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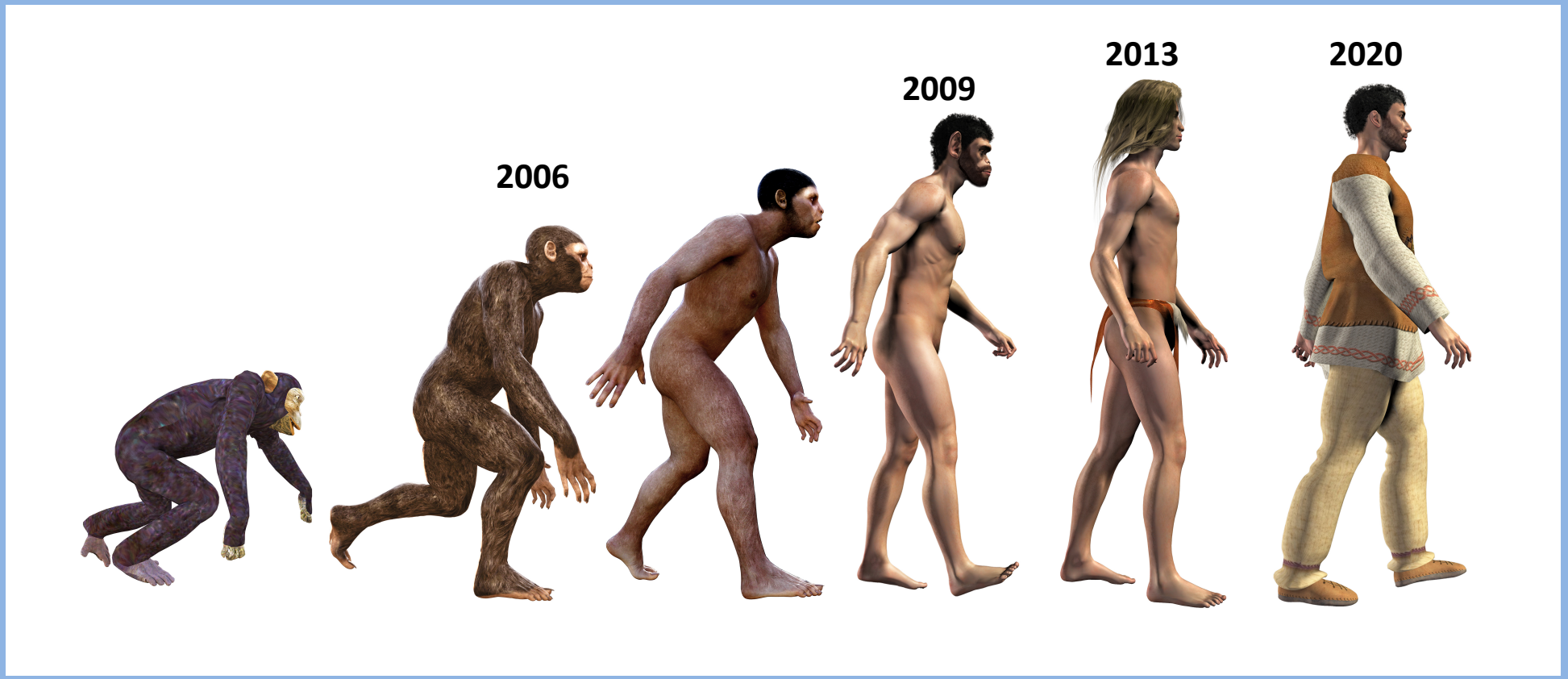
Evolution of ELN Recommendations for CML



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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			

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		

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	

ELN Recommendations for CML: 2013

	2006	2009	2013	2020
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
	• Short follow-up • Possibility • Emerging mutations	Risk of emerging mutations decreasing	TFR, mainly inside the frame of RCTs	• Ponatinib dose optimization proposed • Asciminib announced

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Leukemia
https://doi.org/10.1038/s41375-020-0776-2

REVIEW ARTICLE

Chronic myelogenous leukemia

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]

