Chronic Myeloid Leukemia, Version 2.2021

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ABSTRACT

Chronic myeloid leukemia (CML) is defined by the presence of Philadelphia chromosome (Ph) which results from a reciprocal translocation between chromosomes 9 and 22 [t(9;22)] that gives rise to a *BCR-ABL1* fusion gene. CML occurs in 3 different phases (chronic, accelerated, and blast phase) and is usually diagnosed in the chronic phase. Tyrosine kinase inhibitor therapy is a highly effective first-line treatment option for all patients with newly diagnosed chronic phase CML. This manuscript discusses the recommendations outlined in the NCCN Guidelines for the diagnosis and management of patients with chronic phase CML.

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Individual disclosures for the NCCN Chronic Myeloid Leukemia Panel members can be found on page 1415. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

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

^b Consider qualitative RT-PCR for the detection of atypical *BCR-ABL1* transcripts. See Discussion. Referral to centers with expertise in the management of rare hematologic malignancies is recommended.

^c Hepatitis B virus reactivation has been reported in patients receiving TKI therapy. However, it is not always possible to reliably estimate the frequency or establish a relationship to drug exposure because these incidences are reported voluntarily from a population of uncertain size.

^d See Definitions of Accelerated Phase and Blast Phase (CML-B*).

^e For patients with accelerated phase or blast phase, consider myeloid mutation panel.

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CML-1

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 2020, an estimated 8,450 people will be diagnosed with CML in the United States, and 1,130 people will die of the disease.¹

CML is defined by the presence of Philadelphia chromosome (Ph) in a patient with a myeloproliferative neoplasm (MPN). Ph results from a reciprocal translocation between chromosomes 9 and 22 [t(9;22)] that gives rise to a *BCR-ABL1* fusion gene.² In most patients, the chromosomal break points are located in intron 13 or 14 of the *BCR* gene on chromosome 22 (major break point cluster region; *M-BCR*); in the *ABL1* gene they are located between the 2 alternative *ABL1* exons 1b and 1a, 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 break point cluster region; *m-BCR*),

or e19a2 encoding for p230 (involving the micro break point 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 “*BCR-ABL1* Transcript Variants in CML” (page 1388).

CML occurs in 3 different phases (chronic, accelerated, and blast phase) and is usually diagnosed in the chronic phase in the developed world. 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

CLINICAL PRESENTATION

^f See Management of CML During Pregnancy (CML-C).

⁹ Based on preliminary data from the BFORE trial and long-term follow-up data from the DASISION and ENESTnd trials, second-generation TKIs (bosutinib, dasatinib, or nilotinib) are preferred for patients with an intermediate- or high-risk score, especially for young women whose goal is to achieve a deep and rapid molecular response and eventual drug discontinuation of TKI therapy for family planning purposes.

^h Imatinib may be preferred for older patients with comorbidities such as cardiovascular disease.

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

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CML-2

CP-CML to AP-CML.⁶ The activation of beta-catenin signaling pathway in CML granulocyte-macrophage progenitors (which enhances the self-renewal activity and leukemic potential of these cells) may be a key pathobiologic event in the evolution to BP-CML.⁷

The full NCCN Guidelines for CML (available at NCCN.org) 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 MPN is recommended for all patients with *BCR-ABL1*-negative MPN. The diagnosis and management of CP-CML is included in this discussion.

Diagnosis and Workup

Initial evaluation should consist of a history and physical exam, including palpation of spleen, complete blood count with differential, chemistry profile, and hepatitis 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.

Bone marrow cytogenetics should be done at initial workup to detect additional chromosomal abnormalities in Ph-positive cells (*ACA/Ph*⁺), also known as clonal cytogenetic evolution.⁸ If bone marrow evaluation is not feasible, fluorescence in situ hybridization (FISH) on a peripheral blood specimen with dual probes for *BCR* and *ABL1* genes is an acceptable method to confirm the diagnosis of CML. Interphase FISH is performed on peripheral blood but can be associated with a false-positive rate of 1%–5% depending on the specific probe used in the assay.⁹ 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.¹⁰ Double-fusion FISH is associated with low false-positive rates and can detect all variant translocations of the Ph-chromosome.¹¹

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 $\geq 100,000$ normal cells. qPCR results can be expressed in various ways, for

EARLY TREATMENT RESPONSE MILESTONES^{i,j}

<i>BCR-ABL1</i> (IS)	3 months	6 months	12 months ^k
>10% ^l	YELLOW	RED	
>1%–10%	GREEN		YELLOW
>0.1%–1%	GREEN		LIGHT GREEN
≤0.1%	GREEN		

COLOR	CONCERN	CLINICAL CONSIDERATIONS	RECOMMENDATIONS
RED	TKI-resistant disease	<ul style="list-style-type: none"> Evaluate patient compliance and drug interactions Consider mutational analysis 	Switch to alternate TKI (CML-5) and evaluate for allogeneic HCT
YELLOW	Possible TKI resistance	<ul style="list-style-type: none"> Evaluate patient compliance and drug interactions Consider mutational analysis Consider bone marrow cytogenetic analysis to assess for MCyR at 3 mo or CCyR at 12 mo 	Switch to alternate TKI (CML-5) or Continue same TKI (other than imatinib) (CML-G) ^m or Increase imatinib dose to a max of 800 mg and Consider evaluation for allogeneic HCT
LIGHT GREEN	TKI-sensitive disease	<ul style="list-style-type: none"> If treatment goal is long-term survival: >0.1%–1% optimal If treatment goal is treatment-free remission: ≤0.1% optimal 	<ul style="list-style-type: none"> If optimal: continue same TKI If not optimal: shared decision-making with patient^{n,o}
GREEN	TKI-sensitive disease	Monitor response (CML-D) and side effects	Continue same TKI (CML-G) ^p

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

^j See Criteria for Hematologic, Cytogenetic, and Molecular Response and Relapse (CML-E).

^k *BCR-ABL1* ≤0.1% at 12 months is associated with a very low probability of subsequent loss of response and a high likelihood of achieving a subsequent deep molecular response (MR4.0; ≤0.01% *BCR-ABL1* IS), which is a prerequisite for a trial of treatment-free remission.

^l Patients with *BCR-ABL1* only slightly >10% at 3 months and/or with a steep decline from baseline may achieve <10% at 6 months and have generally favorable outcomes. Therefore, it is important to interpret the value at 3 months in this context before making drastic changes to the treatment strategy.

^m Achievement of response milestones must be interpreted within the clinical context. Patients with more than 50% reduction compared to baseline or minimally above the 10% cutoff can continue the same dose of dasatinib, nilotinib, or bosutinib for another 3 months. Continuation of imatinib 400 mg is not recommended.

ⁿ Switching from imatinib to a second-generation TKI improves response, but is associated with increased toxicity.

^o Consider referral to specialized CML center and/or enrollment in clinical trial.

^p Discontinuation of TKI with careful monitoring is feasible in selected patients. See Discontinuation of TKI Therapy (CML-F).

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CML-3

instance as the ratio of *BCR-ABL1* transcript numbers to the number of control gene transcripts.¹² 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.¹³ In recent years, IS has become the gold standard of expressing qPCR values. More details on monitoring with qPCR using IS are provided in “Standardization of Molecular Monitoring Using the IS” (page 1397). Qualitative RT-PCR for the detection of atypical *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).

BCR-ABL1 transcripts in the peripheral blood at very low levels (1–10 of 10⁸ peripheral blood leukocytes) can be detected in approximately 30% of normal individuals, 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 are indicated.^{14,15}

BCR-ABL1 Transcript Variants in CML

In an international retrospective analysis of a large cohort with newly diagnosed CML (>45,000 patients), e13a2 and e14a2 transcripts (both encoding for p210) were identified in 38% and 62% of patients, respectively; e13a2 was more frequent in males and the proportion decreased with age in both sexes.¹⁶ Unusual or atypical transcripts were identified in about 2% of patients (e1a2, e19a2, e13a3, and e14a3 were the most frequently identified transcripts).¹⁶ 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.^{17–20} While some studies have demonstrated a trend toward better survival outcomes with e14a2 transcript,^{18,19} in other studies the type of transcript did not have any significant impact on long-term survival outcomes.^{17,21} There are very limited data regarding the impact of these transcripts on response to second-generation TKI therapy.¹⁸ In the study that included 213 patients treated with dasatinib or nilotinib, among patients with e13a2 transcripts, cytogenetic and molecular response rates were

TREATMENT RECOMMENDATIONS BASED ON BCR-ABL1 MUTATION PROFILE

- Patients with disease resistant to primary treatment with imatinib should be treated with bosutinib, dasatinib, or nilotinib in the second-line setting, taking into account BCR-ABL1 mutation status.
- Patients with disease resistant to primary treatment with bosutinib, dasatinib, or nilotinib can be treated with an alternate TKI (other than imatinib) in the second-line setting, taking into account BCR-ABL1 mutation status. The durability of these responses is frequently limited.
- The table below lists the BCR-ABL1 mutations that should NOT be treated with bosutinib, dasatinib, or nilotinib in the second-line setting.

THERAPY	CONTRAINDICATED MUTATIONS ^u
Bosutinib	T315I, V299L, G250E, or F317L ^v
Dasatinib	T315I/A, F317L/V/I/C, or V299L
Nilotinib	T315I, Y253H, E255K/V, F359V/C/I, or G250E
Ponatinib, ^w Omacetaxine, ^x allogeneic HCT (CML-6), or clinical trial	None

^u Mutations contraindicated for imatinib are too numerous to include. There are compound mutations that can cause resistance to ponatinib, but those are uncommon following treatment with bosutinib, dasatinib, or nilotinib.

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

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

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

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CML-5

higher in patients receiving dasatinib or nilotinib compared with those treated with imatinib.¹⁸ These findings suggest that initial treatment with second-generation TKIs might be beneficial for patients with e13a2 transcripts, although this needs to be confirmed in a prospective study.

The presence of e1a2 transcript (encoding for p190) is associated with higher risk of disease progression and inferior cytogenetic and molecular responses to TKI therapy.^{22–26} In multivariate analysis, e1a2 transcript was also identified as an independent predictor of inferior survival outcomes.²⁴ It is important to be aware that these data refer to the presence of dominant e1a2 transcript, not to the presence of low-level e1a2 transcripts in patients with dominant e13a2 or e14a2 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.^{25–27} Referral to centers with expertise in the management of CML is recommended.

