Disclosures

• Consultant for Ariad, BMS, Gilead, and Incyte
• We do not intend to discuss the unlabeled use of a product or a product under investigational use.
Objectives

• Discuss the process of diagnosing Chronic Myelogenous Leukemia (CML)
• Describe clinical challenges associated with the management of CML
• Evaluate factors that inform evidence-based treatment planning
• Recognize the clinical application of novel therapies in the treatment of newly diagnosed CML
• Assess side-effect profile of novel therapies for CML
• Discuss interventions to manage side-effects related to TKI therapy
• Evaluate when it is appropriate to discontinue TKI therapy
2001

TIME

There is new ammunition in the war against cancer. These are the bullets.

Revolutionary new pills like GLEEVEC combat cancer by targeting only the diseased cells. Is this the breakthrough we've been waiting for?

2016

DAILY Mirror

CML TREXIT

WE'RE OUT

We vote to quit TKIs
Chronic Myelogenous Leukemia

- Chronic myelogenous leukemia (CML) accounts for 15% of adult leukemias.
- The median age of disease onset is 67 years; however, CML occurs in all age groups (SEER statistics).
- In 2015, an estimated 6,660 people will be diagnosed with CML in the United States, and 1,140 people will die from the disease.
- CML is characterized by the presence of Philadelphia chromosome (Ph) resulting from a reciprocal translocation between chromosomes 9 and 22 [t(9;22)].
The Ph Chromosome and the \textit{Bcr-Abl} Gene

- \textit{t}(9;22) translocation
- \textit{Bcr-Abl} gene structure

Diagnosing CML

WORKUP

- H&P, including spleen size by palpation (cm below costal margin)
- CBC with differential, platelets
- Chemistry profile
- Bone marrow evaluation\(^a\)
  - Aspirate and biopsy for morphologic review
- Cytogentic
  - FISH (blood, if bone marrow not available)\(^b\)
- Molecular
  - Quantitative RT-PCR (QPCR) using International Scale (IS) for BCR-ABL1 (blood)
  - ECG for prolonged QTc
  - Hepatitis panel

CLINICAL PRESENTATION

- Chronic phase CML
  - Ph positive or BCR-ABL1 positive
  - Ph negative and BCR-ABL1 negative

- Advanced phase CML
  - Accelerated phase\(^c\)

- Blast phase\(^d\)

ADDITIONAL EVALUATION

- Determine risk score (See Risk Calculation Table CML-A) → See Primary Treatment (CML-2)
- Additional testing
  - Flow cytometry to determine cell lineage
  - Mutational analysis
  - HLA testing, if considering allogeneic HCT (See CML-6)

Evaluate for diseases other than CML (See NCCN Guidelines for Myeloproliferative Neoplasms)
Phases of CML

- **Chronic**
  - Average duration of 5 to 6 years
  - There are mostly mature leukemia WBCs in the blood and bone marrow and there may be no symptoms of leukemia.

- **Accelerated**
  - Average duration of 6 to 9 months
  - There are some immature leukemia WBCs in the blood and bone marrow (between 5 percent and 30 percent). Patients may have fever, poor appetite and weight loss.

- **Blast**
  - Average duration of 3 to 6 months
  - In this phase, there are mostly immature WBCs in the blood and bone marrow. Symptoms such as anemia and recurring infections are typical.
## Risk Calculation

<table>
<thead>
<tr>
<th>Study</th>
<th>Calculation</th>
<th>Risk Definition by Calculation</th>
</tr>
</thead>
</table>
| Sokal et al, 1984    | $\text{Exp } 0.0116 \times (\text{age in years} - 43.4) + (\text{spleen} - 7.51) + 0.188 \times \left(\frac{\text{platelet count}}{700}\right)^2 - 0.563 + 0.0887 \times (\text{blast cells} - 2.10)$ | Low: <0.8  
Intermediate: 0.8 - 1.2  
High: >1.2 |
| Hasford et al, 1998  | $0.666 \text{ when age } \geq \text{50 years} + \left(0.042 \times \text{spleen}\right) + 1.0956 \text{ when platelet count } > \text{1500 x} \text{109/L} + \left(0.0584 \times \text{blast cells}\right) + 0.20399 \text{ when basophils } > 3\% + \left(0.0413 \times \text{eosinophils}\right) \times 100$ | Low: $\leq 780$  
Intermediate: 781 - 1480  
High: >1480 |
Primary Treatment

