NCCN Guidelines® Insights

Chronic Myelogenous Leukemia, Version 1.2014

Featured Updates to the NCCN Guidelines

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Abstract

The 2014 NCCN Clinical Practice Guidelines in Oncology for Chronic Myelogenous Leukemia recommend quantitative reverse-transcription polymerase chain reaction (QPCR) standardized to International Scale (IS) as the preferred method for monitoring molecular response to tyrosine kinase inhibitor (TKI) therapy. A *BCR-ABL1* transcript level of 10% or less (IS) is now included as the response milestone at 3 and 6 months. Change of therapy to an alternate TKI is recommended for patients with *BCR-ABL1* transcript levels greater than 10% (IS) at 3 months after primary treatment with imatinib. Continuing the same dose of TKI or switching to an alternate TKI are options for patients with *BCR-ABL1* transcript levels greater than 10% (IS) at 3 months after primary treatment with dasatinib or nilotinib. The guidelines recommend 6-month evaluation with QPCR (IS) for patients with *BCR-ABL1* transcript levels greater than 10% at 3 months. Monitoring with QPCR (IS) every 3 months is recommended for all patients, including those who meet response milestones at 3, 6, 12, and 18 months (*BCR-ABL1* transcript level ≤10% [IS] at 3 and 6 months, complete cytogenetic response at 12 and 18 months). (*JNCCN* 2013;11:1327–1340)

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Please Note: These NCCN Guidelines Insights were written before the FDA announcement of safety concerns regarding ponatinib. Consequently, the agent is listed as an option in these Insights. However, at time of publication, ponatinib had been removed from the NCCN Guidelines for CML until further discussion by the NCCN Guidelines Panel. The current status of ponatinib, as a treatment option for CML, is available in the NCCN Guidelines at NCCN.org.

Disclosures for the NCCN Chronic Myelogenous Leukemia Panel

Individual disclosures of potential conflicts of interest for the NCCN Chronic Myelogenous Leukemia Panel members can be found on page 1328.

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. **The NCCN Guidelines® Insights highlight important changes in the NCCN Guidelines® recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further understanding of these changes by summarizing salient portions of the panel's discussion, including the literature reviewed.**

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Chronic Myelogenous Leukemia, Version 1.2014

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Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to NCCN Guidelines for Chronic Myelogenous Leukemia
- Describe the rationale behind the decision-making process for recent updates to the NCCN Guidelines for Chronic Myelogenous Leukemia

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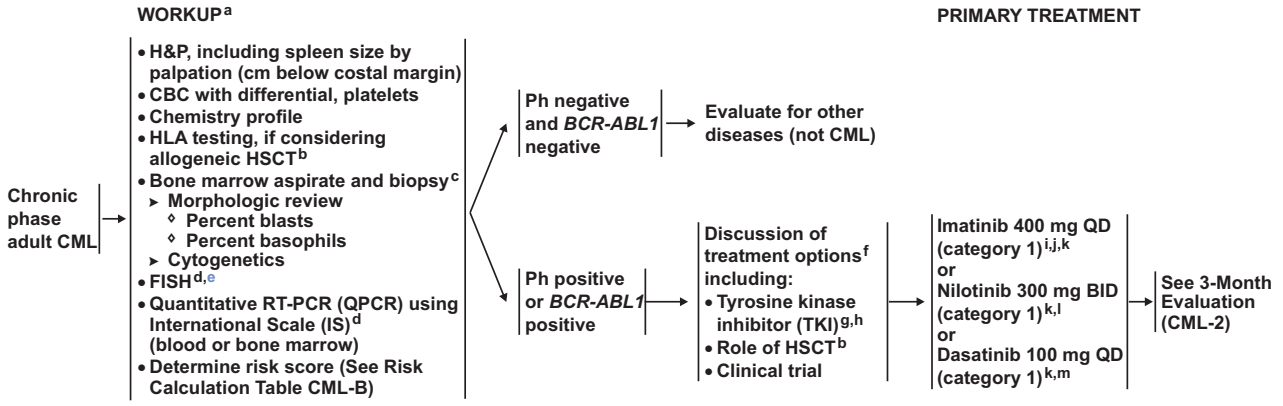
Chronic Myelogenous Leukemia, Version 1.2014



[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]Bone marrow should be done for the initial workup, not only to provide morphologic review, but also to detect chromosomal abnormalities that are not detectable on peripheral blood FISH.
[d]See Discussion for further details.
[e]If collection of bone marrow is not feasible.
[f]For patients with symptomatic leukocytosis or thrombocytosis, see Supportive Care Strategies (CML-C).
[g]There are 8-year follow-up data from the IRIS study that show clear evidence of excellent survival benefit with imatinib.
[h]There are 36- to 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 yet been established. Preliminary data from these studies also suggest that patients with an intermediate- or high-risk Sokal or Hasford score may preferentially benefit from dasatinib or nilotinib. See Discussion for additional information.
[i]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.
[j]See Management of Imatinib Toxicity (CML-D).
[k]Consider bosutinib, ponatinib, IFN/PEG-IFN, allogeneic HSCT, or clinical trial for rare patients unable to tolerate imatinib, dasatinib, or nilotinib. Bosutinib and ponatinib are not approved for first-line therapy.
[l]See Management of Nilotinib Toxicity (CML-E).
[m]See Management of Dasatinib Toxicity (CML-F).

