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Grupo
ONCOCLÍNICAS
Sua vida. Nossa vida.

Entenda as medidas bem-sucedidas e não tão bem-sucedidas na descontinuação da terapia na LMC

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Estimated TFR Rates (Western World)

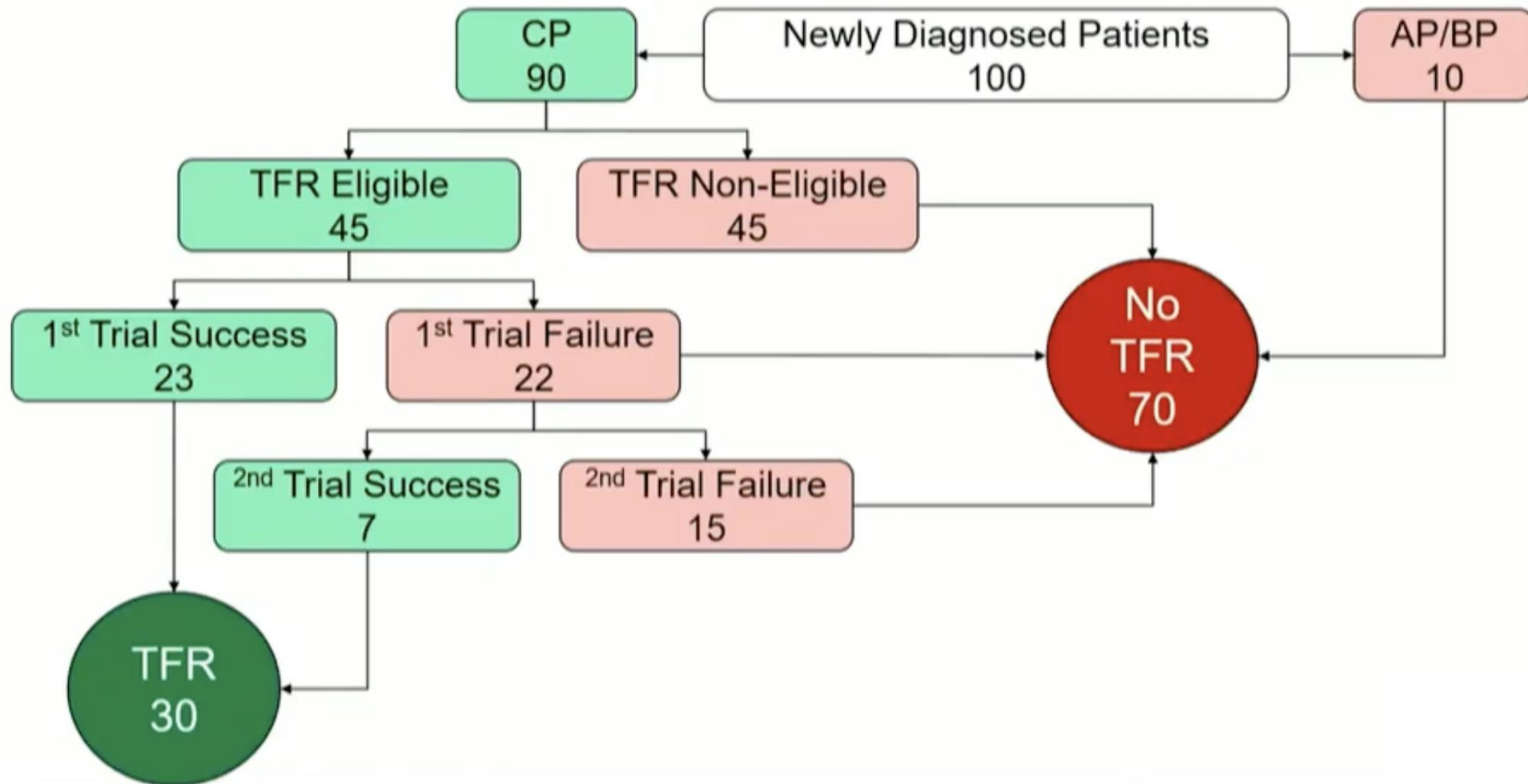


Table 2. TKI discontinuation studies.

Study	TKI	N	Eligibility criteria			Molecular recurrence-free survival
			Depth of MR	Minimum Tx. (y)	Minimum MR (y)	
STIM1 [20, 21]	Imatinib	100	MR ^{5.0}	3	2	38% at 5 years
STIM2 [26, 27]	Imatinib	200	MR ^{4.5}	2	2	50% at 2 years
A-STIM [28]	Imatinib	80	MR ^{5.0}	3	2	64% at 2 years
TWISTER [22]	Imatinib	40	MR ^{4.5}	3	2	45% at 42 months
KID study [25]	Imatinib	90	MR ^{4.5}	3	2	58.5% at 2 years
TRAD [32]	Imatinib	108	MR ^{4.5}	3	2	56.8% at 12 months
DASFREE [29]	Dasatinib	84	MR ^{4.5}	2	1	46% at 2 years
D-STOP [30]	Dasatinib	54	MR ^{4.0}	2	2	62.9% at 12 months
DADI [31]	Dasatinib	63	MR ^{4.0}	1	1	49% at 6 months
NILST [33]	Nilotinib	90	MR ^{4.5}	2	2	58.9% at 1 year
ENSESTfreedom [34-37]	Nilotinib	190	MR ^{4.5}	2	2	48.2% at 5 years
ENESTop [38]	Nilotinib	126	MR ^{4.5}	3	1	42.9% at 5 years
STOP 2G-TKI [39]	Dasatinib/nilotinib	60	MR ^{4.5}	3	2	53.6% at 4 years
EURO SKI [40]	Any TKI	755	MR ^{4.0}	2	1	40% at 2 years
Summary		2,040	≥MR^{4.0}	1-3	1-2	38-64%

MR⁴, BCR::ABL1 ≤ 0.01%; MR^{4.5}, BCR::ABL1 ≤ 0.0032%; MR^{5.0}, BCR::ABL1 ≤ 0.001%.

Abbreviations: INF-α, interferon-α; MR, molecular response; TKI, tyrosine kinase inhibitor; Tx., treatment; y, year(s).

Table 3. Criteria for TKI discontinuation in guidelines with modifications.

Criteria	European LeukemiaNet 2020	NCCN V1. 2023
I. Mandatory		
Disease status	Chronic phase only	Same
Patient communication	Motivated patient	Same
<i>BCR::ABL1</i> test	High-quality quantitative PCR using the international scale with a rapid turnaround of test results	Same
Monitoring	Monthly for the first 6 months, every 2 months for 7–12, and every 3 months thereafter	Same
II. Stop allowed		
Line of therapy	First-line, second-line if intolerance was the reason for the change	NS
Type of transcript	Typical e13a2 or e14a2	Quantifiable
Duration of TKI	> 5 years (> 4 yr for 2G TKI)	> 3 years
Duration of DMR	> 2 years	Same
III. Stop recommended for consideration		
Duration of TKI	> 5 years	> 6 years
Duration of DMR	> 3 years if MR ⁴ > 2 years if MR ^{4.5}	same NS

