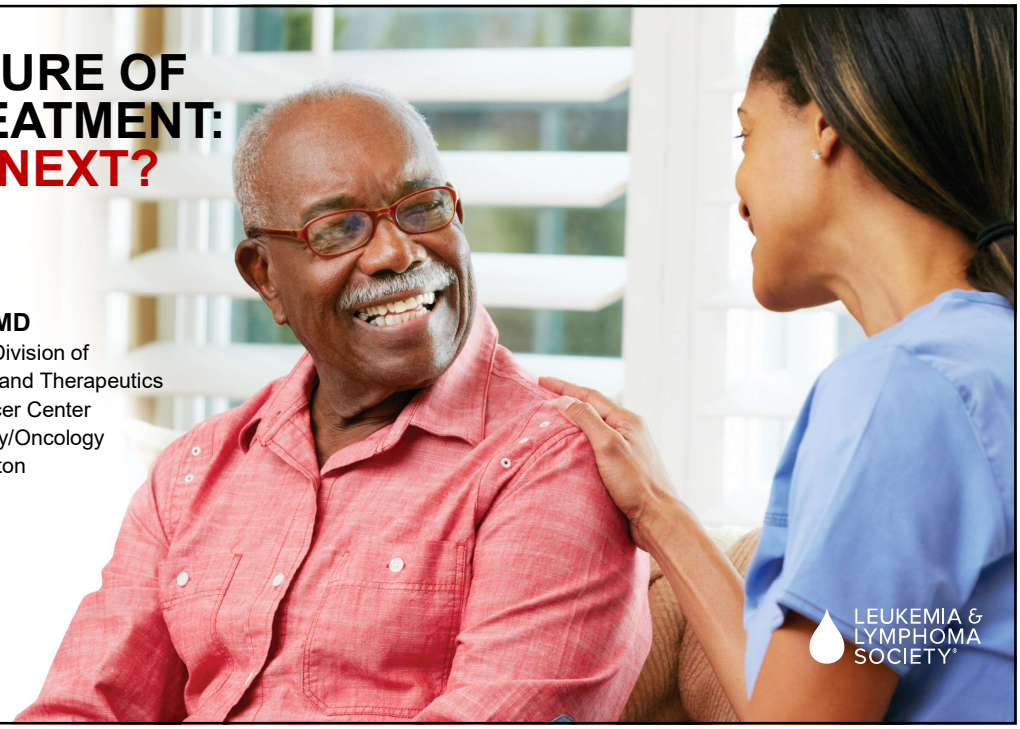
THE FUTURE OF CML TREATMENT: WHAT'S NEXT?



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University of Washington
Seattle, WA

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WELCOMING REMARKS

THE FUTURE OF CML TREATMENT: WHAT'S NEXT?

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FACULTY

THE FUTURE OF CML TREATMENT: WHAT'S NEXT?

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DISCLOSURES

THE FUTURE OF CML TREATMENT: WHAT'S NEXT?

Vivian G. Oehler, MD has the following disclosures; Ascentage Pharma, Novartis, Pfizer, Inc and Terns Pharma *(Consultant).*

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Fred Hutch Cancer Center

The Future of CP CML Treatment: What's Next?

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Translational Science and Therapeutics, Fred Hutchinson Cancer Center
Division of Hematology-Oncology, University of Washington

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Objectives

1. What disease-specific risk factors at chronic phase chronic myeloid leukemia (CP CML) diagnosis may influence first-line therapy selection?
2. What is new in the therapeutic landscape of CP CML?
3. When can we use lower dose tyrosine kinase inhibitor (TKI) therapy?
4. Who is eligible for therapy discontinuation and what are outcomes?

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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.

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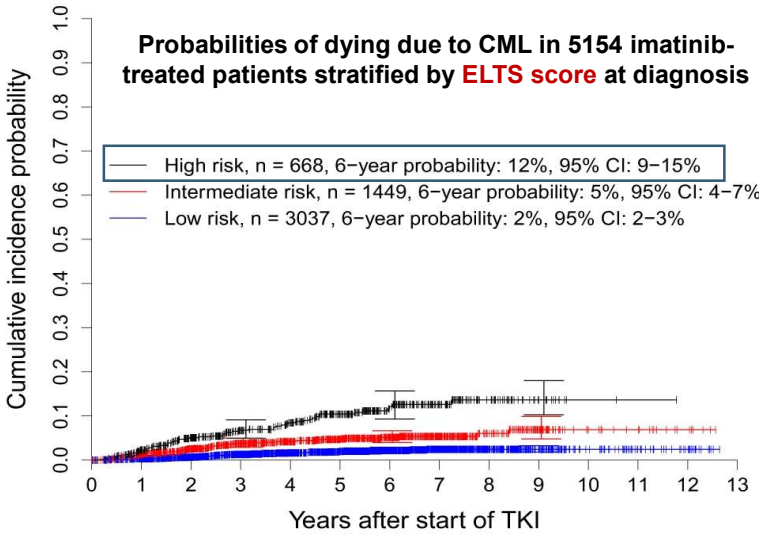
Clinical risk at diagnosis: EUTOS Long-Term Survival Score



Recommended by ELN

1. Better at identifying patients at risk of dying of CML
2. Classifies fewer patients as high-risk
3. Newer model recently proposed also includes genetic features

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

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What defines higher risk at CP CML at diagnosis: molecular features

Prognostic

- Higher clinical risk scores are associated with poorer OS
- Additional clonal chromosomal abnormalities (~3-7% of patients)
- p190-associated transcript e1a2
- 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*. 2016;127:1269-1275; 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.

2024 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)**	●
~~**Oma[illegible]xine**~~	~~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.

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)	●
Oma[illegible]xine	Pr[illegible]thesis [illegible]or			

*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.

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CML Treatment Goals: Talk to your team!

