MAYO CLINIC

# A second and third look at TKI management in CML

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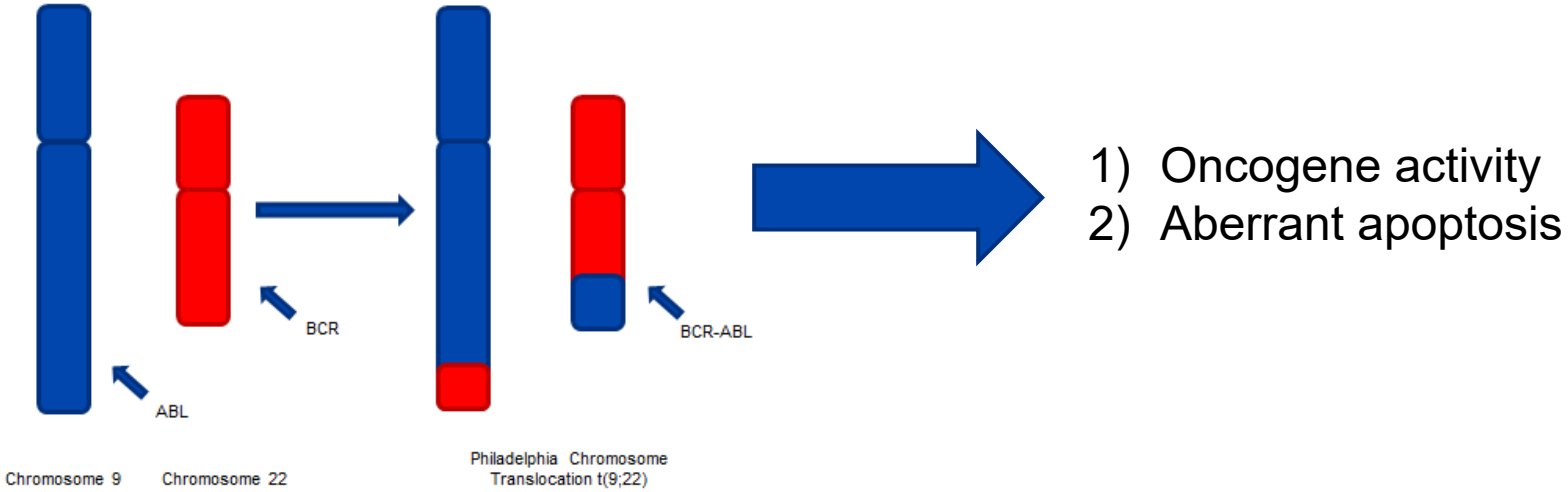
# Objectives

- Compare the safety and efficacy profiles of the tyrosine kinase inhibitors used in the treatment of chronic myeloid leukemia
- Review the data supporting tyrosine kinase inhibitor discontinuation in chronic myeloid leukemia
- Develop an understanding of which patients are appropriate to consider for tyrosine kinase inhibitor discontinuation and the monitoring that is required following discontinuation

# Chronic Myeloid Leukemia (CML)

- **Incidence**
  - Accounts for 15% adult leukemias
  - New cases: 9,000 per year
  - Deaths: 1,000 per year
- **Pathogenesis**

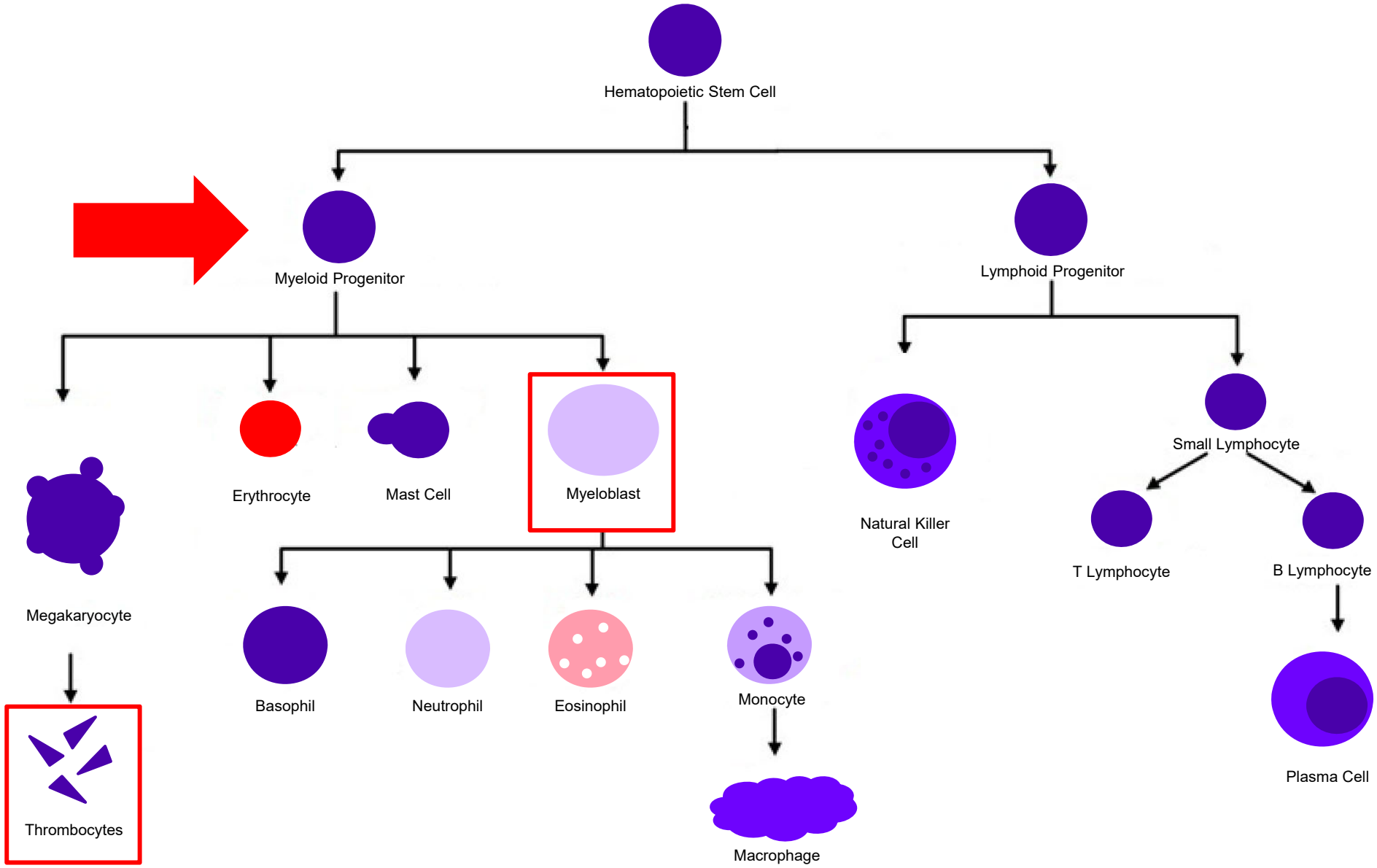



1) Oncogene activity
2) Aberrant apoptosis



Jabbour et al. Am J Hematol. 2018;93:442-459.

