Chronic Myeloid Leukemia in 2020

Vivian G. Oehler, MD
Associate Member, Fred Hutch
Associate Professor, Division of Hematology, University of Washington

ASH, ASCO and beyond

1. Identifying higher risk chronic phase CML at diagnosis

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

3. Stopping TKI therapy: who is eligible, who succeeds, and how to qualify

4. Updates on TKI toxicities

5. New therapeutic strategies

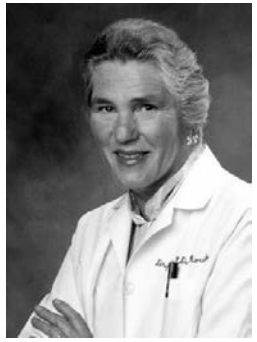
CML epidemiology

- 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 people ages 65 to 74 years.

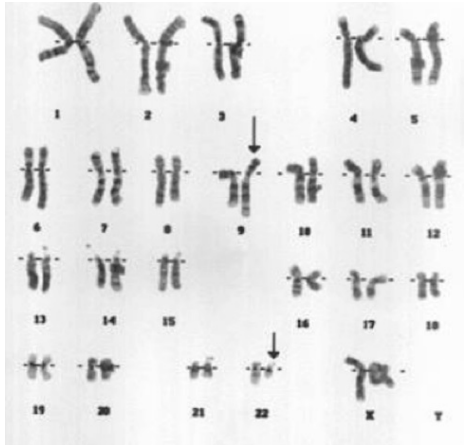
Huang X, et al. *Cancer*. 2012; 118:3123-3127.
Bower H, et al. *J Clin Oncol*. 2016;34:2851-2857
O'Hare T, et al. *Nat Rev Cancer.* 2012;12:513-526.
NCI. SEER Stat Fact Sheets: Chronic Myeloid Leukemia (CML). https://seer.cancer.gov/statfacts/html/cmyl.html. Accessed July 1, 2020.

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

David Hungerford and Peter Nowell

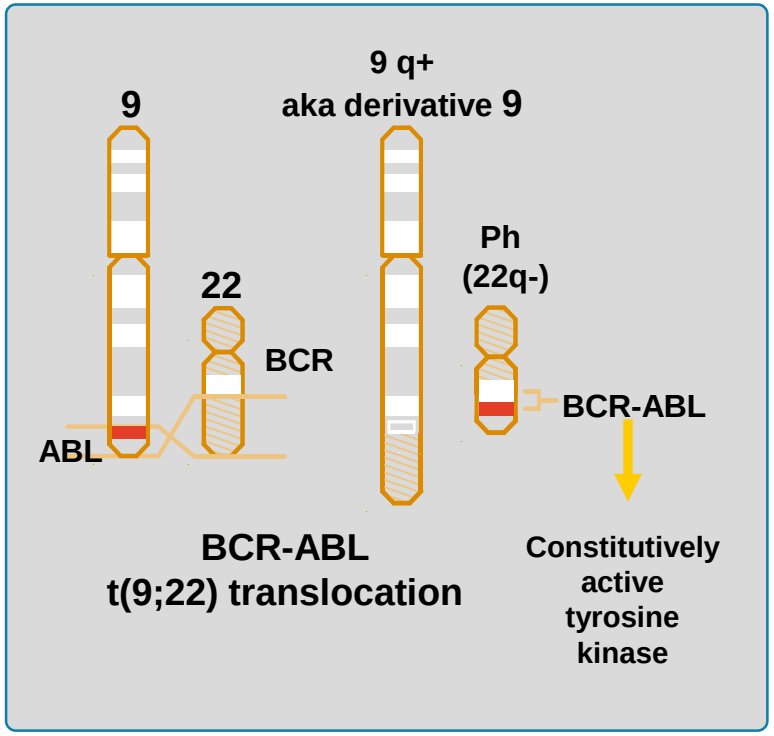


Janet Rowley

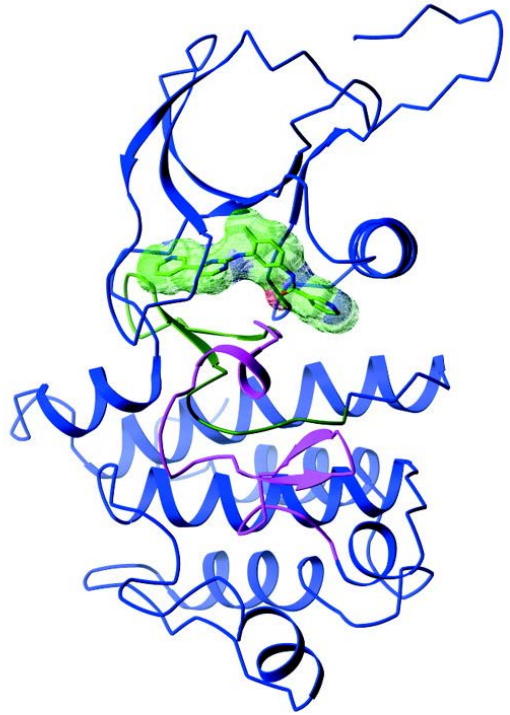


- The first chromosomal abnormality
- The first cytogenetic rearrangement

- The first targeted therapy



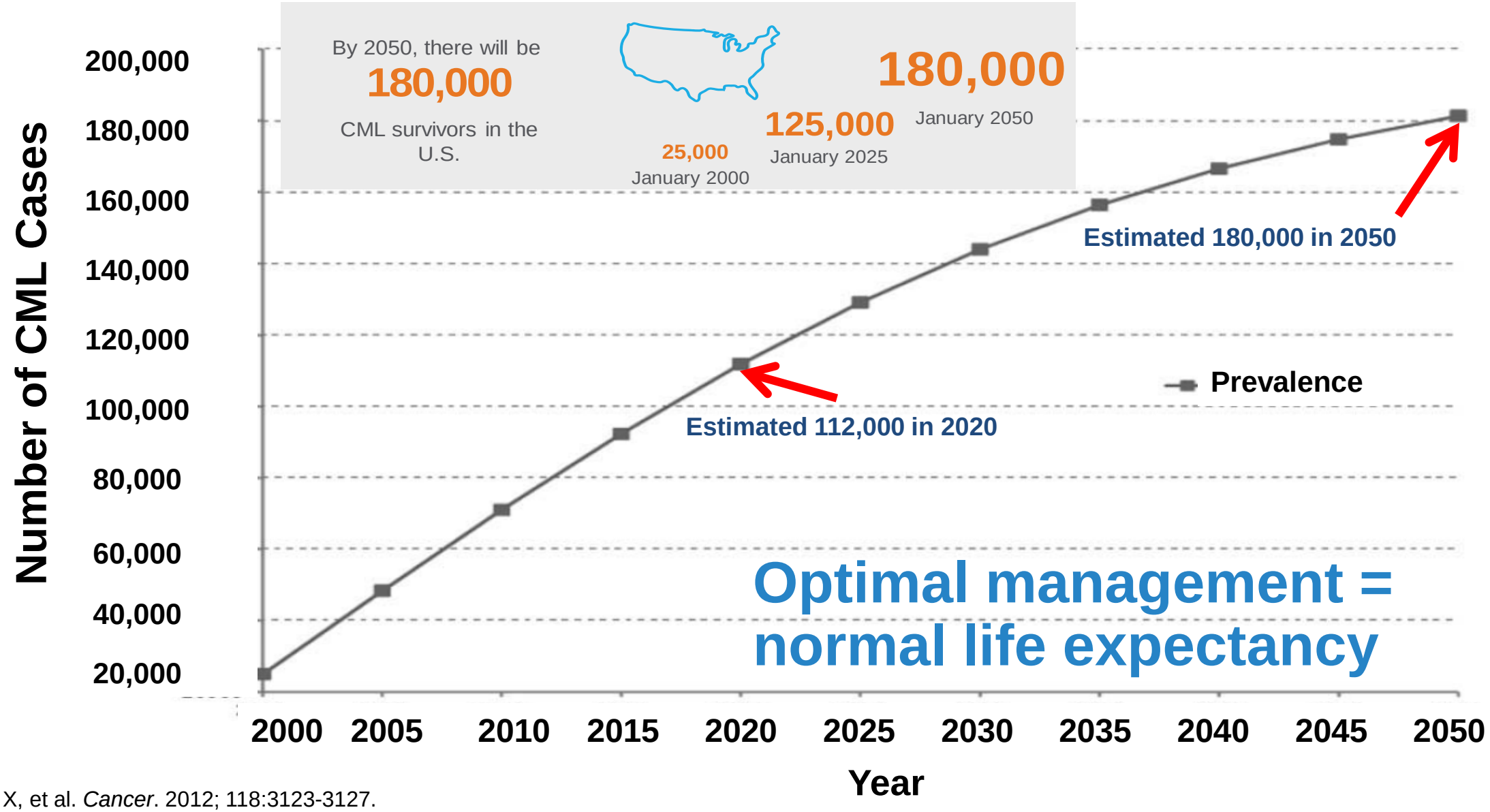
Crystal structure of the catalytic domain of Abl complexed to imatinib



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/

The Uncommon Becomes Common



Huang X, et al. *Cancer*. 2012; 118:3123-3127.
Bower H, et al. *J Clin Oncol*. 2016;34:2851-2857

CML treatment choices in 2020

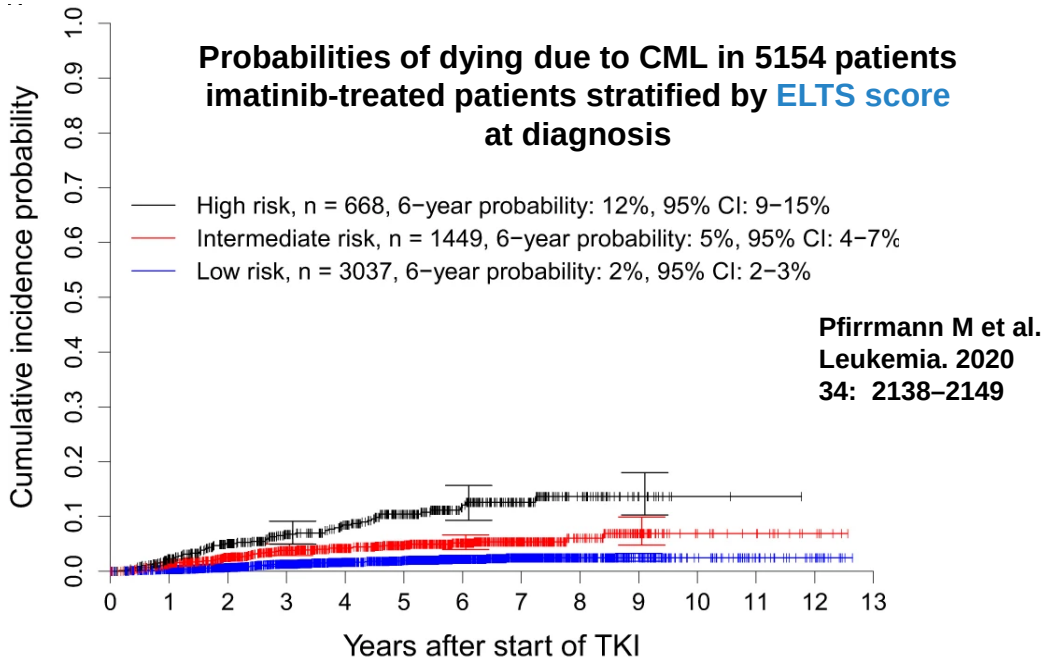
Compound	TKI Generation	First Line	Second Line	Third Line
Imatinib	First	●		
Dasatinib	Second	●	●	●
Nilotinib	Second	●	●	●
Bosutinib	Second	●	●	●
Ponatinib	Third		● (T315I)	● (T315I or “for whom no other tyrosine kinase inhibitor therapy is indicated”)
Omacetaxine	NA			●

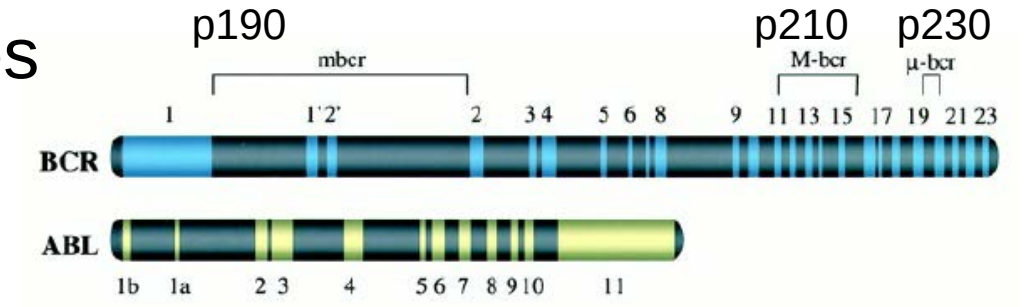
Identifying higher-risk patients at diagnosis:

Risk scores, cytogenetic and molecular abnormalities

Identifying risky CP CML patients at diagnosis

- Sokal, Hasford (*EURO)*
- **NEW: EUTOS Long-term survival Score (ELTS)**
  1. Same clinical and lab parameters as Sokal, but weighting is different
  2. Classifies fewer patients as high-risk and is better at identifying patients at risk for dying of CML
- Additional chromosomal abnormalities
- p190 transcript has been associated with poorer outcomes



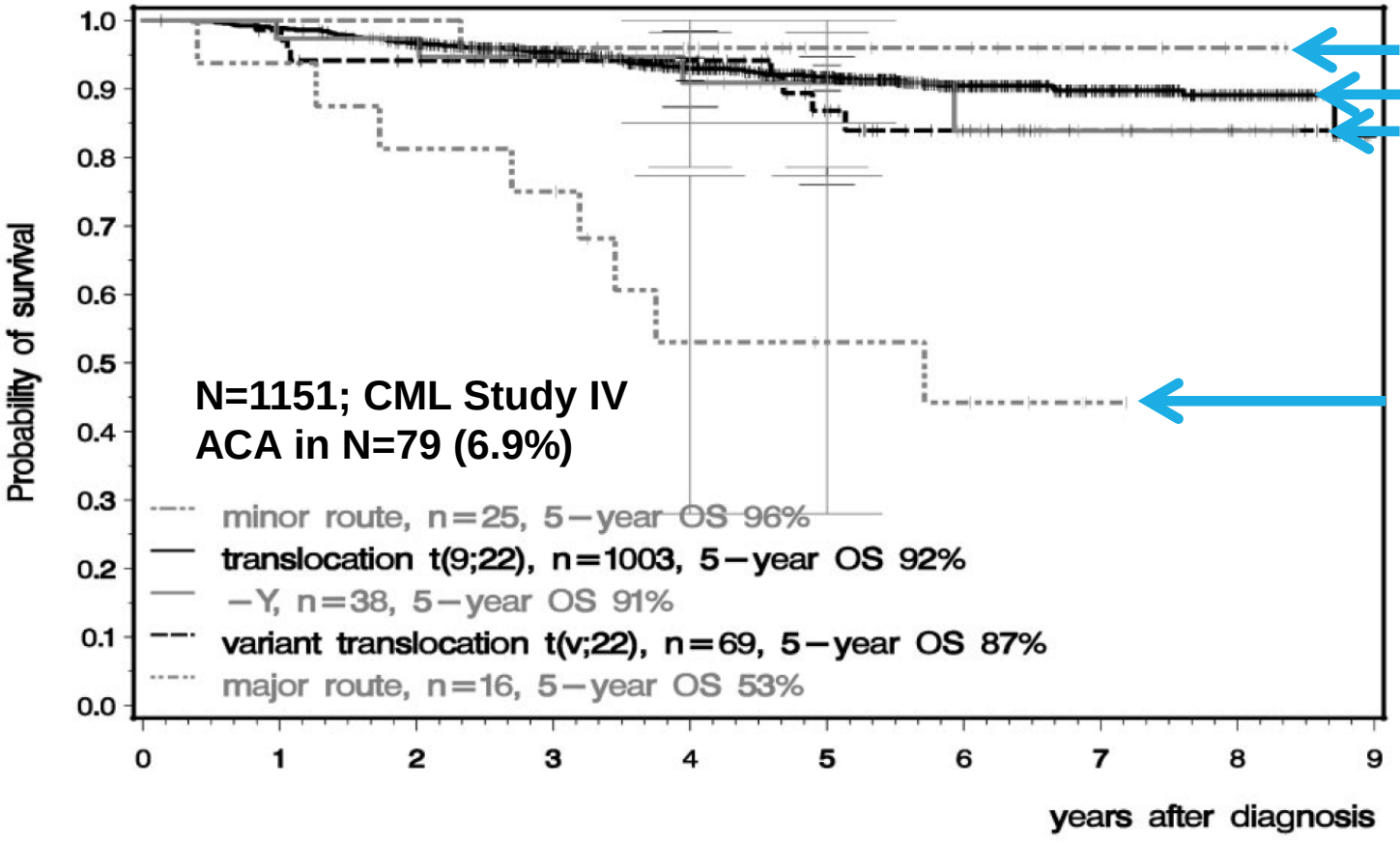


Castagnetti et al. J Clin Oncol. 2010; 28(16): 2748
Quintas-Cardama et al. Cancer. 2011; 117: 5085
Jain P et al. Blood, 2016 127:1269-1275
Geelen IGP et al. Leukemia. 2018;32(10):2299-2303.

Testoni et al. Blood. 2011; 117: 6793
Verma et al. Blood. 2009; 114: 2232
Eunice Laurent et al. Cancer Res 2001; 61:2343-2355

Additional cytogenetic abnormalities (ACA) at diagnosis or acquired during therapy impact TKI response

Major Route (more common)	Minor Route (rarer)
trisomy 8, second Ph chromosome, isochromosome (17)(q10)], and complex karyotype	t(3;12), t(4;6), t(2;16), and t(1;21)



Minor route ACA - 5-year OS 96%
t(9;22) alone – 5-year OS 92%
Variant translocation 5-year OS 87%

Major route ACA 5-year OS 53%

Consider patients with the following higher-risk

1. isochrome(17q), -7/del7q, 11q23, 3q26.2 aberrations, or complex aberrant karyotypes
2. *trisomy 8, 2nd Ph-chromosome, trisomy 19* may be less worrisome

Fabarius et al. Blood. 2011 Dec 22;118(26):6760-8.
Fabarius et al. Ann Hematol. 2015;94(12):2015-2024.
Wang W et al. Blood. 2016;127(22):2742-2750.