1. Life expectancy not impacted by CML	→ **Recognize higher risk CML at diagnosis: risk score, molecular features Are treatment goals associated with normal life expectancy achieved?**
2. Limit impact of TKI therapy on comorbidity outcomes	→ **Medical history matters: history of cardiovascular or pulmonary disease?**
3. Quality of life and minimizing adverse events	→ **Medical history matters: history of IBS, pancreatitis, other? Emerging side effects on therapy – is dose reduction an option?**
4. Treatment-free remission	→ **What responses are needed for how long before stopping?**
5. Limiting costs	→ **Managing out of pocket costs: Generics (imatinib, *dasatinib*) vs other 2G and 3G therapies?**
6. Family planning	→ **2G and 3G therapies for patients who can give birth?**

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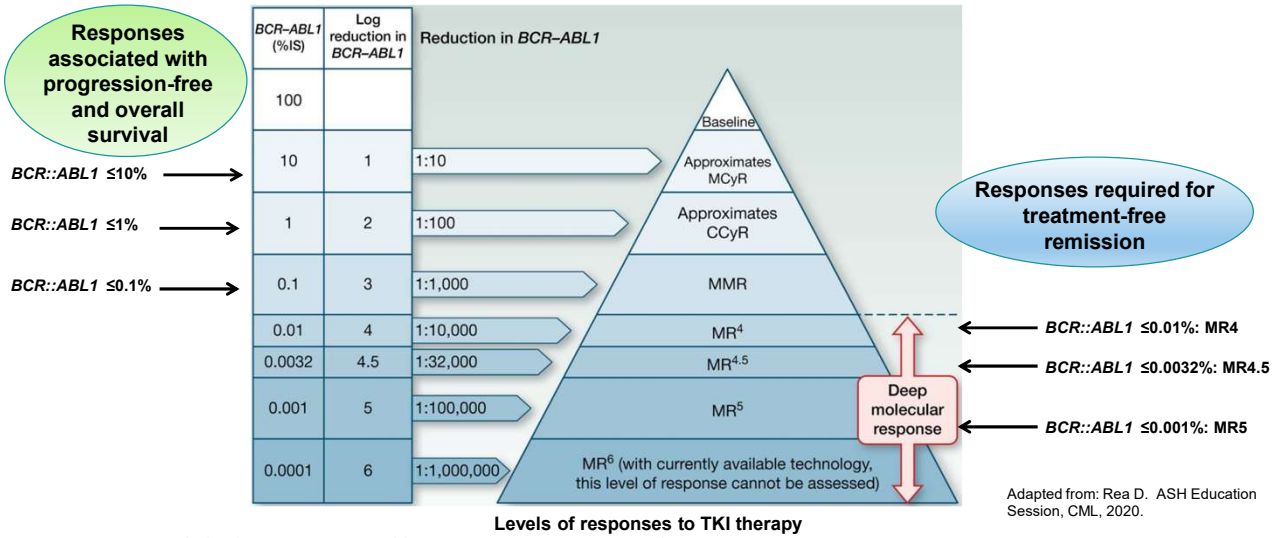
Treatment Goals and Molecular Response Milestones



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

Levels of responses to TKI therapy

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.

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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.

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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.

**** 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.

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First-Line 2nd Generation (2G) TKI: fewer progressions 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.

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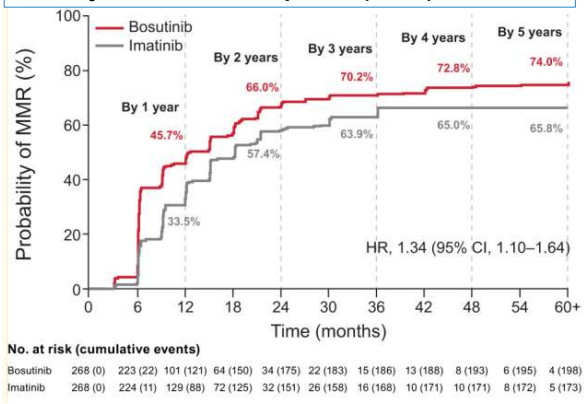
First-line 2G TKI: more patients with MMR or deeper molecular response at specific time points

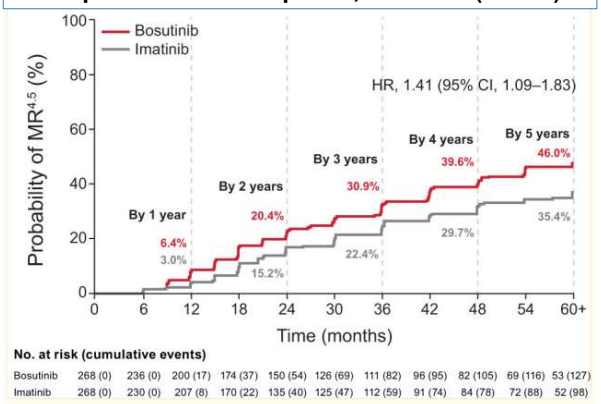
- Phase 3 randomized BFORE Study
- Primary endpoint: MMR rate at 12 months

Similar data for dasatinib and nilotinib vs imatinib

Major molecular response (MMR), ≤ 0.1%



Deeper molecular response, ≤ 0.003% (MR4.5)



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.

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Common and Unique Toxicities CML Therapies

Cardiovascular, cerebrovascular and peripheral arterial vascular events

Requires close follow-up

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

Asciminib: pancreatic enzyme ↑, arthralgias, GI side effects (nausea, diarrhea)

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

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

Common Effects
Myelosuppression
Headache
Rash
Fatigue

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

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

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

Adapted from Dr. Michael J. Mauro, MD

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

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2nd (and 3rd) Generation Therapy Selection Based on Co-Morbidities and Risks

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

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

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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.

