Chronic Myeloid Leukemia in 2021

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Overall Talk Objectives

1. Selecting first-line therapy: first vs. second generation tyrosine kinase inhibitors

2. Stopping TKI therapy: who is eligible and who succeeds

3. Selecting next-line therapy: expectations and outcomes

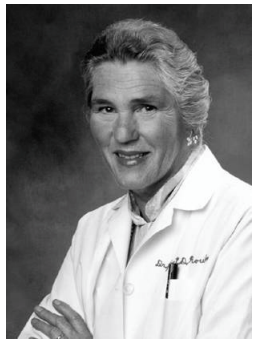
CML epidemiology

- Clonal disorder arising in a hematopoietic stem cell driven by the fusion protein Bcr-Abl
- It is estimated 8,450 people in the US will be diagnosed with CML in 2020, accounting for ~15% of new cases of leukemia
- In the US, CML is most frequently diagnosed in individuals between the ages 65 to 74 years

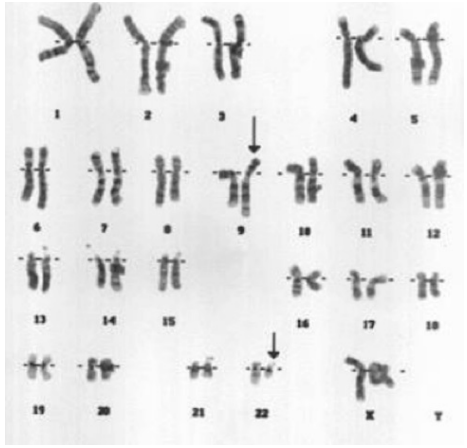
Huang X, et al. *Cancer*. 2012; 118:3123-3127.
Bower H, et al. *J Clin Oncol*. 2016;34:2851-2857
O'Hare T, et al. *Nat Rev Cancer.* 2012;12:513-526.
NCI. SEER Stat Fact Sheets: Chronic Myeloid Leukemia (CML). https://seer.cancer.gov/statfacts/html/cmyl.html. Accessed July 1, 2020.

The Philadelphia story: Bcr-Abl, the hallmark and driver of CML

David Hungerford and Peter Nowell

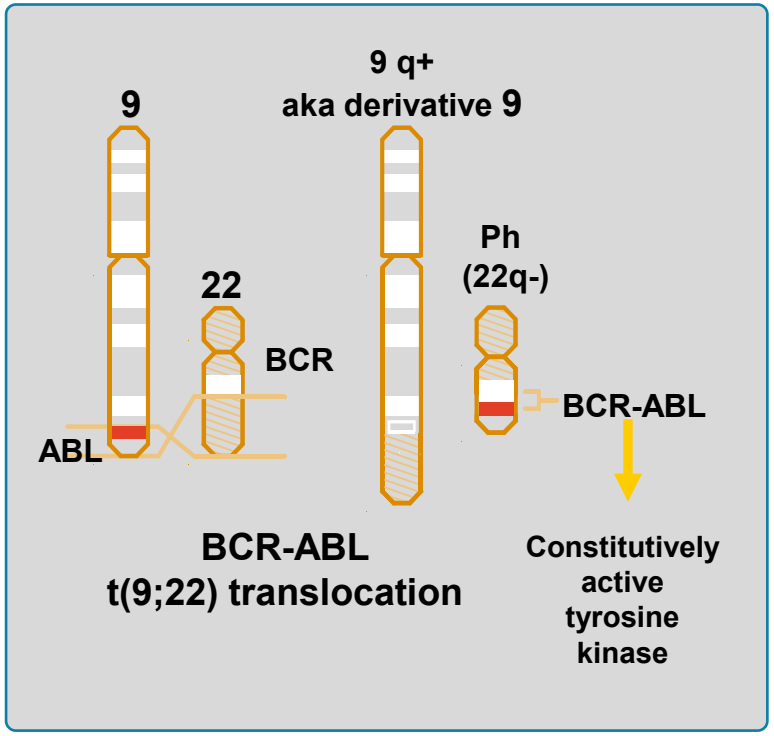


Janet Rowley

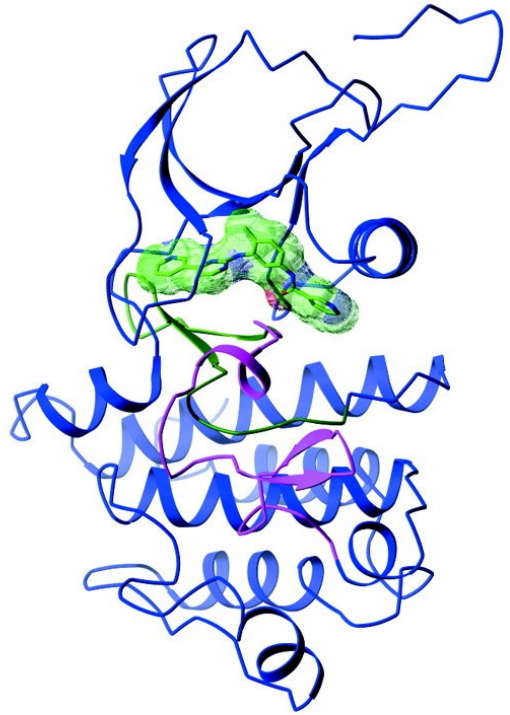


- The first chromosomal abnormality
- The first cytogenetic rearrangement

- The first targeted therapy



Crystal structure of the catalytic domain of Abl complexed to imatinib



Schindler et al. *Science*. 2000;289:1938-1942.

https://www.oncolink.org/cancers/leukemia/chronic-myelogenous-leukemia-cml/the-philadelphia-chromosome.
http://www.ohsu.edu/xd/health/services/cancer/about-us/druker/

First-line TKI selection

Learning objectives

1. Identify disease-specific risk factors at chronic phase chronic myeloid leukemia (CP CML) diagnosis that influence first-line tyrosine kinase inhibitor (TKI) selection

2. Examine how first-line TKI selection impacts outcomes

3. Delineate patient comorbidities that impact first-line TKI selection

CML treatment choices in 2020

Compound	TKI Generation	First Line	Second Line	Third Line
Imatinib	First	●		
Dasatinib	Second	●	●	●
Nilotinib	Second	●	●	●
Bosutinib	Second	●	●	●
Ponatinib	Third		● (T315I)	● (T315I or “for whom no other tyrosine kinase inhibitor therapy is indicated”)
Omacetaxine	NA			●

Selecting first-line therapy: NCCN 3.2021

Risk stratify: Sokal, Hasford, and EUTOS long-term survival (ELTS) scores

Chronic phase CML

Low-risk score →

Imatinib or generic imatinib 400 mg QD or
Bosutinib 400 mg QD or
Dasatinib 100 mg QD or
Nilotinib 300 mg BID

Intermediate- or high-risk score →

Preferred regimens*
Bosutinib 400 mg QD or
Dasatinib 100 mg QD or
Nilotinib 300 mg BID

Other recommended regimen**
Imatinib or generic imatinib 400 mg QD

* Based on follow-up data from the BFORE, DASISION and ENESTnd trials, **second-generation TKIs** (bosutinib, dasatinib, or nilotinib) **are preferred for patients with an intermediate- or high-risk score** especially for young women whose goal is to achieve a deep and rapid molecular response and eventual drug discontinuation of TKI therapy for family planning purposes

** **Imatinib may be preferred** for older patients with **comorbidities** such as cardiovascular disease

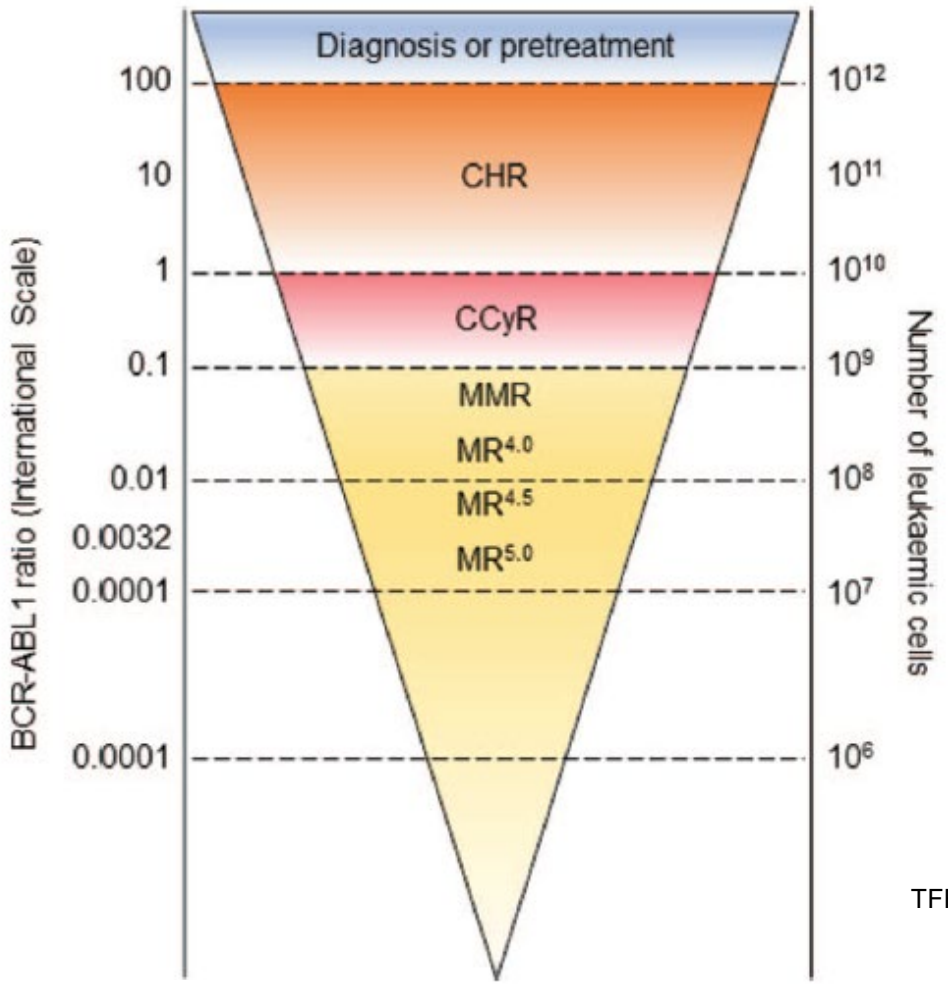
Clinical trial, if available can be considered for all patients

Treatment goals and molecular response milestones in CML

***BCR-ABL1* ≤10%** →

***BCR-ABL1* ≤1%** →

***BCR-ABL1* ≤0.1%** →



Levels of responses to TKI therapy

Response levels required for treatment-free remission

Deep molecular responses

← ***BCR-ABL1* ≤0.01%: MR4**

← ***BCR-ABL1* ≤0.0032%: MR4.5**

← ***BCR-ABL1* ≤0.001%: MR5**

Optimal responses for progression-free survival and near normal life expectancy

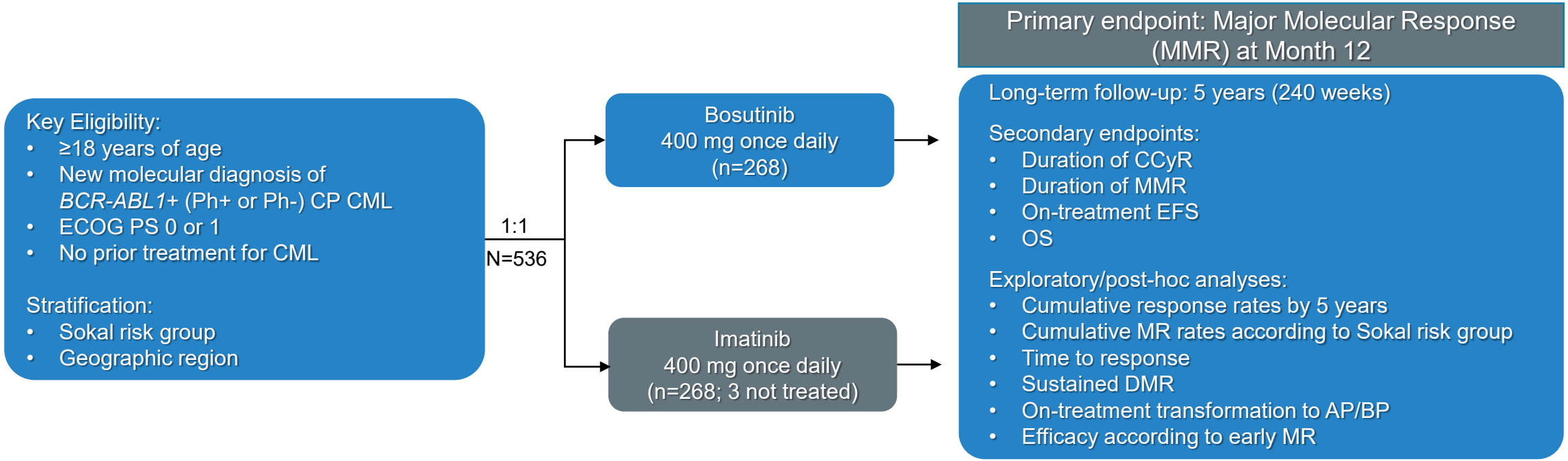
TFR: treatment-free remission

Adapted from:
Deininger MW. Hematology 2015 (ASH). 257-263
Rea D. ASH Education Session, CML, 2020.

Deininger MW, et al. JNCCN 2020; 18: 1385-1415
Hochhaus A, et al. Leukemia 2020; 34(4): 966-984.
Branford S, et al. Haematologica 202; 105(12):2730-2737.

Bosutinib: BFORE Study Design

BFORE (NCT02130557) an open-label, randomized, multicenter, phase 3 trial



- This analysis evaluated efficacy in the ITT population (all randomized patients), with the exception of cytogenetic endpoints which were evaluated in the modified ITT population (Ph+ patients with e13a2/e14a2 transcripts)

This final analysis was based on a last patient last visit of April 17, 2020 (June 12, 2020 database lock), 5 years after the last enrolled patient.

AP=accelerated phase; BP=blast phase; CCyR=complete cytogenetic response; DMR=deep molecular response; ECOG PS=Eastern Cooperative Oncology Group performance status; EFS=event free survival; MMR=major molecular response; MR=molecular response; OS=overall survival

Brümmendorf TH et al. ASH Annual Meeting Abstracts. 2020. Abstract 46.

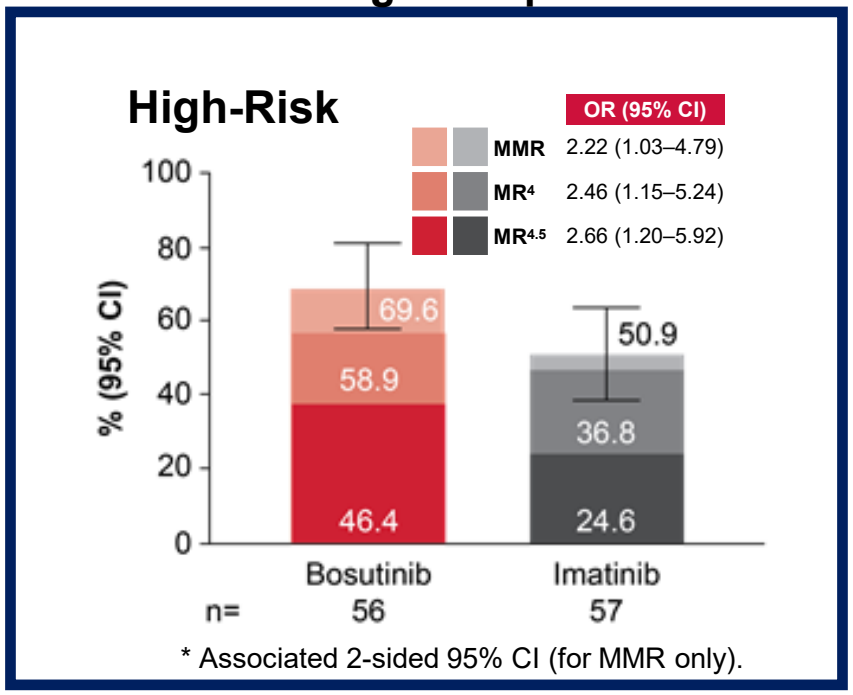
Cumulative Molecular Response

Cumulative response rates by 60 months, % (95% CI)*	Bosutinib n=268	Imatinib n=268	OR (95% CI)
MMR	73.9 (68.6–79.1)	64.6 (58.8–70.3)	1.57 (1.08–2.28)
MR^4	58.2 (52.3–64.1)	48.1 (42.2–54.1)	1.50 (1.07–2.12)
$MR^{4.5}$	47.4 (41.4–53.4)	36.6 (30.8–42.3)	1.57 (1.11–2.22)

Bosutinib updates: low risk for AOE

Abstract 3076. Cortes JE et al. Long-Term Cardiac, Vascular, and Hypertension Safety of Bosutinib (BOS) Versus Imatinib (IMA) for Newly Diagnosed Chronic Myeloid Leukemia (CML): Results from the Bfore Trial.

The greatest improvement in MR with bosutinib (vs imatinib) was observed in Sokal high-risk patients



* Associated 2-sided 95% CI (for MMR only).

Brümmendorf TH et al. ASH Annual Meeting Abstracts. 2020. Abstract 46.

CML treatment goals discussion

1. Life expectancy not impacted by CML: higher-risk CML → **Sokal Score: high risk (>1.2)**
2. Limit impact of TKI therapy on comorbidity outcomes → **• Diabetes mellitus, pulmonary disease, cardiovascular disease? • 10-year atherosclerotic cardiovascular disease risk (ASCVD score)?**
3. Quality of life and minimizing adverse events → **Gastrointestinal issues, pancreatitis, history of chronic active hepatitis B?**
4. Treatment-free remission → **Strong desire to attempt to stop TKI therapy?**
5. Limiting costs → **Always a consideration**
6. Family planning

Oehler VG. Hematology Am Soc Hematol Educ Program (2020) 2020 (1): 228–236.

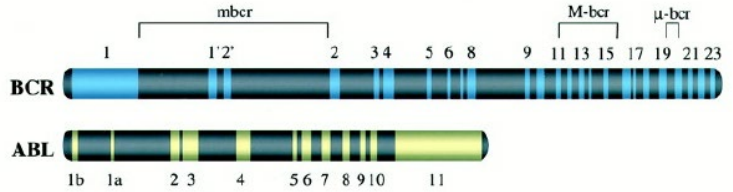
Identifying higher risk CP CML patients at diagnosis: prognostic markers

Prognostic

- Clinical risk scores
- p190-associated transcript e1a2 is associated with poorer outcomes
- p210-associated transcript e13a2 vs. e14a2?
  - *e13a2 transcripts reported to have a lower rate of deep molecular responses on imatinib and nilotinib*

Likely Not Prognostic

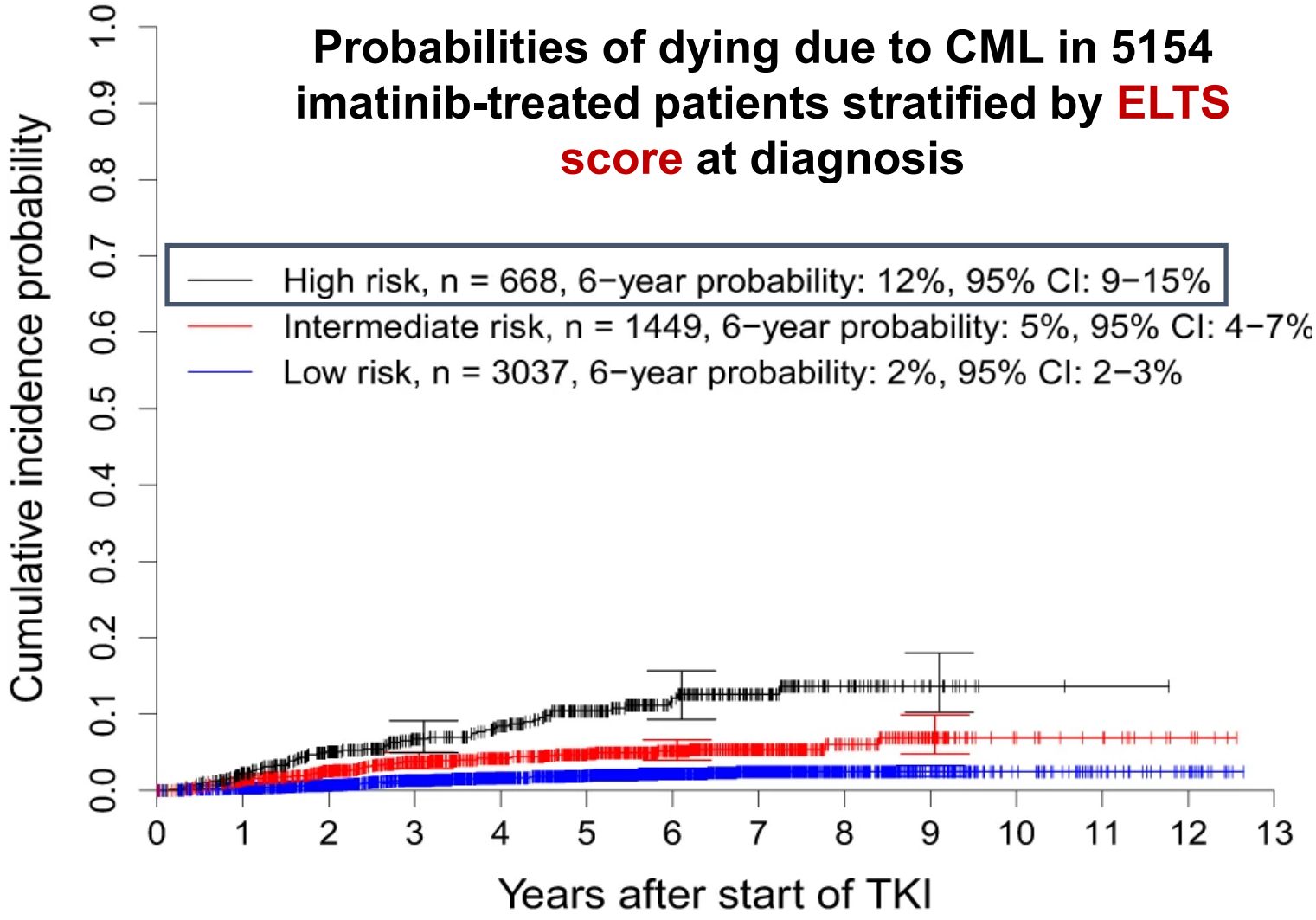
- Deletion derivative 9 chromosome
- Most variant translocations- (e.g. 3-way)
- Other transcript variants?



