ASSOCIAZIONE ITALIANA

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AIL President: G. Toro
Coordinators: A.M. Carella, S. Amadori

The New Guidelines for the Management of CML

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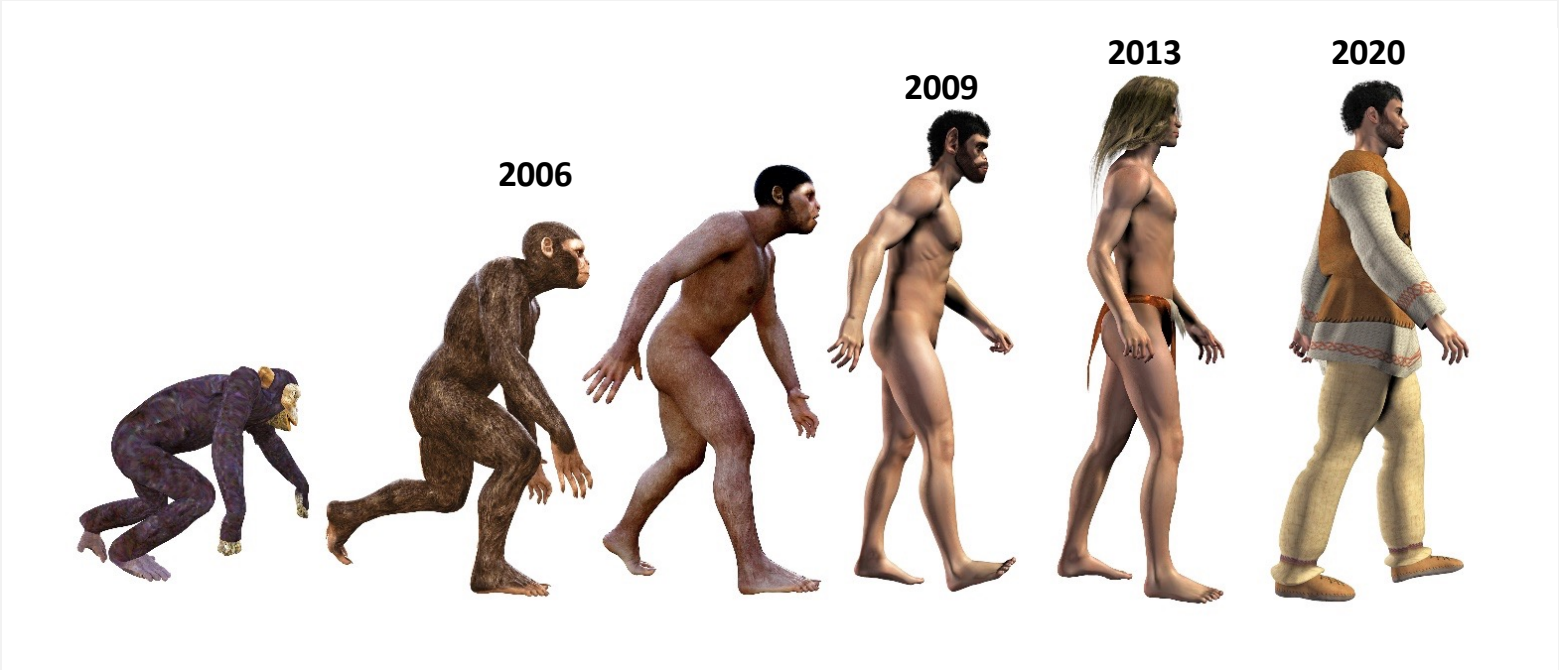
ISTITUTO SCIENTIFICO ROMAGNOLO PER LO STUDIO E LA CURA DEI TUMORI

Evolution of ELN Recommendations for CML



ELN Recommendations for CML: 2006

	2006	2009	2013	2020
1° line	Imatinib			
2° line	None (high-dose imatinib)			
Alt. Options	IFN/allogeneic SCT			
Salvage	Allogeneic SCT			
Milestones	CCyR			
Concerns/ Considerations	• Short follow-up • Possibility of emerging mutations			