CML-1

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.

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

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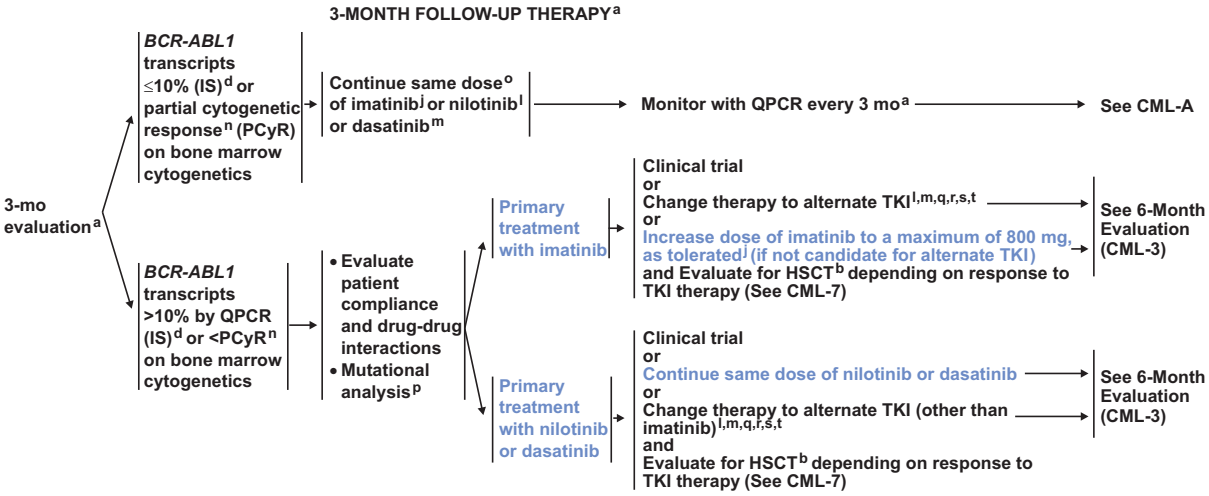
Overview

Chronic myelogenous leukemia (CML) is characterized by the presence of Philadelphia chromosome (Ph) resulting from a reciprocal translocation between chromosomes 9 and 22 [t(9;22]. This translocation results in the fusion of the breakpoint cluster region (*BCR*) gene on chromosome 22 and the Abelson murine leukemia (*ABL1*) gene located on chromosome 9.[1] The



[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.
[d] See Discussion for further details.
[j] See Management of Imatinib Toxicity (CML-D).
[l] See Management of Nilotinib Toxicity (CML-E).
[m] See Management of Dasatinib Toxicity (CML-F).
[n] See Criteria for Hematologic, Cytogenetic, Molecular Response, and Relapse (CML-J).
[o] 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.
[p] See Treatment Options Based on BCR-ABL KD Mutation Status (CML-K).
[q] Consider IFN/PEG-IFN, allogeneic HSCT, omacetaxine, or clinical trial for rare patients unable to tolerate TKI therapy.
[r] See Management of Bosutinib Toxicity (CML-G).
[s] See Management of Ponatinib Toxicity (CML-H).
[t] 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.

CML-2

product of the *BCR-ABL* fusion gene, the p210 fusion protein with deregulated tyrosine kinase activity, plays a central role in the pathogenesis of CML. Another fusion protein, p190 is also produced, usually in the setting of Ph^+ acute lymphoblastic leukemia. p190 is detected only in 1% of patients with CML.[2]

Tyrosine kinase inhibitor (TKI) therapy (with imatinib, dasatinib, or nilotinib) is the standard first-line treatment for patients with newly diagnosed chronic-phase CML (see CML-1, page 1329).[3–5] Early molecular response to first-line TKI therapy is emerging as an effective prognostic indicator of long-term durable responses and survival, necessitating the use of molecular monitoring to identify patients who would benefit from alternate TKI therapy. Dasatinib and nilotinib are effective second-line therapy options for patients resistant or intolerant to imatinib.[6–8] Bosutinib and ponatinib were recently approved for patients resistant or intolerant to prior TKI therapy, including imatinib, dasatinib or nilotinib.[9,10] Monitoring molecular response using quantitative reverse-transcription polymerase chain reaction (QPCR) is particularly important to evaluate treatment effectiveness.

These NCCN Guidelines Insights present the major changes to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for CML and discuss the clinical data that support these changes.