NCCN Guidelines Version 1.2017
Chronic Myeloid Leukemia

CLINICAL PRESENTATION

Chronic phase CML

Low-risk score
(See Risk Calculation Table CML-A)

Intermediate- or high-risk score
(See Risk Calculation Table CML-A)

PRIMARY TREATMENT

<table>
<thead>
<tr>
<th>Low-risk score</th>
<th>Dasatinib 100 mg QD (category 1) or Imatinib 400 mg QD (category 1) or Nilotinib 300 mg BID (category 1) or Clinical trial</th>
</tr>
</thead>
</table>

Treatment Considerations:
- Patient comorbidities and drug toxicities
- Monitor response
- Evaluate patient compliance and drug interactions
- Early toxicity monitoring

<table>
<thead>
<tr>
<th>Intermediate- or high-risk score</th>
<th>Dasatinib 100 mg QD (preferred) or Nilotinib 300 mg BID (preferred) or Imatinib 400 mg QD or Clinical trial</th>
</tr>
</thead>
</table>

See Response Milestones and Treatment Options (CML-3)
Primary Treatment (cont.)

NCCN Guidelines Version 1.2017
Chronic Myeloid Leukemia

**CLINICAL PRESENTATION**

- Advanced phase CML
  - Accelerated phase
  - Blast phase

- Lymphoid
  - Clinical trial or TKI (CML-G) or Omacetaxine

- Myeloid
  - Clinical trial or AML-type induction chemotherapy + TKI (CML-G) (See NCCN Guidelines for Acute Myeloid Leukemia) or TKI (CML-G)

**TREATMENT CONSIDERATIONS**

- Role of allogeneic HCT should be discussed based on response.
- Disease progression to advanced phase while on TKI therapy has worse prognosis than presenting with advanced phase CML.
- Treatment options are based on patient comorbidities and age.
- Selection of TKI is based on prior therapy and/or BCR-ABL mutation profile.
- CNS involvement has been described in blast phase CML. Lumbar puncture and CNS prophylaxis is recommended for lymphoid blast phase.
# Defining Response

<table>
<thead>
<tr>
<th>Type of Response</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHR</td>
<td>Complete Hematologic Response</td>
</tr>
<tr>
<td></td>
<td>Normal differential, WBC, platelets ≤ ULN</td>
</tr>
<tr>
<td>MCyR</td>
<td>Major Cytogenetic Response</td>
</tr>
<tr>
<td></td>
<td>0-35% Ph+ marrow metaphases</td>
</tr>
<tr>
<td>CCyR</td>
<td>Complete Cytogenetic Response</td>
</tr>
<tr>
<td></td>
<td>0% Ph+ marrow metaphases</td>
</tr>
<tr>
<td>MMR</td>
<td>Major Molecular Response</td>
</tr>
<tr>
<td></td>
<td>BCR-ABL/ABL ≤ 0.1% (International Scale)</td>
</tr>
<tr>
<td>CMR</td>
<td>Complete Molecular Response</td>
</tr>
<tr>
<td></td>
<td>Undetectable BCR-ABL (test of sensitivity ≥ 4.5 logs)</td>
</tr>
</tbody>
</table>
# Monitoring Response to TKI Therapy and Mutational Analysis

