



III Simpósio Internacional
de Onco-Hematologia

12, 13 E 14 MARÇO
DE 2020

Hotel Pullman São Paulo Vila Olímpia





Grupo
ONCOCLÍNICAS
Dua vida. Nossa vida.

INSTITUTO
ONCOCLÍNICAS

ONCO
CLÍNICA
CENTRO DE TRATAMENTO
ONCOLÓGICO

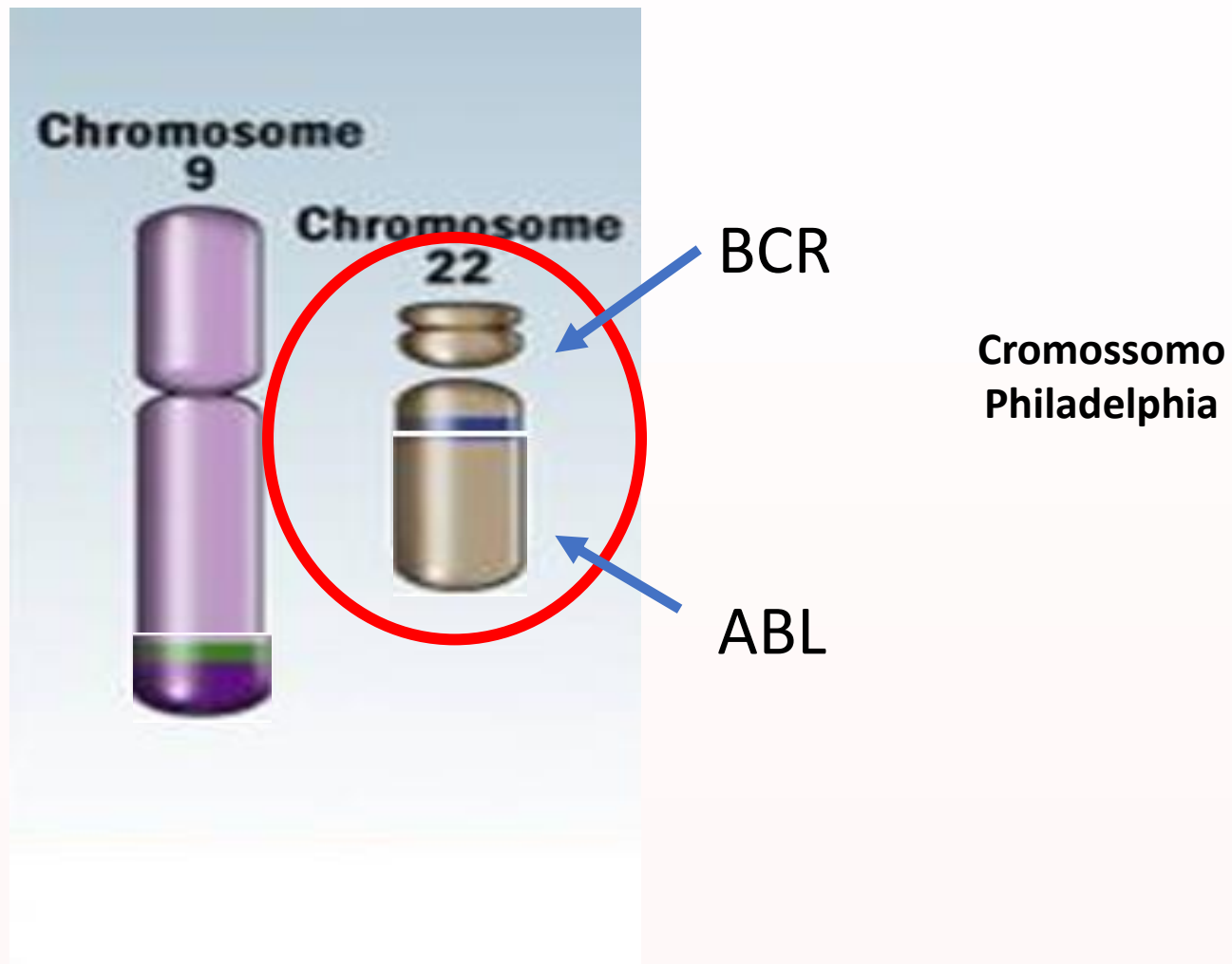
Por que o resultado do BCR/ABL não tem um valor de referência?
É positivo ou negativo?
Como entender?

Carla Boquimpani – HEMORIO / Oncoclínica RJ

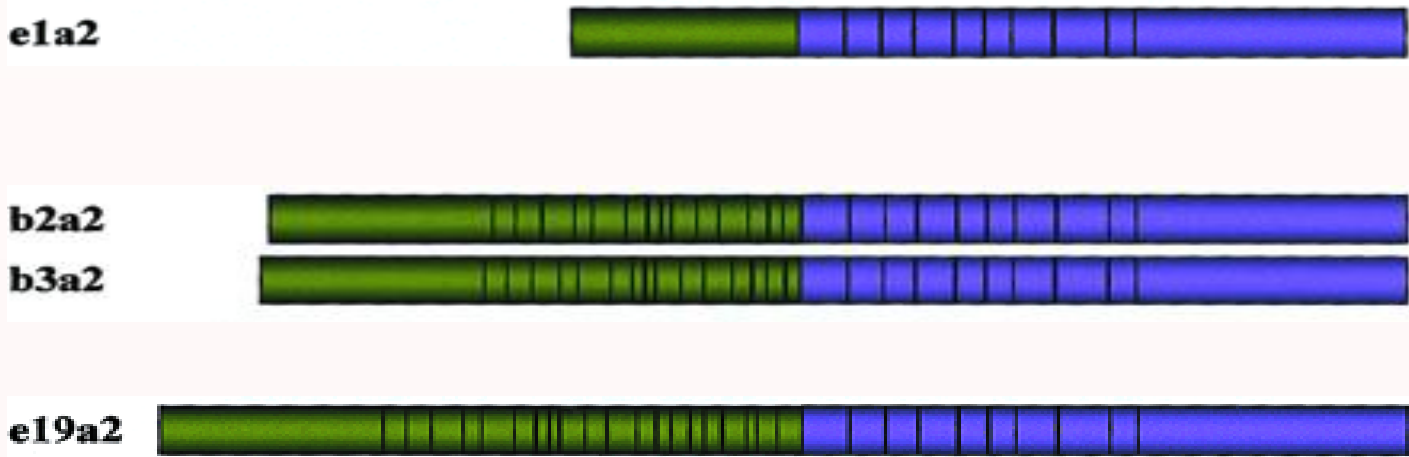
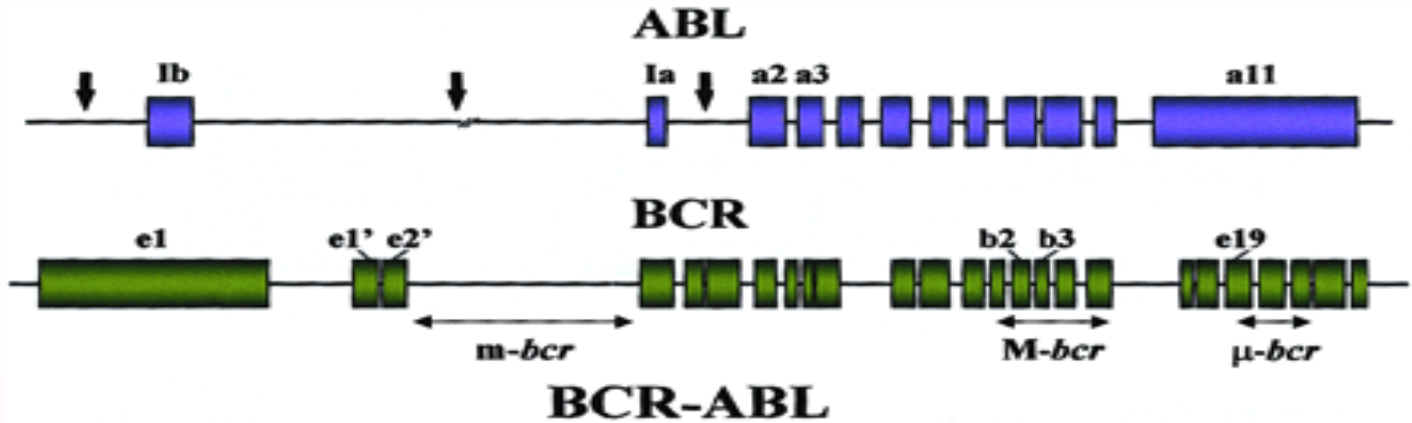
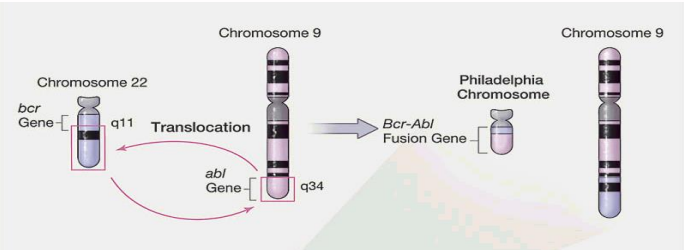


