Fred Hutch Cancer Center

Chronic Myelogenous Leukemia: Management in 2024

Jacob Appelbaum, MD/PhD (on behalf of Vivian Oehler, MD)
Assistant Professor, Hematology/Oncology

September 26, 2024

Disclosures

- None

Objectives

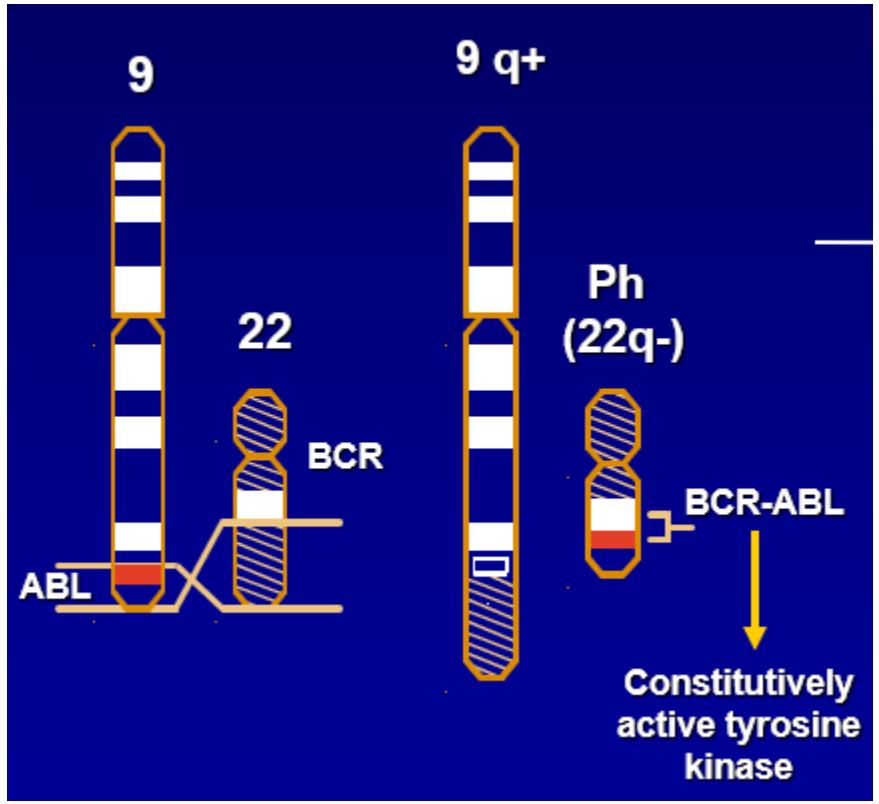
1. Identify disease-specific risk factors at chronic phase chronic myeloid leukemia (CP CML) diagnosis that influence first-line therapy
2. Recognize how first-line therapy selection impacts outcomes including deep molecular response
3. Optimize treatment selection in patients resistant to imatinib and 2nd generation tyrosine kinase inhibitors (TKIs)
4. Understand who may consider dose reduction and review eligibility for, monitoring of, and outcomes in patients who discontinue TKI therapy

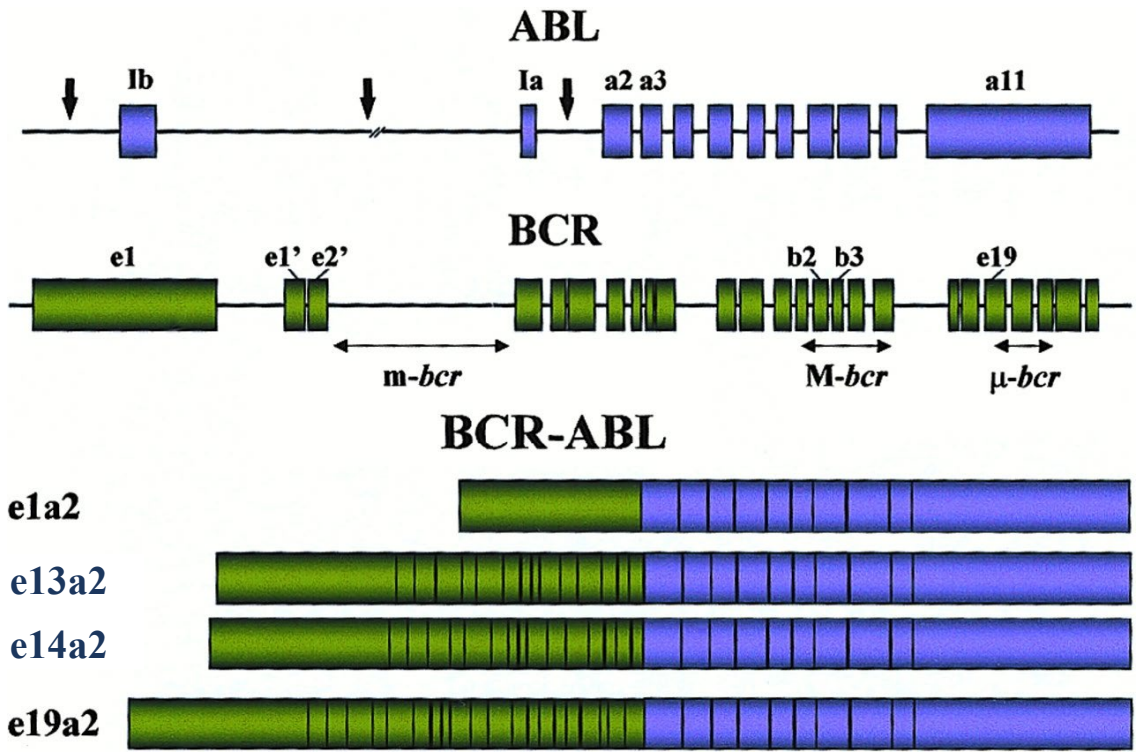
Epidemiology

- ~8,930 people in the US will be diagnosed with CML in 2024
- ~15% of new cases of leukemia
- 5-year relative survival is 70.6% (2013-2019)
- Median age at diagnosis N. America and Europe: 65 to 74 years

NCI. SEER Stat Fact Sheets: Chronic Myeloid Leukemia (CML). https://seer.cancer.gov/statfacts/html/cmyl.html. Accessed January 18, 2024.
Deininger et al. Blood (2000) 96 (10): 3343–3356.

Biology





NCI. SEER Stat Fact Sheets: Chronic Myeloid Leukemia (CML). https://seer.cancer.gov/statfacts/html/cmyl.html. Accessed January 18, 2024.
Deininger et al. Blood (2000) 96 (10): 3343–3356.

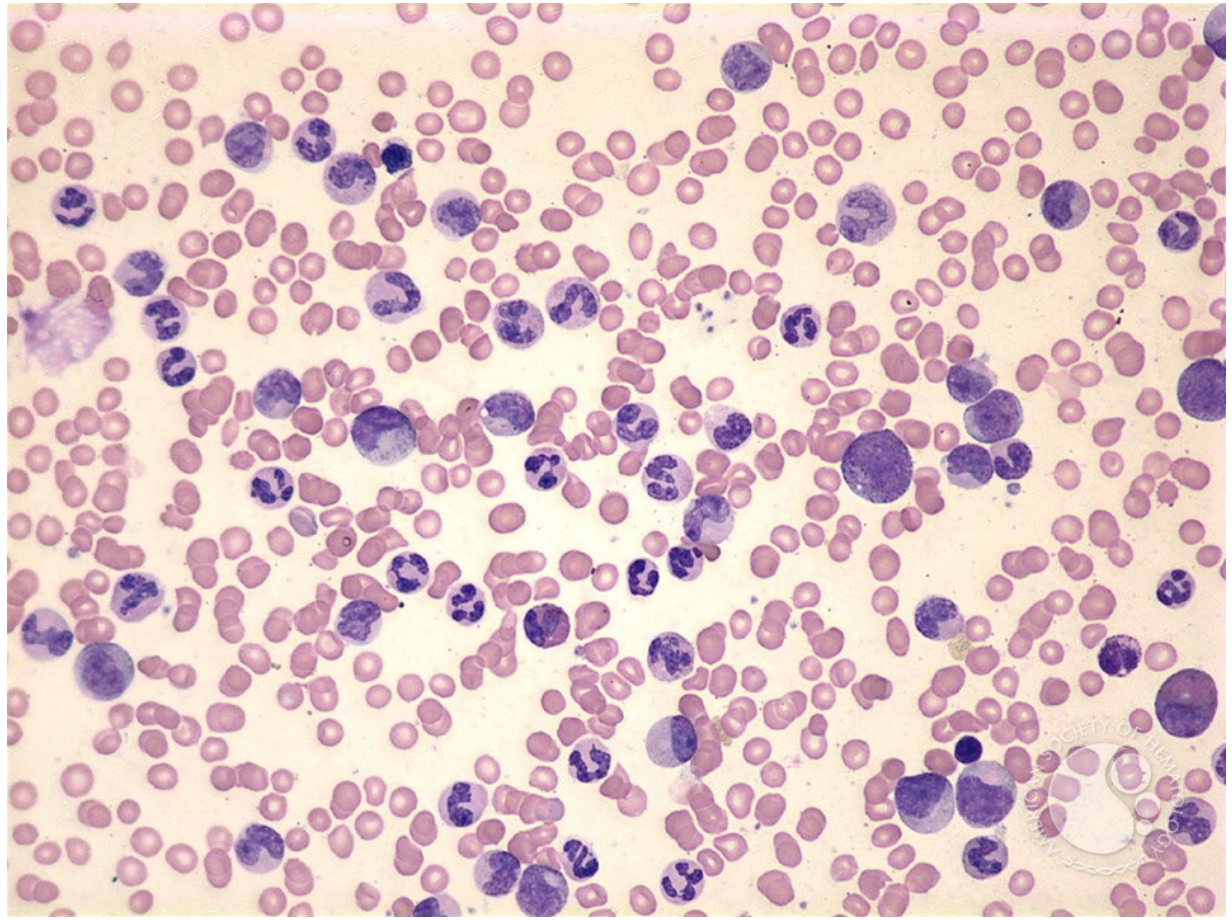
Peripheral Blood Smear

Hx:

- Lethargy & fatigue (anemia), “mental fog”, vision changes, headaches.
- Abdominal fullness, petechiae/bruising

CBC:

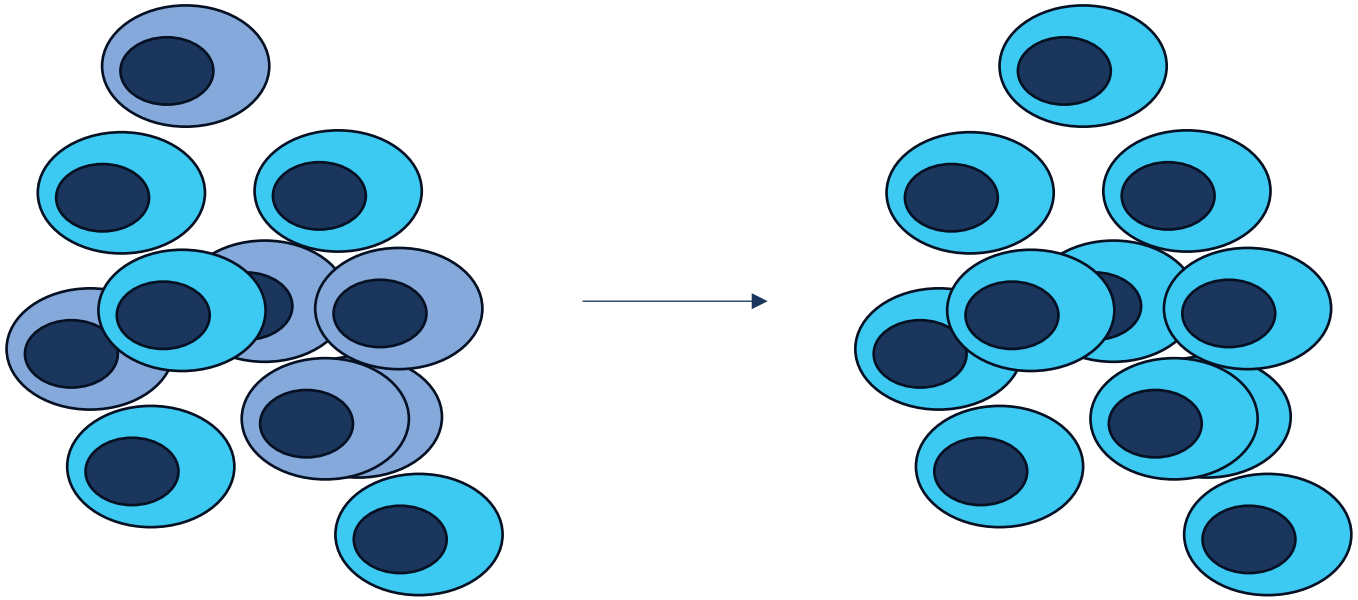
- Elevated WBC count.
- Myeloid cells at all stages of maturation.
- Increased marrow reticulin fibrosis is common (but not diagnostic of MF).
- Pseudo-Gaucher cells and sea-blue histiocytes



CML: Connecting genetics to Neoplasia

G6PD Heterozygous Females: Marrow cells exhibit *clonal* G6PD type (A or B) due to X-chromosome lyonization.

CML colonies = exclusively one type.



Case Presentation

MB is a 54-year-old male diagnosed with CP CML

- Diagnostic peripheral blood *BCR::ABL1*: 95% (e13a2 transcript)
- Medical history is notable for hypertension managed with lisinopril and hyperlipidemia managed with rosuvastatin
- No tobacco use or history of tobacco use

Distinguishing AP from CP

AP Criteria	Blast (%)	Basophils (%)	Additional clonal cytogenetic abnormalities*
WHO	*10-19%*	≥ 20%	**present**
2022 International Consensus Classification	*10-19%*	≥ 20%	**present**
ELN	*15-29%*	≥ 20%	**present**
MD Anderson	*15-29%*	≥ 20%	**present**

*Second Ph, trisomy 8, isochromosome 17q, trisomy 19, complex karyotype, or abnormalities of 3q26.2

Arber D et al. Blood. 2022 Sep 15;140(11):1200-1228.

Distinguishing AP from CP: no more AP in WHO

	AP Criteria	Blast (%)	Basophils (%)	Additional clonal cytogenetic abnormalities
2022	WHO	*10-19%*	≥ 20%	**Present (High-risk CP CML)**
2022	International Consensus Classification*	*10-19%*	≥ 20%	**present**
	ELN	*15-29%**	≥ 20%	**present**
	MD Anderson	*15-29%**	≥ 20%	**present**

*Second Ph, trisomy 8, isochromosome 17q, trisomy 19, complex karyotype, or abnormalities of 3q26.2

Arber D et al. Blood. 2022 Sep 15;140(11):1200-1228.
Khoury JD et al. 2022. Leukemia, 36, 1703–1719.

Distinguishing AP from CP: no more AP in WHO

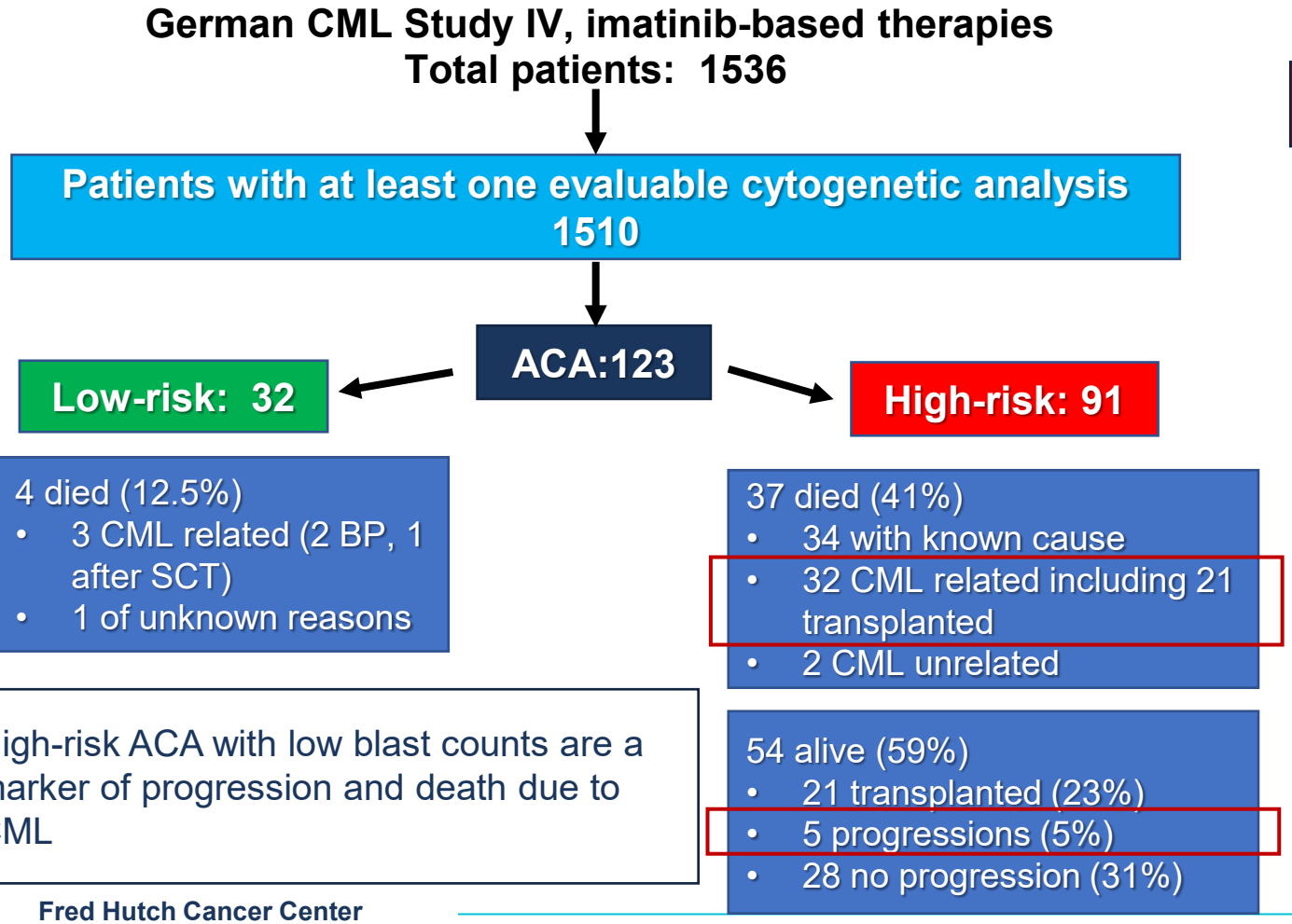
	AP Criteria	Blast (%)	Basophils (%)	Additional clonal cytogenetic abnormalities
2022	WHO	*10-19%*	≥ 20%	**Present (High-risk CP CML)**
2022	International Consensus Classification*	*10-19%*	≥ 20%	**present**
	ELN	*15-29%**	≥ 20%	**present**
	MD Anderson	*15-29%**	≥ 20%	**present**

- In keeping with how we view CML disease progression mechanistically
- Confusing clinically

- **For clinical outcomes: The MD Anderson and European LeukemiaNet (ELN) definitions have been used to define CP vs. AP CML for most clinical trials**
- **NCCN discussion uses MD Anderson criteria**

Arber D et al. Blood. 2022 Sep 15;140(11):1200-1228.
Khoury JD et al. 2022. Leukemia, 36, 1703–1719.

Additional clonal chromosomal abnormalities (ACAs) at diagnosis or acquired during therapy impact TKI response



- High-risk ACA with low blast counts are a marker of progression and death due to CML

Bold=ICC ACA

High-risk ACA:

- 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**

Fabarius et al. Blood. 2011 Dec 22;118(26):6760-8. Hehlmann R et al. Leukemia. 2020; 34(8): 2074–2086.
Fabarius et al. Ann Hematol. 2015;94(12):2015-2024. Wang W et al. Blood. 2016;127(22):2742-2750.