<table>
<thead>
<tr>
<th>Test</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone Marrow Cytogenetics</td>
<td>• At diagnosis&lt;br&gt;• Failure to reach response milestones&lt;br&gt;• Any sign of loss of response (defined as hematologic or cytogenetic relapse)</td>
</tr>
<tr>
<td>Quantitative RT-PCR (QPCR) using IS</td>
<td>• At diagnosis&lt;br&gt;• Every 3 months after initiating treatment. After BCR-ABL1 0.1% – &lt;1% (IS) has been achieved, every 3 months for 2 years and every 3–6 months thereafter&lt;br&gt;• If there is 1-log increase in BCR-ABL1 transcript levels with MMR, QPCR should be repeated in 1–3 months</td>
</tr>
<tr>
<td>BCR-ABL kinase domain mutation analysis</td>
<td>• Chronic phase&lt;br&gt;• Failure to reach response milestones&lt;br&gt;• Any sign of loss of response (defined as hematologic or cytogenetic relapse)&lt;br&gt;• 1-log increase in BCR-ABL1 transcript levels and loss of MMR&lt;br&gt;• Disease progression to accelerated or blast phase</td>
</tr>
</tbody>
</table>
Monitoring Response

A goal in CML treatment is to reduce the amount of bcr-abl to less than 0.0032% of the original amount.
## Response Milestones

### NCCN Guidelines Version 1.2017

#### Chronic Myeloid Leukemia

<table>
<thead>
<tr>
<th>BCR-ABL1 (IS)</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
<th>&gt;12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10%&lt;sup&gt;h&lt;/sup&gt;</td>
<td>YELLOW</td>
<td>RED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1%-10%</td>
<td>GREEN</td>
<td>YELLOW</td>
<td>RED</td>
<td></td>
</tr>
<tr>
<td>0.1%-&lt;1%</td>
<td>GREEN</td>
<td></td>
<td></td>
<td>YELLOW</td>
</tr>
<tr>
<td>&lt;0.1%</td>
<td>GREEN</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Clinical Considerations

<table>
<thead>
<tr>
<th>RESPONSE MILESTONES&lt;sup&gt;l,g&lt;/sup&gt;</th>
<th>SECOND-LINE AND SUBSEQUENT TREATMENT OPTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>RED</td>
<td>Switch to alternate TKI (CML-5) and Evaluate for HCT (CML-6)</td>
</tr>
<tr>
<td>YELLOW</td>
<td>Switch to alternate TKI (CML-5) or Continue same TKI (CML-G)&lt;sup&gt;i&lt;/sup&gt; or Dose escalation of imatinib (to a max of 800 mg) and Evaluate for HCT (CML-6)</td>
</tr>
<tr>
<td>GREEN</td>
<td>Continue same TKI (CML-G)&lt;sup&gt;j&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>h</sup> The table uses color coding to indicate response milestones. **RED** indicates a higher response, **YELLOW** indicates a moderate response, and **GREEN** indicates a lower response. The table is used to monitor and manage the response of patients to treatment for Chronic Myeloid Leukemia.

<sup>l</sup> NCCN Guidelines

<sup>g</sup> Table of Contents

<sup>i</sup> Discussion

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**The Miracle of Science with Soul**

City of Hope
Response Summary

• >10% at 3 months is a poor risk category
• Not all patients with a BCR-ABL1 value >10% at 3 months have a high ongoing risk of treatment failure.
• Any reduction below 10% by 6 months may improve outcome.
• The rate of reduction over the first 3 months is an important factor for outcome and could be considered in therapeutic decisions.
The Spectrum of CML TKI Toxicities

Imatinib
- Fluid retention (ascites, edema, pleural and pericardial effusion)
- Muscle Cramps
- Hypophosphatemia
- GI effects (diarrhea, nausea)
- Renal changes
- Hepatotoxicity

Ponatinib
- Vascular Occlusion
- Heart Failure, Hypertension
- Hepatotoxicity, Pancreatic enzyme elevation
- Fluid retention (ascites, edema, pleural and pericardial effusion)

