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Starting & stopping therapy in Chronic Myeloid Leukemia: What more is needed?

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  - Epizyme (DSMB)
  - Novartis

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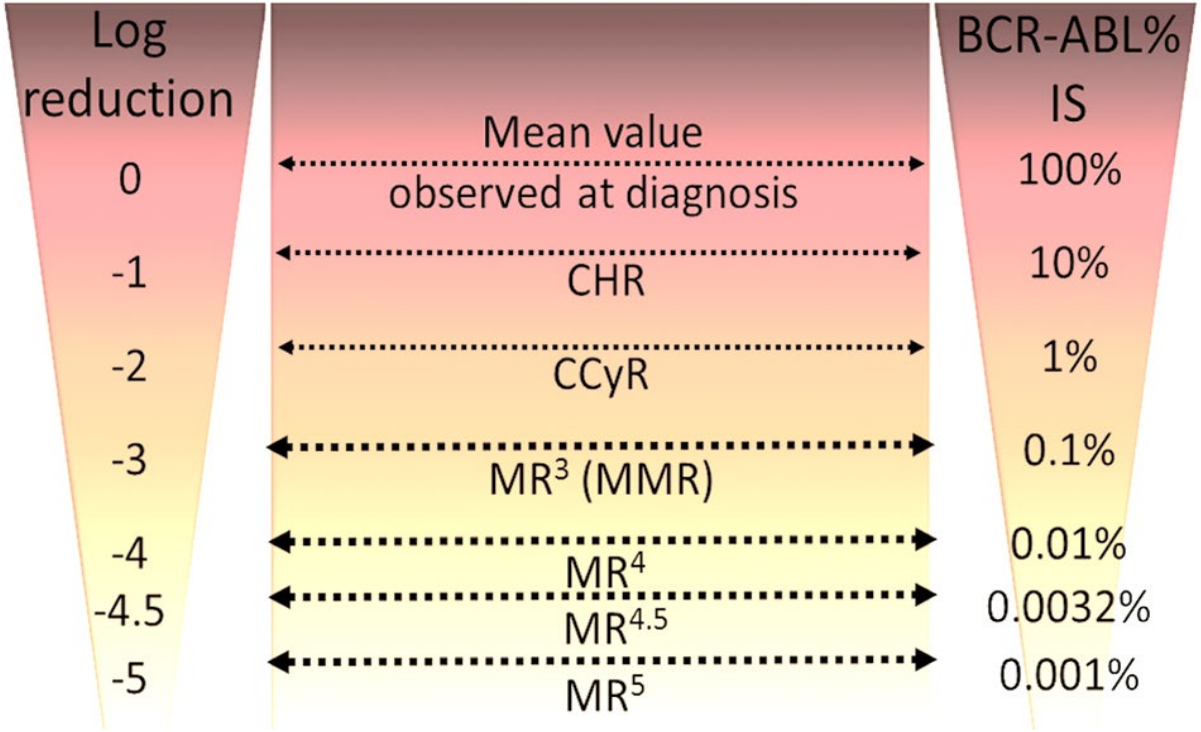
Investigational product: asciminib

CML: What questions remain?