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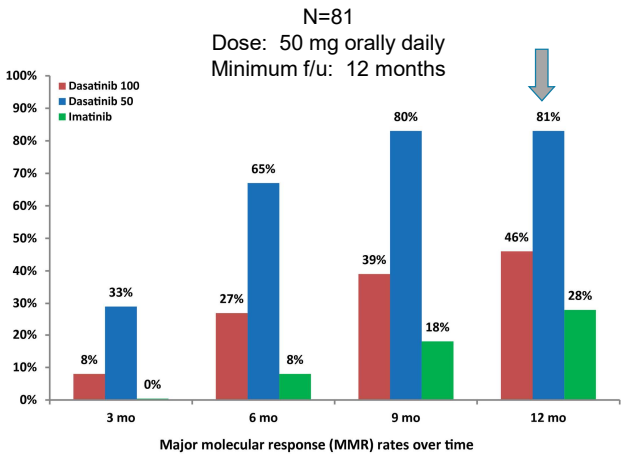
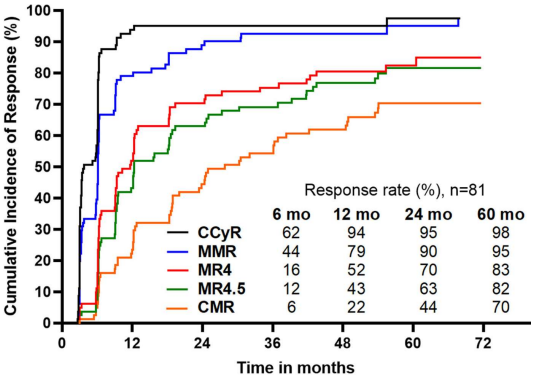
Mitigating treatment related side effects: starting lower dose dasatinib first-line



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.

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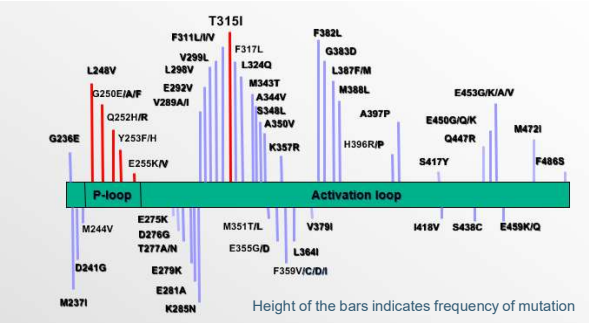
BCR::ABL1 kinase domain mutations

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, Om[illegible]ne,[bb] or allogeneic HCT (CML-6)	None[cc]



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.

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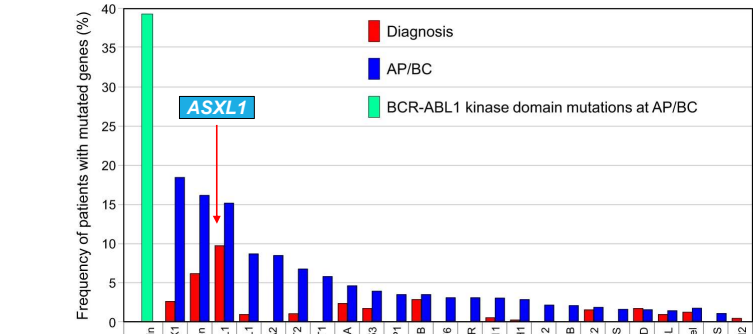
Mutational landscape in CML at diagnosis and at disease progression



	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		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**

Branford S, et al. *Leukemia*. 2019;33:1835–1850; 23
Ochi Y, et al. *Nat Commun*. 2021;14:2833.

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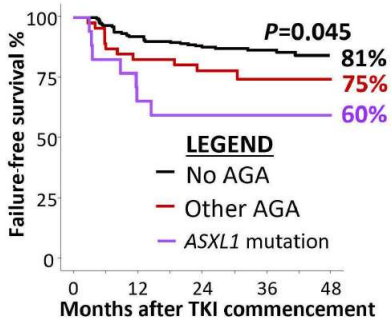
ASXL1 and outcomes

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

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

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[2,3], 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.

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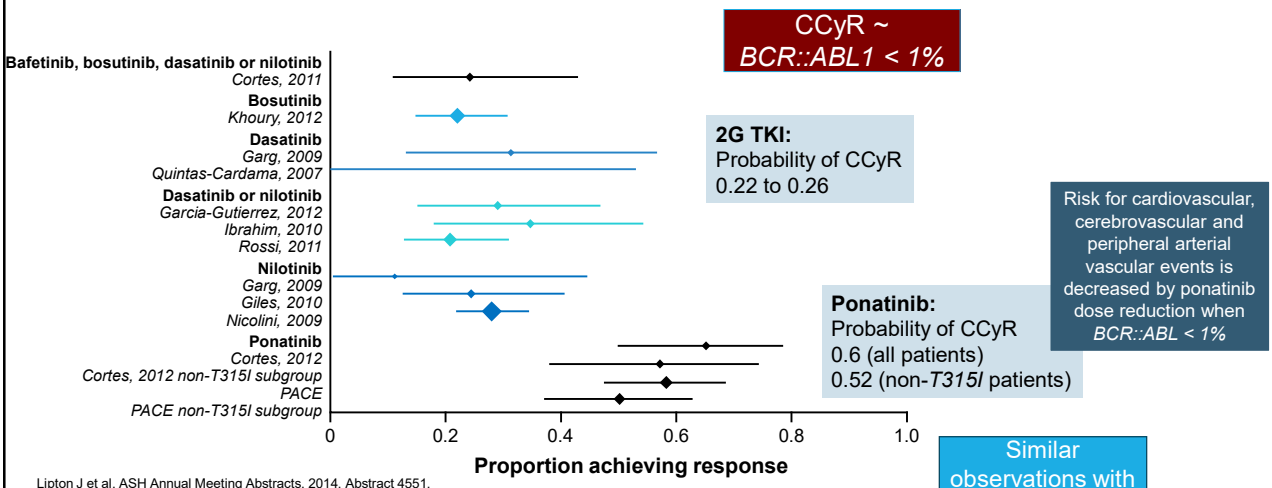
3G therapy is optimal choice after 2G resistance or intolerance

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

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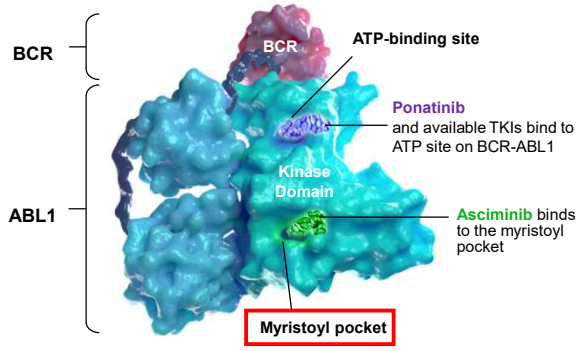
Asciminib, a BCR::ABL1 inhibitor with a distinct allosteric mechanism of action



