Chronic Myelogenous Leukemia

Version 4.2013

NCCN.org
NCCN Guidelines Version 4.2013 Panel Members
Chronic Myelogenous Leukemia

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**Summary of Guidelines Updates (Updates)**

- Workup (CML-1)
- Primary Treatment (CML-1)
- 3-Month Follow-up Therapy (CML-2)
- 12-Month Follow-up Therapy (CML-3)
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**Recommendations for Monitoring Response to TKI Therapy and Mutational Analysis (CML-A)**

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- Management of Nilotinib Toxicity (CML-E)
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- Management of Bosutinib Toxicity (CML-G)
- Management of Ponatinib Toxicity (CML-H)
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**Criteria for Hematologic, Cytogenetic, and Molecular Response (CML-J)**

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**Definitions of Accelerated Phase (CML-L)**

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**NCCN Guidelines Version 4.2013 Updates**

**Chronic Myelogenous Leukemia**

**Summary of changes in the 4.2013 version of the NCCN Chronic Myelogenous Leukemia Guidelines from the 3.2013 version include:**

**CML-1**
- Footnote “g” modified: “There is 24-36 36-48 month follow-up data for dasatinib (DASISION study) and nilotinib (ENESTnd study) demonstrating superior cytogenetic and molecular response rates at certain time points and lower rates of progression to accelerated or blast phase compared to imatinib.”
- Footnote “j” modified: “Consider bosutinib, ponatinib, IFN/PEG-IFN, allogeneic HSCT or clinical trial for rare patients unable to tolerate imatinib, dasatinib, or nilotinib, or bosutinib. Bosutinib and ponatinib are not approved for first-line therapy.”

**CML-2**
- Response wording modified: “BCR-ABL transcript levels ≤10% by RT-PCR using the International Scale (IS)...” and “BCR-ABL/ABL >10% by RT-PCR using the International Scale (IS)...”
- Previous listing of “Change therapy to alternate second generation TKI” modified to “Change therapy to alternate second generation TKI (other than imatinib)”
- Footnote “p” added: “Consider IFN/PEG-IFN, allogeneic HSCT, omacetaxine, or clinical trial for rare patients unable to tolerate TKI therapy.” (also applies to CML-3, CML-4)
- Footnote “r” added: “See Management of Ponatinib Toxicity (CML-H)” (also applies to CML-3, CML-4, CML-5, CML-6)
- Footnote “s” modified: Patients with failure to first-line imatinib should be treated with nilotinib, dasatinib, bosutinib, or ponatinib in the second-line setting. Patients with failure to first-line nilotinib or dasatinib could be treated with an alternate second-generation TKI (other than imatinib) in the second-line setting. (also applies to CML-3, CML-4, CML-5)

**CML-3**
- Complete cytogenetic response and partial cytogenetic response
  - Recommendation modified to “Continue same dose of TKI”
- Partial cytogenetic response, minor or no cytogenetic response and cytogenetic relapse
  - Change therapy recommendation modified to “Change therapy to alternate TKI (preferred) (other than imatinib)”
- Partial cytogenetic response, minor or no cytogenetic response and cytogenetic relapse
  - Recommendation for “Increase dose of imatinib to a maximum of 800 mg, as tolerated” modified, “if not a candidate for alternate TKI dasatinib, nilotinib, bosutinib, or omacetaxine.”

**CML-4**
- Complete cytogenetic response and partial cytogenetic response
  - Recommendation modified to “Continue same dose of TKI”
  - Partial cytogenetic response and molecular relapse
  - Change therapy recommendation modified to “Change therapy to alternate TKI (preferred) (other than imatinib)”

**CML-5**
- Workup
  - Mutational analysis clarified “in TKI pretreated patients”
  - Accelerated phase
  - Ponatinib 45 mg once daily added as a treatment option.

**CML-6**
- Follow-up Therapy
  - Ponatinib added as a treatment option.
- Footnote “cc” modified: “There are data to support the use of posttransplant imatinib but not in patients who have previously failed imatinib. Other TKIs may be more appropriate. Very limited data are available on the use of dasatinib and nilotinib in a small number of patients posttransplant relapse. There are no data for the use of bosutinib, ponatinib, or omacetaxine for patients posttransplant.”

**CML-A**
- Molecular responses with ponatinib in patients with Philadelphia chromosome positive (Ph+) leukemia: results from the PACE trial. ASH Annual Meeting Abstracts 2012;120:3763.
- Footnote “4” added: “Omacetaxine is a treatment option for patients with resistance and/or intolerance to two or more tyrosine kinase inhibitors (TKIs).”

**CML-H**
- New page added listing information related to the management of ponatinib toxicity.

**CML-K**
- Treatment Recommendations changed to Treatment Options.
- Mutation T315I: Ponatinib added as a “preferred” treatment option.
- All other mutations: Ponatinib added as a treatment option.
- Footnote “4” added: “Omacetaxine is a treatment option for patients with resistance and/or intolerance to two or more tyrosine kinase inhibitors (TKIs).”

**MS-1**
- The Discussion section updated to reflect the changes in the algorithm.
Summary of changes in the 3.2013 version of the NCCN Chronic Myelogenous Leukemia Guidelines from the 2.2013 version include:

CML-1
- Footnote “j” modified: “Consider IFN/PEG-IFN, allogeneic HSCT or clinical trial for rare patients unable to tolerate imatinib, dasatinib, nilotinib, or bosutinib. (also applies to CML-2, CML-3, CML-4)

CML-2
- BCR-ABL transcript levels >10% by QPCR using the International Scale (IS) or < PCyR on bone marrow cytogenetics
  - Previous listing of dasatinib 100 mg once daily and Nilotinib 400 mg BID deleted and replaced with “Change therapy to alternate second generation TKI.”
  - Monitoring added with QPCR at least every 3 mo.
- Footnote “p” added: “See Management of Bosutinib Toxicity (CML-G).” (also applies to CML-3, CML-4, CML-5, CML-6)
- Footnote “q” modified: Patients with failure to first-line imatinib should be treated with nilotinib, dasatinib, or bosutinib in the second-line setting. Patients with failure to first-line nilotinib or dasatinib could be treated with the an alternate second generation TKI in the second-line setting. (also applies to CML-3, CML-4, CML-5, CML-6)
- Footnote “r” added: “Omacetaxine is a treatment option for patients with resistance and/or intolerance to two or more TKIs. See Management of Omacetaxine Toxicity (CML-H).” (also applies to CML-3, CML-4, CML-6)

CML-3
- Complete cytogenetic response
  - Bosutinib added as an option for continuation.
- Partial cytogenetic response and cytogenetic relapse
  - Bosutinib added as an option for continuation.
  - Recommendation for “Increase dose of imatinib to a maximum of 800 mg, as tolerated” modified, if not a candidate for dasatinib, nilotinib, bosutinib, or omacetaxine.

CML-4
- Complete cytogenetic response
  - Bosutinib added as an option for continuation.
- Partial cytogenetic response and cytogenetic relapse
  - Previous listing of dasatinib 100 mg once daily and Nilotinib 400 mg BID deleted and replaced with “Change therapy to alternate second generation TKI.”

CML-5
- Accelerated phase
  - Bosutinib 500 mg once daily added as a treatment option.
  - Omacetaxine added as a treatment option with footnote “y”: “Omacetaxine is a treatment option for patients with disease progression due to resistance and/or intolerance to two or more TKIs. See Management of Omacetaxine Toxicity (CML-H).”

CML-6
- Patients in remission or not in relapse
  - Bosutinib added as a treatment option.
  - Omacetaxine added as a treatment option.
- Footnote “aa” modified: “There are data to support the use of imatinib posttransplant but not in patients who have previously failed imatinib. Other TKIs may be more appropriate although there are no published data to support their use posttransplant. Very limited data are available on the use of dasatinib and nilotinib in a small number of patients with posttransplant relapse. There are no data for the use of bosutinib or omacetaxine for patients posttransplant.”

CML-G
- New page added listing information related to the management of bosutinib toxicity.

CML-H
- New page added listing information related to the management of omacetaxine toxicity.

CML-J
- Mutation T315I: Omacetaxine added as a treatment option
- Mutation V299L placed on separate row with the following treatment recommendation: Consider nilotinib or omacetaxine rather than dasatinib or bosutinib.
- Mutation T315A: Imatinib added as a treatment option with a footnote “If mutation detected following dasatinib.”
- Mutations T315A, F317L/V/I/C: Bosutinib and omacetaxine added as treatment recommendations.
- Any other mutation: Bosutinib and omacetaxine added as treatment recommendations.

MS-1
- The Discussion section updated to reflect the changes in the algorithm.
Summary of changes in the 2.2013 version of the NCCN Chronic Myelogenous Leukemia Guidelines from the 1.2013 version include:

CML-3
- Partial cytogenetic response (PCyR): “preferred” added to “change therapy to alternate second generation TKI.”
- PCyR: “preferred” removed from “continue same dose of nilotinib or dasatinib”
- Minor or no cytogenetic response: “Dasatinib 100 mg once daily or Nilotinib 400 mg BID” removed and replaced with “change therapy to alternate second generation TKI (preferred).”
- Cytogenetic relapse: “Dasatinib 100 mg once daily or Nilotinib 400 mg BID” removed and replaced with “change therapy to alternate second generation TKI (preferred).”

CML-A
- Mutational analysis recommendations modified: If there is inadequate initial response (failure to achieve PCyR or BCR-ABL/ABL ≤10% (IS) at 3 months or < PCyR at 12 or < CCyR at 12 and 18 months), any sign of loss of response (defined as hematologic or cytogenetic relapse or 1 log increase in BCR-ABL transcript levels and loss of MMR).

Summary of changes in the 1.2013 version of the NCCN Chronic Myelogenous Leukemia Guidelines from the 2.2012 version include:

CML-1
- Workup: Differential added to CBC.
- Workup: Consider HLA testing modified: HLA testing, if considering HSCT.
- Workup: QPCR moved to it’s own bullet with option from blood or bone marrow.
- Footnote “b” modified: HSCT = hematopoietic stem cell transplantation. Refers to a matched related or unrelated allogeneic transplant. HLA testing should be performed if considering allogeneic HSCT. Indications and outcomes of allogeneic HSCT are dependent on related and unrelated transplant: age, donor type and transplant center-dependent. Nonmyeloablative HSCT is under investigation and should be performed only in the context of a clinical trial. (also applies to CML-2 through CML-6)
- Footnote “f” modified: There is 8-year follow-up data from the IRIS study which show clear evidence of excellent survival benefit with imatinib.
- Footnote “g” modified: There is 24-36 month follow-up data for dasatinib (DASISION study) or nilotinib (ENESTed study) demonstrating superior cytogenetic and molecular response rates at certain time points and lower rates of progression to accelerated or blast phase compared to imatinib. Long term survival benefit has not been established yet. See discussion for additional information. Preliminary data from these studies also suggest that patients with an intermediate- or high-risk score may preferentially benefit from dasatinib or nilotinib.

CML-2
- 3-month evaluation: response criteria changed from “Complete hematologic response” or “Less than complete hematologic response” to “BCR-ABL transcript levels ≤ 10% by QPCR using the International Scale (IS) or partial cytogenetic response (PCyR) on bone marrow cytogenetics” or “BCR-ABL transcript levels > 10% by QPCR using the International Scale (IS) or < PCyR on bone marrow cytogenetics.”
- For the new category “BCR-ABL transcript levels ≤ 10% by QPCR using the International Scale (IS) or partial cytogenetic response (PCyR) on bone marrow cytogenetics,” the following added: “Monitor with QPCR every 3 mo” with further options for “Relapse” and “No relapse.”
- For the new category “BCR-ABL transcript levels > 10% by QPCR using the International Scale (IS) or < PCyR on bone marrow cytogenetics,” “Consider bone marrow cytogenetics deleted” and “consider” deleted before “mutational analysis.”
Summary of changes in the 1.2013 version of the NCCN Chronic Myelogenous Leukemia Guidelines from the 2.2012 version include:

**CML-2**
- Footnote “n” modified: “Same dose of TKI should be continued indefinitely and not be discontinued. Discontinuation of TKI should only be done in the setting of a clinical trial. See discussion for details.” (also applies to CML-3 and CML-4)
- Footnote “o” modified: There are some data regarding the efficacy of second-generation TKIs against specific mutations. See Treatment Options Based on BCR-ABL KD Mutation Status CML-H. (also applies to CML-3 and CML-4)
- Footnote “p” modified: Patients with failure to first-line imatinib should be treated with nilotinib or dasatinib in the second-line setting. Patients with failure to first-line nilotinib or dasatinib, could be treated with the alternate second generation TKI in the second-line setting. (Also applies to CML-3 through CML-6)

**CML-3**
- 12-mo evaluation with bone marrow cytogenetics if neither complete cytogenetic response (CCyR) nor major molecular response (MMR) is achieved.
  - Partial cytogenetic response: “Evaluate patient compliance and drug-drug interactions” and “Consider mutational analysis” added prior to treatment.
  - Partial cytogenetic response and cytogenetic relapse: “preferred” added to “continue same dose of nilotinib or dasatinib.”
  - Partial cytogenetic response and cytogenetic relapse: “if not candidate for nilotinib or dasatinib” added to “increase dose of imatinib...”

**CML-4**
- 18-mo evaluation bone marrow cytogenetics if not in MMR and lack of CCyR at 12 mo.

**CML-5**
- Workup: Cytochemistry (if available).
- Footnote “v” deleted: Patients presenting with de novo Ph+ acute lymphoblastic leukemia (ALL) or de novo blast phase should be considered for combination chemotherapy + TKI (imatinib or dasatinib) or clinical trial. See NCCN ALL Guidelines.
- Footnote “s” is new to the page: “For de novo accelerated phase, the single agent dose for imatinib is 600 mg.”

**CML-6**
- Footnote “x” deleted: “See Management of IFN Toxicity (CML-K)”

**CML-A**
- Bone marrow cytogenetics, bullets 2, 3, and 4 added:
  - At 3 months from initiation of therapy if QPCR using the International Scale (IS) is not available to assess response to TKI therapy.
  - At 12 months from initiation of therapy, if neither CCyR nor MMR is achieved.
  - At 18 months from initiation of therapy, if not in MMR and lack of CCyR at 12 months.
- BCR-ABL kinase domain mutational analysis, chronic phase modified:
  - If there is inadequate initial response (failure to achieve PCyR or BCR-ABL/ABL ≤10% (IS) at 3 months, major cytogenetic response at 12 months or < PCyR at 12 or < CCyR at 18 months), any sign of loss of response (defined as hematologic or cytogenetic relapse or 1 log increase in BCR-ABL transcript levels and loss of MMR).
Discussion

Summary of changes in the 1.2013 version of the NCCN Chronic Myelogenous Leukemia Guidelines from the 2.2012 version include:

**CML-C**
- Dasatinib or nilotinib added as treatment options for symptomatic leukocytosis.

**CML-D**
- The following bullet added: Consider ECG, if patient taking a QT prolonging medication.

**CML-E**
- The following information added: **Rare but serious toxicities**: Peripheral arterial occlusive disease: Nilotinib may be associated with an increased risk of vascular adverse events, including peripheral arterial occlusive disease (PAOD). Evaluate patients for pre-existing PAOD and for vascular risk factors prior to initiating nilotinib and during treatment. If PAOD is confirmed, nilotinib should be permanently discontinued.
- The following bullet added: Consider ECG, if patient taking a QT prolonging medication.

**CML-F**
- The following information added: **Rare but serious toxicities**: Pulmonary Arterial Hypertension: Dasatinib may increase the risk of developing pulmonary arterial hypertension (PAH) which may occur anytime 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.

**CML-G**
- Molecular response, the following added: QPCR with a sensitivity of at least 4.5 logs below the standardized baseline.

**CML-H**

**CML-I**
- The following footnote added: “The above table refers to myeloblasts. Any increase in lymphoblasts is concerning for (nascent) blast crisis.”

**CML-J**

**CML-K**
- The attachment page “Management of Interferon Toxicity” deleted.
**WORKUP**

- **H&P, including spleen size by palpation (cm below costal margin)**
- **CBC with differential, platelets**
- **Chemistry profile**
- **HLA testing, if considering allogeneic HSCT**
- **Bone marrow aspirate and biopsy**
  - Morphologic review
  - Percent blasts
  - Percent basophils
- **Cytogenetics**
- **FISH**
- **Quantitative RT-PCR (QPCR) using International Scale (IS)** (blood or bone marrow)
- **Determine risk score** ([See Risk Calculation Table CML-B](#))

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**PRIMARy TREATMENT**

![Flowchart showing treatment options](#)

- **Ph negative and BCR-ABL negative**
  - Evaluate for other diseases (not CML)

- **Ph positive or BCR-ABL positive**
  - Discussion of treatment options
    - Tyrosine kinase inhibitor (TKI)
    - Role of HSCT
    - Clinical trial
  - Imatinib 400 mg (category 1)
  - Nilotinib 300 mg BID (category 1)
  - Dasatinib 100 mg daily (category 1)

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**Discussion**

- There are data suggesting a faster time to MMR with a higher dose of imatinib, but whether this is an important endpoint in long-term outcome is unknown. Cortes JE, Baccarani M, Guilhot F, et al. Phase III, randomized, open-label study of daily imatinib mesylate 400 mg versus 800 mg in patients with newly diagnosed, previously untreated chronic myeloid leukemia in chronic phase using molecular end points: tyrosine kinase inhibitor optimization and selectivity study. J Clin Oncol 2010;28:424-430.

- There is 8-year follow-up data from the IRIS study which show clear evidence of excellent survival benefit with imatinib.

- There is 36-48 month follow-up data for dasatinib (DASISION study) and nilotinib (ENESTnd study) demonstrating superior cytogenetic and molecular response rates at certain time points and lower rates of progression to accelerated or blast phase compared to imatinib. Long term survival benefit has not been established yet. Preliminary data from these studies also suggest that patients with an intermediate- or high-risk score may preferentially benefit from dasatinib or nilotinib. See discussion for additional information.

