THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

# Chronic Myeloid Leukemia – Changing Goals

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# Disclosures – Richard A. Larson, MD

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  - Astellas
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  - Rafael Pharma
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  - Celgene/BMS (DSMB)
  - CVS/Caremark
  - Epizyme (DSMB)
  - Novartis (DSMB)

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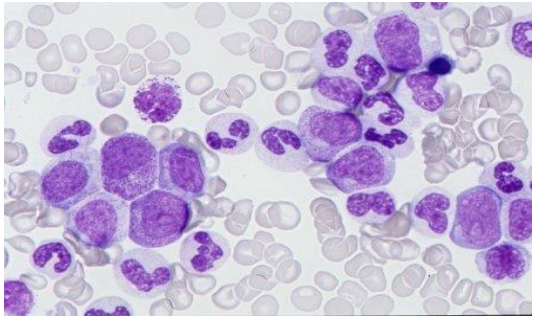
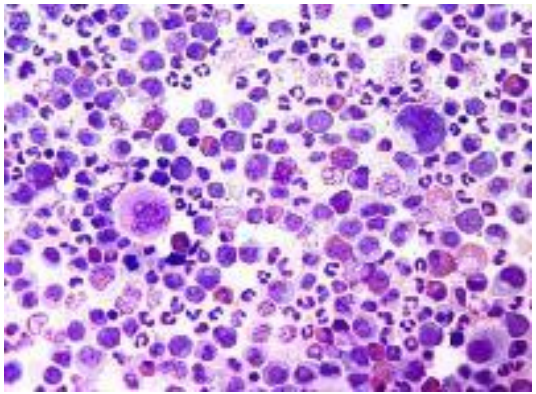
Investigational product: asciminib

# 2021 Learning Objectives

- Survival now approaches that of the general population.
- Risk assessment is still important.
- New biologic predictors of response
- Investigational agent -- asciminib
- Changing goals to treatment-free remission





# 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)<br>+ 0.0345 × (**spleen** - 7.51)<br>+ 0.188 × [(**platelet count**/700)$^2$ - 0.563]<br>+ 0.0887 × (**blood blasts** - 2.10) | Low-risk: < 0.8<br>Intermediate-risk: 0.8 - 1.2<br>High-risk: > 1.2 |
| **ELTS** | 0.0025 × (**age**/10)$^3$<br>+ 0.0615 × **spleen size**<br>+ 0.1052 × **peripheral blood blasts**<br>+ 0.4104 × (**platelet count**/1000)$^{-0.5}$ | Low-risk: < 1.5680<br>Intermediate-risk:1.5680- 2.2185<br>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 ($10^9$/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.

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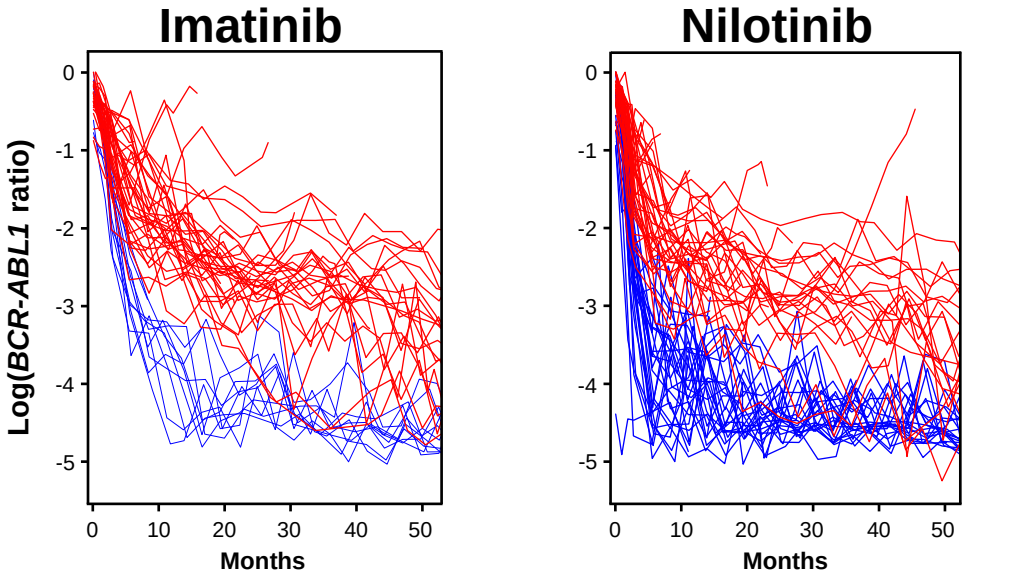
Hochhaus et al. ELN 2020 recommendations for treating CML. Leukemia 2020.