Monitoring Molecular Response to TKI Therapy

Molecular response is determined by the decrease in the amount of *BCR-ABL* mRNA using reverse-transcription polymerase chain reaction (RT-PCR). This assay measures the levels of *BCR-ABL1* transcripts in the peripheral blood or in the bone marrow, and can detect one CML cell in a

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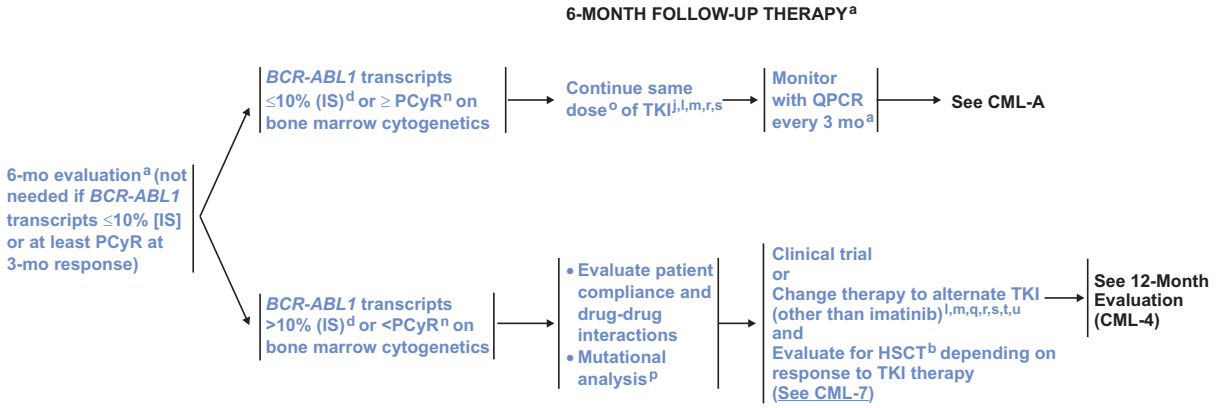

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[r] See Management of Bosutinib Toxicity (CML-G).
[s] See Management of Ponatinib Toxicity (CML-H).
[t] Patients with failure to first-line imatinib should be treated with nilotinib, dasatinib, bosutinib, or ponatinib in the second-line setting. Patients with failure to first-line nilotinib or dasatinib could be treated with an alternate TKI (other than imatinib) in the second-line setting.
[u] Omacetaxine is a treatment option for patients with resistance and/or intolerance to two or more TKIs. See Management of Omacetaxine Toxicity (CML-I).

CML-3

background of 100,000 or greater normal cells. Qualitative RT-PCR assay is reported as being either positive or negative; it is rarely used in the context of monitoring. In contrast, a QPCR assay reports the actual percentage of *BCR-ABL1* mRNA transcripts.[11]

QPCR is the most sensitive assay available for the measurement of *BCR-ABL1* mRNA. A major advantage of the 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. QPCR with either peripheral blood or bone marrow should be performed before initiation of TKI therapy to establish the presence of quantifiable *BCR-ABL1* mRNA transcripts at baseline. The *BCR-ABL1* mRNA transcripts typically remain detectable after complete cytogenetic response (CCyR) is achieved. Therefore, a QPCR assay is the only tool capable of monitoring responses after patients have achieved CCyR.

In the QPCR assay, results are expressed as the ratio of *BCR-ABL1* transcript numbers to the number of control gene transcripts.[12] Alternatively, this ratio is also expressed as a percentage whereby equal copy numbers of the *BCR-ABL1* gene and the control gene at diagnosis would be expressed as 100%.[12] Thus, the choice of an appropriate control gene is important for generating reliable and reproducible data. *BCR*, *ABL*, ß-glucuronidase (*GUSB*), and $ß_2$ microglobulin (*B2M*) have been widely studied for *BCR-ABL1* quantification.[13–15] *BCR* was used as the control gene in the IRIS trial.[13]

Standardization Using the International Scale

A substantial effort has been made to standardize *BCR-ABL1* testing and reporting across academic and private laboratories.[12,16,17] In 2006, the National Institutes of Health Consensus group proposed the use of an International Scale (IS) to standardize

RECOMMENDATIONS FOR MONITORING RESPONSE TO TKI THERAPY AND MUTATIONAL ANALYSIS[1]

Test	Recommendation
Bone marrow cytogenetics[2]	• 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 and 6 months from initiation of therapy if QPCR using IS is not available to assess response to TKI therapy. • At 12 months from initiation of therapy, if CCyR or MMR is not achieved. Absence of MMR in the presence of a CCyR is not considered a failure. • At 18 months from initiation of therapy, if not in MMR or lack of CCyR at 12 months. Absence of MMR in the presence of a CCyR is not considered a failure. Bone marrow cytogenetics are not necessary if patient in MMR at 12 months. • 1-log increase in *BCR-ABL1* transcript levels without 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 1-log increase in *BCR-ABL1* transcript levels with 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-ABL1* ≤10% [IS] at 3 and 6 months or CCyR at 12 and 18 months) ➤ 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.