Identifying Higher Risk CP CML Patients at Diagnosis: Prognostic Markers

Prognostic

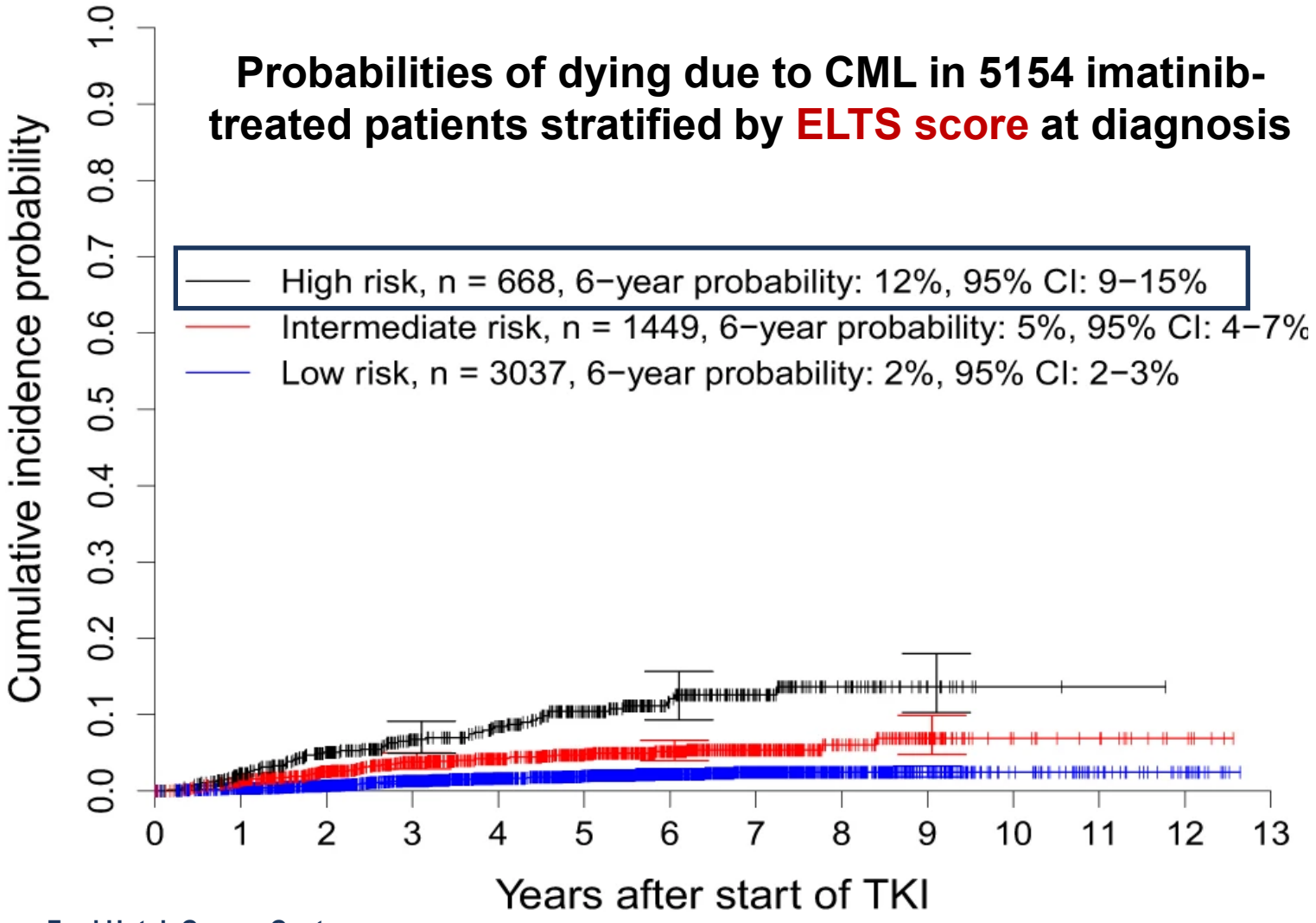
- Higher clinical risk scores are associated with poorer OS
- p190-associated transcript e1a2 associated with poorer outcomes
- p210-associated transcript e13a2 vs e14a2?
  - e13a2 lower rates of deep molecular response on imatinib and nilotinib

Likely Not Prognostic

- Deletion derivative 9 chromosome
- Most variant translocations (e.g., 3-way)
- Other transcript variants?
  - *No dedicated QPCR monitoring assays*

Jain P, et al. *Blood Cancer J.* 2016;6:e469-1275; Genthon A, et al. *Oncotarget.* 2020;11(26):2560-2570; Quintas-Cardama A, et al. *Cancer.* 2011;117:5085-5093; Castagnetti F, et al. *J Clin Oncol.* 2010; 28(16):2748-Testoni N, et al. *Blood.* 2011;117:6793-6800; Verma D, et al. *Blood.* 2009;114:2232-2235; Laurent E, et al. *Cancer Res.* 2001;61:2343-2355.

EUTOS Long-Term Survival Score (ELTS)



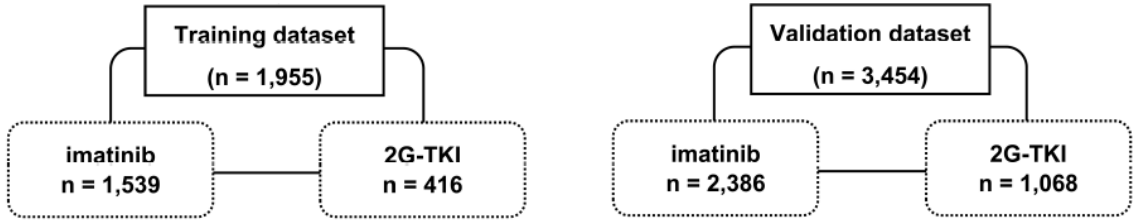
Recommended by ELN

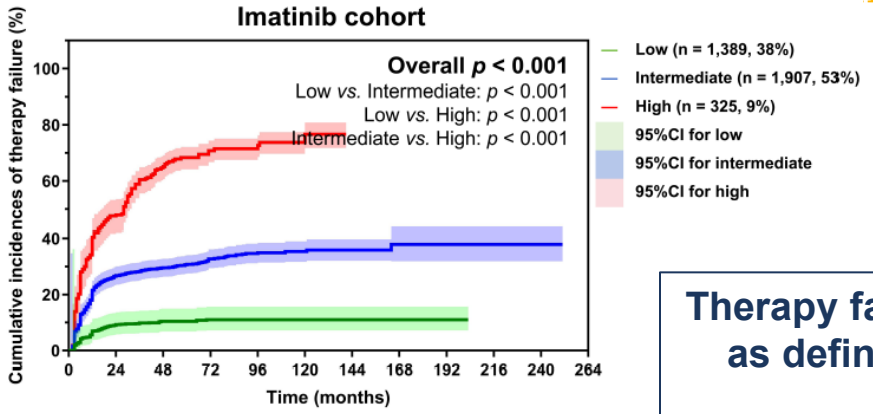
1. Better at identifying patients at risk of dying of CML
2. Classifies fewer patients as high-risk
3. ELTS score (vs Sokal) better prediction of MR4, MR4.5 and CML-related survival, particularly in patients receiving 2G-TKIs

Variables: age, spleen size (cm) below the costal margin, peripheral blood blasts, and platelet count

Pfirrmann M, et al. *Leukemia.* 2020;34:2138–2149; Zhang XS, et al. *Leukemia.* 36, 482–491 (2022).

A(nother) predictive model for therapy failure in CML





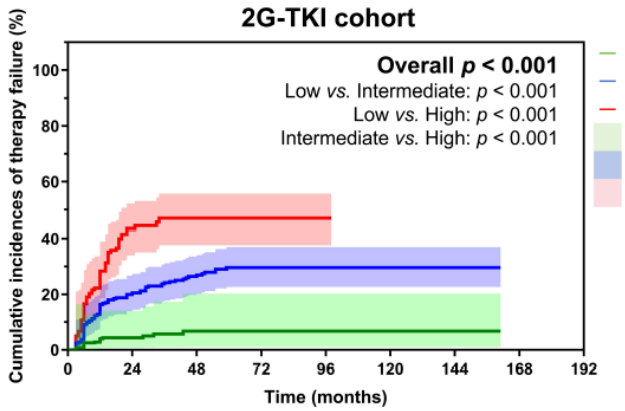
Cumulative incidences of therapy-failure at different years of observation

Years	1	2	3	4	5
Low	6	9	10	10	10
Intermediate	21	27	29	30	34
High	40	48	60	64	68

Therapy failure (vs survival) as defined by ELN 2020

Multi-variable Cox analyses

Co-variates	Regression coefficient	HR (95%CI)	*p*-value
Male	0.2026	1.2 (1.0, 1.5)	0.02
Age/100, years	1.5668	4.8 (2.3, 9.8)	< 0.001
(Hemoglobin/100)^-2, g/L	0.3108	1.4 (1.3, 1.5)	< 0.001
Blood blasts, %	0.1085	1.1 (1.1, 1,2)	< 0.001
Spleen size, cm below costal margin	0.0675	1.1 (1.0, 1.1)	< 0.001
High-risk ACAs in Ph^+ cells*	0.5458	1.7 (1.1, 2.8)	0.03



Cumulative incidences of therapy-failure at different years of observation

Years	1	2	3	4	5
Low	4	4	7	7	7
Intermediate	16	20	23	27	29
High	28	42	46	47	47

Zhang X et al. Blood. 2024, published online 29 July 2024. https://doi.org/10.1182/blood.2024024761.

Case Presentation

MB is a 54-year-old male diagnosed with CP CML

- Diagnostic peripheral blood *BCR-ABL1*: 95% (e13a2 transcript)
- Medical history is notable for hypertension managed with lisinopril and hyperlipidemia managed with rosuvastatin
- No tobacco use or history of tobacco use
- Sokal and EUTOS long-term survival scores: **high-risk**
- Bone marrow cytogenetic exam shows t(9;22)(q34;q11), but no additional cytogenetic abnormalities

CML Treatment Goals Discussion: MB

1. Life expectancy not impacted by CML: higher-risk CML → **ELTS score and Sokal score: High-risk**
2. Limit impact of TKI therapy on comorbidity outcomes → **Hypertension and hyperlipidemia**
3. Quality of life and minimizing adverse events
4. Treatment-free remission
5. Limiting costs
6. Family planning

Treatment?

Treatment Options in CP-CML

Compound	TKI Type / Generation	First Line	Second Line	≥ Third Line
Imatinib	ATP-competitive 1st generation	●		
Dasatinib	ATP-competitive 2nd generation	●	●	●
Nilotinib	ATP-competitive 2nd generation	●	●	●
Bosutinib	ATP-competitive 2nd generation	●	●	●
Ponatinib	ATP-competitive 3rd generation		●* (T315I)	●
Asciminib	ABL Myristoyl Pocket STAMP inhibitor		●† (T315I)	●
Omacetaxine	Protein synthesis inhibitor			

*Approved in US for a patients after ≥ 2 TKIs or for patients with T315I CP-CML in any line. †Approved for a patients after ≥ 2 TKIs or for patients with T315I CP-CML in any line. ‡Only available in the US.

Hochhaus A, et al. *Leukemia* 2020; 34: 966-984; NCCN Guidelines. Chronic Myeloid Leukemia. V3.2022.

Common and Unique Toxicities of TKIs in CML

Cardiovascular, cerebrovascular and peripheral arterial vascular events

Requires close follow-up

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

Ponatinib
Arterial occulsive events, pancreatic enzymes ↑, hypertension, ocular toxicity

Imatinib
Edema/fluid retention, myalgia, hypophosphatemia, GI effects (nausea), transaminitis

Asciminib:
fatigue, headache, increased lipase, nausea, arthralgias, diarrhea, rash, and thrombocytopenia

Common Effects
Myelosuppression
Electrolyte Δ
Rash
Fatigue

Bosutinib
GI effects (diarrhea and nausea), pancreatic enzyme ↑, transaminitis

Nilotinib
Arterial occlusive events, pancreatic enzyme ↑, hyperglycemia
QT prolongation, transaminitis

Dasatinib
Pleural/pericardial effusions, bleeding risk, pulmonary arterial hypertension

Medical comorbidities and older age may make it more difficult to use some 2nd generation TKIs front-line

Adapted from Dr. Michael J. Mauro, MD
Fred Hutch Cancer Center

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

2nd Generation TKI Selection Based on 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.

Selecting First-Line Therapy: NCCN 2.2024

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, 2G TKIs (bosutinib, dasatinib, or nilotinib) are preferred for patients with an intermediate or high-risk score**. 2G TKIs should also be considered for specific subgroups (based on the assessment of treatment goals and benefit/risks), for example, younger patients who are interested in ultimately discontinuing treatment and especially young patients assigned female at birth whose goal is to achieve a deep and rapid molecular response and eventual discontinuation of TKI therapy for family planning purposes.

Fred Hutch Cancer Center

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

Clinical trial, if available can be considered for all patients

NCCN Guidelines. Chronic Myeloid Leukemia. V2.2024.

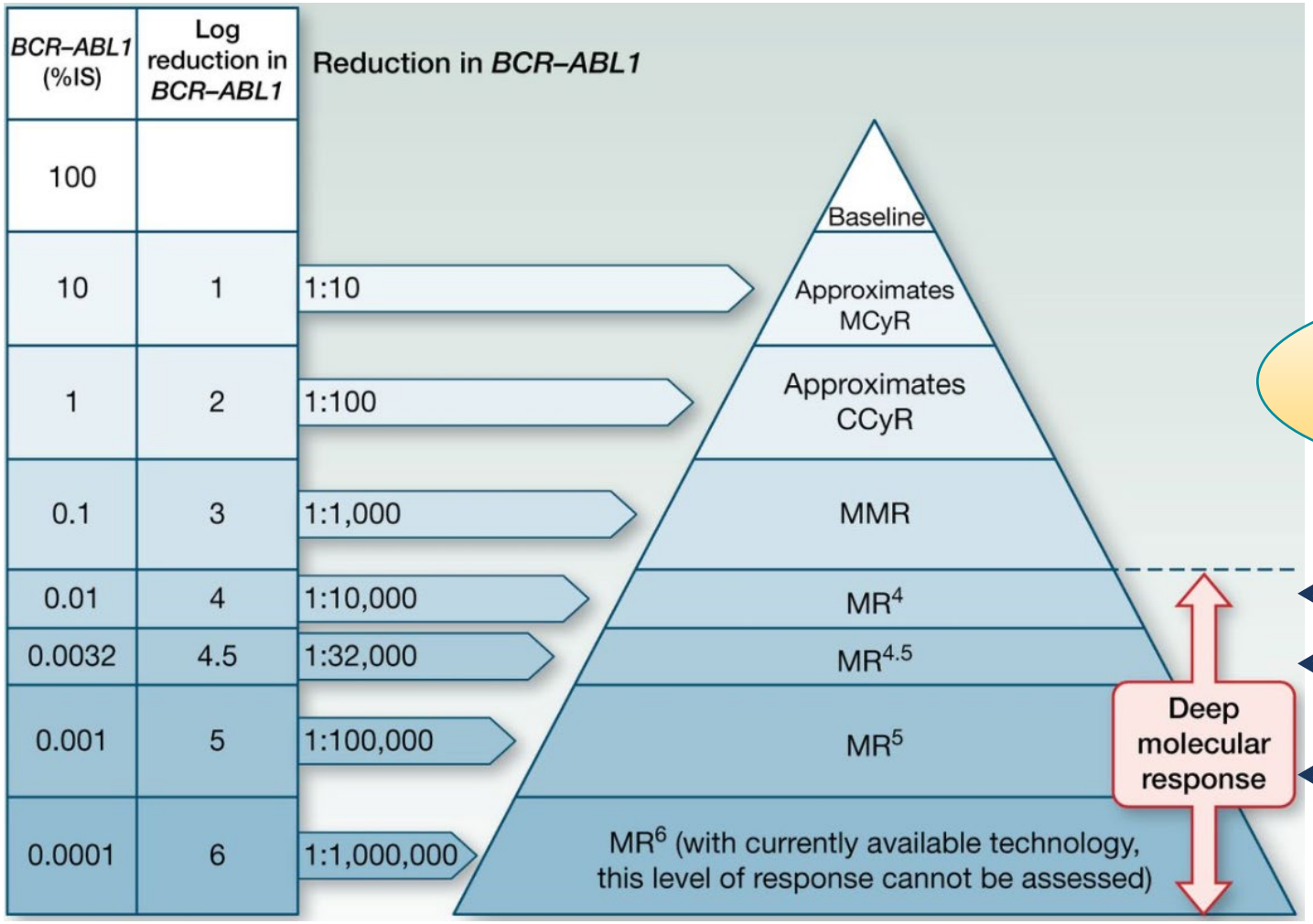
Treatment Goals and Molecular Response Milestones in CML

Responses associated with progression-free and overall survival

***BCR::ABL1* ≤10%** →

***BCR::ABL1* ≤1%** →

***BCR::ABL1* ≤0.1%** →



Responses required for treatment-free remission

← ***BCR::ABL1* ≤0.01%: MR4**

← ***BCR::ABL1* ≤0.0032%: MR4.5**

← ***BCR::ABL1* ≤0.001%: MR5**

Levels of responses to TKI therapy

Adapted from: Rea D. ASH Education Session, CML, 2020.

Mahon FX and Etienne G. *Clin Cancer Res.* 2014;15;20(2):310-322; Deininger MW, et al. *J Natl Compr Canc Netw*. 2020;18:1385-1415; Hochhaus A, et al. *Leukemia.* 2020;34(4):966-984.

First-Line 2nd Generation TKI: 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

Hochhaus A, et al. *Leukemia.* 2016;30:1044-1054; NCCN Guidelines. Chronic Myeloid Leukemia. V1.2024.

First-Line 2nd Generation TKI: 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

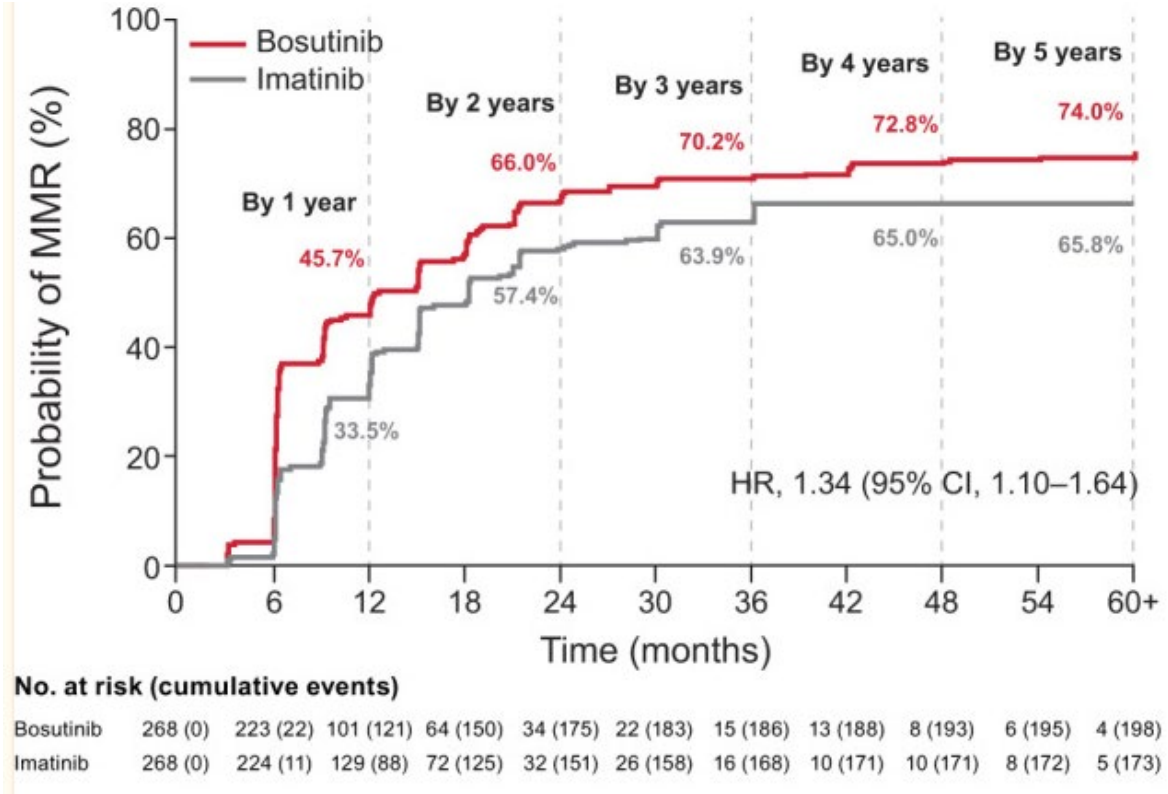
ENESTnd Study Arms	Low-risk			Intermediate-risk			High-risk		
	Disease progression, n (%)	PFS	OS	Disease progression, n (%)	PFS	OS	Disease progression, n (%)	PFS	OS
Nilotinib 300 mg BID	1 (1%)	96.0%	97.0%	2(2%)	92.9%	93.8%	7 (9%)	86.2%	88.8%
Nilotinib 400 mg BID	1 (1%)	99.0%	99.0%	1(1%)	96.9%	96.9%	4 (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%

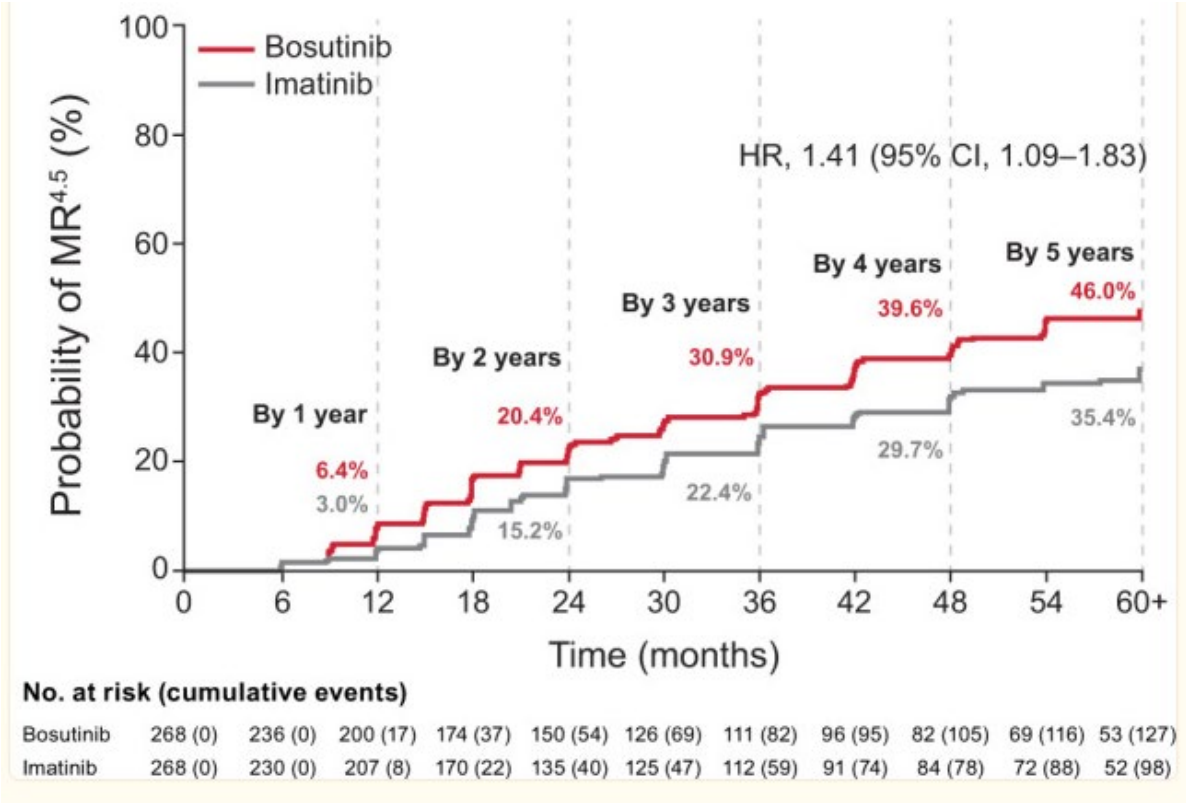
Hochhaus A, et al. *Leukemia.* 2016;30:1044-1054; NCCN Guidelines. Chronic Myeloid Leukemia. V1.2024.

