

Can We Give our Patients a Treatment-Free Interval? **YES**

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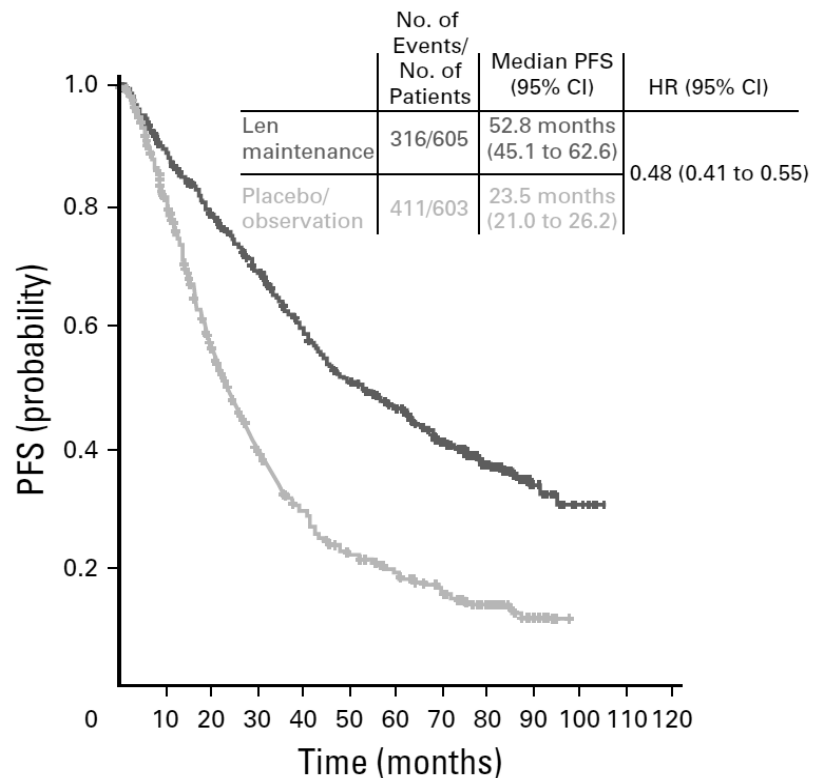
Disclosures

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- Honorarium: Amgen, Janssen, Sanofi, Karyopharm, BMS, Astra Zeneca

Current Paradigm = Continuous Therapy

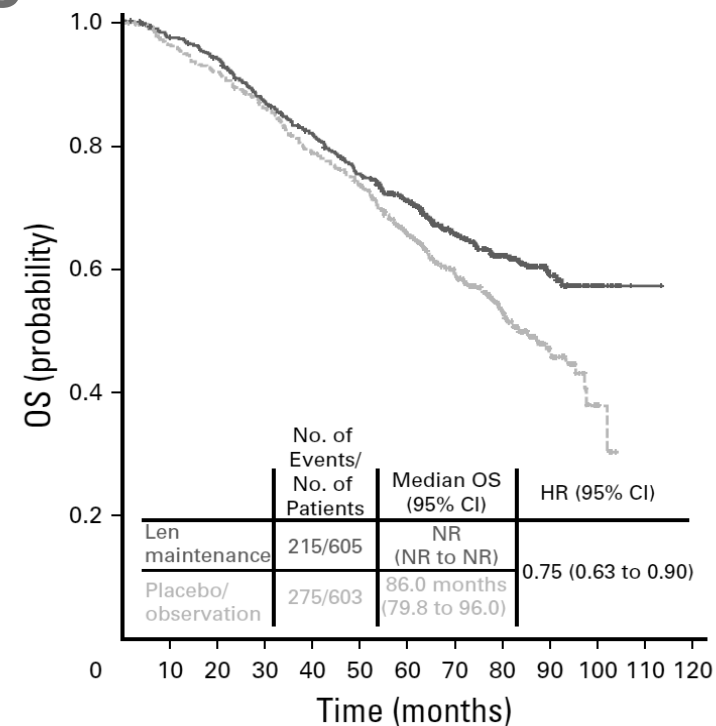
Knowledge that will change your world

PFS



No. at risk:	0	10	20	30	40	50	60	70	80	90	100	110	120
Len maintenance	605	499	428	353	293	244	191	131	83	28	5	0	
Placebo/ observation	603	419	275	179	125	90	71	52	30	9	0		