[1]Hughes T, Deininger M, Hochhaus A, et al. Monitoring CML patients responding to treatment with tyrosine kinase inhibitors: review and recommendations for harmonizing current methodology for detecting BCR-ABL transcripts and kinase domain mutations and for expressing results. Blood 2006;108(1):28-37.
[2]FISH has been inadequately studied for monitoring response to treatment.

CML-A

molecular monitoring with QPCR across different laboratories.[12] This group recommended the use of 1 of 3 control genes (*BCR*, *ABL*, or *GUSB*) and a QPCR assay with a sensitivity of at least 4-log reduction from the standardized baseline.

In the IS, the standardized baseline (defined as the median value of *BCR-ABL1* mRNA at the time of diagnosis in 30 patients with CML as established in the IRIS study) is taken to represent 100%. Major molecular response (MMR), 3-log reduction in the *BCR-ABL1* transcripts from this standardized baseline, is fixed at 0.1%.[12,16] A 2-log reduction (*BCR-ABL1* transcripts 1% IS) and 1-log reduction (*BCR-ABL1* transcripts 10% IS) from the standardized baseline generally correlate with threshold responses indicative of CCyR and major cytogenetic response (MCyR), respectively. Complete molecular response (CMR) is defined as undetectable *BCR-ABL1* transcripts as assessed by QPCR with a sensitivity of 4.5-log reduction or more from the standardized baseline.

The *BCR-ABL1* transcript levels obtained in a given laboratory are converted to the IS by applying a laboratory-specific conversion factor (CF).[12,18] To obtain a laboratory-specific CF, each laboratory typically has to exchange 20 to 30 pretreatment samples with a reference laboratory. Both laboratories analyze the samples and the results are plotted on a log scale for comparison. The anti-log of the estimated mean bias between the methods is designated as the CF.[18] Once a laboratory-specific CF is established, it is validated again through a second sample exchange with the reference laboratory.

QPCR (IS) is still not available in many laboratories because the process is relatively cumbersome, time-consuming, and not considered practical if the laboratory does not have a high volume of assays to perform, or if the prescribing physicians

Chronic Myelogenous Leukemia, Version 1.2014

CRITERIA FOR HEMATOLOGIC, CYTOGENETIC, MOLECULAR RESPONSE AND RELAPSE

Complete hematologic response[1]
- **Complete normalization of peripheral blood counts with leukocyte count <10 cells x 10^9/L**
- **Platelet count <450 cells 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-ABL1* mRNA by QPCR (IS) using an assay with a sensitivity of at least 4.5 logs below the standardized baseline.**
- **Major molecular response - *BCR-ABL1* transcripts 0.1% by QPCR (IS) or ≥3-log reduction in *BCR-ABL1* mRNA from the standardized baseline, if QPCR (IS) is not available.**

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.**

[1]Faderl S et al: Chronic myelogenous leukemia: Biology and therapy. Ann Intern Med 1999;131:207-219. The American College of Physicians-American Society of Internal Medicine is not responsible for the accuracy of the translation.
[2]A minimum of 20 metaphases should be examined.
[3]O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 2003;348:994-1004.
[4]Hughes TP, Kaeda J, Branford S, et al. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. N Engl J Med 2003;349:1423-1432.
[5]Hughes T, Deininger M, Hochhaus A, et al. Monitoring CML patients responding to treatment with tyrosine kinase inhibitors: review and recommendations for harmonizing current methodology for detecting BCR-ABL transcripts and kinase domain mutations and for expressing results. Blood 2006;108:28-37.

CML-J

do not demand it. Alternatively, laboratories with no access to QPCR (IS) assays may establish their own standardized baseline based on a large number of pretreatment samples. Molecular response to TKI therapy is measured as the log-reduction of *BCR-ABL1* mRNA from the standardized baseline (not a reduction from the actual baseline level in an individual patient; see CML-J, page 1333). This is an effective method, and was used in the IRIS trial to establish the 3-log reduction in the *BCR-ABL1* transcript levels from the standardized baseline (not a reduction from the actual baseline level in an individual patient) as the MMR.[13] In addition, this technique was recently used in the US Intergroup CML trial.[19]

Rising *BCR-ABL1* Transcripts and Mutational Analysis

Point mutations in the ABL kinase domain are a frequent mechanism of resistance to TKI therapy. Dasatinib and nilotinib are active against most mutations that confer resistance to imatinib, except for the *T315I* mutation. In addition, mutations at position F317 and V299 are resistant to dasatinib,[20] and Y253H, E255, and F359 substitutions are resistant to nilotinib.[21] Bosutinib has shown potent activity in patients with *BCR-ABL1* mutations that confer resistance to dasatinib (F317L) and nilotinib (Y253H and F359).[9] Ponatinib has demonstrated activity in patients with *BCR-ABL1* mutations resistant to dasatinib or nilotinib (F317L, E255K, F359V, and G250E), including patients with *T315I* mutations.[22,23] Mutational analysis is helpful in selecting subsequent TKI therapy for patients who have an inadequate initial response to first-line or second-line TKI therapy (see CML-K, page 1334).[24,25]

