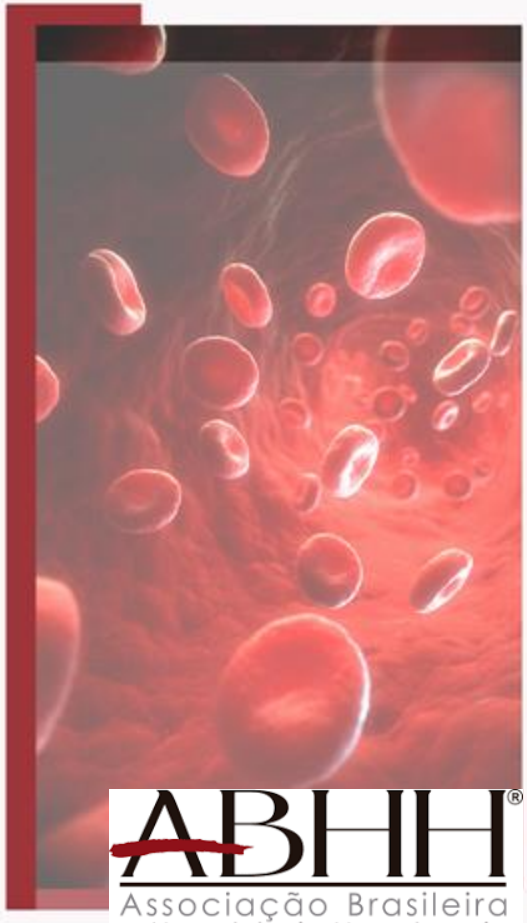

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DIFICULDADES NO TRATAMENTO DA LEUCEMIA MIELÓIDE CRÔNICA NO BRASIL

Renato Sampaio Tavares

CRM: 6538 GO

Prof. Dr. Adjunto de Hematologia da Fac. Medicina da UFG

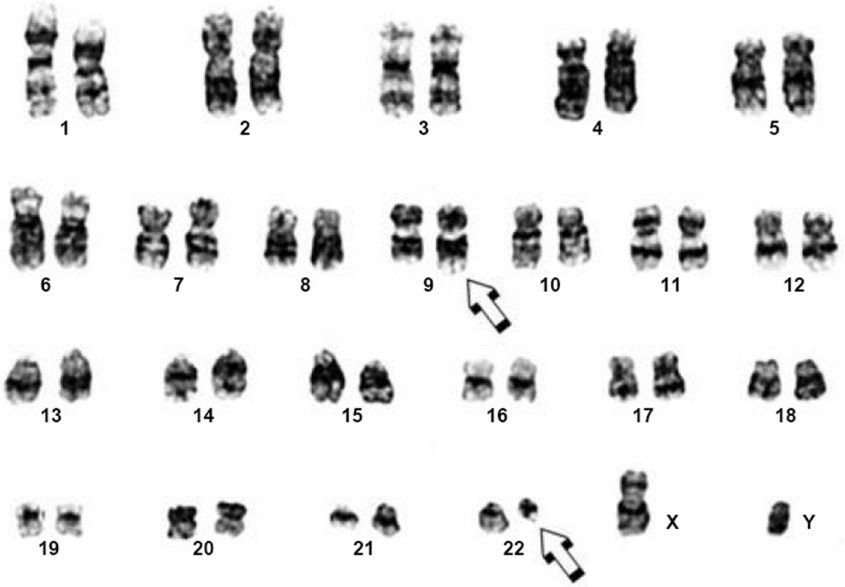
Diretor de Comunicação da ABHH

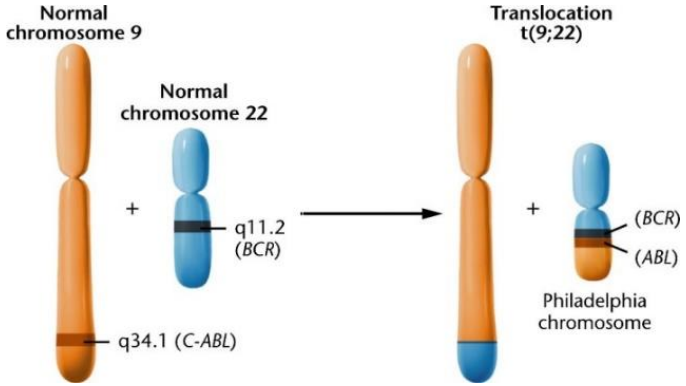
LEUCEMIA MIELÓIDE CRÔNICA

- **Neoplasia hematológica maligna rara** (CID: C 92.1)
- Resultante da fusão dos genes BCR com o gene ABL
- Produção descontrolada da série mieloide, em especial linhagem granulocítica
- 1 a 2 casos para 100 mil habitantes
- Idade média – 50 anos
- Modos de apresentação
  - Crônica – **85%**
  - Acelerada e Blástica – **15%**