First-line 2nd Generation TKI: Cumulative Molecular Response and deeper molecular responses

- Phase 3 randomized BFORE Study
- Primary endpoint: MMR rate at 12 months

Similar data for dasatinib and nilotinib vs imatinib





MMR: *BCR-ABL1* IS ≤0.1%. MR[4]: *BCR-ABL1* IS ≤0.01%. MR[4.5]: *BCR-ABL1* IS ≤0.0032%.

Brümmendorf TH et alLeukemia. 2022 Jul;36(7):1825-1833.

CML Treatment Goals Discussion

1. Life expectancy not impacted by CML: higher-risk CML → **ELTS score and Sokal score: High-risk**
2. Limit impact of TKI therapy on comorbidity outcomes → **Hypertension and hyperlipidemia**
3. Quality of life and minimizing adverse events
4. Treatment-free remission
5. Limiting costs
6. Family planning

- **First-line:** Bosutinib 400 mg orally daily

What data support consideration for lower dose TKI use upfront?

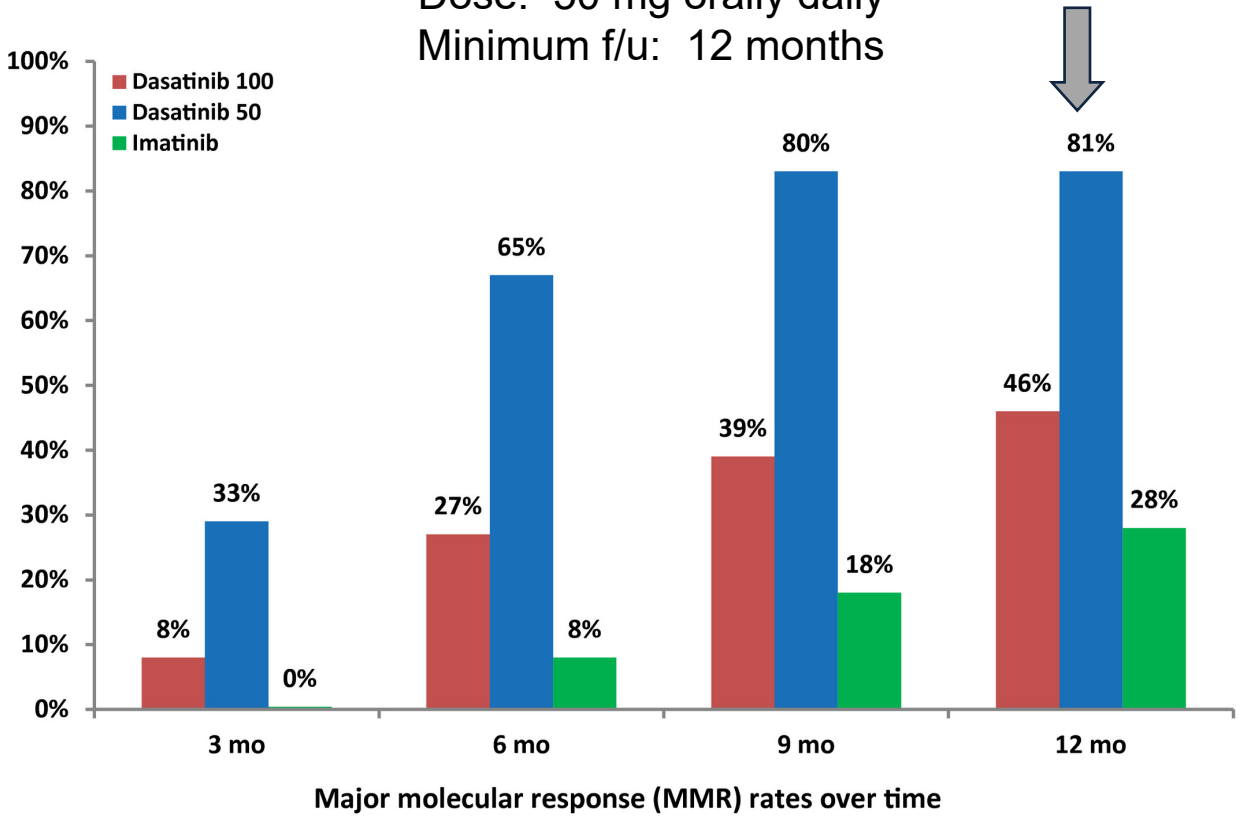
TKI	Study	Patient Characteristics	TKI Dose	Study Findings
Dasatinib	Single center Pilot Study[249]	81 evaluable patients (majority of patients had low-risk (n = 55; 66%) or intermediate-risk (n = 21; 25%) disease by Sokol score Minimum follow up: 12 months	50 mg/day	The cumulative rates for MMR, MR4, and MR4.5 at 12 months were achieved in 81%, 55%, and 49% of patients respectively.
	DAVLEC (Phase II study)[252]	52 patients; aged >70 years; Median follow-up of 366 days	20 mg/day	MMR at 12 months was achieved in 60% of patients.

1. Lower dose dasatinib first-line in low/ intermediate risk or older CP CML patients
2. Retrospective data of dose modifications with durable response in the setting of intolerance

NCCN Guidelines. Chronic Myeloid Leukemia. V2.2024.

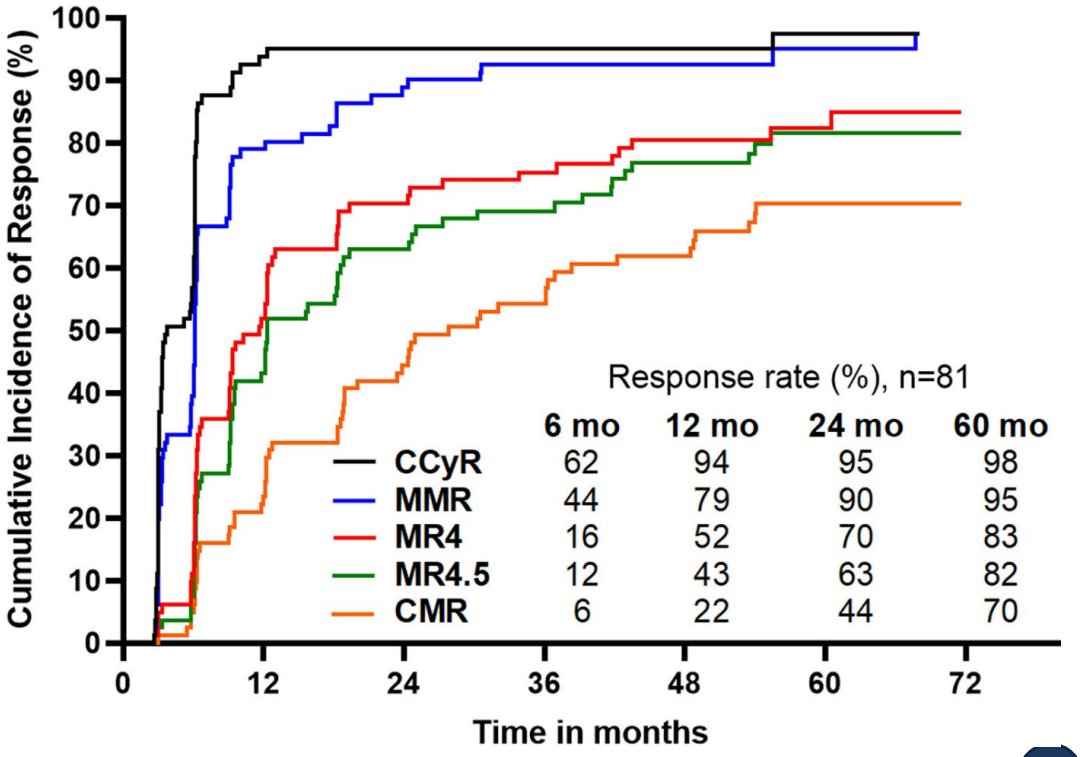
Mitigating treatment related AEs: starting lower dose dasatinib first-line

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



Major molecular response (MMR) rates over time

5-year follow-up



11 patients (13%) developed pleural effusion

Naqvi K et al. Cancer. 2020 Jan 1;126(1):67-75.
Gener-Ricos. Clin Lymphoma Myeloma Leuk. 2023 May 23:S2152-2650(23)00167-2.

What data support consideration for lower dose TKI use upfront?

TKI	Study	Patient Characteristics	TKI Dose	Study Findings
Dasatinib	Single center Pilot Study[249]	81 evaluable patients (majority of patients had low-risk (n = 55; 66%) or intermediate-risk (n = 21; 25%) disease by Sokol score Minimum follow up: 12 months	50 mg/day	The cumulative rates for MMR, MR4, and MR4.5 at 12 months were achieved in 81%, 55%, and 49% of patients respectively.
	DAVLEC (Phase II study)[252]	52 patients; aged >70 years; Median follow-up of 366 days	20 mg/day	MMR at 12 months was achieved in 60% of patients.

1. Lower dose dasatinib first-line in low/ intermediate risk or older CP CML patients

2. Retrospective data of dose modifications with durable response in the setting of intolerance

- **? First-line:** Bosutinib 200-300 mg orally daily

NCCN Guidelines. Chronic Myeloid Leukemia. V2.2024.

Oehler VG, Huang IJ, Siu C, Kim M et al. Dose modifications in the management of chronic phase chronic myeloid leukemia: who, what, and when. 2024 JNCCN invited review, in press.

Case: Treatment

- **First-line:** Bosutinib 400 mg orally daily
- *BCR::ABL1* transcripts at 3 months: 35%
- MB is adherent to therapy but struggles with fatigue. Diarrhea was managed with anti-diarrheal medications for the first 2 months and improved after week 10 of therapy with diet modifications
- *BCR::ABL1* transcripts at 6 months: 29%

Next steps?

NCCN Guidelines Version 2.2024: Early Treatment Response Milestones

Assess for mutations in ABL

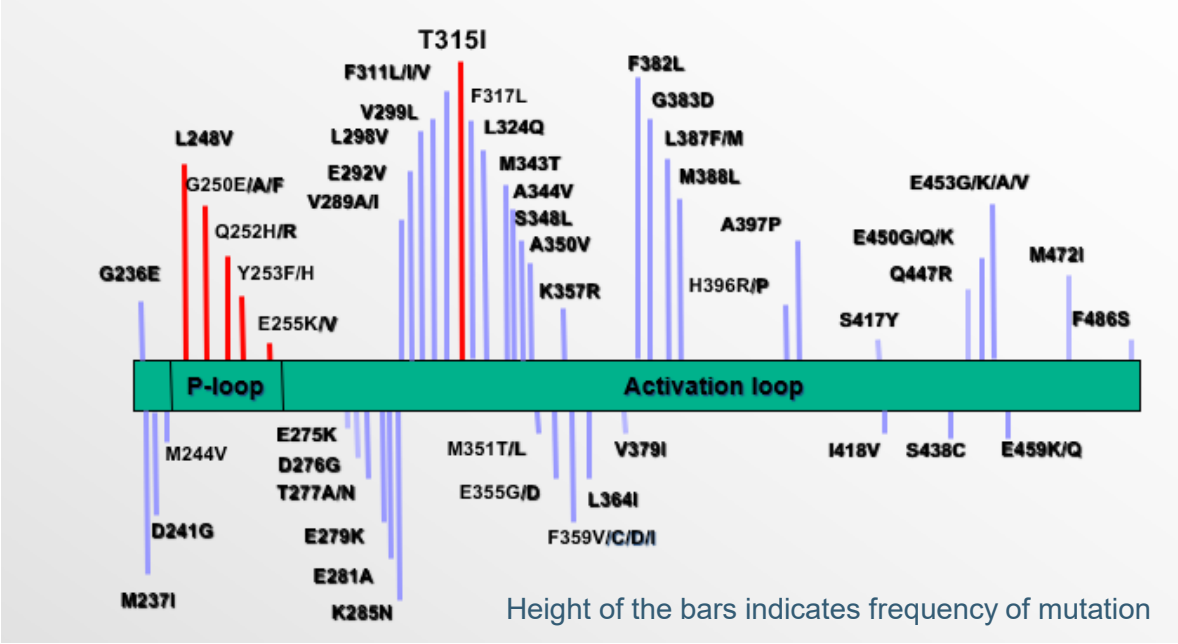
BCR::ABL1	3 months	6 months	12 months
>10%	NCCN Possible TKI Resistance	NCCN TKI-resistant	NCCN TKI-resistant
>1% - 10%	NCCN TKI sensitive	NCCN TKI sensitive	NCCN Possible TKI Resistance
>0.1 - 1%	NCCN TKI sensitive	NCCN TKI sensitive	*NCCN TKI sensitive**
≤ 0.1%	NCCN TKI sensitive	NCCN TKI sensitive	NCCN TKI sensitive

COLOR	CONCERN	CLINICAL CONSIDERATIONS	SECOND-LINE TREATMENT
RED	TKI-resistant disease	• Evaluate patient adherence and drug interactions • Consider *BCR::ABL1* kinase domain mutational analysis • Consider bone marrow cytogenetic analysis to assess for additional chromosomal abnormalities	Switch to alternate TKI (other than imatinib) and evaluate for allogeneic HCT
YELLOW	Possible TKI resistance	• Evaluate patient adherence and drug interactions • Consider *BCR::ABL1* kinase domain mutational analysis • Consider bone marrow cytogenetic analysis to assess for MCyR at 3 months or CCyR at 12 months	Switch to alternate TKI or Continue same TKI and Consider evaluation for allogeneic HCT
LIGHT GREEN	TKI-sensitive disease	• *Evaluate patient adherence and drug interactions* • *If treatment goal is long-term survival: ≤ 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 • Evaluate patient adherence and drug interactions	Continue same TKI

NCCN Guidelines. Chronic Myeloid Leukemia. V2.2024.

BCR::ABL1 kinase domain mutations

THERAPY	CONTRAINDICATED MUTATIONS[z]
Asciminib	A337T, P465S, or F359V/I/C
Bosutinib	T315I, V299L, G250E, or F317L[aa]
Dasatinib	T315I/A, F317L/V/I/C, or V299L
Nilotinib	T315I, Y253H, E255K/V, or F359V/C/I
Ponatinib, Omacetaxine,[bb] or allogeneic HCT (CML-6)	None[cc]



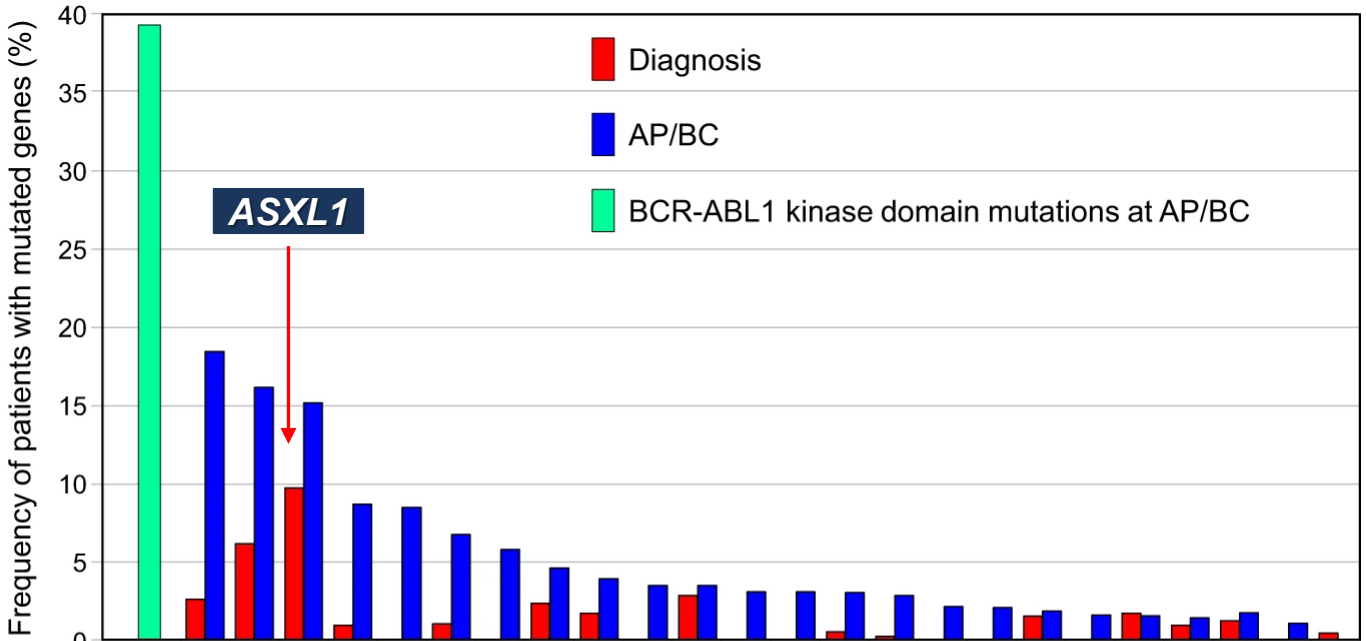
Height of the bars indicates frequency of mutation

1. Acquired resistance
2. Primary resistance

- [aa]Bosutinib has minimal activity against F317L mutation. Nilotinib may be preferred over bosutinib in patients with F317L mutation.
- [cc]There are compound mutations (defined as harboring ≥2 mutations in the same *BCR::ABL1* allele that can cause resistance to ponatinib, but these are uncommon after 2nd generation TKI use

NCCN Guidelines. Chronic Myeloid Leukemia. V1.2025.

Mutational landscape in CML at diagnosis and at disease progression

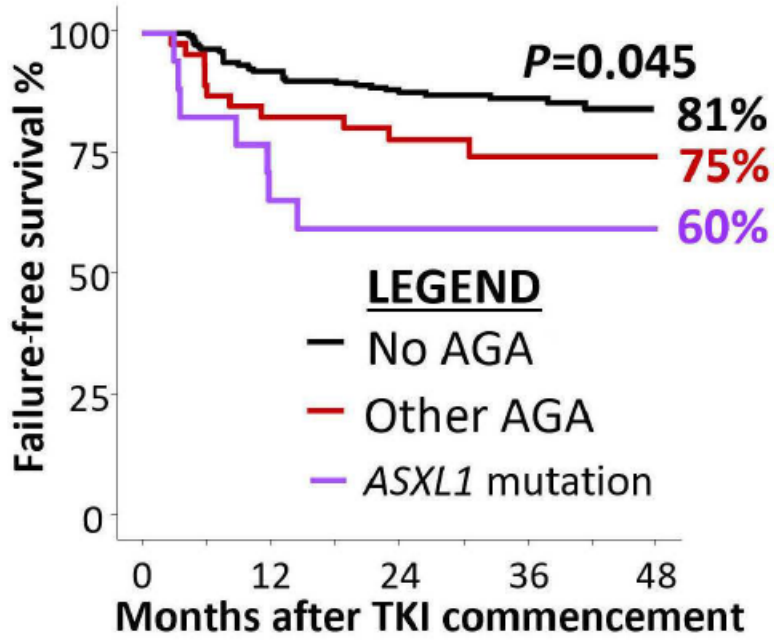


	BCR-ABL1 kinase domain	RUNX1	IKZF1 exon deletion	ASXL1	BCORL1	GATA2	TET2	WT1	DNMT3A	TP53	SETBP1	SETD1B	PHF6	BCOR	PTPN11	IDH1	IDH2	CBLB	JAK2	NRAS	KMT2D	CBL	IKZF1 SNV/indel	KRAS	EZH2
Diagnosis																									
No. of patients tested		3499	493	51850	1091	1090	4394	2240	3488	2374	2090	1093	2090	2090	2091	4891	4890	2090	3235	2240	3334	2242	3334	2240	3482
No. with variants																									
%		**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**

Branford S, et al. *Leukemia*. 2019;33:1835–1850;
Ochi Y, et al. *Nat Commun*. 2021;14:2833.

ASXL1 and outcomes

Mutant *ASXL1* and failure-free survival



Number at risk

No AGA	139	124	111	69	32
Other AGA	43	36	29	17	6
ASXL1	18	15	12	9	3

ARTICLE OPEN

Check for updates

Prognostic impact of *ASXL1* mutations in chronic phase chronic myeloid leukemia

Aram Bidikian[1], Hagop Kantarjian[1], Elias Jabbour[1], Nicholas J. Short[1], Keyur Patel[2], Farhad Ravandi[1], Koji Sasaki[1] and Ghayas C. Issa[1]

ARTICLE OPEN

Check for updates

ASXL1 mutations predict inferior molecular response to nilotinib treatment in chronic myeloid leukemia

Lioba Schönfeld[1,8], Jenny Rinke[1,8], Anna Hinze[1], Saskia N. Nagel[1], Vivien Schäfer[1], Thomas Schenk[1], Christian Fabisch[1], Tim H. Brümmendorf[2], Andreas Burchert[3], Philipp le Coutre[4], Stefan W. Krause[5], Susanne Saussele[6], Fatemeh Safizadeh[7], Markus Pfirrmann[7], Andreas Hochhaus[1] and Thomas Ernst[1]

Failure-free survival per ELN: failure to achieve time-dependent molecular milestones, acquisition of *BCR::ABL1* kinase domain mutations, AP/BP and death by any cause.

AGA includes mutations and other structural variants in BCR::ABL1

Shanmuganathan N et al. Haematologica. 2023 Sep 1;108(9):2380-2395.
Bidikian A et al. Blood Cancer Journal. 2022; 12: 144.
Schönfeld L et al. Leukemia. 2022 Sep;36(9):2242-2249.