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The ELN panel for recommendations in CML comprises 34 experts from Europe, America, and the Asian-Pacific areas. The panel met six times at international meetings of the American Society of Hematology (2015, 2016), the European School of Hematology (2017), the ELN (2019), the European Investigators on CML (2019), and the European School of Hematology/International CML Foundation (2019). Five sets of key questions were submitted to panel members to complement the meetings. Discordant opinions were harmonized by email discussions, and a consensus of 75–100% was reached in most, but not all instances. Unresolved controversies are described in the discussion section. The costs of the meetings and the preparation of the interim and final reports were born entirely by ELN, a research network of excellence initiated by the European Union, now funded by donations and projects of ELN participants. There was no financial support from industry for any activity. Treatment recommendations are

years. Most patients
molecular response
convened an expert
endations. First-line
ib are available first-
-effects of all TKIs
m survival (ELTS)-
ssible. A change of
not reached. Greater
on continues to be a
egnancy. Treatment

ficacy, tolerability,
More recently, there
of life and avoiding
ticular, the identifi-
the possibility of
-called "treatment-
esource-poor coun-
rugs and essential
goal of treatment

eutic scenarios con-
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Leukemia. 2020 Apr;34(4):966-984.

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Diagnostic work-up, baseline.

Physical examination with particular reference to spleen and liver size

Complete blood cell count with microscopic differential

Bone marrow aspirate for cytologic examination and cytogenetics; core biopsy if dry tap

Chromosome banding analysis (CBA)

Fluorescence in-situ hybridization (FISH) only in case of Ph-negativity

Qualitative reverse transcriptase polymerase chain reaction (PCR) for the detection of BCR-ABL1 transcripts and identification of the transcript type

Electrocardiogram

Standard biochemical profile with hepatitis B-serology

Relative risk of CML patients according to clinical and haematological data at diagnosis

	SOKAL Overall Survival CHT	EURO Overall Survival α – IFN	EUTOS CCyR at 18M IMATINIB	EUTOS Long-term Survival CML-related Survival IMATINIB
Age (yrs)	**0,0166 x (Age-43,4)**	0.666 x Age (> 50)	-	**0.0025 x (Age/10)^3**
Spleen (cm)	**0,0345 x (Spleen-7,51)**	0.042 x Spleen	4 x Spleen	**0.0615 x Spleen**
Platelets (10^3/µL)	**0,188 x [(PLT/700)^2-0,563]**	1.0956 x PLT (> 1500)	-	**0.4104 x (PLT count/1000)$^{-0.5}$**
Myeloblast (%)	**0,0887 x (MB-2,1)**	0.0584 x MB	-	**0.1052 x MB**
Eosinophils (%)	-	0.20399 x Bas (> 3)	7 x Bas	
Basophils (%)	-	0.0413 x Eos	-	

Relative risk				
Low	≤ 0.80	≤ 780	≤ 87	< 1.5680
Intermediate	0.81 – 1.20	781-1480	-	1.568 - 2.2185
High	> 1.21	> 1481	> 87	2.2185

SOKAL et al. Blood 1984; 63: 789-799
HASFORD et al. JNCI 1998; 90: 850-858
HASFORD et al. Blood 2011; 118: 686-692
PFIRRMANN M et al, LEUKEMIA 2016;30:48-56