Evolution of ELN Recommendations Moving Forward From 2006 to 2009

CML now compatible with a normal life span (concept reinforced)

Compliance—a potential problem for patients

General mood: Freedom from “cage” of allogeneic SCT

ELN Recommendations for CML: 2009

	2006	2009	2013	2020
1° line	Imatinib	Imatinib		
2° line	None (high-dose imatinib)	Nilotinib, dasatinib, high-dose imatinib		
Alt. Options	IFN/allogeneic SCT	None		
Salvage	Allogeneic SCT	Allogeneic SCT, nilotinib, dasatinib		
Milestones	CCyR	CCyR → MR		
	• Short follow-up • Possibility • Emerging mutations	Risk of emerging mutations decreasing		

Evolution of ELN Recommendations Moving Forward From 2009 to 2013

Phase 1-2 trials of bosutinib and ponatinib published (2011-2012)

A bitter taste of long-term toxicities

The first steps toward treatment-free remission

ELN Recommendations for CML: 2013

	2006	2009	**2013**	2020
1° line	Imatinib	Imatinib	Imatinib, nilotinib, dasatinib	
2° line	None (high-dose imatinib)	Nilotinib, dasatinib, high-dose imatinib	• Ima → nilo, dasa, bosu, pona • Dasa → nilo, bosu, pona • Nilo → dasa, bosu, pona • T315I: pona	
Alt. Options	IFN/allogeneic SCT	None	None	
Salvage	Allogeneic SCT	Allogeneic SCT, nilotinib, dasatinib	Allogeneic SCT	
Milestones	CCyR	CCyR → MR	MMR, major and stable	
	• Short follow-up • Possibility • Emerging mutations	Risk of emerging mutations decreasing	TFR, mainly inside the frame of RCTs	

Evolution of ELN Recommendations Moving Forward From 2013 to 2020

With generic imatinib, avoid alternating different brands

Early and long-term toxicities AND efficacy are the basis of any TKI choice

TFR may be considered in clinical practice if a stable DMR is achieved

ELN Recommendations for CML: 2020

	2006[1]	2009[2]	2013[3]	2020[4]
1° line	Imatinib	Imatinib	Imatinib, nilotinib, dasatinib	Imatinib, nilotinib, dasatinib, bosutinib
2° line	None (high-dose imatinib)	Nilotinib, dasatinib, high-dose imatinib	• Ima → nilo, dasa, bosu, pona • Dasa → nilo, bosu, pona • Nilo → dasa, bosu, pona • T315I: pona	• Ima → nilo, dasa, bosu, pona • Dasa → nilo, bosu, pona • Nilo → dasa, bosu, pona • Bosu → dasa, nilo, pona • T315I: pona
Alt. Options	IFN/allogeneic SCT	None	None	None
Salvage	Allogeneic SCT	Allogeneic SCT, nilotinib, dasatinib	Allogeneic SCT	Allogeneic SCT
Milestones	CCyR	CCyR → MR	MMR, major and stable	MMR → DMR
Concerns/ Considerations	• Short follow-up • Emerging mutations	Risk of emerging mutations ↓	TFR, mainly inside the frame of RCTs	Side effects

Alt, alternative; bosu, bosutinib; CCyR, complete cytogenetic response; CML, chronic myeloid leukaemia; dasa, dasatinib; DMR, deep molecular response; ELN, European LeukemiaNet; HU, hydroxyurea;
IFN, interferon; ima, imatinib; MMR, major molecular response; MR, molecular response;
NA, not applicable; nilo, nilotinib; pona, ponatinib▼; RCT, randomised controlled trial;
SCT, stem cell transplant; TFR, treatment-free survival.

1. Baccarani M, et al. *Blood*. 2006;108:1809–20;
2. Baccarani M, et al. *J Clin Oncol*. 2009;27:6041–51;
3. Baccarani M, et al. *Blood*. 2013;122:872–84;
4. Hochhaus A, et al. *Leukemia*. 2020;34:966–84.