Identifying risky CP CML patients at diagnosis

NOT PROGNOSTIC

- Most variant translocations- (e.g. 3-way rearrangements of the Philadelphia chromosome)
- Other transcripts besides p210 or p190
  - *But much harder to monitor*

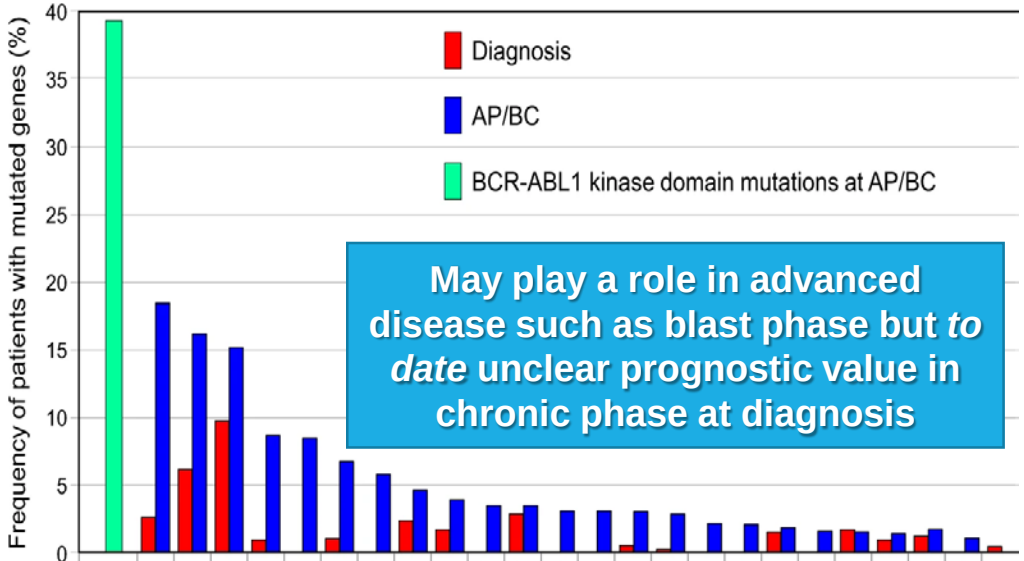
Castagnetti et al. J Clin Oncol. 2010; 28(16): 2748
Quintas-Cardama et al. Cancer. 2011; 117: 5085
Jain P et a. Blood 2016 127:1269-1275
Testoni et al. Blood. 2011; 117: 6793
Verma et al. Blood. 2009; 114: 2232
Eunice Laurent et al. Cancer Res 2001;61:2343-2355

The mutational landscape in CML at diagnosis and at disease progression

Chronic phase	Accelerated phase	Blast crisis
Driven by Bcr-Abl	Additional cytogenetic changes	Development of acute leukemia
Cell differentiation is intact	Increasing blasts %	Block in differentiation
Median duration 3-5 years	Median duration 6-9 months	Median survival 3-6 months

Median survival is ~7-12 months with TKI therapy

ASXL1 (CDS), CBL (CDS), CSF3R (Exons 14, 15, 17), DNMT3A (CDS), EZH2 (Exons 15-20), FBXW7 (CDS), FGFR1 (Exons 4, 11-17, partial 18), FLT3 (p.D835H), GATA1 (Exons 2-3), GATA2 (Exons 3-5), HRAS (Exon 1-2), Hotspot, IDH1(p.R132), IDH2 (Exon 4), JAK2 (Exon 12, 14, 16), KIT (8-18), KMT2A (CDS), KRAS (CDS), MAP2K1 (Exons 2, 3, 6), MPL (Exon 10), MYD88 (Exon 3-5), NGS, NOTCH1 (Exons 20, 26, 27), NPM1 (Exon 12), NRAS (CDS), PDGFRA (Exons 12-18), PHF6 (CDS), PTEN (CDS), RB1 (CDS), RUNX1 (Exon 4-8), SF3B1 (Exon 14-16), SRSF2 (Exon 1), STAG2 (CDS), STAT3 (Exons 20-21), TET2 (CDS), TP53 (CDS), U2AF1 (Exons 2, 6), WT1 (CDS), ZRSR2 (CDS)



	BCR-ABL1 kinase domain	RUNX1	IKZF1 exon deletion	ASXL1	BCORL1	GATA2	TET2	WT1	DNMT3A	TP53	SETBP1	SETD1B	PHF6	BCOR	PTPN11	IDH1	IDH2	CBLB	JAK2	NRAS	KMT2D	CBL	IKZF1 SNV/indel	KRAS	EZH2
Diagnosis																									
No. of patients tested		349	49	518	109	109	439	224	348	237	209	109	209	209	209	489	489	209	323	224	333	224	333	224	348
No. with variants		9	3	50	1	0	4	0	8	4	0	3	0	0	1	1	0	0	5	0	4	2	4	0	2
%		2.6	6.1	9.7	0.9	0	0.9	0	2.3	1.7	0	2.8	0	0	0.5	0.2	0	0	1.5	0	1.2	0.9	1.2	0	0.6
AP/BC																									
No. of patients tested	89	191	106	199	58	143	165	105	66	206	58	58	66	66	67	285	285	98	111	191	66	145	126	191	67
No. with variants	35	35	17	30	5	12	11	6	3	8	2	2	2	2	2	8	6	2	2	2	1	2	1	2	0
%	39.3	18.3	16.0	15.1	8.6	8.4	6.7	5.7	4.5	3.9	3.4	3.4	3.0	3.0	3.0	2.8	2.1	2.0	1.8	1.6	1.5	1.4	0.8	1.0	0

- Increased frequency of these mutations as CML progresses from chronic phase to accelerated or blast phase
- Most common mutations detected are RUNX1, IKZF1, and ASXL1

Branford et al. Leukemia (2019) 33:1835–1850.

Selecting 1st line therapy

Selecting first-line therapy: NCCN 1.2021

Risk stratify: Sokal, Hasford, and EUTOS long-term survival 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

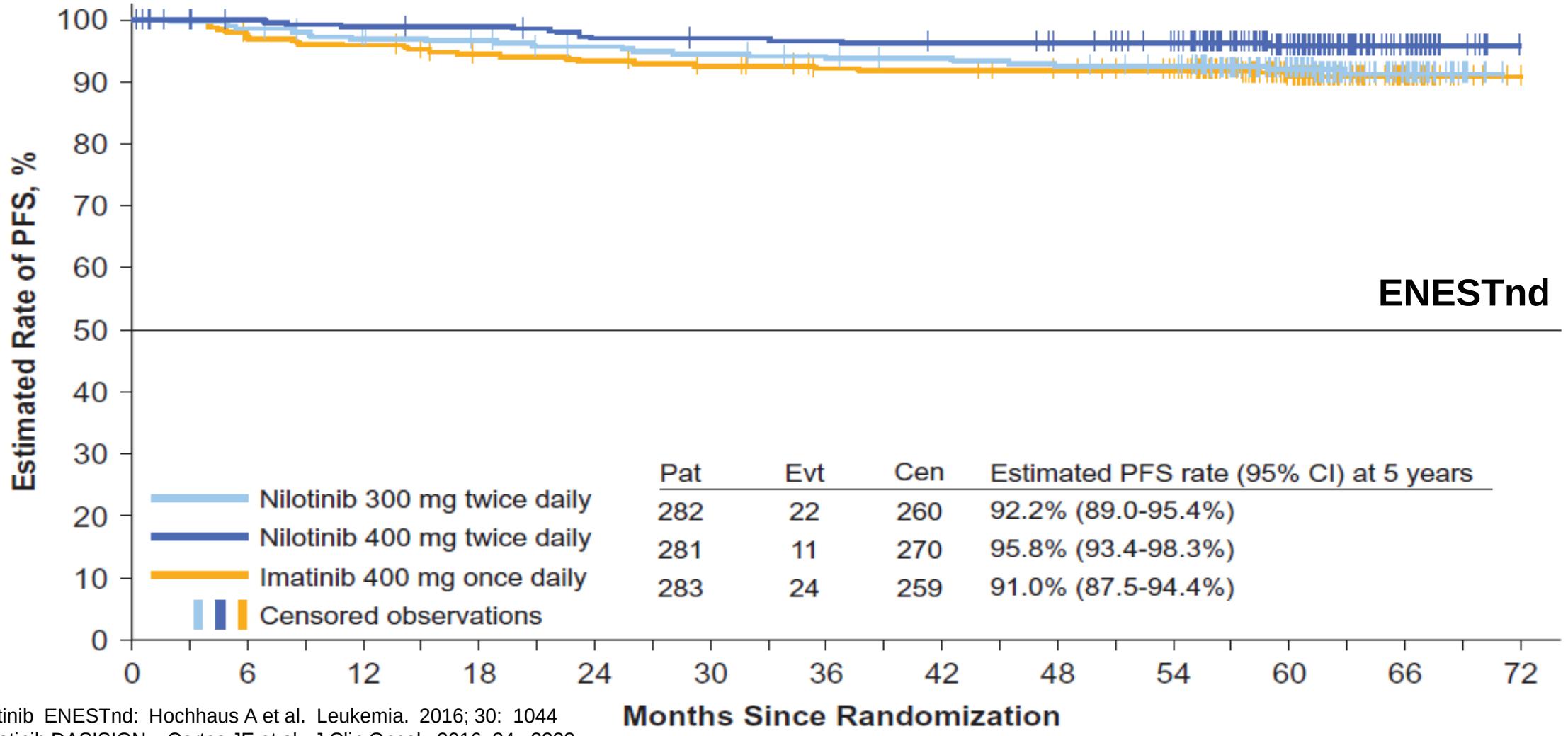
Other recommended regimen:**
- Imatinib or generic imatinib 400 mg QD

* Based on preliminary data from the BFORE trial and long-term follow-up data from the DASISION and ENESTnd trials, **second-generation TKIs 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

No difference in PFS or OS for 1st vs. 2nd generation TKIs



Nilotinib ENESTnd: Hochhaus A et al. Leukemia. 2016; 30: 1044
Dasatinib DASISION : Cortes JE et al. J Clin Oncol. 2016; 34: 2333
Bosutinib BFORE: Cortes JE et al. J Clin Oncol. 2018 2018; 36: 231

Benefits of first-line 2nd generation TKI use: fewer mutations

ENESTnd

	Nilotinib 300 mg twice daily (n = 282), n	Nilotinib 400 mg twice daily (n = 281), n	Imatinib 400 mg once daily (n = 283), n
Patients with mutations	12	11	22
New mutations by Sokal score			
Low	1	2	1
Intermediate	5	3	8
High	6	6	13

Hochhaus A et al. Leukemia. 2016 May;30(5):1044-54

Benefits of first-line 2nd generation TKI use: fewer cases of progression to AP or BC on nilotinib

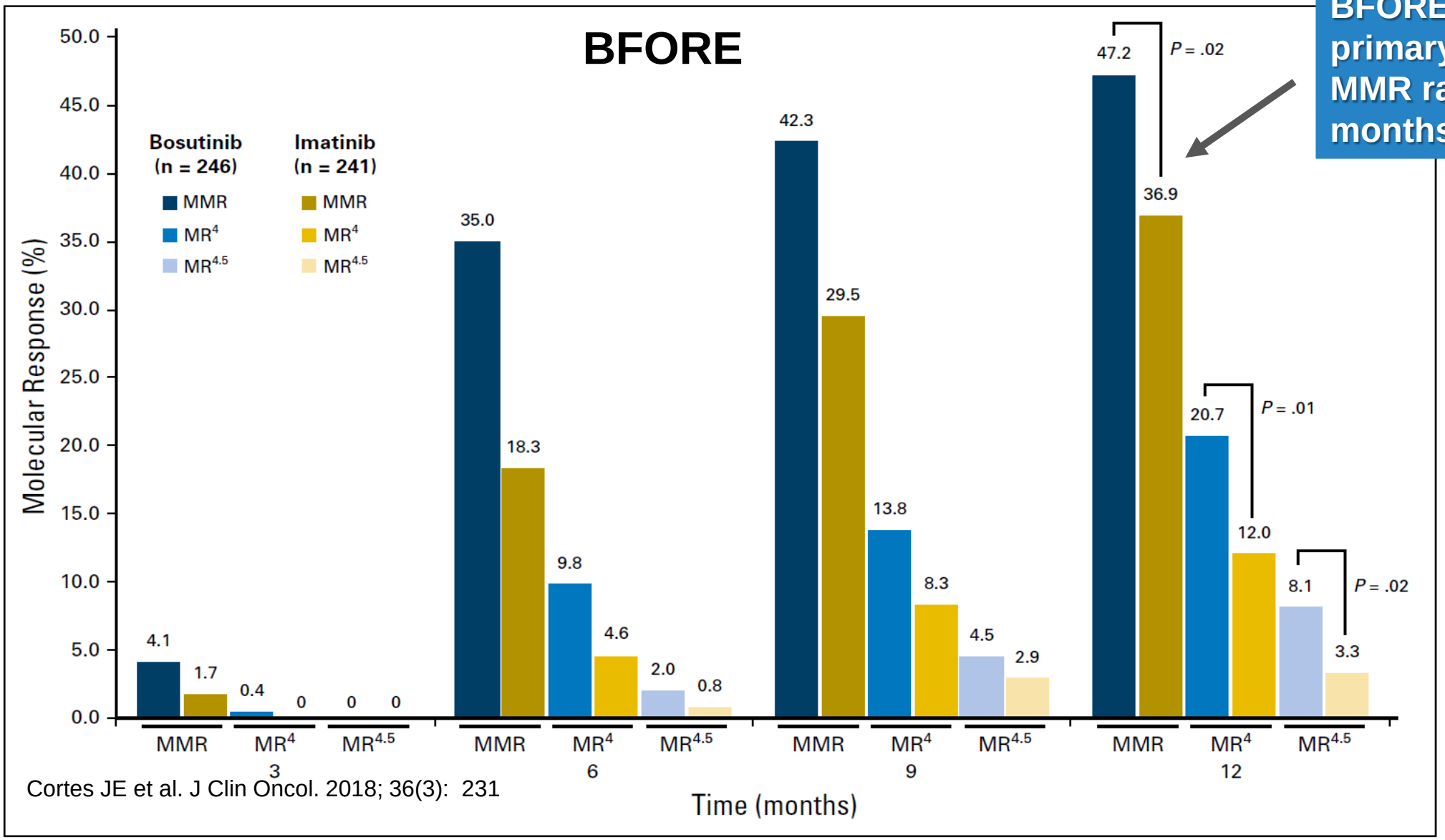
Table 1. Long-term patient outcomes

	Nilotinib 300 mg twice daily (n = 282)	*Nilotinib 400 mg twice daily (n = 281)*	*Imatinib 400 mg once daily (n = 283)*
Progression to AP/BC			
Progression to AP/BC on core treatment, *n*	2	3	12
Estimated 5-year freedom from progression to AP/BC on core treatment, % (95% CI)[a]	99.3 (98.2–100)	98.7 (97.2–100)	95.2 (92.6–97.9)
HR vs imatinib (95% CI)[b]	0.1599 (0.0358–0.7143)	0.2457 (0.0693–0.8713)	—
P vs imatinib[c]	0.0059	0.0185	—
Progression to AP/BC on study, *n*	10	6	21
Estimated 5-year freedom from progression to AP/BC on study, % (95% CI)[a]	96.3 (94.1–98.6)	97.8 (96.0–99.5)	92.1 (88.8–95.3)
HR vs imatinib (95% CI)[b]	0.4636 (0.2183–0.9845)	0.2753 (0.1111–0.6821)	—
P vs imatinib[c]	0.0403	0.0028	—

- *On core treatment: 69 (59.9%), 174 (61.9%) and 141 (49.8%) patients in the nilotinib 300-mg twice-daily, nilotinib 400-mg twice-daily and imatinib arms, respectively, remained on core treatment*
- *On study: on treatment or in follow-up after discontinuation of study treatment*

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

Benefits of first-line 2nd generation TKI use: more rapid MMR and deeper MR



BFORE study primary endpoint MMR rate at 12 months

Cortes JE et al. J Clin Oncol. 2018; 36(3): 231

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.

Increased risk for pulmonary arterial hypertension on dasatinib

- Incidence estimated at less than 1%
- 41 cases of PAH confirmed by right heart catheterization
- 68% presented with synchronous pleural effusion
- No clear relationship with dasatinib dose
- Occurred anywhere from < 1 month to 7 years
- 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

Nilotinib and increased risk for arterial vascular events

ENESTnd 6-year Update

Patients With an Event, n (%)	Nilotinib 300 mg BID n = 279	Nilotinib 400 mg BID n = 277	Imatinib 400 mg QD n = 280
	Total, n (%)	Total, n (%)	Total, n (%)
Peripheral arterial occlusive disease (PAOD)	12 (4.3%)	9 (3.2%)	0
Ischemic heart disease	14 (5%)	28 (10.1%)	6 (2.1%)
Ischemic cerebrovascular events	4 (1.4%)	9 (3.2%)	1 (0.4%)
Other	4 (1.4%)	3 (1.1%)	0
	28 (10%)	44 (15.9%)	7 (2.5%)

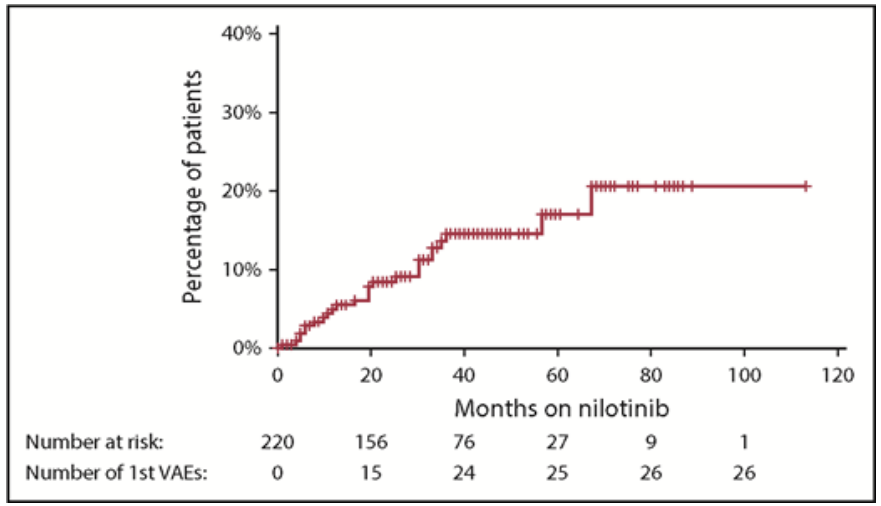
Larson RA, et al. Blood. 2014:[American Society of Hematology Meeting 2014, abstract 4541]
Hochhaus A et al. Leukemia (2016) 30, 1044–1054
Steegman JL et al. Leukemia. 2016 Aug;30(8):1648-71

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%)

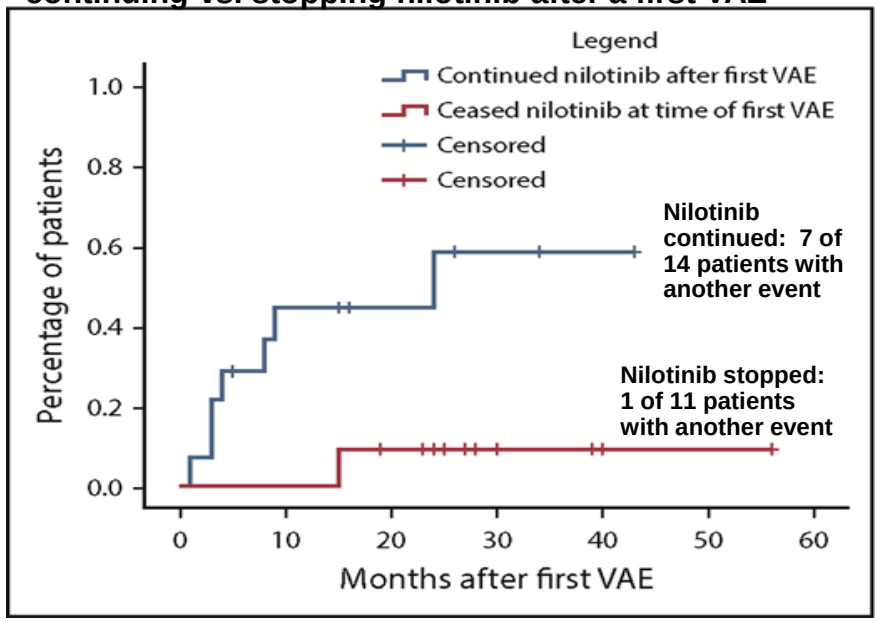
220 patients treated with nilotinib for chronic myeloid leukaemia in chronic phase at 17 Australian institutions

Cumulative incidence of first VAE



26 patients with first arterial vascular event

Cumulative incidence of second VAEs in patients continuing vs. stopping nilotinib after a first VAE



- 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.