OS



No. at risk:	0	10	20	30	40	50	60	70	80	90	100	110	120
Len maintenance	605	577	555	508	473	431	385	282	200	95	20	1	0
Placebo/ observation	603	569	542	505	459	425	351	270	174	71	10	0	

Caveats of continuous therapy

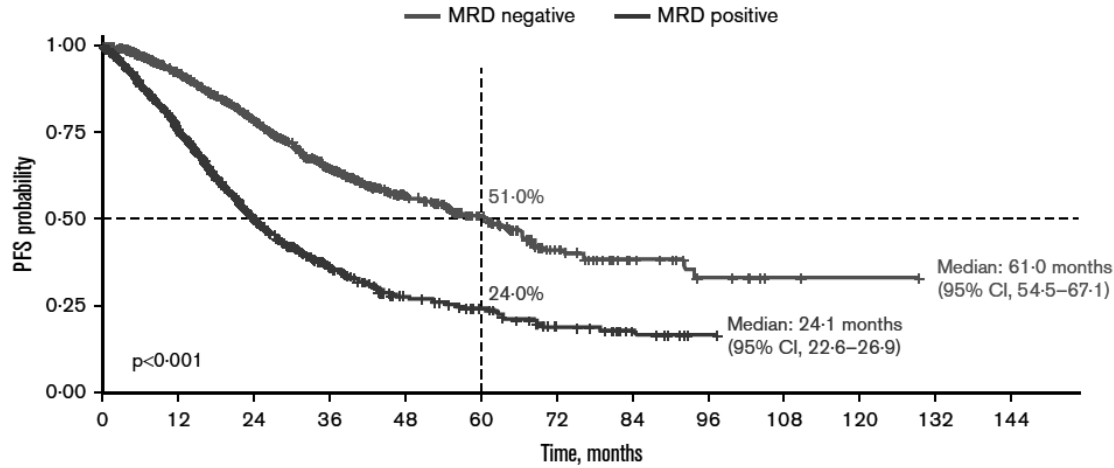
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- Intent vs. Reality
 - RWD, median duration of lenalidomide maintenance as little as **21 months**
- Cost
 - €277,456/QALY to €1,502,780/QALY
- One size does not fit all.
- Evidence for continuous therapy defined in setting of less active therapy

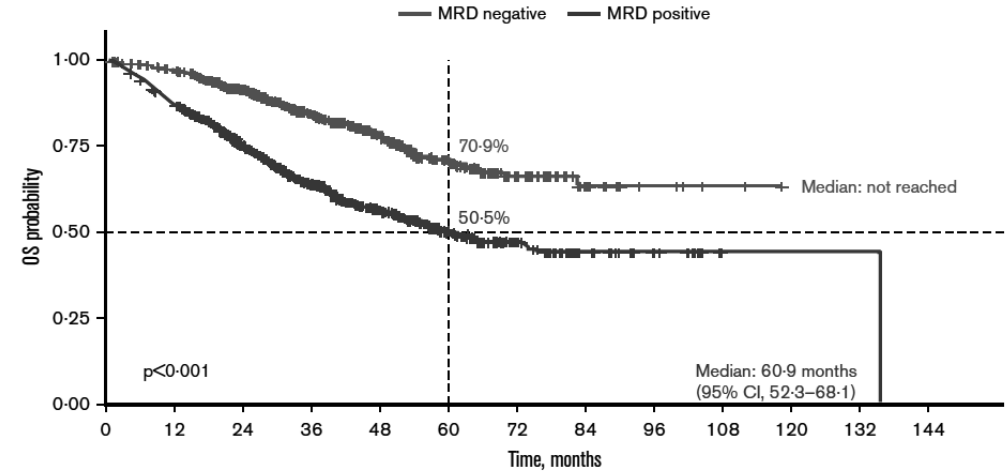
Hari et al. Future Oncol 15:4045, 2019

de Labry Lima et al. Bone Marrow Transplant 54:1908, 2019

MRD Strongly Predicts outcomes



	0	12	24	36	48	60	72	84	96	108	120	132	144
MRD-	1515	1055	589	332	164	95	47	22	10	3	1	0	0
MRD+	1180	719	317	153	72	50	30	13	2	0	0	0	0