Fardel S, et al, *NEJM*, 1999

LEUCEMIA MIELÓIDE CRÔNICA – DIAGNÓSTICO





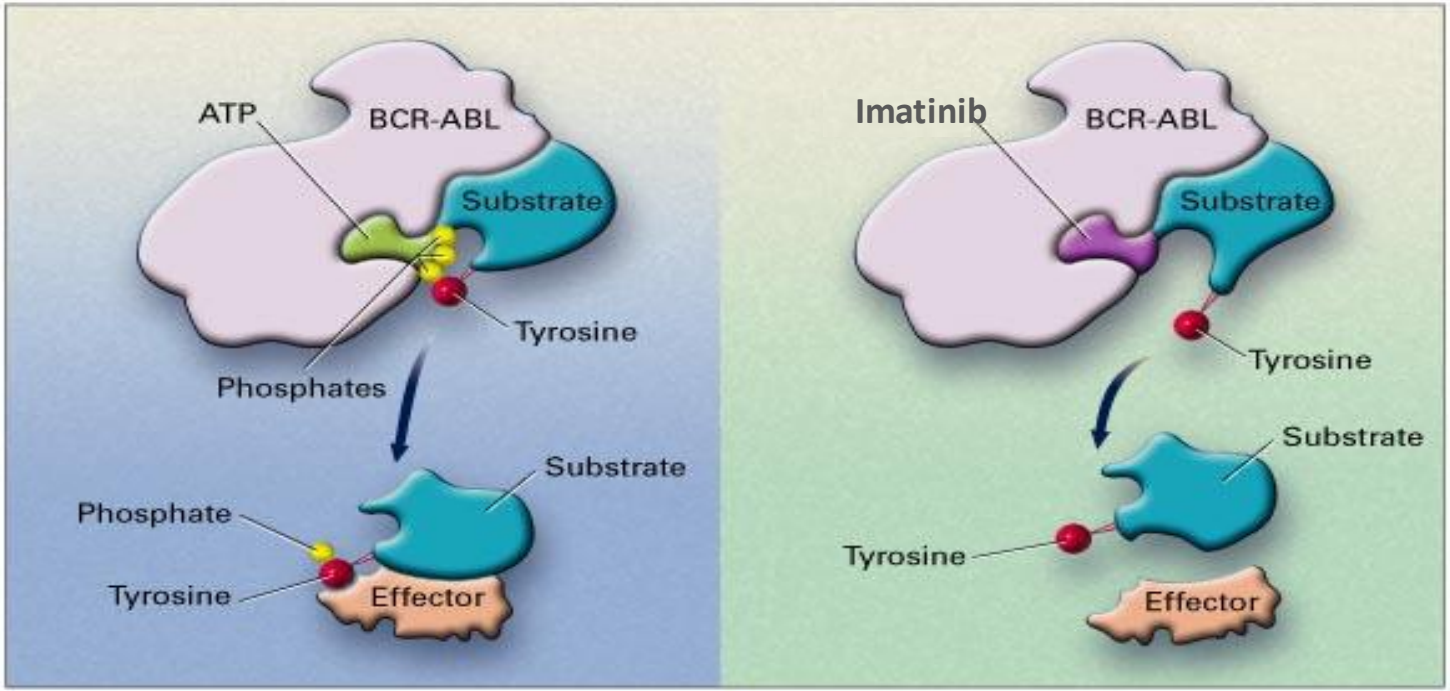
Sawyers CL. *N Engl J Med*. 1999;340:1330-1340

LEUCEMIA MIELÓIDE CRÔNICA NO BRASIL

- Terapia de escolha em primeira linha – **IMATINIBE**
- Cerca de **49%** dos casos irá descontinuar o Imatinibe
- Aproximadamente **20%** dos casos irá para terapia de segunda linha
  - **Dasatinibe** ou **Nilotinibe**
  - Aproximadamente **52%** dos casos em segunda linha irá descontinuar o Nilotinibe / Dasatinibe

Milojkovic D, et al, *Blood*, 2012

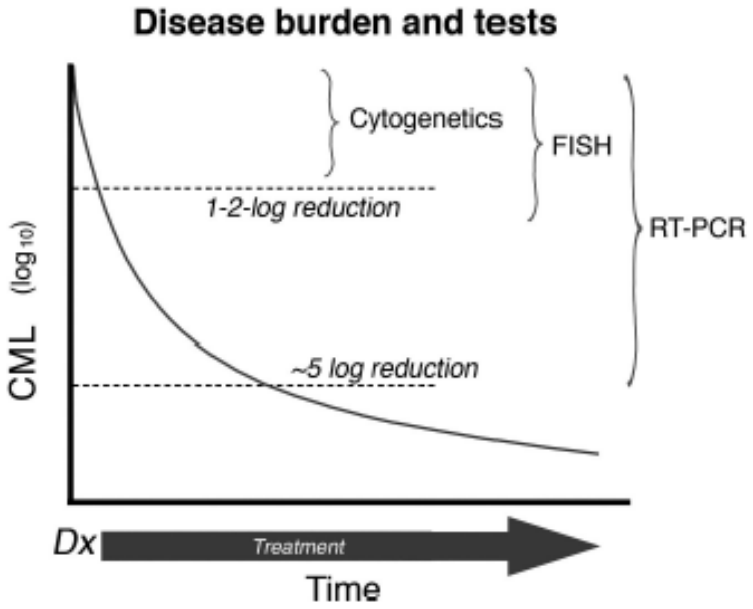
INIBIÇÃO DA ATIVIDADE QUINASE DO BCR-ABL PELO IMATINIBE