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

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

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

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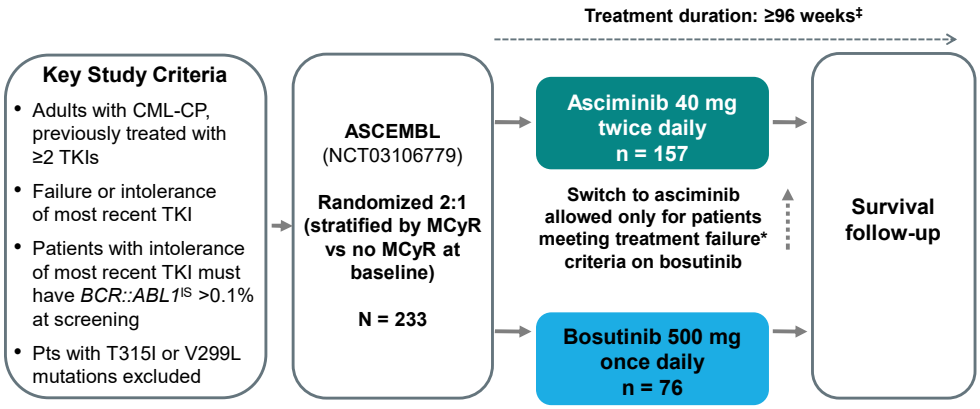
ASCEMBL: Asciminib vs Bosutinib in CML after 2 Prior TKIs, Phase 3 Randomized Study

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. 27

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Demographics and Baseline Characteristics

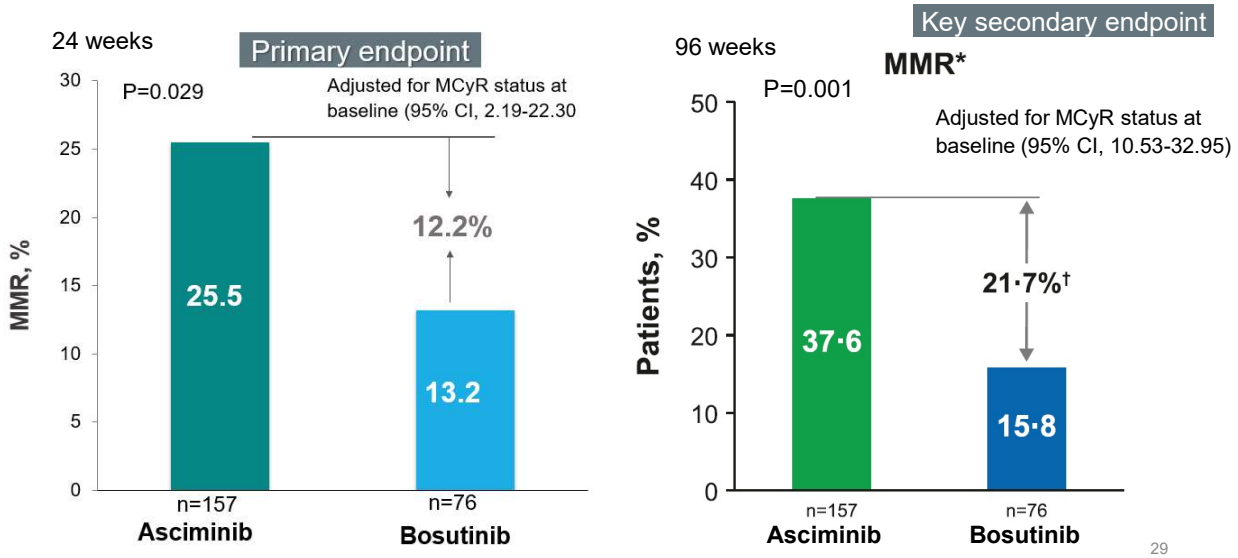
Variable	Asciminib 40 mg Twice Daily (n=157)	Bosutinib 500 mg Once Daily (n=76)	All Patients (N=233)
Median age, years (range)	52.0 (24-83)	52.0 (19-77)	52.0 (19-83)
Female sex, n (%)	75 (47.8)	45 (59.2)	120 (51.5)
MCyR, n (%)	46 (29.3)	22 (28.9)	68 (29.3)
Reason for discontinuation of last TKI, n (%)			
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. 28

28

ASCEMBL: MMR rates at 24 and 96 weeks

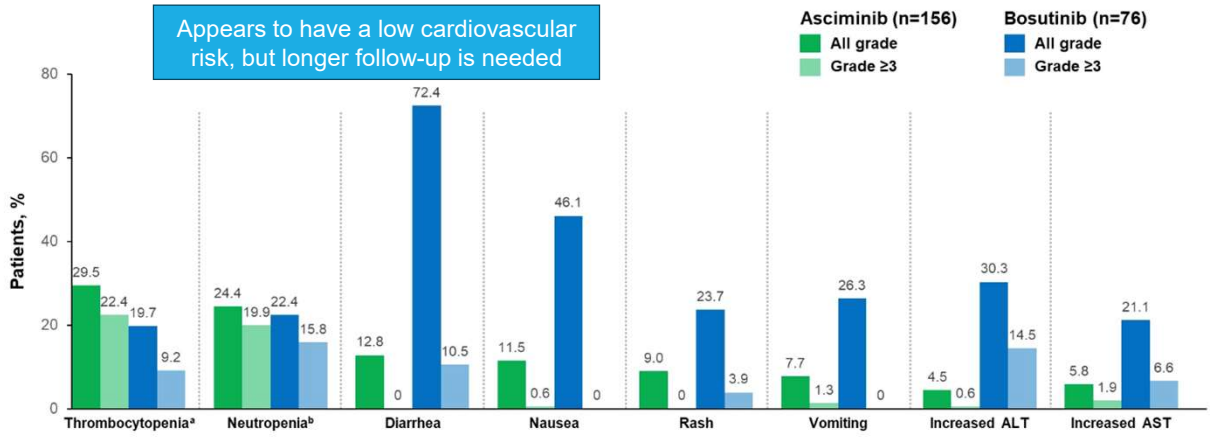


Réa D, et al. *Blood*. 2021;138(21):2031-2041, Hochhaus A et al. *Leukemia*. 2023; 37(3): 617–626.