Jain P et a. Blood 2016 127:1269-1275
Genthon A et al. Oncotarget. 2020;11(26):2560-2570.
Quintas-Cardama A et al. Cancer. 2011; 117: 5085
Castagnetti F et al. J Clin Oncol. 2010; 28(16): 2748
Testoni N et al. Blood. 2011; 117: 6793
Verma D et al. Blood. 2009; 114: 2232
Laurent E et al. Cancer Res 2001;61:2343-2355

Eutos Long-term Survival Score

Probabilities of dying due to CML in 5154 imatinib-treated patients stratified by ELTS score at diagnosis



Can we better identify patients at risk for death due to CML?

EUTOS Long-term survival Score (ELTS):

$$0.0025 \times (\text{age in completed years}/10)^{3} + 0.0615 \times \text{spleen size below costal margin} + 0.1052 \times \text{blasts in peripheral blood} + 0.4104 \times (\text{platelet count}/1000)^{-0.5}$$

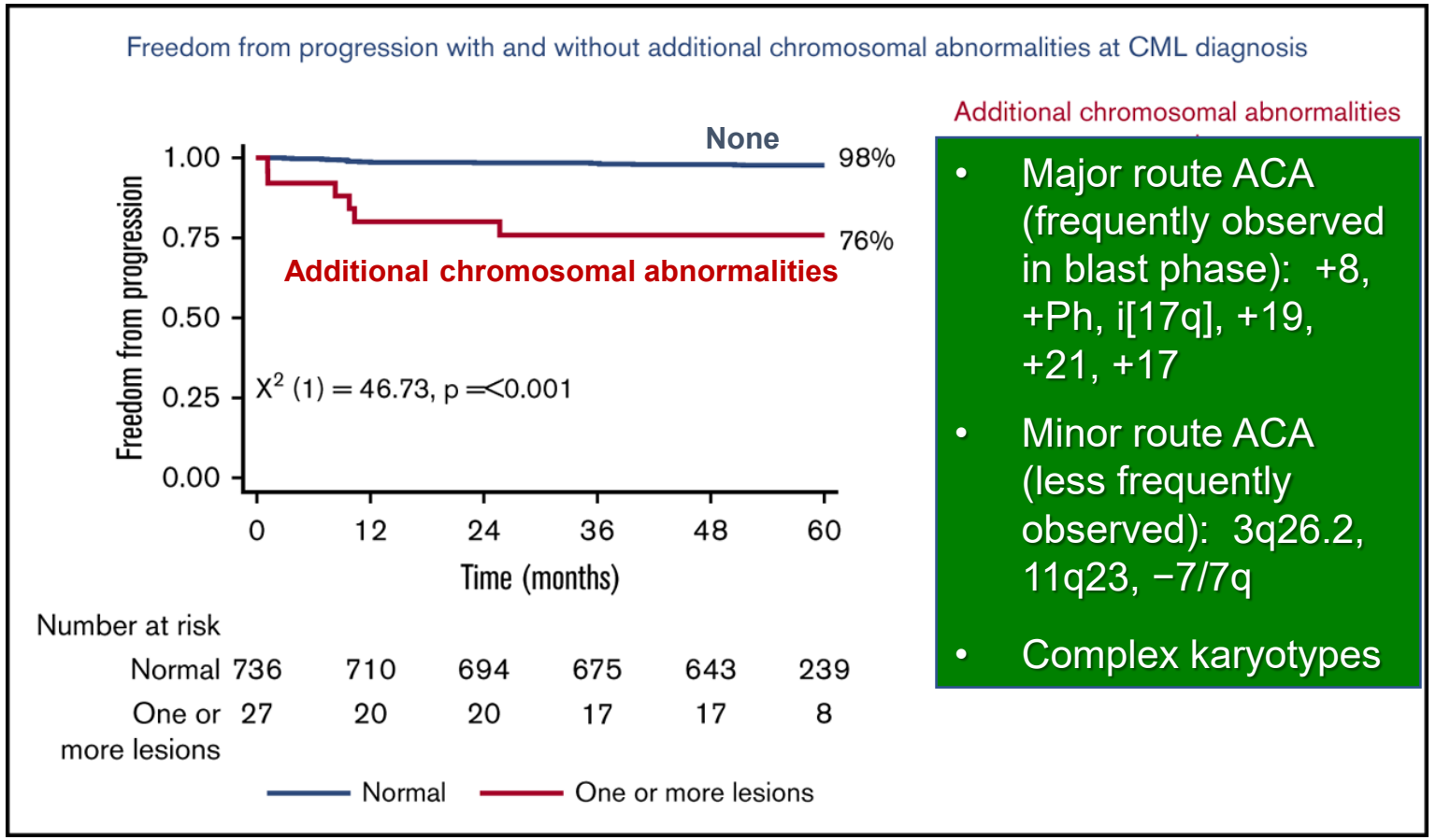
1. Better at identifying patients at risk for dying of CML
2. Classifies fewer patients as high-risk

Pfirrmann M et al. Leukemia. 2020 34: 2138–2149

ACAs at CML Diagnosis Predict an Increased Risk of Progression

Why diagnostic bone marrow metaphase karyotype is important at CML diagnosis

1. SPIRIT2 trial comparing imatinib 400 mg daily with dasatinib 100 mg daily
2. 27/763 (3.5%) with ACA
3. No association was seen between the Sokal or European Treatment and Outcome Study long-term survival (ELTS) scores and the presence of ACAs



Additional chromosomal abnormalities

- Major route ACA (frequently observed in blast phase): +8, +Ph, i[17q], +19, +21, +17
- Minor route ACA (less frequently observed): 3q26.2, 11q23, −7/7q
- Complex karyotypes

Technically, ACAs are a feature of accelerated phase CML

Image used with permission from Clark RE et al. Blood Adv (2021) 5 (4): 1102–1109.

First-line 2nd generation TKI: fewer cases of progression to AP or BP

ENESTnd 5-year results

	Nilotinib 300 mg twice daily (n=282)	Nilotinib 400 mg twice daily (n=281)	Imatinib 400 mg once daily (n=283)
Progression to AP/BP on study, n	10	6	21
Estimated 5-year freedom from progression to AP/BP on study, % (95% CI)	96.3 (94.1-98.6)	97.8 (96.0-99.5)	92.1 (88.8-95.3)
HR vs imatinib (95% CI)	0.4636 (0.2183-0.9845)	0.2753 (0.1111-0.6821)	
P vs imatinib	0.0403	0.0028	

On study: on treatment or in follow-up after discontinuation of study treatment

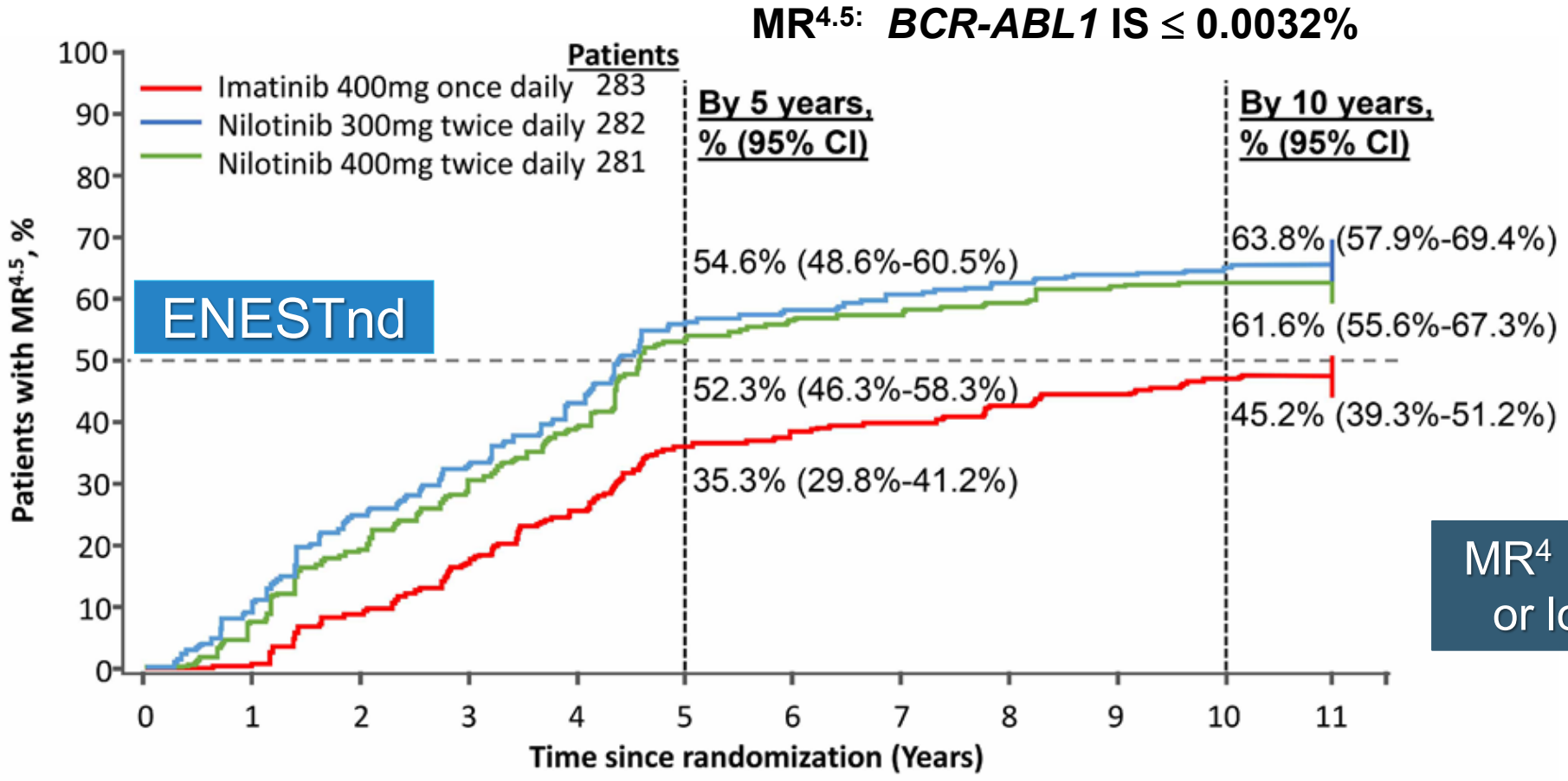
Sokal Score

ENESTnd Study Arms	Low-risk			Intermediate-risk			High-risk		
	Disease progression, n (%)	PFS	OS	Disease progression, n (%)	PFS	OS	Disease progression, n (%)	PFS	OS
Nilotinib 300 mg twice daily	1 (1%)	96.0%	97.0%	2(2%)	92.9%	93.8%	7 (9%)	86.2%	88.8%
Nilotinib 400 mg twice daily	1 (1%)	99.0%	99.0%	1(1%)	96.9%	96.9%	4 (5.1%)	90.0%	91.5%
Imatinib (400 mg)	0	100.0%	100.0%	10 (9.9%)	87.9%	88.5%	11 (14.1%)	82.6%	84.2%

Hochhaus A et al. Leukemia (2016) 30, 1044-1054.

National Comprehensive Cancer Network (NCCN). Chronic myeloid leukemia,version 1.2021. Posted August 28, 2020 at https://www.nccn.org/professionals/physician_gls/default.aspx.

First-line 2nd generation TKI: higher cumulative incidence of $MR^{4.5}$



MR^4 (*BCR-ABL1* IS ≤ 0.01%) or lower NEEDED for TFR

[a] Cumulative $MR^{4.5}$ results were analyzed by combining all data from the core and extension studies; results were ascribed to each patient's assigned core study treatment arm.

Hughes TP et. *Blood*. 2019. Blood (2019) 134 (Supplement_1): 2924.

NCCN Guidelines Version 3.2021: Early treatment response milestones

	3 months		6 months		12 months
>10%	NCCN Possible TKI Resistance		NCCN TKI-resistant		NCCN TKI-resistant
>1% - 10%	NCCN TKI sensitive		NCCN TKI sensitive		NCCN Possible TKI Resistance
>0.1 - 1%	NCCN TKI sensitive		NCCN TKI sensitive		*NCCN TKI sensitive**
≤ 0.1%	NCCN TKI sensitive		NCCN TKI sensitive		NCCN TKI sensitive

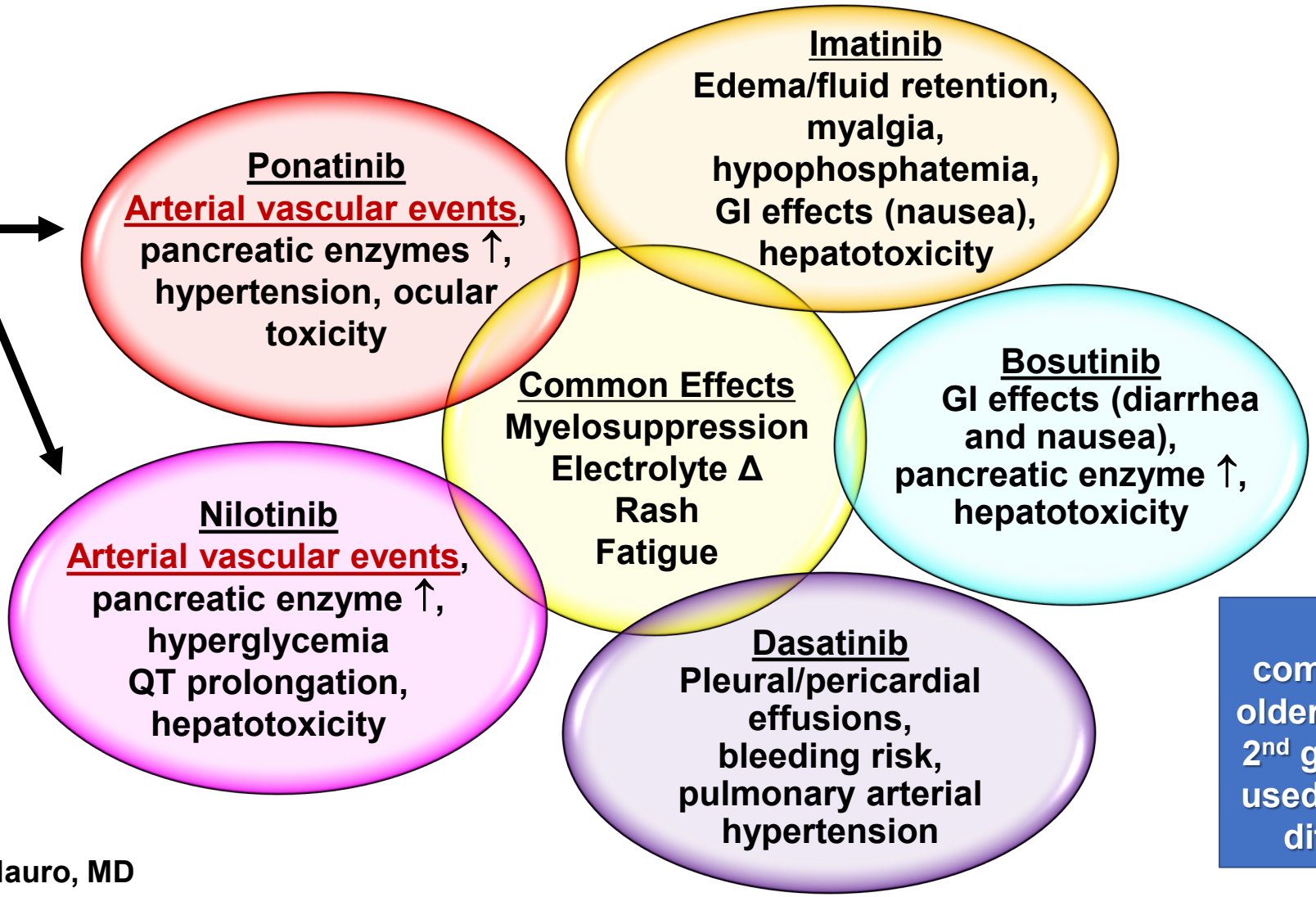
COLOR	CONCERN	CLINICAL CONSIDERATIONS	SECOND-LINE TREATMENT
RED	TKI-resistant disease	• Evaluate patient compliance and drug interactions • Consider mutational analysis	Switch to alternate TKI and evaluate for allogeneic HCT
YELLOW	Possible TKI resistance	• Evaluate patient compliance and drug interactions • Consider mutational analysis • Consider bone marrow cytogenetic analysis to assess for MCyR at 3 mo or CCyR at 12 mo	Switch to alternate TKI or Continue same TKI (other than imatinib) 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*
GREEN	TKI-sensitive disease	• Monitor response and side effects	Continue same TKI

Common and unique toxicities of TKIs in CML

Cardiac and arterial vascular occlusive events

Requires close follow-up

1. Blood pressure
2. Fasting lipid panel
3. Hemoglobin A1c



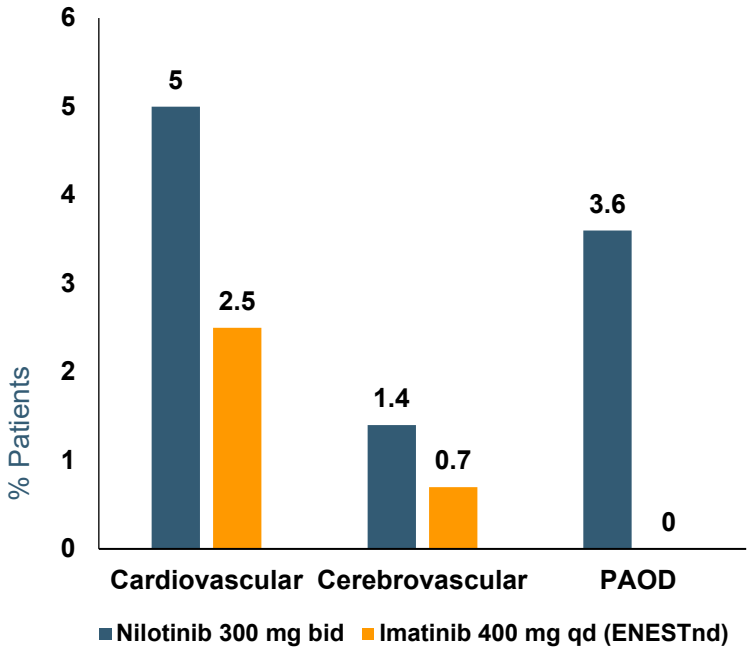
Medical comorbidities and older age may make 2nd generation TKIs used first-line more difficult to use

Adapted from Dr. Michael J. Mauro, MD

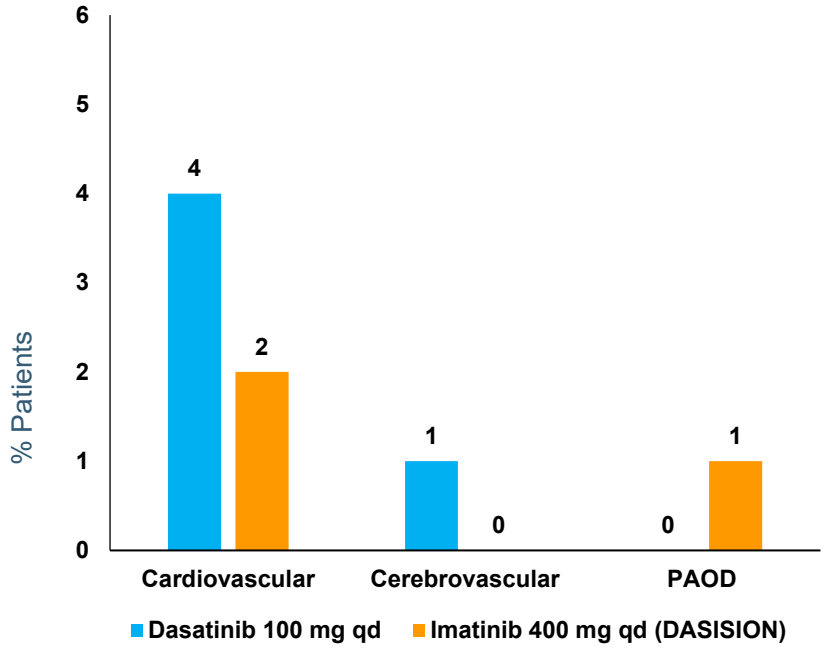
Cortes JE, et al. *J Clin Oncol*. 2012;30(28):3486-3492
Kantarjian H, et al. *J Clin Oncol*. 2014;32(5 suppl):abstr 7081.
Saglio G, et al. *N Engl J Med*. 2010;362(24):2251-2259
Kantarjian H, et al. *N Engl J Med*. 2010;362(24):2260-2270

Ischemic Events by TKI From Randomized Trials

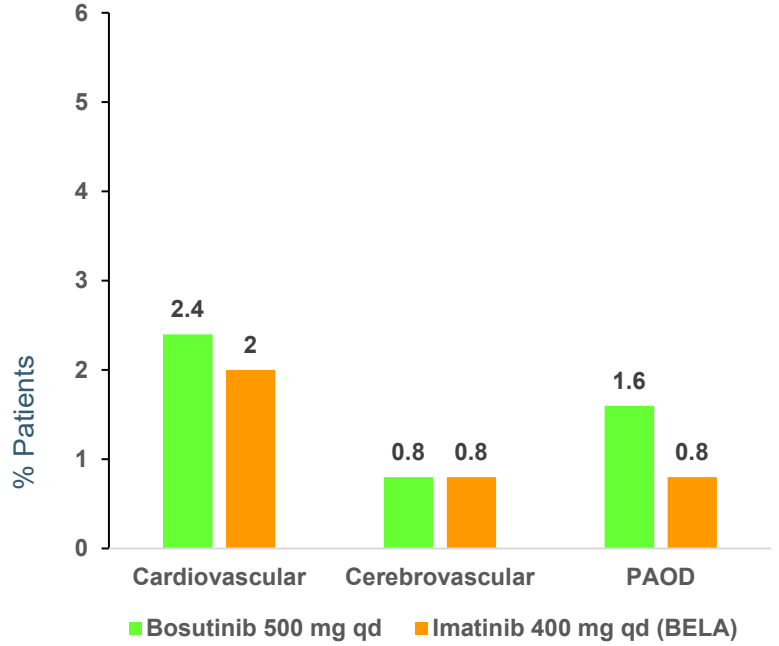
ENESTnd[1]



DASISION[2]



BELA[3*]



* Median exposure 55 months (0.03-69.4)

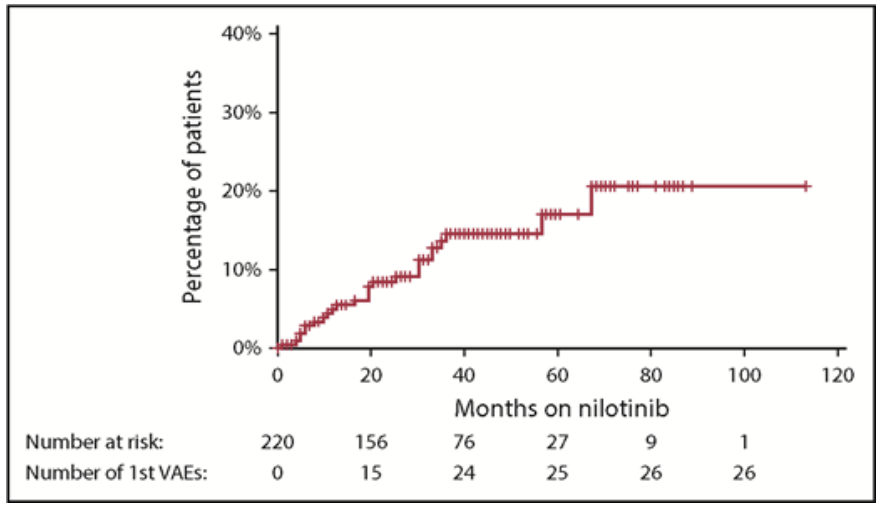
[1]Hochhaus et al. Leukemia 2016; 30: 1044-54;
[2]Cortes et al. JCO 2016; 34: 2333-40;
[3] Cortes JE, et al. Am J Hematol. 2016;91(6):606-616

Continued risk for arterial vascular adverse events over time on nilotinib in CP CML patients

Therapy line	N (%)
First	76 (35%)
Second	112 (51%)
Third	32 (14%)

220 patients treated with nilotinib for chronic myeloid leukaemia in chronic phase at 17 Australian institutions

Cumulative incidence of first VAE



26 patients with first arterial vascular event

- Events more common in older patients
- Smoking history and dyslipidemia are independent risk factors for events
- High rate of recurrence if nilotinib continued after an event even with appropriate management

Minson AG et al. Blood Adv. 2019 Apr 9; 3(7): 1084–1091.

