Chronic Myeloid Leukemia, Version 2.2024

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ABSTRACT

Chronic myeloid leukemia (CML) is defined by the presence of Philadelphia chromosome resulting from a reciprocal translocation between chromosomes 9 and 22 [t9;22] that gives rise to a BCRABL1 fusion gene. CML occurs in 3 different phases (chronic, accelerated, and blast phase) and is usually diagnosed in the chronic phase in developed countries. Tyrosine kinase inhibitor (TKI) therapy is a highly effective treatment option for patients with chronic phaseCML. The primary goal of TKI therapy in patients with chronic phaseCML is to prevent disease progression to accelerated phaseCML or blast phaseCML. Discontinuation of TKI therapy with careful monitoring is feasible in selected patients. This manuscript discusses the recommendations outlined in the NCCN Guidelines for the diagnosis and management of patients with chronic phaseCML.


NCCN GUIDELINES PANEL

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The complete NCCN Guidelines for Chronic Myeloid Leukemia are not printed in this issue of JNCCN but can be accessed online at NCCN.org.

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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 69. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

The complete and most recent version of these guidelines is available free of charge at NCCN.org.
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 2023, an estimated 8,930 people will be diagnosed with CML in the United States, and 1,310 people will die of the disease.¹

CML is defined by the presence of the Philadelphia chromosome (Ph) in a patient with a myeloproliferative neoplasm. Ph results from a reciprocal translocation between chromosomes 9 and 22 [t9;22] that gives rise to a BCR::ABL1 fusion gene.² In most patients, the chromosomal breakpoints are located in intron 13 or 14 of the BCR gene on chromosome 22 (major breakpoint cluster region; M-BCR). In the ABL1 gene they are located between the 2 alternative ABL1 exons lb and Ia, or between ABL1 exons 1 and 2.³,⁴ Irrespective of the precise ABL1 breakpoint, splicing almost invariably fuses ABL1 exon 2 with BCR exons 13 or 14, resulting in e13a2 and e14a2 transcripts that code for a protein, p210, with deregulated tyrosine kinase activity, which causes CML.

Unusual BCR::ABL1 transcripts, e1a2 encoding for p190 (involving the minor breakpoint cluster region; m-BCR), or e19a2 encoding for p230 (involving the micro breakpoint cluster region; μ-BCR), are found infrequently.³,⁴ p190 is usually produced in the setting of Ph-positive acute lymphoblastic leukemia, and p230 is associated with enhanced neutrophil differentiation. Atypical BCR::ABL1 transcripts (eg, e13a3, e14a3, e6a2) have also been detected in about 1%-2% of patients with CML. The proportion of different BCR::ABL1 transcripts and the impact of BCR::ABL1 transcript type on response to tyrosine kinase inhibitor (TKI) therapy are discussed in the section “BCR::ABL1 Transcript Variants in CML” (page 46).

CML occurs in 3 different phases (chronic, accelerated, and blast phase) and is usually diagnosed in the chronic phase in developed countries. Untreated chronic phase CML (CP-CML) will eventually progress to accelerated phase CML (AP-CML) or blast phase CML (BP-CML) in 3 to 5 years on average.⁵ Progression to AP-CML and BP-CML bridges a continuum of clinical features (ie, fever, bone pain, spleen size), cytogenetic changes, and blast count. Gene expression profiling has shown a close correlation of gene expression between AP-CML and BP-CML indicating that the bulk of the genetic changes in progression occur in the transition from CP-CML to AP-CML.⁶ The activation of the beta-catenin signaling pathway in CML granulocyte-macrophage progenitors (which enhances the self-renewal activity and leukemic potential of these cells) may be a key pathobiologic event in the evolution to BP-CML.⁷
**The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for CML discuss the clinical management of CML in all 3 phases (chronic, accelerated, or blast phase). Evaluation for diseases other than CML as outlined in the NCCN Guidelines for Myeloproliferative Neoplasms is recommended for all patients with BCR::ABL1-negative myeloproliferative neoplasm.**

**Diagnosis and Workup**

Initial evaluation should consist of a history and physical examination, including palpation of the spleen, complete blood count with differential, chemistry profile, and hepatits B panel. Bone marrow aspirate and biopsy for morphologic and cytogenetic evaluation and quantitative reverse transcription 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 page CML-1).

Bone marrow cytogenetics with a minimum of 20 metaphases is useful to detect additional chromosomal abnormalities (ACAs) in Ph-positive cells, also known as clonal cytogenetic evolution (discussed in next section). If bone marrow evaluation is not feasible, fluorescence in situ hybridization (FISH) on the bone marrow or a peripheral blood specimen with dual probes for BCR and ABLI genes can be used to confirm the diagnosis of CML. Interphase FISH is performed on peripheral blood but can be associated with a false-positive rate of 1%–5% depending on the specific probe used in the assay. 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. Double-fusion FISH is associated with low false-positive rates and can detect all variant translocations of the Ph-chromosome.

Quantitative RT-PCR (qPCR) should be done at initial workup to establish the presence of quantifiable BCR::ABL1 mRNA transcripts. qPCR, usually done on peripheral blood, is the most sensitive assay available for the measurement of BCR::ABL1 mRNA and it can detect one CML cell in a background of $100,000$ normal cells. qPCR results can be expressed in various ways, such as the ratio of BCR::ABL1 transcript numbers to the number of control gene transcripts. An International Scale (IS) has been established 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. IS has become the gold standard of expressing qPCR values. More details on monitoring with qPCR using the IS are provided in a later section.
Qualitative RT-PCR for detecting atypical \( \text{BCR::ABL1} \) transcripts should be considered if there is discordance between FISH and qPCR results. See the section on “BCR::ABL1 Transcript Variants in CML” (next section).

\( \text{BCR::ABL1} \) transcripts in the peripheral blood at very low levels (1–10 of \( 10^8 \) peripheral blood leukocytes) can be detected in approximately 30% of individuals without CML, and the incidence of this increases with age. The risk of developing CML for these individuals is extremely low, and neither continued monitoring nor therapy is indicated.18,19

**BCR::ABL1 Transcript Variants in CML**

e13a2 and e14a2 transcripts (both encoding for p210) were the most common \( \text{BCR::ABL1} \) transcript variants identified in about 39% and 62% of patients, respectively; e13a2 was more frequent in males and the proportion decreased with age in both sexes.20,21 Unusual or atypical transcripts were identified in about 2% of patients, with e1a2, e19a2, e13a3, and e14a3 being the most frequently identified transcripts.20 The incidence of these atypical transcripts was higher in females and the proportion decreased with age in both genders. The presence of e14a2 at baseline was associated with higher molecular response rates to imatinib.22–28 Although some studies have shown a trend toward better survival outcomes with e14a2 transcript,24,25 in other studies the type of transcript did not have any significant impact on long-term survival outcomes.23,26,29

Limited available data from studies that evaluated the impact of \( \text{BCR::ABL1} \) transcript variants on response to second-generation (2G) TKI therapy suggest that nilotinib may be associated with inferior molecular response rates in patients with e13a2 as well as e14a2 transcripts compared with imatinib 800 mg or dasatinib.24,30 The results of another study indicate that the difference in the amplification characteristics between the e13a2 and e14a2 transcripts can affect the measurement of residual disease, thus emphasizing the need to consider sequential measurement of minimal residual disease in addition to the achievement of response milestones at specific timepoints.31

The presence of e1a2 transcript (encoding for p190) is associated with a higher risk of disease progression, inferior cytogenetic and molecular responses to TKI therapy, and the presence of frequent mutations in epigenetic modifiers genes.32–38 In a multivariate analysis, the e1a2 transcript was also identified as an independent predictor of inferior survival outcomes.34 It is important to be aware that these data refer to the presence of dominant e1a2

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**Criteria for Response and Relapse**