Case: Treatment

- ***First-line:*** *Bosutinib 400 mg orally daily*
- *BCR::ABL1 transcripts at 3 months: 35%*
- *MB is adherent to therapy but struggles with fatigue. Diarrhea was managed with anti-diarrheal medications for the first 2 months and improved after week 10 of therapy with diet modifications*
- *BCR:ABL1 transcripts at 6 months: 29%*
- No mutations in ABL detected
- Bone marrow exam was not performed

Treatment?

Response to 2nd-line therapy after imatinib

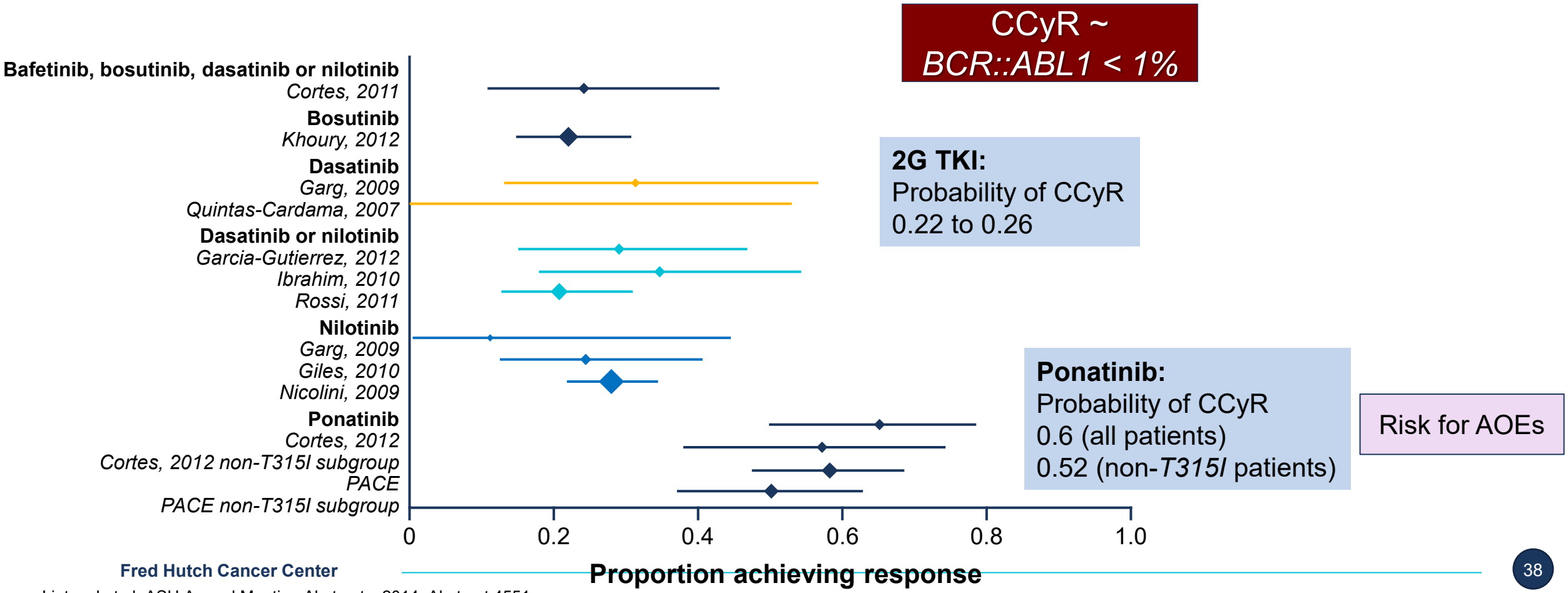
- Resistance to frontline imatinib is associated with lower CCyR rates compared with intolerance to imatinib*
  - Dasatinib (100 mg once daily, 2-year follow-up): imatinib-resistant, 44%; imatinib-intolerant, 67%
  - Nilotinib (400 mg twice daily, 2-year follow-up): imatinib-resistant, 41%; imatinib-intolerant,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

*** 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.

Treatment responses after failing imatinib and a 2nd generation TKI

Proportion of patients achieving CCyR (post 2G TKI setting)



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

Treatment Options in CP-CML

Compound	TKI Type / Generation	First Line	Second Line	≥ Third Line
Imatinib	ATP-competitive 1st generation	●		
Dasatinib	ATP-competitive 2nd generation	●	●	●
Nilotinib	ATP-competitive 2nd generation	●	●	●
Bosutinib	ATP-competitive 2nd generation	●	●	●
Ponatinib	ATP-competitive 3rd generation		●* (T315I)	●
Asciminib	ABL Myristoyl Pocket STAMP inhibitor		●† (T315I)	●
Omacetaxine	Protein synthesis inhibitor			

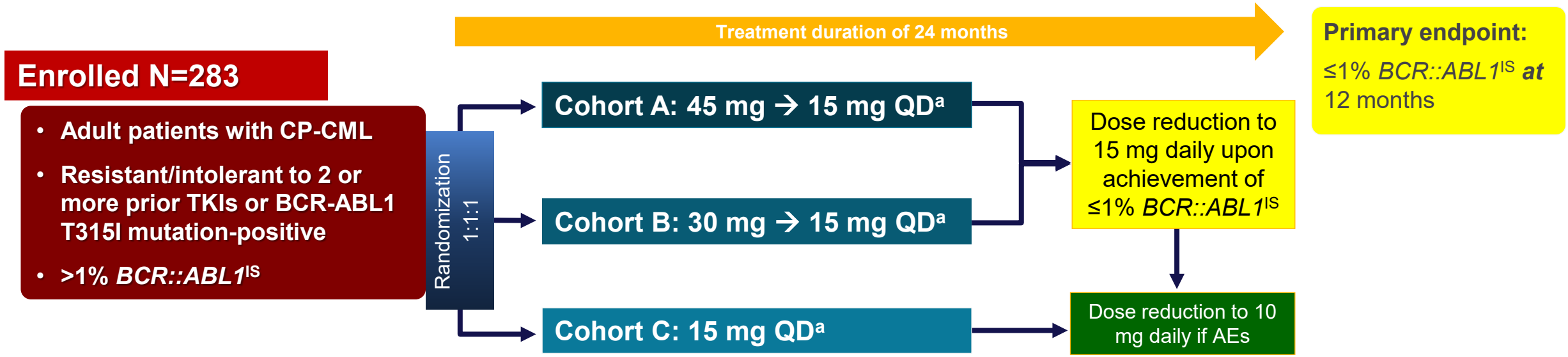
*Approved in US for a patients after ≥ 2 TKIs or for patients with T315I CP-CML in any line. †Approved for a patients after ≥ 2 TKIs or for patients with T315I CP-CML in any line. ‡Only available in the US.

Hochhaus A, et al. *Leukemia* 2020; 34: 966-984; NCCN Guidelines. Chronic Myeloid Leukemia. V3.2022.

Phase 2 OPTIC trial of ponatinib

FDA Label Change

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



- **More than 50% of the patients had received 3 or more TKIs**
- **More than 90% were resistant to their last TKI**

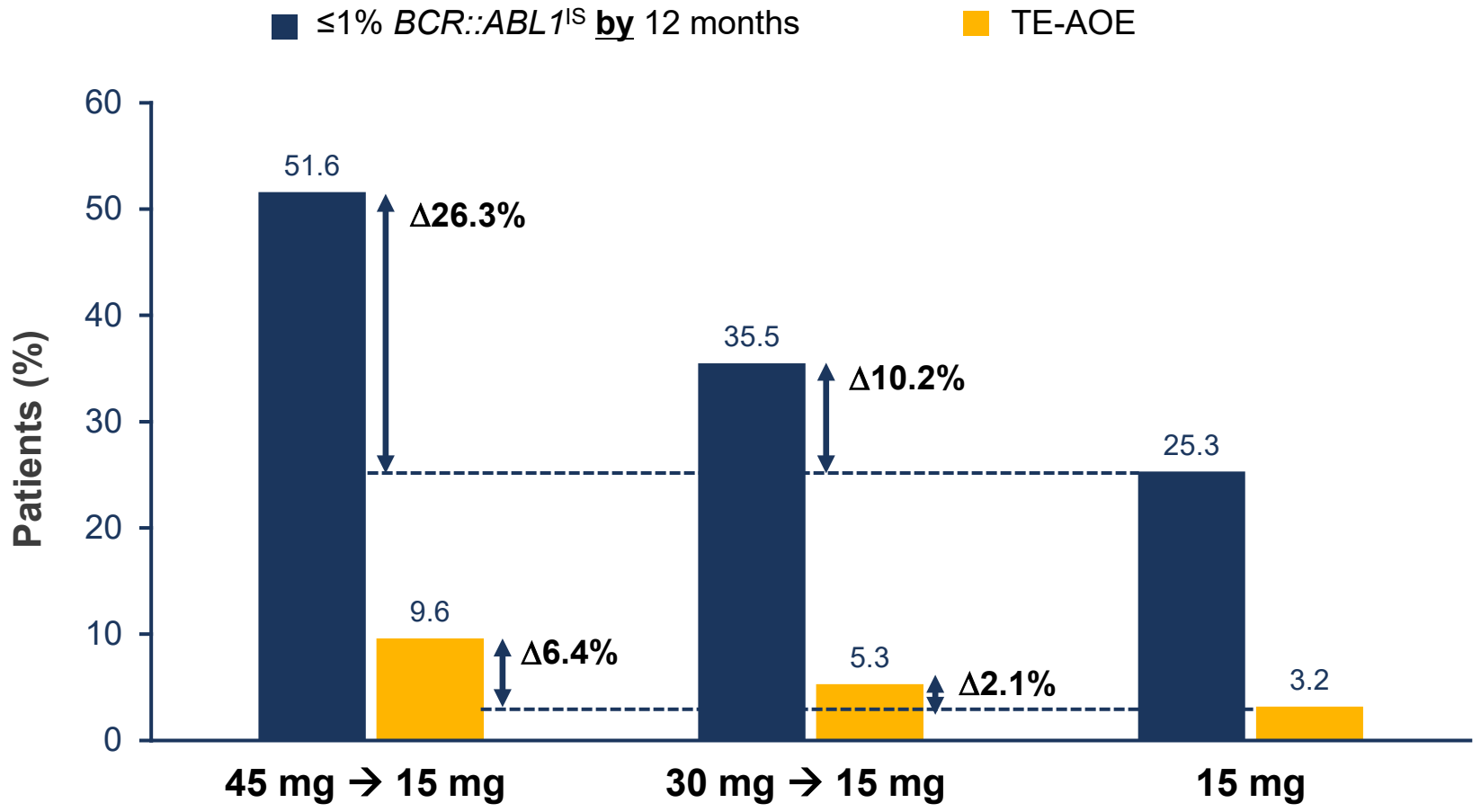
[a] Dose reductions due to AEs were permitted

→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 J et al. Blood. 2021 Nov 25;138(21):2042-2050.

OPTIC: Overall Safety and Efficacy by Starting Dose



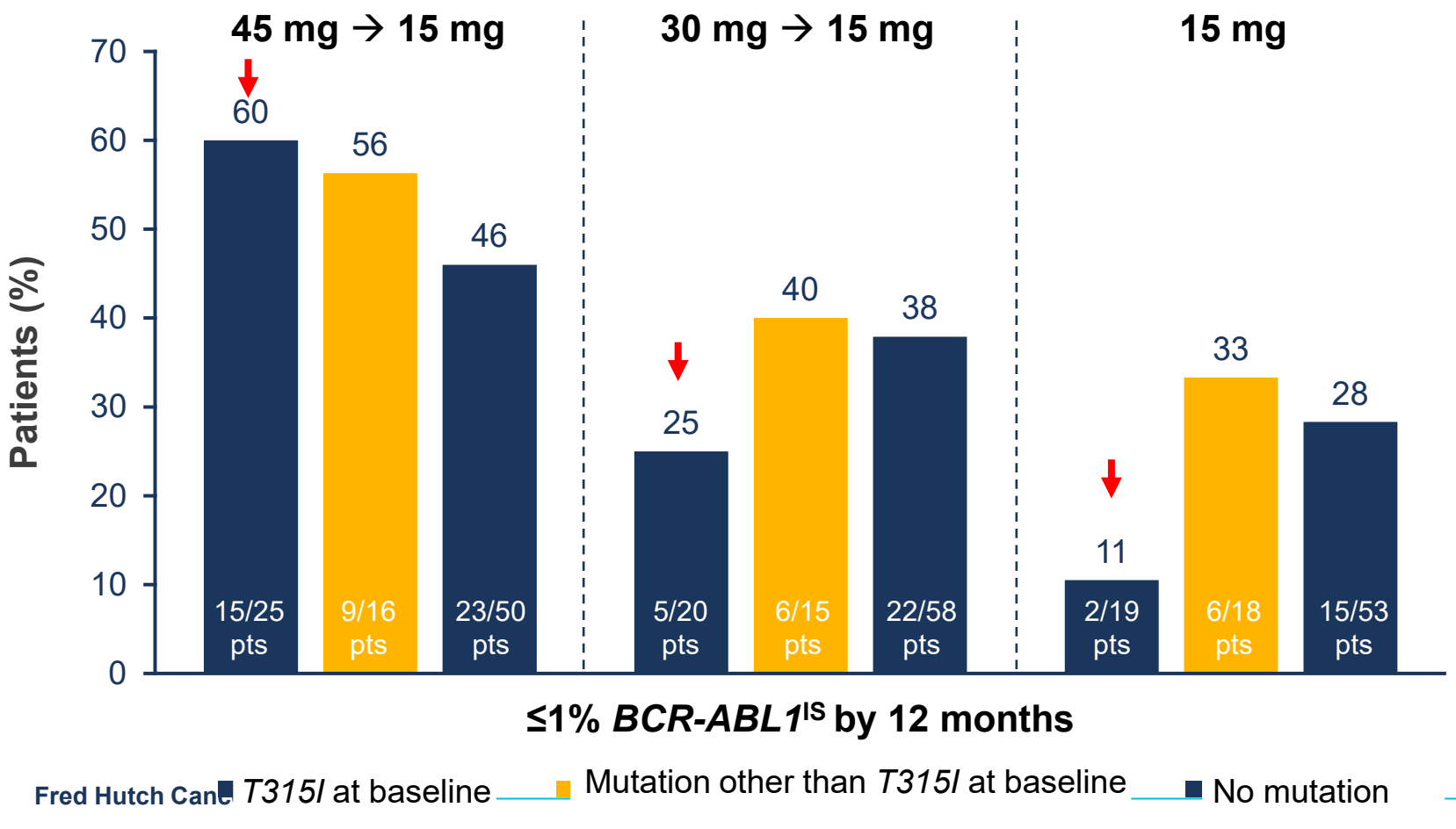
FDA Label Change

- Dose dependent impact on AOEs was observed
- BUT lower incidence of AOEs relative to what was observed in the PACE study which did not include dose reduction (17%, independent adjudication)*
- Propensity score analysis

The primary end point (≤1% *BCR-ABL1*^{IS} **at** 12 months) was achieved in 44.1% (31.7-57.0) in the 45-mg cohort, 29.0% (18.4-41.6) in the 30-mg cohort, and 23.1% (13.4-35.3) in the 15-mg cohort.

Cortes J et al. Blood. 2021 Nov 25;138(21):2042-2050.
*Januzzi JL et al. J Hematol Oncol 15, 1 (2022).

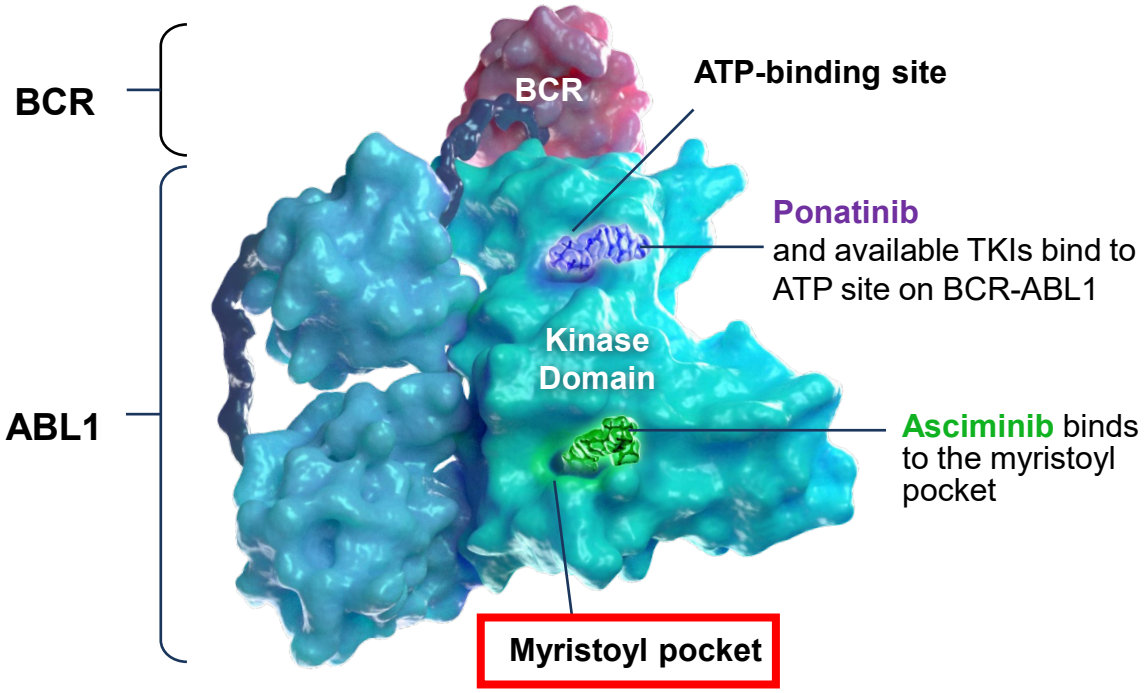
OPTIC: ≤1% *BCR::ABL1*^{IS} Response Rate by 12 Months by *T315I* Baseline Status



1. Starting higher dose important for patients harboring T315I mutations
2. Fewer patients achieved *BCR::ABL1* ≤1% when started at 30 or 15 mg

Cortes J, et al. *Blood*. 2021;138(21):2042-2050.

Asciminib, a BCR::ABL1 inhibitor with a distinct allosteric mechanism of action



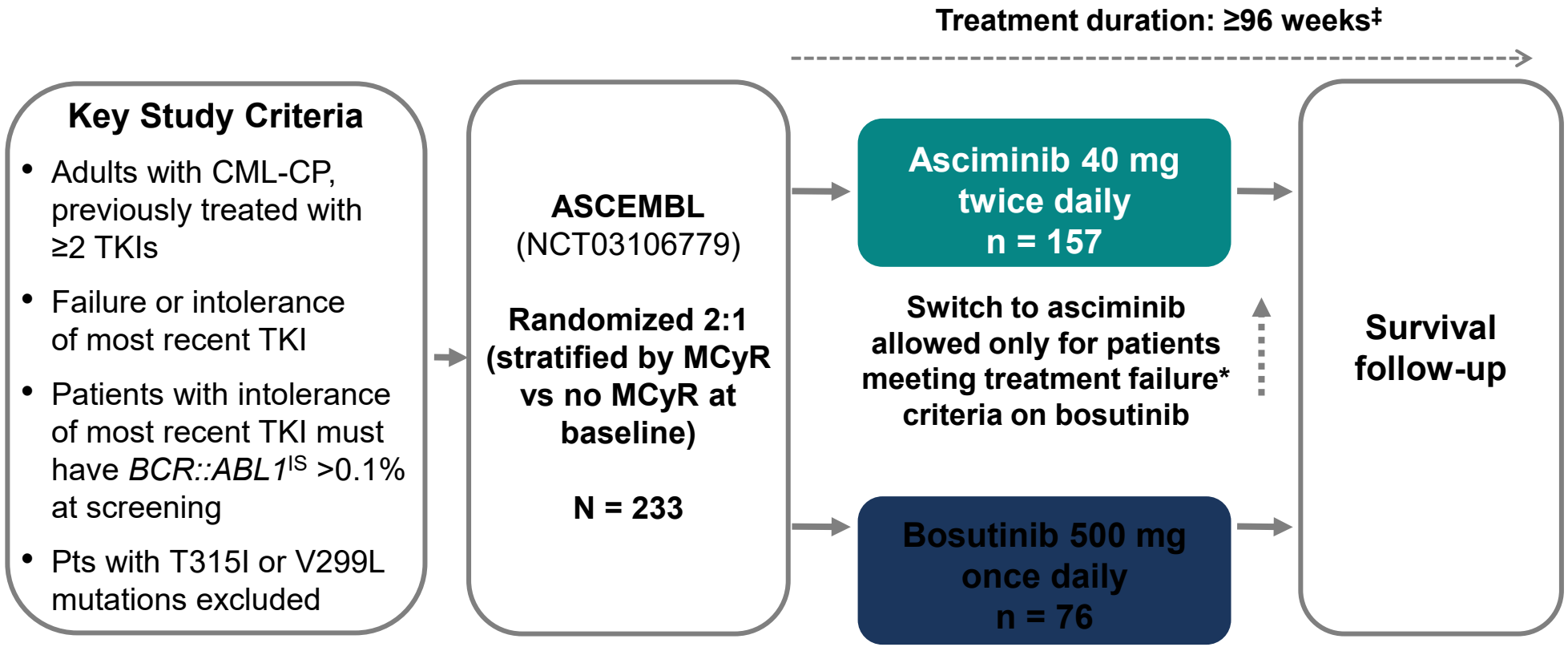
1. Very high selectivity with narrow target profile
2. Active against many *BCR::ABL1* mutations that confer resistance to TKIs, including T315I
3. FDA approved 2021 [3] 3-line in intolerant and resistant CP CML based on ASCEMBL study

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

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

ASCEMBL: Asciminib vs Bosutinib in CML after 2 Prior TKIs, Phase 3 Randomized Study

Primary Endpoint: MMR rate at 24 weeks while on study treatment



*Patients on bosutinib meeting lack of efficacy criteria were allowed to switch to asciminib. NOT included in these analyses.