# Gene expression profiling at baseline (N=112)



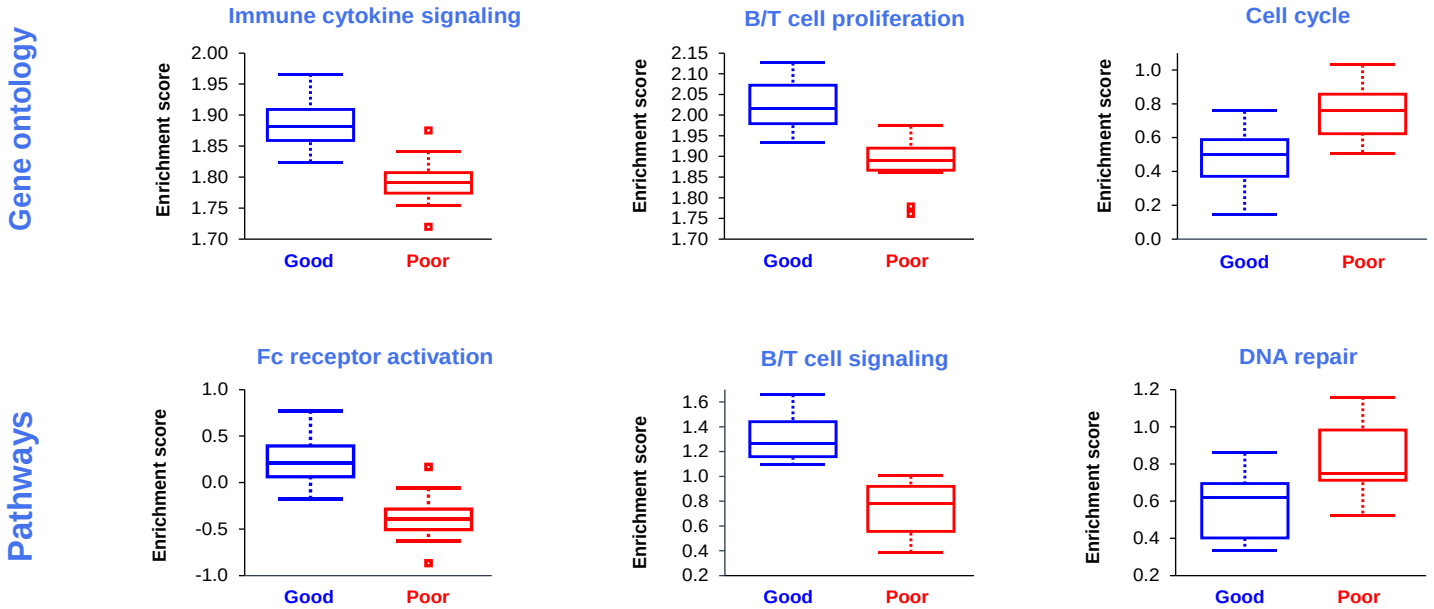

**Good responders:**
**Patients having achieved Major Molecular Response (MMR) by 12 months**

**Poor responders:**
**Patients not having achieved MMR by 12 months or still >10% at 3 months**

- Stratification of samples based on molecular response at 12 months translated into the probability of DMR (deep molecular remission) at 5 years
- This gene analysis was not powered to distinguish response between nilotinib and imatinib

Radich et al. Gene Expression Signature Predicts Deep Molecular Response in CML: Biomarker Analysis from ENESTnd. ASH 2019

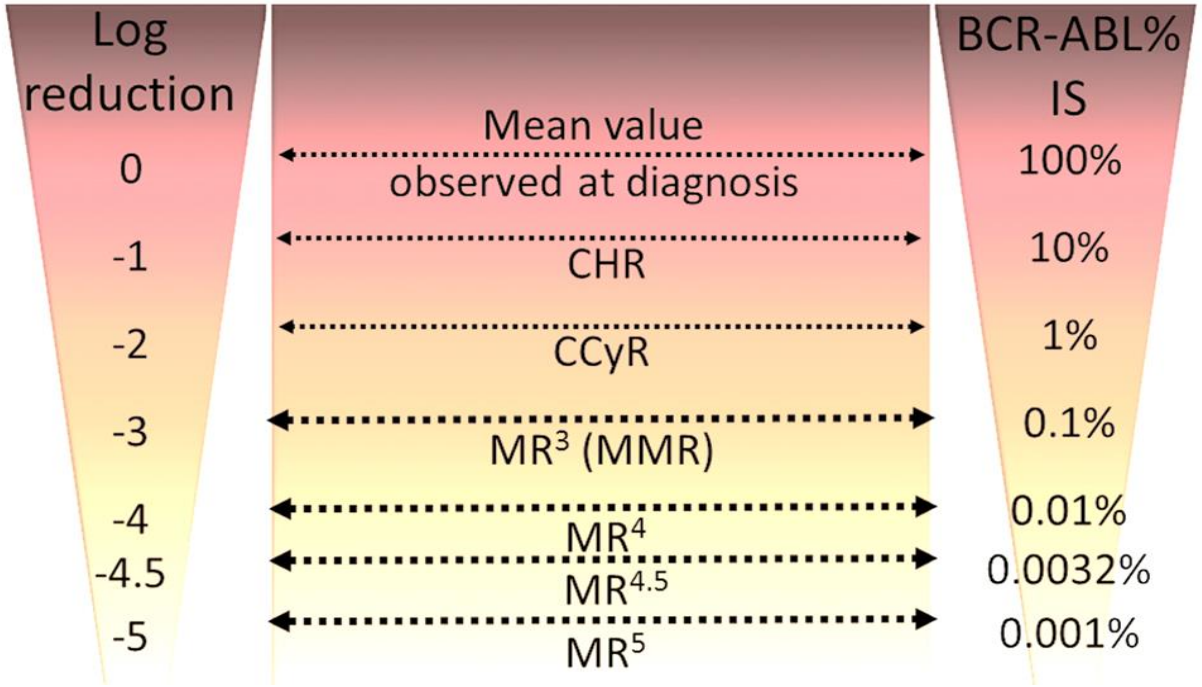
# Pathway Clustering Validated Prediction




**Multiple pathways associated with immune response were found to be predictive of good response**

Radich et al. Gene Expression Signature Predicts Deep Molecular Response in CML: Biomarker Analysis from ENESTnd. ASH 2019

