CML TREATMENT

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HEMATOLOGIST&ONCOLOGIST

INTRODUCTION

- Review of pathophysiology
- History of IMATINIB
- Which of TKI is better for initiation??
- Response criteria
- Defining failure ,suboptimal response and optimal response
- Discontinuation of TKI therapy ??
- Imatinib in pregnancy

- Diagnostic challenge at presentation

Initial treatment with a TKI

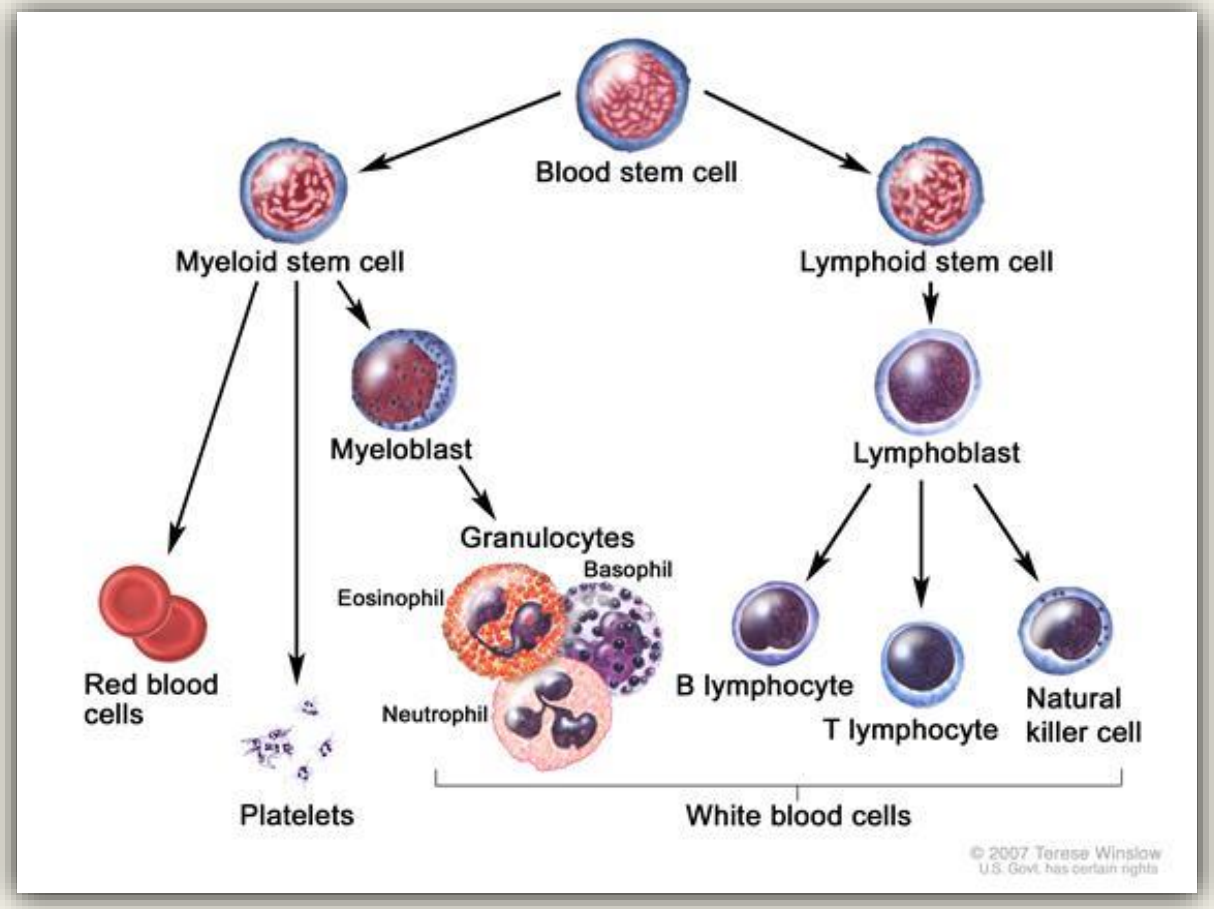
GOALS OF CARE

- Achieve clinical remission
- Maintain long-term disease control
- Avoid disease progression to accelerated phase or blast crisis
- Optimizing quality of life by limiting treatment-related toxicity

- ✓ For certain patient who achieve a sustained and deep molecular remission,a trial of discontinuation of therapy to achieve a treatment-free remission is a long term goal of management

The stem cells

– Ph chromosome
is found on myeloid
monocytic, erythroid
megakaryocytic
B-cells
sometimes T-cell



Prognostic scoring systems for newly diagnosed chronic myeloid leukemia*

Scoring system	Calculator Link	Risk groups
EUTOS score [1]	www.leukemia-net.org/content/leukemias/cml/eutos_score/	Low risk, high risk
Euro (Hasford) score [2]	www.leukemia-net.org/content/leukemias/cml/euro_and_sokal_score/	Low risk, intermediate risk, high risk
Sokal score [3]	www.leukemia-net.org/content/leukemias/cml/euro_and_sokal_score/	Low risk, intermediate risk, high risk
The EUTOS long-term survival score (ELTS) [4]	www.leukemia-net.org/content/leukemias/cml/elts_score/	Low risk, intermediate risk, high risk

- ELTS was derived from survival data that reflect treatment of CML with TKI and it provides the best discrimination for the probabilityof CML-specific death
- additional chromosome abnormalities in Ph+ cells (ACA) +8, a second Ph-chromosome (+Ph), i(17q), +19, −7/7q-, 11q23, or 3q26.2 aberrations, and complex aberrant karyotypes predict a poorer response to TKIs and a higher risk of progression

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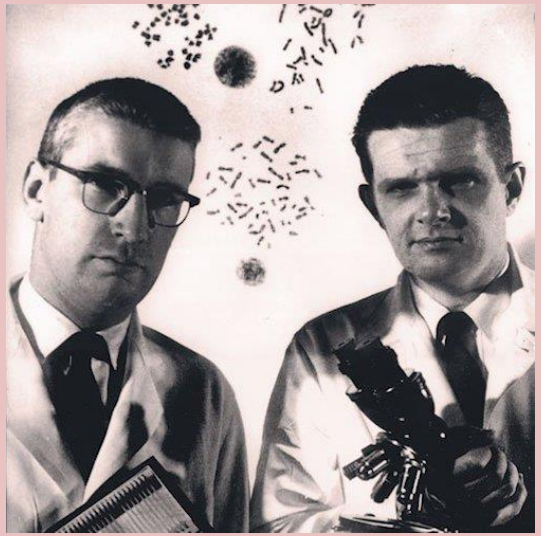
- additional chromosome ab… …lls … progression

In the last version of ELN, mentioned as a “warning”
Currently, the panel recommends classifying ACA and treating patients with high-risk ACA as high-risk patients.



- In 1960, Drs. Nowell and Hungerford
- The discovery of the Philadelphia chromosome and BCR-ABL, supported in part by NCI, demonstrated for the first time that a genetic alteration could cause cancer.

- A few years later, Nora Heisterkamp, M.D discovered that when the Philadelphia chromosome forms, two genes that are normally separated get fused together.
- The hybrid (called a fusion gene) is known as BCR-ABL.

- In 1998, Dr. Druker and his colleagues tested imatinib in a phase 1 clinical trial partially funded by NCI.

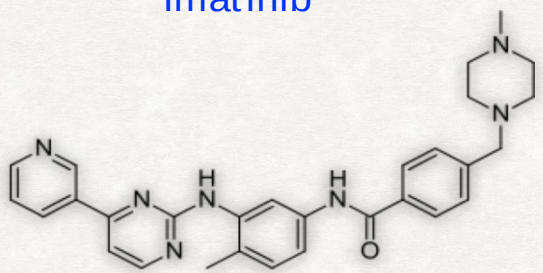
CHOOSING A TKI

2. Tyrosine Kinase inhibitor therapy

First generation

Second generation

Imatinib



Dasatinib

(Sprycel®, Bristol-Myers Squibb)

