Overview

Chronic myeloid leukemia (CML) accounts for 15% of adult leukemias. The median age of disease onset is 67 years; however, CML occurs in all age groups (SEER statistics). In 2018, an estimated 8,430 people will be diagnosed with CML in the United States, and 1,090 people will die of the disease.¹

CML is defined by the presence of Philadelphia chromosome (Ph) in a patient with myeloproliferative neoplasm (MPN). Ph results from a reciprocal translocation between chromosomes 9 and 22 \([t(9;22)]\) that gives rise to a BCR-ABL1 fusion gene. CML occurs in 3 different phases (chronic, accelerated, and blast phase) and is usually diagnosed in the chronic phase. Tyrosine kinase inhibitor (TKI) therapy is a highly effective first-line treatment option for all patients with newly diagnosed chronic phase CML (CP-CML). The selection of TKI therapy should be based on the risk score, toxicity profile of TKI, patient’s age, ability to tolerate therapy, and the presence of comorbid conditions. This manuscript discusses the recommendations outlined in the NCCN Guidelines for the diagnosis and management of patients with CP-CML.

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient’s care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way. The full NCCN Guidelines for Chronic Myeloid Leukemia are not printed in this issue of JNCCN but can be accessed online at NCCN.org.

© National Comprehensive Cancer Network, Inc. 2018. All rights reserved. The NCCN Guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN.

Disclosures for the NCCN Chronic Myeloid Leukemia Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Chronic Myeloid Leukemia Panel members can be found on page 1135. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit NCCN.org.
[t(9;22] that gives rise to a BCR-ABL1 fusion gene; the product of this fusion gene is a protein with deregulated tyrosine kinase activity (p210) that plays a central role in the pathogenesis of CML. Another fusion protein, p190, is also produced, usually in the setting of Ph-positive acute lymphoblastic leukemia. p190 is detected only in 1% of patients with CML.

CML occurs in 3 different phases (chronic, accelerated, and blast phases) and is usually diagnosed in the chronic phase. Untreated chronic phase CML (CP-CML) will eventually progress to advanced phase in 3 to 5 years. Gene expression profiling has shown a close correlation of gene expression between 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.

The NCCN Guidelines for CML discuss the clinical management of CML in all 3 phases (chronic, accelerated, and blast). Evaluation for diseases other than CML, as outlined in the NCCN Guidelines for MPN, is recommended for all patients with BCR-ABL1–negative MPN (to view the most recent version of these guidelines, visit NCCN.org).

### Diagnosis and Workup

Initial evaluation should consist of a history and physical exam, including palpation of spleen,
Chronic Myeloid Leukemia, Version 1.2019

WORKUP

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

CLINICAL PRESENTATION

- Ph positive or BCR-ABL1 positive
- Ph negative and BCR-ABL1 negative
- Chronic phase CML
- Advanced phase CML
- Determined risk score (See Risk Calculation Table CML-A*)

ADDITIONAL EVALUATION

- Accelerated phase
- Blast phase
- Additional testing
  - Flow cytometry to determine cell lineage
  - Mutational analysis
  - HLA testing, if considering allogeneic HCT (See CML-6)
- See Primary Treatment (CML-2)
- See Primary Treatment (CML-4*)

*Available online, in these guidelines, at NCCN.org

---

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

See Definitions of Accelerated Phase and Blast Phase (CML-B, available online, in these guidelines, at NCCN.org).
*Available online, in these guidelines, at NCCN.org

See Monitoring Response to TKI Therapy and Mutational Analysis (CML-C).

Based on long-term follow-up data from the DASISION and ENESTnd trials and preliminary data from the BFORE trial, second-generation TKIs (dasatinib, nilotinib, or bosutinib) are preferred for patients with an intermediate- or high-risk Sokal or Hasford score, especially for young women whose goal is to achieve a deep and rapid molecular response and eventual drug discontinuation of TKI therapy for fertility purposes.

Imatinib may be preferred for older patients with comorbidities such as cardiovascular disease.
Chronic Myeloid Leukemia, Version 1.2019

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

© JNCCN—Journal of the National Comprehensive Cancer Network | Volume 16 | Number 9 | September 2018
### TREATMENT OPTIONS BASED ON BCR-ABL1 MUTATION PROFILE

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

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

Ponatinib is a treatment option for patients with a T315I mutation or for patients for whom no other TKI is indicated.

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

*Available online, in these guidelines, at NCCN.org

---

*© JNCCN—Journal of the National Comprehensive Cancer Network | Volume 16 Number 9 | September 2018*
### MONITORING RESPONSE TO TKI THERAPY AND MUTATIONAL ANALYSIS

<table>
<thead>
<tr>
<th>Test</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| Bone marrow cytogenetics¹        | • At diagnosis  
|                                  | • Failure to reach response milestones  
|                                  | • Any sign of loss of response (defined as hematologic or cytogenetic relapse)                                                                |
| qPCR using IS                    | • At diagnosis  
|                                  | • Every 3 months after initiating treatment. After BCR-ABL1 (IS) ≤1% (>0.1%–1%) has been achieved, every 3 months for 2 years and every 3–6 months thereafter  
|                                  | • If there is 1-log increase in BCR-ABL1 transcript levels with MMR, qPCR should be repeated in 1–3 months                                      |
| BCR-ABL kinase domain mutation analysis | • Chronic phase  
|                                  | ▶ Failure to reach response milestones  
|                                  | ▶ Any sign of loss of response (defined as hematologic or cytogenetic relapse)                                                                 
|                                  | ▶ 1-log increase in BCR-ABL1 transcript levels and loss of MMR                                                                                  
|                                  | ▶ Disease progression to accelerated or blast phase                                                                                           |

¹FISH has been inadequately studied for monitoring response to treatment.
CRITERIA FOR HEMATOLOGIC, CYTOGENETIC, AND MOLECULAR RESPONSE AND RELAPSE

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

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

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

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

---

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

CML-D
DISCONTINUATION OF TKI THERAPY

• Discontinuation of TKI therapy appears to be safe in select CML patients.
• Clinical studies that have evaluated the safety and efficacy of TKI discontinuation have employed strict eligibility criteria and have mandated more frequent molecular monitoring than typically recommended for patients on TKI therapy.
• Some patients have experienced significant adverse events that are believed to be due to TKI discontinuation.
• Discontinuation of TKI therapy should only be performed in consenting patients after a thorough discussion of the potential risks and benefits.

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

1 The feasibility of treatment-free remission (TFR) following discontinuation of bosutinib or ponatinib has not yet been evaluated in clinical studies. It is reasonable to assume that the likelihood of TFR following discontinuation would be similar irrespective of TKI in patients who have achieved and maintained deep molecular response (MR4.0; ≤0.01% BCR-ABL1 IS) for ≥2 years, as documented in at least 4 tests, performed at least 3 months apart.2

2 Data from the EURO-SKI study suggest that MR4.0 (BCR-ABL1 ≤0.01% IS) for 3 years or more was the most significant predictor for successful discontinuation of imatinib. Total duration of imatinib therapy for at least 6 years was also predictive of successful discontinuation (Saussele S, Richter J, Guilhot J, et al. Lancet Oncol 2018;19:747-757).
CBC with differential, chemistry profile, and hepatitis panel. Bone marrow aspirate and biopsy for morphologic and cytogenetic evaluation and quantitative reverse transcriptase polymerase chain reaction (RT-PCR) to establish the presence of quantifiable BCR-ABL1 mRNA transcripts at baseline are recommended to confirm the diagnosis of CML (see CML-1; page 1110).