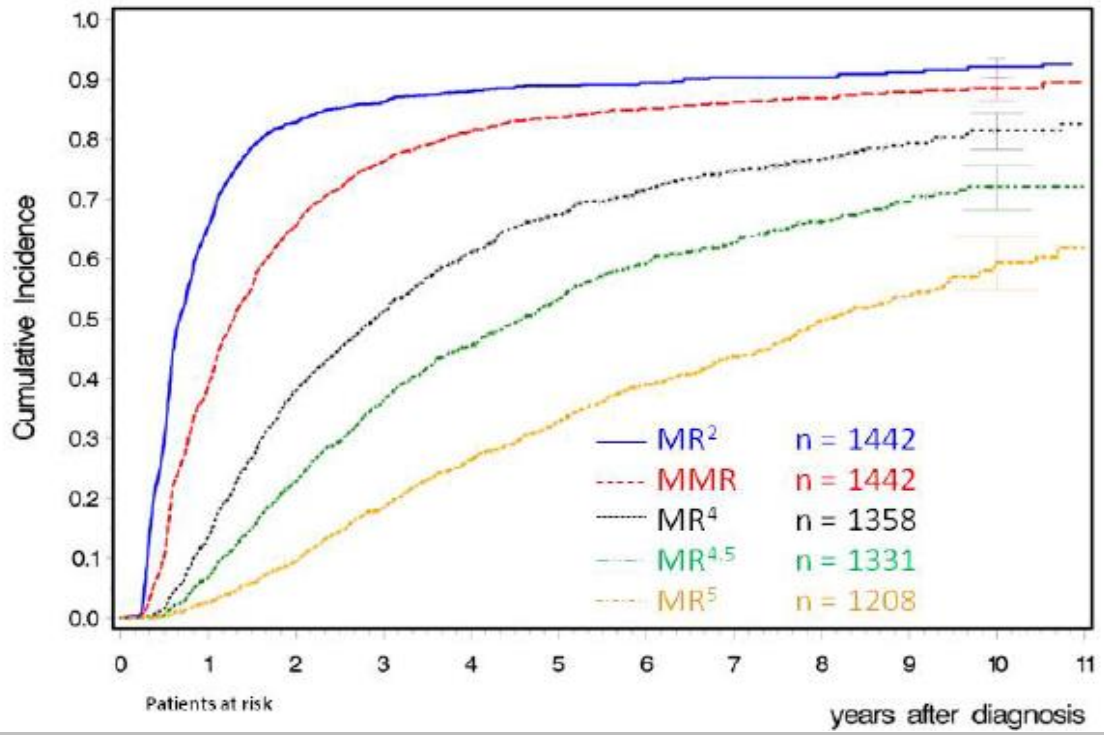
# Quantitative reverse transcriptase polymerase chain reaction (RT-PCR) for BCR-ABL1 transcripts (International Scale)






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

# Safety and Efficacy of Imatinib over 10 years – German CML IV trial






Kalmanti et al. German CML Study Group. Leukemia 2015

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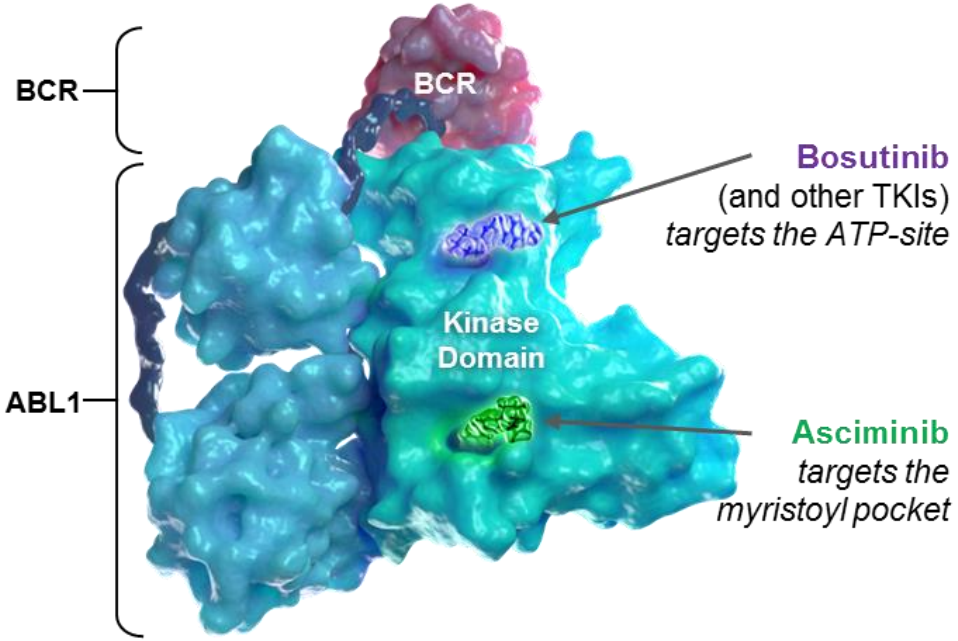
Baccarani et al. Blood 2013 Aug 8; 122(6): 872-84
Hochhaus, et al. Leukemia 2020