29

29

Longer follow-up confirms tolerability of asciminib

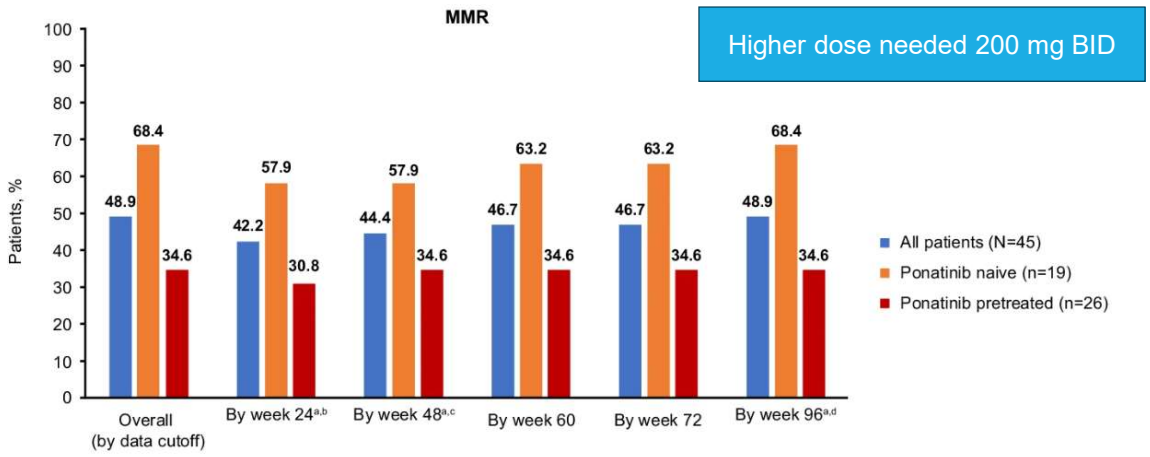


- Asciminib continues to be well tolerated with few GI side effects
- AEs were generally more generally more frequent within the first 18 months of starting asciminib
- Hematologic toxicities similar to bosutinib were frequent in this heavily pre-treated group of patients

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

30

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



Cortes JE, et al. Leukemia. 2024 Jul;38(7):1522-1533. 31

31

ASCEMBL study caveats:

- Was bosutinib the best comparator arm in patients failing prior 2G-TKI?
  - Ponatinib?
- High discontinuation rate in ASCEMBL vs other bosutinib studies

32

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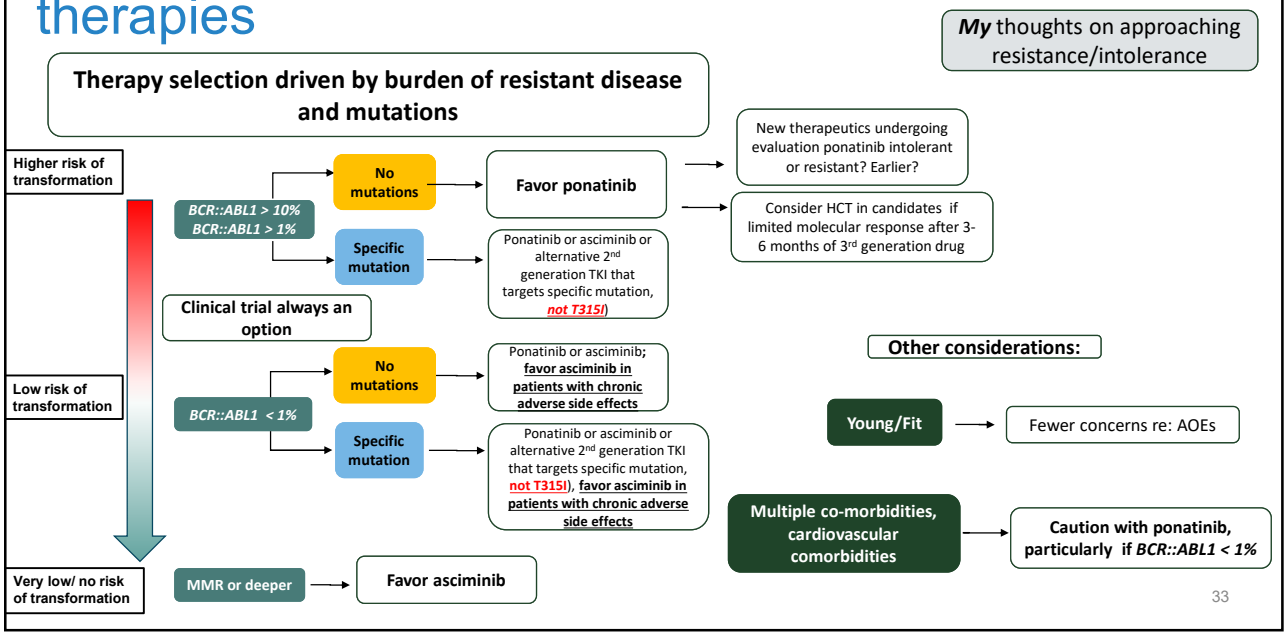
Personal reflections on sequencing new potent therapies



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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)	●
Oma[illegible]xine	Pr[illegible]thesis [illegible]or			

*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.

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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. 35

Oral presentation at: 2024 ASCO Annual Meeting; May 31-June 4, 2024; Chicago, Illinois, and virtual.

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

	Asciminib			IS-TKI		
Variable	**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.