Evolution of ELN Recommendations Moving Forward From 2020 to 2023

Ponatinib dose optimization

Asciminib moving forward

Dose optimization of other TKIs

European LeukemiaNet recommendations for the management of chronic myeloid leukemia (2013)

Recommendations for cytogenetic and molecular monitoring

At diagnosis	Chromosome banding analysis (CBA) of marrow cell metaphases FISH in case of Ph negativity to identify variant and/or cryptic translocation Qualitative PCR (identification of transcript type)
During treatment	Quantitative real time PCR (RQ-PCR), and/or CBA of marrow cell metaphases (at least 20 metaphases) to be performed at 3, 6 and 12 months until a CCyR has been achieved. Once a CCyR is achieved, then every 12 months. Once a CCyR is achieved, FISH on blood cells can be done .
Failure, progression	RQ-PCR, mutational analysis, and CBA of marrow cell metaphases, immunophenotyping in BP.
Warning	Molecular and cytogenetic tests to be performed more frequently. CBA of marrow cell metaphases recommended in case of myelodysplasia or CCA/Ph- (with chromosome 7 involvement)

European LeukemiaNet recommendations for the management of chronic myeloid leukemia (2020)

Recommendations for cytogenetic and molecular monitoring

At diagnosis	**Chromosome banding analysis (CBA) of marrow cell metaphases** **FISH in case of Ph negativity to identify variant and/or cryptic translocation** **Qualitative PCR (identification of transcript type)**
During treatment	**Quantitative real time PCR (RQ-PCR) to be performed at 3, 6 and 12 months even after an MMR is achieved and confirmed, because close monitoring of molecular response is required to assess eligibility for treatment discontinuation.** **CBA of marrow cell metaphases (at least 20 metaphases) may be useful when performed, but alone is not sufficiently sensitive to monitor response.**
Failure, progression	**RQ-PCR, mutational analysis, and CBA of marrow cell metaphases, immunophenotyping in BP.**
Warning	**Molecular and cytogenetic tests to be performed more frequently.** **CBA of marrow cell metaphases recommended in case of myelodysplasia or CCA/Ph- (with chromosome 7 involvement)**

ELN 2020 Recommendations for response

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

For patients aiming at TFR, the optimal response (at any time) is BCR-ABL1 ≤0.01% (MR^4).

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.