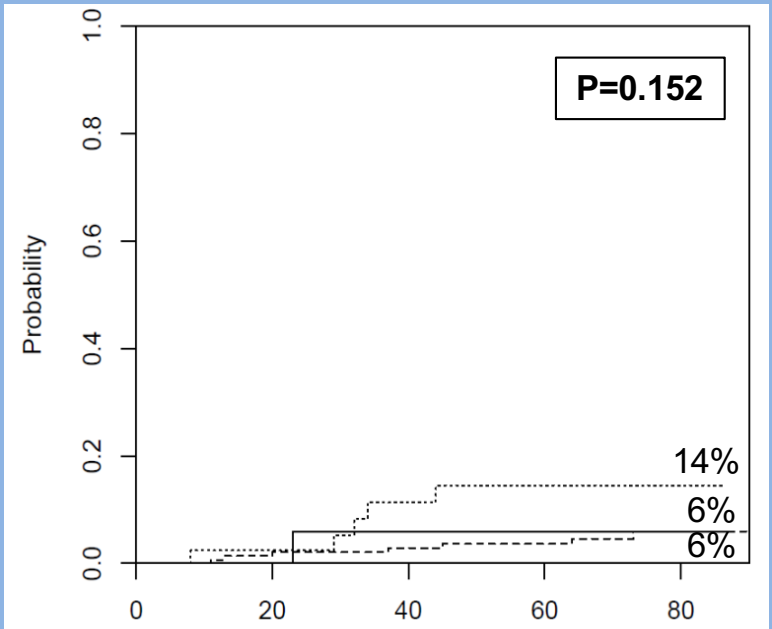
Outcome according to risk scores

Risk strata proportions and outcome						
	Low risk		Intermediate risk		High risk	
$n = 5154$	Sokal	ELTS	Sokal	ELTS	Sokal	ELTS
%	38	55	38	28	23	13
10-year OS	89%	88%	81%	79%	75%	68%
6-year LRD	3%	2%	4%	5%	8%	12%

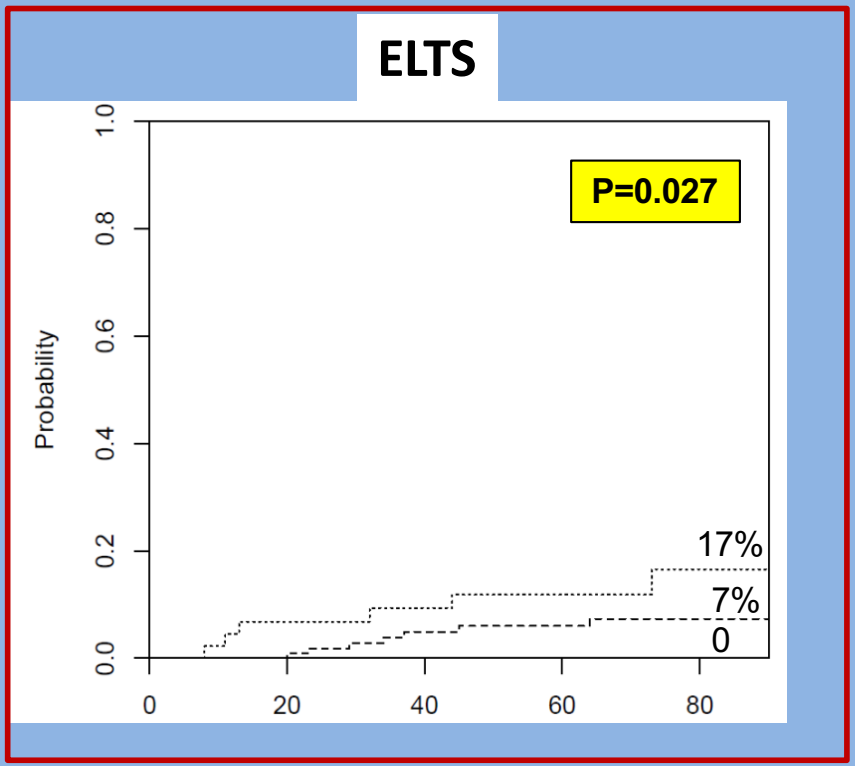
Pfirrmann M, Baccarani M, Saussele S, Guilhot J, Cervantes F, Ossenkoppele G, et al. Prognosis of long-term survival considering disease-specific death in patients with chronic myeloid leukemia. Leukemia. 2016;30:48–56.