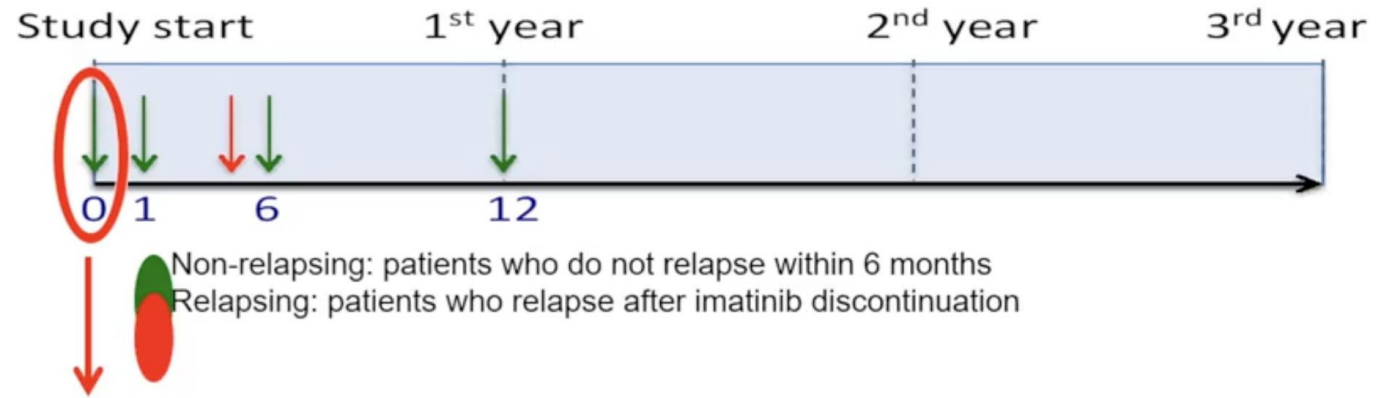
Biological background

CML stem cells

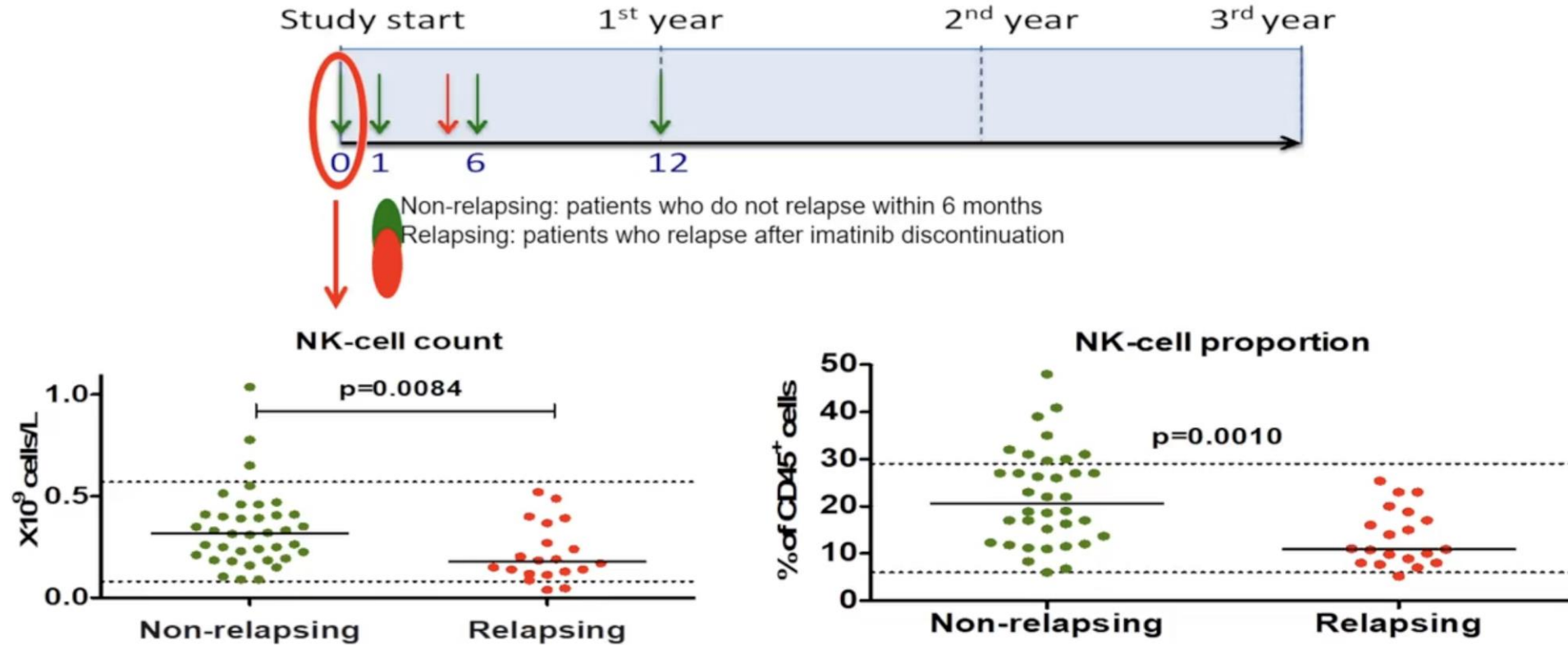


Immunology

NK-cell counts at the time of TKI discontinuation



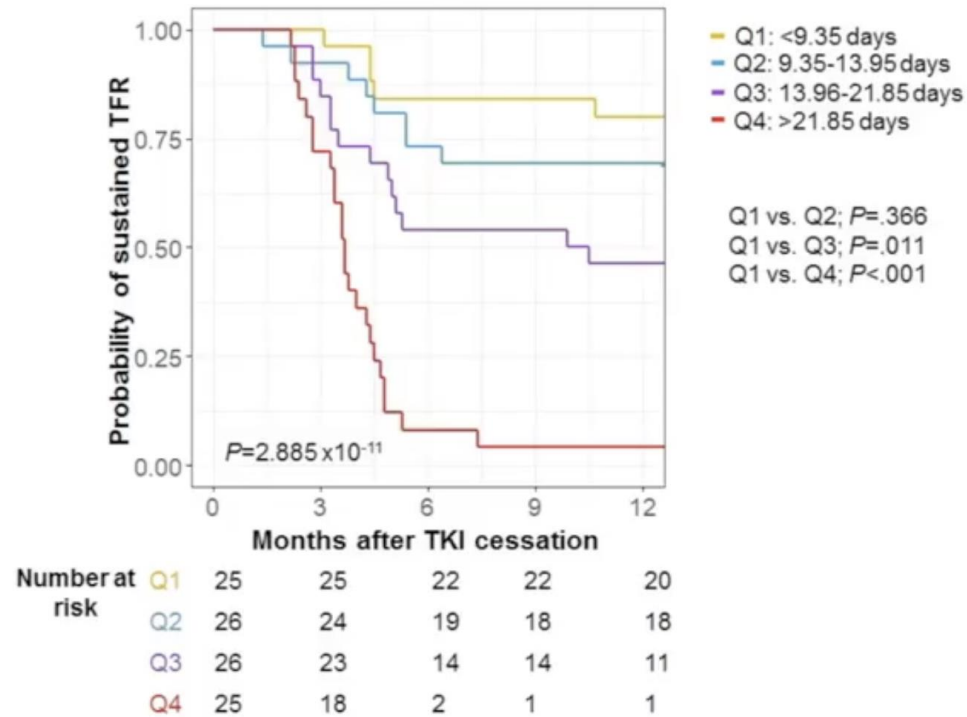
NK-cell counts at the time of TKI discontinuation