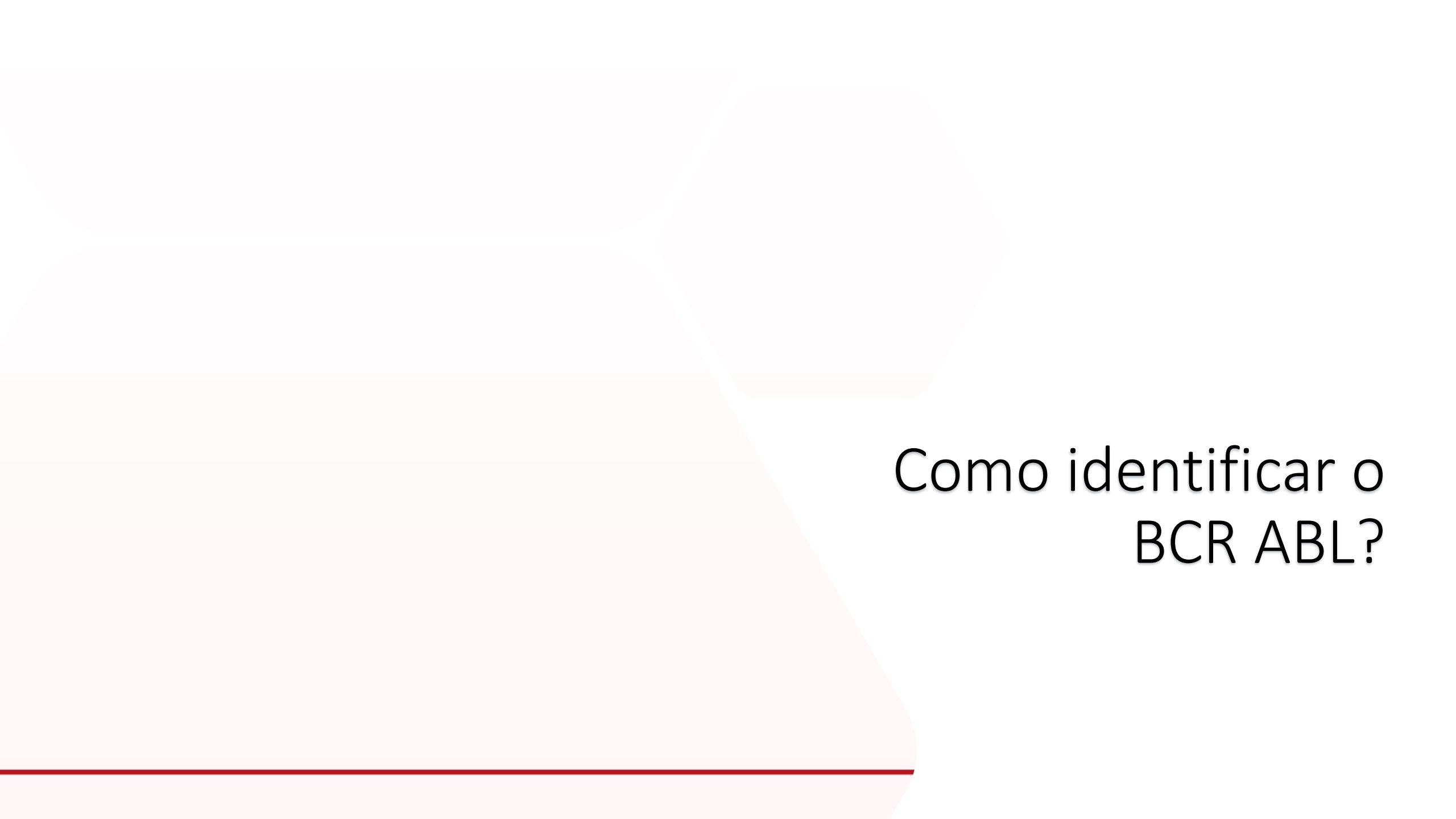
O que é BCR ABL?

Como ocorre a formação do BCR ABL



Anatomia Molecular do Gene *BCR-ABL1*





Como identificar o
BCR ABL?

