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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Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

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

Disclosures for the NCCN Chronic Myeloid Leukemia Panel

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

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

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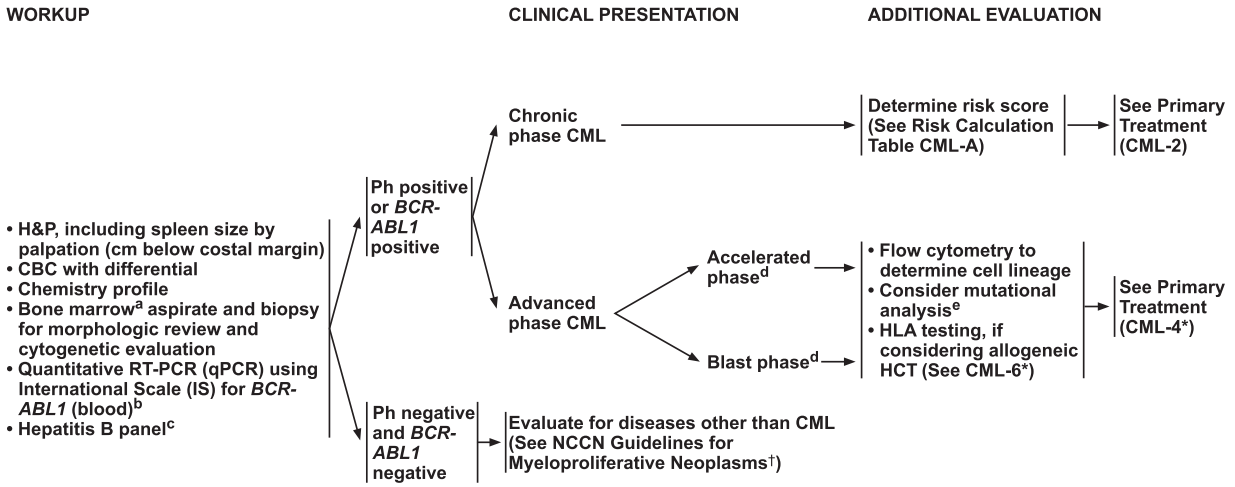

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[a] Bone marrow evaluation should be done for the initial workup, to provide morphologic review, and also to detect chromosomal abnormalities in addition to the Ph chromosome. Fluorescence in situ hybridization (FISH) can be used if cytogenetic evaluation 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.

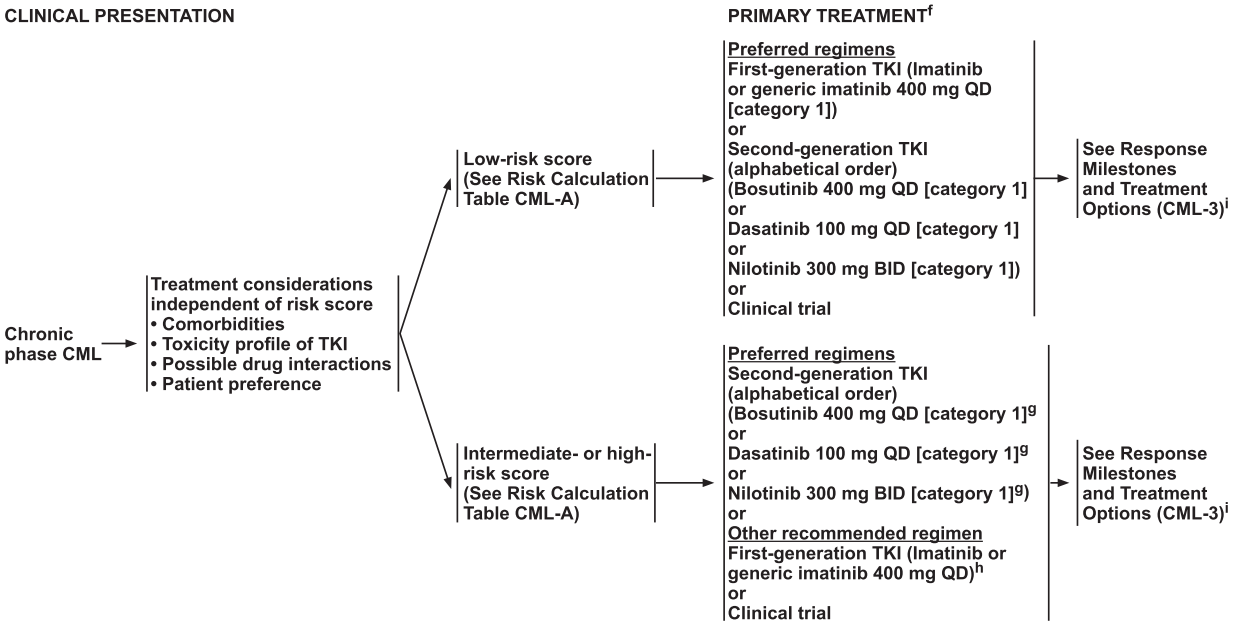
CML-1

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 Ib and Ia, or between *ABL1* exons 1 and 2.[3,4] Irrespective of the precise *ABL1* breakpoint, splicing almost invariably fuses *ABL1* exon 2 with *BCR* exons 13 or 14, resulting in e13a2 and e14a2 transcripts that code for a protein, p210, with deregulated tyrosine kinase activity, which causes CML. Unusual *BCR-ABL1* transcripts, e1a2 encoding for p190 (involving the minor 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



[f] See Management of CML During Pregnancy (CML-C).
[g] 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).

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 ≥100,000 normal cells. qPCR results can be expressed in various ways, for

EARLY TREATMENT RESPONSE MILESTONES[i,j]

BCR-ABL1 (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	• Evaluate patient compliance and drug interactions • Consider mutational analysis	Switch to alternate TKI (CML-5) and evaluate for allogeneic HCT
YELLOW	Possible TKI resistance	• 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	• If treatment goal is long-term survival: >0.1%–1% optimal • If treatment goal is treatment-free remission: ≤0.1% optimal	• 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).

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 10^8 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.

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

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 ≥MR4.0; ≤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 1 OF 2

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 Sokol 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