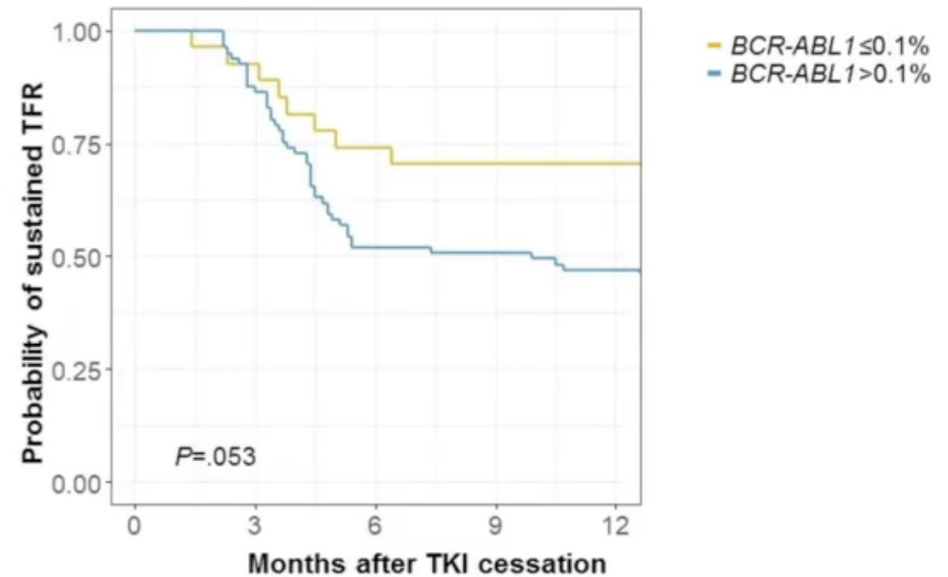
Patients who relapsed after the TKI discontinuation had decreased amount of NK-cells already at the study start when still treated with TKI therapy

EARLY BCR-ABL1 KINETICS ARE PREDICTIVE OF SUBSEQUENT ACHIEVEMENT OF TFR IN CML

C. Probability of sustained TFR based on halving time quartiles



F. Probability of sustained TFR based on the 3-month *BCR-ABL1* value; *BCR-ABL1* ≤0.1% vs. *BCR-ABL1* >0.1%



Risk factors for TFR at 36 months

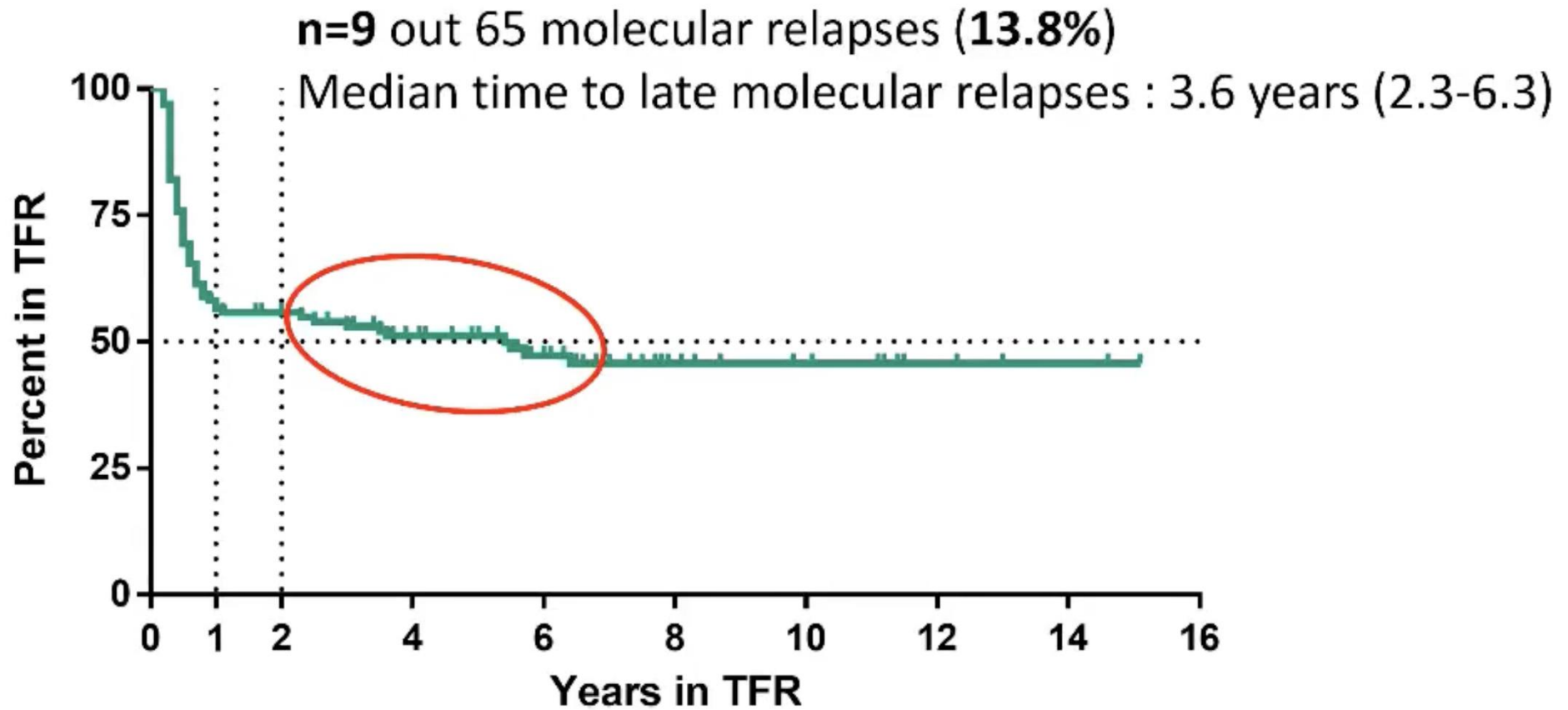
Univariate Models	EURO-SKI				STIM2			
	n	OR	95% CI	p-value	n	OR	95% CI	p-value
Duration of TKI treatment (years)	510	1.124	1.046-1.207	1.0014	184	1.192	1.045-1.360	0.0087
DMR duration under TKI (years)	510	1.102	1.022-1.187	1.0110	184	1.211	1.041-1.410	0.0134
Blasts in peripheral blood (%)	413	0.889	0.809-0.976	1.0137	175	0.760	0.593-0.972	0.0291
S Transcript, e14a(+e13a2) vs. e13a2	392	2.064	1.243-3.427	1.0051	158	2.378	1.139-4.935	0.0211

- **TKI exposure / DMR duration**
- **% of blasts in peripheral blood at diagnosis : more relapses**
- **Transcript type : e14a2**