Qualitative RT-PCR, nested RT-PCR, or Sanger sequencing are useful for the identification of atypical

BCR-ABL1 transcripts.^{28,29} 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 *BCR-ABL1* transcripts.^{30,31} The utility of multiplex PCR assays and patient-specific genomic DNA quantitative PCR assay for monitoring atypical *BCR-ABL1* transcripts has been demonstrated in some reports.^{32–36}

Clonal Cytogenetic Evolution

The prognostic significance of ACA/Ph⁺ is related to the specific chromosomal abnormality and other features of accelerated phase.^{37–41} The presence of “major route” ACA/Ph⁺ (trisomy 8, isochromosome 17q, second Ph, and trisomy 19) at diagnosis may have a negative prognostic impact on survival and disease progression to accelerated or blast phase.^{42–44} However, in a more recent analysis that evaluated the outcomes of patients with CP-CML (with or without ACA) treated with TKI therapy in prospective studies, the presence of ACA/Ph⁺ at the time

RISK CALCULATION TABLE

Risk Score	Calculation	Risk Category
Sokal score ¹	$\text{Exp } 0.0116 \times (\text{age} - 43.4) + 0.0345 \times (\text{spleen} - 7.51) + 0.188 \times [(\text{platelet count} \div 700)^2 - 0.563] + 0.0887 \times (\text{blasts} - 2.10)$	Low <0.8 Intermediate 0.8 – 1.2 High >1.2
Hasford (EURO) score ²	$(0.6666 \times \text{age [0 when age <50 years; 1, otherwise]} + 0.042 \times \text{spleen size [cm below costal margin]} + 0.0584 \times \text{percent blasts} + 0.0413 \times \text{percent eosinophils} + 0.2039 \times \text{basophils [0 when basophils <3\%; 1, otherwise]} + 1.0956 \times \text{platelet count [0 when platelets <1500} \times 10^9/\text{L; 1, otherwise]}) \times 1000$	Low ≤780 Intermediate >780 – ≤1480 High >1480
EUTOS long-term survival (ELTS) score ³	$0.0025 \times (\text{age}/10)^3 + 0.0615 \times \text{spleen size cm below costal margin} + 0.1052 \times \text{blasts in peripheral blood} + 0.4104 \times (\text{platelet count}/1000)^{-0.5}$	Low ≤1.5680 Intermediate >1.5680 but ≤2.2185 High >2.2185

Calculation of relative risk based on Sokal or Hasford (EURO) score can be found at:
https://www.leukemia-net.org/content/leukemias/cml/euro_and_sokal_score/index_eng.html

Online calculator for the ELTS score can be found at: https://www.leukemia-net.org/content/leukemias/cml/elts_score/index_eng.html

¹ Sokal J, Cox EB, Baccarani M, et al. Prognostic discrimination in "good-risk" chronic granulocytic leukemia. *Blood* 1984;63:789-799.

² Hasford J, Pfirrmann M, Hehlmann R, et al. A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alfa. Writing Committee for the Collaborative CML Prognostic Factors Project Group. *J Natl Cancer Inst* 1998;90:850-858.

³ Pfirrmann M, Baccarani M, Saussele S, et al. Prognosis of long-term survival considering disease-specific death in patients with chronic myeloid leukemia. *Leukemia* 2016;30:48-56.

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CML-A

of diagnosis was not associated with worse prognosis.⁴⁵ Survival outcomes were not statistically significantly different among patients with ACA/Ph⁺ based on TKI therapy (imatinib vs second-generation TKIs) or imatinib dose (400 vs 800 mg). It remains uncertain if second-generation TKIs or high-dose imatinib would be more beneficial for patients with ACA/Ph⁺. Patients with ACA/Ph⁺ at diagnosis should be watched carefully for evidence of therapy failure.

Clonal cytogenetic evolution in Ph-negative cells has also been reported in a small subset of patients treated with TKI therapy.^{46–57} The most common abnormalities include trisomy 8 and loss of Y chromosome. Previous work suggested that the overall prognosis of Ph-negative CML with clonal evolution is good and is dependent on response to imatinib therapy.⁵⁰ Recently, however, the presence of chromosome abnormalities other than loss of Y chromosome has been associated with decreased survival in patients with CP-CML treated with various TKIs, suggesting that closer follow-up is indicated.⁵⁸ Progression to myelodysplastic syndromes and acute myeloid leukemia have been reported in patients with monosomy 7 (del 7q).^{59–61}

Role of Next Generation Sequencing

Next generation sequencing (NGS) allows for the detection of low-level BCR-ABL1 kinase domain mutations as well as resistance mutations in genes other than *BCR-ABL1* that may confer resistance to TKIs or portend disease progression.^{62–65} In a recent prospective, multicenter study (NEXT-in-CML) that assessed the feasibility of NGS in detection of low-level mutations in 236 consecutive patients with CML and inadequate response to TKI therapy, NGS was more effective than conventional Sanger sequencing in the detection of low-level mutations.⁶⁵ 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.⁶⁵ NGS with myeloid mutation panel should be considered for patients with no identifiable *BCR-ABL1* mutations.

Additional Evaluation

Chronic Phase CML

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

MANAGEMENT OF CML DURING PREGNANCY

Tyrosine Kinase Inhibitor (TKI) Therapy and Conception

- TKI therapy appears to affect some male hormones at least transiently, but does not appear to have a deleterious effect on male fertility and the miscarriage or fetal abnormality rate is not elevated in female partners of men on TKI therapy.¹⁻⁵
- TKI therapy for women during pregnancy has been associated with both a higher rate of miscarriage and fetal abnormalities. A prolonged wash out period prior to pregnancy, and prompt consideration of holding TKI therapy (if pregnancy occurs while on TKI therapy) and close monitoring should be considered.⁶⁻¹⁰
- Discontinuation of TKI therapy because of pregnancy in women who were not in deep molecular response (DMR $\geq$ MR4.0; $\leq$ 0.01% *BCR ABL1* IS) has only been reported in small series of patients.¹¹⁻¹⁴ Conception while on active TKI therapy is strongly discouraged due to the risk of fetal abnormalities.
- Prior to attempting pregnancy, women and their partners should be counseled about the potential risks and benefits of discontinuation of TKI therapy and possible resumption of TKI therapy should CML recur during pregnancy. Fertility preservation should be discussed with all patients of childbearing age prior to the initiation of TKI therapy. Referral to a CML specialty center and consultation with a high-risk obstetrician is recommended.

Treatment and Monitoring During Pregnancy

- **Men:** TKI therapy need not be discontinued if a pregnancy is planned. Sperm banking can also be performed prior to starting TKI therapy, although there are no data regarding the quality of sperm in men with untreated CML.
- **Women:** TKI therapy should be stopped prior to natural conception and the patient should remain off therapy during pregnancy.⁶⁻⁸ Referral to an in vitro fertilization (IVF) center is recommended in coordination with the patient's obstetrician. TKI should be stopped prior to attempting a natural pregnancy or oocyte retrieval, but the optimal timing of discontinuation is unknown.

- The use of TKI therapy, particularly during the first trimester, should be avoided. If TKI therapy is considered during pregnancy, the potential risks and benefits must be carefully evaluated in terms of maternal health and fetal risk on an individual basis prior to initiation of TKI therapy during pregnancy.
- It is preferable to initiate treatment with interferon alfa and the panel recommends against the use of hydroxyurea during pregnancy, especially in the first trimester, if possible.¹⁵⁻²³ If introduced earlier, the use of interferon can preserve molecular remission after discontinuation of TKI.²⁴ Data are insufficient to establish the use of peginterferon alfa-2a (risk category C) in pregnancy and it should be used only if benefits outweigh potential risk to the fetus.²⁵
- Leukapheresis can be used for a rising white blood cell (WBC) count, although there are no data that recommend at what level of WBC count leukapheresis should be initiated.^{22,26-28}
- Low-dose aspirin or low-molecular-weight heparin can be considered for patients with thrombocytosis.^{29,30}
- Monthly monitoring with qPCR and initiating treatment if the *BCR ABL1* IS increases to $>1.0\%$ is recommended.

Breastfeeding

- TKI therapy can be restarted after delivery. However, women on TKI therapy should be advised not to breastfeed, as TKIs pass into human breast milk.³¹⁻³⁴
- Breastfeeding without TKI treatment may be safe with molecular monitoring, but preferably in those patients with CML who have durable DMR. It may be acceptable to avoid TKIs for the short period of the first 2–5 days after labor to give the child colostrum.^{34,35}
- Close molecular monitoring is recommended for women 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.³⁴

**References
(CML-C 2 of 2)****CML-C
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evaluating TKIs (CML-A).^{66,67} The Sokal score is based on the patient's age, spleen size on clinical exam, platelet count, and percentage of blasts in the peripheral blood.⁶⁶ The Euro score includes eosinophils and basophils in the peripheral blood in addition to the same clinical variables used in the Sokal score.⁶⁷

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.⁶⁸ 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, as many patients with CML die of non-CML causes, reflecting the efficacy of TKI therapy.

Determination of risk score using either the Sokal or Euro or ELTS scoring systems prior to initiation of TKI therapy is recommended for patients diagnosed with CP-CML.⁶⁶⁻⁶⁸

Management of Chronic Phase 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 1.⁶⁹⁻⁷² In summary, (1) all TKIs are highly effective in newly diagnosed CP-CML, with long-term OS approaching that of aged-matched controls; (2) second-generation TKIs, compared with imatinib, generally result in faster cytogenetic and molecular responses, with less progression to advanced phase CML; and (3) as of yet, in randomized clinical trials, there are no significant differences in OS in patients who start imatinib versus a second-generation 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 risk score, toxicity profile, patient age, ability to tolerate therapy, and presence of comorbid conditions.

MANAGEMENT OF CML DURING PREGNANCY – REFERENCES

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CML-C
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Allogeneic HCT is no longer recommended as a first-line treatment for patients with CP-CML.

Imatinib 800 mg is not recommended as initial therapy, given the recent data showing superior efficacy of second-generation TKIs in newly diagnosed CP-CML. Data from randomized phase III studies that have evaluated high-dose imatinib as first-line therapy for CP-CML suggest that imatinib 800 mg was not associated with lower rates of disease progression than imatinib 400 mg in any of these studies, despite improved early responses.^{73–75} 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 the studies. However, patients who were able to tolerate the higher dose of imatinib experienced higher response rates than those receiving standard-dose imatinib.⁷⁶

Clinical Considerations for the Selection of First-Line Therapy

Risk Stratification

Imatinib (400 mg daily) and second-generation 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.^{69–72}

Disease progression is more frequent in patients with intermediate- or high-risk score, and prevention of disease progression to AP-CML or BP-CML is the primary goal of TKI therapy in patients with CP-CML. Second-generation TKIs are associated with lower risk of disease progression than imatinib and are therefore preferred for patients with an intermediate- or high-risk Sokal or Euro score.