[1] Ramasamy K, Hayden J, Lim Z, et al. Successful pregnancies involving men with chronic myeloid leukaemia on imatinib therapy. Br J Haematol 2007;137:374-375.
[2] Breccia M, Cannella L, Montefusco E, et al. Male patients with chronic myeloid leukemia treated with imatinib involved in healthy pregnancies: report of five cases. Leuk Res 2008;32:519-520.
[3] Oweini H, Otrock ZK, Mahfouz RAR, Bazarbachi A. Successful pregnancy involving a man with chronic myeloid leukemia on dasatinib. Arch Gynecol Obstet 2011;283:133-134.
[4] Ghalaut VS, Prakash G, Bansal P, et al. Effect of imatinib on male reproductive hormones in BCR-ABL positive CML patients: A preliminary report. J Oncol Pharm Pract 2014;20:243-248.
[5] Alizadeh H, Jaafar H, Rajnics P, et al. Outcome of pregnancy in chronic myeloid leukaemia patients treated with tyrosine kinase inhibitors: short report from a single centre. Leuk Res 2015;39:47-51.
[6] Pye SM, Cortes J, Ault P, et al. The effects of imatinib on pregnancy outcome. Blood 2008;111:5505-5508.
[7] Cortes JE, Abruzzese E, Chelysheva E, et al. The impact of dasatinib on pregnancy outcomes. Am J Hematol 2015;90:1111-1115.
[8] Barkoulas T, Hall PD. Experience with dasatinib and nilotinib use in pregnancy. J Oncol Pharm Pract 2018;24:121-128.
[9] Salem W, Li K, Krapp C, et al. Imatinib treatments have long-term impact on placentation and embryo survival. Sci Rep 2019;9:2535.
[10] Madabhavi I, Sarkar M, Modi M, Kadakol N. Pregnancy outcomes in chronic myeloid leukemia: A single center experience. J Glob Oncol 2019;5:1-11.
[11] Ault P, Kantarjian H, O'Brien S, et al. Pregnancy among patients with chronic myeloid leukemia treated with imatinib. J Clin Oncol 2006;24:1204-1208.
[12] Kuwabara A, Babb A, Ibrahim A, et al. Poor outcome after reintroduction of imatinib in patients with chronic myeloid leukemia who interrupt therapy on account of pregnancy without having achieved an optimal response. Blood 2010;116:1014-1016.
[13] Lasica M, Willcox A, Burbury K, et al. The effect of tyrosine kinase inhibitor interruption and interferon use on pregnancy outcomes and long-term disease control in chronic myeloid leukemia. Leuk Lymphoma 2019;60:1796-1802~~:1-7~~.
[14] Stella S, Tirro E, Massimino M, et al. Successful management of a pregnant patient with chronic myeloid leukemia receiving standard dose imatinib. In Vivo 2019;33:1593-1598.
[15] Haggstrom J, Adriansson M, Hybbinette T, et al. Two cases of CML treated with alpha-interferon during second and third trimester of pregnancy with analysis of the drug in the new-born immediately postpartum. Eur J Haematol 1996;57:101-102.
[16] Kuroiwa M, Gondo H, Ashida K, et al. Interferon-alpha therapy for chronic myelogenous leukemia during pregnancy. Am J Hematol 1998;59:101-102.
[17] Lipton JH, Derzko CM, Curtis J. Alpha-interferon and pregnancy in a patient with CML. Hematol Oncol 1996;14:119-122.
[18] Baykal C, Zengin N, Coskun F, et al. Use of hydroxyurea and alpha-interferon in chronic myeloid leukemia during pregnancy: a case report. Eur J Gynaecol Oncol 2000;21:89-90.
[19] Thauvin-Robinet C, Maingueneau C, Robert E, et al. Exposure to hydroxyurea during pregnancy: a case series. Leukemia 2001;15:1309-1311.
[20] Fadilah SA, Ahmad-Zailani H, Soon-Keng C, Norlaila M. Successful treatment of chronic myeloid leukemia during pregnancy with hydroxyurea. Leukemia 2002;16:1202-1203.
[21] Al Bahar S, Pandita R, Nath SV. Pregnancy in chronic myeloid leukemia patients treated with alpha interferon. Int J Gynaecol Obstet 2004;85:281-282.
[22] Koh LP, Kanagalingam D. Pregnancies in patients with chronic myeloid leukemia in the era of imatinib. Int J Hematol 2006;84:459-462.
[23] Balsat M, Etienne M, Elhamri M, et al. Successful pregnancies in patients with BCR-ABL-positive leukemias treated with interferon-alpha therapy during the tyrosine kinase inhibitors era. Eur J Haematol 2018;101:774-780.
[24] Abruzzese E, Turkina AG, Apperley JF, et al. Pregnancy management in CML patients: To treat or not to treat? Report of 224 outcomes of the European Leukemia Net (ELN) Database [abstract]. Blood 2019;134:Abstract 498.
[25] Beauverd Y, Radia D, Cargo C, et al. Pegylated interferon alpha-2a for essential thrombocythemia during pregnancy: outcome and safety. A case series. Haematologica 2016;101:e182-184.
[26] Ali R, Ozkalemkas F, Ozkocaman V, et al. Successful pregnancy and delivery in a patient with chronic myelogenous leukemia (CML), and management of CML with leukapheresis during pregnancy: a case report and review of the literature. Jpn J Clin Oncol 2004;34:215-217.
[27] Palani R, Milojkovic D, Apperley JF. Managing pregnancy in chronic myeloid leukaemia. Ann Hematol 2015;94 Suppl 2:S167-176.
[28] Staley EM, Simmons SC, Feldman AZ, et al. Management of chronic myeloid leukemia in the setting of pregnancy: when is leukocytapheresis appropriate? A case report and review of the literature. Transfusion 2018;58:456-460.
[29] James AH, Brancazio LR, Price T. Aspirin and reproductive outcomes. Obstet Gynecol Surv 2008;63:49-57.
[30] Deruelle P, Coulon C. The use of low-molecular-weight heparins in pregnancy--how safe are they? Curr Opin Obstet Gynecol 2007;19:573-577.
[31] Russell MA, Carpenter MW, Akhtar MS, et al. Imatinib mesylate and metabolite concentrations in maternal blood, umbilical cord blood, placenta and breast milk. J Perinatol 2007;27:241-243.
[32] Ali R, Ozkalemkas F, Kimya Y, et al. Imatinib use during pregnancy and breast feeding: a case report and review of the literature. Arch Gynecol Obstet 2009;280:169-175.
[33] Drugs and Lactation Database (LactMed) [Internet]. Bethesda (MD): National Library of Medicine (US); 2006-.
[34] Chelysheva E, Aleshin S, Polushkina E, et al. Breastfeeding in patients with chronic myeloid leukaemia: Case series with measurements of drug concentrations in maternal milk and literature review. Mediterr J Hematol Infect Dis 2018;10:e2018027.
[35] Abruzzese E, Trawinska MM, Perrotti AP, De Fabritiis P. Tyrosine kinase inhibitors and pregnancy. Mediterr J Hematol Infect Dis 2014;6:e2014028.

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; ≤0.1% *BCR-ABL1* IS) and deep molecular response (DMR; MR4.5 [≤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]	• At diagnosis • Failure to reach response milestones • Any sign of loss of response (defined as hematologic or cytogenetic relapse)
qPCR using IS	• At diagnosis • Every 3 months after initiating treatment. After *BCR-ABL1* (IS) ≤1%[2] has been achieved, every 3 months for 2 years and every 3–6 months thereafter • If there is 1-log increase in *BCR-ABL1* transcript levels with MMR, qPCR should be repeated in 1–3 months
BCR-ABL1 kinase domain mutation analysis	• Chronic phase ‣ Failure to reach response milestones ‣ Any sign of loss of response (defined as hematologic or cytogenetic relapse) ‣ 1-log increase in *BCR-ABL1* transcript levels and loss of MMR • Disease progression to accelerated or blast phase[3]

[1] FISH has been inadequately studied for monitoring response to treatment.
[2] CCyR correlates with *BCR-ABL1* (IS) ≤1%.
[3] Consider myeloid mutation panel to identify *BCR-ABL1*–independent resistance mutations in patients with no BCR-ABL1 kinase domain mutations.

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 response[1]
- **Complete normalization of peripheral blood counts with leukocyte count <10 x 10^9/L**
- **Platelet count <450 x 10^9/L**
- **No immature cells, such as myelocytes, promyelocytes, or blasts in peripheral blood**
- **No signs and symptoms of disease with resolution of palpable splenomegaly**

Cytogenetic response[2,3]
- **Complete cytogenetic response (CCyR) - No Ph-positive metaphases**[4]
- **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) ≤10% at 3 and 6 months**
- **Major molecular response (MMR) - *BCR-ABL1* (IS) ≤0.1% or ≥3-log reduction in *BCR-ABL1* mRNA from the standardized baseline, if qPCR (IS) is not available**
- **Deep molecular response (DMR) is defined as MR4.0: *BCR-ABL1* (IS) ≤0.01% or MR4.5: *BCR-ABL1* (IS) ≤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) ≤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.