Réa D, et al. *Blood*. 2021;138(21):2031-2041.
Hochhaus A et al. *Leukemia*. 2023; 37(3): 617–626.

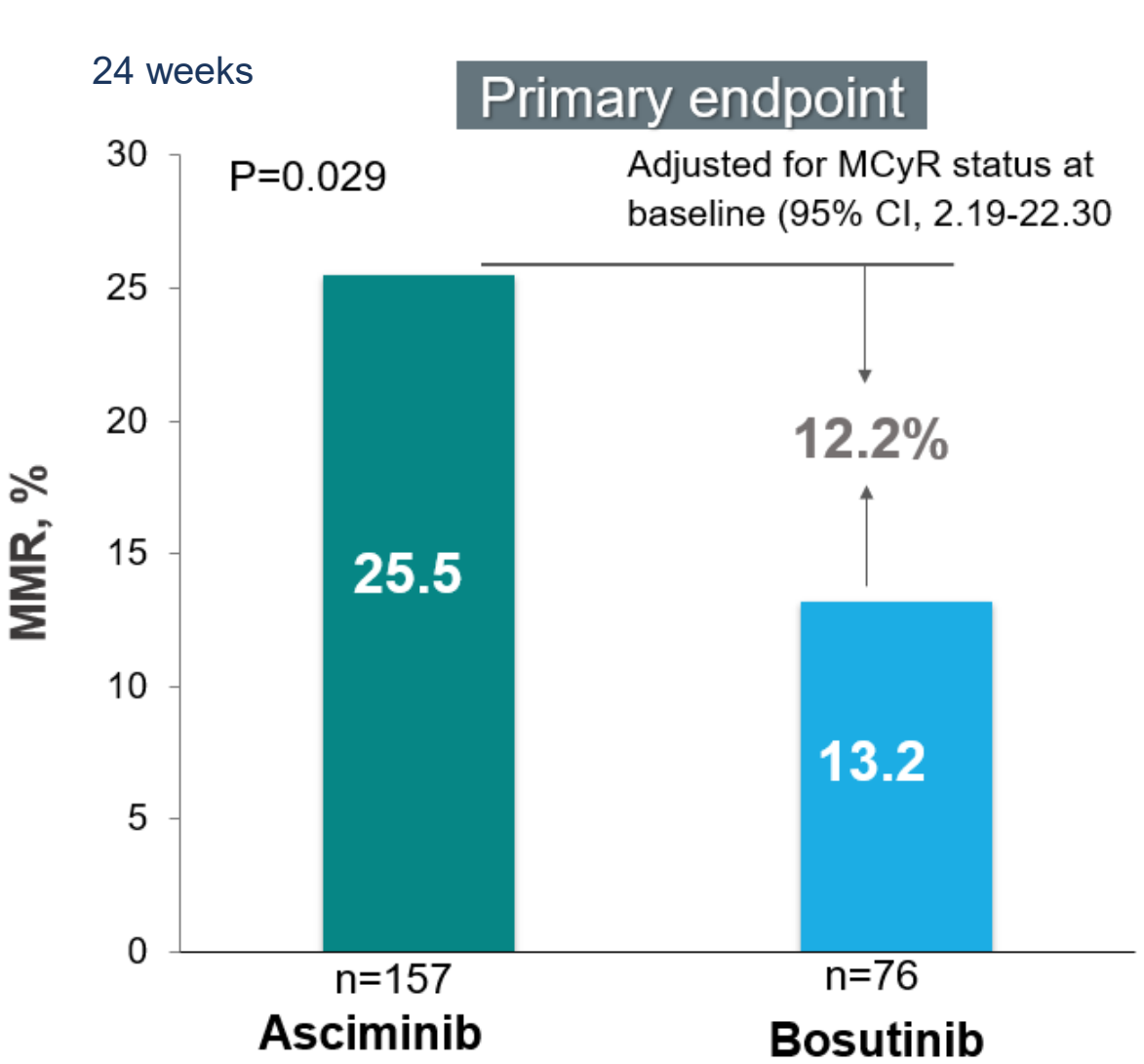
Demographics and Baseline Characteristics

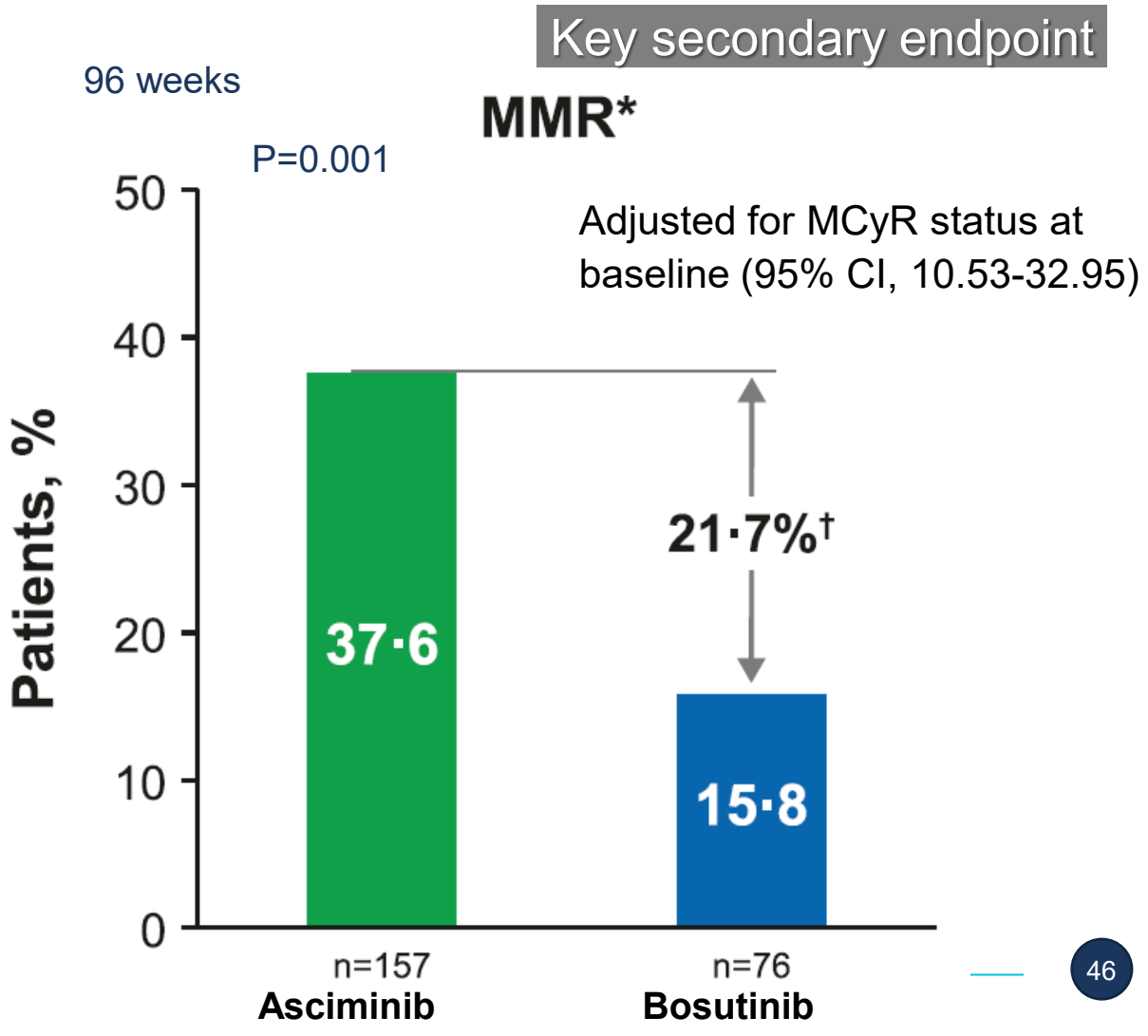
Variable	Asciminib 40 mg Twice Daily (n=157)	Bosutinib 500 mg Once Daily (n=76)	All Patients (N=233)
Median age, years (range)	52.0 (24-83)	52.0 (19-77)	52.0 (19-83)
Female sex, n (%)	75 (47.8)	45 (59.2)	120 (51.5)
MCyR, n (%)	46 (29.3)	22 (28.9)	68 (29.3)
Reason for discontinuation of last TKI, n (%)			
Lack of efficacy	95 (60.5)	54 (71.1)	149 (63.9)
Lack of tolerability	59 (37.6)	22 (28.9)	81 (34.8)
Other*	3 (1.9)	0	3 (1.3)
Number of lines of prior TKI therapy, n (%)			
2	82 (52.2)	30 (39.5)	112 (48.1)
≥3	75 (47.8)	46 (60.5)	121 (51.9)
BCR::ABL^{IS} at baseline, n (%)			
>0.1% to ≤1%†	15 (9.6)	4 (5.3)	NA
>1% to ≤10%	45 (28.7)	23 (30.3)	NA
>10%	97 (61.8)	49 (64.5)	NA
Patients with any BCR::ABL1 mutation, n (%)	20 (12.7)	13 (17.1)	33 (14.2)
Patients with multiple BCR::ABL1 mutations, n (%)	3 (1.9)	1 (1.3)	4 (1.7)

NA, not applicable. * Includes improper assignment of study medication, lack of efficacy and tolerability, and optimal response not reached after 5 years of treatment.
† All patients with *BCR-ABL*^{IS} <1% at baseline were intolerant to the last TKI, except 1 in the asciminib arm (who deviated from the protocol).

Réa D, et al. *Blood*. 2021;138(21):2031-2041.

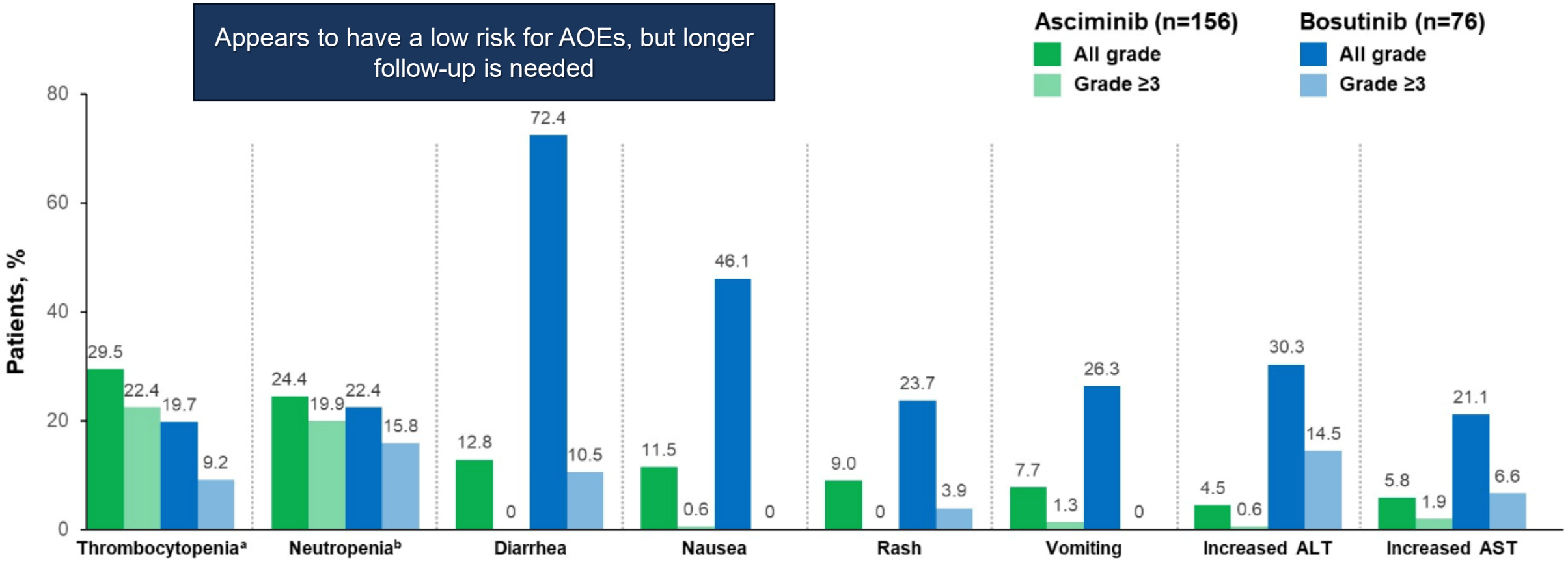
ASCEMBL: MMR rates at 24 and 96 weeks





Réa D, et al. *Blood*. 2021;138(21):2031-2041, Hochhaus A et al. *Leukemia*. 2023; 37(3): 617–626.

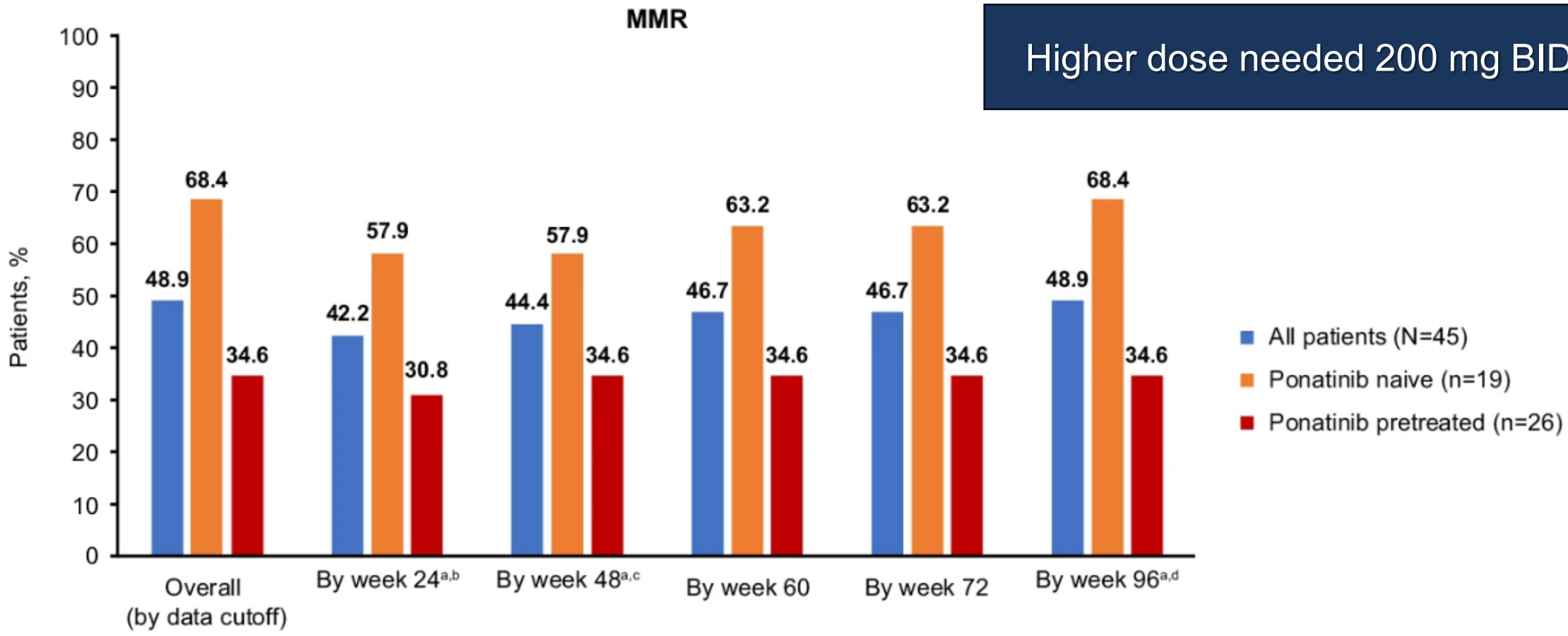
Longer follow-up confirms tolerability of asciminib



- Asciminib continues to be well tolerated with few GI side effects
- AEs were generally more generally more frequent within the first 18 months of starting asciminib
- Hematologic toxicities similar to bosutinib were frequent in this heavily pre-treated group of patients

Hochhaus A et al. *Leukemia.* 2023; 37(3): 617–626.

Asciminib monotherapy in patients with chronic-phase chronic myeloid leukemia with the T315I mutation after ≥1 prior tyrosine kinase inhibitor: 2-year follow-up results



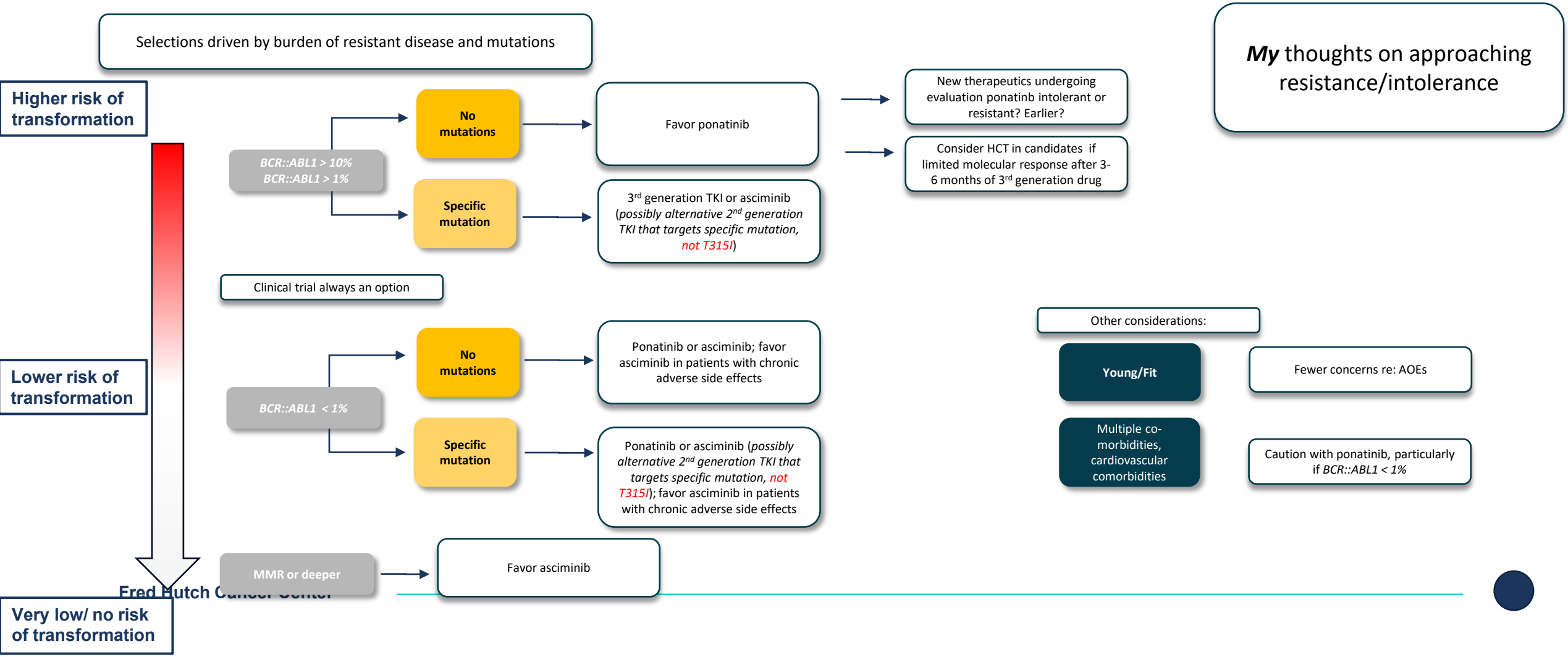
Higher dose needed 200 mg BID

Cortes JE, et al. Leukemia. 2024 Jul;38(7):1522-1533.

ASCEMBL study caveats:

- Was bosutinib the best comparator arm in patients failing prior 2G-TKI?
  - Ponatinib?
    - Is ponatinib (or other 3rd generation drug) a better choice for patients without mutations with *BCR::ABL1* > 10% (> 1%?)
- High discontinuation rate in ASCEMBL vs other bosutinib studies
- Does asciminib have an AOE signal with longer-term follow-up?

Personal reflections on 3rd line therapy and sequencing new potent therapies



Future Treatment Options in CP-CML

Compound	TKI Type / Generation	First Line	Second Line	≥ Third Line
Imatinib	ATP-competitive 1st generation	●		
Dasatinib	ATP-competitive 2nd generation	●	●	●
Nilotinib	ATP-competitive 2nd generation	●	●	●
Bosutinib	ATP-competitive 2nd generation	●	●	●
Ponatinib	ATP-competitive 3rd generation		●* (T315I)	●
Asciminib	ABL Myristoyl Pocket STAMP inhibitor	●	●† (T315I)	●
Omacetaxine	Protein synthesis inhibitor			

*Approved in US for a patients after ≥ 2 TKIs or for patients with T315I CP-CML in any line. †Approved for a patients after ≥ 2 TKIs or for patients with T315I CP-CML in any line. ‡Only available in the US.

Hochhaus A, et al. *Leukemia* 2020; 34: 966-984; NCCN Guidelines. Chronic Myeloid Leukemia. V3.2022.

ASC4FIRST, a head-to-head study comparing asciminib vs all standard-of-care TKIs in newly diagnosed patients with CML

NCT04971226

Key inclusion criteria

- Newly diagnosed Ph+ CML-CP with ***no*** prior TKIs[a]
- Age ≥18 years

Prerandomization TKI selection

- The TKI a patient will take if randomized to the investigator-selected (IS-TKI) arm
- Selected by the physician in consultation with the patient

Stratification by:

- Prerandomization TKI selection (IMA or 2G TKI)
- ELTS risk category (high, intermediate, low)

R 1:1

N=405

Asciminib (ASC) 80 mg QD

- Imatinib stratum: **ASC^{IMA}**
- 2G TKI stratum: **ASC^{2G}**

All IS-TKIs at label doses

- Imatinib stratum: **IS-TKI^{IMA}**
- 2G TKI stratum: **IS-TKI^{2G}**

End of study: LPFT + 5 years[b]

Data cutoff: Nov. 28, 2023

Primary endpoints:

- **MMR at week 48 for asciminib vs all investigator-selected TKIs**
- **MMR at week 48 for asciminib vs investigator-selected TKI within the imatinib stratum**

ASC, asciminib; ELTS, EUTOS long-term survival score; EUTOS, European Treatment and Outcome Study; IMA, imatinib; LPFT, last person first treatment; Ph, Philadelphia chromosome; QD, once daily; R, randomized.