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Jabbour et al. Am J Hematol. 2018;93:442-459.

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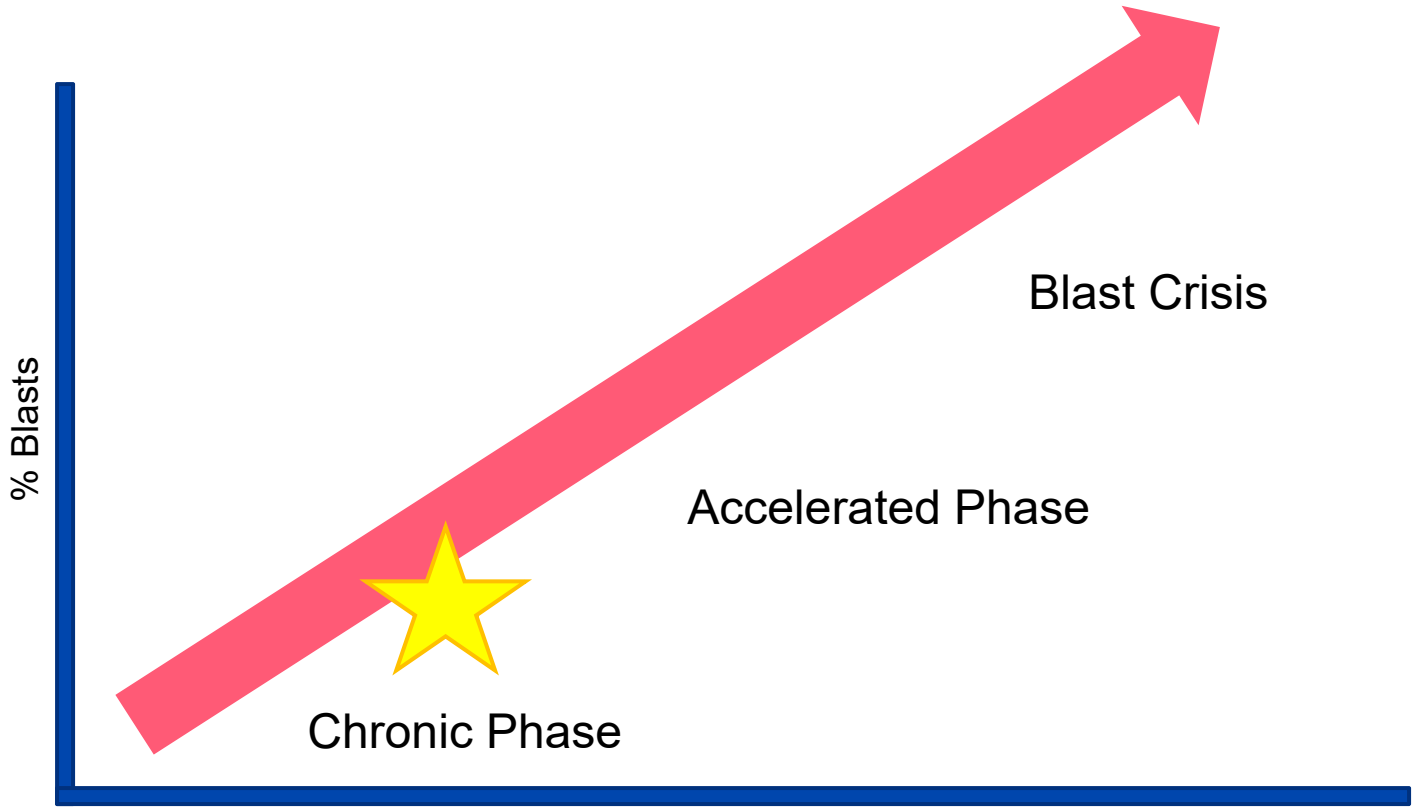
# CML Phases

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Jabbour et al. Am J Hematol. 2018;93:442-459.

# CML Diagnosis

- Peripheral blood:
  - Quantitative BCR-ABL1 PCR
- Bone marrow biopsy:
  - Philadelphia chromosome with t(9,22) identified via cytogenetics testing

**OR**

  - Molecular abnormality BCR-ABL1 identified via FISH testing

FISH = fluorescence in situ hybridization
PCR = polymerase chain reaction

Jabbour et al. Am J Hematol. 2018;93:442-459.

 

# Risk Scoring

## Sokal Score

- Age, spleen, blast cells, platelet count

## Hasford Score

- Age, spleen, blast cells, platelet count, basophils, eosinophils

## EUTOS Score

- Age, spleen, blast cells, platelet count



NCCN. Chronic Myeloid Leukemia. Accessed January 15, 2020.

 

# Cytogenetic Response

| Philadelphia-positive Metaphases (%) | Response |
|---|---|
| 0 | Complete cytogenetic response (CCyR) |
| 0 – 35 | Major cytogenetic response (MCyR) |
| 1 – 35 | Partial cytogenetic response (PCyR) |
| > 35 | Minor cytogenetic response |



Mahon et al. Clin Cancer Res. 2014;20(2):310-322.
NCCN. Chronic Myeloid Leukemia. Accessed January 15, 2020.

 

# Molecular Response

| BCR-ABL1 % | Log Reduction | Level of Response |
|---|---|---|
| 100 | n/a | Baseline |
| 10 | 1 | Approximates MCyR |
| 1 | 2 | Approximates CCyR |
| 0.1 | 3 | MMR |
| 0.01 | 4 | MR 4 |
| 0.0032 | 4.5 | MR 4.5 |
| 0.001 | 5 | MR 5 |
| 0.0001 | 6 | MR 6 |



