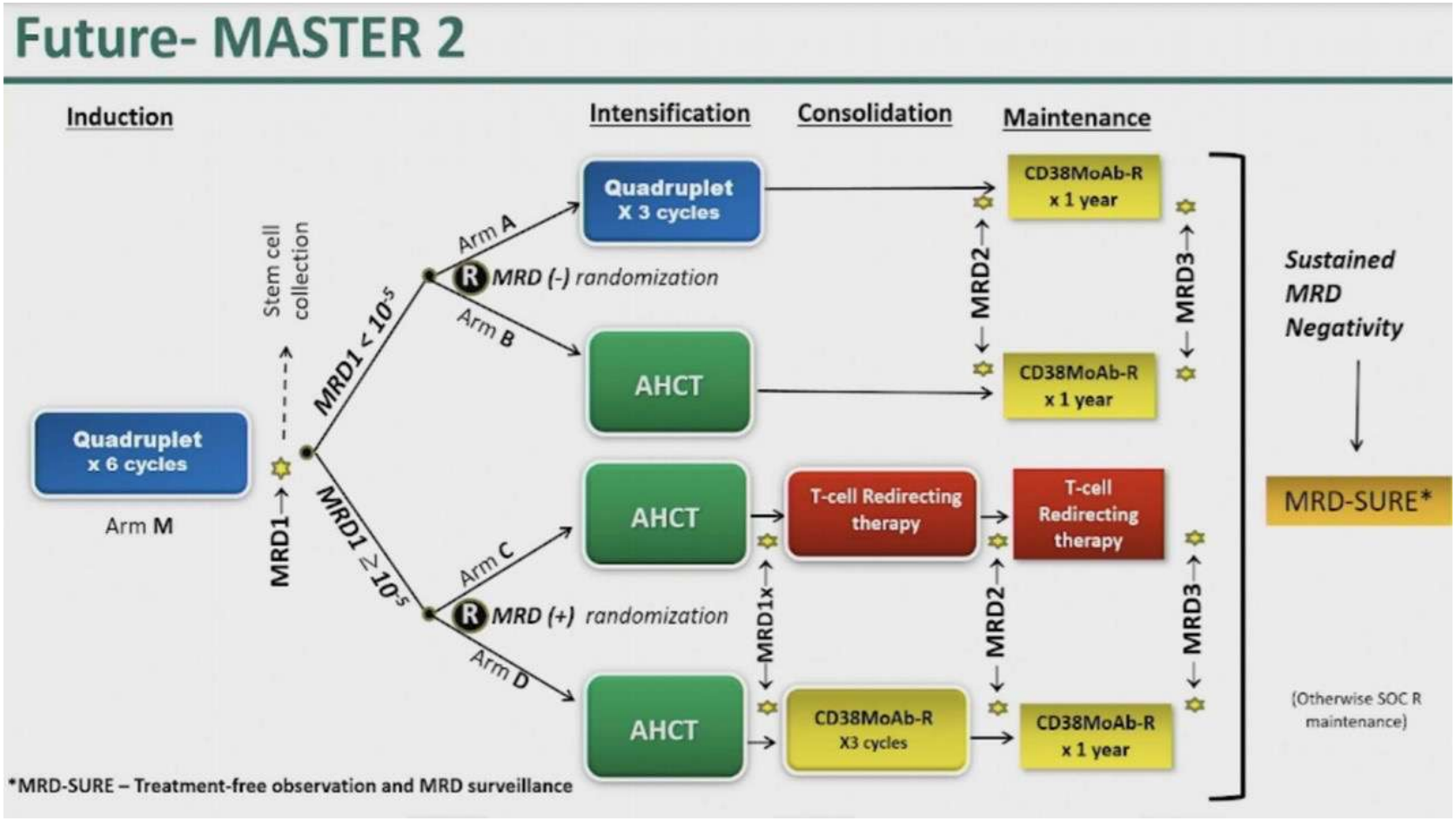
No. at risk:				
0 HRCA	33	31	23	12
1 HRCA	36	24	21	14
2+ HRCA	15	23	5	0

Costa L et al. IMW 2021; ASH 2021; JCO 2021

MIDAS study : MInimal res Disease Adapted Strategy



Moreau P IMW 2021



Costa L et al. ASH 2021

Minimal Residual Disease in MM: Application for Clinical Care and New Drug Registration

- The biological plausibility and prognostic value of MRD are well understood and have been supported by multiple studies.
- MRD negativity is achievable across the entire disease spectrum.
- MRD has the potential to be a surrogate for patient outcome.
- Almost 50 Phase III trials are currently actively enrolling using MRD-directed treatment assignment or MRD as an endpoint

Anderson KC et al. Clin Cancer Res 2021

Standardization depends on the application of MRD

Patient prognostication vs treatment decisions vs clinical trials

	Patient prognostication	Treatment decisions	Clinical trials
Methodology	Preferably IMWG	Ideally IMWG	Ideally IMWG
Sensitivity	10^{-5} - 10^{-6}	10^{-6}	10^{-5} - 10^{-6}
Timing	The latter the better	Immediate (eg. consolidation)	Adapted to study design
Sustainability	At least 1y?	More than 2y?	Depends on treatment schema