# 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

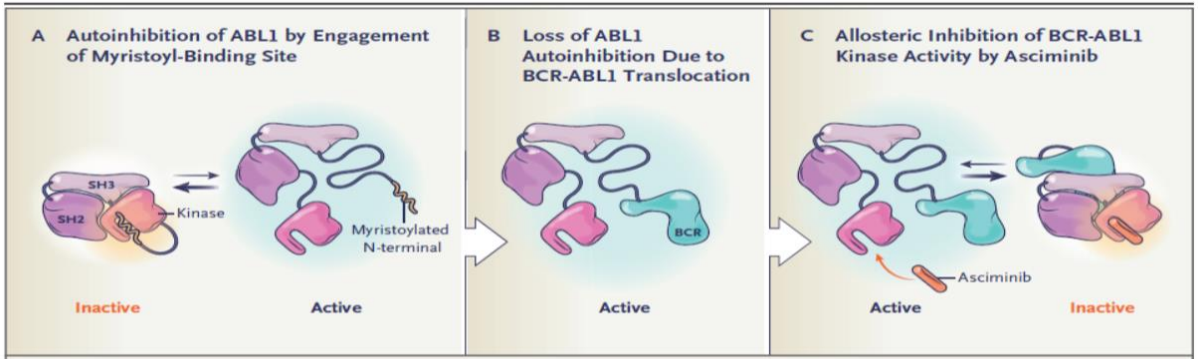
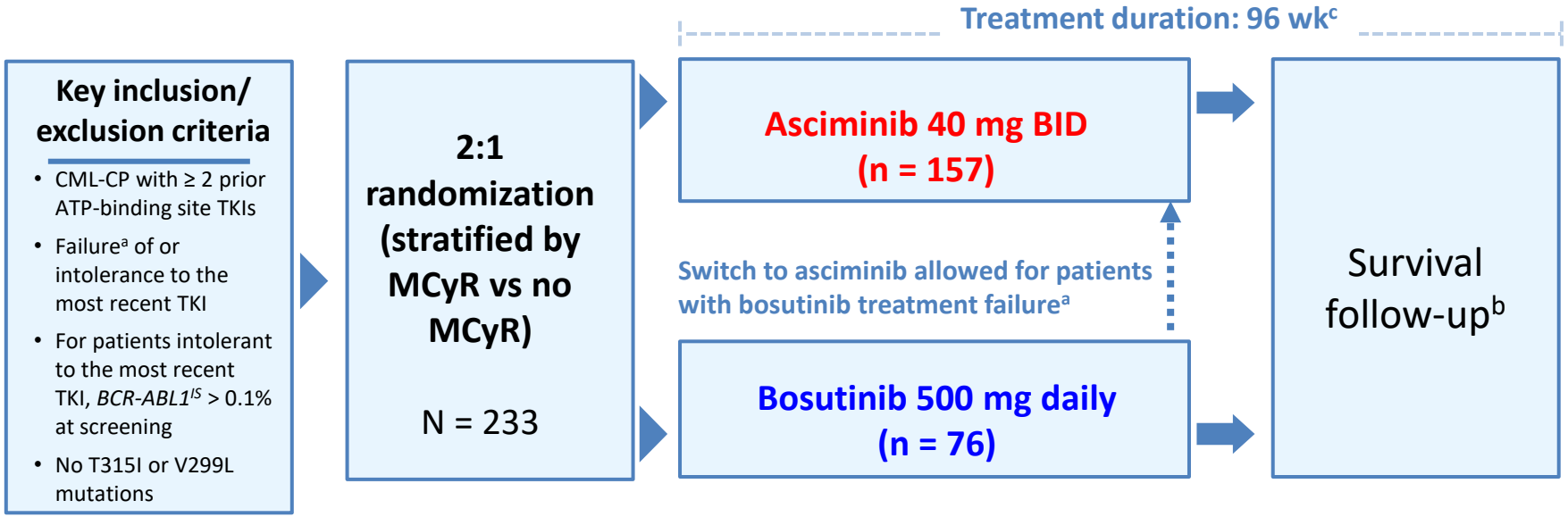



**Figure 1. Binding of the Myristoyl Site of the BCR-ABL1 Protein by Asciminib.**
Autoinhibition of the ABL1 kinase occurs through engagement of the myristoyl-binding site by the myristoylated N-terminal — a negative regulatory motif that locks the ABL1 kinase in the inactive state (Panel A). On fusion 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.

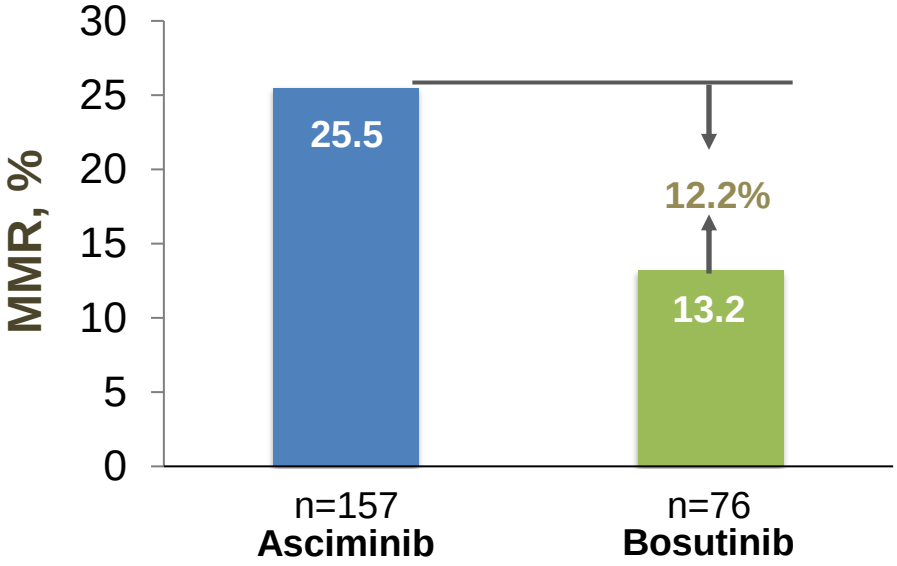
# ASCEMBL Study Design and Key Eligibility Criteria




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

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 Hochhaus A, et al. ASH 2020. Abstract LBA4.