[a]Loss of MMR (BCR-ABL1 >0.1%) indicates failure after TFR

Hochhaus A et al , Leukemia. 2020;34:966–984

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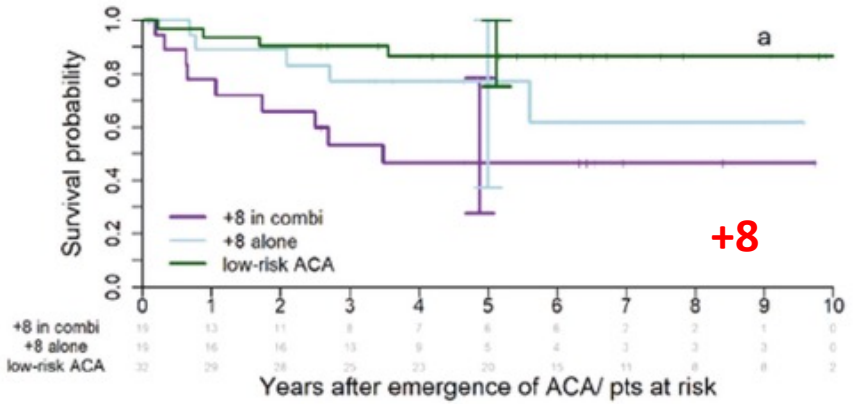
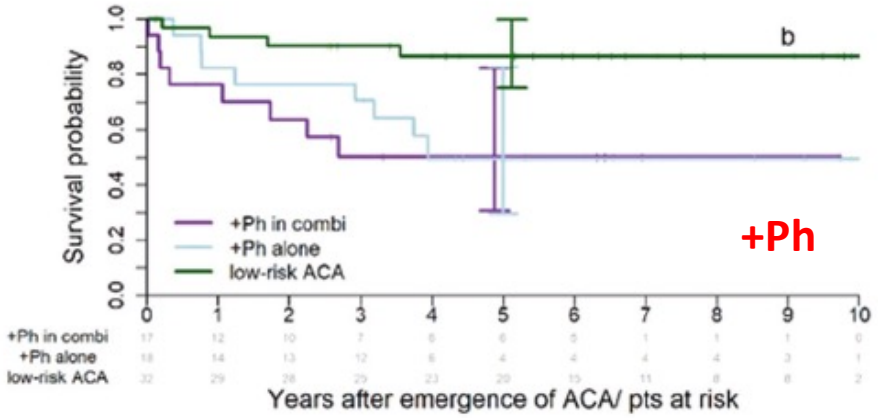
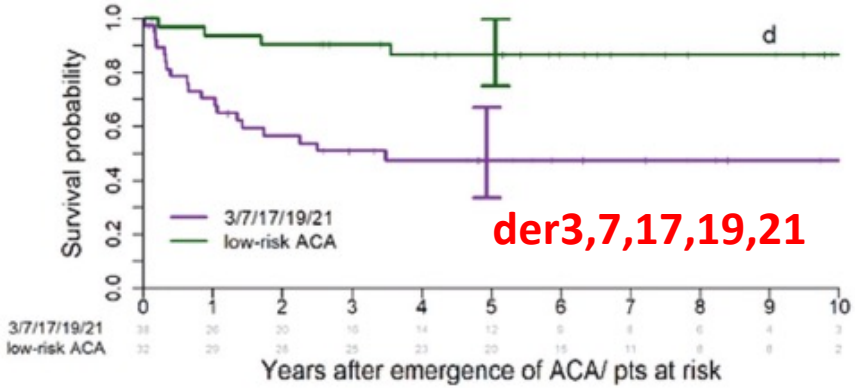
