MRD concepts, methodology and application

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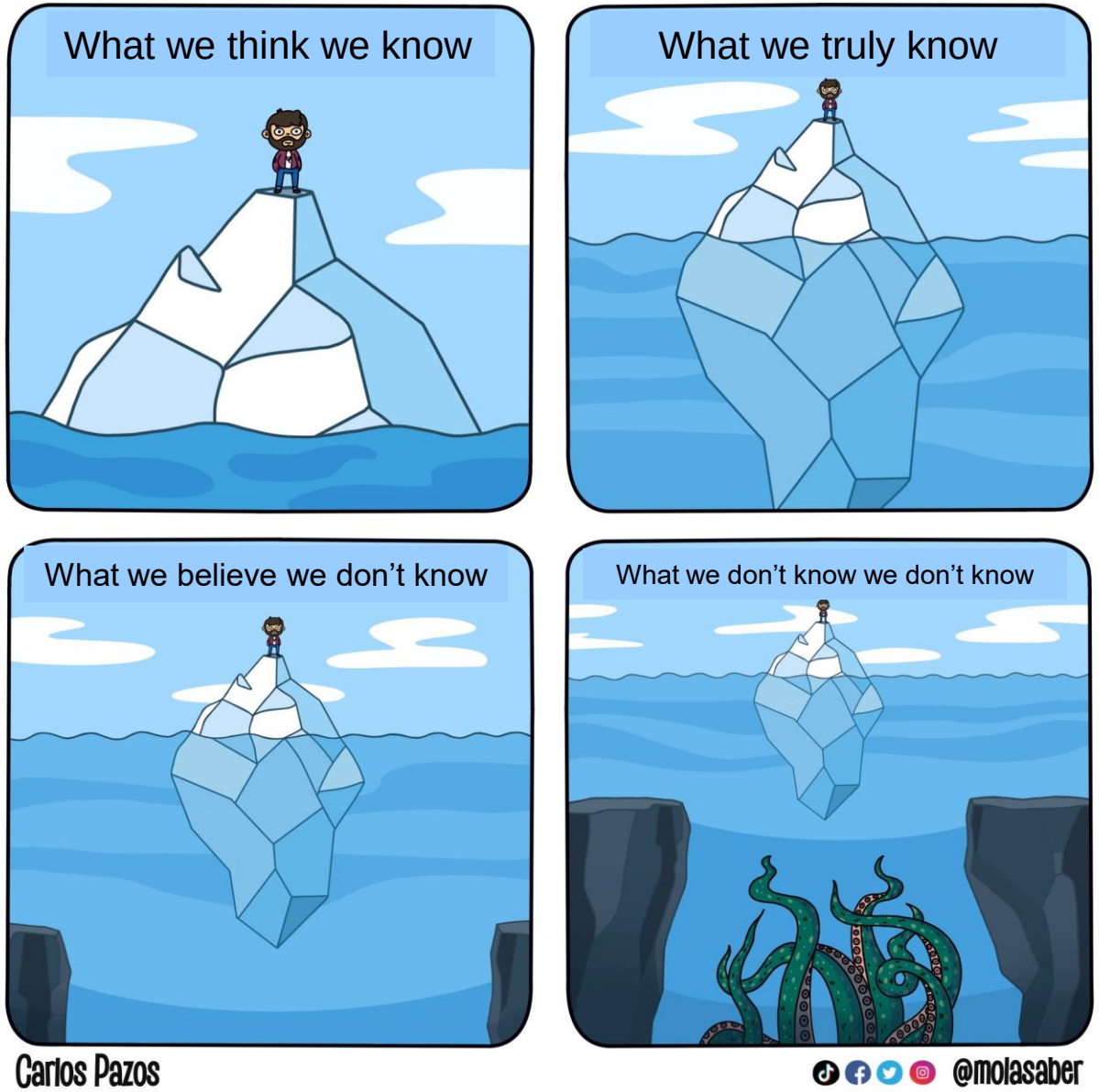
Disclosures

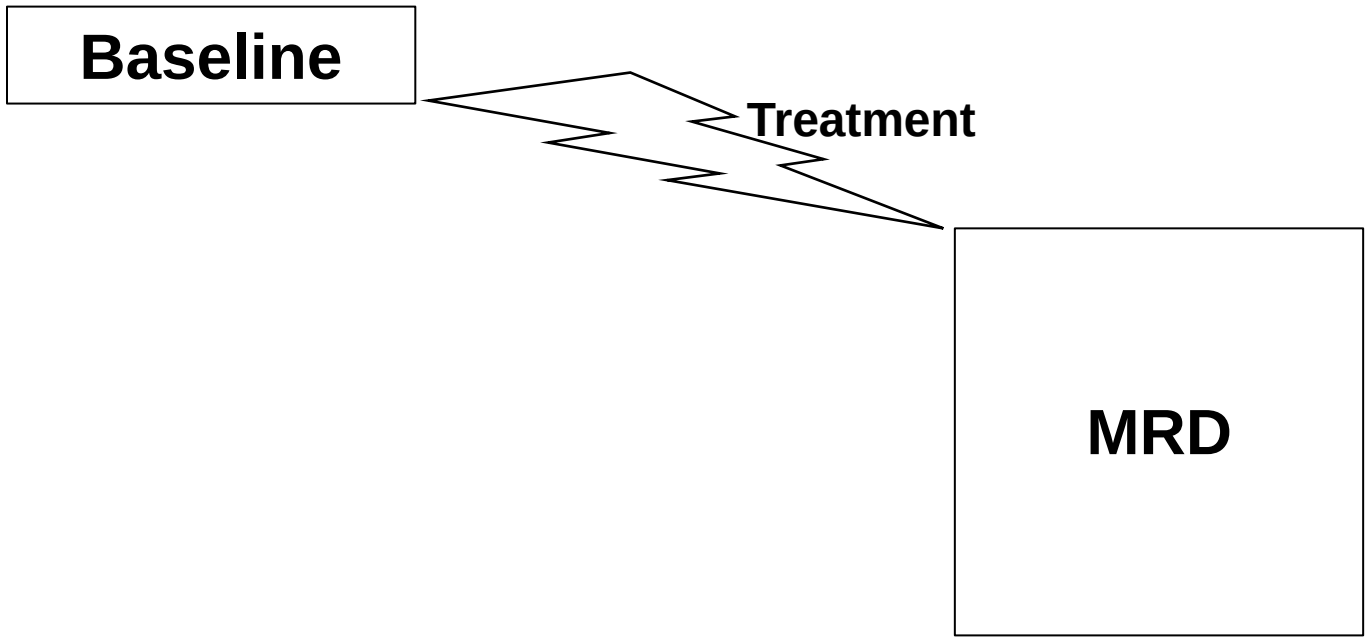
Company	Relationship
Adaptive	Honoraria
Amgen	Honoraria
Becton Dickinson	Honoraria
BMS-Celgene	Consultant, Honoraria, Research Grant, Scientific Advisory Board
GSK	Honoraria, Research Grant, Scientific Advisory Board
Janssen	Consultant, Honoraria, Scientific Advisory Board
Roche	Research Grant
Sanofi	Consultant, Honoraria, Research Grant, Scientific Advisory Board
Takeda	Consultant

My true disclosure about the role of MRD



Established role of MRD as prognostic marker

Intensive research efforts in the last decades



- Measures direct effect of treatment on tumor cells

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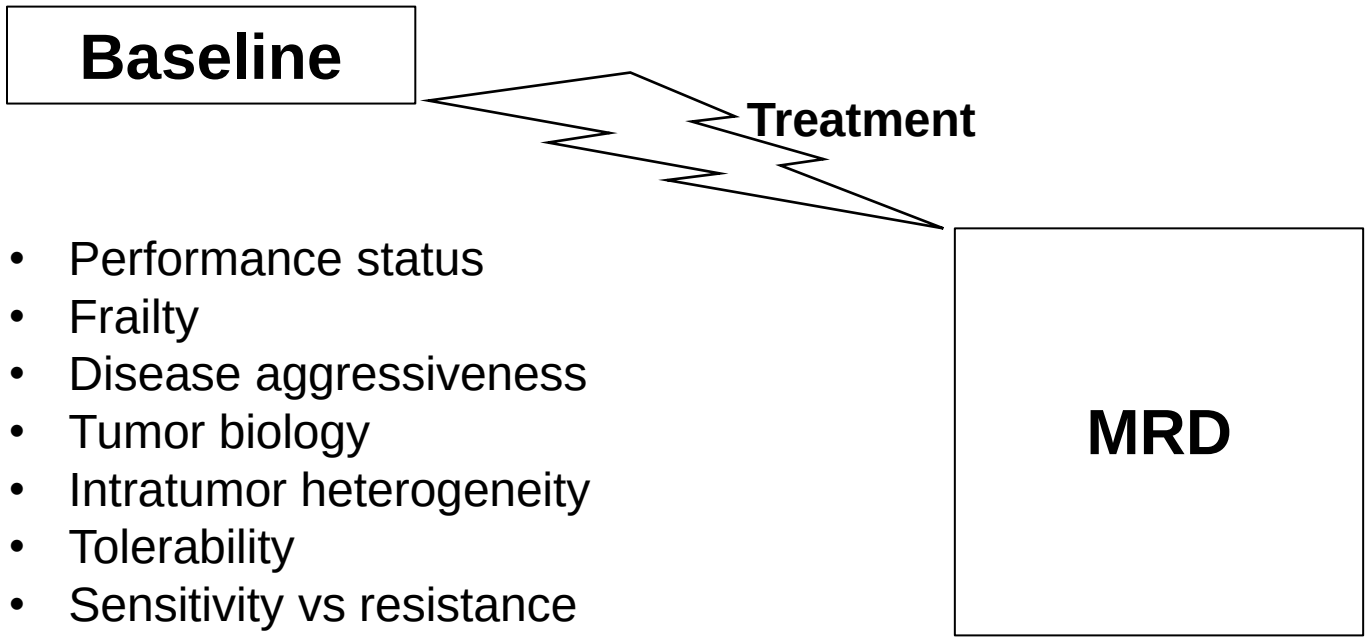