Considerations when selecting 1st line therapy

Goals:	Tyrosine kinase inhibitor:
• Life expectancy not impacted by CML	• Imatinib, 2nd generation TKI
• Overcome higher risk CML	• ***2nd generation TKI,*** imatinib
• Treatment-free remission	• **2nd generation TKI,** imatinib
• Limit impact of TKI therapy on co-morbidity outcomes	• **Imatinib,** 2nd generation TKI
• Quality of life/minimizing adverse events	• Imatinib, 2nd generation TKI
• Family planning	• **2nd generation TKI,** imatinib
• Limiting costs	• **Imatinib**

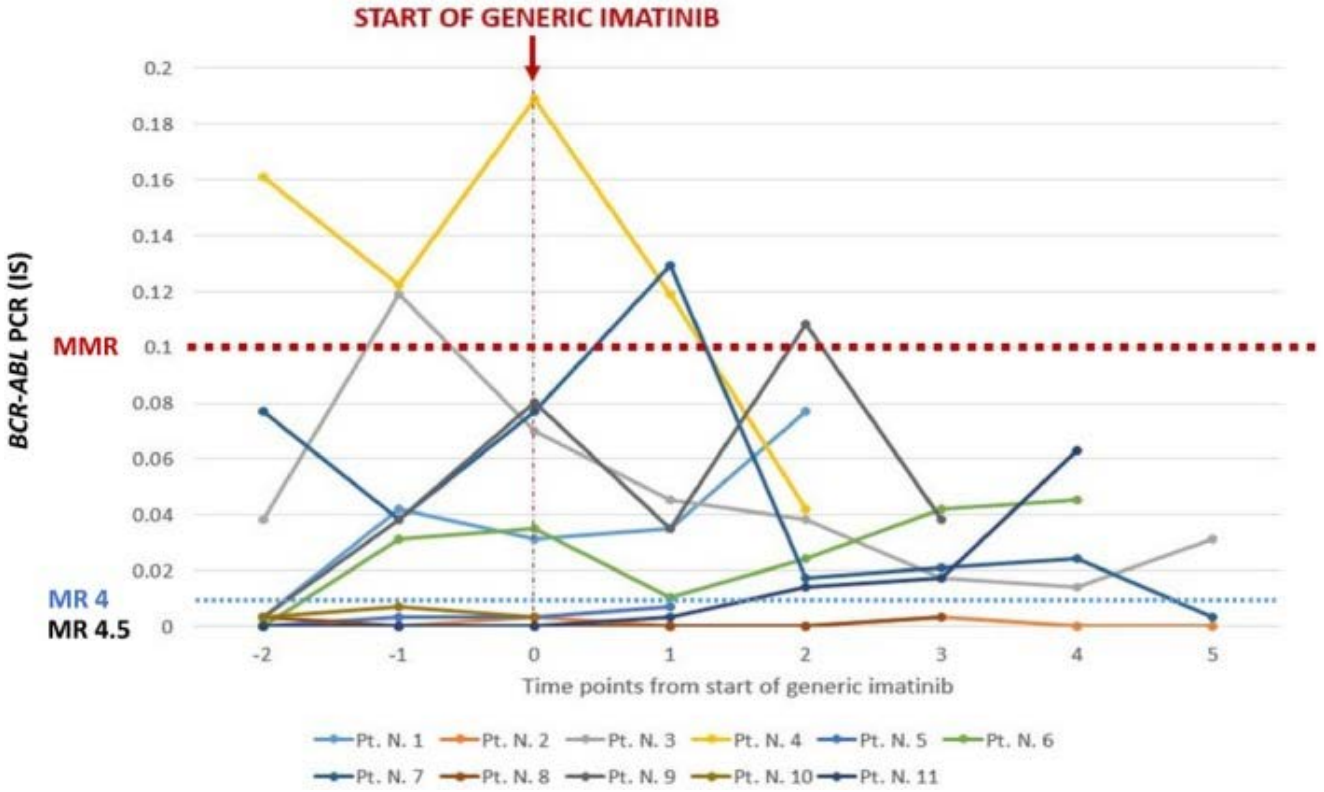
- Imatinib is generic and had an excellent safety profile
- Medical comorbidities may make nilotinib, dasatinib, or bosutinib a less optimal choice vs. imatinib
  1. Atherosclerotic cardiovascular disease, tobacco, T2DM, early family history – *increased risk with nilotinib*
  2. Pulmonary hypertension or pleural effusion – *increased risk with dasatinib*
  3. Hepatitis, liver disease, pancreatitis –*increased risk for transaminitis with nilotinib or bosutinib*
  4. IBD – *increased risk of diarrhea with bosutinib*

Requires close follow-up

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

Oehler VG. First Generation vs. Second Generation TKI - Which is Best At Diagnosis of Chronic Phase Chronic Myeloid Leukemia? ASH Annual Meeting 2020. CML Education Session

No difference between generic and branded imatinib after switch



- **Change from original to generic imatinib appears to maintain efficacy and safe**
- 38 patients
  - 100% CCyR
  - 95% MMR
  - 74% MR4.5
- Received generic IM for median of 19.4 mos (range 3.4-46.3 mos)
- Response after switch
  - Stable: 89%
  - Improved: 8%
  - Worsened: 3%
- Adverse events were mild, **although side effect may vary**

Dalle et al. Cancer Med. 2019 Nov;8(15):6559-6565.

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

NCCN Guidelines Version 1.2021: 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

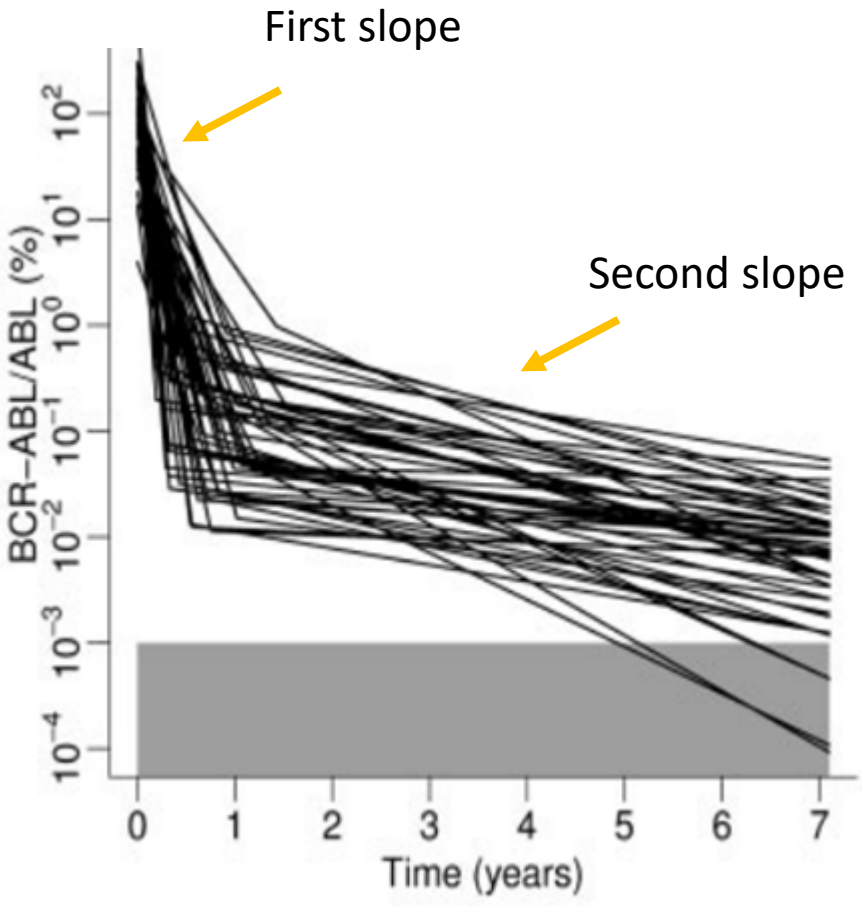
COLOR	CONCERN	CLINICAL CONSIDERATIONS	SECOND-LINE TREATMENT
RED	TKI-resistant disease	• Evaluate patient compliance and drug interactions • Consider mutational analysis	Switch to alternate TKI and evaluate for allogeneic HCT
YELLOW	Possible TKI resistance	• Evaluate patient compliance and drug interactions • 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

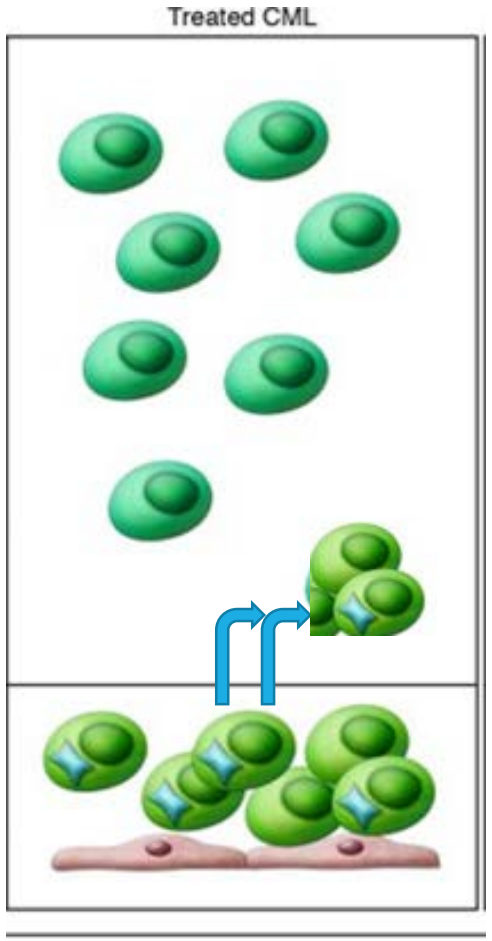
Maintaining quality of life and response: TKI cessation and dose reduction

Benefits of treatment-free remission

- Limit long-term adverse events
- Improve quality of life
- Family planning
- Minimize costs

CML stem cell eradication





Progenitor cell compartment: ***sensitive to TKI***

Stem cell eradication

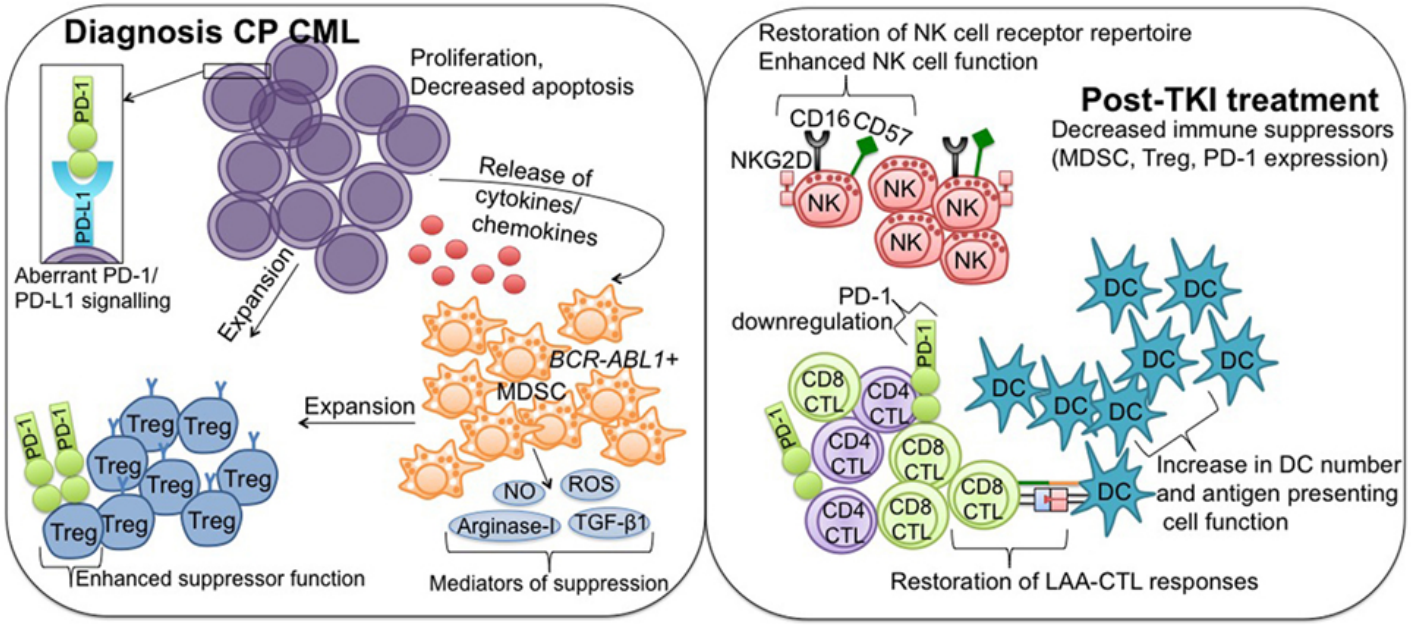
CML stem cell compartment: ***resistant to TKI***

During treatment inactive CML cells persist in the stem cell compartment

- **CML stem cell erosion/eradication on TKI therapy**
  - Over time some of the inactivated CML stem cells become activated
  - This leads to a slow eradication of CML stem cells on continued TKI treatment
  - Partly explains why longer treatment with TKI is associated with better success at stopping TKI

Horn M et al. Blood. 2013 Jan 10;121(2):378-84.
Tang M et al. Blood. 2011 Aug 11; 118(6): 1622-1631

Immunological control that helps sustain treatment-free remission

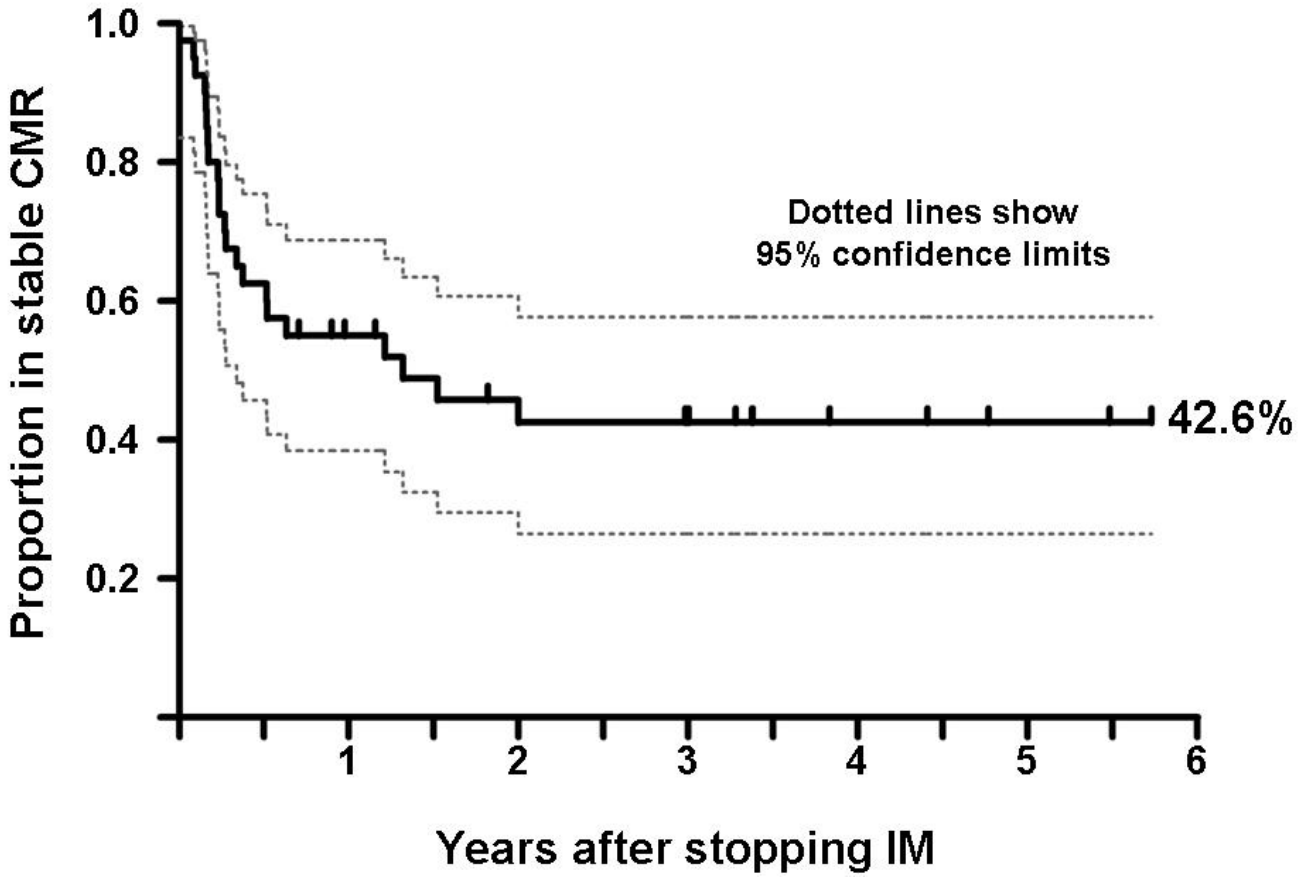


- Patients with deep molecular response have a different immune environment as compared to patients at diagnosis
  - Increased immune activators/surveillance
  - Decreased immune suppressors
- Possible immune cell signature to predict better TKI treatment response and success at stopping therapy

Hughes A and Yong ASM. Front Immunol. 2017; 8: 469.
Hughes et al. Blood. 2017 Mar 2;129(9):1166-1176
Bruck O et al. Leukemia. 2018. 32, pages1643–1656.