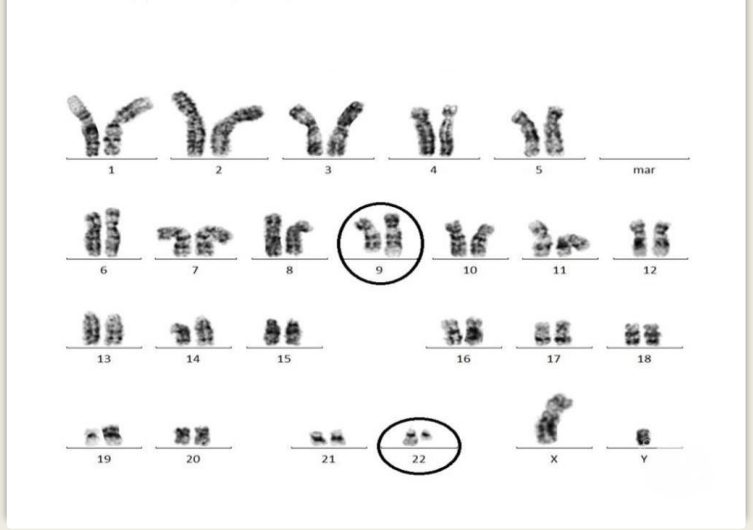
Nilotinib

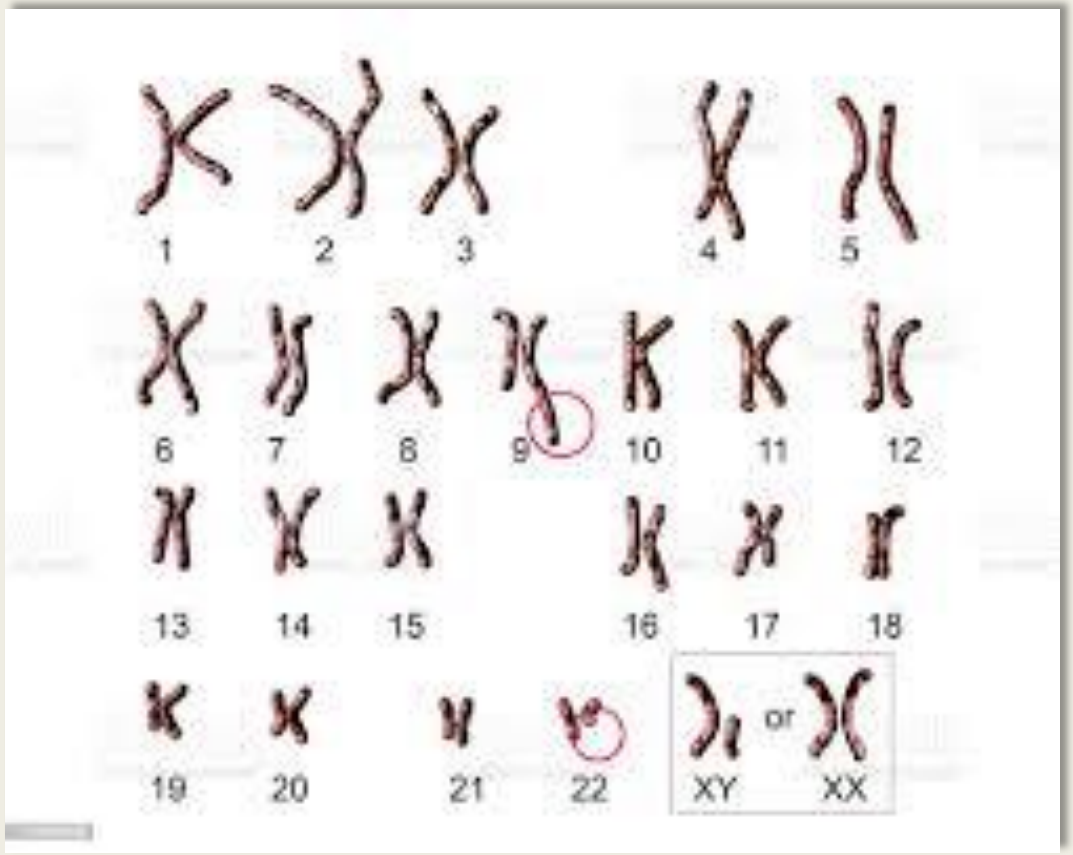
(Tasigna®, Novartis)

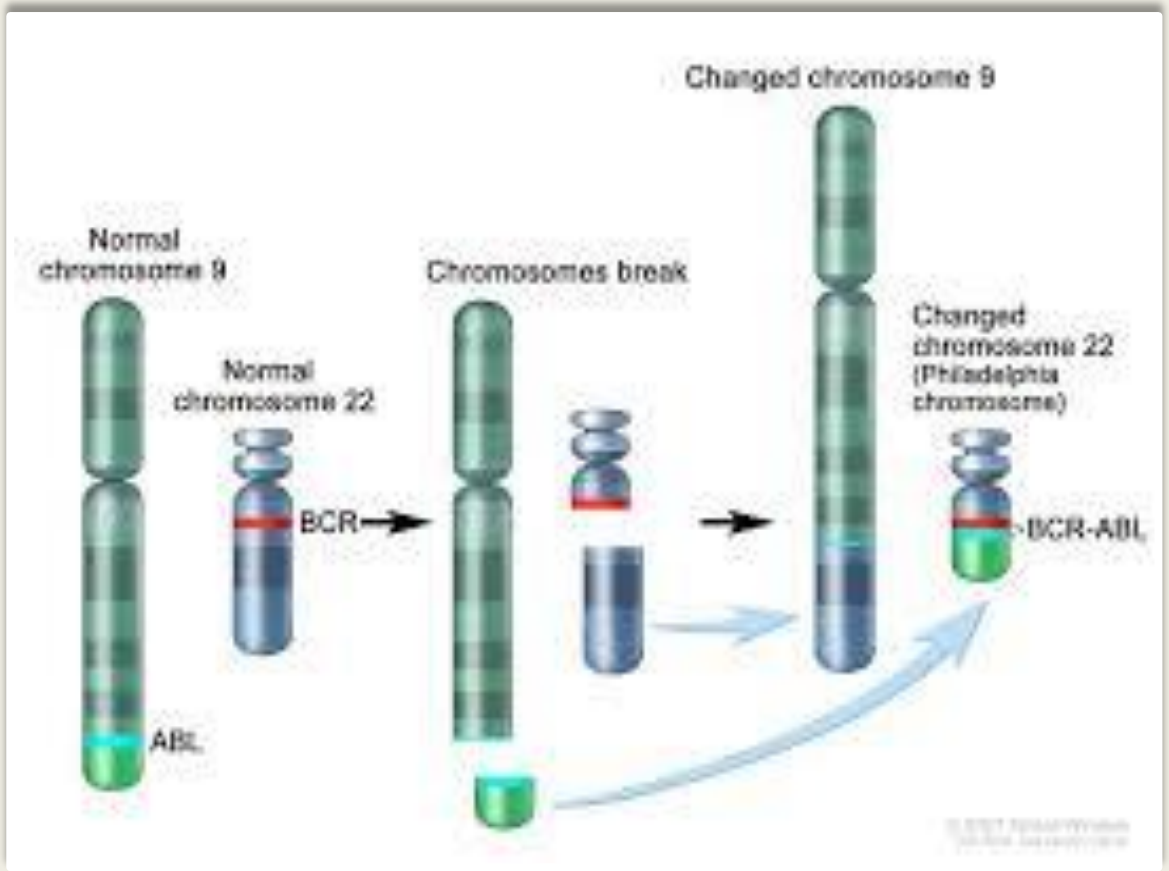
Bosutinib

(Bosulif®, Pfizer)

pathophysiology







doi: 10.1200/JCO.2015.64.8899.

SISION: T
in Treatm
nts Trial

Michele Baccara
s Casanova [2], Br

2021 ANNU

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hew Stenger
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Updated: 6/2/2016 11:11:06 AM