Bosutinib
- Diarrhea/nausea
- Transaminitis
- Fluid Retention (ascites, edema, pleural and pericardial effusion)

Nilotinib
- Peripheral Arterial Occlusive Disease (PAOD)
- Hyperglycemia, Lipids
- QT Interval Prolongation
- Hyperglycemia
- Pancreatic enzyme elevation
- Hepatotoxicity

Dasatinib
- Fluid Retention (ascites, edema, pleural and pericardial effusion)
- Pulmonary Arterial Hypertension (PAH)
- GI Upset
Interventions to Manage Toxicities

Imatinib
- Diuretics, Supportive Care, Echo
- Calcium Supplement, Tonic Water
- Antidiarrheal, Antinausea meds
- Take with food, large glass of water
  - Monitor Renal Function
  - Monitor LFTs

Ponatinib
- Interrupt or stop immediately for vascular occlusion or heart failure
- Monitor and manage blood pressure
  - Monitor LFTs and pancreatic enzymes
  - Diuretics, Supportive Care

Nilotinib
- Evaluate for PAOD and if diagnosed, D/C permanently
- Monitor glucose level
  - (antiglycemic agents if indicated)
- Monitor LFTs and pancreatic enzymes
- Avoid food 2 hrs before and 1 hour after taking dose

Bosutinib
- Antidiarrheal, Antinausea meds
- Take with food, large glass of water
  - Diuretics, Supportive Care
  - Monitor LFTs

Dasatinib
- Diuretics, Supportive Care
- Steroids if pleural or pericardial effusion causing significant symptoms
- D/C permanently if PAH diagnosed
- Take with food, large glass of water
  - Monitor glucose level
  - (antiglycemic agents if indicated)
  - Monitor LFTs and pancreatic enzymes
  - Avoid food 2 hrs before and 1 hour after taking dose

Monitor Laboratory Studies (CBC, CMP, Electrolytes)
- Topical or systemic
<table>
<thead>
<tr>
<th></th>
<th>IRIS (IM400)</th>
<th>IM400 ENEST/DASISION</th>
<th>TIDEL I (IM600)</th>
<th>TIDEL II (IM600)</th>
<th>SPIRIT FRANCE (IM600)</th>
<th>ENESTnd (NIL)</th>
<th>DASISION (DAS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10% at 3 mos</td>
<td>---</td>
<td>33%/36%</td>
<td>24%</td>
<td>12%</td>
<td>---</td>
<td>9%</td>
<td>16%</td>
</tr>
<tr>
<td>CCyR at 12mos</td>
<td>69%</td>
<td>65%/73%</td>
<td>88%</td>
<td>87%</td>
<td>65%</td>
<td>80%</td>
<td>85%</td>
</tr>
<tr>
<td>MMR at 12mos</td>
<td>40%</td>
<td>27%/28%</td>
<td>47%</td>
<td>64%</td>
<td>49%</td>
<td>55%</td>
<td>46%</td>
</tr>
<tr>
<td>MMR at 24 mos</td>
<td>55%</td>
<td>44%/46%</td>
<td>73%</td>
<td>73%</td>
<td>53%</td>
<td>71%</td>
<td>64%</td>
</tr>
<tr>
<td>MR4.5 at 12mos</td>
<td>---</td>
<td>4%/---</td>
<td>18%</td>
<td>19%</td>
<td>22%</td>
<td>11%</td>
<td>5%</td>
</tr>
<tr>
<td>MR4.5 at 24mos</td>
<td>---</td>
<td>9%/8%</td>
<td>---</td>
<td>34%</td>
<td>26%</td>
<td>25%</td>
<td>17%</td>
</tr>
<tr>
<td>OS at 3 yrs</td>
<td>92%</td>
<td>94%/93%</td>
<td>---</td>
<td>96%</td>
<td>---</td>
<td>95%</td>
<td>94%</td>
</tr>
</tbody>
</table>
Practical Approach to a Patient With Resistance (or Intolerance +/-Resistance)