Stopping first-line imatinib therapy

Australian CML8 study (TWISTER)

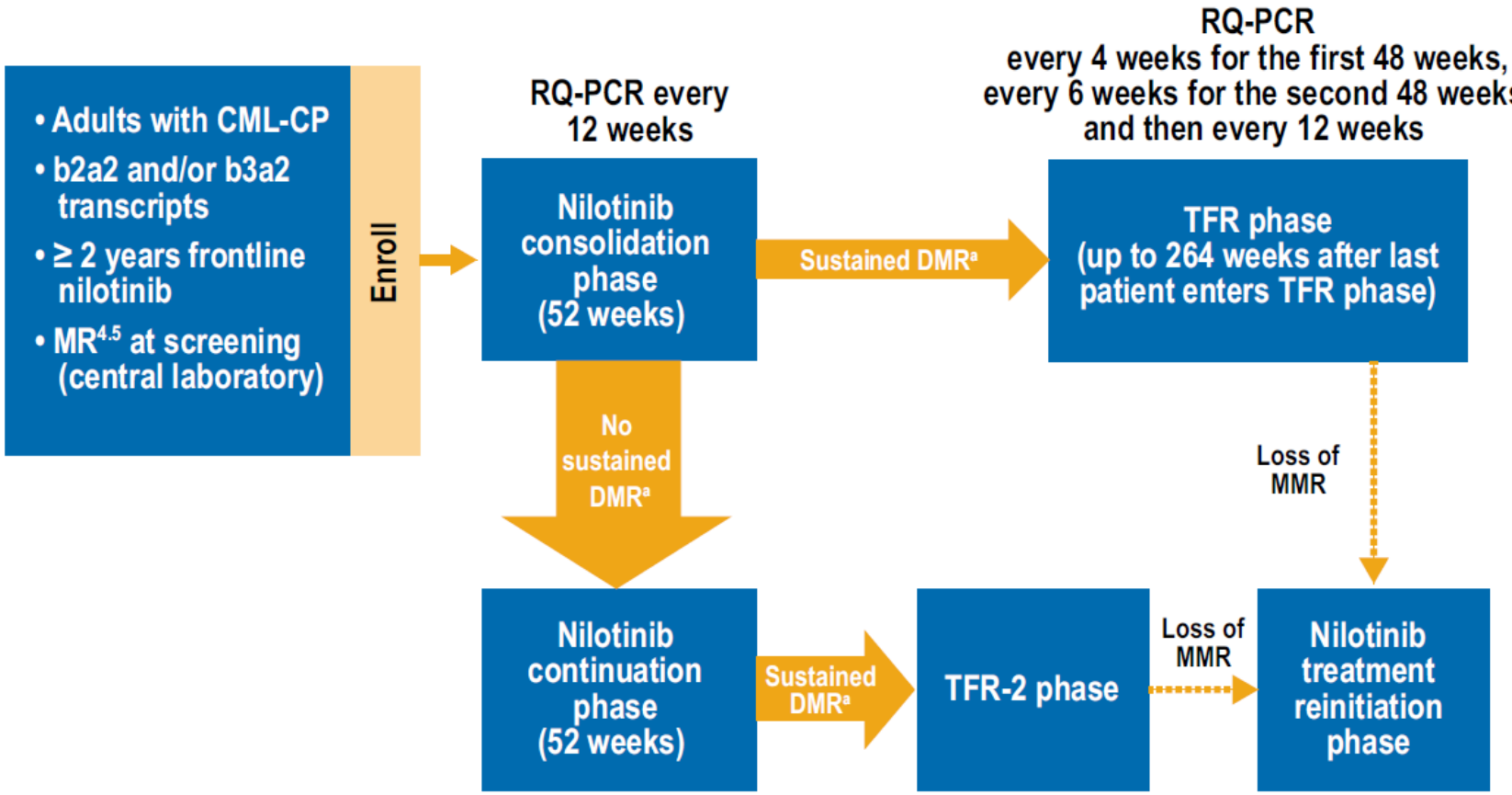


N=40
Entry criteria: BCR-ABL1 IS ≤ 0.0032% (MR4.5 for two years or longer

- Earlier studies stopping IM: **STIM1, STIM2, TWISTER**
  - Very consistent TFR rate at ~45%-50%
  - Most patients restarting therapy achieved former responses
- Stopping 2nd generation TKI
  - STOP-2G TKI: TFR at 48 months 53.6%

Ross DM et al. Blood. 2013 Jul 25;122(4):515-22. Rea D et al. Blood. 2017; 129(7): 846-854.

ENESTfreedom: Stopping 1st-line nilotinib



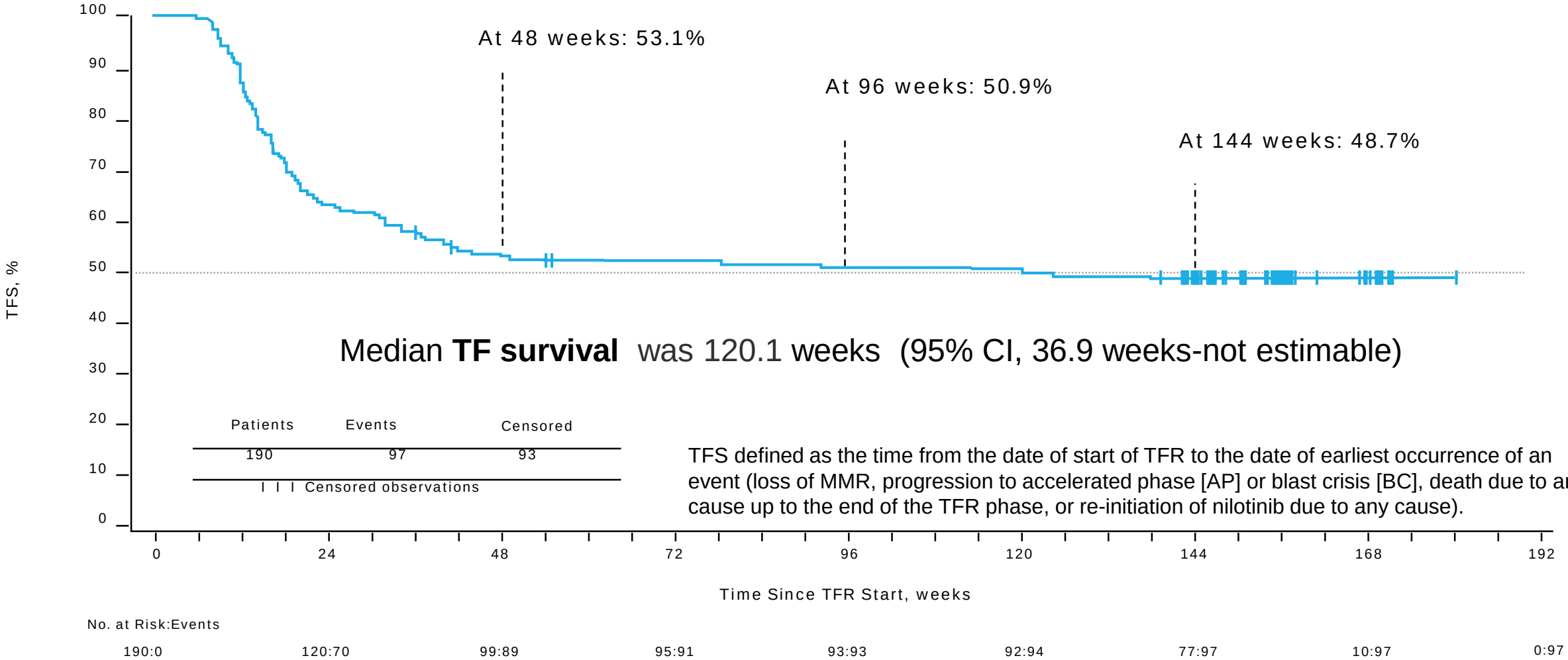
Nilotinib label update includes treatment discontinuation recommendations for CML with sustained molecular responses based on ENESTfreedom and ENESTop

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).

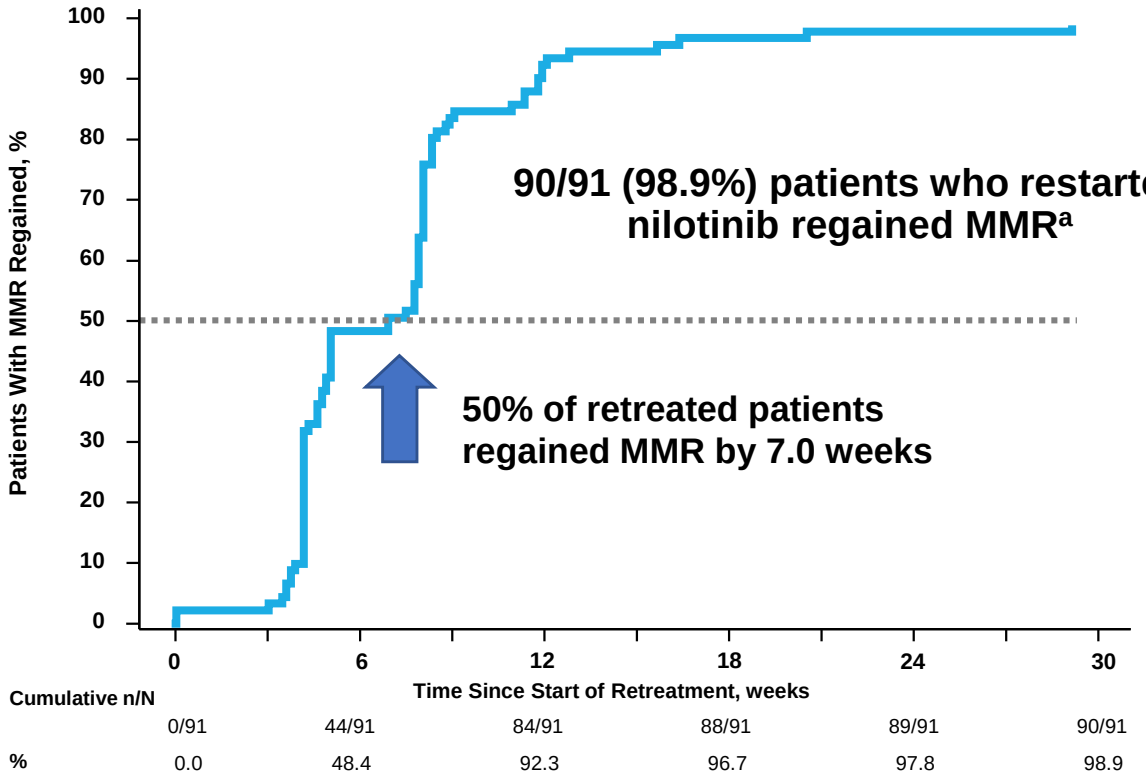
TFS, treatment-free survival.

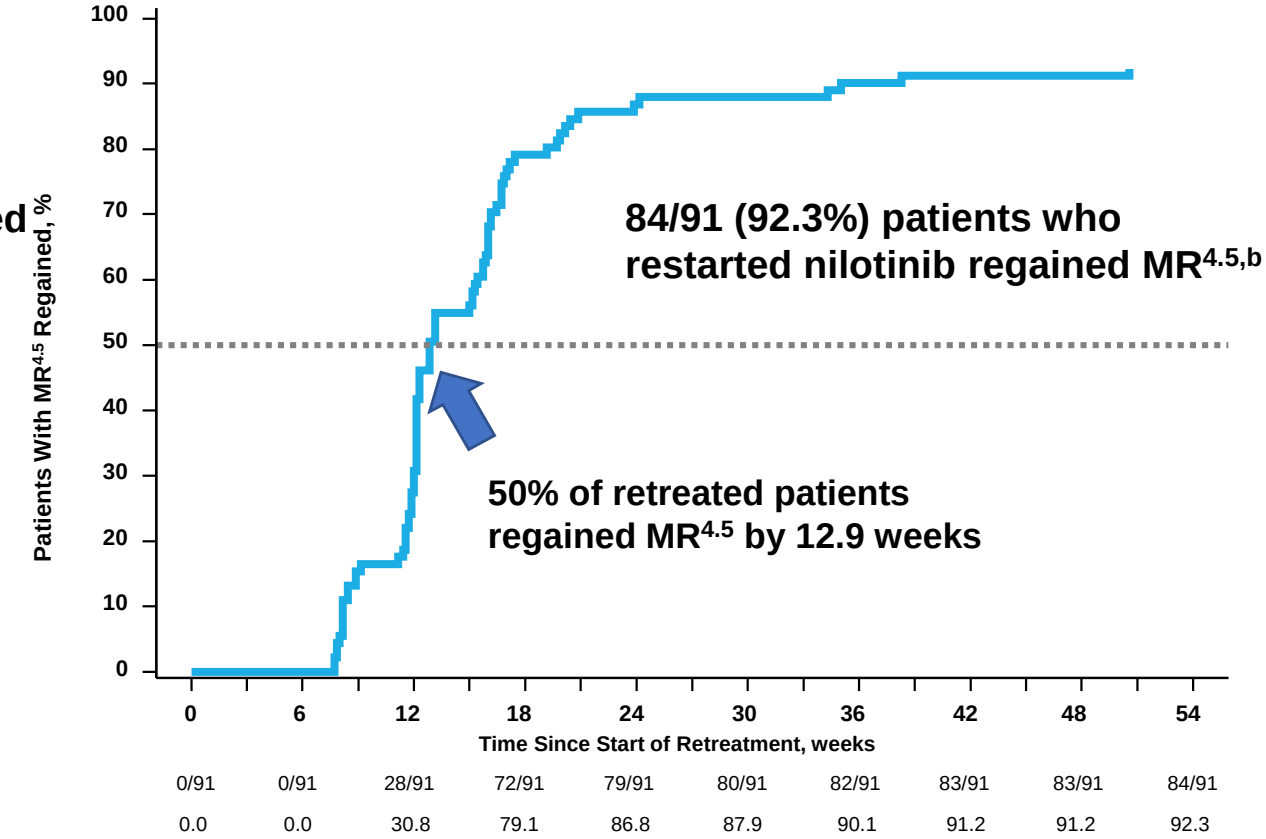
[a] TFS was estimated using the Kaplan-Meier method and was defined as the time from the date of start of TFR to the date of earliest occurrence of an event (loss of MMR, progression to accelerated phase [AP] or blast crisis [BC], death due to any cause up to the end of the TFR phase, or reinitiation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





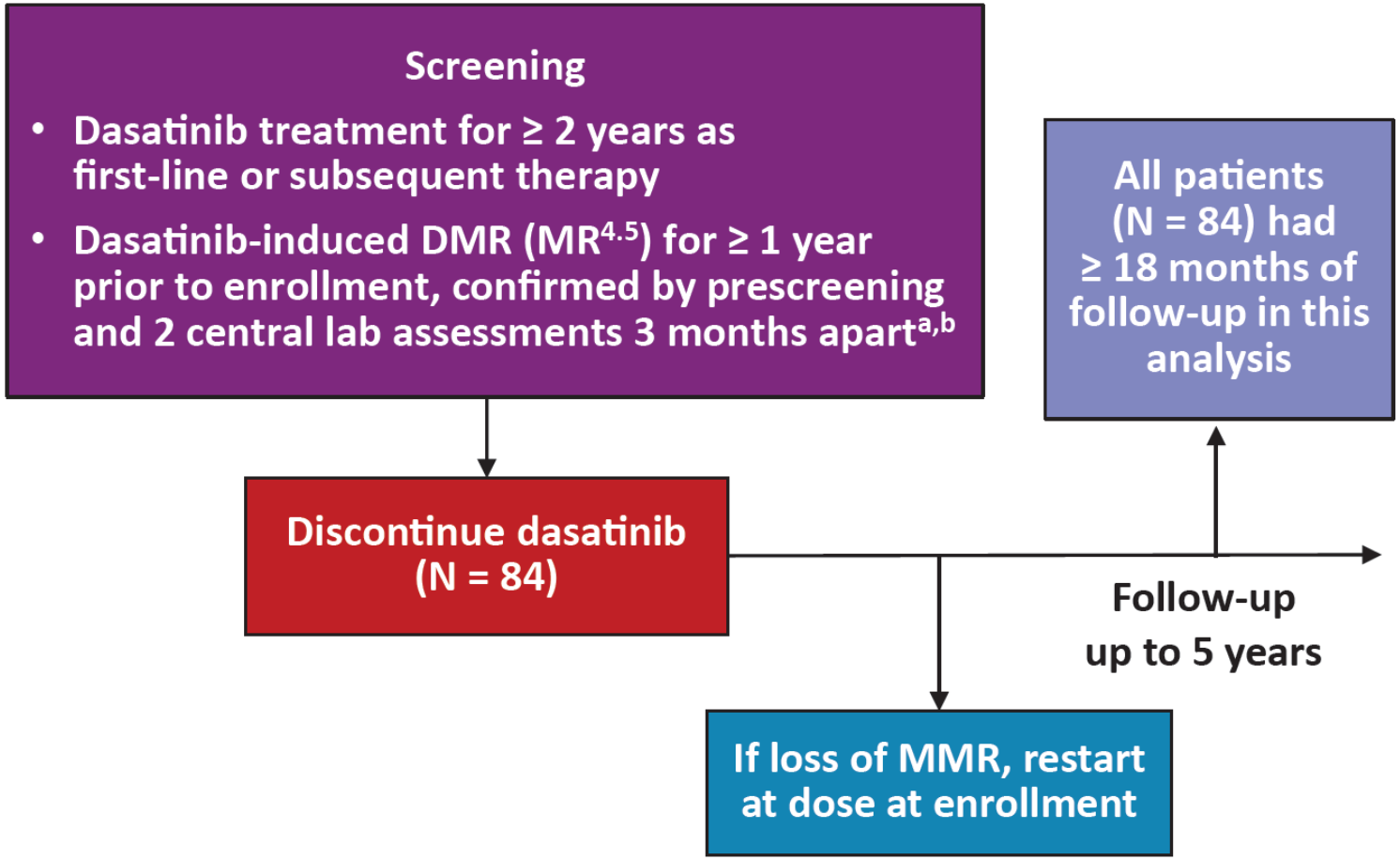
[a] 1 patient discontinued from the study after 7.1 weeks of retreatment without regaining MMR. [b] Of the 6 patients who regained MMR but not $MR^{4.5}$, 1 remained in the reinitiation phase at the data cutoff, and 5 had discontinued from the study (2 due to AEs, 1 due to physician decision, 1 due to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

DASFREE: Stopping dasatinib 1st and 2nd line

- **DASFREE is a phase 2, open-label, single-arm study conducted in North America and Europe**
- ***TFR (proportion of subjects who maintained MMR [BCR-ABL < 0.1%])***



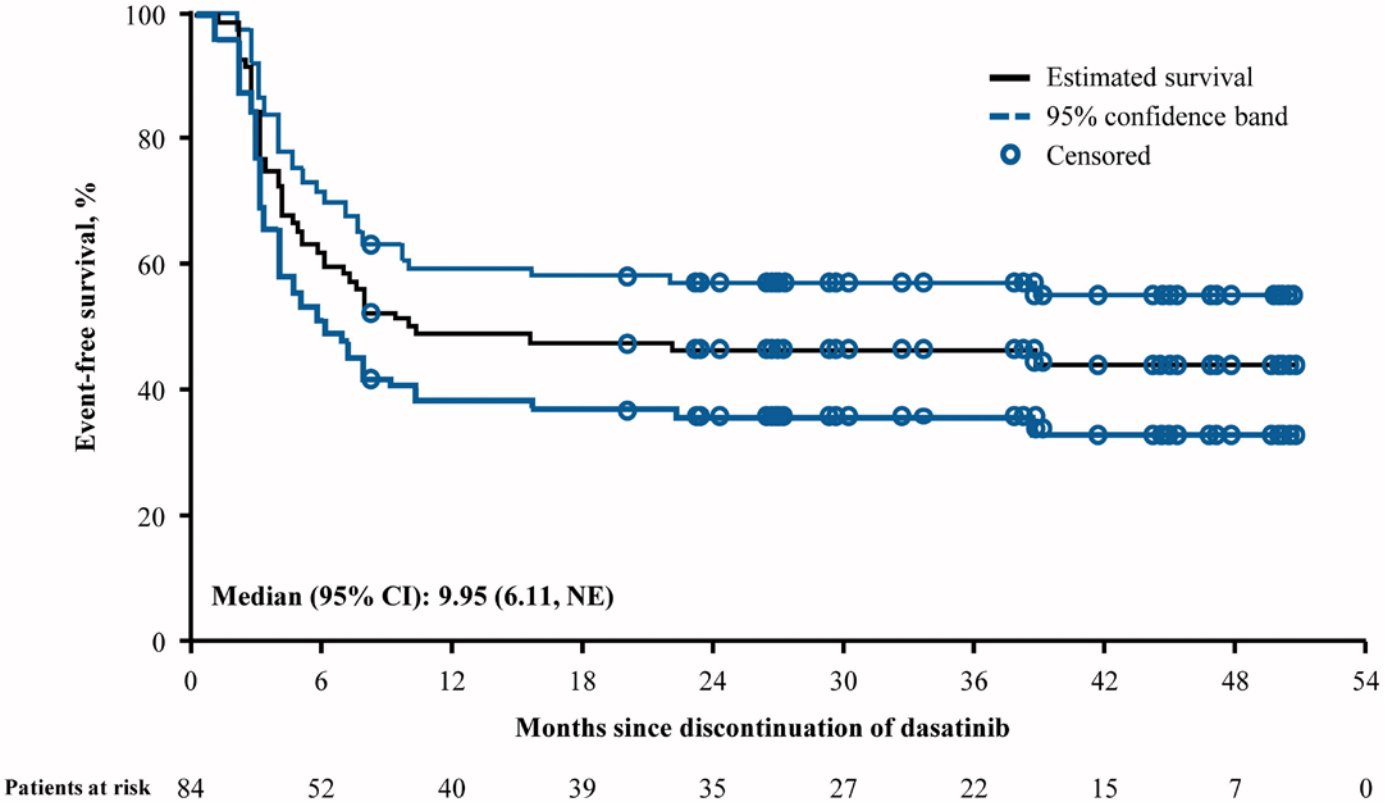
[a] Adults with dasatinib-induced stable DMR for ≥ 9 months, documented by ≥ 3 assessment conducted 2 to 6.5 months apart at a local lab were screened.