[a] Either imatinib, bosutinib, dasatinib, or nilotinib is allowed for up to 2 weeks prior to randomization. Treatment with other TKIs prior to randomization was not permitted.

[b] Patients will remain on study for 5 years after the last patient first dose, unless they have discontinued early due to treatment failure, disease progression, pregnancy, intolerance, or investigator or patient decision.

Hochhaus A, et al. N Engl J Med. 2024 May 31. doi: 10.1056/NEJMoa2400858. Epub ahead of print. PMID: 38820078.

Baseline characteristics were well balanced between asciminib and all IS-TKIs

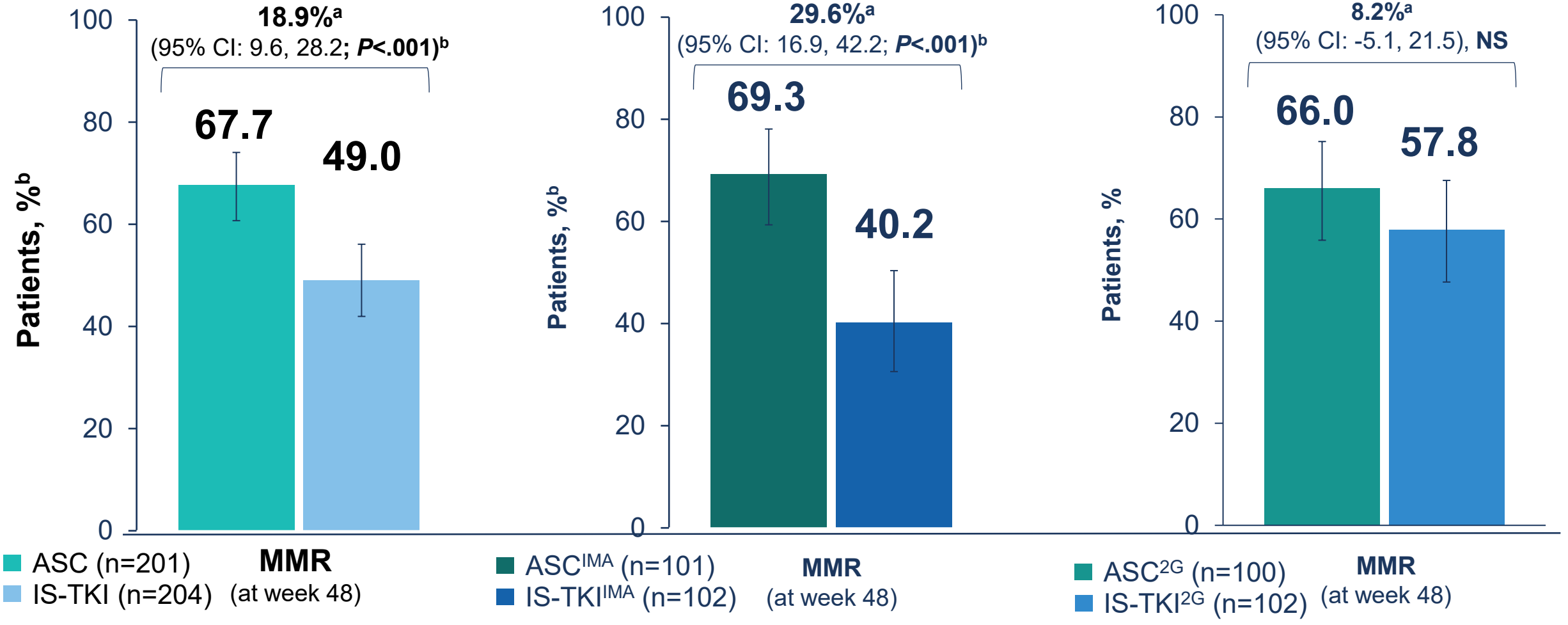
Variable	Asciminib			IS-TKI		
	All asciminib (n=201)	Imatinib stratum (n=101)	2G TKI stratum (n=100)	All IS-TKI (n=204)	Imatinib stratum (n=102)	2G TKI stratum (n=102)
Median age (range), years	52.0 (18.0-79.0)	56.0 (21.0-79.0)	43.0 (18.0-76.0)	50.5 (19.0-86.0)	54.5 (20.0-86.0)	43.0 (19.0-83.0)
Age group, %						
18 to <65 years	77.1	68.3	86.0	76.0	68.6	83.3
65 to <75 years	17.9	23.8	12.0	16.7	21.6	11.8
≥75 years	5.0	7.9	2.0	7.4	9.8	4.9
Male, %	65.2	61.4	69.0	61.3	63.7	58.8
Framingham CV risk score, %[a]						
Low risk (<10%)	54.2	40.6	68.0	54.9	39.2	70.6
Intermediate risk (10%-20%)	15.9	20.8	11.0	21.6	28.4	14.7
High risk (≥20%)	29.9	38.6	21.0	23.5	32.4	14.7
ELTS, %[b]						
Low	60.7	61.4	60.0	61.3	62.7	59.8
Intermediate	27.9	29.7	26.0	27.9	29.4	26.5
High	11.4	8.9	14.0	10.8	7.8	13.7

[a] Framingham estimated 10-year cardiovascular disease risk categories.
[b] Based on randomization data.

Hochhaus A, et al. N Engl J Med. 2024 May 31. doi: 10.1056/NEJMoa2400858. Epub ahead of print. PMID: 38820078.

MMR rate at week 48 was superior with asciminib vs all IS-TKIs and vs IS-TKI^{IMA}

A higher proportion of patients achieved early and deep molecular responses with asciminib vs all IS-TKIs

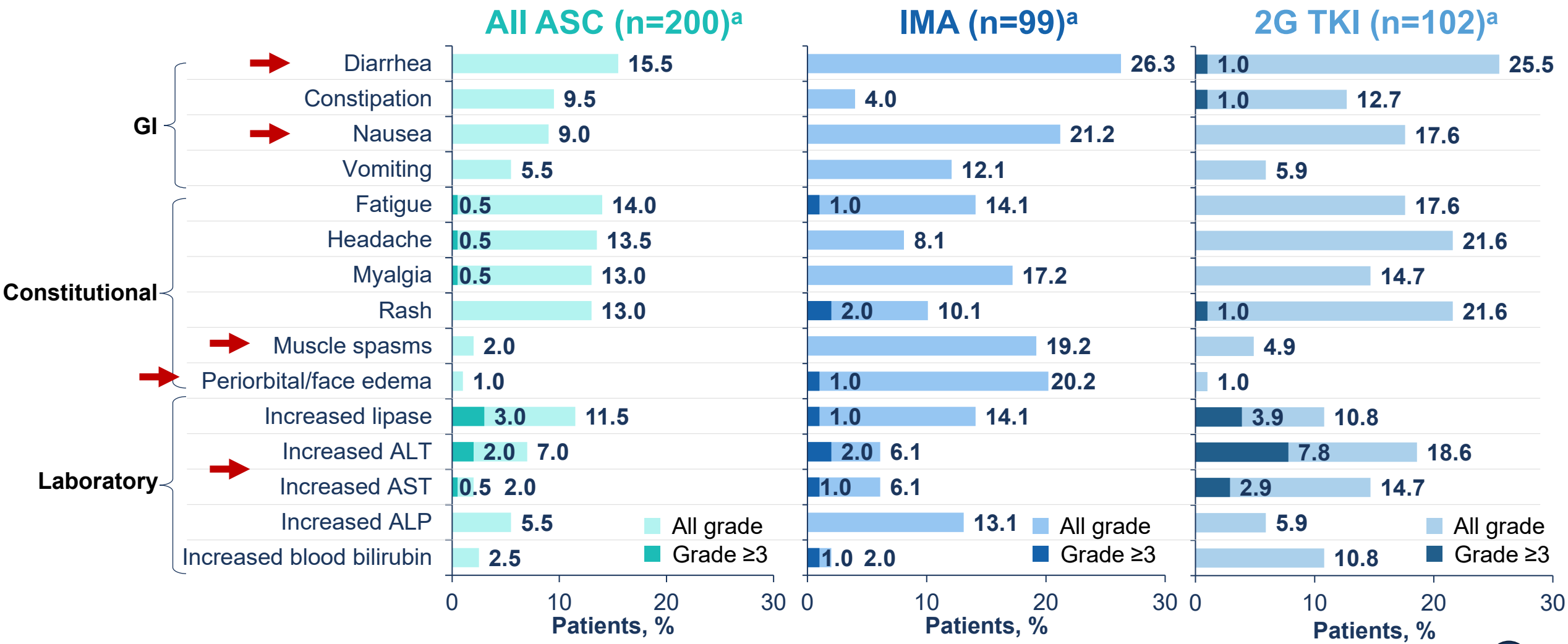


IRT, interactive response technology.
Error bars represent 95% CIs.

[a] The common treatment difference and its 95% CI are estimated using the Mantel-Haenszel method after stratifying for (a) pre-randomization selected TKI, and (b) baseline ELTS risk groups (both IRT data).

[b] Adjusted 1-sided p-value calculated based on the graphical gatekeeping procedure. The null hypothesis is rejected if the adjusted p-value is ≤0.025.

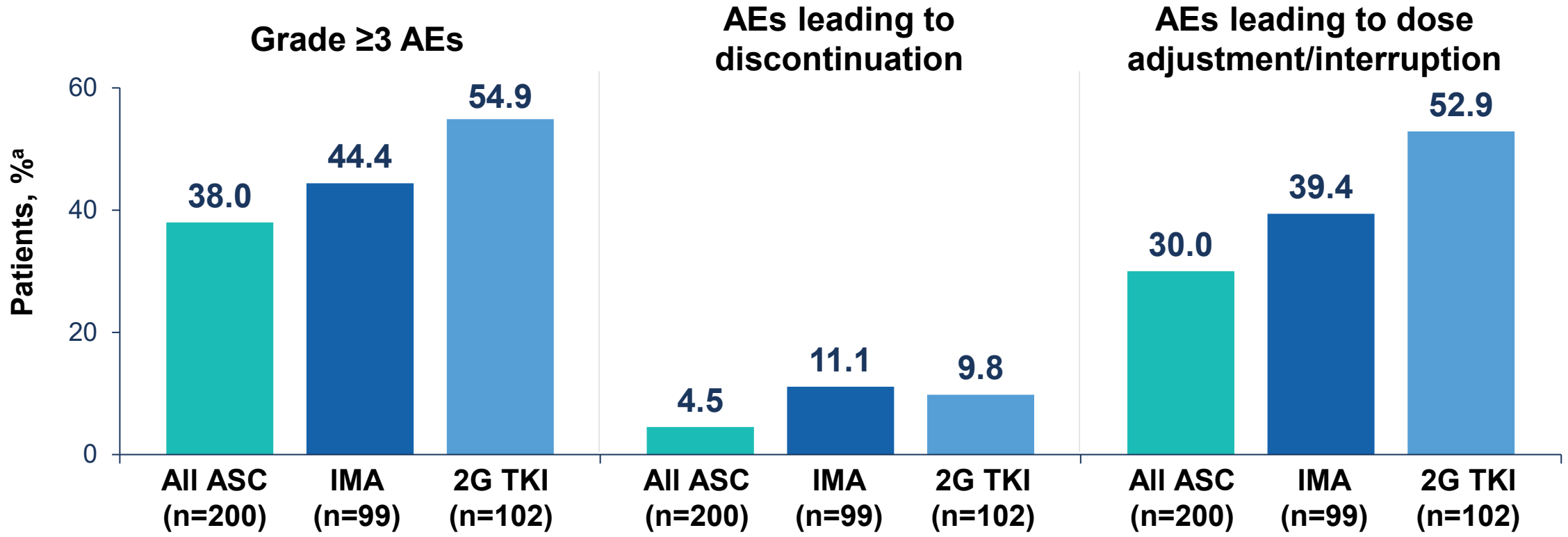
Rates of most non-hematologic toxicities were lower with asciminib



ALP, blood alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GI, gastrointestinal.

[a] Safety analyses consisted of patients who received ≥1 dose of study drug; numbers represent counts of patients. Shown are AEs that occurred during treatment or within 30 days after receiving the last dose of treatment. A patient with multiple severity grades for an AE is only counted under the maximum grade. AEs are ordered by system organ class. COVID-19 and upper respiratory tract infection are not shown.

Asciminib demonstrated favorable safety and tolerability vs IMA and 2G TKIs



- The median dose intensity was 80.0 mg/day with ASC, 400.0 mg/day with IMA, 595.1 mg/day with NIL, 98.9 mg/day with DAS, and 341.8 mg/day with BOS
- The most common AEs leading to treatment discontinuation were increased lipase with ASC (1.5%), diarrhea and lymphopenia with IMA (2.0% each), and pleural effusion with 2G TKIs (2.0%)

BOS, bosutinib; DAS, dasatinib; NIL, nilotinib.
[a] Safety analyses consisted of patients who received ≥1 dose of study drug. Patients were analyzed according to the study treatment received. A patient with multiple severity grades for an AE is only counted under the maximum grade.

Possible Future Treatment Options in CP-CML

Compound	TKI Type / Generation	First Line	Second Line	≥ Third Line
Imatinib	ATP-competitive 1st generation	●		
Dasatinib	ATP-competitive 2nd generation	●	●	●
Nilotinib	ATP-competitive 2nd generation	●	●	●
Bosutinib	ATP-competitive 2nd generation	●	●	●
Ponatinib	ATP-competitive 3rd generation		●* (T315I)	●
Asciminib	ABL Myristoyl Pocket STAMP inhibitor	●	●† (T315I)	●
Omacetaxine	Protein synthesis inhibitor			

Clinical trials:
1. Olverembatinib

1. Tgrx-678
2. TERN-701

*Approved in US for a patients after ≥ 2 TKIs or for patients with T315I CP-CML in any line. †Approved for a patients after ≥ 2 TKIs or for patients with T315I CP-CML in any line. ‡Only available in the US.

Hochhaus A, et al. *Leukemia* 2020; 34: 966-984; NCCN Guidelines. Chronic Myeloid Leukemia. V3.2022.

Case: Treatment

- **Second-line:** Dasatinib 100 mg orally daily
- *BCR::ABL1* transcripts after 2 months: 32%
- MB is fully adherent to therapy
- *BCR::ABL1* transcripts at 3 months: 30%
- No mutations in ABL detected
- Next steps?

Case: Treatment

- ***Second-line:*** *Dasatinib 100 mg orally daily*
- *BCR::ABL1 transcripts after 2 months: 32%*
- *MB is fully adherent to therapy*
- *BCR::ABL1 transcripts at 3 months: 30%*
- *No mutations in ABL detected*
- Bone marrow exam
  - Blasts 2% by morphology and 1% by flow cytometry
  - Metaphase karyotype with Philadelphia chromosome (t(9;22)) in 20/20 cells and a second clone with Ph and inversion 3 (abnormality of 3q26.2) in 6/20 cells
  - *RUNX1*_Arg107Cys mutation, allele frequency 38% (no family history of hematologic malignancy)
- Brother was identified as a 10/10 HLA allele-match for hematopoietic cell transplant

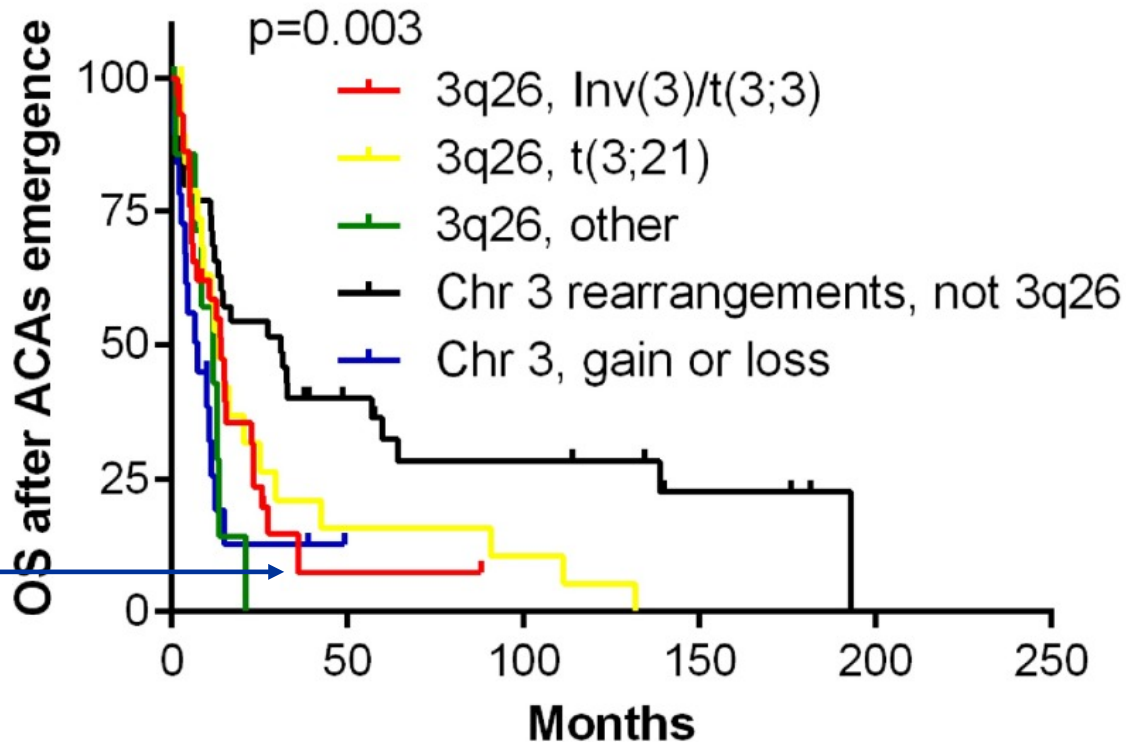
Next steps and treatment?

Additional Chromosomal Abnormalities (ACA) at Diagnosis or Acquired During Therapy Impact TKI Response

High risk ACA with low blast counts are a marker of progression and death due to CML

High-risk ACA:

- 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



Wang W et al. Blood. 2015 Oct 1; 126(14): 1699–1706.
Fabarius et al. Blood. 2011 Dec 22;118(26):6760-8.
Fabarius et al. Ann Hematol. 2015;94(12):2015-2024.
Hehlmann R et al. Leukemia. 2020; 34(8): 2074–2086.
Wang W et al. Blood. 2016;127(22):2742-2750.

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 BP →

- HCT using alternate TKI (+/- induction chemotherapy in BP) to bridge

***de novo* AP patients** →

- Type patient and siblings; use first-line TKI therapy with close monitoring for optimal response as some *de novo* AP patients without high-risk ACA do well. HCT in patients with high-risk ACA*; for others HCT when optimal milestones are not met.*

BP patients →

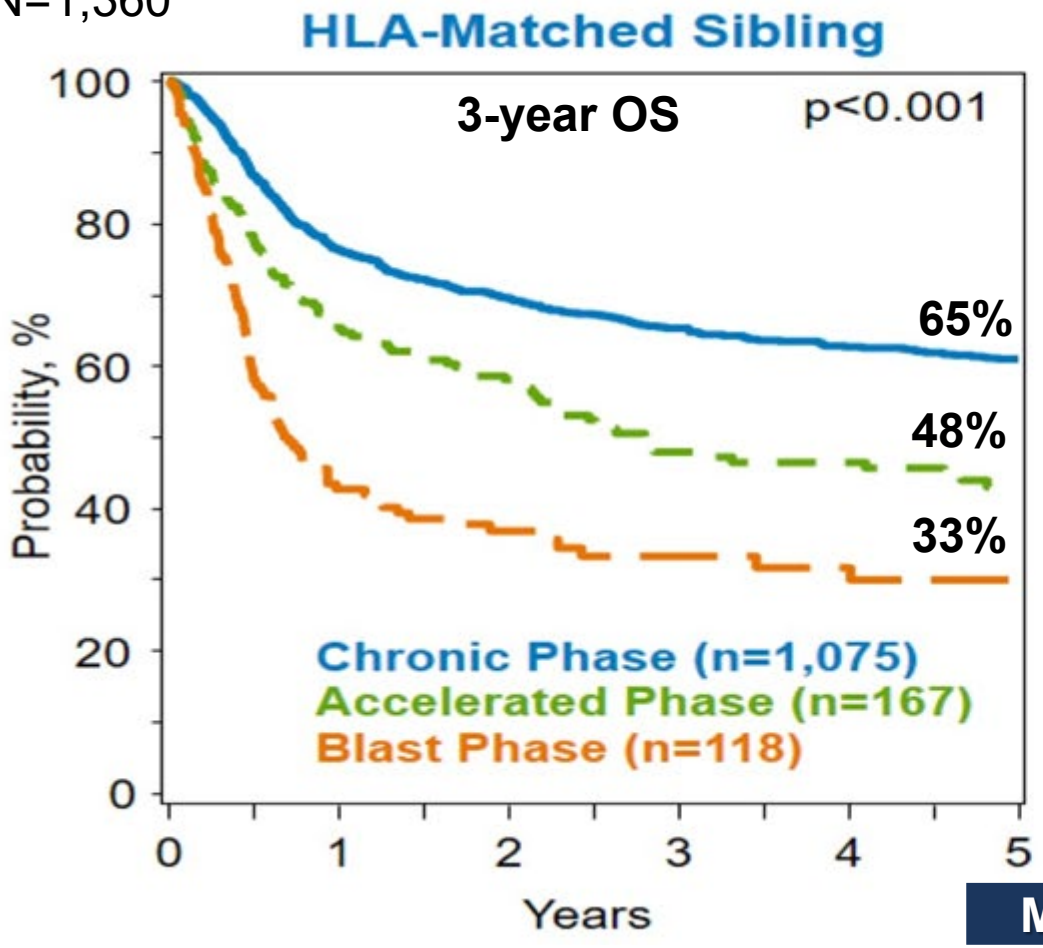
Median survival is ~7-12 months with TKI-based therapy

- HCT after TKI therapy +/- induction chemotherapy. I favor induction chemotherapy + TKI in most HCT candidates.

