NCCN Guidelines Version 1.2019
Chronic Myeloid Leukemia

NCCN Chronic Myeloid Leukemia Panel Members
Summary of Guidelines Updates

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Updates in Version 1.2019 of the NCCN Guidelines for Chronic Myeloid Leukemia from Version 4.2018 include:

**CML-2**
- Footnote d modified: "Long-term follow-up data from the DASISION and ENESTnd trials and preliminary data from the BFORE trial suggest that patients with an intermediate- or high-risk Sokal or Hasford score may preferentially benefit from second-generation TKI (dasatinib, nilotinib, or bosutinib). See Discussion for additional information. Based on long-term follow-up data from the DASISION and ENESTnd trials and preliminary data from the BFORE trial, second-generation TKIs (dasatinib, nilotinib, or bosutinib) are preferred for patients with an intermediate- or high-risk Sokal or Hasford score, especially for young women whose goal is to achieve a deep and rapid molecular response and eventual drug discontinuation of TKI therapy for fertility purposes."
- Footnote e added: "Imatinib may be preferred for older patients with comorbidities such as cardiovascular disease."

**CML-3**
- Early Treatment Response Milestones
  - Last column changed from ">12" to ">15" months
  - Last row removed (≤0.1%)
  - Third row **BCR-ABL1** category changed from ">0.1%–1%" to "≤1%"
    - ◊ Green category added across milestones
- "Concern" category added to the color legend
  - RED - "TKI-resistant disease"
  - YELLOW - "Possible TKI resistance"
  - GREEN - "TKI-sensitive disease"
- Clinical Considerations
  - RED - "Consider mutational analysis"
  - YELLOW - "Consider mutational analysis"
    - ◊ Added bullet: "Consider bone marrow cytogenetic analysis to assess for MCyR at 3 mo or CCyR at 12 mo"
- Second-line and Subsequent Treatment Options
  - YELLOW
    - ◊ "Continue same TKI (other than imatinib)"
    - ◊ "Consider evaluation for allogeneic HCT"
- Footnote g added: "**BCR-ABL1** 0.1% at 12 months is associated with a very low probability of subsequent disease progression and a high likelihood of achieving a subsequent MR4.0, which may facilitate discontinuation of TKI therapy."
- Footnote i modified with addition of this sentence: "Continuation of imatinib 400 mg is not recommended."

**CML-4**
- Bullet removed: "Treatment options are based on patient comorbidities and age."
- The following added after Treatment: "Allogeneic HCT (CML-6)"
- Footnote l added: "Patients who present with accelerated phase at diagnosis should be treated with a TKI, followed by evaluation for allogeneic HCT."

Continued
Updates in Version 1.2019 of the NCCN Guidelines for Chronic Myeloid Leukemia from Version 4.2018 include:

**CML-B**
- Definitions of Accelerated Phase
  - "Blasts" clarified as "myeloblasts"
  - Footnote 1 modified with removal of "This table refers to myeloblasts."
- Definitions of Blast Phase
  - Footnote 6 modified: "World Health Organization (WHO) criteria may be included in some reports (Jaffe ES, Harris NL, Stein H, et al. WHO Classification of Tumours, Pathology, and Genetics of Tumours of Haematopoietic and Lymphoid Tissues, IARC, Lyon, 2001): Blasts ≥20% of peripheral white blood cells or of nucleated bone marrow cells; Extramedullary blast proliferation; Large foci or clusters of blasts in the bone marrow biopsy. However, it should be noted that IBMTR criteria were used in most clinical trials leading to the approval of TKIs."
  - Criteria for WHO moved to footnote.

**CML-D**
- Cytogenetic response
  - Minor cytogenetic response modified: ">35%–65% Ph-positive metaphases"

**CML-E**
- Criteria for TKI Discontinuation
  - Bullet 3 modified: "On approved TKI therapy (imatinib, dasatinib, nilotinib, bosutinib, or ponatinib) for at least 3 years"
  - Footnote 1 added: "The feasibility of treatment-free remission (TFR) following discontinuation of bosutinib or ponatinib has not yet been evaluated in clinical studies. It is reasonable to assume that the likelihood of TFR following discontinuation would be similar irrespective of TKI in patients who have achieved and maintained deep molecular response (MR4.0; ≤0.01% BCR-ABL1 IS) for ≥2 years, based on the extrapolation of findings from the studies that have evaluated TFR following discontinuation of imatinib, dasatinib, or nilotinib."
  - Footnote 2 added: "Data from the EURO-SKI study suggest that MR4.0 (BCR-ABL1 ≤0.01% IS) for 3 years or more was the most significant predictor for successful discontinuation of imatinib. Total duration of imatinib therapy for at least 6 years was also predictive of successful discontinuation (Saussele S, Richter J, Guilhot J, et al. Lancet Oncol 2018;19:747-757)."

**MS-1**
- The discussion section has been updated to reflect the changes in the algorithm.
WORKUP

- H&P, including spleen size by palpation (cm below costal margin)
- CBC with differential
- Chemistry profile
- Bone marrow\(^a\) aspirate and biopsy for morphologic and cytogenetic evaluation
- Quantitative RT-PCR (qPCR) using International Scale (IS) for BCR-ABL1 (blood)
- Hepatitis panel (hepatitis B surface antigen [HBsAg], hepatitis B surface antibody [HBsAb], hepatitis B core antibody [anti-HBc], IgM anti-HBc, IgG anti-HBc)

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CLINICAL PRESENTATION

<table>
<thead>
<tr>
<th>Chronic phase CML</th>
<th>Ph positive or BCR-ABL1 positive</th>
<th>Determined risk score (See Risk Calculation Table CML-A)</th>
<th>See Primary Treatment (CML-2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Advanced phase(^b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ph negative and BCR-ABL1 negative</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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ADDITIONAL EVALUATION

<table>
<thead>
<tr>
<th>Advanced phase(^b)</th>
<th>Evaluate for diseases other than CML (See NCCN Guidelines for Myeloproliferative Neoplasms)</th>
<th>Additional testing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>- Flow cytometry to determine cell lineage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Mutational analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- HLA testing, if considering allogeneic HCT (See CML-6)</td>
</tr>
</tbody>
</table>

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\(^a\) Bone marrow evaluation should be done for the initial workup, to provide morphologic review, and also to detect other chromosomal abnormalities in addition to Ph chromosome. Fluorescence in situ hybridization (FISH) can be used if cytogenetic evaluation is not possible.

\(^b\) See Definitions of Accelerated Phase and Blast Phase (CML-B).

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CLINICAL PRESENTATION

Chronic phase CML

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

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

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

Second-generation TKI (Bosutinib 400 mg QD [category 1]d or Dasatinib 100 mg QD [category 1]d or Nilotinib 300 mg BID [category 1]d) or First-generation TKI (Imatinib or generic imatinib 400 mg QD) or Clinical trial

Second-generation TKI (Bosutinib 400 mg QD [category 1]d or Dasatinib 100 mg QD [category 1]d or Nilotinib 300 mg BID [category 1]d) or First-generation TKI (Imatinib or generic imatinib 400 mg QD) or Clinical trial

PRIMARY TREATMENT

First-generation TKI (Imatinib or generic imatinib 400 mg QD) (category 1) or
Second-generation TKI (Bosutinib 400 mg QD [category 1] or Dasatinib 100 mg QD [category 1] or Nilotinib 300 mg BID [category 1]) or Clinical trial

See Response Milestones and Treatment Options (CML-3)c

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### EARLY TREATMENT RESPONSE MILESTONES\(^c,^f\)

<table>
<thead>
<tr>
<th>BCR-ABL1 (IS)</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months(^g)</th>
<th>&gt;15 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10(^h)</td>
<td>YELLOW</td>
<td></td>
<td>RED</td>
<td></td>
</tr>
<tr>
<td>&gt;1(–10%</td>
<td>GREEN</td>
<td>YELLOW</td>
<td>RED</td>
<td></td>
</tr>
<tr>
<td>(\leq1%</td>
<td>GREEN</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### COLOR | CONCERN | CLINICAL CONSIDERATIONS | SECOND-LINE TREATMENT
--- | --- | --- | ---
RED | TKI-resistant disease | • Evaluate patient compliance and drug interactions  
• Consider mutational analysis | Switch to alternate TKI (CML-5)  
and evaluate for allogeneic HCT (CML-6) |
YELLOW | Possible TKI resistance | • Evaluate patient compliance and drug interactions  
• Consider mutational analysis  
• Consider bone marrow cytogenetic analysis to assess for MCyR at 3 mo or CCyR at 12 mo | Switch to alternate TKI (CML-5)  
or Continue same TKI (other than imatinib) (CML-F)\(^i\)  
or Dose escalation of imatinib (to a max of 800 mg)  
and  
Consider evaluation for allogeneic HCT (CML-6) |
GREEN | TKI-sensitive disease | • Monitor response (CML-F) and side effects | Continue same TKI (CML-F)\(^j\) |

\(^c\)See Monitoring Response to TKI Therapy and Mutational Analysis (CML-C).
\(^f\)See Criteria for Hematologic, Cytogenetic, and Molecular Response and Relapse (CML-D).
\(^g\)BCR-ABL1 0.1% at 12 months is associated with a very low probability of subsequent disease progression and a high likelihood of achieving a subsequent MR4.0, which may facilitate discontinuation of TKI therapy.
\(^h\)Patients with BCR-ABL1 only slightly >10% at 3 months and/or with a steep decline from baseline may achieve <10% at 6 months and have generally favorable outcomes. Therefore, it is important to interpret the value at 3 months in this context before making drastic changes to the treatment strategy.
\(^i\)Achievement of response milestones must be interpreted within the clinical context. Patients with more than 50% reduction compared to baseline or minimally above the 10% cutoff can continue the same dose of dasatinib, nilotinib, or bosutinib for another 3 months. Continuation of imatinib 400 mg is not recommended.
\(^j\)Discontinuation of TKI with careful monitoring is feasible in selected patients. See Discontinuation of TKI Therapy (CML-E).
**Clinical Presentation**

- **Advanced phase CML**
  - **Treatment Considerations**
    - Disease progression to advanced phase while on TKI therapy has worse prognosis than presenting with advanced phase CML.
    - Evaluate for allogeneic HCT
    - Selection of TKI is based on prior therapy and/or BCR-ABL1 mutation profile.
    - CNS involvement has been described in blast phase CML. Lumbar puncture and CNS prophylaxis is recommended for lymphoid blast phase.

- **Clinical trial or TKI (CML-F)**
- **Omacetaxine**
  - **Allogeneic HCT**

- **Clinical trial or ALL-type induction chemotherapy + TKI (CML-F)**
  - **See NCCN Guidelines for Acute Lymphoblastic Leukemia**
  - TKI (CML-F) + steroids
  - **Allogeneic HCT**

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

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*bSee Definitions of Accelerated Phase and Blast Phase (CML-B).*

*kOmacetaxine is a treatment option for patients with disease progression to accelerated phase CML. Omacetaxine is not a treatment option for patients who present with accelerated phase CML.*

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# TREATMENT OPTIONS BASED ON BCR-ABL1 MUTATION PROFILE

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Treatment Recommendation&lt;sup&gt;m&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y253H, E255K/V, or F359V/C/I</td>
<td>Dasatinib</td>
</tr>
<tr>
<td>F317L/V/I/C, T315A, or V299L</td>
<td>Nilotinib</td>
</tr>
<tr>
<td>E255K/V, F317L/V/I/C, F359V/C/I, T315A, or Y253H</td>
<td>Bosutinib</td>
</tr>
<tr>
<td>T315I</td>
<td>Ponatinib,&lt;sup&gt;n&lt;/sup&gt; Omacetaxine,&lt;sup&gt;o&lt;/sup&gt; allogeneic HCT (CML-6), or clinical trial</td>
</tr>
</tbody>
</table>

<sup>m</sup>Patients with disease that is resistant to primary treatment with imatinib should be treated with bosutinib, dasatinib, or nilotinib in the second-line setting. Patients with disease that is resistant to primary treatment with bosutinib, dasatinib, or nilotinib could be treated with an alternate TKI (other than imatinib) in the second-line setting.

<sup>n</sup>Ponatinib is a treatment option for patients with a T315I mutation or for patients for whom no other TKI is indicated.

<sup>o</sup>Omacetaxine is a treatment option for patients with disease that is resistant and/or intolerant to 2 or more TKIs.

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Allogeneic HCT

CCyR\(^f\)

- Monitor with qPCR (peripheral blood) every 3 mo for 2 years, every 3–6 mo thereafter
- Negative
- Positive

Not in CCyR or in relapse\(^f\)

Consider TKI therapy for at least one year in patients with prior accelerated or blast phase CML\(^q\)

Discuss options with transplant team: TKI ± DLI or omacetaxine (CML-F) (choice depending on prior TKI, tolerance, mutation profile, and post-HCT morbidities) or Clinical trial

\(^f\)See Criteria for Hematologic, Cytogenetic, and Molecular Response and Relapse (CML-D).

\(^p\)Indications for allogeneic HCT: Advanced phase CML at presentation or disease progression to blast phase. Outcomes of allogeneic HCT are dependent on age and comorbidities, donor type, and transplant center.

\(^q\)See Discussion.

\(^f\)In patients who have disease that has failed prior TKI therapy, see CML-5 for the selection of post-HCT TKI.

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### RISK CALCULATION TABLE

<table>
<thead>
<tr>
<th>Study</th>
<th>Calculation</th>
<th>Risk Definition by Calculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sokal et al, 1984&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Exp 0.0116 x (age in years - 43.4) + (spleen - 7.51) + 0.188 x [(platelet count ÷ 700)&lt;sup&gt;2&lt;/sup&gt; - 0.563] + 0.0887 x (blast cells - 2.10)</td>
<td>Low &lt; 0.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intermediate 0.8 - 1.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High &gt; 1.2</td>
</tr>
<tr>
<td>Hasford et al, 1998&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.666 when age ≥ 50 years + (0.042 x spleen) + 1.0956 when platelet count &gt; 1500 x 10&lt;sup&gt;9&lt;/sup&gt;/L + (0.0584 x blast cells) + 0.20399 when basophils &gt; 3% + (0.0413 x eosinophils) x 100</td>
<td>Low ≤ 780</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intermediate 781 - 1480</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High &gt; 1480</td>
</tr>
</tbody>
</table>

Calculation of relative risk found at [http://www.icsg.unibo.it/rrcalc.asp](http://www.icsg.unibo.it/rrcalc.asp). Age is in years. Spleen is in centimeter below the costal margin (maximum distance). Blast cells, eosinophils, and basophils are in percents of peripheral blood differential. All factors must be collected prior to any treatment.


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Any increase in lymphoblasts is concerning for (nascent) blast phase.


World Health Organization (WHO) criteria may be included in some reports (Jaffe ES, Harris NL, Stein H, et al. WHO Classification of Tumours: Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues, IARC, Lyon, 2001): Blasts ≥20% of peripheral white blood cells or of nucleated bone marrow cells; Extramedullary blast proliferation; Large foci or clusters of blasts in the bone marrow biopsy. However, it should be noted that IBMTR criteria were used in most clinical trials leading to the approval of TKIs.

