# The promise of stopping TKIs
# Is it ready for prime time?

Ehab Atallah
Associate Professor of Medicine
Medical College of Wisconsin

## Overview

- Why stop tyrosine kinase inhibitors (TKIs)?
- Who can safely stop TKIs?
- How to monitor patients after stopping?
- What is the outcome after stopping?
- When to restart TKIs?
- What next?

# Patient Case

- 67-year-old lady was diagnosed with chronic phase low risk CML in 2008
- Started on a …nib
- Acheived complete cytogenetic remission at 12 months
- PCR for BCR-ABL undetectable since 2012
- Complains of mild fatigue
- Here to discuss stopping therapy

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# Why consider stopping?

- TKI therapy is associated with reduced QOL
- High cost to patient and society
- Some patients may not require lifelong TKIs
- Children and adolescents:
  - Substantial growth abnormalities
  - Effect on pregnancy/fertility
  - Cardiovascular toxicity and thyroid dysfunction

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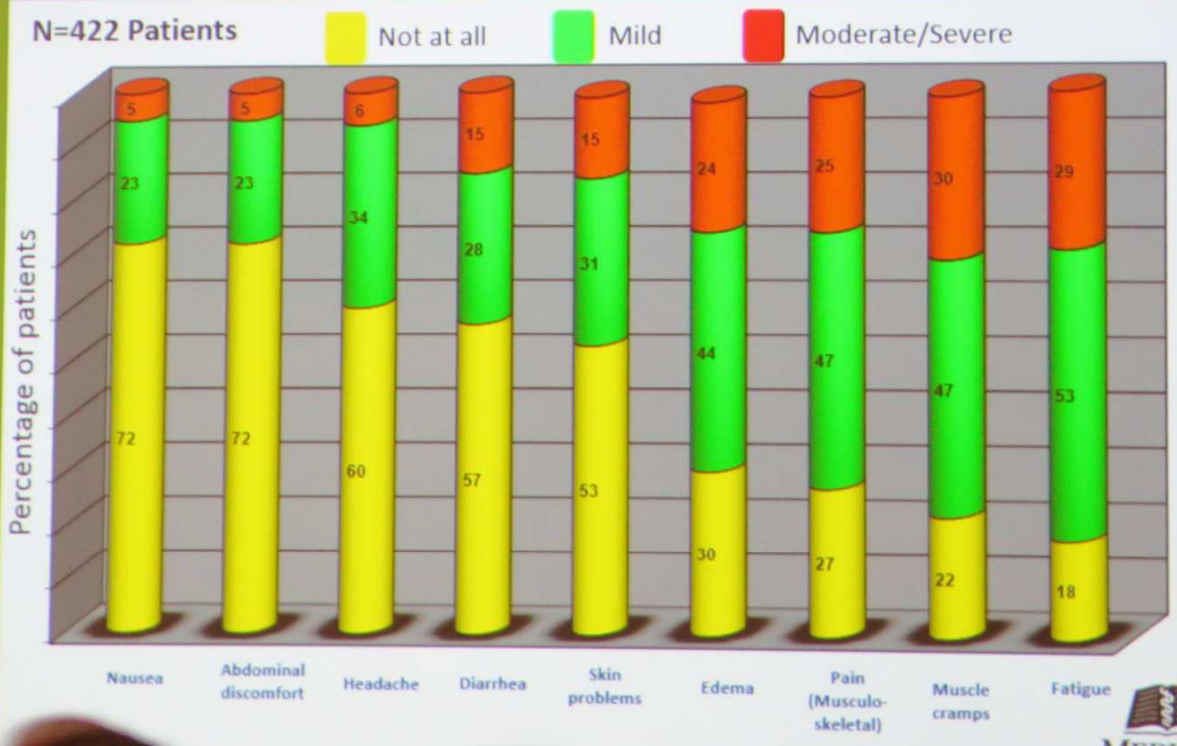
## Patient-Reported Symptom Prevalence in CML Patients Treated with Long-term Imatinib

Duration of imatinib treatment: 5 years (median)




...io Efficace. Blood. 118:4554

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# Price of Drugs

*"Apparently you collapsed when told the price of these ..."*

| Drug | Annual price estimate |
|---|---|
| Imatinib | $ 92,000 |
| Nilotinib | $ 115,500 |
| Dasatinib | $ 123,500 |
| Bosutinib | $ 180,000 |
| Ponatinib | $ 348,000 |

Blood 2013

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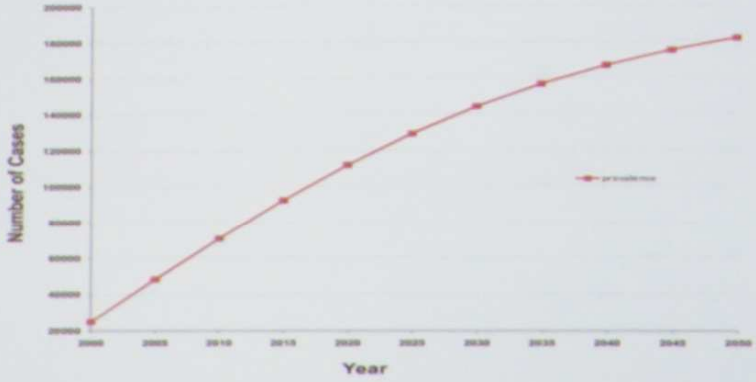
# CML Prevalence in the US




- By 2050 the prevalence of CML will plateau at 180,000
- Current prevalence ≅ 30,000 patients
- Current annual cost of TKIs ≅ $100,000
- Annual cost of drugs in the US ≅ $3,000,000,000

Huang X et al. Cancer. 2012 June 15; 118(12): 3123–3127.