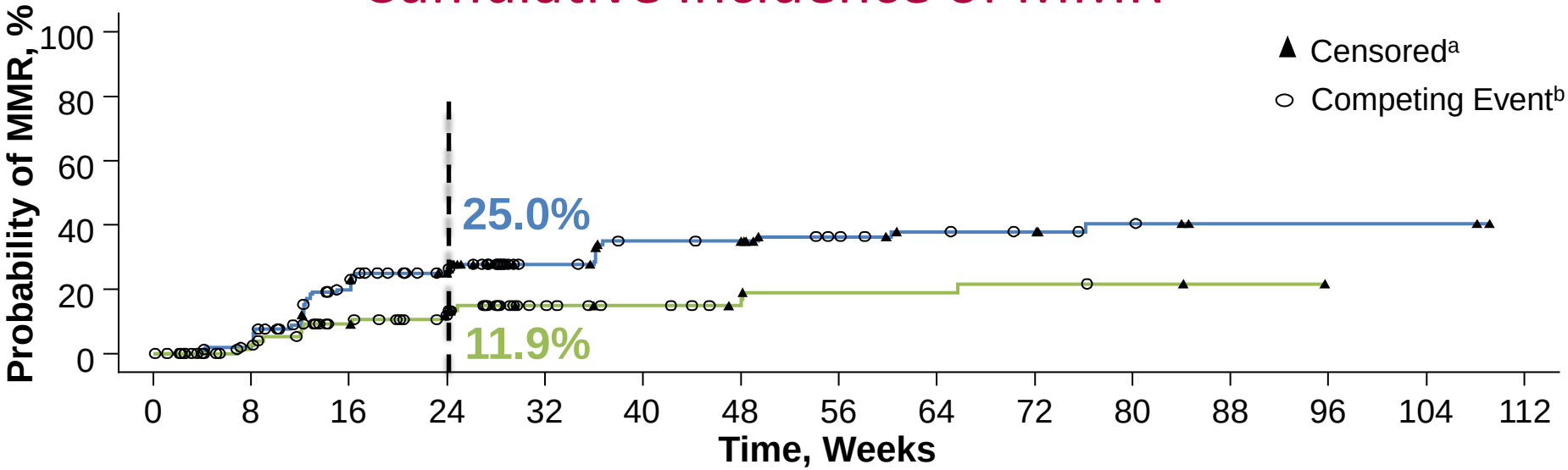
# Major Molecular Response (MMR) Rate at 24 Weeks




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

Presented by Hochhaus A et al. ASH 2020. Abstract LBA4.

# Cumulative Incidence of MMR




**Number of patients still at risk**

| | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Asciminib | 157 | 152 | 145 | 129 | 107 | 92 | 86 | 58 | 47 | 44 | 29 | 29 | 26 | 20 | 18 | 15 | 13 | 12 | 11 | 6 | 5 | 3 | 2 | 2 | 2 | 2 | 2 | 2 | 0 |
| Bosutinib | 76 | 72 | 66 | 60 | 52 | 46 | 39 | 27 | 16 | 12 | 11 | 9 | 6 | 4 | 4 | 4 | 4 | 3 | 3 | 3 | 2 | 2 | 1 | 1 | 0 | 0 | 0 | 0 | 0 |

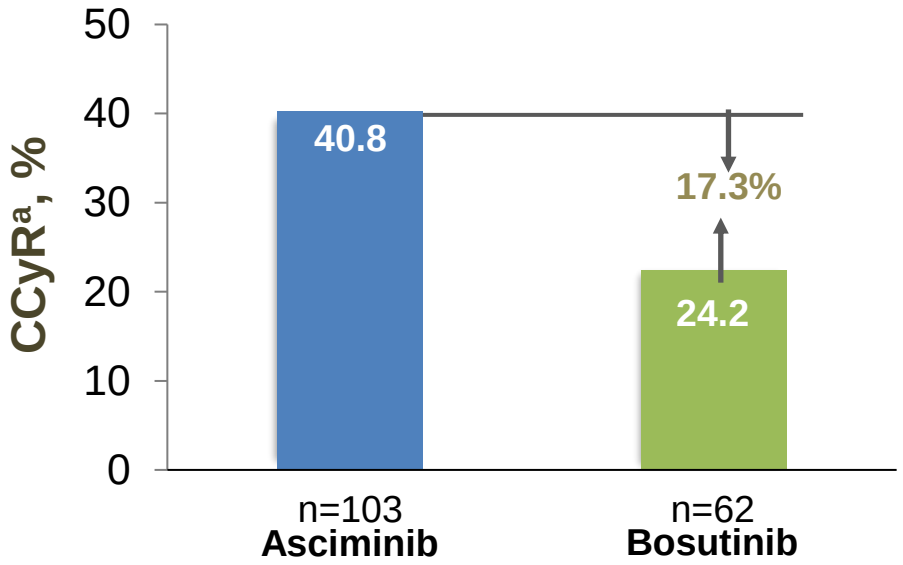
**Cumulative number of competing events**

| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Asciminib | 0 | 5 | 8 | 14 | 18 | 23 | 27 | 35 | 45 | 46 | 47 | 47 | 48 | 48 | 50 | 52 | 52 | 53 | 54 | 55 | 55 | 56 | 56 | 56 | 56 | 56 | 56 | 56 | 56 |
| Bosutinib | 0 | 4 | 8 | 11 | 17 | 20 | 25 | 31 | 41 | 44 | 45 | 47 | 48 | 48 | 48 | 48 | 48 | 48 | 48 | 48 | 49 | 49 | 49 | 49 | 49 | 49 | 49 | 49 | 49 |

[a] Non-responders were censored at their last molecular assessment date. [b] Discontinuation from treatment due to any reason, without prior achievement of MMR, is considered as a competing event.