Bone marrow cytogenetics should be done at initial workup to detect additional chromosomal abnormalities in Ph-positive cells (ACA/Ph+), also known as clonal cytogenetic evolution.7 The prognostic significance of ACA/Ph+ is related to the specific chromosomal abnormality and often other features of accelerated phase.8–12 The presence of “major route” ACA/Ph+ (trisomy 8, isochromosome 17q, second Ph, and trisomy 19) at diagnosis may have a negative prognostic impact on survival and disease progression to accelerated or blast phase.13–15 However, in a more recent analysis that evaluated the outcomes of patients with CP-CML (with or without ACA) treated with tyrosine kinase inhibitors (TKIs) in prospective studies, the presence of ACA/Ph+ at the time of diagnosis was not associated with worse prognosis.16 Patients with ACA/Ph+ at diagnosis should be watched carefully for evidence of therapy failure. Clonal cytogenetic evolution in Ph-negative cells has also been reported in a small subset of patients during the course of imatinib therapy.17–22 The most common abnormalities include trisomy 8 and loss of Y chromosome. Previous work suggested that the overall prognosis of Ph-negative CML with clonal evolution is good and is dependent on response to imatinib therapy.21 Recently, however, the presence of chromosome abnormalities other than loss of Y chromosome has been associated with decreased survival in patients with CP-CML treated with various TKIs, suggesting that closer follow-up is indicated until definitive data are available.23 Progression to myelodysplastic syndromes (MDS) and acute myeloid leukemia have been reported in patients with monosomy 7.24,25

If bone marrow evaluation is not feasible, fluorescence in situ hybridization (FISH) on a peripheral blood specimen with dual probes for BCR and ABL1 genes is an acceptable method to confirm the diagnosis of CML. Interphase FISH is performed on peripheral blood but is associated with a background level of 1%–5% depending on the specific probe used in the assay.26 Hypermetaphase FISH is more sensitive and can analyze up to 500 metaphases at a time, but it is applicable only to dividing cells in the bone marrow.27 Double-fusion FISH is also associated with low false-positive rates and can detect all variant translocations of the Ph-chromosome.28

Quantitative RT-PCR (qPCR) should be performed at initial workup to establish the presence of quantifiable BCR-ABL1 mRNA transcripts at baseline. qPCR, usually performed on peripheral blood, is the most sensitive assay available for the measurement of BCR-ABL1 mRNA and it can detect 1 CML cell in a background of ≥100,000 normal cells. qPCR results can be expressed in various ways, for instance as the ratio of BCR-ABL1 transcript numbers to the number of control gene transcripts.29 An international scale (IS) has been proposed to standardize molecular monitoring with qPCR across different laboratories with the use of 1 of 3 control genes (BCR, ABL1, or GUSB) and a qPCR assay with a sensitivity of at least 4-log reduction from the standardized baseline.30 In recent years, IS has become the gold standard of expressing qPCR values. More details on qPCR monitoring using IS are provided on MS-10 (in these guidelines, at NCCN.org).

BCR-ABL1 transcripts in the peripheral blood at very low levels (1–10 of 106 peripheral blood leukocytes) can also be detected in approximately 30% of normal individuals, and the incidence of BCR-ABL1 transcripts increases with advancing age in healthy individuals.31,32 TKI therapy is not indicated, as the risk of developing CML for these individuals is extremely low.

**Management of Chronic Phase CML**

**Risk Stratification**

Sokal and Euro scoring systems have been used for the risk stratification of patients into 3 risk groups (low, intermediate, and high) in clinical trials evaluating TKIs (see CML-A; available online, in these guidelines, at NCCN.org).33,34 The Sokal score is based on the patient’s age, spleen size, platelet count, and percentage of blasts in the peripheral blood.33 The Euro score includes eosinophils and basophils in the peripheral blood in addition to the same clinical variables used in the Sokal score.34
Chronic Myeloid Leukemia, Version 1.2019

sophils in the blood and spleen size. The predictive value of EUTOS score was validated in a cohort of 2,060 patients enrolled in studies of first-line treatment with imatinib-based regimens.\textsuperscript{15} EUTOS score was better than Sokal and Euro score in predicting the probability of achieving a complete cytogenetic response (CCyR) at 18 months and 5-year progression-free survival (PFS). However, the predictive value of EUTOS score has not been confirmed in subsequent studies by other investigators, and additional studies are needed to validate the EUTOS score.\textsuperscript{36–38}

Determination of risk score using either the Sokal or Hasford (Euro) scoring systems before initiation of TKI therapy is recommended for patients diagnosed with CP-CML (see CML-1; page 1110).

### Primary Treatment

Long-term efficacy data from randomized phase III studies for first-line TKI therapy in patients with newly diagnosed CP-CML are summarized in Table 1.\textsuperscript{39–42} In summary, (1) all TKIs are highly effective in newly diagnosed CP-CML, with long-term overall survival (OS) approaching that of age-matched controls; (2) second-generation TKIs, compared with imatinib, generally result in faster cytogenetic and molecular responses, with less progression to advanced phase CML; and (3) yet, in randomized clinical trials, there are no differences in OS between imatinib and second-generation TKIs.

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

Imatinib, 800 mg, is not recommended as initial therapy, given the recent data showing superior efficacy of second-generation TKIs (dasatinib, nilotinib, and bosutinib) in newly diagnosed CP-CML. Data from randomized phase III studies that have evaluated high-dose imatinib as first-line therapy for CP-CML suggest that imatinib, 800 mg, was not associated with lower rates of disease progression than imatinib, 400 mg, in any of these studies, despite improved early responses (Table 2).\textsuperscript{43–45} Imatinib, 800 mg, was also associated with higher rates of dose interruption, reduction, or discontinuation.

### Table 1. First-Line TKI Therapy for CP-CML: Long-Term Follow-Up Data From Phase III Studies

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study Arms</th>
<th>N</th>
<th>Median Follow-Up</th>
<th>CCyR\textsuperscript{a}</th>
<th>MMR\textsuperscript{b}</th>
<th>Disease Progression, n (%)</th>
<th>PFS Rate\textsuperscript{c}</th>
<th>OS Rate\textsuperscript{d}</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRIS\textsuperscript{40}</td>
<td>Imatinib (400 mg qd)</td>
<td>553</td>
<td>11 y</td>
<td>83%</td>
<td>—</td>
<td>38 (7%)</td>
<td>92%</td>
<td>83%</td>
</tr>
<tr>
<td></td>
<td>Interferon-alpha plus low-dose cytarabine</td>
<td>553</td>
<td>—</td>
<td>—</td>
<td>71 (13%)</td>
<td>—</td>
<td>79%\textsuperscript{f}</td>
<td></td>
</tr>
<tr>
<td>DASISION\textsuperscript{42}</td>
<td>Dasatinib (100 mg qd)</td>
<td>259</td>
<td>5 y</td>
<td>—</td>
<td>76% (P=.002)</td>
<td>12 (5%)</td>
<td>85%</td>
<td>91%</td>
</tr>
<tr>
<td></td>
<td>Imatinib (400 mg qd)</td>
<td>260</td>
<td>—</td>
<td>64%</td>
<td>19 (7%)</td>
<td>86%</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>ENESTnd\textsuperscript{41}</td>
<td>Nilotinib (300 mg bid)</td>
<td>282</td>
<td>5 y</td>
<td>—</td>
<td>77% (P vs imatinib &lt;.0001)</td>
<td>10 (4%)</td>
<td>92%</td>
<td>94%</td>
</tr>
<tr>
<td></td>
<td>Nilotinib (400 mg bid)</td>
<td>281</td>
<td>—</td>
<td>77% (P vs imatinib &lt;.0001)</td>
<td>6 (2%)</td>
<td>96%</td>
<td>96%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Imatinib (400 mg qd)</td>
<td>283</td>
<td>—</td>
<td>60%</td>
<td>21 (7%)</td>
<td>91%</td>
<td>92%</td>
<td></td>
</tr>
<tr>
<td>BFORE\textsuperscript{42}</td>
<td>Bosutinib (400 mg qd)</td>
<td>268</td>
<td>12 mo</td>
<td>77% (P=.0075)</td>
<td>47% (P=.02)</td>
<td>4 (2%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Imatinib (400 mg qd)</td>
<td>268</td>
<td>—</td>
<td>66%</td>
<td>37%</td>
<td>6 (3%)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Abbreviations: CCyR, complete cytogenetic response; CP-CML, chronic phase chronic myeloid leukemia; IS, International Scale; MMR, major molecular response (BCR-ABL1 ≤0.1% IS); OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

\textsuperscript{a}Primary end point of DASISION study: confirmed CCyR rate at 12 mo.