Goldman JM et al. *N Engl J Med.* 2001;344:1084-1086

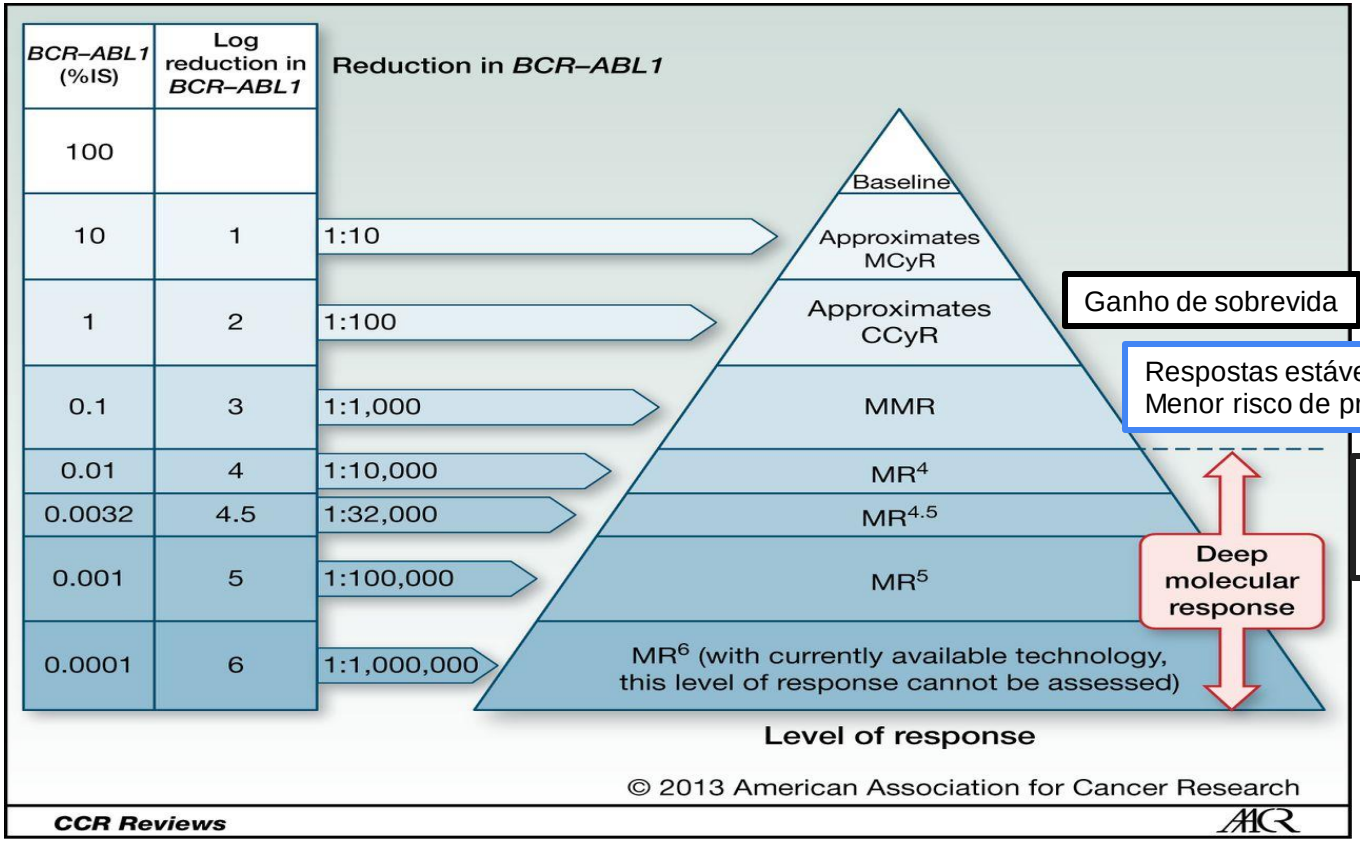
LEUCEMIA MIELÓIDE CRÔNICA – MONITORAMENTO

- Conforme número de células leucêmicas diminui, métodos mais sensíveis são necessários



Radich JP. *Blood*, 2009

Níveis de resposta molecular em LMC e metas no tratamento



Ganho de sobrevida

Respostas estáveis
Menor risco de progressão

Possibilidade de descontinuar a terapia

Adaptado de François-Xavier Mahon, and Gabriel Etienne Clin Cancer Res 2014;20:310-322