**Presented by Hochhaus A, et al. ASH 2020. Abstract LBA4.**

# Complete Cytogenetic Remission (CCyR) Rate at 24 Weeks

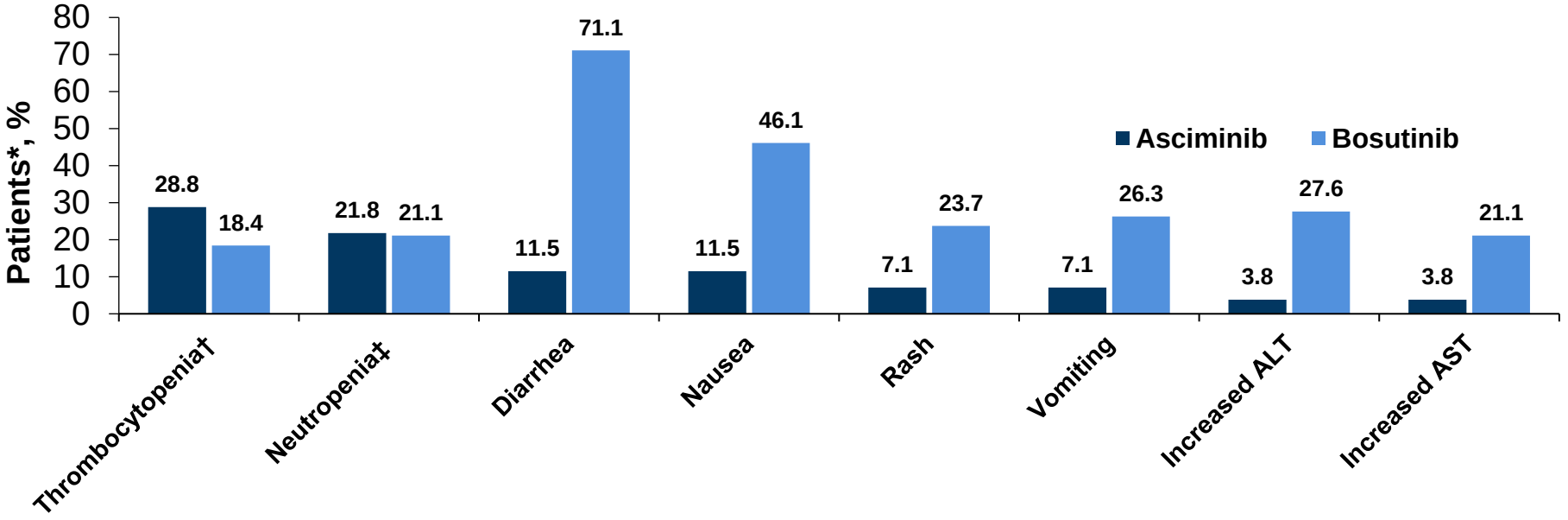



- Common treatment difference after adjusting for MCyR status at baseline was **17.3%** (95% CI, 3.62%-31.0%)

[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.

Presented by Hochhaus A, et al. ASH 2020. Abstract LBA4.

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# 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 | ++++ | ++ | ++++ | ++ | +++ | |
| Pl. Effusion | ++ | + | ++++ | ++ | ++ | + |
| Hyperglycemia | | | | | ++++ | +++ |
| Elevated Lipase | ++++ | ++ | | | ++++ | +++ |
| Elevated ALT | ++++ | ++ | | + | +++++ | +++ |

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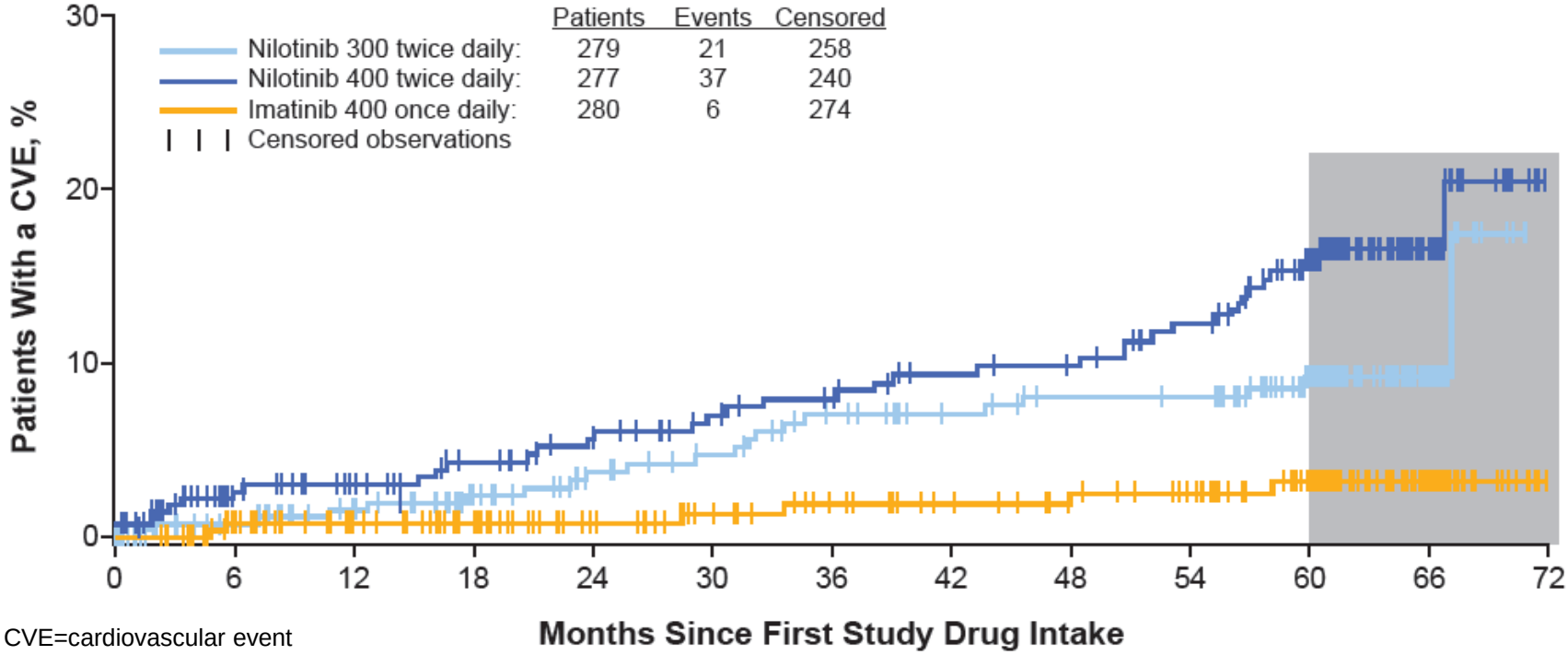
**2+, 1-5%; 3+, 5-10%; 4+, 10-50%; 5+, >50%**