- Performance status
- Frailty
- Disease aggressiveness
- Tumor biology
- Intratumor heterogeneity
- Tolerability
- Sensitivity vs resistance

- Measures direct effect of treatment on tumor cells
- Captures patient heterogeneity in terms of tolerability and response to treatment

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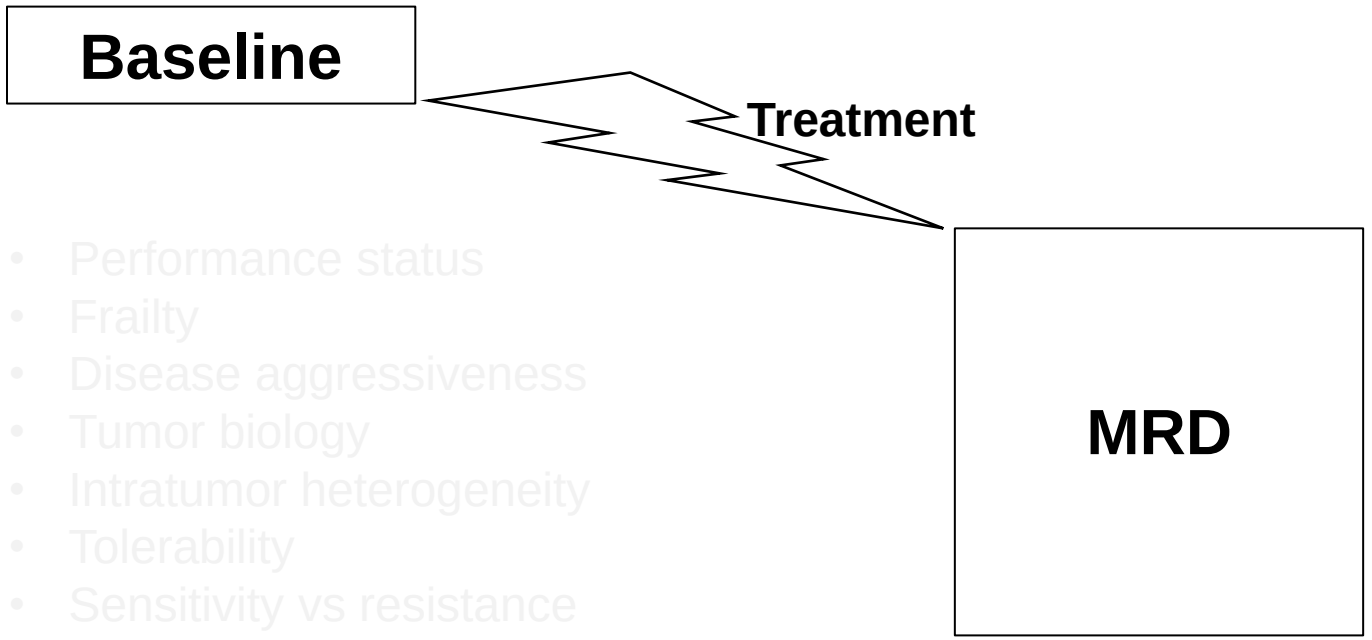

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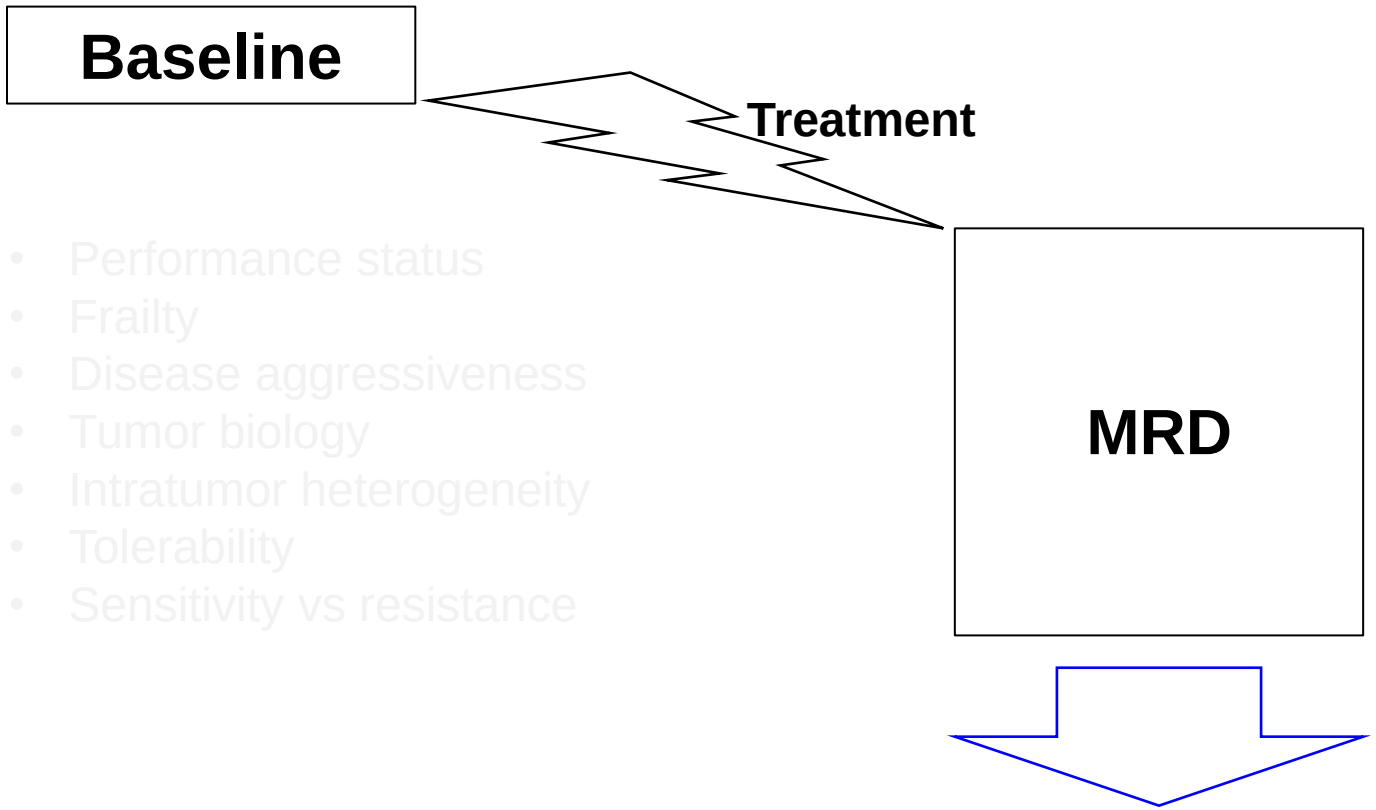

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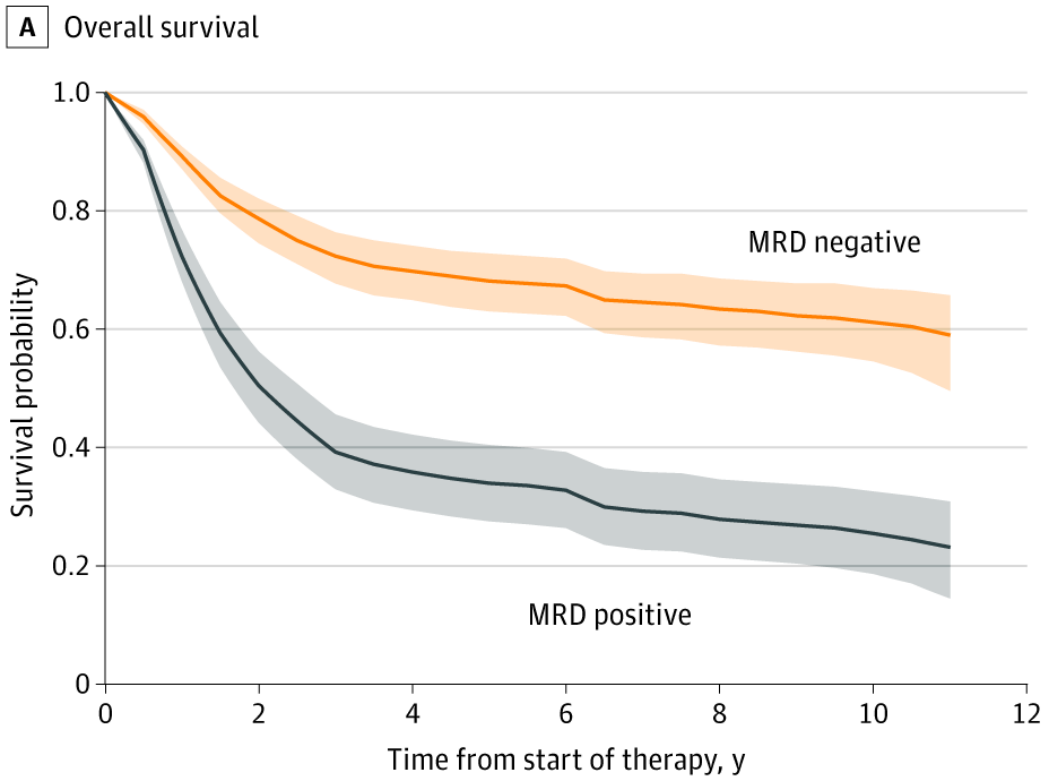
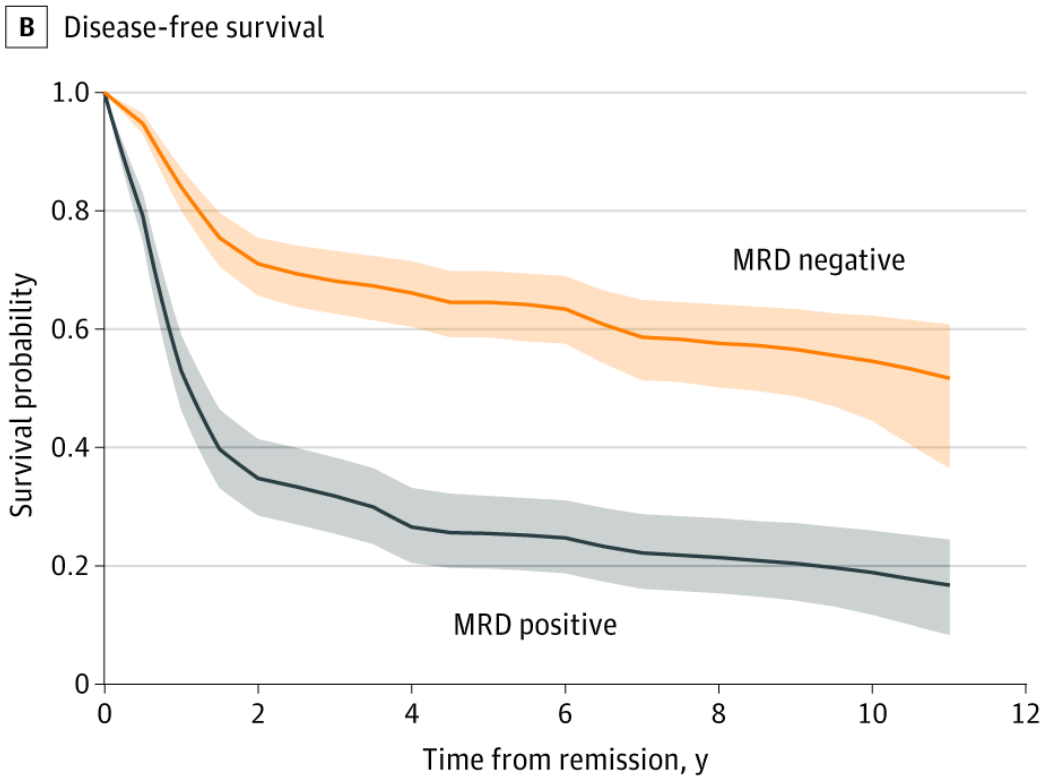
- Measures direct effect of treatment on tumor cells
- Captures patient heterogeneity in terms of tolerability and response to treatment
- Recalibrates patients' risk after treatment
- Dramatic tumor reduction translates into prolonged survival
- Undetectable MRD as a new endpoint of therapy