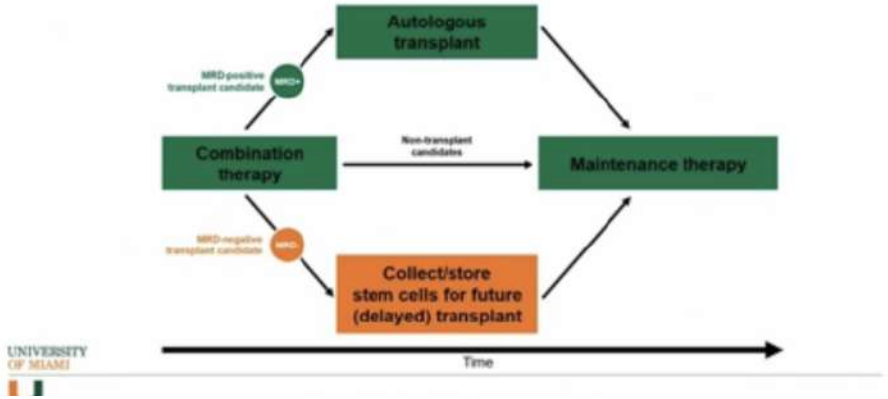
Ready for MRD guided therapy in MM?

- Progress in treatment has made cure a reality for Myeloma patients
- Progress in MRD testing and FDA approved NextGen sequencing and EuroFlow allows for wide clinical applicability
- Sustained MRD negativity with imaging leads to long-term survival

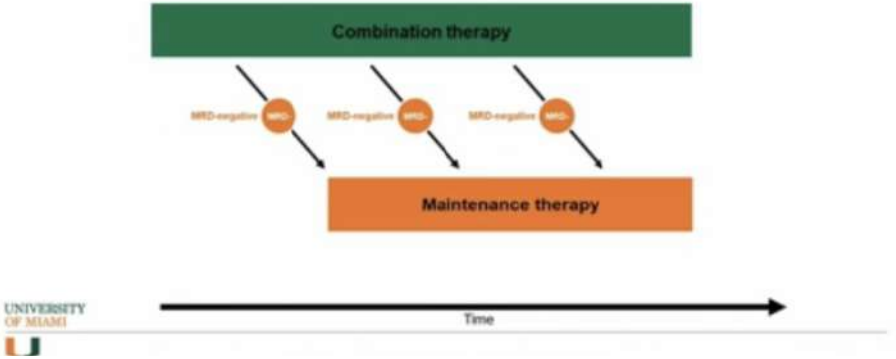
- **YES!** – It is prime time to use MRD guided therapy to make progress towards cure in MM
  - Should be part of every clinical trial
  - Also, part of patient management, especially in patients with high-risk genetics
  - CR at 5 years for stopping maintenance

Ready for MRD guided therapy in MM?

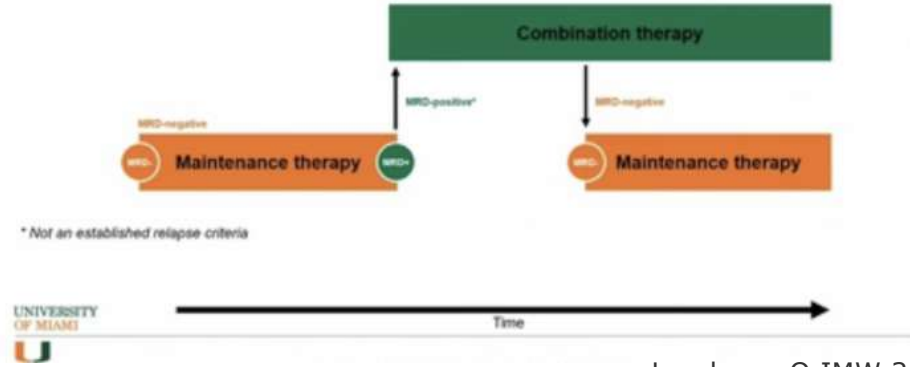
Potential Scenario 1: MRD-guided transplant in multiple myeloma

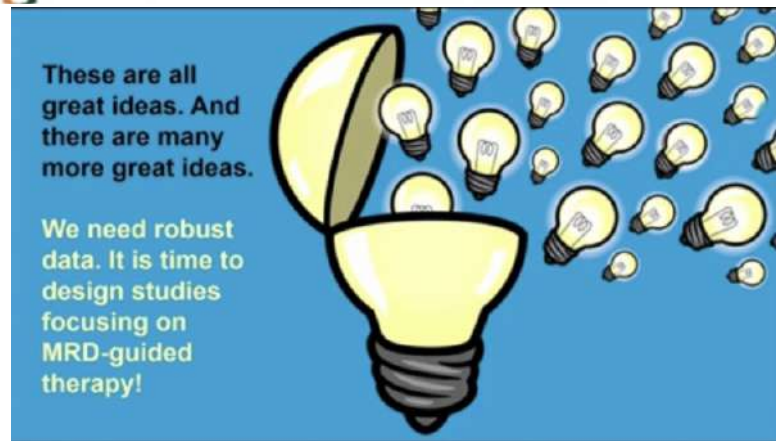


Potential Scenario 2: MRD-guided relapsed/refractory therapy



Potential Scenario 3: starting therapy based on MRD-positivity





Landgren O IMW 2021; Semin Hematol 2018

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1-2 Febbraio 2022
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Royal Hotel Carlton

GRAZIE PER L'ATTENZIONE!

Istituto di Ematologia Seràgnoli

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