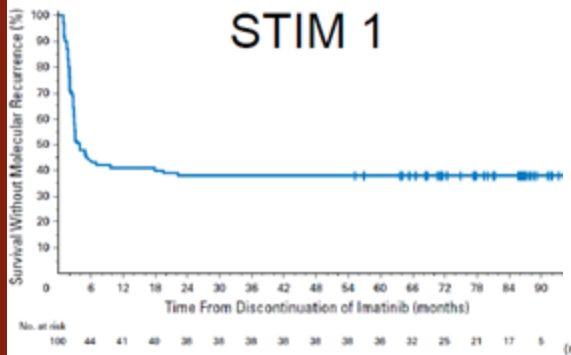
ELN 2020 Respostas ao ITK de primeira linha

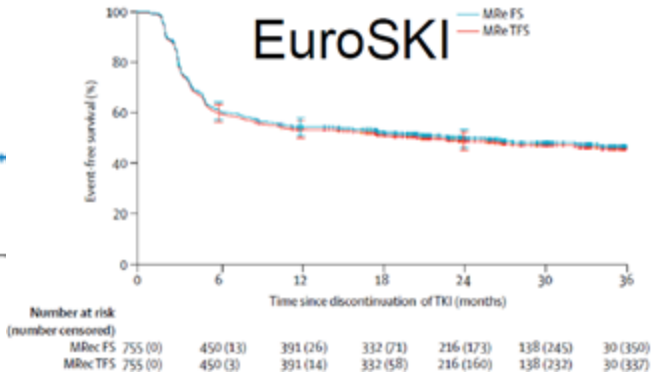
	ÓTIMA	ALERTA	FALHA
BASAL	NA	- ELTS alto risco - ACA/Ph+ (Major route)	NA
3 m	BCR-ABL ≤10%	BCR-ABL ≥10%	BCR-ABL >10% após confirmação em 1-3 meses
6 m	BCR-ABL <1%	BCR-ABL 1%-10%	BCR-ABL >10%
12 m	BCR-ABL≤0.1%	BCR-ABL 0.1%-1 %	BCR-ABL >1%
Qq momento	BCR-ABL ≤0.1%	BCR-ABL >0.1%-1% Perda de ≤0.1% (RMM)	BCR-ABL >1% Mutações - ACA de alto risco

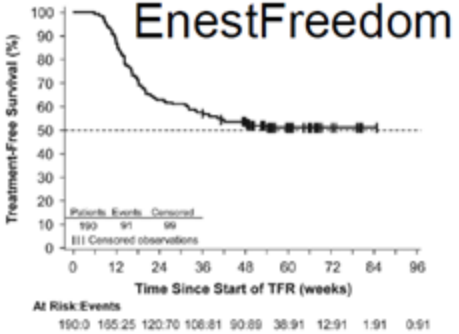
ACA-Alterações citogenéticas adicionais

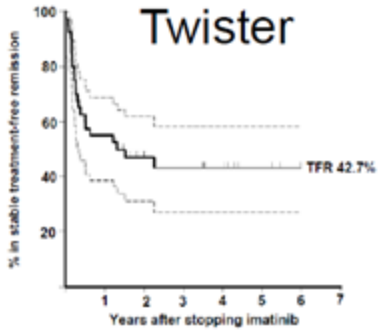
Hochhaus A. et al. Leukemia 2020

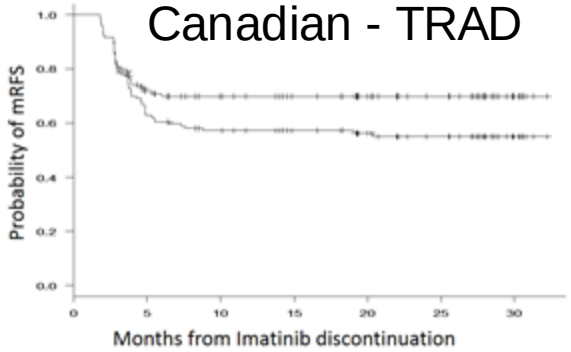
Estudos de descontinuação de ITK
Taxa de sucesso – 50% em pacientes com RM4.0/RM4.5