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

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**3 MONTH FOLLOW-UP THERAPY**

- **BCR-ABL/ABL ≤ 10% (IS) or partial cytogenetic response (PCyR) on bone marrow cytogenetics**
  - Continue same dose of Imatinib or Nilotinib or Dasatinib
  - Evaluate patient compliance and drug-drug interactions
  - Mutational analysis

- **No relapse**
  - Monitor with QPCR every 3 mo

- **See 12-Month Follow-up Therapy (CML-3)**

- **Relapse**
  - Change therapy to alternate TKI (other than imatinib) and Evaluate for HSCT depending on response to second-line therapy
  - See CML-6
  - Monitor with QPCR at least every 3 mo

- **BCR-ABL/ABL > 10% by QPCR (IS) or < PCyR on bone marrow cytogenetics**
  - Evaluate patient compliance and drug-drug interactions
  - Mutational analysis

- **See Recommendations for Monitoring Response to TKI Therapy and Mutational Analysis (CML-A).**
- **HSCT = hematopoietic stem cell transplantation. Indications and outcomes of allogeneic HSCT are dependent on age, donor type and transplant center.**
- **No myeloablative HSCT is under investigation and should be performed only in the context of a clinical trial.**
- **See Management of Imatinib Toxicity (CML-D).**
- **See Management of Nilotinib Toxicity (CML-E).**
- **See Management of Dasatinib Toxicity (CML-F).**
- **See Criteria for Hematologic, Cytogenetic, and Molecular Response (CML-J).**
- **Same dose of TKI should be continued indefinitely. Discontinuation of TKI should only be done in the setting of a clinical trial. See discussion for details.**
- **See Treatment Options Based on BCR-ABL KD Mutation Status CML-K.**
- **Consider IFN/PEG-IFN, allogeneic HSCT, omacetaxine, or clinical trial for rare patients unable to tolerate TKI therapy.**
- **See Management of Bosutinib Toxicity (CML-G).**
- **See Management of Ponatinib Toxicity (CML-H).**
- **Patients with failure to first-line imatinib should be treated with nilotinib, dasatinib, bosutinib, or ponatinib in the second-line setting. Patients with failure to first-line nilotinib or dasatinib could be treated with an alternate TKI (other than imatinib) in the second-line setting.**
- **Omacetaxine is a treatment option for patients with resistance and/or intolerance to two or more TKIs. See Management of Omacetaxine Toxicity (CML-I).**
12 MONTH FOLLOW-UP THERAPY

<table>
<thead>
<tr>
<th>Complete cytogenetic response</th>
<th>Partial cytogenetic response</th>
<th>Minor or no cytogenetic response</th>
<th>Cytogenetic relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continue same dose of TKI</td>
<td>Evaluate patient compliance and drug-drug interactions</td>
<td>Evaluate patient compliance and drug-drug interactions</td>
<td>Evaluate patient compliance and drug-drug interactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mutual analysis of mutational analysis</td>
<td></td>
</tr>
<tr>
<td>Change therapy to alternate TKI (preferred) (other than imatinib)</td>
<td>Change therapy to alternate TKI (preferred) (other than imatinib)</td>
<td>Change therapy to alternate TKI (preferred) (other than imatinib)</td>
<td>Change therapy to alternate TKI (preferred) (other than imatinib)</td>
</tr>
<tr>
<td>or Continue same dose of TKI</td>
<td>or Increase dose of imatinib to a maximum of 800 mg, as tolerated</td>
<td>or Increase dose of imatinib to a maximum of 800 mg, as tolerated</td>
<td>or Increase dose of imatinib to a maximum of 800 mg, as tolerated</td>
</tr>
<tr>
<td>or Evaluate for HSCT depending on response to second-line therapy (See CML-6)</td>
<td>or Clinical trial</td>
<td>or Clinical trial</td>
<td>and Evaluate for HSCT depending on response to second-line therapy (See CML-6)</td>
</tr>
</tbody>
</table>

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**See Recommendations for Monitoring Response to TKI Therapy and Mutational Analysis (CML-A).**

**See Management of Imatinib Toxicity (CML-D).**

**See Management of Dasatinib Toxicity (CML-F).**

**See Criteria for Hematologic, Cytogenetic, and Molecular Response (CML-J).**

**See Treatment Options Based on BCR-ABL KD Mutation Status CML-K.**

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a See Recommendations for Monitoring Response to TKI Therapy and Mutational Analysis (CML-A).
b HSCT = hematopoietic stem cell transplantation. Indications and outcomes of allogeneic HSCT are dependent on age, donor type and transplant center. Nonmyeloablative HSCT is under investigation and should be performed only in the context of a clinical trial.
c See Management of Bosutinib Toxicity (CML-G).
d See Management of Ponatinib Toxicity (CML-H).
e Patients with failure to first-line imatinib should be treated with nilotinib, dasatinib, bosutinib, or ponatinib in the second-line setting. Patients with failure to first-line nilotinib or dasatinib could be treated with an alternate TKI (other than imatinib) in the second-line setting.
f Omacetaxine is a treatment option for patients with resistance and/or intolerance to two or more TKIs. See Management of Omacetaxine Toxicity (CML-I).
g There are no data to support a definitive treatment option for patients with a suboptimal response. Alternate treatment options may be considered.
18 MONTH FOLLOW-UP THERAPY

**Complete cytogenetic response**
- Continue same dose of TKI

**Partial cytogenetic response**
- Evaluate patient compliance and drug-drug interactions
- Mutational analysis

**Cytogenetic relapse**
- Evaluate patient compliance and drug-drug interactions
- Mutational analysis

**See Advanced Phase (CML-5)**

Change therapy to alternate TKI (preferred) (other than imatinib) and Evaluate for HSCT depending on response to second-line therapy (See CML-6) or Clinical trial

Change therapy to alternate TKI (preferred) (other than imatinib) and Evaluate for HSCT depending on response to second-line therapy (See CML-6) or Clinical trial

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

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
HSCT = hematopoietic stem cell transplantation. Indications and outcomes of allogeneic HSCT are dependent on age, donor type and transplant center.

Nonmyeloablative HSCT is under investigation and should be performed only in the context of a clinical trial.

See Management of Nilotinib Toxicity (CML-E).
See Management of Dasatinib Toxicity (CML-F).
See Management of Bosutinib Toxicity (CML-G).
See Management of Ponatinib Toxicity (CML-H).

Patients with failure to first-line imatinib should be treated with nilotinib, dasatinib, bosutinib, or ponatinib in the second-line setting. Patients with failure to first-line nilotinib or dasatinib could be treated with an alternate TKI (other than imatinib) in the second-line setting.

See Definitions of Accelerated Phase (CML-M).
See Definitions of Blast Crisis (CML-M).

In patients with disease progression, the selection of TKI is based on prior therapy and/or mutational testing. There are some data regarding the efficacy of second generation TKIs against specific mutations. See Treatment Options Based on BCR-ABL KD Mutation Status CML-K.

Consider CNS prophylaxis/treatment.

Omacetaxine is a treatment option for patients with disease progression due to resistance and/or intolerance to two or more TKIs. See Management of Omacetaxine Toxicity (CML-I).

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

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

- **Complete cytogenetic remission**
  - QPCR monitoring (peripheral blood) every 3 mo for 2 years, then 6 mo for 3 years
  - Positive
  - Negative

- **Not in remission, or in relapse**
  - Monitored withdrawal of immune suppression

---

**HSCT**
- Hematopoietic stem cell transplantation. Indications and outcomes of allogeneic HSCT are dependent on age, donor type and transplant center. Nonmyeloablative HSCT is under investigation and should be performed only in the context of a clinical trial.

**Discussion options with transplant team:**
- Imatinib or dasatinib
- Nilotinib or bosutinib
- Ponatinib or omacetaxine
- Donor lymphocyte infusion (DLI)
- IFN/PEG-IFN
- Clinical trial

**Omacetaxine**
- A treatment option for patients with resistance and/or intolerance to two or more tyrosine kinase inhibitors (TKIs). See Management of Omacetaxine Toxicity (CML-I).

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

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
## RECOMMENDATIONS FOR MONITORING RESPONSE TO TKI THERAPY AND MUTATIONAL ANALYSIS

<table>
<thead>
<tr>
<th>Test</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| Bone marrow cytogenetics                  | - At diagnosis to establish the disease phase. If collection of bone marrow is not feasible, FISH on a peripheral blood specimen using dual probes for the \( BCR \) and \( ABL \) genes is an acceptable method of confirming the diagnosis of CML.  
- At 3 months from initiation of therapy if QPCR using the International Scale (IS) is not available to assess response to TKI therapy.  
- At 12 months from initiation of therapy, if neither CCyR nor MMR is achieved.  
- At 18 months from initiation of therapy, if not in MMR and lack of CCyR at 12 months.  
- Rising levels of \( BCR-ABL \) transcript (1 log increase) without a MMR. |
| Quantitative RT-PCR (QPCR) using IS       | - At diagnosis  
- Every 3 months when a patient is responding to treatment. After CCyR has been achieved, every 3 months for 3 years and every 3-6 months thereafter.  
- If there is a rising levels of \( BCR-ABL \) transcript (1 log increase) with a MMR, QPCR analysis should be repeated in 1-3 months. |
| BCR-ABL kinase domain mutation analysis    | - Chronic phase  
- If there is inadequate initial response (failure to achieve PCyR or \( BCR-ABL/ABL \leq 10\% \) (IS) at 3 months or CCyR at 12 and 18 months), any sign of loss of response (defined as hematologic or cytogenetic relapse or 1 log increase in \( BCR-ABL \) transcript levels and loss of MMR).  
- Disease progression to accelerated or blast phase. |

---


2FISH has been inadequately studied for monitoring response to treatment.

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

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Calculation</th>
<th>Risk Definition by Calculation</th>
</tr>
</thead>
</table>
| Sokal et al, 1984¹     | \[
Exp 0.0116 \times (\text{age in years} - 43.4) + (\text{spleen} - 7.51) + 0.188 \times \\
[(\text{platelet count} \div 700)^2 - 0.563] + 0.0887 \times (\text{blast cells} - 2.10)\] | Low: < 0.8          |
|                        |                                                                            | Intermediate: 0.8 - 1.2  |
|                        |                                                                            | High: > 1.2            |
| Hasford et al, 1998²   | \[
0.666 \text{ when age} \geq 50 \text{ years} + (0.042 \times \text{spleen}) + 1.0956 \text{ when} \\
\text{platelet count} > 1500 \times 10^6/L + (0.0584 \times \text{blast cells}) + 0.20399 \text{ when} \\
\text{basophils} > 3\% + (0.0413 \times \text{eosinophils}) \times 100\] | Low: ≤ 780         |
|                        |                                                                            | Intermediate: 781 - 1480 |
|                        |                                                                            | High: > 1480          |

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.


SUPPORTIVE CARE STRATEGIES FOR LEUKOCYTOSIS AND THROMBOCYTOSIS

Factors to consider when choosing treatment include: patient’s age, risk factors for thromboembolic disease, and degree of thrombocytosis.

Symptomatic leukocytosis:
- Treatment options include hydroxyurea, apheresis, imatinib, dasatinib, nilotinib, or clinical trial

Symptomatic thrombocytosis:
- Treatment options include hydroxyurea, antiaggregants, anagrelide or apheresis

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

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
MANAGEMENT OF IMATINIB TOXICITY\textsuperscript{1,2}

**Hematologic**

- **Grade 3-4 neutropenia** [absolute neutrophil count (ANC) $< 1000$ mm\(^3\)]: Hold drug until ANC $\geq 1500$ mm\(^3\), then resume imatinib at the starting dose of 400 mg. If recurrence of ANC $< 1000$ mm\(^3\), hold drug until ANC $\geq 1500$ mm\(^3\), then resume imatinib at reduced dose of 300 mg.
- **Grade 3-4 thrombocytopenia** (platelet count $< 50,000$ mm\(^3\)): Hold drug until platelet count $\geq 75,000$ mm\(^3\), then resume imatinib at the starting dose of 400 mg. If recurrence of platelet count $< 50,000$ mm\(^3\), hold drug until platelet count $\geq 75,000$ mm\(^3\), then resume imatinib at reduced dose of 300 mg.
- **Accelerated phase and blast phase**: Patients may have cytopenias related to disease. If cytopenia is unrelated to disease, reduce dose to 400 mg. If cytopenia persists 2 weeks, reduce dose further to 300 mg. If cytopenia persists for 4 weeks, stop imatinib until ANC $\geq 1000$ mm\(^3\) and platelet count $\geq 20,000$ mm\(^3\), and then resume treatment at 300 mg.
- **Growth factors** can be used in combination with imatinib for patients with resistant neutropenia.\textsuperscript{3}
- **Grade 3-4 anemia**\textsuperscript{4}

**Non-hematologic**

- **Grade 2-3**: Use specific interventions, listed above. If not responsive to symptomatic measures, treat as Grade 4.
- **Grade 4**: Hold drug until grade 1 or better, then consider resuming dose at 25-33\% dose reduction (not less than 300 mg). Consider change to dasatinib, nilotinib or clinical trial.

**Consider ECG, if patient taking a QT interval prolonging medication.**

**Non-hematologic - Liver**

- **Grade 2**, hold drug until grade $\leq 1$. Resume at 25-33\% dose reduction (not less than 300 mg). Evaluate for other hepatotoxic drugs that may be contributing to toxicity, including acetaminophen. Consider change to dasatinib, nilotinib or clinical trial.
- **Grade 3-4**: Consider change to dasatinib, nilotinib or clinical trial.

**Specific Interventions**

- **Diarrhea**: supportive care
- **Edema**: diuretics, supportive care
- **Fluid retention** (pleural effusion, pericardial effusion, edema, and ascites): diuretics, supportive care, dose reduction, interruption or discontinuation. Consider echocardiogram to check 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

\textsuperscript{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).

\textsuperscript{2}Many toxicities are self-limiting; consider re-escalating dose at a later time.


\textsuperscript{4}Although erythropoietin is effective, guidelines from the Centers for Medicaid & Medicare Services (CMS) and the Food and Drug Administration (FDA) do not support the use of Erythropoietic Stimulating Agents (ESAs) in myeloid malignancies.
MANAGEMENT OF NILOTINIB TOXICITY\(^1\)

- Nilotinib prolongs the QT interval. Sudden deaths have been reported in patients receiving nilotinib.
- Nilotinib should not be used in patients with hypokalemia, hypomagnesemia, or long QT syndrome. Hypokalemia or hypomagnesemia must be corrected prior to nilotinib administration and should be periodically monitored.
- Drugs known to prolong the QT interval and strong CYP3A4 inhibitors should be avoided.
- ECGs should be obtained to monitor the QTc at baseline, seven days after initiation, and periodically thereafter, as well as following any dose adjustments.
- Patients should avoid food 2 hours before and 1 hour after taking dose.
- A dose reduction is recommended in patients with hepatic impairment.

**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. Resume within 2 weeks at prior dose if QTcF is less than 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 QTc returns to > 480 msec, nilotinib should be discontinued. ECG should be obtained 7 days after any dose adjustment to monitor QTc.

**Hematologic**

- Grade 3-4 neutropenia (absolute neutrophil count [ANC] < 1000/mm\(^3\)): Hold drug until ANC is ≥ 1000/mm\(^3\), resume at prior dose if recovery occurs within 2 weeks, or reduce the dose to 400 mg once daily, if ANC is < 1000/mm\(^3\) for more than 2 weeks.
- Grade 3-4 thrombocytopenia (platelet count < 50,000/mm\(^3\)): Hold drug until the platelet count is ≥ 50,000/mm\(^3\), resume at prior dose if recovery occurs within 2 weeks or reduce the dose to 400 mg once daily, if platelet count is < 50,000/mm\(^3\) for more than 2 weeks.
- Growth factors can be used in combination with nilotinib for patients with resistant neutropenia and thrombocytopenia.
- Grade 3-4 anemia\(^2\)

**Non-hematologic**

- Grade 2-3: Use specific interventions, listed above. If not responsive to symptomatic measures, treat as Grade 4
- Grade 4: Hold drug until grade 1 or better, and then resume at reduced dose level (400 mg once daily). If clinically appropriate, consider escalating dose to 300-400 mg twice daily, depending on starting dose.

**Non-hematologic - Liver**

- Elevated serum levels of lipase, amylase, bilirubin and/or hepatic transaminases (grade ≥ 3): Hold drug until serum levels return to grade ≤ 1. Resume nilotinib at 400 mg once daily.

**Rare but serious toxicities:**

Peripheral arterial occlusive disease: Nilotinib may be associated with an increased risk of vascular adverse events, including peripheral arterial occlusive disease (PAOD). Evaluate patients for pre-existing PAOD and for vascular risk factors prior to initiating nilotinib and during treatment. If PAOD is confirmed, nilotinib should be permanently discontinued.

**Specific Interventions**

- Headache: Supportive care
- Nausea: Supportive care
- Diarrhea: Supportive care
- Rash: Topical or systemic steroids, dose reduction, interruption or discontinuation

\(^1\)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 the Centers for Medicaid & Medicare Services (CMS) and the Food and Drug Administration (FDA) do not support the use of Erythropoietic Stimulating Agents (ESAs) in myeloid malignancies.

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

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

Hematologic

- Grade 4 neutropenia (absolute neutrophil count [ANC] < 500/mm³): Hold drug until ANC ≥ 1000/mm³, resume at original starting dose if recovery occurs within 7 days or reduce one dose level if ANC < 500/mm³ for more than 7 days.
- Grade 3-4 thrombocytopenia (platelet count < 50,000/mm³): Hold drug until platelet count ≥ 50,000/mm³, resume at original starting dose if recovery occurs within 7 days or reduce one dose level if platelet count < 25,000/mm³ for more than 7 days.
- Accelerated phase and blast phase: Patients may have cytopenias related to disease. If cytopenia is unrelated to disease, hold drug until ANC ≥ 1000/mm³ and platelet count ≥ 20,000/mm³, resume at original starting dose or reduce one dose level if cytopenia persists. If cytopenia is related to leukemia, consider dose escalation to 180 daily.

Non-hematologic

- Grade 2-3: Use specific interventions, listed above
- Grade 4: Hold drug until grade 1 or better, and then consider resuming at reduced dose level depending on the severity of the initial event or change to nilotinib.
- Consider ECG, if patient taking a QT prolonging medication.

Rare but serious toxicities:

Pulmonary Arterial Hypertension: Dasatinib may increase the risk of developing pulmonary arterial hypertension (PAH) which may occur anytime 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 (ascites, edema, pleural and pericardial effusion) are managed with diuretics, supportive care
- Pleural/pericardial effusion: diuretics, dose interruption. If patient has significant symptoms, consider short course of steroids (prednisone 20 mg/day x 3); when resolved, reduce one dose level.
- Headache: Supportive care
- GI upset: take medication with a meal and large glass of water
- Diarrhea: supportive care
- Rash: topical or systemic steroids, dose reduction, interruption or discontinuation

1 Please refer to package insert for full prescribing information and monitoring of hematologic or biochemical abnormalities, available at www.fda.gov.

2 Although erythropoietin is effective, recent guidelines from the Centers for Medicaid & Medicare Services (CMS) and the Food and Drug Administration (FDA) do not support the use of Erythropoietic Stimulating Agents (ESAs) in myeloid malignancies.
MANAGEMENT OF BOSUTINIB TOXICITY¹

Hematologic

- Grade 3-4 neutropenia (absolute neutrophil count [ANC] <1000/mm³): Hold drug until ANC is ≥1000/mm³. 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.
- Grade 3-4 thrombocytopenia (platelet count <50,000/mm³): Hold drug until the platelet count is ≥50,000/mm³. 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.

Non-hematologic

- Elevated liver transaminases: If elevations in liver transaminases greater than 5 x institutional upper limit of normal (ULN) occur, withhold bosutinib until recovery to less than or equal to 2.5 x ULN and resume at 400 mg once daily thereafter. If recovery takes longer than 4 weeks, discontinue bosutinib. If transaminase elevations greater than or equal to 3 x ULN occur concurrently with bilirubin elevations greater than 2 x ULN and alkaline phosphatase less than 2 x ULN (Hy’s law case definition), discontinue bosutinib.
- Diarrhea: For NCI CTCAE Grade 3-4 diarrhea (increase of greater than or equal to 7 stools/day over baseline/pretreatment), withhold bosutinib until recovery to Grade less than or equal to 1. Bosutinib may be resumed at 400 mg once daily.
- For other clinically significant, moderate or severe non-hematological 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 concentration 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 (pulmonary and or peripheral edema, pleural and pericardial effusion) are managed with diuretics, supportive care.
- GI upset: take medication with a meal and large glass of water.
- Diarrhea: supportive care.
- 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.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
MANAGEMENT OF PONATINIB TOXICITY¹

Hematologic
- Grade 3-4 neutropenia (absolute neutrophil count [ANC] <1000/mm³): First occurrence: Hold drug until ANC ≥1500/mm³ and resume at initial dose. Second occurrence: Hold drug until ANC ≥1500/mm³ and resume at 30 mg. Third occurrence: Hold drug until ANC ≥1500/mm³ and resume at 15 mg.
- Grade 3-4 thrombocytopenia (platelet count < ): First occurrence: Hold drug until platelet count ≥75,000/mm³ and resume at initial dose. Second occurrence: Hold drug until platelet count ≥75,000/mm³ and resume at 30 mg. Third occurrence: Hold drug until platelet count ≥75,000/mm³ and resume at 15 mg.

Non-Hematologic
- Hepatic Toxicity
  - Elevation of liver transaminase (Grade ≥2): Hold drug until serum levels return to Grade ≤1 and resume at lower dose (30 mg if patient receiving 45 mg; 15 mg if patient receiving 30 mg). Discontinue ponatinib if patient receiving 15 mg.
  - Elevation of AST or ALT ≥3 x upper limit of normal (ULN) concurrent with an elevation of bilirubin >2 x ULN and alkaline phosphatase >2 x ULN: Discontinue ponatinib.
  - Elevation of serum lipase
    - Grade 1 or 2: Consider interruption or dose reduction.
    - Grade 3 or 4: Hold drug until serum levels return to Grade ≤1 and resume lower dose (30 mg if patient receiving 45 mg; 15 mg if patient receiving 30 mg). Discontinue ponatinib if patient receiving 15 mg.

- Pancreatitis
  - Grade 2 or 3: Hold drug until serum lipase levels return to Grade ≤1 and complete resolution of symptoms. Resume at lower dose (30 mg if patient receiving 45 mg; 15 mg if patient receiving 30 mg). Discontinue ponatinib if patient receiving 15 mg.
  - Grade 4: Discontinue ponatinib

Rare but serious toxicities
- Arterial Thrombosis: Cardiovascular, cerebrovascular, and peripheral vascular thromboses, including fatal myocardial infarction and stroke have occurred in patients treated with ponatinib. Interrupt and consider discontinuation of ponatinib in patients who develop arterial thrombotic events.
- Venous Thromboembolism: Venous thromboembolic events including deep venous thrombosis, pulmonary embolism, portal vein thrombosis and retinal vein thrombosis have been reported in patients treated with ponatinib. Consider dose modification or discontinuation of ponatinib in patients who develop serious venous thromboembolism.
- Congestive heart failure or left ventricular dysfunction: Consider discontinuation of ponatinib in patients who develop serious congestive heart failure.
- Hemorrhage: Hemorrhagic events were reported in clinical trials. Cerebral and gastrointestinal hemorrhage were the most commonly reported serious bleeding events. Serious or severe 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 (edema, ascites, pleural and pericardial effusion) are 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.