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# Is TKI Therapy Forever?

- STIM trial
  - RFS after discontinuation of imatinib, N = 100
    - 6-mo: 45%, 12 mo: 43%, 24 mo: 41%


Mahon FX, et al. *Lancet Oncol.* 2010;11(11):1029-1035.

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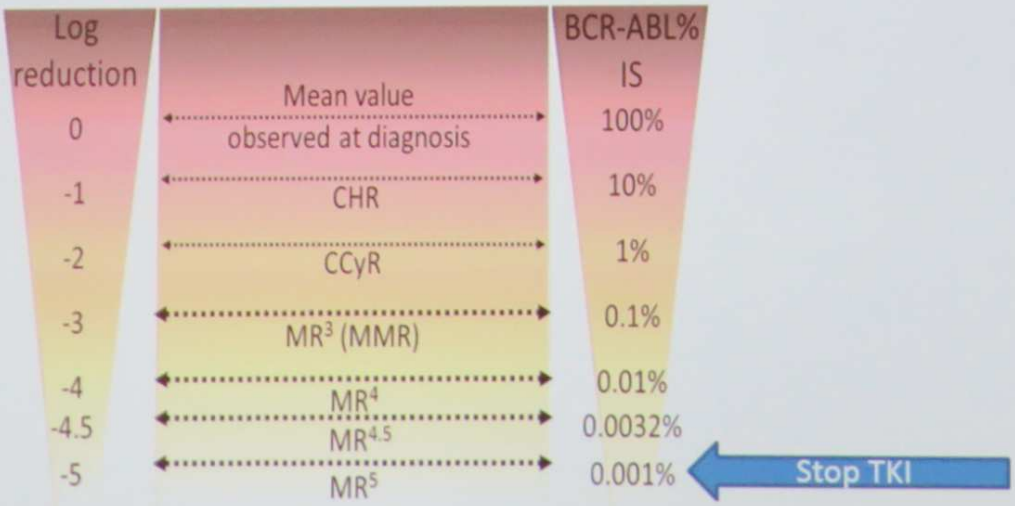
# Depth of Response




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

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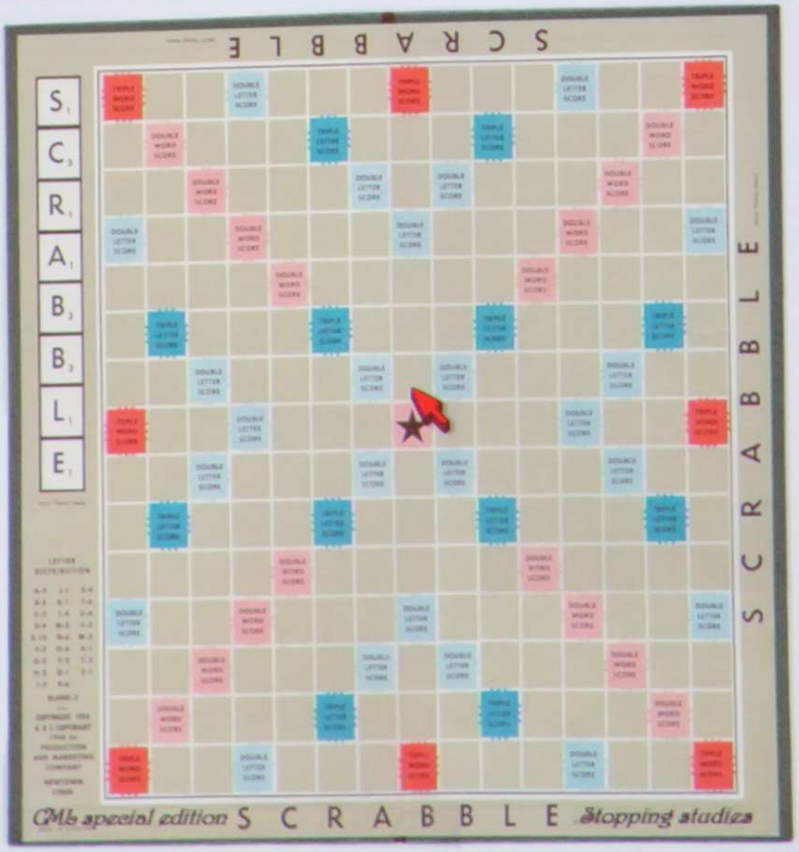