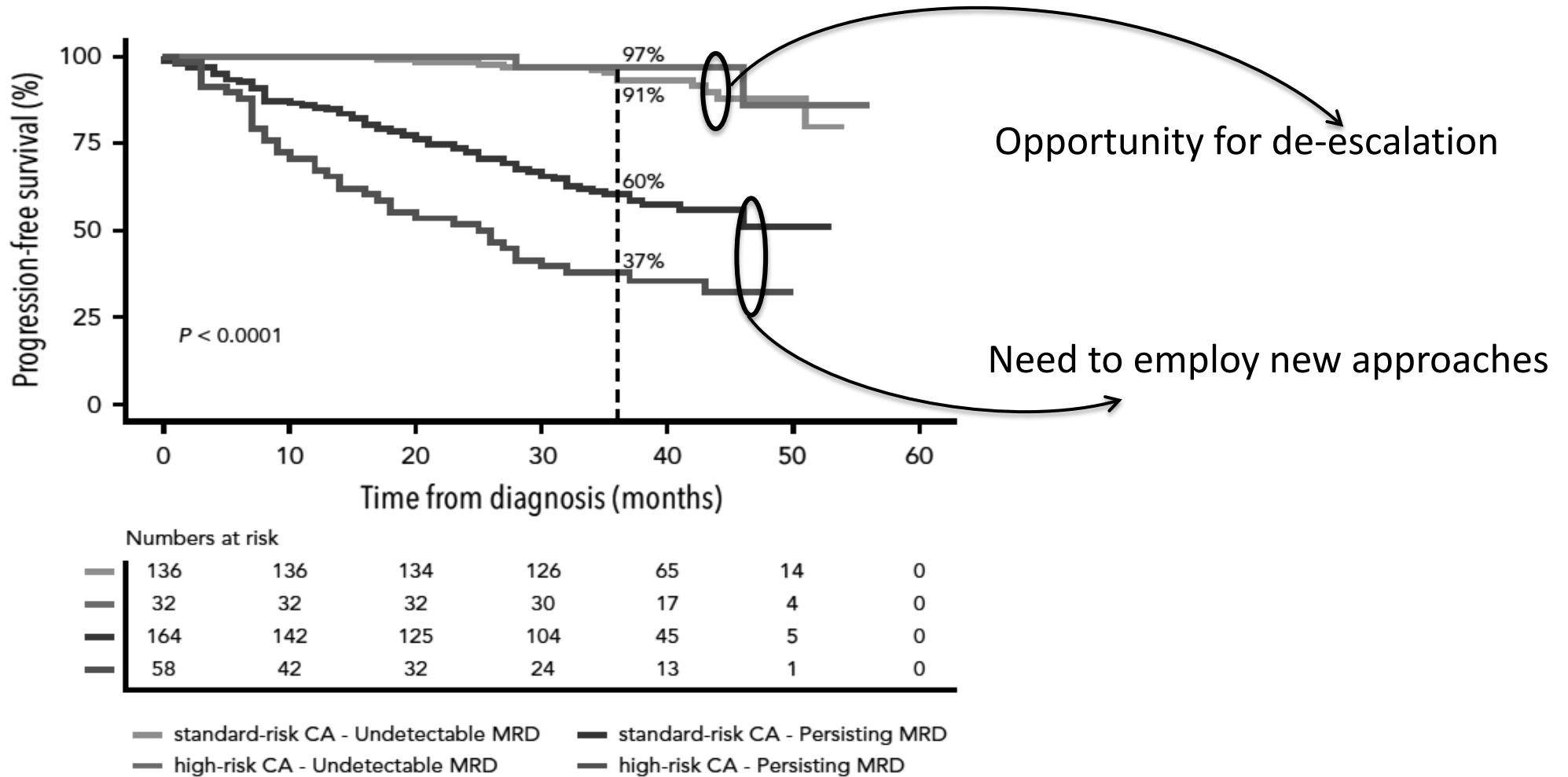
	0	12	24	36	48	60	72	84	96	108	120	132	144
MRD-	794	759	593	380	205	126	45	18	8	5	0	0	0
MRD+	678	584	424	260	140	100	51	26	18	3	3	3	0