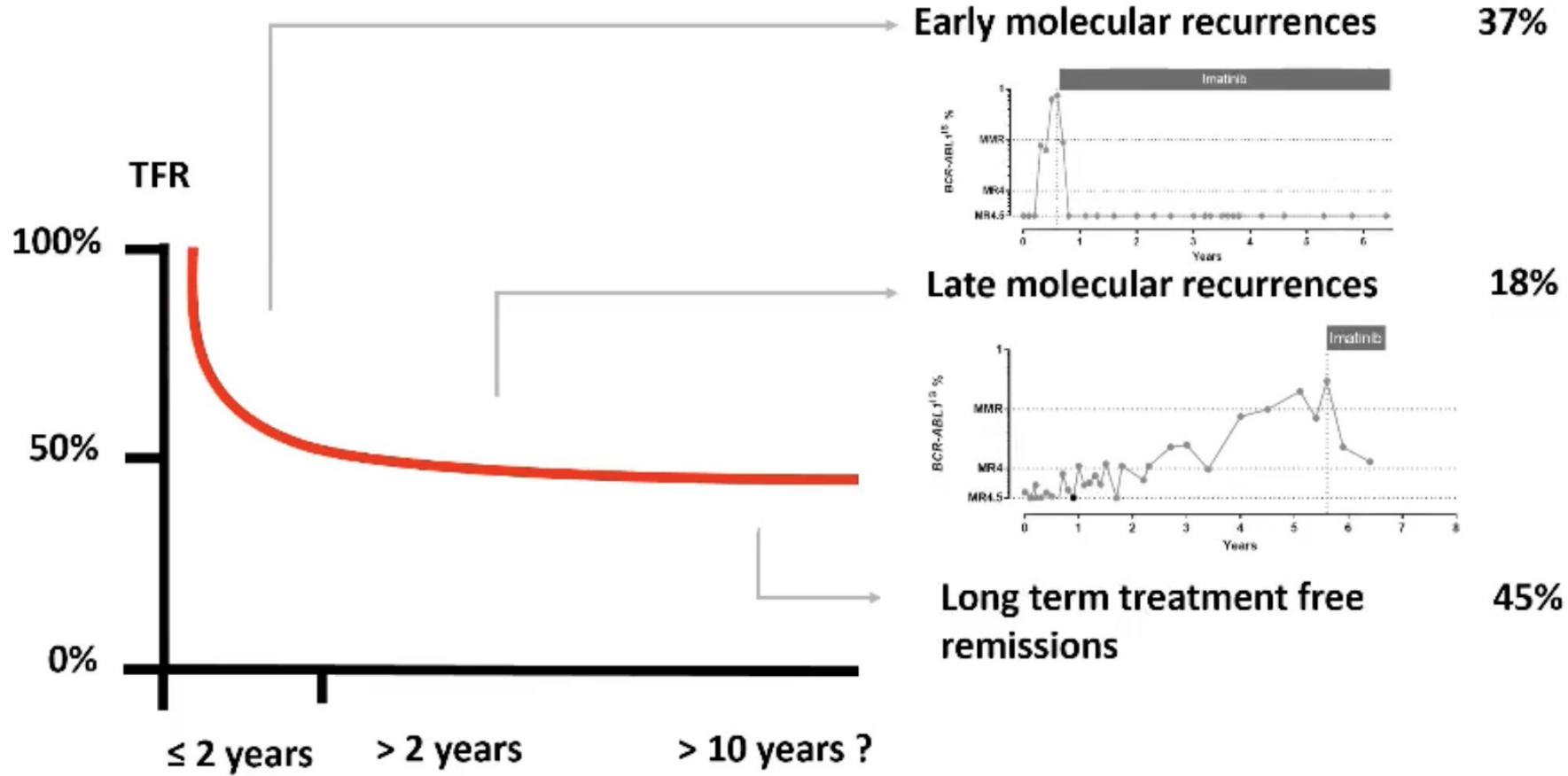


Late molecular relapses (> 2 years in TFR1)

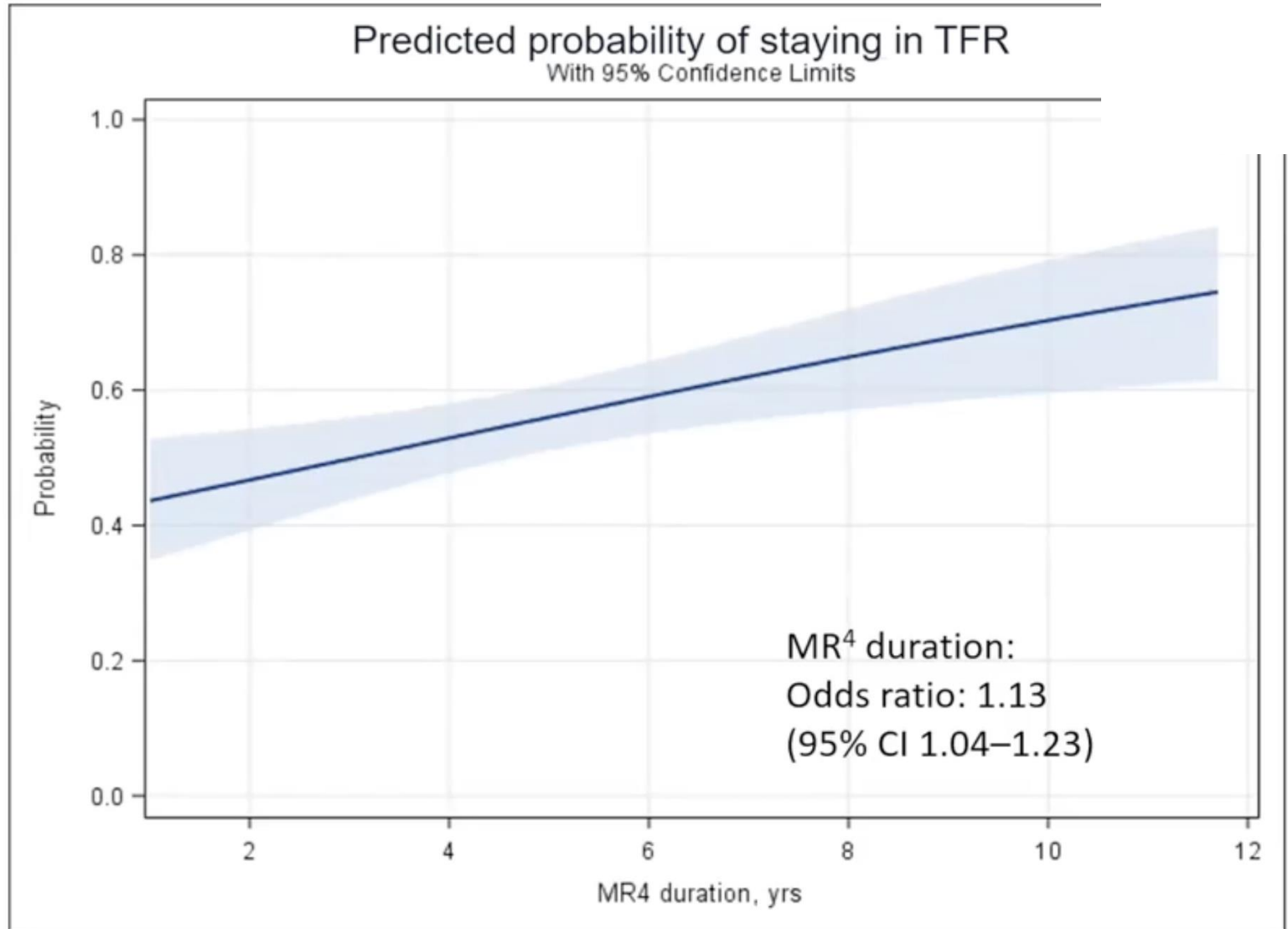
128 patients in TFR, median follow-up in TFR 6.5y