Mahon et al. Clin Cancer Res. 2014;20(2):310-322.
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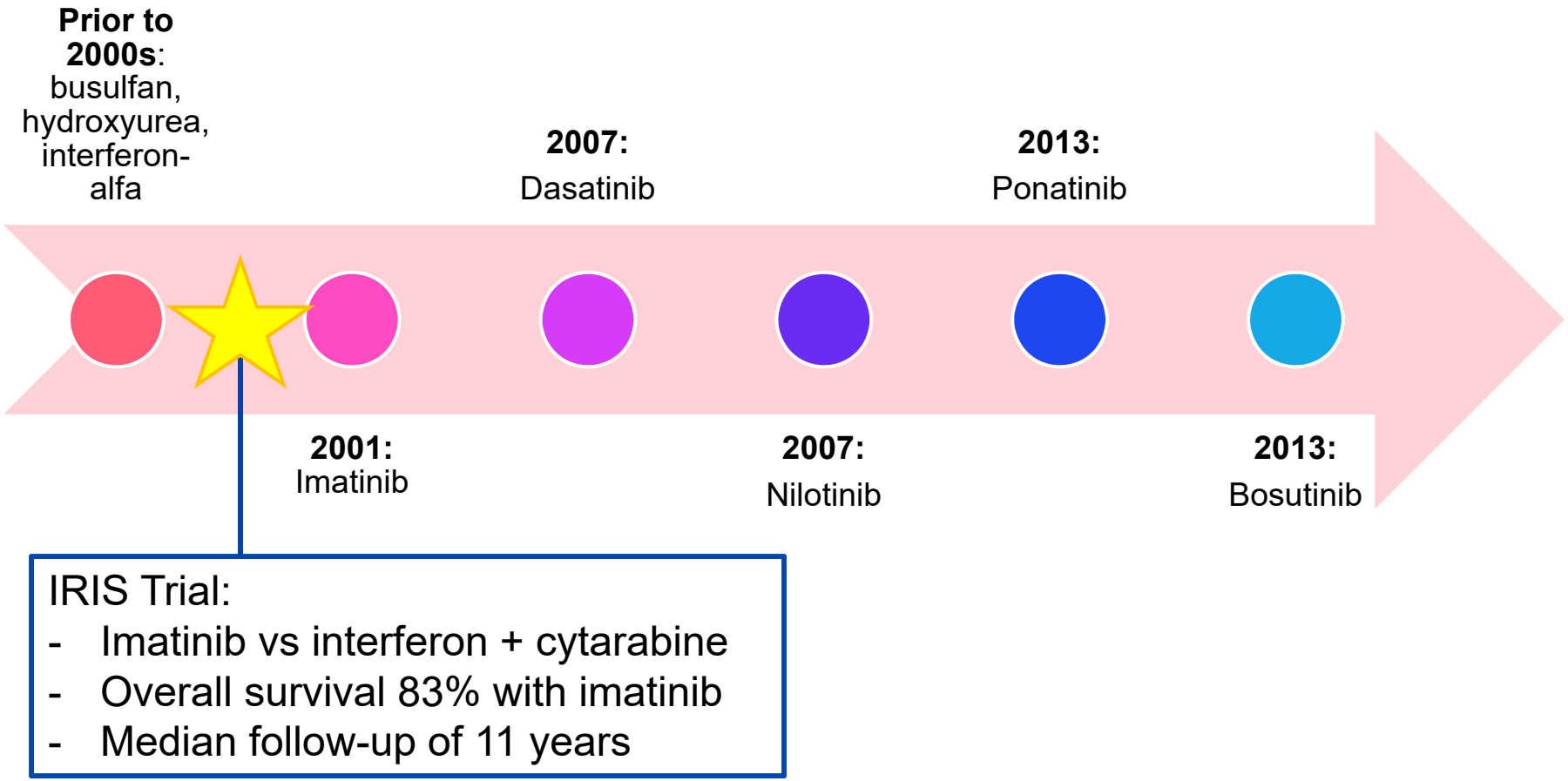
# Treatment Timeline



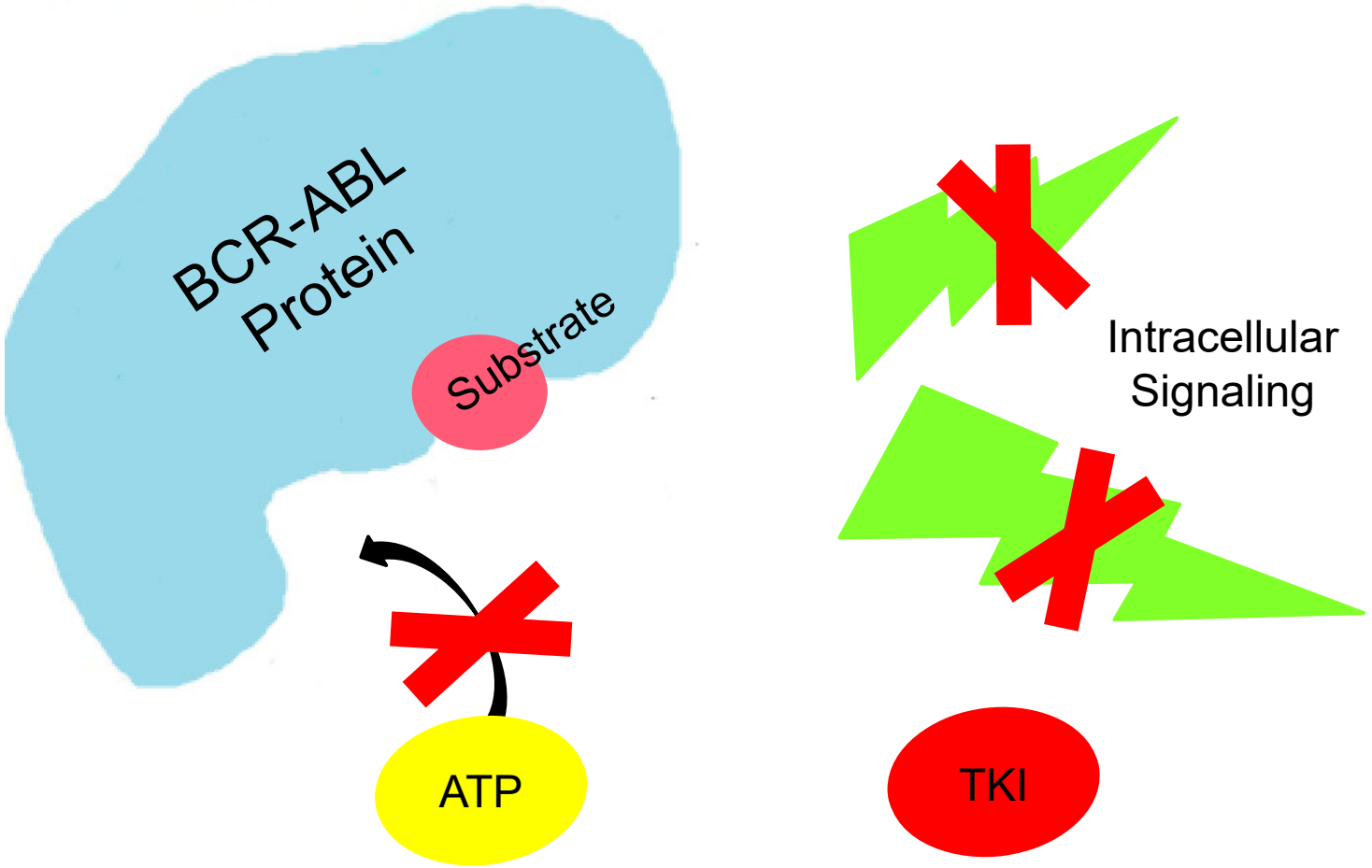

IRIS Trial:
- Imatinib vs interferon + cytarabine
- Overall survival 83% with imatinib
- Median follow-up of 11 years



Hochhaus et al. NEJM. 2017;376(10):917-927.

