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Chronic Myeloid Leukemia – A new drug and new goals

Richard A. Larson, MD
University of Chicago
September 2022

Disclosures – Richard A. Larson, MD

- Research funding to the University of Chicago:
  - Astellas
  - Celgene
  - Daiichi Sankyo
  - Forty Seven/Gilead
  - Novartis (asciminib)
  - Rafael Pharma
- Equity ownership: none
- Royalties: UpToDate, Inc

- Consultancy/ Honoraria:
  - Agios
  - Amgen
  - Ariad/Takeda (DSMB)
  - Astellas
  - Celgene/BMS (DSMB)
  - CVS/Caremark
  - Epizyme (DSMB)
  - Novartis (DSMB)

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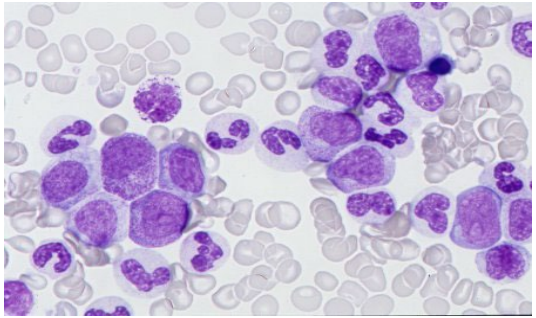
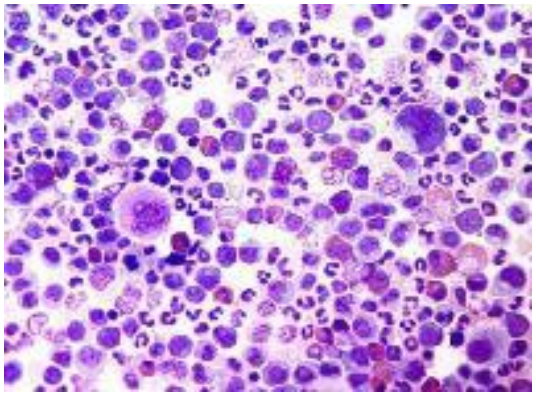
Investigational agents will not be discussed: Olverembatinib HQP1351 (GZD824); ELVN-001 – pure ABL1 inhibitor

Learning Objectives

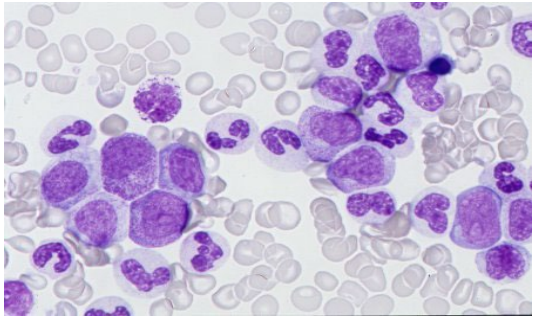
- Survival with CML now approaches that of the general population.
- Risk assessment is still important (Sokal vs ELTS).
- Asciminib – a non-ATP competitive inhibitor of BCR::ABL1
- Should the goal be Survival or Treatment-free Remission (TFR)?
- Discontinuation and Treatment-free Remission.

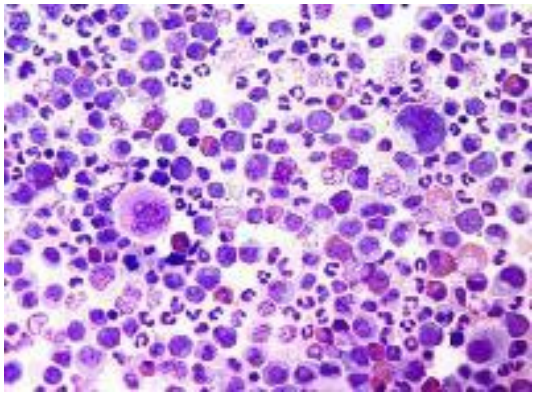




Case History

- 49-year-old man with mild fatigue
- Mild splenomegaly (5 cm) on exam
- WBC 82,000/uL (2% blasts, 3% basophils)
- Hemoglobin 11 g/dL
- Platelets 520,000/uL
- RT-PCR for BCR::ABL1 - positive
- Bone marrow: 95% cellular with granulocytic hyperplasia
- Cytogenetics: 46 XY, t(9;22)(q34;q11)
- Diagnosis:
  chronic myeloid leukemia in chronic phase





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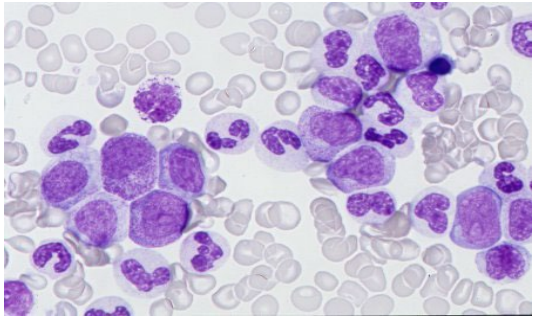
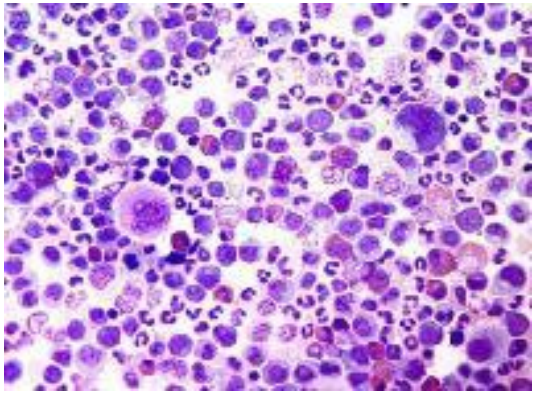
- Diagnosis:
  chronic myeloid leukemia in chronic phase
- Sokal risk score = 0.75 (Low)
- ELTS score = 1.315 (Low)





Comparison of Sokal and ELTS prognostic scores (EUTOS Long Term Survival score)