- First determine what the disease state requires
  - Disease phase
  - Prior TKI exposure
  - Mutational Status
  - T315I unique
  - Select mutations may support role of specific 2nd generation TKIs
  - Predictive potential imprecise
  - “Iceberg” phenomenon
  - More detailed assays forthcoming (like ultra deep sequencing)

- Next balance therapy risk and toxicity potential with known comorbidities
  - Are there true contraindications?
  - Does risk outweigh benefit expected from therapy?
  - Can risk be mitigated or anticipated?
  - Enlist the patient’s insight, trust, and awareness.
Choice of TKI After Resistance

- **T315I**
  - HSCT, ponatinib or investigational drugs
- **V299L, T315A, and F317L/V/I/C**
  - Consider NIL rather than DAS
- **Y253H, E255K/V, and F359V/C/I**
  - Consider DAS rather than NIL
- **Any other mutation**
  - DAS or NIL

BCR-ABL1 Kinase Domain (KD) Mutations

<table>
<thead>
<tr>
<th>IC₅₀ values</th>
<th>Imatinib [nM]</th>
<th>Nilotinib [nM]</th>
<th>Dasatinib [nM]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Native BCR-ABL</td>
<td>260</td>
<td>13</td>
<td>0.8</td>
</tr>
<tr>
<td>M244V</td>
<td>2000</td>
<td>38</td>
<td>1.3</td>
</tr>
<tr>
<td>G250E</td>
<td>1350</td>
<td>48</td>
<td>1.8</td>
</tr>
<tr>
<td>Q252H</td>
<td>1325</td>
<td>70</td>
<td>3.4</td>
</tr>
<tr>
<td>Y253F</td>
<td>&gt;6400</td>
<td>&gt;125</td>
<td>&gt;3.4</td>
</tr>
<tr>
<td>Y253H</td>
<td>&gt;6400</td>
<td>&gt;125</td>
<td>&gt;3.4</td>
</tr>
<tr>
<td>E255K</td>
<td>&gt;6400</td>
<td>&gt;125</td>
<td>&gt;3.4</td>
</tr>
<tr>
<td>E255V</td>
<td>&gt;6400</td>
<td>&gt;125</td>
<td>&gt;3.4</td>
</tr>
<tr>
<td>V299L</td>
<td>540</td>
<td>23</td>
<td>1.3</td>
</tr>
<tr>
<td>F311L</td>
<td>480</td>
<td>23</td>
<td>1.3</td>
</tr>
<tr>
<td>T315A</td>
<td>971</td>
<td>61</td>
<td>1.3</td>
</tr>
<tr>
<td>T315I</td>
<td>&gt;6400</td>
<td>&gt;125</td>
<td>&gt;3.4</td>
</tr>
<tr>
<td>F317L</td>
<td>1050</td>
<td>50</td>
<td>125</td>
</tr>
<tr>
<td>F317V</td>
<td>350</td>
<td>15</td>
<td>7.4</td>
</tr>
<tr>
<td>M315T</td>
<td>880</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>E355G</td>
<td>2300</td>
<td>175</td>
<td>2.2</td>
</tr>
<tr>
<td>F359V</td>
<td>1825</td>
<td>175</td>
<td>2.2</td>
</tr>
<tr>
<td>V379I</td>
<td>1630</td>
<td>51</td>
<td>0.8</td>
</tr>
<tr>
<td>L387M</td>
<td>1000</td>
<td>49</td>
<td>2</td>
</tr>
<tr>
<td>H396P</td>
<td>850</td>
<td>41</td>
<td>0.6</td>
</tr>
<tr>
<td>H396R</td>
<td>1750</td>
<td>41</td>
<td>1.3</td>
</tr>
</tbody>
</table>