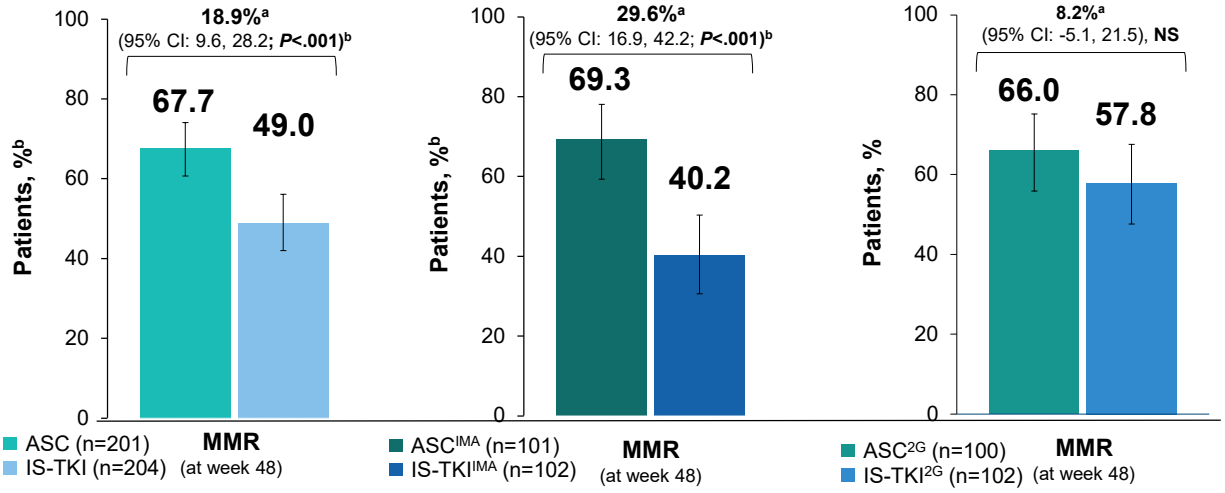
Hochhaus A, et al. N Engl J Med. 2024 May 31. doi: 10.1056/NEJMoa2400858. Epub ahead of print. PMID: 38820078. 36

Oral presentation at: 2024 ASCO Annual Meeting; May 31-June 4, 2024; Chicago, Illinois, and virtual.

36

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.

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Oral presentation at: 2024 ASCO Annual Meeting; May 31-June 4, 2024; Chicago, Illinois, and virtual.

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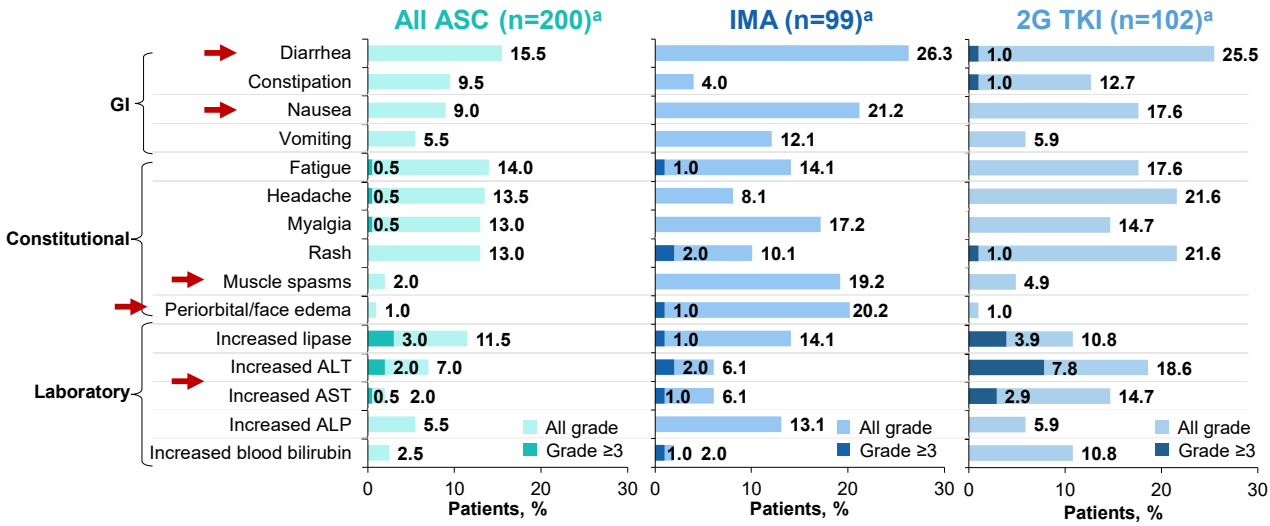
Rates of most non-hematologic toxicities were lower with asciminib



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.

38

Oral presentation at: 2024 ASCO Annual Meeting; May 31-June 4, 2024; Chicago, Illinois, and virtual.

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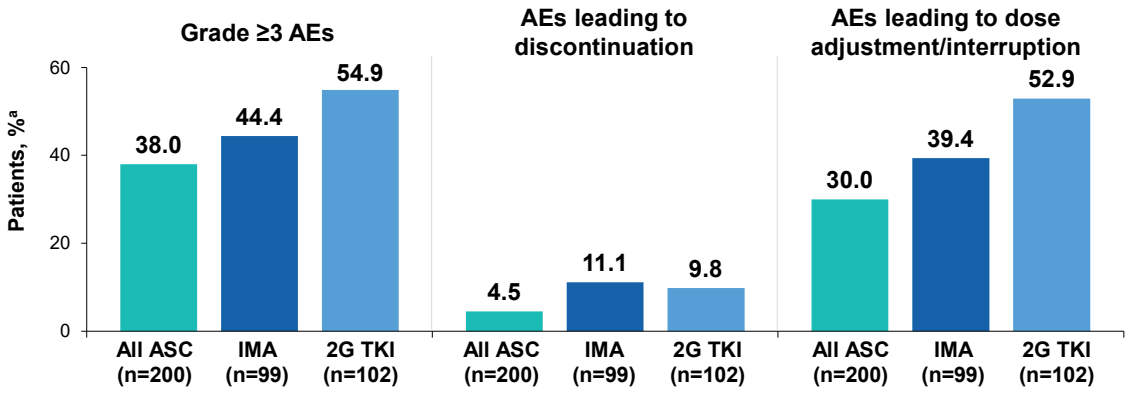
Asciminib demonstrated favorable safety and tolerability vs IMA and 2G TKIs



- 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.

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Oral presentation at: 2024 ASCO Annual Meeting; May 31-June 4, 2024; Chicago, Illinois, and virtual.

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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)	●
Oma[illegible]xine	Pr[illegible]thesis [illegible]or			

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.

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When to consider allogeneic hematopoietic cell transplantation

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

Progression to AP or 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 →
- HCT after TKI therapy +/- induction chemotherapy. I favor induction chemotherapy + TKI in most HCT candidates.