# Tyrosine Kinase Inhibitors (TKIs)





| | Imatinib | Dasatinib | Nilotinib | Bosutinib | Ponatinib |
|---|---|---|---|---|---|
| **Generation** | 1st | 2nd | 2nd | 2nd | 3rd |
| **Landmark Trial** | IRIS<br>OS 83%<br>CCyR 83% | DASISION<br>OS 91%<br>CCyR 96% | ENESTnd<br>OS 94%<br>CCyR 80% | BFORE<br>(ongoing)<br>CCyR 77% | PACE<br>OS 73%<br>CCyR 60% |
| **Key Toxicities** | Fluid retention, pleural effusions | Pleural and pericardial effusions, pulmonary artery HTN, bleeding | Pancreatitis, metabolic syndrome, QT prolongation | GI intolerance | Arterial occlusion, HTN, venous embolus |
| **Cost per month** | $12,000<br>Generic | $16,000 | $17,500 | $18,000 | $20,000 |
| **Dosing** | 400 mg PO daily w/ food | 100 mg PO daily | 300 mg PO twice daily w/o food | 500 mg PO daily w/ food | 45 mg PO daily |
| **Drug Interactions** | CYP3A4 | CYP3A4, Antacids | CYP3A4, QT prolonging drugs | CYP3A4, Antacids | CYP3A4 |

OS = overall survival, MMR = major molecular response, CCyR = complete cytogenetic response, HTN = hypertension



Cortes et al. J Clin Oncol. 2018;36(3):231-237.
Cortes et al. Blood. 2018;132(4):393-404

# Chronic Phase CML – Treatment Pathway

| Low-risk Score | Intermediate or High-risk Score |
|---|---|
| Imatinib<br>Bosutinib<br>Dasatinib<br>Nilotinib<br><br>Other: clinical trial | Bosutinib<br>Dasatinib<br>Nilotinib<br><br>Other: imatinib, clinical trial |

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NCCN. Chronic Myeloid Leukemia. Accessed January 15, 2020.

 

# Chronic Phase CML – Response

| BCR-ABL1 | 3 months | 6 months | 12 months | ≥ 15 months |
|---|---|---|---|---|
| > 10% | YELLOW | RED | | |
| 1-10% | GREEN | | YELLOW | RED |
| ≤ 1% | GREEN | | | |

| Color | Status | Treatment |
|---|---|---|
| RED | TKI-Resistant | • Change TKIs<br>• Evaluate for transplant |
| YELLOW | Possibly TKI-Resistant | • Change TKIs<br>• Continue TKI (if imatinib, increase dose)<br>• Consider transplant |
| GREEN | TKI-Sensitive | • Continue TKI |

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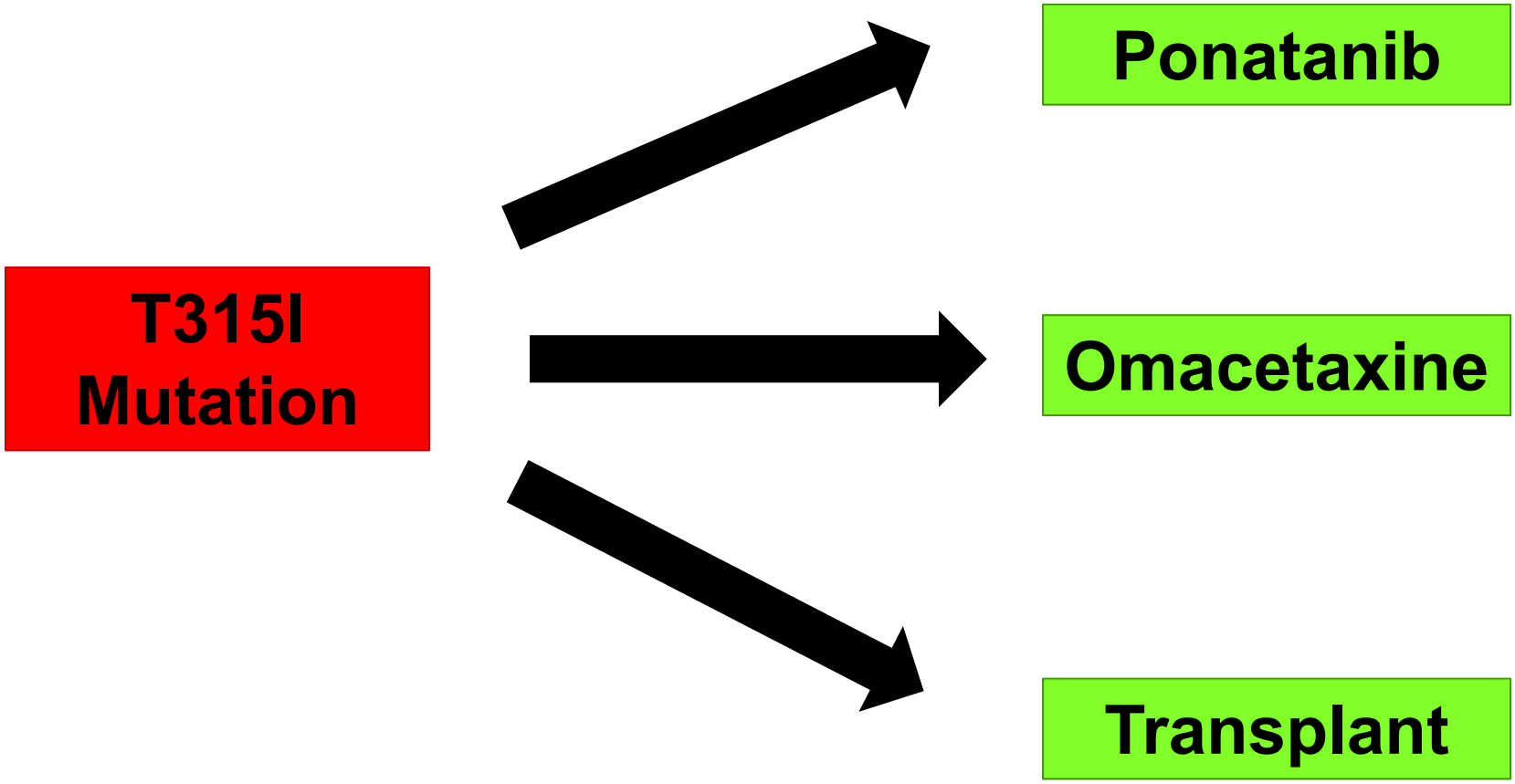
NCCN. Chronic Myeloid Leukemia. Accessed January 15, 2020.

# TKI Resistance






NCCN. Chronic Myeloid Leukemia. Accessed January 15, 2020.

# Advanced Phases – Treatment Pathway

| Accelerated Phase | Blast Phase |
|---|---|
| Clinical trial<br>Bosutinib<br>Dasatinib<br>Nilotinib<br>Ponatinib<br><br>Other: imatinib, omacetaxine | **Lymphoid:**<br>Clinical trial<br>ALL-type chemotherapy<br>TKI<br><br>**Myeloid:**<br>Clinical trial<br>AML-type chemotherapy<br>TKI |

ALL = acute lymphoblastic leukemia
AML = acute myeloid leukemia

NCCN. Chronic Myeloid Leukemia. Accessed January 15, 2020.

# Upcoming TKI – Asciminib

- Novel binding site locking BCR-ABL protein into an inactive confirmation

Phase I dose-escalation study

N = 141, chronic or accelerated phase CML with resistance or unacceptable side effects from at least two previous TKIs

MMR achieved or maintained by 12 months in 48% of patients who could be evaluated (including those with resistance or intolerance to ponatinib) with a dose limiting toxicity of pancreatitis

MMR = major molecular response

Hughes et al. NEJM. 2019;381:2315-2326.