> 2000 patients enrolled on stopping studies

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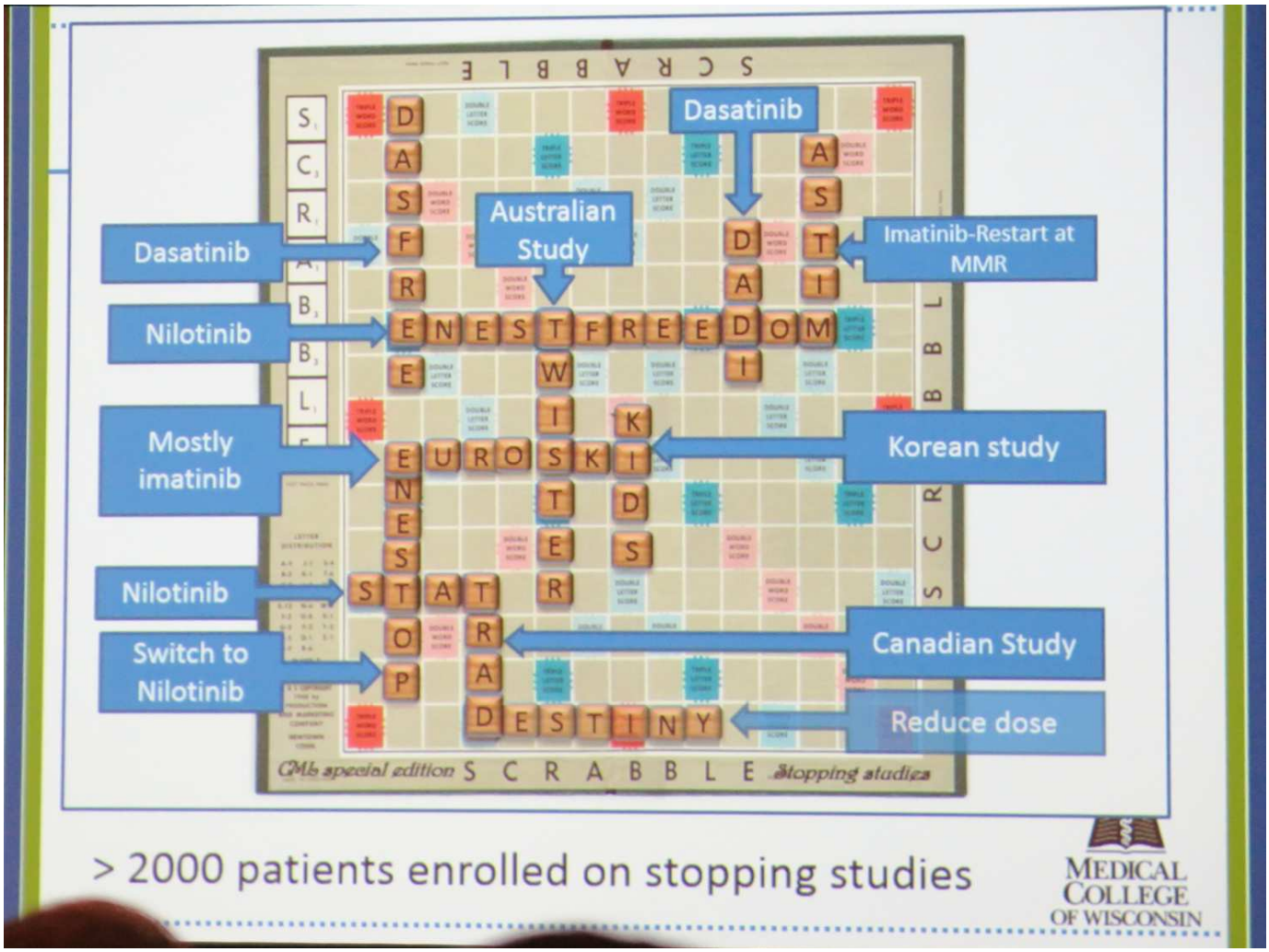
Dasatinib
Australian Study
Dasatinib
Imatinib-Restart at MMR
Nilotinib
Mostly imatinib
Korean study
Nilotinib
Switch to Nilotinib
Canadian Study
Reduce dose
GMs special edition S C R A B B L E Stopping studies
> 2000 patients enrolled on stopping studies
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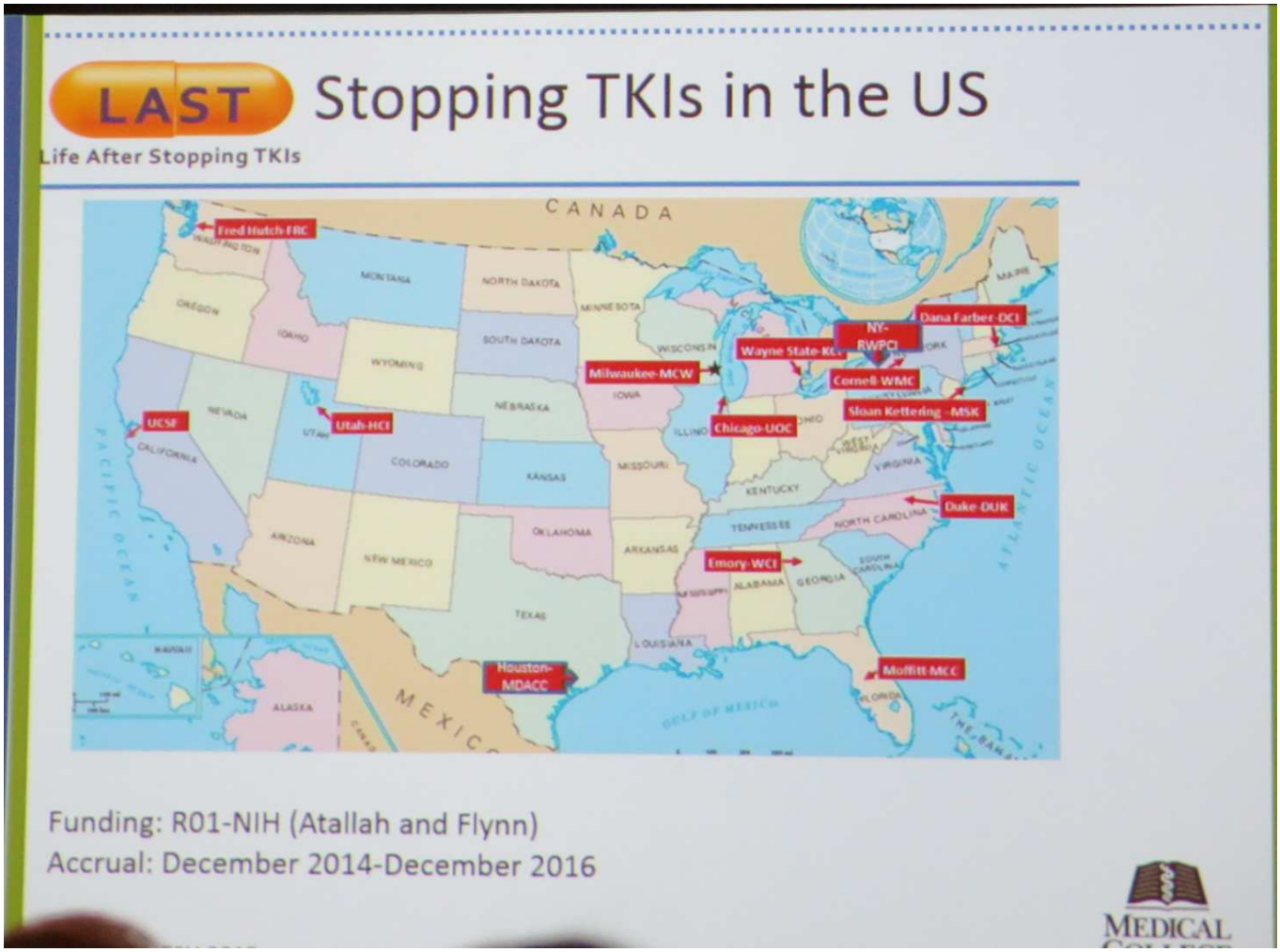
LAST
Stopping TKIs in the US
Life After Stopping TKIs
CANADA
Fred Hutch-FRC
Dana Farber-DCI
NY-RWPCI
Wayne State-KC
Milwaukee-MCW
Cornell-WMC
Sloan Kettering -MSK
UCSF
Utah-HCI
Chicago-UOC
Duke-DUK
Emory-WCI
Houston-MDACC
Moffitt-MCC
Funding: R01-NIH (Atallah and Flynn)
Accrual: December 2014-December 2016
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# Who Can be Considered For Stopping TKIs?