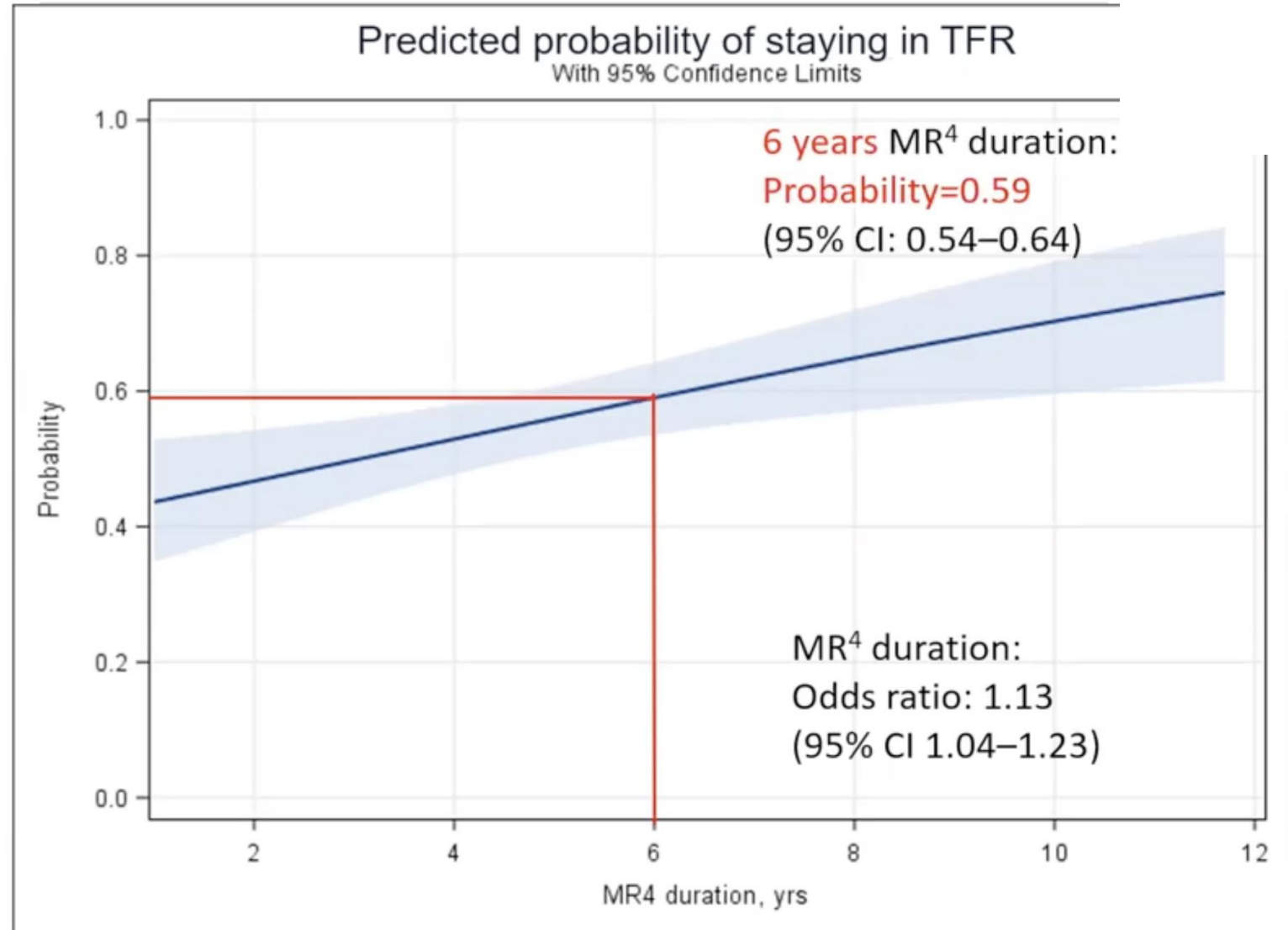
Molecular recurrences during treatment free remission (TFR) in CML patients



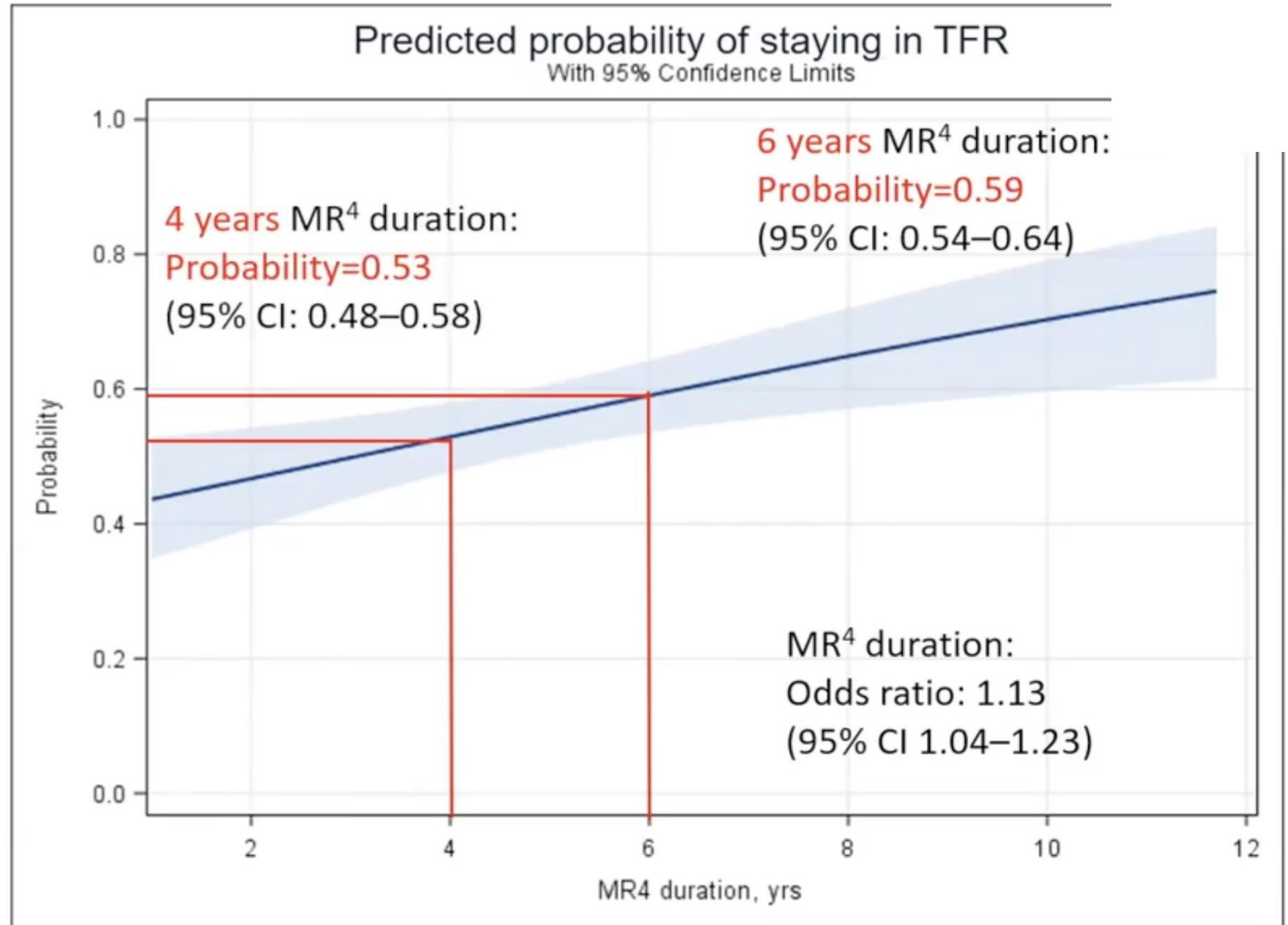
MR⁴ duration (n=405)