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* ≤0.01% IS) for ≥2 years, as documented on at least 4 tests, performed at least 3 months apart.[2]**
- **Access to a reliable qPCR test with a sensitivity of detection of at least MR4.5 (*BCR-ABL1* ≤0.0032% IS) and that provides results within 2 weeks.**
- **Monthly molecular monitoring for the first 6 months following discontinuation, bimonthly during months 7–12, and quarterly thereafter (indefinitely) for patients who remain in MMR (MR3; *BCR-ABL1* ≤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; ≤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* ≤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).

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

Continued on next page

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,

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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.

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 (≤1% *BCR-ABL1* IS; MR2.0) generally correlates with CCyR and a ≥3-log reduction (≤0.1% *BCR-ABL1* IS) is referred to as MMR or MR3.0.[13,108,109]

DMR is defined by the assay's level of sensitivity [≤0.01% *BCR-ABL1* (IS), MR4.0; ≤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 (≤0.1% *BCR-ABL1* IS); OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.
[a]Primary endpoint of DASISION study: confirmed CCyR rate at 12 mo.
[b]Primary endpoint of ENESTnd and BFORE studies: MMR (≤0.1% *BCR-ABL1* IS) rate at 12 mo.
[c]Long-term primary endpoint of IRIS trial in the imatinib group.
[d]Due to the high rate of crossover to imatinib (66%) and the short duration of therapy (<1 y) before crossover among patients who had been randomly assigned to interferon alfa + cytarabine, the long-term follow-up data focused on patients who had been randomly assigned to receive imatinib.
[e]Data include survival among the 363 patients who crossed over to imatinib.
[f]There 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 (≤10% *BCR-ABL1 IS* at 3 and 6 months, ≤1% *BCR-ABL1 IS* at 12 months, and ≤0.1% *BCR-ABL1* IS at >12 months). After CCyR (≤1% *BCR-ABL1 IS)* has been achieved, molecular monitoring is recommended every 3 months for 2 years and every 3 to 6 months thereafter.

Frequent molecular monitoring with qPCR (IS) can help to identify nonadherence to TKI therapy early in the treatment course.[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; ≤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

		Low-Risk		Intermediate-Risk		High-Risk	
Trial	Study Arms	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 (≤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

		Low-Risk			Intermediate-Risk			High-Risk		
Trial	Study Arms	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

		5-y PFS		5-y OS	
Trial	Study Arms	*BCR-ABL1* ≤10%	*BCR-ABL1* >10%	*BCR-ABL1* ≤10%	*BCR-ABL1* >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 (≤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; ≤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 (≤1% *BCR-ABL1* IS, which corresponds to CCyR) or MMR (≤0.1% *BCR-ABL1* IS) within 12 months after first-line TKI therapy. The guidelines emphasize that achievement of response milestones must be interpreted within the clinical context, before making drastic changes to the treatment strategy, especially in ambiguous situations.

The panel has included ≤10% *BCR-ABL1* IS at 3 and 6 months after initiation of first-line TKI therapy as a response milestone, 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 (≤1% *BCR-ABL1* IS, which correlates with CCyR) is considered the optimal response milestone at 12 months if the goal of therapy in an individual patient is long-term survival, whereas the achievement of MMR (≤0.1% *BCR-ABL1* IS) at 12 months should be considered as the optimal response milestone if the treatment goal in an individual patient is TFR. Patients who experience these response milestones are considered to have TKI-sensitive disease, and continuation of the same dose of TKI and assessment of *BCR-ABL1* transcripts with qPCR (IS) every 3 months is recommended for this group of patients.

In patients with a >10% *BCR-ABL1* IS at 3 months and >1% *BCR-ABL1* IS at 12 months, clinical judgment should be used, considering problems with adherence (which can be common given drug toxicity at 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 ≤10% *BCR-ABL1* IS at 3 months or ≤1% *BCR-ABL1* IS at 12 months is associated with a higher risk for disease progression. Patients with >10% *BCR-ABL1* at 3 months or >1% *BCR-ABL1* at 12 months can 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 (≤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-ABL*1 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 (≤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) Imatinib-I (n=95)	4 y	59%	45%	—	57%	78%
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, chromic phase chronic myeloid leukemia; I, intolerant; MCyR, major cytogenetic response; MMR, major molecular response (≤0.1% *BCR-ABL1* IS); OS, overall survival; PFS, progression-free survival; R, resistant; TKI, tyrosine kinase inhibitor.
[a]Primary endpoint: MCyR rate at 6 mo when administered 100 mg once daily vs 70 mg twice daily.
[b]Primary endpoint: MCyR rate in patients with imatinib intolerance or imatinib-resistant disease.
[c]Primary 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 (≤10% *BCR-ABL1* IS) After Second-Line TKI Therapy and Survival Outcomes

		PFS				OS			
		BCR-ABL1 ≤10%		*BCR-ABL1* >10%		*BCR-ABL1* ≤10%		*BCR-ABL1* >10%	
TKI	Median Follow-Up	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 ≤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; ≤0.0032% *BCR-ABL*1 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 (≥MR4.0; ≤0.01% *BCR-ABL1* IS) for ≥2 or more years has been evaluated in several clinical studies. Limited longer-term follow-up data from the TKI discontinuation trials are summarized in Table 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; ≤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 (≤0.1% *BCR-ABL1* IS); MR, molecular response; MR4.0, ≤0.01% *BCR-ABL1* IS; MR4.5, ≤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 (≤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 (≥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* ≤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 (≥MR4.0; ≤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 T3151 (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	**Danusertib** (180 mg/m²; 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/m²/h, 32 mg/m²/h, or 24 mg/m²/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 (≤0.1% *BCR-ABL1* IS); MCyR, major cytogenetic response; MR, molecular response; MR4.0, ≤0.01% *BCR-ABL1* IS; MR4.5, ≤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]