\textsuperscript{b}Primary end point of ENESTnd and BFORE studies: MMR (BCR-ABL1 ≤0.1%) rate at 12 mo.

\textsuperscript{c}Long-term primary end point of IRIS trial in the imatinib group.

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

\textsuperscript{e}Data include survival among the 363 patients who crossed over to imatinib.

\textsuperscript{f}There were no differences in survival rates between the 2 treatment arms after a minimum follow of 12 months; long term follow up is ongoing.
Table 2. High-Dose Imatinib as First-Line Therapy for CP-CML: Long-Term Follow-Up Data From Phase III Studies

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study Arms</th>
<th>Median Follow-Up</th>
<th>MMR %</th>
<th>MR4.5</th>
<th>PFS Rate at 48 mo</th>
<th>OS Rate at 48 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOPS</td>
<td>Imatinib (800 mg qd)</td>
<td>42 mo</td>
<td>79</td>
<td>—</td>
<td>96%</td>
<td>93%</td>
</tr>
<tr>
<td></td>
<td>Imatinib (400 mg qd)</td>
<td></td>
<td>76</td>
<td>—</td>
<td>94%</td>
<td>94%</td>
</tr>
<tr>
<td></td>
<td>Imatinib (400 mg qd)</td>
<td></td>
<td>92</td>
<td>67%</td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td></td>
<td>Imatinib (400 mg qd)</td>
<td></td>
<td>36</td>
<td>9%</td>
<td>80%</td>
<td>90%</td>
</tr>
<tr>
<td>CML IV</td>
<td>Imatinib (800 mg qd)</td>
<td>10 y</td>
<td>89</td>
<td>71%</td>
<td>77%</td>
<td>79%</td>
</tr>
<tr>
<td></td>
<td>Imatinib (400 mg qd)</td>
<td></td>
<td>92</td>
<td>67%</td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td></td>
<td>Imatinib (400 mg qd)</td>
<td></td>
<td>53</td>
<td>19%</td>
<td>92%</td>
<td>95%</td>
</tr>
<tr>
<td></td>
<td>Imatinib (400 mg qd)</td>
<td></td>
<td>36</td>
<td>9%</td>
<td>80%</td>
<td>90%</td>
</tr>
<tr>
<td>SWOG</td>
<td>Imatinib (800 mg qd)</td>
<td>12 mo</td>
<td>53</td>
<td>19%</td>
<td>92%</td>
<td>95%</td>
</tr>
<tr>
<td></td>
<td>Imatinib (400 mg qd)</td>
<td></td>
<td>36</td>
<td>9%</td>
<td>80%</td>
<td>90%</td>
</tr>
</tbody>
</table>

Abbreviations: CP-CML, chronic phase chronic myeloid leukemia; IS, International Scale; MMR, major molecular response (BCR-ABL1 ≤0.1% IS); MR, molecular response; MR4.5: ≥4.5-log reduction in BCR-ABL1 transcripts from baseline; OS, overall survival; PFS, progression-free survival.

- Primary end point: MMR rate at 12 mo (≤0.1% BCR-ABL1), which corresponds to a 3-log reduction in BCR-ABL1 transcripts compared with the standardized baseline established in IRIS study.
- Primary end point: impact of MMR on survival at 12 mo. This study had 5 treatment arms (imatinib, 400 mg qd alone; imatinib, 800 mg bid; imatinib, 400 mg qd with interferon or cytarabine; imatinib after interferon failure). Only the data for imatinib at 400 mg qd alone vs imatinib at 800 mg bid are included in this table.
- Primary end point: MR4.0 (≥4-log reduction in BCR-ABL1 transcripts from baseline) at 12 mo. These are results from the first part of SWOG 50325 study; follow-up after 12 mo was not required for this study.

Due to grade 3 or 4 adverse events in all of the studies. However, patients who can actually tolerate the higher dose of imatinib experience better response rates than those receiving standard-dose imatinib.

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

Clinical Considerations for The Selection of First-Line Therapy

Risk Stratification: Imatinib (400 mg daily) and second-generation TKIs (dasatinib, 100 mg once daily; nilotinib, 300 mg twice daily; and bosutinib, 400 mg daily) are all appropriate options for first-line TKI therapy for patients with CP-CML across all risk scores (see CML-2; page 1112). Disease progression is more frequent in patients with intermediate- or high-risk score, and prevention of disease progression to AP-CML or BP-CML is the primary goal of TKI therapy in patients with CP-CML. Second-generation TKIs are associated with lower risk of disease progression than imatinib and are therefore preferred for patients with an intermediate- or high-risk Sokal or Euro score.

Second-generation TKIs also result in quicker molecular responses and higher rates of deep molecular responses (MMR [BCR-ABL1 ≤0.1% IS] and MR4.5 [≥4.5-log reduction in BCR-ABL1 transcripts from baseline]) in patients with CP-CML across all risk scores (Table 3), which may facilitate subsequent discontinuation of TKI therapy in selected patients. Therefore, second-generation TKIs may be preferred over imatinib for younger patients, particularly women, because the achievement of a deep and rapid molecular response may allow eventual discontinuation of TKI therapy for fertility purposes. Imatinib may be preferred for older patients with comorbidities, especially cardiovascular.

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

Adverse events of first-line TKI therapy in patients with CP-CML reported in phase III random-
ized studies are discussed subsequently and are also summarized in Table 4. See CML-F (available online, in these guidelines, at NCCN.org) for the management of toxicities associated with TKI therapy.

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

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

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

Reversible pulmonary arterial hypertension has been reported as a rare but serious side effect of dasatinib. In the DASISION study, pulmonary hypertension was reported in 5% of patients compared with 0.4% of patients treated with imatinib. Evaluation for signs and symptoms of underlying cardiopulmonary disease before starting and during treatment with dasatinib is recommended. If pulmonary arterial hypertension is confirmed, dasatinib must be permanently discontinued.

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

### Table 3. First-Line TKI Therapy for CP-CML: MR Rates According to Sokal or Euro Risk Score

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study Arms</th>
<th>Low-Risk&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>Intermediate-Risk&lt;sup&gt;a&lt;/sup&gt;</th>
<th>High-Risk&lt;sup&gt;a,b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MMR</td>
<td>MR4.5</td>
<td>MMR</td>
</tr>
<tr>
<td>DASISION&lt;sup&gt;41&lt;/sup&gt;</td>
<td>Dasatinib (100 mg qd)</td>
<td>90%</td>
<td>55%</td>
<td>71%</td>
</tr>
<tr>
<td></td>
<td>Imatinib (400 mg qd)</td>
<td>69%</td>
<td>44%</td>
<td>65%</td>
</tr>
<tr>
<td>ENEStnd&lt;sup&gt;41&lt;/sup&gt;</td>
<td>Nilotinib (300 mg bid)</td>
<td>—</td>
<td>53%</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Nilotinib (400 mg bid)</td>
<td>—</td>
<td>62%</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Imatinib (400 mg qd)</td>
<td>—</td>
<td>38%</td>
<td>—</td>
</tr>
<tr>
<td>BFORE&lt;sup&gt;42&lt;/sup&gt;</td>
<td>Bosutinib (400 mg qd)</td>
<td>58%</td>
<td>—</td>
<td>45%</td>
</tr>
<tr>
<td></td>
<td>Imatinib (400 mg qd)</td>
<td>46%</td>
<td>—</td>
<td>39%</td>
</tr>
</tbody>
</table>

Abbreviations: CP-CML, chronic phase chronic myeloid leukemia; IS, International Scale; MMR, major molecular response (≤0.1% BCR-ABL1 IS); MR, molecular response; MR4.5: 4.5-log reduction in BCR-ABL1 transcripts from baseline; TKI, tyrosine kinase inhibitor.

<sup>a</sup>DASISION study: Risk stratification by Hasford (Euro) risk score.