Key Points

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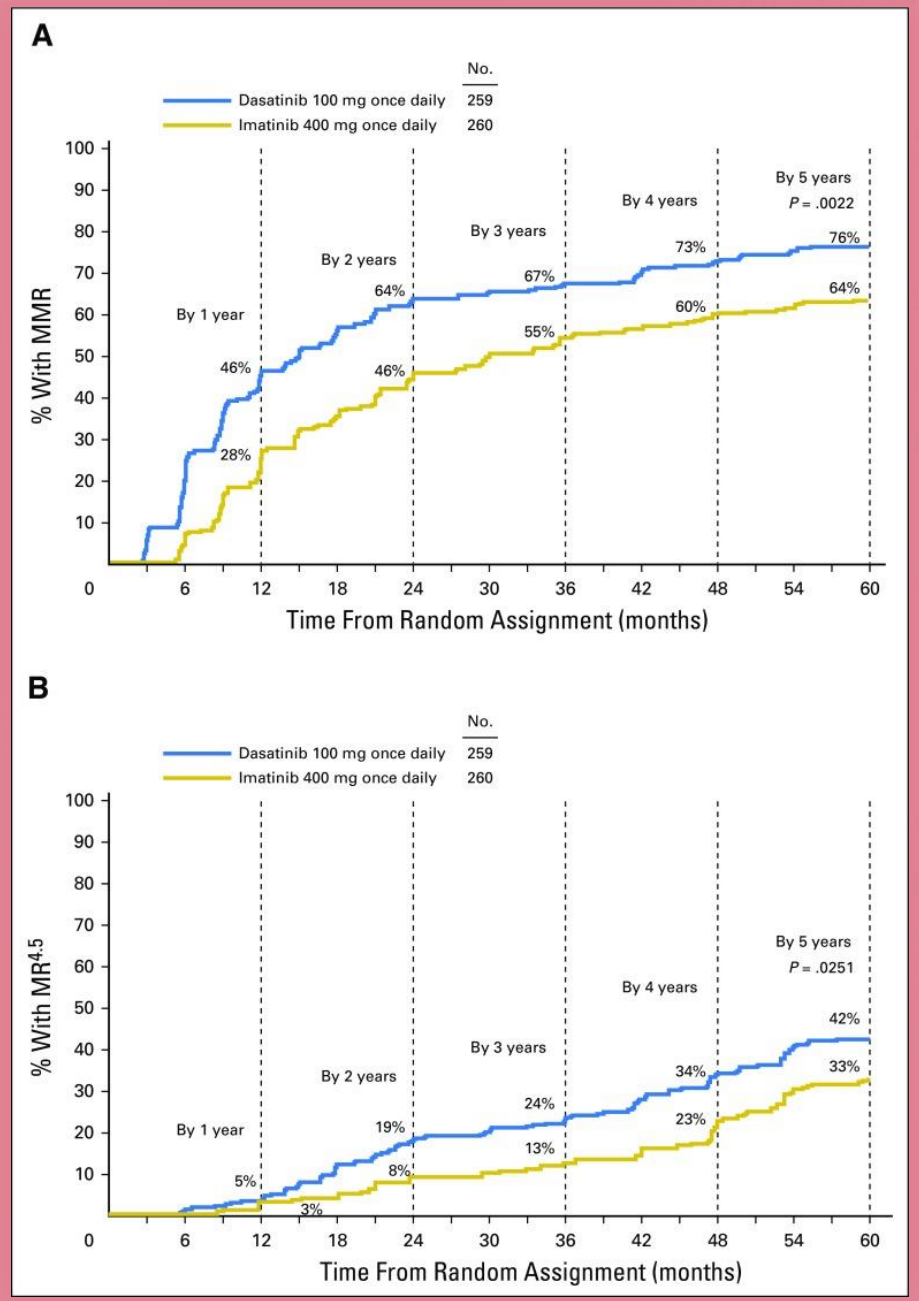
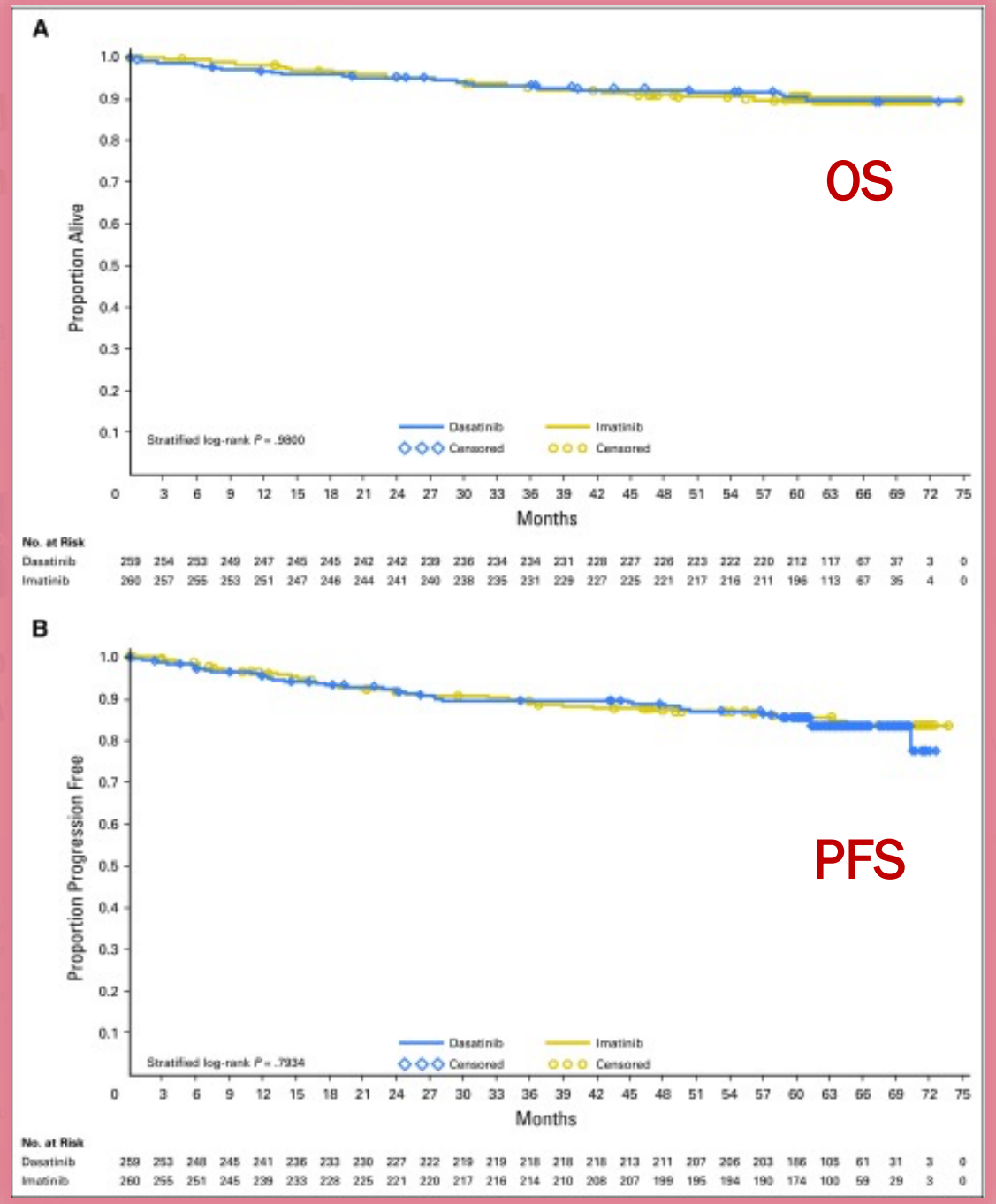
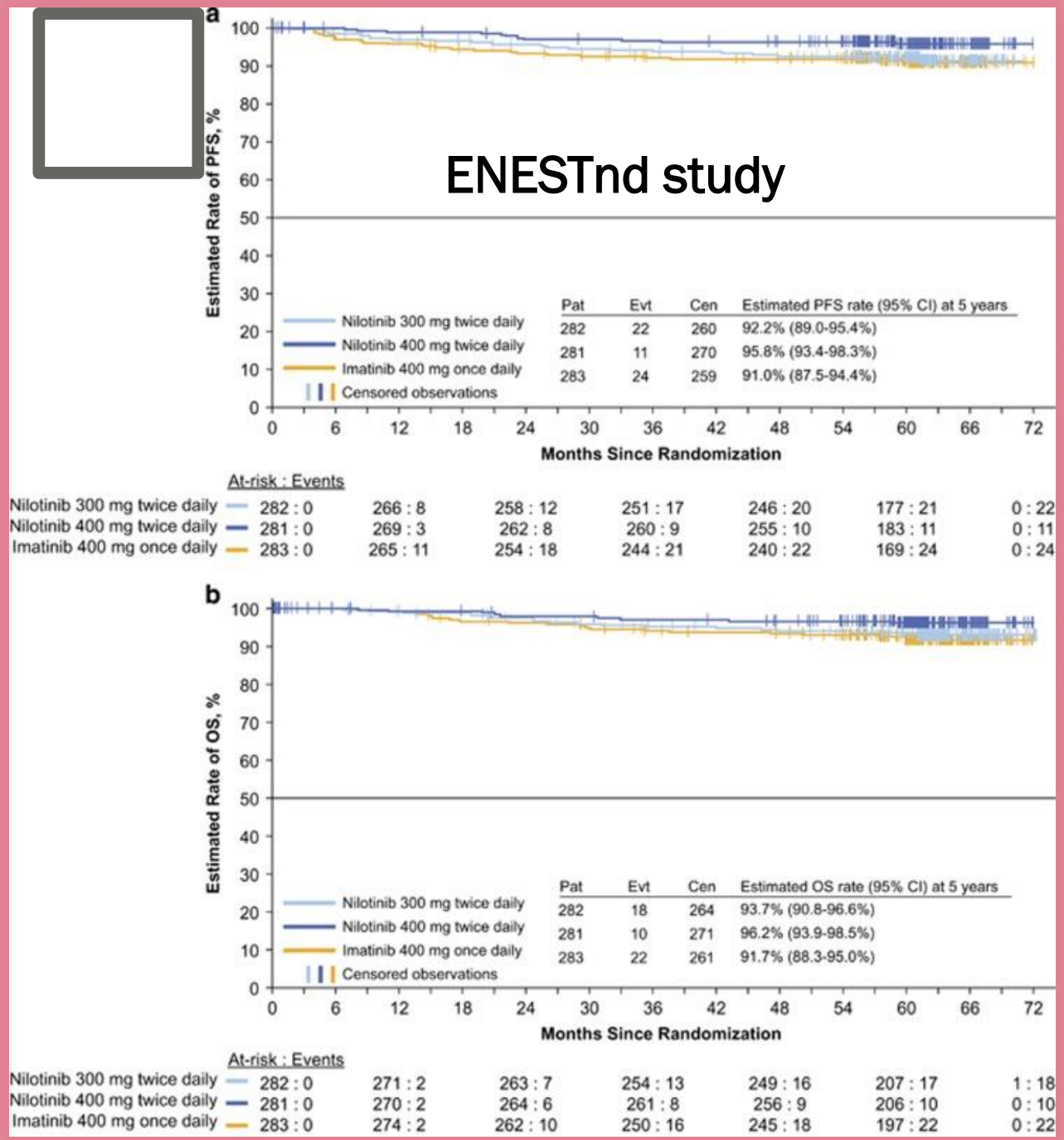