Several studies have shown that rising *BCR-ABL1* transcripts may be associated with an increased likelihood of detecting *BCR-ABL1* mutations and cytogenetic relapse.[26–30] The precise increase in

TREATMENT OPTIONS BASED ON BCR-ABL KD MUTATION STATUS[1-4]

Mutation	Treatment Options
T315I	Ponatinib (preferred), omacetaxine, HSCT, or clinical trial
V299L	Consider ponatinib or nilotinib or omacetaxine[5]
T315A	Consider ponatinib, nilotinib, imatinib,[6] bosutinib, or omacetaxine[5]
F317L/V/I/C	Consider ponatinib, nilotinib, or bosutinib, or omacetaxine[5]
Y253H, E255K/V, F359V/C/I	Consider ponatinib, dasatinib, or bosutinib, or omacetaxine[5]
Any other mutation	Consider ponatinib, high-dose imatinib,[7] dasatinib, nilotinib, bosutinib, or omacetaxine[5]

[1] Soverini S, Hochhaus A, Nicolini FE, et al. Bcr-Abl kinase domain mutation analysis in chronic myeloid leukemia patients treated with tyrosine kinase inhibitors: recommendations from an expert panel on behalf of European LeukemiaNet. Blood 2011;118:1208-1215.
[2] Khoury HJ, Cortes JE, Kantarjian HM, et al. Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib and/or nilotinib therapy failure. Blood 2012;119:3403-3412.
[3] Deininger MWN, Cortes JE, Kim D-W, et al. Impact of baseline mutations on response to ponatinib and end of treatment mutation analysis in patients with chronic myeloid leukemia [abstract]. J Clin Oncol 2013;31(15_suppl):Abstract 7001.
[4] TKIs are preferred over omacetaxine.
[5] Omacetaxine is a treatment option for patients with resistance and/or intolerance to two or more TKIs.
[6] If mutation is detected following dasatinib.
[7] There are no sufficient data on dose escalation available to indicate if mutations with lower IC_{50} values are sensitive to high-dose imatinib.

CML-K

BCR-ABL1 transcripts that warrants a mutation analysis depends on the performance characteristics of QPCR assay in the laboratory.[29] In an analysis of 258 patients with chronic-phase CML treated with imatinib, Kantarjian et al[28] reported that patients with the highest risk were those who lost MMR with more than a 1-log increase in *BCR-ABL1* transcripts, or those who never achieved a MMR and had a 1-log increase in *BCR-ABL1* transcripts.

The NCCN Guidelines recommend mutational analysis for patients with an inadequate initial response (failure to achieve either *BCR-ABL1* transcript levels ≤10% [IS] at 3 and 6 months or CCyR at 12 and 18 months) or any sign of loss of response (hematologic or cytogenetic relapse) or a 1-log increase in *BCR-ABL1* transcripts with loss of MMR (see CML-A, page 1332).

Prognostic Significance of Early Molecular Response to TKI Therapy

First-Line TKI Therapy

The prognostic significance of early molecular response to imatinib was first established in a subset analysis of the IRIS study.[31] The incidence of disease progression was significantly higher in patients who failed to achieve a 1-log reduction in *BCR-ABL1* transcript levels by 3 months or a 2-log reduction in *BCR-ABL1* transcript levels by 6 months. In a subsequent report, Quintas-Cardama et al[32] also showed that patients with a *BCR-ABL1/ABL1* transcript level greater than 10% had a significantly lower probability of achieving a CCyR or MMR, and a higher probability of disease progression compared with those with *BCR-ABL1* transcript levels of 10% or less at the same time point. More recent studies have shown that achievement of *BCR-ABL1* transcript levels of 10% or less after 3 months, or 1% or

less at 6 months after treatment with imatinib, 400 mg, is an effective prognostic indicator for long-term outcomes.[33,34]

In an analysis of 282 patients with chronic-phase CML treated with imatinib, 400 mg, as first-line therapy, Marin et al[33] reported that patients who achieved *BCR-ABL1* transcript levels of 9.84% or less (IS) at 3 months had significantly higher rates of overall survival (OS), progression-free survival (PFS), and event-free survival (EFS) at 8-years than patients with *BCR-ABL1* transcript levels greater than 9.84% (IS) at 3 months ($P<.001$). The OS, PFS, and EFS rates were 93.3%, 92.8%, and 65.0%, respectively, for patients with *BCR-ABL1* transcript levels of 9.84% or less (IS) at 3 months compared with 56.9%, 57.0%, and 6.9%, respectively, for those with *BCR-ABL1* transcript levels greater than 9.84% (IS). In a more recent report, the same investigators also established the superior prognostic value of molecular response assessment at 3 months over molecular response assessment at 6 months.[35] The 8-year probability of OS for those with a low *BCR-ABL1* transcript levels at 3 months and high *BCR-ABL1* transcript levels at 6 months after imatinib therapy was similar to that of patients who had low *BCR-ABL1* transcript levels at both time points (92.4% and 93.5%, respectively; $P=.78$).