Adapted from Blood. 2007;110(7):2242-9.
Second Generation TKIs Have Improved Response But not Changed Overall Survival Over Imatinib

<table>
<thead>
<tr>
<th>Response Landmarks</th>
<th>ENESTnd</th>
<th>DASISION</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete cytogenic response at 12 mos</td>
<td>65%</td>
<td>80%</td>
<td>+15%</td>
</tr>
<tr>
<td></td>
<td>Imatinib</td>
<td>Nilotinib</td>
<td>Gain</td>
</tr>
<tr>
<td></td>
<td>73%</td>
<td>85%</td>
<td>+12%</td>
</tr>
<tr>
<td>Major molecular response at 12 mos</td>
<td>27%</td>
<td>55%</td>
<td>+28%</td>
</tr>
<tr>
<td></td>
<td>Imatinib</td>
<td>Dasatinib</td>
<td>+18%</td>
</tr>
<tr>
<td>Major molecular response at 60 mos</td>
<td>60%</td>
<td>77%</td>
<td>+17%</td>
</tr>
<tr>
<td></td>
<td>64%</td>
<td>76%</td>
<td>+12%</td>
</tr>
<tr>
<td>Complete molecular response at 60 mos</td>
<td>31%</td>
<td>54%</td>
<td>+23%</td>
</tr>
<tr>
<td></td>
<td>33%</td>
<td>42%</td>
<td>+9%</td>
</tr>
<tr>
<td>Overall survival at 60 mos</td>
<td>91.7%</td>
<td>93.7%</td>
<td>+2%</td>
</tr>
<tr>
<td></td>
<td>90%</td>
<td>91%</td>
<td>+1%</td>
</tr>
</tbody>
</table>

Green Indicates Statistically Significant Difference
Red Indicates Nonsignificant Difference
Second Generation TKIs after Imatinib in Chronic Phase CML

<table>
<thead>
<tr>
<th></th>
<th>Dasatinib</th>
<th>Bosutinib</th>
<th>Nilotinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months follow-up</td>
<td>&gt;24</td>
<td>Median of 24</td>
<td>&gt;24</td>
</tr>
<tr>
<td>Complete Hematologic Response</td>
<td>89%</td>
<td>86%</td>
<td>77%</td>
</tr>
<tr>
<td>Major Cytogenetic Response</td>
<td>59%</td>
<td>54%</td>
<td>56%</td>
</tr>
<tr>
<td>Complete Cytogenetic Response</td>
<td>44%</td>
<td>41%</td>
<td>41%</td>
</tr>
<tr>
<td>2-year Progression Free Survival</td>
<td>80%</td>
<td>79%</td>
<td>64%</td>
</tr>
<tr>
<td>2-year Overall Survival</td>
<td>91%</td>
<td>92%</td>
<td>87%</td>
</tr>
</tbody>
</table>
Ponatinib After Second Generation TKI Failure

Figure represents proportion of patients achieving CCyR (post 2G-TKI setting).
Node size represents patient numbers, line signifies derived 95% confidence interval.

Source: Lipton et al. ASH 2013
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 are met.
Reasons to Discontinue TKI

1. Ongoing Toxicity (Fatigue, arthralgias, GI upset, etc.)
2. Financial Toxicity
3. Female patient and pregnancy
## Criteria for TKI Discontinuation