Risks of 2nd generation TKI use: pleural effusions with dasatinib - increasing incidence with age

- DASISION and 034/Dose-optimization randomized studies and a pooled population of 11 trials
  - N= 2712

- Annual risk of pleural effusion ~5-15%
  - **Continued risk over time**
  - At 5 years DASISION: pleural effusion in 28%
  - At 7 years 034/Dose-optimization: 33%

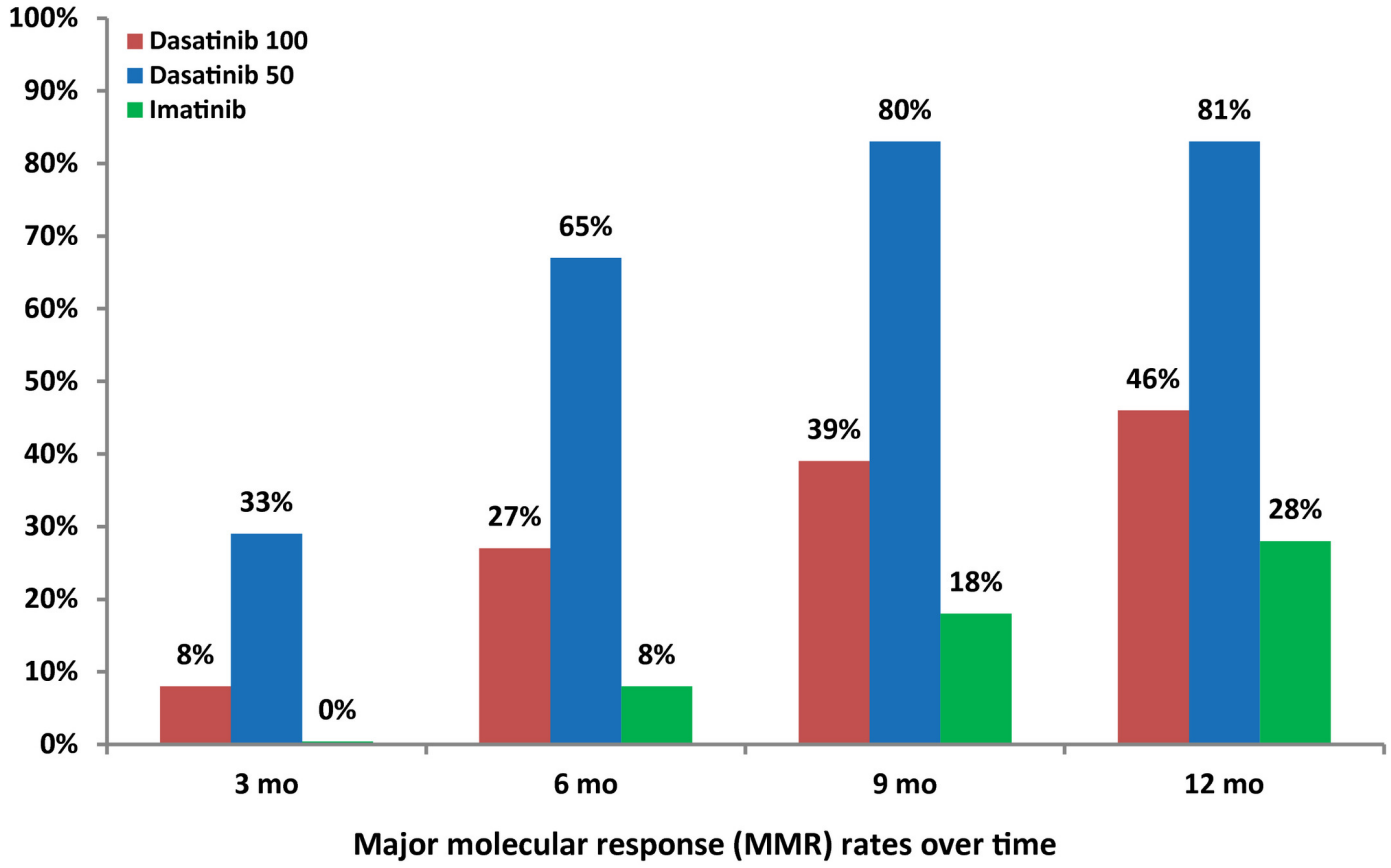
- AGE is the main risk factor
  - *Up to 50% of patients > 60 may develop pleural effusion on doses of 100 mg or higher*
  - *Consider starting patients > 60 years on lower doses*

Porkka K et al. Cancer. 2010 Jan 15;116(2): 377-86
Hughes TP et al. Haematologica. 2019 Jan;104(1):93-101.

Starting lower dose first-line

- Pilot study MD Anderson of newly diagnosed CP CML
- 96% achieved early molecular response at 3 months
- At 12 months
  - 81% MMR
  - 59% MR4
- Mechanism: perhaps safety profile of lower dose dasatinib with fewer treatment interruptions and more continuous dosing
- DASISION study:
  - pleural effusion in up to 28% of the patients
- Low-dose dasatinib:
  - pleural effusion occurred in 6% of patients

N=81
Dose: 50 mg orally daily
Minimum f/u: 12 months



Naqvi K et al. Cancer. 2020 Jan 1;126(1):67-75..

Increased risk for pulmonary arterial hypertension on dasatinib

- 41 cases of PAH confirmed by right heart catheterization
- No clear relationship with dasatinib dose
- Occurred anywhere from < 1 month to 7 years
- 68% presented with synchronous pleural effusion
- 36 cases with follow-up demonstrated that most improved or resolved off therapy (N=34, 94%)

Shah et al. Am J Hematol. 2015 Nov;90(11):1060-4

TKI Selection Based on Selected Co-Morbidities and Risks

History with prior TKI or co-morbidity	Preferred	Less preferred
Diabetes	Dasatinib, Bosutinib	Nilotinib
Pulmonary disease/PAH	Bosutinib, Nilotinib	Dasatinib
GI Issues	Nilotinib, Dasatinib	Bosutinib
Cardiovascular	Bosutinib	Nilotinib, Dasatinib
Peripheral arterial	Bosutinib (Dasatinib?)	Nilotinib
Liver	Dasatinib (Nilotinib?)	Bosutinib
Renal	Nilotinib, Dasatinib	Bosutinib

Cortes J. Blood. 2020 Nov 26;136(22):2507-2512.

Considerations when selecting 1st line therapy

Goals:	**Tyrosine kinase inhibitor:**
1. Life expectancy not impacted by CML: higher-risk CML	1. **2nd generation TKI,** imatinib
2. Limit impact of TKI therapy on comorbidity outcomes	2. **Imatinib,** 2nd generation TKI
3. Quality of life and minimizing adverse events	3. Imatinib, 2nd generation TKI
4. Treatment-free remission	4. **2nd generation TKI,** imatinib
5. Limiting costs	5. **Imatinib**
6. Family planning	6. **2nd generation TKI,** imatinib

- Imatinib is generic and has an excellent safety profile
  - Imatinib-treated patients can achieve deep molecular responses even those with higher risk disease and a switch strategy, if needed, is feasible
  - However, for some high-risk patients a window may be lost with less potent therapy

Oehler VG. Hematology Am Soc Hematol Educ Program (2020) 2020 (1): 228–236.

TKI discontinuation

Learning objectives

1. Identify factors that influence achievement of deep molecular responses (DMR) needed to consider TKI discontinuation

2. Identify factors that influence successful treatment-free remission

Anticipated benefits of treatment-free remission

Patient

- Resolution of TKI-related side effects
- Limit and/or prevent long-term toxicities
- Family planning
- Minimize/eliminate out-of-pocket medical expenses
- Feeling cured

Health care system

- Reduced financial burden of CML treatment

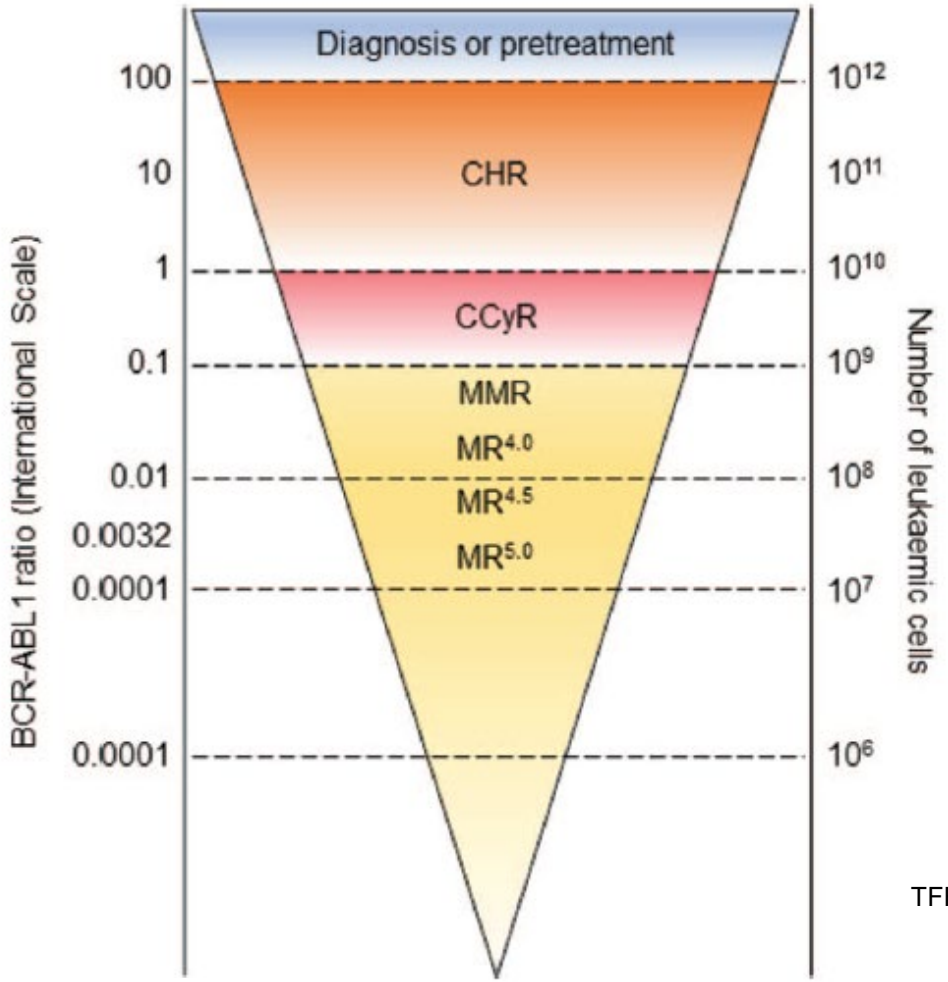
Rea D. Blood Adv (2020) 4 (21): 5589–5594.

Treatment goals and molecular response milestones in CML

***BCR-ABL1* ≤10%** →

***BCR-ABL1* ≤1%** →

***BCR-ABL1* ≤0.1%** →



Levels of responses to TKI therapy

Response levels required for treatment-free remission

Deep molecular responses

← ***BCR-ABL1* ≤0.01%: MR4**

← ***BCR-ABL1* ≤0.0032%: MR4.5**

← ***BCR-ABL1* ≤0.001%: MR5**

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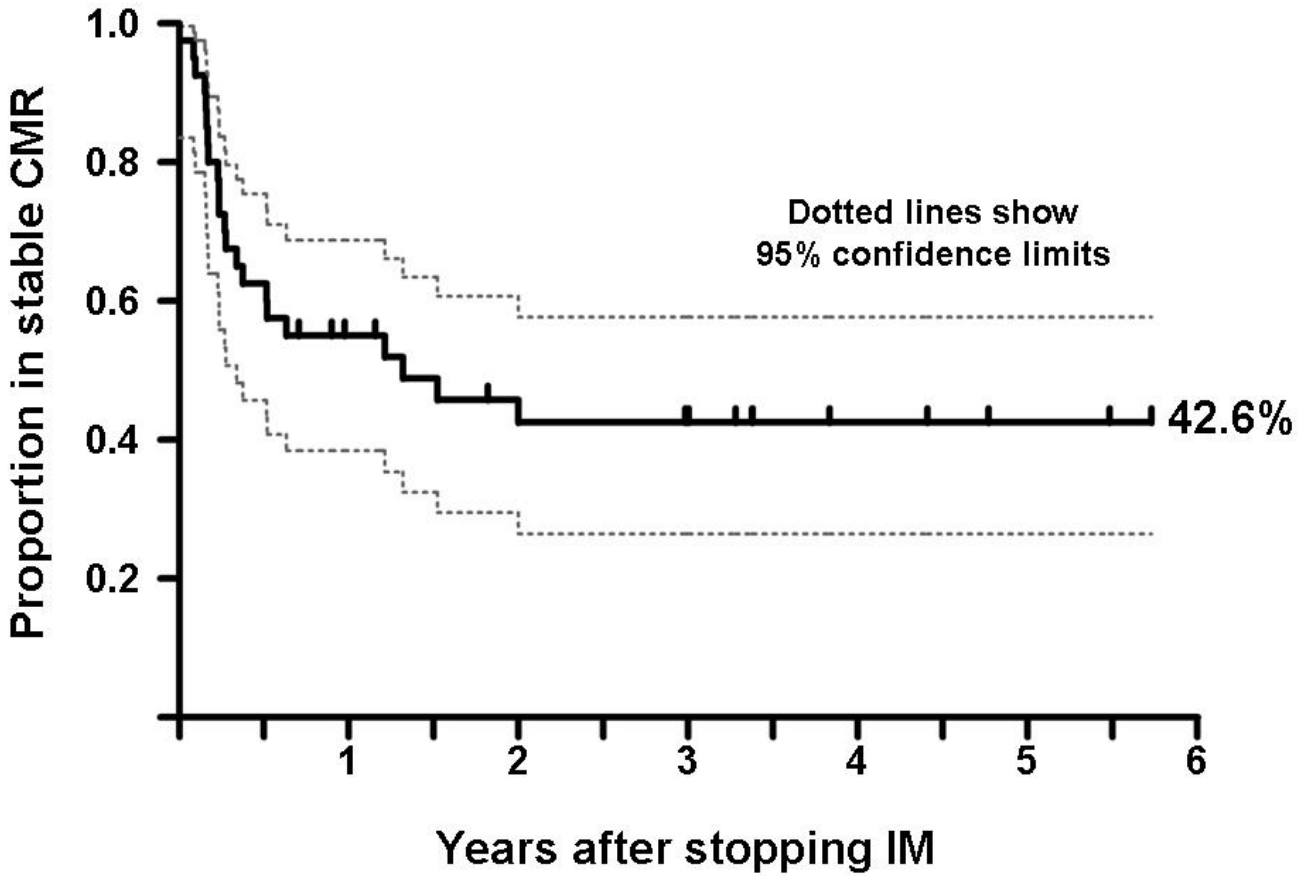
Branford S, et al. Haematologica 202; 105(12):2730-2737.

Stopping first-line imatinib therapy

Australian CML8 study (TWISTER)



N=40

Entry criteria: BCR-ABL1 IS ≤ 0.0032% (MR4.5 for two years or longer)

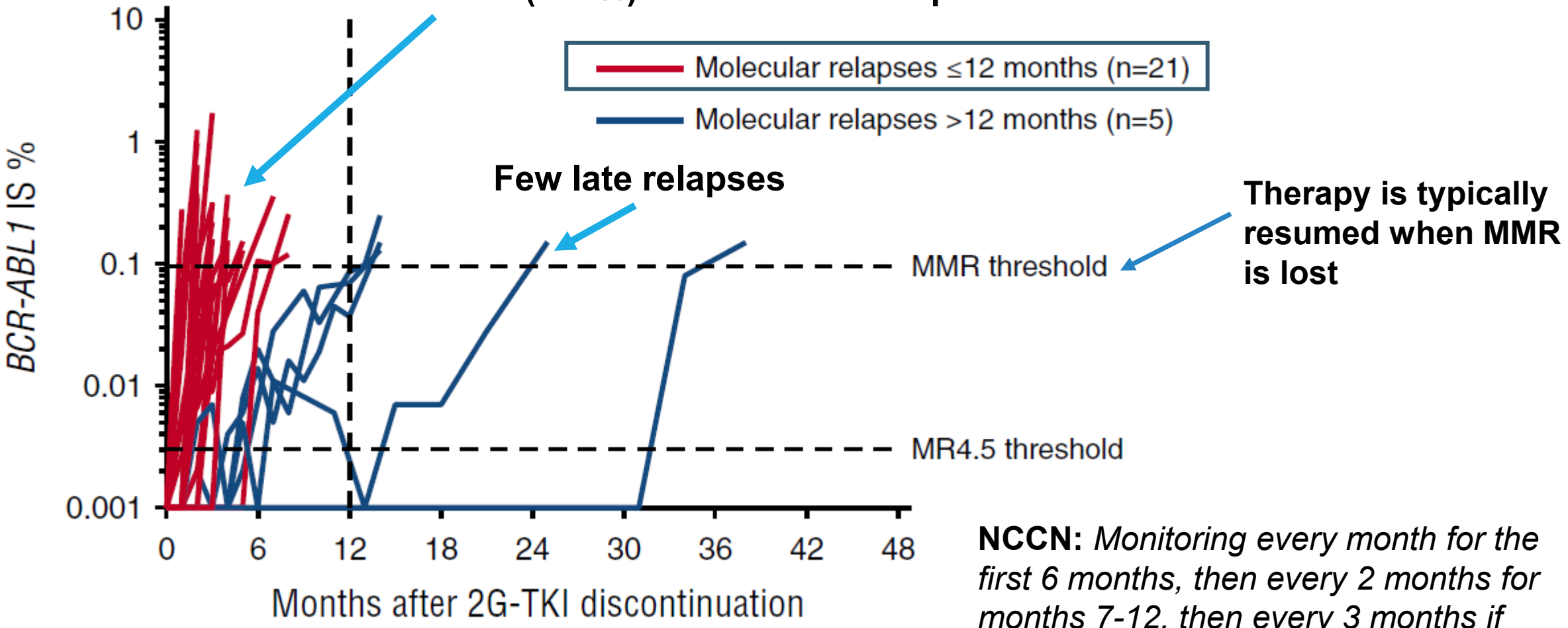
Success rates of TFR attempts in clinical trials range between 40 and 65%

- Earlier studies stopping imatinib: **STIM1, STIM2, TWISTER**
  - Very consistent TFR rate
  - Most patients restarting therapy achieved former responses

Ross DM et al. Blood. 2013 Jul 25;122(4):515-22.