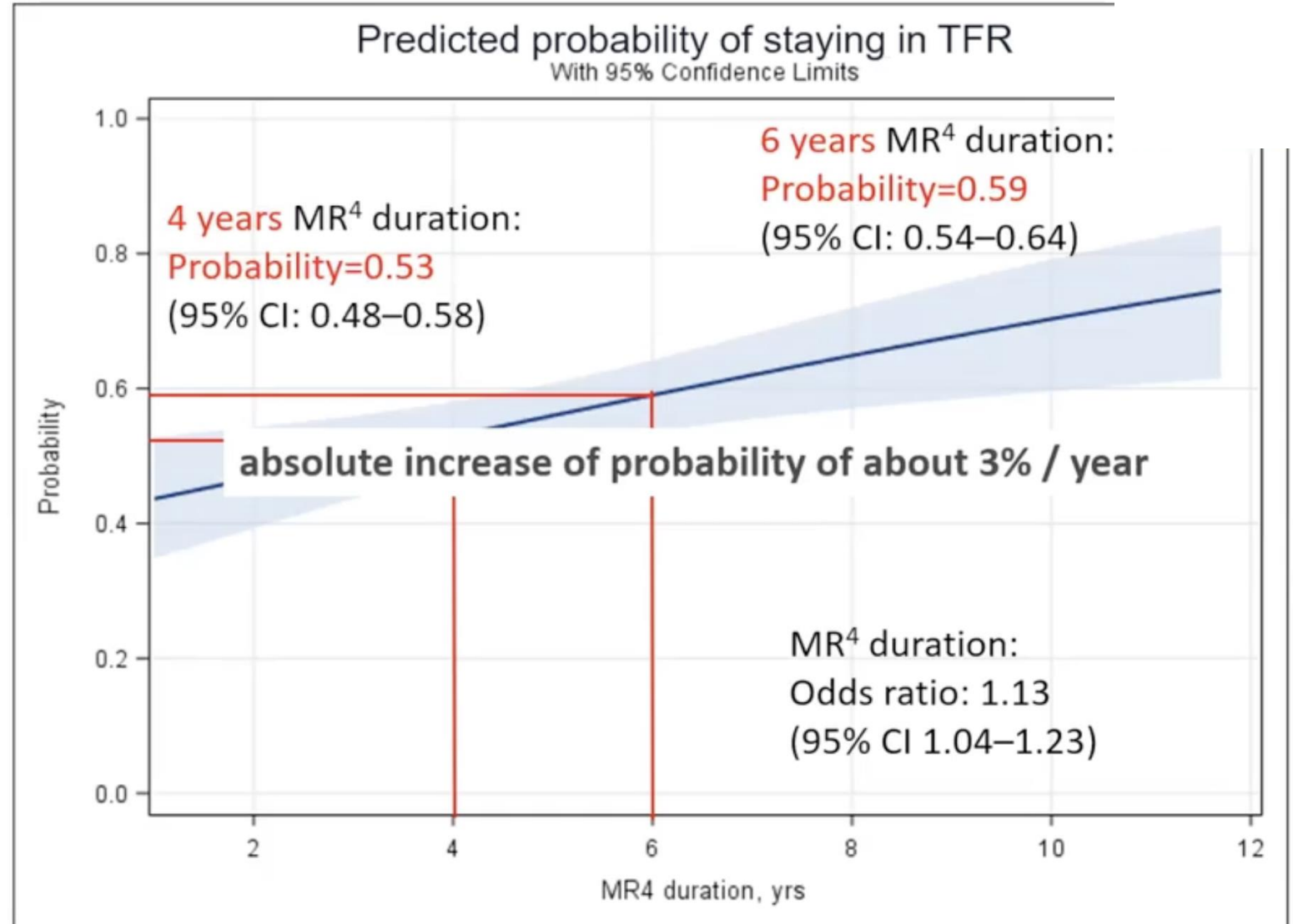
MR⁴ duration (n=405)



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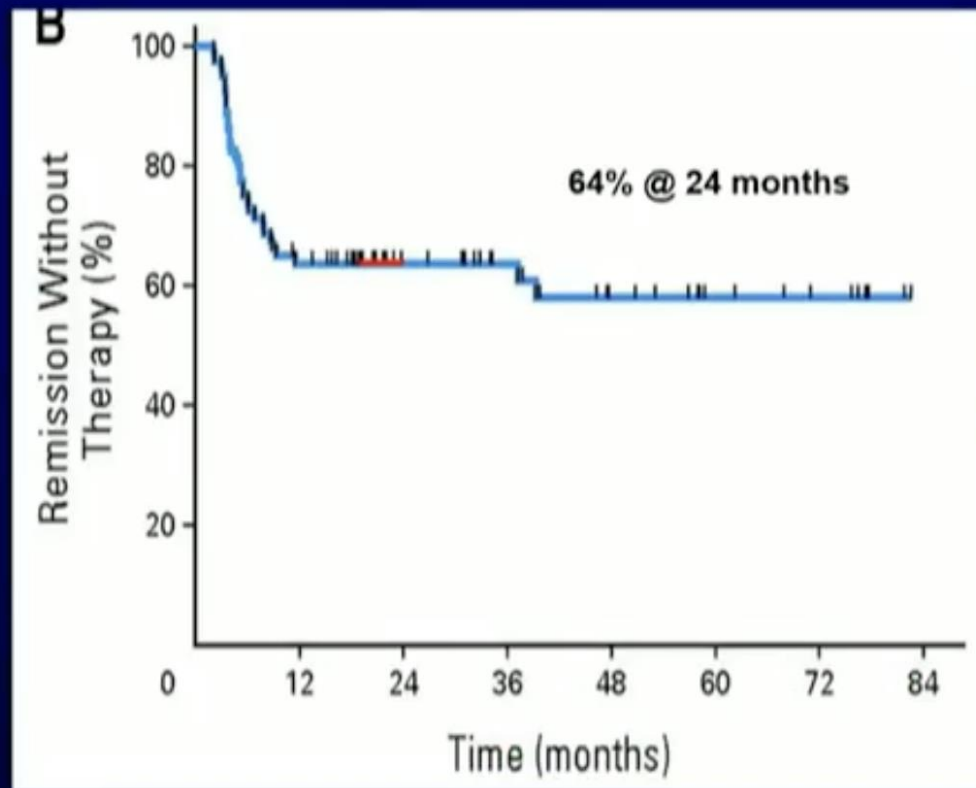
MR⁴ duration (n=405)



How Deep is Deep (MR) for TFR?