High risk additional chromosomal aberrations herald advanced disease and predict survival probability. CML IV cohort.







Hehlmann et al., Leukemia 2020, in press

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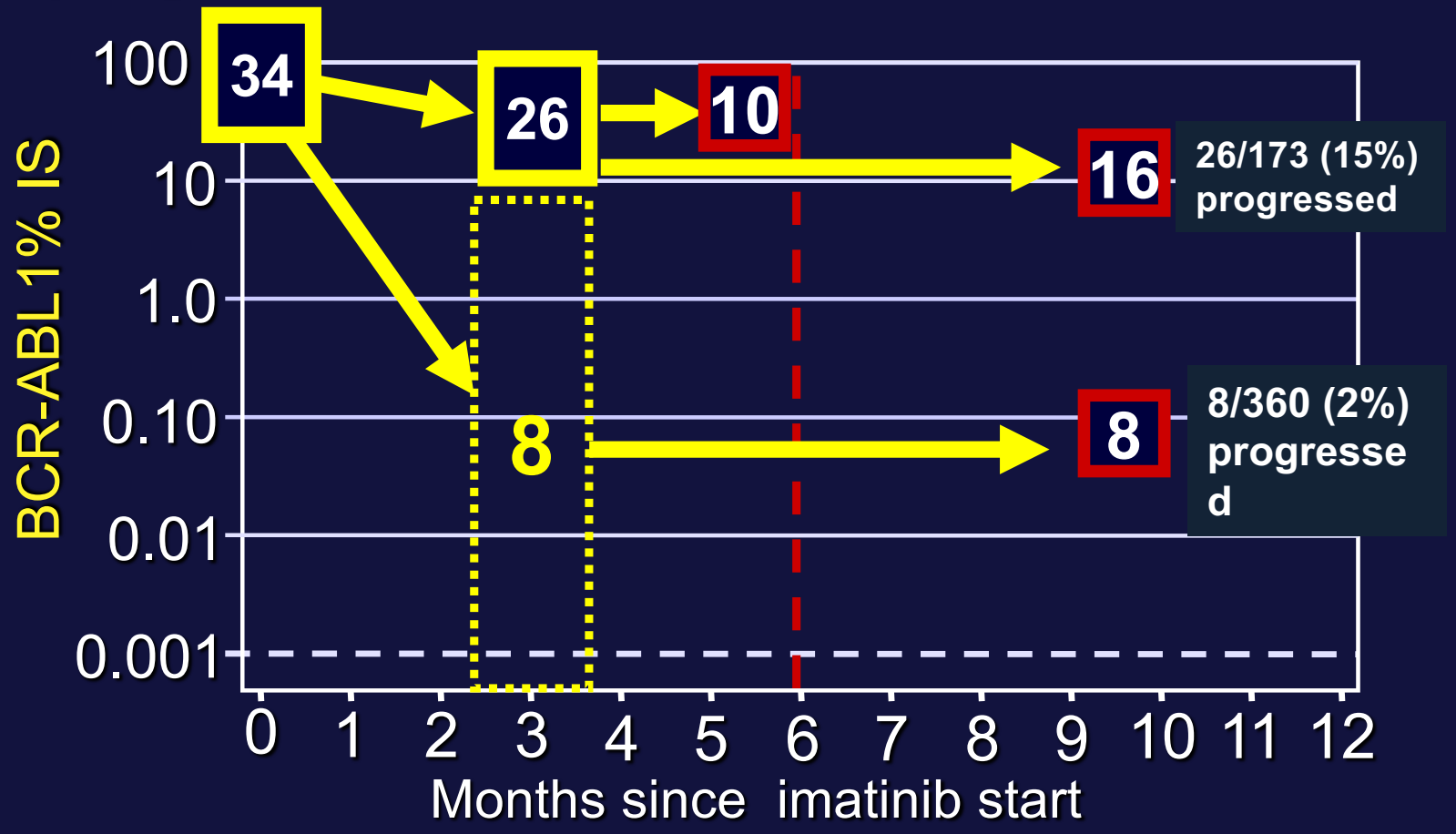
Molecular response in patients who progressed on imatinib *(Dasision & ENESTnd)*