Second-generation TKIs also result in quicker molecular responses and higher rates of major molecular response (MMR; $\leq 0.1\%$ BCR-ABL1 IS) and deep molecular response (DMR; MR4.5 [$\leq 0.0032\%$ BCR-ABL1 IS]) in patients with CP-CML across all risk scores (Table 2), which may facilitate subsequent discontinuation of TKI therapy in select patients.^{70–72} In the ENESTnd study, nilotinib was also associated with lower rates of disease progression and higher progression-free survival (PFS) rates in patients with intermediate- and high-risk score (Table 3).⁷¹

Therefore, second-generation TKIs may be preferred over imatinib for younger patients, particularly women, because the achievement of a deep and rapid molecular response may allow for eventual safe interruption of TKI

MONITORING RESPONSE TO TKI THERAPY AND MUTATIONAL ANALYSIS

Test	Recommendation
Bone marrow cytogenetics ¹	<ul style="list-style-type: none"> • At diagnosis • Failure to reach response milestones • Any sign of loss of response (defined as hematologic or cytogenetic relapse)
qPCR using IS	<ul style="list-style-type: none"> • At diagnosis • Every 3 months after initiating treatment. After <i>BCR-ABL1</i> (IS) $\leq 1\%$² has been achieved, every 3 months for 2 years and every 3–6 months thereafter • If there is 1-log increase in <i>BCR-ABL1</i> transcript levels with MMR, qPCR should be repeated in 1–3 months
<i>BCR-ABL1</i> kinase domain mutation analysis	<ul style="list-style-type: none"> • Chronic phase <ul style="list-style-type: none"> ▸ Failure to reach response milestones ▸ Any sign of loss of response (defined as hematologic or cytogenetic relapse) ▸ 1-log increase in <i>BCR-ABL1</i> transcript levels and loss of MMR • Disease progression to accelerated or blast phase³

¹ FISH has been inadequately studied for monitoring response to treatment.

² CCyR correlates with *BCR-ABL1* (IS) $\leq 1\%$.

³ Consider myeloid mutation panel to identify *BCR-ABL1*-independent resistance mutations in patients with no *BCR-ABL1* kinase domain mutations.

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CML-D

therapy for fertility purposes. Imatinib may be preferred for older patients with comorbidities, especially cardiovascular comorbidities.

Toxicity Profile

All the TKIs are well tolerated. Because bosutinib, dasatinib, and nilotinib have very good efficacy in the upfront setting, differences in their potential toxicity profiles may inform the selection of a specific TKI as initial therapy. 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, heart disease, pancreatitis, or hyperglycemia.

Adverse events of first-line TKI therapy in patients with CP-CML reported in phase III randomized studies are discussed in subsequent sections. See CML-F in the algorithm for the management of toxicities associated with TKI therapy.

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.⁷² 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, no hepatotoxicity-related fatalities were seen 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.⁷⁰ 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,

CRITERIA FOR HEMATOLOGIC, CYTOGENETIC, AND MOLECULAR RESPONSE AND RELAPSE

Complete hematologic response¹

- Complete normalization of peripheral blood counts with leukocyte count $<10 \times 10^9/L$
- Platelet count $<450 \times 10^9/L$
- No immature cells, such as myelocytes, promyelocytes, or blasts in peripheral blood
- No signs and symptoms of disease with resolution of palpable splenomegaly

Cytogenetic response^{2,3}

- Complete cytogenetic response (CCyR) - No Ph-positive metaphases⁴
- Major cytogenetic response (MCyR) - 0%–35% Ph-positive metaphases
- Partial cytogenetic response (PCyR) - 1%–35% Ph-positive metaphases
- Minor cytogenetic response - $>35\%$ –65% Ph-positive metaphases

Molecular response^{5,6,7}

- Early molecular response (EMR) - *BCR-ABL1* (IS) $\leq 10\%$ at 3 and 6 months
- Major molecular response (MMR) - *BCR-ABL1* (IS) $\leq 0.1\%$ or ≥ 3 -log reduction in *BCR-ABL1* mRNA from the standardized baseline, if qPCR (IS) is not available
- Deep molecular response (DMR) is defined as MR4.0: *BCR-ABL1* (IS) $\leq 0.01\%$ or MR4.5: *BCR-ABL1* (IS) $\leq 0.0032\%$

Relapse

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

¹ Faderl S, Talpaz M, Estrov Z, Kantarjian HM. 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 CCyR correlates with *BCR-ABL1* (IS) $\leq 1\%$.

⁵ 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.

⁶ 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.

⁷ Cross NC, White HE, Müller MC, Saglio G, Hochhaus A. Standardized definitions of molecular response in chronic myeloid leukemia. *Leukemia* 2012;26:2172-2175.

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CML-E

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.⁷⁷

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.⁷⁸ 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.⁷⁹ 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.^{80–82} In the DASISION study, pulmonary hypertension was reported in 5% of patients treated with dasatinib compared with $<1\%$ of patients treated with imatinib.⁷⁰ Evaluation for signs and symptoms of underlying cardiopulmonary disease before initiating and

during treatment with dasatinib is recommended. If pulmonary arterial hypertension is confirmed, dasatinib must be permanently discontinued.

The recommended starting dose of dasatinib is 100 mg once daily for patients with newly diagnosed CP-CML. Long-term follow-up results of a single-arm study in a small cohort of patients suggest that dasatinib 50 mg once daily may have similar efficacy.⁸³ Treatment interruption of dasatinib at 100 mg once daily and reintroduction at a lower dose (40 mg twice daily or 60 mg once daily) has been shown to be effective for patients with intolerance to dasatinib at 100 mg once daily.^{84,85} 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 necessitating the discontinuation of dasatinib (eg, pleural effusion, myelosuppression). However, the minimum effective dasatinib dose has not been established in randomized clinical trials.

Imatinib

Chronic fatigue (often correlated with musculoskeletal pain and muscular cramps) is a major factor reducing

DISCONTINUATION OF TKI THERAPY

General Considerations

- Discontinuation of TKI therapy appears to be safe in select CML patients.
- Consultation with a CML specialist to review the appropriateness for TKI discontinuation and potential risks and benefits of treatment discontinuation, including TKI withdrawal syndrome.
- Clinical studies that have evaluated the safety and efficacy of TKI discontinuation have employed strict eligibility criteria and have mandated more frequent molecular monitoring than typically recommended for patients on TKI therapy.
- Some patients have experienced significant adverse events that are believed to be due to TKI discontinuation.
- Discontinuation of TKI therapy should only be performed in consenting patients after a thorough discussion of the potential risks and benefits.
- Consultation with an NCCN Panel member or center of expertise is recommended in the following circumstances:
 - ▶ Any significant adverse event believed to be related to treatment discontinuation.
 - ▶ Progression to accelerated or blast phase CML at any time.
 - ▶ Failure to regain MMR after 3 months following treatment reinitiation.
- Outside of a clinical trial, TKI discontinuation should be considered only if ALL of the criteria included in the list below are met.

Criteria for TKI Discontinuation

- Age ≥ 18 years.
- Chronic phase CML. No prior history of accelerated or blast phase CML.
- On approved TKI therapy for at least 3 years.^{1,2}
- Prior evidence of quantifiable *BCR-ABL1* transcript.
- Stable molecular response (MR4; *BCR-ABL1* $\leq 0.01\%$ IS) for ≥ 2 years, as documented on at least 4 tests, performed at least 3 months apart.²
- Access to a reliable qPCR test with a sensitivity of detection of at least MR4.5 (*BCR-ABL1* $\leq 0.0032\%$ IS) and that provides results within 2 weeks.
- Monthly molecular monitoring for the first 6 months following discontinuation, bimonthly during months 7–12, and quarterly thereafter (indefinitely) for patients who remain in MMR (MR3; *BCR-ABL1* $\leq 0.1\%$ IS).
- Prompt resumption of TKI within 4 weeks of a loss of MMR with monthly molecular monitoring until MMR is re-established, then every 3 months thereafter is recommended indefinitely for patients who have reinitiated TKI therapy after a loss of MMR. For those who fail to achieve MMR after 3 months of TKI resumption, *BCR-ABL1* kinase domain mutation testing should be performed, and monthly molecular monitoring should be continued for another 6 months.

¹ The feasibility of treatment-free remission (TFR) following discontinuation of bosutinib or ponatinib has not yet been evaluated in clinical studies. It is reasonable to assume that the likelihood of TFR following discontinuation would be similar irrespective of TKI in patients who have achieved and maintained deep molecular response (MR4.0; $\leq 0.01\%$ *BCR-ABL1* IS) for ≥ 2 years, based on the extrapolation of findings from the studies that have evaluated TFR following discontinuation of imatinib, dasatinib, or nilotinib.

² Data from the EURO-SKI study suggest that MR4.0 (*BCR-ABL1* $\leq 0.01\%$ IS) for 3 years or more was the most significant predictor for successful discontinuation of imatinib. Total duration of imatinib therapy for at least 6 years was also predictive of successful discontinuation (Saussele S, Richter J, Guilhot J, et al. *Lancet Oncol* 2018;19:747-757).

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CML-F

quality of life.⁸⁶ 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.^{87,88} Skin hypopigmentation has also been reported as a side effect of imatinib and is reversible upon discontinuation or dose reduction.^{89,90} Reversible renal dysfunction with prolonged use of imatinib has also been reported.⁹¹

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 imatinib. Conversely, rash and headache were more common with nilotinib.⁷¹ 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.⁸² QT interval prolongation could be managed with dose reduction. Electrolyte abnormalities should be corrected before the start of treatment with nilotinib and electrolytes should be monitored periodically. Drugs that prolong QT interval should be avoided. Electrocardiogram should be obtained to monitor the QT interval at baseline, 7 days after initiation of nilotinib, and periodically thereafter, and after any dose adjustments. Patients with cardiovascular risk factors should be referred to a cardiologist.

Nilotinib is associated with an increased risk of peripheral arterial occlusive disease (PAOD).^{92–96} Patients should be evaluated for preexisting PAOD and vascular risk factors before starting and during treatment with nilotinib. If PAOD is confirmed, nilotinib should be permanently discontinued.

The recommended starting dose of nilotinib is 300 mg twice daily for patients with newly diagnosed

DRUG INTERACTIONS OF TKIs WITH MOST COMMONLY USED DRUGS AND SUPPLEMENTS^{1,5}

Drug interactions with TKIs are not uncommon. It is always important to take a detailed medication history (including herbal supplements) at every visit.