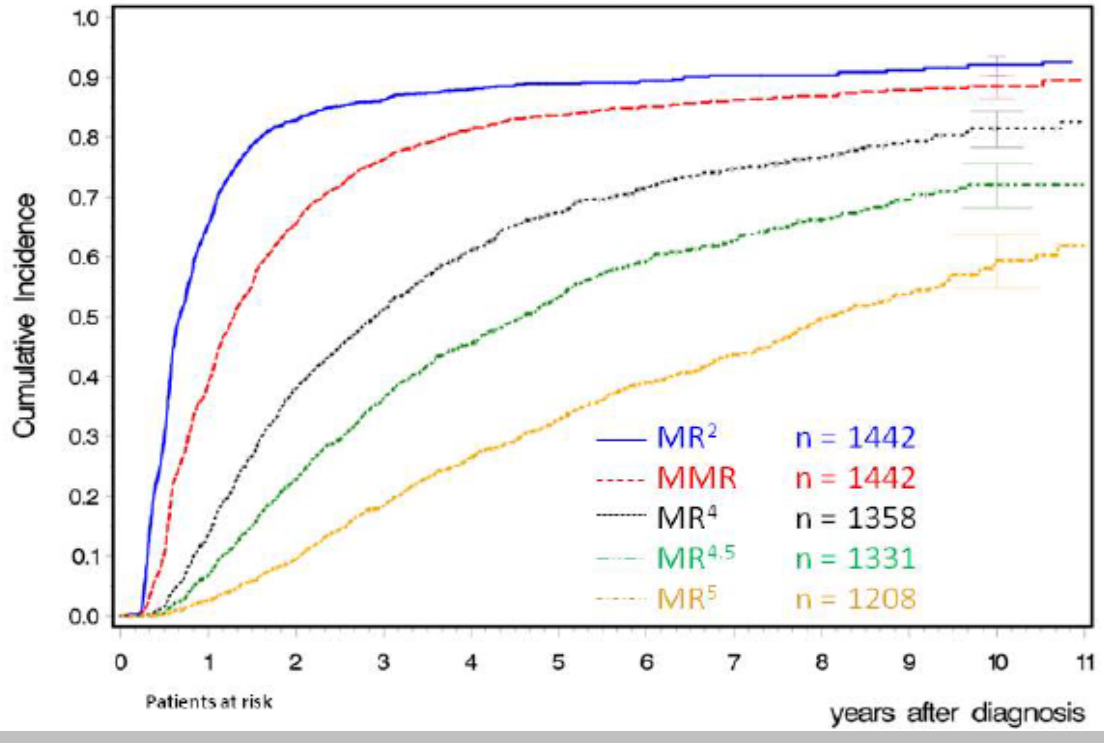
- Risk scores – Sokal or ELTS?
- Which TKI to start?
- Should the goal be Overall Survival or Treatment-free Remission (TFR)?
- Switching based on Early Molecular Response (EMR)
- Reducing dosages to reduce side-effects
- Asciminib (ABL001; Novartis) – a non-ATP competitive inhibitor of BCR/ABL1
- Discontinuation studies (18 so far)

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



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

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



Kalmanti et al. German CML Study Group. Leukemia 2015

Comparison of Sokal and ELTS prognostic scores
(European Treatment & Outcome Study [EUTOS] Long Term Survival score)

Score	Clinical parameters	Risk Groups
Sokal (1984)	Age Spleen size on physical exam Platelet count Peripheral blood blasts (%)	Low: <0.8 Intermediate: 0.8 – 1.2 High: >1.2
ELTS (2016)	Age Spleen size on physical exam Platelet count Peripheral blood blasts (%)	Low: <1.5680 Intermediate: 1.568 – 2.2185 High: >2.2185

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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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.

Recommended tyrosine kinase inhibitors in case of BCR-ABL1 resistance mutations

Mutation	Recommended TKI
T315I	Ponatinib
F317L/V/I/C, T315A	Nilotinib, bosutinib, ponatinib
V299L	Nilotinib, ponatinib
Y253H, E255V/K, F359V/I/C	Dasatinib, bosutinib, ponatinib

- These mutations are not detectable when chronic phase CML is first diagnosed.
- Occult subclones emerge under selective pressure from TKI therapy.

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

What is an Early Molecular Response?

- *BCR/ABL1* transcript level ≤10% (International Scale)
  - At 3 months
  - At 6 months
- Importance: predicts for MMR and Survival
- Limitations: not yet clear whether altering therapy for qRT-PCR level >1% leads to a better outcome.
- However, switching at 3 or 6 months if the *BCR/ABL1* level is still >10% seems reasonable.