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70:7–30.
2. Faderl S, Talpaz M, Estrov Z, et al. The biology of chronic myeloid leukemia. N Engl J Med 1999;341:164–172.
3. Melo JV. The diversity of BCR-ABL fusion proteins and their relationship to leukemia phenotype. Blood 1996;88:2375–2384.
4. Melo JV. BCR-ABL gene variants. Baillieres Clin Haematol 1997;10: 203–222.
5. Sawyers CL. Chronic myeloid leukemia. N Engl J Med 1999;340:1330–1340.
6. Radich JP, Dai H, Mao M, et al. Gene expression changes associated with progression and response in chronic myeloid leukemia. Proc Natl Acad Sci USA 2006;103:2794–2799.
7. Jamieson CHM, Ailles LE, Dylla SJ, et al. Granulocyte-macrophage progenitors as candidate leukemic stem cells in blast-crisis CML. N Engl J Med 2004;351:657–667.
8. Mitelman F. The cytogenetic scenario of chronic myeloid leukemia. Leuk Lymphoma 1993; 11(sup1, Suppl 1)11–15.
9. Douet-Guilbert N, Morel F, Le Charpentier T, et al. Interphase FISH for follow-up of Philadelphia chromosome-positive chronic myeloid leukemia treatment. Anticancer Res 2004;24:2535–2539.
10. Seong DC, Kantarjian HM, Ro JY, et al. Hypermetaphase fluorescence in situ hybridization for quantitative monitoring of Philadelphia chromosome-positive cells in patients with chronic myelogenous leukemia during treatment. Blood 1995;86:2343–2349.
11. Dewald GW, Wyatt WA, Juneau AL, et al. Highly sensitive fluorescence in situ hybridization method to detect double BCR/ABL fusion and monitor response to therapy in chronic myeloid leukemia. Blood 1998;91: 3357–3365.
12. Kantarjian HM, Talpaz M, Cortes J, et al. Quantitative polymerase chain reaction monitoring of BCR-ABL during therapy with imatinib mesylate (STI571; gleevec) in chronic-phase chronic myelogenous leukemia. Clin Cancer Res 2003;9:160–166.
13. 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.
14. Biernaux C, Loos M, Sels A, et al. Detection of major bcr-abl gene expression at a very low level in blood cells of some healthy individuals. Blood 1995;86:3118–3122.
15. Bose S, Deininger M, Gora-Tybor J, et al. The presence of typical and atypical BCR-ABL fusion genes in leukocytes of normal individuals: biologic significance and implications for the assessment of minimal residual disease. Blood 1998;92:3362–3367.
16. Baccarani M, Castagnetti F, Gugliotta G, et al. The proportion of different BCR-ABL1 transcript types in chronic myeloid leukemia. An international overview. Leukemia 2019;33:1173–1183.
17. Hanfstein B, Lauseker M, Hehlmann R, et al. Distinct characteristics of e13a2 versus e14a2 BCR-ABL1 driven chronic myeloid leukemia under first-line therapy with imatinib. Haematologica 2014;99: 1441–1447.
18. Jain P, Kantarjian H, Patel KP, et al. Impact of BCR-ABL transcript type on outcome in patients with chronic-phase CML treated with tyrosine kinase inhibitors. Blood 2016;127:1269–1275.
19. Castagnetti F, Gugliotta G, Breccia M, et al. The BCR-ABL1 transcript type influences response and outcome in Philadelphia chromosome-positive chronic myeloid leukemia patients treated frontline with imatinib. Am J Hematol 2017;92:797–805.
20. Ercaliskan A, Eskazan AE. The impact of BCR-ABL1 transcript type on tyrosine kinase inhibitor responses and outcomes in patients with chronic myeloid leukemia. Cancer 2018;124:3806–3818.
21. Pfirrmann M, Evtimova D, Saussele S, et al. No influence of BCR-ABL1 transcript types e13a2 and e14a2 on long-term survival: results in 1494 patients with chronic myeloid leukemia treated with imatinib. J Cancer Res Clin Oncol 2017;143:843–850.
22. Verma D, Kantarjian HM, Jones D, et al. Chronic myeloid leukemia (CML) with P190 BCR-ABL: analysis of characteristics, outcomes, and prognostic significance. Blood 2009;114:2232–2235.
23. Arun AK, Senthamizhselvi A, Mani S, et al. Frequency of rare BCR-ABL1 fusion transcripts in chronic myeloid leukemia patients. Int J Lab Hematol 2017;39:235–242.
24. Gong Z, Medeiros LJ, Cortes JE, et al. Clinical and prognostic significance of e1a2 BCR-ABL1 transcript subtype in chronic myeloid leukemia. Blood Cancer J 2017;7:e583.
25. Qin YZ, Jiang Q, Jiang H, et al. Prevalence and outcomes of uncommon BCR-ABL1 fusion transcripts in patients with chronic myeloid leukaemia: data from a single centre. Br J Haematol 2018;182:693–700.
26. Xue M, Wang Q, Huo L, et al. Clinical characteristics and prognostic significance of chronic myeloid leukemia with rare BCR-ABL1 transcripts. Leuk Lymphoma 2019;60:3051–3057.