Score	Calculation	Definition of risk groups
Sokal	Exp 0.0116 × (**age** - 43.4) + 0.0345 × (**spleen** - 7.51) + 0.188 × [(**platelet count**/700)^2 - 0.563] + 0.0887 × (**blood blasts** - 2.10)	Low-risk: < 0.8 Intermediate-risk: 0.8 - 1.2 High-risk: > 1.2
ELTS	0.0025 × (**age**/10)^3 + 0.0615 × **spleen size** + 0.1052 × **peripheral blood blasts** + 0.4104 × (**platelet count**/1000)$^{-0.5}$	Low-risk: < 1.5680 Intermediate-risk:1.5680- 2.2185 High-risk: > 2.2185

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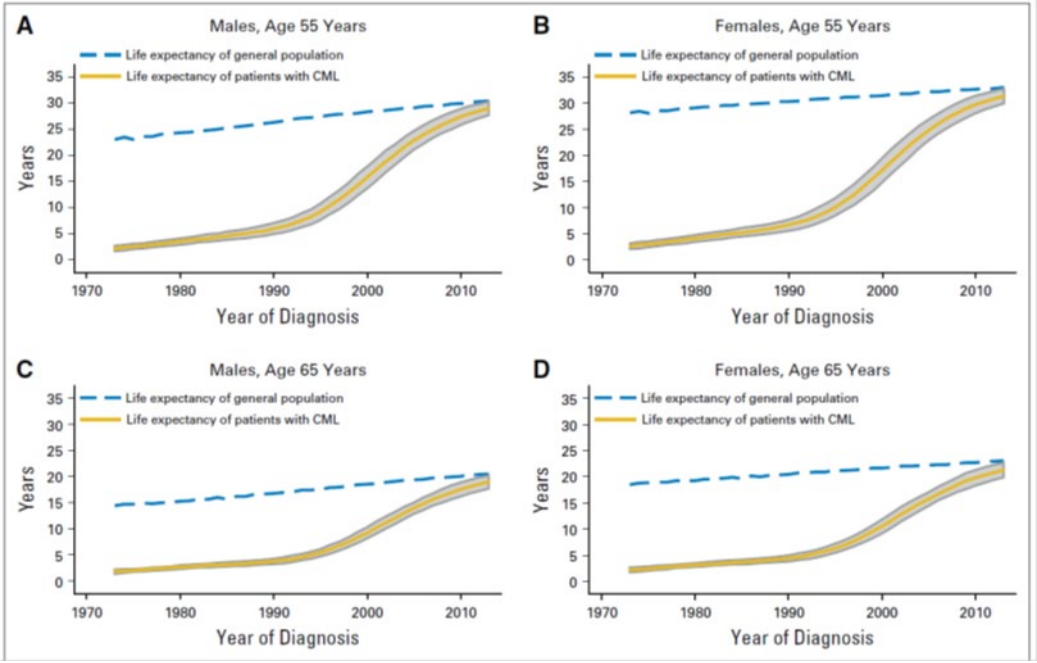
To calculate Sokal and ELTS scores, go to http://www.leukemia-net.org/content/leukemias/cml/elts_score/index_eng.html.

Which is better – Sokal or ELTS?

N = 5154 patients	Low Risk		Intermediate Risk		High Risk	
	Sokal	ELTS	Sokal	ELTS	Sokal	ELTS
% of patients	38%	55%	38%	28%	23%	13%
10-yr OS	89%	88%	81%	79%	75%	68%
6-yr Leukemia-related death	3%	2%	4%	5%	8%	12%

- ELTS: EUTOS score for **long-term survival considering leukemia-related death**; age given in years; spleen size in cm below costal margin measured by palpation; blasts in percent of peripheral blood differential; platelet count, 10E9/L. All values are pre-treatment.
- To calculate Sokal and ELTS scores, go to http://www.leukemia-net.org/content/leukemias/cml/elts_score/index_eng.html ; or UpToDate.

Life expectancy of the general population and of patients with CML in Sweden, over year of diagnosis, by age at diagnosis and sex.



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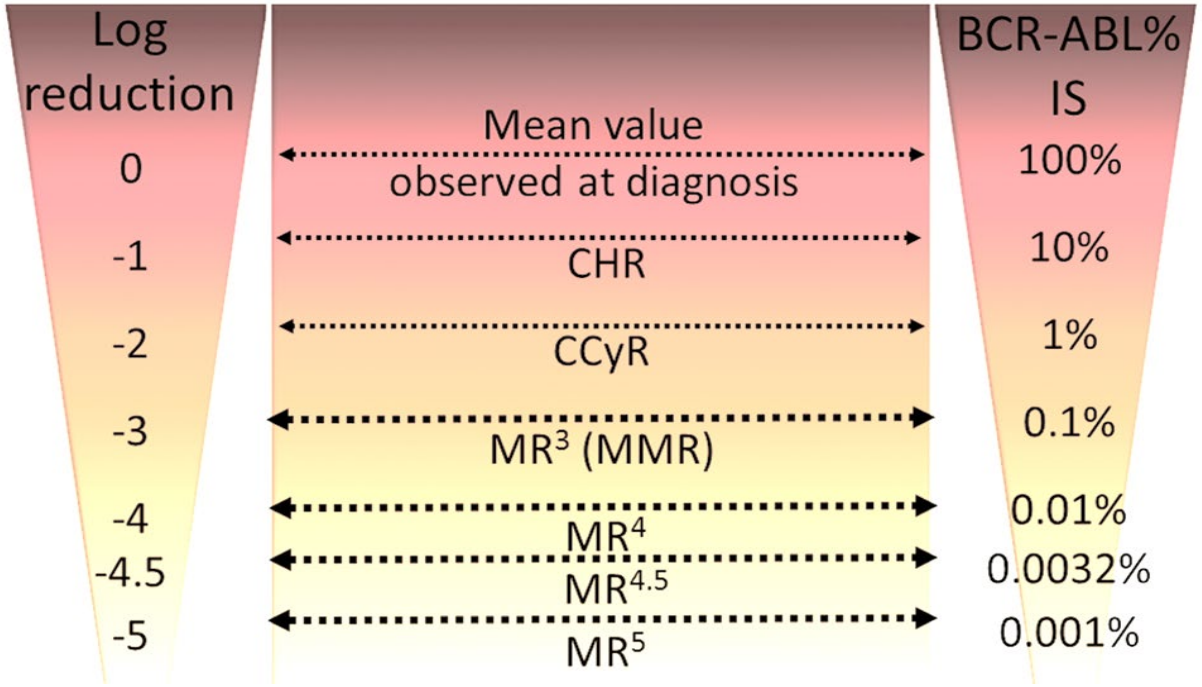
Bower et al. Life expectancy of patients with CML approaches the life expectancy of the general population. J Clin Oncol 2016; 34(24): 2851-2857.