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

Nilotinib labeling contains a black box warning regarding the risk of QT interval prolongation, and sudden cardiac death has been reported in patients receiving nilotinib. QT interval prolongation could be managed with dose reduction. Electrolyte abnormalities should be corrected before start of treatment with nilotinib, and electrolytes should be monitored periodically. Drugs that prolong QT interval should be avoided. Electrocardiogram should be obtained to monitor the QT interval at baseline, 7 days after start of nilotinib, and periodically thereafter, and after any dose adjustments. Patients with cardiovascular risk factors should be referred to a cardiologist. Nilotinib is associated with an increased risk of peripheral arterial occlusive disease (PAOD). Patients should be evaluated for pre-existing PAOD and vascular risk factors before starting and during

| Table 4. Adverse Events of First-Line TKI Therapy in CP-CML |
|-----------------|-----------------|-----------------|-----------------|
|                  | **Dasatinib**, 100 mg qd | **Imatinib**, 400 mg qd | **Nilotinib**, 300 mg bid | **Imatinib**, 400 mg qd | **Bosutinib**, 400 mg qd | **Imatinib**, 400 mg qd |
| **Toxicity**     |                  |                  |                  |                  |                  |                  |
| Hematologic toxicities (grade 3/4) |                  |                  |                  |                  |                  |                  |
| Anemia           | 13%              | 9%               | 4%               | 6%               | 3%               | 5%               |
| Neutropenia      | 29%              | 24%              | 12%              | 22%              | 7%               | 12%              |
| Thrombocytopenia | 22%              | 14%              | 10%              | 9%               | 14%              | 6%               |
| Biochemical abnormalities (grade 3/4) |                  |                  |                  |                  |                  |                  |
| Increased lipase | NR               | NR               | 9%               | 4%               | 13%              | 6%               |
| Increased glucose| NR               | NR               | 7%               | <1%              | 2%               | 2%               |
| Decreased phosphate | 7%            | 28%              | 8%               | 10%              | 5%               | 17%              |
| Increased ALT    | NR               | NR               | 4%               | 2%               | 23%              | 3%               |
| Increased AST    | NR               | NR               | NR               | NR               | 12%              | 3%               |
| Nonhematologic toxicities (any grade)* |                  |                  |                  |                  |                  |                  |
| Rash             | 13%              | 18%              | 38%              | 19%              | 20%              | 13%              |
| Headache         | 13%              | 11%              | 32%              | 23%              | 19%              | 13%              |
| Fatigue          | 9%               | 11%              | 23%              | 20%              | 19%              | 18%              |
| Muscle spasms    | 23%              | 41%              | 12%              | 34%              | 2%               | 26%              |
| Peripheral edema | 13%              | 37%              | 9%               | 20%              | 4%               | 14%              |
| Pleural effusion | 28%              | <1%              | 2%               | 1%               | NR               | NR               |
| Hypertension     | NR               | NR               | 10%              | 4%               | NR               | NR               |
| Pulmonary hypertension | 5%       | <1%              | 0%               | 0%               | NR               | NR               |
| Diarrhea         | 21%              | 22%              | 19%              | 46%              | 70%              | 34%              |
| Constipation     | NR               | NR               | 20%              | 8%               | NR               | NR               |
| Nausea           | 10%              | 24%              | 22%              | 41%              | 35%              | 39%              |
| Vomiting         | 5%               | 11%              | 15%              | 27%              | 18%              | 16%              |

Abbreviations: ALT, alanine amino transferase; AST, aspartate amino transferase; CP-CML, chronic phase chronic myeloid leukemia; NR, not reported; TKI, tyrosine kinase inhibitor.

*Nonhematologic toxicities reported for the DASISION study (except pleural effusion) are from the 3-y follow-up. No new adverse events were observed with 5-y follow-up.
treatment with nilotinib. If PAOD is confirmed, nilotinib should be permanently discontinued.

Bosutinib: In the BFORE study, diarrhea, increased alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were more common with bosutinib, whereas muscle spasms and peripheral edema were more common with imatinib. Grade 3/4 thrombocytopenia was higher with bosutinib and grade 3/4 neutropenia was higher with imatinib. Grade 3/4 anemia was similar in both groups. Discontinuation of therapy because of drug-related adverse events occurred in 14% of patients in the bosutinib group compared with 11% in the imatinib group. Increased ALT (5%) and increased AST increase (2%) were the most common adverse events leading to discontinuation of bosutinib. However, no hepatotoxicity-related fatalities occurred during the study.42

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

Assessment of reticulocyte count, ferritin, iron saturation, vitamin B12, and folate and correction of nutritional deficiencies if present is recommended for patients with grade 3/4 anemia. Red blood cell transfusions are indicated in symptomatic patients. Myeloid growth factor support can be used in combination with TKI therapy for the management of neutropenia.62,63 The use of erythropoiesis-stimulating agents (ESAs) did not impact survival or cytogenetic response rate, but was associated with a higher thrombosis rate in patients with CP-CML.64 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.

Monitoring Response to TKI Therapy
Response to TKI therapy is determined by the measurement of hematologic (normalization of peripheral blood counts), cytogenetic (decrease in the number of Ph-positive metaphases using bone marrow cytogenetics), and molecular responses (decrease in the amount of BCR-ABL1 chimeric mRNA using qPCR). The criteria for hematologic, cytogenetic, and molecular response are summarized in CML-D (page 1115).

Conventional bone marrow cytogenetics is the standard method for monitoring cytogenetic responses, and clinical trial response analyses are most often based on conventional bone marrow cytogenetics. If conventional bone marrow cytogenetics showed no analyzable metaphases, cytogenetic response can be evaluated by FISH; however, it has a false-positive rate of 1% to 10%.65,66 Although some investigators have reported that interphase FISH can be used to monitor CCyR, end points for TKI failure have not been defined on the basis of FISH analysis.67,68 The panel feels that FISH has been inadequately studied for monitoring response to TKI therapy. Therefore, FISH is not generally recommended for monitoring response if conventional cytogenetics or qPCR are available.

qPCR is the only tool capable of monitoring responses after the patient has experienced CCyR, because BCR-ABL1 transcripts typically remain detectable after CCyR is achieved. A major advantage of qPCR is the strong correlation between the results obtained from the peripheral blood and the bone marrow, allowing molecular monitoring without bone marrow aspirations.69,70

Standardization of Molecular Monitoring Using the IS: In the IS, the standardized baseline (defined as the average expression of BCR-ABL1 transcripts in 30 patients treated on the IRIS trial) is set to 100%. Molecular response is expressed as log-reduction from 100%. For example, ≥3-log reduction (≤0.1% BCR-ABL1 IS) is referred to as MMR or MR3.0.30,71,72 A 2-log reduction generally correlates with CCyR (≤1% BCR-ABL1 IS).

The sensitivity of a qPCR assay depends not only on the performance of the assay, but also on the quality of a given sample. As such the term “complete molecular response” to denote undetectable BCR-ABL1 transcripts (a negative qPCR test) should be abandoned, because it may refer to very different levels of response, dependent on the quality of the sample. Laboratories can use their individual assays, but the BCR-ABL1 transcripts obtained in a given laboratory should be converted to the IS by applying a laboratory-specific conversion factor.30,73

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

Monitoring with qPCR (IS) every 3 months is recommended for all patients after initiating TKI therapy, including those who meet response milestones at 3, 6, and 12 months (≤10% BCR-ABL1 IS at 3 and 6 months, ≤1% BCR-ABL1 IS at 12 months, and ≤0.1% BCR-ABL1 IS at >12 months). After CCyR (≤1% BCR-ABL1 IS) has been achieved, molecular monitoring is recommended every 3 months for 2 years and every 3 to 6 months thereafter (see CML-C, page 1114).