Molecular relapse after discontinuation

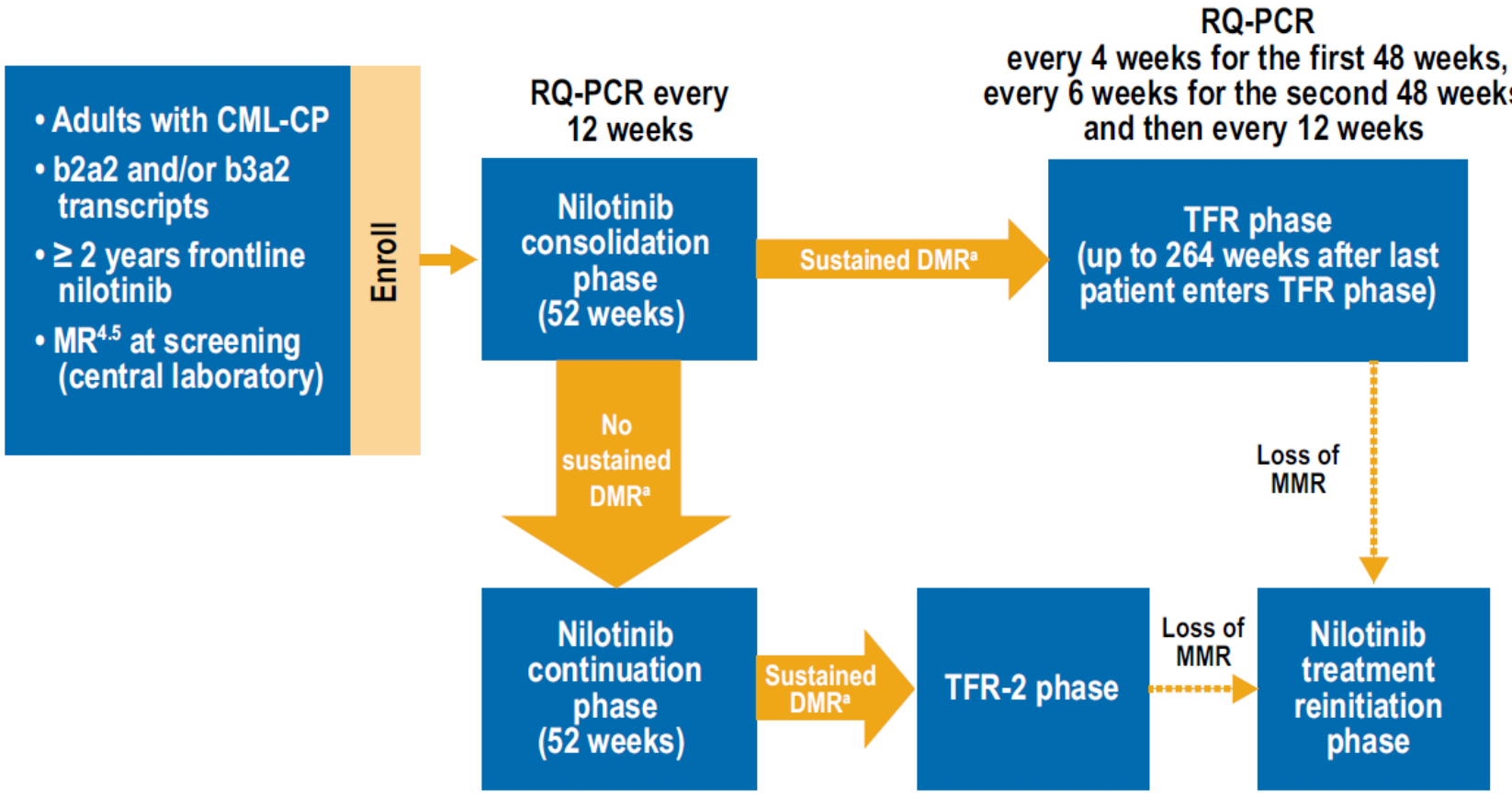
STOP 2G-TKI study



NCCN: *Monitoring every month for the first 6 months, then every 2 months for months 7-12, then every 3 months if MMR is maintained indefinitely*

Rea D et al. Blood. 2017; 129(7): 846-854.

ENESTfreedom: Stopping 1st-line nilotinib



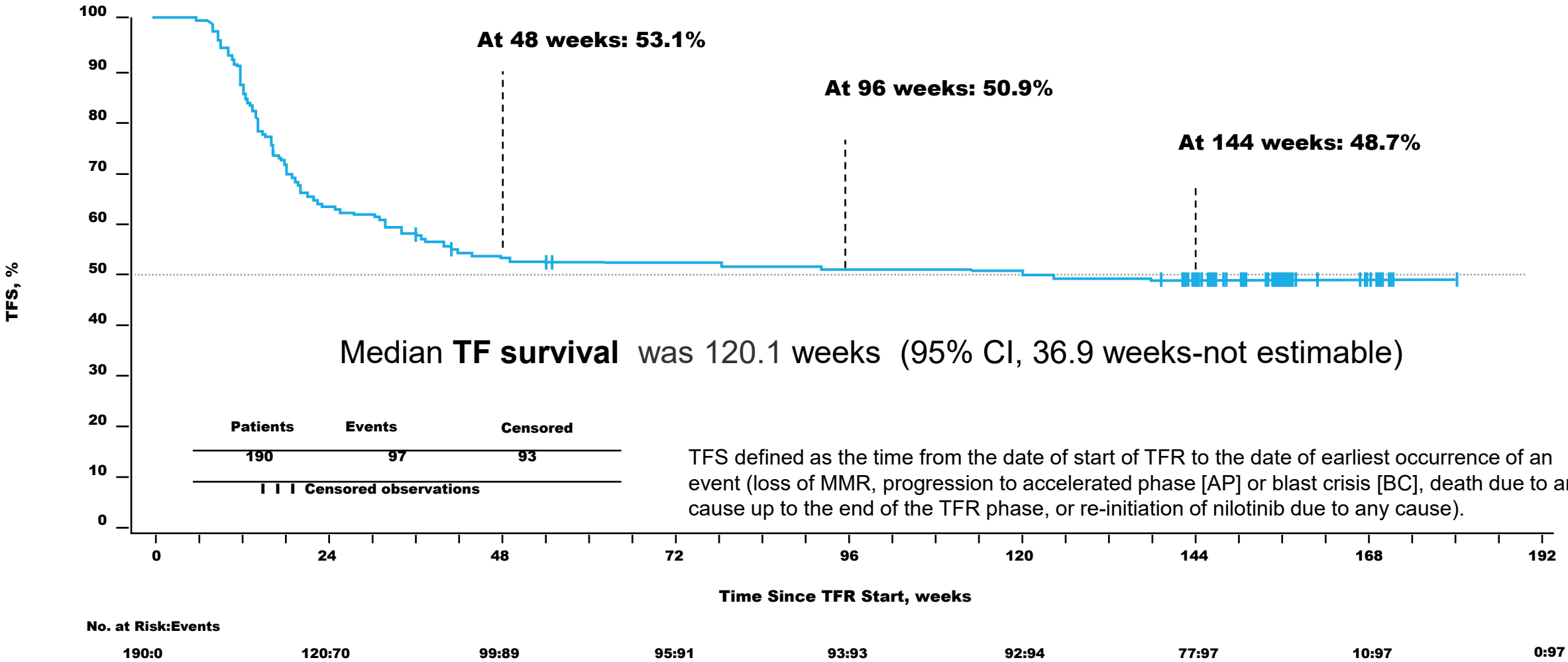
Nilotinib label update includes treatment discontinuation recommendations for CML with sustained molecular responses based on ENESTfreedom and ENESTop

1. Median total nilotinib duration prior to TFR phase was 43.5 months (range 32.9 – 88.7 months)
2. Median time from first MR4.5 to entering TFR phase was 30.4 months (range 12.3 – 83.0 months)

Sustained MR4.5 during a one-year consolidation

Ross DM et al. J Cancer Res Clin Oncol 2018 May;144(5):945-954

ENESTfreedom: Treatment-Free Survival[a]



Median **TF survival** was 120.1 weeks (95% CI, 36.9 weeks-not estimable)

TFS defined as the time from the date of start of TFR to the date of earliest occurrence of an event (loss of MMR, progression to accelerated phase [AP] or blast crisis [BC], death due to any cause up to the end of the TFR phase, or re-initiation of nilotinib due to any cause).

TFS, treatment-free survival.

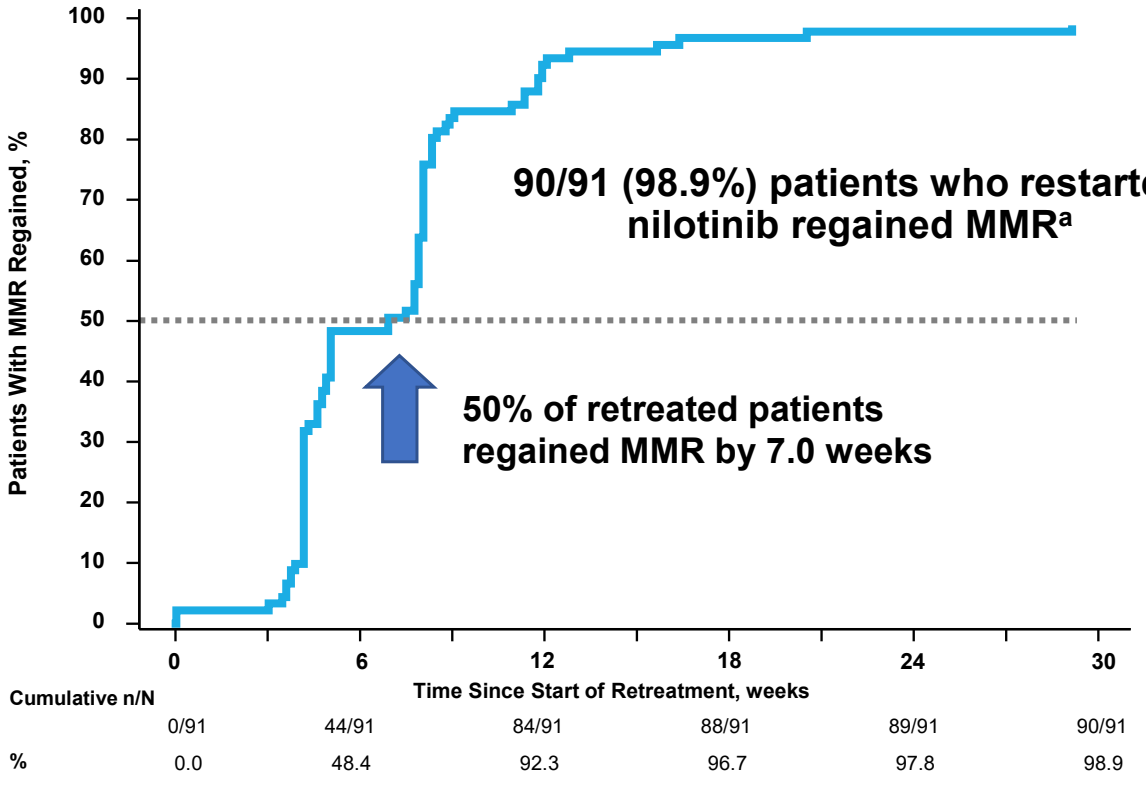
[a] TFS was estimated using the Kaplan-Meier method and was defined as the time from the date of start of TFR to the date of earliest occurrence of an event (loss of MMR, progression to accelerated phase [AP] or blast crisis [BC], death due to any cause up to the end of the TFR phase, or reinitiation of nilotinib due to any cause).

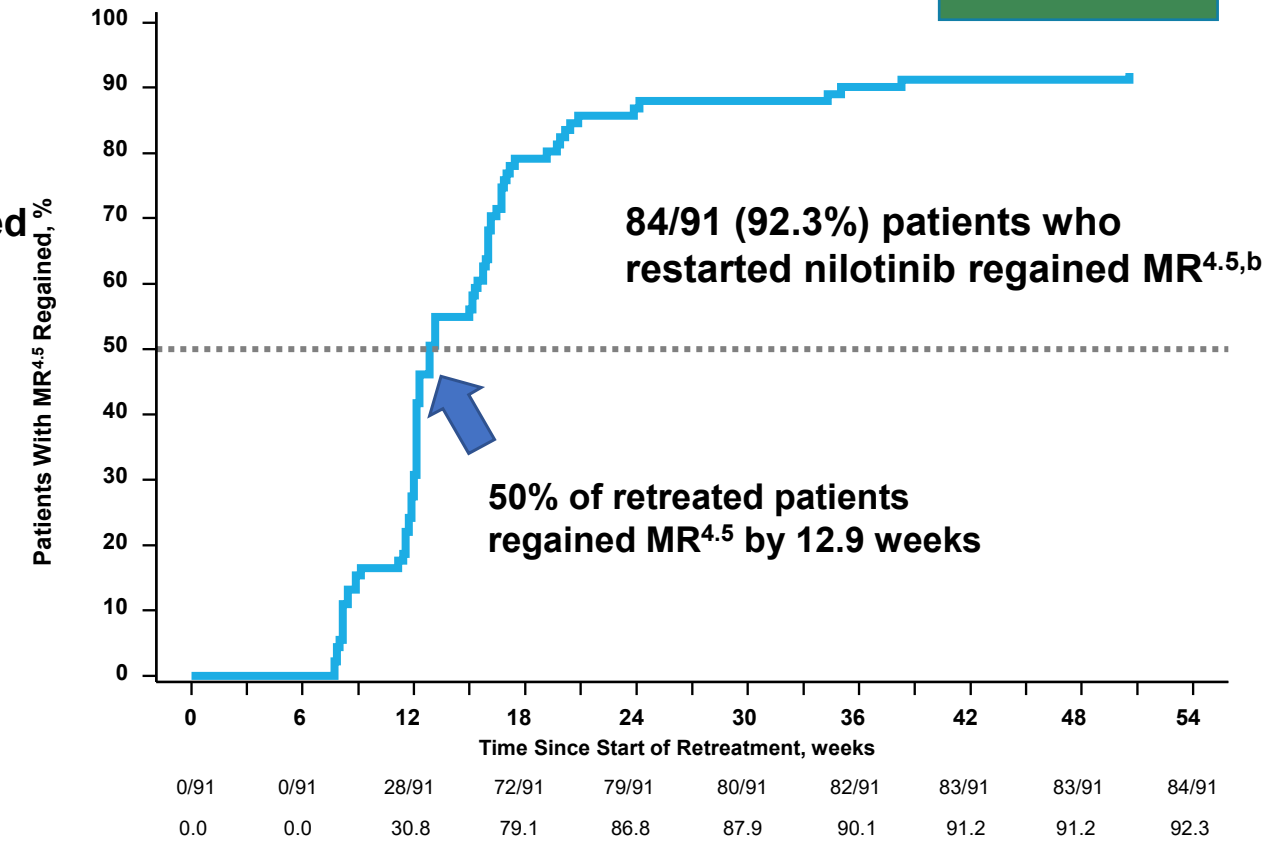
[b] Defined as no loss of MMR and no reinitiation of nilotinib in the first 48 weeks of TFR.

1. Hochhaus A, et al. *Leukemia*. 2017;31:1525-1531.

ENESTfreedom: Cumulative Rate of MMR and $MR^{4.5}$ Regained in Nilotinib Reinitiation Phase

DASFREE





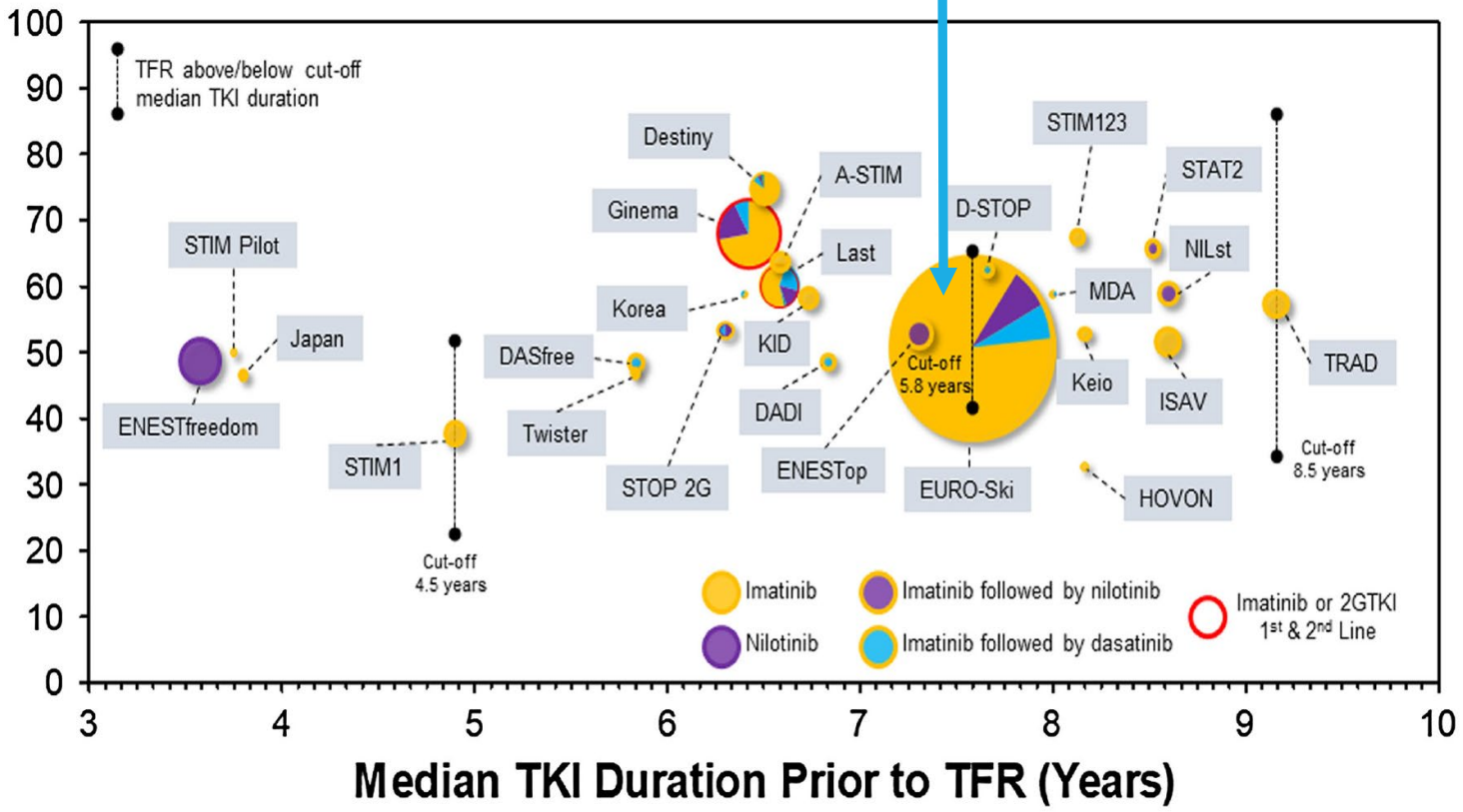
[a] 1 patient discontinued from the study after 7.1 weeks of retreatment without regaining MMR. [b] Of the 6 patients who regained MMR but not $MR^{4.5}$, 1 remained in the reinitiation phase at the data cutoff, and 5 had discontinued from the study (2 due to AEs, 1 due to physician decision, 1 due to patient decision, and 1 due to lack of efficacy [after regaining and then losing MMR; patient was found to have an F359V mutation[1]]).

1. Hochhaus A, et al. *Leukemia*. 2017;31:1525-1531.

Radich et al. Clinical Lymphoma, Myeloma, & Leukemia. 2018; 18(Supplement 1): S226
Shah NP et al . Leuk Lymphoma. 2019 Oct 24:1-10

Factors associated with successful TFR

Prospective EURO-SKI trial:
Imatinib discontinuation after at least 3 years of treatment and 1 year in MR4
Prespecified interim analysis



Positively associated with sustained TFR

- Longer duration of TKI use
- Longer duration of DMR

No impact on sustained TFR

- Depth of response when stopping TKI: MR 4.0 vs. MR4.5

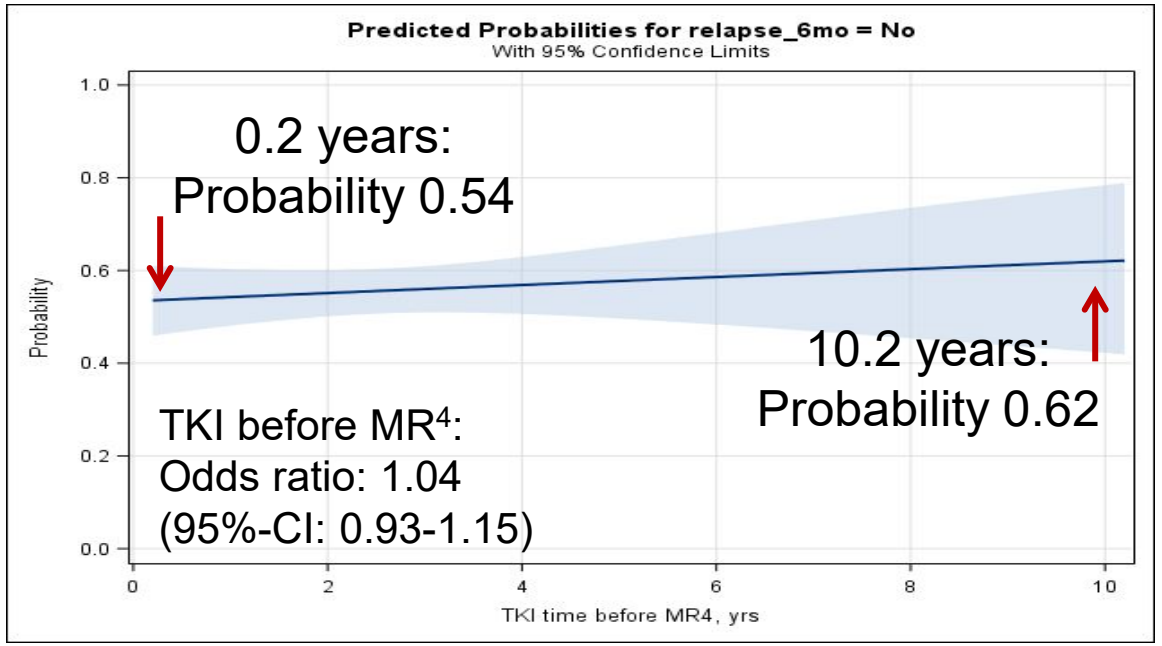
Size of dot indicates study size

Saussele et al. Lancet Oncol. 2018 Jun;19(6):747-757.
Laneuville P. Curr. Treat. Options in Oncol. (2018) 19: 15

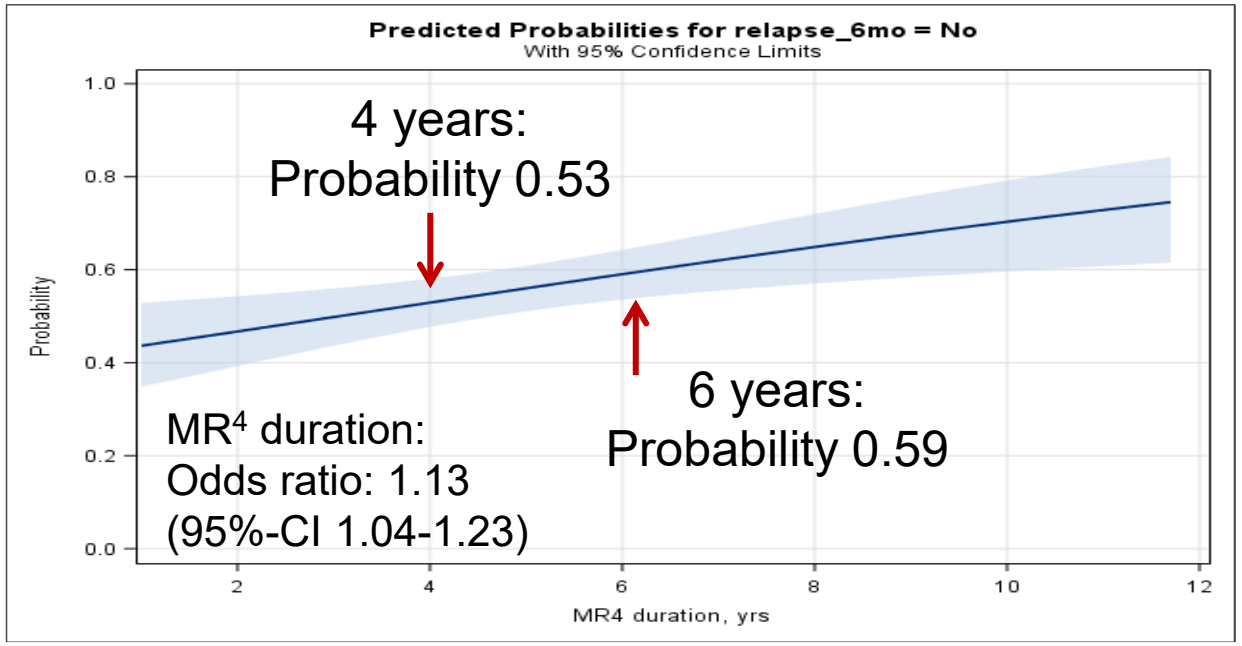
Deep molecular response on TKI is associated with sustained TFR