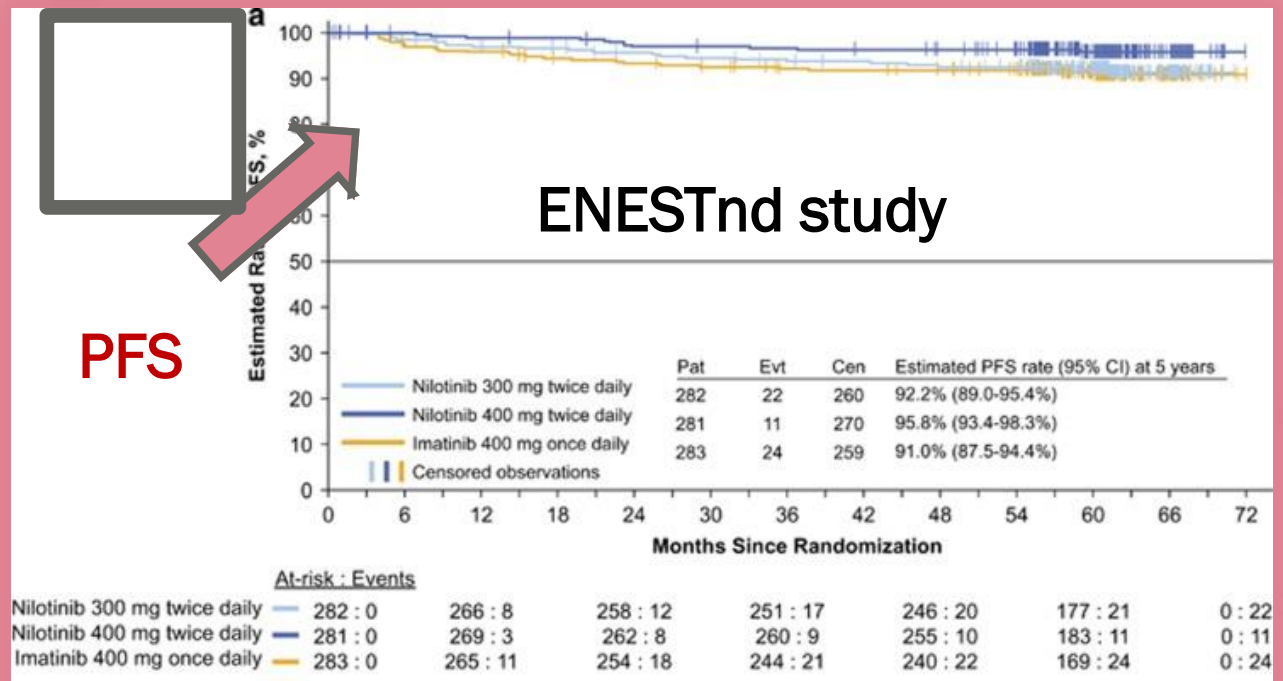


ENESTnd study



ENESTnd study

PFS



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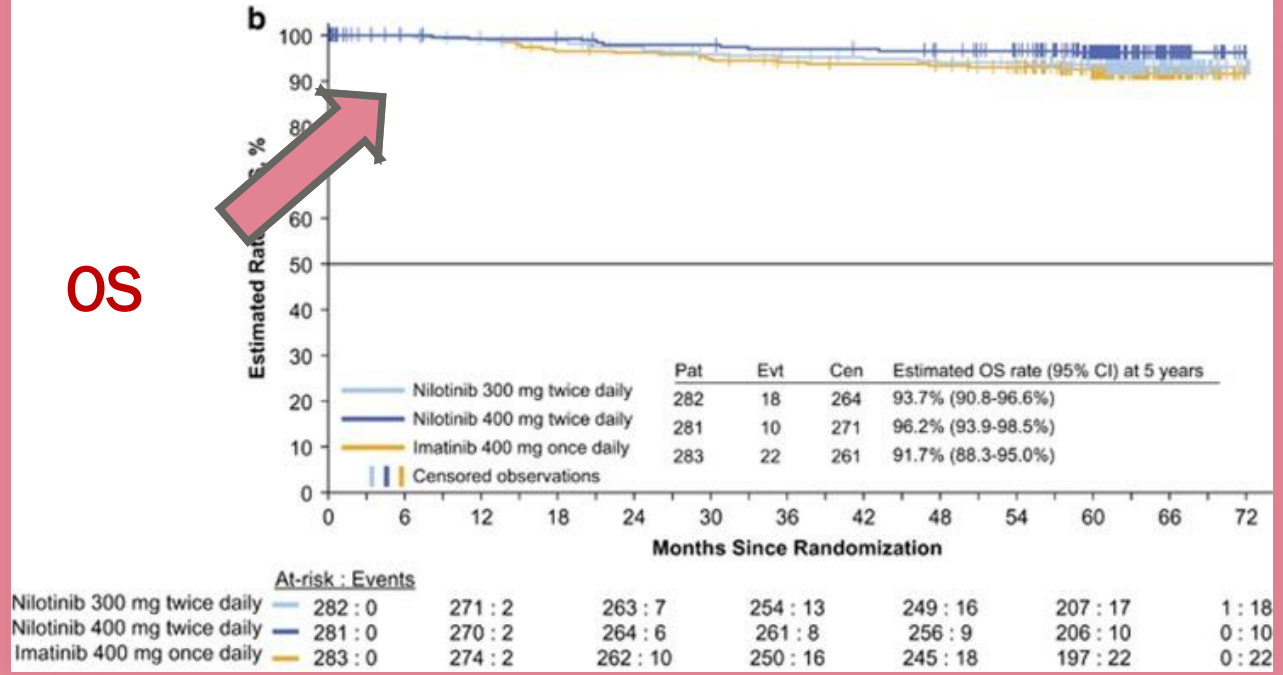

PERSPECTIVE

Transgender Women on
Athletic Teams — The
Lindsay Hecox

ORIGINAL ARTICLE

Newly Diagn
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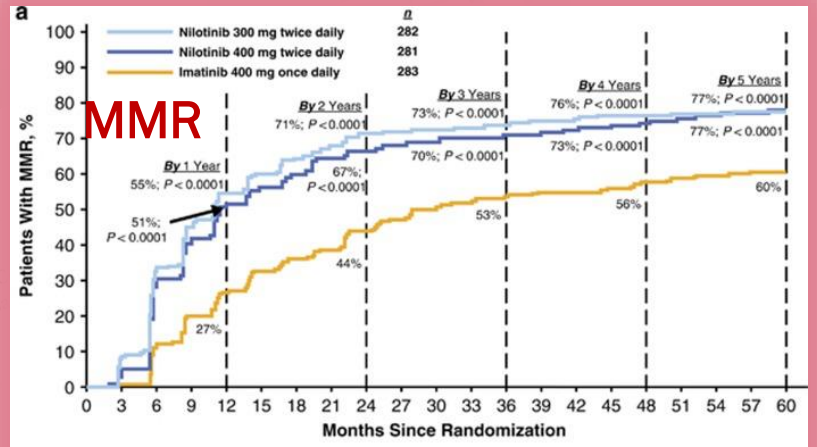
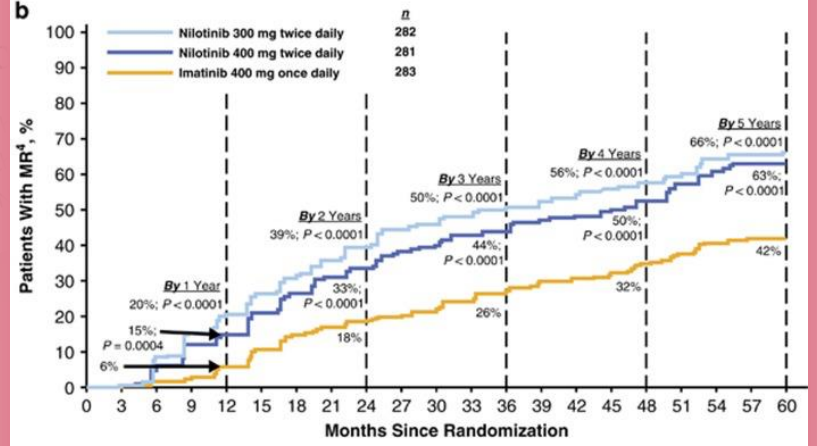
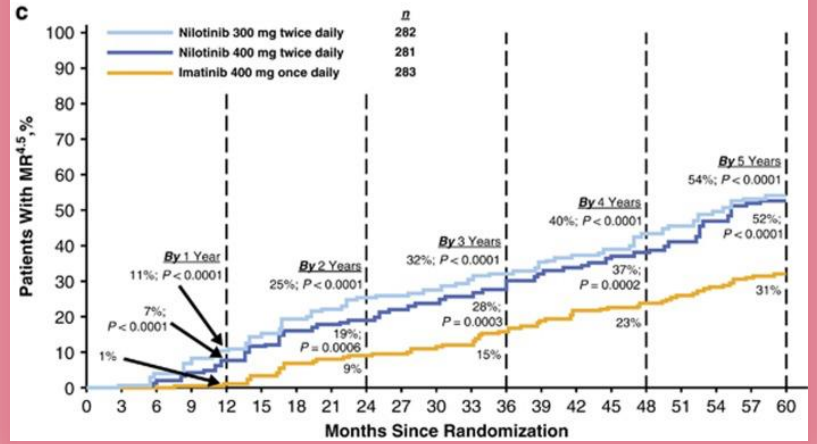
MMR