In the CML IV study (1303 patients with newly diagnosed CML treated with imatinib), Hanfstein et al[34] showed that failure to achieve *BCR-ABL1* transcript levels less than 10% (IS) at 3 months and *BCR-ABL1* transcript levels less than 1% (IS) at 6 months after imatinib treatment correlated with significantly lower OS and PFS rates at 5 years. At 3 months, the 5-year OS rate was 87% for patients with a *BCR-ABL1* transcript level greater than 10% (IS) compared with 95% for those who achieved a *BCR-ABL1* transcript level of 10% or less at 3 months ($P<.0001$). The 5-year PFS rates were 87% and 92%, respectively ($P=.037$). Similarly, at 6 months, the 5-year OS rate was 89% for those with a *BCR-ABL1* transcript level greater than 1% (IS) compared with 97% for patients with a *BCR-ABL1* transcript level of 1% or less (IS; $P<.0001$). The corresponding 5-year PFS rates were 89% and 96%, respectively ($P=.006$).

Landmark analyses from the DASISION and ENESTnd studies have also demonstrated the prognostic significance of early molecular response to first-line therapy with dasatinib or nilotinib in patients with newly diagnosed chronic-phase CML.[36,37]

In the DASISION study, patients with a *BCR-ABL1* transcript level of 10% or less (IS) at 3 months had significantly better 3-year PFS (93% vs 68% for dasatinib, $P=.0003$; 96% vs 75% for imatinib, $P<.0001$).[36] Progression was defined as transformation to accelerated or blast phase, death as a result of any cause, or loss of complete hematologic response or MCyR.[38] The rate of transformation was 3.0% (6 of 198 patients) for patients with *BCR-ABL1* transcript levels of 10% or less at 3 months compared with 13.5% for those who did not reach this response milestone at 3 months. The DASISION study also demonstrated the predictive value molecular response at 6 months.[36] The 3-year PFS was significantly better for patients with *BCR-ABL1* transcript levels of 1% or less at 6 months (95% vs 85% for dasatinib, $P=0020$; 97% vs 84% for imatinib, $P=.0016$). The rate of transformation was 2.0% (3 of 164 patients) for patients with *BCR-ABL1* transcript levels of 1% or less at 6 months compared with 9.7% for patients with *BCR-ABL1* transcript levels greater than 1%.

In the ENESTnd study, patients with *BCR-ABL1* transcript levels of 10% or less at 3 months had significantly improved 4-year PFS compared with those with *BCR-ABL1* transcript levels greater than 10% at 3 months (95% vs 83% for nilotinib 300 mg, $P=.0061$; 98% vs 83% for imatinib, $P<.0001$).[37] Progression was defined as transformation to accelerated or blast phase, or CML-related death.[39]

Jain et al[40] also reported the importance of achieving molecular response at 3 months in patients with chronic-phase CML treated with imatinib (800 mg), dasatinib, or nilotinib as first-line therapy. The 3-year EFS probability was significantly lower for patients with *BCR-ABL1* transcript levels greater than 10% (IS) at 3 months than for those with lower transcript levels (61% vs 95% and 98% for those with *BCR-ABL1* transcript levels less than 1%, or greater than 1% to 10% at 3 months, respectively; $P<.001$).

Second-Line TKI Therapy

The 3-month molecular response after initiation of second-line TKI therapy has also been reported to be a predictor of OS and EFS in patients who are still in chronic phase after experiencing treatment failure while on imatinib.[7,41,42]

In an analysis of 119 patients treated with dasatinib or nilotinib after failure on imatinib, Milojkovic et al[41] reported significantly superior OS (91.3% vs 72.1%; *P*=.02), and EFS (49.3% vs 13.0%; *P*<.001) rates for patients with a *BCR-ABL1* transcript level of 10% or less (IS) at 3 months compared with those with a *BCR-ABL1* transcript level greater than 10% (IS). Branford et al[42] also reported that molecular response at 3 months after second-line nilotinib was predictive of EFS in patients with chronic-phase CML who are resistant or intolerant to imatinib. The estimated 24-month EFS rates were 82% and 48%, respectively, for patients with *BCR-ABL1* transcript levels of 1% or less (IS) and those with *BCR-ABL1* transcript levels greater than 10% (IS) at 3 months after second-line therapy with nilotinib.

Exploratory analyses of the dasatinib dose-optimization study also suggest that achievement of *BCR-ABL1* transcript levels of 10% or less at 1 or 3 months after initiation of dasatinib, 100 mg, is associated with a higher 5-year PFS rate in patients with resistance or intolerance to imatinib.[7]

In a recent analysis of 112 patients with chronic-phase CML treated with dasatinib or nilotinib after imatinib failure, Kim et al[43] reported that *BCR-ABL1* transcript levels at 3 months provide a better prediction of long-term survival than *BCR-ABL1* transcript levels at 6 months after second-line TKI therapy.