2020 European LeukemiaNet Recommendations for newly diagnosed CML

Time:	Optimal Response	Warning	Failure
3 months	BCR/ABL1 ≤10%	BCR/ABL1 > 10%	BCR/ABL1 > 10%, if confirmed
6 months	BCR/ABL1 < 1%	BCR/ABL1 < 1-10%	BCR/ABL1 > 10%
12 months	BCR/ABL1 ≤0.1% (MMR)	BCR/ABL1 < 0.1-1%	BCR/ABL1 > 1%
Thereafter, >12 months	Major Molecular Response [MMR] or better; Tolerating the drug; good adherence; monitored every 3 mos	BCR/ABL1 > 0.1-1%	BCR/ABL1 > 1% ABL1 mutations. New chromosome abnormalities

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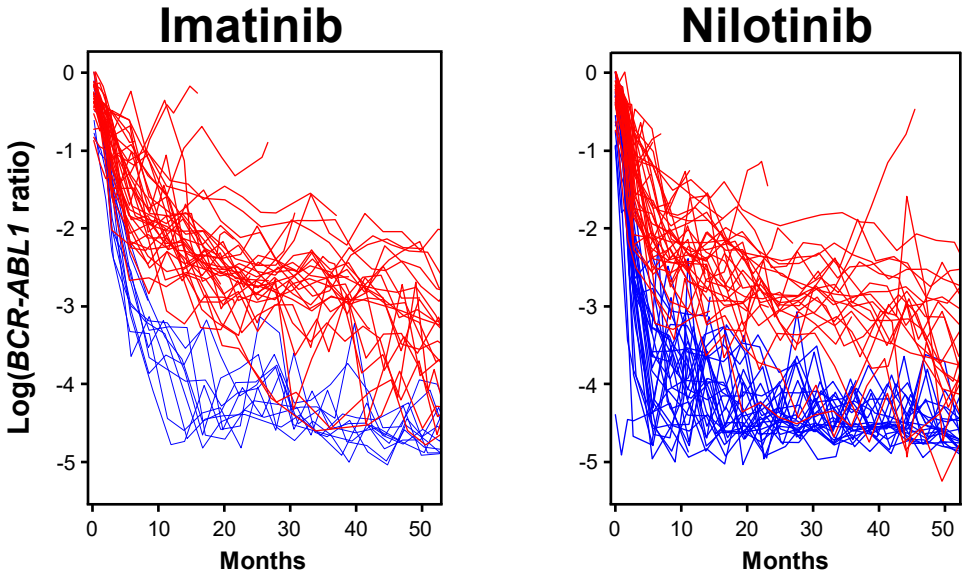
Baccarani, et al. Blood 2013 Aug 8; 122(6): 872-84
Hochhaus, et al. Leukemia 2020; 34: 966–984

Gene expression profiling at baseline (N=112)



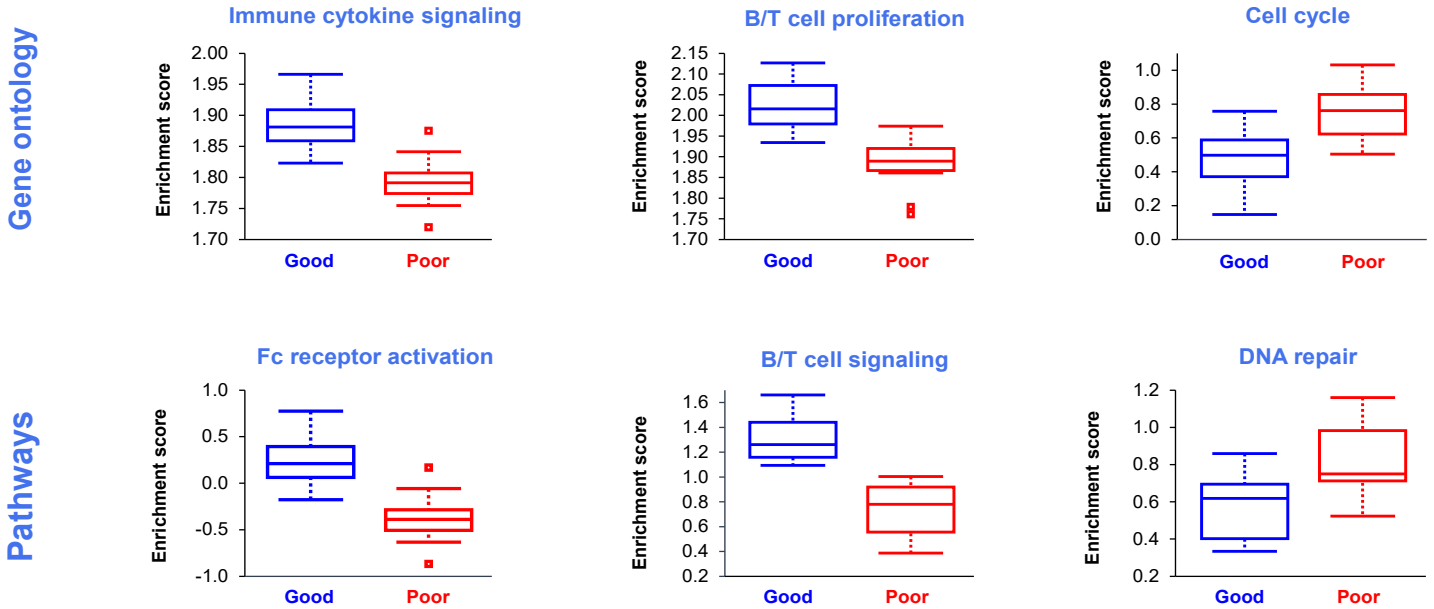
Good responders:
Patients having achieved MMR by 12 months