Jabbour E et al. Blood 2014, 123 (4):494-500; Hughes TP et al. Blood 2014, 123 (9)

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Prevedere una QPCR al terzo e quarto/quinto mese

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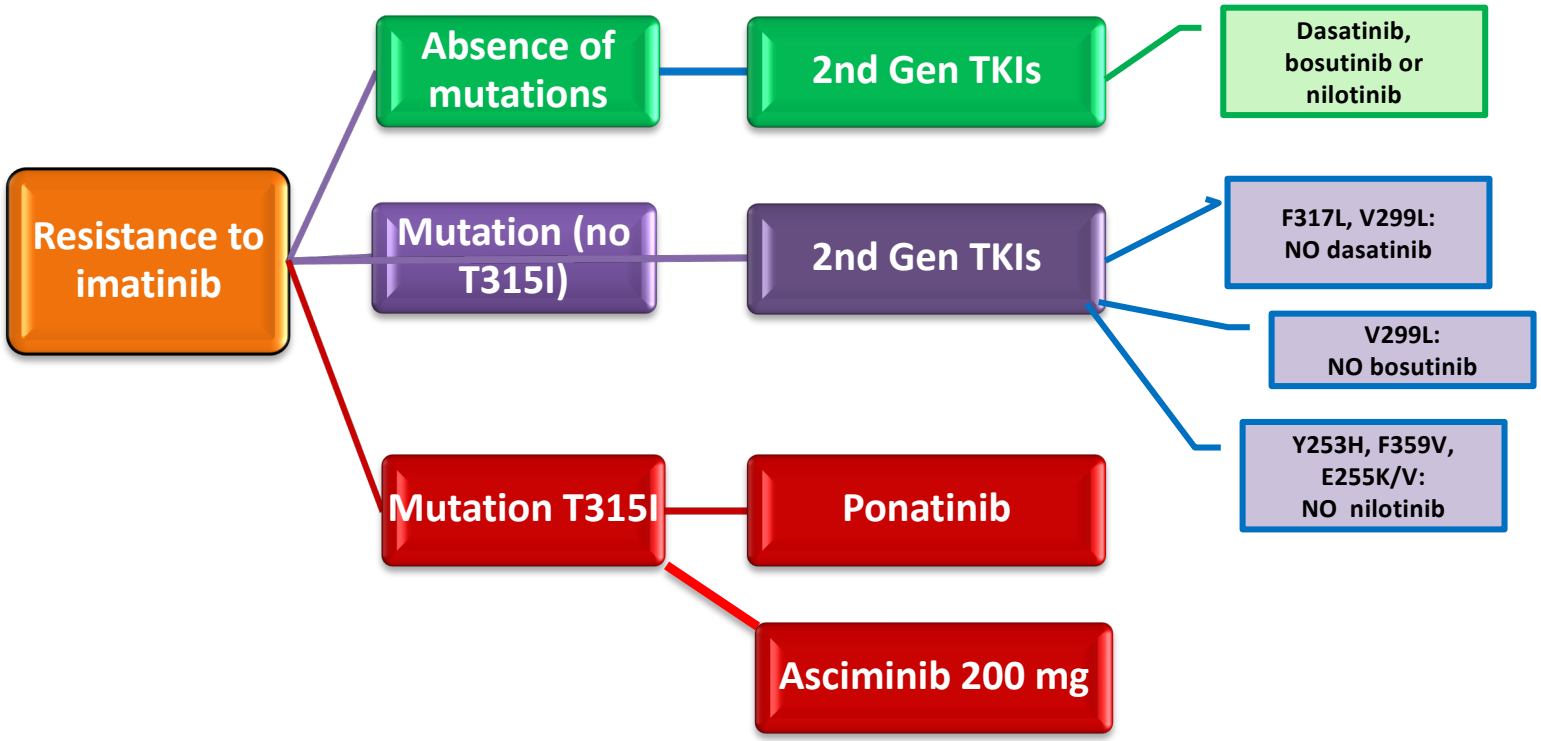
First line therapy ?