- Chronic phase CML
- Duration of TKI: at least 3 years
- Duration of low level BCR-ABL by PCR: 1-2 years
- Depth of response: at least $MR^4$


Ross DM, et al. ASH Annual Meeting abstracts 2013.
Mahon FX et. ASH Annual Meeting abstracts 2016
Pfirrmann M et al. ASH Annual Meeting abstracts 2016
Chat SY et al. ASH Annual Meeting abstracts 2013.
al JCO 2013


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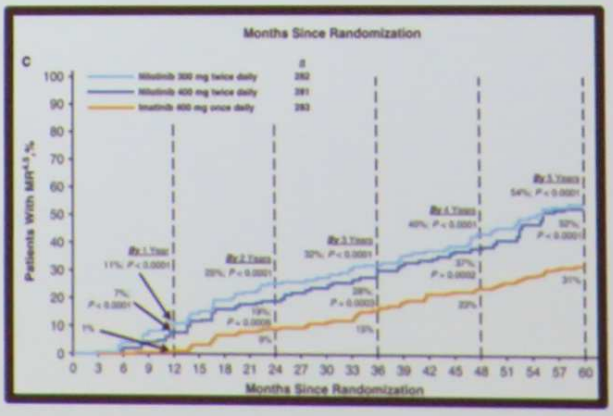
# Cumulative Incidence of $MR^{4.5}$

- DASISION (Dasatinib vs. Imatinib)
- ENESTnd (Nilotinib vs. Imatinib)
- 30-50% of patients would achieve $MR^{4.5}$



Hochhaus A et al. Leukemia 2016 May;30(5):1044-54
Cortes J et al. J Clin Oncol 2016 Jul 10;34(20):2333-40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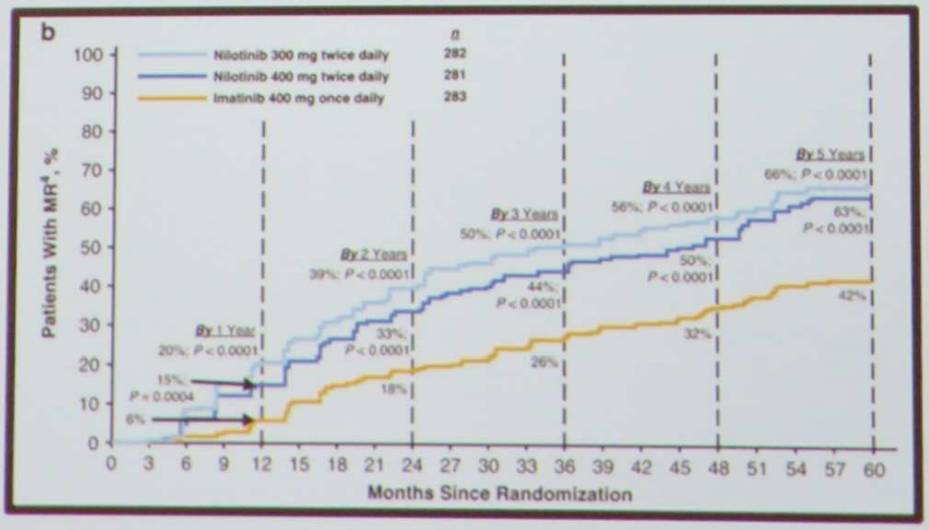
# Cumulative Incidence of MR$^4$