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

Prognostic Significance of Cytogenetic and Molecular Response

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

Recently, studies have suggested that the rate of decline in BCR-ABL1 transcripts correlates with longer-term response. Among patients with >10% BCR-ABL1 IS after 3 months of treatment with imatinib, those with a faster decline in BCR-ABL1 (BCR-ABL1 halving time <76 days) had a superior outcome compared with those with a slower decline (4-year PFS rate was 92% vs 63%, respectively). A rapid initial BCR-ABL1 decline also identifies a subgroup of Sokal high-risk patients with outcomes similar to those of Sokal low-risk patients. Among Sokal high-risk patients, a BCR-ABL1 halving time of ≤11 days was associated with significantly improved FFS (4-year FFS rate was 79% for patients with halving time of ≤11 days vs 53% for those with halving time of >11 days; P=0.03). In the German CML IV study, lack of a half-log reduction of BCR-ABL1 transcripts at 3 months was associated with a higher risk of disease progression on imatinib therapy. The results of the D-First study also showed that in patients treated with dasatinib, BCR-ABL1 halving time of ≤14 days was a significant predictor of MMR by 12 months and deep molecular response (BCR-ABL1 IS at 0.1% IS) by 18 months. Achievement of CCyR (≤1% BCR-ABL1 IS) within 12 months after first-line TKI therapy is an established prognostic indicator of long-term survival. In the IRIS study, the estimated 6-year PFS rate was 97% for patients achieving a CCyR at 6 months compared with 80% for patients with no cytogenetic response at 6 months. In an analysis of patients with newly diagnosed CP-CML treated with imatinib or second-generation TKIs, the 3-year event-free survival and OS rates were 98% and 99% for patients who experienced CCyR at 12 months compared with 67% and 94% in patients who did not experience a CCyR. The prognostic significance of MMR (0.1% BCR-ABL1 IS) after first-line imatinib has also been evaluated in several studies. In all of these studies, the analyses were done for different outcomes measures at multiple time points, but failed to adjust for multiple comparisons, thereby reducing the validity of the conclusions. The synoptic conclusion from these studies is that MMR is moderately superior to CCyR in predicting long-term PFS and OS. However, with longer
follow-up, CCyR becomes an ever stronger indicator of MMR. The achievement of MMR is also not a significant prognosticator of long-term outcome in patients who are in stable CCyR after first-line treatment with dasatinib or nilotinib.90,91 These findings suggest that MMR may not be of prognostic significance in patients who have achieved CCyR and absence of MMR in the presence of a CCyR is not considered a treatment failure. Achievement of MMR (0.1% BCR-ABL1 IS) at 12 months, however, is associated with a very low probability of subsequent disease progression and a high likelihood of achieving a subsequent deep molecular response (MR4.0; ≤0.01% BCR-ABL1 IS) which may facilitate discontinuation of TKI therapy. TKI de-escalation has also been shown to be feasible in patients who had received TKI therapy for ≥3 years with either a stable MMR or MR4.0 for ≥12 months.92

Response Milestones after First-Line TKI Therapy

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

The panel has included ≤10% BCR-ABL1 IS at 3 and 6 months and ≤1% BCR-ABL1 IS at 12 and 15 months as response milestones after first-line TKI therapy (see CML-3; page 1112). Patients who experience these response milestones are considered to have TKI-sensitive disease, and continuation of the same dose of TKI and assessment of BCR-ABL1 transcripts with qPCR (IS) every 3 months is recommended for this group of patients.

In patients with a >10% BCR-ABL1 IS at 3 months and >1% BCR-ABL1 IS at 12 months, clinical judgement should be used, considering problems with adherence (which can be common given drug toxicity at start of therapy), rate of decline in BCR-ABL1 (the faster, the better), and how far from the 10% cutoff the BCR-ABL1 value falls. That being said, failure to experience ≤10% BCR-ABL1 IS at 3 months or ≤1% BCR-ABL1 IS at 12 months is associated with a higher risk for disease progression.

Patients with >10% BCR-ABL1 IS at 3 months or >1% BCR-ABL1 IS at 12 months can continue the same dose of dasatinib or nilotinib or bosutinib for another 3 months. Mutational analysis and evaluation for allogeneic HCT should be considered. Bone marrow cytogenetics should be considered to assess for MCyR at 3 months or CCyR at 12 months.

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

Second-Line Therapy

Long-term efficacy data from phase II/III studies on second-line TKI therapy for CP-CML are summarized in Table 6.91–96

Early molecular response (≤10% BCR-ABL1 IS at 3 and 6 months) after second-line TKI therapy with dasatinib or nilotinib has also been reported to be a prognosticator of OS and PFS (Table 7). Patients who do not experience cytogenetic or molecular responses at 3, 6, or 12 months after second-line and subsequent TKI therapy should be considered for alternative therapies or allogeneic HCT if deemed eligible.
Management of Patients With Inadequate Response to Imatinib: Switching to an alternate TKI is recommended for patients with disease that is resistant to imatinib 400 mg daily. Dasatinib, nilotinib, and bosutinib are active against many of the imatinib-resistant BCR-ABL1 kinase domain mutants, except T315I, and are effective treatment options for patients with CP-CML intolerant to imatinib or those with CP-CML resistant to imatinib.93-95

Dose escalation of imatinib up to 800 mg daily has been shown to overcome some of the primary resistance and is particularly effective in patients with cytogenetic relapse who had achieved cytogenetic response with imatinib, 400 mg daily, although the duration of responses has typically been short.97-100 However, it is unlikely to benefit patients with hematologic failure or those who never had a cytogenetic response with imatinib 400 mg daily. Switching to nilotinib has been shown to result in higher rates of cytogenetic and molecular response than dose escalation of imatinib in patients with inadequate response to imatinib, 400 mg.101,102 In the TIDEL-II study, the cohort of patients with >10% BCR-ABL1 IS at 3 months after imatinib, 400 mg, who were switched directly to nilotinib had higher rates of MMR and CMR at 12 months (but not at 24 months) than the cohort of patients who received dose escalation of imatinib before switching to nilotinib.101 Although dose escalation of imatinib has been shown to be beneficial for patients in CCyR with no MMR, no randomized studies have shown that a change of therapy would improve PFS or event-free survival in this group of patients.103,104

Management of Patients with Inadequate Response to Dasatinib, Nilotinib or Bosutinib: Switching to an alternate TKI (other than imatinib) in the second-line setting could be considered for patients with disease that is resistant to dasatinib, nilotinib, or bosutinib. However, no clear evidence supports that switching to alternate TKI therapy would improve long-term clinical outcome for this group of patients. Ponatinib is an option for patients with T315I mutation and for those with disease that has not responded to several TKIs.96 Long-term efficacy data from phase II/III studies evaluating bosutinib or ponatinib in patients with pretreated CP-CML are summarized in Table 6.

In the PACE trial, serious arterial occlusive events (cardiovascular, cerebrovascular, and peripheral vascular) and venous thromboembolic events occurred in 31% and 6% of patients, respectively.96 Cardiovascular occlusion, cerebrovascular occlusion, and peripheral arterial occlusive events were reported in 16%, 13%, and 14% of patients, respectively. Ponatinib labeling contains a black box warning regarding vascular occlusion, heart failure, and hepatotoxicity. Cardiovascular risk factors (eg, diabetes mellitus, hypertension, hyperlipidemia, smoking, estrogen use) should be identified and controlled before starting ponatinib. Patients should be monitored

<p>| Table 6. Second-line and Subsequent TKI Therapy for CP-CML: Long-Term Follow-Up Data From Phase II/III Studies |</p>
<table>
<thead>
<tr>
<th>TKI</th>
<th>N</th>
<th>Median Follow-Up</th>
<th>MCyR</th>
<th>CCyR</th>
<th>MMR</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dasatinib (100 mg qd) Imatinib-R (n=124)</td>
<td>7 y</td>
<td>—</td>
<td>—</td>
<td>43%</td>
<td>39%</td>
<td>63%</td>
<td></td>
</tr>
<tr>
<td>Imatinib-I (n=43)</td>
<td>4 y</td>
<td>59%</td>
<td>45%</td>
<td>—</td>
<td>57%</td>
<td>78%</td>
<td></td>
</tr>
<tr>
<td>Nilotinib (400 mg bid) (Imatinib-R, n=226; Imatinib-I, n=95)</td>
<td>4 y</td>
<td>39%</td>
<td>22%</td>
<td>—</td>
<td>—</td>
<td>67%</td>
<td></td>
</tr>
<tr>
<td>Bosutinib (400 mg qd) Imatinib and dasatinib-R (n=38)</td>
<td>4 y</td>
<td>42%</td>
<td>40%</td>
<td>—</td>
<td>—</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>Imatinib and dasatinib-I (n=50)</td>
<td>38%</td>
<td>31%</td>
<td>—</td>
<td>—</td>
<td>87%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imatinib and nilotinib-R (n=26)</td>
<td>56%</td>
<td>49%</td>
<td>35%</td>
<td>52% at 5 y</td>
<td>76% at 5 y</td>
<td>66% at 5 y</td>
<td></td>
</tr>
<tr>
<td>Ponatinib (45 mg qd) Dasatinib- or nilotinib-R or I (n=203)</td>
<td>57 mo</td>
<td>72%</td>
<td>70%</td>
<td>58%</td>
<td>50% at 5 y</td>
<td>66% at 5 y</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CCyR, complete cytogenetic response; I, intolerant; IS, International Scale; MCyR, major cytogenetic response; MMR, major molecular response (≤ 0.1% BCR-ABL1 IS); R, resistant; OS, overall survival; PFS, progression-free survival.