One of the most powerful prognostic factors

Association of MRD with survival outcomes in AML

A Systematic Review and Meta-analysis in 11,151 patients

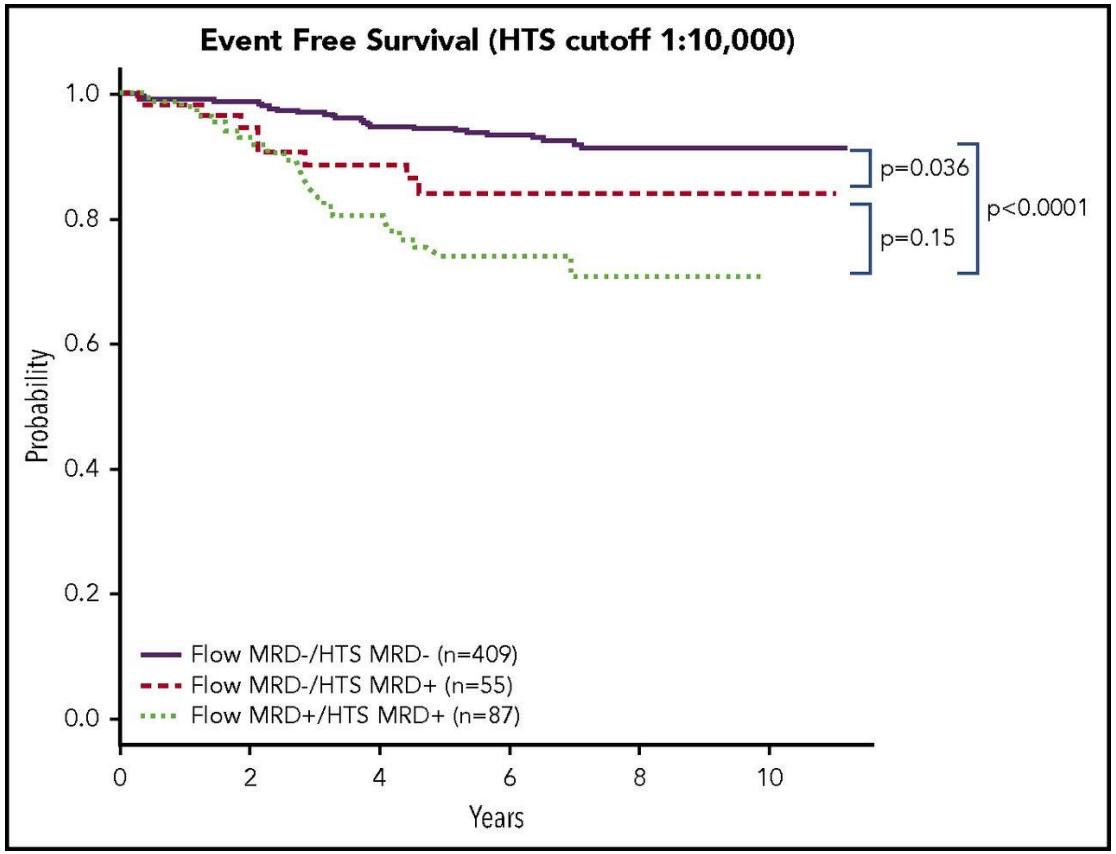




Short NJ, et al. JAMA Oncol. 2020;6(12):1890-1899.

Sensitivity matters

MRD with NGS vs MFC in pediatric BCP-ALL



Wood B, et al. Blood. 2018;131(12):1350-1359.

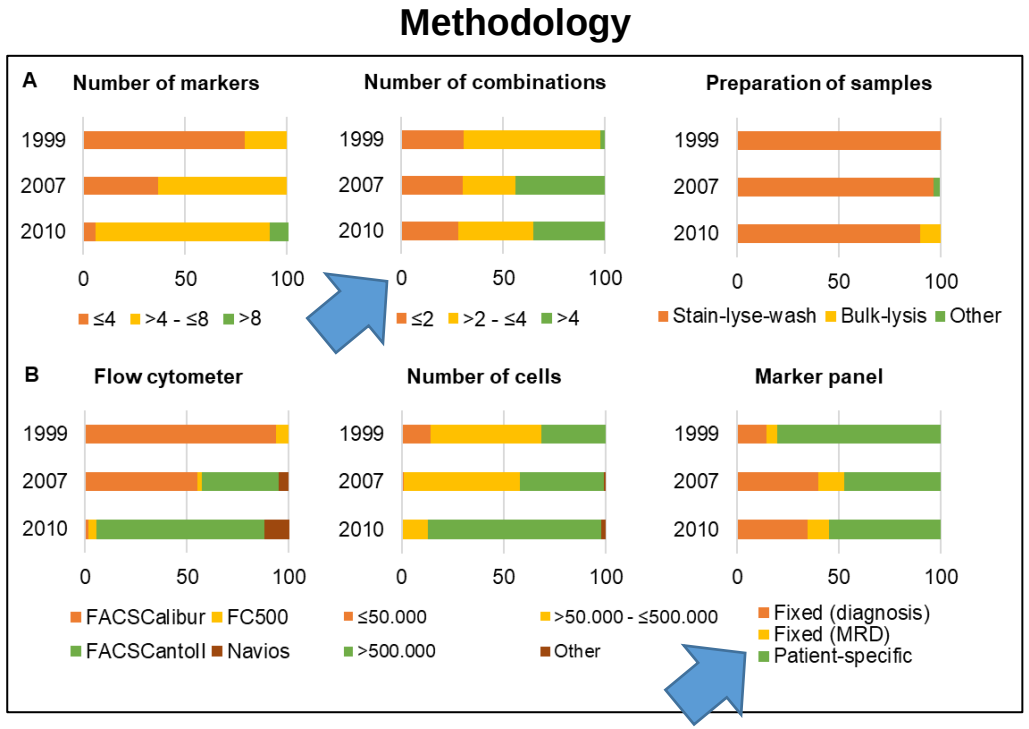
MRD assessment in hematological malignancies

Remains controversial

- Dramatic improvement in treatment efficacy only took place in the last decade for some diseases (no need for MRD if CR rates are low)
- False-expectation about the concept of MRD (it may be the pathway to, but negative MRD does not mean cure)
- Lack of standardization in the field of MRD (suboptimal results)

Heterogeneity of decentralized MRD using MFC in AML

Absence of harmonization nor standardization at the national level



Paiva B, Vidriales MB, Sempere A, et al. Leukemia. 2021;35(8):2358-2370.