Recommendations for Monitoring Response to TKI Therapy

The NCCN Guidelines recommend molecular monitoring with QPCR (IS) with a sensitivity of 4.5-log reduction or more from the standardized baseline (see CML-J, page 1333). The guidelines emphasize that QPCR (IS) is the preferred method for measuring *BCR-ABL1* transcript levels. The panel members agreed that the goal is for all institutions to use QPCR (IS) for molecular monitoring. If QPCR (IS) is not available, it is acceptable to use the log-reduction from the laboratory-specific standardized baseline to monitor molecular response.

Monitoring with QPCR (IS) every 3 months is recommended for all patients undergoing medical therapy, including those who meet response milestones at 3, 6, 12, and 18 months (*BCR-ABL1* transcript levels ≤10% [IS] at 3 and 6 months, CCyR at 12 and 18 months) (see CML-A, page 1332). After CCyR has been achieved, molecular monitoring is recommended every 3 months for 3 years and every 3 to 6 months thereafter.

Three-Month Evaluation

Based on the recent data demonstrating the prognostic significance of early molecular response at 3 months, the panel has included *BCR-ABL1* transcript levels of 10% or less (IS) as a response milestone at 3 months. If QPCR (IS) is not available, the guidelines have included partial cytogenetic response on bone marrow cytogenetics as a response milestone at 3 months. In the German CML IV study, failure to achieve partial cytogenetic response at 3 months and CCyR at 6 months on imatinib correlated with lower OS rates.[34]

The NCCN Guidelines recommend continuation of the same dose of TKI therapy (imatinib, dasatinib, nilotinib) and assessment of *BCR-ABL*1 transcript levels every 3 months for patients with *BCR-ABL1* transcript levels of 10% or less (IS) (see CML-2, page 1330). For patients with *BCR-ABL1* transcript levels greater than 10%, the second-line treatment options are based on the TKI they received as first-line therapy. Evaluation of patient compliance and drug interactions is recommended before changing therapy in patients with inadequate initial response.

Management of Patients With* BCR-ABL1 *Transcript Levels Greater Than 10% After First-Line Imatinib: The CML IV study group identified patients with *BCR-ABL1* transcript levels greater than 10% (IS) at 3 months as a high-risk group based on their prognosis, and recommended switching TKI therapy for this group of patients.[34] In the TIDEL-II study, an early switch to nilotinib in patients who failed to achieve molecular response milestones at 3 and 6 months after imatinib therapy was associated with higher rates of MMR and transformation-free survival.[44] The cohort of patients with *BCR-ABL1* transcript levels greater than 10% (IS) at 3 months after imatinib who were switched directly to nilotinib had higher rates of MMR and CMR at 12 months (but not at 24 months) than those who received dose-escalation of imatinib before switching to nilotinib. Long-term data from clinical studies that have evaluated dasatinib and nilotinib as second-line therapy have reported durable cytogenetic responses and high transformation-free survival rates in patients with chronic-phase CML who are resistant or intolerant to imatinib.[6–8]

The panel consensus was to recommend change of therapy to an alternate TKI (dasatinib, nilotinib, bosutinib, or ponatinib) for patients with *BCR-ABL1* transcript levels greater than 10% (IS) after initial treatment with imatinib.[34,44] Given some of the serious side effects associated with newer TKIs (eg, pulmonary arterial hypertension with dasatinib,[45] peripheral arterial occlusive disease with nilotinib,[46] cardiovascular side effects with ponatinib[47]), the NCCN Guidelines have included dose-escalation of imatinib as an option for patients who are not candidates for alternate TKI.

Management of Patients With* BCR-ABL1 *Transcript Levels Greater Than 10% After First-Line Dasatinib or Nilotinib: Early landmark analyses from DASISION and ENESTnd studies suggest that patients who do not achieve *BCR-ABL1* transcript levels of 10% or less (IS) at 3 months after first-line therapy with dasatinib or nilotinib could be considered for early intervention strategies with an alternate TKI.[36,37] In the DASISION and ENESTnd studies, 9% to 16% of patients treated with dasatinib or nilotinib failed to meet the 3-month response milestone (*BCR-ABL1* ≤10%).

Although the long-term PFS and OS rates were significantly better for patients with *BCR-ABL1* transcript levels of 10% or less at 3 months compared with those with *BCR-ABL1* transcript levels greater than 10% at 3 months after initial treatment with dasatinib and nilotinib, only a small difference was seen in OS rates between the groups (*BCR-ABL1* transcript levels ≤10% vs *BCR-ABL1* transcript levels >10%). In the DASISION study, the 3-year OS rates were 95.9% versus 85.9%, respectively, for patients with *BCR-ABL1* transcript levels of 10% or less and *BCR-ABL1* transcript levels of greater than 10% at 3 months (P=.0348).[36] In the ENESTnd study, the corresponding 4-year OS rates were 97% and 87%, respectively, for patients treated with nilotinib, 300 mg twice daily (P=.0116).[37] The difference in long-term OS rates between the groups (*BCR-ABL1* transcript levels ≤10% vs *BCR-ABL1* transcript levels >10%) was more significant in the imatinib arm in both studies (99% vs 84% in the ENESTnd study, P≤.0001; 96.0% vs 88.0% in the DASISION study, P=.0036).[36,37]