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

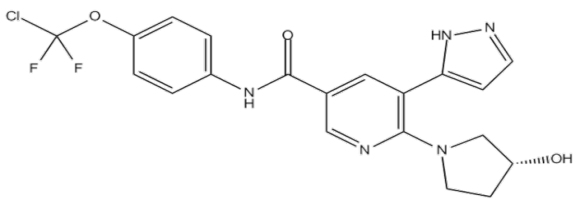
Pathway Clustering Validated Prediction



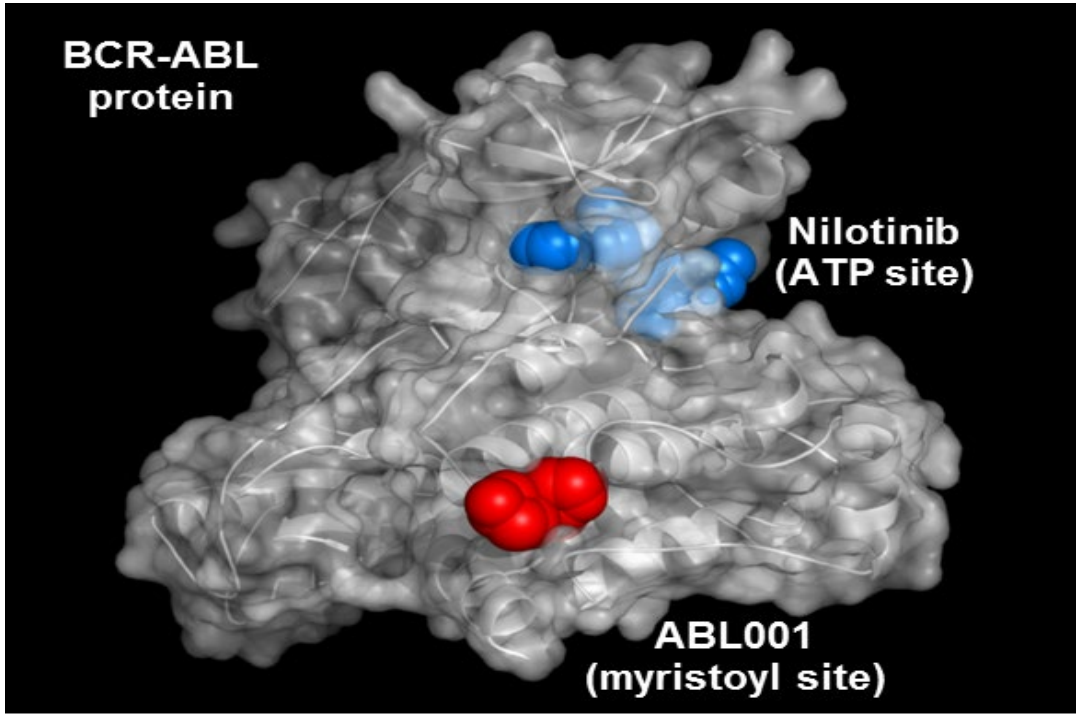
Multiple pathways associated with immune response were found to be predictive of good response