Primary end point: MCyR rate in patients with imatinib-I or imatinib-R disease.

Primary end point: MCyR at any time within the first 12 mo.

© JNCCN—Journal of the National Comprehensive Cancer Network | Volume 16 Number 9 | September 2018
for high blood pressure, evidence of arterial occlusive or thromboembolic events, and reduced cardiac function. Ponatinib should be interrupted or stopped immediately for vascular occlusion and for new or worsening heart failure. Patients with cardiovascular risk factors should be referred to a cardiologist.

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

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

Clinical Considerations For The Selection Of Second-Line Therapy

BCR-ABL kinase domain mutation analysis (see subsequent section), evaluation of drug interactions, and compliance to therapy are recommended before the start of second-line TKI therapy.

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

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

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

Adherence to Therapy: Treatment interruptions and nonadherence to therapy may lead to undesirable clinical outcomes. In the ADAGIO study, non-
adherence to imatinib was associated with poorer response. Patients with suboptimal response missed significantly more imatinib doses (23%) than did those with optimal response (7%).110 Adherence to imatinib therapy has been identified as the only independent predictor for achieving complete molecular response (CMR) on standard-dose imatinib.111 Poor adherence to imatinib therapy has also been identified as the most important factor contributing to cytogenetic relapse and imatinib failure.112 Patients with adherence of ≤85% had a higher probability of losing CCyR at 2 years than those with adherence of >85% (27% and 2%, respectively). Poor adherence to therapy has also been reported in patients receiving dasatinib and nilotinib after imatinib failure.113,114

Patient education on adherence to therapy and close monitoring of patient's adherence is critical to achieving optimal responses. In a significant proportion of patients with TKI-induced toxicities, responses have been observed with doses well below their determined maximum tolerated doses.115 Short interruptions or dose reductions, when medically necessary, may not have a negative impact on disease control or other outcomes. Adequate and appropriate management of side effects and scheduling appropriate follow-up visits to review side effects may be helpful to improve patient adherence to therapy.116 Switching to an alternate TKI because of intolerance might be beneficial for selected patients with acute grade 3/4 nonhematologic toxicities or in those with low-grade, chronic, and persistent adverse events that are not manageable with adequate supportive care measures.117

Resistance to TKI Therapy: Aberrant expressions of drug transporters and plasma protein binding of TKIs121–123 could contribute to primary resistance by altering the intracellular and plasma concentration of TKI. Monitoring imatinib plasma levels may be useful in determining patient adherence to therapy. However, there are no data to support that change of therapy based on plasma imatinib levels will affect treatment outcomes. Pretreatment levels of organic cation transporter 1 (OCT1) have been reported as the most powerful predictor of response to imatinib.124 Conversely, cellular uptake of dasatinib or nilotinib seems to be independent of OCT1 expression, suggesting that patients with low hOCT1 expression might have better outcomes with dasatinib or nilotinib than with imatinib.125–128

**BCR-ABL Kinase Domain Mutation Analysis:** Point mutations in the BCR-ABL1 kinase domain are a frequent mechanism of secondary resistance to TKI therapy and are associated with poor prognosis and higher risk of disease progression.129–134 Among the BCR-ABL1 kinase domain mutations, the T315I mutation confers the complete resistance to imatinib, dasatinib, nilotinib, and bosutinib.135,136

F317L and V299L mutants are resistant to dasatinib and Y253H, E255K/V, and F359V/C mutants are resistant to nilotinib.137–140 E255K/V, F359C/V, Y253H, and T315I mutants are most commonly associated with disease progression and relapse.140 Bosutinib has demonstrated activity in patients with BCR-ABL1 mutants resistant to dasatinib (F317L) and nilotinib (Y253H, E255K/V, and F359C/I/V).95 T315I, G250E, and V299L mutants are resistant to bosutinib. Ponatinib is active against other BCR-ABL1 mutants resistant to dasatinib or nilotinib, including E255V, Y253H, and F359V, in addition to T315I.96,141 Response rates based on BCR-ABL mutation status are listed in Table 8.

BCR-ABL kinase domain mutational analysis is helpful in the selection of subsequent TKI therapy for patients with inadequate initial response to first- or second-line TKI therapy.142 Treatment options based on BCR-ABL1 mutation status are outlined on CML-5 (page 1113). BCR-ABL mutational analysis provides additional guidance in the selection of subsequent TKI therapy only in patients with identifiable mutations. In patients with no identifiable mutations, the selection of subsequent TKI therapy should be based on the toxicity profile of TKI, patient's age, ability to tolerate therapy, and the presence of comorbid conditions. Adverse events of second-line TKI therapy in patients with CP-CML are summarized in Table 9.

The use of an alternate second-generation TKI after treatment failure with 2 prior TKIs, including a second-generation TKI, is not associated with durable responses, except in occasional patients with CP-CML.143 The guidelines recommend BCR-ABL1 mutational analysis for patients who do not experience response milestones, for those with any sign of loss of response (hematologic or cytogenetic relapse), and if there is a 1-log increase in BCR-ABL1 level with loss of MMR.

**Rising BCR-ABL1 Transcript Levels:** Rising BCR-ABL1 transcript levels are associated with an in-
creased likelihood of detecting BCR-ABL1 kinase domain mutations and cytogenetic relapse. In patients who had achieved very low levels of BCR-ABL1 transcripts, emergence of BCR-ABL1 mutations was more frequent in those who had more than a 2-fold increase in BCR-ABL1 levels compared with those with stable or decreasing BCR-ABL1. A serial rise has been reported to be more reliable than a single ≥2-fold increase in BCR-ABL1 transcripts.

The precise increase in BCR-ABL1 transcripts that warrants a mutation analysis depends on the performance characteristics of the qPCR assay. Some laboratories have advocated a 2- to 3-fold range, whereas others have taken a more conservative approach (5- to 10-fold). Among patients in CCyR with a ≥0.5-log increase in BCR-ABL1 transcripts on at least 2 occasions, the highest risk of disease progression was associated with loss of MMR and a more than 1-log increase in BCR-ABL1 transcripts.