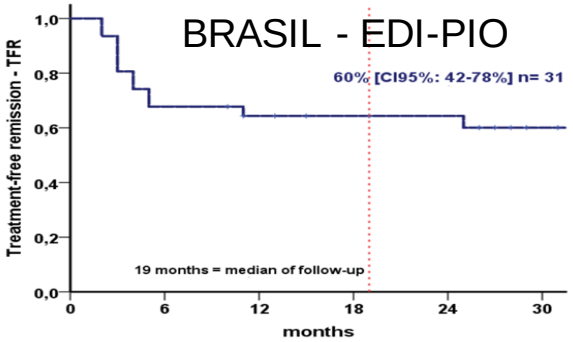










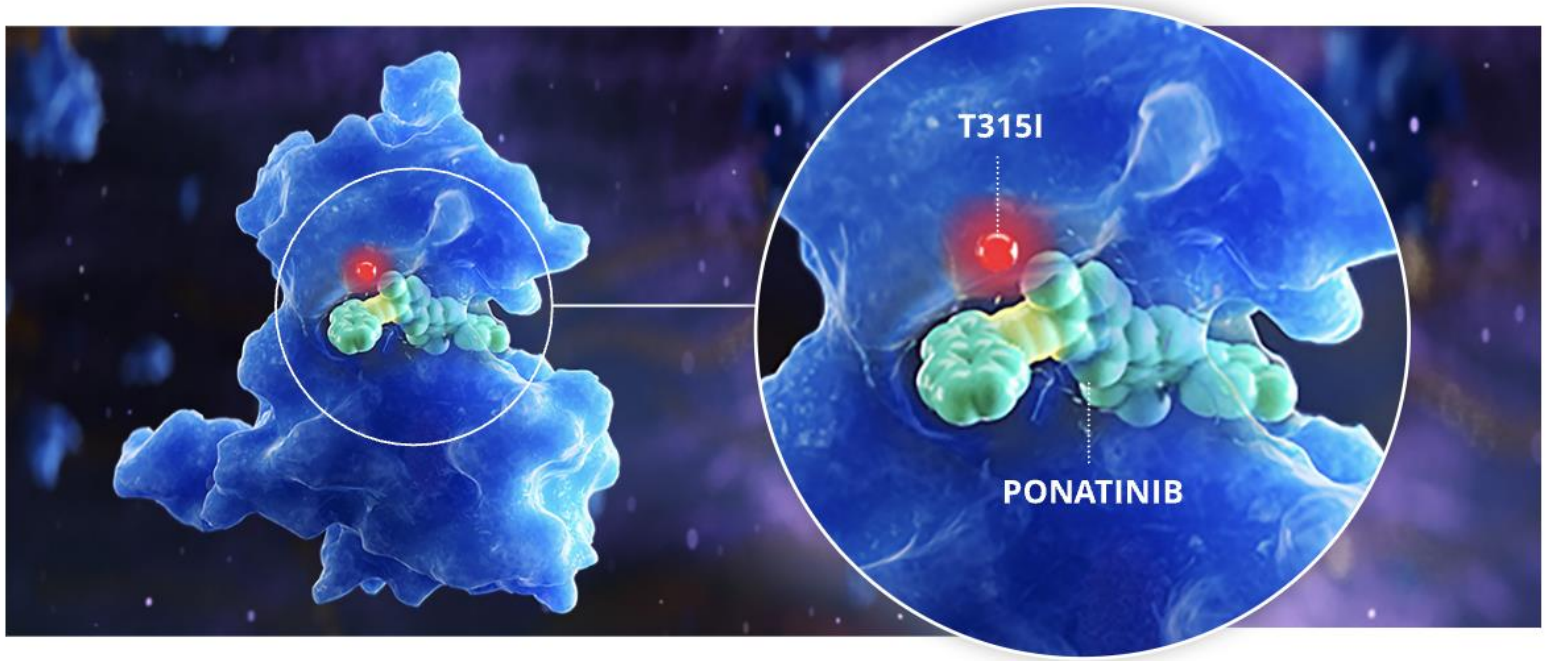


Pagnano et al. Am J Hematol, 2020

PRINCIPAIS DIFICULDADES NO BRASIL

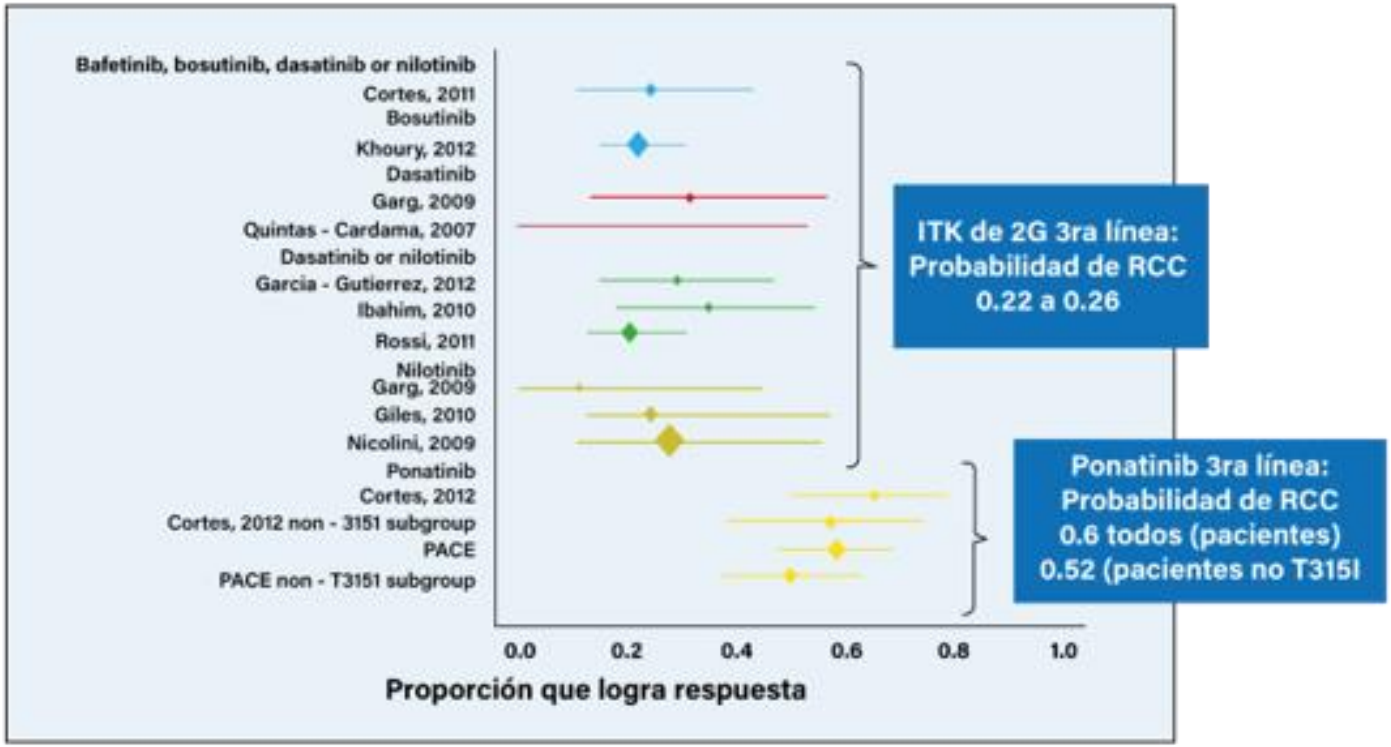
- Não há **Cariótipo** para o Diagnóstico
- Não conseguimos acompanhamento Molecular pelo BCR-ABL
  - Não há controle adequado do tratamento
  - Falha em detector precocemente falhas na terapia
- Não conseguimos **Descontinuação do Tratamento**
  - **Necessita monitoramento regular para ser Seguro**
  - **Teria grande impacto financeiro positive para o Estado**
- Tratamento de 3ª Linha
  - **NECESSIDADE MÉDICA NÃO ATENDIDA**

PONATINIBE



https://www.iclusig.com/hcp/cml/mechanism-of-action

Taxas de Resposta Citogenética em 3ª linha



Lipton JH, et al. Blood. 2013; 122 [abstract 4010].