Quantitative RT-PCR for BCR-ABL1 transcripts (International Scale)



Baccarani M et al. Am Soc Clin Oncol Education Book. 2014: 167-75.

2020 European LeukemiaNet Recommendations for newly diagnosed CML

Time:	Optimal Response	Warning	Failure
3 months	BCR/ABL ≤10%	BCR/ABL >10%	>10% if confirmed
6 months	BCR/ABL <1%	BCR/ABL >1-10%	BCR/ABL >10%
12 months	BCR/ABL ≤0.1% (MMR)	BCR/ABL >0.1-1%	BCR/ABL >1%
Thereafter, >12 months	Major Molecular Response [MMR] or better; Tolerating the drug; good adherence; monitored every 3 mos	BCR/ABL >0.1% -7 or del(7q) in Ph- cells	BCR/ABL >1% ABL mutations. New chromosome abnormalities

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Baccarani et al. Blood 2013 Aug 8; 122(6): 872-84
Hochhaus, et al. Leukemia 2020

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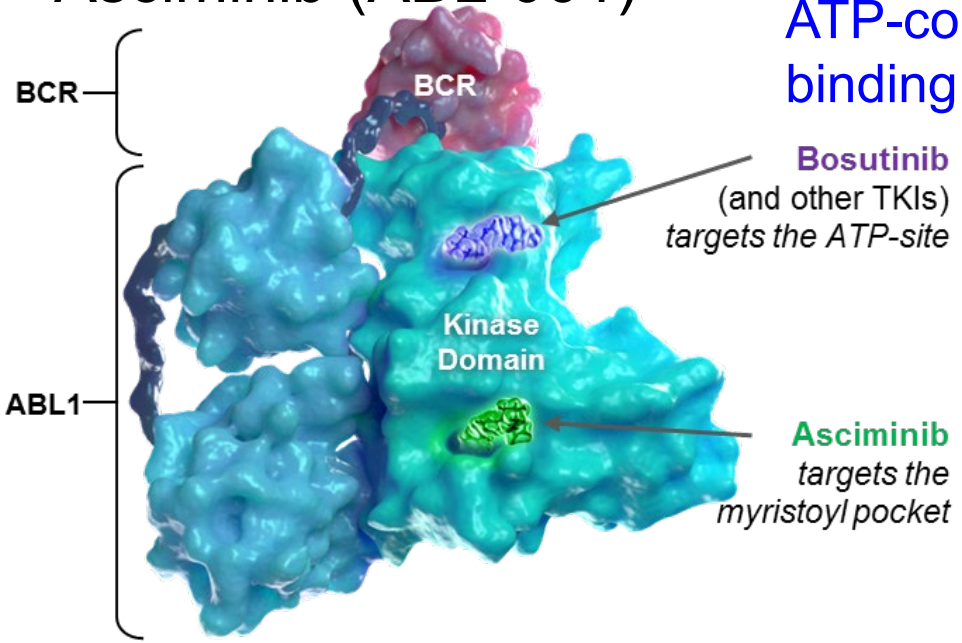
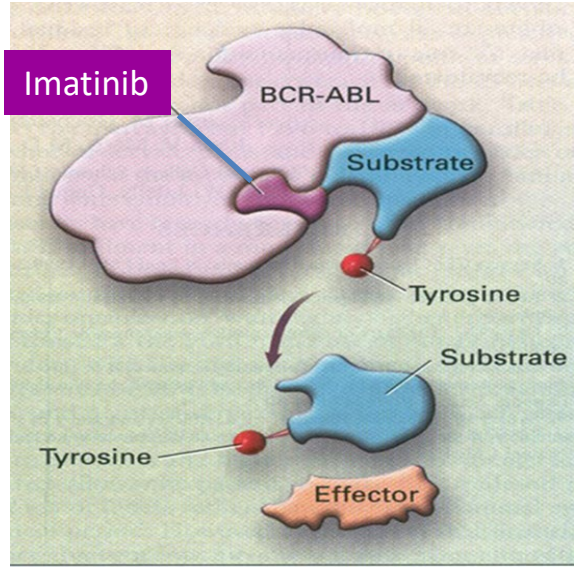
Will Asciminib and its novel mechanism of action change the outcome in CML?

- Asciminib (ABL-001)



ATP-competitive binding site



Non-ATP-competitive binding site – myristoyl pocket locks the inactive isoform

Manley PW, et al. *Leuk Res* 2020; 98:106458

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Asciminib in Chronic Myeloid Leukemia after ABL Kinase Inhibitor Failure

T.P. Hughes, M.J. Mauro, J.E. Cortes, H. Minami, D. Rea, D.J. DeAngelo, M. Breccia, Y.-T. Goh, M. Talpaz, A. Hochhaus, P. le Coutre, O. Ottmann, M.C. Heinrich, J.L. Steegmann, M.W.N. Deininger, J.J.W.M. Janssen, F.-X. Mahon, Y. Minami, D. Yeung, D.M. Ross, M.S. Tallman, J.H. Park, B.J. Druker, D. Hynds, Y. Duan, C. Meille, F. Hourcade-Potelleret, K.G. Vanasse, F. Lang, and D.-W. Kim

