NCCN Clinical Practice Guidelines in Oncology
(NCCN Guidelines®)

Chronic Myeloid Leukemia

Overall management of Chronic Myeloid Leukemia from diagnosis through relapse is described in the full NCCN Guidelines® for Chronic Myeloid Leukemia. Visit NCCN.org to view the complete library of NCCN Guidelines.
### RESPONSE MILESTONES\(^{c,e}\)

<table>
<thead>
<tr>
<th>BCR-ABL1 (IS)</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
<th>&gt;12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10%(^{f})</td>
<td>YELLOW</td>
<td></td>
<td>RED</td>
<td></td>
</tr>
<tr>
<td>&gt;1%–10%</td>
<td></td>
<td>GREEN</td>
<td>YELLOW</td>
<td>RED</td>
</tr>
<tr>
<td>&gt;0.1%–1%</td>
<td>GRE    (\text{en}\)N</td>
<td></td>
<td>GREEN</td>
<td>YELLOW</td>
</tr>
<tr>
<td>≤0.1%</td>
<td>GRE    (\text{en}\)N</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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#### CLINICAL CONSIDERATIONS

- **RED**
  - Evaluate patient compliance and drug interactions
  - Mutational analysis

- **YELLOW**
  - Evaluate patient compliance and drug interactions
  - Mutational analysis

- **GREEN**
  - Monitor response (CML-F) and side effects

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#### SECOND-LINE AND SUBSEQUENT TREATMENT OPTIONS

- Switch to alternate TKI (CML-5) and Evaluate for HCT (CML-6)
- Switch to alternate TKI (CML-5) or Continue same TKI (CML-F)\(^{g}\) or Dose escalation of imatinib (to a max of 800 mg) and Evaluate for HCT (CML-6)
- Continue same TKI (CML-F)\(^{h}\)

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\(^{c}\)See Monitoring Response to TKI Therapy and Mutational Analysis (CML-C).

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

\(^{f}\)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.

\(^{g}\)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.

\(^{h}\)Discontinuation of TKI with careful monitoring is feasible in selected patients. See Discontinuation of TKI Therapy (CML-E).

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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.
### TREATMENT OPTIONS BASED ON BCR-ABL1 MUTATION PROFILE

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

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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>Bone marrow cytogenetics(^1)</td>
<td>• At diagnosis</td>
</tr>
<tr>
<td></td>
<td>• Failure to reach response milestones</td>
</tr>
<tr>
<td></td>
<td>• Any sign of loss of response (defined as hematologic or cytogenetic relapse)</td>
</tr>
<tr>
<td>Quantitative RT-PCR (qPCR) using IS</td>
<td>• At diagnosis</td>
</tr>
<tr>
<td></td>
<td>• 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</td>
</tr>
<tr>
<td></td>
<td>• If there is 1-log increase in BCR-ABL1 transcript levels with MMR, qPCR should be repeated in 1–3 months</td>
</tr>
<tr>
<td>BCR-ABL kinase domain mutation analysis</td>
<td>• Chronic phase</td>
</tr>
<tr>
<td></td>
<td>‣ Failure to reach response milestones</td>
</tr>
<tr>
<td></td>
<td>‣ Any sign of loss of response (defined as hematologic or cytogenetic relapse)</td>
</tr>
<tr>
<td></td>
<td>‣ 1-log increase in BCR-ABL1 transcript levels and loss of MMR</td>
</tr>
<tr>
<td></td>
<td>• Disease progression to accelerated or blast phase</td>
</tr>
</tbody>
</table>

\(^1\)FISH 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 109/L
- Platelet count <450 x 109/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
- Partial cytogenetic response (PCyR) - 1%–35% Ph-positive metaphases
- Major cytogenetic response - 0%–35% Ph-positive metaphases
- Minor cytogenetic response - >35% 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)

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

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MANAGEMENT OF PONATINIB TOXICITY1

- Vascular occlusion: Arterial and venous thrombosis and occlusions, including fatal myocardial infarction and stroke, have occurred in patients treated with ponatinib. Monitor for evidence of thromboembolism and vascular occlusion. Interrupt or stop ponatinib immediately for vascular occlusion.
- 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 (e.g., diabetes mellitus [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.
- Ponatinib is also associated with grade ≥3 skin rash and pancreatitis leading to dose modifications (dose delays or dose reductions).

Dosing

- The recommended initial dose of ponatinib is 45 mg once daily. However, an initial starting dose of 30 mg may be a safer and effective dose for patients with risk factors. Safety and efficacy of ponatinib at initial doses lower than 45 mg is being evaluated in a randomized clinical trial.

Dose Adjustments:

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.
- Growth factors can be used in combination with ponatinib for patients with resistant neutropenia and thrombocytopenia.
- 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

- Liver transaminase >3 x ULN (grade ≥2): Monitor hepatic function. Hold drug until serum levels are <3 x IULN. Resume at lower dose after recovery (30 mg if patient receiving 45 mg; 15 mg if patient receiving 30 mg). Discontinue ponatinib if patient receiving 15 mg.
- AST or ALT ≥3 x ULN concurrent with bilirubin ≥2 x ULN and alkaline phosphatase ≥2 x ULN: Discontinue ponatinib.

- Rash: topical or systemic steroids, dose reduction, interruption, or discontinuation of ponatinib as clinically indicated.
- Hypertension: Monitor and manage blood pressure elevations.
- Fluid retention events (i.e., edema, ascites, pleural and pericardial effusion) are managed with dose interruption, dose reduction, or discontinuation of ponatinib as clinically indicated.
- Pancreatitis (symptomatic), grade 3: Hold drug until serum lipase levels are ≥3 x ULN. Resume at lower dose after recovery (30 mg if patient receiving 45 mg; 15 mg if patient receiving 30 mg). Discontinue ponatinib if patient receiving 15 mg.
- Pancreatitis (symptomatic), grade 4: Discontinue ponatinib if patient receiving 15 mg.
- 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

- Serum lipase elevation, grade 1 or 2 (asymptomatic): Consider dose interruption or reduction. Serum lipase elevation, grade 3 or 4 (>2 x IULN) (asymptomatic) or asymptomatic radiologic pancreatitis: Hold drug until serum levels are <1.5 x ULN. Resume at lower dose after recovery (30 mg if patient receiving 45 mg; 15 mg if patient receiving 30 mg). Discontinue ponatinib if patient receiving 15 mg.
- Heart failure has occurred in patients treated with ponatinib.
- 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 (e.g., diabetes mellitus [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.
- Ponatinib is also associated with grade ≥3 skin rash and pancreatitis leading to dose modifications (dose delays or dose reductions).

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 the Centers for Medicare & Medicaid Services (CMS) and the U.S. Food and Drug Administration (FDA) do not support the use of erythropoiesis-stimulating agents (ESAs) in myeloid malignancies.

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