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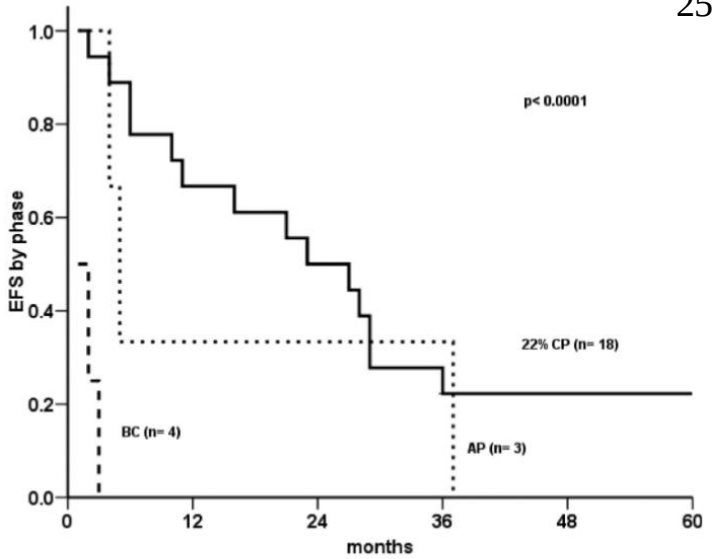
Treatment with dasatinib or nilotinib in chronic myeloid leukemia patients who failed to respond to two previously administered tyrosine kinase inhibitors – a single center experience

Beatriz Felicio Ribeiro, Eliana C.M. Miranda, Dulcinéia Martins de Albuquerque, Márcia T. Delamain, Gislaine Oliveira-Duarte, Maria Helena Almeida, Bruna Vergílio, Rosana Antunes da Silveira, Vagner Oliveira-Duarte, Irene Lorand-Metze, Carmino A. De Souza, Katia B.B. Pagnano*

Universidade de Campinas (Unicamp), Centro de Hematologia e Hemoterapia Campinas/SP, Brazil.

25 CMLpatients - 3rd TKI



gure 3 - Kaplan-Meier survival analysis. Five-year event-free survival of chronic myeloid leukemia patients treated with a 3rd tyrosine ase inhibitor according to disease phase.