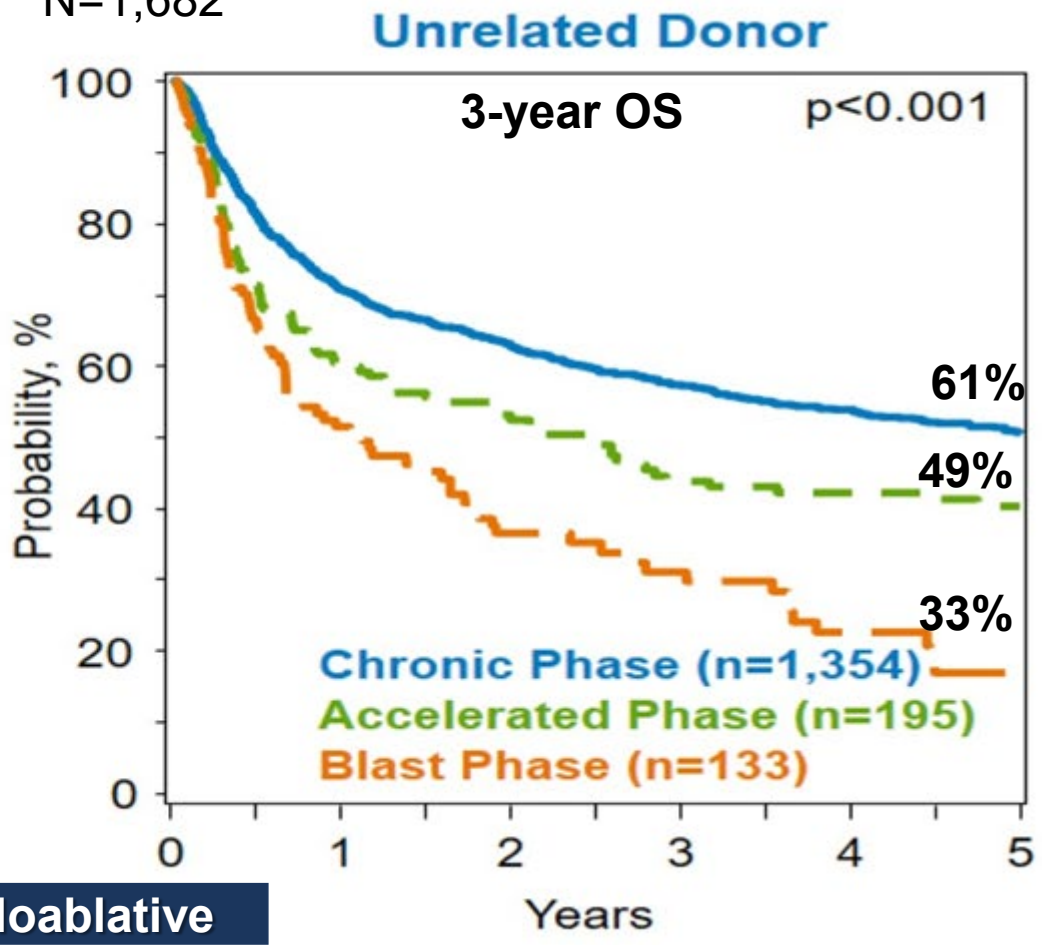
Ohanian et al. Clin Lymphoma Myeloma Leuk. 2014 Apr;14(2):155-162

Survival after HCT for CML, 2007-2017

N=1,360



N=1,682



Myeloablative

Center for International Blood and Marrow Transplant Research (CIBMTR)

Chhabra S et al. *Blood Adv* (2018) 2 (21): 2922–2936.

CML Treatment Goals Discussion

1. Life expectancy not impacted by CML: higher-risk CML → **ELTS score and Sokal score: High-risk**
2. Limit impact of TKI therapy on comorbidity outcomes → **Hypertension and hyperlipidemia**
3. Quality of life and minimizing adverse events
4. Treatment-free remission
5. Limiting costs
6. Family planning

- **First-line:** Bosutinib 400 mg orally daily
- Achieves MMR at 9 months and *BCR::ABL1* ≤0.0032% (MR4.5) at 18 months present for a subsequent 2.5 years

TKI Discontinuation

- Imatinib discontinuation: STIM1, STIM2, TWISTER
  - TFR rate at ~40%-50%

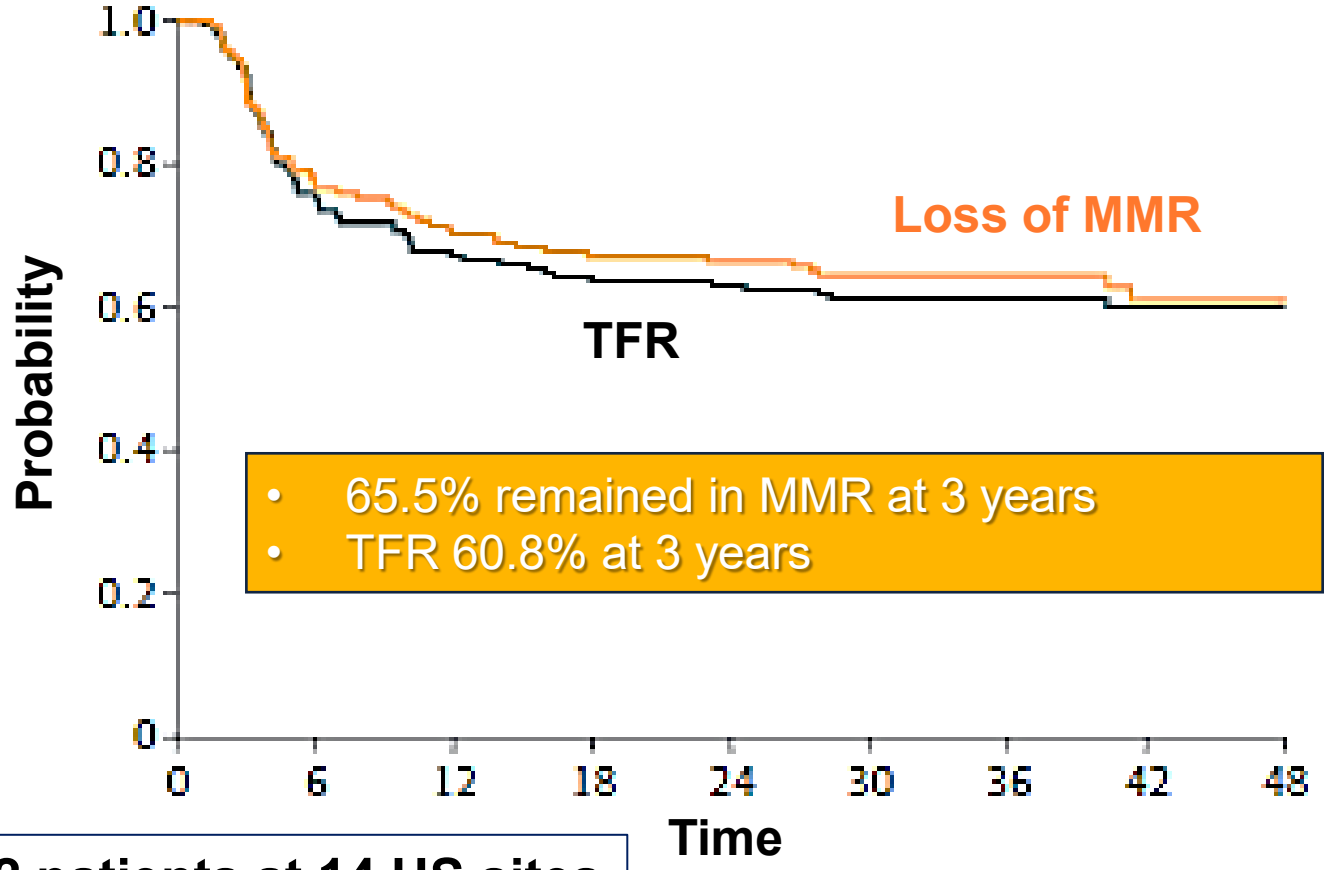
- 2nd Generation TKI discontinuation: similar results
  - ENESTfreedom and ENESTop (nilotinib)
  - DASFREE (dasatinib)
  - STOP 2G-TKI (dasatinib and nilotinib)
  - US LAST Study (imatinib, dasatinib, nilotinib, bosutinib)

- Success rates of TFR attempts in clinical trials range between 40 and 65%
  - Quite consistent even with varying entry criteria (e.g., duration of TKI use and molecular response and depth of response)

Rea D et al. Blood Cancer J. 2017; 7(12): 643
Fred Hutch Cancer Center. 846-854
Rousselot P et al. Blood Adv (2020) 4 (13): 3034–3040
Ross DM et al. Blood. 2013; 122(4); 515-533
Radich JP et al. Leukemia . 2021; 35(5): 1344-1355
Hughes TP et al. Leukemia. 2021; 35(6): 1631-1642
Shah NP et al. LeukLymphoma. 2020; 61(3): 650-659
Atallah E et al. JAMA Oncol. 2021;7(1):42-50

US Life After Stopping TKIs (LAST) Trial

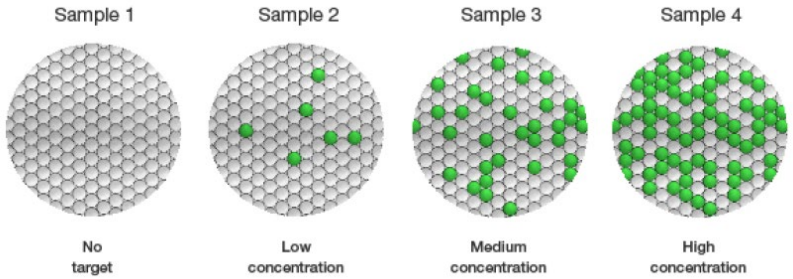
TKI discontinuation after at least 3 years of treatment and 2 years MR4



- 65.5% remained in MMR at 3 years
- TFR 60.8% at 3 years

172 patients at 14 US sites

Droplet Digital PCR



Principle of enhanced sensitivity for rare targets

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

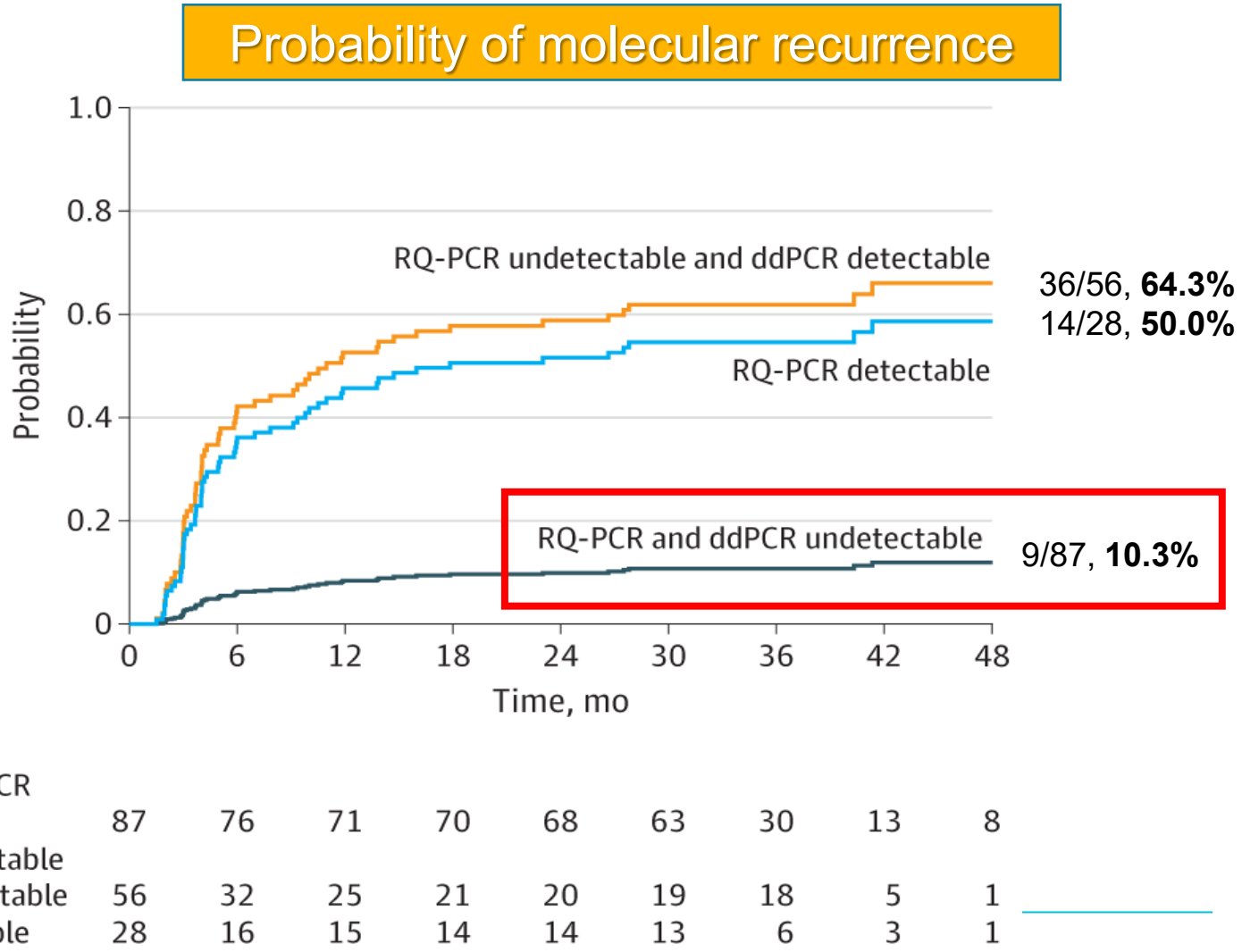
ddPCR offers approximately 0.5 to 1 log greater sensitivity in *BCR::ABL1* detection

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

Probability of Molecular Recurrence by RQ-PCR and Sensitive Droplet Digital PCR Prior to Discontinuation

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



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

TKI Discontinuation Criteria: NCCN and ELN

TKI discontinuation may be considered (NCCN/ELN) if:

At least 3 years of TKI treatment

and

At least 2 years MR4

Optimal TKI discontinuation Conditions (ELN) if:

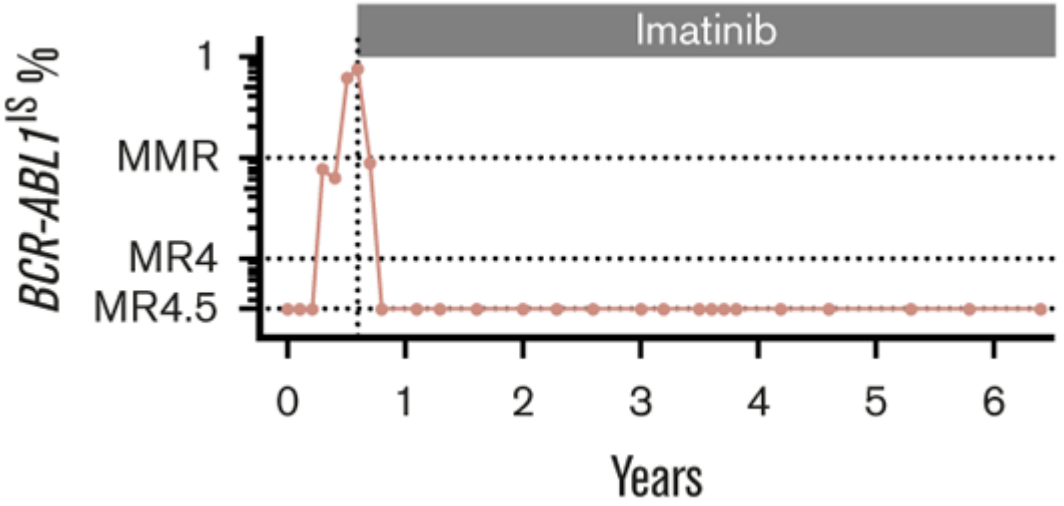
At least 5 years of TKI treatment

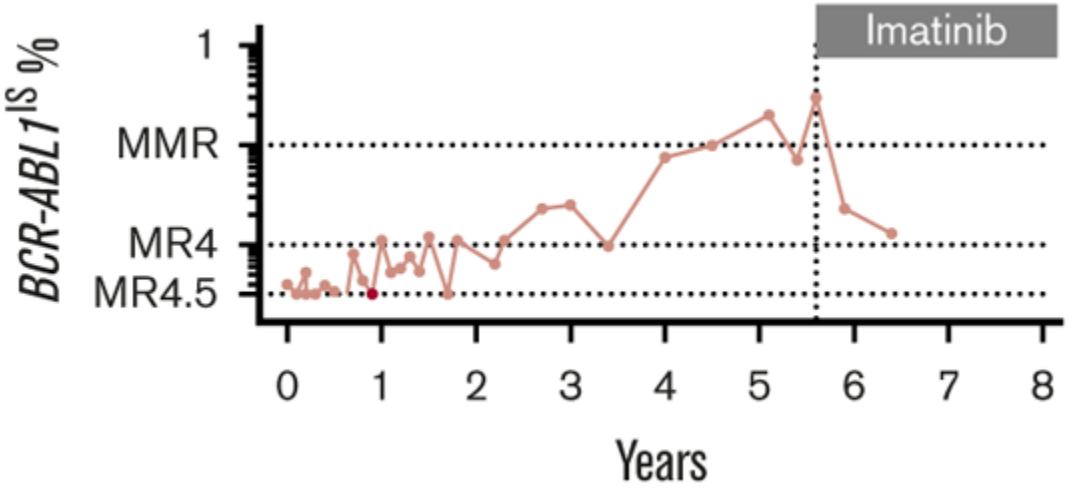
and

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

Rea D. Blood Adv. (2020) 4 (21): 5589–5594.
Hochhaus A, et al. *Leukemia*. 2020;34(4):966-984.
NCCN Guidelines. Chronic Myeloid Leukemia. V3.2022.

Molecular Recurrence (Loss of MMR) After TKI Discontinuation: Long-term STIM1 follow-up





- 65 of 128 (51%) patients in STIM1 had molecular recurrence while off therapy
- Most within the first 6-12 months after discontinuation
- Most regain prior deep molecular response after restarting

- 9 of 65 (14%) patients with late molecular recurrence
- At 2.3, 2.5, 3, 3.5, 3.6, 5.4, 5.5, 5.7, and 6.4 years (median time to LMRec, 3.6 years)

NCCN: *Monitoring 1-2 months for the first 6 months, then every 2 months for months 7-12, then every 3 months if MMR is maintained indefinitely*

Rousselot P et al. *Blood Adv* (2020) 4 (13): 3034–3040.

Risks of TKI discontinuation?

- **Loss of TKI sensitivity upon TFR failure:**
  - Exceptionally reported. Usually, MMR and DMR regained within 3 to 6 months after TKI re-introduction

- **CML progression:**
  - Exceptionally rare cases of “sudden blast phase” either during the treatment-free phase or soon after TKI reintroduction have been reported; mostly lymphoid blast crisis.

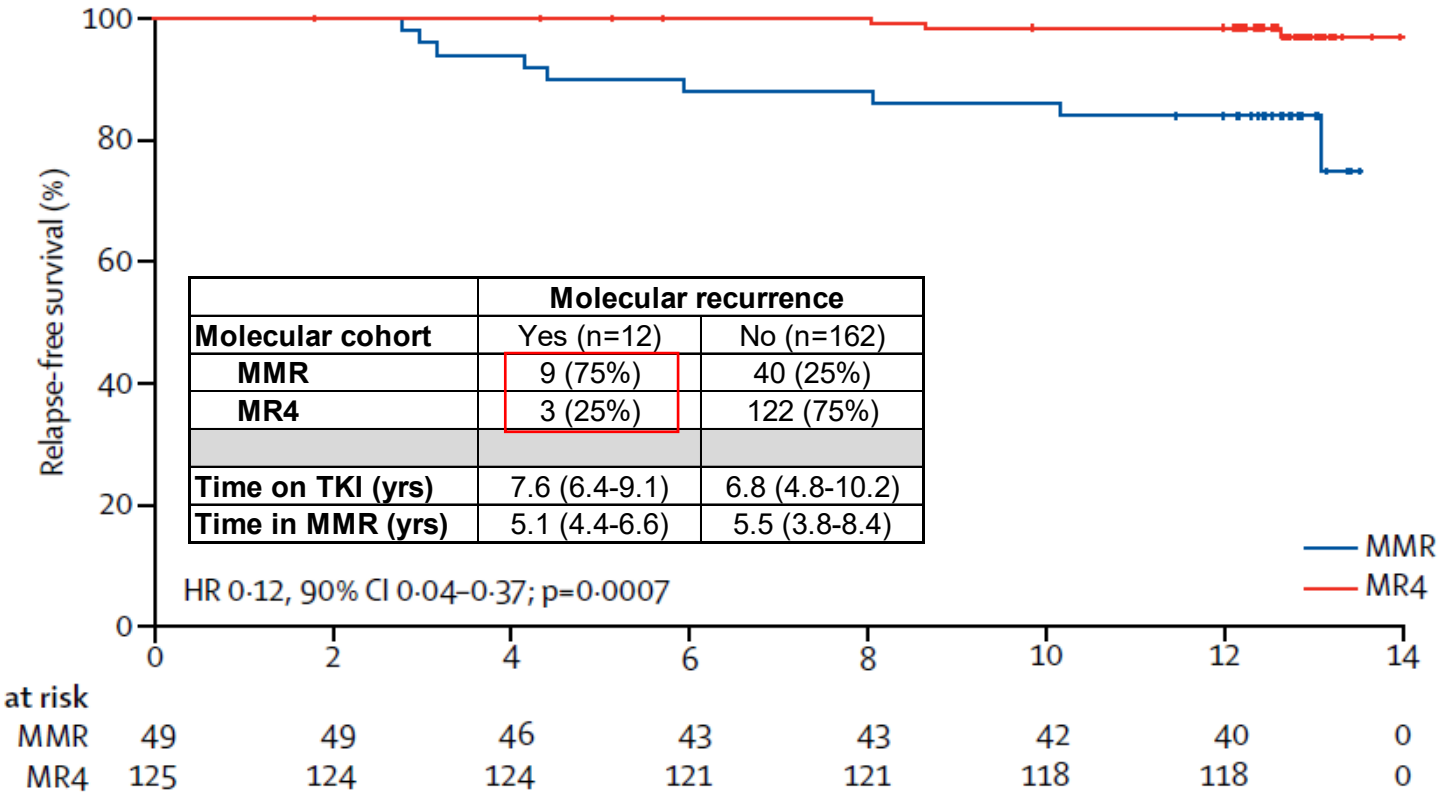
- **TKI withdrawal syndrome**

Alfayez M, et al. Br J Haematol 2019; 187: 543-545.
Richter J, et al. Leuk Lymphoma 2014; 55: 2821-2823.
Rea D, et al. Cancer 2018; 124: 2956-2963.
Rea D. Blood Adv (2020) 4 (21): 5589–5594.
https://doi.org/10.1182/bloodadvances.2020002538

Dose reduction followed by TKI discontinuation: 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)

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

Oehler VG, Huang IJ, Siu C, Kim M et al. Dose modifications in the management of chronic phase chronic myeloid leukemia: who, what, and when. 2024 JNCCN invited review, in press.