<table>
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<tr>
<th>Response/Relapse</th>
<th>Definition</th>
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| **Complete hematologic response (CHR)**<sup>1</sup> | - 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 resolution of palpable splenomegaly |
| **Cyto genetic response**<sup>2,3,4</sup> | - Complete cytogenetic response (CCyR): No Ph-positive metaphases  
- Major cytogenetic response (MCyR): 0%–35% Ph-positive metaphases  
- Partial cytogenetic response (PCyR): 1%–35% Ph-positive metaphases  
- Minor cytogenetic response: >35% Ph-positive metaphases |
| **Molecular response**<sup>5,6,7</sup> | - Early molecular response (EMR): \( \text{BCR::ABL1} (\text{IS}) \leq 10\% \) at 3 and 6 months  
- Major molecular response (MMR): \( \text{BCR::ABL1} (\text{IS}) \leq 0.1\% \) or ≥3-log reduction in \( \text{BCR::ABL1} \) transcripts from the standardized baseline, if qPCR (IS) is not available  
- Deep molecular response (DMR): \( \text{MR4.0}: \text{BCR::ABL1} (\text{IS}) \leq 0.01\% \) or \( \text{MR4.5}: \text{BCR::ABL1} (\text{IS}) \leq 0.0032\% \) |

**Relapse**

- Any sign of loss of hematologic response  
- Any sign of loss of CCyR or its molecular response correlate (MR2.0: \( \text{BCR::ABL1} (\text{IS}) \leq 1\% \)) – defined as an increase in \( \text{BCR::ABL1} \) transcript to >1%  
- 1-log increase in \( \text{BCR::ABL1} \) transcript levels with loss of MMR<sup>8</sup>

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2. A minimum of 20 metaphases should be examined.  
4. CCyR correlates with BCR::ABL1 (IS) ≤1% (MR2.0).
8. The loss of MMR in the presence of a CCyR does not necessarily indicate inadequate response to treatment.
transcript, not to the presence of low-level e1a2 transcripts in patients with dominant e1a2 or e1a2 transcripts. The presence of e19a2 transcript (encoding for p230) is associated with lower rates of cytogenetic and molecular response to TKIs and inferior survival outcomes, despite previous reports of an indolent disease course in the pre-TKI era.\textsuperscript{35,36,39} Referral to centers with expertise in the management of CML is recommended.

Qualitative RT-PCR, nested RT-PCR, or Sanger sequencing are useful for identifying atypical \textit{BCR::ABL1} transcripts.\textsuperscript{40,41} qPCR using log-reduction from standardized baseline can be used to monitor e1a2 transcripts, and monitoring e19a2 transcripts is usually performed using qualitative RT-PCR or nested RT-PCR. However, there are no standardized qPCR assays for monitoring molecular response to TKI therapy in patients with atypical \textit{BCR::ABL1} transcripts.\textsuperscript{52,53} The utility of multiplex PCR assays and patient-specific genomic DNA quantitative PCR assays for monitoring atypical \textit{BCR::ABL1} transcripts has been demonstrated in some reports.\textsuperscript{44–48}

**Clonal Cytogenetic Evolution**

The prognostic significance of ACAs in Ph-positive cells is related to the specific chromosomal abnormality and other features of the accelerated phase.\textsuperscript{8–12} The presence of “major route” ACAs in Ph-positive cells (trisomy 8, iso-chromosome 17q, second Ph, trisomy 19, and chromosome 3 abnormalities) at diagnosis may have a negative prognostic impact on survival and disease progression to accelerated or blast phase.\textsuperscript{49–52} However, in another analysis that evaluated the outcomes of patients with CP-CML (with or without ACAs) treated with TKI therapy in prospective studies, the presence of ACAs in Ph-positive cells at the time of diagnosis was not associated with worse prognosis.\textsuperscript{53} Survival outcomes were not significantly different among patients with ACAs in Ph-positive cells based on TKI therapy (imatinib vs 2G TKIs) or imatinib dose (400 vs 800 mg). It remains uncertain if 2G TKIs or high-dose imatinib would be more beneficial for patients with ACAs in Ph-positive cells. Patients with ACAs in Ph-positive cells at diagnosis should be monitored carefully for evidence of resistance to TKI therapy, and follow-up metaphase karyotype analysis should be performed if resistance is evident.

Clonal cytogenetic evolution in Ph-negative cells has also been reported in a small subset of patients treated with TKI therapy.\textsuperscript{54,55} The most common abnormalities include trisomy 8 and loss of the Y chromosome. Previous work suggested that the overall prognosis of Ph-negative clonal evolution is good and depends on response to
imatinib therapy. However, the presence of chromosome abnormalities other than loss of the Y chromosome has been associated with decreased survival in patients with CP-CML treated with various TKIs, suggesting that closer follow-up is indicated. Progression to myelodysplastic syndromes and acute myeloid leukemia have been reported in patients with monosomy 7 (del 7q).

**Additional Evaluation**

**CP-CML: Risk Stratification**

Sokal and Hasford (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. The Sokal score is based on the patient’s age, spleen size on clinical examination, platelet count, and percentage of blasts in the peripheral blood. The Euro score includes eosinophils and basophils in the peripheral blood in addition to the same clinical variables used in the Sokal score.

The European Treatment and Outcome Study long-term survival (ELTS) score is based on the same variables as the Sokal score and provides the most useful predictor of CML-related death in patients treated with first-line imatinib. The ELTS score has been validated in a cohort of 1,120 patients with CP-CML treated with imatinib in 6 clinical trials. Higher age, higher peripheral blasts, bigger spleen, and low platelet counts were significantly associated with increased probabilities of dying of CML. Patients in the intermediate- and high-risk groups had significantly higher probabilities of dying of CML than those in the low-risk group, and the probabilities were also significantly different between the intermediate- and high-risk groups. Unlike other scoring systems, the ELTS score is focused on CML-specific overall survival (OS). This is important, because many patients with CML die of non-CML causes, reflecting the efficacy of TKI therapy.

**Myeloid Mutational Analysis**

Mutations in epigenetic modifier genes (eg, ASXL1, IKZF1, BCOR, TET1/2, IDH1/2, DNMT3A/3B, EZH2) have been described in patients with CML, and the presence of epigenetic gene mutations at diagnosis has also been associated with lower rates of molecular/cytogenetic responses and lower rates of progression-free survival (PFS)/event-free survival (EFS). Mutations in the ASXL1 gene are the most commonly described secondary alterations in patients with CML.
TREATMENT RECOMMENDATIONS BASED ON BCR::ABL1 MUTATION PROFILE

- Patients with disease resistant to primary treatment with imatinib should be treated with a 2G TKI (bosutinib, dasatinib, or nilotinib) in the second-line setting, taking into account BCR::ABL1 kinase domain mutation status.
- Patients with disease resistant to primary treatment with bosutinib, dasatinib, or nilotinib can be treated with an alternate TKI (other than imatinib), taking into account BCR::ABL1 kinase domain mutation status. Subsequent therapy with an alternate 2G TKI would be effective only in patients with identifiable BCR::ABL1 mutations that confer resistance to TKI therapy. Ponatinib is preferred for patients with no identifiable BCR::ABL1 mutations.
- Ponatinib is the preferred treatment option for patients with a T315I mutation in any phase. It is also a treatment option for CP-CML with resistance or intolerance to at least two prior TKIs or for patients with AP-CML or BP-CML for whom no other TKI is indicated.
- Ascalimib is a treatment option for CP-CML patients with the T315I mutation and/or CP-CML with resistance or intolerance to at least two prior TKIs.
- BCR::ABL1 kinase domain mutations that should NOT be treated with ascalimib, bosutinib, dasatinib, or nilotinib are listed in the table below.

<table>
<thead>
<tr>
<th>THERAPY</th>
<th>CONTRAINDIATED MUTATIONS†</th>
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<tbody>
<tr>
<td>Ascalimib</td>
<td>A337T, P465S, or F359V/Ic</td>
</tr>
<tr>
<td>Bosutinib</td>
<td>T315I, V299L, G250E, or F317Laa</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>T315I/A, F317L/Ic, or V299L</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>T315I, Y253H, E255K/V, or F359V/Ci</td>
</tr>
<tr>
<td>Ponatinib, Omacetaxine,bb or allogeneic HCT</td>
<td>Nonebbc</td>
</tr>
</tbody>
</table>

† Mutations contraindicated for imatinib are too numerous to include. BCR::ABL359I has been reported in patients with disease not responding to imatinib; however, there are not enough data to confirm that 2G TKIs could overcome this resistance (Berman E, et al. Leuk Res 2018;49:158-112).

aa Bosutinib has minimal activity against F317L mutation. Nilotinib may be preferred over bosutinib in patients with F317L mutation.

bb Omacetaxine is a treatment option for patients with chronic or AP-CML that is resistant and/or intolerant to two or more TKIs.

bbc There are compound mutations (defined as harboring 2 mutations in the same BCR::ABL1 allele) that can cause resistance to ponatinib, but those are uncommon following treatment with bosutinib, dasatinib, or nilotinib.