		No. of patients		PFS hazard ratio (95% CI)	p value ^a
MRD sensitivity threshold ^b	10 ⁻⁴	2127	■	0.38 (0.32-0.45)	<0.001
	10 ⁻⁵	5361	■	0.31 (0.27-0.36)	<0.001
	10 ⁻⁶	1469	■	0.22 (0.16-0.29)	<0.001
Cytogenetic risk	High-risk ^c	495	■	0.45 (0.36-0.58)	<0.001
	Standard-risk ^d	583	■	0.40 (0.26-0.60)	0.001

MRD May Abrogate Other Risk Factors = Optimal Dynamic Risk Assessment Tool

Knowledge that will change you

PETHEMA/GEM2012
(MRD 2×10^{-6})



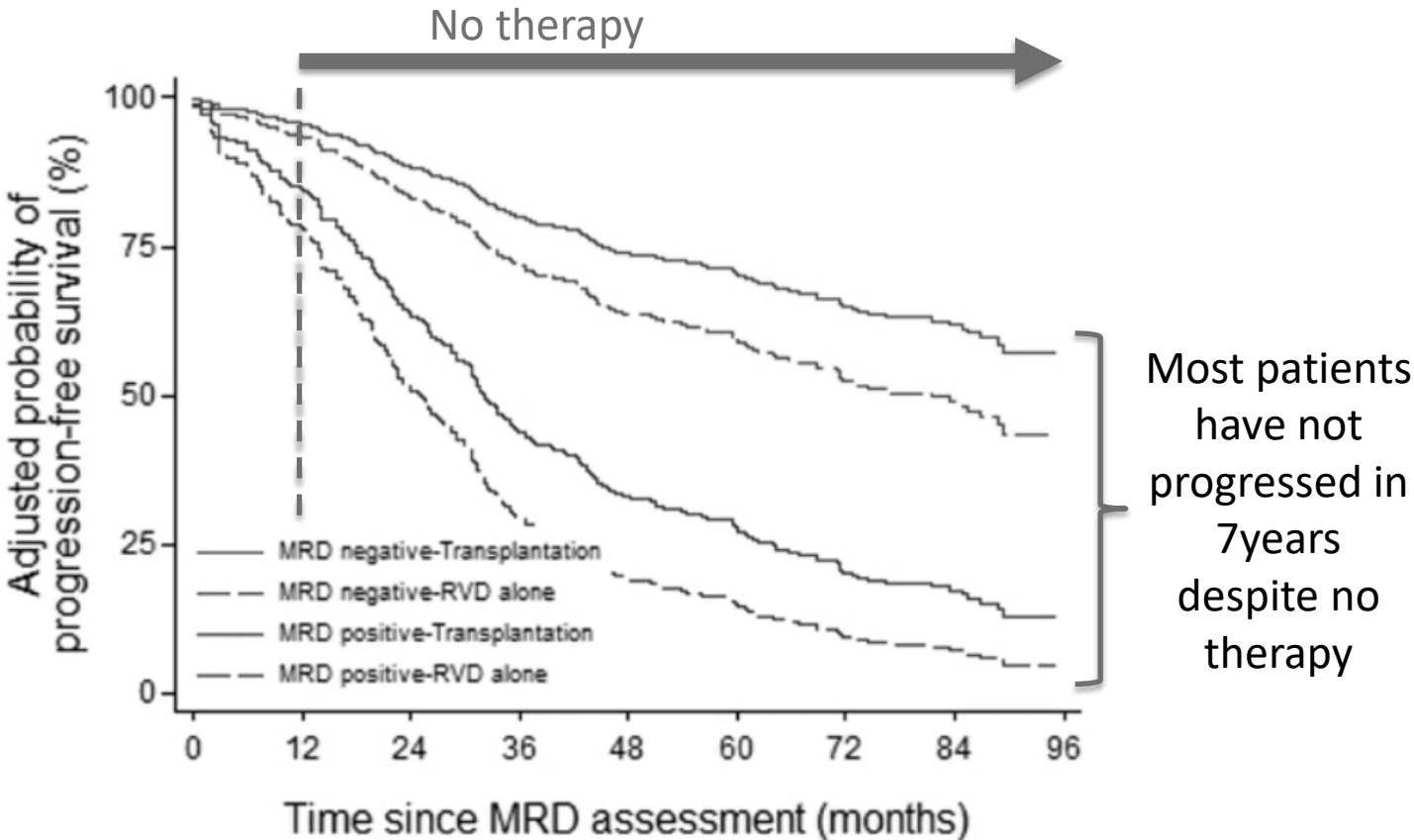
UAB THE UNIVERSITY OF ALABAMA AT BIRMINGHAM Downsides of Maintenance Therapy