27. Verstovsek S, Lin H, Kantarjian H, et al. Neutrophilic-chronic myeloid leukemia: low levels of p230 BCR/ABL mRNA and undetectable BCR/ABL protein may predict an indolent course. Cancer 2002;94:2416–2425.
28. Langabeer SE, McCarron SL, Kelly J, et al. Chronic myeloid leukemia with e19a2 BCR-ABL1 transcripts and marked thrombocytosis: the role of molecular monitoring. Case Rep Hematol 2012;2012:458716.
29. Crampe M, Haslam K, Kelly J, et al. Characterization of a novel variant BCR-ABL1 fusion transcript in a patient with chronic myeloid leukemia: Implications for molecular monitoring. Hematol Oncol Stem Cell Ther 2017;10:85–88.
30. Langabeer SE. Standardized molecular monitoring for variant BCR-ABL1 transcripts in chronic myeloid leukemia. Arch Pathol Lab Med 2015;139:969.
31. Shanmuganathan N, Hughes TP. Molecular monitoring in CML: how deep? How often? How should it influence therapy? Hematology (Am Soc Hematol Educ Program) 2018;2018:168–176.
32. Burmeister T, Reinhardt R. A multiplex PCR for improved detection of typical and atypical BCR-ABL fusion transcripts. Leuk Res 2008;32:579–585.
33. Bennour A, Ouahchi I, Moez M, et al. Comprehensive analysis of BCR/ABL variants in chronic myeloid leukemia patients using multiplex RT-PCR. Clin Lab 2012;58:433–439.
34. Mir R, Ahmad I, Javid J, et al. Simple multiplex RT-PCR for identifying common fusion BCR-ABL transcript types and evaluation of molecular response of the a2b2 and a2b3 transcripts to Imatinib resistance in north Indian chronic myeloid leukemia patients. Indian J Cancer 2015;52:314–318.
35. Pagani IS, Dang P, Saunders VA, et al. Clinical utility of genomic DNA Q-PCR for the monitoring of a patient with atypical e19a2 *BCR-ABL1* transcripts in chronic myeloid leukemia [published online June 6, 2020]. Leuk Lymphoma,doi: 10.1080/10428194.2020.1772476
36. Petiti J, Lo Iacono M, Dragani M, et al. Novel multiplex droplet digital PCR assays to mnitor minimal residual disease in chronic myeloid leukemia patients showing atypical *BCR-ABL1* transcripts. J Clin Med 2020;9:1457.
37. Cortes JE, Talpaz M, Giles F, et al. Prognostic significance of cytogenetic clonal evolution in patients with chronic myelogenous leukemia on imatinib mesylate therapy. Blood 2003;101:3794–3800.
38. O'Dwyer ME, Mauro MJ, Blasdel C, et al. Clonal evolution and lack of cytogenetic response are adverse prognostic factors for hematologic relapse of chronic phase CML patients treated with imatinib mesylate. Blood 2004;103:451–455.
39. Wang W, Cortes JE, Lin P, et al. Clinical and prognostic significance of 3q26.2 and other chromosome 3 abnormalities in CML in the era of tyrosine kinase inhibitors. Blood 2015;126:1699–1706.
40. Wang W, Tang G, Cortes JE, et al. Chromosomal rearrangement involving 11q23 locus in chronic myelogenous leukemia: a rare phenomenon frequently associated with disease progression and poor prognosis. J Hematol Oncol 2015;8:32.
41. Wang W, Cortes JE, Tang G, et al. Risk stratification of chromosomal abnormalities in chronic myelogenous leukemia in the era of tyrosine kinase inhibitor therapy. Blood 2016;127:2742–2750.
42. Verma D, Kantarjian H, Shan J, et al. Survival outcomes for clonal evolution in chronic myeloid leukemia patients on second generation tyrosine kinase inhibitor therapy. Cancer 2010;116:2673–2681.
43. Fabarius A, Kalmanti L, Dietz CT, et al. Impact of unbalanced minor route versus major route karyotypes at diagnosis on prognosis of CML. Ann Hematol 2015;94:2015–2024.
44. Fabarius A, Leitner A, Hochhaus A, et al. Impact of additional cytogenetic aberrations at diagnosis on prognosis of CML: long-term observation of 1151 patients from the randomized CML Study IV. Blood 2011;118:6760–6768.
45. Alhuraiji A, Kantarjian H, Boddu P, et al. Prognostic significance of additional chromosomal abnormalities at the time of diagnosis in patients with chronic myeloid leukemia treated with frontline tyrosine kinase inhibitors. Am J Hematol 2018;93:84–90.
46. Bumm T, Müller C, Al-Ali H-K, et al. Emergence of clonal cytogenetic abnormalities in Ph- cells in some CML patients in cytogenetic remission to imatinib but restoration of polyclonal hematopoiesis in the majority. Blood 2003;101:1941–1949.
47. Feldman E, Najfeld V, Schuster M, et al. The emergence of Ph-, trisomy -8+ cells in patients with chronic myeloid leukemia treated with imatinib mesylate. Exp Hematol 2003;31:702–707.
48. Medina J, Kantarjian H, Talpaz M, et al. Chromosomal abnormalities in Philadelphia chromosome-negative metaphases appearing during imatinib mesylate therapy in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase. Cancer 2003;98:1905–1911.
49. Terre C, Eclache V, Rousselot P, et al. Report of 34 patients with clonal chromosomal abnormalities in Philadelphia-negative cells during imatinib treatment of Philadelphia-positive chronic myeloid leukemia. Leukemia 2004;18:1340–1346.
50. Deininger MW, Cortes J, Paquette R, et al. The prognosis for patients with chronic myeloid leukemia who have clonal cytogenetic abnormalities in Philadelphia chromosome-negative cells. Cancer 2007;110:1509–1519.
51. Jabbour E, Kantarjian HM, Abruzzo LV, et al. Chromosomal abnormalities in Philadelphia chromosome negative metaphases appearing during imatinib mesylate therapy in patients with newly diagnosed chronic myeloid leukemia in chronic phase. Blood 2007;110:2991–2995.
52. Vignetti M, Fazi P, Cimino G, et al. Imatinib plus steroids induces complete remissions and prolonged survival in elderly Philadelphia chromosome-positive patients with acute lymphoblastic leukemia without additional chemotherapy: results of the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) LAL0201-B protocol. Blood 2007;109:3676–3678.
53. Fabarius A, Haferlach C, Müller MC, et al. Dynamics of cytogenetic aberrations in Philadelphia chromosome positive and negative hematopoiesis during dasatinib therapy of chronic myeloid leukemia patients after imatinib failure. Haematologica 2007;92:834–837.
54. Baldazzi C, Luatti S, Marzocchi G, et al. Emergence of clonal chromosomal abnormalities in Philadelphia negative hematopoiesis in chronic myeloid leukemia patients treated with nilotinib after failure of imatinib therapy. Leuk Res 2009;33:e218–e220.
55. Wang H, Jin J, Wang Y, et al. Clonal chromosomal abnormalities in Philadelphia-negative cells in chronic myeloid leukemia patients treated with nilotinib used in first-line therapy. Ann Hematol 2013;92:1625–1632.
56. Ni H, Sun X, Xu Y, et al. Clinical implications of clonal chromosomal abnormalities in Philadelphia negative cells in CML patients after treated with tyrosine kinase inhibitors. Cancer Genet 2019;238:44–49.
57. Sheng G, Xue M, Wang Q, et al. Occurrence of chromosomal abnormalities in Philadelphia chromosome-negative metaphases in patients with chronic-phase chronic myeloid leukemia undergoing TKI treatments. Leuk Lymphoma 2019;60:3503–3511.
58. Issa GC, Kantarjian HM, Gonzalez GN, et al. Clonal chromosomal abnormalities appearing in Philadelphia chromosome-negative metaphases during CML treatment. Blood 2017;130:2084–2091.
59. Karimata K, Masuko M, Ushiki T, et al. Myelodysplastic syndrome with Ph negative monosomy 7 chromosome following transient bone marrow dysplasia during imatinib treatment for chronic myeloid leukemia. Intern Med 2011;50:481–485.
60. Navarro JT, Feliu E, Grau J, et al. Monosomy 7 with severe myelodysplasia developing during imatinib treatment of Philadelphia-positive chronic myeloid leukemia: two cases with a different outcome. Am J Hematol 2007;82:849–851.
61. Bidet A, Dulucq S, Smol T, et al. Poor prognosis of chromosome 7 clonal aberrations in Philadelphia-negative metaphases and relevance of potential underlying myelodysplastic features in chronic myeloid leukemia. Haematologica 2019;104:1150–1155.
62. Soverini S, De Benedittis C, Castagnetti F, et al. In chronic myeloid leukemia patients on second-line tyrosine kinase inhibitor therapy, deep sequencing of BCR-ABL1 at the time of warning may allow sensitive detection of emerging drug-resistant mutants. BMC Cancer 2016;16:572.
63. Kizilors A, Crisà E, Lea N, et al. Effect of low-level BCR-ABL1 kinase domain mutations identified by next-generation sequencing in patients with chronic myeloid leukaemia: a population-based study. Lancet Haematol 2019;6:e276–e284.
64. Soverini S, Abruzzese E, Bocchia M, et al. Next-generation sequencing for BCR-ABL1 kinase domain mutation testing in patients with chronic myeloid leukemia: a position paper. J Hematol Oncol 2019;12:131.
65. Soverini S, Bavaro L, De Benedittis C, et al. Prospective assessment of NGS-detectable mutations in CML patients with nonoptimal response: the NEXT-in-CML study. Blood 2020;135:534–541.
66. Sokal JE, Cox EB, Baccarani M, et al. Prognostic discrimination in "good-risk" chronic granulocytic leukemia. Blood 1984;63:789–799.
67. Hasford J, Pfirrmann M, Hehlmann R, et al. A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alfa. J Natl Cancer Inst 1998;90:850–858.