[b]For any patient not eligible for enrollment because both assessments at the central lab did not confirm DMR, rescreening was allowed ≥ 9 months after the last central lab screening failure.

DMR = deep molecular response; IS = International Scale; MMR = major molecular response; $MR^{4.5}$ = BCR-ABL1 ≤ 0.0032% on the International Scale.

Shah NP et al. *Blood.* 2018; 132: ASH Meeting Abstract 4253
Shan NP et al . Leuk Lymphoma. 2019 Oct 24:1-10

DASFREE: TFR at 2 years



	2-year TFR, % (95% CI)
Patients on first-line dasatinib	51 (35, 67)
Patients on subsequent lines of dasatinib	42 (28,57)
Resistant	44 (25, 64)
Intolerant	44 (22, 67)

French STOP-2G TKI Study

- 60-month TFR rate 29.8% for patients with prior resistance *versus* 63.6% if no such history

ENESTop stopping 2nd line nilotinib after imatinib

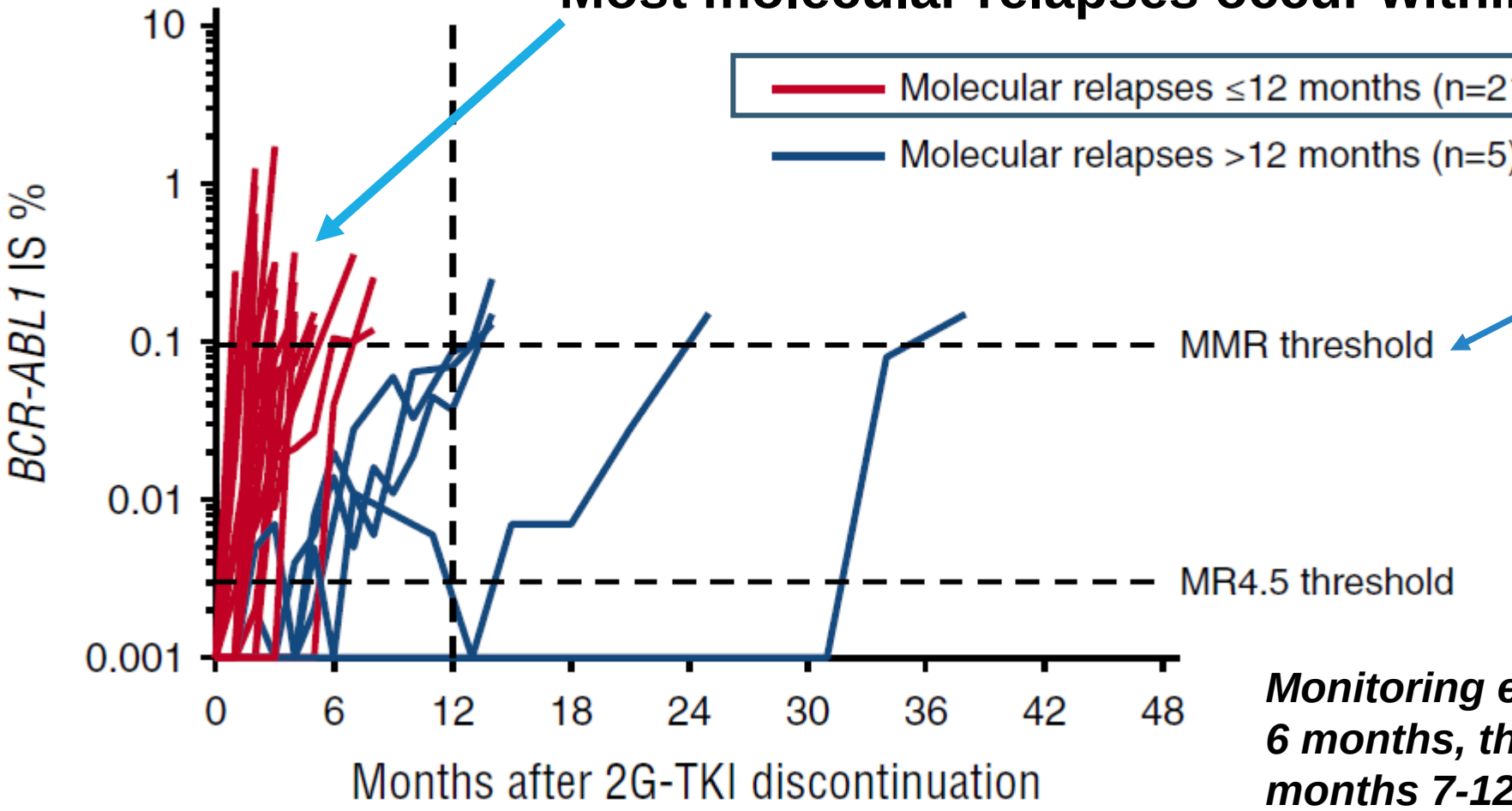
- NO difference in TFR rates if stopping for resistance or intolerance

Shah NP et al. *Blood.* 2018; 132: ASH Meeting Abstract 4253
Shan NP et al . Leuk Lymphoma. 2019 Oct 24:1-10
Rea et al. ASH Annual Meeting 2019, abstract 30

Monitoring is critical

STOP 2G-TKI study

Most molecular relapses occur within 12 months



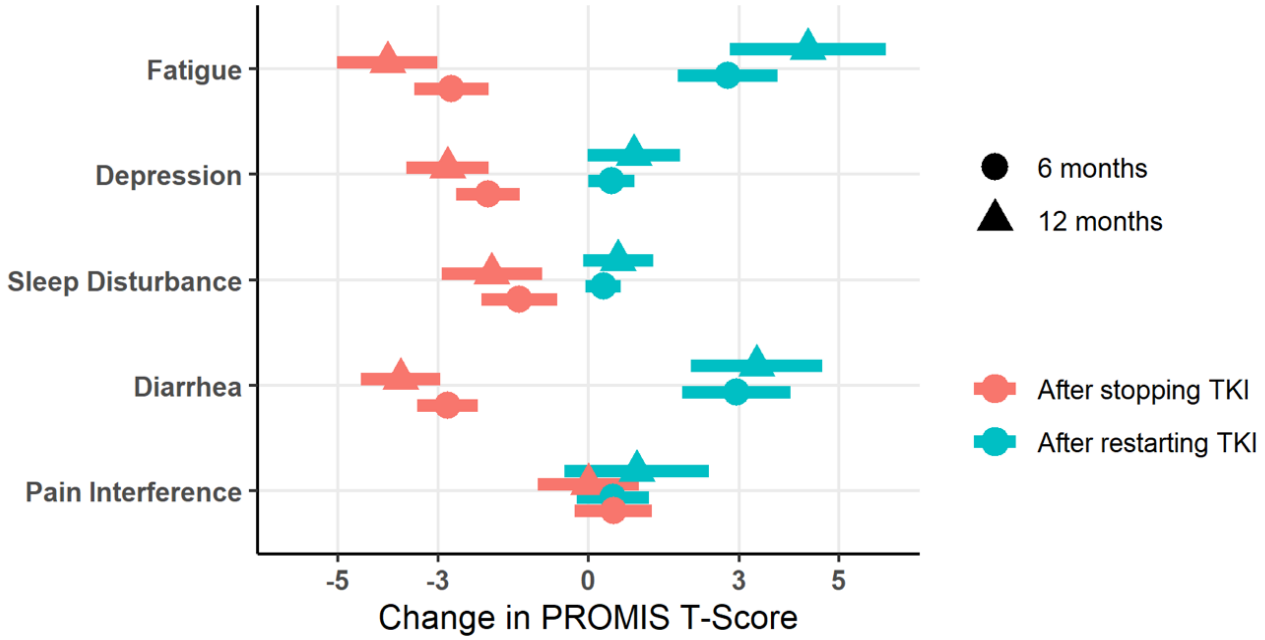
Therapy is typically resumed when MMR is lost

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.

U.S. Life after Stopping TKIs (LAST) Study

First study to prospectively assess patient-reported outcomes (PROs) after stopping (and restarting) TKIs

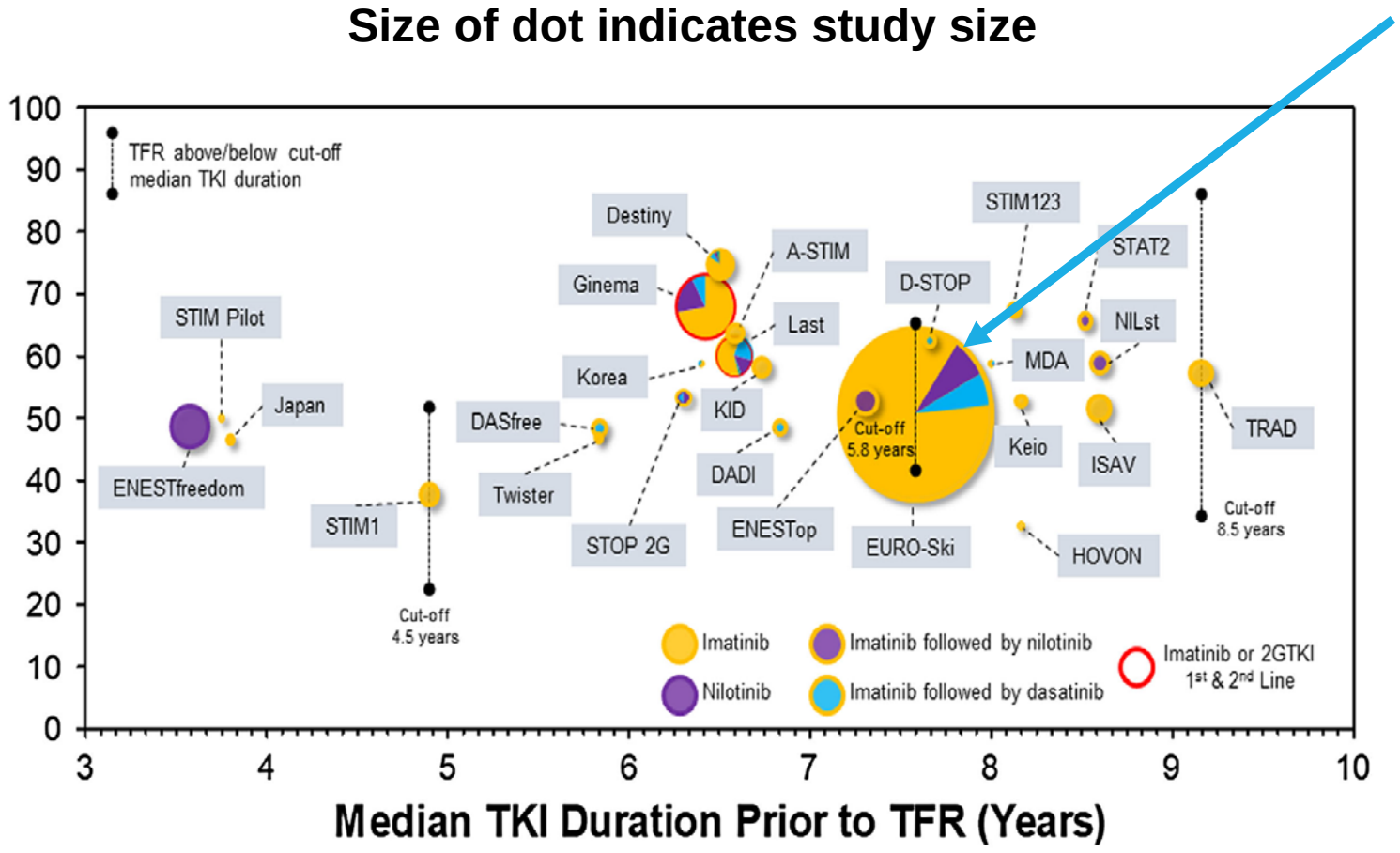


Mean changes (and 95% confidence intervals) in PROs after TKI discontinuation and TKI restart at 6 and 12 mos.

1. 172 patients at 14 US sites
2. 60% TFR at 3 years
3. Significant improvements in fatigue, depression, sleep, and GI symptoms off therapy
4. Molecular relapse occurred most frequently within the first 12 months
5. Rare late relapses were seen
   - 10.2% between 12-24 months
   - 5.1% between 24-36 months
   - 3.4% after 36 months

Atallah E et al. JAMA Oncology. 2020 *in press*

Factors associated with successful TFR



- EURO-Ski

1. **LONGER TKI use**
   - Cut-off >5.8 yrs vs < 5.8 yrs
     - TFR 57% vs. 34%
2. **LONGER period of deep molecular response**
   - For each additional year of MR 4.0 – odds of remaining in MMR by 6 months increased by 13%
3. **No difference:** depth of response when stopping TKI: MR 4.0 vs. MR4.5 v. MR5.0

Laneuville P. Curr. Treat. Options in Oncol. (2018) 19: 15

One downside of treatment-free remission: withdrawal syndrome

LAST study: 3 patients restarted therapy due to 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

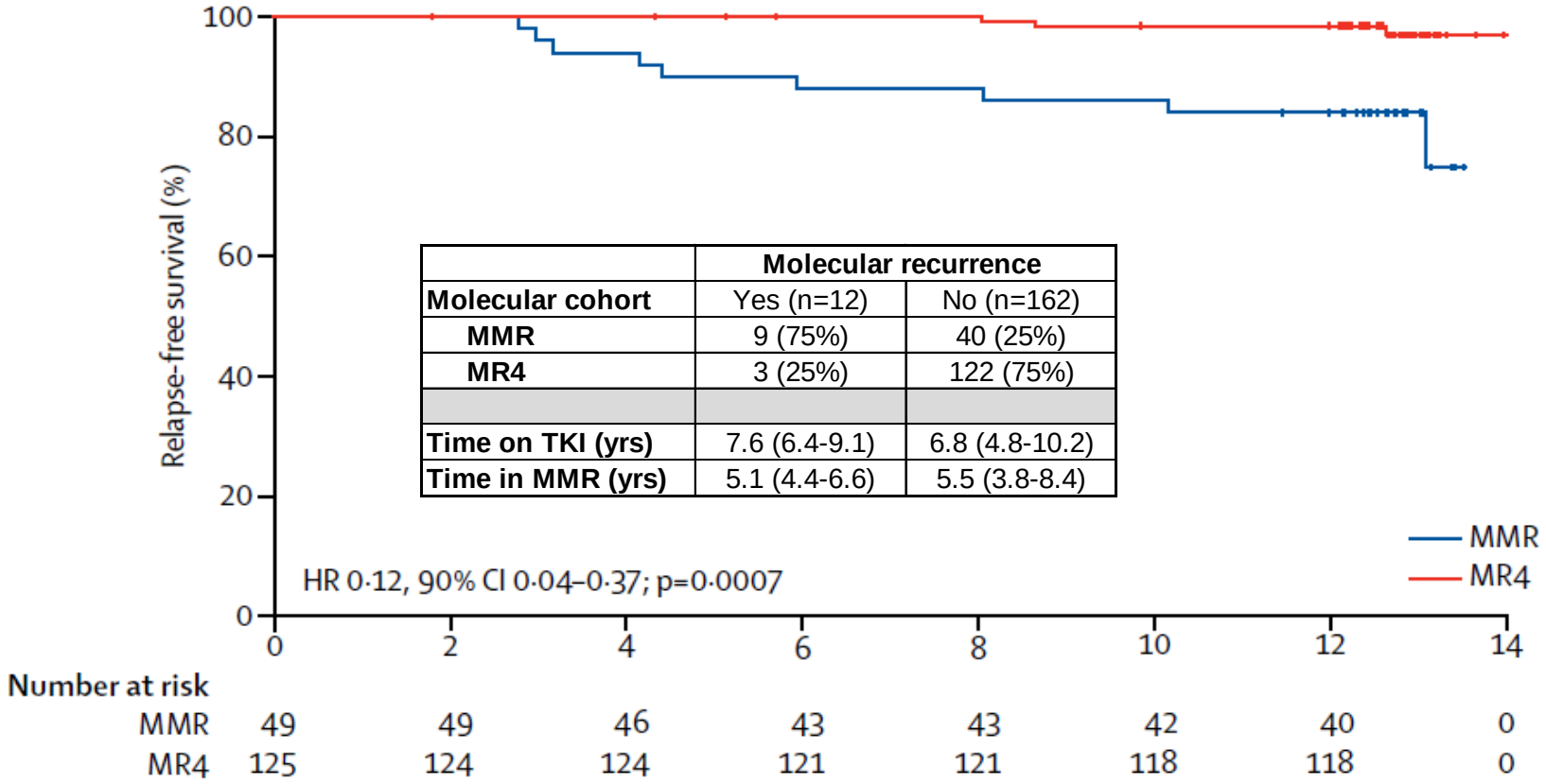
- Management:
  - NSAIDs
  - Prednisone

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]