EURO-SKI trial: imatinib discontinuation after at least 3 years of treatment and 1 year in MR4

Imatinib duration *BEFORE* MR4



Imatinib duration *SINCE* MR4

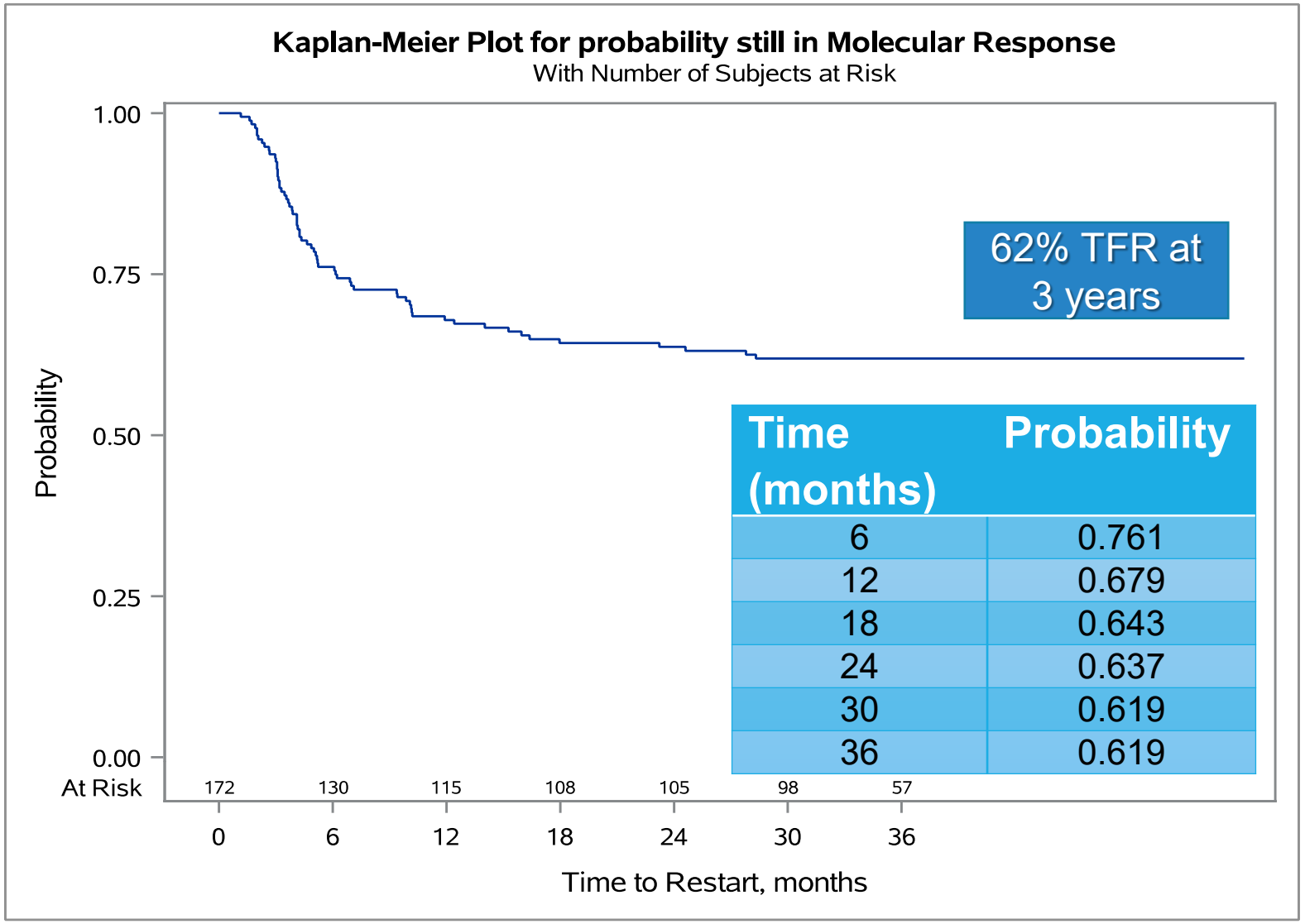


Each additional year in DMR leads to an absolute increase of 2-3% in molecular relapse-free survival

Figure adapted from Dr. Delphine Rea. 2020. ASH Education Session. Handling Challenging Questions in the Management of Chronic Myeloid Leukemia

Saussele S, et al. Blood (ASH) 2017.
Saussele S, et al. Lancet Oncol. 2018;19(6):747-757.

U.S. Life after Stopping TKIs (LAST): TFR at 3-years



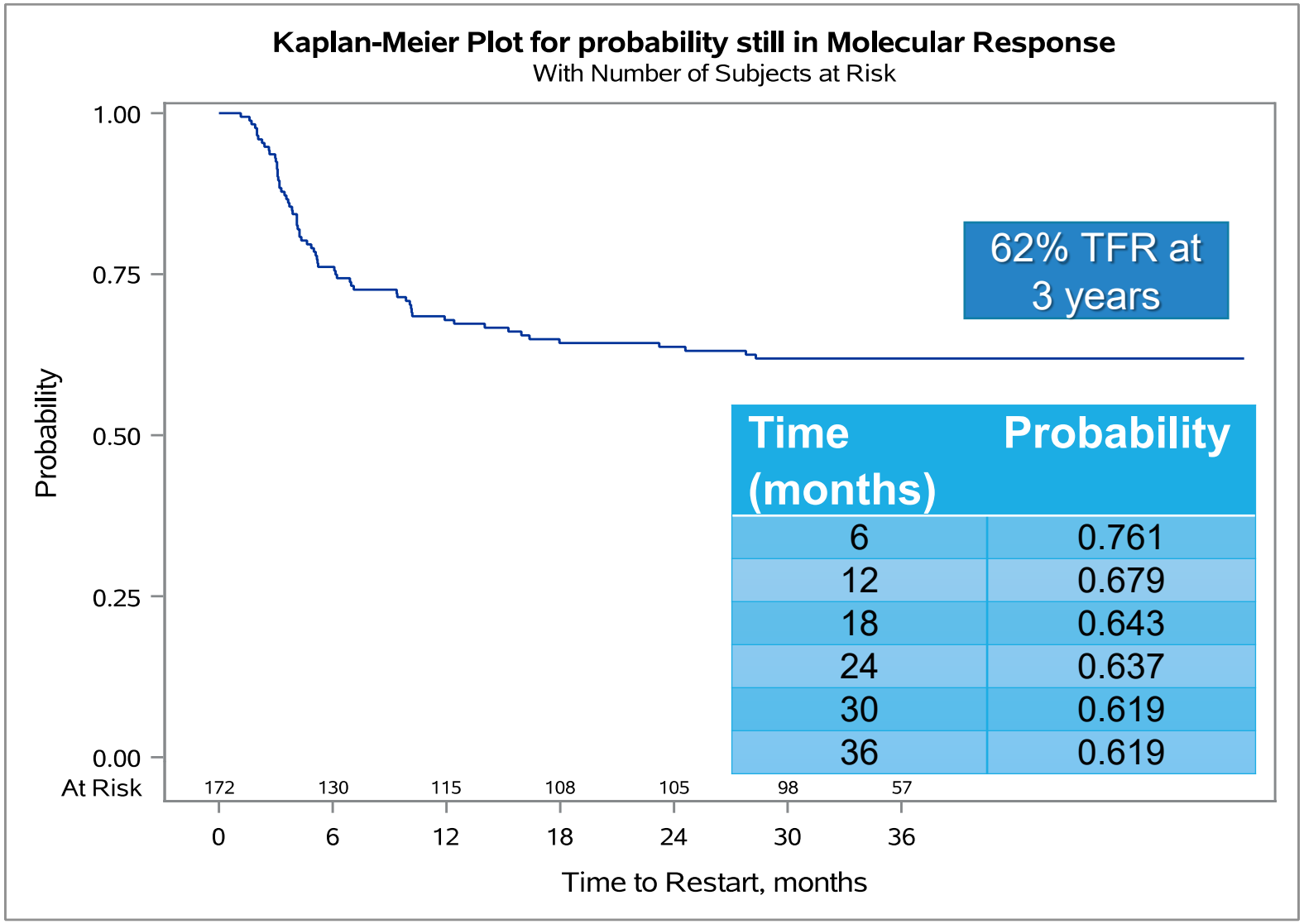
172 patients at 14 US sites

Key inclusion criteria

- ≥ 18 years
- On TKI therapy for 3+ years **including imatinib, dasatinib, bosutinib, and nilotinib**
- Well controlled; ≥ 2 years of documented *BCR-ABL1* < 0.01% by PCR
- No previous TKI resistance
- Switching for intolerance permitted

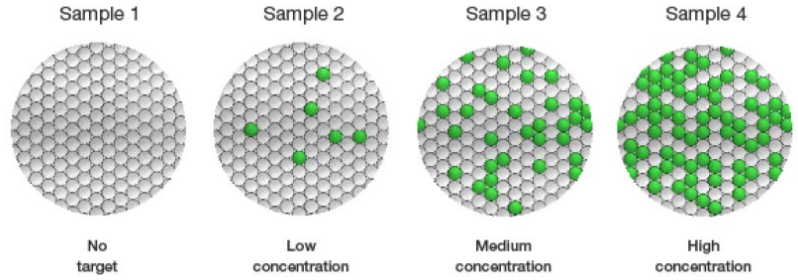
Atallah E et al. JAMA Oncology. JAMA Oncol. 2021 Jan 1;7(1):42-50.

U.S. Life after Stopping TKIs (LAST): TFR at 3-years



Time (months)	Probability
6	0.761
12	0.679
18	0.643
24	0.637
30	0.619
36	0.619

Bio-Rad droplet digital PCR (ddPCR)



Principle of enhanced sensitivity for rare targets

- Partitioning increases the effective concentration of single copies by decreasing background

ddPCR offers approximately 0.5 to 1 log greater sensitivity in *BCR-ABL1* detection

Atallah E et al. JAMA Oncology. JAMA Oncol. 2021 Jan 1;7(1):42-50.

Probability of molecular recurrence by RQ-PCR and sensitive droplet digital PCR prior to discontinuation

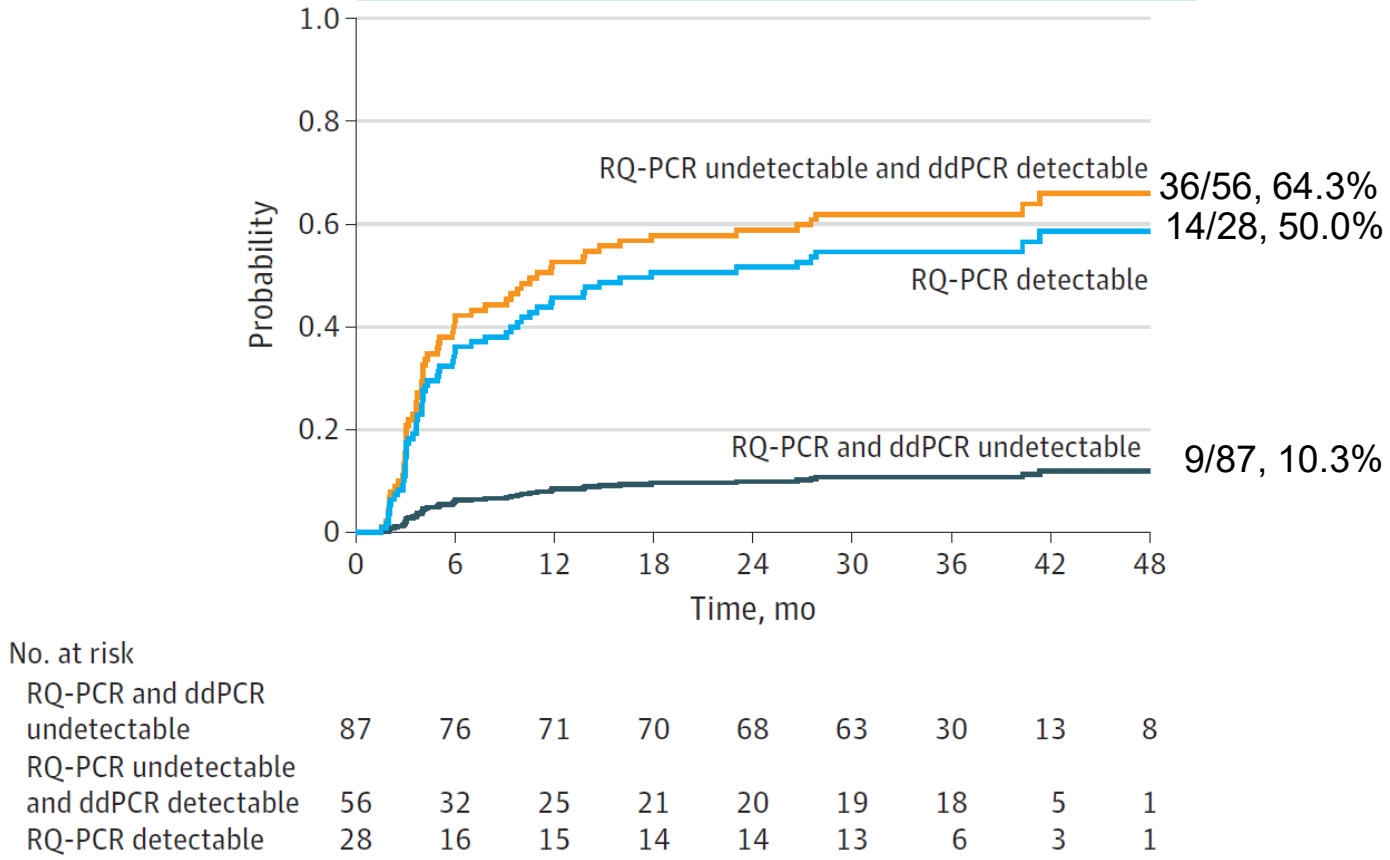
1. Molecular recurrence (MRec) for patients with detectable *BCR-ABL1* transcripts by RQ-PCR was **50.0%**

2. MRec for patients with undetectable *BCR-ABL1* transcripts by RQ-PCR but detectable by ddPCR was **64.3%**

3. **MRec for patients with undetectable *BCR-ABL1* transcripts by both dd PCR and RQPCR was 10.3% (*P* ≤.001)**

Suggests that depth of response DOES matter

ddPCR offers approximately 0.5 to 1 log greater sensitivity in *BCR-ABL1* detection

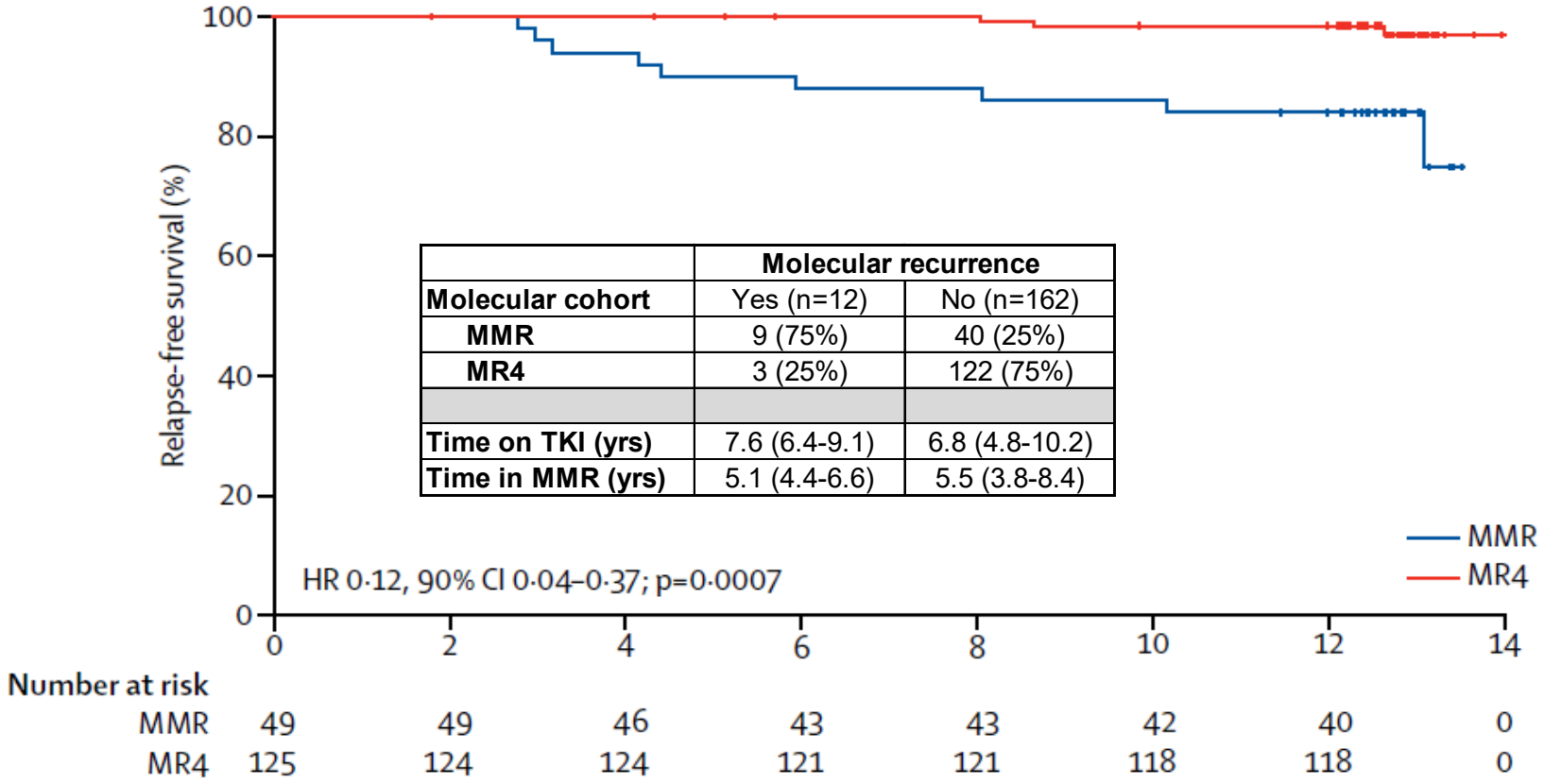


Atallah E et al. JAMA Oncol. 2020 Nov 12;e205774. doi: 10.1001/jamaoncol.2020.5774.

Dose reductions and continued durable response: DESTINY

174 patients

	MMR (n=49)	MR4 (n=125)	Overall
Time on TKI (years)	7.7 (5.1-10.7)	6.5 (4.8-10.2)	6.9 (4.8-10.2)



	Molecular recurrence	
Molecular cohort	Yes (n=12)	No (n=162)
MMR	9 (75%)	40 (25%)
MR4	3 (25%)	122 (75%)
Time on TKI (yrs)	7.6 (6.4-9.1)	6.8 (4.8-10.2)
Time in MMR (yrs)	5.1 (4.4-6.6)	5.5 (3.8-8.4)

- General improvement in adverse side effect
- All regained MMR within 4 months of resumption of full dose TKI

TKI discontinuation phase:

Recurrence-free survival was 72% at 3 years after study entry for patients with MR4

- Longer duration of TKI?
- Other biological factors?
- Small group analyses?

De-Escalation and Stopping Treatment with Imatinib, Nilotinib, or sprYcel (DESTINY) study: TKI treatment was deescalated to half the standard dose for 12 months, then stopped for a further 24 months

Clark RE et al. Lancet Hematol. 2017 Jul;4(7):e310-e316.
Clark RE et al. Lancet Haematol. 2019 Jul;6(7):e375-e383.

Risks of TKI discontinuation

1. Loss of TKI sensitivity upon TFR failure is very rare

2. CML progression is extremely rare
   - Rare reports of “sudden” blast phase have been reported during the treatment-free phase or soon after TKI reintroduction.

LAST study: 3 patients restarted therapy due to withdrawal syndrome

3. **TKI withdrawal syndrome**
   - 25 -30% of patients after stopping TKIs
   - Low-grade musculoskeletal pain
   - Typically, within the first one to two months
   - Duration – median 6 months, range 1-36 months (Korean Imatinib Discontinuation Study (KIDS))
   - Duration of TKI use (>93 months) and prior history of osteoarticular symptoms predispose to withdrawal syndrome

- Management:
  - NSAIDs
  - Prednisone

Lee SE et al. Haematologica. 2016; 101(6):717-723
Berger MG et al. Br J Haematol. 2019 Jul 4. doi: 10.1111/bjh.16083. [Epub ahead of print]
Alfayez M, et al. Br J Haematol 2019; 187: 543-545.
Richter J, et al. J Clin Oncol 2014; 32: 2821-2823.
Rea D, et al. Cancer 2018; 124: 2956-2963.
Rea D. Blood Adv (2020) 4 (21): 5589–5594.