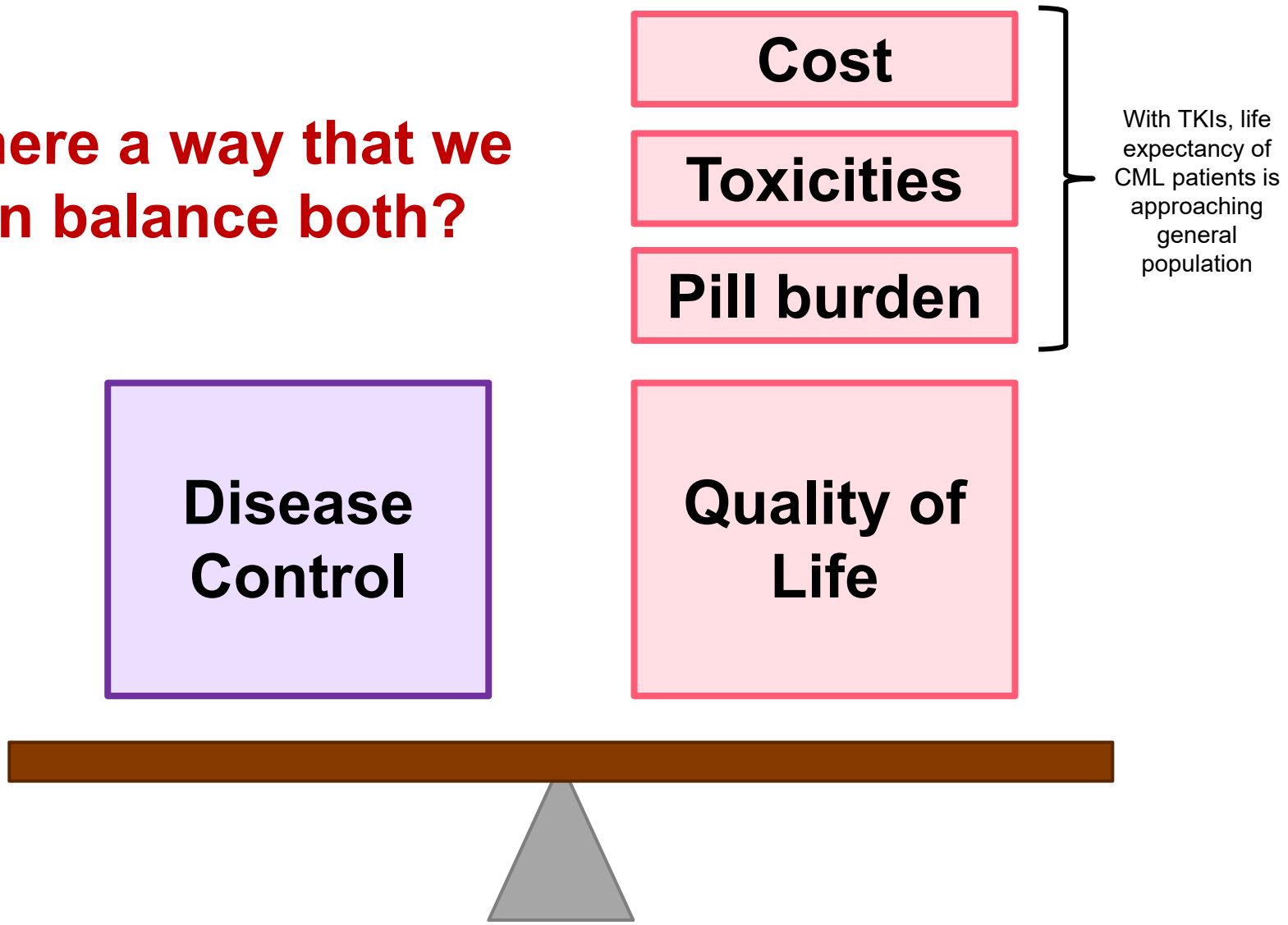
# Poll Everywhere Question #1

A 38 year old female is incidentally found to have an elevated WBC and is diagnosed with CML with intermediate score features. Which of the following treatment options is most appropriate?