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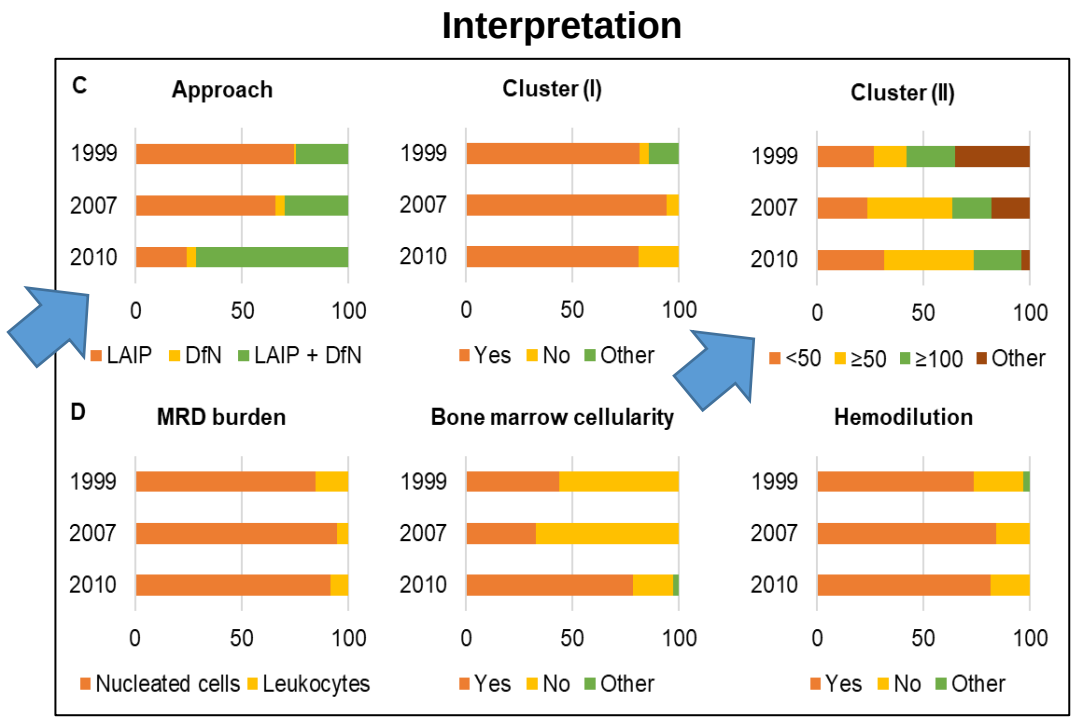

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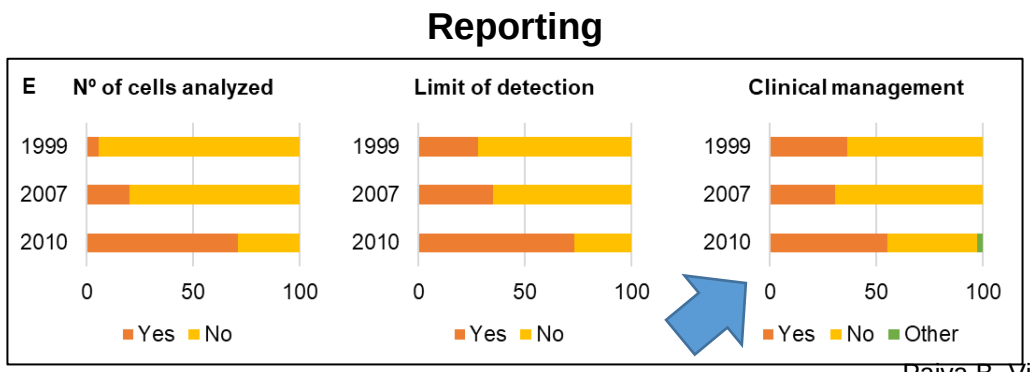
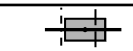


Paiva B, Vidriales MB, Sempere A, et al. Leukemia. 2021;35(8):2358-2370.

Heterogeneity in virtually all aspects of MFC based MRD testing impacted in its ability to discriminate patients with different outcome

Question	Answer	No. of patients	Reduced risk of CIR	HR (95% CI)	*P* value	*P* value for interaction
No. of combinations	≤2	265		0.9 (0.6 – 1.3)	.590	.002
	>2 - ≤4	375		0.7 (0.5 – 0.9)	.008	
	>4	326		0.6 (0.4 – 0.9)	.007	
No. of cells measured	≤50.000	26		NA	NA	.016
	>50.000 - ≤500.000	327		0.8 (0.6 – 1.1)	.210	
	>500.000	600		0.7 (0.5 – 0.9)	.002	
	Other	13		NA	NA	
Approach	LAIP	424		0.8 (0.6 – 1.0)	.099	.109
	DfN	50		0.3 (0.1 – 0.7)	.010	
	LAIP + DfN	492		0.7 (0.5 – 0.9)	.016	
MRD burden	Nucleated cells	886		0.7 (0.6 – 0.9)	.006	.001
	Leukocytes ($CD45^{+}$)	80		0.5 (0.3 – 1.0)	.063	
Overall	-	966		0.7 (0.6 – 0.9)	<.001	

1

Paiva B, Vidriales MB, Sempere A, et al. Leukemia. 2021;35(8):2358-2370.

MRD assessment across some hematological malignancies

Application depending on clinical need and methodological robustness

	ALL	AML	CML	CLL	MM
Complexity	Intermediate	High	Low	Intermediate	Intermediate
Standardization	High	Low	High	Low	Intermediate
Clinical trials	Yes	Yes	Yes	Yes	Yes
Routine practice	Yes	Yes	Yes	Infrequent	Intermediate
Treatment decisions	Yes	Yes	Yes	Infrequent	Infrequent

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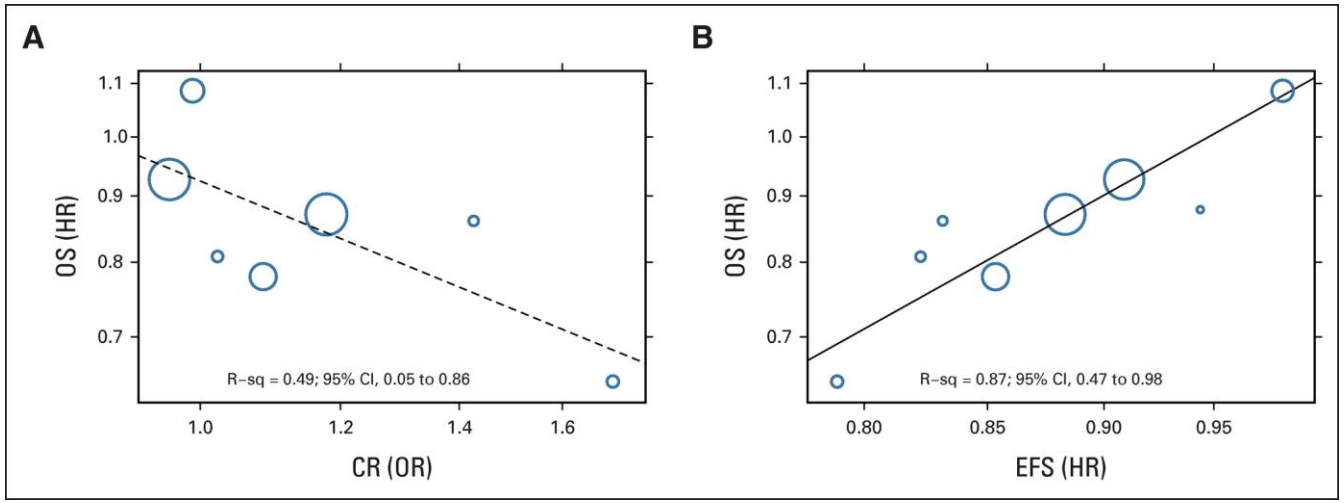
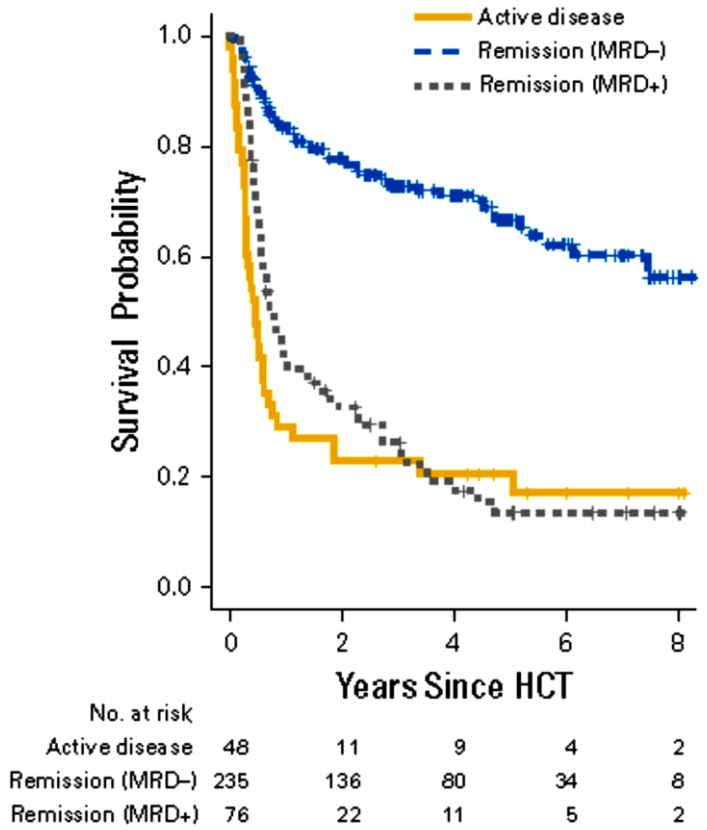
Evolving treatment landscapes

MRD and surrogacy

Association of treatment effects on OS, CR and EFS in AML[1]

CR but persistent MRD = NO CR[2]