- ENESTnd (Nilotinib vs. Imatinib)
- 40-60% of patients achieve MR$^4$




Hochhaus A et al. Leukemia 2016 May;30(5):1044-54

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# Patients' Perception

| Patient Characteristics (N=22) | N (%) |
|---|---|
| Men | 9 (40%) |
| Age 65+ | 5 (23%) |
| Ever on imatinib | 18 (82%) |
| Years on TKI, median (range) | 6.75 (2-15) |
| Discussed stopping with doctor | 18 (82%) |
| Stopped TKI | 11 (50%) |
| Do not want to stop TKI | 11 (50%) |

Flynn et al. ESH 2016

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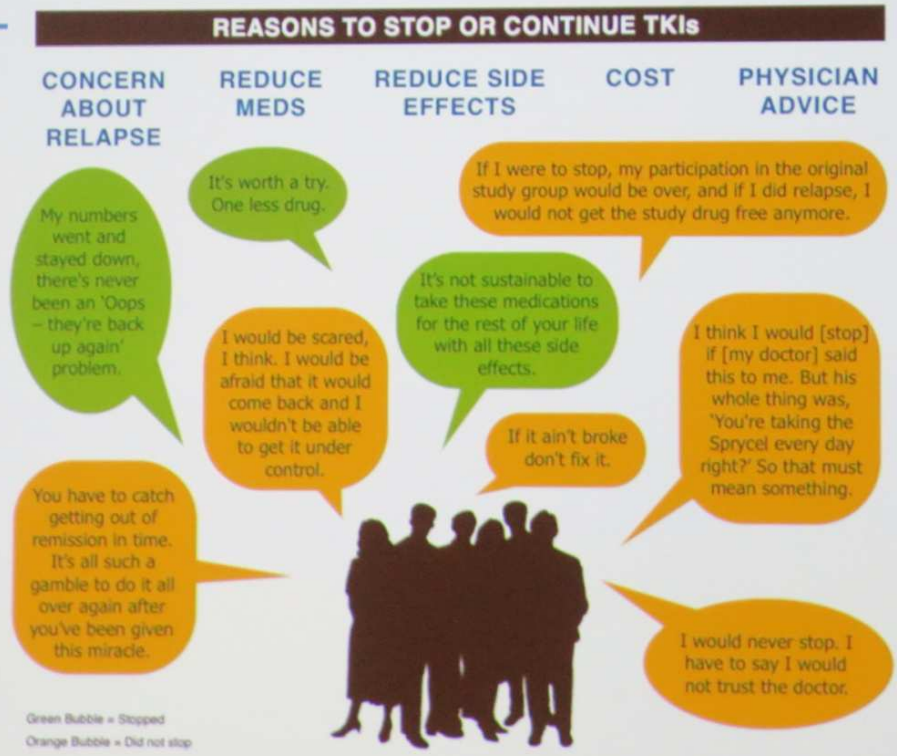
# Patients' Perceptions




Courtesy of Dr. Flynn. ESH 2016

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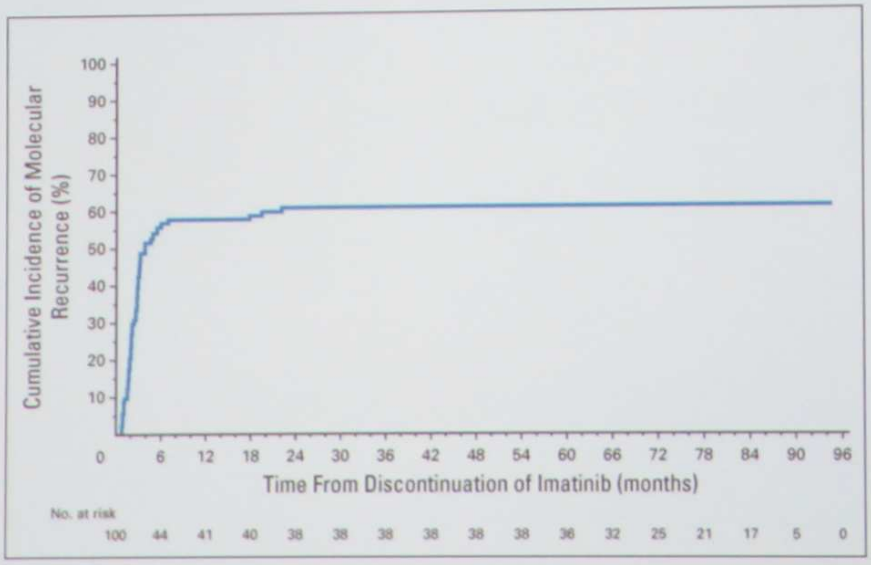
# Monitoring




- Monthly for first 6 months
- Every 2 months for 18 months
- Every 3 months thereafter

Etienne G et al. J Clin Oncol.2017 Jan 20;35(3):298-305.

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# Outcome of Select Discontinuation Studies

| Study | # | TKI | RFS % (years) |
|---|---|---|---|
| STIM1 | 100 | IFN/Imatinib | 38 (7) |
| TWISTER | 40 | Imatinib | 45 (3.5) |
| STIM2* | 124 | Imatinib | 46 (2) |
| KIDS** | 78 | Imatinib | 58 (2) |
| Euro-SKI | 750 | Imatinib | 52 (2) |
| Dasfree | 130 | Dasatinib | 63 (1) |
| ENESTfreedom | 190 | Nilotinib | 52 (4) |

*No prior therapy with IFN, **21 patients had prior HCT


Etienne G et al. J Clin Oncol.2017
Ross et al. Blood 2013 122:515-522
Mahon FX, *et al.* ASH Annual Meeting abstracts 2013
Lee SE et al. Am J Hematology. 2013;88:449-454
Mahon FX, *et al.* ASH Annual Meeting abstracts 2016
Shah N et al. ASH Annual Meeting abstracts 2016
Hochhaus A et al. ASH Annual Meeting abstracts 2016


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# When to Restart?