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

Hematologic
- Complete blood counts (CBCs) should be performed weekly during induction and initial maintenance cycles. After initial maintenance cycles, monitor CBCs every two weeks or as clinically indicated. Monitor platelet counts as part of the CBC monitoring as recommended.
- Grade 4 neutropenia (absolute neutrophil count [ANC] less than 0.5 x 10^9/L): Delay starting the next cycle until ANC is greater than or equal to 1.0 x 10^9/L and reduce the number of dosing days by 2 days for the next cycle.
- Grade 3 thrombocytopenia (platelet counts less than 50 x 10^9/L): Delay starting the next cycle until platelet count is greater than or equal to 50 x 10^9/L and reduce the number of dosing days by 2 days for the next cycle. Avoid anticoagulants, aspirin, and non-steroidal anti-inflammatory drugs (NSAIDs) when the platelet count is less than 50,000/µL as they may increase the risk of bleeding.

Non-hematologic
- 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 until good glycemic control has been established.
- Manage other clinically significant non-hematologic toxicity symptomatically. Interrupt and/or delay omacetaxine until toxicity is resolved.

Specific Interventions
- Diarrhea: supportive care.

Please refer to package insert for full prescribing information and monitoring of hematologic or biochemical abnormalities, available at www.fda.gov.
CRITERIA FOR HEMATOLOGIC, CYTOGENETIC AND MOLECULAR RESPONSE

Complete hematologic response 1
- 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 2,3
- Complete- No Ph-positive metaphases
- Partial- 1%-35% Ph-positive metaphases
- Major- 0%-35% Ph-positive metaphases (complete + partial)
- Minor- >35% Ph-positive metaphases

Molecular response 4,5
- Complete molecular response - no detectable BCR-ABL mRNA by QPCR (International scale) using an assay with a sensitivity of at least 4.5 logs below the standardized baseline.
- Major molecular response - ≥3-log reduction in International Scale of BCR-ABL mRNA

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2A minimum of 20 metaphases should be examined.


### TREATMENT OPTIONS BASED ON BCR-ABL KD MUTATION STATUS

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>T315I</td>
<td>Ponatinib (preferred), omacetaxine, HSCT, or clinical trial</td>
</tr>
<tr>
<td>V299L</td>
<td>Consider ponatinib or nilotinib or omacetaxine(^4)</td>
</tr>
<tr>
<td>T315A</td>
<td>Consider ponatinib, nilotinib, imatinib,(^5)bosutinib, or omacetaxine(^4)</td>
</tr>
<tr>
<td>F317L/V/I/C</td>
<td>Consider ponatinib, nilotinib, or bosutinib, or omacetaxine(^4)</td>
</tr>
<tr>
<td>Y253H, E255K/V, F359V/C/I</td>
<td>Consider ponatinib, dasatinib, or bosutinib, or omacetaxine(^4)</td>
</tr>
<tr>
<td>Any other mutation</td>
<td>Consider ponatinib, high dose imatinib,(^6) dasatinib, nilotinib, bosutinib, or omacetaxine(^4)</td>
</tr>
</tbody>
</table>

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4. Omacetaxine is a treatment option for patients with resistance and/or intolerance to two or more tyrosine kinase inhibitors (TKIs).
5. If mutation detected following dasatinib.
6. There are not sufficient data on dose escalation available to indicate if mutations with lower IC\(_{50}\) values are sensitive to high dose imatinib.

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

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

<table>
<thead>
<tr>
<th>Criteria of Sokal et al&lt;sup&gt;1&lt;/sup&gt;</th>
<th>International Bone Marrow Transplant Registry Criteria&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Criteria Used at M.D. Anderson Cancer Center&lt;sup&gt;3&lt;/sup&gt;</th>
<th>World Health Organization (WHO) Criteria&lt;sup&gt;4&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Peripheral blood or marrow blasts ≥ 5%</td>
<td>• Leukocyte count difficult to control with hydroxyurea or busulfan</td>
<td>• Peripheral blood blasts ≥ 15%</td>
<td>• Blasts 10-19% of WBCs in peripheral and/or nucleated bone marrow cells</td>
</tr>
<tr>
<td>• Basophils &gt; 20%</td>
<td>• Rapid leukocyte doubling time (&lt; 5 days)</td>
<td>• Peripheral blood blasts and promyelocytes ≥ 30%</td>
<td>• Peripheral blood basophils ≥ 20%</td>
</tr>
<tr>
<td>• Platelet count ≥ 1000 x 10⁹/L despite adequate therapy</td>
<td>• Peripheral blood or marrow blasts ≥ 10%</td>
<td>• Peripheral blood basophils ≥ 20%</td>
<td>• Persistent thrombocytopenia (&lt; 100 x 10⁹/L) unrelated to therapy, or persistent thrombocytosis (&gt; 1000 x 10⁹/L) unresponsive to therapy</td>
</tr>
<tr>
<td>• Clonal evolution</td>
<td>• Peripheral blood or marrow blasts and promyelocytes ≥ 20%</td>
<td>• Platelet count ≤ 100 x 10⁹/L unrelated to therapy</td>
<td>• Increasing spleen size and increasing WBC count unresponsive to therapy</td>
</tr>
<tr>
<td>• Frequent Pelger-Huet-like neutrophils, nucleated erythrocytes, megakaryocyte nuclear fragments</td>
<td>• Peripheral blood basophils and eosinophils ≥ 20%</td>
<td>• Clonal evolution</td>
<td>• Cytogenetic evidence of clonal evolution</td>
</tr>
<tr>
<td>• Marrow collagen fibrosis</td>
<td>• Anemia or thrombocytopenia unresponsive to therapy</td>
<td>• Progressive splenomegaly</td>
<td></td>
</tr>
<tr>
<td>• Anemia or thrombocytopenia unrelated to therapy</td>
<td>• Leukocyte doubling time &lt; 5 days</td>
<td>• Development of myelofibrosis</td>
<td></td>
</tr>
<tr>
<td>• Progressive splenomegaly</td>
<td>• Fever of unknown origin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The above table refers to myeloblasts. Any increase in lymphoblasts is concerning for (nascent) blast crisis.

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**DEFINITIONS OF BLAST CRISIS**

<table>
<thead>
<tr>
<th>World Health Organization (WHO) Criteria</th>
<th>International Bone Marrow Transplant Registry</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blasts ≥ 20% of peripheral blood white cells or of nucleated bone marrow cells</strong></td>
<td><strong>≥ 30% blasts in the blood, marrow, or both</strong></td>
</tr>
<tr>
<td><strong>Extramedullary blast proliferation</strong></td>
<td><strong>Extramedullary infiltrates of leukemic cells</strong></td>
</tr>
<tr>
<td><strong>Large foci or clusters of blasts in the bone marrow biopsy</strong></td>
<td></td>
</tr>
</tbody>
</table>

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1 Adapted from Swerdlow SH, Campo E, Harris NL, et al. WHO classification of Tumours of Haematopoietic and Lymphoid Tissues, IARC, Lyon, 2008.


---

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

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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 3-5 years. Gene expression profiling has shown a close correlation of gene expressions 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. 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.

Sokal and Hasford are the two prognostic scoring systems available for the risk stratification of patients with CML (Table 1). The Sokal score is based on the patient’s age, spleen size, platelet count, and percentage of blasts in the peripheral blood. The Hasford model includes eosinophils and basophils in the peripheral blood in addition to the same clinical variables used in the Sokal model. Both of these scoring systems stratify patients into three risk groups (low, intermediate, and high) and have been used for the risk stratifications of patients in clinical trials evaluating tyrosine kinase inhibitors (TKIs).

The NCCN Guidelines for CML discuss the clinical management of patients in chronic phase, disease progression to accelerated or blast phase, and monitoring response to treatment.

**Tyrosine Kinase Inhibitor Therapy for CML**

**Imatinib**

Imatinib is a selective inhibitor of the BCR-ABL tyrosine kinase. Initial clinical trials evaluated the efficacy of imatinib as second-line therapy for patients with CP-CML who had failed interferon or those with
AP-CML or BP-CML. At 5-year follow-up, complete cytogenetic response (CCyR) was seen in 41% of patients and 44% of patients remained on imatinib. Estimated rates of freedom from progression (FFP) to accelerated or blast phase and overall survival (OS) at 6 years were 61% and 76%, respectively.

Newly diagnosed patients were evaluated in the IRIS trial. In this trial, 1106 patients were randomized to receive initial therapy with either imatinib 400 mg or interferon-alpha plus low-dose cytarabine. Crossover was allowed for treatment failure or intolerance. With a median follow-up of 19 months, the best observed major cytogenetic response (MCyR) rate was 85.2% in the imatinib group compared to 22.1% in the interferon plus cytarabine group (P < .001). The CCyR rate was 73.8% and 8.5%, respectively (P < .001). The estimated rate of FFP was significantly higher in the imatinib than in the interferon plus cytarabine arm (96.7% and 91.5%, respectively; P < .001). Imatinib was also much better tolerated than the combination of interferon plus cytarabine.

In May 2001, the FDA (U.S. Food and Drug Administration) first approved imatinib mesylate for the advanced stages of CML. In December 2002, based on the results of the IRIS study, imatinib was approved for the first-line treatment of patients with CML.

Long-term follow-up data of the IRIS trial are now available. With a median follow-up of 60 months, the best observed MCyR and CCyR rates were 89% and 82%, respectively. Only 7% of patients had progressed to accelerated or blast phase and the OS rate was 89%. The estimated 8-year event-free survival (EFS), FFP to accelerated or blast phase and OS were 81%, 92%, and 85%, respectively. Major molecular response (MMR) rate increased from 24% at 6 months to 39% at 12 months, and the best observed MMR rate was 86% with 8-year follow-up. None of the patients with documented MMR at 12 months progressed to accelerated or blast phase. These results demonstrate that continuous treatment with imatinib induces high durable responses with a decreasing rate of relapse in a large proportion of patients with CP-CML. However, due to the high rate of crossover (90%) from interferon-alpha to imatinib within a year of study, survival benefit for imatinib vs. interferon could not be demonstrated in the IRIS trial. In historical comparisons, survival benefit was significantly better for imatinib compared to interferon. Recently, Guilhot and colleagues reported the safety and efficacy of imatinib in 359 patients who crossed over from interferon-alpha plus cytarabine to imatinib in the IRIS study. After a median follow-up of 54 months on imatinib, 93% achieved complete hematologic response (CHR); MCyR and CCyR were observed in 86% and 81% of patients, respectively. Estimated rates of FFP to accelerated or blast phase and OS were 91% and 89%, respectively, at 48 months after starting imatinib.

Toxicity
Imatinib is generally well tolerated. Frequently reported grade 3 or 4 toxicities include neutropenia and thrombocytopenia. Most frequently reported adverse events include gastrointestinal disturbances, edema, rash, and musculoskeletal complaints, but none of these led to discontinuation of treatment. Hypophosphatemia, with associated changes in bone and mineral metabolism, has been noted in a small group of patients.

Erythropoietin and filgrastim have been shown to be effective in patients who develop imatinib-induced anemia and neutropenia, respectively. In a recent report, the use of erythropoietin 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 Centers for Medicare & Medicaid Services (CMS)
and the FDA do not support the use of ESAs in patients with myeloid malignancies. See “Management of Imatinib Toxicity” in the guidelines.

In a recent trial, long-term treatment with imatinib was associated with congestive heart failure (CHF) and cardiotoxicity. However, this appears to be very rare, as shown by the recent analysis of 1276 patients treated with imatinib at MD Anderson Cancer Center. After a median follow-up of 47 months, 22 (1.7%) patients were found to have CHF during imatinib therapy. Out of these patients, 13 of them had received prior treatment with cardiotoxic drugs. The authors concluded that CHF is uncommon among patients receiving imatinib, and its incidence rates are similar to those that occur in the general population. Patients with previous cardiac history should be monitored carefully. Aggressive medical therapy is recommended for symptomatic patients. Electrocardiogram (ECG) should be considered for patients taking QT interval-prolonging medication.

**High-dose Imatinib**

Most patients retain variable levels of residual molecular disease at the 400 mg dose of imatinib. Several studies have evaluated the efficacy of high-dose imatinib in newly diagnosed patients. Imatinib 600 or 800 mg daily was well tolerated and was also associated with significantly better cytogenetic and molecular response rates.

The investigators of the TIDEL trial also reported superior response rates (MMR at 12 and 24 months were 55% and 77%, respectively) in patients receiving imatinib 600 mg as the initial dose compared to those receiving less than 600 mg (MMR at 12 and 24 months were 32% and 53%, respectively).

In a phase II multicenter study, newly diagnosed patients (n = 115; 70% Sokal low-risk) treated with imatinib 400 mg twice daily achieved rapid and deep responses. CHR at 6, 12, and 18 months was achieved and maintained in 93%, 94%, and 93% of evaluable patients, respectively.

The rate of MCyR at 12 and 18 months was 90% and 96%, respectively, and the corresponding CCyR rates were 85% and 83%, respectively. MMR rates were 48% and 54% at 6 months and 12 months, respectively. The response rates were also higher in this trial compared to historic controls that received 400 mg daily in the IRIS trial. At 12 months, MMR was 54% for patients in the RIGHT trial compared with an estimated 39% for the historical control group. At 18 months, MCyR and CCyR rates were 90% and 85%, respectively, in the RIGHT trial compared with 85% and 74%, respectively, in the historical control group in the IRIS trial.

The TOPS trial is an open-label, phase III, randomized trial comparing the efficacy of higher dose imatinib and standard-dose imatinib in patients with newly diagnosed CP-CML. This trial randomized 476 patients to receive either high-dose imatinib (800 mg; 400 mg twice daily) or standard-dose imatinib (400 mg once daily). High-dose imatinib was well tolerated in most patients and was also associated with more rapid responses than the standard dose. However, MMR and CCyR at 12 months were comparable between arms (MMR: 46% vs. 40%, respectively; CCyR: 70% vs. 66%, respectively). In patients with high Sokal risk scores, MMR rates at 12 months were 51% for high-dose imatinib compared to 31% for standard-dose imatinib. The MMR rate also correlated with average dose intensity. At 12 months, MMR was observed in 83 (62%) of 134 patients with an average dose intensity of 600 to 799 mg/day, and it was observed in 26 (38%) of 69 patients with an average dose intensity of 400 to 599 mg/day.

The German CML IV study also reported significantly faster response rates with imatinib 800 mg as compared to imatinib 400 mg with or without interferon. The incidence of MMR at 12 months was also
significantly higher with imatinib 800 mg/day (59% vs. 44% and 46% for imatinib 800 mg, imatinib 400 mg, and imatinib 400 mg with interferon, respectively). More rapid achievement of MMR with imatinib 800 mg was observed in low- and intermediate-risk patients, but not in high-risk patients. At 3 years, the OS (95%) and progression-free survival (PFS) (94%) rates for all patients were not different between treatment arms.

The efficacy of imatinib 800 mg as front-line therapy in intermediate and high Sokal risk patients with CP-CML was evaluated by the GIMEMA CML Working Party and the European LeukemiaNet Study group, respectively. The results of the phase II trial by the GIMEMA CML Working Party indicated that high-dose imatinib is effective in inducing rapid cytogenetic and molecular responses in intermediate Sokal risk patients. The response rates at 12 months were better than those documented in the IRIS study for intermediate-risk patients treated with 400 mg imatinib. The European LeukemiaNet Study, which randomized high Sokal risk patients to receive 800 mg or 400 mg of imatinib, did not show a significant benefit for high-dose imatinib.

In newly diagnosed patients, high-dose imatinib induces higher and faster CCyR and MMR compared to standard-dose imatinib early on, but there is no difference in response rates between the two arms at 12 months. Imatinib 800 mg has not been shown to have lower rates of disease progression than standard-dose imatinib in any of the studies, despite improved early responses. High-dose imatinib is associated with higher rates of dose interruption, reduction, or discontinuation in a substantial number of patients due to grade 3 or 4 adverse events. However, the data suggest that patients who can actually tolerate the higher dose of imatinib do achieve better response rates than those receiving standard-dose imatinib.

Dasatinib
Dasatinib is a potent, orally available small molecule dual inhibitor of ABL and SRC family of kinases. Dasatinib has an added advantage in that it can bind to both the active and inactive conformation of the ABL kinase domain. As a result, dasatinib is active against nearly all BCR-ABL mutations resistant to imatinib, in vitro, except T315I.

First-line Therapy
The efficacy and safety of dasatinib as first-line therapy for newly diagnosed patients with CP-CML was first confirmed in a phase II trial. Fifty patients with newly diagnosed CP-CML were randomly assigned to dasatinib 100 mg once daily or 50 mg twice daily. With a median follow-up of 24 months, 98% of evaluable patients had achieved CCyR and 82% had achieved MMR. In historical comparison, the CCyR rates at 3, 6, and 12 months were comparable to those achieved with high-dose imatinib and better than those achieved with standard-dose imatinib. There were no significant differences in response rate and toxicity between the two arms, and the median dose at 12 months was 100 mg.

The efficacy and safety of dasatinib (100 mg once daily) and imatinib (400 mg once daily) among patients with newly diagnosed CP-CML were compared in a multinational randomized study (DASISION trial). In this study, 519 patients with newly diagnosed CP-CML were randomized to receive dasatinib (100 mg once daily; 259 patients) or imatinib (400 mg once daily; 260 patients). After a minimum follow-up of 12 months, the confirmed CCyR (77% vs. 66%, respectively) and MMR (46% vs. 28%) rates were higher for dasatinib than for imatinib. Responses were achieved in a shorter time with dasatinib. The CCyR
rates at 3, 6, and 9 months after initiation of therapy were 54%, 73%, and 78%, respectively, for dasatinib, and the corresponding response rates were 31%, 59%, and 67%, respectively, for imatinib. The rates of MMR at 3, 6, and 9 months after dasatinib treatment were 8%, 27%, and 39%, respectively, and the corresponding rates for imatinib were 0.4%, 8%, and 18%, respectively. Although there was a trend in favor of dasatinib, progression to the accelerated or blast phase was not statistically different between the two groups; 5 patients on dasatinib (2%) and 9 patients who were receiving imatinib (3.5%) met the definition of progression. The safety profiles were similar in both treatment arms.

In October 2010, based on the results of the DASISION trial, the FDA approved dasatinib (100 mg once daily) for the treatment of adult patients with newly diagnosed Ph-positive CP-CML.

Long-term follow-up (24-36 months) data confirmed that dasatinib induces faster and deeper cytogenetic and molecular responses with fewer progressions to accelerated or blast phase than imatinib in newly diagnosed patients with CP-CML. The 3-year follow-up data showed that more patients in the dasatinib arm achieved a PCyR or CCyR at 3 months (81% vs.67% with imatinib) and at 6 months (91% vs. 81% with imatinib). MMR rates (BCR-ABL transcript levels \(\leq 0.1\%\)) were also significantly higher for dasatinib compared to imatinib (68% and 55%, respectively; \(P < .0001\)). BCR-ABL transcript levels of \(\leq 10\%\) at 3 months were achieved in 84% of patients on dasatinib compared to 64% of patients on imatinib (\(P < .0001\)). MMR rates were also higher with dasatinib across all the risk groups (as determined by Hasford score). At 24-month follow-up, MMR rates for dasatinib were 73%, 61%, and 57% for patients with low-, intermediate-, and high-risk scores. The corresponding MMR rates for imatinib were 56%, 50%, and 38%, respectively.

In the Intergroup phase II randomized trial (S0325; \(n = 250\)), dasatinib (100 mg once daily) induced more complete cytogenetic and deeper molecular responses, compared with imatinib (400 mg once daily) in patients with newly diagnosed CP-CML. The molecular response rates (3-log reductions in BCR-ABL transcript level) at 12 months were 59% and 44% respectively for dasatinib and imatinib; \(P = .059\) and with a median follow-up of 3 years, the OS and PFS were similar in both arms.

**Second-line Therapy**

In a phase I dose escalation study, dasatinib induced hematologic and cytogenetic responses in patients with CML or Ph-positive ALL, resistant or intolerant to imatinib. This result led to the initiation of several phase II studies (START trial) of dasatinib in patients with Ph-positive leukemias, resistant or intolerant to imatinib. Resistance to imatinib was defined as failure to achieve a CHR within 3-6 months, an absence of a MCyR at 12 months, or disease progression following prior response to imatinib. Dasatinib was administered at 70 mg twice daily on a continuous basis. Interruption of treatment and dose modifications were allowed for the management of disease progression or toxicity after one cycle of treatment.