DISCUSSION

Our data show that only 22% of patients in the CP stage showed long-term benefits from the administration of a 3rd TKI after imatinib and a 2nd TKI failure. We found that 89% of our patients in the CP stage achieved CHR, 13% achieved CCyR, and 24% achieved MMR; however, 50% of those patients lost CHR within a median of 23 months. All patients with CCyR lost their response after 12 months, and 25% of patients lost MMR after 7 months.

CLINICS 2015;70(8):550-555

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Treatment with dasati
leukemia patients v
previously administe
a single center exper

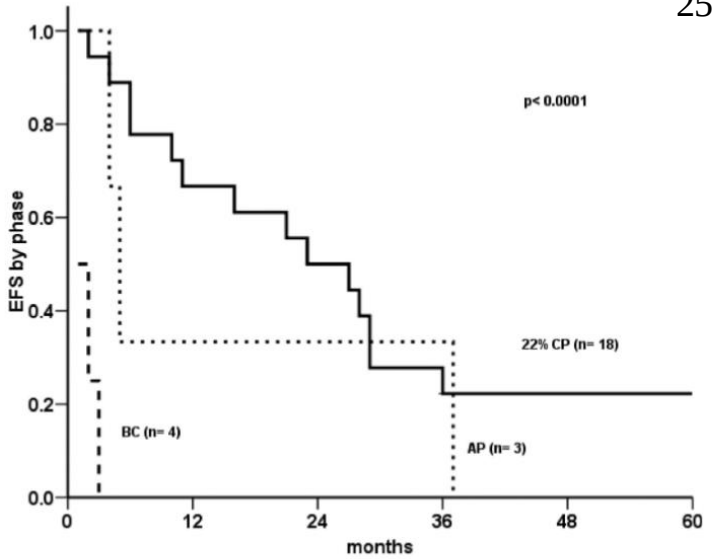
Beatriz Felicio Ribeiro, Eliana C.M. Mirand
Gislaine Oliveira-Duarte, Maria Helena Al
Vagner Oliveira-Duarte, Irene Lorand-Met

Ponatinib efficacy and safety in Philadelphia chromosome–positive leukemia: final 5-year results of the phase 2 PACE trial

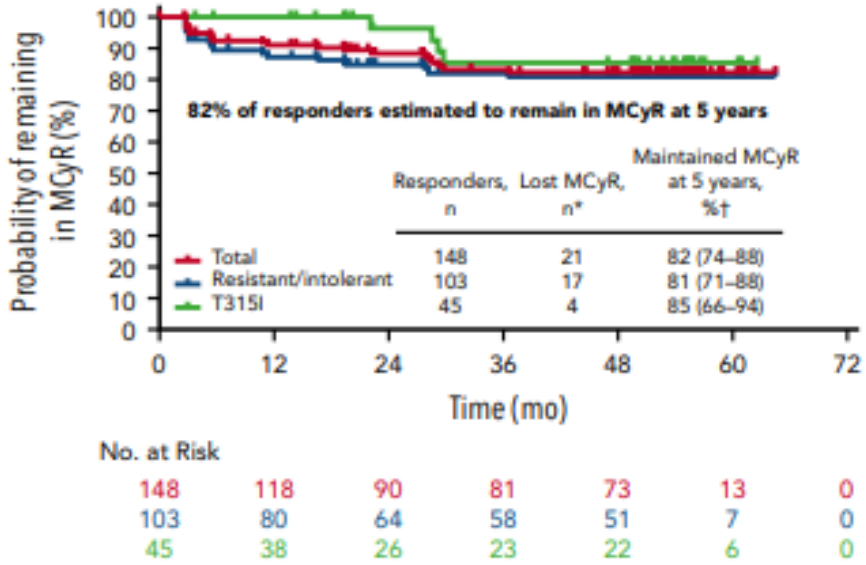
Jorge E. Cortes,[1] Dong-Wook Kim,[2] Javier Pinilla-Ibarz,[3] Philipp D. le Coutre,[4] Ronald Paquette,[5] Charles Chuah,[6] Franck E. Nicolini,[7] Jane F. Apperley,[8] H. Jean Khoury,[9] Moshe Talpaz,[10] Daniel J. DeAngelo,[11] Elisabetta Abruzzese,[12] Delphine Rea,[13] Michele Baccarani,[14] Martin C. Müller,[15] Carlo Gambacorti-Passerini,[16] Stephanie Lustgarten,[17] Victor M. Rivera,[17] Frank G. Haluska,[17] François Guilhot,[18,19] Michael W. Deininger,[20] Andreas Hochhaus,[21] Timothy P. Hughes,[22] Neil P. Shah,[23] and Hagop M. Kantarjian[1]

Universidade de Campinas (Unicamp), Centro de Hematologia e Hemoterapia Campinas/SP, Brazil.

25 CMLpati



B



gure 3 - Kaplan-Meier survival analysis. Five-year event-free survival of chronic myeloid leukemia patients treated with a 3rd tyrosine ase inhibitor according to disease phase.