Elderly patients (≥ 65 yrs) N = 202
Leukemia-related survival by risk

SOKAL



ELTS



Castagnetti et al, ASH 2018

ELN treatment milestones 2020

	Optimal	Warning	Failure
Baseline	NA	High-risk ACA, high-risk ELTS score	NA

Cytogenetics-based risk prediction of blastic transformation of chronic myeloid leukemia in the era of TKI therapy

Zimu Gong,[1] L. Jeffrey Medeiros,[1] Jorge E. Cortes,[2] Zi Chen,[1] Lan Zheng,[1] Yan Li,[1] Shi Bai,[1] Pei Lin,[1] Roberto N. Miranda,[1] Jeffrey L. Jorgensen,[1] Timothy J. McDonnell,[1] Wei Wang,[1] Hagop M. Kantarjian,[2] and Shimin Hu[1]

2326 patients: : 570 pts with ACAs (24,5%) (at dx and later)

High–risk group: 3q26 rearrangement, -7/7q-, i(17q) isolated or as a component of complex k

Int-2 group: other complex k without a HR component

Int-1 group: +8,+Ph, or other single ACAs

SR group: without ACAs

blood advances 12 DECEMBER 2017 • VOLUME 1, NUMBER 26

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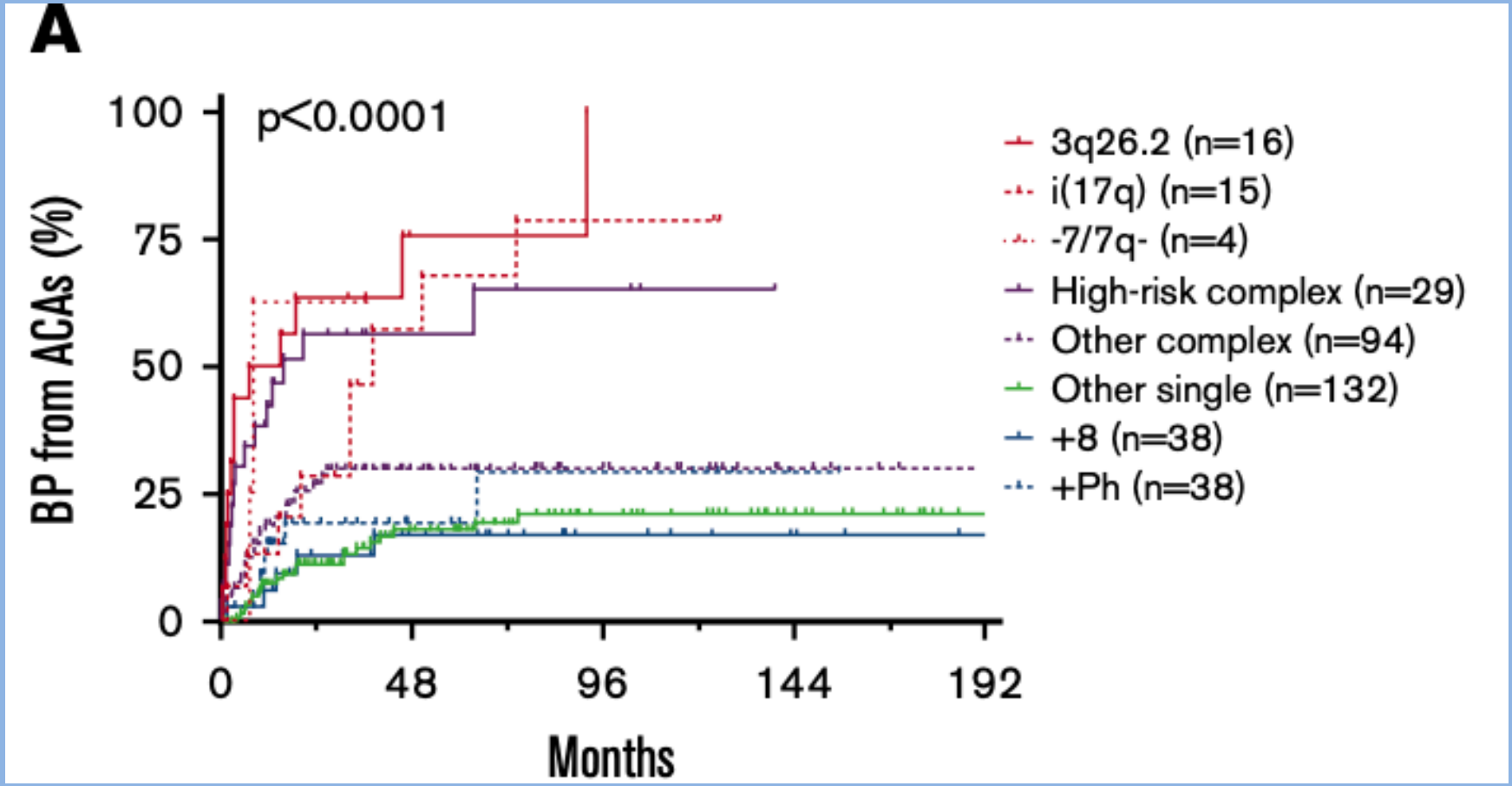
2326 patients: 164 at initial diagnosis (7%)