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**DEFINITIONS OF ACCELERATED PHASE**

<table>
<thead>
<tr>
<th>Modified Criteria Used at MD Anderson Cancer Center (most commonly used in clinical trials)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Peripheral blood myeloblasts ≥15% and &lt;30%</td>
</tr>
<tr>
<td>• Peripheral blood myeloblasts and promyelocytes combined ≥30%</td>
</tr>
<tr>
<td>• Peripheral blood basophils ≥20%</td>
</tr>
<tr>
<td>• Platelet count ≤100 x 10⁹/L unrelated to therapy</td>
</tr>
<tr>
<td>• Additional clonal cytogenetic abnormalities in Ph+ cells</td>
</tr>
</tbody>
</table>

**DEFINITIONS OF BLAST PHASE**

<table>
<thead>
<tr>
<th>International Bone Marrow Transplant Registry (most commonly used in clinical trials)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ≥30% blasts in the blood, marrow, or both</td>
</tr>
<tr>
<td>• Extramedullary infiltrates of leukemic cells</td>
</tr>
</tbody>
</table>

---

1 Any increase in lymphoblasts is concerning for (nascent) blast phase.
6 World Health Organization (WHO) criteria may be included in some reports (Jaffe ES, Harris NL, Stein H, et al. WHO Classification of Tumours: Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues, IARC, Lyon, 2001): Blasts ≥20% of peripheral white blood cells or of nucleated bone marrow cells; Extramedullary blast proliferation; Large foci or clusters of blasts in the bone marrow biopsy. However, it should be noted that IBMTR criteria were used in most clinical trials leading to the approval of TKIs.

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### MONITORING RESPONSE TO TKI THERAPY AND MUTATIONAL ANALYSIS

<table>
<thead>
<tr>
<th>Test</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bone marrow cytogenetics</strong>¹</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><strong>qPCR using IS</strong></td>
<td>- At diagnosis&lt;br&gt;- Every 3 months after initiating treatment. After $BCR-ABL1$ (IS) ≤1% (&gt;0.1%–1%) 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><strong>BCR-ABL kinase domain mutation analysis</strong></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>

¹FISH has been inadequately studied for monitoring response to treatment.

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CRITERIA FOR HEMATOLOGIC, CYTOGENETIC, AND MOLECULAR RESPONSE AND RELAPSE

**Complete hematologic response**

- Complete normalization of peripheral blood counts with leukocyte count <10 x 10^9/L
- Platelet count <450 x 10^9/L
- No immature cells, such as myelocytes, promyelocytes, or blasts in peripheral blood
- No signs and symptoms of disease with disappearance of palpable splenomegaly

**Cytogenetic response**

- Complete cytogenetic response (CCyR) - No Ph-positive metaphases
- Major cytogenetic response (MCyR) mostly approves for this version - 0%–35% Ph-positive metaphases
- Partial cytogenetic response (PCyR) - 1%–35% Ph-positive metaphases
- Minor cytogenetic response - >35%–65% Ph-positive metaphases

**Molecular response**

- Early molecular response (EMR) - BCR-ABL1 (IS) ≤10% at 3 and 6 months
- Major molecular response (MMR) - BCR-ABL1 (IS) ≤0.1% or ≥3-log reduction in BCR-ABL1 mRNA from the standardized baseline, if qPCR (IS) is not available
- Complete molecular response (CMR) is variably described, and is best defined by the assay's level of sensitivity (eg, MR4.5)

**Relapse**

- Any sign of loss of response (defined as hematologic or cytogenetic relapse)
- 1-log increase in BCR-ABL1 transcript levels with loss of MMR should prompt bone marrow evaluation for loss of CCyR but is not itself defined as relapse (eg, hematologic or cytogenetic relapse)

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2 A minimum of 20 metaphases should be examined.
4 CCyR typically correlates with BCR-ABL1 (IS) ≤1% (>0.1%–1%).
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.

Criteria for TKI Discontinuation (Outside of a clinical trial, TKI discontinuation should be considered only if ALL of the criteria included in the list below are met)
• Age ≥18 years.
• Chronic phase CML. No prior history of accelerated or blast phase CML.
• On approved TKI therapy for at least 3 years.1,2
• Prior evidence of quantifiable BCR-ABL1 transcript.
• Stable molecular response (MR4; BCR-ABL1 ≤0.01% IS) for ≥2 years, as documented on at least 4 tests, performed at least 3 months apart.2
• Access to a reliable qPCR test with a sensitivity of detection of at least MR4.5 (BCR-ABL1 ≤0.0032% IS) and that provides results within 2 weeks.
• Monthly molecular monitoring for one year, then every 6 weeks for the second year, and every 12 weeks thereafter (indefinitely) is recommended for patients who remain in MMR (MR3; BCR-ABL1 ≤0.1% IS) after discontinuation of TKI therapy.
• Prompt resumption of TKI within 4 weeks of a loss of MMR with molecular monitoring every 4 weeks until MMR is re-established, then every 12 weeks thereafter is recommended indefinitely for patients who have reinitiated TKI therapy after a loss of MMR. For those who fail to achieve MMR after 3 months of TKI resumption, BCR-ABL1 kinase domain mutation testing should be performed, and monthly molecular monitoring should be continued for another 6 months.
• 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.
• Reporting of the following to an NCCN CML Panel Member is strongly encouraged:
  ▶ Any significant adverse event believed to be related to treatment discontinuation.
  ▶ Progression to accelerated or blast phase CML at any time.
  ▶ Failure to regain MMR after 3 months following treatment reinitiation.

1The feasibility of treatment-free remission (TFR) following discontinuation of bosutinib or ponatinib has not yet been evaluated in clinical studies. It is reasonable to assume that the likelihood of TFR following discontinuation would be similar irrespective of TKI in patients who have achieved and maintained deep molecular response (MR4.0; ≤0.01% BCR-ABL1 IS) for ≥2 years, based on the extrapolation of findings from the studies that have evaluated TFR following discontinuation of imatinib, dasatinib, or nilotinib.

2Data from the EURO-SKI study suggest that MR4.0 (BCR-ABL1 ≤0.01% IS) for 3 years or more was the most significant predictor for successful discontinuation of imatinib. Total duration of imatinib therapy for at least 6 years was also predictive of successful discontinuation (Saussele S, Richter J, Guilhot J, et al. Lancet Oncol 2018;19:747-757).
MANAGEMENT OF TOXICITIES

BOSUTINIB (CML-F 1 of 6)

DASATINIB (CML-F 2 of 6)

IMATINIB (CML-F 3 of 6)

NILOTINIB (CML-F 4 of 6)

OMACETAXINE (CML-F 5 of 6)

PONATINIB (CML-F 6 of 6)
MANAGEMENT OF BOSUTINIB TOXICITY

Dose Adjustments:

Hematologic Toxicities

• Absolute neutrophil count (ANC) <1.0 x 10^9/L or platelets <50 x 10^9/L: Hold bosutinib until ANC ≥1.0 x 10^9/L and platelets ≥50 x 10^9/L. Resume treatment with bosutinib at the same dose if recovery occurs within 2 weeks. If blood counts remain low for greater than 2 weeks, upon recovery reduce dose by 100 mg and resume treatment. If cytopenia recurs, reduce dose by an additional 100 mg upon recovery and resume treatment. Doses less than 300 mg/d have not been evaluated.

• Growth factors can be used in combination with bosutinib for patients with resistant neutropenia and thrombocytopenia.

• Grade 3-4 anemia: Check reticulocyte count, ferritin, iron saturation, B12, folate, and correct nutritional deficiencies if present. Transfusion support should be used if patient is symptomatic.

Non-Hematologic Toxicities

• Liver transaminases >5 x IULN: Hold bosutinib until recovery to ≤2.5 x IULN and resume dose at 400 mg once daily thereafter. If recovery takes longer than 4 weeks, discontinue bosutinib. If transaminase elevations ≥3 x IULN occur concurrently with bilirubin elevations >2 x IULN and alkaline phosphatase <2 x IULN (Hy’s law case definition), discontinue bosutinib.

• Diarrhea: For NCI Common Terminology Criteria for Adverse Events (CTCAE) Grade 3-4 diarrhea (increase of ≥7 stools/day over baseline/pretreatment), withhold bosutinib until recovery to Grade ≤1. Bosutinib may be resumed at 400 mg once daily.

• For other clinically significant, moderate, or severe non-hematologic toxicity, withhold bosutinib until the toxicity has resolved, then consider resuming bosutinib at 400 mg once daily. If clinically appropriate, consider re-escalating the dose of bosutinib to 500 mg once daily.

Special Populations

• In patients with pre-existing mild, moderate, and severe hepatic impairment, the recommended dose of bosutinib is 200 mg daily. A daily dose of 200 mg in patients with hepatic impairment is predicted to result in an area under the curve (AUC) similar to the AUC seen in patients with normal hepatic function receiving 500 mg daily. However, there are no clinical data for efficacy at the dose of 200 mg once daily in patients with hepatic impairment and CML.

Specific Interventions

• Fluid retention events (ie, pulmonary and/or peripheral edema; pleural and pericardial effusion): Diuretics, supportive care.

• GI upset: Take medication with a meal and large glass of water.

• Rash: Topical or systemic steroids, dose reduction, interruption, or discontinuation.
MANAGEMENT OF DASATINIB TOXICITY

Dose Adjustments:

Hematologic Toxicities

- Chronic phase ANC <0.5 x 10^9/L or platelets <50 x 10^9/L: Hold dasatinib until ANC ≥1.0 x 10^9/L and platelets ≥50 x 10^9/L, then resume dasatinib at the starting dose if recovery occurs in ≤7 days. If platelets <25 x 10^9/L or recurrence of ANC <0.5 x 10^9/L for >7 days, hold drug until ANC ≥1.0 x 10^9/L and platelets ≥50 x 10^9/L, then resume dasatinib at reduced dose of 80 mg once daily for second episode. For third episode, further reduce dose to 50 mg once daily (for newly diagnosed patients) or discontinue dasatinib (for patients with disease that is resistant or intolerant to prior therapy including imatinib).
- Accelerated phase and blast phase, ANC <0.5 x 10^9/L and/or platelets <10 x 10^9/L: Patients may have cytopenias related to disease. If cytopenia is unrelated to disease, hold dasatinib until ANC ≥1.0 x 10^9/L and platelets ≥20 x 10^9/L, and resume at original starting dose. If recurrence, hold dasatinib until ANC ≥1.0 x 10^9/L and platelets ≥20 x 10^9/L, and resume dasatinib at reduced dose of 100 mg once daily (second episode) or 80 mg once daily (third episode).
- Growth factors can be used in combination with dasatinib for patients with resistant neutropenia and thrombocytopenia.
- Grade 3-4 anemia: Check reticulocyte count, ferritin, iron saturation, B12, folate, and correct nutritional deficiencies if present. Transfusion support should be used if patient is symptomatic.

Non-Hematologic Toxicities

- If a severe, non-hematologic, adverse reaction develops with dasatinib, treatment must be held until the event has resolved or improved. Thereafter, treatment can be resumed as appropriate at a reduced dose depending on the initial severity of the event.

Rare But Serious Toxicities

- Pulmonary arterial hypertension (PAH): Dasatinib may increase the risk of developing PAH, which may occur any time after initiation, including after more than one year of treatment. PAH may be reversible on discontinuation of dasatinib. Evaluate patients for signs and symptoms of underlying cardiopulmonary disease prior to initiating dasatinib and during treatment. If PAH is confirmed, dasatinib should be permanently discontinued.

Specific Interventions

- Fluid retention events (ie, ascites, edema, pleural and pericardial effusion): Diuretics, supportive care.
- Pleural/pericardial effusion: Diuretics, dose interruption. If patient has significant symptoms, consider short course of steroids (prednisone 20–50 mg/d x 3–4 days, may taper with 20 mg/d x 3–4 days); when resolved, reduce one dose level.
- GI upset: Take medication with a meal and large glass of water.
- Rash: Topical or systemic steroids, dose reduction, interruption, or discontinuation.

1Please refer to package insert for full prescribing information and monitoring of hematologic or biochemical abnormalities, available at www.fda.gov.
2Although erythropoietin is effective, recent guidelines from CMS and the FDA do not support the use of ESAs in myeloid malignancies.
MANAGEMENT OF IMATINIB TOXICITY¹,³

Dose Adjustments:

Hematologic Toxicities
• Chronic phase ANC <1.0 x 10⁹/L, and/or platelets <50 x 10⁹/L: Hold imatinib until ANC ≥1.5 x 10⁹/L and platelets ≥75 x 10⁹/L, then resume imatinib at the starting dose of 400 mg. If recurrence of ANC <1.0 x 10⁹/L and/or platelets <50 x 10⁹/L, hold drug until ANC ≥1.5 x 10⁹/L and platelets ≥75 x 10⁹/L, then resume imatinib at reduced dose of 300 mg.
• Accelerated phase and blast phase, ANC <0.5 x 10⁹/L and/or platelets <10 x 10⁹/L: Patients may have cytopenias related to disease. If cytopenia is unrelated to disease, reduce dose to 400 mg. If cytopenia persists for 2 weeks, reduce dose further to 300 mg. If cytopenia persists for 4 weeks, stop imatinib until ANC ≥1.0 x 10⁹/L and platelet count ≥20 x 10⁹/L and then resume treatment at 300 mg.
• Growth factors can be used in combination with imatinib for patients with resistant neutropenia.⁴
• Grade 3-4 anemia:² Check reticulocyte count, ferritin, iron saturation, B12, folate, and correct nutritional deficiencies if present. Transfusion support should be used if patient is symptomatic.

Non-Hematologic Toxicities
• Bilirubin >3 x institutional upper limit of normal (IULN) or liver transaminases >5 x IULN: Hold imatinib until bilirubin <1.5 x IULN and transaminase levels <2.5 x IULN. Resume imatinib at a reduced daily dose (400–300 mg, 600–400 mg, or 800–600 mg).
• Severe hepatotoxicity or severe fluid retention: Hold imatinib until the event has resolved. Treatment can be resumed as appropriate depending on the severity of the event.
• Patients with moderate renal impairment (creatinine clearance [CrCl] = 20–39 mL/min) should receive a 50% decrease in the recommended starting dose and future doses can be increased as tolerated. Doses greater than 600 mg are not recommended in patients with mild renal impairment (CrCl = 40–59 mL/min). For patients with moderate renal impairment, doses greater than 400 mg are not recommended. Imatinib should be used with caution in patients with severe renal impairment.

Specific Interventions
• Fluid retention (ie, pleural effusion, pericardial effusion, edema, ascites): Diuretics, supportive care, dose reduction, interruption, or discontinuation. Consider echocardiogram to check left ventricular ejection fraction (LVEF).
• GI upset: Take medication with a meal and large glass of water.
• Muscle cramps: Calcium supplement, tonic water.
• Rash: Topical or systemic steroids, dose reduction, interruption, or discontinuation.

¹Please refer to package insert for full prescribing information and monitoring of hematologic or biochemical abnormalities, available at www.fda.gov.
³Many toxicities are self-limiting; consider re-escalating dose at a later time.
²Although erythropoietin is effective, recent guidelines from CMS and the FDA do not support the use of ESAs in myeloid malignancies.
MANAGEMENT OF NILOTINIB TOXICITY

- Nilotinib prolongs the QT interval. Prior to administration of nilotinib and periodically, monitor for hypokalemia or hypomagnesemia and correct deficiencies. Electrocardiograms (ECGs) should be obtained to monitor the QTc at baseline, 7 days after initiation, and periodically thereafter, as well as following any dose adjustments.
- Sudden deaths have been reported in patients receiving nilotinib.
- Avoid use of concomitant drugs known to prolong the QT interval and strong CYP3A4 inhibitors.
- Patients should avoid food 2 hours before and 1 hour after taking dose.

**QT Interval Prolongation**

- ECGs with a QTc >480 msec: Hold drug. If serum potassium and magnesium levels are below lower limit of normal, correct with supplements to within normal limits. Review concomitant medication usage. Resume within 2 weeks at prior dose if QTcF is <450 msec and within 20 msec of baseline. If QTcF is between 450 and 480 msec after 2 weeks, resume at reduced dose (400 mg once daily). Following dose reduction, if QTcF returns to >480 msec, nilotinib should be discontinued. ECG should be obtained 7 days after any dose adjustment to monitor QTc.