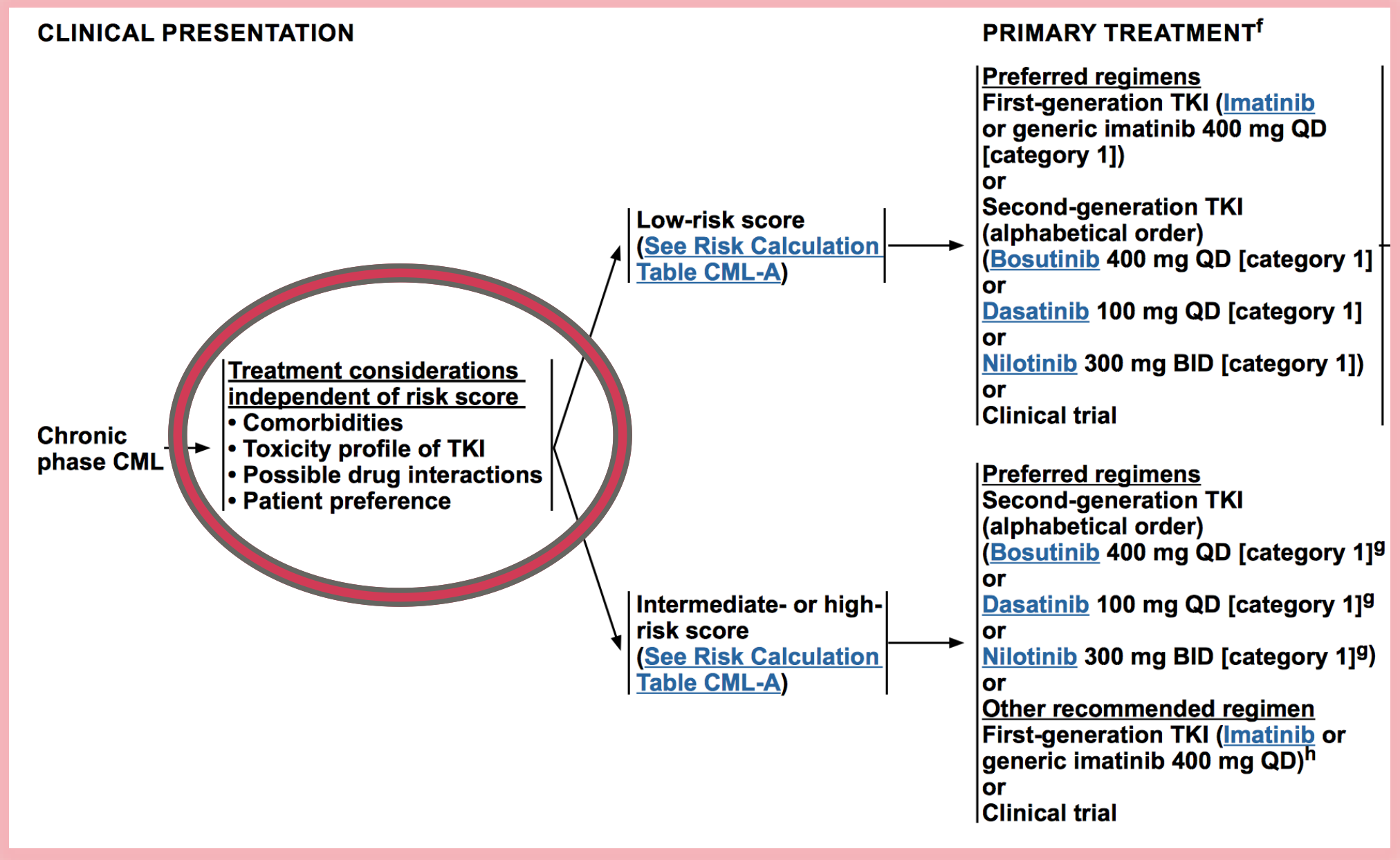




Management of Patients with Inadequate Response to Imatinib

- Should be evaluated for adherence to treatment and possible drug interaction
- Evidence of loss of response should be confirmed with repeat studies befor treatment changes are initiated
- If there is a 1-log increase in bcr-abl1 after achieving mmr (mr3),this should be confirmed by repeating q pcr in one to three months

NCCN Guidelines Version 2.2021 Chronic Myeloid Leukemia



Clinical Trial > J Clin Oncol. 2016 Jul 10;34(20):2333-40. doi: 10.1200/JCO.2015.64.8899.
Epub 2016 May 23.

Final 5-Year Study Results of DASISION: The Dasatinib Versus Imatinib Study in Treatment-Naïve Chronic Myeloid Leukemia Patients Trial

Jorge E Cortes [1], Giuseppe Saglio [2], Hagop M Kantarjian [2], Michele Baccarani [2], Jiří Mayer [2], Concepción Boqué [2], Neil P Shah [2], Charles Chuah [2], Luis Casanova [2], Brigid Bradley-Garelik [2], George Manos [2], Andreas Hochhaus [2]

Affiliations + expand

PMID: 27217448 PMCID: PMC5118045 DOI: 10.1200/JCO.2015.64.8899

Free PMC article

INITIAL TREATMENT with imatinib:

- 400 mg once daily with a meal and a large glass of water
- Dispersed in water or apple juice
- Should be adjusted for liver or renal impairment
- Concurrent use of strong CYP3A4 inducers should be avoided
- At higher dosage, providing benchmarks for deep molecular responses

TOXICITY

- Cytopenia,Edema,Nausea,Diarrhea,Rash,Muscle cramp (generally mild)
- HEART FAILURE
- HEPATOTOXICITY