- General improvement in adverse side effects
- Prospective (DESTINY) and retrospective data support dose reductions from standard dose in MMR or with deeper molecular response likely do not compromise outcomes

TKI discontinuation phase:

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

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

CML Treatment Goals Discussion

1. Life expectancy not impacted by CML: higher-risk CML → **ELTS score and Sokal score: High-risk**
2. Limit impact of TKI therapy on comorbidity outcomes → **Hypertension and hyperlipidemia**
3. Quality of life and minimizing adverse events
4. Treatment-free remission
5. Limiting costs
6. Family planning

- **First-line:** Bosutinib 400 mg orally daily
- Achieves MMR at 9 months and *BCR::ABL1* ≤0.0032% (MR4.5) for a subsequent 2.5 years
- ***My approach: Decrease bosutinib to 200 mg daily for 6-12 months then discontinue***

Conclusions

Goals:	Tyrosine kinase inhibitor:
1. Life expectancy not impacted by CML: high-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, *dasatinib, nilotinib***
6. Family planning	6. **2nd generation TKI,** imatinib

1. Patient-oriented and care provider-directed framework to guide first-line TKI therapy selection in CP CML based on current evidence

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

Conclusions

2. TFR is an important goal for many patients, but many don't achieve durable deep molecular response or fail TKI discontinuation. Long-term quality of life on TKI therapy is important.

3. Third generation TKIs (or asciminib) are more likely to result in *BCR-ABL1* < 1% or MMR in patients resistant to a 2nd generation TKI without specific mutations

   - Potent 3G TKI and allosteric inhibitors are under evaluation in clinical trials BUT *don't forget HCT for eligible CP CML patients in ≥ 3rd line who don't respond.*

Question 1:

TS is a 52-year-old male with no other medical problems recently diagnosed with CP CML with a high-risk ELTS score. Bosutinib 400 mg daily is started. Blood counts and splenomegaly normalize over 4 weeks. Three months after initiating therapy molecular response is assessed and *BCR::ABL1* transcripts are reported at 45% IS. The patient is adherent to therapy and has not missed any doses. ABL mutation studies are ordered. A T315I mutation is detected.

Appropriate treatment strategies include which of the following?

A. Stop bosutinib and start asciminib at 40 mg twice daily
B. Stop bosutinib and start dasatinib 140mg daily
C. Stop bosutinib and start nilotinib 400mg twice daily
D. Stop bosutinib and start ponatinib at 45 mg daily
E. Choices A and D

Scan the QR or use link to join

https://forms.office.com/r/y16AnFviuR

Copy link

0 response submitted

Appropriate treatment strategies include which of the following?

- Stop bosutinib and start asciminib at 40 mg twice daily
- Stop bosutinib and start dasatinib 140mg daily
- Stop bosutinib and start nilotinib 400mg twice daily
- Stop bosutinib and start ponatinib at 45 mg daily
- Choices A & D

Treemap | Bar

1 of 1

We'd love your feedback!

We have just two questions for you.

Question 1 (Revisited) – Collaborator Link:
https://forms.office.com/Pages/DesignPageV2.aspx?subpage=design&FormId=6qNUAJSzi0GtGhdBOCMf1swzZxL0t79JiwHGksy17f1UNEFOUlNYWU1JVVJNUEpJOVlLSjdZSThSUy4u&Token=d427b834eebe4731a9c0bd6cdc609c83

Question 1: Answer

ABL mutation studies are ordered. A T315I mutation is detected.

Appropriate treatment strategies include which of the following?

A. Stop bosutinib and start asciminib at 40 mg twice daily
B. Stop bosutinib and start dasatinib 140mg daily
C. Stop bosutinib and start nilotinib 400mg twice daily
D. Stop bosutinib and start ponatinib at 45 mg daily
E. Choices A and D

ANSWER D.
The T315I mutation is resistant to all currently FDA approved ABL-targeted therapies except ponatinib and asciminib. **However, a higher dose of asciminib is needed to effectively treat T315I mutated CML and the FDA approved dose is 200 mg twice daily**. Consequently, choice A is incorrect. The OPTIC study of ponatinib dosing reported that higher ponatinib dose at therapy initiation resulted in higher rates of *BCR::ABL1* < 1% by 12 months and that ponatinib response for T315I mutated CML was particularly dependent on the dose initiated. Enrollment on a clinical trial is also reasonable.

Question 2:

CA is a 68-year-old female diagnosed with low-risk ELTS score CP CML 4 years ago and is treated with imatinib 400 mg daily. Past medical history is notable for hypertension and intermittent chest pain (negative cardiac workup). CA is a non-smoker. Family history is notable for a father who died of an MI at age 50. Recently, CA has struggled with side effects on imatinib including periorbital and peripheral edema and nausea requiring anti-emetic therapy once a week. Durable MR4 (*BCR::ABL1* transcripts $\leq$ 0.01%) was achieved 12 months ago.

Which of the following statement(s) are accurate in counseling the patient on next steps?

A. The risk for pleural effusion on dasatinib is only within the first 12 months of treatment.

B. Dose reduction of imatinib in patients with durable major molecular or deeper molecular responses is associated with a high rate of loss of molecular response.

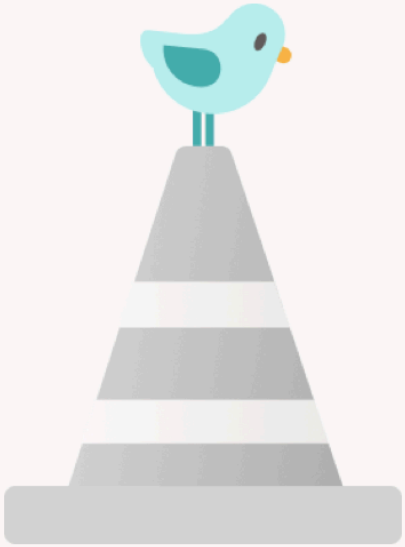
C. Bosutinib is associated with high rates of nausea and diarrhea and expert panels recommend initiatin dose (e.g., 200-300 mg daily) and titrating dose as needed to achieve molecular response.

D. Choices A, B, C

E. Choices A, B

F. Choices A, C

G. Choices B, C



Sorry, something went wrong

Please make sure you have permission to access this form.

Technical details

Question 2 (Revisited) – Collaborator Link:
https://forms.office.com/Pages/DesignPageV2.aspx?subpage=design&FormId=6qNUAJSzi0GtGhdBOCMf1swzZxL0t79JiwHGksy17f1UNUVPVENVTTBHRzQwQ0dQMzY2WEtaU1pMRS4u&Token=876340b5c87f467e8672fe13c0f3a1e1

Question 2: Answer

Which of the following statement(s) are accurate in counseling the patient on next steps?

A. The risk for pleural effusion on dasatinib is only within the first 12 months of treatment.

B. Dose reduction of imatinib in patients with durable major molecular or deeper molecular responses is associated with a high rate of loss of molecular response.

C. Bosutinib is associated with high rates of nausea and diarrhea and expert panels recommend initiating therapy at a lower dose (e.g., 200-300 mg daily) and titrating dose as needed to achieve molecular response.

D. Choices A, B, C

E. Choices A, B

F. Choices A, C

G. Choices B, C

Answer C.

The rate of pleural effusion in imatinib intolerant and resistant patients treated with 2nd line dasatinib on the CA180-034 studies was 28% in patients receiving 100 mg daily. Pleural effusion can occur ***at any time*** during treatment with dasatinib. The risk for effusion increases with increasing dasatinib dose and increasing age. Earlier studies reported the rate is 50% or higher in patients 70 years or older receiving doses of 100 mg daily or higher. The UK DESTINY study enrolled patients with durable MMR or MR4 for at least 12 months and reduced TKI dose by 50%. After 12 months of reduced dose among patients with durable MMR 19% lost MMR and among patients with MR4 only 3 patients (2.48%) lost MMR. Among patients with MR4 who then discontinued therapy after dose reduction, molecular recurrence-free survival was 72%. For bosutinib-treated patients the rates of all grade nausea and diarrhea were 18% and 70%, respectively, on the first-line BFORE study with similar observations in later-line studies. Consequently, expert panels have suggested initiating bosutinib at lower dose and titrating as needed to achieve desired molecular response.

Question 3:

Which of the following statements are accurate?

A. Asciminib binds to the ATP site of the ABL kinase

B. Blood pressure increases within the first few weeks after ponatinib initiation due to targeting of VEGFR

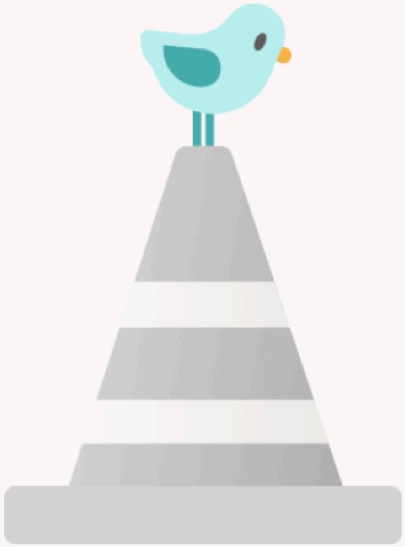
C. Ponatinib dose reduction from 45 or 30 mg daily to 15 mg daily once *BCR::ABL1 < 1%* is achieved compromises response but is recommended to limit the risk for arterial occlusive events (AOEs).

D. A, B, C

E. A, B

F. A, C

G. B, C



Sorry, something went wrong

Please make sure you have permission to access this form.

Technical details

Question 3 (Revisited) – Collaborator Link:
https://forms.office.com/Pages/DesignPageV2.aspx?subpage=design&FormId=6qNUAJSzi0GtGhdBOCMf1swzZxL0t79JiwHGksy17f1URTEyVjJWNVBPR1k4NVpTTENKMU9CVzNBMS4u&Token=0c592fac99a64d2bb82f2b37460caf78

Question 3: Answer

Which of the following statements are accurate?

A. Asciminib binds to the ATP site of the ABL kinase

B. Blood pressure increases within the first few weeks after ponatinib initiation due to targeting of VEGFR

C. Ponatinib dose reduction from 45 or 30 mg daily to 15 mg daily once *BCR::ABL1 < 1%* is achieved compromises response but is recommended to limit the risk for arterial occlusive events (AOEs).

D. A, B, C

E. A, B

F. A, C

G. B, C

Answer B. Asciminib is an allosteric inhibitor that binds to the myristoyl pocket of the ABL1 portion of the fusion protein and locks it into an inactive conformation. It does not bind to the ATP site. Ponatinib has a potent inhibitory effect on VEGFR-2 leading to a decrease in nitric oxide production (i.e., a potent vasodilator) and an increase in endothelin production. This can be seen quickly after ponatinib initiation. Hypertension with ponatinib can be seen in up to 68% of patients. On the OPTIC study, which examined 3 doses of ponatinib (15, 30, and 45 mg daily) with a mandated dose reduction to 15 mg daily once *BCR::ABL1 < 1%,* responses after dose reduction to 15 mg daily (median follow-up, 32 months) were durable and maintained in 73% and 79% of patients reducing dose from 45 or 30 mg, respectively. A recent analysis estimated that response-adjusted dosing reduced the risk for AOEs by ~60%.

Fred Hutch
Cancer Center

Thank you

voehler@uw.edu
voehler@fredhutch.org

Fred Hutch Cancer Center

Extra slides

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.

Molecular response with long-term follow-up

Table 3. Molecular response with long-term follow-up

Trial	Study arms	No. of patients	Median follow-up	EMR at 3 mo	CCyR by 12 mo	MMR 12 mo*,†	MMR by 2 y	MR4 by 2 y	MR4.5 by 2 y	MR4 by 5 y	MR 4.5 by 5 y	MR4 by 10 y	MR4.5 by 10 y
IRIS‡	Imatinib (400 mg)	553	11 y	—	69%*	39%*	—	—	—	—	40.2%§	—	63.2%§
	Interferon/ cytarabine	553		—			—	—	—	—	—	—	—
German CML Study IV	Imatinib (400 mg) arm (all)	400 (1551)	9.5 y	68.5%‖	67.5%	36.7%	—	—	—	65.7%	49.4%	81%	67.2%
DASISION¶	Dasatinib (100 mg)	259	5 y	84%	83.0%	46.0%	64.0%	—	17.0%	—	42.0%	—	—
	Imatinib (400 mg)	260		64%	72.0%	28.0%	46.0%	—	8.0%	—	33.0%	—	—
ENESTnd#	Nilotinib 300 mg twice daily	282	5 y	91%	80.0%	44%†	71.0%	39.0%	25.0%	65.6%	53.5%	73%	64%
	Nilotinib 400 mg twice daily	281		89%	78.0%	43%†	67.0%	33.0%	19.0%	63.0%	52.3%	—	—
	Imatinib (400 mg)	283		67%	65.0%	22%†	44.0%	18.0%	9.0%	41.7%	31.4%	56%	44%
BFORE#,**	Bosutinib (400 mg)	268	2 y	75%	77.2%	47.2%†	61.2%	32.8%	13.1%	—	—	—	—
	Imatinib (400 mg)	268		57%	66.4%	36.9%†	50.7%	25.7%	10.8%	—	—	—	—

Data from 4 first-line phase 3 randomized registration studies (IRIS, DASISION, ENESTnd, and BFORE) and the first-line imatinib 400 mg daily arm of the German CML Study IV are shown. MRs at various time points are shown. These trials cannot be directly compared, because different methods of trial evaluation were used (eg, rates at a specific time point vs cumulative incidence estimates).
CCyR, complete cytogenetic response (no Philadelphia chromosome–positive metaphases by bone marrow examination); EMR, early molecular response; MMR, major molecular response; MR, molecular response.
*Estimated rate.
†Rate at 12 months (ie, not cumulative).
‡The primary endpoint for IRIS was event-free survival (survival without transformation to accelerated phase/blast phase, loss of complete hematologic response, loss of major cytogenetic response, or increased white blood cell count); survival outcomes include 363 patients who crossed over to imatinib.
§Rate at the specific time point (eg, at 5 years and at 10 years).
‖Includes all patients in all arms.
¶The primary endpoint for the DASISION study was confirmed complete cytogenetic response by 12 months.
#The primary endpoint of the ENESTnd and BFORE studies was MMR rate at 12 months.
**Twenty-four-month BFORE trial updates have been presented in abstract format.[41]

Oehler VG. First-generation vs second-generation tyrosine kinase inhibitors: which is best at diagnosis of chronic phase chronic myeloid leukemia? Hematology Am Soc Hematol Educ Program. 2020 Dec 4;2020(1):228-236

Disease progression, PFS, and OS with long-term follow-up

Table 4. Disease progression, progression-free survival, and overall survival with long-term follow-up

Trial	Study arms	No. of patients	Median follow-up	Disease progression, n (%)	PFS	OS
IRIS*	Imatinib (400 mg)	553	11 y	38 (6.9%)	92.1%	83.3%
	Interferon/cytarabine	553		71 (12.8%)	—	78.8%
German CML Study IV	Imatinib (400 mg) arm (all)	400 (1551)	9.5 y	17 (4.2%)	80.0%	80.0%
DASISION	Dasatinib (100 mg)	259	5 y	12 (5%)	85.0%	91.0%
	Imatinib (400 mg)	260		19 (7%)	86.0%	90.0%
ENESTnd†	Nilotinib 300 mg twice daily	282	5 y	10 (4%)	92.0%	94.0%
	Nilotinib 400 mg twice daily	281		6 (2%)	96.0%	96.0%
	Imatinib (400 mg)	283		21 (7%)	91.0%	92.0%
BFORE‡	Bosutinib (400 mg)	268	2 y	6 (2%)	—	99.2%
	Imatinib (400 mg)	268		7 (3%)	—	97.0%

Data from 4 first-line phase 3 randomized registration studies (IRIS, DASISION, ENESTnd, and BFORE) and the first-line imatinib 400 mg daily arm of the German CML Study IV are shown. PFS, OS, and disease progression (defined as progression to accelerated phase or blast phase) are shown. OS, overall survival; PFS, progression-free survival. Adapted with permission from the NCCN Guidelines® for Chronic Myeloid Leukemia V.1.2021. © 2021 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

*Survival outcomes include 363 patients who crossed over to imatinib.

†Progression to accelerated phase/blast phase during the study.

‡Twenty-four-month BFORE trial updates have been presented in abstract format.[41]

Oehler VG. First-generation vs second-generation tyrosine kinase inhibitors: which is best at diagnosis of chronic phase chronic myeloid leukemia? Hematology Am Soc Hematol Educ Program. 2020 Dec 4;2020(1):228-236

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: Imodium
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

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)

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

Scenarios where lower dose therapy may be considered either preemptively or in the setting of TEAEs

Low or intermediate-risk ELTS* or Sokal score at diagnosis

→ Dasatinib 50 mg QD[b]
Bosutinib 200-300 mg QD[c]
Nilotinib 300 mg BID[d]

Frail/elderly Multiple co-morbidities

→ Imatinib 300 mg daily[e]
Bosutinib 200-300 mg QD[c]
Dasatinib 20-50 mg QD[b,f]

*EUTOS long-term survival (ELTS)

a. For patients with limited side effects dose reductions may be considered, for example, prior to TKI discontinuation or for risk mitigation.
b. Naqvi K, et al. Cancer. 2020;126(1):67-75. Gener-Ricos G, et al. Clin Lymphoma Myeloma Leuk. 2023;23(10):742-748.
c. Cortes JE, et al. Expert panel review. J Hematol Oncol. 2018;11(1):143. Caution with 200 mg dose recommended.
d. Reduced dose in later-line in intolerant patients. Hiwase D, et al. Leuk Res. 2018;67:109-115.
e. Ohnishi K, et al. Cancer Sci. 2012;103(6):1071-1078.
f. DAVLEC study reported dasatinib 20 mg daily dosing in older Asian patients. Murai K, et al. Lancet Haematol. 2021;8(12):e902-e911.
g. UK DESTINY study examined dose reduction in patients with durable responses >12 months. Dose reduction decisions are influenced by duration/durability of MMR, desire to attempt TFR, and degree of side effects. Clark RE, et al. Lancet Haematol. 2017;4(7):e310-e316.
h. Per OPTIC, ponatinib starting dose 30-45 mg daily, 45 mg may be preferred for T315I, with dose reduction once *BCR::ABL1* ≤1%. Dose reduction is recommended to reduce risk for AOEs. Cortes J, et al. Blood. 2021;138(21):2042-2050.
i. UK DESTINY study reduced imatinib dose to 200 mg daily, dasatinib to 50 mg daily, and nilotinib to 200 mg BID in patients with durable MMR or MR4 for >12 months.
j. Retrospective review of front-line and later line therapy supports 300 mg daily bosutinib dosing. Kota V, et al. Leuk Res. 2021;111:106690.
k. In patients starting at dasatinib dose >50 mg daily.
l. NILO-RED observational study reported on dose reduction to 400-450 mg daily. Rea D, et al. Blood. 2017;130(Supplement 1):318.
m. May consider low dosing longer-term for patients who successfully regain deep molecular response after TKI discontinuation failure; limited data for very low dose TKI dosing in these settings.

Once *BCR::ABL1* ≤1% is achieved

→ Ponatinib 15 mg QD[h]

Once *BCR::ABL1* ≤0.1%[g] is achieved

→ Imatinib 200-300 mg QD[i]
Bosutinib 200-300 mg QD[j]
Dasatinib 50 mg Qd[i,k]
Nilotinib 400-450 mg Qd[i,l]
Ponatinib 15 mg QD[h]

Once *BCR::ABL1* ≤0.01%[g] is achieved

→ Imatinib 200 mg QD[i]
Bosutinib 200 mg QD[j,m]
Dasatinib 20 mg QD[f,m]
Nilotinib 200-400 mg QD[l,m]

Oehler VG, Huang IJ, Siu C, Kim M et al. Dose modifications in the management of chronic phase chronic myeloid leukemia: who, what, and when. 2024 JNCCN invited review, in press.

Fred Hutch
Cancer Center

Thank you