- STIM1 and STIM 2: Loss of MMR or ≥ 1 log increase in BCR-ABL
- TWISTER: Loss or MMR or two consecutive samples positive at any value
- A-STIM, LAST, EURO-SKI: Loss of MMR
- KIDS: Confirmed loss of MMR


Ross DM, et al. ASH Annual Meeting abstracts 2013.
Mahon FX, *et al.* ASH Annual Meeting abstracts 2013
Mahon FX, *et al.* ASH Annual Meeting abstracts 2016
Atallah et al. ESH 2015
Choi SY et al. ASH Annual Meeting abstracts 2013.
Rousselot P et al JCO 2013


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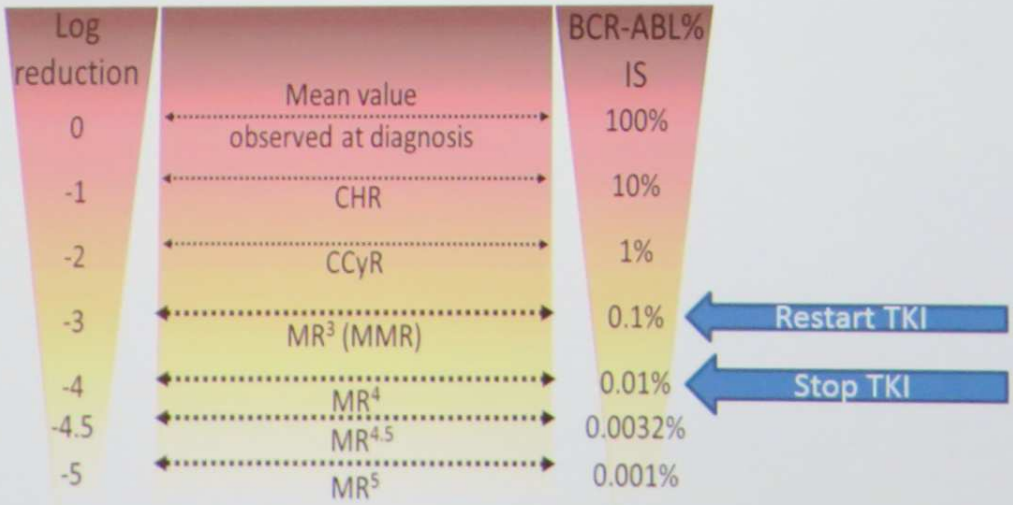
# Restart




carani M et al. Am Soc Cli... Book. 2014:167-75

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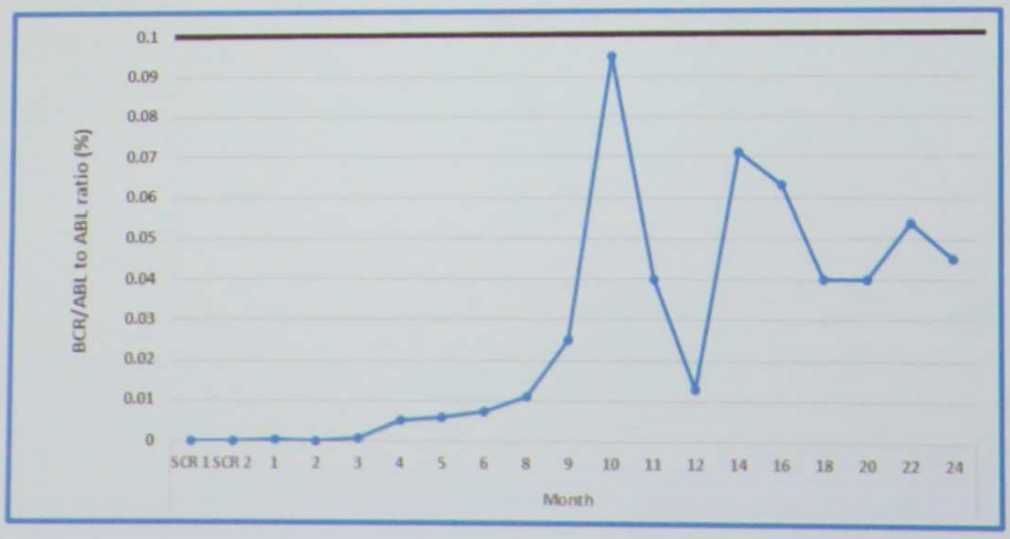
# When to Restart?




Restart

Patient from LAST study, unpublished data

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# Withdrawal Syndrome

- TKI withdrawal syndrome:
  - Musculoskeletal pain/joint pain
  - 30% of patients
  - Median duration 6 months
  - Less likely to relapse

Lee et al. Haematologica. 2016 Jun;101(6):717-23.
Richter et al. J Clin Oncol. 2014;32(25):2821–2823.