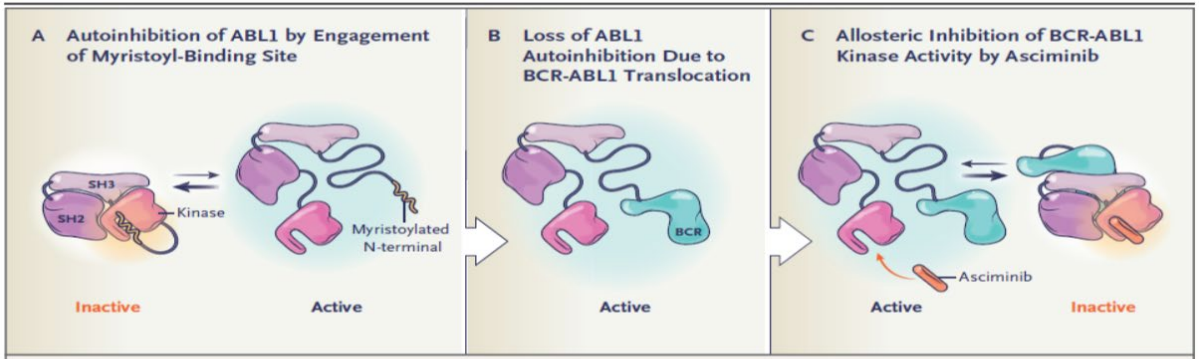


Figure 1. Binding of the Myristoyl Site of the BCR-ABL1 Protein by Asciminib.
Autoinhibition of the ABL1 kinase occurs through engagement of the myristoyl-binding site by the myristoylated N-terminal — a negative regulatory motif that locks the ABL1 kinase in the inactive state (Panel A). On fusion of ABL1 to BCR, the myristoylated N-terminal is lost and the ABL1 kinase is activated (Panel B). By allosterically binding the myristoyl site, asciminib mimics myristate and restores inhibition of BCR-ABL1 kinase activity (Panel C).

N Engl J Med
Dec 12, 2019;
381:2315-26.

Phase I study of asciminib in chronic phase CML without a T315I mutation

Variable	No. of patients (n / evaluable)	Percent responding
Chronic Phase	113	
Median follow up	72 weeks (0.1-167)	
Complete Hematologic Response	34/37	92
CCyR	77/110	70
MMR by 6 mos	37/99	37
MMR by 12 mos	44/91	48

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Hughes et al. N Engl J Med Dec 12, 2019; 381: 2315-26.

Phase I study of asciminib in chronic or accelerated phase CML with T315I mutation

Variable	No of patients (n / evaluable)	Percent responding
CP/AP	33*	
Median follow up	37 weeks (0.7-167)	
Complete Hematologic Response	18/23	78
CCyR	12/30	40
MMR by 6 mos	6/25	24
MMR by 12 mos	6/23	26

* Only 9 patients received 200 mg twice daily

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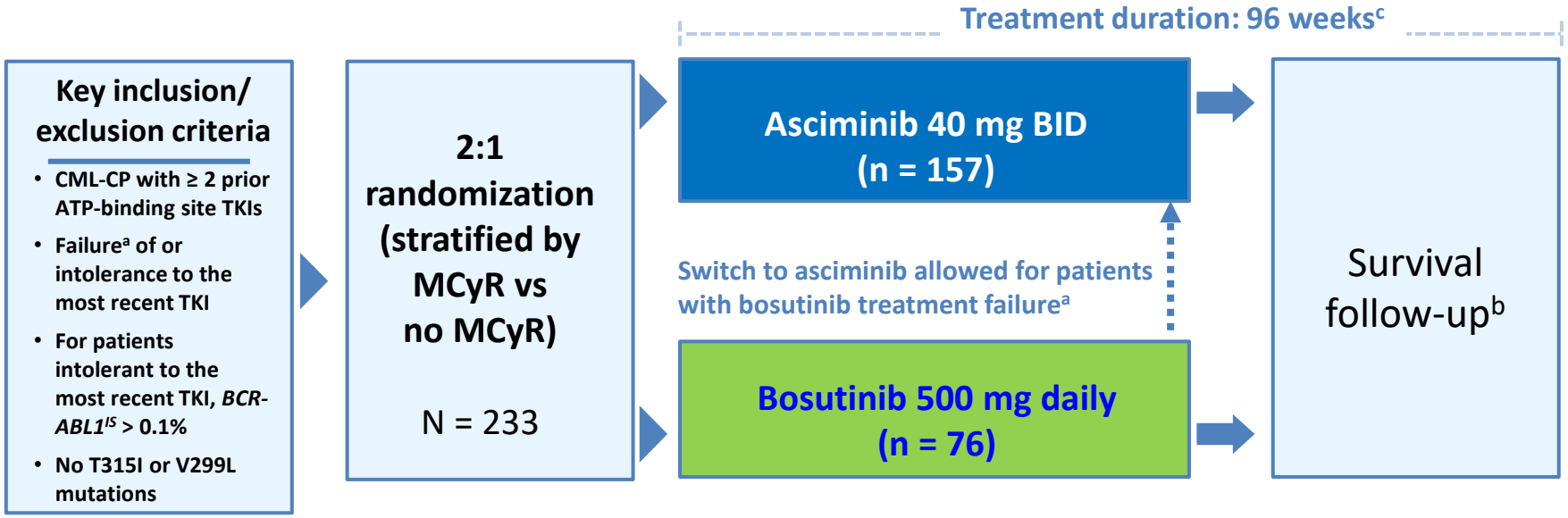
Hughes et al. N Engl J Med Dec 12, 2019; 381: 2315-26.