Histórico da evolução da monitorização da LMC

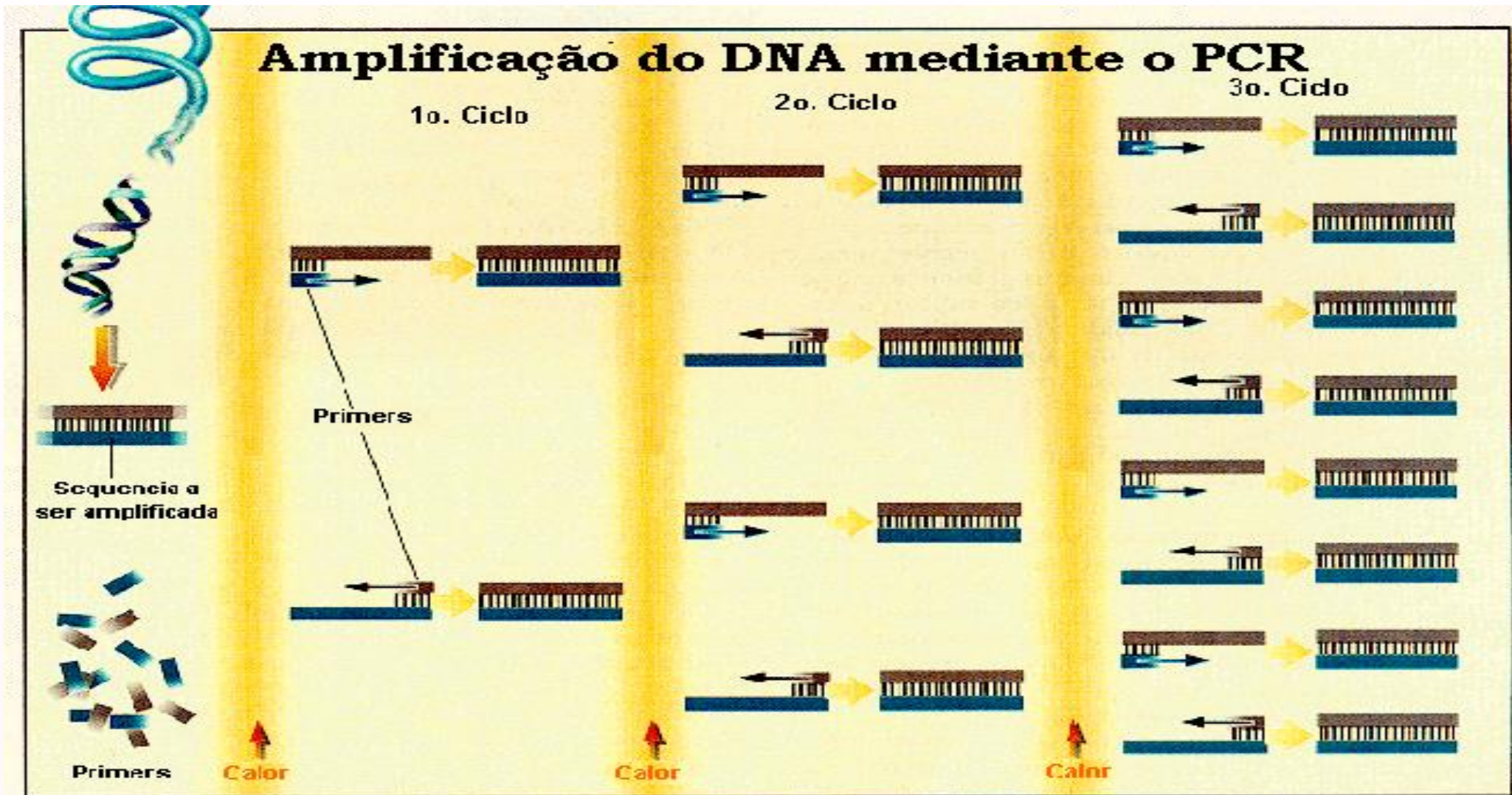
- ❖ Metade do século XIX LMC entidade diferenciada das demais leucemias
- ❖ Em 1960 identificado o cromossoma Philadelphia
- ❖ Nos 30 anos seguintes monitoramento por mensuração do número de metáfases Ph positivas
- ❖ Início do PCR qualitativo para BCR ABL para evidência da existência ou ausência do transcrito
- ❖ PCR em primeiro passo e em segundo passo (Nested) pra amplificação e aumento da sensibilidade
- ❖ 1993 Nick Cross iniciou o uso do PCR quantitativo relação de BCR-ABL/ABL
- ❖ 2003 Hughes introduziu o conceito de redução logarítmica
- ❖ 2005 Bethesda NIH – início do uso de IS na liberação de resultados do RT

PCR



Entendendo o PCR

PCR - Reação em Cadeia da Polimerase



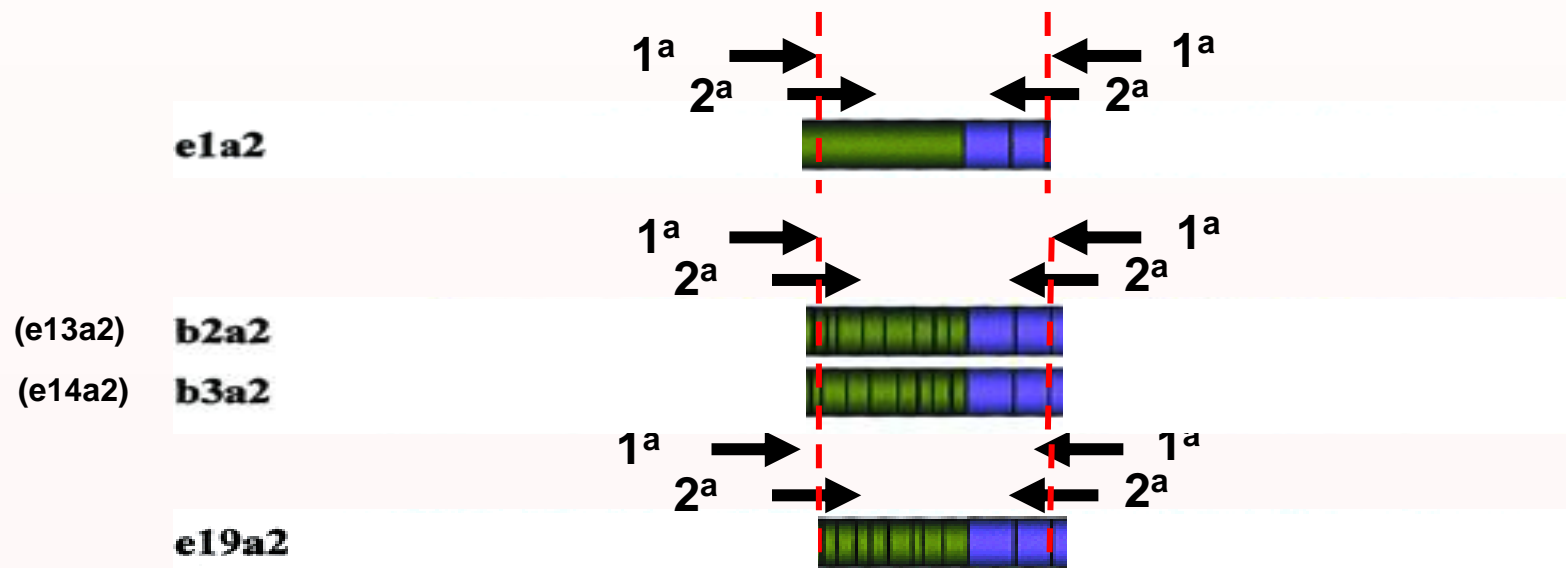
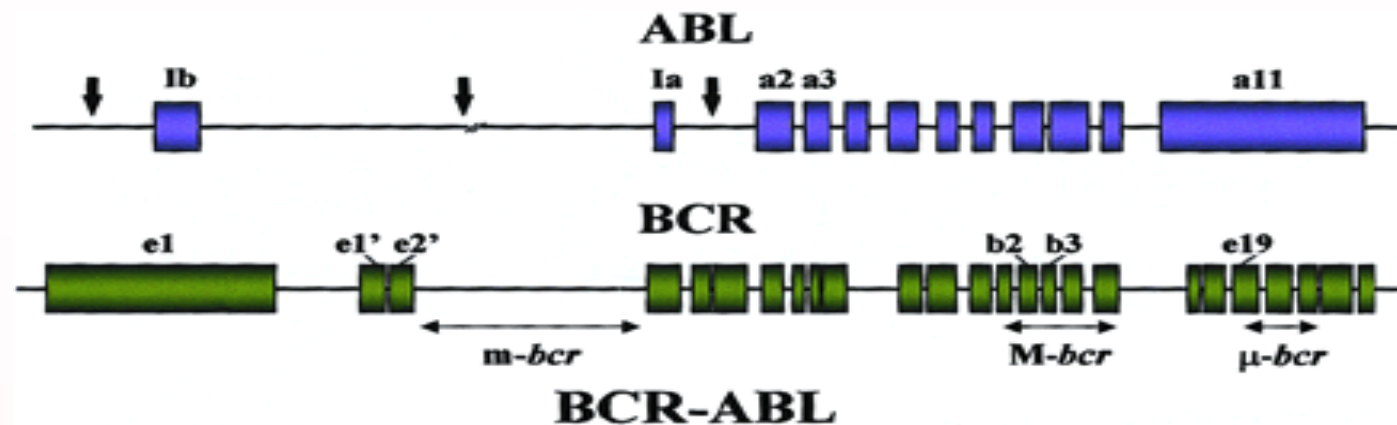
Cortesia Dr. Israel Bendict