Progression to accelerated phase / blast crisis

5-year risk (ITT)	n
Dasatinib vs Imatinib	12 vs 19
Nilotinib vs Imatinib	10 vs 21
1 year risk	
Bosutinib vs Imatinib	4 vs 6

Cortes et al. DASISION. JCO 2016
Hochhaus et al. ENESTnd. LEUKEMIA 2016
Cortes et al. BFORE. Lancet Oncol. 2018

Molecular response

	MMR by 5 years	MR$^{4.5}$	≤10% EMR, at 3 months
DAS vs IM	**76%** 64%	**42%** 33%	**84%** 64%
NIL vs IM	**77%** 60%	**54%** 31%	**91%** 67%
	by 2 years		
BOS vs IM	**66%** **57**%	**20%** 15%	**75%** 57%

Hochhaus et al. ENESTnd. LEUKEMIA 2016
Cortes et al. DASISION. JCO 2016
Cortes et al. BFORE. Lancet Oncol. 2018; updated

REGULAR ARTICLE

blood advances

Managing chronic myeloid leukemia for treatment-free remission: a proposal from the GIMEMA CML WP

Michele Baccarani,[1] Elisabetta Abruzzese,[2] Vincenzo Accurso,[3] Francesco Albano,[4] Mario Annunziata,[5] Sara Barulli,[6] Germana Beltrami,[7] Micaela Bergamaschi,[7] Gianni Binotto,[8] Monica Bocchia,[9] Giovanni Caocci,[10] Isabella Capodanno,[11] Francesco Cavazzini,[12] Michele Cedrone,[13] Marco Cerrano,[14] Monica Crugnola,[15] Mariella D'Adda,[16] Chiara Elena,[17] Carmen Fava,[14] Paola Fazi,[2] Claudio Fozza,[18] Sara Galimberti,[19] Valentina Giai,[20] Antonella Gozzini,[21] Gabriele Gugliotta,[1] Alessandra Iurlo,[22] Gaetano La Barba,[23] Luciano Levato,[24] Alessandro Lucchesi,[25] Luigia Luciano,[26] Francesca Lunghi,[27] Monia Lunghi,[28] Michele Malagola,[29] Roberto Marasca,[30] Bruno Martino,[31] Angela Melpignano,[32] Maria Cristina Miggiano,[33] Enrico Montefusco,[34] Caterina Musolino,[35] Fausto Palmieri,[36] Patrizia Pregno,[37] Davide Rapezzi,[38] Giovanna Rege-Cambrin,[14] Serena Rupoli,[39] Marzia Salvucci,[40] Rosaria Sancetta,[41] Simona Sica,[42] Raffaele Spadano,[43] Fabio Stagno,[44] Mario Tiribelli,[45] Simona Tomassetti,[46] Elena Trabacchi,[47] Massimiliano Bonifacio,[48] Massimo Breccia,[2] Fausto Castagnetti,[1] Fabrizio Pane,[26] Domenico Russo,[29] Giuseppe Saglio,[14] Simona Soverini,[1] Paolo Vigneri,[44] and Gianantonio Rosti[1]