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IFM 2009

Deferring Lenalidomide for 7 years:

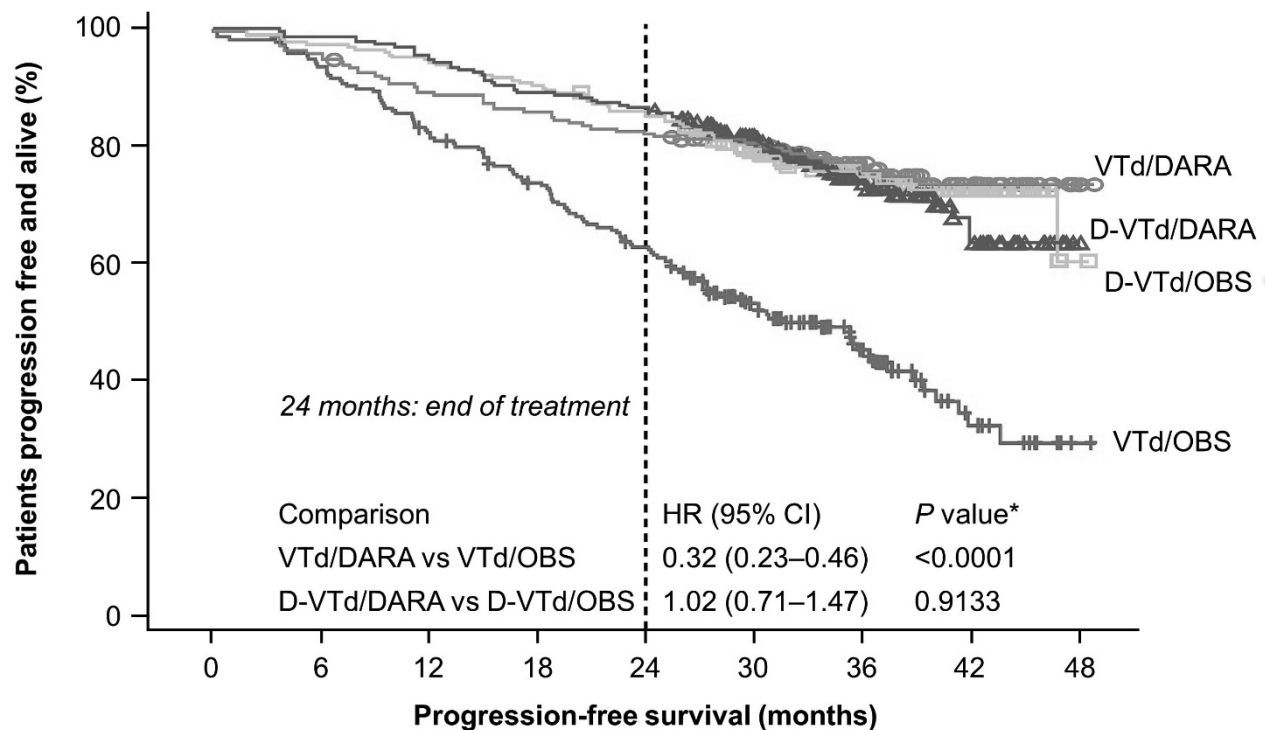
- "Saving" of US\$ 1.5 million!
- Avoid ~3.5% absolute increase in risk of SPM
- Avoid dozens of extra lab checks/MD visits
- Avoid diarrhea, fatigue, rash
- Avoid "daily reminder I have cancer"