The START-C trial evaluated dasatinib (70 mg twice daily) in 387 patients with CP-CML resistant or intolerant to imatinib. After a median follow-up of 15.2 months, CHR, MCyR, and CCyR were observed in 91%, 59%, and 49% of patients, respectively; only 3% of patients experienced disease progression after achieving MCyR. The 15-month PFS and OS rates were 90% and 96%, respectively.
Extended follow-up data have confirmed the durability of cytogenetic responses with dasatinib.\textsuperscript{42,43} After a follow-up of 24 months, CHR, MCyR, CCyR, and MMR were observed in 91\%, 62\%, 53\%, and 47\% of patients, respectively. OS and PFS rates at 24 months were 94\% and 80\%, respectively.\textsuperscript{42} Among patients resistant to imatinib, median time to MCyR and CCyR was 2.9 months and 5.5 months, respectively. Among patients intolerant to imatinib, median times to achieve MCyR and CCyR were both 2.8 months. The majority of patients resistant (84\% for MCyR and 86\% for CCyR) or intolerant (97\% for MCyR and 98\% for CCyR) to imatinib had maintained their responses at 24 months.\textsuperscript{43}

Dasatinib is associated with higher response rates and EFS when administered early after imatinib failure.\textsuperscript{44} In the retrospective analysis of data from phase II studies of dasatinib in CP-CML patients resistant or intolerant to imatinib, EFS was higher for those who went on dasatinib after the loss of MCyR on imatinib than those who received dasatinib after the loss of both MCyR and CHR (89\% and 29\%, respectively).\textsuperscript{44}

The efficacy of high-dose imatinib and dasatinib was evaluated in a phase II trial (START-R) in which 150 patients with CP-CML resistant to imatinib were randomized to receive 140 mg (70 mg twice a day) of dasatinib or 800 mg of imatinib.\textsuperscript{45,46} In the initial report from the START-R trial, dasatinib was clearly superior to 800 mg of imatinib if patients had already failed treatment with 600 mg of imatinib, whereas response rates were equivalent for high-dose imatinib and dasatinib in patients who had failed treatment with 400 mg of imatinib.\textsuperscript{45} However, the 2-year follow-up data suggested that dasatinib is clearly superior to imatinib 800 mg in patients resistant to imatinib at doses of 400 or 600 mg daily.\textsuperscript{46} At a minimum follow-up of 2 years, dasatinib demonstrated higher rates of CHR (93\% vs. 82\%), MCyR (53\% vs. 33\%), and CCyR (44\% vs. 18\%) compared to high-dose imatinib. MMR was also more frequent with dasatinib than with high-dose imatinib (29\% vs. 12\%) and the estimated PFS also favored dasatinib, indicating that dasatinib is an effective treatment for patients with CP-CML resistant to standard-dose as well as high-dose imatinib.

The START-A trial evaluated the safety and efficacy of dasatinib (70 mg twice daily) in patients with accelerated phase CML (AP-CML) resistant or intolerant to imatinib.\textsuperscript{47} At 8-month follow-up (for the first 107 patients enrolled in the study), major hematologic response (MaHR) was achieved in 64\% of patients, MCyR was achieved in 33\% of the treated population, and 76\% of patients remained progression-free. Follow-up data from the full patient cohort of 174 patients have confirmed the efficacy and safety of dasatinib in patients with imatinib resistant or intolerant to AP-CML.\textsuperscript{48} The 12-month PFS and OS rates were 66\% and 82\%, respectively.

The efficacy of dasatinib in imatinib-resistant or intolerant patients with CML in myeloid blast crisis (MBC) or in lymphoid blast crisis (LBC) was evaluated in START-B and START-L trials, respectively.\textsuperscript{49} In patients with MBC-CML, 32\% had achieved MaHR at 6-month follow-up, which increased to 34\% at 8-month follow-up and was maintained at 12-month follow-up.\textsuperscript{50} MCyR was achieved in 31\% of patients. In the LBC-CML group, 31\% achieved MaHR at 6-month follow-up, and this rate increased to 35\% at 12-month follow-up.\textsuperscript{50} After a minimum follow-up of 12 months, MCyR was achieved in 33\% (MBC-CML) and 52\% (LBC-CML) of patients and CCyR was achieved in 26 and 46\% of patients, respectively. Median PFS and OS for patients with MBC were 6.7 and 11.8 months, respectively. In patients with LBC, the corresponding survival rates were 3.0 and 5.3 months, respectively.\textsuperscript{50}
In June 2006, based on the favorable results of the above-mentioned four single-arm phase II studies, FDA approved dasatinib (70 mg twice daily) for patients with CML resistant or intolerant to imatinib.

In a recent dose-optimization randomized study (CA180-034), dasatinib dosed at 100 mg once daily was equally as effective as 70 mg twice daily in patients (n = 167) with CP-CML resistant or intolerant to imatinib. At 24 months, the CCyR (50% vs. 54%) and MCyR (63% vs.61%), PFS (80% vs. 76%), and OS (91% and 88%) rates for patients who received dasatinib 100 mg once daily were comparable to those seen in patients who received dasatinib at 70 mg twice daily. The incidences of grade 3/4 toxicities (pleural effusion [2% vs. 5%] and thrombocytopenia [23% vs. 38%]) were also lower with 100 mg daily dose, and fewer patients required dose interruption (62% vs. 77%), dose reduction (39% vs. 62%), and toxicity-related discontinuation (16% vs. 23). Based on the results of this study, FDA has approved 100 mg once daily as the starting dose. Six-year follow-up data confirmed the long-term safety and durability of cytogenetic responses in patients with CP-CML resistant or intolerant to imatinib treated with dasatinib100 mg once daily. At 6-year follow-up, the MMR, PFS, and OS rates were 42%, 49%, and 71%, respectively. The rate of progression to accelerated or blast phase was 6% (n =10).

Kantarjian et al recently reported that once daily dosing of dasatinib at 140 mg has similar efficacy to 70 mg twice daily dosing with an improved safety profile in patients with AP-CML. Recently, 2-year follow-up data from a phase III trial showed that dasatinib 140 mg once daily demonstrates equivalent efficacy and improved safety compared with 70 mg twice daily in patients with BP-CML.

The recommended starting dose of dasatinib is 100 mg once daily for patients with CP-CML resistant or intolerant to imatinib and 140 mg once daily for patients with disease progression to AP-CML or BP-CML.

Toxicity

Dasatinib is also well tolerated. Nonhematologic adverse events are mild to moderate and cytopenias, although more common, are manageable with dose modification. ECG should be considered for patients taking QT interval-prolonging medications. See “Management of Dasatinib Toxicity” in the guidelines. Dasatinib, however, is associated with significant but reversible inhibition of platelet aggregation that may contribute to bleeding in some patients receiving the drug. Pleural effusion can be an adverse effect of dasatinib.

Recently, Quintas-Cardama and colleagues from MD Anderson Cancer Center performed an analysis of patients with CML treated with varying doses of dasatinib in phase I and phase II studies. Pleural effusion occurred in 29% of patients with CP-CML, 50% of patients with AP-CML, and 33% of patients with BP-CML. Pleural effusion led to dose interruption in 83% of patients and dose reduction was necessary in 71% patients. Patients with prior cardiac history, patients with hypertension, and those receiving twice-a-day dosing of dasatinib at 70 mg are at increased risk of developing pleural effusion. Close monitoring and timely intervention are necessary for patients at risk of developing pleural effusion.

Reversible pulmonary arterial hypertension has been reported as a rare but serious side effect associated with dasatinib. 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 should be permanently discontinued.
Lymphocytosis from the clonal expansion of NK/T-cells has been reported during dasatinib treatment in patients with all stages of CML resistant or intolerant to imatinib, and it has been associated with increased incidence of pleural effusion. Cytogenetic response rates to dasatinib were higher in this group of patients. Similar effects were also observed among patients treated with dasatinib as first-line therapy in the DASISION study. Further studies are needed to confirm these preliminary findings.

Nilotinib

Nilotinib is a highly selective inhibitor of BCR-ABL tyrosine kinase that is more potent than imatinib (20-50 times more potent in imatinib-resistant cell lines and 3-7 times more potent in imatinib-sensitive cell lines).

First-line Therapy

The efficacy and safety of nilotinib as first-line therapy in early chronic phase patients were initially evaluated in 2 separate phase II studies. Nilotinib at 400 mg twice daily induced high rates of CCyR and MMR, with most patients reaching these responses early during their therapy.

In a phase III, randomized, open-label, multicenter trial (ENESTnd trial), the efficacy and safety of nilotinib (300 mg twice daily; n = 282 or 400 mg twice daily; n = 281) was compared with that of imatinib (400 mg once daily; n = 283) in patients with newly diagnosed CP-CML. At 12 months, the MMR (the primary endpoint) rates were 44%, 43%, and 22%, respectively, for nilotinib (300 mg and 400 mg) and imatinib. The CCyR rates by 12 months (80% for the 300 mg dose and 78% for the 400 mg dose vs. 65% for imatinib) were also higher for nilotinib than for imatinib. Patients receiving nilotinib at either of the two dose levels had a significant improvement in the time to progression to the accelerated or blast phase, as compared with those receiving imatinib. The rate of progression to accelerated or blast phase was 4% with imatinib and less than 1% with nilotinib (P = .01 for the 300 mg and P = .004 for the 400 mg). Superior rates of CCyR and MMR were observed in both nilotinib arms compared with the imatinib arm across all Sokal risk groups. Among patients with a high Sokal risk, CCyR rates by 12 months were 74%, 63%, and 49% among patients receiving 300 mg of nilotinib, 400 mg of nilotinib, and 400 mg of imatinib, respectively. MMR at 12 months in these patients was 41%, 32%, and 17% for patients receiving 300 mg of nilotinib, 400 mg of nilotinib, and 400 mg of imatinib, respectively. The 300 mg dose of nilotinib had the lowest rate of discontinuation due to adverse events or laboratory abnormalities among the 3 study groups.

In June 2010, based on the results of the ENESTnd trial, FDA approved nilotinib (300 mg twice daily) for the treatment of adult patients with newly diagnosed Ph-positive CP-CML.

Long-term follow-up data (24-48 months) confirmed that nilotinib induces superior molecular responses with significantly fewer progressions to accelerated or blast phase in patients with newly diagnosed CML. At 3 years, significantly more patients in the nilotinib arms achieved MMR than with imatinib (73% and 70%, respectively, for nilotinib 300 mg and 400 mg twice daily vs. 53% for imatinib 400 mg once daily; P < .0001). Among patients with high Sokal risk, the MMR rate at 3 years was 67%, 64%, and 39%, respectively, for patients receiving 300 mg of nilotinib, 400 mg of nilotinib, and imatinib. The rates of progression to accelerated or blast phase were also significantly lower for nilotinib 300 mg twice daily (2 patients; 0.7%; P = .0059) and nilotinib 400 mg twice daily (3 patients; 1.1%; P = .016) than imatinib (12 patients; 4%). The estimated 3-year rate of freedom-from-progression was 99.3%, 98.7%, and 95.2%, respectively, for the 3 treatment groups. The 3-year PFS rate was 93.3%, 96.7% and 92%, respectively for patients receiving 300 mg of
nilotinib, 400 mg of nilotinib, and imatinib. The corresponding 3-year OS rates were 95.1%, 97% and 94% respectively.

**Second-line Therapy**

In a phase I study, nilotinib was found to be active in imatinib-resistant CML with a favorable safety profile. Following this study, a phase II open-label trial evaluated the safety and efficacy of nilotinib (400 mg twice daily) in patients with CP-CML (n = 280) and AP-CML (n = 119) resistant or intolerant to imatinib. The efficacy endpoint for CP-CML was MCyR and the endpoint for AP-CML was MaHR.

In patients with CP-CML, at 6-month follow-up, MCyR was observed in 48% of patients and CCyR was observed in 31% of patients. Long-term follow-up results from this study confirmed that these responses are durable with no change in safety profile. At the 2-year follow-up, the overall MMR, MCyR, and CCyR rates were 28%, 59%, and 44% of patients, respectively, and the responses were durable with 84% maintaining CCyR and 77% maintaining MCyR at 24 months. The estimated overall PFS and OS rates at 24 months were 64% and 87%, respectively. MCyR, MMR, and PFS rates were higher in patients with CHR at study entry (73%, 38%, and 77%, respectively) compared to 52%, 22%, and 56%, respectively, among patients without CHR at study entry. At 48 months, patients with baseline CHR had a significantly higher PFS rate than those without baseline CHR (71% vs. 49%, respectively; P = .001). Disease progression was observed only in 3% of patients and the estimated OS rate was 78%.

In patients with AP-CML, hematologic response was observed in 47% of patients and MCyR was observed in 29% of patients. OS rate among the 119 patients after 12 months of follow-up was 79%. Non-hematologic adverse events were mostly mild to moderate. Grade 3 or higher bilirubin and lipase elevations occurred in 9% and 18% of patients. Long-term follow-up results confirmed that nilotinib induces rapid and durable responses with a favorable risk/benefit profile in patients with AP-CML who were intolerant or resistant to prior imatinib. Among patients with at least 24-month follow-up (n = 137), confirmed hematologic response was observed in 55% of patients and 31% had CHR (30% of imatinib-resistant and 37% of imatinib-intolerant patients achieved CHR). MCyR and CCyR were achieved in 32% and 20% of patients, respectively. Cytogenetic and molecular responses were also durable, with 66% of patients maintaining MCyR at 24 months and 83% of patients maintaining CCyR at 12 months. The estimated PFS and OS rates at 24 months were 70% and 33%, respectively.

Nilotinib has also been evaluated in patients with BP-CML. In a phase II study of 136 patients (MBC, n = 105; LBC, n = 31), after a minimum follow-up of 24 months, MaHR was observed in 60% of patients with MBC and 59% of patients with LBC. MCyR was achieved in 38% of patients with MBC and 52% of patients with LBC. CCyR was seen in 30% of patients with MBC and 32% of patients with LBC. The OS rate was 42% at 12 months and 27% at 24 months. However, the responses were not durable. The duration of MCyR was 11 months for patients with MBC and 3 months for those with LBC.

Nilotinib (400 mg twice daily) is approved for the treatment of CP-CML and AP-CML in patients resistant or intolerant to imatinib. However, it is not yet approved for the treatment of patients with BP-CML.

**Toxicity**

Nilotinib was rarely associated with fluid retention, edema, or muscle cramps. Neutropenia and thrombocytopenia (grade 3-4) were reported only in 29% of patients with CP-CML. Grade 3 or 4 elevations in lipase and bilirubin, hypophosphatemia, and hyperglycemia were observed in 17%, 8%, 16%, and 12% of patients with CP-CML, respectively.
However, these abnormalities were transient and clinically asymptomatic. See “Management of Nilotinib Toxicity” in the guidelines.

QT interval prolongation is a nonhematologic adverse reaction associated with nilotinib, which could be managed with dose reduction. 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. Electrolyte abnormalities should be corrected prior to initiation of treatment with nilotinib and should be monitored periodically. Drugs that prolong QT interval should be avoided. 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.

Nilotinib may be associated with an increased risk of vascular adverse events, including 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

Bosutinib, a member of the dual ABL/SRC family of kinases has demonstrated activity against many of the BCR-ABL kinase domain mutations resistant to imatinib, dasatinib, and nilotinib, except T315I, with minimal inhibition of KIT and PDGFR.

First-line Therapy

The phase III randomized trial (BELA trial) compared the efficacy of bosutinib (n = 250; 500 mg once daily) with imatinib (n = 252; 400 mg once daily) in newly diagnosed patients with CP-CML. At 12 months, bosutinib was associated with a higher MMR rate (41% vs. 27% for imatinib; P < .001), fewer transformations to accelerated or blast phase CML (2% vs. 4% on imatinib) and faster times to CCyR and MMR. However, this trial did not meet its primary end point of CCyR at 12 months. The CCyR rates at 12 months were 70% and 68% respectively, for bosutinib and imatinib (P = .601). Further follow-up is needed to assess the duration of response, transformation to AP-CML or BP-CML and overall survival, as well as the tolerability of bosutinib in newly diagnosed patients with CML.

Bosutinib is currently not recommended as first-line therapy for this group of patients.

Second-line Therapy

The safety and efficacy of bosutinib (500 mg once daily) was evaluated in a single-arm multicenter phase I-II trial, in a total of 570 patients with resistance or intolerance to prior TKI therapy (288 patients with CP-CML following prior imatinib only; 118 patients with CP-CML pretreated with imatinib followed by dasatinib and/or nilotinib; 164 patients with accelerated and blast phase CML and ALL). The primary endpoint was MCyR at 24 weeks for patients with CP-CML and CHR by 8 weeks for patients with advanced phase CML and ALL.

In the cohort of 288 patients with CP-CML treated with imatinib alone (200 patients resistant to imatinib and 88 patients intolerant to imatinib), MCyR was achieved in 31% of patients (33% patients resistant to imatinib and 27% patients intolerant to imatinib) at 24 weeks. After a median follow-up of 24 months, CHR, MCyR and CCyR were achieved in 86%, 53% and 41% of patients respectively. Molecular response was evaluable only in a small subset of patients. Among patients in CCyR, 64% had a MMR and 53% achieved complete molecular response. The 2-year PFS and OS rates were 79% (including 73% for patients resistant to imatinib and 95% for patients intolerant to imatinib) and 92%
(89% for patients resistant to imatinib and 98% for patients intolerant to imatinib), respectively. \(^{89}\)

In the cohort of 118 patients with CP-CML pretreated with more than one TKI (imatinib followed by dasatinib and/or nilotinib), with a median follow-up of 28.5 months, CHR, MCyR and CCyR were achieved in 73%, 32%, and 24% of patients, respectively. \(^{89}\) In a sub-group analysis of 33 patients who were in CCyR, MMR and CMR were observed in 49% (16 of 33) and 36% (12 of 33) of patients respectively. The median duration of MCyR and CHR has not been reached at the time of median follow-up. Patients intolerant to dasatinib had a trend towards higher rates of CHR (67% vs. 50%), CCyR (28% vs. 14%) and MMR (25% vs. 3%) compared to those resistant to dasatinib. The rate of disease progression to AP-CML and BP-CML was 4% and 0%, respectively. The estimated PFS and OS rates at 2 years were 73% and 83%, respectively.

In the cohort of patients with AP-CML (n = 63) and BP-CML (n = 48), bosutinib induced CHR and MCyR in patients with and without BCR-ABL mutations. \(^{91}\) Among patients with AP-CML evaluable for response, CHR, MCyR, and CCyR were observed in 61% (20 of 33), 48% (13 of 27), and 33% (9 of 27) of patients, respectively. The corresponding response rates in patients with BP-CML evaluable for response were 32% (7 out of 22), 52% (11 out of 22), and 29% (6 out of 22), respectively. Median follow-up for the entire cohort was 8.3 months.

Based on the results of this study, the FDA approved bosutinib for the treatment of patients in all three phases of CML, resistant or intolerant to prior TKI therapy.

### Toxicity

Bosutinib has a favorable toxicity profile. Diarrhea, nausea, vomiting, and rash were the most common non-hematologic grade 1 or 2 adverse events. \(^{89-91}\) Grade 3 or 4 diarrhea and rash were reported in 8% and 4% of patients, respectively. Thrombocytopenia (25%), neutropenia (19%), and anemia (8%) were the most common grade 3 or 4 hematologic toxicities. Bosutinib was also associated with minimal effects on QTc interval prolongation and a low incidence of pleural effusions, muscle cramps, musculoskeletal events, and cardiac toxicities that may be seen with other TKIs. See “Management of Bosutinib Toxicity” in the guidelines for specific interventions.

### Ponatinib

Ponatinib is a potent, orally available multitargeted kinase inhibitor active against many of the BCR-ABL kinase domain mutations including T315I. \(^{92,93}\)

A single arm multicenter phase II trial (PACE trial) evaluated the safety and efficacy of ponatinib (45 mg once daily) in a total of 449 patients with resistance or intolerance to prior TKI therapy or with the T315I mutation (270 patients with CP-CML; 85 patients with AP-CML; 94 patients BP-CML or ALL). \(^{94}\) The primary endpoint was MCyR at anytime within 12 months after initiation of treatment in patients with CP-CML and MaHR at any time within 6 months after initiation of treatment for patients with advanced phase CML.

In the cohort of patients with CP-CML, ponatinib induced durable MCyR, CCyR and MMR in 56%, 46% and 34% of patients respectively. \(^{91}\) The response rates were higher in patients with T315I mutation (MCyR rates were 50% in patients resistant/intolerant to prior TKI and 70% in patients with T315I mutation). \(^{94}\) In a post hoc analysis, younger age in patients with T315I mutation, exposure to fewer prior
TKI therapy, and shorter duration of leukemia were identified as predictors of response. Response rates were higher in patients who were exposed to fewer prior TKIs (MCyR, CCyR and MMR rates were 84%, 79% and 53% respectively for patients treated with one prior TKI compared to 46%, 38% ad 29% respectively for those treated with 3 prior TKIs). The difference in MCyR rates were statistically significant between the groups (P = .003) whereas the differences in MMR rates were not statistically significant (P = .062). Among patients treated with 3 prior TKIs and who achieved MCyR and MMR with ponatinib, responses were durable in 83% and 80%, respectively at 12 months. The PFS and OS rates at 12 months were 80% and 94% respectively.