Reação em Cadeia da Polimerase (PCR)

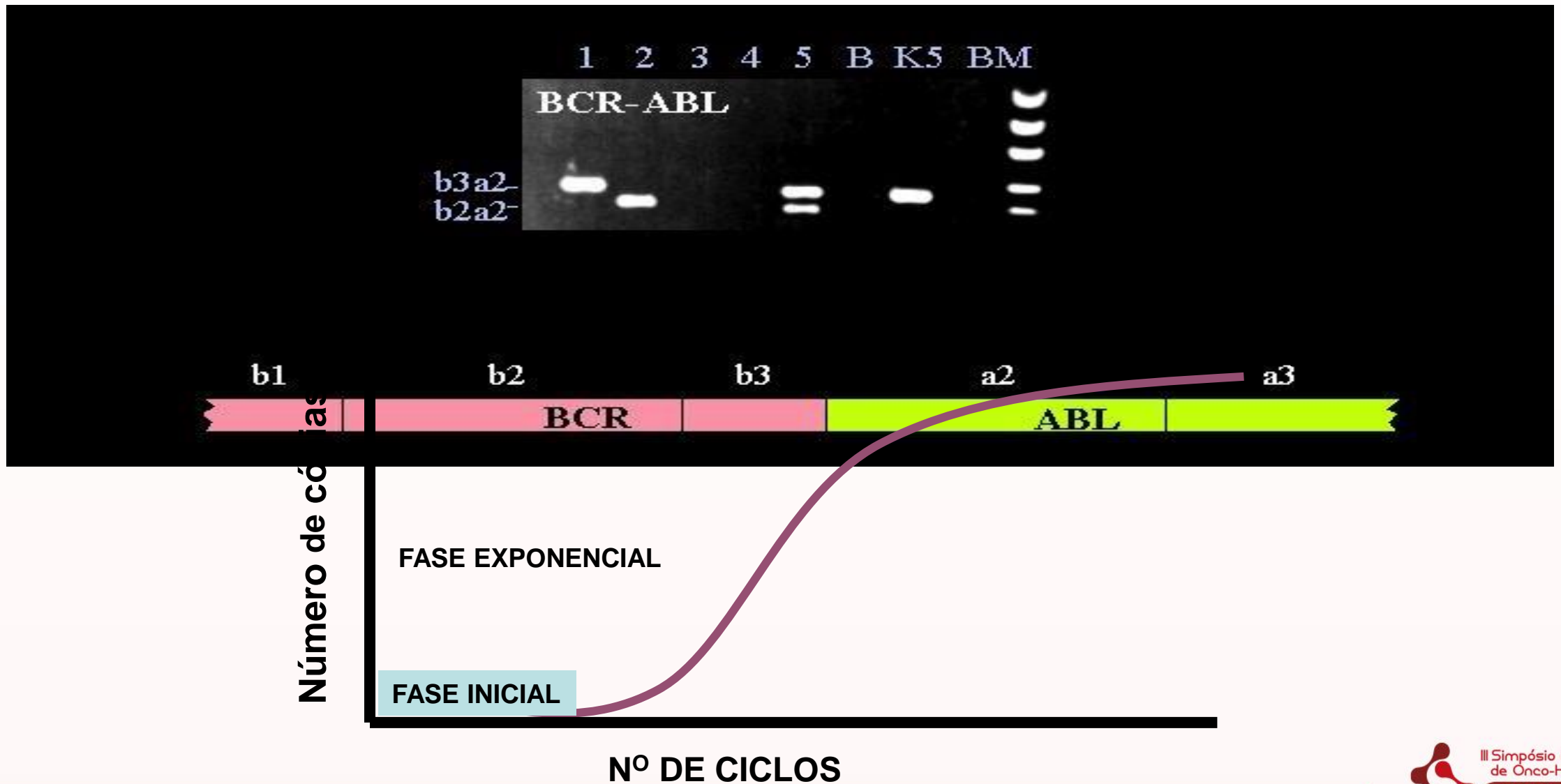
1) Qualitativo

{ Fase única
{ Duas fases (“nested”)