1. Interferon alpha
2. Imatinib
3. Dasatinib
4. Ponatinib

## Is there a way that we can balance both?

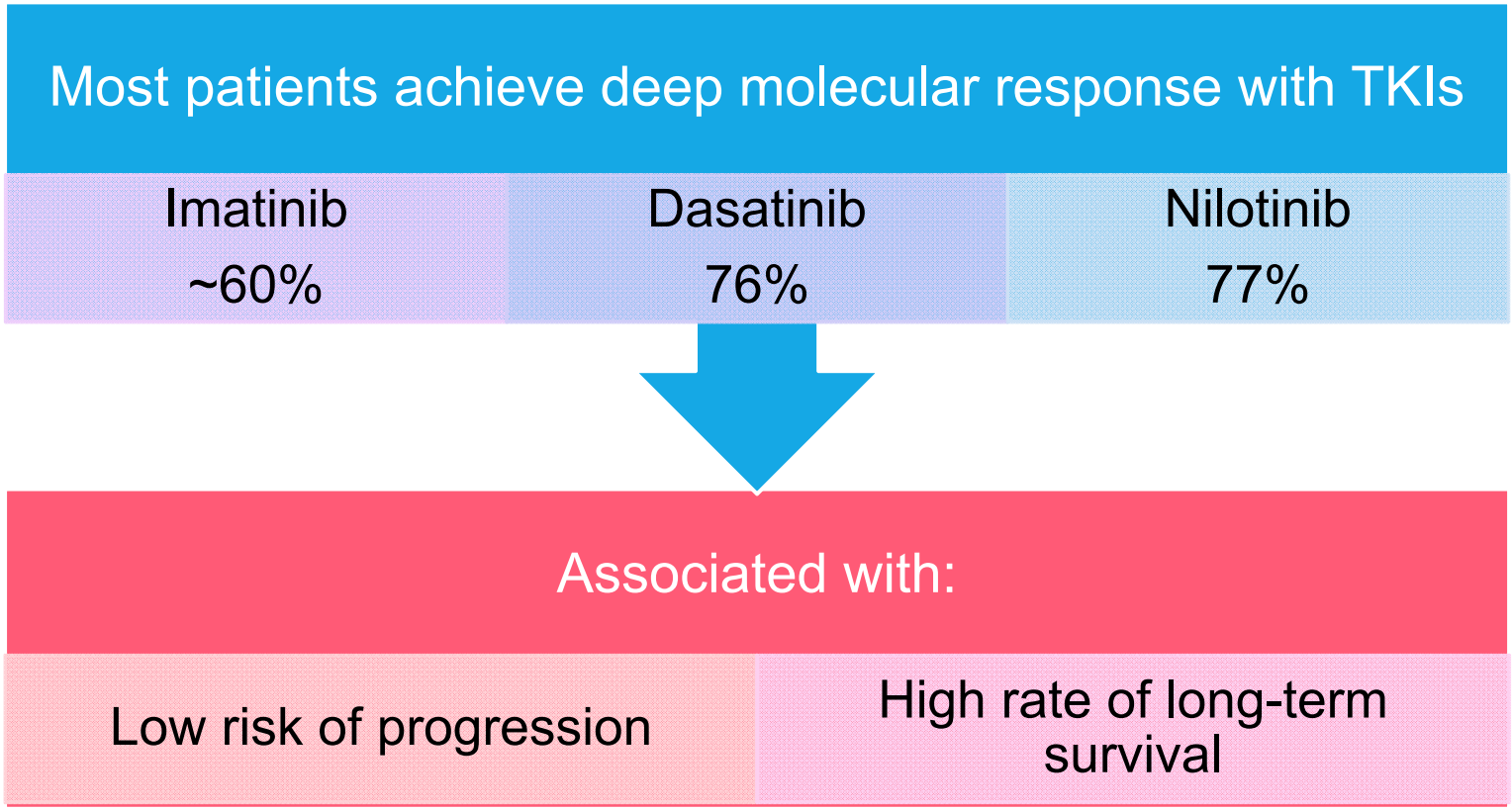



Bower et al. J Clin Oncol. 2016;34(24):2851-2858.



# TKI Discontinuation






Hughes et al. Blood. 2010;116:3758-3765.
Hehlmann et al. J Clin Oncol. 2014;32:415-423.

# STIM Discontinuation Trial

## Design

- Prospective
- Multicenter
- Non-randomized
- Single-arm
- Open-label
- N = 100

## Inclusion

- Adults ≥18 years of age
- Ph(+) CML in chronic or accelerated phase
- Imatinib ≥3 years
- May have received previous treatment
- MR of 5.0, sustained CMR ≥2 years

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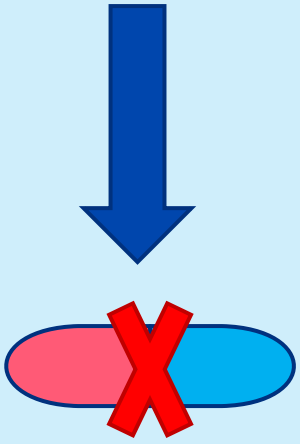
Ph(+) = philadelphia chromosome positive
MR = molecular response
CMR = complete molecular response

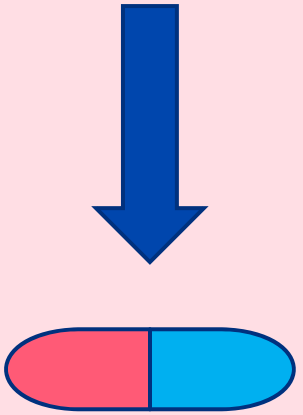
Mahon et al. Lancet Oncol. 2010;11(11):1029-1035.
Etienne et al. J Clin Oncol. 2017;35(3):298-305.

# STIM Discontinuation Trial

| Study Intervention | Monitoring | Response to Monitoring |
|---|---|---|
| **Imatinib ≥ 3 years**<br>**MR 5.0 x 2 years** | **Monthly**<br>**1 year** | **Loss of MR 5.0** |
| | **Every two months**<br>**1 year** | |
| | **Every three months**<br>**Indefinitely** | |





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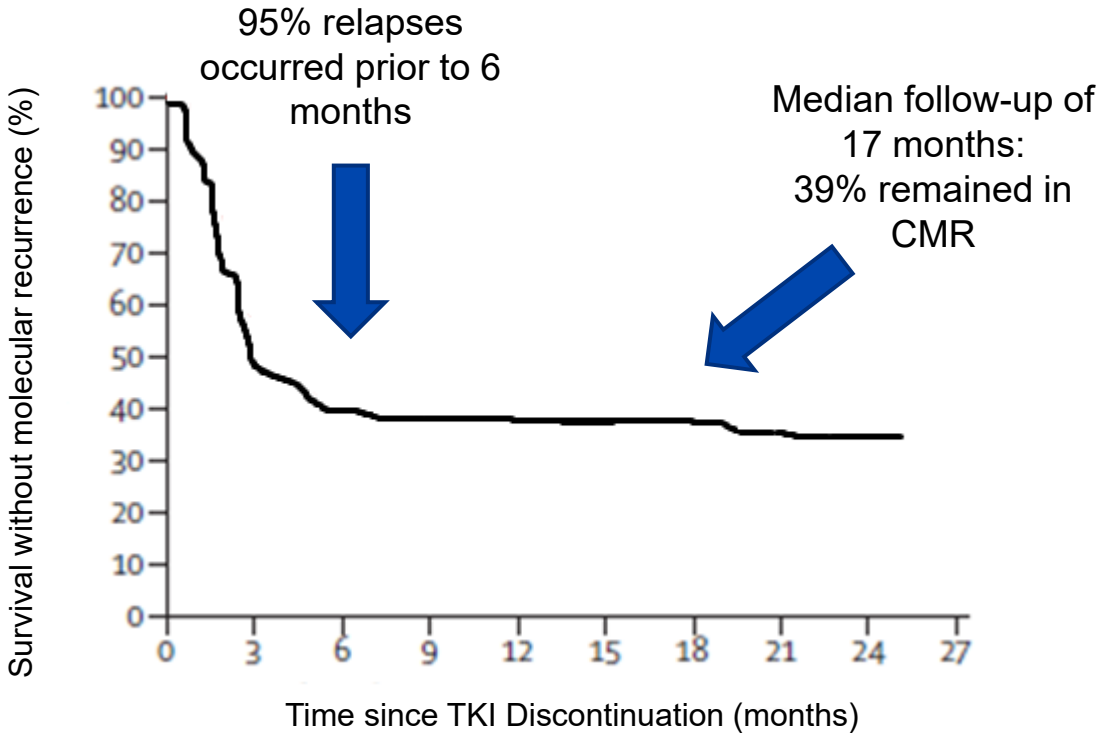
MR = molecular response

Mahon et al. Lancet Oncol. 2010;11(11):1029-1035.
Etienne et al. J Clin Oncol. 2017;35(3):298-305.