Ponatinib also induced hematologic and cytogenetic responses across all cohorts in patients with advanced phase CML. Among patients with AP-CML resistant or intolerant to dasatinib or nilotinib, MaHR, MCyR and CCyR were observed in 50%, 56% and 33% of patients respectively. The corresponding response rates were 58%, 34% and 22% respectively for patients with T315I mutation. The estimated median PFS was 80 weeks; the probability of maintaining PFS at 6 and 12 months was 80% and 57%, respectively. Among patients with BP-CML resistant or intolerant to dasatinib or nilotinib, MaHR, MCyR and CCyR were observed in 29%, 29% and 21% of patients respectively. The corresponding response rates were 32%, 18% and 16% respectively for patients with T315I mutation. The estimated median PFS was 18 weeks, with the probability of maintaining PFS at 6 and 12 months 34% and 20%, respectively.

Based on the results of this study, the FDA approved ponatinib for the treatment of patients in all three phases of CML, resistant or intolerant to prior TKI therapy.

**Toxicity**

Ponatinib was well tolerated. The most common non-hematologic adverse events were rash, dry skin, abdominal pain, headache and pancreatitis. Thrombocytopenia and neutropenia were the most common grade 3-4 hematologic toxicities. Thrombocytopenia, neutropenia, and pancreatitis were typically reported early in treatment and were managed with dose modification. Ponatinib was also associated with fluid retention events (edema, ascites, pleural and pericardial effusion) which could be managed with dose interruption, dose reduction or discontinuation of ponatinib as clinically indicated.

Arterial Thrombosis (cardiovascular, cerebrovascular, and peripheral vascular thromboses, including fatal myocardial infarction) and venous thromboembolic events (deep venous thrombosis, pulmonary embolism, portal vein thrombosis and retinal vein thrombosis) have also been reported in clinical studies. Dose interruptions, modifications or discontinuation as clinically indicated should be considered in patients with arterial and venous thromboembolic events.

Hepatotoxicity, liver failure and death have been rarely reported in patients treated with ponatinib. Liver function tests should be done at baseline, and at least monthly or as clinically indicated during treatment. Dose interruption and dose reductions or discontinuation of ponatinib should be considered for hepatotoxicity.

See “Management of Ponatinib Toxicity” in the guidelines for specific interventions.

**TKI Therapy and Conception**

Imatinib has been shown to be teratogenic and embryotoxic in animal studies. There are some reports in literature indicating that patients who receive imatinib at the time of conception may have normal
Pye and colleagues recently reported the outcome of pregnancies in 180 women exposed to imatinib during pregnancy. Fifty percent 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 by Ault and colleagues, of the 10 women who discontinued imatinib due to pregnancy, 6 had an increase in Ph-positive metaphases. Only 3 women had CCyR at 18 months after resuming therapy. Imatinib is not known to be a genotoxic. However, spermatogenesis was impaired in animal studies. In the clinical experience, male fertility seems to be preserved in patients receiving imatinib. However, there are isolated reports of oligospermia in men receiving imatinib therapy.

Dasatinib and nilotinib are known to cause embryonic or fetal toxicities in animals. There have been isolated reports in literature regarding the outcome of pregnancy in patients receiving dasatinib or nilotinib. In a report from Cortes and colleagues involving 16 patients, among the 8 female patients who became pregnant while on dasatinib, induced or spontaneous abortion was reported in 3 and 2 patients, respectively. The outcome and pregnancy course in the other 3 patients was normal. Among the 8 male patients treated with dasatinib whose partners became pregnant while on treatment, normal pregnancy was reported for 7 cases and the outcome was unknown in one case.

At the present time, enough evidence is not available to favor the continuation of TKI therapy during pregnancy. Potential benefit of TKI therapy for the mother or its potential risk to the fetus must be carefully evaluated on an individual basis prior to administering imatinib, dasatinib, or nilotinib for pregnant women. Men desiring conception should consider sperm cryopreservation prior to initiation of TKI therapy.

**Drug Interactions**

Imatinib, dasatinib, nilotinib, bosutinib and ponatinib are extensively metabolized in the liver by cytochrome P450 (CYP) enzymes. Drugs that induce or inhibit CYP3A4 or CYP3A5 enzymes may alter the therapeutic effect of TKIs.

**Imatinib**

Drugs that induce CYP3A4 or CYP3A5 enzyme levels such as anticonvulsants and steroids may decrease the therapeutic plasma concentration of imatinib. These should be used with caution in patients receiving imatinib, and appropriate alternatives should be explored to maximize treatment outcome. Conversely, drugs that inhibit CYP3A4 enzyme activity and drugs that are metabolized by the CYP3A4 or CYP3A5 enzyme might result in increased plasma levels of imatinib. Imatinib is also a weak inhibitor of the CYP2D6 and CYP2C9 isoenzymes; therefore, drugs metabolized by these enzymes (eg, warfarin) should be used with caution. Please refer to the package insert for full prescribing information and drug interactions, available at www.fda.gov.

**Dasatinib**

CYP3A4 inducers may decrease plasma concentration of dasatinib. CYP3A4 inhibitors and drugs that are metabolized by this enzyme may increase the concentration of dasatinib. Therefore, concomitant administration with CYP3A4 inhibitors or inducers should be avoided. If coadministration cannot be avoided, a dose adjustment and close monitoring for toxicity should be considered. In addition, the solubility of dasatinib is pH-dependent, and long-term suppression of gastric acid secretion reduces dasatinib exposure. Concomitant use with H2 blockers or proton pump inhibitors is not recommended. Please refer to
the package insert for full prescribing information and drug interactions, available at [www.fda.gov](http://www.fda.gov).

**Nilotinib**

Drugs that induce CYP3A4 may decrease nilotinib plasma concentrations. If nilotinib needs to be administered with a CYP3A4 inducer, dose increase should be considered. Concomitant administration of strong inhibitors of CYP3A4 may increase the plasma concentration of nilotinib. If coadministration cannot be avoided, nilotinib should be interrupted or dose reduction should be considered. In addition, nilotinib is a competitive inhibitor of CYP2C8, CYP2C9, CYP2D6, and UGT1A1, potentially increasing the plasma concentrations of drugs eliminated by these enzymes. Please refer to the package insert for full prescribing information and drug interactions, available at [www.fda.gov](http://www.fda.gov).

**Bosutinib**

CYP3A4 inducers and proton pump inhibitors (PPIs) may decrease bosutinib plasma concentrations. Concomitant administration of strong or moderate CYP3A4 inducers with bosutinib should be avoided. The use of short-acting antacids or H2 blockers instead of PPIs should be considered to avoid reduction in bosutinib plasma concentrations. Concomitant use of strong or moderate inhibitors of CYP3A4 should also be avoided since these drugs may increase the plasma concentration of bosutinib. Please refer to the package insert for full prescribing information and drug interactions, available at [www.fda.gov](http://www.fda.gov).

**Ponatinib**

CYP3A4 inducers may decrease ponatinib plasma concentrations. Coadministration of strong CYP3A inducers with ponatinib should be avoided unless the benefit outweighs the possible risk of ponatinib underexposure. CYP3A4 inhibitors may increase the plasma concentration of ponatinib. Dose reduction to 30 mg is recommended when ponatinib has to be coadministered with strong CYP3A inhibitors. Elevated gastric pH may reduce the bioavailability of ponatinib. Coadministration of ponatinib with drugs that could elevate the gastric pH (PPIs, H2 blockers, or antacids) should be avoided unless the benefit outweighs the possible risk of ponatinib underexposure. Please refer to the package insert for full prescribing information and drug interactions, available at [www.fda.gov](http://www.fda.gov).

**Chronic Phase CML**

**Initial Workup**

Initial evaluation of patients with CP-CML should include history and physical (H&P), including palpation of spleen, complete blood count (CBC) with differential, chemistry profile, bone marrow aspirate, and biopsy.

Bone marrow cytogenetics and measurement of *BCR-ABL* transcript levels by quantitative real-time polymerase chain reaction (QPCR) is recommended before initiation of treatment as well as for monitoring response to therapy. Conventional bone marrow cytogenetics should be done for initial work-up; it not only provides morphologic review, but also detects chromosomal abnormalities other than Ph-chromosome that are not detectable using peripheral blood. If collection of bone marrow is not feasible, fluorescence in-situ hybridization (FISH) on a peripheral blood specimen with dual probes for *BCR* and *ABL* genes is an acceptable method for confirming the diagnosis of CML.

Patients who are *BCR-ABL*-negative do not have CML. These patients have a significantly worse prognosis than those with *BCR-ABL*-positive CML. Therefore, further evaluation of other diseases is warranted for patients who are *BCR-ABL*-negative. Patients with *BCR-ABL*-positive
CML (by bone marrow cytogenetics, FISH, or QPCR) are the focus of this NCCN guideline.

**Primary Treatment**

Imatinib (400 mg once daily) is still recommended as a reasonable first-line therapy (category 1) for newly diagnosed patients with CP-CML. Based on the recent FDA approval of nilotinib (300 mg twice daily) and dasatinib (100 mg once daily), the guidelines have also included nilotinib or dasatinib as first-line therapy options (category 1) for newly diagnosed patients. This recommendation is based on the data from randomized trials demonstrating that dasatinib and nilotinib are associated with superior cytogenetic and molecular response rates at certain time points and lower rates of disease progression compared to imatinib. Long-term survival benefit has yet not been established.  

Preliminary data from DASISION and ENESTnd studies also suggest that intermediate- and high-risk patients (as determined by Sokal or Hasford score) may preferentially benefit from dasatinib or nilotinib since they are associated with lower risk of disease progression in this patient population. Therefore, the guidelines recommend determination of risk status as part of initial workup (See Table 1). Longer term follow-up is needed to determine whether second-generation TKIs should be implemented as standard first-line therapy in such a risk-adapted fashion.

Since both dasatinib and nilotinib have very good efficacy in the upfront setting, differences in their potential toxicity profiles may be helpful in the selection of a second-generation TKI over imatinib as first-line therapy. In general, the choice of first-line therapy in a given patient may depend on risk score, physician’s experience, age, ability to tolerate therapy, and the presence of comorbid conditions. For example, based on the toxicity profile, nilotinib may be preferred for patients with a history of lung disease or deemed to be at risk of developing pleural effusions. Alternatively, dasatinib may be preferred in patients with a history of arrhythmias, heart disease, pancreatitis, or hyperglycemia.

Given the recent data showing superior efficacy of nilotinib and dasatinib in newly diagnosed patients, high-dose imatinib is currently not recommended as initial therapy for patients with newly diagnosed CML. The NCCN Member Institutions believe that interferon should no longer be considered as initial therapy for patients with newly diagnosed CML. In patients treated with interferon, CCyR is achieved in 10% to 15% of patients with a median survival of more than 10 years and some of these patients may actually be cured. However, EFS benefit is seen mainly in low-risk patients with a CCyR. Given this small percentage, most of the panel believed that these data for interferon do not outweigh the significant benefits seen with TKI therapy. In phase II/III studies, pegylated interferon-alpha 2a and alpha 2b have been shown to be active as initial treatment in patients with CP-CML. In very rare patients who are not able to tolerate TKI therapy, interferon, or PEG-interferon, allogeneic hematopoietic stem cell transplant (HSCT) or participation in a clinical can be considered.

Participation in a clinical trial or allogeneic HSCT is a reasonable treatment option for patients with T315I mutation, since this mutation is associated with resistance to imatinib, dasatinib, and nilotinib.

**Monitoring Response to TKI Therapy**

Monitoring disease response to TKI therapy is one of the key management strategies of CML. Response to TKI therapy is determined by the measurement of hematologic, cytogenetic, and molecular responses. The goal of TKI therapy is to achieve a CCyR.
within 12 months of initiation of therapy, to eventually achieve a MMR, and to prevent disease progression to accelerated or blast phase.

**Hematologic Response**
CHR is defined as complete normalization of peripheral blood counts with no immature blood cells, leukocyte count less than \(10 \times 10^9/L\), and platelet count less than \(450 \times 10^9/L\). The patient is free of signs and symptoms of the disease with the disappearance of splenomegaly. Partial hematologic response indicates the presence of immature blood cells and/or platelet count less than 50% of pretreatment count but more than \(450 \times 10^9/L\) and/or persistent splenomegaly (but less than 50% of pretreatment). The majority of patients in CP-CML will achieve a CHR with TKI therapy.

**Cytogenetic Response**
Cytogenetic response is determined by the decrease in the number of Ph-positive metaphases, as determined by bone marrow aspirate and cytogenetics. CCyR indicates that there are no Ph-positive metaphases. MCyR indicates that 0% to 35% of the cells still have Ph-positive metaphases, and in the case of partial cytogenetic response (PCyR) 1% to 34% of the cells have Ph-positive metaphases.

Cytogenetic monitoring is the most widely used technique for monitoring response in patients with CML. Conventional bone marrow cytogenetics for Ph-positive metaphases is the standard for monitoring cytogenetic responses in CML, and clinical trial response analyses are most often based on conventional bone marrow cytogenetics. It is widely available and reliable. However, the sensitivity is approximately 5% if only 20 metaphases are examined. If conventional bone marrow cytogenetics showed no analyzable metaphases, cytogenetic response can be further evaluated by more sensitive techniques such as FISH; however, endpoints for failure to imatinib have not been defined on the basis of FISH analysis. FISH uses 5'-BCR and 3'-ABL probes and has a false-positive rate of 1% to 10%. Interphase or hypermetaphase FISH can be performed on peripheral blood or bone marrow aspirates, respectively. Interphase FISH does not require cell division. It is applicable to a larger number of cells but is associated with a background level of 1% to 5% (depending on the specific probe used in the assay). Hypermetaphase FISH is applicable only to dividing cells in the bone marrow. Hypermetaphase FISH is more sensitive and can analyze up to 500 metaphases at a time. Techniques such as double-fusion FISH can detect all variant translocations of the Ph-chromosome and are also associated with low false-positive rates.

**Prognostic Significance of Cytogenetic Response**
Achievement of cytogenetic response is an important prognostic indicator of long-term survival in patients treated with imatinib. In the IRIS study, PFS was significantly better for patients who achieved any cytogenetic response at 6 months and a MCyR at 12 months, compared to those with no cytogenetic response at 6 months or less than a MCyR at 12 months. At the median follow-up of 60 months, PFS rate was better for patients who achieved a CCyR or PCyR at 12 months compared to those who did not have a MCyR at 12 months (97%, 93%, and 81%, respectively). At 8 year follow-up, of the 456 patients who achieved CCyR on imatinib, only 15 patients (3%) had progressed to accelerated or blast phase during study treatment. The updated results of the IRIS trial also confirmed that patients with minor cytogenetic response at 3 months, PCyR at 6 and 12 months, and CCyR at 18 months were associated with stable CCyR over the...
observation period. Patients with minor to PCyR at 3 months and those with PCyR at 6 and 12 months were more likely to achieve a stable CCyR than have an event. de Lavallade and colleagues also identified cytogenetic response after 1 year of imatinib therapy as the major prognostic factor for OS and PFS. In the German CML IV study, failure to achieve a PCyR at 3 months and CCyR at 6 months on imatinib correlated with lower rates of OS. The 5-year OS rates were 95% and 97%, respectively, for patients with a PCyR at 3 months and CCyR at 6 months. The corresponding survival rates were 87% and 91%, respectively, for those with no PCyR or CCyR at these time points.

Early cytogenetic response to initial therapy with second-generation TKIs is also predictive of long-term survival in newly diagnosed patients with CP-CML. Jabbour et al recently reported that the achievement of a CCyR at 3, 6, and 12 months remains a major prognostic factor for outcome in patients with early CP-CML regardless of the TKI (imatinib 400 mg, imatinib 800 mg, or second-generation TKI). Patients with CCyR at 3, 6, and 12 months had significantly better 3-year EFS (98%, 97%, and 98%) and OS rates (99%, 99%, and 99%) compared to 83%, 72%, and 67% and 90%, respectively, in patients who did not achieve a CCyR at these time points.

Molecular Response
Molecular response is determined by the decrease in the amount of \( BCR-ABL \) chimeric mRNA. RT-PCR (reverse transcriptase polymerase chain reaction) is the most sensitive assay available for the \( BCR-ABL \) chimeric mRNA. This assay measures the levels of \( BCR-ABL \) transcripts in the peripheral blood or in the bone marrow, and it can detect one CML cell in a background of \( \geq 100,000 \) normal cells. Qualitative RT-PCR assay is reported as either positive or negative; it is rarely used in the context of monitoring patients since it is only a “yes or no” answer. In contrast, a QPCR assay reports the actual percentage of \( BCR-ABL \) mRNA transcripts. A major advantage of QPCR assay is the strong correlation between the results obtained from the peripheral blood and the bone marrow, allowing molecular monitoring without the necessity of obtaining bone marrow aspirations.

In the QPCR assay, results are expressed as the ratio of \( BCR-ABL \) transcript numbers to the number of control gene transcripts. Thus, the choice of an appropriate control gene is important for generating reliable and reproducible data. \( BCR, ABL, \) beta glucuronidase (\( GUSB \)), and beta-2-microglobulin are the 4 control genes that have been widely studied for \( BCR-ABL \) quantification. Amongst institutions and laboratories that perform this test there are differences in techniques as well as the use of various internal controls that make quantification of the assay variable. A substantial effort has been made to standardize \( BCR-ABL \) testing and reporting across academic and private laboratories. In 2006, the National Institutes of Health Consensus group proposed an international scale (IS) for \( BCR-ABL \) measurement. This group recommended the use of one of three control genes- \( BCR, ABL, \) or \( GUSB \).

\( BCR \) was used as the control gene in the IRIS trial, and more recently \( ABL \) has also been used as the control gene for the determination of molecular response to imatinib. In the IRIS trial, the standardized baseline was calculated by measuring the level of \( BCR-ABL/BCR \) in the peripheral blood collected from 30 patients with newly diagnosed CP-CML prior to the initiation of any treatment. The same 30 samples were assayed in the 3 laboratories. The median value was used as the standardized baseline at each laboratory, and at least a 3-log reduction from this baseline was defined as the MMR. Thus, MMR is defined as a 3-log reduction or greater in the \( BCR-ABL \) transcript levels from the standardized baseline and not a reduction from the actual baseline level.
in an individual patient. Complete molecular response (CMR) occurs when there is no detectable \textit{BCR-ABL} chimeric mRNA as assessed by QPCR using IS with a sensitivity of 4.5-log reduction or more from the standardized baseline.

The majority of patients initially treated with imatinib, dasatinib, nilotinib, or allogeneic HSCT will achieve a CCyR and a smaller percentage will achieve a CMR identified by the absence of \textit{BCR-ABL} chimeric mRNA transcripts. The \textit{BCR-ABL} mRNA transcripts typically fall slowly after complete cytogenetic remission is reached. Therefore, QPCR assay is useful to establish a baseline \textit{BCR-ABL} for monitoring molecular responses after the patient has achieved CCyR.

**Prognostic Significance of Molecular Response**

Several studies have reported that achievement of MMR after treatment with imatinib is associated with durable long-term cytogenetic remission\textsuperscript{137-140} and a lower rate of disease progression.\textsuperscript{13,140-142} Cortes et al reported that a significantly lower portion of patients (5% with MMR and 4% with CMR) lost their CCyR compared to 37% who did not reach these levels of molecular response.\textsuperscript{137} In the 7-year follow-up of the IRIS study, the probability of loss of CCyR by 7 years was only 3% for patients in MMR at 18 months compared to 26% for those with CCyR but not MMR.\textsuperscript{140} The GIMEMA study group reported similar findings.\textsuperscript{138,139} Patients with a stable MMR have a significantly lower risk of losing the CCyR than patients with unstable MMR (4% vs. 21%, respectively; \(P = .03\)) and those with no MMR (4% vs. 33%, respectively, \(P < .0001\)).\textsuperscript{139}

The 5-year follow-up of the IRIS trial showed that no patient who had a CCyR and a MMR at 12 months had progressed to the accelerated or blast phase.\textsuperscript{13} The estimated PFS rate at 24 months was 100% for patients with a CCyR and at least a 3-log reduction in the \textit{BCR-ABL} transcript level at 12 months, compared to 95% for those with CCyR and a less than 3-log reduction of \textit{BCR-ABL} at 12 months. The 7-year follow-up of the IRIS study also showed that progression is very rare in patients who achieved MMR (\textit{BCR-ABL [IS]} \(\leq 0.1\%\)) at any time point during imatinib therapy.\textsuperscript{140} The estimated EFS rate at 84 months was 95\% for patients who had a MMR at 18 months compared to 86\% in those with less than MMR at this time point (86\% for those with \textit{BCR-ABL [IS]} \(> 0.1\% \text{ to } \leq 1.0\%\); \(P = .01\) and 65\% for those with \textit{BCR-ABL [IS]} \(> 1.0\%)\).\textsuperscript{140} Press and colleagues also reported that failure to achieve at least a 2-log reduction in \textit{BCR-ABL} mRNA at the time of CCyR or a 3-log reduction any time thereafter is associated with a significantly shorter PFS,\textsuperscript{141} and a minimal half-log increase in the \textit{BCR-ABL} or a loss of MMR predicts shorter relapse-free survival in patients who were in CCyR on imatinib.\textsuperscript{142}

Although some investigators have reported that dose escalation of imatinib might benefit patients in CCyR with no MMR,\textsuperscript{143} no randomized studies have shown that a change of therapy would improve survival, PFS, or EFS in this group of patients.\textsuperscript{144} Some investigators have also suggested that MMR may not be of prognostic significance in patients who have achieved CCyR at 12 months with imatinib.\textsuperscript{29,127,145} de Lavallade et al reported that in patients achieving CCyR at 12 months with imatinib,\textsuperscript{29,127,145} Marin et al also confirmed that among patients with CCyR, even though patients who did not have a MMR at 18 months had a higher chance of losing CCyR, this did not translate into difference in PFS.\textsuperscript{145} Recently, Hehlman et al from a German CML study group reported that independent of the treatment approach, MMR at 12 months was associated with a better PFS (99\% vs. 94\%; \(P = .0023\)) and OS (99\% vs. 93\%; \(P = .0011\)) at 3 years when compared with
**Discussion**

**BCR-ABL (IS) >1% or no MMR.**

However, there was no difference in PFS and OS when compared with the **BCR-ABL (IS) 0.1% to 1% group** (which closely correlates with CCyR). The 3-year survival rates for MMR at 12 months and **BCR-ABL (IS) 0.1% to 1% at 12 months were 99% and 98%, respectively,** implying that MMR is not of prognostic significance in patients who have achieved CCyR at 12 months. Jabbour et al also reported that achievement of MMR may not be a significant prognostic indicator of outcome in patients who are in stable CCyR after treatment with second-generation TKIs.  