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

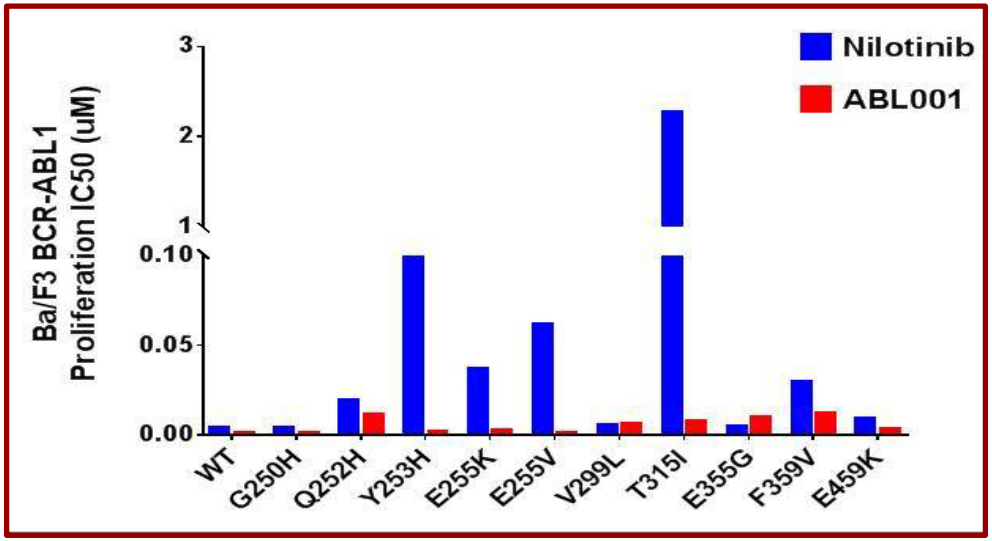
Asciminib (ABL001) Is a Potent, Specific Inhibitor of BCR-ABL1 with a Distinct Allosteric Mechanism of Action



- Developed to gain potent BCR-ABL1 inhibition
- Maintain inhibition against BCR-ABL1 mutations that confer resistance to TKIs
- Combine with TKIs to prevent emergence of BCR-ABL1 mutations and to increase the depth of molecular response in a greater number of patients compared with single-agent treatment



In contrast to nilotinib, ABL001 maintained activity against all BCR-ABL constructs, regardless of mutation, at concentrations below 50 nM.