**Hematologic Toxicities**

- Chronic or accelerated phase, ANC <1.0 x 10^9/L, and/or platelets <50 x 10^9/L: Hold nilotinib and monitor blood counts. Resume within 2 weeks at prior dose if ANC >1.0 x 10^9/L and platelets >50 x 10^9/L. If blood counts remain low for >2 weeks, reduce dose to 400 mg once daily.
- Growth factors can be used in combination with nilotinib for patients with resistant neutropenia and thrombocytopenia.
- Grade 3-4 anemia: Check reticulocyte count, ferritin, iron saturation, B12, folate, and correct nutritional deficiencies if present. Transfusion support should be used if patient is symptomatic.

**Non-Hematologic Toxicities**

- Elevated serum lipase, amylase, bilirubin, or hepatic transaminases grade ≥3: Hold nilotinib and monitor serum levels. Resume nilotinib at 400 mg once daily if serum levels return to grade ≤1.

**Hepatic Impairment:**

- Consider alternate therapies. See prescribing information for dose adjustments related to hepatic impairment.

**Glucose:**

- Assess glucose levels before initiating treatment and monitor treatment as clinically indicated.

**Rare But Serious Toxicities**

- Peripheral arterial occlusive disease (PAOD): Nilotinib is associated with an increased risk of vascular adverse events, including PAOD, and should be used with caution in patients with cardiovascular risk factors or a history of PAOD. Evaluate patients for a history of PAOD and for vascular risk factors prior to initiating nilotinib and during treatment. If PAOD is confirmed, nilotinib should be permanently discontinued.

**Specific Interventions**

- Rash: Topical or systemic steroids, dose reduction, interruption, or discontinuation.

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1Please refer to package insert for full prescribing information and monitoring of hematologic or biochemical abnormalities, available at [www.fda.gov](http://www.fda.gov).

2Although erythropoietin is effective, recent guidelines from CMS and the FDA do not support the use of ESAs in myeloid malignancies.
MANAGEMENT OF OMACETAXINE TOXICITY

Dose Adjustments:
Hematologic Toxicities
- Complete blood counts (CBCs) should be performed weekly during induction and initial maintenance cycles. After initial maintenance cycles, monitor CBCs every 2 weeks or as clinically indicated. ANC <0.5 x 10^9/L or platelet count <50 x 10^9/L: Delay starting the next cycle until ANC ≥1.0 x 10^9/L and platelet count ≥50 x 10^9/L and reduce the number of dosing days by 2 days for the next cycle.

Non-Hematologic Toxicities
- Grade 3 or 4 hyperglycemia: Monitor blood glucose levels frequently, especially in patients with diabetes or risk factors for diabetes. Avoid omacetaxine in patients with poorly controlled diabetes mellitus (DM) until good glycemic control has been established.
- Manage other clinically significant non-hematologic toxicity symptomatically. Interrupt and/or delay omacetaxine until toxicity is resolved.

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

1Please refer to package insert for full prescribing information and monitoring of hematologic or biochemical abnormalities, available at www.fda.gov.
MANAGEMENT OF PONATINIB TOXICITY\(^1\)

**Hematologic Toxicities**
- **ANC <1.0 x 10^9/L or platelets <50 x 10^9/L**
  - First occurrence: Hold ponatinib until ANC ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L and resume at initial dose of 45 mg.
  - Second occurrence: Hold ponatinib until ANC ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L and resume at 30 mg.
  - Third occurrence: Hold ponatinib until ANC ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L and resume at 15 mg.
- **Grade 3-4 anemia:** Check reticulocyte count, ferritin, iron saturation, B12, folate, and correct nutritional deficiencies if present. Transfusion support should be used if patient is symptomatic.
- **Heart failure:** Has occurred in patients treated with ponatinib. Monitor cardiac function. Interrupt or stop ponatinib for new or worsening heart failure.
- **Hepatotoxicity:** Hepatotoxicity, liver failure, and death have occurred in patients treated with ponatinib. Monitor hepatic function prior to and during treatment. Interrupt ponatinib if hepatotoxicity is suspected.
- **Cardiovascular risk:** Identify and control traditional risk factors for atherosclerosis (eg, DM, hypertension, hyperlipidemia, smoking, estrogen use) before starting ponatinib. Patients with cardiovascular risk factors should be referred to a cardiologist. Consider the use of low-dose aspirin if there is no contraindication.
- **Non-Hematologic Toxicities**
  - **Rash:** Topical or systemic steroids, dose reduction, interruption, or discontinuation of ponatinib.
  - **Hypertension:** Monitor and manage blood pressure elevations.
  - **Fluid retention events (ie, edema, ascites, pleural and pericardial effusion):** Managed with dose interruption, dose reduction, or discontinuation of ponatinib as clinically indicated.
  - **Hypertension:** Monitor and manage blood pressure elevations.
  - **Rash:** Topical or systemic steroids, dose reduction, interruption, or discontinuation.

**Rare But Serious Toxicities**
- **Hemorrhage:** Hemorrhagic events were reported in clinical trials. Cerebral and gastrointestinal hemorrhage were the most commonly reported serious bleeding events. Serious hemorrhage should be managed with dose interruption.
- **Cardiac arrhythmias:** Advise patients to report signs and symptoms suggestive of alterations in heart rate (fainting, dizziness, chest pain, or palpitations).
- **Tumor lysis syndrome:** Ensure adequate hydration and correct high uric acid levels prior to initiating therapy with ponatinib in patients with advanced-phase CML.

**Specific Interventions**
- **Fluid retention events (ie, edema, ascites, pleural and pericardial effusion):** Managed with dose interruption, dose reduction, or discontinuation of ponatinib as clinically indicated.
- **Hypertension:** Monitor and manage blood pressure elevations.
- **Rash:** Topical or systemic steroids, dose reduction, interruption, or discontinuation.

**Note:** All recommendations are category 2A unless otherwise indicated.

**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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\(^1\)Please refer to package insert for full prescribing information and monitoring of hematologic or biochemical abnormalities, available at [www.fda.gov](http://www.fda.gov).

\(^2\)Although erythropoietin is effective, recent guidelines from CMS and the FDA do not support the use of ESAs in myeloid malignancies.
Discussion

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.
Overview

Chronic myeloid 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 2018, an estimated 8,430 people will be diagnosed with CML in the United States, and 1090 people will die from the disease.¹

CML is defined by the presence of Philadelphia chromosome (Ph) in a patient with a myeloproliferative neoplasm (MPN). Ph results from a reciprocal translocation between chromosomes 9 and 22 [t(9;22)] that gives rise to a *BCR-ABL1* fusion gene; the product of this fusion gene is a protein with deregulated tyrosine kinase activity (p210) that plays a central role in the pathogenesis of CML.² Another fusion protein, p190, is also produced, usually in the setting of Ph-positive acute lymphoblastic leukemia (ALL). p190 is detected only in 1% of patients with CML.³

CML occurs in three different phases (chronic, accelerated, and blast phase) and is usually diagnosed in the chronic phase. Untreated chronic phase CML (CP-CML) will eventually progress to advanced phase in 3 to 5 years.⁴ Gene expression profiling has shown a close correlation of gene expression between the accelerated phase CML (AP-CML) and blast phase CML (BP-CML). The bulk of the genetic changes in progression occur in the transition from CP-CML to AP-CML.⁵ The activation of beta-catenin signaling pathway in CML granulocyte-macrophage progenitors (which enhances the self-renewal activity and leukemic potential of these cells) may also be a key pathobiologic event in the evolution to BP-CML.⁶

The NCCN Guidelines for CML discuss the clinical management of CML in all three phases (chronic, accelerated, or blast phase). Evaluation for diseases other than CML as outlined in the NCCN Guidelines for MPN is recommended for all patients with *BCR-ABL1*-negative MPN.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for Chronic Myelogenous Leukemia, an electronic search of the PubMed database was performed to obtain key literature in Chronic Myelogenous Leukemia published between April 2017 and March 2018 using the following search terms: chronic myeloid leukemia or chronic myelogenous leukemia. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.⁷

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 213 citations and their potential relevance was examined. The data from key PubMed articles selected by the panel for review during the Guidelines update meeting as well as articles from additional sources deemed as relevant to these Guidelines have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.
Diagnosis and Workup (CML-1)

Initial evaluation should consist of a history and physical exam, including palpation of spleen, complete blood count (CBC) with differential, chemistry profile, and hepatitis panel. Bone marrow aspirate and biopsy for morphologic and cytogenetic evaluation and quantitative reverse transcriptase polymerase chain reaction (RT-PCR) to establish the presence of quantifiable \( BCR-ABL1 \) mRNA transcripts at baseline are recommended to confirm the diagnosis of CML.

Bone marrow cytogenetics should be done at initial workup to detect additional chromosomal abnormalities in Ph-positive cells (ACA/Ph+), also known as clonal cytogenetic evolution.\(^8\) If bone marrow evaluation is not feasible, fluorescence in situ hybridization (FISH) on a peripheral blood specimen with dual probes for \( BCR \) and \( ABL1 \) genes is an acceptable method to confirm the diagnosis of CML. Interphase FISH is performed on peripheral blood but is associated with a background level of 1%–5% depending on the specific probe used in the assay.\(^9\) Hypermetaphase FISH is more sensitive and can analyze up to 500 metaphases at a time, but it is applicable only to dividing cells in the bone marrow.\(^10\) Double-fusion FISH is also associated with low false-positive rates and can detect all variant translocations of the Ph-chromosome.\(^11\)

Quantitative RT-PCR (qPCR) should be done at initial workup to establish the presence of quantifiable \( BCR-ABL1 \) mRNA transcripts at baseline. qPCR, usually done on peripheral blood is the most sensitive assay available for the measurement of \( BCR-ABL1 \) mRNA and it can detect one CML cell in a background of \( \geq 100,000 \) normal cells. qPCR results can be expressed in various ways, for instance as the ratio of \( BCR-ABL1 \) transcript numbers to the number of control gene transcripts.\(^12\) An International Scale (IS) has been proposed to standardize molecular monitoring with qPCR across different laboratories with the use of one of three control genes (\( BCR, ABL1 \), or \( GUSB \)) and a qPCR assay with a sensitivity of at least 4-log reduction from the standardized baseline.\(^13\) In recent years, IS has become the gold standard of expressing qPCR values. More details on monitoring with qPCR using IS are provided on MS-10.

\( BCR-ABL1 \) transcripts in the peripheral blood at very low levels (1–10 out of \( 10^8 \) peripheral blood leukocytes) can also be detected in approximately 30% of normal individuals, and the incidence of \( BCR-ABL1 \) transcripts increases with advancing age in healthy individuals.\(^14,15\) Tyrosine kinase inhibitor (TKI) therapy is not indicated, as the risk of developing CML for these individuals is extremely low.

Clonal Cytogenetic Evolution

The prognostic significance of ACA/Ph+ is related to the specific chromosomal abnormality and often other features of accelerated phase.\(^16-20\) The presence of "major route" ACA/Ph+ (trisomy 8, isochromosome 17q, second Ph, and trisomy 19) at diagnosis may have a negative prognostic impact on survival and disease progression to accelerated or blast phase.\(^21-23\) However, in a more recent analysis that evaluated the outcomes of patients with CP-CML (with or without ACA) treated with TKIs in prospective studies, the presence of ACA/Ph+ at the time of diagnosis was not associated with...
worse prognosis.\textsuperscript{24} Patients with ACA/Ph\textsuperscript{+} at diagnosis should be watched carefully for evidence of therapy failure.

Clonal cytogenetic evolution in Ph-negative cells has also been reported in a small subset of patients during the course of imatinib therapy.\textsuperscript{25-30} The most common abnormalities include trisomy 8 and loss of Y chromosome. Previous work suggested that the overall prognosis of Ph-negative CML with clonal evolution is good and is dependent on response to imatinib therapy.\textsuperscript{29} Recently, however, the presence of chromosome abnormalities other than loss of Y chromosome has been associated with decreased survival in patients with CP-CML treated with various TKIs, suggesting that closer follow-up is indicated until definitive data are available.\textsuperscript{31} Progression to myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) have been reported in patients with monosomy 7.\textsuperscript{32,33}

### Additional Evaluation

#### Chronic Phase CML (CML-1)

Determination of risk score using either the Sokal or Hasford (Euro) scoring systems prior to initiation of TKI therapy is recommended for patients diagnosed with CP-CML. Sokal and Euro scoring systems have been used for the risk stratification of patients into three risk groups (low, intermediate, and high) in clinical trials evaluating TKIs (CML-A).\textsuperscript{34,39} The Sokal score is based on the patient’s age, spleen size, platelet count, and percentage of blasts in the peripheral blood.\textsuperscript{34} The Euro score includes eosinophils and basophils in the peripheral blood in addition to the same clinical variables used in the Sokal score.\textsuperscript{35}

European Treatment and Outcome Study (EUTOS) score is based only on the percentage of basophils in the blood and spleen size. The predictive value of EUTOS score was validated in a cohort of 2060 patients enrolled in studies of first-line treatment with imatinib-based regimens.\textsuperscript{36} EUTOS score was better than Sokal and Euro score in predicting the probability of achieving a complete cytogenetic response (CCyR) at 18 months and 5-year progression-free survival (PFS). However, the predictive value of EUTOS score has not been confirmed in subsequent studies by other investigators, and additional studies are needed to validate the EUTOS score.\textsuperscript{37-39}

#### Advanced Phase CML (CML-1)

Flow cytometry to determine cell lineage, mutational analysis, and human leukocyte antigen (HLA) testing, if considering allogeneic hematopoietic cell transplant (HCT), are recommended for patients with advanced phase CML. Progression to AP-CML and BP-CML bridges a continuum of clinical features (fever, bone pain, spleen size), cytogenetic changes, and blast count.

AP-CML defined only by clonal cytogenetic evolution is associated with a better prognosis than AP-CML defined by clonal cytogenetic evolution and additional features of progression.\textsuperscript{21,40} The modified MD Anderson Cancer Center criteria for AP-CML (15% and <30% peripheral blood or bone marrow blasts, ≥30% or more of peripheral blood blasts and promyelocytes, ≥20% peripheral blood or bone marrow basophils, platelet count ≤100 x 10\textsuperscript{9}/L unrelated to therapy, and clonal cytogenetic evolution in Ph\textsuperscript{+} cells) are used in clinical trials that have evaluated the efficacy of TKIs (CML-B).\textsuperscript{41} The revised 2016 WHO diagnostic criteria for AP-CML include a “provisional” response to TKI criteria in addition to
hematologic and cytogenetic criteria. These diagnostic criteria require validation in prospective clinical trials.

The International Bone Marrow Transplant Registry (IBMTR) criteria define blast phase as the presence of ≥30% blasts in the blood, bone marrow, or both, or as the presence of extramedullary disease (CML-B). IBMTR was used in most of the clinical trials leading to the approval of TKIs, and is best aligned with prognostication systems derived from these studies. The WHO diagnostic criteria (presence of ≥20% blast cells in the peripheral blood or bone marrow, the presence of extramedullary blast proliferation, and large foci or clusters of blasts in the bone marrow biopsy) may be included in some reports.

Management of Chronic Phase CML

Primary Treatment (CML-2)

Long-term efficacy data from randomized phase III studies for first-line TKI therapy in patients with newly diagnosed CP-CML are summarized in Table 1. In summary, 1) all TKIs are highly effective in newly diagnosed CP-CML, with long-term overall survival (OS) approaching that of aged-matched controls; 2) second generation TKIs, compared to imatinib, generally result in faster cytogenetic and molecular responses, with less progression to advanced phase CML; 3) yet, in randomized clinical trials, there are no differences in OS between imatinib, and second generation TKIs (dasatinib, nilotinib and bosutinib).

The selection of first-line TKI therapy (bosutinib, dasatinib, imatinib or nilotinib) in a given patient should be based on the risk score, toxicity profile of TKI, patient’s age, ability to tolerate therapy, and the presence of comorbid conditions. Allogeneic HCT is no longer recommended as a first-line treatment option for patients with CP-CML.