68. 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.
69. Hochhaus A, Larson RA, Guilhot F, et al. Long-term outcomes of imatinib treatment of chronic myeloid leukemia. N Engl J Med 2017;376: 917–927.
70. Cortes JE, Saglio G, Kantarjian HM, et al. Final 5-year study results of DASISION: the dasatinib versus imatinib study in treatment-naive chronic myeloid leukemia patients trial. J Clin Oncol 2016;34: 2333–2340.
71. Hochhaus A, Saglio G, Hughes TP, et al. Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. Leukemia 2016; 30:1044–1054.
72. Cortes JE, Gambacorti-Passerini C, Deininger MW, et al. Bosutinib versus imatinib for newly diagnosed chronic myeloid leukemia: results from the randomized BFORE trial. J Clin Oncol 2018;36:231–237.
73. Baccarani M, Druker BJ, Branford S, et al. Long-term response to imatinib is not affected by the initial dose in patients with Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase: final update from the Tyrosine Kinase Inhibitor Optimization and Selectivity (TOPS) study. Int J Hematol 2014;99:616–624.
74. Deininger MW, Kopecky KJ, Radich JP, et al. Imatinib 800 mg daily induces deeper molecular responses than imatinib 400 mg daily: results of SWOG S0325, an intergroup randomized PHASE II trial in newly diagnosed chronic phase chronic myeloid leukaemia. Br J Haematol 2014;164:223–232.
75. Hehlmann R, Lauseker M, Saußele S, et al. Assessment of imatinib as first-line treatment of chronic myeloid leukemia: 10-year survival results of the randomized CML study IV and impact of non-CML determinants. Leukemia 2017;31:2398–2406.
76. Hoffmann VS, Hasford J, Deininger M, et al. Systematic review and meta-analysis of standard-dose imatinib vs. high-dose imatinib and second generation tyrosine kinase inhibitors for chronic myeloid leukemia. J Cancer Res Clin Oncol 2017;143:1311–1318.
77. Quintás-Cardama A, Han X, Kantarjian H, et al. Tyrosine kinase inhibitor-induced platelet dysfunction in patients with chronic myeloid leukemia. Blood 2009;114:261–263.
78. Hughes TP, Laneuville P, Rousselot P, et al. Incidence, outcomes, and risk factors of pleural effusion in patients receiving dasatinib therapy for Philadelphia chromosome-positive leukemia. Haematologica 2019;104: 93–101.
79. Porkka K, Khoury HJ, Paquette RL, et al. Dasatinib 100 mg once daily minimizes the occurrence of pleural effusion in patients with chronic myeloid leukemia in chronic phase and efficacy is unaffected in patients who develop pleural effusion. Cancer 2010;116:377–386.
80. Montani D, Bergot E, Günther S, et al. Pulmonary arterial hypertension in patients treated by dasatinib. Circulation 2012;125:2128–2137.
81. Orlandi EM, Rocca B, Pazzano AS, et al. Reversible pulmonary arterial hypertension likely related to long-term, low-dose dasatinib treatment for chronic myeloid leukaemia. Leuk Res 2012;36:e4–e6.
82. Cirmi S, El Abd A, Letinier L, et al. Cardiovascular toxicity of tyrosine kinase inhibitors used in chronic myeloid leukemia: an analysis of the FDA adverse event reporting system database (FAERS). Cancers (Basel) 2020;12:826.
83. Naqvi K, Jabbour E, Skinner J, et al. Long-term follow-up of lower dose dasatinib (50 mg daily) as frontline therapy in newly diagnosed chronic-phase chronic myeloid leukemia. Cancer 2020;126:67–75.
84. Bergeron A, Réa D, Levy V, et al. Lung abnormalities after dasatinib treatment for chronic myeloid leukemia: a case series. Am J Respir Crit Care Med 2007;176:814–818.
85. Serpa M, Sanabani SS, Bendit I, et al. Efficacy and tolerability after unusually low doses of dasatinib in chronic myeloid leukemia patients intolerant to standard-dose dasatinib therapy. Clin Med Insights Oncol 2010;4:155–162.
86. Efficace F, Baccarani M, Breccia M, et al. Chronic fatigue is the most important factor limiting health-related quality of life of chronic myeloid leukemia patients treated with imatinib. Leukemia 2013;27:1511–1519.
87. Berman E, Nicolaides M, Maki RG, et al. Altered bone and mineral metabolism in patients receiving imatinib mesylate. N Engl J Med 2006; 354:2006–2013.
88. Berman E, Girotra M, Cheng C, et al. Effect of long term imatinib on bone in adults with chronic myelogenous leukemia and gastrointestinal stromal tumors. Leuk Res 2013;37:790–794.
89. Tsao AS, Kantarjian H, Cortes J, et al. Imatinib mesylate causes hypopigmentation in the skin. Cancer 2003;98:2483–2487.
90. Aleem A. Hypopigmentation of the skin due to imatinib mesylate in patients with chronic myeloid leukemia. Hematol Oncol Stem Cell Ther 2009;2:358–361.
91. Sakurai M, Kikuchi T, Karigane D, et al. Renal dysfunction and anemia associated with long-term imatinib treatment in patients with chronic myelogenous leukemia. Int J Hematol 2019;109:292–298.
92. Aichberger KJ, Herndlhofer S, Schernthaner G-H, et al. Progressive peripheral arterial occlusive disease and other vascular events during nilotinib therapy in CML. Am J Hematol 2011;86:533–539.
93. Tefferi A, Letendre L. Nilotinib treatment-associated peripheral artery disease and sudden death: yet another reason to stick to imatinib as front-line therapy for chronic myelogenous leukemia. Am J Hematol 2011;86:610–611.
94. Giles FJ, Mauro MJ, Hong F, et al. Rates of peripheral arterial occlusive disease in patients with chronic myeloid leukemia in the chronic phase treated with imatinib, nilotinib, or non-tyrosine kinase therapy: a retrospective cohort analysis. Leukemia 2013;27:1310–1315.
95. Assunção PM, Lana TP, Delamain MT, et al. Cardiovascular risk and cardiovascular events in patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors. Clin Lymphoma Myeloma Leuk 2019;19: 162–166.
96. Caocci G, Mulas O, Bonifacio M, et al. Recurrent arterial occlusive events in patients with chronic myeloid leukemia treated with second- and third-generation tyrosine kinase inhibitors and role of secondary prevention. Int J Cardiol 2019;288:124–127.
97. Tokuhira M, Kimura Y, Sugimoto K, et al. Efficacy and safety of nilotinib therapy in patients with newly diagnosed chronic myeloid leukemia in the chronic phase. Med Oncol 2018;35:38.
98. Quintas-Cardama A, Kantarjian H, O'Brien S, et al. Granulocyte-colony-stimulating factor (filgrastim) may overcome imatinib-induced neutropenia in patients with chronic-phase chronic myelogenous leukemia. Cancer 2004;100:2592–2597.
99. Quintás-Cardama A, De Souza Santos FP, Kantarjian H, et al. Dynamics and management of cytopenias associated with dasatinib therapy in patients with chronic myeloid leukemia in chronic phase after imatinib failure. Cancer 2009;115:3935–3943.
100. Santos FP, Alvarado Y, Kantarjian H, et al. Long-term prognostic impact of the use of erythropoietic-stimulating agents in patients with chronic myeloid leukemia in chronic phase treated with imatinib. Cancer 2011; 117:982–991.
101. Reinhold U, Hennig E, Leiblein S, et al. FISH for BCR-ABL on interphases of peripheral blood neutrophils but not of unselected white cells correlates with bone marrow cytogenetics in CML patients treated with imatinib. Leukemia 2003;17:1925–1929.
102. Fugazza G, Miglino M, Bruzzone R, et al. Cytogenetic and fluorescence in situ hybridization monitoring in Ph+ Chronic Myeloid Leukemia patients treated with imatinib mesylate. J Exp Clin Cancer Res 2004;23: 295–299.
103. Landstrom AP, Ketterling RP, Knudson RA, et al. Utility of peripheral blood dual color, double fusion fluorescent in situ hybridization for BCR/ABL fusion to assess cytogenetic remission status in chronic myeloid leukemia. Leuk Lymphoma 2006;47:2055–2061.
104. Testoni N, Marzocchi G, Luatti S, et al. Chronic myeloid leukemia: a prospective comparison of interphase fluorescence in situ hybridization and chromosome banding analysis for the definition of complete cytogenetic response: a study of the GIMEMA CML WP. Blood 2009;114: 4939–4943.
105. Lima L, Bernal-Mizrachi L, Saxe D, et al. Peripheral blood monitoring of chronic myeloid leukemia during treatment with imatinib, second-line agents, and beyond. Cancer 2011;117:1245–1252.
106. Hughes TP, Hochhaus A, Branford S, et al. Long-term prognostic significance of early molecular response to imatinib in newly diagnosed chronic myeloid leukemia: an analysis from the International Randomized Study of Interferon and STI571 (IRIS). Blood 2010;116: 3758–3765.
107. Akard LP, Cortes JE, Albitar M, et al. Correlations between cytogenetic and molecular monitoring among patients with newly diagnosed chronic myeloid leukemia in chronic phase: post hoc analyses of the Rationale and Insight for Gleevec High-Dose Therapy study. Arch Pathol Lab Med 2014;138:1186–1192.
108. Branford S, Cross NCP, Hochhaus A, et al. Rationale for the recommendations for harmonizing current methodology for detecting BCR-ABL transcripts in patients with chronic myeloid leukaemia. Leukemia 2006;20:1925–1930.
109. Cross NC. Standardisation of molecular monitoring for chronic myeloid leukaemia. Best Pract Res Clin Haematol 2009;22:355–365.