Next-generation sequencing (NGS) allows for the detection of low-level BCR::ABL1 kinase domain mutations and mutations in genes other than BCR::ABL1 that may confer resistance to TKIs or portend disease progression.89-90 In a prospective, multicenter study (NEXT-in-CML) that assessed the feasibility of NGS to detect low-level mutations in 236 consecutive patients with CML and an inadequate response to TKI therapy, NGS was more effective than conventional Sanger sequencing in the detection of low-level mutations.90 Prospective monitoring of mutation kinetics demonstrated that TKI-resistant low-level mutations are invariably selected if the patients are not switched to another TKI or if they are switched to an inappropriate TKI or TKI dose.90 NGS with myeloid mutation panel should be considered for patients with no identifiable BCR::ABL1 mutations.

Testing for BCR::ABL1–independent mutations using NGS with myeloid mutation panel may be useful for patients with CP-CML who do not experience optimal response milestones due to the presence of cytopenias, for those patients with TKI-resistant disease and for patients with advanced phase–CML.80,83 However, there are very limited data on the impact of BCR::ABL1–independent mutations in patients with newly diagnosed CP-CML.

CP-CML and are an independent predictor of inferior molecular/cytogenetic responses and EFS rates after TKI therapy (including 2G-TKI therapy).86,87 In an analysis of 222 patients with CP-CML (prospectively enrolled in the CML-V study), an ASXL1 mutation was detected in 20 patients at the time of diagnosis. All patients had received nilotinib-based TKI therapy. The probability of experiencing major molecular response (MMR) or better at 12 months was significantly lower for patients with an ASXL1 mutation (55%; P = .0036) compared with 85% for patients with no mutations and 82% for patients with other non-ASXL1 mutations.87 However, in another study of 124 patients with newly diagnosed CP-CML, mutations in epigenetic modifier genes (including ASXL1 mutation) were predictive of response rates only in patients treated with imatinib but did not have any impact on the outcomes in patients treated with 2G TKIs.81

IKZF1 exon deletions and mutations in ASXL1, RUNX1, and BCOR genes were the most frequently described secondary alterations in advanced phase–CML, while IDH1/2 mutations were detected at a markedly lower frequency.74-79,82,84,85 IKZF1, RUNX1, and DNMT3A alterations were identified as important markers of disease progression to advanced phase–CML and risk of relapse after discontinuation of TKI.73-75,79,88
Additionally, BCR::ABL1–independent gene mutations have also been frequently described in Ph-negative clones.91 The impact of mutations is also variable depending on whether they occur in Ph-positive or Ph-negative clones.

Myeloid mutational analysis using NGS can be considered for patients with CP-CML and advanced phase–CML at diagnosis. This is a category 2B recommendation for patients with newly diagnosed CP-CML.

Management of CP-CML

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 S1 in the Supplementary material (available online with this article).92–96 In summary, (1) all TKIs recommended are highly effective in newly diagnosed CP-CML, with long-term OS expected to be similar to that of aged-matched controls; (2) 2G TKIs, compared with imatinib, generally result in faster cytogenetic and molecular responses, with less progression to advanced phase–CML; and (3) as of yet, in randomized clinical trials, there are no significant differences in OS in patients who start imatinib versus a 2G TKI (dasatinib, nilotinib, and bosutinib).

The selection of first-line TKI therapy (bosutinib, dasatinib, imatinib, or nilotinib) in a given patient should be based on the risk score, toxicity profile, patient’s age, ability to tolerate therapy, and the presence of comorbid conditions (see page CML-2). Allogeneic hematopoietic cell transplantation (HCT) is no longer recommended as a first-line treatment of patients with CP-CML.

Clinical Considerations for the Selection of First-Line Therapy

Risk Stratification

Imatinib (400 mg daily) and 2G TKIs (bosutinib [400 mg daily], dasatinib [100 mg once daily], and nilotinib [300 mg twice daily]) are all appropriate options for first-line TKI therapy for patients with CP-CML across all risk scores.92–96

The generic version of innovator drug (imatinib) has been shown to be noninferior to innovator drug (imatinib) in terms of efficacy with an acceptable toxicity profile.97–99 A US FDA-approved generic version is an appropriate substitute for an innovator drug (imatinib).100 Innovator and generic drugs approved by the regulatory authorities based on pharmacokinetic equivalence can be used interchangeably.
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, despite improved early responses (see Supplementary Table S2). Imatinib 800 mg was also associated with higher rates of dose interruption, reduction, or discontinuation due to grade 3 or 4 adverse events in all of the studies. However, patients who could tolerate the higher dose of imatinib achieved higher response rates than those receiving standard-dose imatinib. Imatinib 800 mg is not recommended as initial therapy, given the data showing superior efficacy of 2G TKIs in newly diagnosed CP-CML.

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. 2G TKIs are associated with a lower risk of disease progression than imatinib and are preferred for patients with an intermediate- or high-risk Sokal or Euro score; 2G TKIs also result in quicker molecular responses and higher rates of MMR (=0.1 BCR::ABL1 IS) and deep molecular response (DMR) (MR4.0 \(=0.01\%\) BCR::ABL1 IS) or MR4.5 \(=0.0032\%\) BCR::ABL1 IS) in patients with CP-CML across all risk scores (see Supplementary Table S3), which may facilitate subsequent discontinuation of TKI therapy in selected patients. Therefore, 2G TKIs may be preferred over imatinib for younger patients, particularly females since the achievement of a deep and rapid molecular response may allow for eventual safe interruption of TKI therapy for fertility purposes. Imatinib may be preferred for older patients with comorbidities, especially cardiovascular comorbidities.

Toxicity Profile

All the TKIs are generally well tolerated. Since bosutinib, dasatinib, and nilotinib have very good efficacy in the upfront setting, differences in their potential toxicity profiles may inform the selection of a specific TKI as initial therapy. Adverse events of first-line TKI therapy in patients with CP-CML reported in phase III randomized studies are discussed below and are summarized in Supplementary Table S4.

Nilotinib or bosutinib may be preferred for patients with a history of lung disease or deemed to be at risk for developing pleural effusions. Dasatinib or bosutinib may be preferred in patients with a history of arrhythmias, cardiovascular disease, pancreatitis, or hyperglycemia.
Bosutinib
In the BFORE study, diarrhea, increased alanine aminotransferase, and aspartate aminotransferase 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 due to drug-related adverse events occurred in 14% of patients in the bosutinib group compared with 11% in the imatinib group. Increased alanine aminotransferase (5%) and increased aspartate aminotransferase (2%) were the most common adverse events leading to discontinuation of bosutinib. However, there were no hepatotoxicity-related fatalities during the study.

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 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 also more common with dasatinib (28% in the DASISION study compared with <1% with imatinib and 33% in a dose optimization study) and age has been identified as a significant risk factor for the development of pleural effusion. 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, with hypertension, and receiving dasatinib 70 mg twice daily are at increased risk of developing pleural effusions. Close monitoring and timely intervention are necessary for patients at risk for developing pleural effusions.

Largely reversible pulmonary arterial hypertension has been reported as a rare but serious side effect of dasatinib. In the DASISION study, pulmonary hypertension was reported in 5% of patients treated with dasatinib compared with <1% 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.

Imatinib
Chronic fatigue (often correlated with musculoskeletal pain and muscular cramps) is a major factor in reducing quality of life in patients who take imatinib. Hypophosphatemia and decrease in bone mineral density have 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. Reversible renal dysfunction with prolonged use of imatinib has also been reported.