Recent studies have suggested that early molecular response (<10% reduction in BCR-ABL transcript levels after 3 months of first-line TKI therapy) is an effective prognostic indicator for long-term durable responses and survival. Marin et al reported that assessment of **BCR-ABL** transcript levels at 3 months was a strong predictor of failure to imatinib therapy; 8-year probability of OS was significantly lower in patients with **BCR-ABL (IS) >9.84% at 3 months than those with BCR-ABL (IS) ≤9.84% (57% and 93%, respectively; P < .001).** In the CML IV study, **BCR-ABL (IS) >10% at 3 months after imatinib therapy correlated with lower OS rates at 5 years compared to BCR-ABL (IS) 1% to 10% and <1% (87%, 94%, and 97%, respectively).** In the DASISION study, **BCR-ABL (IS) of ≤10% at 3 months was associated with a higher probability of achieving CCyR by 12 months (96% vs. 27% for dasatinib; 90% vs. 45% for imatinib), MMR by 24 months (76% vs. 16% for dasatinib; 66% vs. 19% for imatinib), significantly better 3-year PFS (93% vs. 68% for dasatinib; 96% vs. 75% for imatinib) and 3-year OS (dasatinib: 96% vs. 86% for dasatinib; 96% vs. 88% for imatinib) compared to those who did not reach this response milestone.**

**Rising BCR-ABL Levels**

Several studies have shown that a rising **BCR-ABL** level may be associated with an increased risk of **BCR-ABL** mutations in the future and cytogenetic relapse. Branford and colleagues reported that in patients who had achieved very low levels of **BCR-ABL** transcripts, emergence of **BCR-ABL** mutations was more frequent in those who had more than a 2-fold increase in **BCR-ABL** levels compared to those with stable or decreasing **BCR-ABL.** In contrast, Wang reported that a serial rise is more reliable than a single 2-fold or greater rise in **BCR-ABL transcript levels.** In an analysis of 258 patients with CP-CML on imatinib therapy, Kantarjian et al studied 116 patients in CCyR and who experienced an increase in **BCR-ABL** transcript levels of half log or more on at least two occasions. Eleven of 116 (9%) patients had CML progression. The patients with the highest risk were those who lost MMR with a >1 log increase in **BCR-ABL**, or those who never achieved a MMR and had a one log rise in **BCR-ABL**.

The amount of **BCR-ABL** increase that warrants concern, and should trigger mutation testing, is not known. Some labs have advocated a 2 to 3 fold range, while others have taken a more conservative approach (0.5-1 log). Obviously, some common sense must prevail, since the amount of change in absolute terms depends on the MMR level. For example, a finding of any **BCR-ABL** compared to CMR is an infinite increase in **BCR-ABL** level, though a change from CMR to a barely detectable level is clearly different than a 5-fold increase in a case hovering at the MMR level.

Currently there are no specific guidelines for changing therapy based on rising **BCR-ABL** transcripts as detected by QPCR. Changes of therapy based solely on rising **BCR-ABL** transcripts should be done only in the context of a clinical trial.
Resistence to TKIs

**Primary Resistance**

Primary hematologic resistance to TKI therapy (failure to achieve hematologic remission within 3 to 6 months of initiation of treatment) is very rare in newly diagnosed patients with Ph-positive CP-CML, whereas primary cytogenetic resistance to imatinib (failure to achieve any level of cytogenetic response at 6 months, MCyR at 12 months, or CCyR at 18 months) is evident in 15% to 25% of patients.

**Plasma protein Binding**

Imatinib, dasatinib, and nilotinib are all more than 90% bound to the plasma proteins, albumin as well as alpha-1 acid glycoprotein (AGP). Available data indicate that inadequate plasma concentration of imatinib may be one of the causes for primary resistance.

Gambacorti-Passerine and colleagues observed that excessive binding of imatinib to AGP may reduce the therapeutic effect of imatinib. Picard and colleagues also observed that trough plasma levels of imatinib were significantly higher in patients achieving CCyR and MMR at 12 months. In a subanalysis of the IRIS study, plasma levels of imatinib following the first month of treatment proved to be a significant prognostic factor for long-term clinical response. However, other investigators have suggested that plasma levels of imatinib in patients receiving different dose schedules had no correlation with response to therapy.

The clinical value of monitoring plasma levels of imatinib remains to be defined. Monitoring imatinib plasma levels may be useful in determining patient adherence to therapy. However, at the present time, there is no data to support that change of therapy based on plasma imatinib levels will affect treatment outcomes. Therefore, the panel does not recommend routine imatinib plasma level testing.

**Intracellular Concentration of TKIs**

Aberrant expressions of drug transporters such as multidrug resistance ATP-binding cassette (ABC) transporters (MDR1 or ABCB1 and ABCG2) and human organic cation transporter-1 (hOCT1) also contribute to resistance by altering the intracellular concentration of TKIs. Imatinib, dasatinib, and nilotinib have been identified as substrates for ABCB1 and ABCG2. Overexpression of the multidrug resistance gene (MDR1) has been associated with decreased intracellular concentration of imatinib, which may confer resistance to imatinib. Recent reports also suggest that ABCB1 and ABCG2 can confer resistance to dasatinib and nilotinib. Further clinical studies are needed to confirm these preliminary findings.

Pretreatment levels of hOCT1 have been reported as the most powerful predictor of response to imatinib. White and colleagues recently reported that most patients with suboptimal response to imatinib have low hOCT1 activity. In the updated analysis of patients enrolled in the TIDEL trial, MMR rate at 60 months was higher for patients with high hOCT1 activity compared to those with low hOCT1 activity (89% vs. 55%, respectively). Low hOCT1 activity was also associated with a significantly lower OS (87% vs. 96%) and EFS (48% vs. 74%) as well as a higher kinase domain mutation rate (21% vs. 4%). These differences were highly significant in patients who averaged less than 600 mg/day of imatinib. Similar findings were also reported in the subset analysis of the TOPS trial. Among patients receiving 400 mg of imatinib daily, MMR rates at 24 months were significantly higher for patients with high hOCT1 activity than those with low hOCT1 activity (100% and 57%, respectively; P < .001) but this difference was not significant in patients receiving 800 mg of imatinib. The corresponding MMR rates were 95% and 68%, respectively (P = .073). On the other hand, cellular uptake of dasatinib or nilotinib seems to be independent
of hOCT1 expression, suggesting that patients with low hOCT1 expression might have better outcomes with dasatinib or nilotinib.\textsuperscript{168-171}

**Secondary Resistance**

The most common mechanism for secondary resistance is the reactivation of \textit{BCR-ABL} activity.\textsuperscript{154} This occurs most often by mutations in the ABL tyrosine kinase domain of the \textit{BCR-ABL} gene (resulting in conformational changes in the fusion protein that affect the binding site of imatinib on the tyrosine kinase), and less frequently by \textit{BCR-ABL} gene amplification or increased \textit{BCR-ABL} expression.\textsuperscript{172-174} In the \textit{START-C} study, 46% of patients with imatinib-resistant CP-CML did not carry \textit{BCR-ABL} mutations, thus confirming that resistance to imatinib is multifactorial. Other mechanisms that are independent of \textit{BCR-ABL} include activation of the SRC family of kinases or cytogenetic clonal evolutions characterized by additional chromosomal abnormalities in the Ph-positive cells.\textsuperscript{154,173}

**ABL Kinase Domain Mutations**

Point mutations in the ABL kinase domain are emerging as the most frequent mechanism of resistance to TKI therapy. In a large study of 319 chronic-phase patients, Khorashad et al found that kinase domain mutations were the only independent predictor for the loss of CCyR and a higher risk progression (3.8- and 3.7-fold, respectively) when compared to patients without a mutation.\textsuperscript{175} Patients with P-loop mutations were associated with a particularly high risk of progression. Other studies have also reported that mutations in the ATP phosphate-binding loop (P-loop) are associated with poor prognosis and high risk of progression among patients treated with imatinib.\textsuperscript{176-179} However, Jabbour and colleagues could not confirm these findings.\textsuperscript{180} In the \textit{START} trials, dasatinib induced similar rates of major hemato logical and cytogenetic responses irrespective of the presence of P-loop or other mutations in imatinib-resistant patients with accelerated or BP-CML.\textsuperscript{47,49} Branford and colleagues observed that although there was a higher incidence of P-loop mutations in the accelerated phase, the difference in the frequency of mutation was significant between early chronic phase and accelerated phase, compared to that between accelerated phase and late chronic phase.\textsuperscript{176}

Among the mutations in the ABL kinase domain, the presence of T315I mutation confers the highest resistance to imatinib, dasatinib, and nilotinib. Some reports have suggested that T315I is associated with disease progression and poor survival.\textsuperscript{181,182} Jabbour and colleagues reported that survival of patients with T315I is dependent on the stage of the disease, with many chronic phase patients having an indolent course.\textsuperscript{181} Patients in the chronic phase had a 2-year survival rate of 87%. In patients in the accelerated phase and blast phase, survival rates were similarly poor irrespective of their T315I mutational status. Available clinical evidence indicates that in addition to T315I, mutations F317 and V299 are resistant to dasatinib and mutations Y253H, E255, and F359 are resistant to nilotinib.\textsuperscript{183-185} Among patients with \textit{BCR-ABL} mutations resistant to imatinib, clinically relevant mutations less sensitive to nilotinib (Y253H, E255K/V, and F359V/C) or dasatinib (F317L and V299L) or both (T315I) occurred in 43% of cases including 14% with T315I.\textsuperscript{183}

Muller et al recently reported the results of the largest analysis of clinical response to dasatinib after imatinib failure in 1043 patients with CP-CML according to the pre-existing \textit{BCR-ABL} mutations.\textsuperscript{186} The presence of T315I and F317L mutations at baseline was associated with less favorable responses. A few responses (CHR and MCyR) were observed in patients with a T315I mutation but no CCyRs. Patients with an F317L mutation had a high rate of CHR (93%) but low rates of MCyR and CCyR (14% and 7%, respectively), whereas
favorable CCyR rates were achieved in patients with highly imatinib-resistant mutations such as E255K/V (38%) and L248V (40%). Other studies have also reported similar findings in patients with F317 mutations at baseline.\textsuperscript{187,188} In one study, F315 and/or F317 mutations were associated with resistance to dasatinib.\textsuperscript{188} In another study, patients with a F317L mutation had a similar survival compared with patients with other mutations with outcome dependent on the CML phase; this mutation was sensitive to other TKIs.\textsuperscript{187}

Hughes et al assessed the occurrence and impact of baseline BCR-ABL mutations on nilotinib therapy in patients with imatinib-resistant CP-CML.\textsuperscript{189} Patients with Y253H, E255V/K, and F359V/C mutations achieved less favorable MCyR rates (13%, 43%, and 9%, respectively) and none of them achieved CCyR within 12 months of therapy. E255K/V, F359C/V, Y253H, and T315I mutations were most commonly associated with disease progression. Consistent with these findings, F359V, Y253H, and E255K/V mutations were associated with relapse to nilotinib in the study reported by Soverini et al.\textsuperscript{190}

In the phase I/II study that evaluated the efficacy of bosutinib in patients with CP-CML, AP-CML and BP-CML, resistant or intolerant to prior TKI therapy, bosutinib was active in patients with BCR-ABL mutations.\textsuperscript{90} The most common baseline mutations were T315I, F359C/I/S/V, F317L, G250E, Y253F/H and M351T. T315I and V299L were the most common emergent mutations, both of which are resistant to bosutinib. Among patients with baseline mutations, CHR and MCyR were observed in those with mutations resistant to dasatinib (F317L) and nilotinib (Y253H, E255K/V and F359C/I/V).\textsuperscript{90}

In the PACE trial, in addition to T315I, ponatinib was also active against other BCR-ABL mutations resistant to dasatinib or nilotinib, including F317L, E255K, F359V and G250E. In patients with CP-CML, MMR rates were 41%, 50%, 31% and 38% respectively for patients with F317L, E255K, F359V and G250E mutations.\textsuperscript{191}

Taken in full, the data suggest that identification of mutations supports the diagnosis of resistance to TKI therapy and mutational analysis would be helpful in identifying a subgroup of patients who demand careful monitoring, as these patients are at a higher risk of progression. Mutational status at the time of loss of response to TKI therapy may be helpful in selection of subsequent TKI therapy. Mutational analysis would also be helpful to identify the subset of patients who will be eligible for allogeneic HSCT. See Table 2, Treatment options based on KD mutational status.

### Clonal Evolution

Clonal evolution is defined by the presence of additional cytogenetic abnormalities (ACA) besides the Ph-chromosome and is considered to be a feature of AP-CML.\textsuperscript{192} In an analysis of patients who developed cytogenetic clonal evolution on interferon therapy (prior to the use of imatinib), Majlis and colleagues from MD Anderson Cancer Center concluded that the prognostic significance of clonal evolution is not uniform, but it is related to the specific chromosomal abnormality and the presence of other features of accelerated phase.\textsuperscript{193} In this study, presence of chromosome 17 abnormality, predominance of abnormal metaphases (≥ 36%), and the other accelerated features were identified as the worst prognostic factors.

In patients with accelerated phase treated with imatinib, clonal evolution resulted in lower response rates and a shorter time to treatment failure. However, in a subset of patients, clonal evolution was associated with a
better prognosis when it was considered as the only criteria for accelerated phase disease. With a median follow-up of 12 months, the MCyR and CCyR rates were 73% (11 of 15) and 60% (9 of 15), respectively. In a subsequent report, of 141 patients treated with imatinib after failing interferon, O’Dwyer and colleagues identified clonal evolution, an elevated platelet count, and failure to achieve MCyR by 6 months as adverse prognostic factors for hematologic relapse. In a large trial of 498 patients in chronic or accelerated phase, cytogenetic clonal evolution was not an important factor for achieving MCyR or CCyR with imatinib, but it was an independent poor prognostic factor for survival in both CP-CML and AP-CML.

In the German CML IV study, patients with cytogenetic abnormalities including trisomy 8, second Ph-chromosome and isochromosome 17q at the time of diagnosis had longer times to cytogenetic and molecular responses and shorter PFS and OS than in patients with t(9;22) [major-route ACA]. After a median observation follow-up of 5 years, the PFS and OS rates were 90% and 92%, respectively, for patients with t(9;22), and the corresponding survival rates were 50% and 53%, respectively, for those with major-route ACA.

Clonal cytogenetic abnormalities in Ph-negative cells have also been reported in a small subset of patients during the course of imatinib therapy. The significance of these chromosomal abnormalities is unclear, but the most common abnormalities include trisomy 8, an abnormality frequently seen in patients with myelodyplastic syndrome (MDS). Only rare cases of MDS or acute myeloid leukemia (AML) have been reported in patients with these abnormalities, usually in those who had received interferon as well as prior chemotherapy. Some of these abnormalities may persist only in a small percentage of metaphases or may be transient and disappear with continued therapy in patients who have achieved CCyR. In a recent report, Deininger and colleagues concluded that the overall prognosis for patients with Ph-negative CML and clonal cytogenetic evolution was good and was dependent on patients’ response to imatinib therapy. In newly diagnosed patients with CP-CML treated with imatinib, chromosomal abnormalities in Ph-negative cells appeared in 9% of the patients. Loss of Y chromosome was most common. The significance of loss of Y chromosome in this setting is unclear. It has been reported that this phenomenon is a common occurrence among aging males.

Management of Resistance
Dose escalation of imatinib up to 800 mg daily has been shown to overcome some of the primary resistance, but the duration of responses has typically been short. Jabbour and colleagues assessed the long-term efficacy of imatinib dose escalation after hematologic or cytogenetic failure in 84 patients with CP-CML. After a median follow-up of 61 months, the estimated 2- and 3-year EFS and OS rates were 57% and 47% and 84% and 76%, respectively. Responses were also durable; 88% of patients with MCyR sustained their response beyond 2 years. Dose escalation was particularly effective in patients with cytogenetic relapse who had achieved cytogenetic response with
standard-dose imatinib. In this group of patients, CCyR and MCyR rates were 73% and 87%, respectively, compared to 52% and 60% for the overall group of patients with cytogenetic failure. In a retrospective analysis of 106 patients with newly diagnosed CP-CML from the IRIS trial who received imatinib at a dose of 400 mg daily, and subsequently underwent dose escalation to either 600 mg or 800 mg daily, the rates of FFP to accelerated or blast phase and OS were 89% and 84% at 3 years after dose increase, respectively. These results indicate that dose escalation of imatinib is unlikely to benefit those with hematologic failure or those who never had a cytogenetic response with standard-dose imatinib; dose escalation of imatinib might be beneficial for patients with cytogenetic relapse or suboptimal cytogenetic response to imatinib 400 mg daily (See the section on “Suboptimal Response”).

Dasatinib, nilotinib, and bosutinib are active against many of the imatinib-resistant BCR-ABL kinase domain mutations, except T315I and are effective treatment options for patients with CP-CML resistant to standard-dose imatinib. The results of the START-R trial demonstrated that dasatinib is also effective for patients with CP-CML resistant to high-dose imatinib. Bosutinib has shown potent activity in patients with BCR-ABL mutations resistant to dasatinib (F317L) and nilotinib (Y253H and F359). Ponatinib has demonstrated activity in patients with BCR-ABL mutations resistant to dasatinib or nilotinib (F317L, E255K, F359V and G250E) including T315I.

Omacetaxine (Homoharringtonine, a cephalotaxus alkaloid) is a protein synthesis inhibitor with demonstrated activity against CML lines including those harboring the T315I mutation. The efficacy of omacetaxine in patients with CP-CML or AP-CML resistant to 2 or more TKI therapies was evaluated in a multicenter phase II trial (n = 122; 62 patients had received 2 TKIs (imatinib, dasatinib or nilotinib and 60 patients had received all 3 approved TKIs). In the subset analysis of patients with CP-CML who had failed prior therapy with 2 or more TKIs (45 patients in the 2 TKI group and 36 patients in the 3 TKI group), MCyR was observed in 27% of patients treated with 2 prior TKI therapy (median survival was 30 months) and in 11% of patients treated with all three 3 TKIs (median survival was not reached). The MCyR rates were 19% (median duration not reached), 29% (median duration 7.4 months) and 20% (median duration 17.7 months) for patients with resistance, intolerance and resistance/intolerance to prior TKI therapy. The median OS in these 3 groups of patients was 34 months, not reached, and 25 months respectively. Among patients with AP-CML (17 patients in the 2 TKI group and 24 patients in the 3 TKI group), MaHR was observed in 35% and 21% of patients in the 2 and 3 TKI groups respectively. Median survival was 12 months and 24.6 months respectively.

Omacetaxine was also safe and effective in the treatment for patients with T315I mutation and failure to prior TKI therapy. Among 62 evaluable patients with CP-CML, CHR, MCyR and CCyR were seen in 77%, 23% and 16% of patients, respectively. MMR was achieved in 17% of patients and the T315I clone was reduced to below detection limits in 61% of patients. Median duration of CHR and MCyR was 9 and 7 months, respectively. After a median follow-up of 19 months, median PFS was 7.7 months and the median OS had not yet been reached.