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# Predictors of Molecular Relapse

- Sokal risk
  - High vs. low
- Duration of TKI
  - > 5.8 vs. ≤ 5.8 years.
- Age
  - Older vs. Younger

Ilander M et al. Leukemia. 2017 May;31(5):1108-1116
Etienne G et al. J Clin Oncol.2017 Jan 20;35(3):298-305
Mahon FX, *et al.* ASH Annual Meeting abstracts 2016

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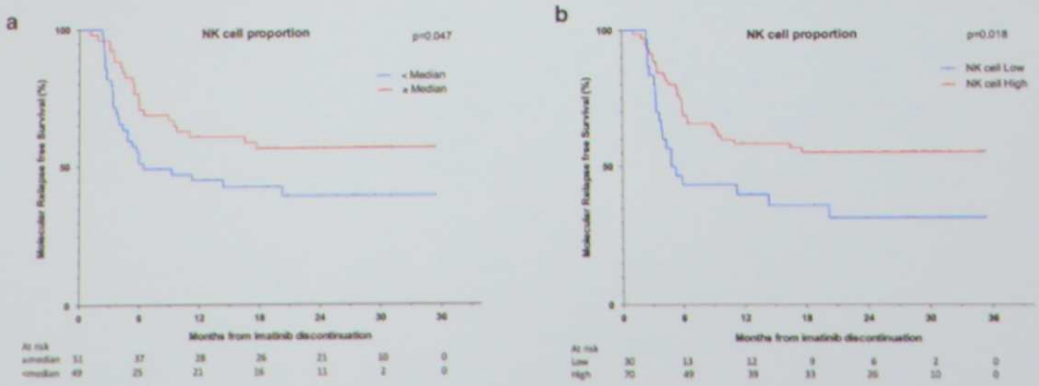
# Predictors of Molecular Relapse
# NK cell number




Ilander M et al. Leukemia. 2017 May;31(5):1108-1116.

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# Additional pre-requisites for stopping TKI

- Patient involvement
- Multi-team approach with a designated healthcare provider to permit effective communication with patients
- Clinical team that understands/interprets IS reports

Courtesy of Dr. Jean Khoury

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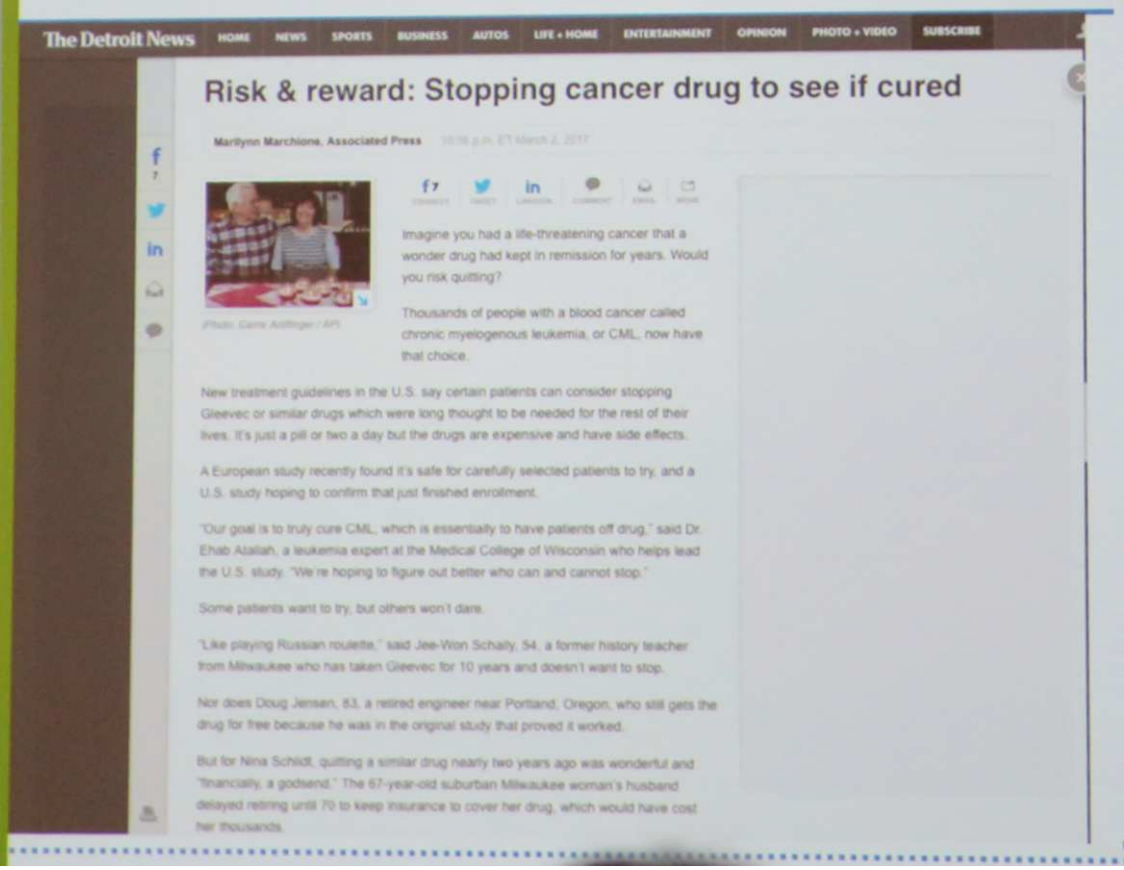
# Patient Case Continued



The Detroit News HOME NEWS SPORTS BUSINESS AUTOS LIFE + HOME ENTERTAINMENT OPINION PHOTO + VIDEO SUBSCRIBE

## Risk & reward: Stopping cancer drug to see if cured

Marilynn Marchione, Associated Press

Imagine you had a life-threatening cancer that a wonder drug had kept in remission for years. Would you risk quitting?

Thousands of people with a blood cancer called chronic myelogenous leukemia, or CML, now have that choice.

New treatment guidelines in the U.S. say certain patients can consider stopping Gleevec or similar drugs which were long thought to be needed for the rest of their lives. It's just a pill or two a day but the drugs are expensive and have side effects.