ENESTnd study

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2021 ANNU

5-Year Results Dasatinib vs Im

By Matthew Stenger

Posted: 6/2/2016 11:11:06 AM

Last Updated: 6/2/2016 11:11:06 AM

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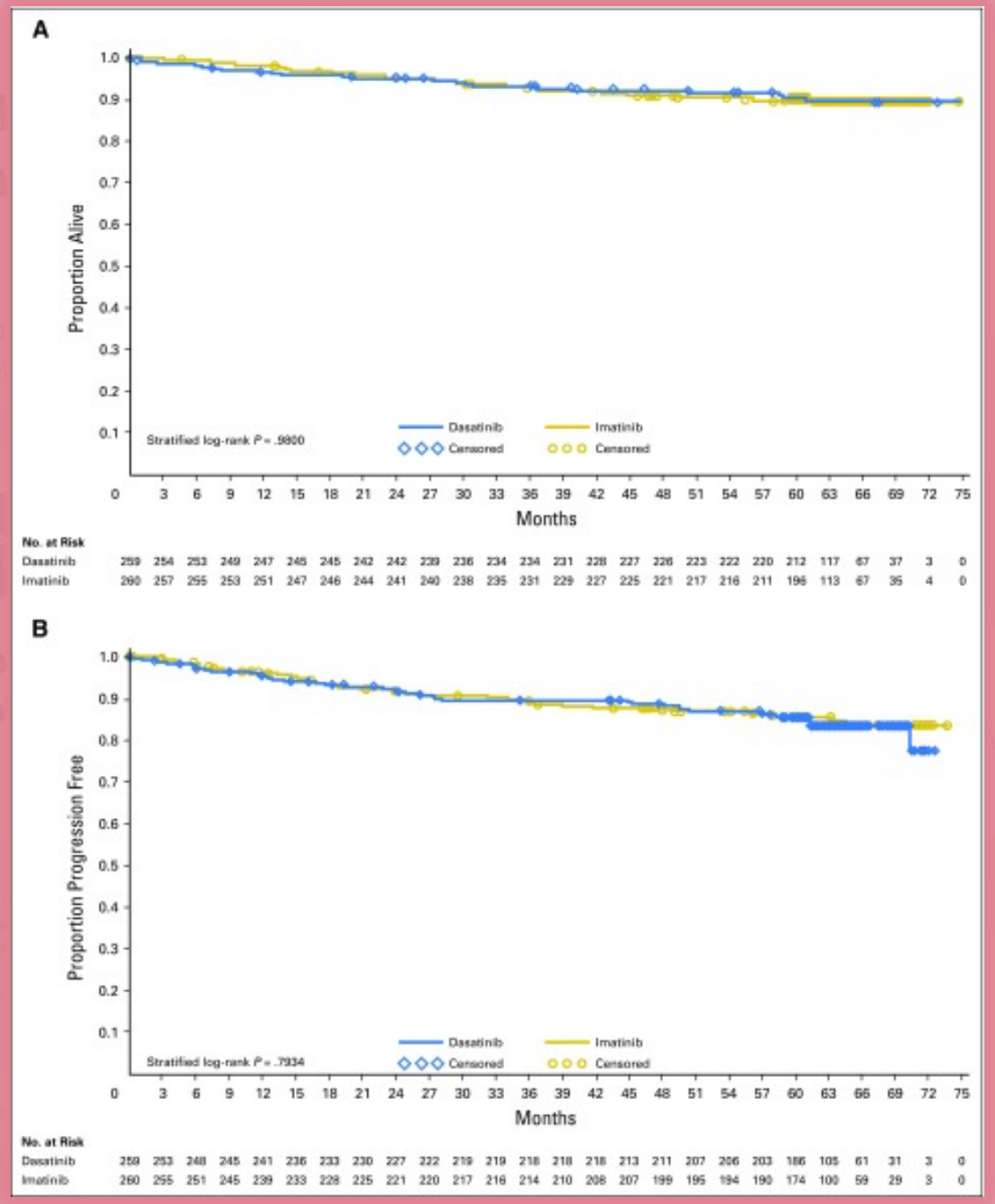
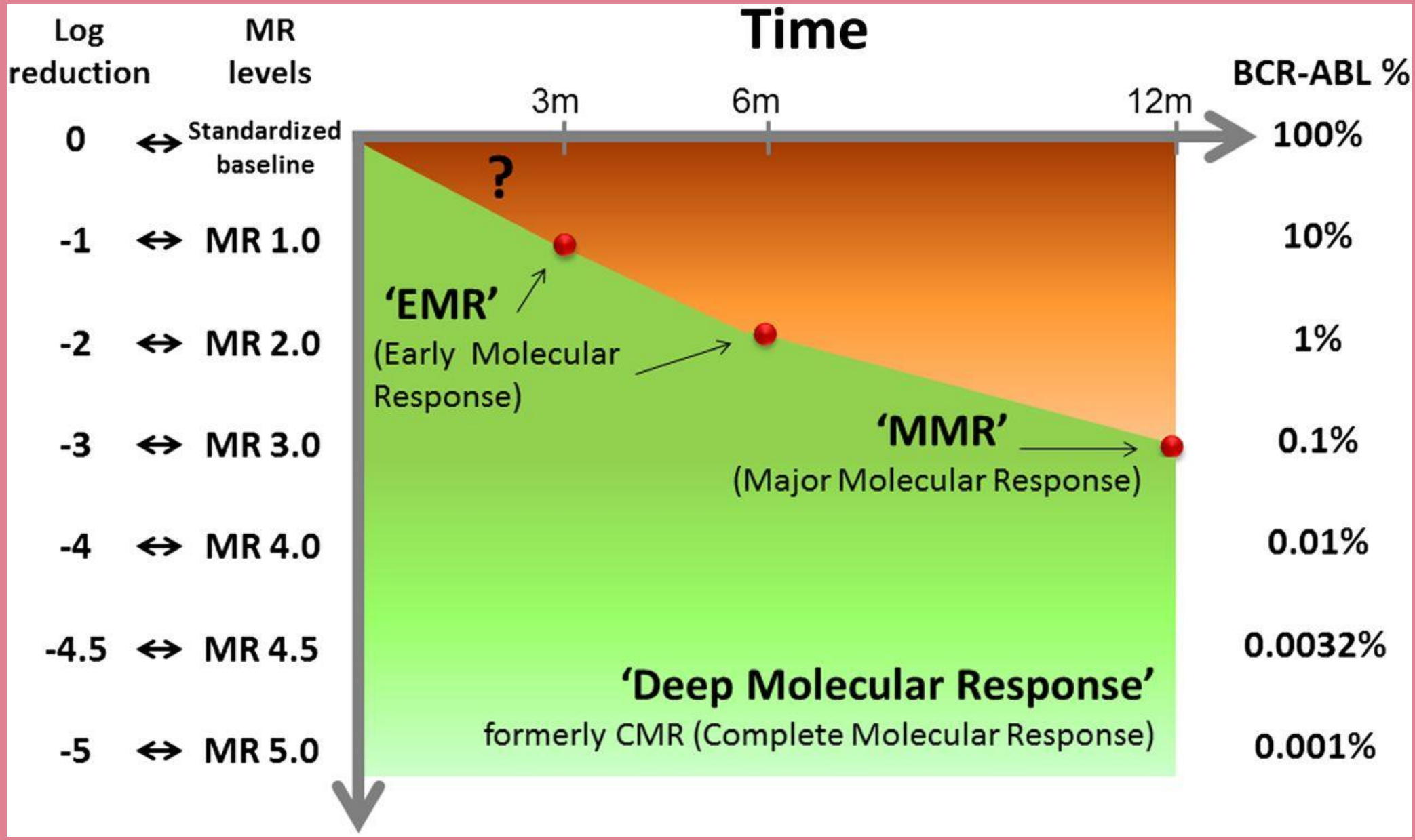
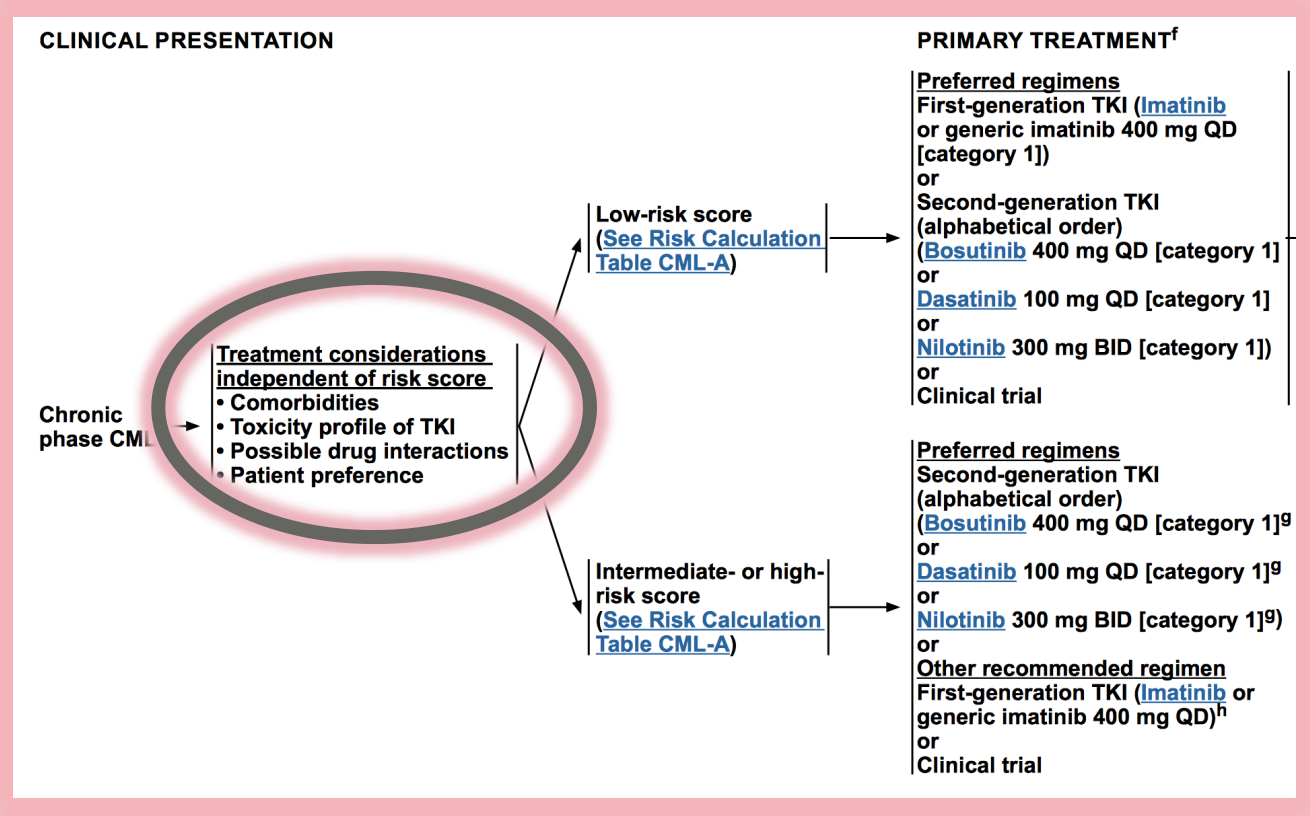