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

# Incidence of Adverse Vascular Events on ENESTnd




CVE=cardiovascular event

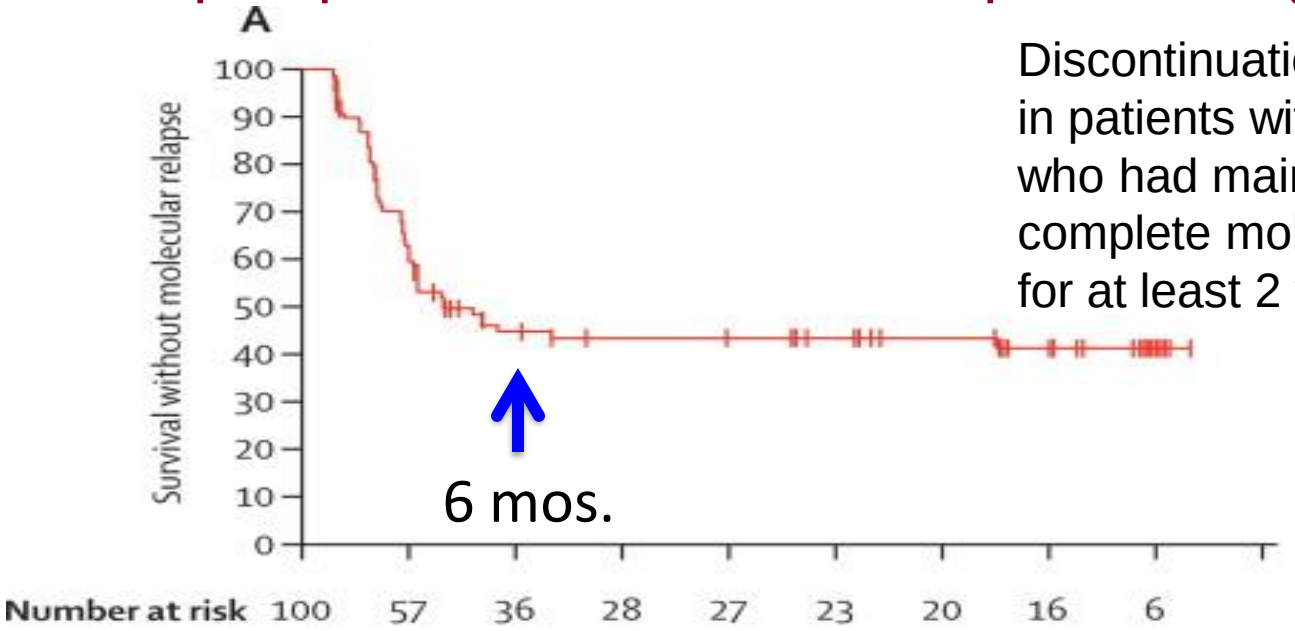
# What is “treatment-free remission” (TFR) and when it is appropriate to consider?

- Prospective discontinuation of TKI therapy with more frequent molecular monitoring.
  - Goal is to maintain deep molecular remission
  - 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.

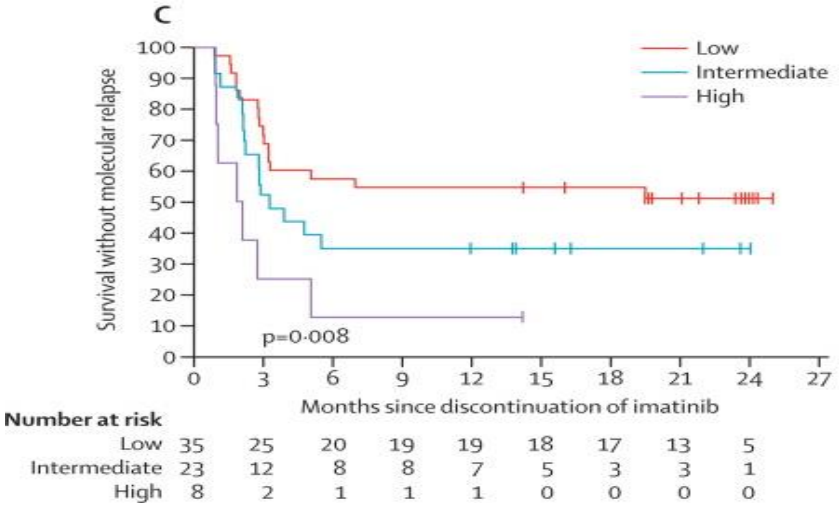
For 100 patients, the estimated molecular relapse-free survival was 45% (95% CI 34–55) at 6 months, 43% (33–53) at 12 months, and 41% (34–55) at 24 months.