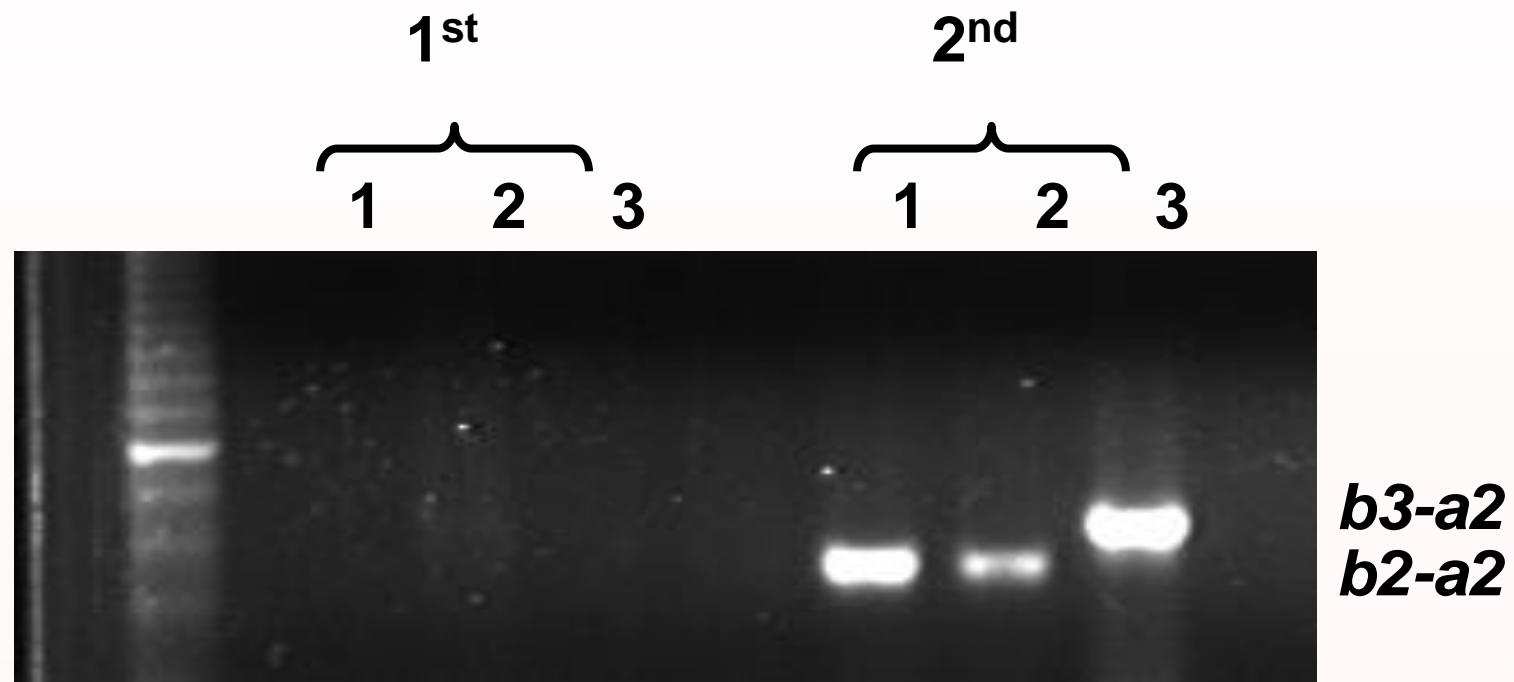
Anatomia Molecular do Gene *BCR-ABL1*



PCR QUALITATIVO



REAÇÃO DA POLIMERASE EM CADEIA “nested”



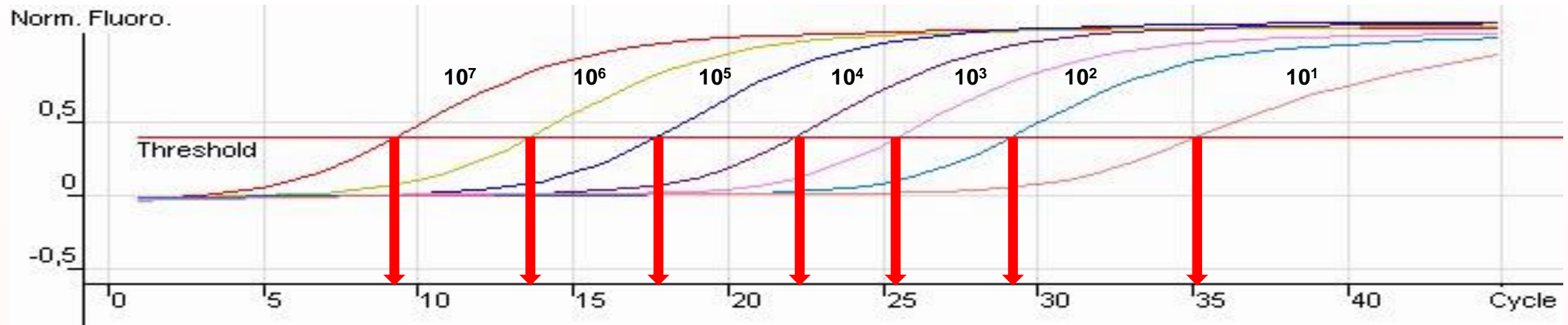
Reação em Cadeia da Polimerase (PCR)

1) Qualitativo

{ Fase única
{ Duas fases (“nested”)

2) Quantitativo

PCR QUANTITATIVO

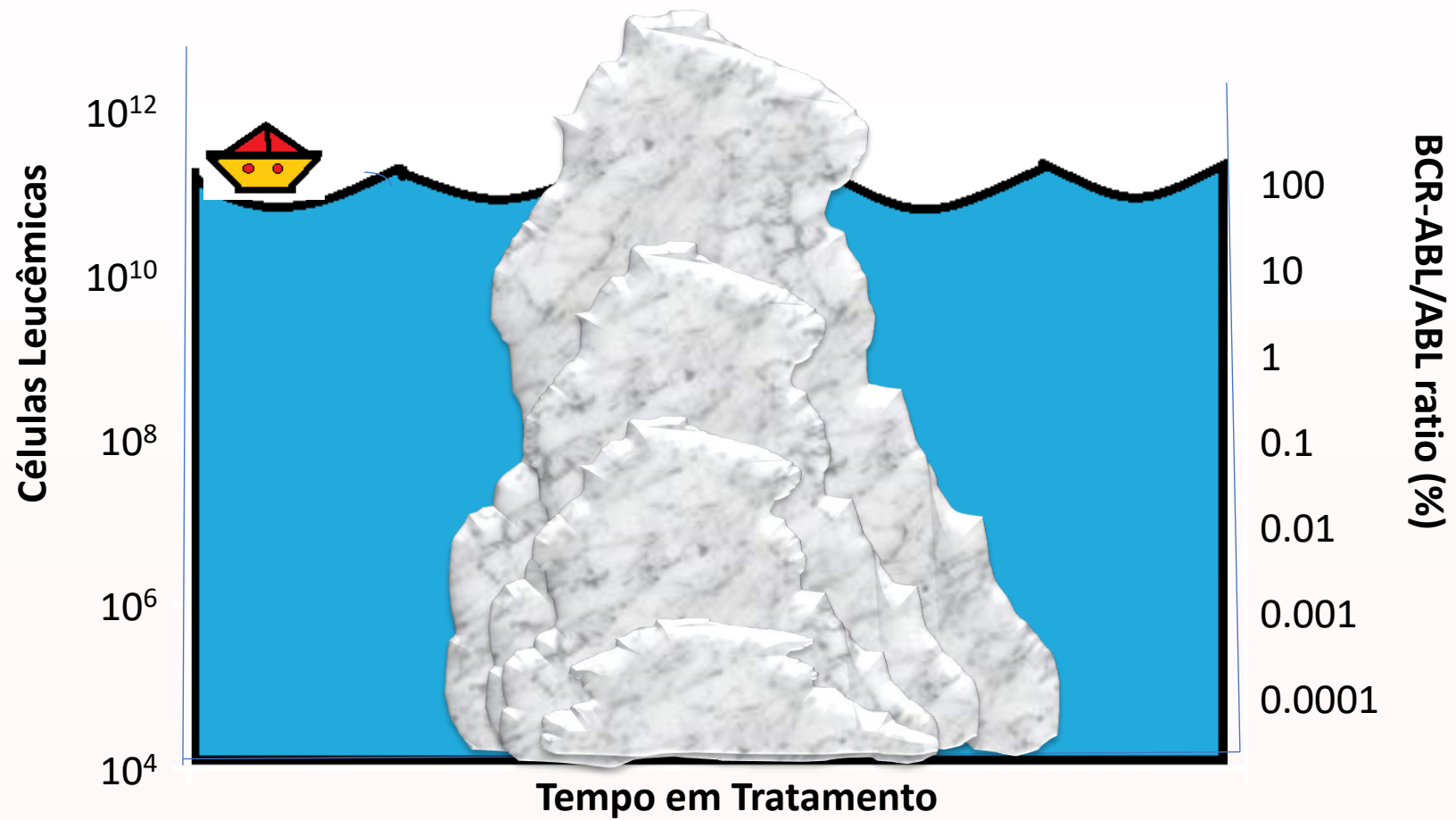


Por que o monitoramento é tão importante?