Nilotinib
In the ENESTnd study, rates of nonhematologic adverse events such as nausea, diarrhea, vomiting, muscle spasm, and peripheral edema of any grade were higher for patients receiving nilotinib. Conversely, rash and headache were more common with nilotinib. Grade 3 or 4 neutropenia was more frequently observed in the imatinib group, whereas thrombocytopenia and anemia were similar in both groups. Electrolyte abnormalities and elevations in lipase, glucose, and bilirubin were more frequent with nilotinib than with imatinib. Patients with a previous history of pancreatitis may be at greater risk of elevated serum lipase. The overall incidences of adverse events leading to discontinuation of therapy were comparable in the nilotinib 300 mg twice-daily 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 starting 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 initiation of nilotinib, and periodically thereafter, as well as after any dose adjustments.

Nilotinib is associated with an increased risk of ischemic heart disease, ischemic cerebrovascular disease and peripheral arterial occlusive disease. The 10-year follow-up data from ENESTnd study showed a higher rate of cardiovascular events with nilotinib (17% and 24%, respectively for nilotinib 300 mg twice daily and nilotinib 400 mg twice daily) versus imatinib (4%). Evaluation for pre-existing cardiovascular risk factors before starting treatment with nilotinib and close monitoring for any cardiovascular events during treatment with nilotinib is recommended for all patients. Patients with cardiovascular risk factors should be referred to a cardiologist.

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 assessments (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 46).

Conventional bone marrow cytogenetics is the standard method for monitoring cytogenetic responses, and many clinical trial response analyses have been based on conventional bone marrow cytogenetics. With the advent of qPCR, bone marrow cytogenetic analyses to assess response are rarely performed. If conventional bone marrow cytogenetics yield no analyzable metaphases, cytogenetic response can be evaluated by FISH, preferably with a dual color probe to minimize false-positive rates. FISH and cytogenetic results are correlated, but are not superimposable. Although some investigators have reported that interphase FISH can be used to monitor complete cytogenetic response (CCyR), inadequate response to TKI therapy has not been defined on the basis of FISH analysis. The panel feels that FISH has been inadequately studied for monitoring response to TKI therapy and 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, since BCR::ABL1 transcripts typically remain detectable after CCyR is achieved. A major advantage of qPCR is the strong correlation between the results obtained from the peripheral blood and the bone marrow, allowing for molecular monitoring without bone marrow aspirations.

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 with untreated CML enrolled in the IRIS trial) is set to 100%. Molecular response is expressed as log-reduction from 100%. For example, a 2-log reduction or greater (≥1% BCR::ABL1 IS; MR2.0) generally correlates with CCyR and a ≥3-log reduction (≥0.1% BCR::ABL1 IS) is referred to as MMR or MR3.0. DMR is defined by the assay’s level of sensitivity (≤0.01% BCR::ABL1 [IS], MR4.0; ≤0.0032% BCR::ABL1 [IS], MR4.5). The sensitivity of a qPCR assay depends not only on the performance of the assay, but also on the quality of a given sample.

As such, the term complete molecular response to denote undetectable BCR::ABL1 transcripts (a negative qPCR test) should be abandoned, as it may refer to very different levels of response, dependent on the quality of the sample and sensitivity of the test. 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.

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 to measure BCR::ABL1 transcripts (See CML-E, page 47). In patients with prolonged myelosuppression who may not be in complete hematologic response (CHR) due to persistent cytopenias or an unexplained drop in blood counts during therapy, bone marrow cytogenetics is indicated to confirm response to TKI therapy and exclude other pathology, such as myelodysplastic syndrome or the presence of chromosomal abnormalities other than Ph. Given the risk for transient myelosuppression that can occur during early disease responses, TKI therapy should not be held while bone marrow evaluation is pending.

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.

Frequent molecular monitoring with qPCR (IS) can help to identify nonadherence to TKI therapy early in the treatment course. Since adherence to TKI therapy is associated with better clinical outcomes, frequent molecular monitoring is essential if there are concerns about the patient’s adherence to TKI therapy. 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. Molecular monitoring of response to TKI therapy more frequently than every 3 months is not presently recommended.

Prognostic Significance of Cytogenetic and Molecular Response

Early molecular response (EMR; ≤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 (see Supplementary Table S5). Some reports suggest that EMR at 3 months has a superior prognostic value and supports 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 transcripts 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 (eg, 11%–15% at 3 months), it is reasonable to reassess at 6 months before considering major changes to the treatment strategy.

Some 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). 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 or less was a significant predictor of MMR by 12 months and DMR (MR4.0; IS) by 18 months.

Achievement of CCyR or ≤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 experiencing 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 2G TKIs, the 3-year EFS 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.

MMR (≤0.1% BCR::ABL1 IS) as a predictor of PFS and OS 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 general conclusion from these studies is that the achievement of MMR is associated with durable long-term cytogenetic remission and lower rate of disease progression, but MMR is not a significant predictor of superior OS in patients with a stable CCyR. Importantly, with longer follow-up, CCyR becomes an ever-stronger indicator of MMR, reducing the added prognostic value of MMR. Although the CML IV study showed that MR4.5 (≤0.0032% BCR::ABL1 IS) at 4 years was associated with a significantly higher OS (independent of therapy) than MR2.0 (≤1% BCR::ABL1 IS, which corresponds to CCyR), this study demonstrated no significant differences in OS in patients who experienced MMR (≤0.1% BCR::ABL1 IS) and those who experienced MR2.0 (≤1% BCR::ABL1 IS).

The absence of MMR in the presence of a CCyR is therefore not considered as an inadequate response to treatment. Although some investigators have reported that dose escalation of imatinib might benefit patients in CCyR with no MMR, no randomized studies are available to show that a change of therapy would improve survival, PFS, or EFS in this group of patients. However, the achievement of MMR (≤0.1% BCR::ABL1 IS) at 12 months is associated with a very low probability of subsequent loss of response and a high likelihood of experiencing a subsequent DMR (MR4.0; ≤0.01% BCR::ABL1 IS), which may facilitate discontinuation of TKI therapy.

In view of the ongoing evolution of treatment goals (OS vs treatment-free remission [TFR]), expert panels have emphasized the importance of joint decision-making between patient and provider, particularly in ambiguous situations.

**Response Milestones After First-Line TKI Therapy**

The most important goals of TKI therapy are to prevent disease progression to AP-CML or BP-CML and to achieve either MR2.0 (≤1% BCR::ABL1 IS, which corresponds to CCyR) or MMR (≤0.1% BCR::ABL1 IS) within 12 months after first-line TKI therapy. The guidelines emphasize that achievement of response milestones must be interpreted within the clinical context, before making drastic changes to the treatment strategy, especially in ambiguous situations.

The panel has included ≤10% BCR::ABL1 IS at 3 and 6 months after initiation of first-line TKI therapy as a response milestone, because the achievement of EMR after first-line TKI therapy is an effective prognosticator of favorable long-term PFS (see CML-3, page 48). Achievement of >0.1%–1% BCR::ABL1 IS (≤1% BCR::ABL1 IS, which correlates with CCyR) is considered the optimal response milestone at 12 months if the goal of therapy in an individual patient is long-term survival, whereas the achievement of MMR (≤0.1% BCR::ABL1 IS) at 12 months should be considered as the optimal response milestone if the treatment goal in an individual patient is TFR. 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 judgment should be used, considering problems with adherence (which can be common given drug toxicity at the start of therapy), rate of decline in BCR::ABL1 (the faster, the better), and how far from the cutoff the BCR::ABL1 value falls. Inability to reach ≤10% BCR::ABL1 IS at 3 months or ≤1% BCR::ABL1 IS at 12 months is associated with a higher risk for disease progression. Patients with >10% BCR::ABL1 at 3 months or >1% BCR::ABL1 at 12 months can switch to alternate TKI or continue the same dose of TKI (bosutinib, dasatinib, imatinib, or nilotinib) for another 3 months. BCR::ABL1 mutational analysis and evaluation for allogeneic HCT should be considered. Bone marrow cytogenetics should be
considered to assess for major cytogenetic response (MCyR) at 3 months or CCyR at 12 months.