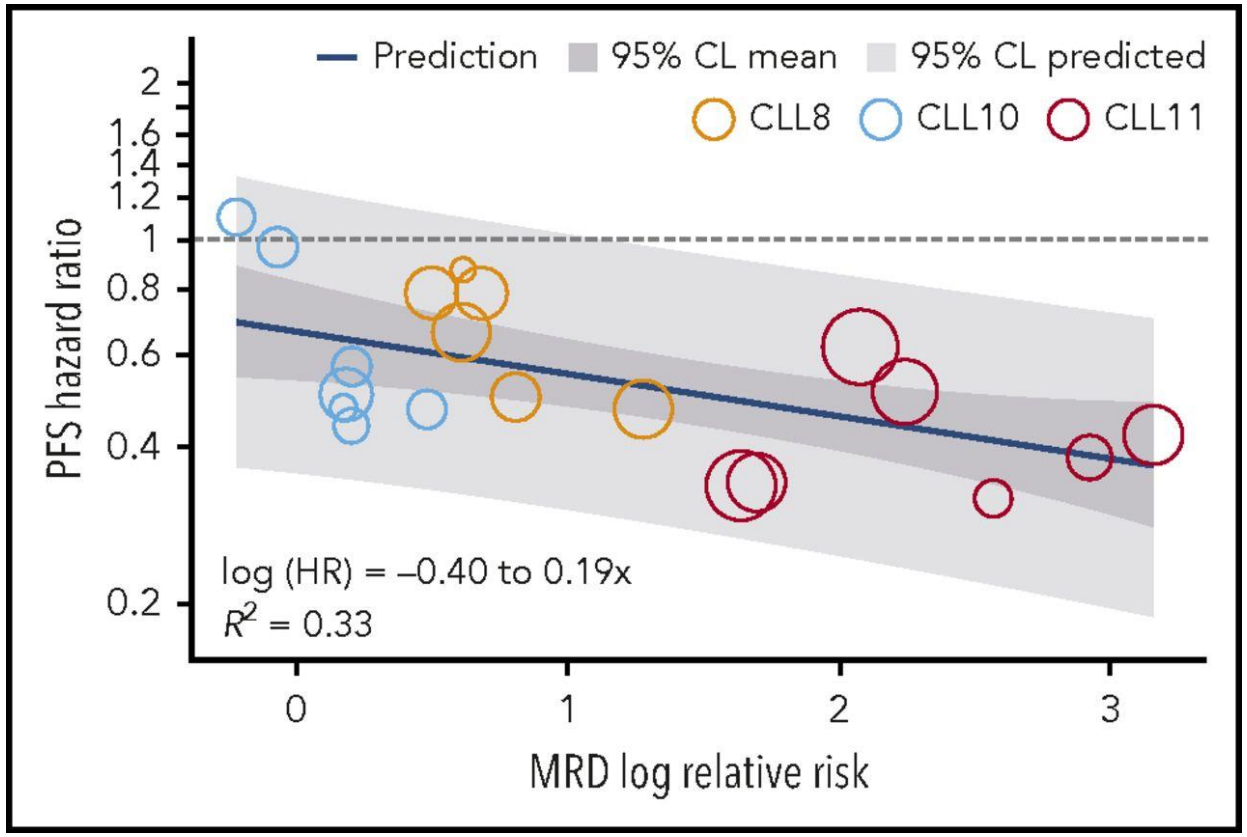




1. Norsworthy KJ, et al. J Clin Oncol. 2022;40(8):847-854.
2. Araki D, et al. J Clin Oncol 2015;34:329-336.

Predicting treatment effect on PFS using MRD surrogate end point

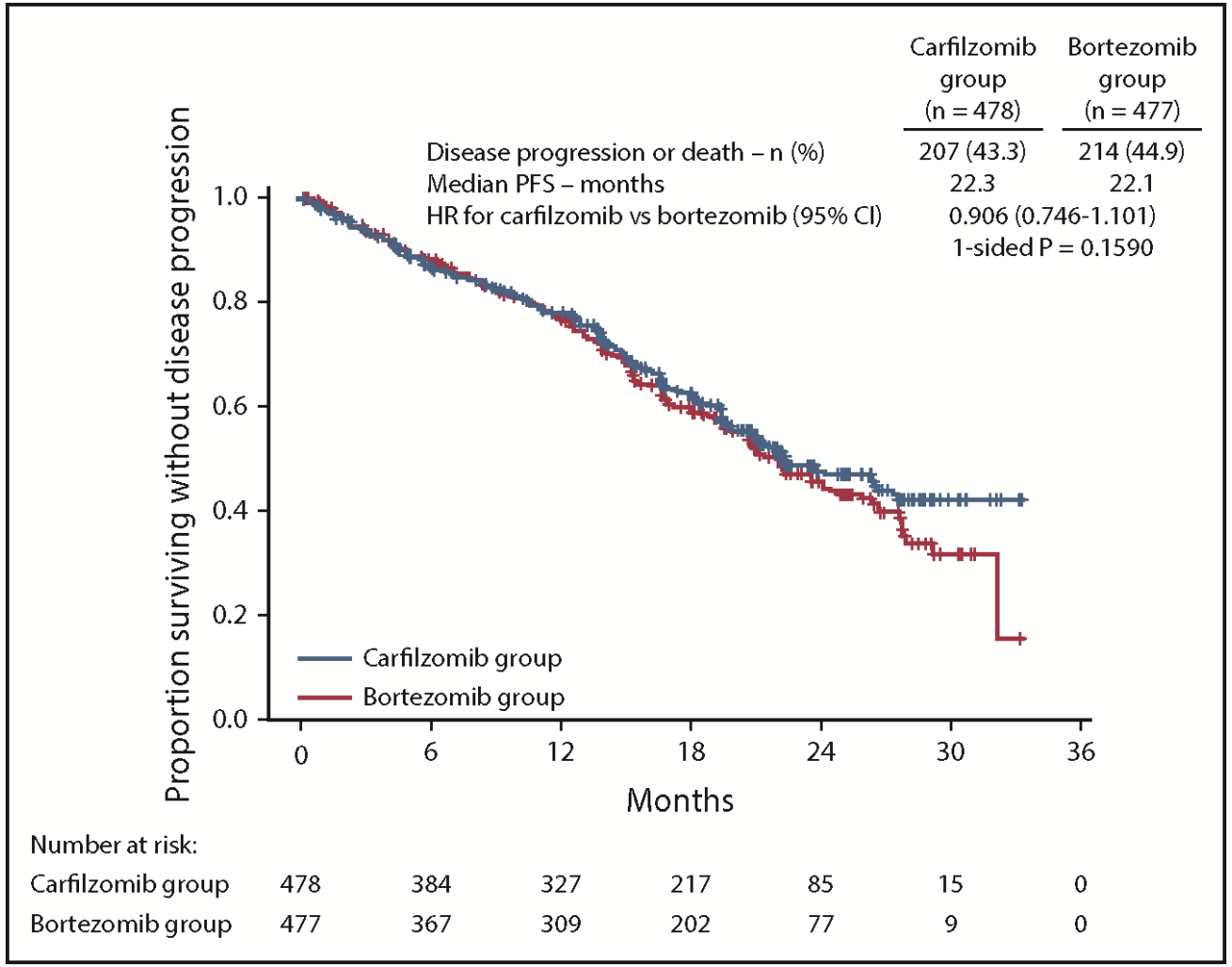
The example of CLL (chemoimmunotherapy)



Dimier N, et al. Blood. 2018;131(9):955-962.

MRD rates using NGF in the CLARION trial

15.7% KMP vs 15.5% VMP



Facon T, et al. Blood. 2019;133(18):1953–1963

MRD rates in the investigational vs control arm

Dara effect in Maia, Alcyone, Pollux and Castor (~5-fold difference)

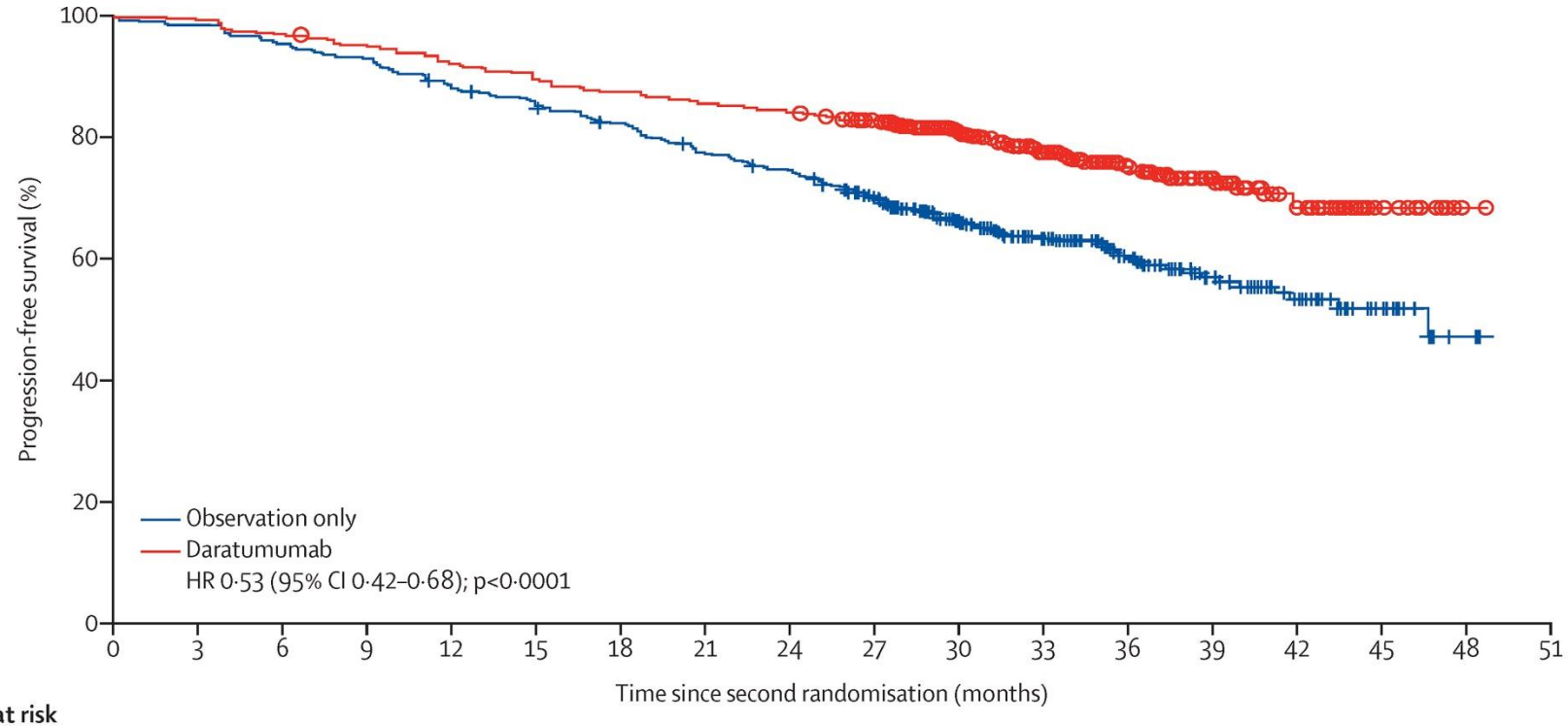
	ALCYONE			MAIA		
MRD negativity (10^{-5})	**D-VMP**	**VMP**	***P* value**	**D-Rd**	**Rd**	***P* value**
ITT	28%	7%	<.0001	29%	9%	<.0001
≥CR	59%	28%	<.0001	58%	34%	.0001

	POLLUX			CASTOR		
MRD negativity (10^{-5})	**D-Rd**	**Rd**	***P* value**	**D-Vd**	**Vd**	***P* value**
ITT	32.5%	7%	<.0001	15%	2%	<.0001
≥CR	57%	29%	.0001	53%	17%	.0035

Cavo M, et al. Blood 2021;139(6):835-844.