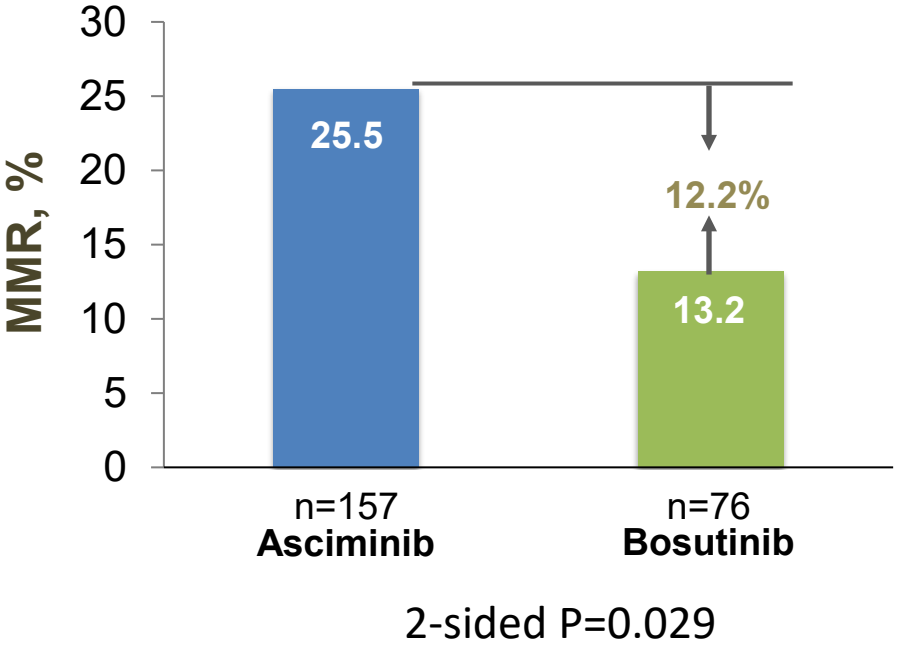
ASCEMBL 3rd Line Study Design and Key Eligibility Criteria



- Data cutoff for current analysis: May 25, 2020 (all patients completed the Week 24 visit or discontinued before). Pts still on treatment: 54% ASC vs 20% BOS.
- Median duration of follow-up: 14.9 months from randomization to cutoff

AP, accelerated phase; BC, blast crisis; BID, twice daily; CP, chronic phase; IS, international scale; MCyR, major cytogenetic response; QD, once daily.
[a] Must meet the definition of treatment failure per the 2013 European LeukemiaNet guidelines (Baccarani M, et al. Blood. 2013;122[6]:872-884); [b] Patients who discontinue study treatment at any time will continue to be followed up for survival and progression to AP/BC for up to 5 years after the last patient's first dose; [c] Patients will continue to receive study treatment for up to 96 weeks after the last patient's first dose. **Presented by Delphine Rea at EHA in June 2022. Abstract S155.**

Major Molecular Response (MMR) Rate at 24 Weeks



2-sided P=0.029

Key Secondary Endpoint: MMR at week 96

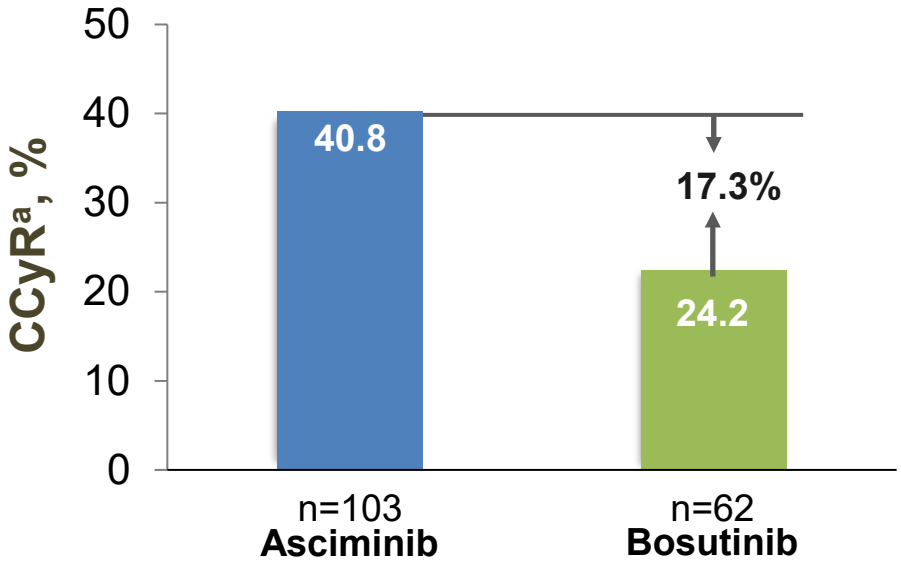
Asciminib	38%
Bosutinib	16%
Difference	22% (2-sided P=0.001)

Deep Molecular Response (MR^4) at week 96

Asciminib	17%
Bosutinib	11%

Presented by Delphine Rea at EHA June 2022. Abstract S155.