Log reduction
MR levels
Time
BCR-ABL %
3m
6m
12m
0 ↔ Standardized baseline
100%
?
-1 ↔ MR 1.0
10%
'EMR'
(Early Molecular Response)
-2 ↔ MR 2.0
1%
'MMR'
(Major Molecular Response)
-3 ↔ MR 3.0
0.1%
-4 ↔ MR 4.0
0.01%
-4.5 ↔ MR 4.5
0.0032%
'Deep Molecular Response'
formerly CMR (Complete Molecular Response)
-5 ↔ MR 5.0
0.001%

CHOOSING A TKI



No individual TKI is preferred for initial treatment of all patients with CP CML

Selection of a TKI based on :

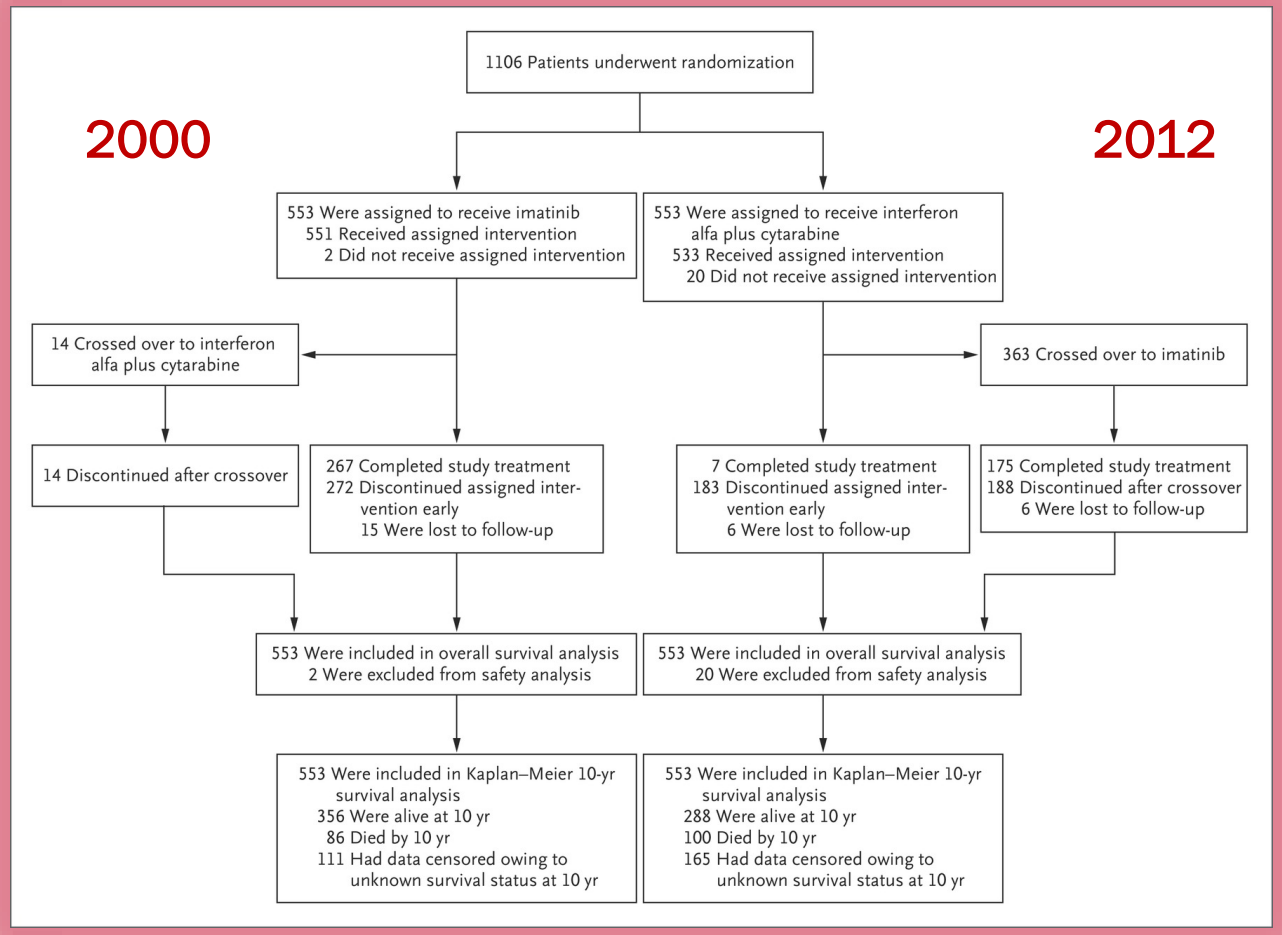
- CML risk score
- Side effect profile
- Comorbid illnesses
- Patient preference
- Cost

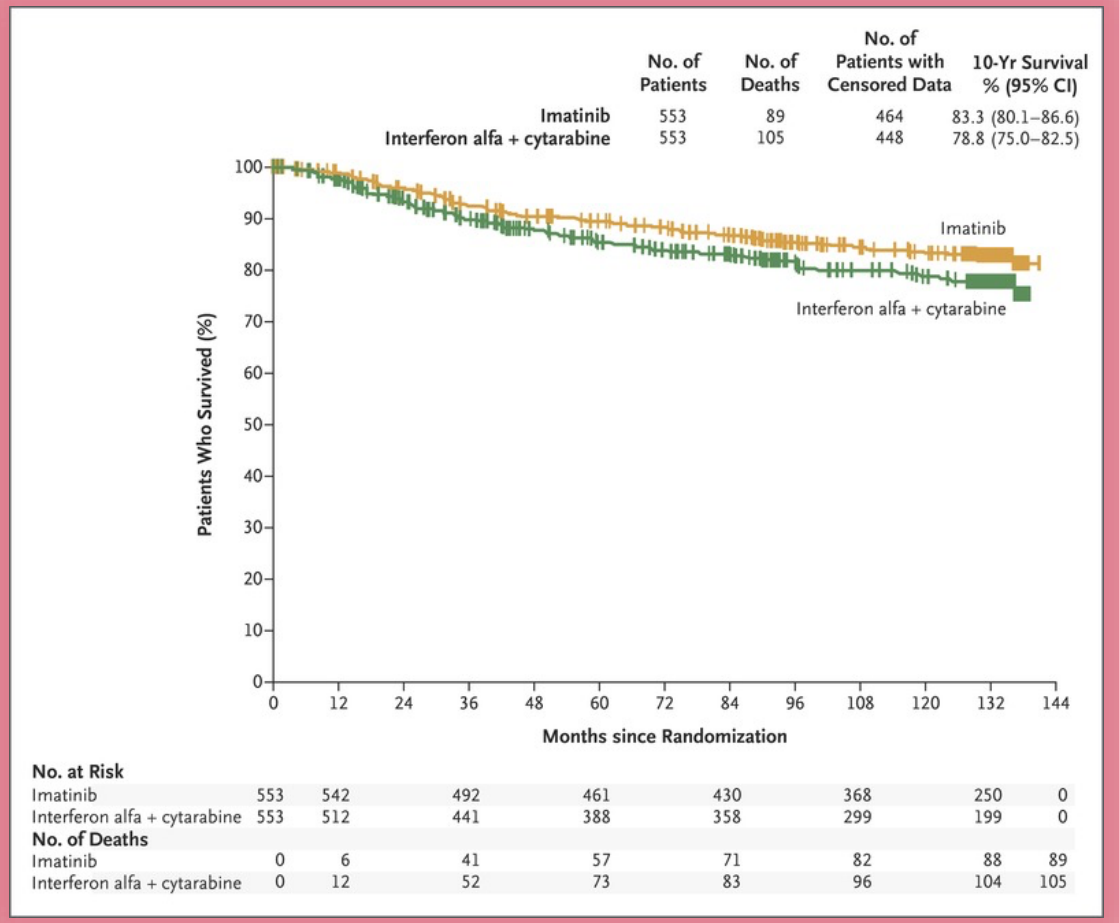
- Imatinib and second-generation TKIs achieve comparable rates of OS,PFS,AEs