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Bosutinib</th>
<th>Dasatinib</th>
<th>Nilotinib</th>
<th>Ponatinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>E255K</td>
<td>NR</td>
<td>9/16 (56%)</td>
<td>3/7 (43%)</td>
<td>8/13 (62%)</td>
</tr>
<tr>
<td>E255V</td>
<td>NR</td>
<td>4/11 (36%)</td>
<td></td>
<td>1/4 (25%)</td>
</tr>
<tr>
<td>E459K</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>3/7 (43%)</td>
</tr>
<tr>
<td>F317L</td>
<td>1/7 (14%)</td>
<td>2/14 (14%)</td>
<td>NR</td>
<td>13/29 (45%)</td>
</tr>
<tr>
<td>F359C</td>
<td>1/2 (50%)</td>
<td>3/5 (60%)</td>
<td>11/1 (9%)</td>
<td>1/7 (14%)</td>
</tr>
<tr>
<td>F359V</td>
<td>2/3 (67%)</td>
<td>17/27 (63%)</td>
<td>11/20 (55%)</td>
<td></td>
</tr>
<tr>
<td>F359H</td>
<td>2/2 (100%)</td>
<td>10/12 (83%)</td>
<td>NR</td>
<td>3/4 (75%)</td>
</tr>
<tr>
<td>G250E</td>
<td>0/5 (0%)</td>
<td>29/60 (48%)</td>
<td>3/5 (60%)</td>
<td>8/12 (67%)</td>
</tr>
<tr>
<td>H396R</td>
<td>NR</td>
<td>17/33 (52%)</td>
<td>NR</td>
<td>1/5 (20%)</td>
</tr>
<tr>
<td>L248V</td>
<td>NR</td>
<td>10/15 (67%)</td>
<td>NR</td>
<td>1/2 (50%)</td>
</tr>
<tr>
<td>M244V</td>
<td>2/3 (67%)</td>
<td>27/27 (59%)</td>
<td>NR</td>
<td>4/9 (56%)</td>
</tr>
<tr>
<td>M351T</td>
<td>NR</td>
<td>28/54 (52%)</td>
<td>NR</td>
<td>1/2 (50%)</td>
</tr>
<tr>
<td>Y253H</td>
<td>5/6 (83%)</td>
<td>15/23 (65%)</td>
<td>1/8 (13%)</td>
<td>1/2 (50%)</td>
</tr>
<tr>
<td>V299L</td>
<td>0/2 (0%)</td>
<td>NR</td>
<td>NR</td>
<td>3/8 (38%)</td>
</tr>
</tbody>
</table>

Abbreviation: NR, not reported.

Increased

Table 8. Responses Based on BCR-ABL1 Mutations Status

Table 9. Adverse Events of Second-Line and Subsequent TKI Therapy in CP-CML

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

Abbreviations: ALT, alanine amino transferase; AST, aspartate amino transferase; CP-CML, chronic phase chronic myeloid leukemia; TKI, tyrosine kinase inhibitor.

Discontinuation of TKI Therapy

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

The possibility of treatment-free remission (TFR) after discontinuation of imatinib was first evaluated in the Stop Imatinib (STIM1) study in 100 patients with a CMR for at least 2 years (5-log
The results of the RE-STIM study demonstrated the safety of a second TKI discontinuation after a first unsuccessful attempt. The rate of molecular relapse after the first TKI discontinuation attempt was the only factor significantly associated with outcome. The TFR rate at 24 months after second TKI discontinuation was higher for patients who remained in deep molecular response within the first 3 months after the first TKI discontinuation (72% vs 32% for other patients).

Approximately 40% to 60% of patients who discontinue TKI therapy after achieving deep molecular response experience recurrence within 6 months of treatment cessation, in some cases as early as 1 month after discontinuation of TKI therapy. Resumption of TKI therapy immediately after recurrence results in the achievement of undetectable disease in almost all patients. TKI withdrawal syndrome (aggravation or new development of musculoskeletal pain and/or pruritus after discontinuation of TKI therapy) has been reported during the TFR period in some TKI discontinuation studies, and the occurrence of imatinib withdrawal syndrome was associated with a lower rate of molecular relapse in the KID study.

In the STIM study, molecular relapse (trigger to resume TKI therapy) was defined as positivity for BCR-ABL1 transcripts by qPCR confirmed by

---

**Table 10. Summary of Limited Longer-Term Follow-Up Data From the TKI Discontinuation Trials**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment Prior to Discontinuation</th>
<th>N</th>
<th>Depth and Duration of MR Required for Discontinuation</th>
<th>Trigger to Resume TKI Therapy</th>
<th>Median Follow-Up</th>
<th>Treatment-Free Remission Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>STIM1</td>
<td>Imatinib ± interferon</td>
<td>100</td>
<td>MR5.0 for at least 2 y</td>
<td>Loss of MR5.0</td>
<td>77 mo</td>
<td>38% at 60 mo</td>
</tr>
<tr>
<td>TWISTER</td>
<td>Imatinib ± interferon</td>
<td>40</td>
<td>MR4.5 for at least 2 y</td>
<td>Loss of MR5.0</td>
<td>42 mo</td>
<td>47% at 24 mo</td>
</tr>
<tr>
<td>HOVON1</td>
<td>Imatinib + cytarabine</td>
<td>15</td>
<td>MR4.5 for at least 2 y</td>
<td>Loss of MR4.5</td>
<td>36 mo</td>
<td>33% at 24 mo</td>
</tr>
<tr>
<td>ASTIM1</td>
<td>Imatinib ± interferon</td>
<td>80</td>
<td>MR5.0 for at least 2 y</td>
<td>Loss of MMR</td>
<td>31 mo</td>
<td>61% at 36 mo</td>
</tr>
<tr>
<td>ISAV1</td>
<td>Imatinib (after failure of interferon or hydroxyurea)</td>
<td>108</td>
<td>CMR for at least 18 mo</td>
<td>Loss of MMR</td>
<td>36 mo</td>
<td>52% at 36 mo</td>
</tr>
<tr>
<td>KID1</td>
<td>Imatinib ± interferon</td>
<td>90</td>
<td>MR4.5 for at least 2 y</td>
<td>Loss of MMR</td>
<td>27 mo</td>
<td>59% at 24 mo</td>
</tr>
<tr>
<td>Stop 2GTKI1</td>
<td>Dasatinib/Nilotinib (first or secondline)</td>
<td>60</td>
<td>MR4.5 for at least 24 mo</td>
<td>Loss of MMR</td>
<td>47 mo</td>
<td>54% at 48 mo</td>
</tr>
<tr>
<td>ENESTfreedom1</td>
<td>Nilotinib (firstline)</td>
<td>190</td>
<td>MR4.5 for 12 mo</td>
<td>Loss of MMR</td>
<td>96 wk</td>
<td>49% at 96 wk</td>
</tr>
<tr>
<td>ENESTTop1</td>
<td>Nilotinib (secondline)</td>
<td>126</td>
<td>MR4.5 for 12 mo</td>
<td>Loss of MMR</td>
<td>96 wk</td>
<td>53% at 96 wk</td>
</tr>
<tr>
<td>DADI1</td>
<td>Dasatinib (secondline)</td>
<td>63</td>
<td>MR4.0 for at least 12 mo</td>
<td>Loss of MR4.0</td>
<td>44 mo</td>
<td>44% at 36 mo</td>
</tr>
<tr>
<td>EUROSKI1</td>
<td>Any TKI</td>
<td>758</td>
<td>MR4.0 for at least 1 y</td>
<td>Loss of MMR</td>
<td>27 mo</td>
<td>50% at 24 mo</td>
</tr>
</tbody>
</table>

Abbreviations: CMR, complete molecular response (undetectable BCR-ABL1 by qPCR as determined by local laboratories; IS, International Scale; MMR, major molecular response (≤0.1% BCRABL1 IS); MR, molecular response; MR4.0, ≤0.01% BCRABL1 IS; MR4.5, ≤0.0032% BCRABL1 IS or ≥4.5log reduction of BCRABL1 and undetectable minimal residual disease on qPCR with a sensitivity of ≥4.5log reduction; MR5.0, ≥4.5log reduction in BCRABL1 levels and undetectable minimal residual disease on qPCR with a sensitivity of ≥4.5log reduction; TKI, tyrosine kinase inhibitor.

reduction in BCR-ABL1 levels and undetectable minimal residual disease on qPCR with a sensitivity of ≥4.5-log reduction from the standardized baseline. With a median follow-up of 77 months after discontinuation of imatinib, the molecular recurrence-free survival was 43% at 6 months and 38% at 60 months. Other subsequent studies that have evaluated discontinuation of imatinib have also reported similar findings.