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)



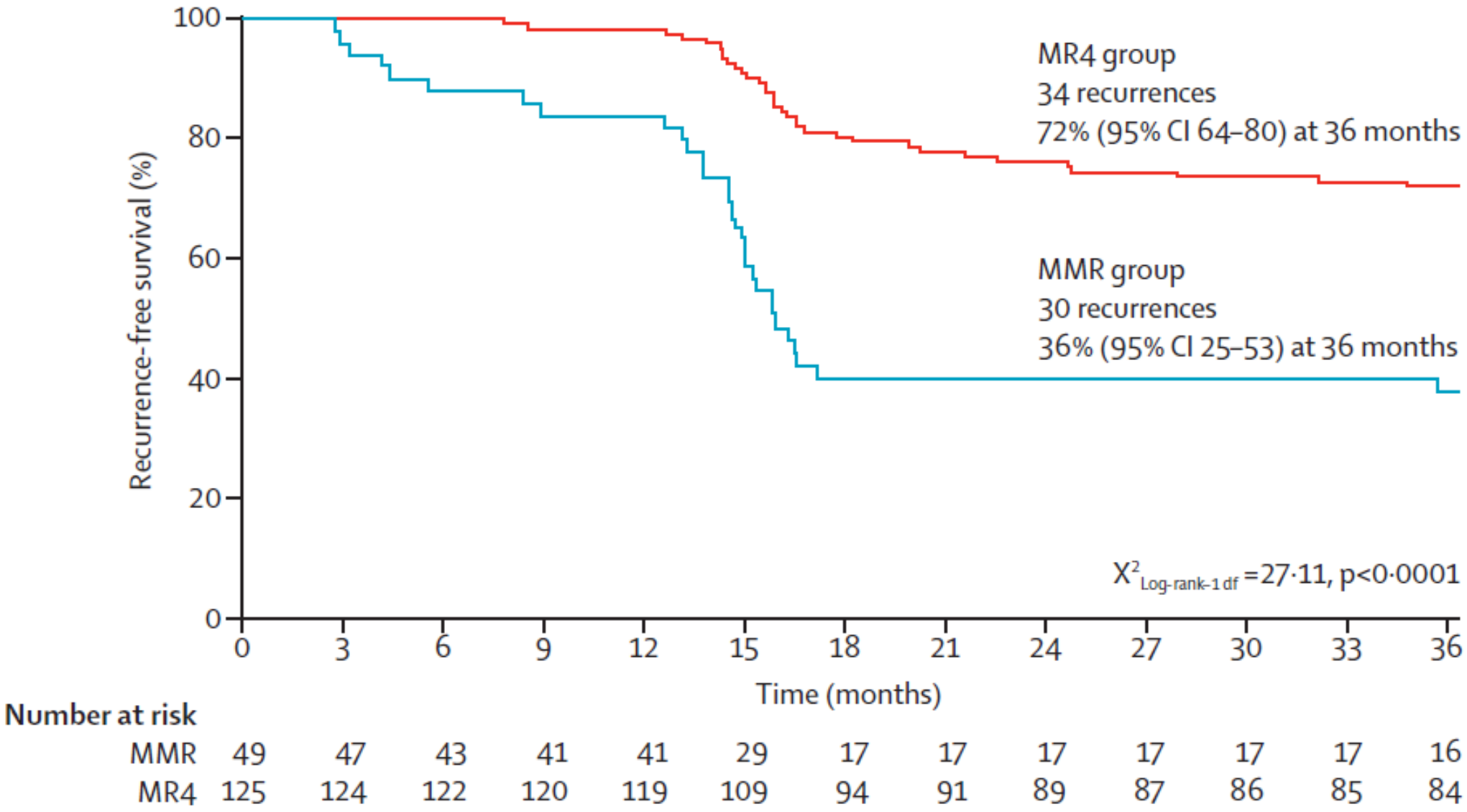
	Molecular recurrence	
Molecular cohort	Yes (n=12)	No (n=162)
MMR	9 (75%)	40 (25%)
MR4	3 (25%)	122 (75%)
Time on TKI (yrs)	7.6 (6.4-9.1)	6.8 (4.8-10.2)
Time in MMR (yrs)	5.1 (4.4-6.6)	5.5 (3.8-8.4)

1. General improvement in adverse side effects
2. Limited MSK symptoms vs. complete TKI withdrawal
3. All regained MMR within 4 months of resumption of full dose TKI

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.

DESTINY: TKI cessation phase

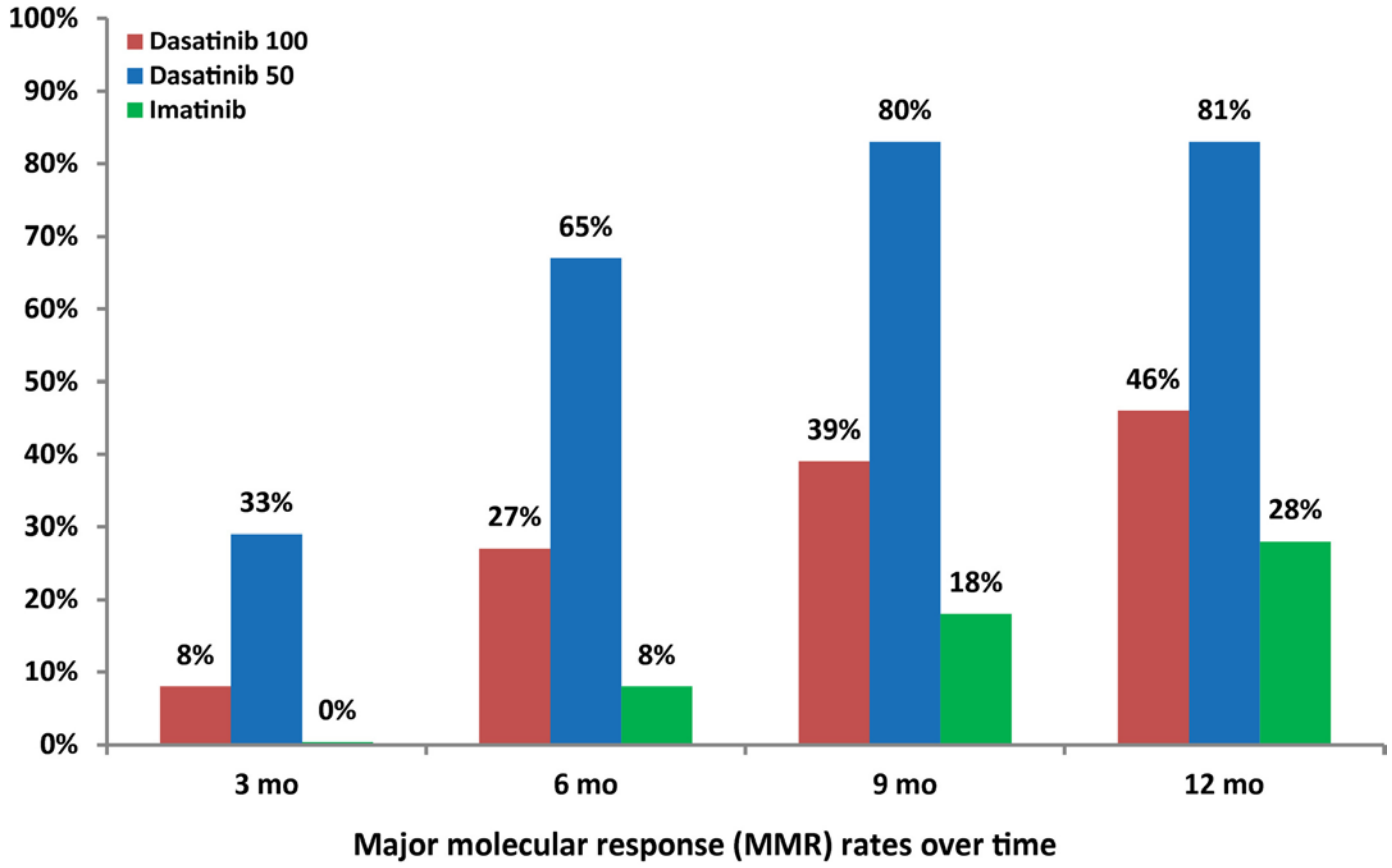


Clark RE et al. Lancet Hematol. 2017 Jul;4(7):e310-e316.
Clark RE et al. Lancet Haematol. 2019 Jul;6(7):e375-e383.

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

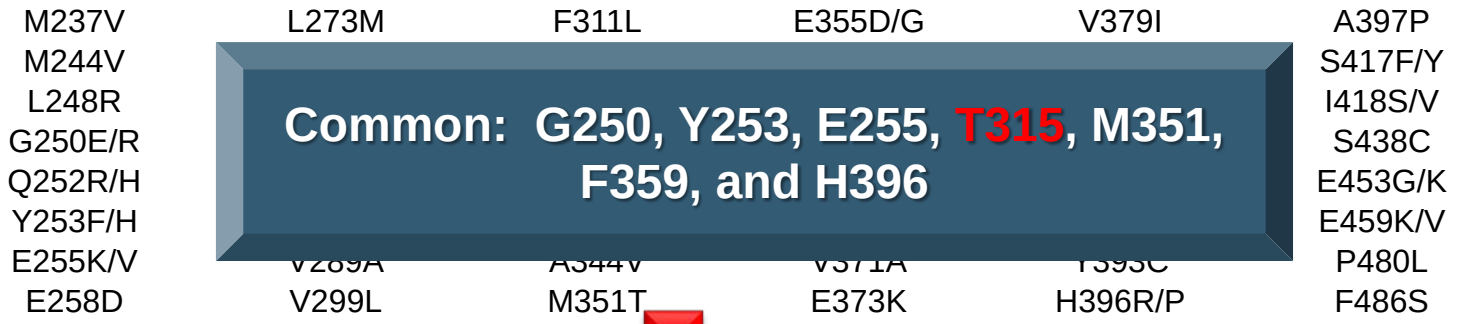
N=81
Dose: 50 mg orally daily
Minimum f/u: 12 months



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

Next-line therapy

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%

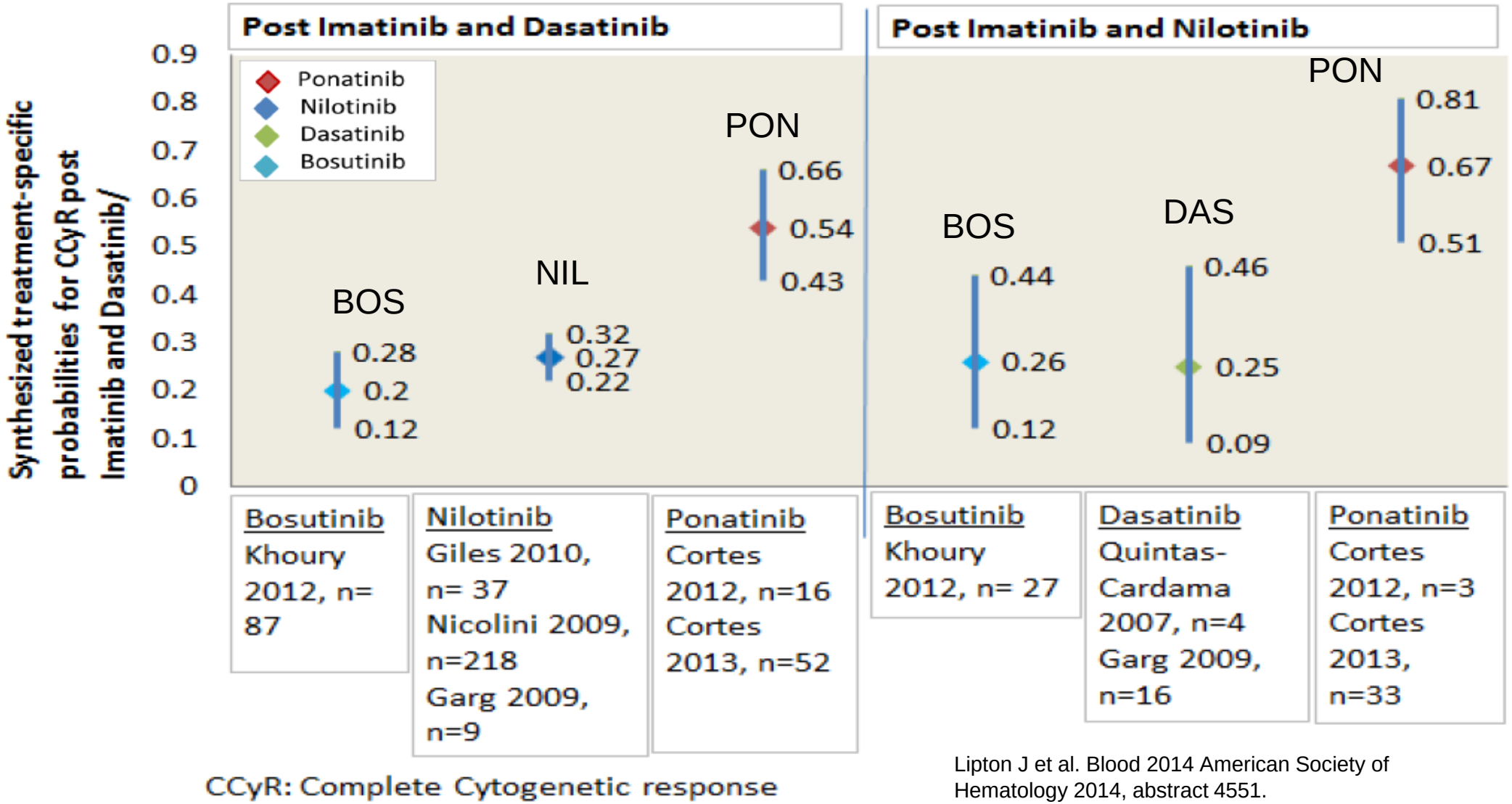
- Patients treated second-line with either dasatinib or nilotinib experience lower long-term overall survival rates compared with patients treated first-line with these TKIs*
  - Dasatinib: first-line 5-year OS, 91%; second-line 5-year OS, ~75%
  - Nilotinib: first-line 5-year OS, 96%; second-line 4-year 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.

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



CCyR: Complete Cytogenetic response

Lipton J et al. Blood 2014 American Society of Hematology 2014, abstract 4551.
Lipton J et al. Leuk Res. 2015 Jan;39(1):58-64

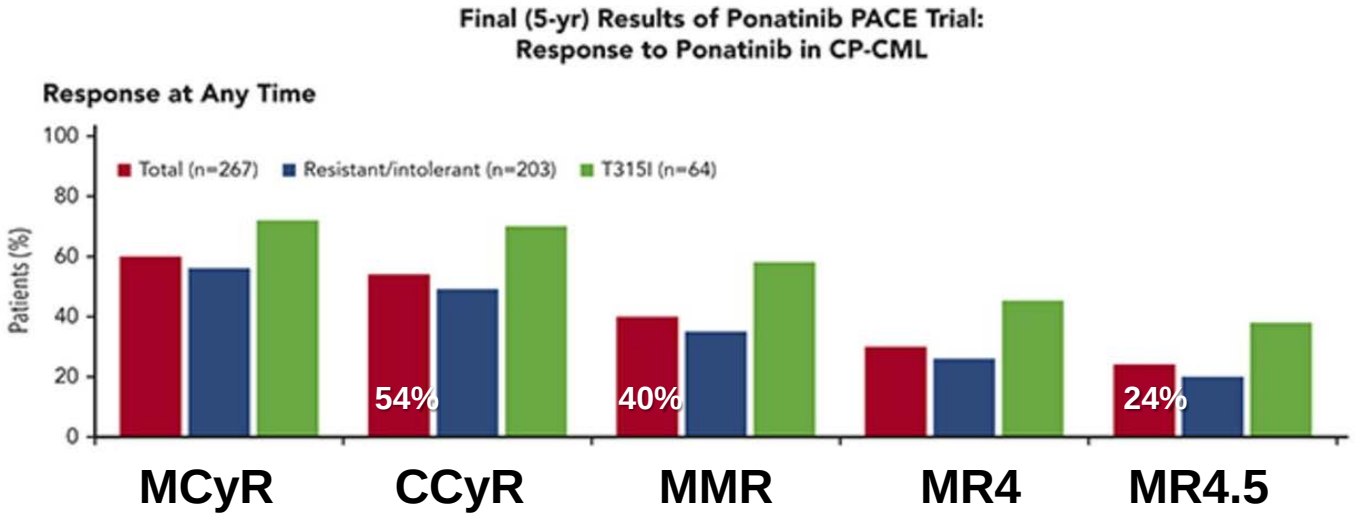
When to consider ponatinib?

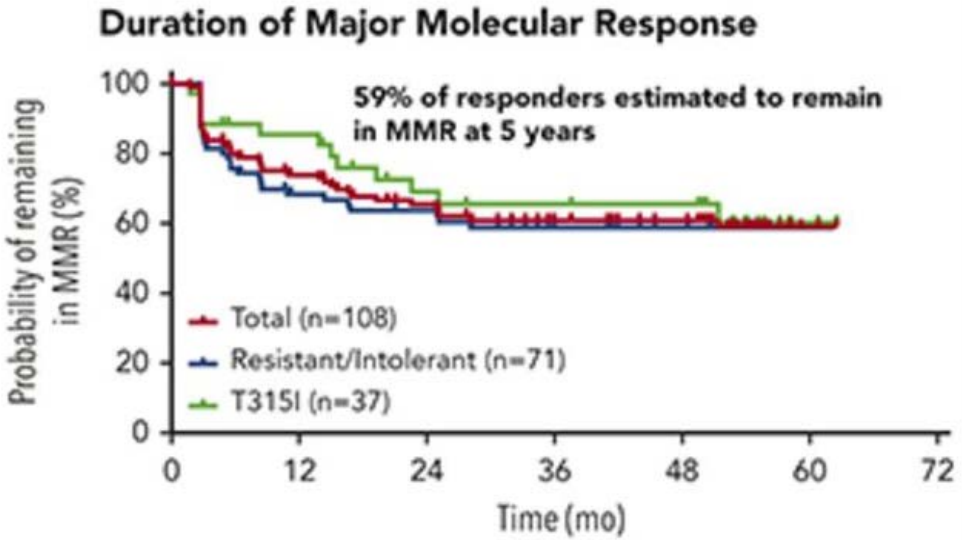
- Label: T315I mutated CML and “for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated”
- Consider: Progression to advanced phase (bridge to transplant)
- Consider: after failure of two 2nd generation TKIs (NCCN)
  - Response to a third 2nd generation TKI is usually low
- *Consider: in CP CML patients who fail first-line 2nd generation TKI therapy with primary resistance* ***and no mutations***
  - *Consider brief trial of 2nd line 2nd generation TKI*
  - *Worrisome group who may need early consideration for allogeneic stem cell transplantation*

Arterial occlusion has occurred in at least 35% of ICLUSIG® (ponatinib)-treated patients including fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures.