Drug Class/ Medications	Change in TKI Level				
	Bosutinib	Dasatinib	Imatinib	Nilotinib	Ponatinib
Proton Pump Inhibitors (PPIs) • Lansoprazole • Rabeprazole • Esomeprazole • Omeprazole • Pantoprazole	Decrease in exposure	Decrease in exposure	No major interaction	Decrease in exposure	Minor decrease in exposure; Monitor
Histamine 2 Receptor Antagonists (H2RAs) • Famotidine • Ranitidine • Nizatidine	Decrease in exposure; AVOID; If absolutely necessary consider once-daily H2RA ≥2 hours after taking bosutinib	Decrease in exposure; AVOID; If absolutely necessary consider once-daily H2RA ≥2 hours after taking dasatinib	No major interaction	Decrease in exposure; AVOID; If absolutely necessary consider once-daily H2RA ≥2 hours after or ≥10 hours before taking nilotinib	No major interaction
Antacids	Decrease in exposure if concomitant; Use antacids at least 2 hours before or at least 2 hours after taking bosutinib	Decrease in exposure if concomitant; Use antacids at least 2 hours before or at least 2 hours after taking dasatinib	No major interaction	Decrease in exposure if concomitant; Use antacids at least 2 hours before or at least 2 hours after taking nilotinib	No major interaction
Antidepressants • Fluoxetine • Bupropion • Citalopram	Minor increase in exposure; Monitor QTc monitoring	Minor increase in exposure; Monitor QTc monitoring	Minor increase in exposure; Monitor QTc monitoring	AVOID if possible due to cumulative QTc prolongation risk	Minor increase in exposure; Monitor QTc monitoring
Cardiovascular Medications • Amiodarone • Diltiazem • Verapamil	Increase in exposure and arrhythmia risk; Strongly consider alternative cardiac medication or TKI dose adjustment	Increase in exposure and arrhythmia risk; Strongly consider alternative cardiac medication or TKI dose adjustment	Increase in exposure; Strongly consider alternative cardiac medication or TKI dose adjustment	Increase in exposure and arrhythmia risk; AVOID	Increase in exposure; Strongly consider alternative cardiac medication or TKI dose adjustment

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CML-G
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CP-CML. Limited data from small cohorts of patients suggest that lower doses of nilotinib (<600 mg per day) may be associated with better safety and efficacy than nilotinib 300 mg twice daily.⁹⁷ However, as with dasatinib, the minimum effective dose of nilotinib has not been established in randomized clinical trials.

Management of Hematologic Toxicities of TKI Therapy
Cytopenias (anemia, neutropenia, and thrombocytopenia) should be managed with transient interruptions of TKI therapy and dose modifications. Full prescribing information can be found on the package insert (available at www.accessdata.fda.gov/scripts/cder/daf/) for the recommended dose modifications of specific TKI therapy.

Assessment of reticulocyte count, ferritin, iron saturation, vitamin B12, and folate and correction of nutritional deficiencies if present is recommended for patients with grade 3–4 anemia. Red blood cell transfusions are indicated in symptomatic patients. Myeloid growth factor support can be used in combination with TKI therapy for the management of neutropenia.^{98,99} The use of erythropoiesis-stimulating agents did not impact survival or cytogenetic response rate but was associated

with a higher thrombosis rate in patients with CP-CML.¹⁰⁰ Recent guidelines from the U.S. Centers for Medicare & Medicaid Services and the FDA do not support the use of erythropoiesis-stimulating agents in patients with myeloid malignancies.

Monitoring Response to TKI Therapy

Response to TKI therapy is determined by the measurement of hematologic (normalization of peripheral blood counts), cytogenetic (decrease in the number of Ph-positive metaphases using bone marrow cytogenetics), and molecular assessments (decrease in the amount of *BCR-ABL1* chimeric mRNA using qPCR). The criteria for hematologic, cytogenetic, and molecular response are summarized in the algorithm (see CML-D, page 1393).

Conventional bone marrow cytogenetics is the standard method for monitoring cytogenetic responses, and many clinical trial response analyses were based on conventional bone marrow cytogenetics. With the advent of qPCR, bone marrow cytogenetic analyses to assess response are rarely performed at this time. If conventional bone marrow cytogenetics yield no analyzable metaphases, cytogenetic response can be evaluated by FISH,

DRUG INTERACTIONS OF TKIs WITH MOST COMMONLY USED DRUGS AND SUPPLEMENTS^{1,5}

Drug interactions with TKIs are not uncommon. It is always important to take a detailed medication history (including herbal supplements) at every visit.

Drug Class/ Medications	Change in TKI Level				
	Bosutinib	Dasatinib	Imatinib	Nilotinib	Ponatinib
Anti-infectives • Azole Antifungals ▶ Fluconazole ≥200 mg ▶ Voriconazole ▶ Itraconazole ▶ Posaconazole ▶ Isavuconazole • Clarithromycin • Telithromycin • Ritonavir	Increase in exposure; Strongly consider alternative anti-infective or TKI dose adjustment	Increase in exposure; Strongly consider alternative anti-infective or TKI dose adjustment	Increase in exposure; Strongly consider alternative anti-infective or TKI dose adjustment	Increase in exposure; Strongly consider alternative anti-infective or TKI dose adjustment	Increase in exposure; Strongly consider alternative anti-infective or TKI dose adjustment
Anti-infectives • Fluoroquinolones ▶ Levofloxacin ▶ Moxifloxacin ▶ Ciprofloxacin	QTc monitoring	QTc monitoring	No major interaction	Use with caution	No major interaction
Herbal Supplements^{6,7} • Curcumin (Turmeric) • Ginkgo Biloba • Green Tea Extract	Increase in exposure; Strongly consider supplement discontinuation	Increase in exposure; Strongly consider supplement discontinuation	Increase in exposure; Strongly consider supplement discontinuation	Increase in exposure; Strongly consider supplement discontinuation	Increase in exposure; Strongly consider supplement discontinuation
Herbal Supplements^{6,7} • St. John's Wort	Decrease in exposure; AVOID	Decrease in exposure; AVOID	Decrease in exposure; AVOID	Decrease in exposure; AVOID	Decrease in exposure; AVOID

¹ Please refer to package insert for full prescribing information and drug interactions: <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>.

⁵ van Leeuwen RW, van Gelder T, Mathijssen RH, et al. Drug-drug interactions with tyrosine-kinase inhibitors: a clinical perspective. *Lancet Oncol* 2014;15:e315-e326.

⁶ Zhang W, Lim LY. Effects of spice constituents on P-glycoprotein-mediated transport and CYP3A4-mediated metabolism in vitro. *Drug Metab Dispos* 2008;36:1283-1290.

⁷ Scott GN, Elmer GW. Update on natural product-drug interactions. *Am J Health Syst Pharm* 2002;59:339-347.

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CML-G
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preferably with a dual color probe to minimize false-positive rates. FISH and cytogenetic results are correlated, but not superimposable.^{101–103} Although some investigators have reported that interphase FISH can be used to monitor complete cytogenetic response (CCyR), endpoints for TKI failure have not been defined on the basis of FISH analysis.^{104,105} The panel believes 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 achieved 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.^{106,107}

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 ($\leq 1\%$ *BCR-ABL1* IS; MR2.0) generally correlates with CCyR and a ≥ 3 -log reduction ($\leq 0.1\%$ *BCR-ABL1* IS) is referred to as MMR or MR3.0.^{13,108,109}

DMR is defined by the assay's level of sensitivity [$\leq 0.01\%$ *BCR-ABL1* (IS), MR4.0; $\leq 0.0032\%$ *BCR-ABL1* (IS), MR4.5].¹¹⁰ 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. 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.^{13,111}

Recommendations for Monitoring Response to TKI Therapy

qPCR (IS) is the preferred method to monitor response to TKI therapy. qPCR assays with a sensitivity

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

Trial	Study Arms	No. of Patients	Median Follow-Up	CCyR ^a	MMR ^b	Disease Progression n (%)	PFS ^c	OS ^c
IRIS ^{69,d}	Imatinib (400 mg once daily)	553	11 y	83%	—	38 (7%)	92%	83%
	Interferon alpha + low-dose cytarabine	553		—	—	71 (13%)	—	79% ^e
DASISION ⁷⁰	Dasatinib (100 mg once daily)	259	5 y	—	76% (P=.002)	12 (5%)	85%	91%
	Imatinib (400 mg once daily)	260		—	64%	19 (7%)	86%	90%
ENESTnd ⁷¹	Nilotinib (300 mg twice daily)	282	5 y	—	77% (P<.0001)	10 (4%)	92%	94%
	Imatinib (400 mg once daily)	283		—	60%	21 (7%)	91%	92%
BFORE ^{72,f}	Bosutinib (400 mg once daily)	268	12 mo	77% (P=.0075)	47% (P=.02)	4 (2%)	—	—
	Imatinib (400 mg once daily)	268		66%	37%	6 (3%)	—	—

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

^aPrimary endpoint of DASISION study: confirmed CCyR rate at 12 mo.

^bPrimary endpoint of ENESTnd and BFORE studies: MMR ($\leq 0.1\%$ *BCR-ABL1* IS) rate at 12 mo.

^cLong-term primary endpoint of IRIS trial in the imatinib group.

^dDue to the high rate of crossover to imatinib (66%) and the short duration of therapy (<1 y) before crossover among patients who had been randomly assigned to interferon alpha + cytarabine, the long-term follow-up data focused on patients who had been randomly assigned to receive imatinib.

^eData include survival among the 363 patients who crossed over to imatinib.

^fThere were no differences in survival rates between the 2 treatment arms after a minimum follow-up of 12 mo; long-term follow-up is ongoing.

of ≥ 4.5 -log reduction from the standardized baseline are recommended for the measurement of *BCR-ABL1* transcripts. In patients with prolonged myelosuppression who may not be in complete hematologic response (CHR) due to persistent cytopenias or unexplained drop in blood counts during therapy, bone marrow cytogenetics is indicated to confirm response to TKI therapy and exclude other pathology, such as myodysplastic syndromes or the presence of chromosomal abnormalities other than Ph.