In patients with >0.1%–1% BCR::ABL1 IS at 12 months, shared decision-making is recommended depending on the goal of therapy in individual patients (longer-term survival vs TFR). As discussed previously, although not associated with increased OS, MMR at 12 months is associated with a lower rate of disease progression and a higher likelihood of achieving DMR, which is a prerequisite for TFR. Switching to a 2G TKI from imatinib might be considered to increase the probability of achieving MMR (≤0.1% BCR::ABL1 IS) at 12 months. However, there is a possibility that a switch may be associated with increased toxicity. Referral to specialized CML centers and/or enrollment in a clinical trial should be considered.

Patients with >10% BCR::ABL1 IS at 6 and 12 months are considered to have TKI-resistant disease. Evaluation for allogeneic HCT (ie, a discussion with a transplant specialist, which might include HLA testing) is recommended. Bone marrow cytogenetic analysis to assess ACAs should be considered. Alternative treatment options should be considered as described subsequently.

**Second-Line Therapy**

Dose escalation of imatinib up to 800 mg daily has been shown to overcome some cases of primary resistance and is particularly effective for cytogenetic relapse in patients who had experienced cytogenetic response with imatinib 400 mg daily, although the duration of responses has typically been short. However, it is unlikely to benefit patients who do not experience hematologic response or those who never had a cytogenetic response with imatinib 400 mg daily. In patients with >10% BCR::ABL1 IS at 3 months after imatinib 400 mg, switching to nilotinib or dasatinib has been shown to result in higher rates of MMR at 12 months than dose escalation of imatinib. Although dose escalation of imatinib has been shown to be beneficial for patients in CCyR without MMR, no randomized studies have shown that a change of therapy would improve PFS or EFS in this group of patients.

Dasatinib, nilotinib, and bosutinib, which are more potent than imatinib in vitro and retain activity against many of the imatinib-resistant BCR::ABL1 kinase domain mutants except T315I, are effective treatment options for patients who are intolerant to imatinib or CP-CML that is resistant to imatinib. Bosutinib also has shown activity in patients with CP-CML that is resistant to multiple TKIs (imatinib, dasatinib, and nilotinib). Ponatinib and asciminib (specifically targeting the ABL myristoyl pocket inhibitor) are active against most of the resistant BCR::ABL1 kinase domain mutants including T315I.

Long-term efficacy data from clinical trials on second-line and subsequent TKI therapy for CP-CML are summarized in Supplementary Table S6.

Ponatinib was initially approved as a treatment option for patients with a T315I mutation and/or for patients for whom no other TKI is indicated based on the results of the PACE trial. The recommended initial dose of ponatinib was 45 mg once daily. The high-dose intensity of ponatinib was associated with increased risk of arterial occlusive events (AOE) and the incidence of cardiovascular adverse events was highest among patients with pre-existing cardiovascular risk factors. In the PACE trial, serious AOE (cardiovascular, cerebrovascular, and peripheral vascular) and venous thromboembolic events occurred in 31% and 6% of patients, respectively. Cardiovascular, cerebrovascular, and peripheral AOE were reported in 16%, 13%, and 14% of patients, respectively.

In the OPTIC trial that evaluated the safety and efficacy of response-adjusted dosing regimens, patients were randomized to ponatinib starting doses of 45 mg, 30 mg, and 15 mg, with dose reduction to 15 mg with experience of ≤1% BCR::ABL1 (IS) in the 45 mg and 30 mg cohorts. Ponatinib was effective at all 3 dose levels (45 mg, 30 mg, and 15 mg) and the maximum benefit was observed with 45 mg. After a median follow-up of 32 months, BCR::ABL1 (IS) ≤1% at 12 months was achieved in 44% of patients in the 45 mg cohort compared with 29% and 23% in the 30 mg and 15 mg cohorts, respectively. After response-based dose reduction to 15 mg, responses were maintained in 73% and 79% of patients in the 45 mg and 30 mg cohorts, respectively. The rate of any AOE reported in the OPTIC trial (10% in the 45 mg cohort; 5% and 3% in the 30 mg and 15 mg cohorts, respectively) was lower than that reported for ponatinib 45 mg in the PACE trial. Based on the results of the OPTIC trial, the FDA has approved a response-adjusted dosing regimen for ponatinib (starting dose of 45 mg once daily with a reduction to 15 mg on achievement of BCR::ABL1 (IS) ≤1%) for patients with CP-CML with resistance or intolerance to ≥2 prior kinase inhibitors.

Cardiovascular risk factors (eg, diabetes mellitus, hypertension, hyperlipidemia, smoking, estrogen use) should be identified and controlled before starting ponatinib. Patients should be monitored for high blood pressure, evidence of arterial occlusive or thromboembolic events, and reduced cardiac function. Ponatinib should be interrupted or stopped immediately for vascular occlusion and for new or worsening heart failure. Patients with cardiovascular risk factors should be referred to a cardiologist. Asciminib is approved for patients with CP-CML having the T315I mutation and/or CP-CML with resistance or intolerance to ≥2 prior TKIs.

In the phase III randomized study (ASCEMBL), asciminib 40 mg twice daily achieved higher molecular response rates (MMR, MR4.0, and MR4.5) than bosutinib 500 mg once daily in patients with CP-CML previously treated with ≥2 prior TKIs. The incidence of adverse
events leading to treatment discontinuation was also lower with asciminib (6% vs 21%). Gastrointestinal toxicities (diarrhea, nausea, and vomiting) and biochemical abnormalities (increased alanine aminotransferase and aspartate aminotransferase levels) were notably higher with bosutinib. AOE were reported in 3% and 1% of patients treated with asciminib and bosutinib, respectively. Patients with a history of cardiovascular risk factors or cardiovascular signs and symptoms should be carefully monitored, and appropriate treatment should be started as clinically indicated. The recommended initial dose of asciminib is 80 mg once daily or 40 mg twice daily in patients without a T315I mutation and 200 mg twice daily for patients with a T315I mutation. In the phase I study, most patients with a T315I mutation experiencing CCyR and MMR had received >150 mg twice-daily asciminib.

Omacetaxine is a treatment option for patients with CP-CML resistant or intolerant to ≥2 TKIs including those with a T315I mutation. Omacetaxine resulted in MCyR, CCyR, and MMR rates of 23%, 16%, and 17%, respectively. The T315I clone declined to below detection limits in 61% of patients with CP-CML resistant to prior TKI therapy and the T315I mutation (CML 202 study; n=62). The median PFS was 8 months and the median OS had not yet been reached. In the cohort of patients with CP-CML resistant or intolerant to ≥2 TKIs (CML 203 study; n=46), the MCyR and CCyR rates were 22% and 4%, respectively. The median PFS and OS were 7 months and 30 months, respectively. The response rates and survival outcomes, however, were substantially lower than those observed with ponatinib in the PACE trial. 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 TKI Therapy

Switching to a 2G TKI (based on the BCR::ABL1 kinase domain mutation status) is recommended for patients with disease that is resistant to imatinib 400 mg daily. Patients with disease that is resistant to bosutinib, dasatinib, or nilotinib could be switched to an alternate 2G TKI. However, there is no clear evidence to support that switching to alternate 2G TKI therapy would improve long-term clinical outcome for this group of patients. Subsequent therapy with an alternate 2G TKI is expected to be effective only in patients with identifiable BCR::ABL1 mutations that confer resistance to TKI therapy. Ponatinib is the preferred treatment option for patients with a T315I mutation in any phase. Ponatinib is also preferred for patients with no identifiable BCR::ABL1 mutations. Evaluation of allogeneic HCT or enrollment in a clinical trial should be considered for this group of patients.

EMR (≤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 (see Supplementary Table S7). 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.

BCR::ABL1 kinase domain mutation analysis (see later section), evaluation of drug interactions, and compliance to therapy are recommended before the start of second-line TKI therapy. As discussed earlier, myeloid mutational analysis using NGS to identify BCR::ABL1–independent mutations may also be useful for patients with CP-CML who do not experience optimal response milestones due to the presence of cytopenias and for those with TKI resistant disease.