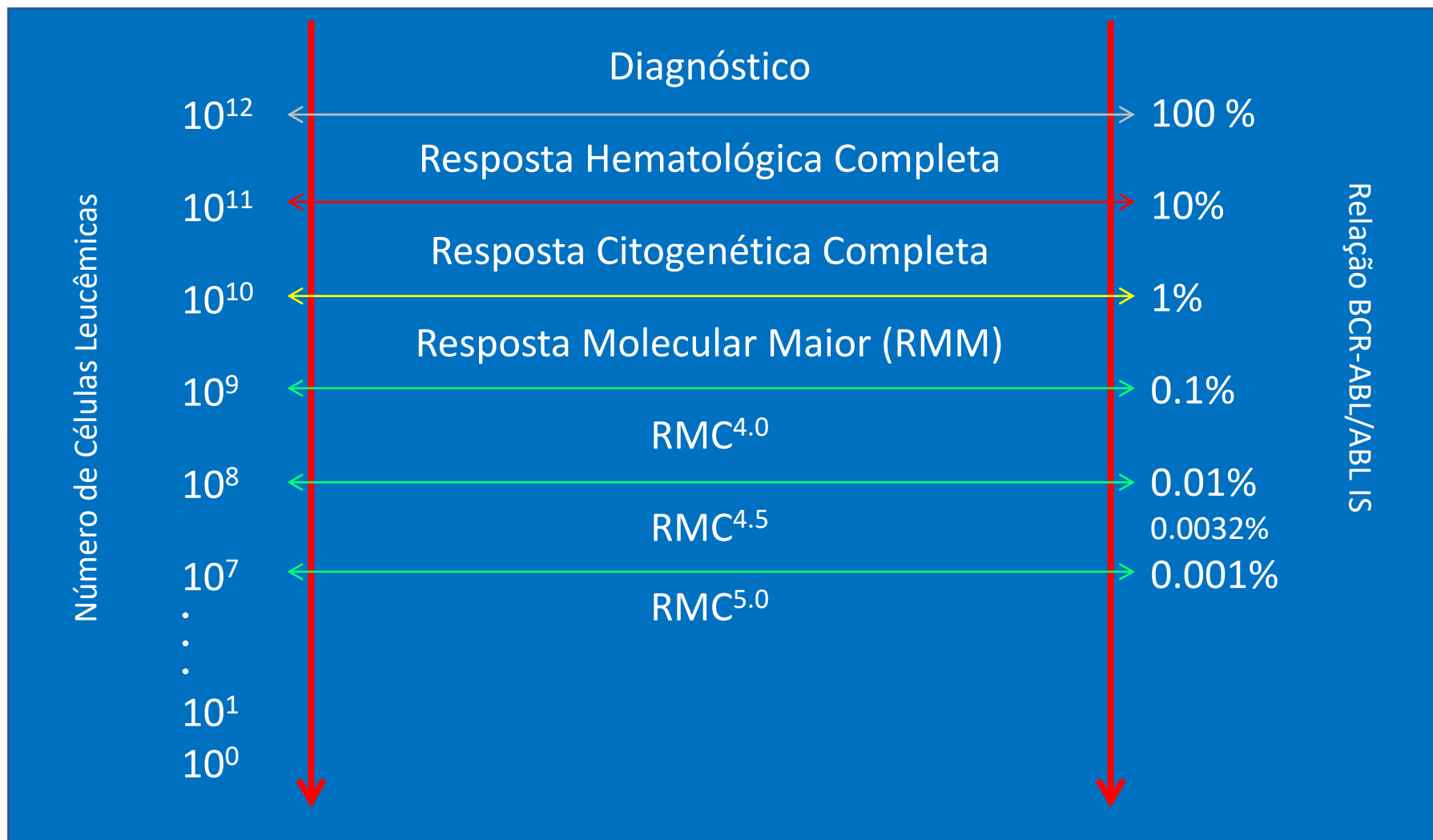
Objetivos do Tratamento



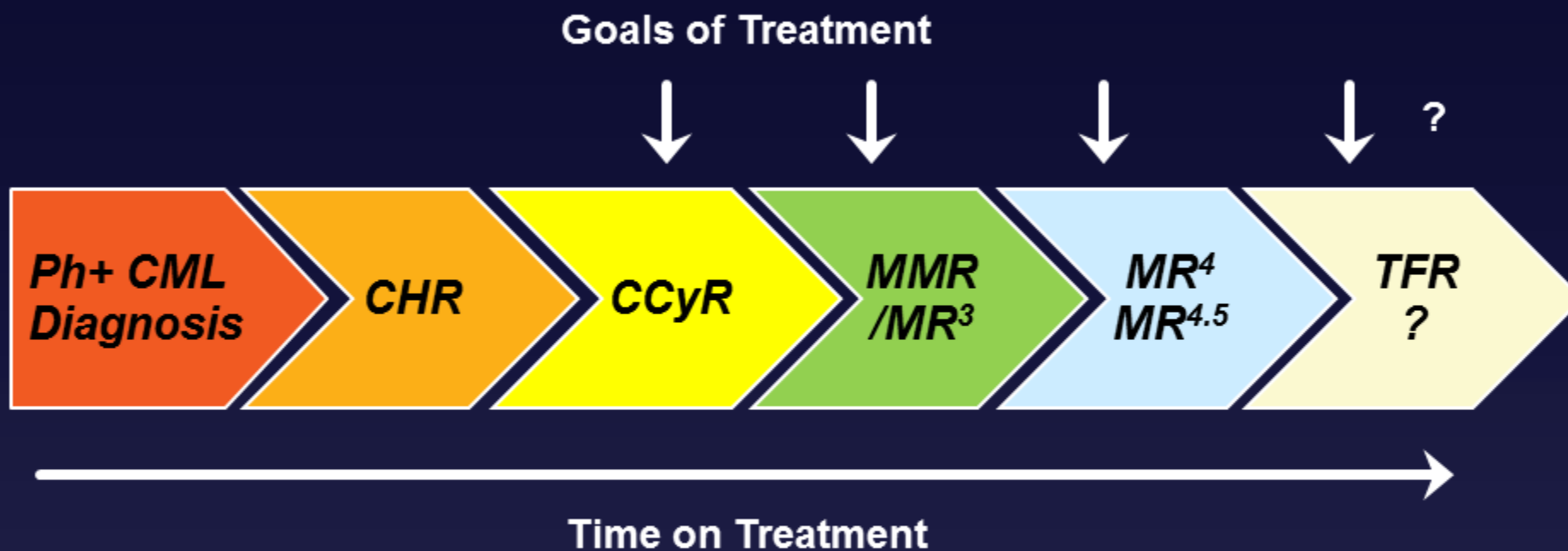
Adapted from Kaeda J, et al. *Acta Haematol.* 2002;107:64–75.
Baccarani M, et al. *Blood.* 2006;108:1809–1820.

National Comprehensive Cancer Network. Clinical practice guidelines in oncology: chronic myelogenous leukemia. V.2.2009.