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

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

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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. 2017; 129(7): 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

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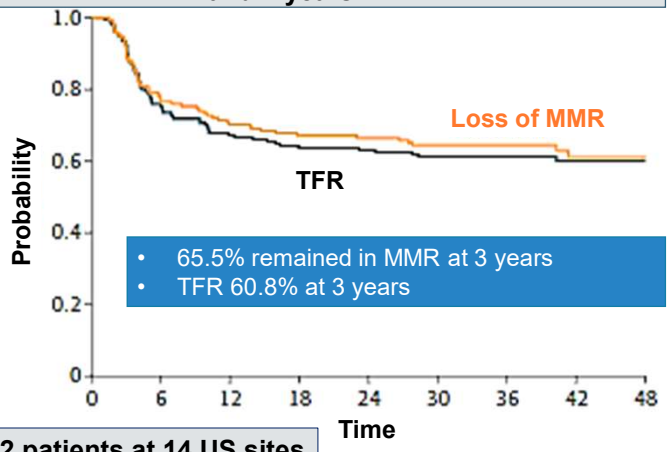
US Life After Stopping TKIs (LAST) Trial

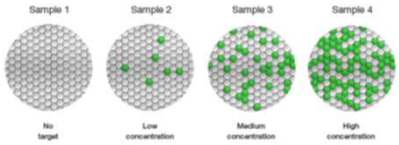
TKI discontinuation after at least 3 years of treatment and 2 years MR4



- 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.

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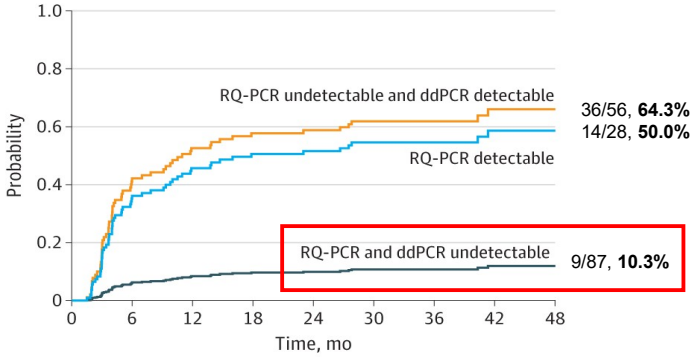
Probability of Molecular Recurrence by RQ-PCR and Sensitive Droplet Digital PCR Prior to Discontinuation

MRec for patients with undetectable *BCR::ABL1* transcripts by both dd PCR and RQPCR was 10.3% ($P \leq .001$)

Suggests that depth of response DOES matter

Probability of molecular recurrence



36/56, **64.3%**
14/28, **50.0%**
9/87, **10.3%**

No. at risk

RQ-PCR and ddPCR undetectable	87	76	71	70	68	63	30	13	8
RQ-PCR undetectable and ddPCR detectable	56	32	25	21	20	19	18	5	1
RQ-PCR detectable	28	16	15	14	14	13	6	3	1

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

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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 4-5 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.

45

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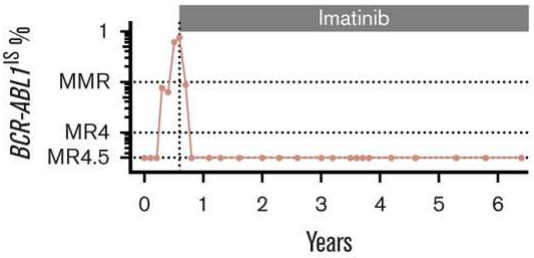
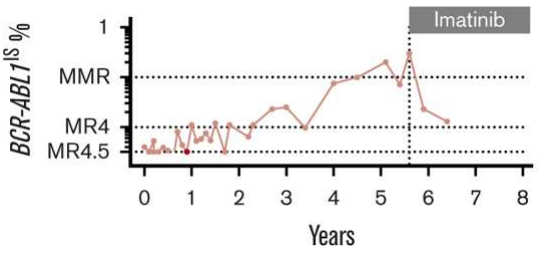
Molecular Recurrence (Loss of MMR) After TKI Discontinuation: Long-term STIM1 follow-up



- 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.

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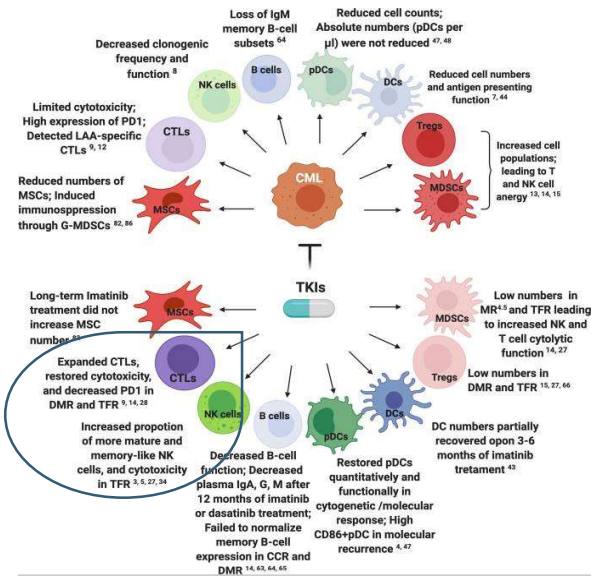
Risks of TKI discontinuation?