Chronic phase CML

Don't stop TKI if:

- History of CML progression

or

- TKI treatment for less than 3 years

or

- DMR for less than 2 years

or

- Unwillingness to comply to post TKI discontinuation monitoring

or

- No access to frequent *BCR-ABL1* monitoring, no quantifiable *BCR-ABL1*

or

- No DMR

TKI discontinuation may be considered if:

- TKI for 3 to less than 5 years

and

- MR4 for 2 to less than 3 years

Optimal TKI discontinuation conditions if:

- At least 5 years of TKI treatment

and

- > 3 years of MR4 or > 2 years of MR4.5

Investigational DMR-inducing strategies

- Switch to another TKI
- Switch to combined treatment
- Add-on therapy

Other research directions

- Upfront combination therapies
- Therapeutic interventions based on EMR levels
- Better understanding of predictors of TFR eligibility and success in order to adapt clinical interventions

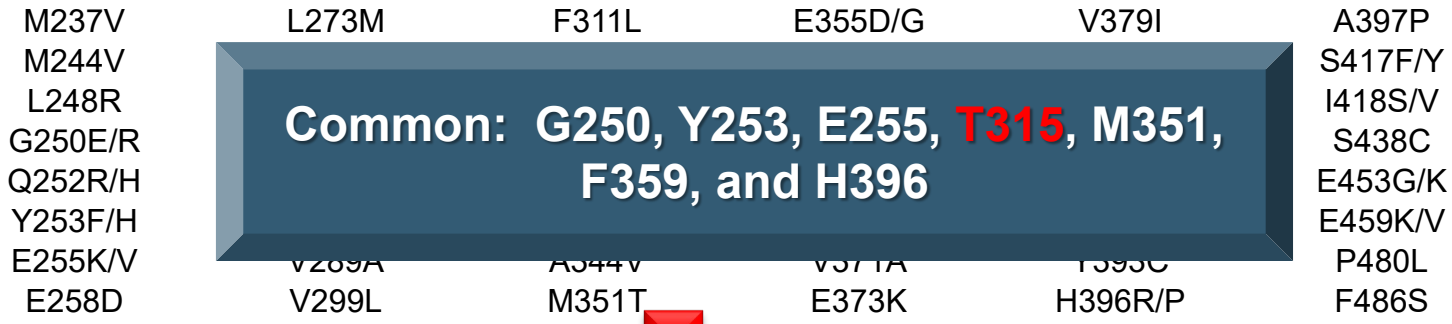
Rea D. Blood Adv (2020) 4 (21): 5589–5594.

Next-line therapy

Learning objectives

1. Understand mechanisms of resistance
2. Recognize poorer response and OS after multiple lines of therapy
3. Examine strategies to treat CP CML resistant or intolerant of 2nd generation TKIs

Mutations associated with tyrosine kinase inhibitor resistance



1st Generation: Imatinib

Y253H
E255K/V
T315I
F359V/I/C

Nilotinib

V299L
T315I
F317L/V/I/C

Dasatinib

L248V
G250E
E255K
V299L

T315I
F359C

Bosutinib

2nd Generation

Ponatinib
Treats T315I

3rd Generation

NCCN recommendations for next-line treatment based on BCR-ABL kinase domain mutation status

THERAPY	CONTRAINDICATED mutations[u]
Bosutinib	*T315I, V299L, G250E or F317L*[v]
Dasatinib	*T315I/A, F317L/V/I/C* or *V299L*
Nilotinib	*T315I, Y253H, E255K/V, F359V/C/I or G250E*
Ponatinib,[w] Omacetaxine,[x] allogeneic HCT (CML-6), or clinical trial	None

BUT NOT ALL RESISTANCE IS MUTATION DRIVEN

- BCR-ABL–independent mechanisms
- **Harder to treat**

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Chronic Myeloid Leukemia. Version 1.2021.

Summary response to 2nd-line therapy after imatinib

- Resistance to frontline imatinib is associated with lower CCyR rates compared with intolerance to imatinib*
  - Dasatinib (100 mg once daily, 2-year follow-up): imatinib-resistant, 44%; imatinib-intolerant, 67%
  - Nilotinib (400 mg twice daily, 2-year follow-up): imatinib-resistant, 41%; imatinib-intolerant, 51%
  - Bosutinib (500 mg once daily, 2-year follow-up): imatinib-resistant, 46%; imatinib-intolerant, 54%

- Patients treated second-line with either dasatinib or nilotinib experience lower long-term overall survival rates compared with patients treated first-line with these TKIs*
  - Dasatinib: first-line 5-year OS, 91%; second-line 5-year OS, ~75%
  - Nilotinib: first-line 5-year OS, 96%; second-line 4-year OS, 78%
  - Overall survival at 5-year on bosutinib was 84% for the imatinib resistant group

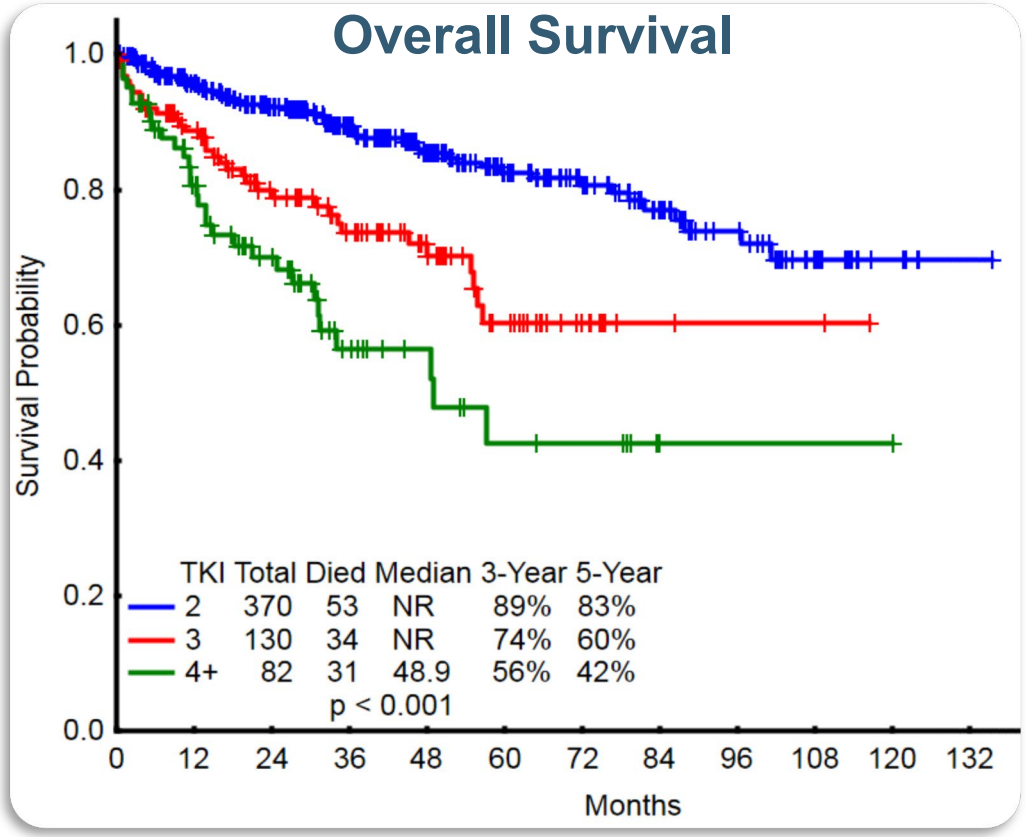
*** These trials cannot be directly compared due to different methods of trial evaluation**

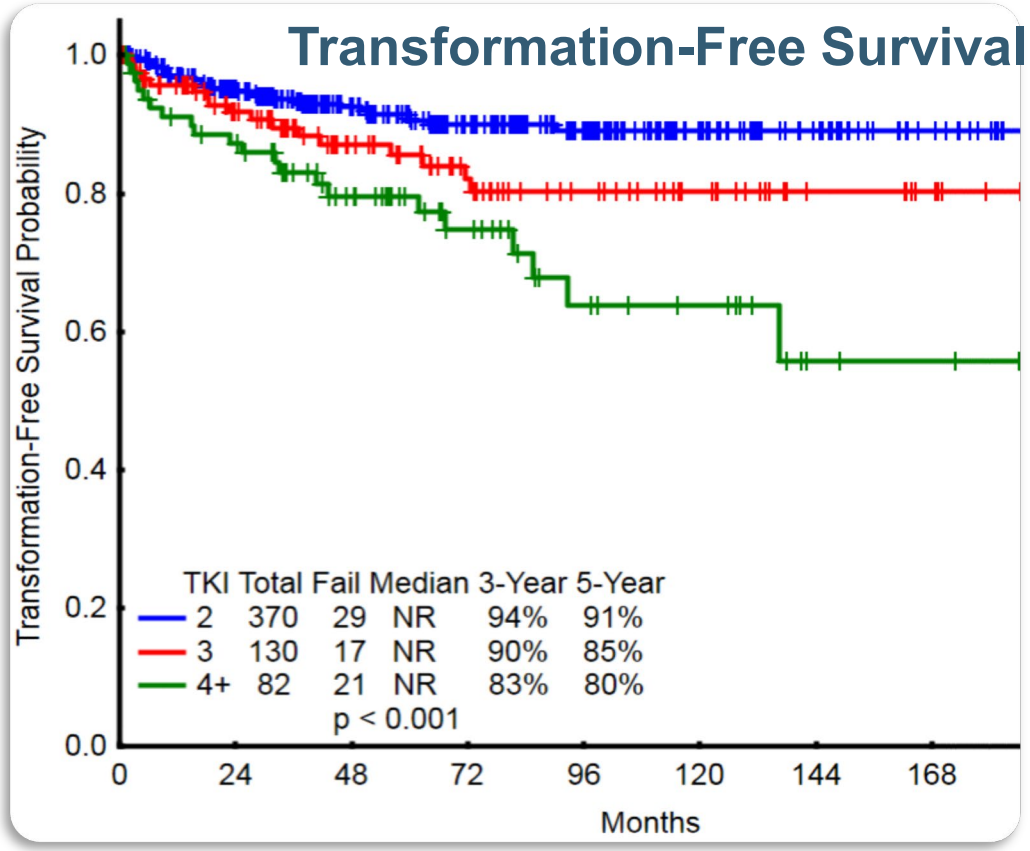
Shah NP et al. *Haematologica*. 2010;95(2):232-240.
Kantarjian HM et al. *Blood*. 2011;117(4):1141-1145.
Gambacorti-Passerini C, et al. *Am J Hematol*. 2014;89(7):732-742.
Cortes JE et al. *J Clin Oncol*. 2016;34(10):2333-2340.

Shah NP, et al. *Am J Hematol*. 2016;91(9):869-874.
Hochhaus A, et al. *Leukemia*. 2016;30(5):1044-1054.
Giles FJ, et al. *Leukemia*. 2013;27(1):107-112.
Gambacorti-Passerini C, et al. *Haematologica*. 2018;103(8):1298-1307.

Outcomes for CP CML patients on later line therapy

CML-related death increases with each subsequent line of therapy

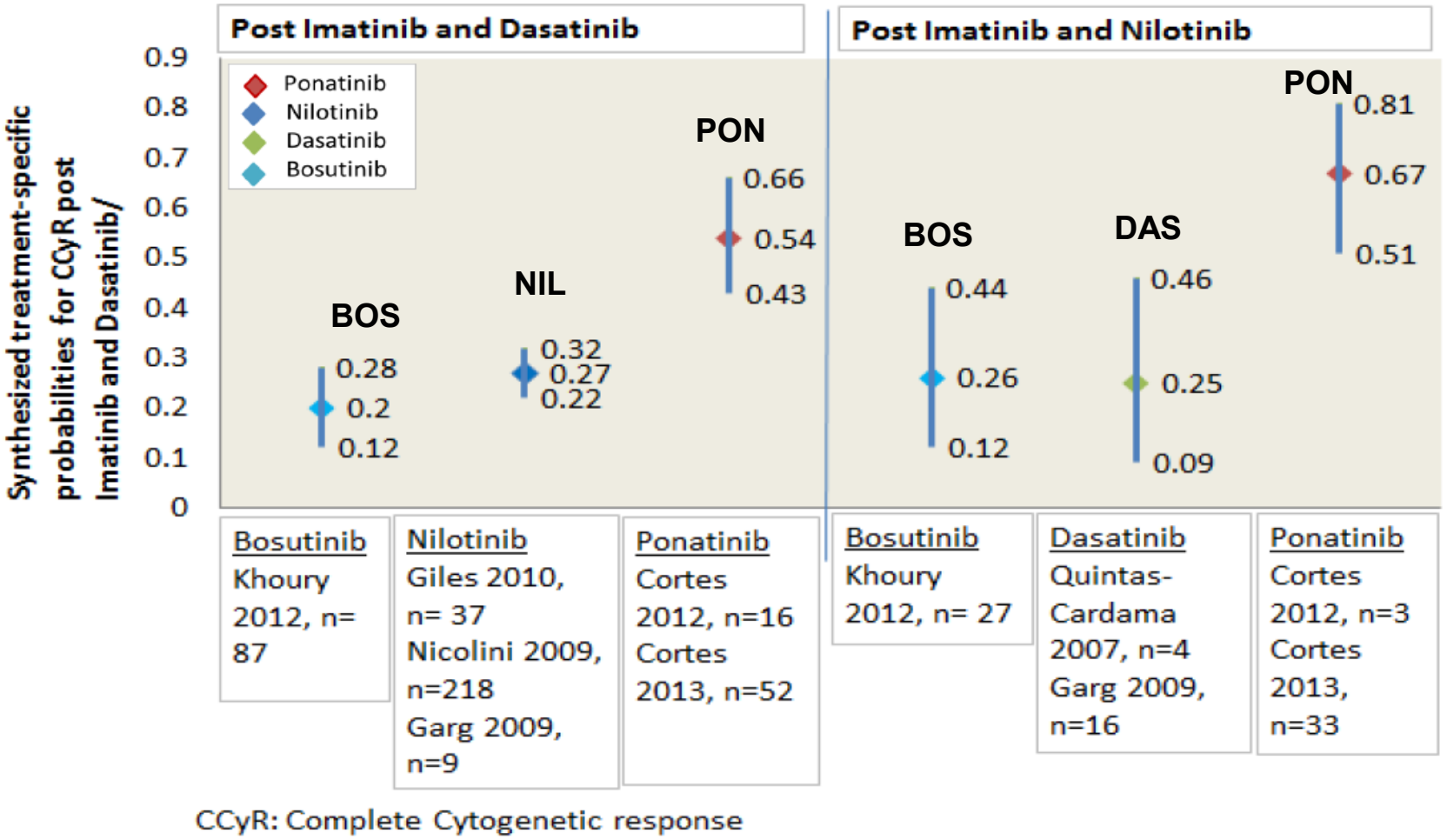




- **582 CP CML patients at MD Anderson (2/2000 to 7/2015) who received > 1 TKI**
- **2TKIs (n=370), 3TKIs (n=130), and 4+TKIs (n=82 ; 4 TKI n=59, 5 TKI n=20, 6 TKI n=1, 7 TKI n=2)**

Akosile BA et al. ASH Annual Meeting Abstracts. Blood (2015) 126 (23): 1587.

Responses after 2nd generation TKI : CCyR on third-line TKI therapy



CCyR: Complete Cytogenetic response

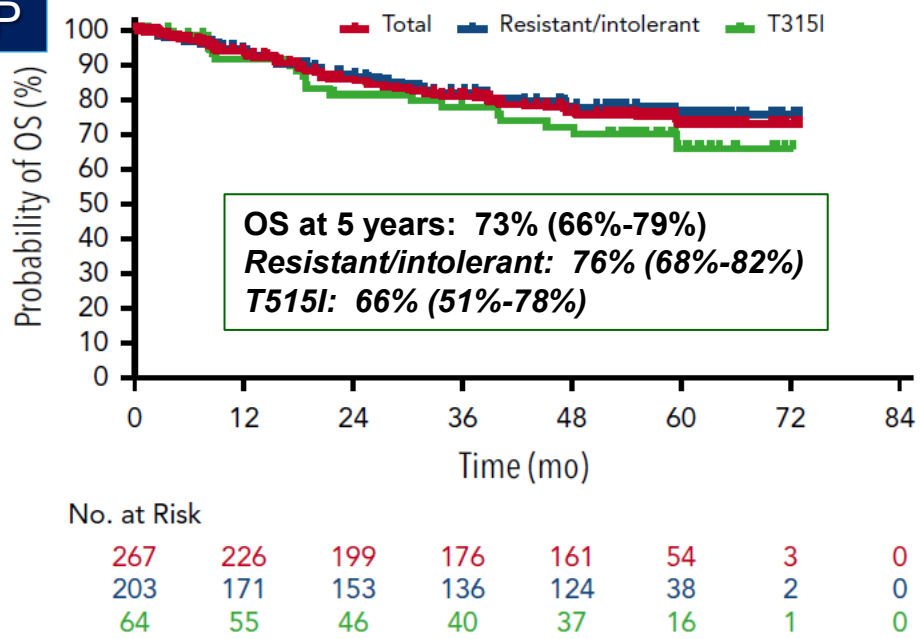
CCyR ~ *BCR-ABL1* < 1%

CCyR rates are higher with ponatinib vs treatment with another 2nd generation TKI

Lipton J et al. ASH Annual Meeting Abstracts. 2014. Abstract 4551.
Lipton J et al. Leuk Res. 2015 Jan;39(1):58-64

Good OS but increased arterial occlusive events (AOEs) on ponatinib

CP



5-year results PACE study CP CML patients

CP CML (n=270)	AE	SAE
AOEs, n (%)	84 (31)*	69 (26)**
Cardiovascular	42 (16)	33 (12)
Cerebrovascular	35 (13)	28 (10)
Peripheral vascular	38 (14)	31 (11)
Exposure-adjusted AOEs, no. of patients with events per 100 patient-years	14.1	10.9

*Forty-six patients had >1 AOE. **Thirty-one patients had >1 serious AOE.

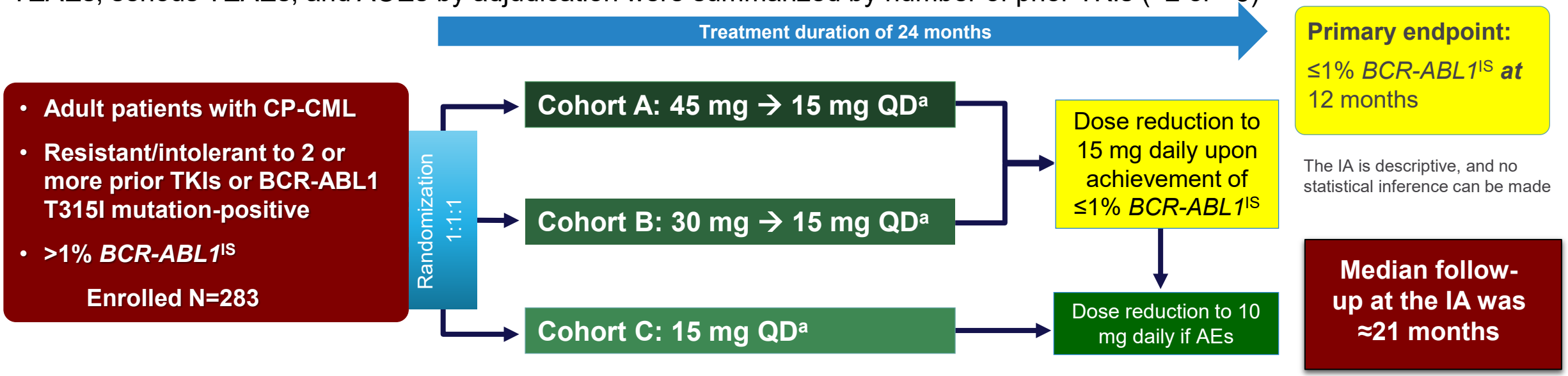
1. Lower incidence of AOEs in later years on lower ponatinib dose
2. Modeling predicts risk for AOEs may be dose related

Cortes JE et al. Blood. 2018 Jul 26;132(4):393-404.

Phase 2 OPTIC Trial

What is the optimal ponatinib dose to maintain efficacy but minimize AOEs?

- Outcomes were analyzed by baseline mutation status (none, any, T315I, and mutation other than T315I) and number of prior TKIs (≤2 or ≥3) in the ITT population
  - Mutation status was determined by a central lab
- TEAEs, serious TEAEs, and AOEs by adjudication were summarized by number of prior TKIs (≤2 or ≥3)



[a] Dose reductions due to AEs were permitted

→15 mg, Cohort A is referred to as 45 mg → 15 mg and Cohort B as 30 mg → 15 mg because the study design has a dose reduction to 15 mg upon achievement of ≤1% BCR-ABL1IS. There also were patients in Cohorts A and B who dose-reduced to different dose levels (30, 15, and 10 mg) due to safety

IA, interim analysis; ITT, intent to treat; QD, daily; TEAE, treatment-emergent adverse event

Cortes JE et al. ASH Annual Meeting Abstracts. 2020. Abstract 48

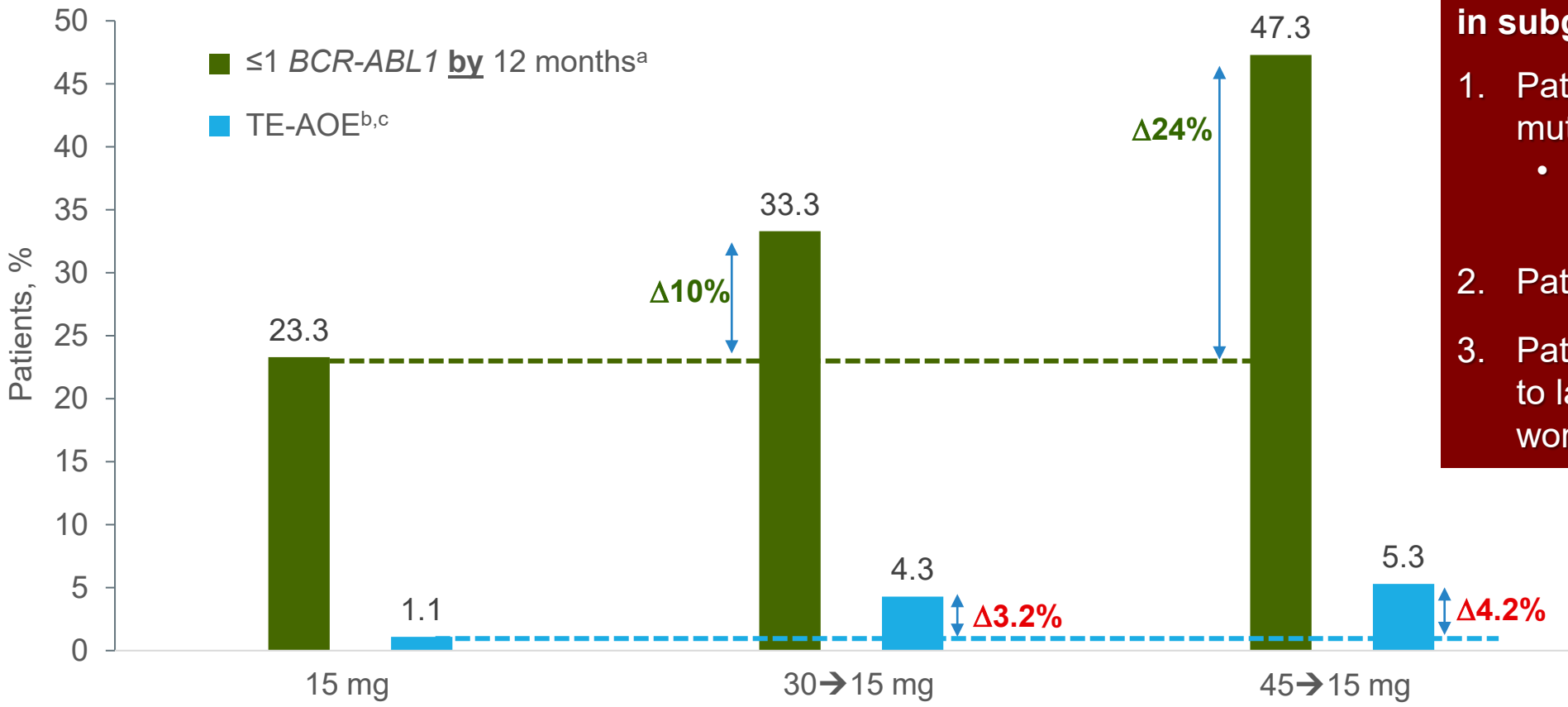
Demographics and Baseline Disease Characteristics (Part 2)

Characteristic	15 mg (n=94)	30 mg→15 mg (n=94)	45 mg→15 mg (n=94)
Reason for prior therapy stopped, resistance, n (%)	94 (100)	94 (100)	92 (98)
Prior TKIs, n (%)			
1	4 (4)	1 (1)	1 (1)
2	42 (45)	37 (39)	43 (46)
≥3	48 (51)	56 (60)	50 (53)
Prior 2G-TKIs, n (%)			
≥1	90 (96)	93 (99)	93 (99)
≥2	56 (60)	64 (68)	56 (60)

CHR, complete hematologic response.