Complete Cytogenetic Remission (CCyR) Rate at 24 Weeks

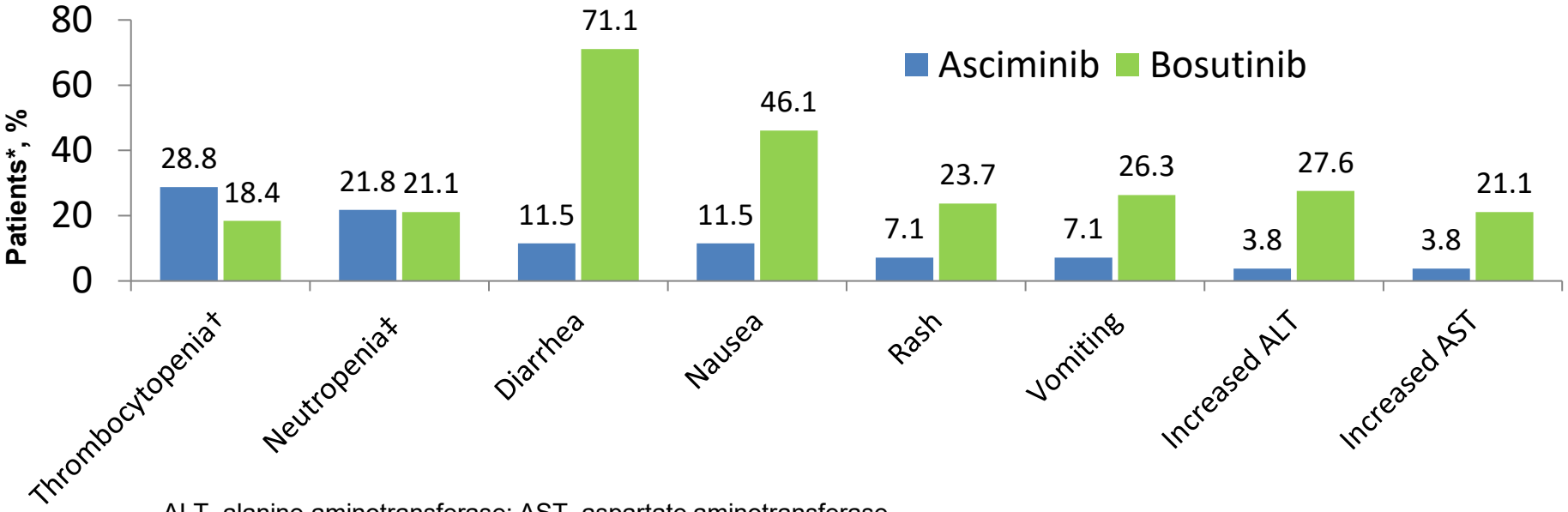


- Common treatment difference after adjusting for MCyR status at baseline was **17.3%** (95% CI, 3.62%-31.0%)

[a] CCyR at 24 weeks is based on patients not in CCyR at baseline (asciminib n = 103, bosutinib n = 62). Cytogenetic response is based on the percentage of Ph+ bone marrow metaphases with at least 20 examined. CCyR was imputed from MMR on a specific date if there was no valid cytogenetic assessment. **Presented by Hochhaus A, et al. ASH 2020. Abstract LBA4.**

Most Frequent All-Grade Adverse Events (AEs occurring in ≥20% of patients in either treatment arm)

- All-grade AEs occurred in 90% of patients on asciminib and 96% on bosutinib.



ALT, alanine aminotransferase; AST, aspartate aminotransferase.

* Numbers represent counts of patients. A patient with multiple severity grades for an adverse event is only counted under the maximum grade. † Grouped term that includes AEs reported by investigator as thrombocytopenia and platelet count decreased. ‡ Grouped term that includes AEs reported by investigator as neutropenia, neutrophil count decreased, and febrile neutropenia.

Delphine Rea et al. A phase 3, open-label, randomized study of asciminib, a STAMP inhibitor, vs bosutinib in CML after 2 or more prior TKIs. BLOOD 25 Nov 2021; 138 (21): 2031-42.

Potential impact of asciminib

- Asciminib is currently approved for third-line therapy at 80 mg daily, or for T315I mutant CML at 200 mg BID.
- Ongoing studies:
  - Front-line trial of asciminib vs physician's choice of imatinib/dasatinib/nilotinib
  - Combination therapy of imatinib + asciminib
  - Asciminib plus dexamethasone for newly diagnosed Ph+ acute lymphoblastic leukemia.

Stopping TKI Therapy in CML

Why discontinue tyrosine kinase inhibitor (TKI) therapy?

Common side-effects from TKIs in CML

	Imatinib		Dasatinib		Nilotinib	
	All grades	**Gr 3&4**	All grades	**Gr 3&4**	All grades	**Gr 3&4**
Fatigue	++++	**+**	+++	**+**	++++	**+**
Skin rash	++++	**++**	+++	**+**	++++	**+**
Nausea	++++		++++		+++	**+**
Diarrhea	++++	**++**	++++	**+**	+++	**+**
Myalgia	+++++		++++			
Headache	+++		++++		++++	
Edema	++++	**++**	++++	**++**	+++	
Pleural. Effusion	++	**+**	++++	**++**	++	**+**
Hyperglycemia					++++	**+++**
Elevated Lipase	++++	**++**			++++	**+++**
Elevated ALT	++++	**++**		**+**	+++++	**+++**

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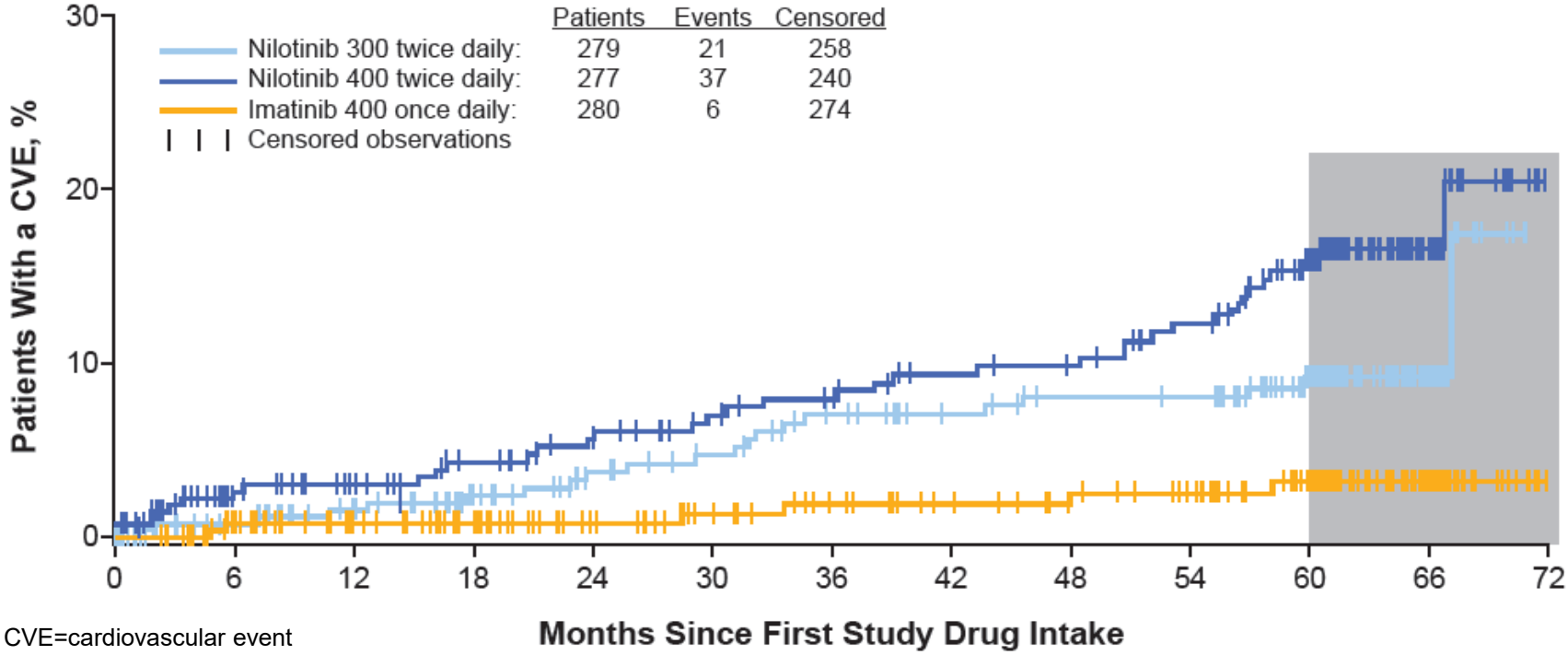
2+, 1-5%; 3+, 5-10%; 4+, 10-50%; 5+, >50%