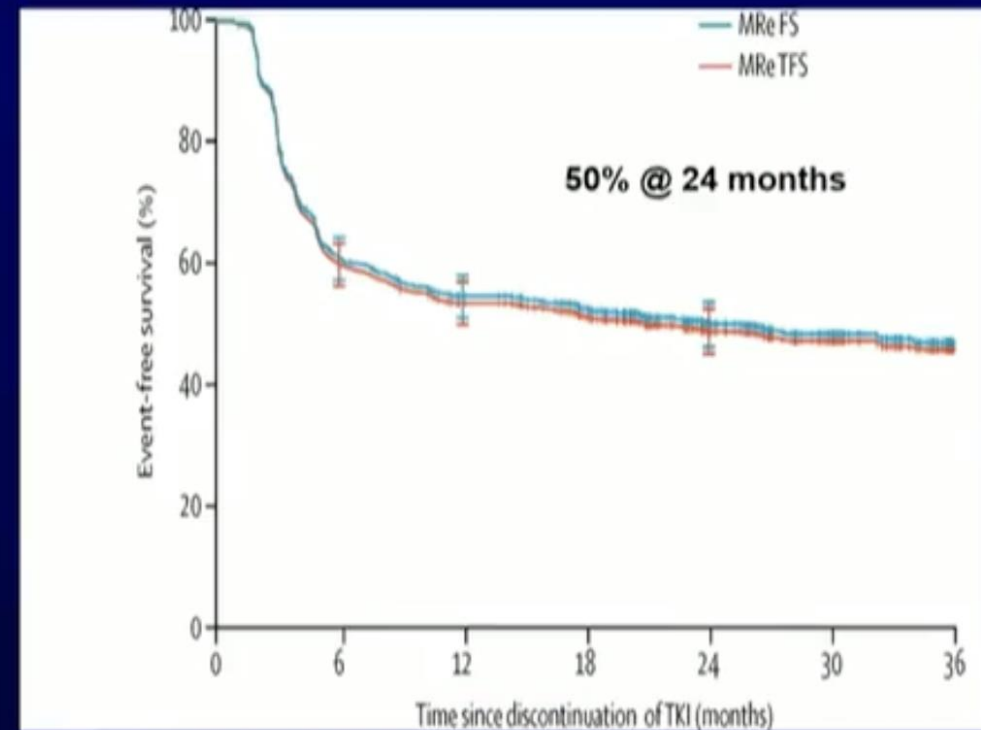
A-STIM

- MR4.5
- ≥ 2 years



EURO-Ski

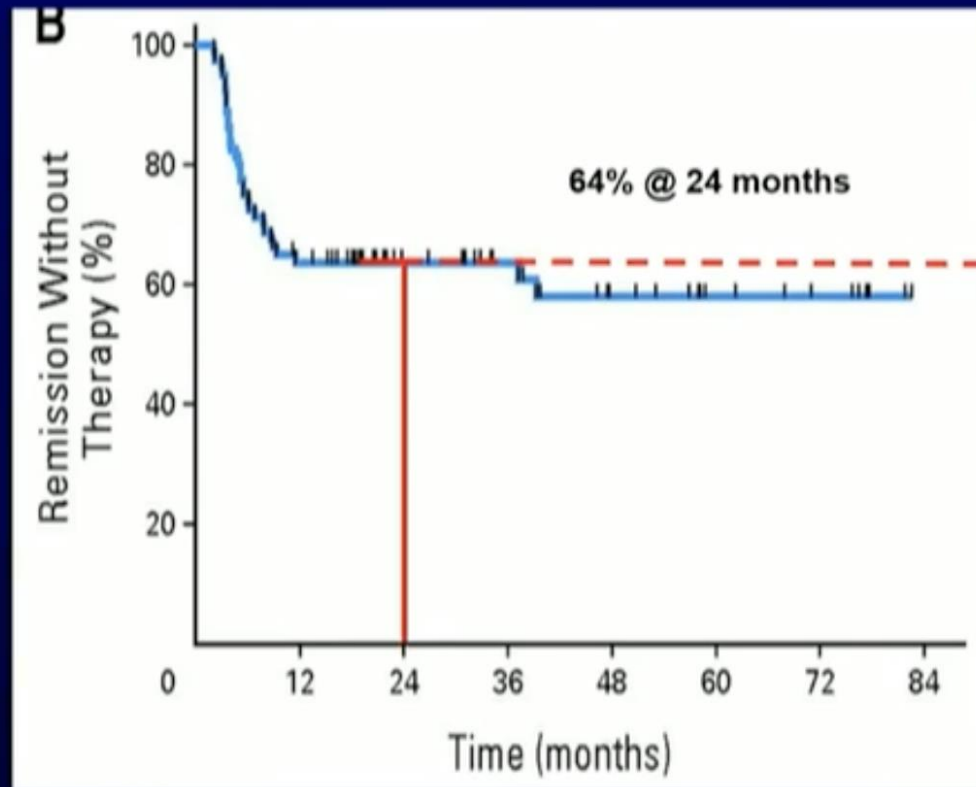
- MR4
- ≥ 1 years



How Deep is Deep (MR) for TFR?