110. Cross NC, White HE, Müller MC, et al. Standardized definitions of molecular response in chronic myeloid leukemia. Leukemia 2012;26:2172–2175.
111. Branford S, Fletcher L, Cross NC, et al. Desirable performance characteristics for BCR-ABL measurement on an international reporting scale to allow consistent interpretation of individual patient response and comparison of response rates between clinical trials. Blood 2008;112:3330–3338.
112. Guérin A, Chen L, Dea K, et al. Association between regular molecular monitoring and tyrosine kinase inhibitor therapy adherence in chronic myelogenous leukemia in the chronic phase. Curr Med Res Opin 2014;30:1345–1352.
113. Hanfstein B, Müller MC, Hehlmann R, et al. Early molecular and cytogenetic response is predictive for long-term progression-free and overall survival in chronic myeloid leukemia (CML). Leukemia 2012;26:2096–2102.
114. Marin D, Ibrahim AR, Lucas C, et al. Assessment of BCR-ABL1 transcript levels at 3 months is the only requirement for predicting outcome for patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors. J Clin Oncol 2012;30:232–238.
115. Neelakantan P, Gerrard G, Lucas C, et al. Combining BCR-ABL1 transcript levels at 3 and 6 months in chronic myeloid leukemia: implications for early intervention strategies. Blood 2013;121:2739–2742.
116. Nazha A, Kantarjian H, Jain P, et al. Assessment at 6 months may be warranted for patients with chronic myeloid leukemia with no major cytogenetic response at 3 months. Haematologica 2013;98:1686–1688.
117. Branford S, Yeung DT, Parker WT, et al. Prognosis for patients with CML and >10% BCR-ABL1 after 3 months of imatinib depends on the rate of BCR-ABL1 decline. Blood 2014;124:511–518.
118. Hanfstein B, Shlyakhto V, Lauseker M, et al. Velocity of early BCR-ABL transcript elimination as an optimized predictor of outcome in chronic myeloid leukemia (CML) patients in chronic phase on treatment with imatinib. Leukemia 2014;28:1988–1992.
119. Iriyama N, Fujisawa S, Yoshida C, et al. Shorter halving time of BCR-ABL1 transcripts is a novel predictor for achievement of molecular responses in newly diagnosed chronic-phase chronic myeloid leukemia treated with dasatinib: Results of the D-first study of Kanto CML study group. Am J Hematol 2015;90:282–287.
120. Hochhaus A, O'Brien SG, Guilhot F, et al. Six-year follow-up of patients receiving imatinib for the first-line treatment of chronic myeloid leukemia. Leukemia 2009;23:1054–1061.
121. Jabbour E, Kantarjian H, O'Brien S, et al. The achievement of an early complete cytogenetic response is a major determinant for outcome in patients with early chronic phase chronic myeloid leukemia treated with tyrosine kinase inhibitors. Blood 2011;118:4541–4546., quiz 4759.
122. Druker BJ, Guilhot F, O'Brien SG, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. N Engl J Med 2006;355:2408–2417.
123. Press RD, Galderisi C, Yang R, et al. A half-log increase in BCR-ABL RNA predicts a higher risk of relapse in patients with chronic myeloid leukemia with an imatinib-induced complete cytogenetic response. Clin Cancer Res 2007;13:6136–6143.
124. de Lavallade H, Apperley JF, Khorashad JS, et al. Imatinib for newly diagnosed patients with chronic myeloid leukemia: incidence of sustained responses in an intention-to-treat analysis. J Clin Oncol 2008;26:3358–3363.
125. Marin D, Milojkovic D, Olavarria E, et al. European LeukemiaNet criteria for failure or suboptimal response reliably identify patients with CML in early chronic phase treated with imatinib whose eventual outcome is poor. Blood 2008;112:4437–4444.
126. Jabbour E, Kantarjian HM, O'Brien S, et al. Front-line therapy with second-generation tyrosine kinase inhibitors in patients with early chronic phase chronic myeloid leukemia: what is the optimal response? J Clin Oncol 2011;29:4260–4265.
127. Hehlmann R, Müller MC, Lauseker M, et al. Deep molecular response is reached by the majority of patients treated with imatinib, predicts survival, and is achieved more quickly by optimized high-dose imatinib: results from the randomized CML-study IV. J Clin Oncol 2014;32:415–423.
128. Saussele S, Hehlmann R, Fabarius A, et al. Defining therapy goals for major molecular remission in chronic myeloid leukemia: results of the randomized CML Study IV. Leukemia 2018;32:1222–1228.
129. Cervantes F, López-Garrido P, Montero MI, et al. Early intervention during imatinib therapy in patients with newly diagnosed chronic-phase chronic myeloid leukemia: a study of the Spanish PETHEMA group. Haematologica 2010;95:1317–1324.
130. Kantarjian H, Cortes J. Considerations in the management of patients with Philadelphia chromosome-positive chronic myeloid leukemia receiving tyrosine kinase inhibitor therapy. J Clin Oncol 2011;29:1512–1516.
131. Hochhaus A, Baccarani M, Silver RT, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia 2020;34:966–984.
132. Shah NP, Rousselot P, Schiffer C, et al. Dasatinib in imatinib-resistant or -intolerant chronic-phase, chronic myeloid leukemia patients: 7-year follow-up of study CA180-034. Am J Hematol 2016;91:869–874.
133. Giles FJ, le Coutre PD, Pinilla-Ibarz J, et al. Nilotinib in imatinib-resistant or imatinib-intolerant patients with chronic myeloid leukemia in chronic phase: 48-month follow-up results of a phase II study. Leukemia 2013;27:107–112.
134. Gambacorti-Passerini C, Cortes JE, Lipton JH, et al. Safety and efficacy of second-line bosutinib for chronic phase chronic myeloid leukemia over a five-year period: final results of a phase I/II study. Haematologica 2018;103:1298–1307.
135. Cortes JE, Kim D-W, Pinilla-Ibarz J, et al. Ponatinib efficacy and safety in Philadelphia chromosome-positive leukemia: final 5-year results of the phase 2 PACE trial. Blood 2018;132:393–404.
136. Kantarjian HM, Talpaz M, O'Brien S, et al. Dose escalation of imatinib mesylate can overcome resistance to standard-dose therapy in patients with chronic myelogenous leukemia. Blood 2003;101:473–475.
137. Marin D, Goldman JM, Olavarria E, et al. Transient benefit only from increasing the imatinib dose in CML patients who do not achieve complete cytogenetic remissions on conventional doses. Blood 2003;102:2702–2703., author reply 2703–2704.
138. Jabbour E, Kantarjian HM, Jones D, et al. Imatinib mesylate dose escalation is associated with durable responses in patients with chronic myeloid leukemia after cytogenetic failure on standard-dose imatinib therapy. Blood 2009;113:2154–2160.
139. Kantarjian HM, Larson RA, Guilhot F, et al. Efficacy of imatinib dose escalation in patients with chronic myeloid leukemia in chronic phase. Cancer 2009;115:551–560.
140. Yeung DT, Osborn MP, White DL, et al. TIDEL-II: first-line use of imatinib in CML with early switch to nilotinib for failure to achieve time-dependent molecular targets. Blood 2015;125:915–923.
141. Cortes JE, De Souza CA, Ayala M, et al. Switching to nilotinib versus imatinib dose escalation in patients with chronic myeloid leukaemia in chronic phase with suboptimal response to imatinib (LASOR): a randomised, open-label trial. Lancet Haematol 2016;3:e581–e591.
142. Cortes JE, Khoury HJ, Kantarjian HM, et al. Long-term bosutinib for chronic phase chronic myeloid leukemia after failure of imatinib plus dasatinib and/or nilotinib. Am J Hematol 2016;91:1206–1214.
143. García-Gutiérrez V, Milojkovic D, Hernandez-Boluda JC, et al. Safety and efficacy of bosutinib in fourth-line therapy of chronic myeloid leukemia patients. Ann Hematol 2019;98:321–330.
144. Jain P, Kantarjian H, Boddu PC, et al. Analysis of cardiovascular and arteriothrombotic adverse events in chronic-phase CML patients after frontline TKIs. Blood Adv 2019;3:851–861.
145. Caocci G, Mulas O, Abruzzese E, et al. Arterial occlusive events in chronic myeloid leukemia patients treated with ponatinib in the real-life practice are predicted by the Systematic Coronary Risk Evaluation (SCORE) chart. Hematol Oncol 2019;37:296–302.
146. Casavecchia G, Galderisi M, Novo G, et al. Early diagnosis, clinical management, and follow-up of cardiovascular events with ponatinib. Heart Fail Rev 2020;25:447–456.
147. Cortes JE, Kantarjian H, Shah NP, et al. Ponatinib in refractory Philadelphia chromosome-positive leukemias. N Engl J Med 2012;367:2075–2088.
148. Dorer DJ, Knickerbocker RK, Baccarani M, et al. Impact of dose intensity of ponatinib on selected adverse events: Multivariate analyses from a pooled population of clinical trial patients. Leuk Res 2016;48:84–91.
149. Iurlo A, Cattaneo D, Orofino N, et al. Low-dose ponatinib in intolerant chronic myeloid leukemia patients: a safe and effective option. Clin Drug Investig 2018;38:475–476.
150. Garg RJ, Kantarjian H, O'Brien S, et al. The use of nilotinib or dasatinib after failure to 2 prior tyrosine kinase inhibitors: long-term follow-up. Blood 2009;114:4361–4368.
151. Cortes J, Lipton JH, Rea D, et al. Phase 2 study of subcutaneous omacetaxine mepesuccinate after TKI failure in patients with chronic-phase CML with T315I mutation. Blood 2012;120:2573–2580.