Apperley. Lancet Dec 5, 2014;
Steegmann et al. Leuk Lymph 2012; 53:2351

Incidence of Adverse Vascular Events on ENESTnd



CVE=cardiovascular event

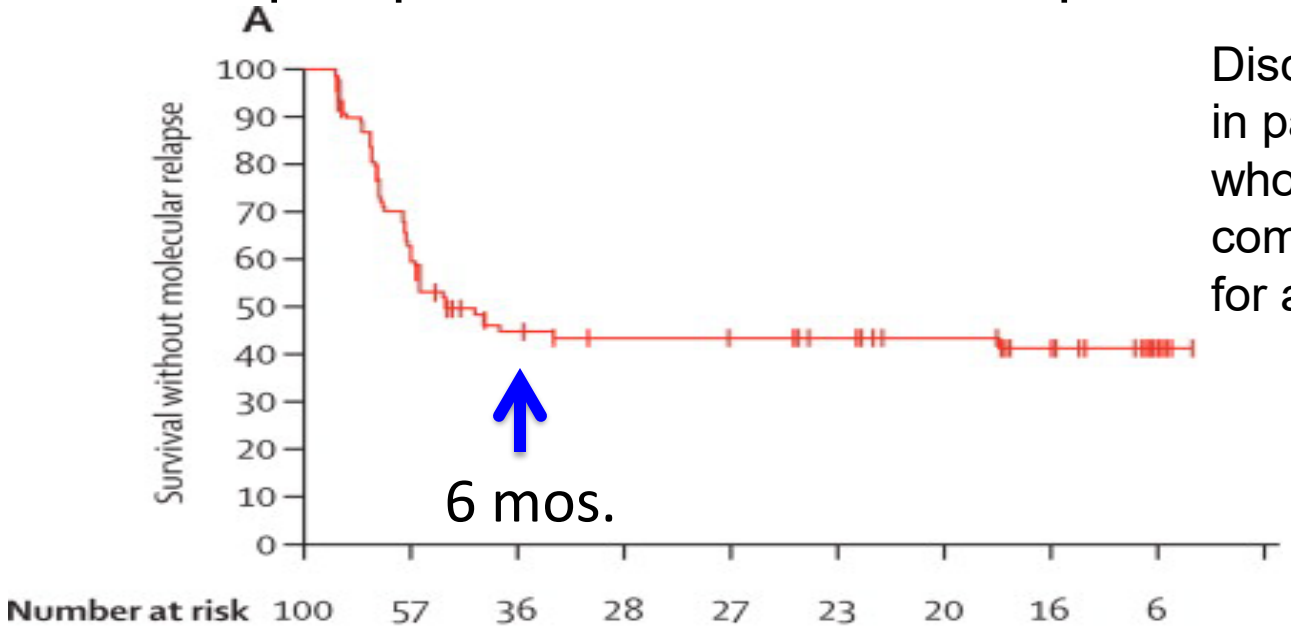
What is “treatment-free remission” (TFR) and when it is appropriate to consider?

- Prospective discontinuation of TKI therapy with more frequent molecular monitoring.
  - Goal is to maintain deep molecular remission without treatment.
  - Eliminate chronic side-effects (e.g. fatigue, rash, GI)
  - Reduce complications of treatment (vascular toxicity)
  - Reduce costs
- Best results are achieved after >5 years of total therapy and >2 years in deep molecular remission (<0.01% transcript level)

TFR – warnings!

- Psychological stress and anxiety
- Non-adherence to follow up (monitoring is mandatory)
- “TKI withdrawal” syndrome
- Molecular recurrence and hematologic relapse
- Need for retreatment

- The prospective, multicenter Stop Imatinib (STIM) Trial



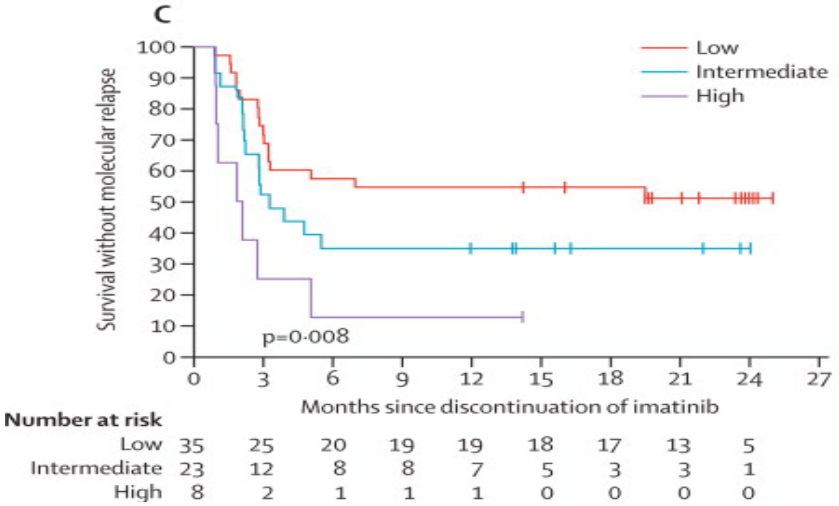
Discontinuation of imatinib in patients with CML who had maintained complete molecular remission for at least 2 years.