Monitoring with qPCR (IS) every 3 months is recommended for all patients after initiating TKI therapy, including those who meet response milestones at 3, 6, and 12 months ($\leq 10\%$ *BCR-ABL1* IS at 3 and 6 months, $\leq 1\%$ *BCR-ABL1* IS at 12 months, and $\leq 0.1\%$ *BCR-ABL1* IS at >12 months). After CCyR ($\leq 1\%$ *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.¹¹² 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; $\leq 10\%$ *BCR-ABL1* IS at 3 and 6 months) after first-line TKI therapy has emerged as an effective prognosticator of favorable long-term PFS

Table 2. First-Line TKI Therapy for CP-CML: Molecular Response Rates According to Risk Score

Trial	Study Arms	Low-Risk		Intermediate-Risk		High-Risk	
		MMR	MR4.5	MMR	MR4.5	MMR	MR4.5
DASISION ⁷⁰ (Euro risk score)	Dasatinib (100 mg once daily)	90%	55%	71%	43%	67%	31%
	Imatinib (400 mg once daily)	69%	44%	65%	28%	54%	30%
ENESTnd ⁷¹ (Sokal risk score)	Nilotinib (300 mg twice daily)	—	53%	—	60%	—	45%
	Imatinib (400 mg once daily)	—	37%	—	33%	—	23%
BFORE ⁷² (Sokal risk score)	Bosutinib (400 mg once daily)	58%	—	45%	—	34%	—
	Imatinib (400 mg once daily)	46%	—	39%	—	17%	—

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

Table 3. First-Line TKI Therapy for CP-CML: 5-Year Outcomes According to Sokal Risk Score

Trial	Study Arms	Low-Risk			Intermediate-Risk			High-Risk		
		Disease Progression n (%)	PFS	OS	Disease Progression n (%)	PFS	OS	Disease Progression n (%)	PFS	OS
ENESTnd ⁷¹ (Sokal risk score)	Nilotinib (300 mg twice daily)	1 (1%)	96%	97%	2 (2%)	93%	94%	7 (9%)	86%	89%
	Imatinib (400 mg once daily)	0%	100%	100%	10 (10%)	88%	89%	11 (14%)	83%	84%

Abbreviations: CP-CML, chronic phase chronic myeloid leukemia; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

and OS (Table 4).^{70,71,75,113} Some reports suggest that EMR at 3 months has a superior prognostic value and support the use of early intervention strategies based on the *BCR-ABL1* transcript level at 3 months.^{114,115} However, other studies yielded partially conflicting results regarding the predictive value of *BCR-ABL1* transcripts at 3 months.¹¹⁶ From a practical perspective, it is important to consider these data points within the clinical context. For instance, if *BCR-ABL1* transcript level is minimally above the 10% cutoff (11% at 3 months), it is reasonable to reassess at 6 months before considering major changes to the treatment strategy.

Quite recently, studies have suggested that the rate of decline in *BCR-ABL1* transcripts correlates with longer-term response.^{117–119} 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).¹¹⁷ 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.¹¹⁸ The results of the D-First study also showed that in patients treated with dasatinib, *BCR-ABL1* halving time of ≤14 days was a significant predictor of MMR by 12 months and DMR (MR4.0; ≤0.01% *BCR-ABL1* IS) by 18 months.¹¹⁹

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.^{120,121} In the IRIS study, the estimated 6-year PFS rate was 97% for patients achieving a CCyR at 6 months compared with 80% for patients with no cytogenetic response at 6 months.¹²⁰ In an analysis of patients with newly diagnosed CP-CML treated with imatinib or second-generation TKIs, the 3-year event-free survival and OS rates were 98% and 99% for patients who experienced CCyR at 12 months compared with 67% and 94% in patients who did not experience a CCyR.¹²¹

MMR (≤0.1% *BCR-ABL1* IS) as a predictor of PFS and OS has also been evaluated in several studies.^{106,122–128} 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 who are in 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 achieved MMR (≤0.1% *BCR-ABL1* IS) and those who achieved MR2.0 (≤1% *BCR-ABL1* IS).¹²⁷

Table 4. Early Molecular Response (≤10% *BCR-ABL1* IS at 3 mo) After First-Line TKI Therapy and Survival Outcomes

Trial	Study Arms	5-y PFS		5-y OS	
		<i>BCR-ABL1</i> ≤10%	<i>BCR-ABL1</i> >10%	<i>BCR-ABL1</i> ≤10%	<i>BCR-ABL1</i> >10%
DASISION ⁷⁰	Dasatinib (100 mg once daily)	89%	72%	94%	81%
	Imatinib (400 mg once daily)	93%	72%	95%	81%
ENESTnd ⁷¹	Nilotinib (300 mg twice daily)	95%	78%	98%	82%
	Nilotinib (400 mg twice daily)	96%	89%	96%	93%
	Imatinib (400 mg once daily)	98%	79%	99%	79%
CML IV Study ¹¹³	Imatinib (400 mg once daily)	92%	87%	94%	87%

Abbreviations: OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

The absence of MMR in the presence of a CCyR is therefore not considered a treatment failure. Although some investigators have reported that dose escalation of imatinib might benefit patients in CCyR with no MMR,¹²⁹ there are no randomized studies to show that a change of therapy would improve survival, PFS, or event-free survival in this group of patients.¹³⁰ However, the achievement of MMR ($\leq 0.1\%$ *BCR-ABL1* IS) at 12 months is associated with a very low probability of subsequent loss of response and a high likelihood of achieving a subsequent DMR (MR4.0; $\leq 0.01\%$ *BCR-ABL1* IS), which may facilitate discontinuation of TKI therapy.^{31,128} 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.¹³¹

Response Milestones After First-Line TKI Therapy (CML-3)

The most important goals of TKI therapy are to prevent disease progression to AP-CML or BP-CML and to achieve either MR2.0 ($\leq 1\%$ *BCR-ABL1* IS, which corresponds to CCyR) or MMR ($\leq 0.1\%$ *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 $\leq 10\%$ *BCR-ABL1* IS at 3 and 6 months after initiation of first-line TKI therapy as a response milestone, since the achievement of EMR after first-line TKI therapy is an effective prognosticator of favorable long-term PFS. Achievement of $>0.1\%$ – 1% *BCR-ABL1* IS ($\leq 1\%$ *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 ($\leq 0.1\%$ *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 initiation of therapy), rate of decline in *BCR-ABL1* (the faster, the better), and how far from the cutoff the *BCR-ABL1* value falls. That being said, failure to achieve $\leq 10\%$ *BCR-ABL1* IS at 3 months or $\leq 1\%$ *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 continue the same dose of dasatinib, nilotinib, or bosutinib 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, MMR at 12 months is associated with lower rate of disease progression and a higher likelihood of achieving DMR, which is a prerequisite for TFR. Switching to a second-generation TKI from imatinib might be considered to increase the probability of achieving MMR ($\leq 0.1\%$ *BCR-ABL1* IS) at 12 months. However, it is also 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 (that is, a discussion with a transplant specialist, which might include HLA testing) is recommended. Alternate treatment options should be considered as described subsequently.

Second-line Therapy

Long-term efficacy data from phase II/III studies on second-line TKI therapy for CP-CML are summarized in Table 5.^{132–135}

EMR ($\leq 10\%$ *BCR-ABL1* IS at 3 and 6 months) after second-line TKI therapy with dasatinib or nilotinib has also been reported to be a prognosticator of OS and PFS (Table 6). Patients who do not experience cytogenetic or molecular responses at 3, 6, or 12 months after second-line and subsequent TKI therapy should be considered for alternative therapies or allogeneic HCT if deemed eligible.

Management of Patients With Inadequate Response to Imatinib

Switching to an alternate TKI is recommended for patients with disease that is resistant to imatinib 400 mg daily. Dasatinib, nilotinib, and bosutinib, 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 with CP-CML intolerant or resistant to imatinib.^{132–134}

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.^{136–139}

Table 5. Second-Line and Subsequent TKI Therapy for CP-CML: Long-Term Follow-Up Data From Phase II/III Studies

TKI	No. of Patients	Median Follow-Up	MCyR	CCyR	MMR	PFS	OS
Dasatinib ^{132,a} (100 mg once daily)	Imatinib-R (n=124)	7 y	—	—	43%	39%	63%
	Imatinib-I (n=43)		—	—	55%	51%	70%
Nilotinib ^{133,b} (400 mg twice daily)	Imatinib-R (n=226)	4 y	59%	45%	—	57%	78%
	Imatinib-I (n=95)						
Bosutinib ^{142,b} (400 mg once daily)	Imatinib and dasatinib-R (n=38)	4 y	39%	22%	—	—	67%
	Imatinib and dasatinib-I (n=50)		42%	40%	—	—	80%
	Imatinib and nilotinib-R (n=26)		38%	31%	—	—	87%
Ponatinib ^{135,c} (45 mg once daily)	Dasatinib or nilotinib-R or -I (n=203)	57 mo	56%	49%	35%	52% at 5 y	76% at 5 y
	T315I mutation (n=64)		72%	70%	58%	50% at 5 y	66% at 5 y

Abbreviations: CCyR, complete cytogenetic response; CP-CML, chronic phase chronic myeloid leukemia; I, intolerant; MCyR, major cytogenetic response; MMR, major molecular response ($\leq 0.1\%$ BCR-ABL1 IS); OS, overall survival; PFS, progression-free survival; R, resistant; TKI, tyrosine kinase inhibitor.

^aPrimary endpoint: MCyR rate at 6 mo when administered 100 mg once daily vs 70 mg twice daily.

^bPrimary endpoint: MCyR rate in patients with imatinib intolerance or imatinib-resistant disease.

^cPrimary endpoint: MCyR at any time within the first 12 mo.

However, it is unlikely to benefit patients with hematologic failure or those who never had a cytogenetic response with imatinib 400 mg daily. In patients with inadequate response to imatinib 400 mg, switching to nilotinib has been shown to result in higher rates of cytogenetic and molecular response than dose escalation of imatinib.^{140,141} In the TIDEL-II study, the cohort of patients with $>10\%$ BCR-ABL1 IS at 3 months after imatinib 400 mg who were switched directly to nilotinib had higher rates of MMR and complete molecular response at 12 months (but not at 24 months) than the cohort of patients who received dose escalation of imatinib before switching to nilotinib.¹⁴⁰ Although dose escalation of imatinib has been shown to be beneficial for patients in CCyR with no MMR, no randomized studies have shown that a change of therapy would improve PFS or event-free survival in this group of patients.^{129,130}

Management of Patients With Inadequate Response to Dasatinib, Nilotinib, or Bosutinib

Switching to an alternate TKI (other than imatinib) in the second-line setting could be considered for patients with

disease that is resistant to dasatinib, nilotinib, or bosutinib. Bosutinib has demonstrated activity in patients with CP-CML resistant/intolerant to multiple TKIs (imatinib, dasatinib, and nilotinib).^{142,143} However, there is no clear evidence to support that switching to alternate TKI therapy would improve long-term clinical outcome for this group of patients.

Ponatinib is an option for patients with a T315I mutation and for those with disease that has not responded to several TKIs.¹³⁵ Long-term efficacy data from phase II/III studies evaluating bosutinib or ponatinib in patients with pretreated CP-CML are summarized in Table 5.