Perrot A et al. ASH meeting 2020

UAB THE UNIVERSITY OF ALABAMA AT BIRMINGHAM A Lesson from Cassiopeia Part 2

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D-VTD/OBS arm -
 ~3/4 of patients without progression 3.5 years after end of therapy

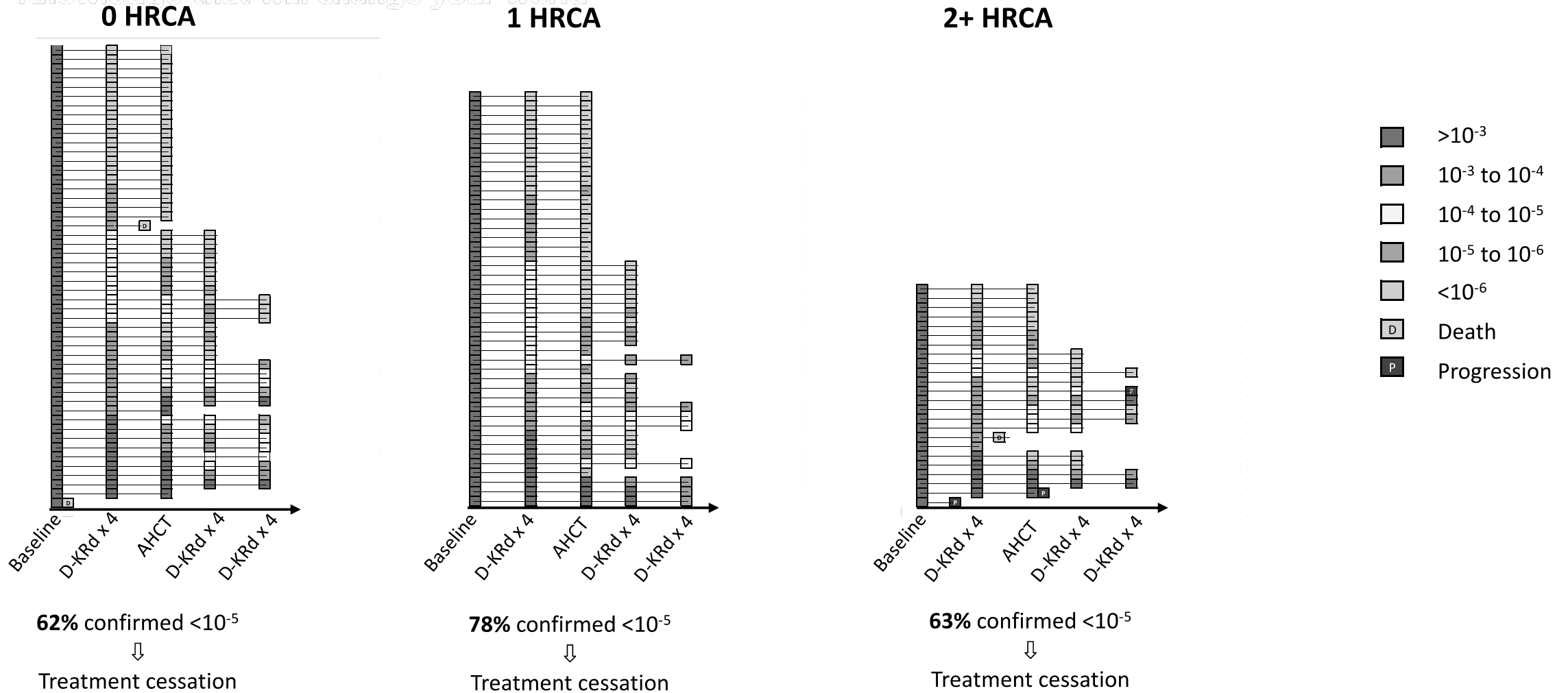
Patients at risk

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

Confirmed MRD(-) is Achievable in ~80% with Response-Adapted therapy

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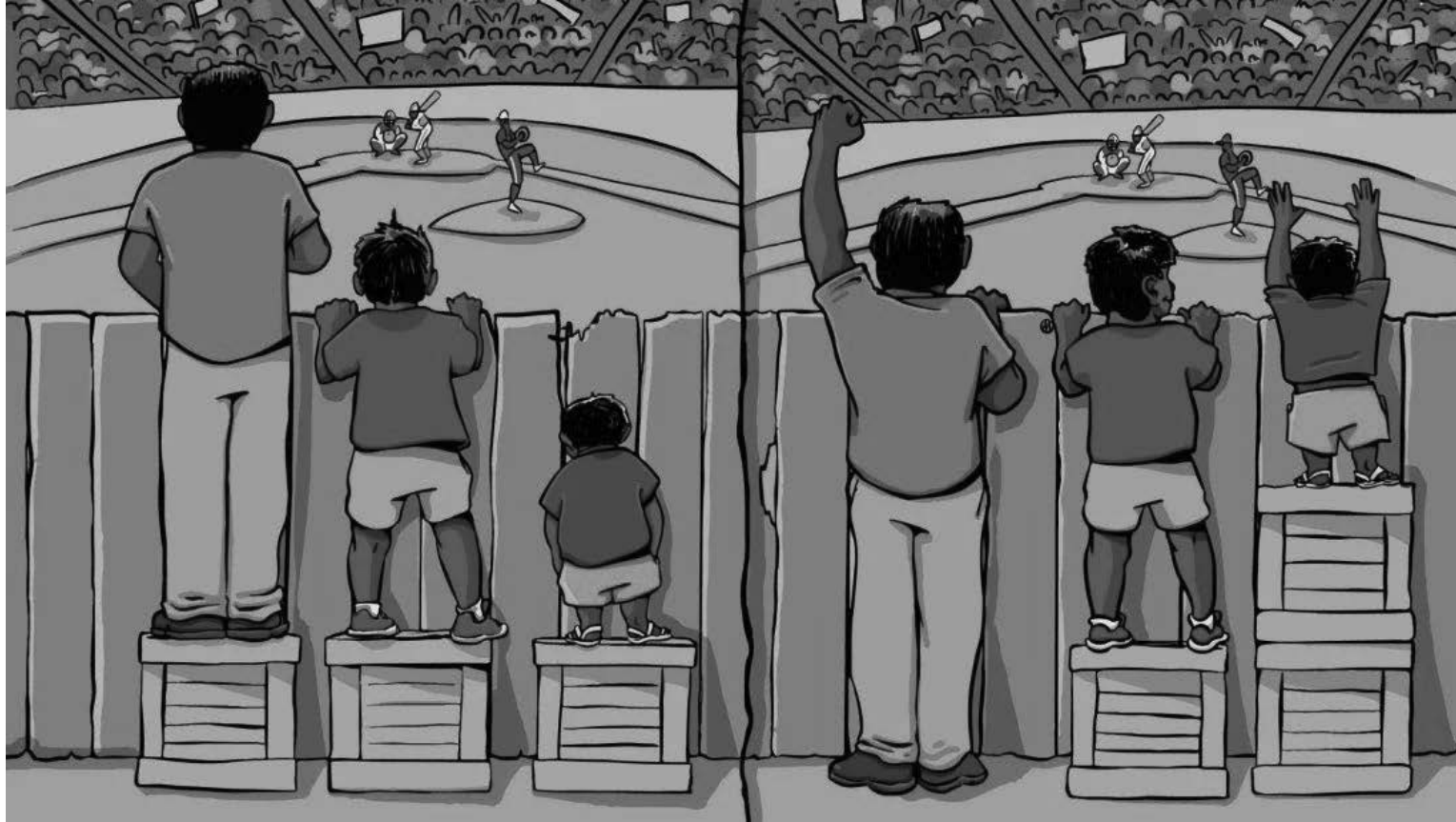
HRCA = gain/amp 1q, t(4;14), t(14;16), t(14;20) or del(17p)

Costa et al IMW 2021

MASTER trial

UAB THE UNIVERSITY OF ALABAMA **Same treatment for all vs. Individualized**

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**Lenalidomide maintenance
until progression**

**Risk and response-adapted
therapy**

Treatment-Free Observation and MRD surveillance

- Alternative to continuous therapy
- Should be pursued in confirmed MRD(-) patients
- MRD surveillance to mitigate risk from omitting maintenance
- Risk of omitting maintenance balanced against
 - QOL
 - Cost
 - Toxicity from continuous therapy (including SPM)
- Golden opportunity to study undisturbed interplay of immune reconstitution and MRD.