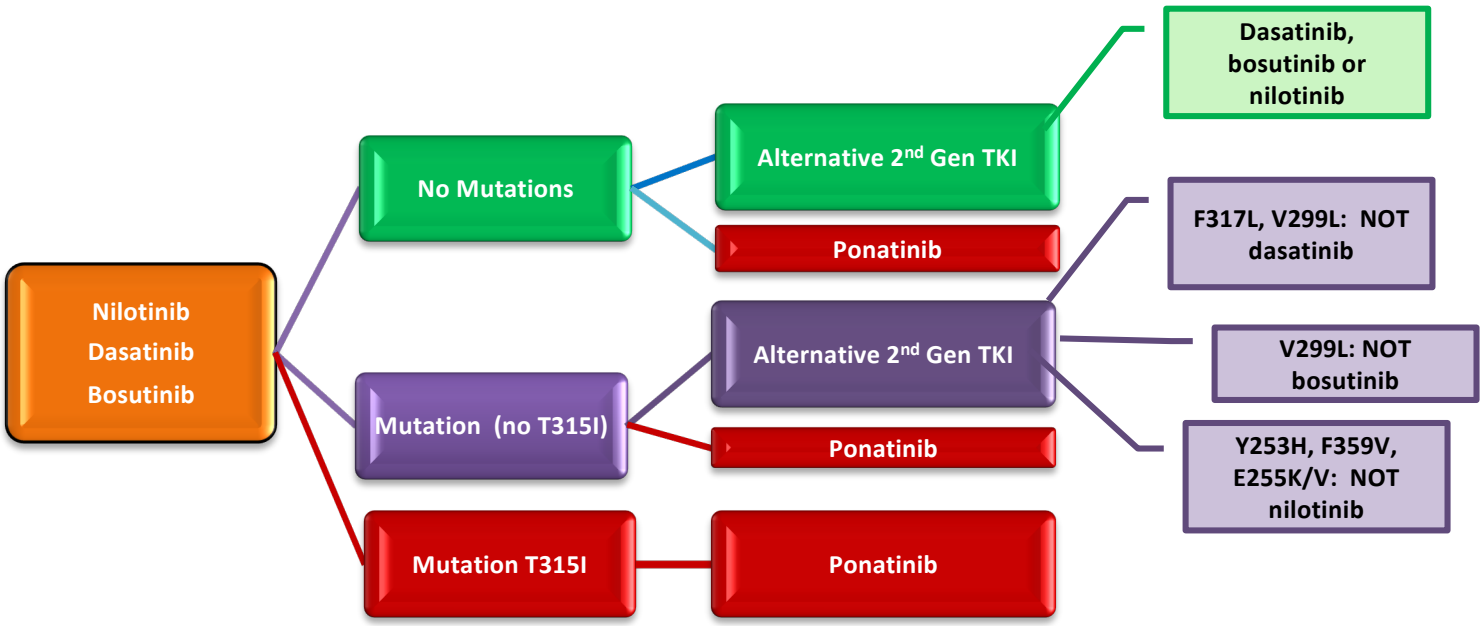
BCR-ABL+ CML in CP

Options	#1	#2	#3
Imatinib 400 (-800) mg (incl. generics)	for all	for low-risk pat.	Choice of First line therapy according to individual aim and additional diseases
Nilotinib 2x300 mg	-	for higher risks	
Dasatinib 100 mg	-		
Bosutinib 400 mg	-		

Resistance to imatinib, options (2023)