A European study recently found it's safe for carefully selected patients to try, and a U.S. study hoping to confirm that just finished enrollment.

"Our goal is to truly cure CML, which is essentially to have patients off drug," said Dr. Ehab Atallah, a leukemia expert at the Medical College of Wisconsin who helps lead the U.S. study. "We're hoping to figure out better who can and cannot stop."

Some patients want to try, but others won't dare.

"Like playing Russian roulette," said Jee-Won Schaily, 54, a former history teacher from Milwaukee who has taken Gleevec for 10 years and doesn't want to stop.

Nor does Doug Jensen, 63, a retired engineer near Portland, Oregon, who still gets the drug for free because he was in the original study that proved it worked.

But for Nina Schildt, quitting a similar drug nearly two years ago was wonderful and "financially, a godsend." The 67-year-old suburban Milwaukee woman's husband delayed retiring until 70 to keep insurance to cover her drug, which would have cost her thousands.

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# Summary

- Most patients with CML will do well with current therapy
- Stopping TKIs is ready for prime time
  - A select group of patients
  - With proper monitoring
- Multi-team approach is a key component to the success and safety of TFR

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NCCN Cancer Network®

## Chronic Myeloid Leukemia

Table of Contents
Discussion

### DISCONTINUATION OF TKI THERAPY

- Discontinuation of TKI therapy appears to be safe in select CML patients.
- Clinical studies that have evaluated the safety and efficacy of TKI discontinuation have employed strict eligibility criteria and have mandated more frequent molecular monitoring than typically recommended for patients on TKI therapy.
- Some patients have experienced significant adverse events that are believed to be due to TKI discontinuation.
- Discontinuation of TKI therapy should only be performed in consenting patients after a thorough discussion of the potential risks and benefits.
- Outside of a clinical trial, TKI discontinuation should be considered only if ALL of the criteria included in the list below are met.

Criteria for TKI Discontinuation

- Age ≥18 years.
- Chronic phase CML. No prior history of accelerated or blast phase CML.
- On approved TKI therapy (imatinib, dasatinib, nilotinib, bosutinib, or ponatinib) for at least three years.
- Prior evidence of quantifiable *BCR-ABL1* transcript.
- Stable molecular response (MR4; ≤0.01% IS) for ≥2 years, as documented on at least four tests, performed at least three months apart.
- No history of resistance to any TKI.
- Access to a reliable QPCR test with a sensitivity of detection of ≥4.5 logs that reports results on the IS and provides results within 2 weeks. Monthly molecular monitoring for the first six months following discontinuation, bimonthly during months 7–24, and quarterly thereafter (indefinitely) for patients who remain in MMR (MR3; ≤0.1% IS).
- Consultation with a CML Specialty Center to review the appropriateness for TKI discontinuation and potential risks and benefits of treatment discontinuation, including TKI withdrawal syndrome.
- Prompt resumption of TKI, with a monthly molecular monitoring for the first six months following resumption of TKI and every 3 months thereafter is recommended indefinitely for patients with a loss of MMR. For those who fail to achieve MMR after six months of TKI resumption, BCR-ABL1 kinase domain mutation testing should be performed, and monthly molecular monitoring should be continued for another six months.
- Reporting of the following to a member of the NCCN CML panel is strongly encouraged:
  - Any significant adverse event believed to be related to treatment discontinuation.
  - Progression to accelerated or blast phase CML at any time.

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# Future Directions

- Investigate causes of loss of molecular response
- Determine the mechanism of CVS and other toxicities
- Understand why some patients have persistent detectable disease with no disease progression
- Cure CML
  - Off therapy with no evidence of disease

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# Is Stopping TKI Realistic?

50% achieve MR4 or MR 4.5

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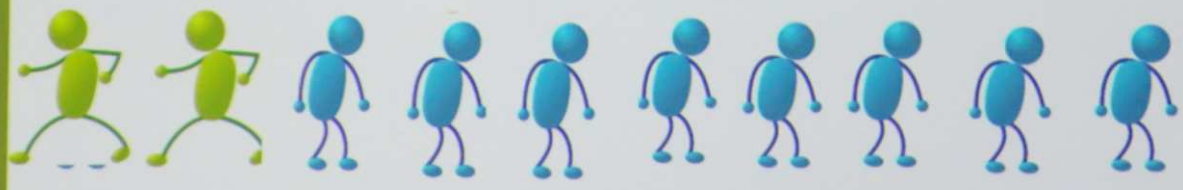
# Is Stopping TKI Realistic?

50% achieve MR4 or MR 4.5



50% restart TKI

70-80% of newly diagnosed patients with CML will need long term TKI therapy

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# The Jean Khoury *Cure CML Consortium*

*"Galvanized by the spectacular collaboration created by the LAST study, the creation of a CML consortium was simply the next logical thing to do"*

Ehab Atallah, MD
Jorge Cortes, MD
Michael Deininger, MD, PhD
Brian Druker, MD
Kathryn Flynn, PhD
Stuart Goldberg, MD
Mary Horowitz, MD
H. Jean Khoury, MD, FACP
Vamsi Kota, MD
Richard Larson, MD
Jeffrey H Lipton, MD, PhD
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Jerald Radich, MD
Javier Pinilla-Ibarz, MD, PhD
Ellen Ritchie, MD
Richard Silver, MD
Charles A. Schiffer, MD
Neil Shah, MD, PhD
James Thompson, MD
Martha Wadleigh, MD

Arielle Baim (Project manager)
Alex Hinman (Multisite manager)
Jessica Guhl (Assistant project manager)
Dan Bullock (Administrative assistant)

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