Drug Interactions

All TKIs are metabolized in the liver by cytochrome P450 (CYP) enzymes, and concomitant use of drugs that induce or inhibit CYP3A4 or CYP3A5 enzymes may alter the therapeutic effect of TKIs. 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. Asciminib is also a CYP2C9 inhibitor and concomitant use of asciminib increases the plasma concentration of other drugs that are CYP2C9 substrates.

Concomitant use of drugs 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.

Adherence to Therapy

Treatment interruptions and nonadherence to therapy may lead to undesirable clinical outcomes. In the ADAGIO study, nonadherence to imatinib was associated with poorer response. Patients with suboptimal response missed significantly more imatinib doses (23%) than did those with optimal response (7%). Adherence to imatinib therapy has been identified as the only independent predictor for achieving complete molecular response on standard-dose imatinib. The 6-year probability of experiencing complete molecular response was significantly higher for patients with ≥90% adherence rate (44% compared with 0% for patients with ≤90% adherence rate; P=.002). Poor adherence to imatinib therapy
has also been identified as the most important factor contributing to cytogenetic relapse and inadequate response to imatinib.\textsuperscript{176} Patients with adherence of 85% or less had a higher probability of losing CCyR at 2 years than those with adherence of greater than 85% (27% and 2%, respectively). Poor adherence to therapy has also been reported in patients receiving dasatinib and nilotinib following inadequate response to imatinib.\textsuperscript{177,178}

Patient education on adherence to therapy and close monitoring of each 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.\textsuperscript{179} 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.\textsuperscript{180} Switching to an alternate TKI because of intolerance is appropriate for patients with disease responding to TKI therapy and it might be beneficial for selected patients with acute grade 3–4 nonhematologic toxicities or in those with chronic, low-grade nonhematologic toxicities that are not manageable with adequate supportive care measures.\textsuperscript{181,182}

**Resistance to TKI Therapy**

Aberrant expressions of drug transporters\textsuperscript{183–185} and plasma protein binding of TKIs\textsuperscript{186–188} could contribute to primary resistance by altering the intracellular and plasma concentration of TKIs.

Pretreatment levels of organic cation transporter 1 (OCT1) have been reported as the most powerful predictor of response to imatinib.\textsuperscript{189} Conversely, cellular uptake of dasatinib or nilotinib seems to be independent of OCT1 expression, suggesting that patients with low OCT1 expression might have better outcomes with dasatinib or nilotinib than with imatinib.\textsuperscript{190–193}

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, and assays that measure plasma levels of imatinib are not widely available.

**BCR::ABL1 Kinase Domain Mutation Analysis**

Point mutations in the $\textit{BCR::ABL1}$ kinase domain are a frequent mechanism of secondary resistance to TKI therapy and are associated with poor prognosis and a higher risk of disease progression.\textsuperscript{194–196} E255K/V, F359C/V, Y253H, and T315I mutants are most commonly associated with disease progression and relapse.\textsuperscript{200–201} Among the $\textit{BCR::ABL1}$ kinase domain mutations, T315I confers complete resistance to imatinib, dasatinib, nilotinib, and bosutinib.\textsuperscript{202,203} The T315A, F317L/I/V/C, and V299L mutants are resistant to dasatinib and the E255K/V, F359V/C, and Y253H mutants are resistant to nilotinib.\textsuperscript{200,204–206} The G250E and V299L mutants are resistant to bosutinib.\textsuperscript{198}

Bosutinib and dasatinib have demonstrated activity in patients with $\textit{BCR::ABL1}$ mutants resistant to nilotinib (Y253H, E255K/V, and F359I/V/C),\textsuperscript{158} bosutinib has minimal activity against the F317L mutation (which is resistant to dasatinib) and nilotinib may be preferred over bosutinib in patients with the F317L mutation.\textsuperscript{200,205,207}

Ponatinib is active against $\textit{BCR::ABL1}$ mutants resistant to dasatinib or nilotinib, including E255V, Y253H, F359V, and T315I.\textsuperscript{160} There are not enough data available regarding the impact of mutations on the efficacy of asciminib because of the heterogeneity of reported mutations and low patient numbers in the ASCEmbl trial.\textsuperscript{163} Patients with detectable bosutinib-resistant $\textit{BCR::ABL1}$ mutations (T315I or V299L) were ineligible to participate in this trial.\textsuperscript{161} In addition to T315I, asciminib has been reported to be active against select $\textit{BCR::ABL1}$ mutants resistant to bosutinib, dasatinib, or nilotinib (G250E, Y253H, E255V). However, F359V/I/C mutations are insensitive to asciminib.\textsuperscript{708} Although new myristoyl-pocket mutations have been detected during asciminib treatment, there is insufficient data to determine their significance.

$\textit{BCR::ABL1}$ compound mutations (variants containing ≥2 mutations within the same $\textit{BCR::ABL1}$ allele that presumably arise sequentially) confer different levels of resistance to TKI therapy, and compound mutants involving T315I confer the highest level of resistance to all TKIs, including ponatinib.\textsuperscript{209,210} In another study that used NGS to detect low-level and $\textit{BCR::ABL1}$ compound mutations in 267 patients with heavily pretreated CP-CML from the PACE trial, no compound mutation was identified that consistently conferred resistance to ponatinib, suggesting that such compound mutations are uncommon following treatment with bosutinib, dasatinib, or nilotinib for CP-CML.\textsuperscript{211}

$\textit{BCR::ABL1}$\textsuperscript{35INS} has been associated with resistance to imatinib.\textsuperscript{212,213} In one study, $\textit{BCR::ABL1}$\textsuperscript{35INS} was detected in 23% of patients (64 of the 284 patients; 45 patients with CP-CML).\textsuperscript{213} Among the 34 patients with CP-CML treated with imatinib, primary refractory disease, disease progression while on imatinib and disease progression after dose interruption were reported in 24% (n = 8), 32% (n = 11), and 12% (n = 4) of patients respectively. $\textit{BCR::ABL1}$\textsuperscript{35INS} was also associated with grade 3 or 4 hematologic toxicity. This study, however, was not powered to determine the efficacy of 2G TKI against $\textit{BCR::ABL1}$\textsuperscript{35INS} since very few patients with this mutation received either dasatinib or nilotinib.

$\textit{BCR::ABL1}$ kinase domain mutational analysis is helpful in the selection of subsequent TKI therapy for patients with inadequate initial response to first-line or...
second-line TKI therapy. The guidelines recommend BCR::ABL1 kinase domain mutational analysis for patients who do not achieve response milestones, for those with any sign of loss of response (hematologic or cytogenetic relapse), and if there is a 1-log increase in BCR::ABL1 level with loss of MMR.

BCR::ABL1 kinase domain mutational analysis provides additional guidance for selecting subsequent TKI therapy only in patients with identifiable mutations. Treatment options based on BCR::ABL1 kinase domain mutation status are outlined on CML-5 (page 49). In patients with no identifiable mutations, the selection of subsequent TKI therapy should be based on the patient’s age, ability to tolerate therapy, presence of comorbid conditions, and toxicity profile of the TKI.

**Rising BCR::ABL1 Transcripts**

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

Rising transcript levels should prompt an investigation of treatment adherence and reassessment of coadministered medications. 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, while others have taken a more conservative approach (5- to 10-fold). Obviously, some common sense must prevail, since the amount of change in absolute terms depends on the level of molecular response. For example, a finding of any BCR::ABL1 after achieving a DMR (MR4.5; ≤0.0032% BCR::ABL1 IS) is an infinite increase in BCR::ABL1 transcripts. However, a change in BCR::ABL1 transcripts from a barely detectable level to MR4.5 is clearly different from a 5-fold increase in BCR::ABL1 transcripts after achieving MMR.

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

**Discontinuation of TKI Therapy**

The feasibility of discontinuation of TKI therapy (dasatinib, imatinib, or nilotinib) with close monitoring in carefully selected patients who have experienced and maintained DMR (≥MR4.0; ≤0.01% BCR::ABL1 IS) for 2 or more years has been evaluated in several clinical studies. Longer-term follow-up data from the TKI discontinuation trials are summarized in Supplementary Table S8.