In the PACE trial, serious arterial occlusive events (cardiovascular, cerebrovascular, and peripheral vascular) and venous thromboembolic events occurred in 31% and 6% of patients, respectively.¹³⁵ Cardiovascular, cerebrovascular, and peripheral arterial occlusive events were reported in 16%, 13%, and 14% of patients, respectively. In an analysis of cardiovascular, arterial, and thrombotic adverse events associated with front-line TKI therapy in prospective clinical trials, the incidence of cardiovascular adverse events was highest among

Table 6. Early Molecular Response ($\leq 10\%$ BCR-ABL1 IS) After Second-Line TKI Therapy and Survival Outcomes

TKI	Median Follow-Up	PFS				OS			
		BCR-ABL1 $\leq 10\%$		BCR-ABL1 $>10\%$		BCR-ABL1 $\leq 10\%$		BCR-ABL1 $>10\%$	
		3 mo	6 mo	3 mo	6 mo	3 mo	6 mo	3 mo	6 mo
Dasatinib ¹³² (100 mg once daily)	7 y	56%	57%	21%	4%	72%	74%	56%	50%
Nilotinib ¹³³ (400 mg twice daily)	4 y	67%	58%	42%	39%	81%	82%	71%	73%

Abbreviations: OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

patients treated with ponatinib and those with preexisting cardiovascular risk factors.¹⁴⁴ The increased incidences of arterial occlusive events among patients treated with ponatinib were also confirmed in another multicenter real-life study.¹⁴⁵

The ponatinib labeling contains a black box warning regarding vascular occlusion, heart failure, and hepatotoxicity. Cardiovascular risk factors (eg, diabetes mellitus, hypertension, hyperlipidemia, smoking, estrogen use) should be identified and controlled before starting ponatinib. Patients should be monitored for high blood pressure, evidence of arterial occlusive or thromboembolic events, and reduced cardiac function.¹⁴⁶ 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.

According to the package insert, the recommended initial dose of ponatinib is 45 mg once daily, the maximum tolerated dose determined in a phase 1 dose-escalation study.¹⁴⁷ As high-dose intensity of ponatinib is associated with increased risk of adverse events, dose modifications may be necessary to prevent or manage adverse events.¹⁴⁸ Recent reports suggest that substantial responses can be observed at lower dose levels (30 mg or 15 mg) with decreased incidence of cardiovascular events; the rates at which MCyR and MMR were maintained were independent of the dose reductions.^{135,149} Thus, an initial dose of 15 mg or 30 mg may be a safer and effective dose for patients with cardiovascular risk factors. The safety and efficacy of ponatinib at initial doses lower than 45 mg are under study in a randomized clinical trial, with results expected in the near future.

The use of an alternate second-generation TKI after treatment failure with 2 prior TKIs, including a second-generation TKI, is not associated with durable responses except in occasional patients with CP-CML.¹⁵⁰

Omacetaxine is a treatment option for patients with CP-CML resistant or intolerant to ≥ 2 TKIs including those with a T315I mutation.^{151,152} In the CML 202 study, among 62 evaluable patients with CP-CML resistant to prior TKI therapy and T315I mutation, after a median follow-up of 19 months, MCyR, CCyR, and MMR rates were 23%, 16%, and 17%, respectively, and the T315I clone declined to below detection limits in 61% of patients.¹⁵¹ The median PFS was 8 months and the median OS had not yet been reached. In the cohort of 46 patients with CP-CML resistant or intolerant to ≥ 2 TKIs (CML 203 study), after a median follow-up of 19 months, the MCyR and CCyR rates were 22% and 4%, respectively. The median PFS and OS were 7 months and 30 months, respectively.¹⁵² The response rates and survival outcomes, however, were substantially lower than that observed with ponatinib in the PACE trial in this patient population (Table 5; the estimated 5-year

PFS rate was 52% for patients with CP-CML resistant or intolerant to ≥ 2 TKIs and 50% for those with a T315I mutation).¹³⁵ Omacetaxine had an acceptable toxicity profile and the most common grade 3/4 adverse events were thrombocytopenia (67%), neutropenia (47%), and anemia (37%).

Clinical Considerations for the Selection of Second-Line Therapy

BCR-ABL1 kinase domain mutation analysis (see subsequent sections), evaluation of drug interactions, and compliance to therapy are recommended before the start of second-line TKI therapy.

Drug Interactions

Bosutinib, dasatinib, imatinib, nilotinib, and ponatinib 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.^{153,154} 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.

Drug interactions between TKIs and some of the most commonly used drugs and supplements are summarized in the algorithm (CML-F, page 1395). Concomitant use of drugs that are metabolized by these enzymes requires caution, and appropriate alternatives should be explored to optimize treatment outcome. If coadministration cannot be avoided, dose modification should be considered.

Adherence to Therapy

Treatment interruptions and nonadherence to therapy may lead to undesirable clinical outcomes.^{155–157} 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%).¹⁵⁵ Adherence to imatinib therapy has been identified as the only independent predictor for achieving complete molecular response on standard-dose imatinib.¹⁵⁶ Poor adherence to imatinib therapy has also been identified as the most important factor contributing to cytogenetic relapse and imatinib failure.¹⁵⁷ Patients with adherence of $\leq 85\%$ had a higher probability of losing CCyR at 2 years than those with adherence of $>85\%$ (27% and 2%, respectively). Poor adherence to therapy has also been

reported in patients receiving dasatinib and nilotinib following imatinib failure.^{158,159}

Patient education on adherence to therapy and close monitoring of patient 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.¹⁶⁰ 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.¹⁶¹ Switching to an alternate TKI because of intolerance might be beneficial for selected patients with acute grade 3/4 nonhematologic toxicities or in those with chronic, low-grade nonhematologic toxicities that are not manageable with adequate supportive care measures.^{162–164}

Resistance to TKI Therapy

Aberrant expressions of drug transporters^{165–167} and plasma protein binding of TKI^{168–170} could contribute to primary resistance by altering the intracellular and plasma concentration of TKI.

Pretreatment levels of organic cation transporter 1 (OCT1) have been reported as the most powerful predictor of response to imatinib.¹⁷¹ On the other hand, 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.^{172–175}

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 BCR-ABL1 kinase domain are a frequent mechanism of secondary resistance to TKI therapy and are associated with poor prognosis and higher risk of disease progression.^{176–181} Among the BCR-ABL1 kinase domain mutations, T315I confers complete resistance to imatinib, dasatinib, nilotinib, and bosutinib.^{182,183} The T315A, F317L/I/V/C, and V299L mutants are resistant to dasatinib and E255K/V, F359V/C, and Y253H mutants are resistant to nilotinib.^{184–187} E255K/V, F359C/V, Y253H, and T315I mutants are most commonly associated with disease progression and relapse.^{187,188} Bosutinib has demonstrated activity in patients with BCR-ABL1 mutants resistant to dasatinib (F317L) and nilotinib (Y253H, E255K/V, and F359C/I/V).¹⁴² However, bosutinib has minimal activity against F317L mutant

while in vitro studies suggest that F317L is highly sensitive to nilotinib.^{185,187,189} Nilotinib may be preferred over bosutinib in patients with F317L mutation. T315I, G250E, and V299L mutants are resistant to bosutinib.¹⁴² Ponatinib is active against *BCR-ABL1* mutants resistant to dasatinib or nilotinib, including E255V, Y253H, and F359V, in addition to T315I.¹³⁵

BCR-ABL1 compound mutations (variants containing ≥ 2 mutations within the same *BCR-ABL1* allele that presumably arise sequentially) confer different levels of resistance to TKI therapy, and T315I-inclusive compound mutants confer the highest level of resistance to all TKIs, including ponatinib.^{190,191} In a more recent study that used NGS to detect low-level and *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.¹⁹²

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.¹⁹³ The guidelines recommend *BCR-ABL1* 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. Treatment options based on BCR-ABL1 kinase domain mutation status are outlined on CML-5 (page 1389).

BCR-ABL1 mutational analysis provides additional guidance in the selection of subsequent TKI therapy only in patients with identifiable mutations. In patients with no identifiable mutations, the selection of subsequent TKI therapy should be based on the toxicity profile of TKI, patient age, ability to tolerate therapy, and the presence of comorbid conditions.

BCR-ABL1-independent Mutations

Mutations in a variety of cancer-associated genes other than *BCR-ABL1* (eg, *ASXL1*, *RUNX1*, *IKZF1*, *TET1/2*, *IDH1/2*, *JAK2*, *DNMT3A/3B*, *EZH2*, *WT1*, *NPM1*, *NRAS*, *KRAS*, *CBL*, *BCOR*, *CREBBP*, and *TP53*) have been described in patients with CML at diagnosis and in patients with AP-CML or BP-CML.^{194–201} *IKZF1* exon deletions and mutations in *ASXL1*, *RUNX1*, and *BCOR* genes were the most frequently described in advanced phase CML, while *IDH1/2* mutations were detected at a markedly lower frequency.^{200,201} *IKZF1* and *RUNX1* alterations, both involved in cell differentiation, were identified as important markers of disease progression from CP-CML to BP-CML.^{194,199} In one study that analyzed the mutation landscape of patients with CML using a panel of 92 genes

associated with myeloid malignancy, the presence of mutations in genes involved in epigenetic regulation pathways at diagnosis (eg, *ASXL1*, *BCOR*, *TET1/2*, *IDH1/2*, *DNMT3A/3B*, and *EZH2*) was associated with poor response to TKI therapy (CCyR at 12 months, $P=.02$; MMR at 24 months, $P=.04$; and MR4.5 at 36 months, $P=.03$) independent of other clinical factors.¹⁹⁷

However, many of these studies did not indicate whether the patients had CP-CML at diagnosis, and the impact of mutations is also variable depending on whether they occur in Ph-positive or Ph-negative clones.²⁰⁰ Therefore, these results are not indicative of the frequency of mutations in cancer-associated genes in patients with CP-CML at diagnosis and results are not definitive.

Rising *BCR-ABL1* Transcripts

Rising *BCR-ABL1* transcripts are associated with an increased likelihood of detecting *BCR-ABL1* kinase domain mutations and cytogenetic relapse.^{202–206} In patients who had achieved very low levels of *BCR-ABL1* transcripts, emergence of *BCR-ABL1* kinase domain mutations was more frequent in those who had >2 -fold increase in *BCR-ABL1* transcripts compared with those with stable or decreasing *BCR-ABL1* transcripts.²⁰² A serial rise has been reported to be more reliable than a single ≥ 2 -fold increase in *BCR-ABL1* transcripts.^{203,204} 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.²⁰⁴

Rising transcript levels should prompt 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.²⁰⁶ Some laboratories have advocated a 2- to 3-fold range,^{125,205,206} while others have taken a more conservative approach (5–10-fold).²⁰⁴ 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; $\leq 0.0032\%$ *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 (with close monitoring) in carefully selected patients who have

achieved and maintained DMR ($\geq \text{MR4.0}$; $\leq 0.01\%$ *BCR-ABL1* IS) for ≥ 2 or more years has been evaluated in several clinical studies. Limited longer-term follow-up data from the TKI discontinuation trials are summarized in Table 7.