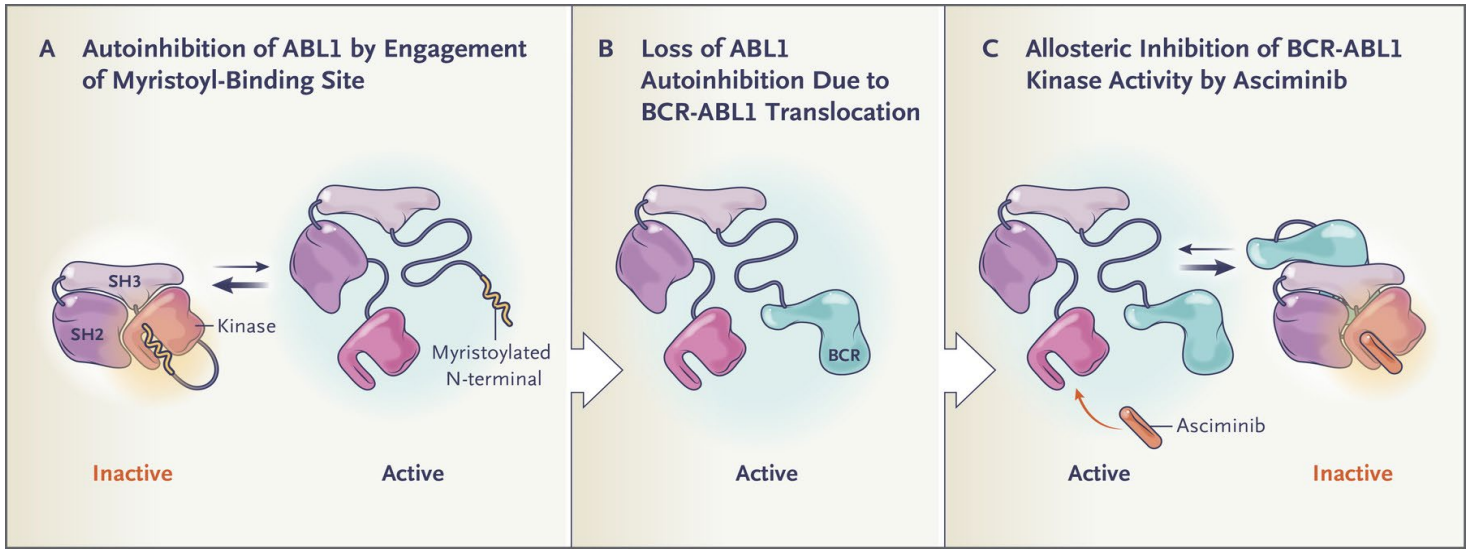
ABL001 inhibited the proliferation of cells with a T315I mutation in the low nanomolar range; in contrast, nilotinib was inactive at concentrations up to 10 μM.

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,



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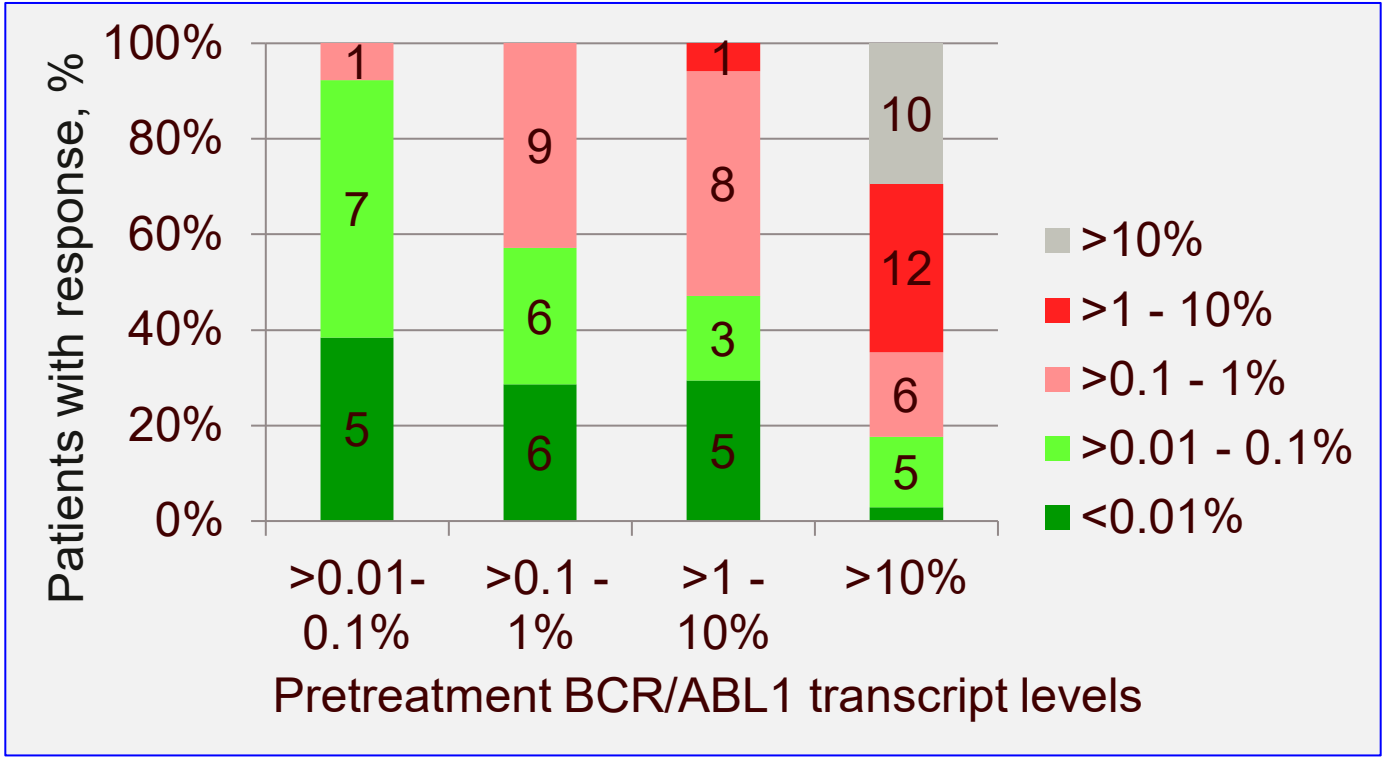
N Engl J Med 2019; 381: 2315-26