The results of the RE-STIM study showed 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 24 months after the second TKI discontinuation was higher for patients who remained in DMR within the first 3 months after the first TKI discontinuation (72% vs 32% for other patients).

Approximately 40%–60% of patients who discontinue TKI therapy after achieving DMR experience recurrence within 12 months of treatment cessation, in some cases as early as 1 month after discontinuation of TKI therapy. Several factors may help predict the risk of recurrence after TKI discontinuation (a higher Sokal risk score, female gender, lower natural killer cell counts, suboptimal response or resistance to imatinib, duration of TKI therapy, and DMR before TKI discontinuation). However, only the duration of TKI therapy and DMR before discontinuation of TKI 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 duration of DMR (MR4.0 for 3 years) were significantly associated with MMR maintenance at 6 months after discontinuation of imatinib and lack of MR4.0 at 36 months after discontinuation of TKI therapy was highly predictive of subsequent loss of MMR. A rapid initial decline in BCR::ABL1 transcripts after initiation of first-line TKI therapy has also been shown to be an independent predictor of TFR eligibility and sustained TFR.

Resumption of TKI therapy immediately after recurrence results in the achievement of DMR in almost all patients. In the STIM study, molecular relapse (trigger to resume TKI therapy) was defined as positivity for BCR::ABL1 transcripts by qPCR confirmed by a 1-log increase in BCR::ABL1 transcripts between 2 successive assessments or loss of MMR at one point. 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 TKI therapy. The estimated probability of MMR loss was 33% at 12 months and 36% at 24 months after discontinuation of imatinib.

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. The occurrence of imatinib withdrawal syndrome was associated with a lower rate of molecular relapse in the KID study.

The feasibility of TFR after discontinuation of TKIs other than dasatinib, imatinib, or nilotinib has not yet been evaluated in clinical trials.
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 DMR (MR4.0: ≤0.01% BCR::ABL1 IS) for 2 or more years.

Clinical studies that have evaluated the safety and efficacy of discontinuation of TKI have used 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 discontinuation of TKI therapy and ascertain their safety.

Based on 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, consenting patients (in early CP-CML) who have achieved and maintained a DMR (≥MR4.0) for 2 or more years. The panel acknowledges that more frequent molecular monitoring is essential following discontinuation of TKI therapy for the early identification of loss of MMR. Frequency of molecular monitoring has varied substantially among different studies, and the optimal frequency of molecular monitoring in patients with a loss of MMR after discontinuation of TKI therapy has not been established.

The criteria for the selection of patients suitable for discontinuation of TKI therapy and recommendations for molecular monitoring in TFR phase are outlined on CML-F (page 50). The panel emphasizes that discontinuation of TKI therapy outside of a clinical trial should be considered only if all the criteria included on the list are met.

**Dose Modifications of TKI Therapy**

Limited available evidence (mostly from nonrandomized studies and retrospective analysis) suggests that initiation of TKIs (bosutinib, dasatinib, nilotinib) at lower doses and/or de-escalation for all TKIs (with close monitoring) in patients who achieve optimal responses are appropriate strategies for the prevention and management of treatment-related adverse events and to avoid long-term toxicities. However, except for ponatinib (OPTIC trial), the minimum effective dose or optimal de-escalation of TKI has not yet been established in prospective phase III randomized clinical trials.

**Initiation of TKIs at Lower Dose**

Low-dose TKIs for first-line or dose modifications for intolerance or resistance have been evaluated mostly in nonrandomized studies and retrospective analyses. Data from selected studies are outlined in Supplementary Table S9 and Supplementary Table S10.

**Bosutinib**

The recommended starting dose of bosutinib is 400 mg daily for patients with newly diagnosed CP-CML (which is better tolerated than the 500 mg daily dose that was used in the initial randomized phase III trial) and 500 mg once daily for intolerant or resistant CP-CML.

In patients with newly diagnosed CP-CML, recommendations from an expert panel suggest initiating bosutinib at 200 to 300 mg once daily (with dose escalation as clinically indicated) in most patients and initiation at 400 mg daily is recommended only for patients with high-risk disease. The results of a retrospective analysis suggest that dose reduction of bosutinib to 300 mg or 400 mg results in better tolerability and improved efficacy in patients with CP-CML resistant imatinib, dasatinib and/or nilotinib.

**Dasatinib**

The recommended starting dose of dasatinib is 100 mg once daily for patients with CP-CML.

Long-term follow-up of a single-arm study (81 evaluable patients) suggests that dasatinib 50 mg once daily may have similar efficacy in patients with low- or intermediate-risk CP-CML. Dasatinib 20 mg once daily has also been shown to be an appropriate starting dose for patients 65 years and over with newly diagnosed CP-CML. Intermittent dosing (on/off treatment with a drug holiday) or dose reduction to 50 mg once daily has also been shown to be effective as second-line and subsequent therapy in patients with CP-CML resistant/intolerant to imatinib.

Dasatinib at 50 mg (20 mg with careful monitoring in selected patients) should be considered for patients with clinically significant intolerance to dasatinib 100 mg once daily to avoid serious adverse events (eg, pleural effusion, myelosuppression), necessitating the discontinuation of dasatinib.

**Imatinib**

The recommended starting dose of imatinib is 400 mg once daily for patients with CP-CML.

In a phase II study that evaluated imatinib 400 mg in 481 patients with newly diagnosed CML, dose reduction was required in 46% of patients due to intolerance and excessive dose reductions to less than 300 mg was associated with inferior response rates and survival outcomes.

**Nilotinib**

The recommended starting dose of nilotinib is 300 mg twice daily for patients with newly diagnosed CP-CML and 400 mg twice daily for resistant or intolerant CP-CML.

In a retrospective analysis of 70 patients with newly diagnosed CP-CML, early dose reduction of nilotinib to
less than 600 mg/day resulted in a lower rate of adverse events and better therapeutic efficacy.²⁴⁹ One-year MMR and overall MR4.5 rates were 90% and 60%, respectively for the 10 patients treated with 600 mg/day of nilotinib throughout the study, with no disease progression to advanced phase.

The ENESTswift study showed that switching to nilotinib 300 mg twice daily (which is lower than the recommended dose of 400 mg daily in the second-line setting) was effective and well-tolerated in most patients with CP-CML with intolerance to imatinib or dasatinib in the first-line setting.²⁵⁰

**Ponatinib**

The recommended initial dose of ponatinib is 45 mg once daily.

In the OPTIC trial, the optimal benefit was observed with 45 mg once daily for all patients including those with the T315I mutation. Ponatinib at lower dose levels (30 mg once daily and 15 mg once daily) resulted in clinical benefit in patients without the T315I mutation (see Supplementary Table S6). These data support initiation of ponatinib at 45 mg once daily for patients with the T315I mutation followed by dose reduction to 15 mg once daily on achievement of BCR::ABL1 (IS) ≤1%.¹⁶¹

The results of a retrospective analysis showed that ponatinib 15 mg daily was associated with a lower incidence of drug-related adverse events with no impact on efficacy.²⁵¹

**De-escalation or Intermittent Dosing of TKI**

TKI de-escalation has been shown to be feasible in patients, primarily those without prior TKI resistance, who had received TKI therapy for 2 or more years with durable MMR or DMR for 12 or more months.²⁵²–²⁵⁹

Data from selected clinical trials that have evaluated this approach are summarized in Supplementary Table S11.

The phase II INTERIM study first established that intermittent dosing of imatinib is feasible in patients 65 years and over in stable MMR or MR4, after 2 or more years of treatment.²⁵² The interim analysis of the phase III OPTKiMA study demonstrated that this approach is also feasible for patients treated with dasatinib or nilotinib.²⁵⁹ OPTKiMA is an ongoing study that is evaluating the potential de-escalation of all TKIs after achieving a stable DMR.