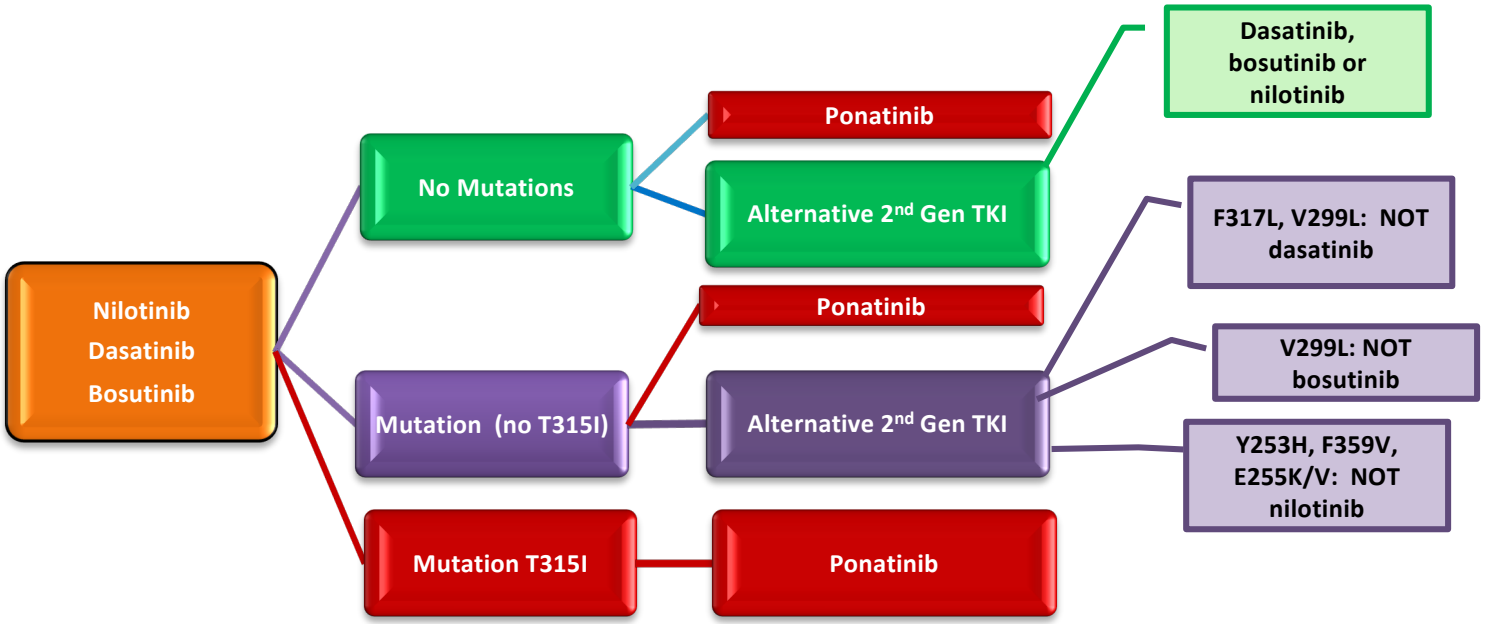


Resistance to a 2nd gen TKI in first line

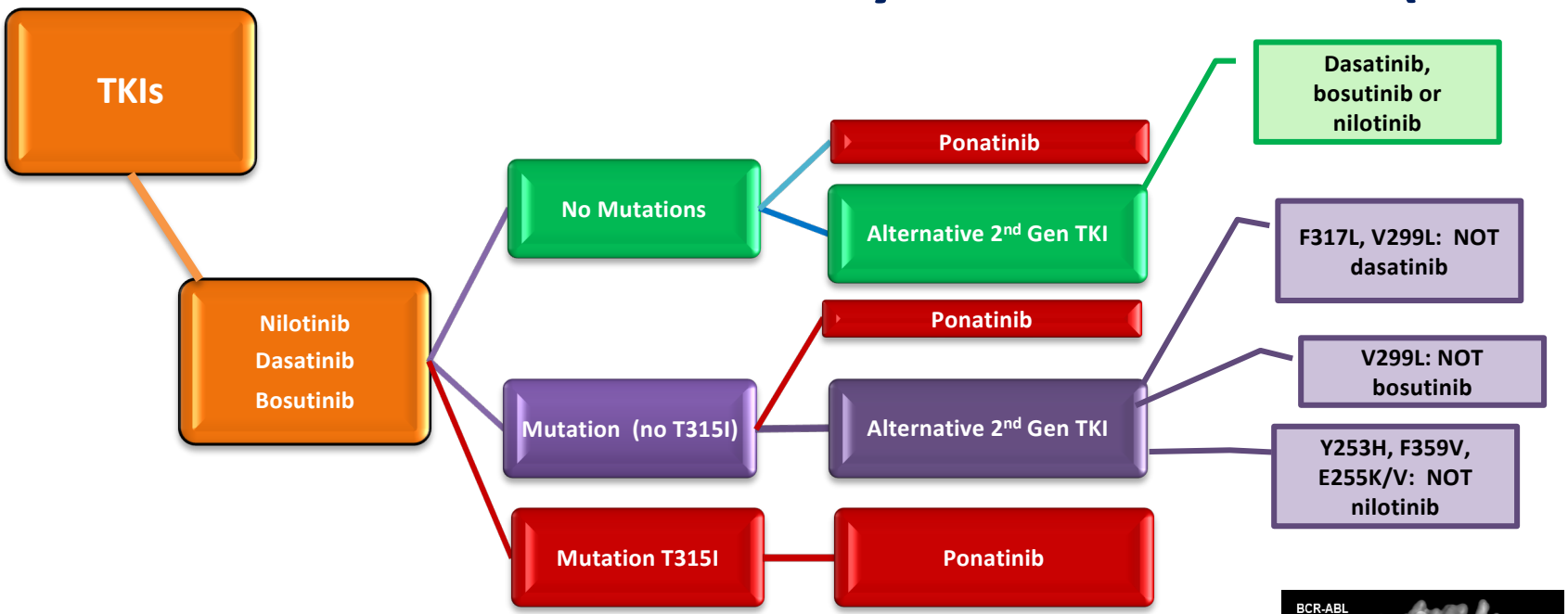


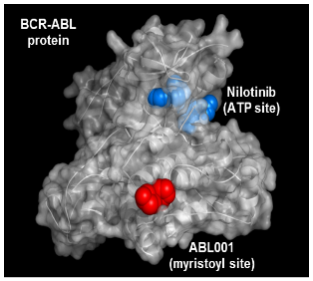
Hochhaus A, et al. Leukemia 2020; 34: 966-984.
NCCN Guidelines https://www.nccn.org/store/login/login.aspx?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf

Resistance to a 2nd gen TKI in first line (2023)



Third line and beyond treatment (2023)





Massimo Breccia

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