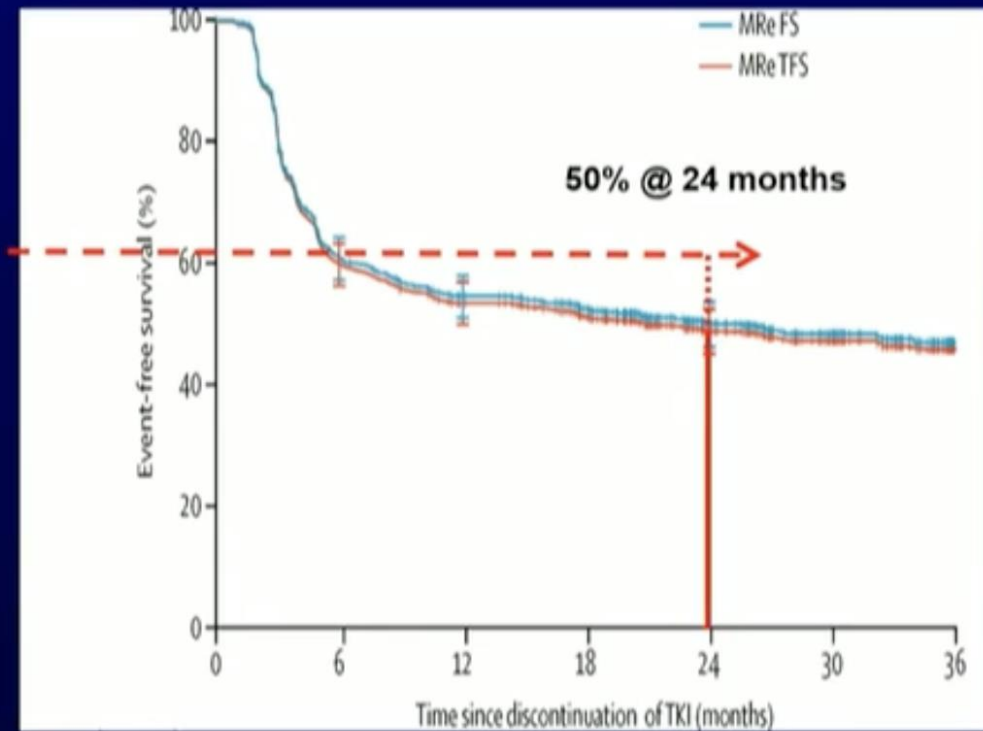
A-STIM

- MR4.5
- ≥ 2 years



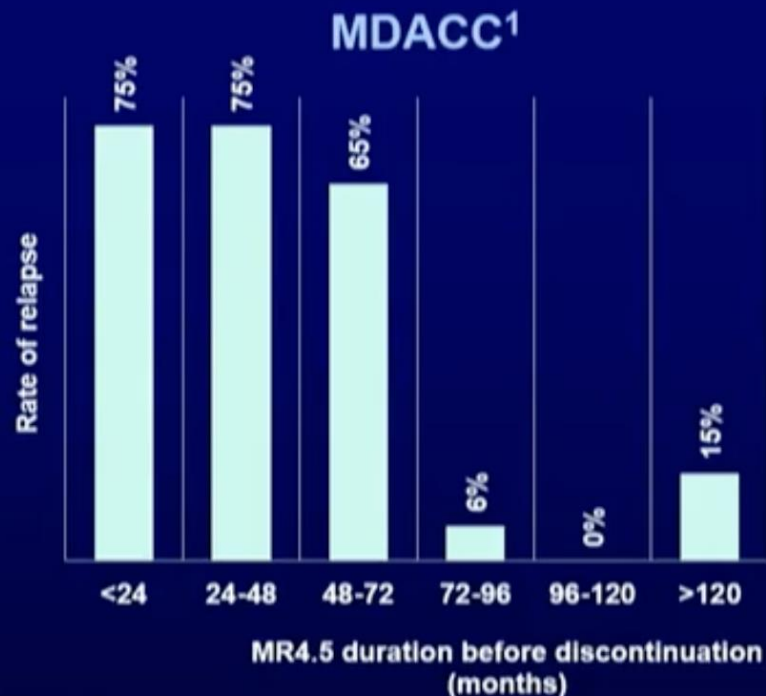
EURO-Ski

- MR4
- ≥ 1 years



How to Improve TFR Success?

- Wait longer



- MVA: MR^{4.5} duration >72 mo before discontinuation only predictor for durable response (p < 0.001, HR 0.08 [CI 95%, 0.02- 0.27])

EURO-SKI²

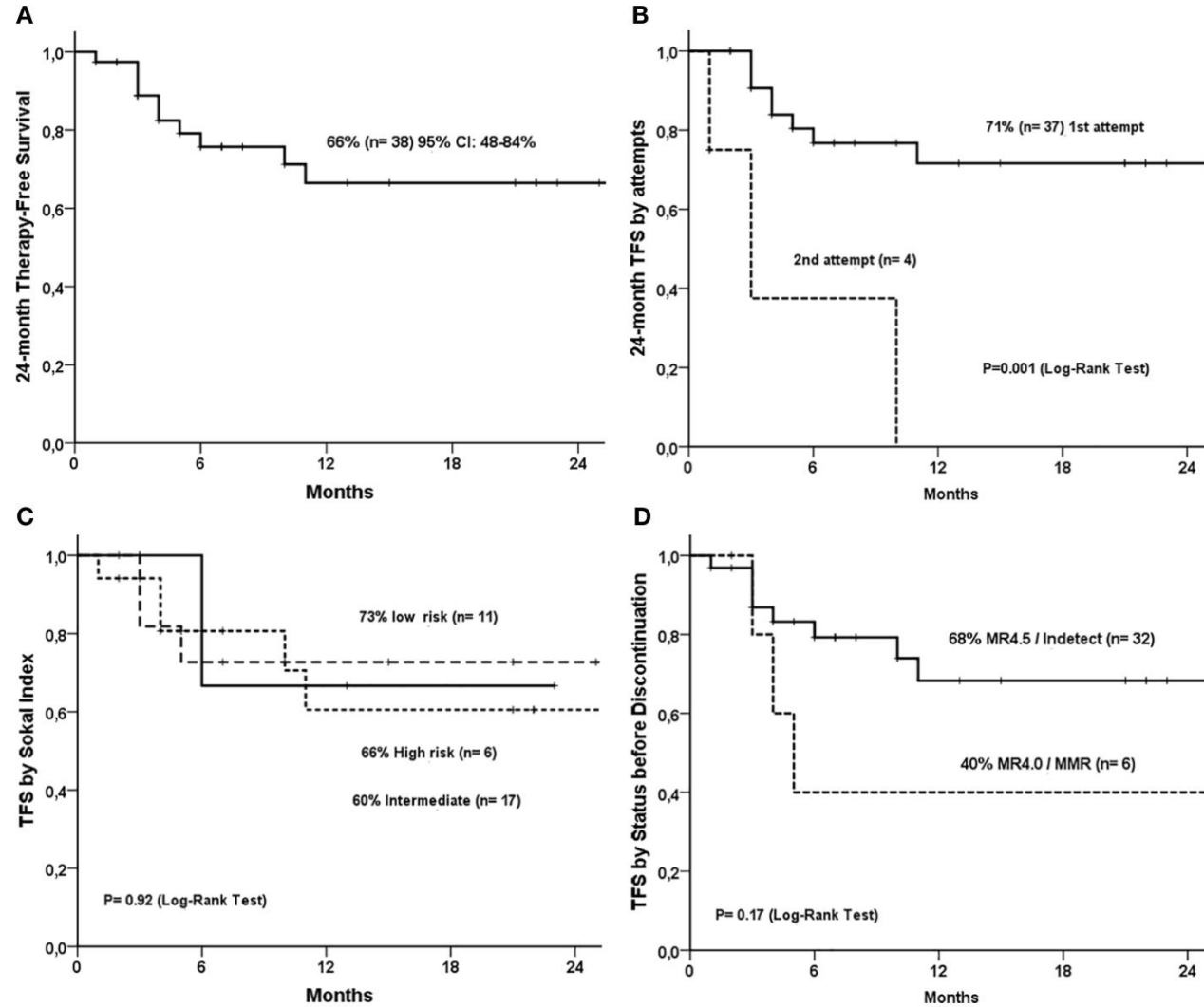
Years DMR	n/N	% (95% CI) without relapse
1-2	13/28	46% (28-66)
>2 to ≤3	17/31	55% (36-73)
>3 to ≤4	22/37	59% (42-75)
>4 to ≤5	11/17	65% (38-86)
>5 to ≤6	14/20	70% (46-88)
>6 to ≤7	9/15	60% (32-84)
>7	15/23	65% (43-84)

Yearly increase of ~3% in the probability of staying in MMR at 6 months over the observed range of DMR durations.

Kinetics of *BCR::ABL1* transcript levels and molecular relapse after tyrosine kinase inhibitors discontinuation in chronic myeloid leukemia patients: preliminary results from the DES-CML study

Bruna Murbach¹, Gislaine Duarte¹, Leonardo Carvalho Palma²,
Eliana Miranda¹, Guilherme Duffles¹, Grazielle Pavan Furlin¹,
Isabella Toni¹, Carmino De Souza¹, Larissa Binelli²,
Vitor Leonardo Bassan³, Fabiola Attie de Castro³,
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and Katia Borgia Barbosa Pagnano^{1*}

DES CML Study



Conclusão

- ❑ A interrupção do tratamento com o TKI tem sido evidenciada nos guidelines como um objetivo do tratamento da LMC
- ❑ A duração do tratamento, a profundidade da resposta e a duração da profundidade da resposta são critérios fundamentais para o sucesso na interrupção do tratamento
- ❑ A disponibilidade da realização de exames de PCR padronizados, com frequência descrita nos protocolos e resultados rápidos é condicional para se permitir iniciar o processo de interrupção do tratamento



Obrigada

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