The DESTINY trial showed the feasibility of de-escalating TKIs (imatinib, dasatinib, or nilotinib) to half the standard dose for 12 months (imatinib 200 mg once daily; dasatinib 50 mg once daily; or nilotinib 200 mg twice daily) in patients achieving MMR or MR4 followed by discontinuation for 24 months (with frequent monitoring).²⁵⁵–²⁵⁶

The NILO-RED study (published only as an abstract) demonstrated the feasibility of maintenance therapy with reduced dose nilotinib (once daily) in patients experiencing MMR on standard-dose nilotinib (twice daily).

**Management of CML During Pregnancy and Breastfeeding**

The median age of disease onset is 65 years, but CML occurs in all age groups. The EUTOS population-based registry has reported that approximately 37% of patients are of reproductive age at diagnosis.²⁶⁰ Clinical care teams should be prepared to address issues relating to fertility and pregnancy as well as counsel these patients about the potential risks and benefits of treatment discontinuation and possible resumption of TKI therapy should CML recur during pregnancy.

**TKI Therapy and Conception**

TKI therapy appears to affect some male hormones at least transiently, but it does not appear to have a deleterious effect on male fertility. Furthermore, the miscarriage or fetal abnormality rate is not elevated in female partners of males on TKI therapy.²⁶¹–²⁶⁵

TKI therapy during pregnancy has been associated with both a higher rate of miscarriage and fetal abnormalities.²⁶⁶–²⁷¹ In one report on the outcome of pregnancies in 180 patients exposed to imatinib during pregnancy, 50% of pregnancies with known outcome were normal and 10% of pregnancies with known outcome had fetal abnormalities.²⁶⁶ Eighteen pregnancies ended in spontaneous abortion. In another report on the outcomes of pregnancy and conception during treatment with dasatinib, among 46 patients treated with dasatinib, 15 patients (33%) delivered a normal infant.²⁶⁷ Elective or spontaneous abortions were reported in 18 (39%) and 8 patients (17%), respectively, and 5 patients (11%) had an abnormal pregnancy. Fetal abnormalities were reported in 7 cases. Among 33 patients who conceived with males who had received treatment with dasatinib, 30 (91%) delivered infants who were normal at birth. In a report of 16 pregnancy cases among patients assigned female at birth treated with bosutinib noted 6 live births, 4 abortions, and 6 unknown outcomes.²⁷²

Although there is a paucity of data regarding the outcome of pregnancy in patients receiving bosutinib, ponatinib, or asciminib at conception, all TKIs also must be considered unsafe for use during pregnancy. Conception while on active TKI therapy is strongly discouraged due to the risk of fetal abnormalities. Close monitoring and prompt consideration of holding TKI therapy (if pregnancy occurs while on TKI therapy) should be considered.

Depending on other factors such as age, a natural pregnancy may occur months after stopping TKI therapy.²⁷³,²⁷⁴ A prolonged washout period before pregnancy should be considered, although there are no data regarding how long a patient should be off TKI therapy before trying to become...
pregnant. There are no published guidelines regarding the optimal depth of molecular response that is considered “safe” to stop TKI therapy before attempting pregnancy.\textsuperscript{275}

Discontinuation of TKI therapy because of pregnancy in patients assigned female at birth who were not in DMR (\(\leq 0.01\% \text{ BCR::ABL1 IS}\)) has only been reported in a small series of patients.\textsuperscript{273,274,276,277} In one series, among 10 patients who stopped imatinib because of pregnancy after a median of 8 months of therapy, 5 of the 9 patients who had experienced a CHR lost the response after stopping therapy, and 6 had an increase in Ph-positive metaphases.\textsuperscript{273} At 18 months after resuming therapy, all 9 patients had achieved a CHR but only 3 females experienced a CCyR and none had experienced an MMR. In another series that reported the outcomes for 7 patients who were not in DMR at the time imatinib was stopped because of pregnancy, 3 were in an MMR.\textsuperscript{274} All 7 patients had disease relapse. The 3 who had an MMR at the time imatinib was stopped could regain the same response once the drug was restarted, whereas the remaining 4 patients did not.

Planning a Pregnancy

In patients assigned male at birth, the general recommendation is that TKI therapy need not be discontinued if a pregnancy is planned. However, experience is limited. Sperm banking can also be performed before starting TKI therapy, but no data are available regarding quality of sperm in males with untreated CML.

In patients assigned female at birth, due to the risk of miscarriage and fetal abnormalities during pregnancy, TKI therapy should be stopped prior to natural conception and patients should remain off therapy during pregnancy.\textsuperscript{266–268}

Fertility preservation should be discussed with all patients of childbearing age before starting TKI therapy. Referral to an in vitro fertilization center is recommended in coordination with the patient’s obstetrician. TKI should be stopped prior to attempting oocyte retrieval, but the optimal timing of discontinuation is unknown. No data are available to recommend how long a patient should be off therapy before oocyte retrieval, although usually at least 1 month off therapy is recommended. In addition to the high incidence of disease recurrence off TKI therapy, patients should also be made aware of the significant obstacles related to in vitro fertilization (eg, lack of access to centers that perform the procedure, high costs associated with drugs, surgical procedures, and embryo/oocyte storage that may not be covered by insurance, variable access to surrogate programs, the need to take family medical leave from work to attend in vitro fertilization appointments).

Before attempting pregnancy, patients and their partners should be counseled that no guidelines exist regarding how best to monitor CML during pregnancy, nor how best to manage progressive disease should it occur during pregnancy. Referral to a CML specialty center and consultation with a high-risk obstetrician is recommended.

Treatment During Pregnancy

Most of the literature regarding treatment during pregnancy consists of case reports. TKI therapy, particularly during the first trimester, should be avoided because of teratogenic risk. If TKI therapy is considered during pregnancy, the potential benefit for the mother and the potential risk to the fetus of continuing TKI therapy versus the risk of treatment interruption leading to the loss of optimal disease response must be carefully evaluated on an individual basis.

Leukapheresis can be used for a rising white blood cell count and/or platelet count, although there are no data that recommend at what level leukapheresis and/or platelet pheresis should be initiated.\textsuperscript{278–281} Low-dose aspirin or low-molecular-weight heparin can be considered for patients with thrombocytosis.\textsuperscript{282,283}

The panel also recommends against the use of hydroxyurea during pregnancy, especially in the first trimester.\textsuperscript{284–286} If treatment is needed during pregnancy, it is preferable to initiate treatment with interferon alfa-2a.\textsuperscript{287} Most data using interferons during pregnancy have been reported in patients with essential thrombocytosis.\textsuperscript{288,289} If introduced earlier, interferons can preserve molecular remission after discontinuation of TKI.\textsuperscript{290,291} Peginterferon alfa-2a is the only interferon available for clinical use in the United States.

Monthly monitoring of complete blood count with differential and frequent monitoring with qPCR (every 1–3 months) would be helpful to guide the timing for initiation of TKI therapy, although specific thresholds for treatment reinitiation have not been defined.

Breastfeeding

TKI therapy can be restarted after delivery. However, patients on TKI therapy should be advised not to breastfeed, as TKIs pass into human breast milk.\textsuperscript{292–295}

Breastfeeding without TKI therapy may be safe with molecular monitoring, preferably in those patients with CML who have durable DMR. It may be acceptable to avoid TKIs for the short period of the first 2 to 5 days after labor to give the child colostrum.\textsuperscript{295,296}

Close molecular monitoring is recommended for females who extend the treatment-free period for breastfeeding. If the loss of MMR after treatment cessation is confirmed, breastfeeding needs to be terminated and TKI should be restarted.\textsuperscript{295}
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<td>Bristol Myers Squibb; Novartis Pharmaceuticals Corporation</td>
<td>None</td>
<td>None</td>
<td>Hematology/Hematology oncology</td>
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<tr>
<td>Steven Tsai, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Hematology/Hematology oncology; Hematopoietic cell transplantation</td>
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<tr>
<td>Jennifer Vaughan, MD, MSPH</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Cogent Pharmaceuticals Inc.</td>
</tr>
<tr>
<td>Jeanna Welborn, MD</td>
<td>None</td>
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<td>None</td>
<td>Medical oncology</td>
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<tr>
<td>David T. Yang, MD</td>
<td>None</td>
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<td>None</td>
<td>Pathology</td>
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The NCCN Guidelines Staff have no conflicts to disclose.