The possibility of TFR after discontinuation of imatinib was first evaluated in the Stop Imatinib (STIM1) study in 100 patients with undetectable *BCR-ABL1* transcripts for at least 2 years (5-log reduction in *BCR-ABL1* transcripts and undetectable minimal residual disease on qPCR with a sensitivity of ≥ 4.5 -log reduction from the standardized baseline).^{207,208} With a median follow-up of 77 months after discontinuation of imatinib, the molecular recurrence-free survival was 43% at 6 months and 38% at 60 months.²⁰⁸ Other subsequent studies that have evaluated the discontinuation of imatinib have also reported similar findings.^{209–213}

More recent studies have also confirmed the feasibility of TFR after discontinuation of dasatinib or nilotinib in patients with CP-CML who have achieved and maintained MR4.5 for 12 months after ≥ 2 years of TKI therapy in the first-line or second-line setting (TFR rates ranging from 44% to 54%; Table 7).^{214–220} The feasibility of TFR after discontinuation of bosutinib or ponatinib has not yet been evaluated in clinical studies. In the EURO-SKI study that evaluated TFR after discontinuation of any first-line TKI therapy (imatinib, dasatinib, or nilotinib) in eligible patients, the type of first-line TKI therapy did not significantly affect molecular relapse-free survival.²¹⁸ Therefore, it is reasonable to assume that the likelihood of TFR after discontinuation would be similar irrespective of TKI in patients who have achieved and maintained DMR (MR4.0; $\leq 0.01\%$ *BCR-ABL1* IS) for ≥ 2 years.

The results of the RE-STIM study demonstrated the safety of a second TKI discontinuation after a first unsuccessful attempt.²²¹ The rate of molecular relapse after the first TKI discontinuation attempt was the only factor significantly associated with outcome. The TFR rate at 24 months after second TKI discontinuation was higher for patients who remained in 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 one month after discontinuation of TKI therapy. Resumption of TKI therapy immediately after recurrence results in the achievement of DMR in almost all patients.^{207–219} 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

Table 7. Summary of Limited Longer-Term Follow-Up Data From the TKI Discontinuation Trials

Trial	Treatment Prior to Discontinuation	No. of Patients	Depth and Duration of MR Required for Discontinuation	Trigger to Resume TKI Therapy	Median Follow-Up	Treatment-Free Remission Rate
STIM1 ²⁰⁸	Imatinib ± interferon	100	MR5.0 for at least 2 y	Loss of MR5.0	77 mo	38% at 60 mo
TWISTER ²¹³	Imatinib ± interferon	40	MR4.5 for at least 2 y	Loss of MR5.0	103 mo	45% (molecular relapse-free survival 45% at 8 y)
HOVON ²⁰⁹	Imatinib + cytarabine	15	MR4.5 for at least 2 y	Loss of MR4.5	36 mo	33% at 24 mo
A-STIM ²¹⁰	Imatinib ± interferon	80	MR5.0 for at least 2 y	Loss of MMR	31 mo	61% at 36 mo
ISAV study ²¹¹	Imatinib (after failure of interferon or hydroxyurea)	108	CMR for at least 18 mo	Loss of MMR	36 mo	52% at 36 mo
KID study ²¹²	Imatinib ± interferon	90	MR4.5 for at least 2 y	Loss of MMR	27 mo	59% at 24 mo
Stop 2G-TKI ²¹⁴	Dasatinib/Nilotinib (first- or second-line)	60	MR4.5 for at least 24 mo	Loss of MMR	47 mo	54% at 48 mo
DASFREE ²¹⁹	Dasatinib (first- or second-line)	84	MR4.5 for 12 mo	Loss of MMR	2 y	46% at 24 mo
ENESTFreedom ²¹⁵	Nilotinib (first-line)	190	MR4.5 for 12 mo	Loss of MMR	96 wk	49% at 96 wk
ENESTop study ²¹⁶	Nilotinib (second-line)	126	MR4.5 for 12 mo	Loss of MMR	96 wk	53% at 96 wk
DADI ²²⁰	Dasatinib (first-line)	68	MR4.5 for at least 24 mo	Loss of MMR	23 mo	55% at 6 mo
DADI ²¹⁷	Dasatinib (second-line)	63	MR4.0 for at least 12 mo	Loss of MR4.0	44 mo	44% at 36 mo
EURO-SKI ²¹⁸	Any TKI	758	MR4.0 for at least 1 y	Loss of MMR	27 mo	50% at 24 mo

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

studies,^{212,215,216,219} and the occurrence of imatinib withdrawal syndrome was associated with a lower rate of molecular relapse in the KID study.²¹²

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.^{207,208} The results of the A-STIM study showed that loss of MMR ($\leq 0.1\%$ *BCR-ABL1* IS) could be used as a practical criterion for restarting therapy. The estimated probability of MMR loss was 35% at 12 months and 36% at 24 months after discontinuation of imatinib.²¹⁰ Several factors may help predict the risk of recurrence after discontinuation of TKI therapy (eg, a higher Sokal risk score, female gender, lower natural killer cell counts, suboptimal response or resistance to imatinib, duration of TKI therapy, and DMR prior to TKI discontinuation).^{207,208,212,214–219,222} However, only the duration of TKI therapy and DMR prior to TKI discontinuation therapy have been associated with TFR with a high level of consistency.^{207,212,218,219} 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.²¹⁸

Based on the available evidence from clinical studies that have evaluated the feasibility of TFR, the panel

members feel that discontinuation of TKI therapy (with close monitoring) is feasible in carefully selected, consenting patients (in early CP-CML) who have achieved and maintained a DMR ($\geq \text{MR4.0}$) for ≥ 2 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* $\leq 0.0032\%$ 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.

The criteria for the selection of patients suitable for discontinuation of TKI therapy are outlined on CML-E (page 1394). The guidelines emphasize that discontinuation of TKI therapy outside of a clinical trial should be considered only if *all* the criteria included on the list are met. 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 panel recommendations for molecular monitoring in TFR phase are outlined on CML-E.

Emerging Treatment Options

Novel BCR-ABL1 inhibitors and small molecule inhibitors targeting several BCR-ABL1-independent pathways have shown efficacy in preliminary clinical trials.^{223,224} These novel agents (either as monotherapy or in combination with currently approved TKIs) are being evaluated in ongoing clinical trials in all 3 phases of CML. Results from selected published clinical trials of novel agents are outlined in Table 8.

The use of low-dose interferon in combination with TKI for a limited period prior to discontinuation of TKI, and gradual de-escalation of TKI before discontinuation of TKI therapy in patients with DMR are also being explored in ongoing clinical trials as potential strategies to improve TFR outcome.^{224,225} Pegylated interferon in combination with TKIs has demonstrated promising results, and ongoing clinical trials are evaluating the combination of second-generation TKIs with various pegylated interferons.²²⁶

Immunologic approaches such as the use of BCR-ABL1 immune peptides, immune checkpoint blockade, leukemia-associated antigens, and dendritic cell vaccines are also being evaluated to improve molecular response.²²³

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 at the time of diagnosis are of reproductive age.²²⁷ 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 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 men on TKI therapy.^{228–232}

The situation is more complex for women, as TKI therapy during pregnancy has been associated with both a higher rate of miscarriage and fetal abnormalities. Limited evidence from case reports on women with CML exposed to imatinib, dasatinib, or nilotinib during pregnancy indicates the need for close monitoring, a prolonged washout period prior to pregnancy, and prompt consideration of holding TKI therapy if pregnancy occurs while on imatinib, nilotinib, or dasatinib.^{233–237} In one report on the outcome of pregnancies in 180 women exposed to imatinib during pregnancy, 50% of pregnancies with

known outcome were normal and 10% of pregnancies with known outcome had fetal abnormalities.²³³ Eighteen pregnancies ended in spontaneous abortion. In another report on the outcomes of pregnancy and conception during treatment with dasatinib, among 46 women treated with dasatinib, 15 women (33%) delivered a normal infant.²³⁴ Elective or spontaneous abortions were reported in 18 women (39%) and 8 women (17%), respectively, and 5 women (11%) had an abnormal pregnancy. Fetal abnormalities were reported in 7 cases. Among 33 women who conceived with dasatinib-treated men, 30 (91%) delivered infants who were normal at birth. Although there are no data regarding the outcome of pregnancy in patients receiving bosutinib or ponatinib at the time of conception, these agents must be considered unsafe for use in pregnant women.

Discontinuation of TKI therapy because of pregnancy in women who were not in DMR ($\geq$ MR4.0; $\leq$ 0.01% BCR-ABL1 IS) has only been reported in small series of patients.^{238–241} In one series, among 10 women who stopped imatinib because of pregnancy after a median of 8 months of therapy, 5 of the 9 women who had achieved a CHR lost the response after stopping therapy, and 6 had an increase in Ph-positive metaphases.²³⁸ At 18 months after resuming therapy, all 9 patients had experienced a CHR but only 3 experienced CCyR and none had experienced an MMR. In another series that reported the outcomes of 7 women who were not in DMR at the time imatinib was stopped because of pregnancy, 3 were in an MMR.²³⁹ All 7 women had disease relapse. The 3 women who had an MMR at the time imatinib was stopped were able to regain the same response once the drug was restarted, whereas the remaining 4 patients were not.

Depending on other factors such as age, a natural pregnancy may occur months after stopping TKI therapy. Assuming the earliest time a woman could conceive and give birth naturally, without any washout period, is 10 months after stopping TKI, the likelihood is about 60% that her PCR will become positive if she was in DMR at the time of getting pregnant.^{238,239}

Conception while on active TKI therapy is strongly discouraged due to the risk of fetal abnormalities. Before attempting pregnancy, women 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. Fertility preservation should be discussed with all patients of childbearing age before the start of TKI therapy. Referral to a CML specialty center and consultation with a high-risk obstetrician is recommended.

Planning a Pregnancy

In men, the general recommendation is that TKI therapy need not be discontinued if a pregnancy is planned.