More recent studies have also confirmed the feasibility of TFR after discontinuation of dasatinib or nilotinib, in patients with CP-CML who have achieved and maintained MR4.5 for 12 months after ≥2 years of TKI therapy in the first-line or second-line setting (TFR rates ranging from 44% to 54%; Table 10). The feasibility of TFR after discontinuation of bosutinib or ponatinib has not yet been evaluated in clinical studies. In the EURO-SKI study that evaluated TFR after discontinuation of any first-line TKI therapy (imatinib, dasatinib, or nilotinib) in eligible patients, the type of first-line TKI therapy did not significantly affect molecular relapse-free survival. Therefore, it is reasonable to assume that the likelihood of TFR after discontinuation would be similar irrespective of TKI in patients who have experienced and maintained deep molecular response (MR4.0; ≤0.01% BCR-ABL1 IS) for ≥2 years.
The results of the A-STIM study showed that loss of MMR (≤0.1% BCR-ABL1 IS) could be used as a practical criterion for restarting therapy. The estimated probability of MMR loss was 35% at 12 months and 36% at 24 months after discontinuation of imatinib. Several factors may help predict the risk of relapse after discontinuation of TKI therapy (eg, a higher Sokal risk score, female sex, lower natural killer cell counts, suboptimal response or resistance to imatinib, duration of TKI therapy, and deep molecular response prior to TKI discontinuation). However, only the duration of TKI therapy and deep molecular response before TKI discontinuation therapy have been associated with TFR with a high level of consistency. In the EURO-SKI study, duration of treatment with imatinib (≥ 6 years) and deep molecular response duration (MR4.0 for 3 years) were significantly associated with MMR maintenance at 6 months after discontinuation of imatinib.

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

The criteria for the selection of patients suitable for discontinuation of TKI therapy are outlined in CML-E (page 1116). The guidelines emphasize that discontinuation of TKI therapy outside of a clinical trial should be considered only if all the criteria included in the list are met. The panel acknowledges that more frequent molecular monitoring is essential after discontinuation of TKI therapy for the early identification of loss of MMR. Frequency of molecular monitoring has varied substantially among different studies, and the optimal frequency of molecular monitoring in patients with a loss of MMR after discontinuation of TKI therapy has not been established. The panel recommendations for molecular monitoring in TFR phase are outlined in CML-E (page 1116).

References


Marin D, Goldman JM, Olavarria E, Apperley JF. Transient benefit only from increasing the imatinib dose in CML patients who do not achieve complete cytogenetic remissions on conventional doses. Blood 2003;102:2702–2704.


## Individual Disclosures for Chronic Myeloid Leukemia

<table>
<thead>
<tr>
<th>Panel Member</th>
<th>Clinical Research Support/Data Safety Monitoring Board</th>
<th>Scientific Advisory Boards, Consultant, or Expert Witness</th>
<th>Promotional Advisory Boards, Consultant, or Speakers Bureau</th>
<th>Date Completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Camille N. Abboud, MD</td>
<td>None</td>
<td>Pfizer Inc.</td>
<td>Agios Pharmaceuticals, Inc.; Cardinal Health; and Jazz Pharmaceuticals</td>
<td>7/12/18</td>
</tr>
<tr>
<td>Jessica K. Altman, MD</td>
<td>None</td>
<td>Astellas Pharma US, Inc.; and Novartis Pharmaceuticals Corporation</td>
<td>None</td>
<td>4/7/18</td>
</tr>
<tr>
<td>Ellin Berman, MD</td>
<td>Bristol-Myers Squibb Company; and Takeda Pharmaceuticals North America, Inc.</td>
<td>ARIAD Pharmaceuticals, Inc.; and Pfizer Inc.</td>
<td>None</td>
<td>4/3/18</td>
</tr>
<tr>
<td>Ravi Bhatia, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>5/1/18</td>
</tr>
<tr>
<td>Bhavana Bhattacharjee, DO</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>4/24/18</td>
</tr>
<tr>
<td>Peter Curtin, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>4/24/18</td>
</tr>
<tr>
<td>Daniel J. DeAngelis, MD, PhD</td>
<td>None</td>
<td>Amgen Inc.; ARIAD Pharmaceuticals, Inc.; Bristol-Myers Squibb Company; Celgene Corporation; GlycoMimetics; Incyte Corporation; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Shire; and Sunesis Pharmaceuticals, Inc.</td>
<td>None</td>
<td>12/13/16</td>
</tr>
<tr>
<td>Michael Deininger, MD, PhD</td>
<td>None</td>
<td>ARIAD Pharmaceuticals, Inc.; Blueprint Medicines Corporation; Galena Biopharma, Inc.; Incyte Corporation; Novartis Pharmaceuticals Corporation; and Pfizer Inc.</td>
<td>None</td>
<td>5/15/18</td>
</tr>
<tr>
<td>Jason Gottlib, MD, MS</td>
<td>Blueprint Medicines Corporation; Celgene Corporation; CTI BioPharma Corp.; Deciphera Pharmaceuticals, Inc.; Gilead Sciences, Inc.; Incyte Corporation; Pharmacyclics, Inc.; Promedior, Inc.; and Seattle Genetics, Inc.</td>
<td>Blueprint Medicines Corporation; Deciphera Pharmaceuticals, Inc.; Gilead Sciences, Inc.; Incyte Corporation; and Novartis Pharmaceuticals Corporation</td>
<td>None</td>
<td>3/15/18</td>
</tr>
<tr>
<td>Gabriela Hobbs, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>3/14/18</td>
</tr>
<tr>
<td>Madan Jagasia, MD</td>
<td>Incyte Corporation; Janssen Pharmaceutica Products, LP; and Kadmon Corporation</td>
<td>Therakos, Inc.</td>
<td>None</td>
<td>4/25/18</td>
</tr>
<tr>
<td>Hagop M. Kantarjian, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>4/30/18</td>
</tr>
<tr>
<td>Lori Maness, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>4/11/18</td>
</tr>
<tr>
<td>Leland Metheny, MD</td>
<td>Incyte Corporation; Pfizer Inc.; and Takeda Pharmaceuticals North America, Inc.</td>
<td>Pfizer Inc.</td>
<td>None</td>
<td>4/24/18</td>
</tr>
<tr>
<td>Joseph O. Moore, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>1/26/18</td>
</tr>
<tr>
<td>Arnel Pallera, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>5/1/18</td>
</tr>
<tr>
<td>Philip Pancari, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>3/15/18</td>
</tr>
<tr>
<td>Mrinal Patnail, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>7/1/18</td>
</tr>
<tr>
<td>Enkhtsetseg Purev, MD, PhD</td>
<td>Juno Therapeutics, Inc.</td>
<td>None</td>
<td>Celgene Corporation</td>
<td>5/10/18</td>
</tr>
<tr>
<td>Jerald P. Radich, MD</td>
<td>None</td>
<td>Novartis Pharmaceuticals Corporation; and Seattle Genetics, Inc.</td>
<td>None</td>
<td>3/18/18</td>
</tr>
<tr>
<td>Michal G. Rose, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>4/29/18</td>
</tr>
<tr>
<td>Neil P. Shah, MD, PhD</td>
<td>Bristol-Myers Squibb Company</td>
<td>None</td>
<td>None</td>
<td>4/24/18</td>
</tr>
<tr>
<td>B. Douglas Smith, MD</td>
<td>None</td>
<td>Celgene Corporation</td>
<td>Novartis Pharmaceuticals Corporation; and Pfizer Inc.</td>
<td>4/3/18</td>
</tr>
<tr>
<td>David S. Snyder, MD</td>
<td>None</td>
<td>Novartis Pharmaceuticals Corporation</td>
<td>None</td>
<td>4/27/18</td>
</tr>
<tr>
<td>Kendra L. Sweet, MD, MS</td>
<td>Cytomix, Inc.; and Stemline Therapeutics</td>
<td>Agios Pharmaceuticals, Inc.; Novartis Pharmaceuticals Corporation; and Pfizer Inc.</td>
<td>Bristol-Myers Squibb Company; Celgene Corporation; Jazz Pharmaceuticals; and Novartis Pharmaceuticals Corporation</td>
<td>5/1/18</td>
</tr>
<tr>
<td>Moshe Talpaz, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>3/14/18</td>
</tr>
<tr>
<td>James Thompson, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>4/24/18</td>
</tr>
<tr>
<td>David T. Yang, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>4/30/18</td>
</tr>
</tbody>
</table>

The NCCN Guidelines Staff have no conflicts to disclose.