# STIM Discontinuation Trial – Interim




Univariate analysis associated Sokal risk and shorter duration of therapy with higher risk of relapse

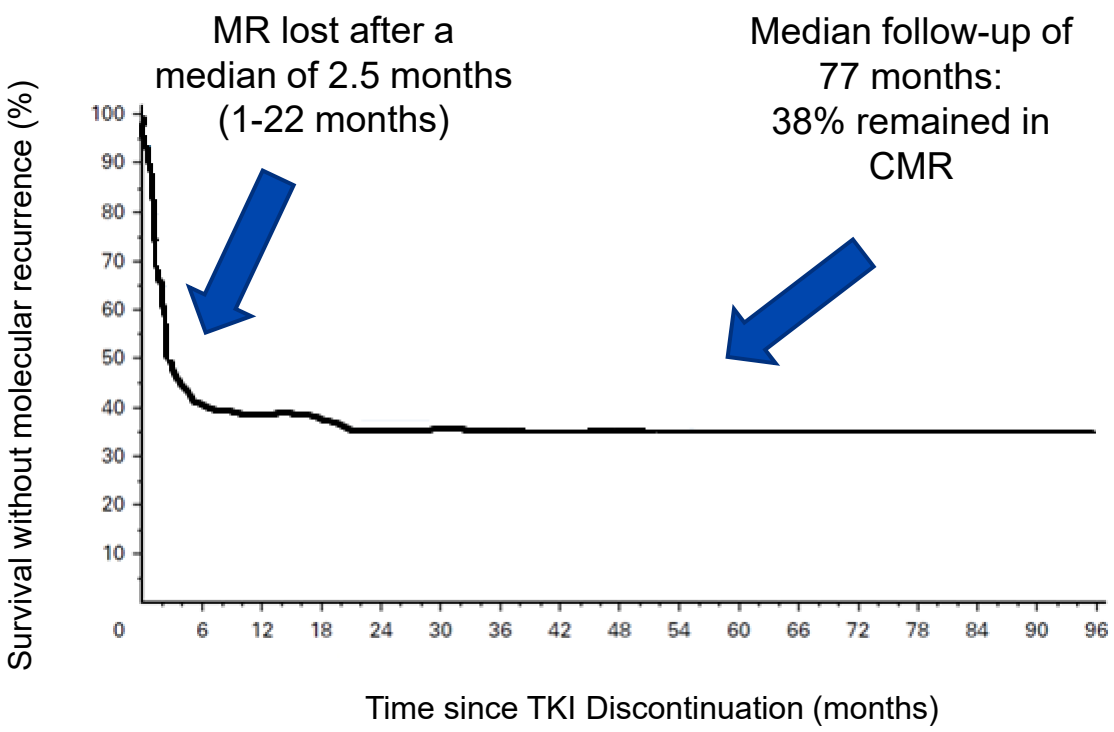
Patients who had molecular relapse following discontinuation retained sensitivity to imatinib

CMR = complete molecular response

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

# STIM Discontinuation Trial – Final




Treatment was restarted in 57 of 61 patients with MR loss

55 patients achieved a second MR with a median time of 4 months (1-16 months)

CMR = complete molecular response

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

# STIM Discontinuation Trial

## Key Takeaways

1. Approximately 40% retained MR
2. Majority of MR loss occurs within first six months
3. Re-initiation of treatment feasible

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MR = molecular response

Mahon et al. Lancet Oncol. 2010;11(11):1029-1035.
Etienne et al. J Clin Oncol. 2017;35(3):298-305.

# Imatinib Discontinuation

| Trial | Prior Treatment | N | MR Depth + Duration | TKI Resume | Median Follow-up | TFR |
|---|---|---|---|---|---|---|
| TWISTER | Imatinib +/- interferon | 40 | MR 4.5 2 years | Loss of MR 5.0 | 42 mo | 47% 24 mo |
| HOVON | Imatinib +/- cytarabine | 15 | MR 4.5 2 years | Loss of MR 4.5 | 36 mo | 33% 24 mo |
| A-STIM | Imatinib +/- interferon | 80 | MR 5.0 2 years | Loss of MMR | 31 mo | 61% 36 mo |
| ISAV | Imatinib + interferon or hydoxyurea | 108 | CMR 18 mo | Loss of MMR | 36 mo | 52% 36 mo |
| KID | Imatinib +/- interferon | 90 | MR 4.5 2 years | Loss of MMR | 27 mo | 59% 24 mo |

CMR = complete molecular response, MR = molecular response, MMR = major molecular response, TFR = treatment-free remission



Ross et al. Blood. 2013;122:515-522.
Thielen et al. Eur J Cancer. 2013;49:3242-3246.
Rousselot et al. J Clin Oncol. 2014;32:424-430.
Mori et al. Am J Hematol. 2015;90:910-914.
Lee et al. Haematologica. 2016;101:717-723.

# Dasatinib and Nilotinib Discontinuation

| Trial | Prior Treatment | N | MR Depth + Duration | TKI Resume | Median Follow-up | TFR |
|---|---|---|---|---|---|---|
| STOP 2G-TKI | Dasatinib or nilotinib | 60 | MR 4.5 24 mo | Loss of MMR | 47 mo | 54% 48 mo |
| ENEST Freedom | Nilotinib | 190 | MR 4.5 12 mo | Loss of MMR | 96 wks | 49% 96 wks |
| ENESTop | Nilotinib | 126 | MR 4.5 12 mo | Loss of MMR | 44 mo | 53% 96 wks |
| DADI | Dasatinib | 63 | MR 4.0 12 mo | Loss of MR 4.0 | 27 mo | 44% 36 mo |

CMR = complete molecular response, MR = molecular response, MMR = major molecular response, TFR = treatment-free remission

No studies have assessed the discontinuation of bosutinib or ponatanib

Rea et al. Blood. 2017;129:846-854.
Ross et al. J Cancer Res Clin Oncol. 2018;144:945-954.
Mahon et al. Ann Intern Med. 2018;168:461-470.
Okada et al. Clin Lymphoma Myeloma Leuk. 2018;18:353-360.

# EURO-SKI Discontinuation Trial

## Design

- Prospective
- Multicenter
- Non-randomized
- Single-arm
- Open-label
- N = 755

## Inclusion

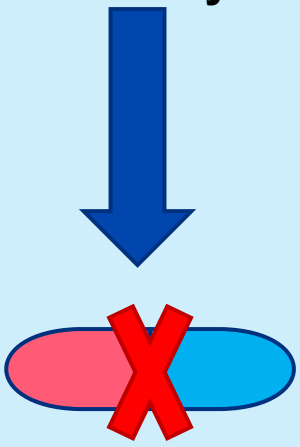
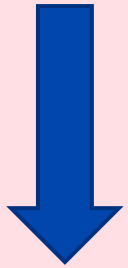
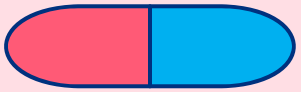
- Adults ≥18 years of age
- Ph(+) CML in chronic phase
- TKI ≥3 years
- May have received previous treatment
- MR of 4.0, sustained CMR ≥1 year

Ph(+) = philadelphia chromosome positive
MR = molecular response
CMR = complete molecular response

Saussele et al. Lancet Oncol. 2018;19:747:757.