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Green</th>
<th>Yellow</th>
<th>Red</th>
</tr>
</thead>
<tbody>
<tr>
<td>Institutional criteria met</td>
<td>Yes</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>Sokal score at diagnosis</td>
<td>Non-high</td>
<td>High</td>
<td>-</td>
</tr>
<tr>
<td>BCR-ABL transcript at diagnosis</td>
<td>Typical - B2A2 or B3A2 (e13a2 or e14a2)</td>
<td>Atypical, but can be accurately quantified</td>
<td>Not quantifiable</td>
</tr>
<tr>
<td>CML past history</td>
<td>CP only</td>
<td>Resistance or KD mutation</td>
<td>Prior AP or BC</td>
</tr>
<tr>
<td>Response to first line TKI therapy</td>
<td>Optimal</td>
<td>Warning</td>
<td>Failure</td>
</tr>
<tr>
<td>Duration of all TKI therapy</td>
<td>&gt; 8 years</td>
<td>3–8 years</td>
<td>&lt; 3 years</td>
</tr>
<tr>
<td>Depth of deep molecular response</td>
<td>MR4.5</td>
<td>MR4.0</td>
<td>Not in MR4.0</td>
</tr>
<tr>
<td>Duration of deep molecular response monitored in a standardized laboratory</td>
<td>&gt; 2 years</td>
<td>1–2 years</td>
<td>&lt; 1 year</td>
</tr>
</tbody>
</table>

**All green lights:** strong recommendation to consider TKI withdrawal  
**Any yellow lights:** only consider TKI withdrawal in high priority circumstances (e.g., significant toxicity or planned pregnancy)  
**Any red lights:** TKI withdrawal not recommended except in clinical trial
TKI Discontinuation: Monitoring

• 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).

• 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.
## Summary of Imatinib Discontinuation Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Number</th>
<th>Treatment before disc.</th>
<th>Response required</th>
<th>Definition of relapse</th>
<th>TFR (different FU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>STIM1</td>
<td>100</td>
<td>IFN then Imatinib for ≥3 years</td>
<td>CMR</td>
<td>Loss of MMR or ≥1-log increase in BCR-ABL&lt;sup&gt;a&lt;/sup&gt;</td>
<td>39 %</td>
</tr>
<tr>
<td>STIM2</td>
<td>200</td>
<td>Imatinib for ≥3 years</td>
<td>As for STIM</td>
<td>As for STIM</td>
<td>46 %</td>
</tr>
<tr>
<td>ALLG CML8</td>
<td>40</td>
<td>Imatinib for ≥3 years</td>
<td>UMRD ≥2 years</td>
<td>Loss of MMR or confirmed loss of MR&lt;sup&gt;4,5&lt;/sup&gt;</td>
<td>45 %</td>
</tr>
<tr>
<td>According to STIM</td>
<td>80</td>
<td>Imatinib for ≥3 years</td>
<td>As for STIM; occasional positive samples eligible</td>
<td>Loss of MMR</td>
<td>64 %</td>
</tr>
<tr>
<td>EUROSKI</td>
<td>868</td>
<td>Imatinib, nilotinib, dasatinib</td>
<td>MR&lt;sup&gt;a&lt;/sup&gt; for ≥1 year; TKI for ≥3 years</td>
<td>Loss of MMR</td>
<td>54 %</td>
</tr>
<tr>
<td>ISTAV</td>
<td>112</td>
<td>Imatinib</td>
<td>Undetectable PCR (3 PCRs)</td>
<td>Loss of MMR</td>
<td>52 %</td>
</tr>
<tr>
<td>DESTINY</td>
<td>168</td>
<td>Imatinib, nilotinib or dasatinib</td>
<td>MR4 and stable response under half standard dose for 12 months</td>
<td>Loss of MMR</td>
<td>In progress</td>
</tr>
</tbody>
</table>
Key Takeaways

- CML is a highly treatable condition
- Generic Imatinib is here; combinations still hold promise
- Early response increasingly predictive of long term success
- Resistance based on mutations can drive treatment choice but is likely quite complex
- Second-line therapy can be highly effective; third-line therapy needs to be carefully chosen (risk/benefit of ponatinib vs other alternatives)
- There are promising results in TKI Discontinuation Studies
- SCT is still a needed option
References


References (cont.)


Mauro, MJ ( ). Chronic Myelogenous Leukemia: applying emerging evidence in practice (PowerPoint slides)
References (cont.)