23 DECEMBER 2019 · VOLUME 3, NUMBER 24

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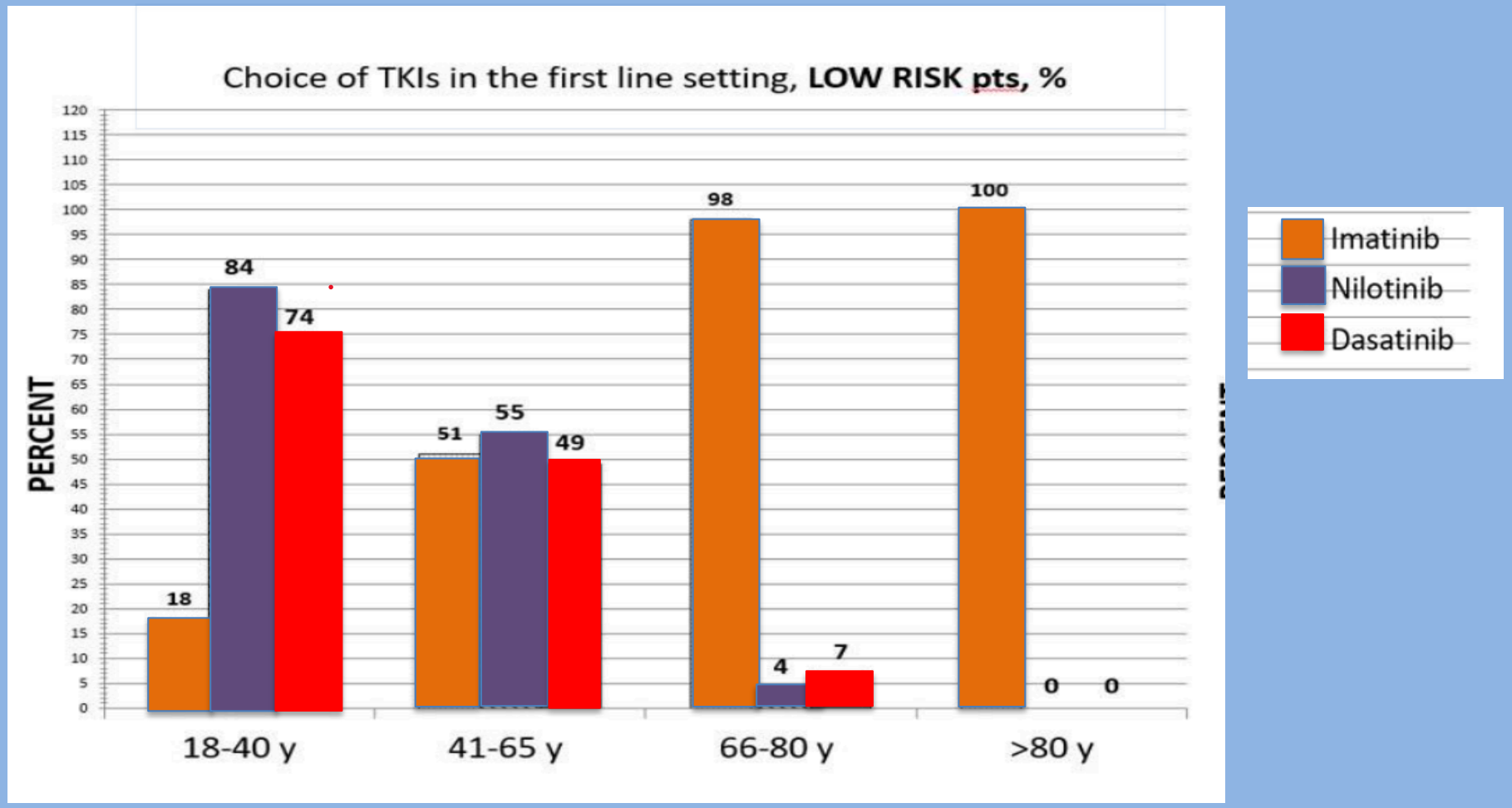