Definições das Respostas na LMC



Os objetivos do tratamento tem se tornado mais ambiciosos ao longo do tempo



CHR, complete hematologic response;

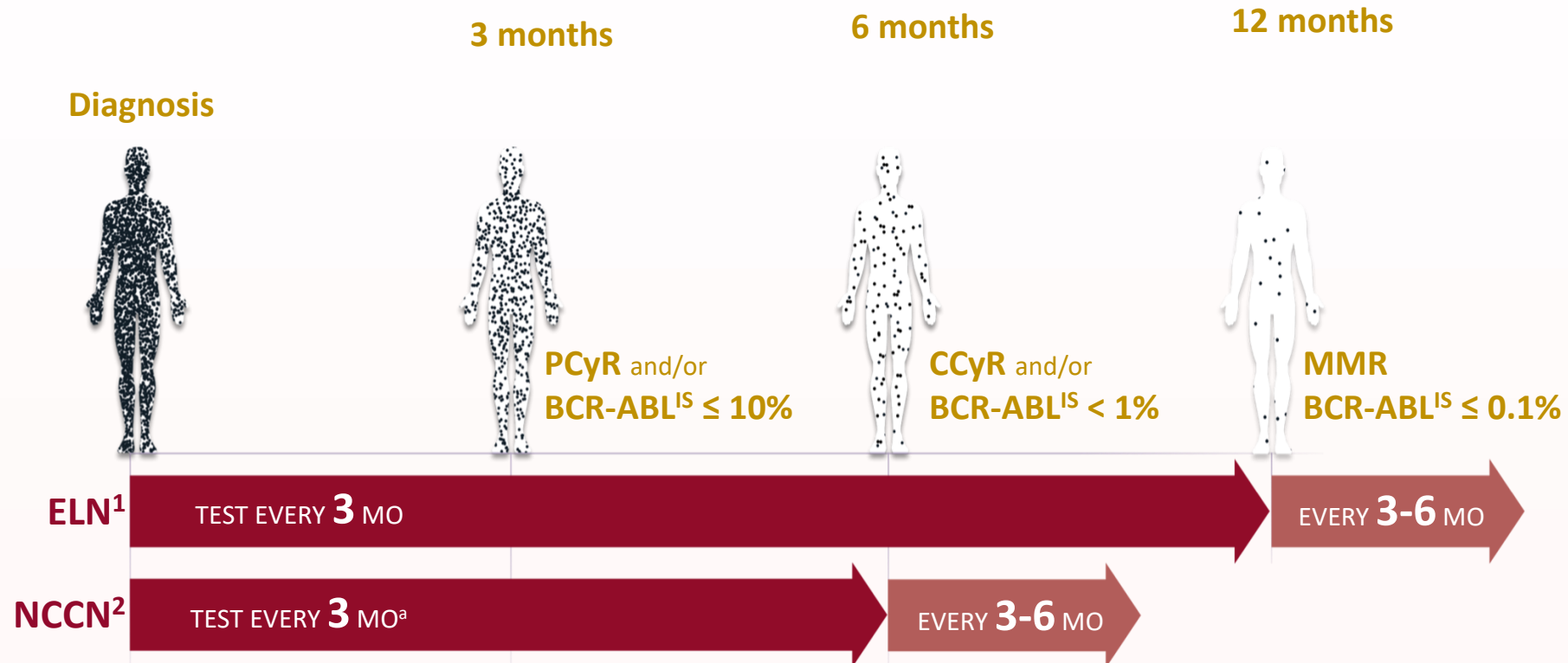
CCyR, complete cytogenetic response;

MMR, major molecular response, 3-log reduction from IRIS baseline (IS);

MR⁴, MR^{4.5}, 4-log / 4.5 log reduction from IRIS baseline (IS)