Shift in molecular responses from baseline after 12 months of asciminib (85 chronic phase patients without T315I mutations)



Hughes et al. N Engl J Med 2019

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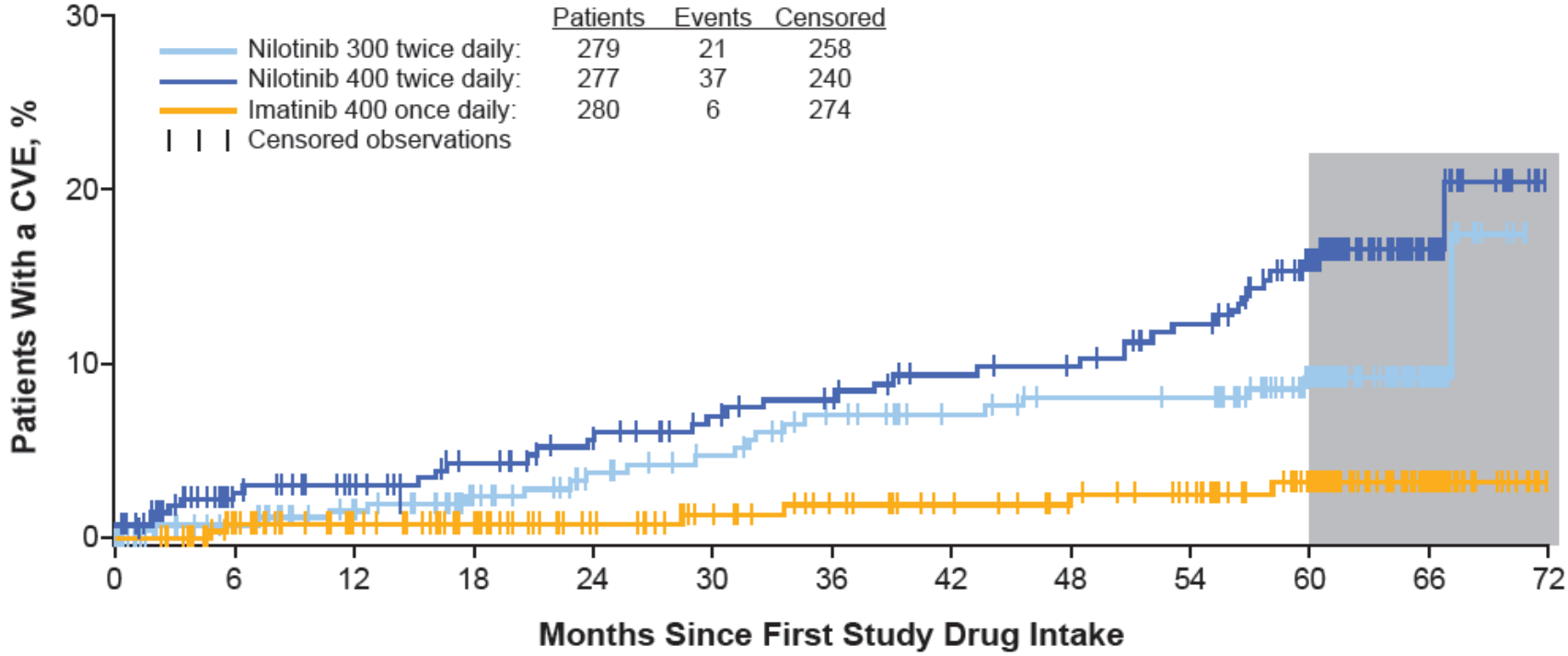
Can TKI therapy ever be reduced or discontinued?