Imatinib 800 mg is not recommended as initial therapy, given the recent data showing superior efficacy of second generation TKIs in newly diagnosed CP-CML. Data from randomized phase III studies that have evaluated high-dose imatinib as first-line therapy for CP-CML suggest that imatinib 800 mg was not associated with lower rates of disease progression than imatinib 400 mg in any of these studies, despite improved early responses (Table 2). Imatinib 800 mg was also associated with higher rates of dose interruption, reduction, or discontinuation due to grade 3 or 4 adverse events in all of the studies. However, patients who can actually tolerate the higher dose of imatinib achieve better response rates than those receiving standard-dose imatinib.

The prospective studies evaluating imatinib 800 mg daily found that increased toxicity of that dose forced decreasing dose to approximately 600 mg daily when considering the actually administered dose intensity. Additionally the French SPIRIT trial reported superior major molecular response (MMR) rates in patients treated with imatinib 600 mg daily compared to 400 mg daily. These data suggest that imatinib 600 mg daily may be closer to the optimal dose than 400 mg.

Clinical Considerations For The Selection of First-Line Therapy

Risk Stratification

Imatinib (400 mg daily) and second generation TKIs (dasatinib [100 mg once daily], nilotinib [300 mg twice daily] and bosutinib [400 mg...
daily]) are all appropriate options for first-line TKI therapy for patients with CP-CML across all risk scores.\textsuperscript{44-47}

Disease progression is more frequent in patients with intermediate- or high-risk score and prevention of disease progression to AP-CML or BP-CML is the primary goal of TKI therapy in patients with CP-CML. Second generation TKIs are associated with lower risk of disease progression than imatinib and are therefore preferred for patients with an intermediate- or high-risk Sokal or Euro score.

Second-generation TKIs also result in quicker molecular responses and higher rates of deep molecular responses (MMR and MR4.5) in patients with CP-CML across all risk scores (Table 3) which may facilitate subsequent discontinuation of TKI therapy in selected.\textsuperscript{45-47} Therefore, second generation TKIs may be preferred over imatinib for younger patients, particularly women since the achievement of a deep and rapid molecular response may allow eventual discontinuation of TKI therapy for fertility purposes. Imatinib may be preferred for older patients with comorbidities, especially cardiovascular.

**Toxicity Profile**

All of the TKIs are fairly well tolerated. Since bosutinib, dasatinib and nilotinib have very good efficacy in the upfront setting, differences in their potential toxicity profiles may inform the selection of either one of these TKIs as initial therapy. Nilotinib or bosutinib may be preferred for patients with a history of lung disease or deemed to be at risk of developing pleural effusions. Dasatinib or bosutinib may be preferred in patients with a history of arrhythmias, heart disease, pancreatitis, or hyperglycemia.

Adverse events of first-line TKI therapy in patients with CP-CML reported in phase III randomized studies are discussed below and are also summarized in Table 4. See CML-F for the management of toxicities associated with TKI therapy.

**Imatinib**

Chronic fatigue (mostly correlated with musculoskeletal pain and muscular cramps) is a major factor reducing quality of life.\textsuperscript{52} Hypophosphatemia and decrease in bone mineral density has been noted in a small group of patients, suggesting that monitoring bone health should be considered for patients taking imatinib.\textsuperscript{53,54} Skin hypopigmentation has also been reported as a side effect of imatinib and is reversible upon discontinuation or dose reduction.\textsuperscript{55,56}

**Dasatinib**

In the DASISION study, the incidences of grade 3/4 hematologic toxicities (anemia, neutropenia and thrombocytopenia) were higher for dasatinib than imatinib. Nonhematologic adverse events such as muscle spasms, peripheral edema and hypophosphatemia were more frequent with imatinib. Discontinuation of therapy because of drug-related adverse events occurred in 16% and 7% of patients in the dasatinib and imatinib arms, respectively. Dasatinib is also associated with significant but reversible inhibition of platelet aggregation that may contribute to bleeding in some patients, especially if accompanied by thrombocytopenia.\textsuperscript{57}

Pleural effusion was more common with dasatinib (28%) than with imatinib (<1%).\textsuperscript{45} The occurrence of pleural effusion is significantly reduced with dasatinib 100 mg once daily compared with 70 mg twice daily.\textsuperscript{58} Patients with prior cardiac history, hypertension, and those
receiving twice-daily dosing of dasatinib at 70 mg are at increased risk of developing pleural effusions. Close monitoring and timely intervention are necessary for patients at risk of developing pleural effusions.

Reversible pulmonary arterial hypertension has been reported as a rare but serious side effect of dasatinib. In the DASISION study, pulmonary hypertension was reported in 5% of patients treated with dasatinib compared to <1% of patients treated with imatinib. Evaluation for signs and symptoms of underlying cardiopulmonary disease prior to initiating and during treatment with dasatinib is recommended. If pulmonary arterial hypertension is confirmed, dasatinib must be permanently discontinued.

The recommended starting dose of dasatinib is 100 mg once daily for patients with CP-CML. Limited data available from small cohorts of patients suggest that lower doses of dasatinib may potentially have similar efficacy. Treatment interruption of dasatinib at standard dose and reintroduction of dasatinib at a lower dose of 40 mg twice daily also resolved all pulmonary complications without recurrence. However, the minimum effective dose has not been established in randomized clinical trials. Re-introduction of dasatinib at 50 mg (20 mg with careful monitoring in selected patients) should be considered for patients with clinically significant intolerance to dasatinib at 100 mg once daily to avoid serious adverse events necessitating the discontinuation of dasatinib (eg, pleural effusion, myelosuppression).

Nilotinib
In the ENESTnd study, nonhematologic adverse events such as nausea, diarrhea, vomiting, muscle spasm, and peripheral edema of any grade were higher for patients receiving imatinib. Conversely, rash and headache were higher with nilotinib. Grade 3 or 4 neutropenia was more frequent in the imatinib group, whereas thrombocytopenia and anemia were similar in both groups. Electrolyte abnormalities and elevations in lipase, glucose and bilirubin were more frequent with nilotinib than with imatinib. Patients with a previous history of pancreatitis may be at greater risk of elevated serum lipase. The overall incidences of adverse events leading to discontinuation of therapy were comparable in the nilotinib 300 mg twice daily arm and imatinib arms (12% and 14% respectively) and slightly higher in nilotinib 400 mg twice daily arm (20%).

Nilotinib labeling contains a black box warning regarding the risk of QT interval prolongation, and sudden cardiac death has been reported in patients receiving nilotinib. QT interval prolongation could be managed with dose reduction. Electrolyte abnormalities should be corrected prior to initiation of treatment with nilotinib and electrolytes should be monitored periodically. Drugs that prolong QT interval should be avoided. Electrocardiogram (ECG) should be obtained to monitor the QT interval at baseline, 7 days after initiation of nilotinib and periodically thereafter, as well as following any dose adjustments. Patients with cardiovascular risk factors should be referred to a cardiologist.

Nilotinib is associated with an increased risk of peripheral arterial occlusive disease (PAOD). Patients should be evaluated for pre-existing PAOD and vascular risk factors prior to initiating and during treatment with nilotinib. If PAOD is confirmed, nilotinib should be permanently discontinued.
**Bosutinib**

In the BFORE study, diarrhea, increased alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were more common with bosutinib whereas muscle spasms and peripheral edema were more common with imatinib. Grade 3/4 thrombocytopenia was higher with bosutinib and grade 3/4 neutropenia was higher with imatinib. Grade 3/4 anemia was similar in both groups. Discontinuation of therapy because of drug-related adverse events occurred in 14% of patients in the bosutinib group compared to 11% in the imatinib group. Increased ALT [5%] and increased AST increase [2%]) were the most common adverse events leading to discontinuation of bosutinib. However, there were no hepatotoxicity-related fatalities during the study.

**Management of Hematologic Toxicities of TKI Therapy**

Cytopenias (anemia, neutropenia, and thrombocytopenia) should be managed with transient interruptions of TKI therapy and dose modifications. Please see the package insert for full prescribing information, available at www.fda.gov, for the recommended dose modifications of specific TKI therapy.

Assessment of reticulocyte count, ferritin, iron saturation, vitamin B12, and folate and correction of nutritional deficiencies if present, is recommended for patients with grade 3-4 anemia. Red blood cell transfusions are indicated in symptomatic patients. Myeloid growth factor support can be used in combination with TKI therapy for the management of neutropenia. The use of erythropoiesis-stimulating agents (ESAs) did not impact survival or cytogenetic response rate, but was associated with a higher thrombosis rate in patients with CP-CML. Recent guidelines from the U.S. Centers for Medicare & Medicaid Services (CMS) and the FDA do not support the use of ESAs in patients with myeloid malignancies.

**Monitoring Response to TKI Therapy**

Response to TKI therapy is determined by the measurement of hematologic (normalization of peripheral blood counts), cytogenetic (decrease in the number of Ph-positive metaphases using bone marrow cytogenetics), and molecular responses (decrease in the amount of BCR-ABL1 chimeric mRNA using qPCR). The criteria for hematologic, cytogenetic, and molecular response are summarized in CML-D.

Conventional bone marrow cytogenetics is the standard method for monitoring cytogenetic responses, and clinical trial response analyses are most often based on conventional bone marrow cytogenetics. If conventional bone marrow cytogenetics showed no analyzable metaphases, cytogenetic response can be evaluated by FISH; however, it has a false-positive rate of 1% to 10%. Although some investigators have reported that interphase FISH can be used to monitor CCyR, endpoints for TKI failure have not been defined on the basis of FISH analysis. The panel feels that FISH has been inadequately studied for monitoring response to TKI therapy. Therefore, FISH is not generally recommended for monitoring response if conventional cytogenetics or qPCR are available.

qPCR is the only tool capable of monitoring responses after the patient has achieved CCyR, since BCR-ABL1 transcripts typically remain detectable after CCyR is achieved. A major advantage of qPCR is the strong correlation between the results obtained from the peripheral
blood and the bone marrow, allowing molecular monitoring without bone marrow aspirations.\textsuperscript{74,75}

**Standardization of Molecular Monitoring Using the International Scale**

In the IS, the standardized baseline (defined as the average expression of $BCR-ABL1$ transcripts in 30 patients treated on the IRIS trial) is set to 100%. Molecular response is expressed as log-reduction from 100%. For example, $\geq 3$-log reduction ($\leq 0.1\%$ $BCR-ABL1$ IS) is referred to as MMR or MR3.0).\textsuperscript{13,76,77} A 2-log reduction generally correlates with CCyR ($\leq 1\%$ $BCR-ABL1$ IS).

The sensitivity of a qPCR assay depends not only on the performance of the assay, but also on the quality of a given sample. As such the term ‘complete molecular response’ to denote undetectable $BCR-ABL1$ transcripts (a negative qPCR test) should be abandoned, as it may refer to very different levels of response, dependent on the quality of the sample. Laboratories can use their individual assays, but the $BCR-ABL1$ transcripts obtained in a given laboratory should be converted to the IS by applying a laboratory-specific conversion factor (CF).\textsuperscript{13,78}

**Recommendations for Monitoring Response to TKI Therapy**

qPCR (IS) is the preferred method to monitor response to TKI therapy. qPCR assays with a sensitivity of $\geq 4.5$-log reduction from the standardized baseline are recommended for the measurement of $BCR-ABL1$ transcripts (CML-C). In patients with prolonged myelosuppression who may not be in complete hematologic response (CHR) due to persistent cytopenias or unexplained drop in blood counts during therapy, bone marrow cytogenetics is indicated to confirm response to TKI therapy and exclude other pathology, such as MDS or the presence of chromosomal abnormalities other than Ph.

Monitoring with qPCR (IS) every 3 months is recommended for all patients after initiating TKI therapy, including those who meet response milestones at 3, 6, and 12 months ($\leq 10\%$ $BCR-ABL1$ IS at 3 and 6 months, $\leq 1\%$ $BCR-ABL1$ IS at 12 months, and $\leq 0.1\%$ $BCR-ABL1$ IS at $>12$ months). After CCyR ($\leq 1\%$ $BCR-ABL1$ IS) has been achieved, molecular monitoring is recommended every 3 months for 2 years and every 3 to 6 months thereafter.

Frequent molecular monitoring with qPCR (IS) can help to identify non-adherence to TKI therapy early in the treatment course.\textsuperscript{79} Since adherence to TKI therapy is associated with better clinical outcomes, frequent molecular monitoring is essential if there are concerns about the patient’s adherence to TKI therapy after CCyR has been achieved. In patients with deeper molecular responses (MMR and better) and who are compliant with TKI therapy, the frequency of molecular monitoring can be reduced, though the optimal frequency is unknown.

**Prognostic Significance of Cytogenetic and Molecular Response**

Early molecular response ($\leq 10\%$ $BCR-ABL1$ IS at 3 and 6 months) after first-line TKI therapy has emerged as an effective prognosticator of favorable long-term PFS and OS, regardless of TKI used (Table 5).\textsuperscript{45,46,50,80} Some reports suggest that early molecular response at 3 months has a superior prognostic value and support the use of early intervention strategies based on the $BCR-ABL1$ transcript level at 3 months.\textsuperscript{81,82} However other studies yielded partially conflicting results regarding the predictive value of $BCR-ABL1$ transcript levels at
3-months. From a practical perspective, it is important to consider these data points within the clinical context. For instance, if BCR-ABL1 transcript level is minimally above the 10% cutoff (11% at 3 months), it is reasonable to re-assess at 6 months before considering major changes to the treatment strategy.

Quite recently, studies have suggested that the rate of decline in BCR-ABL1 transcripts correlates with longer-term response. Among patients with >10% BCR-ABL1 IS after 3 months of treatment with imatinib, those with a faster decline in BCR-ABL1 (BCR-ABL1 halving time <76 days) had a superior outcome compared to those with a slower decline (4-year PFS rate was 92% vs. 63%, respectively). A rapid initial BCR-ABL1 decline also identifies a subgroup of Sokal high-risk patients with outcomes similar to those of Sokal low-risk patients. Among Sokal high-risk patients, a BCR-ABL1 halving time of ≤11 days was associated with significantly improved FFS (4-year FFS rate was 79% for patients with halving time of ≤11 days vs. 53% for those with halving time of > 11 days; \(P = .03\)). In the German CML IV study, lack of a half-log reduction of BCR-ABL1 transcripts at 3 months was associated with a higher risk of disease progression on imatinib therapy. The results of the D-First study also showed that in patients treated with dasatinib, BCR-ABL1 halving time of ≤14 days was a significant predictor of MMR by 12 months and deep molecular response (BCR-ABL1 <0.01% IS) by 18 months.

Achievement of CCyR (≤1% BCR-ABL1 IS) within 12 months after first-line TKI therapy is an established prognostic indicator of long-term survival. In the IRIS study, the estimated 6-year PFS rate was 97% for patients achieving a CCyR at 6 months compared to 80% for patients with no cytogenetic response at 6 months. In an analysis of patients with newly diagnosed CP-CML treated with imatinib or second-generation TKIs, the 3-year EFS and OS rates were 98% and 99% for patients who achieved CCyR at 12 months compared to 67% and 94% in patients who did not achieve a CCyR.

The prognostic significance of MMR (0.1% BCR-ABL1 IS) after first-line imatinib has also been evaluated in several studies. In all of these studies, the analyses were done for different outcomes measures at multiple time points, but failed to adjust for multiple comparisons, thereby reducing the validity of the conclusions. The synoptic conclusion from these studies is that MMR is moderately superior to CCyR in predicting long-term PFS and OS. However, with longer follow-up, CCyR becomes an ever stronger indicator of MMR. The achievement of MMR is also not a significant prognosticator of long-term outcome in patients who are in stable CCyR after first-line treatment with dasatinib or nilotinib. These findings suggest that MMR may not be of prognostic significance in patients who have achieved CCyR and absence of MMR in the presence of a CCyR is not considered a treatment failure. Achievement of MMR (0.1% BCR-ABL1 IS) at 12 months, however, is associated with a very low probability of subsequent disease progression and a high likelihood of achieving a subsequent deep molecular response (MR4.0; ≤0.01% BCR-ABL1 IS) which may facilitate discontinuation of TKI therapy. TKI de-escalation has also been shown to be feasible in patients who had received TKI therapy for ≥3 years with either a stable MMR or MR4.0 for ≥12 months.
Response Milestones after First-Line TKI Therapy

The goal of TKI therapy is to achieve a CCyR (≤1% BCR-ABL1 IS) within 12 months after first-line TKI therapy and to prevent disease progression to AP-CML or BP-CML. The guidelines emphasize that achievement of response milestones must be interpreted within the clinical context, before making drastic changes to the treatment strategy.