Blood Advances, 10.1182/bloodadvances.2019000865

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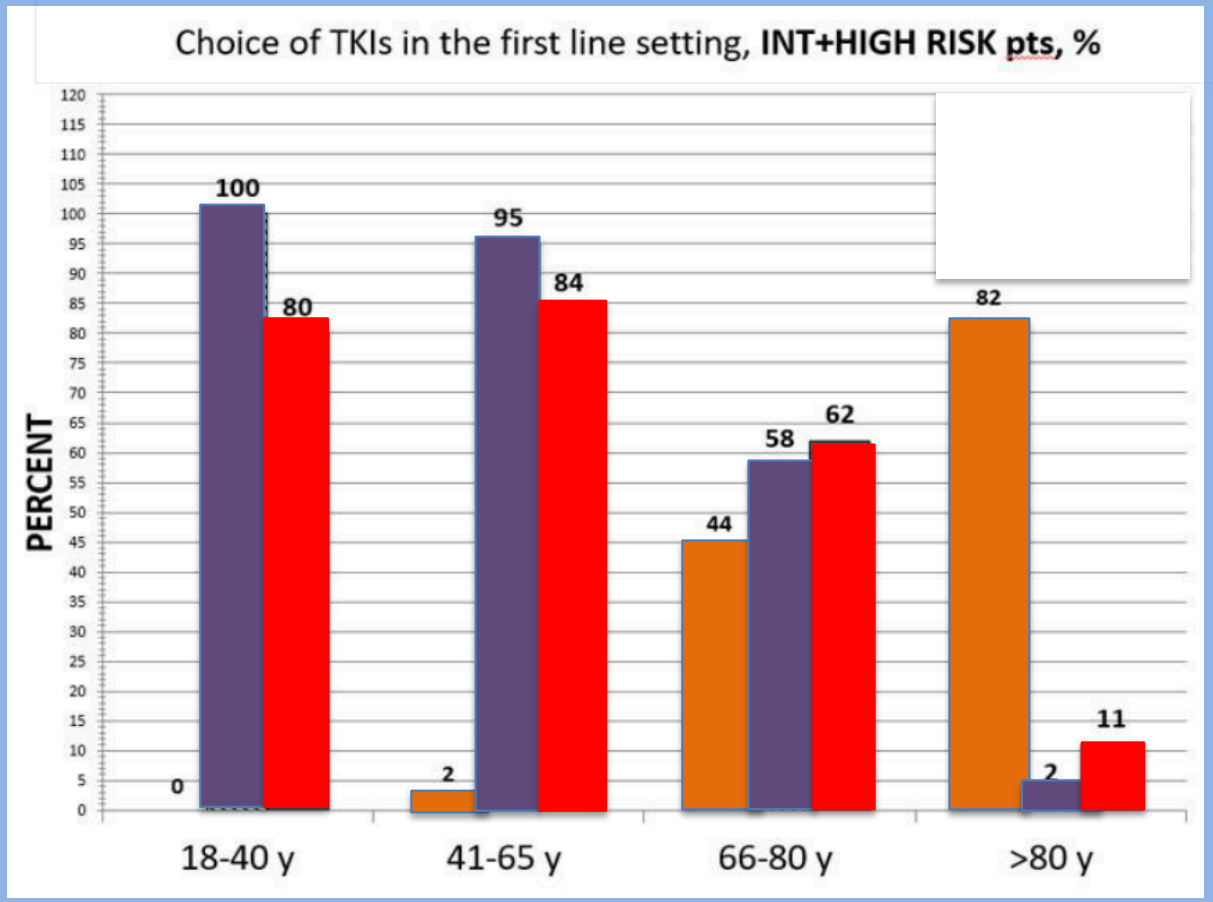
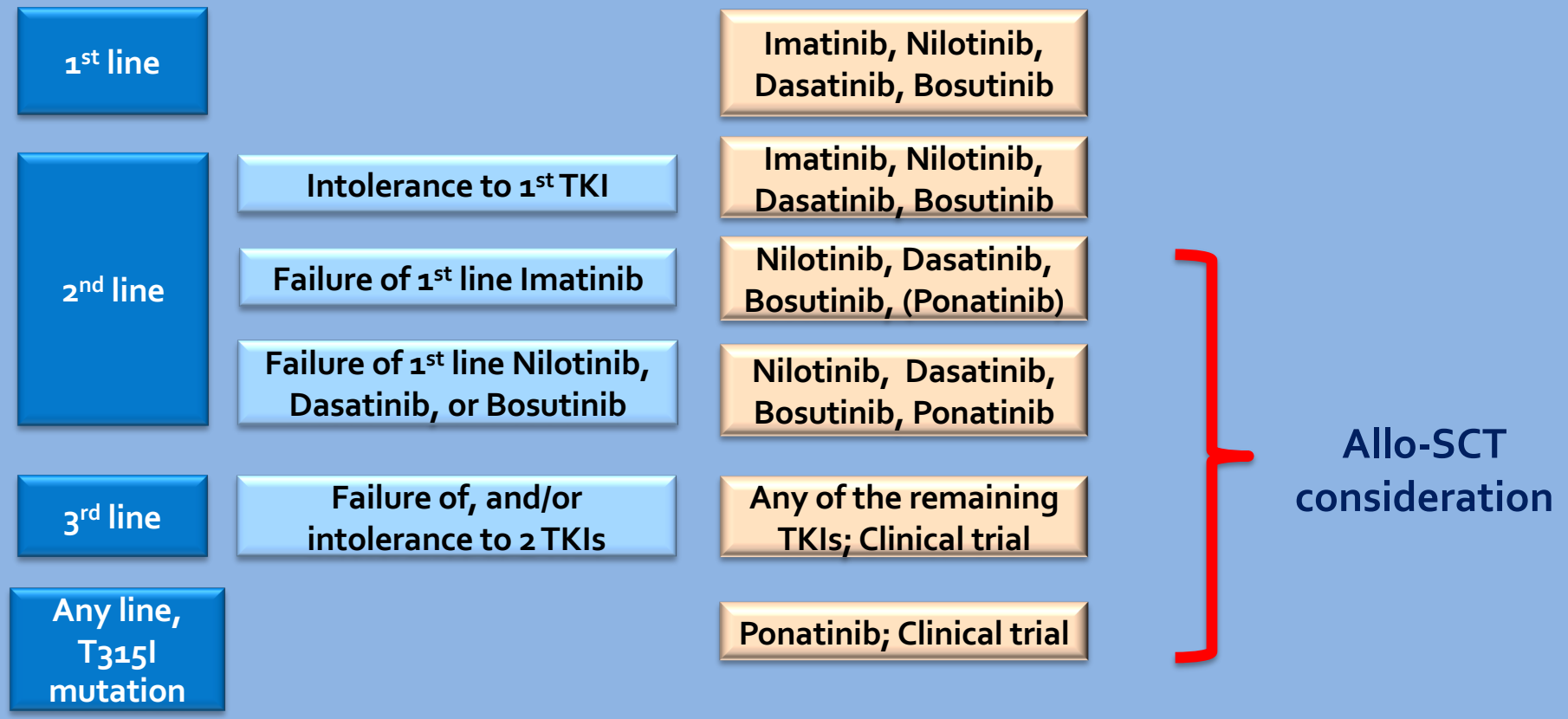


Blood Advances, 10.1182/bloodadvances.2019000865

ELN treatment milestones 2020 (1st line and 2nd line)

	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

Recommendations for Switch: CP-CML



Hochhaus et al., Leukemia 2020, May 4th

ELN, second line policy

«In the absence of BCR-ABL1 KD-mutations, there can be no clear recommendation for any particular 2GTKI: all second-line TKIs are effective, but there are no studies comparing the TKIs with each other»

«In patients with resistance to a 2GTKI without specific mutations ponatinib is preferred rather than an alternative 2GTKI unless cardiovascular risk factors preclude its use»

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CML Resistant to a 2G TKI frontline

nilotinib failure > dasatinib failure > ponatinib

dasatinib failure > nilotinib failure > ponatinib

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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.

LMC, linee guida 2021

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