Incidence of Adverse Vascular Events on ENESTnd



Hochhaus et al. ENESTnd. Leukemia 2016

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)

Cumulative incidence of deep molecular response (MR4 and MR4.5) 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

De-escalation of tyrosine kinase inhibitor dose in patients with CML with stable major molecular response (DESTINY)

- CML in first chronic phase who had received TKI for ≥ 3 years
- Either in stable MR4 (BCR-ABL1:ABL1 transcripts <0.01%) or in stable MMR (consistently <0.1%) for 12 months or longer.
- Patients decreased to half their standard TKI dose (imatinib 200 mg daily, dasatinib 50 mg daily, or nilotinib 200 mg twice daily) for 12 months.
- Molecular recurrence was defined as loss of MMR on two consecutive samples.

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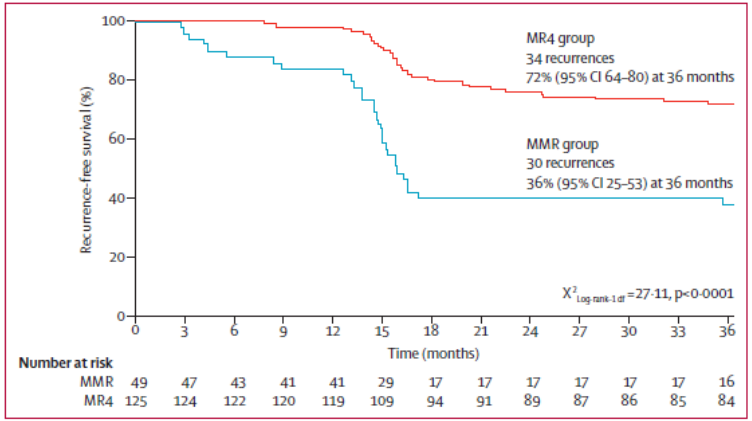
Richard E. Clark et al. Lancet Haematology 2019

De-escalation of tyrosine kinase inhibitor dose in CML with stable major molecular response (DESTINY)

Relapse-free survival

Red = MR4 group

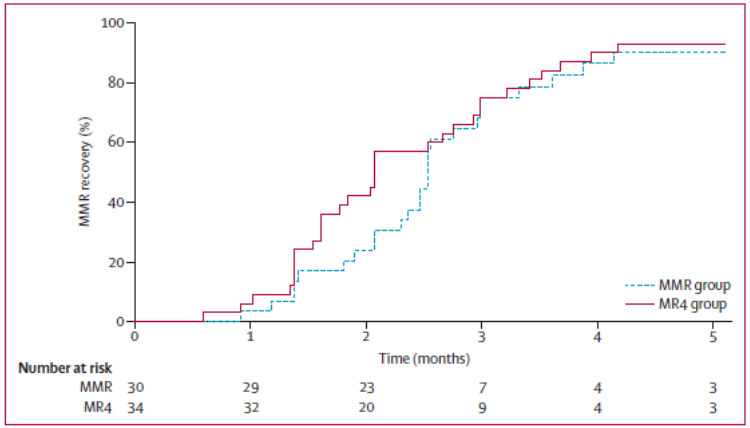
Blue = MMR group



Time to recover MMR

Red = MR4 group

Blue = MMR group



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Richard Clark et al. Lancet Haematol 2019

TFR – warnings!

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

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.
- Identifying which patients can safely stop TKI therapy.
- Developing combination therapies.
- Treating resistant and blast phase disease.