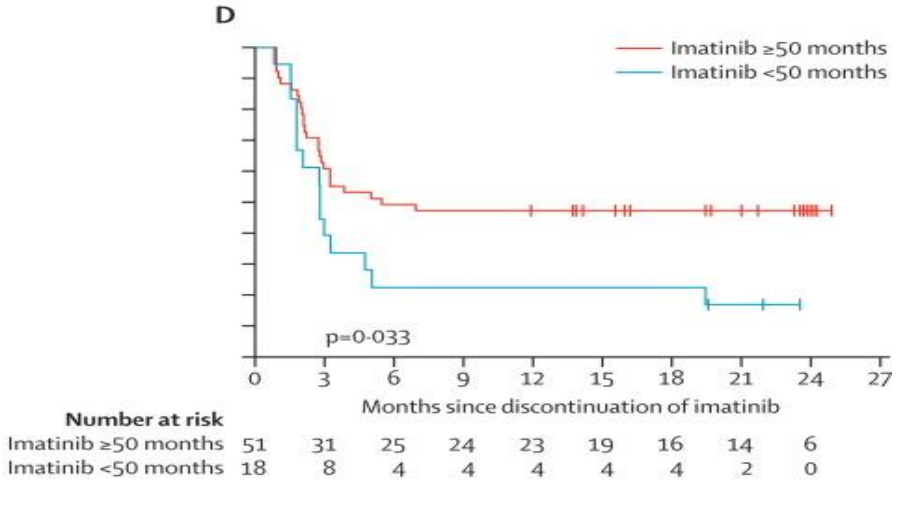
FX Mahon et al. Lancet Oncology 2010; 11: 1029

# The prospective, multicenter Stop Imatinib (STIM) Trial

By initial Sokal Score




By time on Imatinib therapy



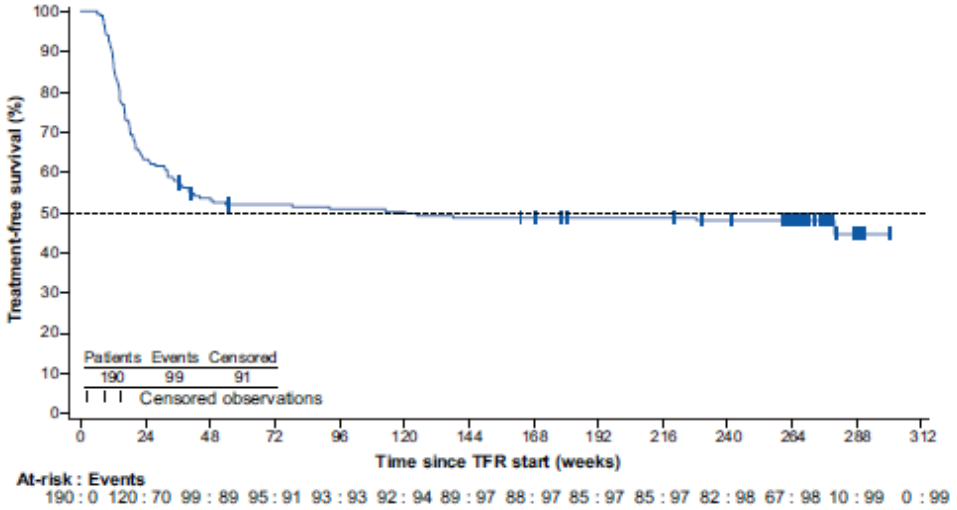



FX Mahon et al. Lancet Oncology 2010; 11: 1029

# 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 | |
|---|---|---|
| Low | 32/63 | 51% |
| Intermediate | 19/50 | 38% |
| High | 8/29 | 28% |
| Missing | 20/48 | 42% |

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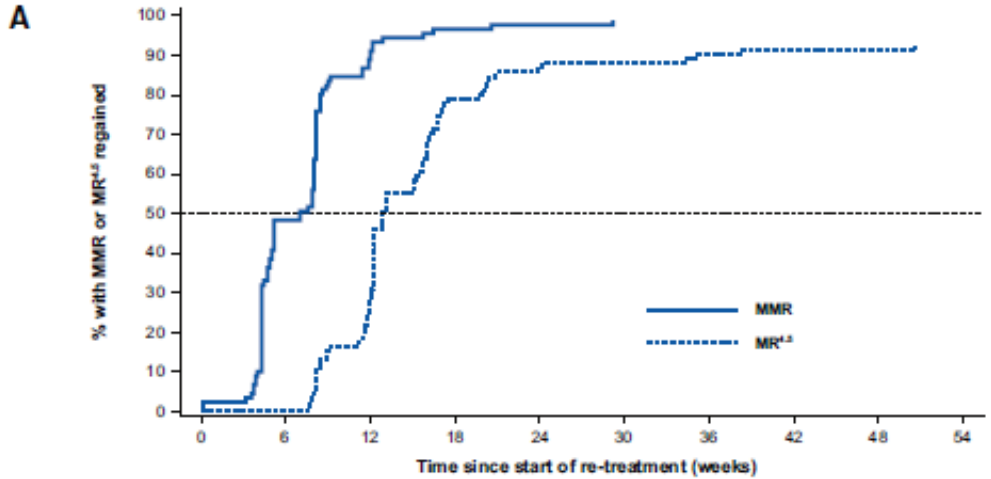
Radich et al. Leukemia 2021

# ENESTfreedom Study: TFR after frontline nilotinib

Cumulative MMR and $MR^{4.5}$ rates following treatment re-initiation




| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| MMR | Cumulative n/N | 0/91 | 44/91 | 83/91 | 88/91 | 89/91 | 90/91 | | | | |
| | Cumulative % | 0.0 | 48.4 | 91.2 | 96.7 | 97.8 | 98.9 | | | | |
| $MR^{4.5}$ | Cumulative n/N | 0/91 | 0/91 | 28/91 | 72/91 | 79/91 | 80/91 | 82/91 | 83/91 | 83/91 | 84/91 |
| | Cumulative % | 0.0 | 0.0 | 30.8 | 79.1 | 86.8 | 87.9 | 90.1 | 91.2 | 91.2 | 92.3 |

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# 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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# Recommendations for safe TKI discontinuation

- CML in first Chronic Phase only (data are lacking outside this setting)
- Motivated patient with good communication
- Patient's agreement to more frequent monitoring after stopping treatment, i.e., monthly for the first 6 months, every 2 months for months 6-12, then every 3 months.
- Access to high quality quantitative RT-PCR using the International Scale (IS)
- Typical e13a2 or e14a2 BCR/ABL1 transcripts

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

# 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

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.