TFR, treatment free remission, maintenance of MMR without therapy

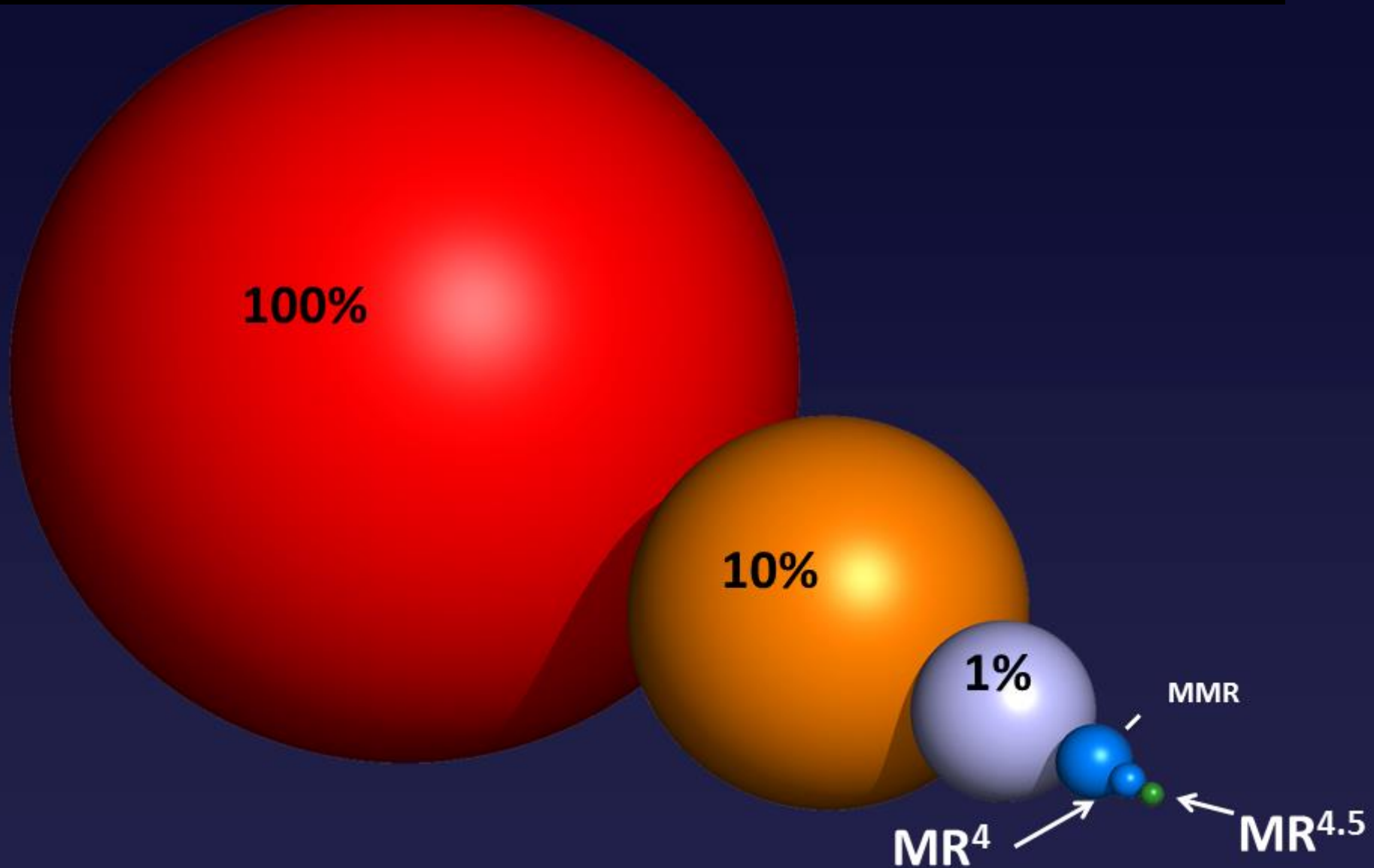
Resposta ótima ao tratamento com TKI



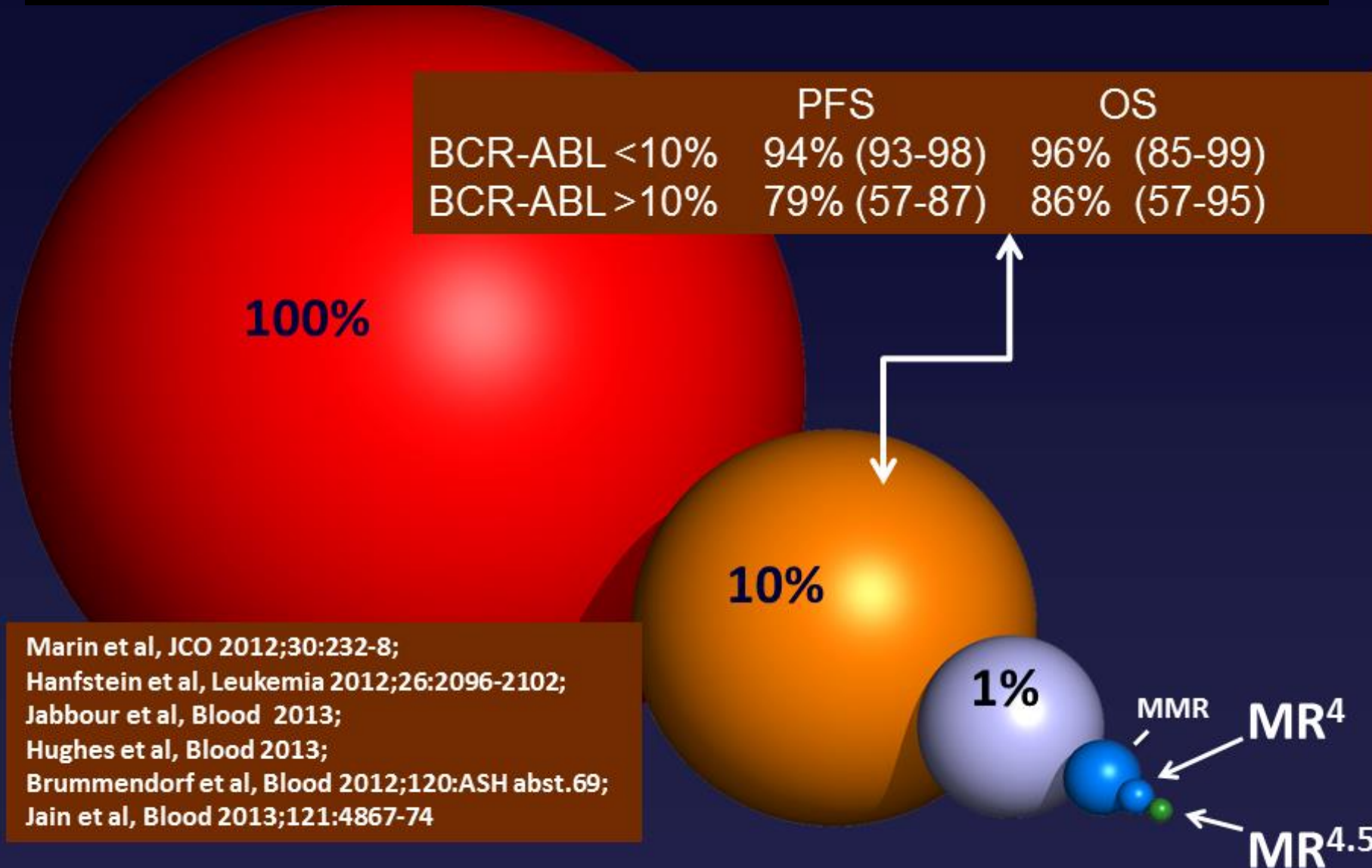
1. Baccarani M, et al. Blood. 2013;122(6):872-884;

2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Chronic Myelogenous Leukemia. V1.2015

Redução precoce leva a resposta profunda com o tempo



Redução precoce leva a resposta profunda com o tempo



Redução precoce leva a resposta profunda com o tempo

BCR-ABL < or > 10% at 3 months *
MMR at 3-6 months †

MR^{4.5}

41% - 5.7% at 4 yrs

83% - 69% at 5 yrs

10%

1%

MMR

MR⁴

MR^{4.5}

*Branford et al., Blood 2014

† Hehlmann et al, JCO 2014



Chronic myelogenous leukemia

European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia

A. Hochhaus¹ · M. Baccarani² · R. T. Silver³ · C. Schiffer⁴ · J. F. Apperley⁵ · F. Cervantes⁶ · R. E. Clark⁷ · J. E. Cortes⁸ · M. W. Deininger⁹ · F. Guilhot¹⁰ · H. Hjorth-Hansen¹¹ · T. P. Hughes¹² · J. J. W. M. Janssen¹³ · H. M. Kantarjian¹⁴ · D. W. Kim¹⁵ · R. A. Larson¹⁶ · J. H. Lipton¹⁷ · F. X. Mahon¹⁸ · J. Mayer¹⁹ · F. Nicolini²⁰ · D. Niederwieser²¹ · F. Pane²² · J. P. Radich²³ · D. Rea²⁴ · J. Richter²⁵ · G. Rosti² · P. Rousselot²⁶ · G. Saglio²⁷ · S. Saußebe²⁸ · S. Soverini² · J. L. Steegmann²⁹ · A. Turkina³⁰ · A. Zaritskey³¹ · R. Hehlmann^{28,32}

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Escore de Resposta Molecular

	MMR	MR ⁴	MR ^{4.5}	MR ⁵
Minimum sum of reference gene transcripts	10,000 ABL1 ^a 24,000 GUSB ^a	10,000 ABL1 24,000 GUSB	32,000 ABL1 77,000 GUSB	100,000 ABL1 240,000 GUSB
BCR-ABL1 transcript level on the IS ^b	≤0.1%	≤0.01%	≤0.0032%	≤0.001%

^aMinimal sensitivity for accurate quantification.

^bInternational Scale, IS.

Leukemia Net 2013 Critérios de resposta

Time	Optimal	Warning	Failure
Diagnosis	–	-High risk, -CCA/Ph+ (Major route)	–
3 months	Ph+ ≤35% and/or BCR-ABL ≤10%	Ph+ 36%–95% and/or BCR-ABL >10%	No CHR and/or Ph+ >95%
6 months	Ph+ 0% and/or BCR-ABL ≤1%	Ph+ 1%–35% and/or BCR-ABL 1%–10%	Ph+ >35% and/or BCR-ABL >10%
12 months	BCR-ABL ≤0.1%	BCR-ABL >0.1%–1%	Ph+ >0% and/or BCR-ABL >1%
Any time	BCR-ABL ≤0.1%	BCR-ABL 0.1%–1%	BCR-ABL >1%

Leukemia Net 2020 Critérios de resposta

	Optimal	Warning	Failure
Baseline	NA	High-risk ACA, high-risk ELTS score	NA
3 months	$\leq 10\%$	$> 10\%$	$> 10\%$ if confirmed within 1–3 months
6 months	$\leq 1\%$	$> 1-10\%$	$> 10\%$
12 months	$\leq 0.1\%$	$> 0.1-1\%$	$> 1\%$
Any time	$\leq 0.1\%$	$> 0.1-1\%$, loss of $\leq 0.1\%$ (MMR) ^a	$> 1\%$, resistance mutations, high-risk ACA

For patients aiming at TFR, the optimal response (at any time) is BCR-ABL1 $\leq 0.01\%$ (MR⁴).

A change of treatment may be considered if MMR is not reached by 36–48 months.

NA not applicable, ACA additional chromosome abnormalities in Ph⁺ cells, ELTS EUTOS long term survival score.

^aLoss of MMR (BCR-ABL1 $> 0.1\%$) indicates failure after TFR

Obrigada

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