The panel members acknowledged that patients failing to achieve *BCR-ABL1* transcript levels of 10% or less (IS) at 3 months after first-line therapy with dasatinib or nilotinib are considered to be at high-risk for disease progression and should be considered for alternate treatment options or enrollment in a clinical trial. However, in the absence of clear evidence supporting an early intervention strategy, there was no uniform consensus among panel members to recommend a definite treatment option for this group of patients. Although some panel members agreed that switching to an alternate TKI may be justified to prevent disease progression for patients with *BCR-ABL1* transcript levels greater than 10% (IS) at 3 months, other panel members were not in favor of a change of therapy based on a single measurement of *BCR-ABL1* transcripts at 3 months.

Therefore, the guidelines have included participation in a clinical trial, continuation of the same dose of dasatinib or nilotinib, or switching to an alternate TKI (after evaluation of patient compliance and drug interactions) as second-line therapy options for patients with *BCR-ABL1* transcript levels greater than 10% (IS) after initial treatment with dasatinib or nilotinib.

Six-Month Evaluation

Nazha et al[48] recently reported that a 6-month molecular response to first-line TKI better discriminates patients with poor outcome. In an analysis of 489 patients with chronic-phase CML treated with first-line TKI therapy (imatinib, dasatinib, or nilotinib), the 5-year OS rate was 88% for those who did not achieve any response (MCyR or *BCR-ABL1* [IS] <10%) at 3 months. The corresponding OS rate was 100% for patients who subsequently achieved a response (MCyR or *BCR-ABL1* [IS] <10%) at 6 months compared with 79% for those who continued to have no response. Available data from clinical studies that have evaluated dasatinib or nilotinib as second-line therapy suggest that achievement of molecular response at 3-months after initiation of second-line TKI therapy is predictive of long-term outcome.[7,41,42] Therefore, 6-month response evaluation would allow for timely intervention for those patients who had been switched to an alternate TKI at 3 months.

Some investigators have suggested *BCR-ABL1* transcript levels of 1% or less as an optimal response milestone at 6 months.[33,34,36] However, the panel members believed that data are insufficient to recommend this value. In their recent report, Kim et al[43] also concluded that *BCR-ABL1* 10% (IS) cutoff

at 3 months after second-line TKI therapy provided better stratification than *BCR-ABL1* 1% (IS) cutoff; PFS (98.7% vs 73.2%; *P*=.001) and OS (100.0% vs 90.7%; *P*<.001) were significantly higher for those with *BCR-ABL1* transcript levels of less than 10% compared with those with *BCR-ABL1* transcript levels greater than 10% at 3 months.

The guidelines recommend a 6-month evaluation with QPCR (IS) for patients with *BCR-ABL1* transcript levels greater than 10% at 3 months, consistent with quarterly evaluation in all patients (see CML-3, page 1331). The panel also included *BCR-ABL1* transcript levels of 10% or less (IS) or partial cytogenetic response on bone marrow cytogenetics, if QPCR (IS) is not available, as a response milestone at 6 months. The NCCN Guidelines recommend continuation of the same dose of TKI therapy and assessment of *BCR-ABL1* transcripts every 3 months for patients with *BCR-ABL1* transcript levels of 10% or less (IS). Clinical trial or switching to an alternate TKI (after evaluation of patient compliance and drug interactions) are included as second-line therapy options for patients with *BCR-ABL1* transcript levels greater than 10% (IS).

Summary

The availability of more potent *BCR-ABL1* TKIs has significantly improved the outcomes of patients with newly diagnosed CML, and the outlook for patients with CML continues to appear promising. Monitoring molecular response with QPCR (IS) provides a more precise and less invasive assessment of response to TKI therapy. The recent updates to the NCCN Guidelines underscore the importance of regular molecular monitoring with QPCR (IS). Informing clinicians about the significance of using QPCR standardized to IS can help institutions successfully implement and integrate molecular monitoring with QPCR (IS) as an essential component in the clinical management of patients with CML.

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Posttest Questions

1. What is the optimal response after 3 months of TKI therapy for patients with chronic-phase CML according to the NCCN Guidelines?
   a. Complete hematologic response
   b. *BCR-ABL/ABL1* transcript level ≤10% (IS) or partial cytogenetic response (PCyR)
   c. Complete cytogenetic response
   d. Major molecular response
2. Which of the following options are appropriate for the management of a patient with *BCR-ABL/ABL1* transcript level of 16% (IS) after 3 months of primary treatment with dasatinib?
   a. Switch to alternate TKI
   b. Continue the same of dasatinib
   c. Evaluate for hematopoietic stem cell transplantation based on response to TKI therapy
   d. All of the above
3. Dose escalation of imatinib can be considered for selected patients with *BCR-ABL1* transcript level >10% (IS) after 3 months following imatinib therapy.
   a. True
   b. False