Table 8. Results from Selected Published Clinical Trials Evaluating Novel Treatment Options

Drug Class	Clinical Trial	TKI	No. of Patients	Median Follow-Up	Response Rates
BCR-ABL1 inhibitors	Phase I (dose-escalation study) ²⁶⁴ CP-CML or AP-CML with resistance or intolerance to at least 2 previous TKIs	Asciminib (10–200 mg once or twice daily)	CP-CML without T315I (n=113)	72 wk	MCyR: 77%; CCyR: 70%
			CP-CML with T315I (n=28)	37 wk	MCyR: 60%; CCyR: 44%
			AP-CML without T315I (n=4)	46 wk	CHR: 100%; CCyR: 0%
			AP-CML with T315I (n=5)	16 wk	CHR: 80%; CCyR: 20%
	Phase III (REPRISE study) ²⁶⁵ Newly diagnosed CP-CML	Radotinib (300 mg twice daily)	n=79	≥48 mo	MMR: 85%; MR4.5: 58%
		Radotinib (400 mg twice daily)	n=81		MMR: 83%; MR4.5: 56%
		Imatinib (400 mg once daily)	n=81		MMR: 75%; MR4.5: 49%
	Phase II ²⁶⁶ CP-CML or AP-CML with resistance or intolerance to imatinib	Radotinib (400 mg twice daily)	n=77	23 mo	MCyR: 65%; CCyR: 47%; MMR: 14%
Aurora kinase inhibitors	Phase I ²⁶⁷ CP-CML or AP/BP-CML after failure of imatinib	Lonafarnib (100 mg twice daily) + imatinib (400 mg once daily)	CP-CML (n=9)		CHR: 9%; CCyR: 4%
		Lonafarnib (100 mg twice daily) + imatinib (600 mg once daily)	AP/BP-CML (n=14)		CHR: 14%; PCyR: 4%
	Phase I ²⁶⁸ CP-CML CML after failure of imatinib	Tipifarnib (300 mg twice daily) + imatinib (400 mg once daily)	n=26		CHR: 68%; CCyR: 12%
Farnesyl transferase inhibitors	Phase I (dose-escalation study) ²⁶⁹ AP-CML or BP-CML with resistance or intolerance to previous TKIs	Danusetib (180 mg/m ² ; 3-hour IV infusion; days 1–7; 14-d cycle)	AP-CML (n=7)		CHR: 3%
			BP-CML (n=9)		CCyR: 4%
	Phase II ²⁷⁰ CP-CML, AP/BP-CML with T315I mutation	Tozasertib (5-day continuous IV infusion every 14 d at 40 mg/m ² /h, 32 mg/m ² /h, or 24 mg/m ² /h)	CP-CML (n=15)		CHR: 7%; MCyR: 13%; CCyR: 13%
			AP-CML (n=14)		MCyR: 7%; CCyR: 7%
			BP-CML (n=11)		MCyR: 9%
JAK2 inhibitors	Phase I (dose-escalation study) ²⁷¹ CP-CML with no history of disease progression to AP-CML or BP-CML	Ruxolitinib (5, 10, and 15 mg) + nilotinib (300 mg or 400 mg twice daily)	n=11		40% had values between MMR and MR4.0; 10% had values between MR4.0 and MR4.5; and 40% had MR4.5

Abbreviations: AP, acute phase; BP, blast phase; CHR, complete hematologic response; CCyR, complete cytogenetic response; CML, chronic myeloid leukemia; CP, chronic phase; IV, intravenous; MMR, major molecular response ($\leq 0.1\%$ *BCR-ABL1* IS); MCyR, major cytogenetic response; MR, molecular response; MR4.0, $\leq 0.01\%$ *BCR-ABL1* IS; MR4.5, $\leq 0.0032\%$ *BCR-ABL1* IS or > 4.5 -log reduction of *BCR-ABL1* and undetectable minimal residual disease on qPCR with a sensitivity of ≥ 4.5 -log reduction; MR5.0, 5-log reduction in *BCR ABL1* levels and undetectable minimal residual disease on qPCR with a sensitivity of ≥ 4.5 -log reduction; TKI, tyrosine kinase inhibitor.

However, experience is limited. Sperm banking can also be performed prior to starting TKI therapy, although there are no data regarding quality of sperm in men with untreated CML.

In women, due to the risk of miscarriage and fetal abnormalities during pregnancy, TKI therapy should be stopped prior to natural conception and the patient should remain off therapy during pregnancy.^{233–235} Referral to an in vitro fertilization (IVF) center is recommended in coordination with the patient's obstetrician. TKI should be stopped before attempting a natural pregnancy or oocyte retrieval, but the optimal timing of discontinuation is unknown. Compounding the high incidence of disease recurrence off TKI therapy are the significant obstacles that exist for women who choose one of the

previously mentioned forms of IVF, chief among which is the lack of access to centers that perform the procedure, high costs associated with the drugs and surgical procedures that may not be covered by insurance, costs of embryo/oocyte storage, and access to surrogate programs. Some women may require more than one IVF cycle to obtain enough potentially viable embryos for implantation. In addition, women may need a family medical leave from work to attend IVF appointments. It is also important to note that not all states allow surrogacy.

Treatment and Monitoring During Pregnancy

Most of the literature regarding treatment during pregnancy consists of case reports. The use of TKI therapy,

particularly during the first trimester, should be avoided. If TKI therapy should be 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 prior to initiation of TKI therapy.

Interferon alpha and hydroxyurea have been used during pregnancy.^{242–250} If treatment is deemed necessary during pregnancy, interferon can induce and maintain hematologic remission; if introduced earlier, interferon can preserve molecular remission after discontinuation of TKI.^{251,252} It is preferable to initiate treatment with interferon and the panel recommends against the use of hydroxyurea during pregnancy, especially in the first trimester, if possible. Data are insufficient to establish the use of peginterferon alfa-2a (risk category C) in pregnancy, and it should be used only if benefits outweigh potential risk to the fetus.²⁵³

Leukapheresis can be used for a rising white blood cell (WBC) count, although there are no data that

recommend at what level of white blood cell count leukapheresis should be initiated.^{249,254–256} Low-dose aspirin or low-molecular-weight heparin can be considered for patients with thrombocytosis.^{257,258}

Monthly monitoring with qPCR and initiating treatment if the *BCR-ABL1* IS increases to >1.0% is recommended.

Breastfeeding

TKI therapy can be restarted after delivery. However, women on TKI therapy should be advised not to breastfeed, as TKIs pass into human breast milk.^{259–262} Breastfeeding without TKI treatment may be safe with molecular monitoring, but 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.^{262,263}

Close molecular monitoring is recommended for women 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.²⁶²

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Individual Disclosures for the NCCN Chronic Myeloid Leukemia Panel

Panel Member	Clinical Research Support/Data Safety Monitoring Board	Scientific Advisory Boards, Consultant, or Expert Witness	Promotional Advisory Boards, Consultant, or Speakers Bureau	Specialties
Jessica K. Altman, MD	Agios Pharmaceuticals, Inc.; Amphivena Therapeutics, Inc.; Aprea Therapeutics AB; Astellas Pharma US, Inc.; BioSight Ltd.; Boehringer Ingelheim GmbH; Celgene Corporation; Fujifilm Corporation; and GlycoMimetics, Inc.	AbbVie, Inc.; Astellas Pharma US, Inc.; BioSight Ltd.; Daiichi-Sankyo, Co.; Phebra Pty, Ltd.; and Theradex	None	Hematology/Hematology Oncology
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Gabriela Hobbs, MD	None	Bristol-Myers Squibb Company; Celgene Corporation; Constellation Pharmaceuticals, Inc.; Jazz Pharmaceuticals Inc.; and Novartis Pharmaceuticals Corporation	None	Hematology/Hematology Oncology, and Medical Oncology
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Monica Mead, MD	None	None	None	Medical Oncology
Leland Metheny, MD	None	Incyte Corporation, and Takeda Pharmaceuticals North America, Inc.	None	Hematology/Hematology Oncology, and Bone Marrow Transplantation
Sanjay Mohan, MD, MSCI	Astex Pharmaceuticals, Inc.	None	None	Hematology/Hematology Oncology
Joseph O. Moore, MD	Novartis Pharmaceuticals Corporation, and Pharmacyclis, Inc.	Novartis Pharmaceuticals Corporation	Pharmacyclis, Inc.	Medical Oncology
Kiran Naqvi, MD, MPH	None	None	None	Hematology/Hematology Oncology
Vivian Oehler, MD	None	None	Bristol-Myers Squibb Company, and Takeda Pharmaceuticals North America, Inc.	Hematology/Hematology Oncology
Arnel M. Pallera, MD	None	None	None	
Mrinal Patnaik, MD	None	Stem Line Pharmaceuticals	None	Medical Oncology
Keith Pratz, MD	AbbVie, Inc.; Agios Pharmaceuticals Inc.; Astellas Pharma US, Inc.; Takeda Pharmaceuticals North America, Inc.	AbbVie, Inc.; Agios Pharmaceuticals, Inc.; Astellas Pharma US, Inc.; Boston Biomedical, Inc.; and Bristol-Myers Squibb Company	None	Medical Oncology
Iskra Pusic MD, MSCI	None	Incyte Corporation, and Kadmon Corporation	None	Medical Oncology
Michal G. Rose, MD	None	None	None	Medical Oncology
Neil P. Shah MD, PhD	Bristol-Myers Squibb Company; PTC Therapeutics, Inc.; and Sierra Oncology	None	None	Hematology/Hematology Oncology
B. Douglas Smith, MD	Celgene Corporation	Agios Pharmaceuticals, Inc.; Jazz Pharmaceuticals Inc.; Novartis Pharmaceuticals Corporation; and Pfizer Inc.	None	Medical Oncology, and Internal Medicine
David S. Snyder, MD	None	None	None	Hematology/Hematology Oncology, and Bone Marrow Transplantation
Kendra L. Sweet, MD, MS	AROG Pharmaceuticals; ImmunoGen, Inc.; and Incyte Corporation	Bristol-Myers Squibb Company; Novartis Pharmaceuticals Corporation; and Takeda Pharmaceuticals North America, Inc.	Astellas Pharma US, Inc., and Stemline Therapeutics, Inc.	Hematology/Hematology Oncology; Medical Oncology; and Internal Medicine
Moshe Talpaz, MD	Takeda Pharmaceuticals North America, Inc.	Celgene Corporation; CTI BioPharma Corp.; and Novartis Pharmaceuticals Corporation	None	Medical Oncology
James Thompson, MD, MS	None	None	None	Hematology/Hematology Oncology
David T. Yang, MD	None	None	None	Pathology

The NCCN Guidelines Staff have no conflicts to disclose.