Cortes JE et al. ASH Annual Meeting Abstracts. 2020. Abstract 48

Overall Safety and Efficacy by Starting Dose



The benefit in efficacy was seen in subgroup analysis:

1. Patients with and without mutations
   - T315 vs other mutation vs no mutation
2. Patients receiving ≥ 3 TKIs
3. Patients whose best response to last prior TKI was CHR or worse

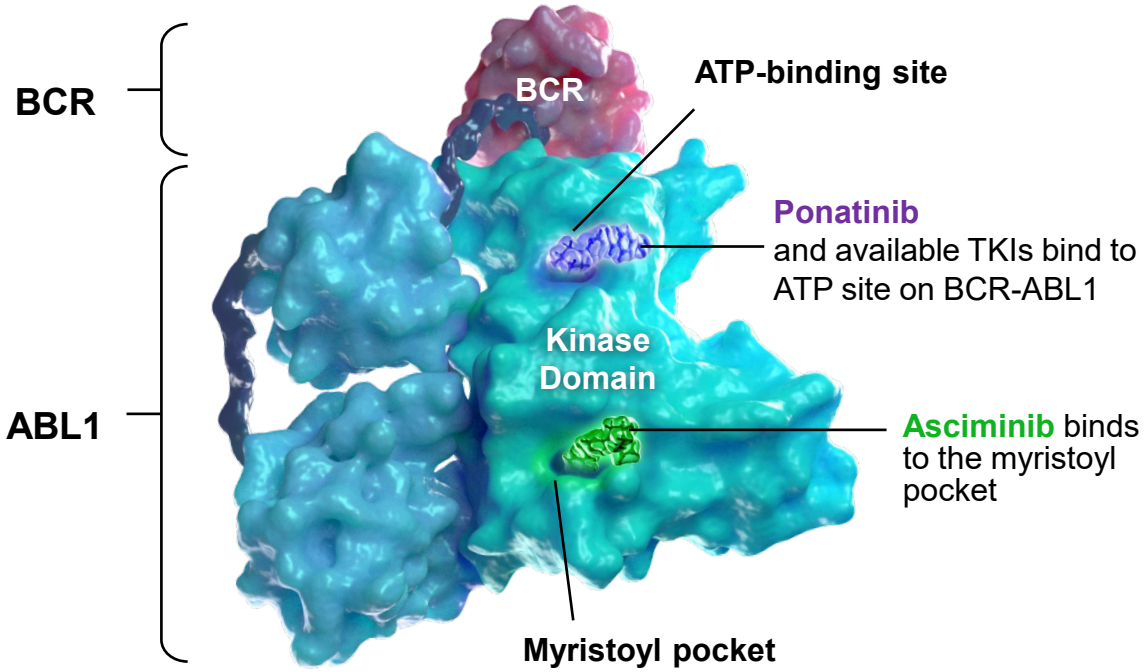
1. Although rates of adjudicated AOEs did increase with higher dose
2. AOEs were low (0%–6%) in all 3 cohorts irrespective of the number of prior TKIs

- There was a trend toward higher serious TEAE rates for patients treated with ≥3 TKIs

[a] Efficacy n's by cohort: 15 mg, n=90; 30 mg and 45 mg, n=93. [b] TE-AOE n's by cohort: all cohorts, n=94. [c] AOEs are based on adjudication

Cortes JE et al. ASH Annual Meeting Abstracts. 2020. Abstract 48

Asciminib a potent, specific inhibitor of BCR-ABL1 with a distinct allosteric mechanism of action



Asciminib has been designated as the first-in-class STAMP (**S**pecifically **T**argeting the **A**BL1 **M**yristoyl **P**ocket) inhibitor

1. Very high selectivity with narrow target profile
2. Active against *BCR-ABL1* mutations that confer resistance to TKIs
3. Efficacy demonstrated in phase 1 study
   - Most common all grade AEs
     - Fatigue, headache, increased lipase, nausea, arthralgias, diarrhea, rash, thrombocytopenia

Hochhaus A et al. ASH Annual Meeting Abstracts. 2020. Abstract LBA-4

Hughes TP, et al. ASH Annual Meeting Abstracts. 2016, abstract 625.
Hughes TP et al. N Engl J Med 2019;381:2315-26.

Phase 3 ASCEMBL: Study Design and Key Eligibility Criteria

Primary Endpoint

- **MMR rate at 24 weeks** while on study treatment without meeting any treatment failure criteria before 24 weeks

Earlier endpoint

Key Study Criteria

- Adults with CML-CP, previously treated with ≥2 TKIs
- Failure* or intolerance† of most recent TKI
- Patients with intolerance of most recent TKI must have *BCR-ABL1*^{IS} >0.1% at screening
- No T315I or V299L mutations

ASCEMBL
(NCT03106779)

Randomized 2:1 (stratified by MCyR vs no MCyR at baseline)

N = 233

Asciminib 40 mg twice daily n = 157

Switch to asciminib allowed only for patients meeting treatment failure* criteria on bosutinib

Bosutinib 500 mg once daily n = 76

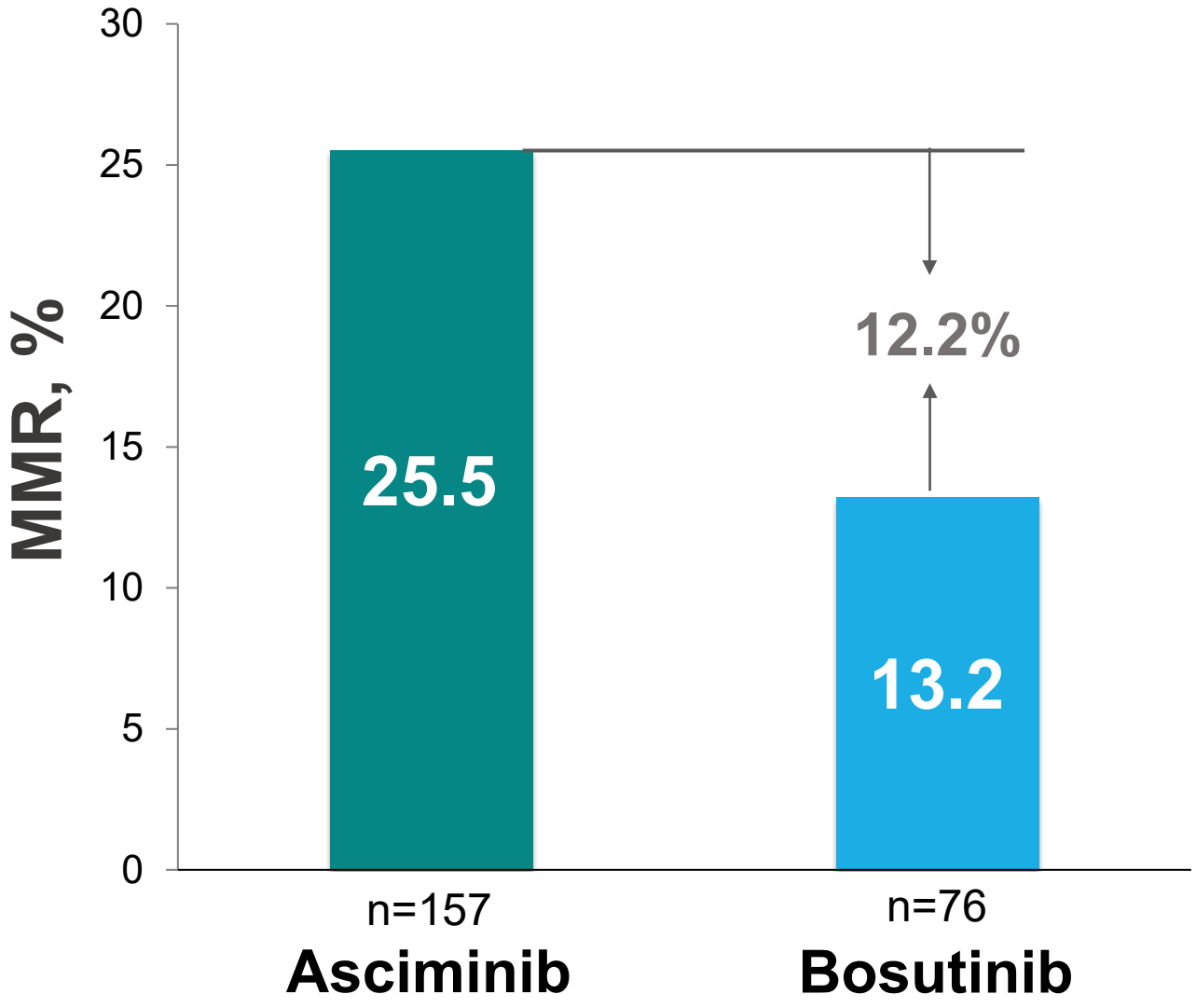
Survival follow-up

- **Data cutoff for current analysis: May 25, 2020 (all patients completed the Week 24 visit or discontinued before)**
- **Median duration of follow-up: 14.9 months from randomization to cutoff**

CML-CP, chronic myeloid leukemia in chronic phase; IS, international scale; MCyR, major cytogenetic response.
* Must meet the definition of treatment failure per the 2013 European LeukemiaNet recommendations. † Defined as nonhematologic grade 3 or 4 toxicity while on therapy, persistent grade 2 toxicity, unresponsive to optimal management, including dose adjustments; or hematologic grade 3 or 4 toxicity while on therapy, recurrent after dose reduction to the lowest recommended dose. ‡ Patients will continue to receive study treatment for up to 96 weeks after the last patient's first dose or 48 weeks after the last patient switches to asciminib, whichever is longer.

Hochhaus A et al. ASH Annual Meeting Abstracts. 2020. Abstract LBA-4

MMR Rate at 24 Weeks



Asciminib was also better tolerated

- Common treatment difference after adjusting for MCyR status at baseline was **12.2%** (95% CI, 2.19-22.3; 2-sided P=0.029)
- Median duration of exposure was 43.4 (range, 0.1-129.9) weeks for asciminib and 29.2 (range, 1.0-117.0) weeks for bosutinib

Treatment effect after adjusting for MCyR and other baseline covariates such as line of therapy and treatment failure vs. intolerance favors asciminib

Hochhaus A et al. ASH Annual Meeting Abstracts. 2020. Abstract LBA-4

Abstract 650: Asciminib, a First-in-Class STAMP Inhibitor, Provides Durable Molecular Response in Patients (pts) with Chronic Myeloid Leukemia (CML) Harboring the T315I Mutation: Primary Efficacy and Safety Results from a Phase 1 Trial

1. Asciminib 200 mg BID has a favorable safety profile and meaningful clinical efficacy in patients with the T315I mutation which confers resistance to all ABL-targeted TKIs except ponatinib

2. Nearly half of the patients achieved MMR, which has been durable in most of the patients

3. Major molecular response was achieved by ponatinib-naive and ponatinib-pretreated patients, with a higher incidence among ponatinib-naive patients

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When to consider allogeneic hematopoietic cell transplantation

CP patients →

- ≥ 3rd line therapy
  - Typing at failure or intolerance of 2nd-line therapy, consider in some when initiating 2nd line therapy (failure of 1st line 2nd gen TKI without mutations)

Progression to AP or BC →

- HCT using alternate TKI to bridge

***de novo* AP patients** →

- Type patient and siblings; use first-line TKI therapy with close monitoring for optimal response as some AP patients do well. HCT in patients with worrisome ACA*; for others HCT when optimal milestones are not met.*

BP patients →

- HCT after TKI therapy +/- induction chemotherapy

Median survival is ~7-12 months with TKI-based therapy

MDACC: First-line TKI Therapy in AP

- 51 patients treated September 1999 through May 2011
- AP criteria:
  - Blasts ≥ 15% (n = 6)
  - basophils ≥ 20% (n = 22),
  - platelets < 100 × 10^9/L (n = 3),
  - cytogenetic clonal evolution (n =20)
- Imatinib: 30 (59%) patients
- 2nd gen TKI: 21 (41%)
  - 16 nilotinib
  - 5 dasatinib

For patients achieving CCyR on first-line therapy for AP: Overall survival 100% and event-free survival 96%

Response	All (n = 51)	Imatinib (n = 30)	2GTKI (n = 21)
CHR	49 (96)	29 (97)	20 (95)
Cytogenetic			
mCyR	1 (2)	1 (3)	0 (0)
PCyR	1 (2)	1 (3)	0 (0)
CCyR	43 (84)	24 (80)	19 (90)
MCyR	44 (86)	25 (83)	19 (90)
Molecular			
MMR	35 (69)	19 (63)	16 (76)
MR4.5	25 (49)	15 (50)	10 (63)
Follow-Up, Months	65 (3-144)	113 (48-144)	28 (3-73)
Months to CHR	1 (0-12)	1 (0-12)	1 (0-3)
Months to MMR	10 (0-44)	12 (3-44)	6 (0-24)
Months to CCyR	3 (2-44)	6 (2-44)	3 (2-6)

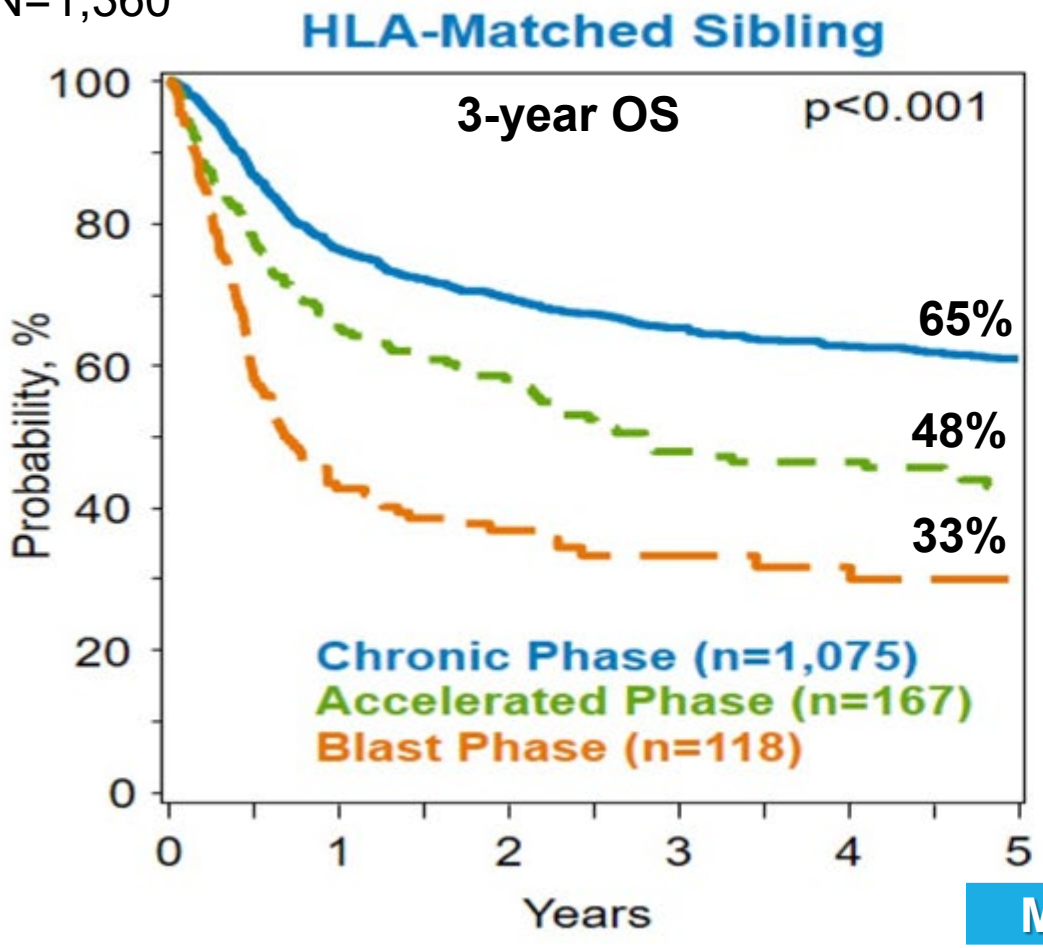
CCyR

MMR

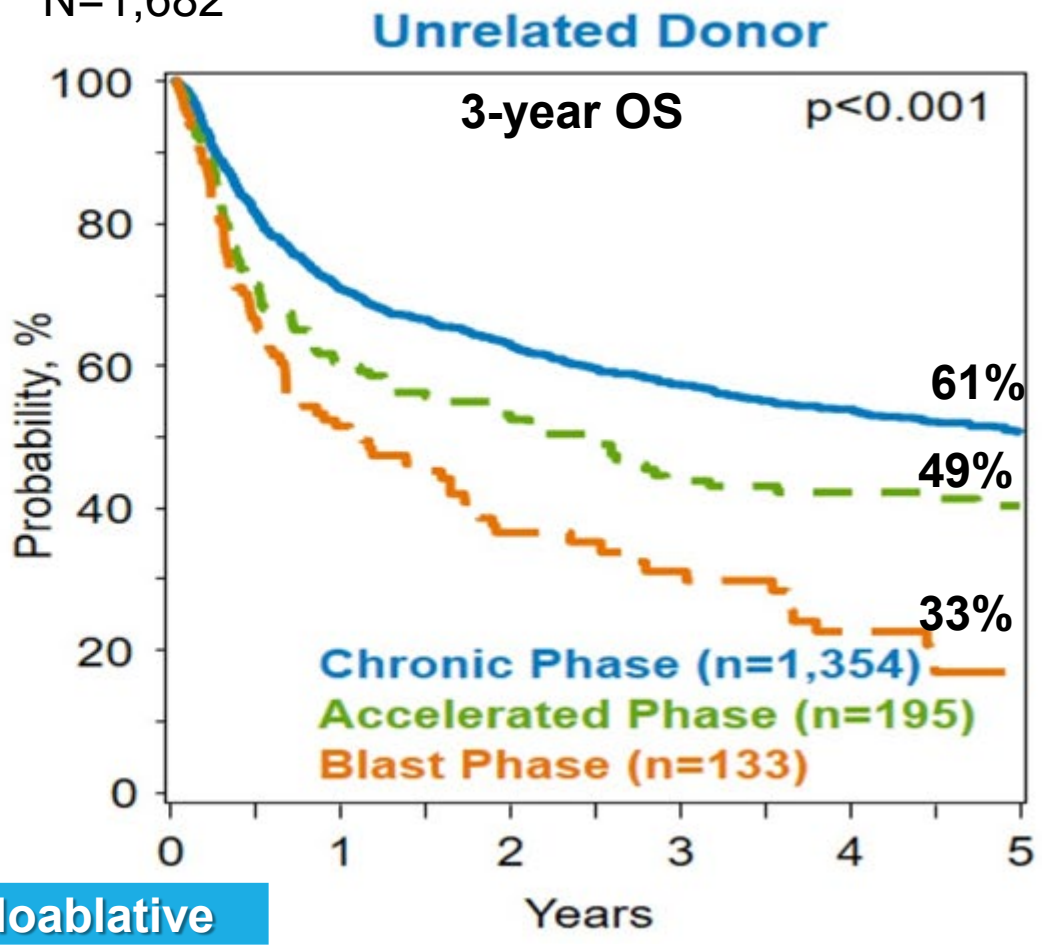
Ohanian et al. Clin Lymphoma Myeloma Leuk. 2014 Apr;14(2):155-162

Survival after HCT for CML, 2007-2017

N=1,360



N=1,682



Myeloablative

Center for International Blood and Marrow Transplant Research (CIBMTR)

Clinical Trials at Fred Hutch/SCCA for CML:

1. Phase 1b Study of PK, safety and efficacy of orally administered HQP1351 (TKI, Ascentage)
2. Treatment Free Remission After Combination Therapy With Ruxolitinib Plus Tyrosine Kinase Inhibitors
3. 2nd TKI discontinuation
4. In development: asciminib first-line

Research studies:

1. Chemogenomic profiing of CML progenitor cells *in vitro* to various TKIs and other agents to identify biomarkers of clinical response and toxicity

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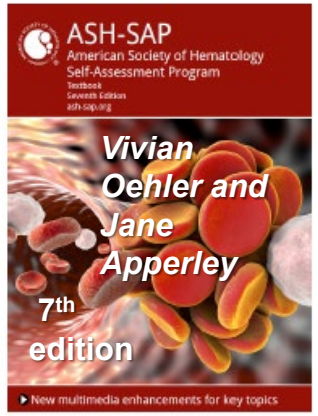

H. JEAN KHOURY CURE CML CONSORTIUM

We are a group of researchers from 17 world-class academic medical centers throughout North America committed to curing CML through innovative research. With feedback from advocates and patients, we strive to meet the needs of the CML community.