MRD rates using NGF in the CASSIOPEIA trial

64% D-VTd vs 44% VTd (CR rates, 39% vs 26%)

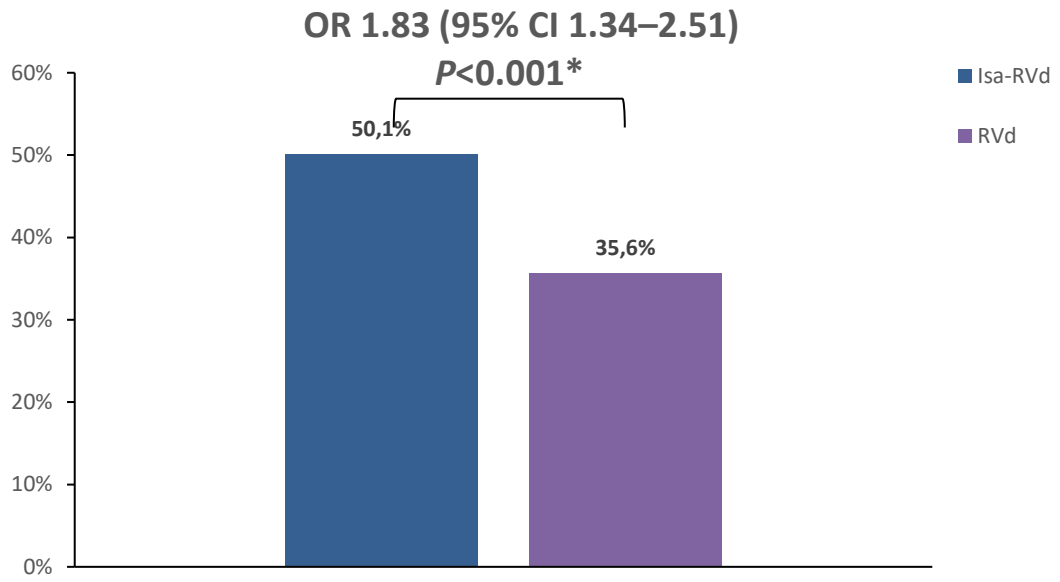


Number at risk (number censored)																	
Observation only	444 (0)	438 (0)	424 (0)	413 (0)	392 (1)	377 (2)	362 (4)	339 (5)	326 (6)	294 (20)	227 (71)	178 (112)	118 (164)	76 (201)	53 (220)	21 (251)	3 (268)	0 (271)
Daratumumab	442 (0)	439 (0)	429 (0)	420 (1)	406 (1)	396 (1)	386 (1)	377 (1)	372 (1)	354 (12)	283 (76)	215 (133)	155 (188)	102 (237)	64 (270)	25 (309)	1 (333)	0 (334)

Moreau P, et al. Lancet Oncol. 2021;22(10):1378-1390.

First primary endpoint, end of induction MRD negativity by NGF (10^{-5}), was met in ITT analysis

Patients with MRD negativity at the end of induction therapy



Low number of not assessable/missing† MRD status: Isa-RVd (10.6%) and RVd (15.2%)

CR rates were 24.2% vs 21.6% (*P*=0.46)

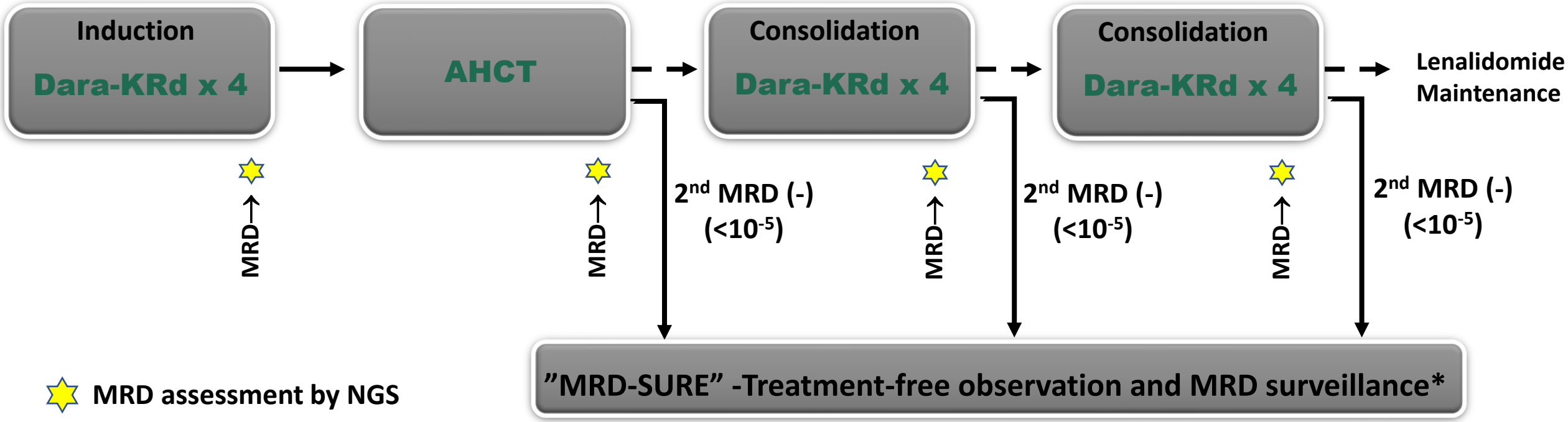
MAT-GLB-2105440 v1.0 Approval Date: 11/2021

*P value derived from stratified conditional logistic regression analysis
†Missing NGF-MRD values were due to either patients' loss to follow-up during induction therapy or to missing bone marrow samples or technical failures in measurement counted as non-responders, i.e. NGF-MRD positive
CI, confidence interval; d, dexamethasone; Isa, isatuximab; ITT, intent-to-treat; MRD, minimal residual disease; NGF, next-generation flow; OR, odds ratio; R, lenalidomide; V, bortezomib

Learning in clinical trials how (or not) to use MRD

MASTER trial

Study design

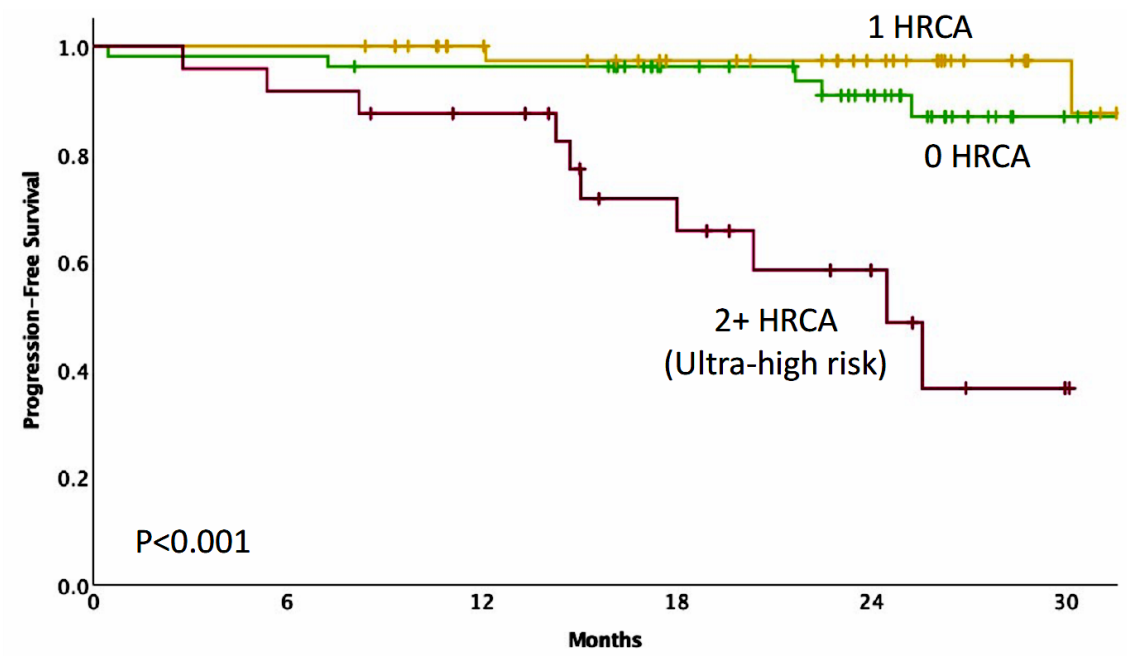


*24 and 72 weeks after completion of therapy

Costa LJ, et al. J Clin Oncol. 2021:JCO2101935.