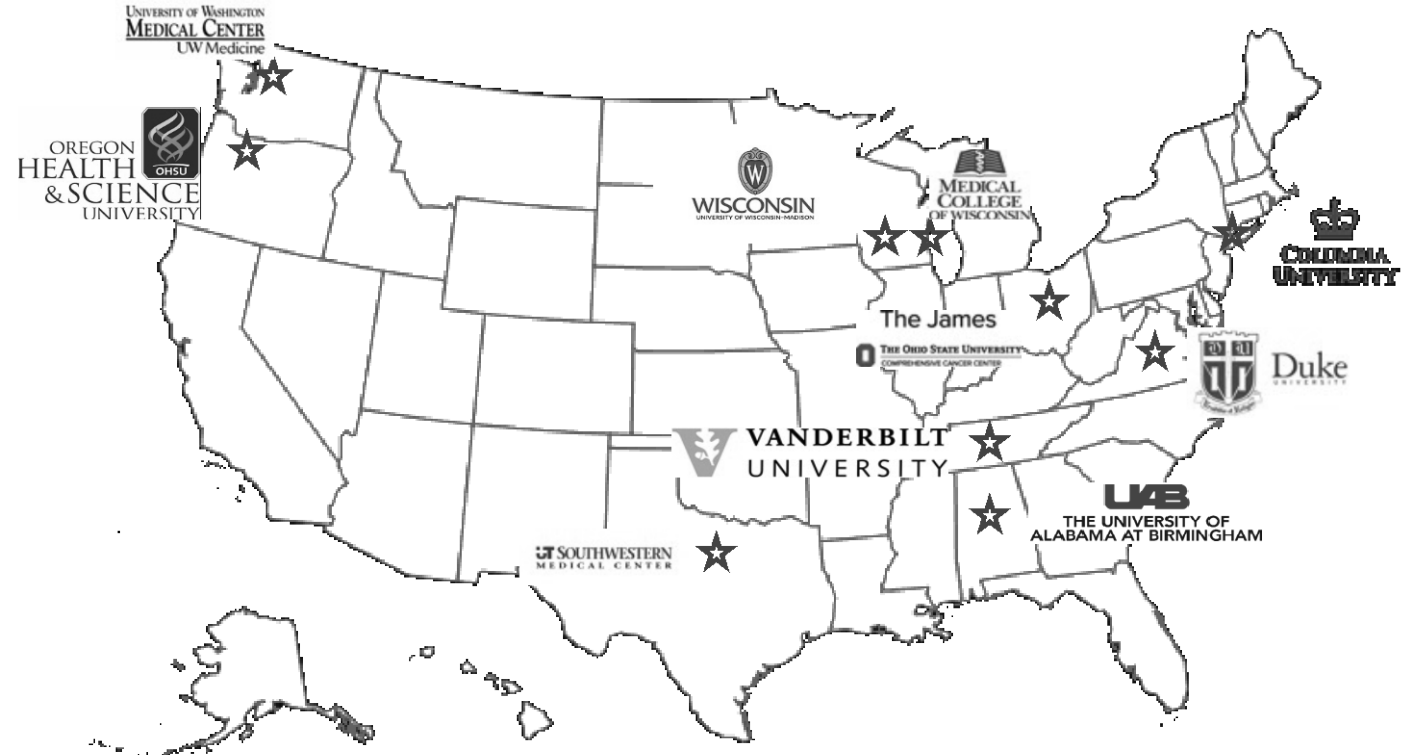
Acknowledgements

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❖ MASTER protocol team

❖ Patient advocates

❖ Patients and family



We can't call it cure until we can stop therapy