Fred Hutchinson Cancer Research Center
Huntsman Cancer Institute
H. Lee Moffitt Cancer Center & Research Institute
Medical College of Wisconsin
MD Anderson Cancer Center
Oregon Health & Science University
John Theurer Cancer Center at Hackensack University
Winship Cancer Institute of Emory University

www.curecml.org

'Galvanized by the spectacular collaboration created by the LAST study, the creation of a CML consortium was simply the next logical thing to do' -H. Jean Khoury

University of Chicago Comprehensive Cancer Center
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Duke Cancer Institute
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Barbara Ann Karmanos Cancer Institute
UCSF Helen Diller Family Comprehensive Cancer Center
Roswell Park Cancer Institute
Dana-Farber Cancer Institute

Extra slides

Helpful reviews and recommendations European LeukemiaNet

REVIEW

European LeukemiaNet recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukaemia

JL Steegmann[1], M Baccarani[2], M Breccia[3], LF Casado[4], V García-Gutiérrez[5], A Hochhaus[6], D-W Kim[7], TD Kim[8], HJ Khoury[9], P Le Coutre[8], J Mayer[10], D Milojkovic[11], K Porkka[12,13], D Rea[14], G Rosti[2], S Saussele[15], R Hehlmann[16] and RE Clark[17]

Leukemia (2016), 1–24

www.nature.com/leu

Most reports on chronic myeloid leukaemia (CML) treatment with tyrosine kinase inhibitors (TKIs) focus on efficacy, particularly on molecular response and outcome. In contrast, adverse events (AEs) are often reported as infrequent, minor, tolerable and manageable, but they are increasingly important as therapy is potentially lifelong and multiple TKIs are available. For this reason, the European LeukemiaNet panel for CML management recommendations presents an exhaustive and critical summary of AEs emerging during CML treatment, to assist their understanding, management and prevention. There are five major conclusions. First, the main purpose of CML treatment is the antileukemic effect. Suboptimal management of AEs must not compromise this first objective. Second, most patients will have AEs, usually early, mostly mild to moderate, and which will resolve spontaneously or are easily controlled by simple means. Third, reduction or interruption of treatment must only be done if optimal management of the AE cannot be accomplished in other ways, and frequent monitoring is needed to detect resolution of the AE as early as possible. Fourth, attention must be given to comorbidities and drug interactions, and to new events unrelated to TKIs that are inevitable during such a prolonged treatment. Fifth, some TKI-related AEs have emerged which were not predicted or detected in earlier studies, maybe because of suboptimal attention to or absence from the preclinical data. Overall, imatinib has demonstrated a good long-term safety profile, though recent findings suggest underestimation of symptom severity by physicians. Second and third generation TKIs have shown higher response rates, but have been associated with unexpected problems, some of which could be irreversible. We hope these recommendations will help to minimise adverse events, and we believe that an optimal management of them will be rewarded by better TKI compliance and thus better CML outcomes, together with better quality of life.

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]

Abstract

The therapeutic landscape of chronic myeloid leukemia (CML) has profoundly changed over the past 7 years. Most patients with chronic phase (CP) now have a normal life expectancy. Another goal is achieving a stable deep molecular response (DMR) and discontinuing medication for treatment-free remission (TFR). The European LeukemiaNet convened an expert panel to critically evaluate and update the evidence to achieve these goals since its previous recommendations. First-line treatment is a tyrosine kinase inhibitor (TKI; imatinib brand or generic, dasatinib, nilotinib, and bosutinib are available first-line). Generic imatinib is the cost-effective initial treatment in CP. Various contraindications and side-effects of all TKIs should be considered. Patient risk status at diagnosis should be assessed with the new EUTOS long-term survival (ELTS)-score. Monitoring of response should be done by quantitative polymerase chain reaction whenever possible. A change of treatment is recommended when intolerance cannot be ameliorated or when molecular milestones are not reached. Greater than 10% BCR-ABL1 at 3 months indicates treatment failure when confirmed. Allogeneic transplantation continues to be a therapeutic option particularly for advanced phase CML. TKI treatment should be withheld during pregnancy. Treatment discontinuation may be considered in patients with durable DMR with the goal of achieving TFR.

Leukemia (2020) 34:966–984
https://doi.org/10.1038/s41375-020-0776-2

REVIEW ARTICLE

Primer of (some) CML clinical trials

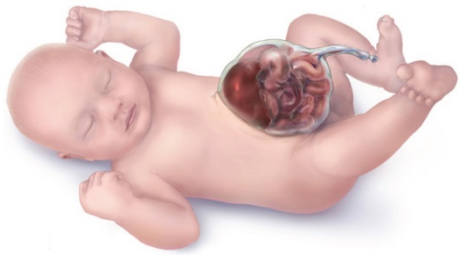
- **IRIS:** Phase 3, front-line imatinib vs. Interferon-α and cytarabine CP CML
- **ENESTnd:** Phase 3, front-line nilotinib vs. imatinib CP CML
- **ENESTFreedom:** Stopping first-line nilotinib
- **ENESTop:** Stopping second-line nilotinib
- **DASISION:** Phase 3, front-line dasatinib vs. imatinib CP CML
- **DASFREE:** Stopping dasatinib
- **BFORE:** Phase 3, front-line bosutinib vs. imatinib CP CML
- **DESTINY:** Phase 2 study de-escalating followed by stopping imatinib, nilotinib, and dasatinib
- **German CML-Study IV:** five-arm randomized trial CP CML comparing first-line imatinib treatment with different dosages and with or without additional non-TKI therapy
  - including - imatinib (400), imatinib (800), imatinib/ara-C, imatinib/interferon
- **PACE:** ponatinib once daily in CML or Ph+ ALL patients with resistance or intolerance to dasatinib or nilotinib, or with the BCR-ABL1 T315I mutation.
- **EPIC:** front-line ponatinib vs. imatinib CP CML
- **OPTIC:** Dose optimization study of ponatinib
- **ASCEMBL:** Asciminib vs bosutinib CP CML 3rd line and beyond.

What to know for the Boards (1)

1. Know when to declare failure, how to assess for resistance, and select next-line therapy

2. Recognize that mutation profile is needed to select appropriate next-line therapy
   - T315I (ponatinib, omacetaxine, transplant, *asciminib*)
   - V299L (nilotinib is good choice)

3. Interferon can be used during 2nd and 3rd trimester
   - TKIs cause birth defects (omphalocele)



http://www.cdc.gov/ncbddd/birthdefects/omphalocele.html
Centers for Disease Control and Prevention, National Center on Birth Defects and Developmental Disabilities

What to know for the Boards (2)

Know expected/important/bad side effects

- Helps you select best therapy for a particular patient
- Early recognition AND intervention will enhance compliance and ultimately impact response

- Pleural and pericardial effusion and dasatinib
- Pulmonary hypertension and dasatinib
- Glucose intolerance and nilotinib
- Liver function test abnormalities and nilotinib and bosutinib
- Diarrhea and bosutinib (usually first 1-2 months)
- Increased vascular events (arterial – CAD, PAD, stroke)
  - Ponatinib ~10-34%
  - Nilotinib – increased, ~ 10-20%
- QTc monitoring
  - Nilotinib: weekly ECG X 3 as strongest effect on QT prolongation, keep potassium and magnesium WNL

Comparison of TKI efficacy in 3 registration phase 3 studies compared with imatinib (*note can not be compared directly)*

Endpoint	Nilotinib (300)	Imatinib	Dasatinib	Imatinib	Bosutinib	Imatinib
	ENESTnd		DASISION		BFORE	
CCyR by 12 months	80	65	85	73	77	66
CCyR by 24 months	87	77	86	82		
MMR by 12 months	53	27	46	28	47	36
MMR by 24 months	69	44	64	46		
MR4.5 by 24 months	23	10	17	8		
Transformation	2.6	6.7	3.5	5.8	1.6	2.5
Death	*3.7*	*6*	*6*	*5*	*0*	*4*
Overall survival	*95.1**	*94**	*95.3***	*95.2***	*99.6****	*97.9****

*Median f/u 36 mo, ** Median f/u 24 mo, *** Median f/u 12 mo

Manage toxicities aggressively: Common adverse events on IRIS, DASISION, ENESTnd and BFORE first-line trials

Grade	All (%)	3 /4 (%)	All %	3 /4 (%)	All %	3 / 4(%)	All %	3 / 4(%)
	imatinib 400 mg QD (n=551)		dasatinib 100 mg QD (n=258)		nilotinib 300 mg BID (n=279)		bosutinib 400 mg QD (n=268)	
Rash	34	2	11	0	31	<1	19.8	0.4
Headache	31	<1	12	0	14	1	18.7	1.1
Nausea	44	<1	8	0	11	<1	35.1	0
Alopecia	4	0			8	0		
Pruritus	7	<1			15	<1		
Myalgia	21	1.5	6	0	10	<1	3	0.4
Fatigue	35	1	8	<1	11	0	19.4	0.4
Vomiting	17	1.5	5	0	5	0	17.9	1.1
Diarrhea	33	2	17	<1	8	1	70.1	7.8
Musculoskeletal Pain	37	3	11	0			29.5	1.9
Muscle Spasm	38	1			7	0	2.2	0
Peripheral Edema	55	1	14	1	5	0	4.1	<1
Eyelid Edema					1	0		
Periorbital Edema					<1	0	1.5	0
Pleural Effusion			10	0			1.9	
Hematologic								
Neutropenia	61	14	65	21	43	12	11.2	6.7
Thrombocytopenia	57	8	70	19	48	10	35.1	13.8
Anemia	45	3	90	10	38	3	18.7	3.4

Rash: anti-histamines, steroid creams, systemic steroids (rarely)

Diarrhea: immodium
Edema: lasix

Pleural effusion: lasix, steroids, thoracentesis

Grade 3/4 : hold drugs, see NCCN, can reintroduce at same dose or if repeat event lower dose. Consider switch for severe toxicities

For hematologic toxicity as marrow recovers and CML disappears typically can slowly push drug dose to therapeutic range

Summary of common toxicities on tyrosine kinase inhibitor therapy extracted from the IRIS, DASISION, ENESTnd and BFORE first-line trials

	imatinib 400 mg QD (n=551)		dasatinib 100 mg QD (n=258)		nilotinib 300 mg BID (n=279)		bosutinib 400 mg QD (n=268)	
Grade	All (%)	3 /4 (%)	All %	3 /4 (%)	All %	3 / 4(%)	All %	3 / 4(%)
Labs								
Increased total bilirubin					53	4		
Increased alkaline phosphatase					21	0		
Decreased phosphate					32	5	43.7	4.5
Increased glucose					36	6	46.3	2.2
Increased lipase					24	6	39.6	13.1
Increased amylase					15	<1	25	2.2
Increase creatinine					5	0		0
Increased ALT	43	5			66	4	63.4	23.1
Increased AST					40	1	49.3	11.9

Omacetaxine: CP or AP CML after failure/intolerance to 2 TKIs

- Consider for patients:
  - With increased vascular risk
  - Non-adherent

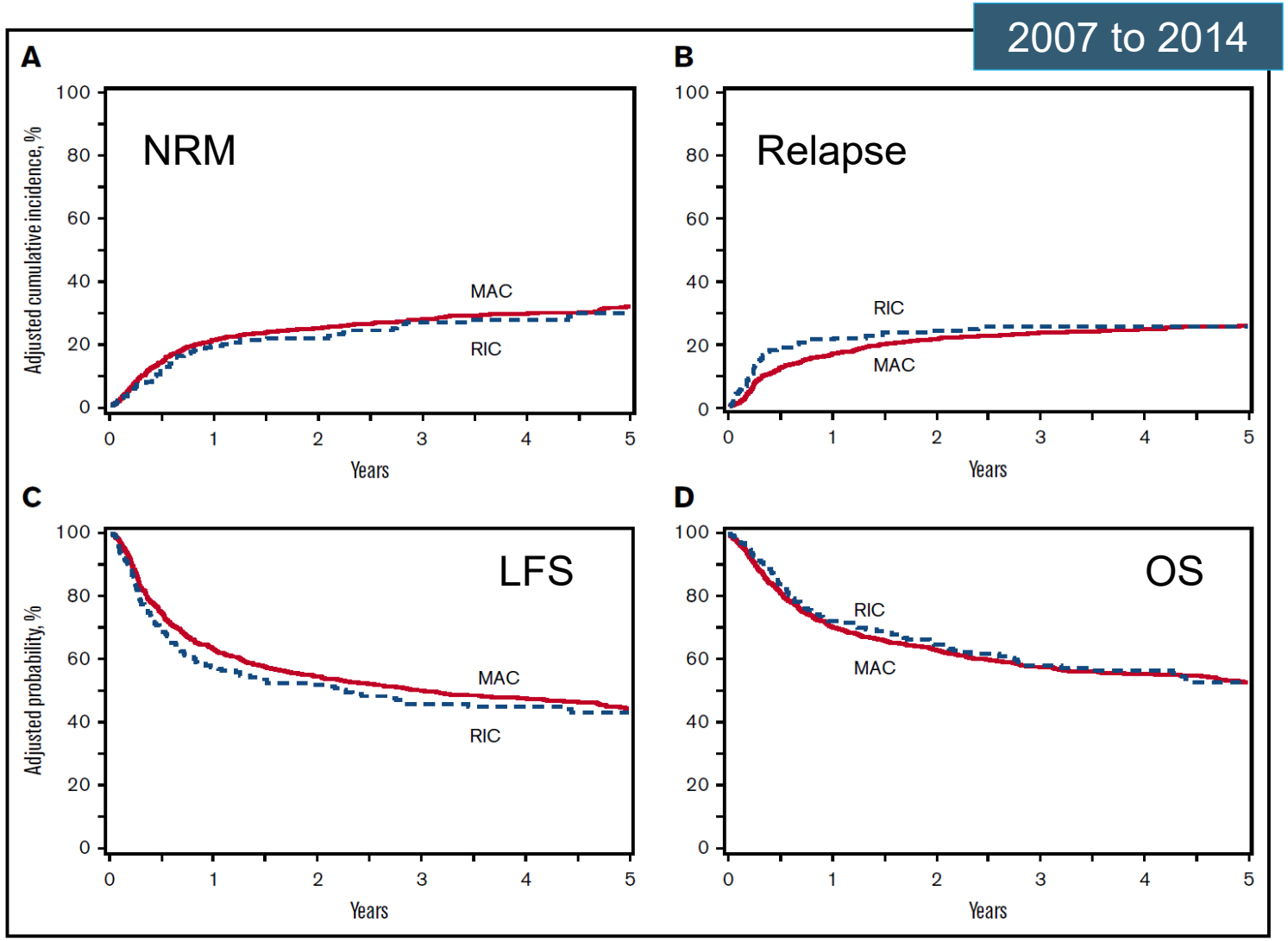
	MCyR			CCyR[a]		
	Overall (n = 76)	Patients With >3 Cycles (n = 50)	Patients With ≥12 Cycles (n = 21)	Overall (n = 76)	Patients With >3 Cycles (n = 50)	Patients With ≥12 Cycles (n = 21)
Response rate, n (%)	14 (18)	11 (22)	6 (29)	7 (9)	6 (12)	6 (29)
All patients	5/22 (23)	3/16 (19)	2/7 (29)	3/22 (14)	2/16 (13)	2/7 (29)
Patients with T315I at baseline	10/40 (25)	7/28 (25)	4/12 (33)	5/40 (13)	4/18 (22)	4/12 (33)
Patients with 2 prior TKIs	4/36 (11)	4/22 (18)	2/9 (22)	2/36 (6)	2/22 (9)	2/9 (22)
Patients with 3 prior TKIs						

vs. ~50% in ponatinib-treated patients

Response to omacetaxine in CP CML patients receiving more than 3 or 12 cycles
Duration of response is mostly < 12 months

Cortes JE et al. Cancer. 2015 May 15;121(10):1637-44.

Myeloablative vs. Reduced-intensity Conditioning Allogeneic HCT for CML



1. 1,395 CML allo-HCT recipients ages 18 to 60 years in CP1, CP2 or greater, or AP
   - MAC (n=1204)
   - RIC (n=191)
2. In multivariable analyses no significant difference in OS, LFS and NRM
3. Compared with MAC, RIC had a higher risk of early relapse after allo-HCT (hazard ratio [HR], 1.85; P = .001)
4. Cumulative incidence of chronic graft-versus-host disease was lower with RIC than with MAC (HR, 0.77; P = .02).

Image used with permission from Chhabra S et al. *Blood Adv* (2018) 2 (21): 2922–2936.

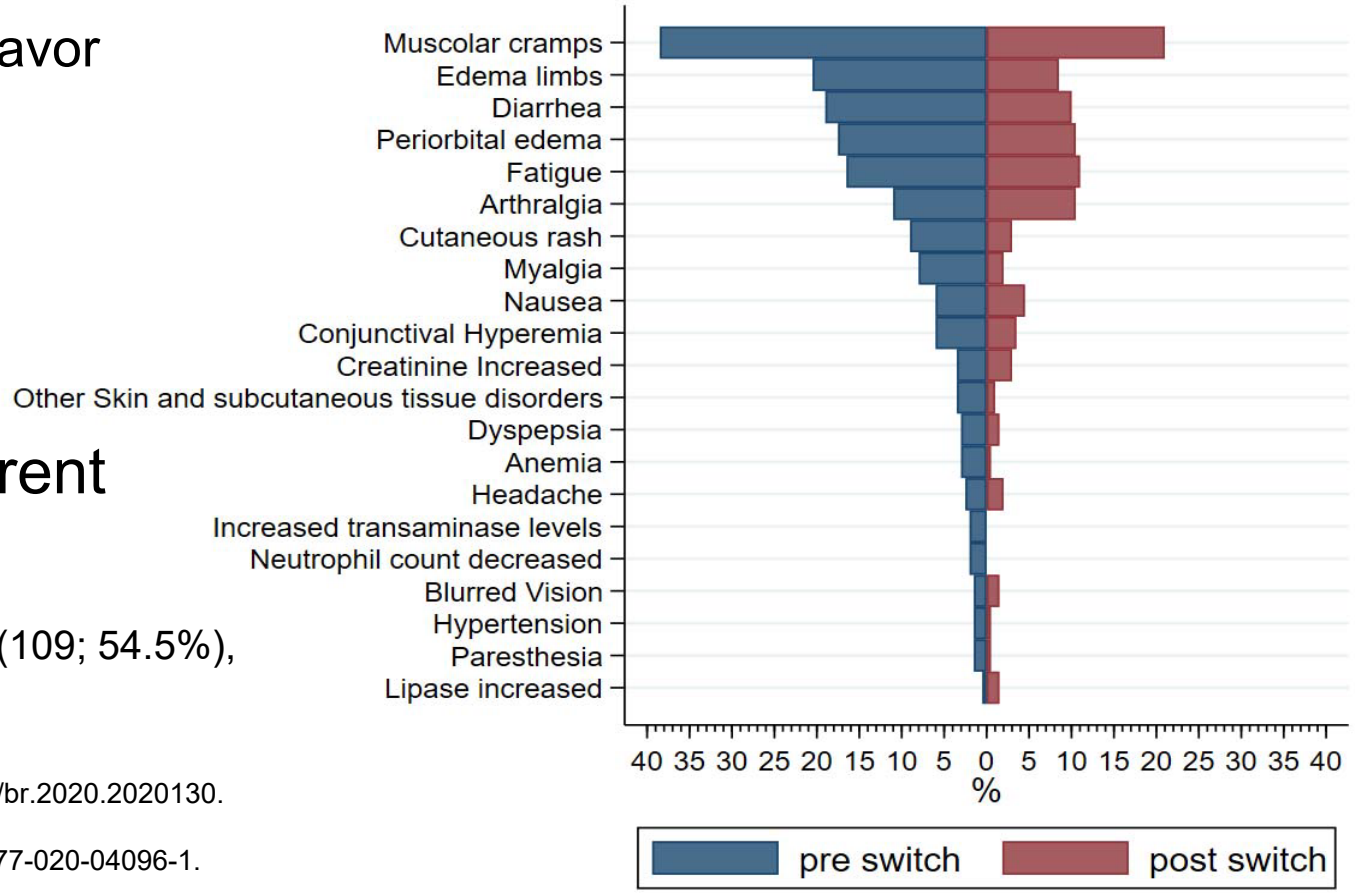
Switching from branded to generic imatinib

Limited data for starting first-line generic imatinib

- Patients may develop new side effect or have improvement of prior side effects
  - Significant difference was found in favor of generic imatinib for:
    - muscular cramps (*P*<0.0001),
    - periorbital edema (*P*=0.0027),
    - edema of the limbs (*P*<0.0001),
    - fatigue (*P*=0.0482),
    - diarrhea (*P*=0.0028)
- Different generics may have different side effects due to excipients

Generic Pharmacies: Accord (117 patients; 58.5%), Teva (109; 54.5%), Sandoz (41; 20.5%), Mylan (1; 0.4%), Reddy (1; 0.4%).

Adverse events (AEs) with frequencies >1% and number and percentage of G3-G4 for each event pre- and post-switch.



Gemelli M et al. Blood Reearch preprint on August 14, 2020, as doi:10.5045/br.2020.2020130.
Dalle et al. Cancer Med. 2019 Nov;8(15):6559-6565
Scalzulli et al,. Ann Hematol preprint on May 28, 2020 at doi: 10.1007/s00277-020-04096-1.

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Managing CML Patients with Co-Morbidities

1. Assess risk factors
2. Eliminate / manage behavioral risk factors (smoking, diet, exercise)
3. Aggressively follow and manage co-morbidities (DM, hypertension, cholesterol, weight)
4. When possible, use drugs with lower risk for patients at higher risk
5. Dose adjustments as needed
6. Monitor ankle-brachial index, statins?
7. Involve specialists early
8. Balance risk: benefit

Monitoring goals summary

- Early molecular response (*BCR-ABL1* IS < 10%) at 3 months
  - ~10% difference in OS or PFS
    - On either 1st or 2nd generation TKIs
  - Three months may be too early to assess response if poor adherence to therapy or multiple doses were held due to AEs early in the treatment course

- *BCR-ABL1* IS < 1% by 12 -15 months (equivalent of CCyR)
  - Associated with large OS and PFS benefits

- MMR (≤ 0.1%) (by 12 months)
  - Associated with (smaller) OS and PFS (as compared to *BCR-ABL1 < 1%*)
  - Limits likelihood of losing response
  - **Goal if treatment-free remission is desired**

- Deep molecular response
  - **Goal if treatment-free remission is desired**
  - No patient achieving MR4.5 on German CML Study IV progressed