Requires close monitoring of blood pressures, glucose and lipid panel with primary care or cardiology

PACE study: final 5-year results





- Start at 30-45 mg for first 3 months and dose reduce to 30 mg if optimal response (MCyR or better)
  - Responses appear to be durable **<u>with</u>** dose reduction
  - Lower risk of arterial events *predicted* with lower dose
- Consider dose reduction to 15 mg for MMR
- *New data:* OPTIC Study: *Ponatinib in Participants With Resistant Chronic Phase Chronic Myeloid Leukemia (CP-CML) to Characterize the Efficacy and Safety of a Range of Doses* – abstract ASCO 2020
  - Starting 45 mg dose appears to be more effective in these resistant patients

Cortes JE et al. Blood 2018;132:393-404.
Cortes JE et al. Interim analysis (IA) of OPTIC: A dose-ranging study of three ponatinib (PON) starting doses. American Society of Clinical Oncology Annual Meeting. 2020, abstract 7502

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.

When to consider allogeneic stem 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** →

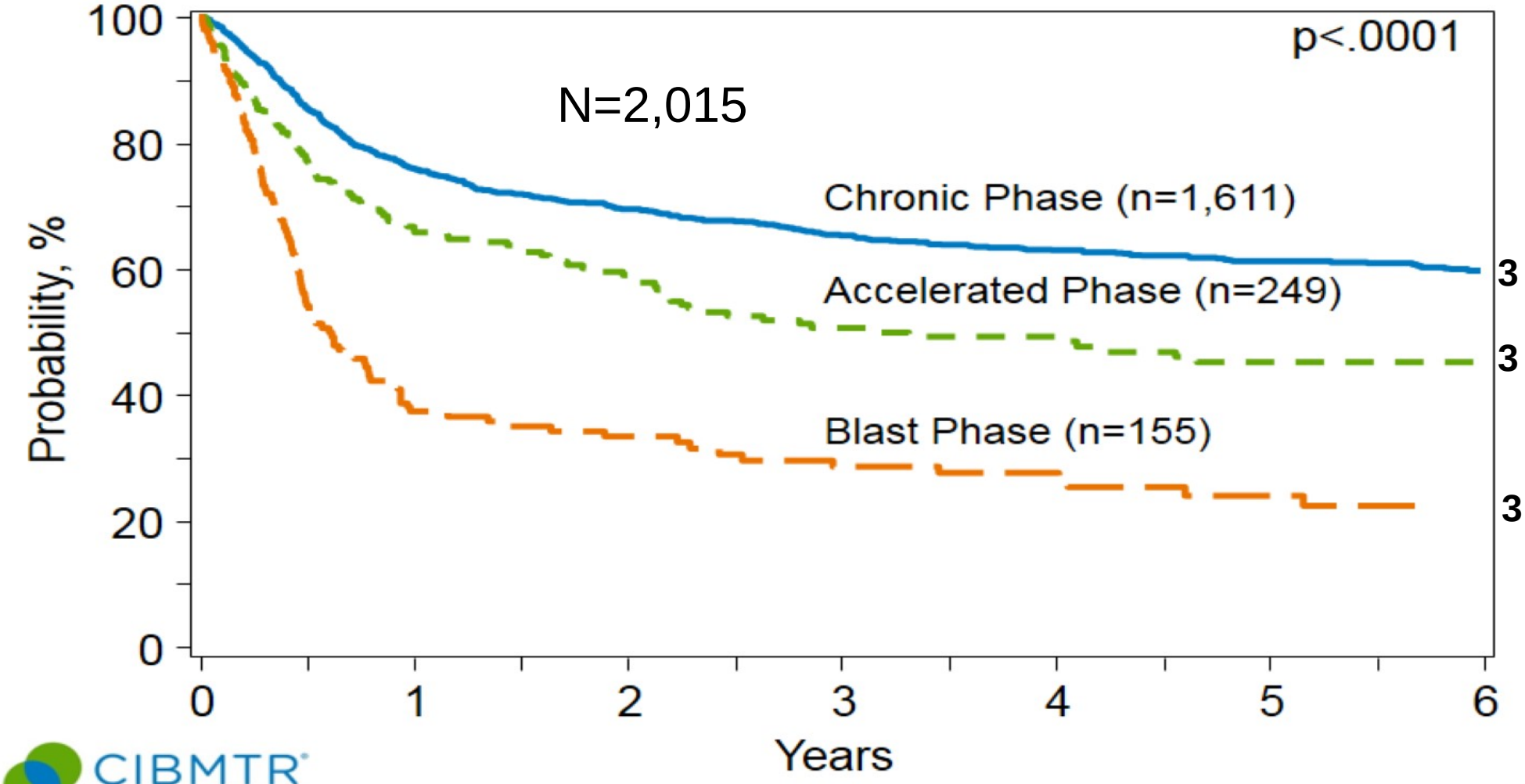
- Type patient and siblings; use first-line TKI therapy with close monitoring for optimal response as some AP patients do well. HCT in patients with worrisome ACA*; for others HCT when optimal milestones are not met.*

BP patients →

- HCT after TKI therapy +/- induction chemotherapy

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

Survival after HLA Matched Sibling HCT for CML, 2005-2015



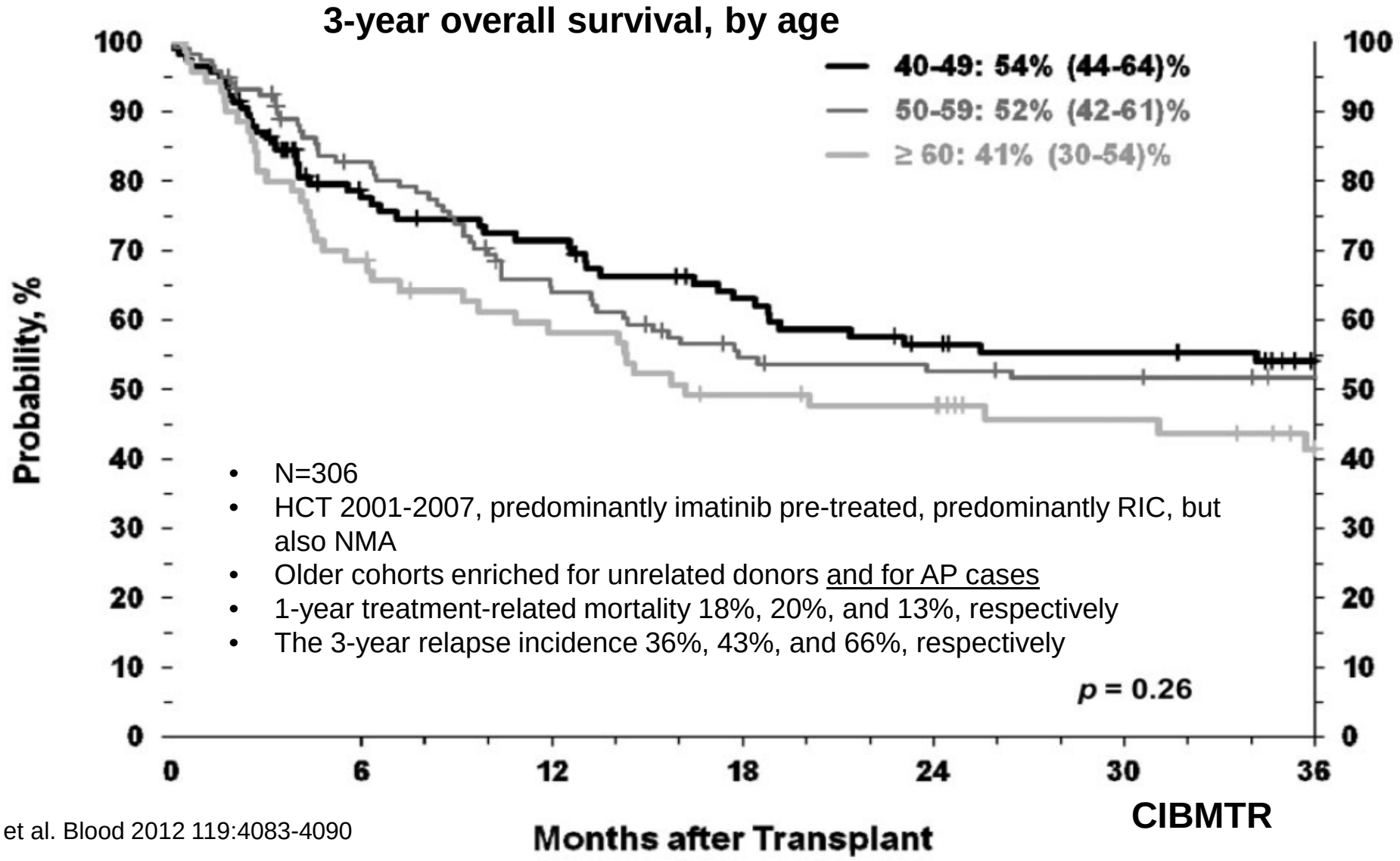
3 yr OS: 66%

3 yr OS: 51%

3 yr OS: 29%

CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Survival after reduced intensity conditioning HCT in CML



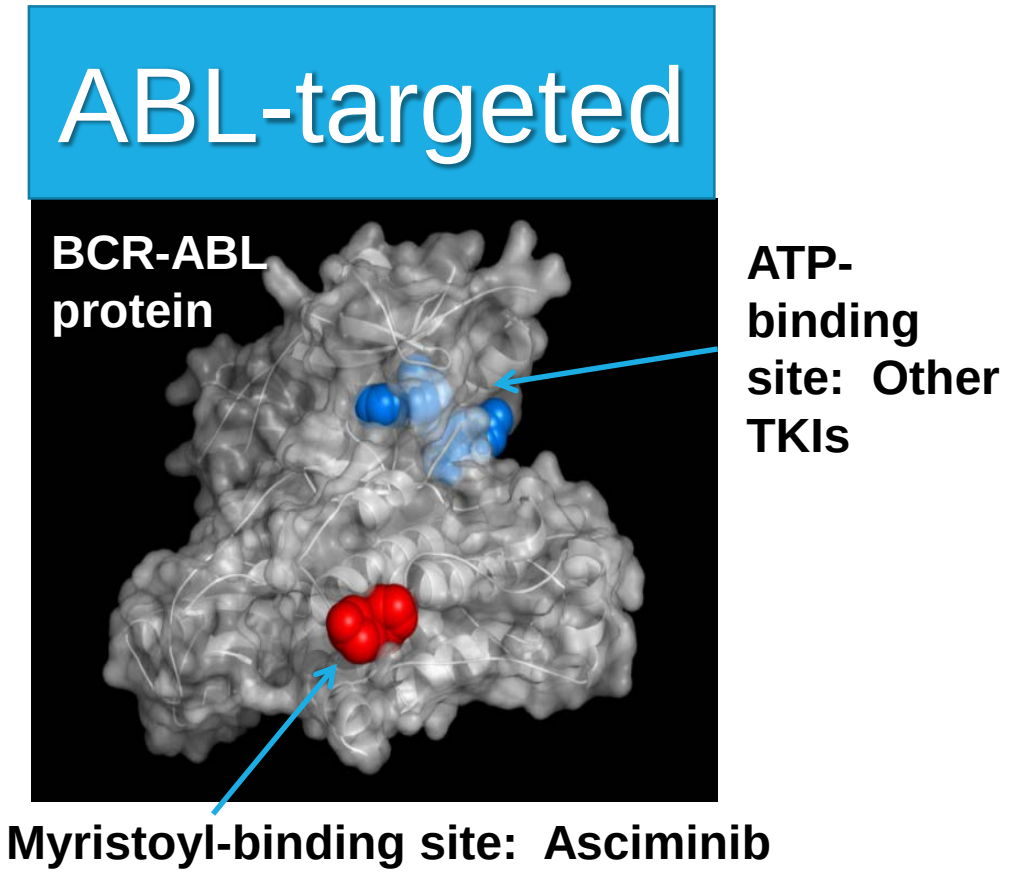
- N=306
- HCT 2001-2007, predominantly imatinib pre-treated, predominantly RIC, but also NMA
- Older cohorts enriched for unrelated donors and for AP cases
- 1-year treatment-related mortality 18%, 20%, and 13%, respectively
- The 3-year relapse incidence 36%, 43%, and 66%, respectively

Warlick E et al. Blood 2012 119:4083-4090

New therapeutic approaches

1. **Other strategies to target BCR-ABL**
2. *Targeting BCR-ABL-independent mechanisms and immune approaches*

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

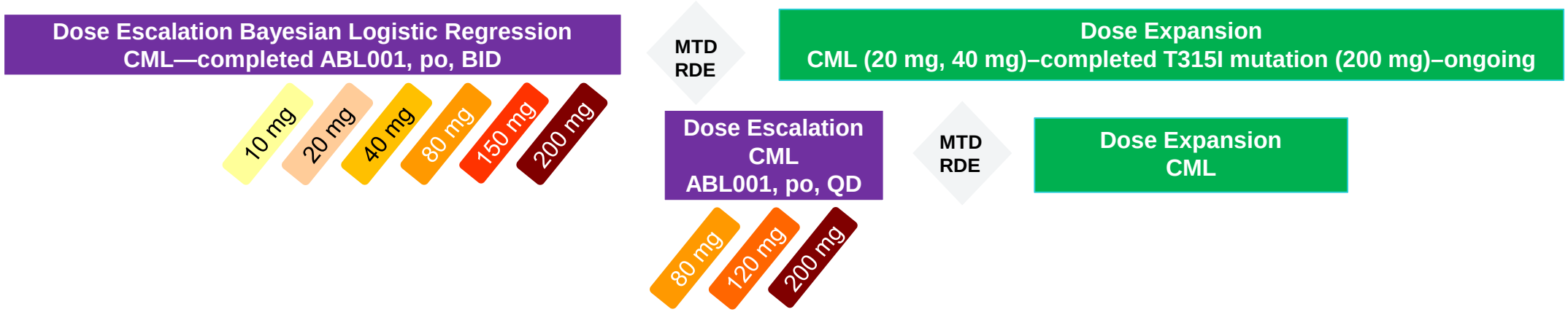


- Very high selectivity with narrow target profile
- Active against BCR-ABL1 mutations that confer resistance to TKIs
- Potential to combine with TKIs to prevent the emergence of *BCR-ABL1* mutations

TKI, tyrosine kinase inhibitor.

Hughes TP, et al. Blood 2016;128 [abstract 625].
Hughes TP et al. N Engl J Med 2019;381:2315-26.

ABL001X2101: a multicenter, phase 1, first-in-human study



- 141 CP and 9 AP patients relapsed or refractory to at least two different TKIs or who had unacceptable side effects on therapy
- Patients with a T315I mutation (33 patients) were eligible after they had received at least one TKI
- **Primary outcome:** estimation of MTD/RDE
- **Secondary outcomes:** safety, tolerability, preliminary anti-CML activity, pharmacodynamics, pharmacokinetic profile

ALL: Acute lymphocytic leukemia; BID: Twice daily; BP: Blast phase; CML: Chronic myeloid leukemia; MTD: Maximum tolerated dose; Ph+: Philadelphia chromosome–positive; po: Peroral; QD: Once daily; RDE: Recommended dose for expansion.
CABL001X2101 study protocol.

Response in CP CML patients without T315I in Phase I Asciminib Trial

Variable - NO T315I	Overall (N=113)
Median follow up (week, range)	72 (0.1-167)
Patients remaining on study N (%)	88 (78%)
CHR, N (%) evaluable	34/37 (92%)
MCyR, N(%) evaluable	85/110 (77%)
CCyR, N (%) evaluable	77/110 (70%)
MMR, N (%)	
In all patients	
By 6 mo	37/99 (37%)
By 12 mo	44/91 (48%)
In patients with 2 or fewer TKI	
By 6 mo	13/25 (53%)
By 12 mo	15/25 (60%)
In patients with more than 2 TKI	
By 6 mo	24/74 (32%)
By 12 mo	29/66 (33%)

Prior TKI	%
1 prior TKI	**2**
2 prior TKIs	**27**
≥ 3 prior TKIs	**72**

Adverse events related to study drug

- Most common all grade AEs
  - Fatigue, headache, increased lipase, nausea, arthralgias, diarrhea, rash, thrombocytopenia
- Most common grade 3/4 AEs
  - Increased lipase, hypertension and thrombocytopenia

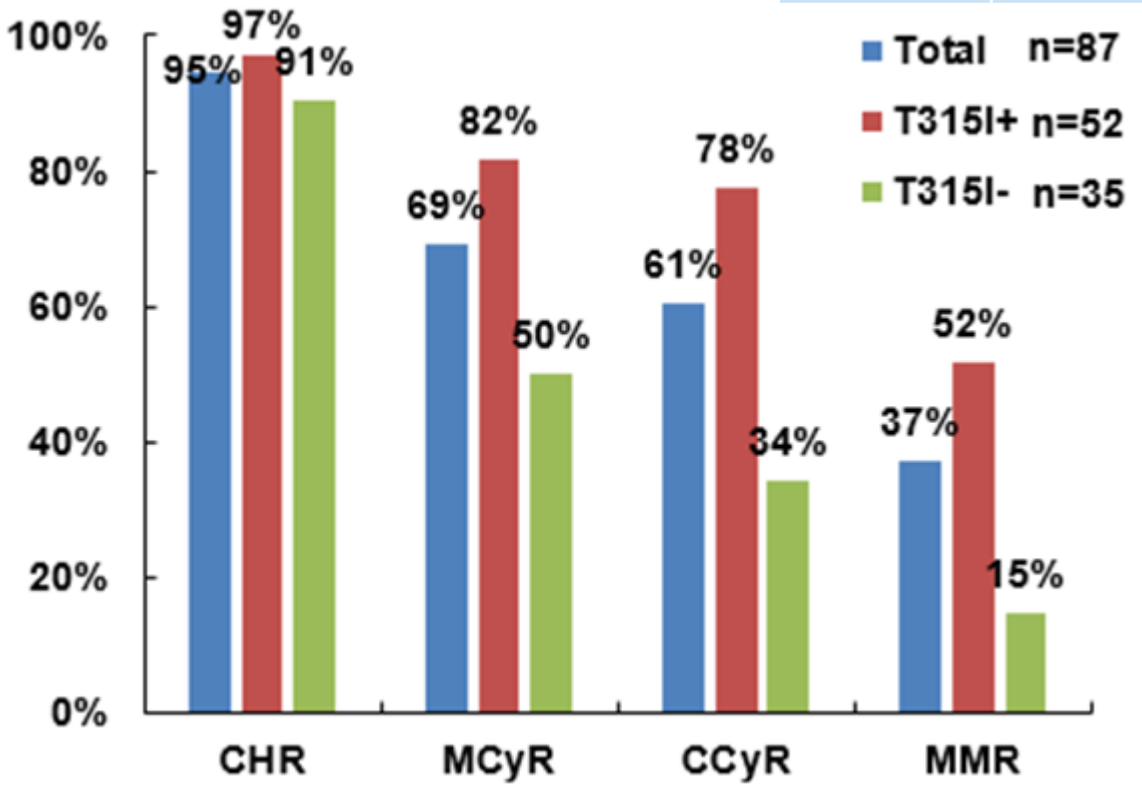
Hughes, Mauro et al N Engl J Med 2019;381:2315-26.