The panel has included ≤10% BCR-ABL1 IS at 3 and 6 months and ≤1% BCR-ABL1 IS at 12 and 15 months as response milestones after first-line TKI therapy. Patients who achieve these response milestones are considered to have TKI sensitive disease, and continuation of the same dose of TKI and assessment of BCR-ABL1 transcripts with qPCR (IS) every 3 months is recommended for this group of patients.

In patients with a >10% BCR-ABL1 IS at 3 months and >1% BCR-ABL1 IS at 12 months, clinical judgement should be used, considering problems with adherence (which can be common given drug toxicity at initiation of therapy), rate of decline in BCR-ABL1 (the faster, the better), and how far from the cutoff the BCR-ABL1 value falls. That being said, failure to achieve ≤10% BCR-ABL1 IS at 3 months or ≤1% BCR-ABL1 IS at 12 months is associated with a higher risk for disease progression. Patients with >10% BCR-ABL1 at 3 months or >1% BCR-ABL1 at 12 months can continue the same dose of dasatinib or nilotinib or bosutinib for another 3 months. Mutational analysis and evaluation for allogeneic HCT should be considered.

In patients with >10% BCR-ABL1 IS at ≥6 months and those with >1% BCR-ABL1 IS at 15 months are considered to have TKI resistant disease. Evaluation for allogeneic HCT (that is, a discussion with a transplant specialist, which might include HLA testing) is recommended. Alternate treatment options should be considered as described below.

Second-line Therapy

Long-term efficacy data from phase II/III studies on second-line TKI therapy for CP-CML are summarized in Table 6.98-101

Early molecular response (≤10% BCR-ABL1 IS at 3 and 6 months) after second-line TKI therapy with dasatinib or nilotinib has also been reported to be a prognosticator of OS and PFS (Table 7). Patients who do not achieve cytogenetic or molecular responses at 3, 6, or 12 months after second-line and subsequent TKI therapy should be considered for alternative therapies or allogeneic HCT if deemed eligible.

Management of Patients with Inadequate Response to Imatinib

Switching to an alternate TKI is recommended for patients with disease that is resistant to imatinib 400mg daily. Dasatinib, nilotinib, and bosutinib are active against many of the imatinib-resistant BCR-ABL1 kinase domain mutants, except T315I, and are effective treatment options for patients with CP-CML intolerant to imatinib or those with CP-CML resistant to imatinib.98-100

Dose escalation of imatinib up to 800 mg daily has been shown to overcome some of the primary resistance and is particularly effective for cytogenetic relapse in patients who had achieved cytogenetic response with imatinib 400 mg daily, although the duration of responses has
Cardiovascular occlusion, cerebrovascular occlusion, and peripheral arterial occlusive events were reported in 16%, 13%, and 14% of patients, respectively. Ponatinib labeling contains a black box warning regarding vascular occlusion, heart failure, and hepatotoxicity. Cardiovascular risk factors (eg, diabetes mellitus, hypertension, hyperlipidemia, smoking, estrogen use) should be identified and controlled before starting ponatinib. Patients should be monitored for high blood pressure, evidence of arterial occlusive or thromboembolic events, and reduced cardiac function. Ponatinib should be interrupted or stopped immediately for vascular occlusion and for new or worsening heart failure. Patients with cardiovascular risk factors should be referred to a cardiologist.

The recommended initial dose of ponatinib is 45 mg once daily. High dose intensity of ponatinib is significantly associated with increased risk of adverse events. Therefore, dose modifications may be necessary for the management of adverse events. In a post hoc analysis of the PACE trial that assessed the clinical impact of dose modification and dose intensity on outcomes of patients with CP-CML, substantial responses were observed at lower dose levels and the rates of maintenance of MCyR and MMR were high irrespective of the dose-reductions. Thus, an initial dose of 30 mg may be a safer and effective dose for patients with cardiovascular risk factors. Safety and efficacy of ponatinib at initial doses lower than 45 mg are being evaluated in a randomized clinical trial.

Omacetaxine is an option for patients with the T315I mutation and in those with CML that is resistant to ≥2 TKIs. In the CML 202 study, among 62 evaluable patients with T315I and CP-CML resistant to prior
TKI therapy, MCyR, CCyR and MMR were achieved in 23%, 16% and 17% of patients, respectively and the T315I clone declined to below detection limits in 61% of patients.\textsuperscript{111} After a median follow-up of 19 months, the median PFS was 8 months and the median OS had not yet been reached. In the cohort of 46 patients with CP-CML that is resistant to ≥2 TKIs (CML 203 study), MCyR and CCyR were achieved in 22% and 4% of patients, respectively. Median PFS and OS were 7 months and 30 months, respectively.\textsuperscript{112} Omacetaxine had an acceptable toxicity profile and the most common grade 3/4 adverse events were thrombocytopenia (67%), neutropenia (47%), and anemia (37%).\textsuperscript{113}

**Clinical Considerations For The Selection Of Second-Line Therapy**

BCR-ABL kinase domain mutation analysis (see below), evaluation of drug interactions and compliance to therapy are recommended prior to the initiation of second-line TKI therapy.

**Drug Interactions**

Bosutinib, dasatinib, imatinib and nilotinib are metabolized in the liver by cytochrome P450 (CYP) enzymes. Drugs that are CYP3A4 or CYP3A5 inducers may decrease the therapeutic plasma concentration of TKIs, whereas CYP3A4 inhibitors and drugs that are metabolized by the CYP3A4 or CYP3A5 enzyme might result in increased plasma levels of TKIs.\textsuperscript{114} In addition, imatinib is also a weak inhibitor of the CYP2D6 and CYP2C9 isoenzymes and nilotinib is a competitive inhibitor of CYP2C8, CYP2C9, CYP2D6, and UGT1A1, potentially increasing the plasma concentrations of drugs eliminated by these enzymes.

Concomitant use of drugs that are metabolized by these enzymes requires caution and appropriate alternatives should be explored to optimize treatment outcome. If coadministration cannot be avoided, dose modification should be considered.

Concomitant use of H2 blockers or proton pump inhibitors (PPIs) is not recommended in patients receiving dasatinib. If their use is inevitable, they should be administered 12 hours prior to the next dasatinib dose. Concomitant use of PPI is not recommended in patients receiving bosutinib. The use of short-acting antacids or H2 blockers should be considered instead of PPIs.

**Adherence to Therapy**

Treatment interruptions and non-adherence to therapy may lead to undesirable clinical outcomes.\textsuperscript{115-117} In the ADAGIO study, non-adherence to imatinib was associated with poorer response. Patients with suboptimal response missed significantly more imatinib doses (23%) than did those with optimal response (7%).\textsuperscript{115} Adherence to imatinib therapy has been identified as the only independent predictor for achieving complete molecular response (CMR) on standard-dose imatinib.\textsuperscript{116} Poor adherence to imatinib therapy has also been identified as the most important factor contributing to cytogenetic relapse and imatinib failure.\textsuperscript{117} Patients with adherence of ≤85% had a higher probability of losing CCyR at 2 years than those with adherence of >85% (27% and 2%, respectively). Poor adherence to therapy has also been reported in patients receiving dasatinib and nilotinib following imatinib failure.\textsuperscript{118,119}

Patient education on adherence to therapy and close monitoring of patient’s adherence is critical to achieving optimal responses. In a significant proportion of patients with TKI-induced toxicities, responses have been observed with doses well below their determined maximum
tolerated doses. Short interruptions or dose reductions, when medically necessary, may not have a negative impact on disease control or other outcomes. Adequate and appropriate management of side effects and scheduling appropriate follow-up visits to review side effects may be helpful to improve patient adherence to therapy. Switching to an alternate TKI because of intolerance might be beneficial for selected patients with acute grade 3/4 non-hematologic toxicities or in those with low-grade, chronic and persistent adverse events that are not manageable with adequate supportive care measures.

Resistance to TKI Therapy
Aberrant expressions of drug transporters and plasma protein binding of TKI could contribute to primary resistance by altering the intracellular and plasma concentration of TKI. Monitoring imatinib plasma levels may be useful in determining patient adherence to therapy. However, there are no data to support that change of therapy based on plasma imatinib levels will affect treatment outcomes. Pretreatment levels of organic cation transporter 1 (OCT1) have been reported as the most powerful predictor of response to imatinib. On the other hand, cellular uptake of dasatinib or nilotinib seems to be independent of OCT1 expression, suggesting that patients with low OCT1 expression might have better outcomes with dasatinib or nilotinib than with imatinib.

BCR-ABL Kinase Domain Mutation Analysis
Point mutations in the BCR-ABL1 kinase domain are a frequent mechanism of secondary resistance to TKI therapy and are associated with poor prognosis and higher risk of disease progression. Among the BCR-ABL1 kinase domain mutations, the T315I mutation confers the complete resistance to imatinib, dasatinib, nilotinib, and bosutinib.

F317L and V299L mutants are resistant to dasatinib and Y253H, E255K/V, and F359C/V mutants are resistant to nilotinib. E255K/V, F359C/V, Y253H, and T315I mutants are most commonly associated with disease progression and relapse. Bosutinib has demonstrated activity in patients with BCR-ABL1 mutants resistant to dasatinib (F317L) and nilotinib (Y253H, E255K/V, and F359C/I/V). T315I, G250E, and V299L mutants are resistant to bosutinib. Ponatinib is active against other BCR-ABL1 mutants resistant to dasatinib or nilotinib, including E255V, Y253H, and F359V, in addition to T315I. Response rates to TKI therapy based on BCR-ABL mutation status are listed in Table 8.

BCR-ABL kinase domain mutational analysis is helpful in the selection of subsequent TKI therapy for patients with inadequate initial response to first-line or second-line TKI therapy. Treatment options based on BCR-ABL1 mutation status are outlined on CML-5. BCR-ABL mutational analysis provides additional guidance in the selection of subsequent TKI therapy only in patients with identifiable mutations. In patients with no identifiable mutations, the selection of subsequent TKI therapy should be based on the toxicity profile of TKI, patient’s age, ability to tolerate therapy, and the presence of comorbid conditions. Adverse events of second-line TKI therapy in patients with CP-CML summarized in Table 9.

The use of an alternate second generation TKI after treatment failure with two prior TKIs, including a second generation TKI is not associated with durable responses, except in occasional patients with
CP-CML. The guidelines recommend BCR-ABL1 mutational analysis for patients who do not achieve response milestones, for those with any sign of loss of response (hematologic or cytogenetic relapse), and if there is a 1-log increase in BCR-ABL1 level with loss of MMR.

**Rising BCR-ABL1 Transcript Levels**

Rising BCR-ABL1 transcript levels are associated with an increased likelihood of detecting BCR-ABL1 kinase domain mutations and cytogenetic relapse. In patients who had achieved very low levels of BCR-ABL1 transcripts, emergence of BCR-ABL1 mutations was more frequent in those who had more than a 2-fold increase in BCR-ABL1 levels compared to those with stable or decreasing BCR-ABL1. A serial rise has been reported to be more reliable than a single ≥2-fold increase in BCR-ABL1 transcripts. Among patients in CCyR with a ≥0.5-log increase in BCR-ABL1 transcripts on at least two occasions, the highest risk of disease progression was associated with loss of MMR and a more than 1-log increase in BCR-ABL1 transcripts.

The precise increase in BCR-ABL1 transcripts that warrants a mutation analysis depends on the performance characteristics of the qPCR assay. Some labs have advocated a 2- to 3-fold range, while others have taken a more conservative approach (5 – 10-fold). Obviously, some common sense must prevail, since the amount of change in absolute terms depends on the level of molecular response. For example, a finding of any BCR-ABL1 after achieving a deep molecular response (MR4.5; ≤0.0032% BCR-ABL1 IS) is an infinite increase in BCR-ABL1 transcripts. However, a change in BCR-ABL1 transcripts from a barely detectable level to MR4.5 is clearly different from a 5-fold increase in BCR-ABL1 transcripts after achieving MMR.

Currently there are no specific guidelines for changing therapy based on rising BCR-ABL1 levels as detected by qPCR. Changes of therapy based solely on rising BCR-ABL1 levels should be done only in the context of a clinical trial.

**Discontinuation of TKI Therapy (CML-E)**

The feasibility of discontinuation of TKI therapy (with close monitoring) in carefully selected patients who have achieved and maintained deep molecular response (≥MR4.0; ≤0.01% BCR-ABL1 IS) for ≥2 or more years has been evaluated in several clinical studies. Limited longer-term follow-up data from the TKI discontinuation trials are summarized in Table 10.

The possibility of treatment-free remission (TFR) after discontinuation of imatinib was first evaluated in the Stop Imatinib (STIM1) study in 100 patients with a CMR for at least 2 years (5-log reduction in BCR-ABL1 levels and undetectable minimal residual disease on qPCR with a sensitivity of ≥4.5-log reduction from the standardized baseline). With a median follow-up of 77 months after discontinuation of imatinib, the molecular recurrence-free survival was 43% at 6 months and 38% at 60 months. Other subsequent studies that have evaluated the discontinuation of imatinib have also reported similar findings.

More recent studies have also confirmed the feasibility of TFR after discontinuation of dasatinib or nilotinib, in patients with CP-CML who have achieved and maintained MR4.5 for 12 months after ≥2 years of...
TKI therapy in the first-line or second-line setting (TFR rates ranging from 44% to 54%; Table 10).\textsuperscript{161-165} The feasibility of TFR following discontinuation of bosutinib or ponatinib has not yet been evaluated in clinical studies. In the EURO-SKI study that evaluated TFR after discontinuation of any first-line TKI therapy (imatinib, dasatinib or nilotinib) in eligible patients, the type of first-line TKI therapy did not significantly affect molecular relapse-free survival.\textsuperscript{161} Therefore, it is reasonable to assume that the likelihood of TFR following discontinuation would be similar irrespective of TKI in patients who have achieved and maintained deep molecular response (MR4.0; ≤0.01% BCR-ABL1 IS) for ≥2 years.

The results of the RE-STIM study demonstrated the safety of a second TKI discontinuation after a first unsuccessful attempt.\textsuperscript{166} The rate of molecular relapse after the first TKI discontinuation attempt was the only factor significantly associated with outcome. The TFR rate at 24 months after second TKI discontinuation was higher for patients who remained in deep molecular response within the first 3 months after the first TKI discontinuation (72% vs 32% for other patients).