# EURO-SKI Discontinuation Trial

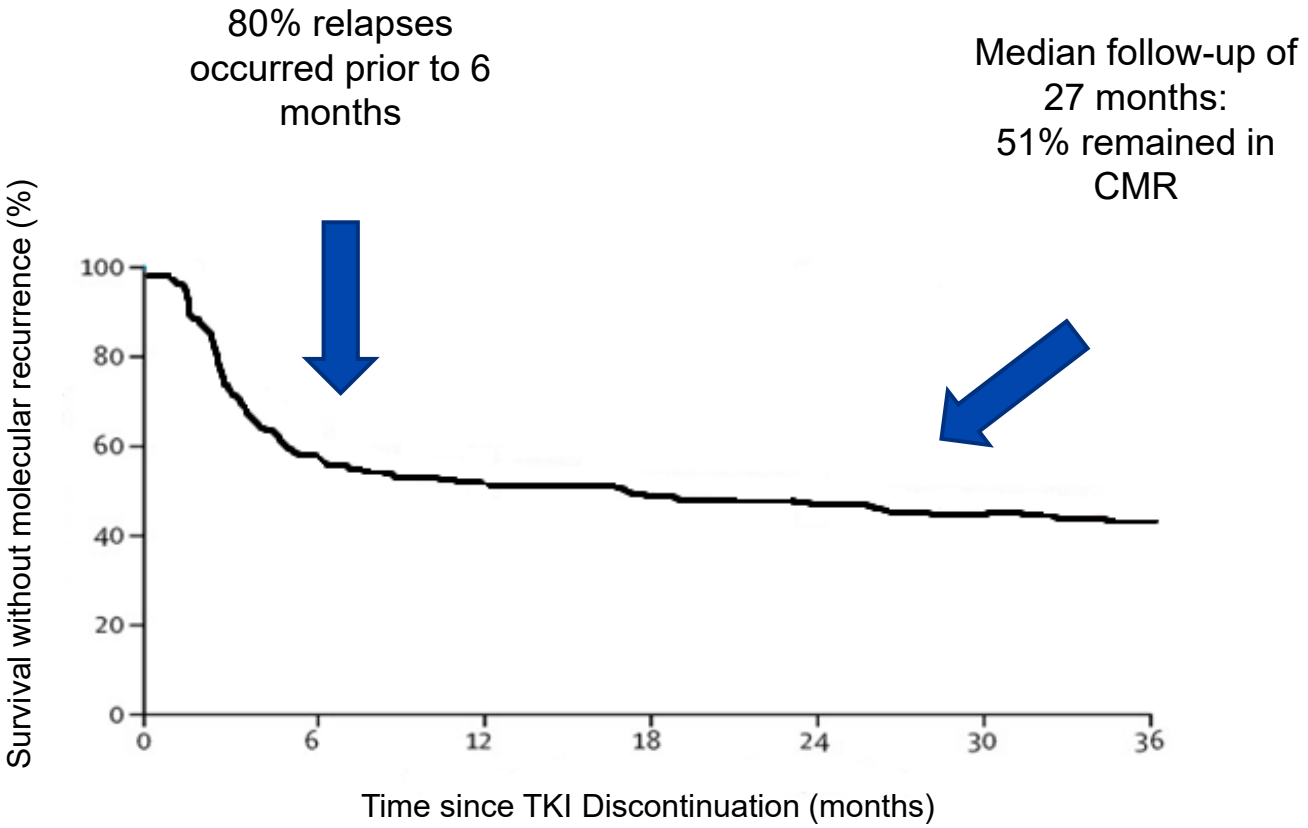
| Study Intervention | Monitoring | Response to Monitoring |
|---|---|---|
| **Imatinib, nilotinib, dasatinib ≥ 3 years MR 4.0 x 1 year**  | **Monthly 6 months**  **Every six weeks 6 months**  **Every three months At least 3 years** | **Loss of MMR BCR-ABL 0.1%**   |

MR = molecular response

Saussele et al. Lancet Oncol. 2018;19:747:757.

# EURO-SKI Discontinuation Trial – Interim




CMR = complete molecular response

Saussele et al. Lancet Oncol. 2018;19:747:757.

# EURO-SKI Discontinuation Trial

| Years of MR | Proportion without Relapse |
|---|---|
| 1 – 2 years | 46% |
| 2 – 3 years | 55% |
| 3 – 4 years | 59% |
| 4 – 5 years | 65% |
| 5 – 6 years | 70% |
| 6 – 7 years | 60% |
| ≥ 7 years | 65% |

Probability of maintaining MR 6 months following TKI discontinuation correlated with duration of deep molecular response (OR 1.13, p = 0.0032)

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MR = molecular response

Saussele et al. Lancet Oncol. 2018;19:747:757.

 

# EURO-SKI Discontinuation Trial

## Key Takeaways

1. Half of patients retained MR
2. Majority of MR loss occurs within first six months
3. Longer duration of deep molecular response prior to discontinuation is associated with lower risk of MR loss at six months



Saussele et al. Lancet Oncol. 2018;19:747:757.

 

# NCCN Criteria for TKI Discontinuation

- Age ≥18 years
- Chronic phase
- TKI therapy ≥3 years
- Prior quantifiable BCR-ABL1
- BCR-ABL1 ≤0.01% ≥2 years
- Monitoring access
- Monitoring adherence
- TKI resumption with relapse

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NCCN. Chronic Myeloid Leukemia. Accessed January 15, 2020.

 

# Poll Everywhere Question #2

Which of the following patients is most appropriate to consider for TKI discontinuation?

1. TKI for 5 months, BCR-ABL 10%
2. TKI for 5 years, diagnosed in accelerated phase
3. TKI for 3.5 years, BCR-ABL1 ≤0.01%
4. 17 year old, TKI for 4 years, BCR-ABL1 ≤0.01%


 

# Post-Discontinuation Monitoring


Test with sensitivity to detect at least BCR-ABL1 ≤ 0.0032% and report within 2 weeks



NCCN. Chronic Myeloid Leukemia. Accessed January 15, 2020.

 

# Post-Discontinuation Monitoring

Resume TKI within 4 weeks if loss of MMR (BCR-ABL ≤ 0.1%)

Monthly until MMR re-established

Every three months indefinitely

Pursue TKI-resistance testing if MMR not achieved by three months

MMR = major molecular response

NCCN. Chronic Myeloid Leukemia. Accessed January 15, 2020.

 

# Poll Everywhere Question #3 Case

CM appropriately discontinued their TKI, dasatinib, four weeks ago. At their follow-up appointment today they continue to be in MMR but do note new musculoskeletal pain that has been present the last 7 -10 days.

You believe that the musculoskeletal pain may be related to their recent TKI discontinuation.


 

# Poll Everywhere Question #3

What is your approach to manage CM's new musculoskeletal pain?

1. Restart dasatinib
2. Initiate ponatinib
3. Initiate high dose steroids
4. Initiate ibuprofen


 

# TKI Withdrawal Syndrome

- Approximately 1/3 of patients experience
- Manifests as musculoskeletal pain
  - Within 4-8 weeks of discontinuation
  - Cessation within ~ 6 months of appearance
  - No significant laboratory derangements
- Treatment approach:
  - Non-steroidal anti-inflammatory drugs
  - Corticosteroids – prednisone 10-20 mg
  - Do not re-start TKI for symptom control



Richter et al. JCO. 2014;32(25):2821-2823.
Lee et al. Haematologica. 2016;101:717-723.

 

# Summary

- Survival for CML has significantly improved since the advent of TKI use
- Each of the five TKIs used in CML has its own unique features
- Certain patients may qualify for discontinuation of long-term TKI use
- Vigilant monitoring strategy must be employed if TKIs are discontinued


 


# Questions and Discussion