HQP1351 a TKI WITH efficacy against T315I

- 101 CML patients
  - 87 CP patients and 14 AP patients
  - The 18-month progression free survival (PFS) rate was 94% in CP and 61% in AP
- The most common non-hematologic adverse events were hypertriglyceridemia, transaminitis, proteinuria, hyperbilirubinemia
- The most common hematologic treatment-related adverse event that was Grade 3/4 was thrombocytopenia (50%)

Prior TKI	N (%)
1	12 (14)
2	47 (54)
3 or more	28 (32)

Responses in CP patients



Ren et al. J Med Chem. 2013 Feb 14;56(3):879-94
Liu et al. Cell Biosci. 2019 Oct 26;9:88

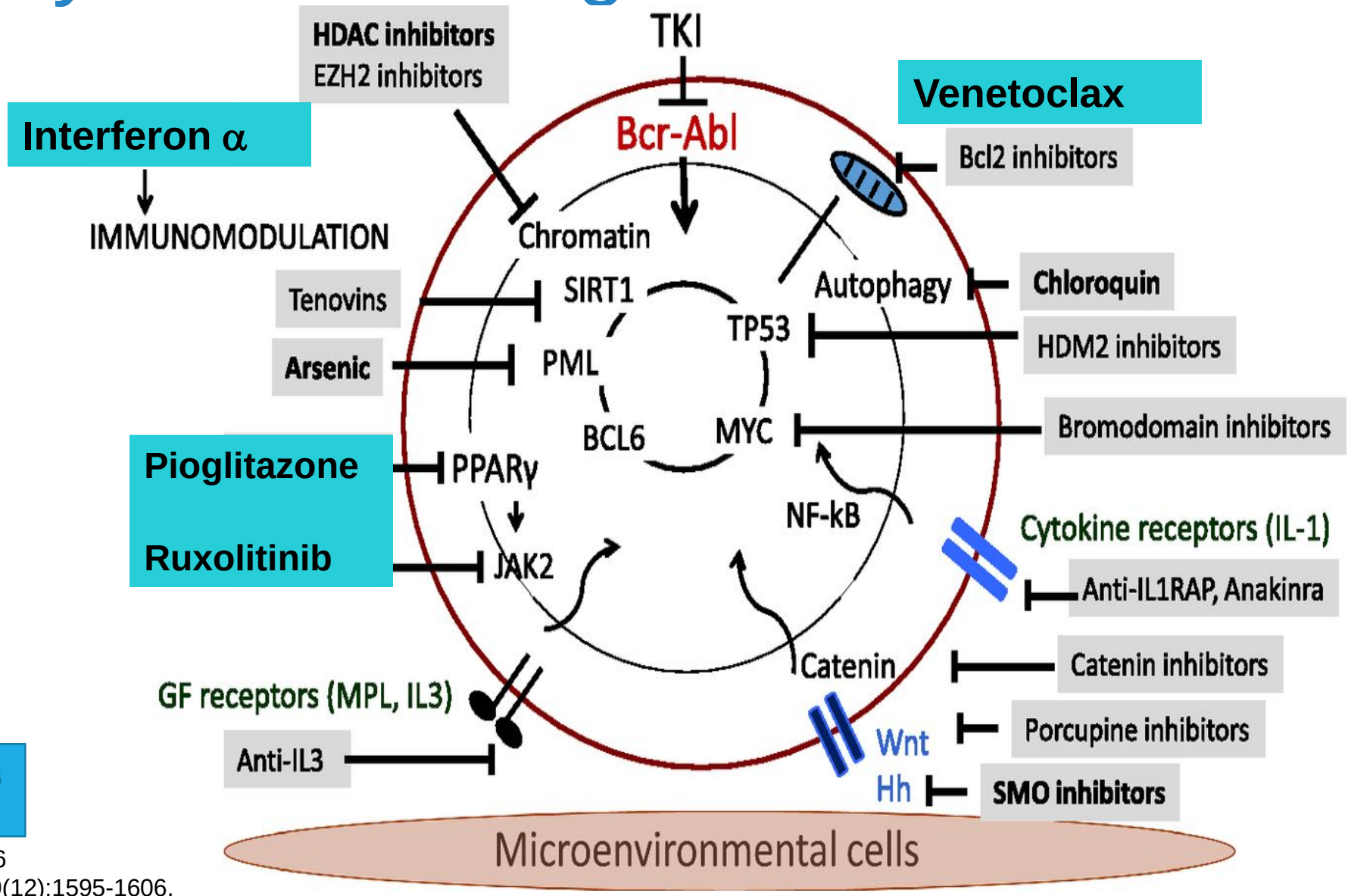
Turkina et al. American Society of Hematology Meeting 2018. Blood (2018) 132 (Supplement 1): 790.
Jiang et al. American Society of Hematology Meeting 2019. Abstract 493.

Other pathways contributing to CML

Targeting BCR-ABL-independent mechanisms to:

1. Combat resistance
2. Eradicate CML stem cells
3. Promote deep response and improve TFR rates
4. Treat advanced disease

Inteferon, JAKi, and PPARγ agonists also likely impact immune function



Massimino et al. Mol Cancer. 2018 Feb 19;17(1):56
Holyoake TL and Vetrie D. Blood. 2017 Mar 23;129(12):1595-1606.
Bhatia R. Hematology Am Soc Hematol Educ Program. 2017 Dec 8;2017(1):115-120

Clinical Trials at Fred Hutch/SCCA for CML:

1. Phase 1b Study of PK, safety and efficacy of orally administered HQP1351 (TKI, Ascentage)
2. BMS: Studying vascular events on TKIs prospectively
3. Treatment Free Remission After Combination Therapy With Ruxolitinib Plus Tyrosine Kinase Inhibitors
4. Pending: 2nd TKI stop
5. 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

voehler@uw.edu

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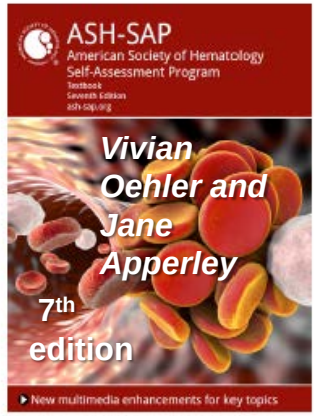


H. JEAN KHOURY CURE CML CONSORTIUM

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
Princess Margaret Cancer Centre
Memorial Sloan Kettering Cancer Center
Duke Cancer Institute
Weill Medical College of Cornell University
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.

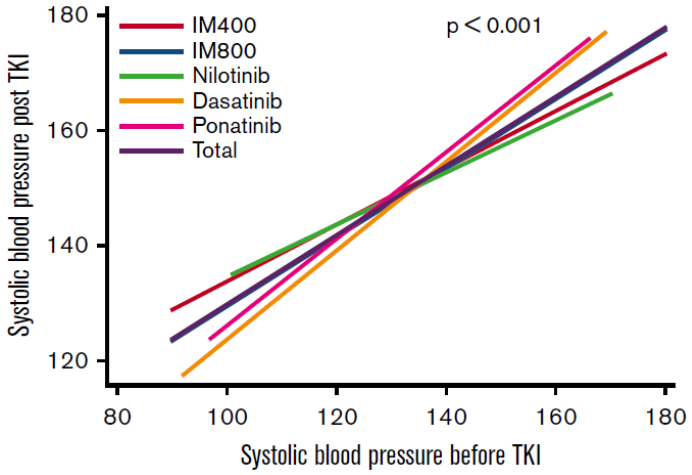
Leukemia (2020) 34:966–984
https://doi.org/10.1038/s41375-020-0776-2

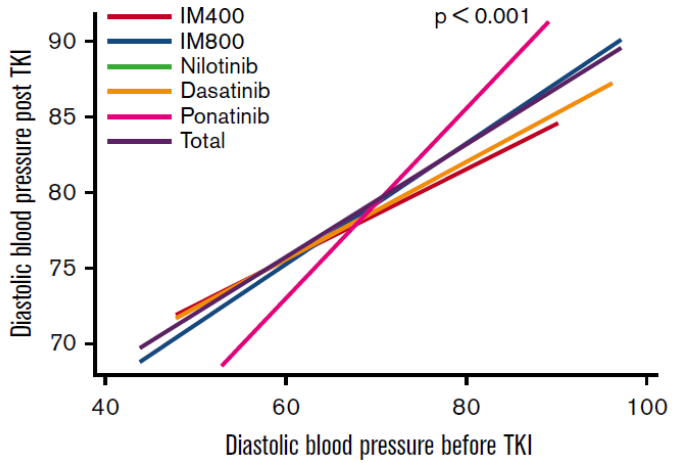
REVIEW ARTICLE

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*
- **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
- ***DESTINY:*** *Phase 2 study de-escalating followed by stopping imatinib, nilotinib, and dasatinib*
- **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

Cardiovascular and arteriothrombotic adverse events after frontline TKIs





NCT03045120: Determining Change in Cardiovascular and Metabolic Risks in Patients With Chronic Phase Chronic Myeloid Leukemia Receiving BCR-ABL Tyrosine Kinase Inhibitor First-Line Therapy in the United States

- Retrospective study of 531 patients treated with frontline TKIs in different prospective trials
- Hypertension was the most common AE seen across all TKIs
  - 175 patients (33%)
    - grade 3/4 in 17%
- Incidence and the risk of CV-AEs and AT-AEs is significantly increased in patients
  - taking second- and third-generation TKIs, and
  - with preexisting cardiovascular risk factors

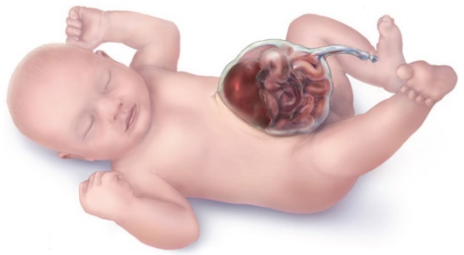
Jain P et al. Blood Adv. 2019 Mar 26;3(6):851-861
Haguet H et al. Expert Opin Drug Saf. 2017;16(1):5-12

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, or transplant)
   - 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 ~27-34%
  - 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

Mechanisms of resistance

Primary resistance: *no initial response*

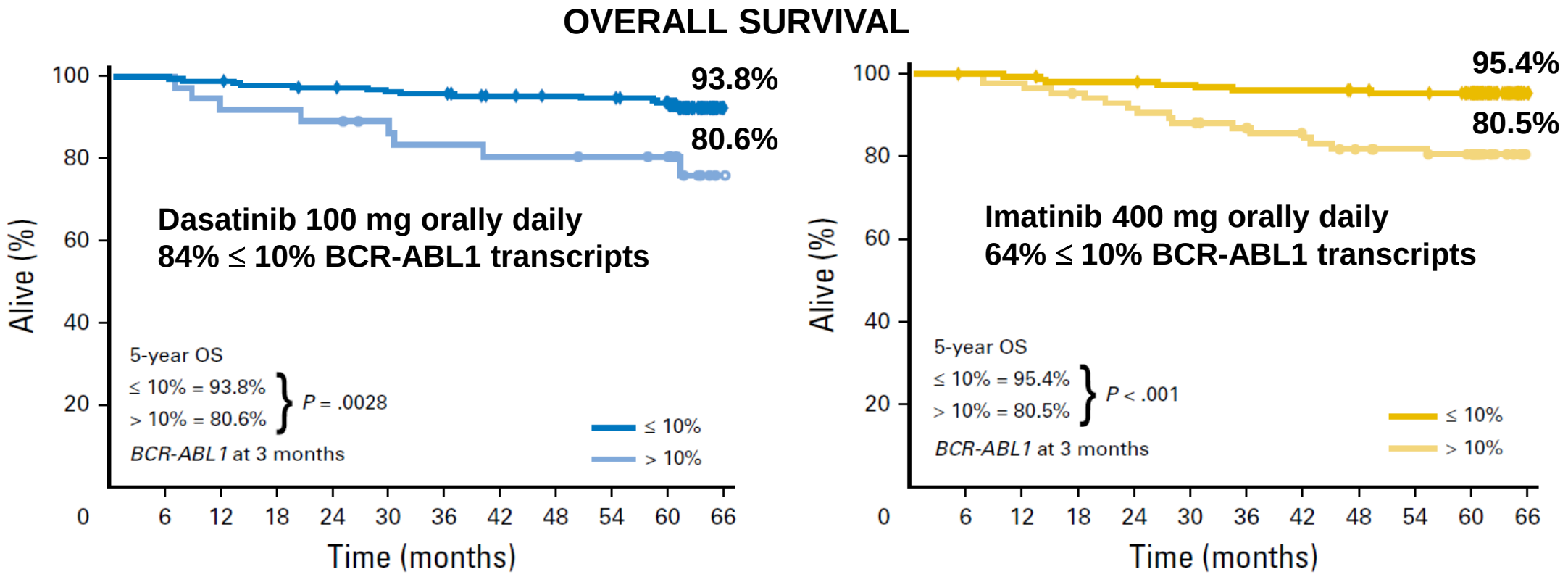
- Insufficient inhibition of Bcr-Abl
  - Low hOCT (OCT1) activity (imatinib)
- BCR-ABL–independent mechanisms
- ABL tyrosine kinase domain (TKD) mutations

Acquired (secondary) resistance: after a response

- ABL TKD mutations (common, *but many DO NOT have*)
- BCR-ABL–independent mechanisms

1. Eide CA, O'Hare T. *Curr Hematol Malig Rep*. 2015;10:158-166.

Early molecular response and outcomes



- Similar results across various studies: ~10-15% difference in OS or PFS
- Impact on outcomes is similar for 1st and 2nd generation TKIs
- However, absence of EMR may be a marker of poor adherence and not only of poor biology

Hanfstein B, et al. *Leuk* . 2012; 26:2096
Marin D, et al. *J Clin Oncol*. 2012;30(3):232
Cortes JE et al. J Clin Oncol. 2016; 34: 2333
Hochhaus A et al. Leukemia. 2016; 30: 1044

Summary of TKI discontinuation trials and retrospective series

Consistent TFR rate across studies (mostly of patients stopping first-line therapy)

Table 1. Summary of TKI discontinuation trials and retrospective series

Study	# Pts	1st-line TKI	2nd-line/ consolidation TKI	Median duration TKI (years)	Stable DMR at STOP	Median duration DMR (years)	Retreatment criteria	Follow-up (years)	Time TFR (years)	Rate TFR (%)
A-STIM [6]	80	I (100%)		6.58	UMRD	3.42	> MMR	2.58	2	64
DADI [7]	63	I (100%)	D (100%)	6.83	0.0069%^{IS}	NR	> 0.0069%^{IS}	1.67	1	48
DASFREE [23]	84	I (85%),D	D (100%)	5.91	MR4.5	NR	> MMR	NR	1	49
Destiny* [15, 29]	117	I (84%), D (8%), N (4%)		6.80	MR4.0*	NR	> MMR	NR	2	77
D-STOP [19]	54	I (61%), D (39%)	D (100%)	7.66	UMRD	4.25	> MR4.0	1.5	1	62.9
ENESTfreedom [22]	190	N (100%)	N (100%)	3.58	MR4.5	2.52	> MMR	NR	1.85	48.9
ENESTop [16]	126	I (100%)	N (100%)	7.3	MR4.5	3.65	> MR4 × 2, > MMR × 1	1.9	1.85	53.2
Euro-Ski [21]	750	I (94%), N/D	15% D/N/I	7.58	MR4.0	2.98	> MMR	0.83	2	51
Ginema [26]	293	I (72%), N (20%), D (8%)		6.42	MR4.0	3.83	Variable	2.83	1	68
Hovon [12]	15	I (100%)		8.17	MR4.5	NR	> 1 log/> MMR	3.6	2	33
ISAV [9]	112	I (100%)		8.59	UMRD	2.14	> UMRD ×2, > MMR	1.8	3	51.9
Japan [28]	43	I (100%)		3.77	UMRD	2.28	> MMR × 2	1.87	5	47
Keio [20]	53	I (91%), N (8%), D (1%)		8.16	UMRD	3.17	> 100 copies *BCRABL*	NR	2	52.8
KID [8]	90	I (100%)		6.73	UMRD	3.32	> MMR × 2	2.22	2	58.5
Korea [27]	24	I (67%), D (21%), B (12%)		6.42	UMRD	4.16	> MMR	3.04	2	59.7
LAST [14]	173	I (60%), N (23%), D (15%), B (2%)		6.58	MR4.0	NR	> MMR	1.025	1	60
MDA** [25]	27	I (77%), D (11%), N (6%), B (6%)		8.0	UMRD	5.25	> UMRD	1.33	1.5	59
NILst [17]	87	I/N	N (100%)	8.6	MR4.5	2–12 Y	> MR4.5 × 2	1.11	1	58.9
STAT2*** [24]	73	I/N	N (100%)	8.52	MR4.5	2$^{\&}$, 2.58$^{\&\&}$	> MR4.5 × 2	NR	1	67.9
STIM1 [4]	100	I (100%)		4.9	UMRD	3.03	> UMRD × 2, > MMR	6.42	5	38
STIM123 [11]	68	I (100%)		8.125	MR4.5	4.5	> MMR	NR	1	67.6
STIM-Pilot [5]	12	I (100%)		3.75	UMRD	2.67	> UMRD × 2	1.5	1.5	50
STOP 2G-TKI [10]	60	D/N 1stL 13.3%, 2ndL 66.7%, 3rdL 20%		6.3	UMRD	2.42	> MMR	3.92	4	53.6
TRAD [18]	123	I (100%)		9.16	MR4.5	NR	> MR4 × 2, > MMR	NR	1	57.5
Twister [13]	40	I (100%)		5.92	UMRD	2.5	> UMRD × 2, > MMR	3.5	2	47.1

 # Pts number of patients, *TKI* tyrosine kinase inhibitor, *DMR* deep molecular response, *TFR* treatment-free remission, *I* imatinib, *D* dasatinib, *N* nilotinib, *B* bosutinib, *UMRD* undetectable molecular residual disease, *MR* molecular response, *MMR* major molecular response, *IS* international standard, *NR* not reported

*MR4 subgroup

**UMDR subgroup

***Median duration TFR from weighted average of SG1$^{\&}$ and SG2$^{\&\&}$ patient groups

Laneuville P. Curr. Treat. Options in Oncol. (2018) 19: 15

Claudiani et al. Haematologica September 2019 : haematol.2019.234179; Doi:10.3324

National Comprehensive Cancer Network (NCCN) recommendations on TKI cessation

1. Age ≥ 18 years
2. CP CML. No prior h/o AP or BP
3. On TKI therapy for at least 3 years
4. Documentation of quantifiable *BCR-ABL1* transcript
5. Stable deep molecular response (MR 4 or better, ≤ 0.01% on at least 4 tests (at least 3 months apart) for ≥ 2 years.
6. Access to a reliable QPCR test with a sensitivity of detection of at least MR4.5 (*BCR-ABL1* ≤ 0.0032% and provides results within 2 weeks.
7. Monthly monitoring for the first 6 months, then every 2 months during months 7-12 and then every 3 months indefinitely if MMR is maintained
8. Discuss with CML Specialty Center to review the appropriateness for TKI discontinuation
9. Resumption of TKI within 4 weeks for loss of MMR with monitoring monthly until MMR is re-established, and then every 3 months

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Chronic Myeloid Leukemia. Version 1.2020