Approximately 40% to 60% of patients who discontinue TKI therapy after achieving deep molecular response experience recurrence within 6 months of treatment cessation, in some cases as early as one month after discontinuation of TKI therapy. Resumption of TKI therapy immediately after recurrence results in the achievement of undetectable disease in almost all patients.\textsuperscript{154-165} TKI withdrawal syndrome (aggravation or new development of musculoskeletal pain and/or pruritus after discontinuation of TKI therapy) has been reported during the TFR period in some TKI discontinuation studies\textsuperscript{160,163,164} and the occurrence of imatinib withdrawal syndrome was associated with a lower rate of molecular relapse in the KID study.\textsuperscript{160}

In the STIM study, molecular relapse (trigger to resume TKI therapy) was defined as positivity for \textit{BCR-ABL1} transcripts by qPCR confirmed by a 1-log increase in \textit{BCR-ABL1} transcripts between two successive assessments or loss of MMR at one point.\textsuperscript{154,155} The results of the A-STIM study showed that loss of MMR (≤0.1% \textit{BCR-ABL1} IS) could be used as a practical criterion for restarting therapy. The estimated probability of MMR loss was 35% at 12 months and 36% at 24 months after discontinuation of imatinib.\textsuperscript{158} Several factors may help predict the risk of relapse after discontinuation of TKI therapy (e.g., a higher Sokal risk score, female gender, lower natural killer cell counts, suboptimal response or resistance to imatinib, duration of TKI therapy and deep molecular response prior to TKI discontinuation).\textsuperscript{154,155,160-165,167} However, only the duration of TKI therapy and deep molecular response prior to TKI discontinuation therapy have been associated with TFR with a high level of consistency.\textsuperscript{154,160,161} In the EURO-SKI study, duration of treatment with imatinib (≥6 years) and deep molecular response duration (MR4.0 for 3 years) were significantly associated with MMR maintenance at 6 months after discontinuation of imatinib.\textsuperscript{161}

Based on the available evidence from clinical studies that have evaluated the feasibility of TFR, the panel members feel that discontinuation of TKI therapy (with close monitoring) is feasible in carefully selected patients (in early CP-CML) who have achieved and maintained a deep molecular response (≥MR4.0) for ≥2 years. Clinical studies that have evaluated the safety and efficacy of discontinuation of
TKI have employed strict eligibility criteria and have mandated more frequent molecular monitoring than typically recommended for patients on TKI therapy. Access to a reliable qPCR (IS) with a sensitivity of detection of at least MR4.5 ($BCR-ABL1 \leq 0.0032\%$ IS) and the availability of test results within 2 weeks is one of the key requirements to monitor patients after discontinuation of TKI therapy and ascertain their safety.

The criteria for the selection of patients suitable for discontinuation of TKI therapy are outlined in CML-E. The guidelines emphasize that discontinuation of TKI therapy outside of a clinical trial should be considered only if ALL of the criteria included in the list are met. The panel acknowledges that more frequent molecular monitoring is essential following discontinuation of TKI therapy for the early identification of loss of MMR. Frequency of molecular monitoring has varied substantially among different studies, and the optimal frequency of molecular monitoring in patients with a loss of MMR after discontinuation of TKI therapy has not been established. The panel recommendations for molecular monitoring in TFR phase are outlined in CML-E.

Management of Advanced Phase CML

Imatinib has induced favorable hematologic and cytogenetic response rates in patients with AP-CML or BP-CML.\textsuperscript{168-172} Dasatinib,\textsuperscript{173,174} nilotinib,\textsuperscript{175,176} bosutinib,\textsuperscript{177} and ponatinib\textsuperscript{101} have demonstrated activity in imatinib-resistant or imatinib-intolerant AP-CML or BP-CML. Long-term follow-up data from phase II/III studies evaluating TKI therapy for disease progression to AP-CML and BP-CML are summarized in Table 11 and Table 12 respectively.

The efficacy of imatinib in combination with decitabine or cytarabine-based chemotherapy in AP-CML and myeloid BP-CML has been demonstrated in several small studies.\textsuperscript{178-181} Hyper-CVAD in combination with imatinib or dasatinib is also effective for patients with lymphoid BP-CML, particularly when followed by allogeneic HCT.\textsuperscript{182,183}

A significant portion of patients with AP-CML or BP-CML treated with TKI therapy achieve a MCyR but not a concomitant CHR because of persistent cytopenias, which in turn is associated with an inferior outcome.\textsuperscript{184} Omacetaxine has shown efficacy in patients with AP-CML that is resistant to multiple TKIs as well as for patients with T315I mutation.\textsuperscript{185} Among the 51 patients with AP-CML, after a median follow-up of 16 months, major hematologic response (MaHR), CHR, and minor cytogenetic response were achieved or maintained in 37%, 29%, and 11% of patients, respectively.\textsuperscript{185} The MaHR rates were 55% and 58%, respectively, for patients with a history of a T315I mutation and for those with confirmed T315I mutation at baseline. The median PFS and OS were 5 months and 18 months, respectively. The most common grade 3/4 hematologic adverse events were thrombocytopenia (51%), anemia (39%), neutropenia (20%), and febrile neutropenia (14%).

Treatment Considerations (CML-4)

Disease progression to AP-CML or BP-CML while on TKI therapy has worse prognosis than de novo AP-CML or BP-CML. Participation in clinical trials and evaluation for allogeneic HCT is recommended for all patients with AP-CML and BP-CML. In patients with disease progression to AP-CML or BP-CML, the selection of TKI therapy is based on prior therapy and/or $BCR-ABL1$ kinase domain mutational analysis.
De-novo AP-CML can often be initially managed like CP-CML with single agent TKI followed by evaluation for allogeneic HCT.\textsuperscript{186,187} However, patients with disease progression from CP-CML to AP-CML while on a TKI therapy have a high rate of progression to BP-CML, with predictably poor survival. These patients should be considered for a clinical trial and/or allogeneic HCT. Treatment with a course of alternate TKI (not received before) will be beneficial as a “bridge” to allogeneic HCT in patients with disease progression. Omacetaxine is also an option for patients with disease progression to AP-CML on TKI therapy.\textsuperscript{185}

TKI in combination with chemotherapy (ALL-type chemotherapy for lymphoid BP-CML and AML-type chemotherapy for myeloid BP-CML) or steroids followed by allogeneic HCT is recommended for de-novo BP-CML and disease progression to BP-CML.

Central nervous system (CNS) involvement has been described in case reports of BP-CML.\textsuperscript{188-191} Lumbar puncture and CNS prophylaxis is recommended for lymphoid BP-CML. Documented CNS involvement in patients with lymphoid BP-CML should be managed according to the standard of care for AML or ALL. Dasatinib has been reported to cross the blood brain barrier and may represent the best TKI option for patients with CNS disease.\textsuperscript{192} TKI therapy has not been optimized for patients with CNS involvement.

**Allogeneic Hematopoietic Cell Transplant**

Allogeneic HCT is a potentially curative treatment for patients with CML. Ongoing advances in alternative donor sources (such as unrelated donors and cord blood), more accurate HLA testing for a stringent selection of unrelated matched donors, and the use of reduced-intensity conditioning regimens have improved outcomes following allogeneic HCT.\textsuperscript{193-199}

Allogeneic HCT is an appropriate treatment option for the very rare patients presenting with BP-CML at diagnosis, patients with disease that is resistant to TKIs, patients with progression to AP-CML or BP-CML while on TKI therapy, and for the rare patients intolerant to all TKIs.\textsuperscript{200-203} Several studies have confirmed that prior TKI therapy does not compromise the outcome following allogeneic HCT or increase transplant-related toxicity.\textsuperscript{204-210}

Disease phase, HLA matching, age and sex of the donor and recipient, and time from diagnosis to transplant have been identified as pretransplant risk factors.\textsuperscript{211} Low HCT comorbidity index has been identified as prognostic indicators of lower non-relapse mortality and an improved survival.\textsuperscript{212} The disease phase at the time of transplant remains an important prognostic factor and the survival outcomes following transplant are clearly better for patients in CP-CML compared to patients with AP-CML or BP-CML.\textsuperscript{213-218} Therefore, the potential use of allogeneic HCT must be tied to faithful monitoring of disease, since the major potential pitfall in delaying transplantation is “missing” the chronic phase interval.

**Monitoring Response after Allogeneic HCT (CML-6)**

BCR-ABL1 transcripts may persist after many years in patients after allogeneic HCT. The prognostic significance of BCR-ABL1 positivity is influenced by the time of testing after allogeneic HCT. A positive qPCR assay for BCR-ABL1 at ≥18 months after allogeneic HCT is associated with a lower risk of relapse than a positive qPCR assay for BCR-ABL1.
at 6 to 12 months after allogeneic HCT. Early detection of BCR-ABL1 transcripts after allogeneic HCT may be useful to identify patients who may be in need of alternative therapies before the onset of a complete relapse.

**Management of Post-transplant Relapse (CML-6)**

Donor lymphocyte infusion (DLI) is effective in inducing durable molecular remissions in the majority of patients with relapsed CML following allogeneic HCT, though it is more effective in patients with chronic phase relapse than advanced phase relapse. However, DLI is associated with complications such as graft-vs-host disease (GVHD), susceptibility to infections, and immunosuppression. Improvements in the methods of detecting BCR-ABL1 transcripts to predict relapse, the development of reduced-intensity conditioning regimens, modified delivery of lymphocytes with the depletion of CD8+ cells, and the use of escalating cell dosage regimens have reduced the incidence of GVHD associated with DLI.

Imatinib induces durable cytogenetic and molecular responses in the majority of patients relapsing with chronic and advanced phase CML following allogeneic HCT, and the response rates are higher in patients with chronic phase relapse than advanced phase relapse. Very limited data are available on the use of dasatinib and nilotinib in patients with post-transplant relapse. There are also data suggesting that the use of DLI in combination with imatinib may be more effective at inducing rapid molecular remissions than either modality alone. Recent retrospective studies have shown that TKIs are superior to DLI alone or in combination with TKI for post-transplant relapse. However, these observations are yet to be confirmed in randomized trials. Post-transplant TKI therapy is also effective to prevent relapse following allogeneic HCT in high-risk patients.

Patients who are in CCyR (qPCR-negative) should undergo regular qPCR monitoring (every 3 months for 2 years, then every 3–6 months thereafter). Given the high risk for hematologic relapse in patients with prior accelerated or blast phase, post-transplant TKI therapy should be considered for at least one year in this cohort of patients who are in remission following allogeneic HCT.

TKI with or without DLI or omacetaxine can be considered for patients who are not in remission or in cytogenetic relapse or those with an increasing level of molecular relapse. The selection of TKI depends on prior TKI, the side effect profile of the TKI under consideration, the presence of comorbidities, and BCR-ABL1 mutational status. Pre-existing mutations in the BCR-ABL1 kinase domain, frequently associated with resistance to TKIs are detectable in the majority of patients who relapse after allogeneic HCT. BCR-ABL1 mutational analysis is therefore essential prior to the selection of TKI for the treatment of post-transplant relapse.

In patients with CML that has previously failed imatinib, there are no data to support the use of post-transplant imatinib, and dasatinib, nilotinib, bosutinib, ponatinib, or omacetaxine may be more appropriate options. However, there are no data to support the use of post-transplant bosutinib, ponatinib, or omacetaxine. CNS relapse of CML following allogeneic HCT has been described in few case reports. Dasatinib may also be an effective treatment for extramedullary relapse following allogeneic HCT. Participation in a clinical trial is highly desirable.
Management of CML During Pregnancy
The median age of disease onset is 67 years, but CML occurs in all age groups. The EUTOS population-based registry has reported that approximately 37% of patients at the time of diagnosis are of reproductive age. Clinical care teams should be prepared to address issues relating to fertility and pregnancy as well as counsel these patients about the potential risks and benefits of treatment discontinuation and possible resumption of TKI therapy should CML recur during pregnancy. Referral to a CML specialty center is recommended.

TKI Therapy and Conception
TKI therapy appears to affect some male hormones at least transiently, but does not appear to have a deleterious effect on fertility in men. Furthermore, the miscarriage or fetal abnormality rate is not higher in female partners of men on TKI therapy.

The situation is more complex for women as TKI therapy during pregnancy has been associated with both a higher rate of miscarriage and fetal abnormalities. Limited evidence from case reports on women with CML exposed to imatinib, dasatinib or nilotinib during pregnancy indicate the need for close monitoring and prompt consideration of holding TKI therapy if pregnancy should occur while on nilotinib or dasatinib. In one report on the outcomes of pregnancies in 180 women exposed to imatinib during pregnancy, 50% of pregnancies with known outcome were normal and 10% of pregnancies with known outcome had fetal abnormalities. Eighteen pregnancies ended in spontaneous abortion. In another report on the outcomes of pregnancy and conception during treatment with dasatinib, among 46 women treated with dasatinib, 15 women (33%) delivered a normal infant. Elective or spontaneous abortions were reported in 18 women (39%) and 8 women (17%), respectively, and 5 women (11%) had an abnormal pregnancy. Fetal abnormalities were reported in 7 cases. Among 33 women fathered by dasatinib-treated men, 30 (91%) delivered infants who were normal at birth. Although there are no data regarding the outcome of pregnancy in patients receiving bosutinib and ponatinib at the time of conception, these agents must be considered unsafe to use in pregnant women.

Discontinuation of TKI therapy because of pregnancy in women who were not in a CMR has only been reported in two small series. In one series, among 10 women who stopped imatinib because of pregnancy after a median of 8 months of therapy, 5 of the 9 women who had achieved a CHR lost the response after stopping therapy, and 6 had an increase in Ph-positive metaphases. At 18 months after resuming therapy, all nine patients had disease progression. The three women who had an MMR at the time imatinib was stopped were able to regain the same response once the drug was restarted, whereas the remaining four patients were not.

Depending on other factors such as age, a natural pregnancy may occur months after stopping TKI therapy. Assuming the earliest time a woman could conceive and give birth naturally, without any wash out period, is 10 months after stopping TKI, the likelihood is about 60% that
her PCR will become positive if she was in a CMR at the time of getting pregnant. It is even higher if she was not in a CMR when she became pregnant.270,271

Planning a Pregnancy

Prior to attempting pregnancy, women and their partners should be counseled that no guidelines exist regarding how best to monitor CML during pregnancy, nor how best to manage progressive disease should it occur during pregnancy. Conception while on active TKI therapy is strongly discouraged due to the risk of fetal abnormalities. Fertility preservation should be discussed with all patients of childbearing age prior to the initiation of TKI therapy.

In men, the general recommendation is that TKI therapy need not be discontinued if a pregnancy is planned. However, experience is limited. Sperm banking can also be performed prior to starting TKI therapy, although there are no data regarding quality of sperm in untreated men with CML.

In women, due to the risk of miscarriage and fetal abnormalities during pregnancy, TKI therapy should be stopped prior to natural conception and the patient should remain off therapy during pregnancy.267-269 Consultation with a high-risk obstetrician is recommended. Referral to an in-vitro-fertilization (IVF) center is recommended in coordination with the patient’s obstetrician. TKI should be stopped prior to attempting a natural pregnancy or oocyte retrieval, but the optimal timing of discontinuation is unknown. Compounding the high incidence of disease recurrence off TKI therapy are the significant obstacles that exist for women who choose one of the above forms of IVF, chief among which is the lack of access to centers that perform the procedure, high costs associated with the drugs and surgical procedures that may not be covered by insurance, costs of embryo/oocyte storage, and access to surrogate programs. Some women may require more than one IVF cycle to obtain enough potentially viable embryos for implantation. In addition, women may need a family medical leave from work to attend IVF appointments. It is also important to note that not all states allow surrogacy.

TKI therapy can be restarted after delivery. If TKI therapy is considered during pregnancy, the potential benefit for the mother and the potential risk to the fetus of continuing TKI therapy vs. the risk of treatment interruption leading to the loss of optimal disease response must be carefully evaluated on an individual basis prior to initiation of TKI therapy. Women on TKI therapy should also be advised not to breast feed, as TKIs pass into human breast milk.272,273

Monitoring and Treatment During Pregnancy

Most of the literature regarding treatment during pregnancy consists of case reports. It is recommended to check monthly blood qPCR, and initiate treatment if the BCR-ABL1 increases to >1.0% IS. Leukapheresis can be used for a rising white blood cell (WBC) count, although there are no data that recommend at what level of WBC count leukapheresis should be initiated.274-277 Low-dose aspirin or low-molecular-weight heparin can be considered for patients with thrombocytosis.278,279

Interferon alpha (in wide range of doses: 3–6 million units every other day to 5–8 million units daily) and hydroxyurea have been used during
pregnancy. The potential risks and benefits should be carefully evaluated in terms of maternal health and fetal risk prior to initiation of treatment during pregnancy, especially during the first trimester.