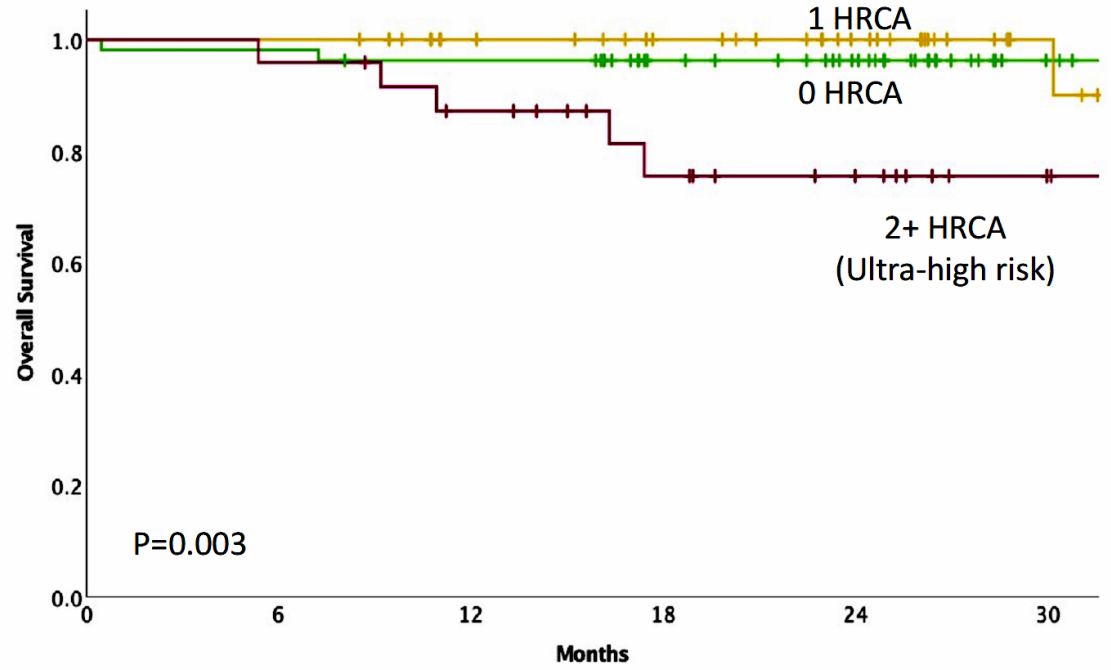
MASTER trial

Progression-free survival 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:

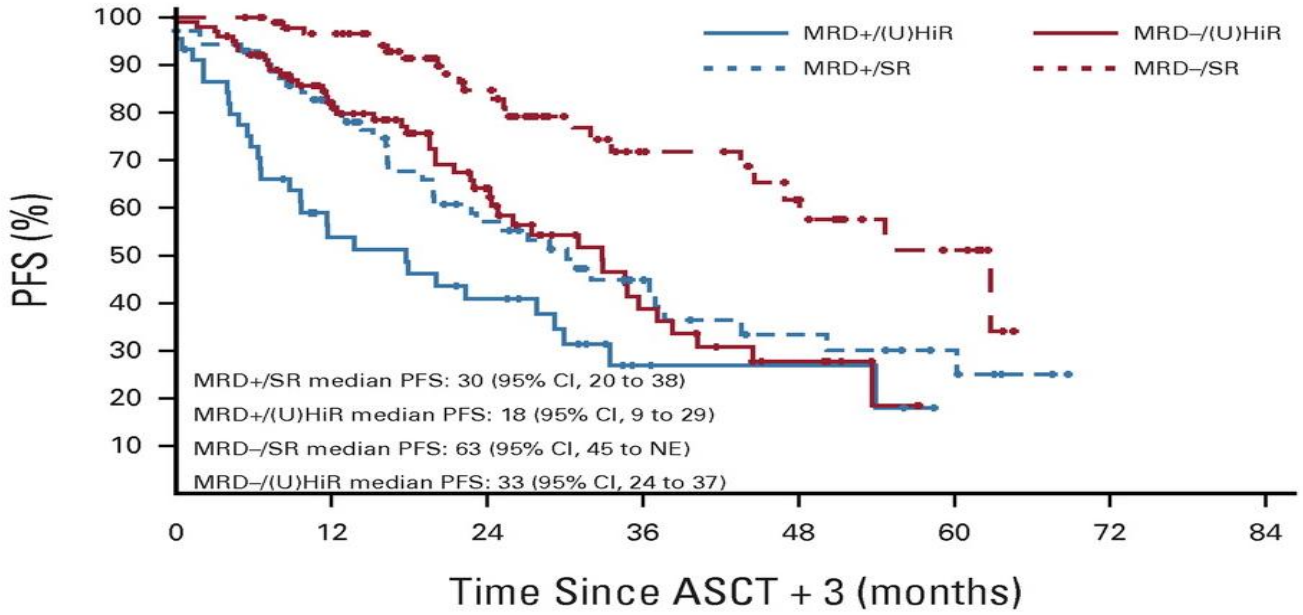
0 HRCA	50	49	46	36	29	11
1 HRCA	44	44	36	30	23	9
2+ HRCA	24	23	19	13	9	3

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

Costa LJ, et al. J Clin Oncol. 2021:JCO2101935.

Lenalidomide vs observation in MRD negative patients

Results from the MRC Myeloma XI trial



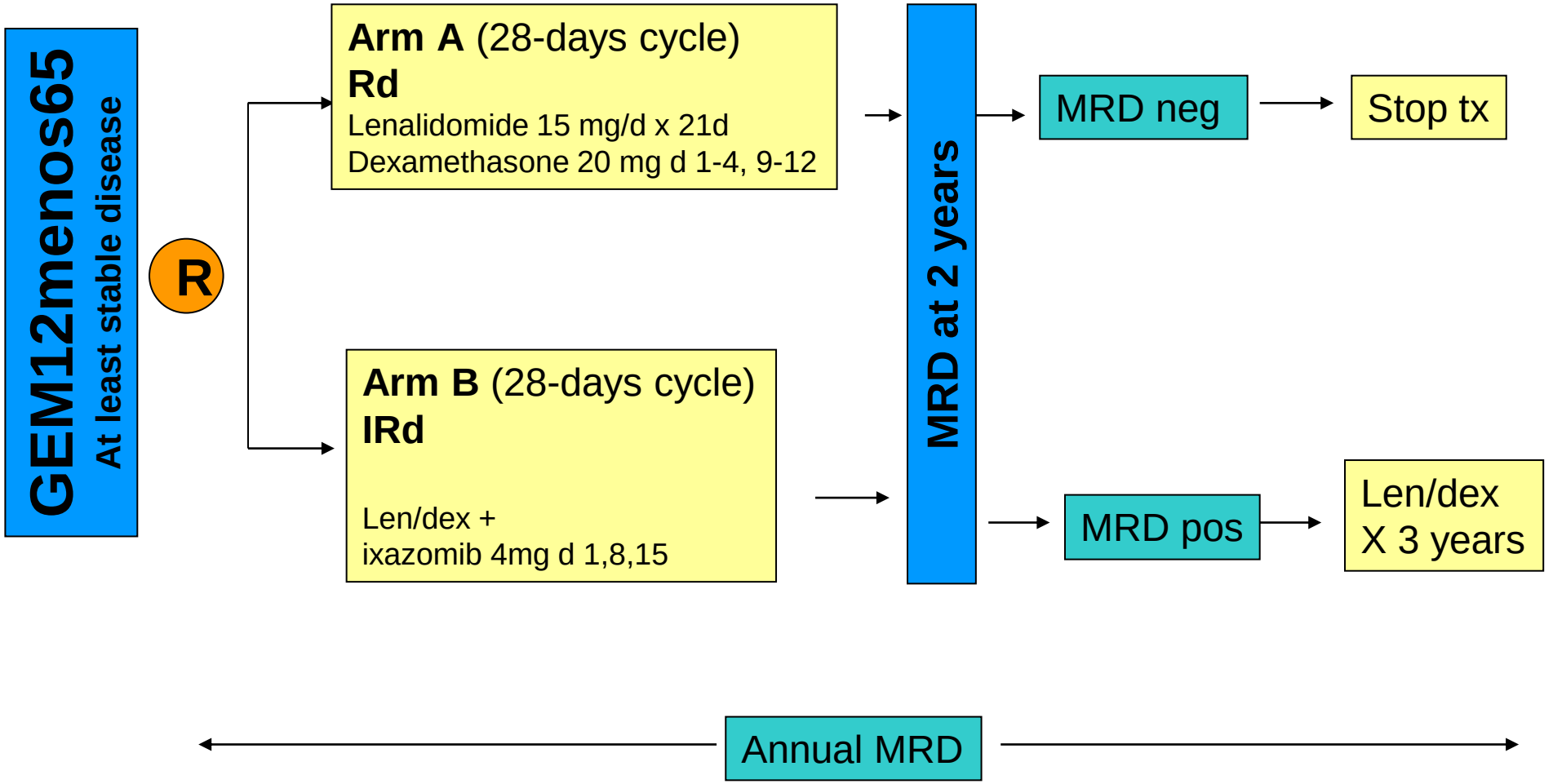
No. at risk (No. censored):

MRD+/(U)HiR	45 (0)	21 (4)	15 (5)	4 (12)	3 (13)	0 (15)	
MRD+/SR	72 (1)	52 (7)	31 (14)	17 (22)	10 (25)	6 (28)	0 (33)
MRD–/(U)HiR	102 (0)	68 (17)	36 (37)	15 (47)	7 (51)	0 (57)	
MRD–/SR	96 (1)	83 (10)	48 (37)	25 (54)	16 (60)	7 (67)	0 (73)

De Tute RM, et al. J Clin Oncol. 2022 Apr 4:JCO2102228.

Can MRD be used to interrupt or prolong treatment?

Results from the GEM2014MAIN trial



Rosiñol L, et al. Blood 2021;138 (Supplement 1): 466.