For 100 patients, the estimated molecular relapse-free survival was 45% (95% CI 34–55) at 6 months, 43% (33–53) at 12 months, and 41% (34–55) at 24 months.

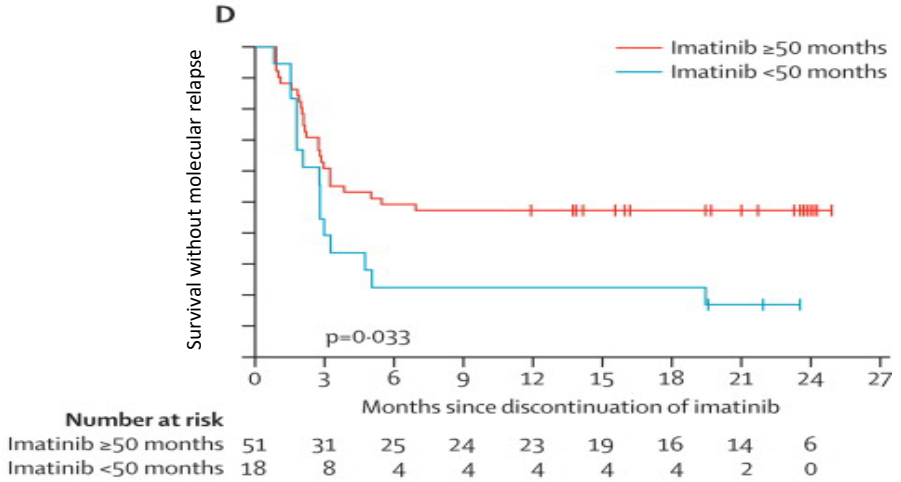
FX Mahon et al. Lancet Oncology 2010; 11: 1029

- The prospective, multicenter Stop Imatinib (STIM) Trial

By initial Sokal Score



By time on Imatinib therapy

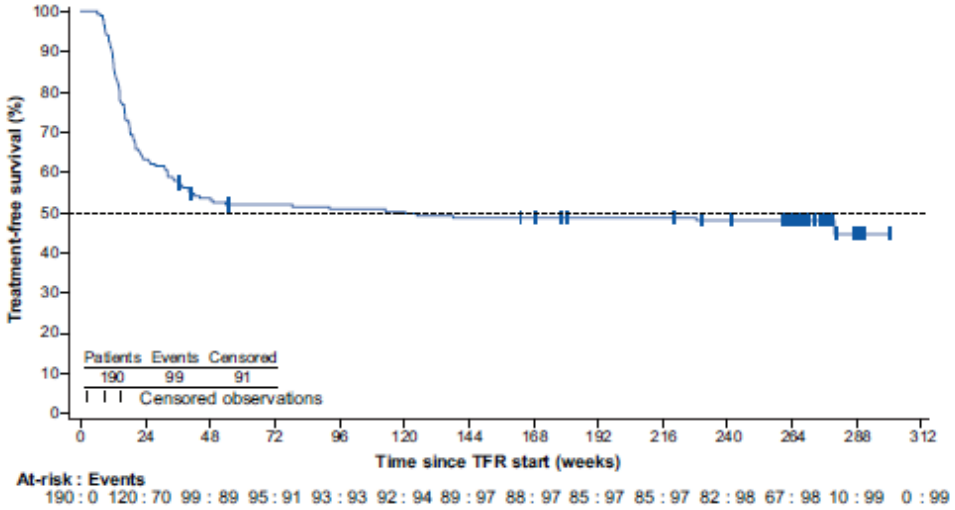


FX Mahon et al. Lancet Oncology 2010; 11: 1029

ENESTfreedom Study: TFR after frontline nilotinib

- Chronic phase CML, n=190
- Frontline nilotinib for >3 years.
- Sustained $MR^{4.5}$ for >1 year.

Sokal score at Diagnosis	TFR at 5 years, n/N (%)	
Low	32/63	51%
Intermediate	19/50	38%
High	8/29	28%
Missing	20/48	42%



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Radich et al. Leukemia 2021

Greatest chance for successful TKI discontinuation

- First-line therapy, or second-line if intolerance was the only reason for changing TKI.
- No prior treatment failure.
- Duration of TKI therapy >5 years (>4 years for 2nd Gen TKI)
- Duration of Deep Molecular Response (DMR) >3 years, if MR4
- Duration of DMR >2 years, if MR4.5

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Hochhaus, et al. Leukemia 2020; 34: 966–984

Cumulative incidence of deep molecular response (MR^4 and $MR^{4.5}$) with imatinib, nilotinib, and dasatinib by 5 and 10 years

Study		5 Years (%)	10 Years (%)
CML Study IV	Imatinib MR4	68	81
	Imatinib MR4.5	53	72
ENESTnd	Imatinib MR4	42	56
	Imatinib MR4.5	35	45
	Nilotinib MR4	66	73
	Nilotinib MR4.5	54	64
DASISION	Imatinib MR4.5	33	NA
	Dasatinib MR4.5	42	NA

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Closing slide

Remaining challenges in CML

- Managing acute and chronic toxicities of TKI therapy.
- Attention to cardiac risk factors and co-morbidities
- Identifying which patients can safely stop TKI therapy.
- Developing combination therapies.
- Treating resistant and blast phase disease.

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Thank you.

rlarson@uchicago.edu