**Specific Considerations for Children with CML**

CML accounts for less than 3% of all pediatric leukemias. In general, children are diagnosed at a median age of 11 to 12 years, with approximately 10% presenting in advanced phase. As a consequence of its rarity, there are no evidence-based recommendations for the management of CML in the pediatric population. Many pediatric oncologists follow treatment guidelines that are designed for adult patients. However, clinical presentations and host factors are different between children and adults, and some factors should be considered when treating pediatric patients with CML.

**Selection of TKI**

Imatinib, dasatinib and nilotinib are currently approved treatment of CML in children. Higher dose imatinib (340 mg/m²) has also been shown to be effective and well tolerated in children. There are very little data on the safety and efficacy of bosutinib and ponatinib in children.

The validity of prognostic scores (eg, Sokal, Euro, and EUTOS) for risk assessment or to make treatment decisions has not been established in the pediatric population. In an analysis that attempted to validate the three prognostic scoring systems in a cohort of 90 children (median age 12 years), there was a high discordance among the scoring methods. The EUTOS long-term survival (ELTS) score has demonstrated better differentiation of PFS than Sokal and Euro scores in children treated with imatinib.

**Monitoring for Long-Term Side Effects**

Children have a much longer life expectancy than adults and TKI therapy may be needed for many decades; therefore, there are potential long-term side effects (such as delayed growth, changes in bone metabolism, thyroid abnormalities, and effects on puberty and fertility) that may not be seen in adults. A number of studies have reported impaired longitudinal growth in children with CML treated with TKI therapy and the effect is more significant in prepubertal children.

Growth should be monitored closely and a bone age x-ray should be obtained if longitudinal growth is delayed. A dual energy X-ray absorptiometry (DEXA) scan should be obtained if bone mineral density is decreased on plain radiograph or if there is unprovoked fracture. Further evaluation and referral to an endocrinologist is also warranted. Discontinuation of TKI therapy has not been evaluated in the pediatric population and is not recommended outside the context of a clinical trial.

**Immunizations**

There are little data on immune function with patients on TKI therapy, and it potentially hinders routine vaccination for children with CML. In general, the use of inactivated killed vaccines to children on TKI therapy is safe, although it is unknown whether responses are comparable to those seen in healthy children. A study showed a higher seroconversion rate to H1N1 influenza vaccine in adult CML patients compared to patients with B-cell malignancies or HCT recipients. Administration of
live vaccines during TKI therapy is not recommended in general, although one study showed that varicella vaccine could be safely given to some children with immune deficiency. Live attenuated annual influenza vaccine (nasal spray) should be avoided, and the inactivated killed vaccine (flu shot) should be used for children receiving TKI therapy. Live vaccines could be considered after stopping TKI therapy for several weeks in patients with a deep molecular response. In the United States, all required live vaccines are completed by the age of 4 to 6 years (http://www.cdc.gov/vaccines/). As CML is rarely seen in children younger than this age, few patients face this issue.
### Table 1: First-line TKI Therapy for CP-CML: Long-term Follow-up data from Phase III studies

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study Arms</th>
<th>No. of patients</th>
<th>Median Follow-up</th>
<th>CCyR&lt;sup&gt;a&lt;/sup&gt;</th>
<th>MMR&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Disease progression ( %)</th>
<th>PFS&lt;sup&gt;c&lt;/sup&gt;</th>
<th>OS&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IRIS</strong>&lt;sup&gt;44,d&lt;/sup&gt;</td>
<td>Imatinib (400 mg once daily)</td>
<td>553</td>
<td>11 years</td>
<td>83%</td>
<td>—</td>
<td>38 (7%)</td>
<td>92%</td>
<td>83%</td>
</tr>
<tr>
<td></td>
<td>Interferon-alpha plus low-dose cytarabine</td>
<td>553</td>
<td></td>
<td></td>
<td></td>
<td>71 (13%)</td>
<td></td>
<td>79%</td>
</tr>
<tr>
<td><strong>DASISION</strong>&lt;sup&gt;45&lt;/sup&gt;</td>
<td>Dasatinib (100 mg once daily)</td>
<td>259</td>
<td>5 years</td>
<td>—</td>
<td>76%</td>
<td>12 (5%)</td>
<td>85%</td>
<td>91%</td>
</tr>
<tr>
<td></td>
<td>Imatinib (400 mg once daily)</td>
<td>260</td>
<td></td>
<td></td>
<td>64%</td>
<td>19 (7%)</td>
<td>86%</td>
<td>90%</td>
</tr>
<tr>
<td><strong>ENESTnd</strong>&lt;sup&gt;46&lt;/sup&gt;</td>
<td>Nilotinib (300 mg twice daily)</td>
<td>282</td>
<td>5 years</td>
<td>—</td>
<td>77%</td>
<td>10 (4%)</td>
<td>92%</td>
<td>94%</td>
</tr>
<tr>
<td></td>
<td>Nilotinib (400 mg twice daily)</td>
<td>281</td>
<td></td>
<td></td>
<td></td>
<td>77%</td>
<td>96%</td>
<td>96%</td>
</tr>
<tr>
<td></td>
<td>Imatinib (400 mg once daily)</td>
<td>283</td>
<td></td>
<td></td>
<td>60%</td>
<td>21 (7%)</td>
<td>91%</td>
<td>92%</td>
</tr>
<tr>
<td><strong>BFORE</strong>&lt;sup&gt;47,f&lt;/sup&gt;</td>
<td>Bosutinib (400 mg once daily)</td>
<td>268</td>
<td>12 months</td>
<td>77%</td>
<td>47%</td>
<td>4 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Imatinib (400 mg once daily)</td>
<td>268</td>
<td></td>
<td>66%</td>
<td>37%</td>
<td>6 (3%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CCyR, complete cytogenetic response; MMR, major molecular response (≤ 0.1% *BCR-ABL1* IS); OS, overall survival; PFS, progression-free survival

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**a.** Primary end point of DASISION study: Confirmed CCyR rate at 12 months.

**b.** Primary endpoint of ENESTnd and BFORE studies: MMR (≤ 0.1% *BCR-ABL1* IS) rate at 12 months.

**c.** Long-term primary end point of IRIS trial in the imatinib group.

**d.** Due to the high rate of crossover to imatinib (66%) and the short duration of therapy (< 1 year) before crossover among patients who had been randomly assigned to interferon alfa plus cytarabine, the long-term follow-up data focused on patients who had been randomly assigned to receive imatinib.

**e.** Data includes survival among the 363 patients who crossed over to imatinib.

**f.** There were no difference in survival rates between the two treatment arms after a minimum follow up was 12 months; long-term follow up is ongoing.
### Table 2: High-dose Imatinib as First-Line Therapy For CP-CML: Long-Term Follow-up Data From Phase III Studies

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study Arms</th>
<th>No. of patients</th>
<th>Median Follow-up</th>
<th>MMR</th>
<th>MR4.5</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TOPS study</strong>48,a</td>
<td>Imatinib (800 mg once daily)</td>
<td>319</td>
<td>42 months</td>
<td>79%</td>
<td>—</td>
<td>96% at 48 months</td>
<td>93% at 48 months</td>
</tr>
<tr>
<td></td>
<td>Imatinib (400 mg once daily)</td>
<td>157</td>
<td></td>
<td>76%</td>
<td>—</td>
<td>94% at 48 months</td>
<td>94% at 48 months</td>
</tr>
<tr>
<td><strong>CML IV study</strong>50,b</td>
<td>Imatinib (800 mg once daily)</td>
<td>420</td>
<td>10 years</td>
<td>89%</td>
<td>71%</td>
<td>77%</td>
<td>79%</td>
</tr>
<tr>
<td></td>
<td>Imatinib (400 mg once daily)</td>
<td>400</td>
<td></td>
<td>92%</td>
<td>67%</td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td><strong>SWOG study</strong>49,c</td>
<td>Imatinib (800 mg once daily)</td>
<td>73</td>
<td>12 months</td>
<td>53%</td>
<td>19%</td>
<td>92% (4-year PFS)</td>
<td>95% (4-year OS)</td>
</tr>
<tr>
<td></td>
<td>Imatinib (400 mg once daily)</td>
<td>72</td>
<td></td>
<td>36%</td>
<td>9%</td>
<td>80% (4-year PFS)</td>
<td>90% (4-year OS)</td>
</tr>
</tbody>
</table>

MMR, major molecular response (≤ 0.1% BCR-ABL1 IS); MR, molecular response; MR4.5: ≥4.5-log reduction in BCR-ABL1 transcripts from baseline; OS, overall survival; PFS, progression-free survival

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a. Primary end point: MMR rate at 12 months (≤ 0.1% BCR-ABL1) which corresponds to a 3-log reduction in BCR-ABL1 transcripts compared with the standardized baseline established in IRIS study.
b. Primary end point: The impact of MMR on survival at 12 months. This study had 5 treatment arms (imatinib 400 mg once daily alone; imatinib 800 mg twice daily; imatinib 400 mg once daily with interferon or cytarabine; Imatinib after interferon failure. Only the data for imatinib 400 mg once daily alone vs imatinib 800 mg twice daily are included in this table.
c. Primary end point: MR4.0 (≥4-log reduction in BCR-ABL1 transcripts from baseline) at 12 months. Results from the first part of SWOG S0325 study; Follow-up after 12 months was not required for this study.
Table 3: First-line TKI Therapy for CP-CML: Molecular Response Rates According To Sokal Or Euro Risk Score

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study Arms</th>
<th>Low-risk&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>Intermediate-risk&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>High-risk&lt;sup&gt;a,b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MMR</td>
<td>MR4.5</td>
<td>MMR</td>
</tr>
<tr>
<td>DASISION45</td>
<td>Dasatinib (100 mg once daily)</td>
<td>90%</td>
<td>55%</td>
<td>71%</td>
</tr>
<tr>
<td></td>
<td>Imatinib (400 mg once daily)</td>
<td>69%</td>
<td>44%</td>
<td>65%</td>
</tr>
<tr>
<td>ENESTnd46</td>
<td>Nilotinib (300 mg twice daily)</td>
<td>—</td>
<td>53%</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Nilotinib (400 mg twice daily)</td>
<td>—</td>
<td>62%</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Imatinib (400 mg once daily)</td>
<td>—</td>
<td>38%</td>
<td>—</td>
</tr>
<tr>
<td>BFORE47</td>
<td>Bosutinib (400 mg once daily)</td>
<td>58%</td>
<td>—</td>
<td>45%</td>
</tr>
<tr>
<td></td>
<td>Imatinib (400 mg once daily)</td>
<td>46%</td>
<td>—</td>
<td>39%</td>
</tr>
</tbody>
</table>

MMR, major molecular response (≤ 0.1% BCR-ABL1 IS); MR, molecular response; MR4.5: 4.5-log reduction in BCR-ABL1 transcripts from baseline;

<sup>a</sup> DASISION study: Risk stratification by Hasford (Euro) risk score.
<sup>b</sup> ENESTnd and BFORE trial: Risk stratification by Sokal risk score.
Table 4. Adverse Events of First-line TKI Therapy in CP-CML

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>DASISION(^{45})</th>
<th>ENESTnd(^{46})</th>
<th>BFORE(^{47})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dasatinib 100 mg QD</td>
<td>Imatinib 400 mg QD</td>
<td>Nilotinib 300 mg BID</td>
</tr>
<tr>
<td>Hematologic toxicities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Grade 3/4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>13%</td>
<td>9%</td>
<td>4%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>29%</td>
<td>24%</td>
<td>12%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>22%</td>
<td>14%</td>
<td>10%</td>
</tr>
<tr>
<td>Biochemical abnormalities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Grade 3/4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased lipase</td>
<td>NR</td>
<td>NR</td>
<td>9%</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>NR</td>
<td>NR</td>
<td>7%</td>
</tr>
<tr>
<td>Decreased phosphate</td>
<td>7%</td>
<td>28%</td>
<td>8%</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>NR</td>
<td>NR</td>
<td>4%</td>
</tr>
<tr>
<td>Increased AST</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Nonhematologic toxicities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Any grade)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>13%</td>
<td>18%</td>
<td>38%</td>
</tr>
<tr>
<td>Headache</td>
<td>13%</td>
<td>11%</td>
<td>32%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9%</td>
<td>11%</td>
<td>23%</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>23%</td>
<td>41%</td>
<td>12%</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>13%</td>
<td>37%</td>
<td>9%</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>28%</td>
<td>&lt;1%</td>
<td>2%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>NR</td>
<td>NR</td>
<td>10%</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>5%</td>
<td>&lt;1%</td>
<td>0%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21%</td>
<td>22%</td>
<td>19%</td>
</tr>
<tr>
<td>Constipation</td>
<td>NR</td>
<td>NR</td>
<td>20%</td>
</tr>
<tr>
<td>Nausea</td>
<td>10%</td>
<td>24%</td>
<td>22%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5%</td>
<td>11%</td>
<td>15%</td>
</tr>
</tbody>
</table>

ALT, alanine amino transferase; AST, aspartate amino transferase; BID, twice daily; QD, once daily.
* Non-hematologic toxicities from the DASISION study (except pleural effusion) are from the 3-year follow-up. No new adverse events were observed with 5-year follow-up.
Table 5. Early Molecular Response (≤10% BCR-ABL1 IS at 3 months) after First-line TKI Therapy and Survival Outcomes

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study Arms</th>
<th>5-year PFS</th>
<th>5-year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>BCR-ABL1 ≤10%</td>
<td>BCR-ABL1 &gt;10%</td>
</tr>
<tr>
<td>DASISION&lt;sup&gt;45&lt;/sup&gt;</td>
<td>Dasatinib (100 mg once daily)</td>
<td>89%</td>
<td>72%</td>
</tr>
<tr>
<td></td>
<td>Imatinib (400 mg once daily)</td>
<td>93%</td>
<td>72%</td>
</tr>
<tr>
<td>ENESTnd&lt;sup&gt;46&lt;/sup&gt;</td>
<td>Nilotinib (300 mg twice daily)</td>
<td>95%</td>
<td>78%</td>
</tr>
<tr>
<td></td>
<td>Nilotinib (400 mg twice daily)</td>
<td>96%</td>
<td>89%</td>
</tr>
<tr>
<td></td>
<td>Imatinib (400 mg once daily)</td>
<td>98%</td>
<td>79%</td>
</tr>
<tr>
<td>CML IV Study&lt;sup&gt;80&lt;/sup&gt;</td>
<td>Imatinib (400 mg once daily)</td>
<td>92%</td>
<td>87%</td>
</tr>
</tbody>
</table>

OS, overall survival; PFS, progression-free survival
### Table 6. Second-line and Subsequent TKI therapy for CP-CML: Long-Term Follow-Up Data From Phase II/III Studies