Omacetaxine has an acceptable toxicity profile in all three phases of CML. In a pooled safety analysis of 207 patients from the phase II studies, (median age, 57 years), 108 patients with CP-CML; 55 patients in AP-CML and 44 patients in BP-CML), the most common adverse events were thrombocytopenia, anemia, diarrhea, neutropenia and nausea. Treatment-related grade 3/4 hematologic adverse events
included thrombocytopenia (52%), neutropenia (31%), anemia (30%), leukopenia (12%), and febrile neutropenia (11%).

Omacetaxine was approved by the FDA in October 2012 for the treatment of patients with CP-CML or AP-CML who are intolerant to other therapy or those who did not respond to prior treatment with 2 or more TKIs.

**Monitoring Response to First-line TKI Therapy**

Most patients receiving TKI therapy will achieve a CHR at 3 months, and CCyR at 6, 12, or 18 months. If there is no hematologic and cytogenetic response at the above-mentioned intervals, mutational analysis should be considered and patient compliance to TKI therapy should be evaluated. In patients with prolonged myelosuppression who may not be in CHR due to persistent cytopenias or unexplained drop in blood counts during therapy, bone marrow cytogenetics may be useful to confirm response to TKI therapy and to look for non-Ph clonal changes and evidence of myelodysplasia.

Bone marrow cytogenetics and QPCR using IS with a sensitivity of 4.5-log reduction or more from the standardized baseline are recommended to monitor cytogenetic and molecular responses respectively to TKI therapy. Hughes et al have reported that routine monitoring of BCR-ABL transcripts, in conjunction with cytogenetic evaluation, provides important information about long-term disease control in patients with CML. Some investigators have reported that interphase FISH can be used to monitor CCyR. However, the panel feels that FISH has been inadequately studied for monitoring response to TKI therapy. Therefore, FISH is not recommended for monitoring response.

Based on the recent data demonstrating the prognostic significance of cytogenetic and molecular responses at 3 months, the panel has included BCR-ABL ≤10% (IS) by QPCR or PCyR on bone marrow cytogenetics (if QPCR [using IS] is not available) as a response milestone at 3 months. QPCR to monitor BCR-ABL transcript levels is recommended every 3 months when a patient is responding to treatment. Bone marrow cytogenetics is recommended at 12 months (for patients who are not in CCyR or MMR) and at 18 months (if not in MMR and there is lack of CCyR at 12 months).

Mutational analysis and evaluation of patient compliance to TKI therapy are recommended for patients with inadequate initial response (ie, failure to achieve a PCyR or BCR-ABL ≤10% [IS] at 3 months; CCyR at 12 and 18 months).

The optimal guidelines for monitoring response to TKI therapy and mutational analysis are outlined in Table 3.

**Suboptimal Response**

In the European LeukemiaNet (ELN) guidelines, suboptimal response to first-line imatinib is defined as no cytogenetic response at 3 months, less than PCyR at 6 months, PCyR at 12 months, and less than MMR at 18 months.

Suboptimal response to imatinib could result from many factors, including poor compliance to imatinib therapy; individual variation in drug metabolism; aberrant expression of drug transporters; differences in the intrinsic biology of the disease, which might result in clonal competition between clones highly sensitive to imatinib; and those resistant. The prognostic implications of suboptimal response may also be different depending on the time point of suboptimal response. Thus, the outcomes of patients with suboptimal response at 6 and 12
months are more similar to those of patients who met the criteria for failure, and the outcomes of patients with a suboptimal response at 18 months are very similar to those of patients with an optimal response. However, other investigators suggest that suboptimal responders at 12 months have an outcome closer to that of patients with an optimal response, with a similar transformation-free survival but with worse EFS. A few early reports have suggested that dose escalation of imatinib to 800 mg as tolerated, or switching to dasatinib or nilotinib, are effective in patients with suboptimal response to imatinib 400 mg.

However, these definitions are not applicable to patients with newly diagnosed CML treated with second-generation TKIs in the first-line setting. Jabbour et al have recently proposed that for this group of patients, CCyR and PCyR at 3 months should be considered as optimal and suboptimal responses, respectively. At the present time, the panel feels that there is no strong evidence to recommend a definite treatment option for patients with suboptimal response. Careful monitoring and may benefit from alternate treatment options. NCCN supports clinical trials that evaluate whether intervention for suboptimal response or molecular relapse affects short- and long-term outcomes.

The guidelines recommend continuation of the same dose of TKI therapy (imatinib, dasatinib, nilotinib) for patients with PCyR (less than 10% of BCR-ABL transcript level by QPCR using the IS) at 3 months. These patients should be assessed by QPCR every 3 months. Change of therapy to alternate second-generation TKI (preferred), continuation of TKI therapy with dasatinib, nilotinib or bosutinib at the same dose or dose escalation of imatinib to 800 mg as tolerated (in patients with contraindications to dasatinib or nilotinib or bosutinib or omacetaxine) are included as options for patients with PCyR at 12 months.

Follow-up Therapy

 Patients not responding to first-line therapy with imatinib should be treated with dasatinib or nilotinib or bosutinib or ponatinib in the second-line setting. Patients not responding to first-line therapy with dasatinib or nilotinib could be treated with an alternate TKI for second-line therapy. At this time, there are no data to recommend a definite treatment option for this group of patients. Omacetaxine is an option for patients with resistance and/or intolerance to two or more TKIs. See Table 4 for the recommendations for follow-up therapy.

The panel believes that at the present time there are not enough data to recommend one TKI over the other as the preferred second-line therapy. Mutational analysis may be helpful in selection of subsequent TKI therapy. See Table 2, Treatment options based on KD mutational status.

Monitoring Response to Second-line TKI Therapy

Early cytogenetic response to second-line TKIs can predict survival and guide subsequent therapy. Tam and colleagues reported that in patients receiving dasatinib or nilotinib, patients achieving MCyR after 12 months of treatment had a significant advantage over those achieving minor cytogenetic response or CHR. Milojkovic and colleagues also reported that among patients with CP-CML who were resistant to imatinib and who were treated with dasatinib or nilotinib, those who had a minimal cytogenetic response at 3 months, PCyR at 6 months, and CCyR at 12 months had significantly better outcomes than patients with lesser degrees of cytogenetic response. At the 12-month landmark analysis, patients with a CCyR at 12 months had significantly superior event-free (97% vs. 80%) and overall (100% vs. 75%) survival.
85%) survival probabilities compared to those who had failed to achieve a CCyR. There were no significant differences in PFS. More recently, Shah et al reported that achievement of CCyR (with or without MMR) at 12 months to dasatinib 100 mg once daily was predictive of PFS. The PFS rate was 87% for those with a CCyR (with or without MMR) at 12 months compared to 78% and 45%, respectively, for those with PCyR or no cytogenetic response at 12 months.

The measurement of BCR-ABL transcript levels at 3 months following second-line TKI therapy has also been reported to be predictive of response and may provide further information about the value of continuing treatment with the second-generation TKIs. BCR-ABL% (IS) at 3 months after nilotinib therapy correlated with MCyR, MMR, and EFS rates regardless of baseline mutational status in patients resistant or intolerant to imatinib. Patients whose BCR-ABL% (IS) levels decreased below 10% at 3 months have a high probability of achieving MMR and MCyR at 24 months. Similarly, patients who achieve early molecular response may also have an increased probability of improved long-term outcomes on nilotinib therapy, while patients with BCR-ABL% (IS) value of greater than 10 at 3 months may have a poorer prognosis. Milojkovic et al reported that molecular response at 3 months was the only independent predictor for OS in patients who received a second-generation TKI as second-line therapy while still in the chronic phase. CCyR (67.2% vs. 11.2%; P = .0001), EFS (49.3% vs. 13.0%; P < .001), and OS (91.3% vs. 72.1%; P = .02) rates were significantly higher for patients with BCR-ABL/ABL (IS) ≤ 10% at 3 months compared to those patients with BCR-ABL/ABL (IS) > 10%. Shah et al also reported similar findings in the 6-year follow-up of dasatinib dose optimization study. The 6-year PFS (64% vs. 26%; P < .001) and OS (83% and 59%; P < .001) rates were significantly higher in patients with BCR-ABL/ABL ≤10% (IS) at 3 months, irrespective of resistance or intolerance to imatinib, mutational status, and baseline response level.

Low Sokal risk score at diagnosis, best cytogenetic response on imatinib, neutropenia at any time during imatinib therapy requiring dose reduction despite growth factor support, and time from detection of imatinib failure to start of second-line TKI have also been identified as predictive factors for achievement of cytogenetic response on second-line TKI therapy. Recently, Jabbour et al identified a lack of any cytogenetic response to imatinib therapy and a poor performance status as independent poor predictive factors of outcome to second-line TKIs.

The use of a alternate TKIs after failure of two prior TKIs may induce responses in some patients, but these are not durable except in occasional patients in chronic phase. Investigational therapies or allogeneic HSCT should be considered for this group of patients. At the present time, there are no definite recommendations for specific time points to switch patients to allogeneic HSCT based on the response to second-line TKI therapy. Based on the available data, patients receiving dasatinib or nilotinib with no cytogenetic or molecular response at 3, 6, or 12 months should be considered for alternative therapies or allogeneic HSCT, if a suitable donor is available.

Adherence to TKI Therapy

Treatment interruptions and non-adherence to TKI therapy may lead to undesirable clinical outcomes. In the ADAGIO (Adherence Assessment with Glivec: Indicators and Outcomes) study, which evaluated the outcomes of non-adherence to imatinib therapy in patients with CML, non-adherence was associated with poorer response to imatinib. Patients with suboptimal response had significantly
higher mean percentages of imatinib not taken (23%) than did those with optimal response (7%). Marin and colleagues recently identified adherence as the only independent predictor for achieving CMR on standard-dose imatinib. Patients whose imatinib doses were increased had poor adherence (86%), and in these patients adherence was the only independent predictor for inability to achieve a MMR. Poor adherence to imatinib therapy has also been identified as the most important factor contributing to cytogenetic relapse and imatinib failure. Patients with an adherence rate of 85% or less had a higher probability of losing their CCyR at 2 years than those with an adherence rate of more than 85% (27% and 1.5%, respectively). BCR-ABL doubling time has been reported as a marker to identify non-adherence to TKI therapy in patients who are still in CP-CML.

Poor adherence to TKI therapy has also been reported in patients receiving dasatinib and nilotinib following imatinib failure. However, the impact of non-adherence to dasatinib and nilotinib on treatment efficacy has not yet been reported. In the absence of such data, findings from the studies involving patients treated with imatinib should be extrapolated to patients receiving second-generation TKI therapy.

Discontinuation of TKI Therapy

TKI therapy has become the standard of care for patients with CML. Imatinib has significantly reduced the annual mortality rate among patients with CML (less than 5% in the first 5-6 years of treatment compared to 10%-20% in the pre-imatinib era), and patients responding to imatinib are likely to maintain their responses on long-term therapy. CCyR can be achieved in most patients with CP-CML receiving imatinib, and CMR has been documented in 40% of patients after 7 years of first-line treatment with imatinib. Recent randomized studies have also shown that dasatinib and nilotinib induce faster and deeper treatment responses than imatinib in the first-line setting. However, the vast majority of patients who achieve a clinically undetectable level of BCR-ABL transcripts (CMR) by the most sensitive PCR measures remain with residual disease that may eventually lead to disease relapse.

Results from recent studies suggest that discontinuation of imatinib (with close molecular monitoring) may be possible in selected patients with a stable CMR for 2 or more years. In a pilot study (12 patients; 10 of 12 had received prior interferon therapy), Rousselot and colleagues suggested that discontinuation of imatinib is feasible in a subset of patients achieving sustained CMR. Similar findings were reported in subsequent prospective non-randomized studies (Stop Imatinib [STIM] study and Australasian CML8 trial).

In the multicenter STIM study, Mahon et al evaluated the possibility of discontinuation of imatinib in 100 patients with a CMR (5-log reduction in BCR-ABL and ABL levels and undetectable transcripts on QPCR) for at least 2 years while on imatinib. Among 69 patients with a follow-up of more than 12 months (median follow-up of 24 months), 39% of patients remained in CMR and 61% of patients relapsed, most within 6
months after discontinuation of imatinib. The molecular relapse-free survival was 41% and 38%, respectively, at 12 months and 2 years. In the updated analysis of the STIM study, the overall probability of maintaining CMR at 24 and 36 months was 39%, and it was significantly better for patients in the low Sokal risk group (55% at 24 months; \( P < .001 \)) compared to those in the intermediate and high-risk groups.\(^{253}\) Sokal risk score and the duration of imatinib therapy were identified as the independent prognostic factors for the prediction of molecular relapse after imatinib discontinuation.

In the Australasian CML8 trial, Ross et al evaluated discontinuation of imatinib in 40 patients (21 had received imatinib after prior interferon and 19 patients received imatinib as front-line therapy) with CP-CML in CMR for 2 or more years.\(^{252}\) At the median follow-up of 33 months, the actuarial molecular relapse-free survival was 42% (50% in patients who received prior interferon and 32% for those treated with imatinib alone). High Sokal risk score and shorter duration of interferon treatment were associated with increased risk of relapse.

Discontinuation of TKI therapy in patients treated with dasatinib or nilotinib following imatinib failure has been reported in only a small number of patients.\(^{254,255}\) Ross et al reported that CMR was maintained for more than 12 months in 2 of 3 patients after discontinuation of dasatinib.\(^{254}\) Rea et al from the French CML Study Group reported that discontinuation of TKI therapy is possible in patients with stable undetectable \( BCR-ABL \) transcripts after treatment with dasatinib or nilotinib following imatinib failure.\(^{255}\) After a median of 13 months, 11 patients remained off-therapy (10 patients with either a stable undetectable or weakly detectable \( BCR-ABL \) transcript); 31% of patients (5/16) lost MMR by 4 months after discontinuation. MMR was rapidly regained after reintroduction of dasatinib or nilotinib. The majority of patients in this study were in the low Sokal risk group. The median duration of TKI therapy prior to discontinuation was 32 months and the median duration of sustained undetectable \( BCR-ABL \) transcripts was 27 months.

Additional prospective studies in larger cohorts with long-term follow-up are needed to determine the optimal duration of TKI therapy in patients who are in CMR. At the present time, the guidelines recommend continuation of TKI therapy indefinitely in responding patients. Discontinuation of TKI therapy should be considered only in the context of a clinical trial.

**Advanced Phase CML**

**Accelerated Phase**

Varying definitions have been used for AP-CML.\(^{256-259}\) See “Definitions for Accelerated Phase” in the guidelines. The most commonly used definition is the World Health Organization (WHO) criteria, which defines accelerated phase as the presence of any of the following features: 10% to 19% of blasts in the peripheral blood or bone marrow, 20% or more of basophils in the peripheral blood, persistent thrombocytopenia (less than 100 x 10^9/L) unrelated to therapy or persistent thrombocytosis (more than 1000 x 10^9/L) unresponsive to therapy, increasing spleen size, and increasing white blood cell (WBC) count unresponsive to therapy.\(^{259}\) Cortes et al have suggested a modification to the WHO criteria (15% or more of peripheral blood blasts, 30% or more of peripheral blood blasts and promyelocytes, 20% or more of basophils, platelet count of 100 x 10^9/L or less, and clonal evolution).\(^{260}\) It should be noted that clinical trials of TKIs have largely reported efficacy data using the modified MD Anderson Cancer Center accelerated phase criteria.\(^{260}\)
Blast Phase

Approximately 50% of all the blast phase cases are of the myeloid subtype, 25% are of the lymphoid subtype, and the rest are undifferentiated. According to the International Bone Marrow Transplant Registry (IBMTR), blast crisis is defined as 30% or greater blasts in the blood, bone marrow, or both, or as the presence of extramedullary disease. In the WHO criteria, blast crisis is defined as 20% or greater 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. See “Definitions for Blast Phase” in the guidelines.

Work-up and Treatment Options

The panel recommends bone marrow cytogenetics and mutational analysis prior to initiation of treatment for patients with AP-CML and BP-CML. Participation in a clinical trial is recommended for all patients with accelerated or blast phase.

High-dose combination chemotherapy has been used in patients with AP-CML or BP-CML resulting in response rates of 25% to 60%. In a study of 48 patients with AP-CML or BP-CML, intensive chemotherapy induced hematologic and cytogenetic responses in 29% and 23% of patients, respectively; CHR was observed in 25% of patients with AP-CML and 33% of patients with BP-CML. Among patients with BP-CML, ALL-type chemotherapy regimens are associated with higher response rates in patients with BP-CML (49% vs. less than 20% for other morphologies;P < .001); however, the responses are not durable.

Imatinib, dasatinib, nilotinib, bosutinib, and ponatinib also induce favorable response rates in patients with AP-CML or BP-CML. Omacetaxine has shown activity in patients with disease progression to AP-CML after prior therapy with 2 or more TKIs. Recent studies have shown that the addition of TKI to chemotherapy improves outcome in patients with BP-CML or minimally treated or newly diagnosed Ph-positive ALL. In a study of 36 patients with myeloid BP-CML, the addition of imatinib to daunorubicin and cytarabine was associated with a hematologic response rate of 78% (CHR rate of 55.5%) with a median follow-up of 6 years. Median OS was 16 months, and the OS in patients with hematologic response was 35.4 months. In another study (n = 32), the combination of the hyperCVAD regimen with dasatinib resulted in an overall response rate of 94% (72% achieving complete remission) and a CMR rate of 43% (33% MMR) in patients with relapsed Ph-positive ALL or lymphoid BP-CML. Among patients with lymphoid BP-CML, at a median follow-up of 85 weeks, the 3-year OS rate was 76%, with 82% remaining in CMR at 3 years.

A significant portion of patients treated with dasatinib or nilotinib achieve a MCyR but not a concomitant CHR because of persistent cytopenias. Fava et al reported that failure to achieve a CHR at the time of MCyR was associated with an inferior outcome. The 2-year survival rate was 37% compared to 77% for patients with MCyR and concomitant CHR. These results suggest that patients with MCyR without a CHR should be considered for alternate therapies.

NCCN Recommendations

Dasatinib (140 mg once daily) or nilotinib (400 mg twice daily) or bosutinib (500 mg once daily) or ponatinib (45 mg once daily) are appropriate options for patients with disease progression to AP-CML following TKI therapy. The selection of TKI therapy is based on prior therapy and/or mutational testing (See Table 2). Allogeneic HSCT can be considered based on response to TKI therapy. Omacetaxine is a
treatment option for patients with disease progression to AP-CML due to resistance and/or intolerance to two or more TKIs.

TKI therapy alone or in combination with chemotherapy followed by allogeneic HSCT (if feasible) is recommended for patients in myeloid or lymphoid blast phase. ALL-type chemotherapy is recommended for patients with lymphoid BP-CML (See NCCN Guidelines for ALL). AML-type chemotherapy is recommended for those with myeloid BP-CML (See NCCN Guidelines for AML).

Allogeneic Hematopoietic Stem Cell Transplant

Allogeneic HSCT is a potentially curative treatment for patients with CML, but the excellent results with TKI therapy have challenged the role of allogeneic HSCT as a first-line therapy. The widespread application of allogeneic HSCT is limited by donor availability and the high toxicity of the procedure in older patients, which limits the age of eligibility at many centers to younger than 65 years. Ongoing advances in alternative donor sources (such as unrelated donors and cord blood), more accurate human leukocyte antigen (HLA) typing of unrelated donors, and less toxic regimens are broadening the use of allogeneic HSCT. Transplants from unrelated matched donors can now be used for many patients with CML. The advent of molecular DNA assessment of HLA typing has enabled a rigorous and stringent selection of unrelated matched donors, and this improvement in typing has translated into greatly improved transplant outcomes, so that results with unrelated, fully matched donors are comparable to those of related matched donors.

Investigational approaches using non-myeloablative reduced-intensity conditioning have been pioneered to engender a graft-versus-leukemia effect without exposing the patient to the toxicity associated with the myeloablative preparative regimen. These studies are still investigational but are quite promising and show that molecular remissions may be achieved with non-myeloablative reduced-intensity conditioning in patients with CML.