- The first generation TKI was tested in the IRIS study
- At higher dosage, providing benchmarks for deep molecular responses
- Served as control arm in six prospective pharmaceutical company-sponsored trials testing dasatinib, nilotinib, bosutinib, and radotinib
- In CP a lower dose of 300mg can be used if 400mg is not tolerated
- A dose of 400 mg twice daily can be used in AP, but in patients with progression to more advanced disease a change to second generation TKI (2GTKI) is recommended

Long-Term Outcomes of Imatinib Treatment for Chronic Myeloid Leukemia

N Engl J Med 2017; 376:917-927





TKI Common toxicities

- **IMATINIB**

  Cytopenia ,Muscle cramps,fatigue,edema,nausea,diarrhea,rash, ⇩ P , ⇩ BMD

- **NILOTINIB**

  Coronary,cerebral,peripheral vascular disease,prolongedQTc interval;hyperglycemia;pancreatitis

- **DASATINIB**

  Pleural effusion,pulmonary

Response criteria

European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia

	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

NCCN Guidelines Version 2.2021
Chronic Myeloid Leukemia

EARLY TREATMENT RESPONSE MILESTONES[i,j]

BCR-ABL1 (IS)	3 months	6 months	12 months[k]
>10%[l]	YELLOW	RED	
>1%–10%	GREEN		YELLOW
>0.1%–1%	GREEN		LIGHT GREEN
≤0.1%	GREEN		

COLOR	CONCERN	CLINICAL CONSIDERATIONS	RECOMMENDATIONS
RED	TKI-resistant disease	• Evaluate patient compliance and drug interactions • Consider mutational analysis	Switch to alternate TKI (CML-5) and evaluate for allogeneic HCT
YELLOW	Possible TKI resistance	• Evaluate patient compliance and drug interactions • Consider mutational analysis • Consider bone marrow cytogenetic analysis to assess for MCyR at 3 mo or CCyR at 12 mo	Switch to alternate TKI (CML-5) or Continue same TKI (other than imatinib) (CML-G)[m] or Increase imatinib dose to a max of 800 mg and Consider evaluation for allogeneic HCT
LIGHT GREEN	TKI-sensitive disease	• If treatment goal is long-term survival: >0.1%–1% optimal • If treatment goal is treatment-free remission: ≤0.1% optimal	• If optimal: continue same TKI • If not optimal: shared decision-making with patient[n,o]
GREEN	TKI-sensitive disease	• Monitor response (CML-D) and side effects	Continue same TKI (CML-G)[p]

Criteria for TKI Discontinuation

. Age ≥18 years.

• Chronic phase CML. No prior history of accelerated or blast phase CML

• On approved TKI therapy for at least 3 years

• Prior evidence of quantifable *BCR-ABL1* transcript

• Stable molecular response (MR4; *BCR-ABL1* ≤0.01% IS) for ≥2 years, as documented on at least 4 tests, performed at least 3 months apart

• Access to a reliable qPCR test with a sensitivity of detection of at least MR4.5 (*BCR-ABL1* ≤0.0032% IS) and that provides results within 2 weeks.

• Monthly molecular monitoring for the rst 6 months following discontinuation, bimonthly during months 7–12, and quarterly thereafter (indefnitely) for patients who remain in MMR (MR3; *BCR-ABL1* ≤0.1% IS).

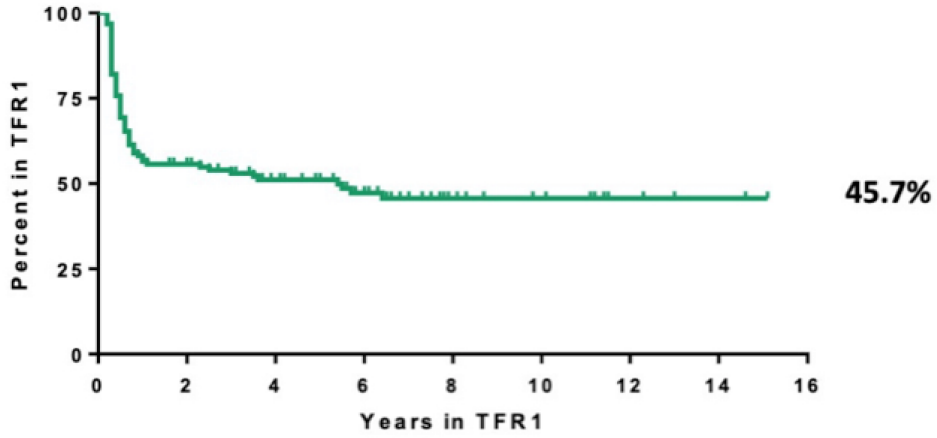
• Prompt resumption of TKI within 4 weeks of a loss of MMR with monthly molecular monitoring until MMR is re-established, then every 3 months thereafter is recommended indefnitely for patients who have reinitiated TKI therapy after a loss of MMR. For those who fail to achieve MMR after 3 months of TKI resumption, BCR-ABL1 kinase domain mutation testing should be performed, and monthly molecular monitoring should be continued for another 6 months

Long term follow-up of patients in TFR

Report from the American Society of Hematology Congress 2019

TFR1 : overall results

Median follow-up in TFR1: 6.5 years



TFR1 : late relapses

(> 2 years in TFR1, MMR loss)

n=9 out 65 molecular relapses (**13.8%**)

Median time to late molecular relapses : 3.6 years (2.3-6.3)

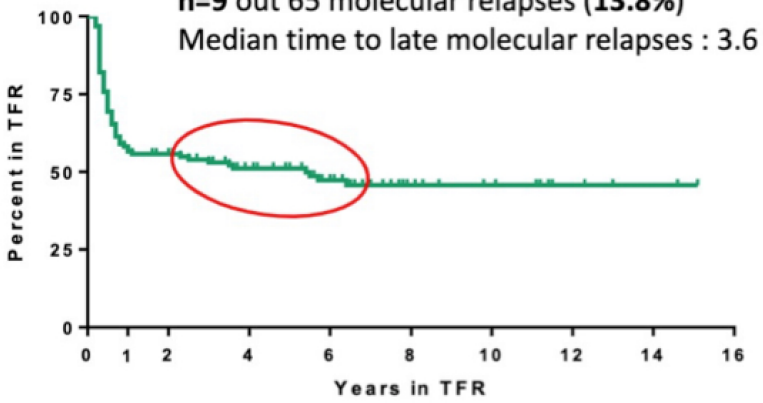


Table 1. Recommended TKI doses approved for children and proportion of patients achieving MMR

Recommended TKI dose for CML-CP treatment	Proportion of pediatric patients with CML-CP treated with first-line TKI who achieved MMR				
	Patients, no.	12 mo	18 mo	24 mo	References
Imatinib					
340 mg/m²/dose, once daily	51	NR	NR	NR	16
300 mg/m²/dose, once daily	140	42%*	59%*	69%*	14
260 mg/m²/dose, once daily	44	31%†	55%*	60%*	15
Nilotinib					
230 mg/m²/dose, twice daily	25	64%*	68%§	NR	18
Dasatinib					
60 mg/m²/dose, once daily	84	52%*	65%*	70%*	17

NR, not reported.

*Results are reported as a cumulative rate at the indicated time point.

†Results are reported as a response rate at the indicated time point.

§Cumulative response rate by data cutoff at 16.6 mo.

options in the case of a suboptimal response (Figure 1). Several factors must be taken into consideration when choosing a TKI.

cohorts demonstrate that molecular responses at months 6 and 12 months are deeper with 2G-TKIs, but at 18 months are similar

Table 2. Initial and follow-up evaluations

Evaluations at diagnosis	Evaluations at follow-up visits
Complete blood count (including differentials) and comprehensive metabolic profile	Complete blood count (including differentials) and comprehensive metabolic profile
Spleen and liver size (should be measured as below costal margin)	Spleen and liver size (should be measured as below costal margin)
Bone marrow aspirate and biopsy (differentials and karyotype)	Bone marrow every 6 mo until complete cytogenetic response
Baseline molecular genetics (qRT-PCR for BCR-ABL1) with transcript type (eg, e14a2)	Molecular monitoring from peripheral blood by qRT-PCR (monthly in the first 3 mo, every 3 mo thereafter)
Categorize stage of disease (CML-CP, CML-AP, CML-BP), identify additional risk factors (eg, additional chromosomal aberrations)	Classify response according to treatment time as recommended by the ELN[44] or NCCN[42] (Table 3) In advanced phases of CML, also monitor bone marrow cytogenetics to detect clonal evolution

qRT, quantitative reverse transcription.

Thank you