<table>
<thead>
<tr>
<th>TKI</th>
<th>No. of Patients</th>
<th>Median Follow-up</th>
<th>MCyR</th>
<th>CCyR</th>
<th>MMR</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dasatinib</strong>&lt;sup&gt;a,98&lt;/sup&gt; (100 mg once daily)</td>
<td>Imatinib-R (n =124)</td>
<td>7 years</td>
<td>—</td>
<td>—</td>
<td>43%</td>
<td>39%</td>
<td>63%</td>
</tr>
<tr>
<td></td>
<td>Imatinib-I (n=43)</td>
<td></td>
<td>—</td>
<td>—</td>
<td>55%</td>
<td>51%</td>
<td>70%</td>
</tr>
<tr>
<td><strong>Nilotinib</strong>&lt;sup&gt;b,99&lt;/sup&gt; (400 mg twice daily)</td>
<td>Imatinib-R (n =226)</td>
<td>4 years</td>
<td>59%</td>
<td>45%</td>
<td>—</td>
<td>57%</td>
<td>78%</td>
</tr>
<tr>
<td></td>
<td>Imatinib (n=95)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bosutinib</strong>&lt;sup&gt;b,100&lt;/sup&gt; (400 mg once daily)</td>
<td>Imatinib and dasatinib-R (n = 38)</td>
<td>4 years</td>
<td>39%</td>
<td>22%</td>
<td>—</td>
<td>—</td>
<td>67%</td>
</tr>
<tr>
<td></td>
<td>Imatinib and dasatinib-I (n =50)</td>
<td></td>
<td>42%</td>
<td>40%</td>
<td>—</td>
<td>—</td>
<td>80%</td>
</tr>
<tr>
<td></td>
<td>Imatinib and nilotinib-R (n=26)</td>
<td></td>
<td>38%</td>
<td>31%</td>
<td>—</td>
<td>—</td>
<td>87%</td>
</tr>
<tr>
<td><strong>Ponatinib</strong>&lt;sup&gt;c,101&lt;/sup&gt; (45 mg once daily)</td>
<td>Dasatinib or nilotinib-R or I (n= 203)</td>
<td>57 months</td>
<td>56%</td>
<td>49%</td>
<td>35%</td>
<td>52% at 5 years</td>
<td>76% at 5 years</td>
</tr>
<tr>
<td></td>
<td>T315I mutation (n= 64)</td>
<td></td>
<td>72%</td>
<td>70%</td>
<td>58%</td>
<td>50% at 5 years</td>
<td>66% at 5 years</td>
</tr>
</tbody>
</table>

R = Resistant; I = Intolerant; CCyR, complete cytogenetic response; MCyR, major cytogenetic response; MMR, major molecular response (≤ 0.1% BCR-ABL1 IS); OS, overall survival; PFS, progression-free survival

**Legend:**
- Primary end point: MCyR rate at 6 months when administered 100 mg once daily vs. 70 mg twice daily.
- Primary endpoint: MCyR rate in patients with imatinib intolerance or imatinib resistant disease.
- Primary endpoint: MCyR at any time within the first 12 months.
Table 7. Early Molecular Response (≤10% BCR-ABL1 IS) after Second-line TKI Therapy and Survival Outcomes

<table>
<thead>
<tr>
<th>TKI</th>
<th>Median Follow-up</th>
<th>Progression-free survival (PFS)</th>
<th>Overall survival (OS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>BCR-ABL1 ≤10%</td>
<td>BCR-ABL1 &gt;10%</td>
</tr>
<tr>
<td></td>
<td>3 months</td>
<td>6 months</td>
<td>3 months</td>
</tr>
<tr>
<td>Dasatinib&lt;sup&gt;98&lt;/sup&gt;</td>
<td>7 years</td>
<td>56%</td>
<td>57%</td>
</tr>
<tr>
<td>(100 mg once daily)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nilotinib&lt;sup&gt;99&lt;/sup&gt;</td>
<td>4 years</td>
<td>67%</td>
<td>58%</td>
</tr>
<tr>
<td>(400 mg twice daily)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 8. Responses Based on BCR-ABL1 Mutations Status

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Major cytogenetic response (MCyR), n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bosutinib\textsuperscript{100}</td>
</tr>
<tr>
<td>E255K\textsuperscript{a}</td>
<td>NR</td>
</tr>
<tr>
<td>E255V\textsuperscript{a}</td>
<td>NR</td>
</tr>
<tr>
<td>E459K</td>
<td>NR</td>
</tr>
<tr>
<td>F317L\textsuperscript{b}</td>
<td>1/7 (14%)</td>
</tr>
<tr>
<td>F359C\textsuperscript{a}</td>
<td>1/2 (50%)</td>
</tr>
<tr>
<td>F359V\textsuperscript{a}</td>
<td>2/3 (67%)</td>
</tr>
<tr>
<td>F359I\textsuperscript{a}</td>
<td>2/2 (100%)</td>
</tr>
<tr>
<td>G250E\textsuperscript{c}</td>
<td>0/5 (0%)</td>
</tr>
<tr>
<td>H396R</td>
<td>NR</td>
</tr>
<tr>
<td>L248V</td>
<td>NR</td>
</tr>
<tr>
<td>M244V</td>
<td>2/3 (67%)</td>
</tr>
<tr>
<td>M351T</td>
<td>NR</td>
</tr>
<tr>
<td>Y253H\textsuperscript{a}</td>
<td>5/6 (83%)</td>
</tr>
<tr>
<td>V299L\textsuperscript{b,c}</td>
<td>0/2 (0%)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} BCR-ABL1 mutations resistant to nilotinib;
\textsuperscript{b} BCR-ABL1 mutations resistant to dasatinib;
\textsuperscript{c} BCR-ABL1 mutations resistant to bosutinib.
### Table 9. Adverse Events of Second-Line and Subsequent TKI Therapy in CP-CML

<table>
<thead>
<tr>
<th>Toxicity (Any grade)</th>
<th>Dasatinib(^{98}) (100 mg QD)</th>
<th>Nilotinib(^{99}) (300 mg BID)</th>
<th>Bosutinib(^{100}) (400 mg QD)</th>
<th>Ponatinib(^{101}) (45 mg QD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>33%</td>
<td>31%</td>
<td>28%</td>
<td>47%</td>
</tr>
<tr>
<td>Headache</td>
<td>—</td>
<td>18%</td>
<td>27%</td>
<td>43%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>37%</td>
<td>21%</td>
<td>24%</td>
<td>30%</td>
</tr>
<tr>
<td>Myalgias/Arthralgias</td>
<td>38%</td>
<td>11%</td>
<td>18%</td>
<td>24%/33%</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>28%</td>
<td>—</td>
<td>17%</td>
<td>—</td>
</tr>
<tr>
<td>Hypertension</td>
<td>—</td>
<td>—</td>
<td>8%</td>
<td>37%</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>26%</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>42%</td>
<td>12%</td>
<td>83%</td>
<td>20%</td>
</tr>
<tr>
<td>Constipation</td>
<td>—</td>
<td>13%</td>
<td>13%</td>
<td>41%</td>
</tr>
<tr>
<td>Nausea</td>
<td>27%</td>
<td>25%</td>
<td>48%</td>
<td>29%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13%</td>
<td>38%</td>
<td>19%</td>
<td></td>
</tr>
<tr>
<td>Increased blood creatinine</td>
<td>—</td>
<td>—</td>
<td>13%</td>
<td>—</td>
</tr>
<tr>
<td>Increased lipase</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>27%</td>
</tr>
<tr>
<td>Increased ALT/AST</td>
<td>—</td>
<td>—</td>
<td>15%</td>
<td>—</td>
</tr>
</tbody>
</table>

ALT, alanine amino transferase; AST, aspartate amino transferase; BID, twice daily; QD, once daily.
### Table 10. Summary of Limited Longer term Follow up Data from the TKI Discontinuation Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment prior to discontinuation</th>
<th>No. of patients</th>
<th>Depth and duration of MR required for discontinuation</th>
<th>Trigger to resume TKI therapy</th>
<th>Median follow-up</th>
<th>Treatment-free remission (TFR) rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>STIM1&lt;sup&gt;155&lt;/sup&gt;</td>
<td>Imatinib ± interferon</td>
<td>100</td>
<td>MR5.0 for at least 2 years</td>
<td>Loss of MR5.0</td>
<td>77 months</td>
<td>38% at 60 months</td>
</tr>
<tr>
<td>TWISTER&lt;sup&gt;156&lt;/sup&gt;</td>
<td>Imatinib ± interferon</td>
<td>40</td>
<td>MR4.5 for at least 2 years</td>
<td>Loss of MR5.0</td>
<td>42 months</td>
<td>47% at 24 months</td>
</tr>
<tr>
<td>HOVON&lt;sup&gt;157&lt;/sup&gt;</td>
<td>Imatinib + cytarabine</td>
<td>15</td>
<td>MR4.5 for at least 2 years</td>
<td>Loss of MR4.5</td>
<td>36 months</td>
<td>33% at 24 months</td>
</tr>
<tr>
<td>A-STIM&lt;sup&gt;158&lt;/sup&gt;</td>
<td>Imatinib ± interferon</td>
<td>80</td>
<td>MR5.0 for at least 2 years</td>
<td>Loss of MMR</td>
<td>31 months</td>
<td>61% at 36 months</td>
</tr>
<tr>
<td>ISAV study&lt;sup&gt;159&lt;/sup&gt;</td>
<td>Imatinib (after failure of interferon or hydroxyurea)</td>
<td>108</td>
<td>CMR for at least 18 months</td>
<td>Loss of MMR</td>
<td>36 months</td>
<td>52% at 36 months</td>
</tr>
<tr>
<td>KID study&lt;sup&gt;160&lt;/sup&gt;</td>
<td>Imatinib ± interferon</td>
<td>90</td>
<td>MR4.5 for at least 2 years</td>
<td>Loss of MMR</td>
<td>27 months</td>
<td>59% at 24 months</td>
</tr>
<tr>
<td>Stop 2G-TKI&lt;sup&gt;162&lt;/sup&gt;</td>
<td>Dasatinib/Nilotinib (first- or second-line)</td>
<td>60</td>
<td>MR4.5 for at least 24 months</td>
<td>Loss of MMR</td>
<td>47 months</td>
<td>54% at 48 months</td>
</tr>
<tr>
<td>ENESTFreedom&lt;sup&gt;163&lt;/sup&gt;</td>
<td>Nilotinib (first-line)</td>
<td>190</td>
<td>MR4.5 for 12 months</td>
<td>Loss of MMR</td>
<td>96 weeks</td>
<td>49% at 96 weeks</td>
</tr>
<tr>
<td>ENESTop study&lt;sup&gt;164&lt;/sup&gt;</td>
<td>Nilotinib (second-line)</td>
<td>126</td>
<td>MR4.5 for 12 months</td>
<td>Loss of MMR</td>
<td>96 weeks</td>
<td>53% at 96 weeks</td>
</tr>
<tr>
<td>DADI&lt;sup&gt;165&lt;/sup&gt;</td>
<td>Dasatinib (second-line)</td>
<td>63</td>
<td>MR4.0 for at least 12 months</td>
<td>Loss of MR4.0</td>
<td>44 months</td>
<td>44% at 36 months</td>
</tr>
<tr>
<td>EURO-SKI&lt;sup&gt;161&lt;/sup&gt;</td>
<td>Any TKI</td>
<td>758</td>
<td>MR4.0 for at least 1 year</td>
<td>Loss of MMR</td>
<td>27 months</td>
<td>50% at 24 months</td>
</tr>
</tbody>
</table>

CMR, complete molecular response (undetectable BCR-ABL1 by qPCR as determined by local laboratories; MMR, major molecular response (≤0.1% BCR-ABL1 IS); MR, molecular response; MR4.0, ≤ 0.01% BCR-ABL1 IS; MR4.5, ≤ 0.0032% BCR-ABL1 IS or >4.5-log reduction of BCR-ABL1 and undetectable minimal residual disease on qPCR with a sensitivity of ≥4.5-log reduction; MR5.0, 5-log reduction in BCR ABL1 levels and undetectable minimal residual disease on qPCR with a sensitivity of ≥4.5-log reduction;
Table 11. TKI Therapy for Disease progression to AP-CML: Long-term follow-up data from Phase II/III studies

<table>
<thead>
<tr>
<th>TKI</th>
<th>No. of Patients</th>
<th>Median Follow-up</th>
<th>MCyR</th>
<th>CCyR</th>
<th>OS</th>
<th>PFS</th>
</tr>
</thead>
</table>
| **Dasatinib**\(^a\)\(^,\)\(^173\)  
(140 mg once daily)          | Imatinib-R (n =117)  | 24 months        | 36%  | 29%  | 63% | 51% |
|                              | Imatinib-I (n=41)  |                  | 46%  | 41%  |     |     |
| **Nilotinib**\(^b\)\(^,\)\(^175\)  
(400 mg twice daily)         | Imatinib-R (n = 109) | 24 months        | 30%  | 19%  | 70% | 33% |
|                              | Imatinib-I (n = 27) |                  | 41%  | 30%  |     |     |
| **Bosutinib**\(^c\)\(^,\)\(^177\)  
(500 mg once daily)          | Prior imatinib only (n = 49) | 48 months   | 48%  | 35%  | 66% |     |
|                              | Imatinib followed by dasatinib or nilotinib (n =30) |       | 27%  | 23%  | 45% |     |
| **Ponatinib**\(^d\)\(^,\)\(^101\)  
(45 mg once daily)           | Dasatinib or nilotinib-R or I (n =65) | 32 months   | 45%  | 28%  | 48% at 5 years | 19% |
|                              | T315I mutation (n= 18) |                  | 67%  | 44%  | 52% at 5 years | 29% |

R = Resistant; I= Intolerant; CCyR, Complete cytogenetic response; MCyR, major cytogenetic response; OS, overall survival; PFS, progression-free survival

---

a. Primary endpoint: Major hematologic response, achieved in 66% and 68% of patients respectively, in the dasatinib, 140 mg once daily and 70 mg twice daily groups.
b. Primary endpoint: Confirmed complete hematologic response rate, achieved in 30% of patients with imatinib-resistant disease and 37% of imatinib-intolerant patients.
c. Primary endpoint: Confirmed overall hematologic response by 48 weeks.
d. Primary endpoint: Major hematologic response at any time within the first 6 months.
### Table 12. TKI Therapy for Disease progression to BP-CML: Long-term follow-up data from Phase II/III studies

<table>
<thead>
<tr>
<th>TKI</th>
<th>No. of Patients</th>
<th>Median Follow-up</th>
<th>MCyR</th>
<th>CCyR</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dasatinib&lt;sup&gt;a,174&lt;/sup&gt; (140 mg once daily)</td>
<td>Lymphoid blast phase (n=33)</td>
<td>24 months</td>
<td>50%</td>
<td>38%</td>
<td>21%</td>
</tr>
<tr>
<td></td>
<td>Myeloid blast phase (n=75)</td>
<td></td>
<td>25%</td>
<td>14%</td>
<td>24%</td>
</tr>
<tr>
<td>Nilotinib&lt;sup&gt;b,176&lt;/sup&gt; (400 mg twice daily)</td>
<td>Lymphoid blast phase (n =31)</td>
<td>24 months</td>
<td>52%</td>
<td>32%</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>Myeloid blast phase (n = 105)</td>
<td></td>
<td>38%</td>
<td>30%</td>
<td>32%</td>
</tr>
<tr>
<td>Bosutinib&lt;sup&gt;c,177&lt;/sup&gt; (500 mg once daily)</td>
<td>Prior imatinib only (n = 36)</td>
<td>48 months</td>
<td>50%</td>
<td>37%</td>
<td>28%</td>
</tr>
<tr>
<td></td>
<td>Imatinib followed by dasatinib or nilotinib (n =28)</td>
<td></td>
<td>21%</td>
<td>17%</td>
<td>17%</td>
</tr>
<tr>
<td>Ponatinib&lt;sup&gt;d,101&lt;/sup&gt; (45 mg once daily)</td>
<td>Dasatinib or nilotinib-R or I (n =38)</td>
<td>6 months</td>
<td>18%</td>
<td>16%</td>
<td>9% at 3 years</td>
</tr>
<tr>
<td></td>
<td>T315I mutation (n= 24)</td>
<td></td>
<td>29%</td>
<td>21%</td>
<td></td>
</tr>
</tbody>
</table>

R = Resistant; I= Intolerant; CCyR, complete cytogenetic response; MCyR, major cytogenetic response; OS, overall survival;

---

<sup>a</sup> Primary endpoint: Major hematologic response  
<sup>b</sup> Endpoints: Duration of major hematologic response and MCyR, and OS.  
<sup>c</sup> Primary endpoint: Confirmed overall hematologic response by 48 weeks.  
<sup>d</sup> Major hematologic response at any time within the first 6 months.
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