- **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. J Clin Oncol 2014; 32: 2821-2823.
Rea D, et al. Cancer 2018; 124: 2956-2963.
Rea D. Blood Adv (2020) 4 (21): 5589–5594.
https://doi.org/10.1182/bloodadvances.2020002538

Immunological control helps sustain treatment-free remission



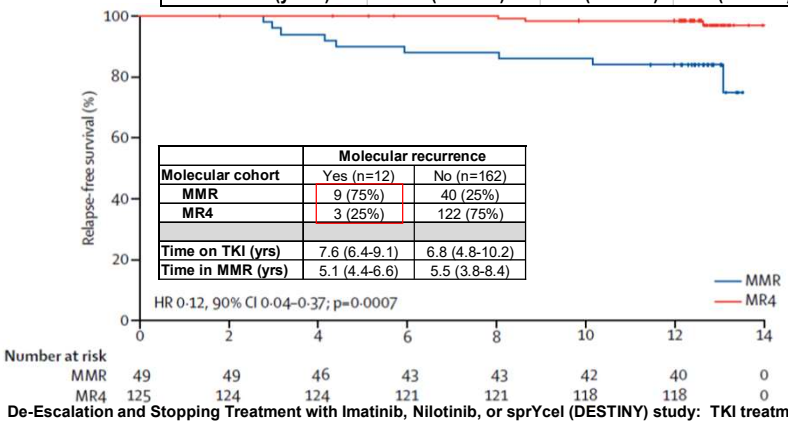
Immune surveillance likely critical in maintaining treatment-free remission

Patterson SD, Copland M. Curr Hematol Malig Rep. 2023 Apr;18(2):19-32.
Hsieh YC, Kirschner K, Copland M. Leukemia. 2021 May;35(5):1229-1242.
Hughes A and Yong ASM. Front Immunol. 2017; 8: 469.
Huuhtanen J et al. Leukemia. 2024 Jan;38(1):109-125.

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

- 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.

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When lower dose therapy may be considered either preemptively or in the setting of side effects

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. Hwasse 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]

Limited data for lower dose asciminib

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.

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Conclusions

Goals:	Therapy:
1. Life expectancy not impacted by CML: high-risk CML	1. **2nd generation TKI or asciminib** vs imatinib
2. Limit impact of TKI therapy on comorbidity outcomes	2. **Imatinib** vs 2nd generation TKI *or asciminib*
3. Quality of life and minimizing adverse events	3. Asciminib vs TKI (role for lower dosing)
4. Treatment-free remission	4. **2nd generation TKI or asciminib,** imatinib
5. Limiting costs	5. **Generics (imatinib, *dasatinib)*** vs others
6. Family planning	6. **2nd generation TKI or asciminib** vs imatinib

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

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

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Conclusions

2. TFR is an important goal for many patients, but not all achieve durable deep molecular response and 40-50% fail therapy discontinuation. **<u>Long-term quality of life on therapy is important.</u>**
3. For patients resistant to 2G TKI, 3G therapeutics are more likely to result in *BCR-ABL1* < 1% or MMR
   - Additional potent 3G TKI and allosteric inhibitors are under evaluation in clinical trials BUT don't forget stem cell transplant for eligible resistant CP CML patients in > 3rd line with high burden of CML or persistent severe hematologic toxicities which limit the ability to treat effectively.

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Fred Hutch Cancer Center

Thank you

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ASK A QUESTION
THE FUTURE OF CML: WHAT'S NEXT?

Ask a question by phone:

Press star (*) then the number 1 on your keypad.

Ask a question by web:

Click "Ask a question"
Type your question
Click "Submit"

Due to time constraints, we can only take one question per person. Once you've asked your question, the operator will transfer you back into the audience line.

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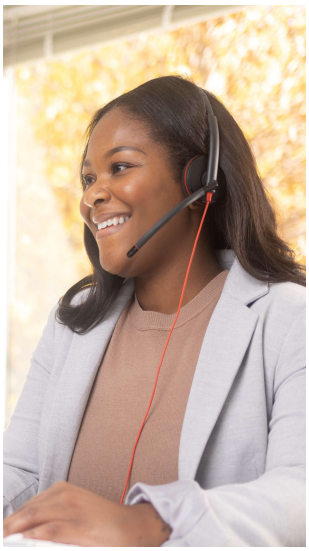
LLS EDUCATION & SUPPORT RESOURCES

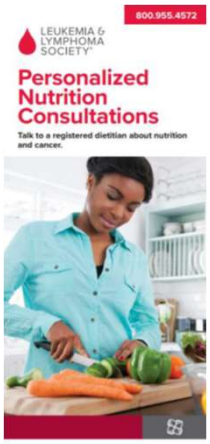


HOW TO CONTACT US:

To contact an **Information Specialist** about disease, treatment and support information, resources and clinical trials:
www.LLS.org/InformationSpecialists

Call: (800) 955-4572
Monday to Friday, 9 a.m. to 9 p.m. ET
Chat live online: www.LLS.org/InformationSpecialists
Monday to Friday, 10 a.m. to 7 p.m. ET
Email: www.LLS.org/ContactUs
All email messages are answered within one business day.

CLINICAL TRIAL SUPPORT CENTER
Work one-on-one with an LLS Clinical Trial Nurse Navigator who will help you find clinical trials and personally assist you throughout the entire clinical-trial process.
www.LLS.org/Navigation



NUTRITION CONSULTATIONS
Our registered dietitian has expertise in oncology nutrition and provides free one-on-one consultations by phone or email.
www.LLSNutrition.org

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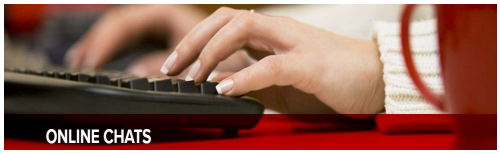

Online Chats

Online Chats are free, live sessions, moderated by oncology social workers. To register for one of the chats below, or for more information, please visit www.LLS.org/Chat

Education Videos

View our free education videos on disease, treatment, and survivorship. To view all patient videos, please visit www.LLS.org/EducationVideos

Patient Podcast

The Bloodline with LLS is here to remind you that after a diagnosis comes hope. To listen to an episode, please visit www.TheBloodline.org

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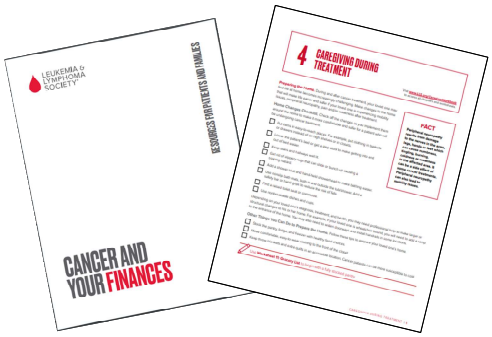
LLS EDUCATION & SUPPORT RESOURCES

The Leukemia & Lymphoma Society (LLS) offers the following financial assistance programs to help individuals with blood cancers: **www.LLS.org/Finances**



To order free materials: **www.LLS.org/Booklets**

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