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TABLE I. Activity of Imatinib, Bosutinib, Dasatinib, Nilotinib, Ponatinib, and DCC-2036 Against Mutated Form of BCR/ABL

		IC50-fold increase (WT = 1)				
		Imatinib	Bosutinib	Dasatinib	Nilotinib	Ponatinib
	Parental	10.8	38.3	568.3	38.4	570.0
	WT	1	1	1	1	1
P-loop	M244V	0.9	0.9	2.0	1.2	3.2
	L248R	14.6	22.9	12.5	30.2	6.2
	L248V	3.5	3.5	5.1	2.8	3.4
	G250E	6.9	4.3	4.4	4.6	6.0
	Q252H	1.4	0.8	3.1	2.6	6.1
	Y253F	3.6	1.0	1.6	3.2	3.7
	Y253H	8.7	0.6	2.6	36.8	2.6
	E255K	6.0	9.5	5.6	6.7	8.4
	E255V	17.0	5.5	3.4	10.3	12.9
C-helix	D276G	2.2	0.6	1.4	2.0	2.1
	E279K	3.6	1.0	1.6	2.0	3.0
	E292L	0.7	1.1	1.3	1.8	2.0
ATP binding region	V299L	1.5	26.1	8.7	1.3	0.6
	T315A	1.7	6.0	58.9	2.7	0.4
	T315I	17.5	45.4	75.0	39.4	3.0
	T315V	12.2	29.3	738.8	57.0	2.1
	F317L	2.6	2.4	4.5	2.2	0.7
	F317R	2.3	33.5	114.8	2.3	4.9
	F317V	0.4	11.5	21.3	0.5	2.3
SH2-contact	M343T	1.2	1.1	0.9	0.8	0.9
	M351T	1.8	0.7	0.9	0.4	1.2
Substrate binding region	F359I	6.0	2.9	3.0	16.3	2.9
	F359V	2.9	0.9	1.5	5.2	4.4
A-loop	L384M	1.3	0.5	2.2	2.3	2.2
	H396P	2.4	0.4	1.1	2.4	1.4
	H396R	3.9	0.8	1.6	3.1	5.9
C-terminal lobe	F486S	8.1	2.3	3.0	1.9	2.1
	L248R + F359I	11.7	39.3	13.7	96.2	17.7

Sensitive	≤2
Moderately resistant	2.1–4
Resistant	4.1–10
Highly resistant	>10

For each mutant the relative IC50 increase over wild type BCR/ABL was calculated. Results represent the average of at least three independent experiments.

Redaelli S, et al. *Am J Hematol* 2012

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European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia

A. Hochhaus[1] · M. Baccarani[2] · R. T. Silver[3] · C. Schiffer[4] · J. F. Apperley[5] · F. Cervantes[6] · R. E. Clark[7] · J. E. Cortes[8] · M. W. Deininger[9] · F. Guilhot[10] · H. Hjorth-Hansen[11] · T. P. Hughes[12] · J. J. W. M. Janssen[13] · H. M. Kantarjian[14] · D. W. Kim[15] · R. A. Larson[16] · J. H. Lipton[17] · F. X. Mahon[18] · J. Mayer[19] · F. Nicolini[20] · D. Niederwieser[21] · F. Pane[22] · J. P. Radich[23] · D. Rea[24] · J. Richter[25] · G. Rosti[2] · P. Rousselot[26] · G. Saglio[27] · S. Saußele[28] · S. Soverini[2] · J. L. Steegmann[29] · A. Turkina[30] · A. Zaritskey[31] · R. Hehlmann[28,32]

Table 6 Management strategy recommendations for end-phase CML.

Prevention by elimination of BCR-ABL1	Assurance of effective TKI treatment
Early: emergence of high-risk ACA	Observe closely, consider intensification of treatment (ponatinib, early allo-SCT)
Primary blast phase	Start with imatinib, change to a 2GTKI according to KD-mutation profile.
Resistance to 2GTKI (first or second line)	Ponatinib or experimental agent. Assessment for allo-SCT, donor search.
Failure to ponatinib	High risk of progression, early allo-SCT recommended
Accelerated phase	To be treated as high-risk patients; proceed to allo-SCT if response not optimal.
Progress to blast phase	Attempt at return to CP2. Outcome with currently available TKI poor. Addition of chemotherapy based on AML regimens for myeloid BP (such as dasatinib or ponatinib + FLAG-IDA) or ALL regimens for lymphoid BP (such as imatinib or dasatinib + hyperfractionated CVAD) recommended. Choice of TKI should be based on prior therapy and BCR-ABL1 KD-mutational status. After CP2 is achieved proceed to allo-SCT without delay.

ACA additional chromosomal aberrations, *allo-SCT* allogeneic stem cell transplantation, *2GTKI* second generation tyrosine kinase inhibitor, *CP1* first chronic phase, *CP2* second chronic phase, *BP* blast phase, *AML* acute myeloblastic leukemia, *ALL* acute lymphoblastic leukemia.

Leukemia (2020) 34:966–984

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Obrigado!!!

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