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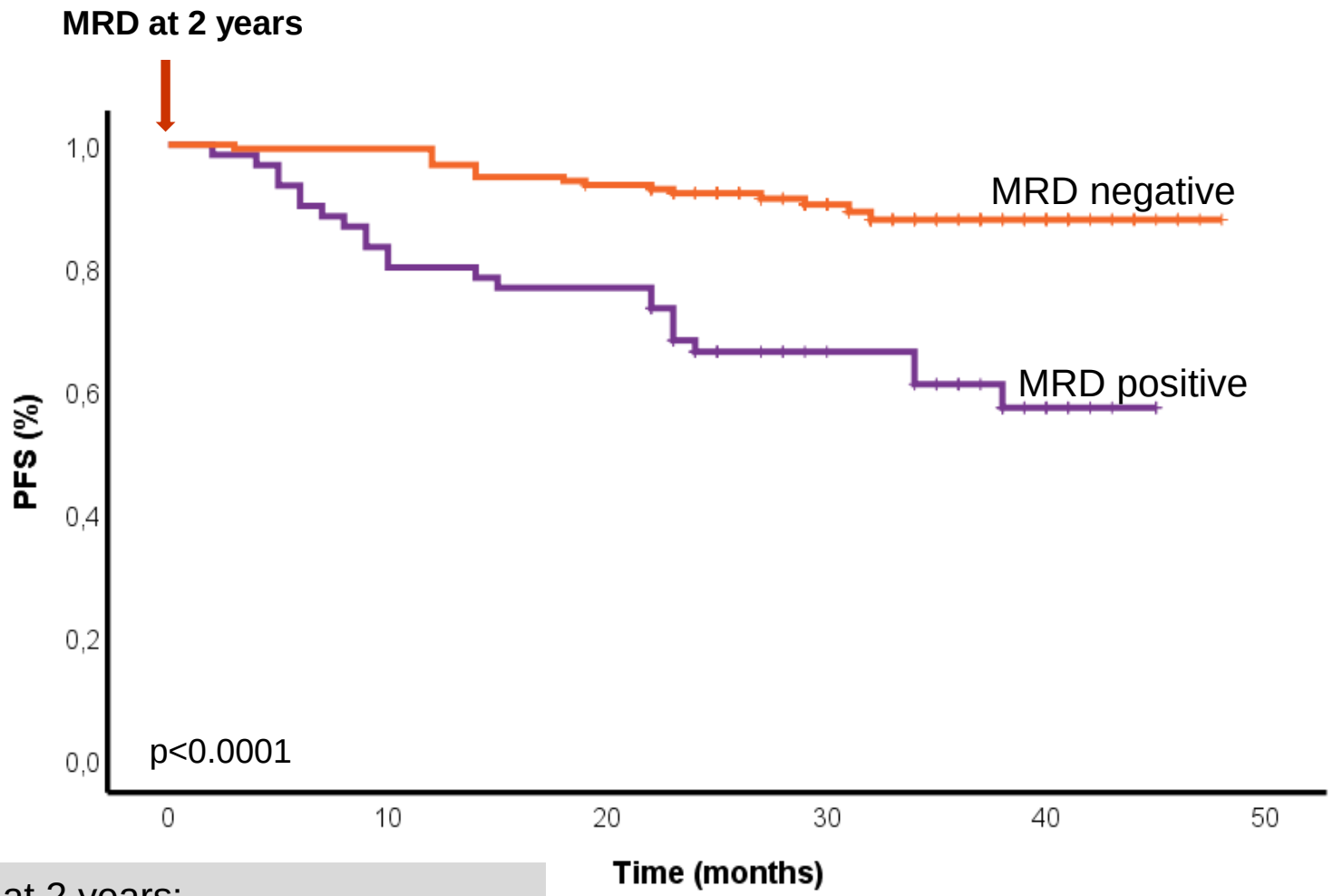


MRD at 2 years:
- negative: stop maintenance
- positive: Rd for 3 additional years

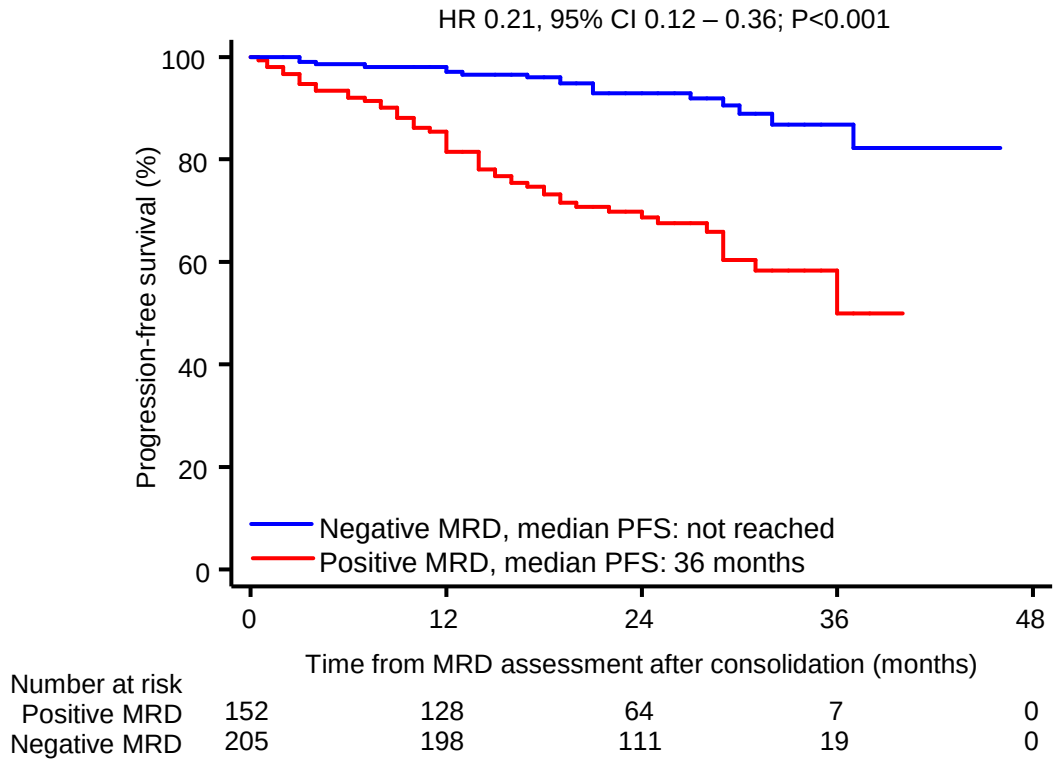
Rosiñol L, et al. Blood 2021;138 (Supplement 1): 466.

Once the lessons are learned, there should be stringent standardization in clinical laboratories

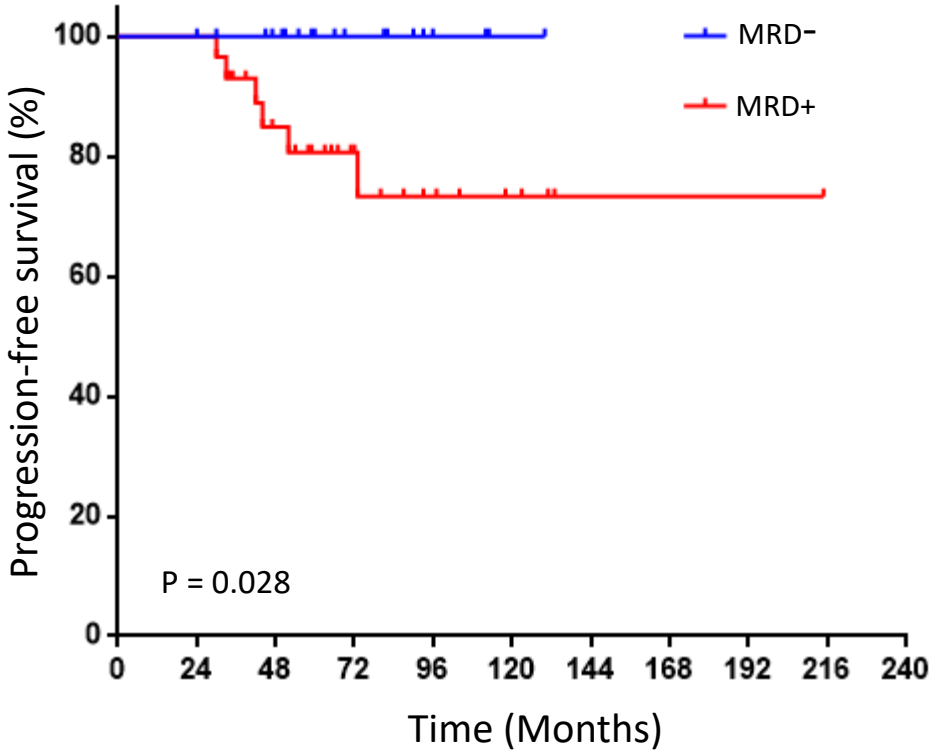
Methods for measuring MRD per IMWG guidelines[1]

NGF

Clinical trials[2,3]



Clinical practice[4]



1. Kumar S, et al. Lancet Oncol. 2016;17:e328-e346.
2. Facon T, et al. Blood. 2019;133(18):1953-1963.
3. Paiva B, et al. J Clin Oncol. 2020;38(8):784-792.
4. Terpos E, et al. Hemasphere. 2019;3(6):e300.

Points for discussion

- MRD is poised to be the most relevant prognostic factor in most hematological malignancies
- There is room for improvement, particularly if authorities promote/enforce complete standardization (IVD)
- Any MRD level matters in terms of risk of relapse
    - True in 90% of patients (long-term survivors with persistent disease)
    - Undetectable MRD should be defined with the highest possible sensitivity
    - Improve the definition of MRD cells (eg, CH mutations) to avoid false-positives
- Per the number of ongoing trials, it is plausible that by 2030 there will be guidelines on how to use MRD for treatment decisions in some hematological malignancies
- With very few exceptions, undetectable MRD rates precede years in advance a benefit in PFS
    - Methodological and treatment heterogeneity are barriers to better statistical outcomes
    - Can you imagine knowing the readout of most trials ~12 months after the last patient enrolled?