Prognostic Factors

The outcome of allogeneic HSCT is influenced by the disease phase, HLA matching, age, sex, and time from diagnosis to transplant. Low HSCT comorbidity index (HCT-CI) and low C-reactive protein were recently identified as prognostic indicators for lower non-relapsed mortality rate and a somewhat improved survival rate. The disease phase at the time of transplant remains an important prognostic factor; outcomes following transplant are clearly better for patients in chronic phase compared to patients with advanced disease; 5-year survival rates after matched-related transplants are approximately 75%, 40%, and 10% for patients in chronic, accelerated, and blast crisis phases, respectively. Patients who receive allogeneic HSCT for CML in first chronic phase and remain in remission for at least 5 years have favorable subsequent long-term survival. Survival remains poor for patients transplanted in accelerated or blast phase compared to those transplanted in chronic phase. Gratwohl et al. reported improved survival across all the EBMT risk groups due to significant reduction in incidences of relapse and treatment-related mortality. However, survival was still poor for patients transplanted in accelerated or blast phase (40%-47% and 16%, respectively) compared to 70% for those transplanted in chronic phase. In the sub-group analysis of the German CML IV Study, among 84 patients who underwent allogeneic HSCT because of either a high-disease risk score at diagnosis, imatinib failure, or disease progression, the 3-year survival rates were 91% for patients with chronic phase and 59% for those with advanced phase, with a treatment-related mortality of 8%. In a more recent report from CIBMTR, disease-free survival rates after allogeneic HSCT were 35%
to 40%, 26% to 27%, and 8% to 11% for patients transplanted in the second chronic phase, accelerated phase, and blast phase, respectively. Multivariate analyses demonstrated that conventional prognostic indicators remain the strongest determinants of transplant outcomes. Therefore, the potential use of transplantation must be tied to faithful monitoring of disease, since the major potential pitfall in delaying transplantation is “missing” the chronic phase interval.

**Effect of Prior TKI Therapy**

There has been concern that previous treatment with imatinib might have a deleterious effect on subsequent allogeneic HSCT outcomes, as previously implicated with busulfan and interferon. However, results from several large studies have confirmed that the use of imatinib prior to allogeneic HSCT is not associated with a significant increase in death, relapse rate, and non-relapse mortality compared to cases who did not receive pre-transplant imatinib. These data suggest that pre-transplant imatinib does not compromise the outcome of a subsequent allogeneic HSCT. In fact, the IBMTR data on 409 patients treated with imatinib before transplant and 900 patients who did not receive imatinib showed that prior use of imatinib was associated with improved survival for patients transplanted in chronic phase, although this was limited to patients who underwent transplant because of intolerance rather than failure on imatinib. Such a survival benefit was not seen in patients transplanted in advanced phase.

Some studies have also shown that the use of second-generation TKI before allogeneic HSCT does not affect the outcome of transplant or increase transplant-related toxicity.

**Indications for Allogeneic HSCT**

Allogeneic HSCT is an appropriate first-line treatment option for the very rare patients presenting with blast phase at diagnosis, patients with T315I and other BCR-ABL mutations that are resistant to all TKIs, and for rare patients intolerant of all TKIs. A recent report from the MD Andersen Cancer Center indicated that allogeneic HSCT is an effective strategy for patients with CML with T315I mutation, particularly in earlier stages; patients who underwent transplant in chronic phase had the best outcome. In a more recent analysis of imatinib-resistant CML patients (chronic phase, n = 34; accelerated phase, n = 9; and blast phase, n = 4) who underwent HSCT at the MD Anderson Cancer Center, the overall response rate was 89% and 68% of patients had MMR. The 2-year EFS rate was 36% for patients with BCR-ABL mutations and 58% for those with no mutations, respectively. The corresponding 2-year OS rate was 44% and 76%, respectively. Nicolini et al also reported similar findings in 64 patients with T315I mutation. At a median follow-up of 26 months, survival probabilities at 24 months after allogeneic HSCT were 59%, 67%, and 30% for patients with chronic, accelerated, and blast phase, respectively. In multivariate analysis, blast phase at the time of transplant and transplants from unrelated donors were identified as adverse prognostic factors for OS.

**NCCN Recommendations**

**Chronic phase CML**

Given the successful induction of durable responses with imatinib in the vast majority of patients and the recent results showing superior early efficacy of nilotinib and dasatinib in newly diagnosed patients, allogeneic HSCT is no longer recommended as a first-line treatment option for patients with CP-CML. In a randomized study, primary HSCT and drug treatment were compared in 621 newly diagnosed patients. Among the 354 patients who were eligible for HSCT based on the availability of a related donor, 123 patients received a HSCT and 219 patients received the best possible drug treatment (interferon until imatinib became available later in the trial; imatinib was offered to
patients failing interferon). Survival with drug therapy was clearly superior for the first 5 years. Survival differences were significant in low-risk patients and no survival difference was observed in intermediate- or high-risk patients.\textsuperscript{316}

Role of allogeneic HSCT should be discussed with the patient. Allogeneic HSCT is recommended for patients with T315I mutation who do not respond to imatinib, dasatinib, or nilotinib. Nonmyeloablative transplant is investigational and it should be performed only in the context of a clinical trial. Evaluation for allogeneic HSCT based on response to second-line TKI therapy is recommended for all patients with failure to first-line TKI therapy, as indicated below:

- **BCR-ABL/ABL >10% (IS) or less than PCyR at 3 months**
- Minor or no cytogenetic response at 12 months
- PCyR at 18 months
- Cytogenetic relapse at 6, 12, or 18 months

**Advanced Phase CML**

Allogeneic HSCT should be considered for patients with disease progression to accelerated or blast phase on TKI therapy. In this group of patients, treatment with a course of alternate TKI (not received before) will be beneficial as a “bridge” to transplantation.

**Monitoring Response after Allogeneic HSCT**

The **BCR-ABL** transcripts persist after many years in most patients after allogeneic HSCT. Several studies have investigated the clinical significance of monitoring **BCR-ABL** transcript levels by QPCR following HSCT.\textsuperscript{317-322} Radich et al reported that PCR-positivity 6 or 12 months after HSCT is associated with a higher risk of disease relapse (42%) compared to only 3% in patients who tested PCR-negative. This study also showed that early PCR-positivity is associated with more aggressive disease and high risk of relapse.\textsuperscript{319} Olavarria et al reported similar findings. QPCR was performed at 3-5 months after allogeneic HSCT. At 3 years after allogeneic HSCT, the cumulative relapse rate was 17% for patients with no evidence of **BCR-ABL** transcripts, 43% for those who had less than 100 **BCR-ABL** transcripts, and 86% for those with more than 100 **BCR-ABL** transcripts.\textsuperscript{321} PCR-positivity at 6 months or less was also highly predictive of relapse in patients who received T-cell depleted transplant.\textsuperscript{320} The prognostic significance of **BCR-ABL** positivity is less evident after a longer period of time following transplantation. Costello et al reported that the relapse rate was only 8% in patients who were **BCR-ABL** positive at more than 36 months after HSCT.\textsuperscript{323} Other investigators have reported that **BCR-ABL** transcripts persist even in patients who are in complete remission for more than 10 years after HSCT.\textsuperscript{324} More recently, Radich et al analyzed 379 consecutive CML patients alive at 18 months or more after HSCT to assess the relapse risk associated with **BCR-ABL** detection in "late" CML survivors.\textsuperscript{322} Ninety of 379 patients (24%) had at least one positive **BCR-ABL** test 18 months after transplantation or later; 13 of 90 **BCR-ABL**-positive patients (14%) and 3 of 289 **BCR-ABL**-negative patients (1.0%) relapsed.

Thus, the prognostic significance of **BCR-ABL** positivity is influenced by the time of testing after allogeneic HSCT. While QPCR assay positive for **BCR-ABL** at 6 to 12 months after transplant is associated with a high risk of relapse, a positive QPCR assay at a much later time point after transplant is associated with a lower risk of relapse. Early detection of **BCR-ABL** transcripts after transplant 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

Donor lymphocyte infusion (DLI) is effective in inducing durable molecular remissions in the majority of patients with relapsed CML following allogeneic HSCT, though it is more effective in patients with chronic phase relapse than advanced phase relapse.\textsuperscript{325-328} The probability of survival at 3 years following DLI was significantly better for patients who achieved molecular remission than for those who did not achieve molecular remission (95% and 53%, respectively; \(P = .0001\)).\textsuperscript{326} However, DLI is associated with complications such as graft-vs-host disease (GVHD), susceptibility to infections, and immunosuppression.\textsuperscript{325} Improvements in the methods of detecting \(BCR-ABL\) transcripts to predict relapse, the development of reduced-intensity conditioning regimens, modified delivery of lymphocytes with the depletion of CD8+ cells, the use of escalating cell dosage regimens, and very-low-dose DLI in combination with alpha-IFN have reduced the incidence of GVHD associated with DLI.\textsuperscript{329-333}

Imatinib has also been very effective in inducing durable remissions in the majority of patients relapsing in all phases of CML following allogeneic HSCT.\textsuperscript{334-338} Complete hematologic and cytogenetic response rates with post-transplant imatinib are higher in patients with chronic phase relapse than advanced phase relapse. More recent studies have also reported durable molecular responses with imatinib in patients relapsing with chronic and advanced phase disease.\textsuperscript{339,340} Imatinib has also been shown to be effective in the prophylactic setting to prevent relapse following HSCT in high-risk patients. In a prospective evaluation of patients with Ph-positive ALL (\(n = 15\)) or CML beyond first chronic phase (\(n = 7\)) in remission following myeloablative allogeneic HSCT, Carpenter et al showed that imatinib can be safely administered during the first 90 days after myeloablative allogeneic HSCT at a dose intensity comparable to that used in primary therapy.\textsuperscript{341} Imatinib was administered for one year following HSCT. At a median follow-up of 1.4 years, the majority of patients (5 patients with CML and 12 patients with ALL) were in molecular remission. Olavarria et al also reported similar findings in patients undergoing reduced-intensity allogeneic HSCT in first chronic phase.\textsuperscript{342}

In a recent retrospective analysis, disease-free survival was significantly higher for patients receiving DLI than for those in the imatinib group.\textsuperscript{343} There was also a trend towards higher rates of complete molecular remissions in the DLI group. Some investigators have suggested that the combination of DLI and imatinib may be more effective at inducing rapid molecular remissions than either modality alone.\textsuperscript{344} These observations are yet to be confirmed in randomized trials.

**NCCN Recommendations**

Patients who are in CCyR (QPCR-negative) should undergo regular QPCR monitoring (every 3 months for 2 years, then 6 months for 3 years). 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 HSCT.\textsuperscript{341}

Imatinib, dasatinib, nilotinib, bosutinib, ponatinib or omacetaxine, DLI, or interferon or PEG-interferon can be considered as options for patients who are not in remission or in cytogenetic relapse or those with an increasing level of molecular relapse. Monitored withdrawal of immune suppression is recommended prior to initiation of therapy for post-transplant relapse.

In patients who have previously failed imatinib, there are no data to support the use of post-transplant imatinib. Very limited data in a small number of patients are available on the use of dasatinib and nilotinib in
patients with post-transplant relapse. Dasatinib may also be an effective treatment for extramedullary relapse following allogeneic HSCT. There are no data for the use of bosutinib, ponatinib or omacetaxine for patients post-transplant.

Dasatinib, nilotinib, bosutinib, ponatinib or omacetaxine may be more appropriate for patients who have previously failed imatinib. Discussion of treatment options with a transplant team is recommended. Participation in a clinical trial should be considered.

Summary

CML is a hematopoietic stem cell disease characterized by the presence of Ph chromosome resulting from the translocation between chromosomes 9 and 22 \([t(9;22)]\). The development of small molecule BCR-ABL TKIs has significantly improved the outcomes of patients with newly diagnosed CML.

The results of the IRIS trial established the safety, efficacy, and excellent survival benefit for imatinib in patients with newly diagnosed CML. Imatinib 400 mg daily is still considered a reasonable first-line treatment for newly diagnosed patients with CP-CML. Dasatinib and nilotinib are also associated with superior cytogenetic and molecular response rates and lower rates of progression to accelerated or blast phase in newly diagnosed patients with CML. The guidelines include dasatinib and nilotinib as first-line treatment options for patients with newly diagnosed CP-CML.

Monitoring treatment response to TKI therapy to identify the subgroup of patients who would benefit from early intervention with alternate treatment options is crucial in the management of patients with CML. The NCCN guidelines recommend monitoring response with QPCR using IS at 3 months from initiation of therapy and every 3 months thereafter in patients responding to TKI therapy. Patients with suboptimal response represent a subgroup that requires careful monitoring and may benefit from alternate treatment options. Continuation of TKI therapy with dasatinib or nilotinib at the same dose, imatinib dose escalation to 800 mg as tolerated, or change of therapy to alternate second-generation TKI are included as options for this group of patients.

Primary hematologic resistance to TKI therapy is very rare in patients with newly diagnosed CP-CML. Some patients will develop secondary resistance to TKI therapy related to the presence of BCR-ABL mutations resulting in disease progression. Dose escalation of imatinib has been shown to overcome resistance in some patients with cytogenetic failure on standard dose imatinib, particularly those with prior cytogenetic response. Dasatinib and nilotinib are effective in patients resistant or intolerant to imatinib. More recently, bosutinib and ponatinib have shown significant activity in patients with all three phases of CML, resistant or intolerant to prior TKI therapy. Bosutinib and ponatinib are effective treatment options for patients with BCR-ABL mutations resistant to dasatinib or nilotinib. In addition, ponatinib is also active against T315I mutation, which is resistant all the other approved TKIs.

Mutational analysis at the time of failure or loss of response to TKI therapy would be helpful in the selection of subsequent TKI therapy. The NCCN guidelines recommend mutational analysis if there is inadequate initial response, any sign of loss of response, or disease progression.

Dasatinib or nilotinib or bosutinib or ponatinib are recommended for patients with disease progression to AP-CML. Allogeneic HSCT should be considered based on response to therapy. TKI therapy
either alone or in combination with chemotherapy followed by allogeneic HSCT is recommended for patients with disease progression to BP-CML.

Omacetaxine is an option for patients in CP-CML and AP-CML with resistance and/or intolerance to two or more TKIs and for those with T315I mutation.

Allogeneic HSCT remains a potentially curative treatment for patients with CML and is recommended for patients with T315I mutation as well as for the rare patients who present with BP-CML at diagnosis. Evaluation for allogeneic HSCT based on response to second-line TKI therapy is recommended for all patients with failure to first-line TKI therapy. For most patients, a trial of alternate TKI (not received before) is reasonable before proceeding to allogeneic HSCT. Post-transplant TKI therapy should be considered for at least one year for patients with prior accelerated or blast phase who are in remission following allogeneic HSCT. Imatinib, dasatinib, nilotinib, bosutinib or ponatinib, omacetaxine, DLI, interferon or PEG-interferon can be considered as options for patients with post-transplant relapse.

Availability of more potent TKIs has widened the treatment options and the outlook for patients with CML continues to look promising. Selection of appropriate TKI therapy will depend on the stage of the disease, the agent's side effect profile, and its relative effectiveness against 

BCR-ABL mutations. Ongoing clinical trials are evaluating alternate treatment options for patients with BCR-ABL mutations resistant to currently approved TKIs including T315I. Consistent with NCCN philosophy, participation in clinical trials is always encouraged.
**Table 1. Calculation of Risk Score**^{1,2}

<table>
<thead>
<tr>
<th>Study</th>
<th>Calculation</th>
<th>Risk Definition by Calculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sokal et al, 1984(^3)</td>
<td>(\text{Exp} 0.0116 \times (\text{age in years} - 43.4) + 0.0345 \times (\text{spleen} - 7.51) + 0.188 \times \left[\frac{(\text{platelet count} \div 700)^2 - 0.563}{\text{platelet count} \div 700} + 0.0887 \times (\text{blast cells} - 2.10)\right])</td>
<td>Low &lt; 0.8 (\text{Intermediate} \ 0.8 - 1.2) (\text{High} &gt; 1.2)</td>
</tr>
<tr>
<td>Hasford et al, 1998(^4)</td>
<td>(0.666 \text{when age} \geq 50 \text{years} + (0.042 \times \text{spleen}) + 1.0956 \text{when platelet count} &gt; 1,500 \times 10^9 L + (0.0584 \times \text{blast cells}) + 0.20399 \text{when basophils} &gt; 3% + (0.0413 \times \text{eosinophils}) \times 100)</td>
<td>Low (\leq 780) (\text{Intermediate} \ 781-1,480) (\text{High} &gt; 1,480)</td>
</tr>
</tbody>
</table>

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1. 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.


### Table 2. Treatment Options Based on BCR-ABL Kinase Domain Mutation Status

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>T315I</td>
<td>Ponatinib (preferred) or omacetaxine, HSCT or clinical trial</td>
</tr>
<tr>
<td>V299L</td>
<td>Consider ponatinib, nilotinib or omacetaxine&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>T315A</td>
<td>Consider ponatinib, nilotinib, imatinib&lt;sup&gt;5&lt;/sup&gt;, bosutinib, or omacetaxine&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>F317L/V/I/C</td>
<td>Consider ponatinib, nilotinib, bosutinib or omacetaxine&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Y253H, E255K/V, F359V/C/I</td>
<td>Consider ponatinib, dasatinib, bosutinib or omacetaxine&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Any other mutation</td>
<td>Consider ponatinib, high-dose imatinib&lt;sup&gt;6&lt;/sup&gt;, dasatinib, nilotinib, bosutinib or omacetaxine&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

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4. Omacetaxine is a treatment option for patients with resistance and/or intolerance to two or more TKIs.

5. If mutation is detected following treatment with dasatinib.

6. There are no sufficient data on dose escalation available to indicate if mutations with lower IC50 values are sensitive to high-dose imatinib.
### Table 3. Recommendations for Monitoring Response to TKI Therapy and Mutational Analysis

<table>
<thead>
<tr>
<th>Test</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow cytogenetics²</td>
<td>At diagnosis to establish the disease phase. If collection of bone marrow is not feasible, FISH on a peripheral blood specimen using dual probes for the BCR and ABL genes is an acceptable method of confirming the diagnosis of CML. At 3 months from initiation of therapy, if QPCR using International Scale (IS) is not available. At 12 months from initiation of therapy, if there is no CCyR or MMR. At 18 months from initiation of therapy, if not in MMR and lack of CCyR at 12 months. Rising levels of BCR-ABL transcript (1-log increase) without a MMR.</td>
</tr>
<tr>
<td>Quantitative RT-PCR (QPCR)</td>
<td>At diagnosis. Every 3 months when a patient is responding to treatment. After CCyR has been achieved, every 3 months for 3 years and every 3-6 months thereafter. If there is a rising level of BCR-ABL transcript (1-log increase) with a MMR, QPCR analysis should be repeated in 1-3 months.</td>
</tr>
</tbody>
</table>
| BCR-ABL kinase domain mutation analysis | • Chronic phase  
  ➢ For patients with inadequate initial response (failure to achieve PCyR or BCR-ABL/ABL ≤ 10% (IS) at 3 months or CCyR at 12 and 18 months).  
  ➢ Any sign of loss of response (defined as hematologic or cytogenetic relapse or 1-log increase in BCR-ABL transcript levels and loss of MMR).  
  • Disease progression to accelerated or blast phase. |

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2. FISH has been inadequately studied for monitoring response to treatment.
## Table 4. Recommendations for Follow-up Therapy

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Response</th>
<th>Treatment Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>BCR-ABL/ABL ≤10% (IS) or PCyR</td>
<td>Continue the same dose of TKI</td>
</tr>
<tr>
<td>3 months</td>
<td>BCR-ABL/ABL &gt;10% (IS) or less than PCyR</td>
<td>Switch to alternate TKI&lt;sup&gt;3&lt;/sup&gt; Evaluate for allogeneic HSCT depending on response to TKI therapy</td>
</tr>
<tr>
<td>12 months</td>
<td>CChyR</td>
<td>Continue the same dose of TKI</td>
</tr>
<tr>
<td>12 months</td>
<td>PCyR&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Switch to alternate TKI (preferred)&lt;sup&gt;3&lt;/sup&gt; Continue same dose of TKI Dose escalation of imatinib to a maximum of 800 mg, as tolerated (if not a candidate for dasatinib, nilotinib, bosutinib, ponatinib or omacetaxine)</td>
</tr>
<tr>
<td>12 months</td>
<td>Minor or no cytogenetic response&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>Switch to alternate TKI (preferred)&lt;sup&gt;3&lt;/sup&gt; Evaluate for allogeneic HSCT depending on response to TKI therapy</td>
</tr>
<tr>
<td>12 months</td>
<td>Cytogenetic relapse&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>Switch to alternate TKI (preferred)&lt;sup&gt;3&lt;/sup&gt; Dose escalation of imatinib to a maximum of 800 mg, as tolerated (if not a candidate for dasatinib, nilotinib, bosutinib, ponatinib or omacetaxine) Evaluate for allogeneic HSCT depending on response to TKI therapy</td>
</tr>
<tr>
<td>18 months</td>
<td>CChyR</td>
<td>Continue the same dose of TKI</td>
</tr>
<tr>
<td>18 months</td>
<td>PCyR or cytogenetic relapse&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>Switch to alternate TKI&lt;sup&gt;3&lt;/sup&gt; Evaluate for allogeneic HSCT depending on response to TKI therapy</td>
</tr>
</tbody>
</table>

1. Evaluation of patient compliance and drug interactions are recommended prior to changing therapy for patients with inadequate initial response.
2. Enrollment in clinical trial is an option for this group of patients.
3. Omacetaxine is a treatment option for patients with resistance and/or intolerance to two or more TKIs.
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