152. Cortes J, Digumarti R, Parikh PM, et al. Phase 2 study of subcutaneous omacetaxine mepesuccinate for chronic-phase chronic myeloid leukemia patients resistant to or intolerant of tyrosine kinase inhibitors. Am J Hematol 2013;88:350–354.
153. 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.
154. Osorio S, Escudero-Vilaplana V, Gómez-Centurión I, et al. Drug-to-drug interactions of tyrosine kinase inhibitors in chronic myeloid leukemia patients. Is it a real problem? Ann Hematol 2018;97:2089–2098.
155. Noens L, van Lierde M-A, De Bock R, et al. Prevalence, determinants, and outcomes of nonadherence to imatinib therapy in patients with chronic myeloid leukemia: the ADAGIO study. Blood 2009;113: 5401–5411.
156. Marin D, Bazeos A, Mahon F-X, et al. Adherence is the critical factor for achieving molecular responses in patients with chronic myeloid leukemia who achieve complete cytogenetic responses on imatinib. J Clin Oncol 2010;28:2381–2388.
157. Ibrahim AR, Eliasson L, Apperley JF, et al. Poor adherence is the main reason for loss of CCyR and imatinib failure for chronic myeloid leukemia patients on long-term therapy. Blood 2011;117:3733–3736.
158. Wu EQ, Guerin A, Yu AP, et al. Retrospective real-world comparison of medical visits, costs, and adherence between nilotinib and dasatinib in chronic myeloid leukemia. Curr Med Res Opin 2010;26:2861–2869.
159. Yood MU, Oliveria SA, Cziraky M, et al. Adherence to treatment with second-line therapies, dasatinib and nilotinib, in patients with chronic myeloid leukemia. Curr Med Res Opin 2012;28:213–219.
160. Quintás-Cardama A, Cortés JE, Kantarjian H. Practical management of toxicities associated with tyrosine kinase inhibitors in chronic myeloid leukemia. Clin Lymphoma Myeloma 2008;8(Suppl 3):S82–S88.
161. Cornelison M, Jabbour EJ, Welch MA. Managing side effects of tyrosine kinase inhibitor therapy to optimize adherence in patients with chronic myeloid leukemia: the role of the midlevel practitioner. J Support Oncol 2012;10:14–24.
162. Cortes JE, Lipton JH, Miller CB, et al. Evaluating the impact of a switch to nilotinib on imatinib-related chronic low-grade adverse events in patients with CML-CP: the ENRICH Study. Clin Lymphoma Myeloma Leuk 2016;16:286–296.
163. Kim DW, Saussele S, Williams LA, et al. Outcomes of switching to dasatinib after imatinib-related low-grade adverse events in patients with chronic myeloid leukemia in chronic phase: the DASPERSE study. Ann Hematol 2018;97:1357–1367.
164. Hiwase D, Tan P, D'Rozario J, et al. Efficacy and safety of nilotinib 300 mg twice daily in patients with chronic myeloid leukemia in chronic phase who are intolerant to prior tyrosine kinase inhibitors: results from the phase IIIb ENESTswift study. Leuk Res 2018;67:109–115.
165. Thomas J, Wang L, Clark RE, et al. Active transport of imatinib into and out of cells: implications for drug resistance. Blood 2004;104: 3739–3745.
166. Mahon FX, Hayette S, Lagarde V, et al. Evidence that resistance to nilotinib may be due to BCR-ABL, Pgp, or Src kinase overexpression. Cancer Res 2008;68:9809–9816.
167. Hegedus C, Ozvegy-Laczka C, Apáti A, et al. Interaction of nilotinib, dasatinib and bosutinib with ABCB1 and ABCG2: implications for altered anti-cancer effects and pharmacological properties. Br J Pharmacol 2009;158:1153–1164.
168. Picard S, Titier K, Etienne G, et al. Trough imatinib plasma levels are associated with both cytogenetic and molecular responses to standard-dose imatinib in chronic myeloid leukemia. Blood 2007;109: 3496–3499.
169. Larson RA, Druker BJ, Guilhot F, et al. Imatinib pharmacokinetics and its correlation with response and safety in chronic-phase chronic myeloid leukemia: a subanalysis of the IRIS study. Blood 2008;111: 4022–4028.
170. Bouchet S, Titier K, Moore N, et al. Therapeutic drug monitoring of imatinib in chronic myeloid leukemia: experience from 1216 patients at a centralized laboratory. Fundam Clin Pharmacol 2013;27:690–697.
171. White DL, Radich J, Soverini S, et al. Chronic phase chronic myeloid leukemia patients with low OCT-1 activity randomized to high-dose imatinib achieve better responses and have lower failure rates than those randomized to standard-dose imatinib. Haematologica 2012;97: 907–914.
172. Giannoudis A, Davies A, Lucas CM, et al. Effective dasatinib uptake may occur without human organic cation transporter 1 (hOCT1): implications for the treatment of imatinib-resistant chronic myeloid leukemia. Blood 2008;112:3348–3354.
173. Hiwase DK, Saunders V, Hewett D, et al. Dasatinib cellular uptake and efflux in chronic myeloid leukemia cells: therapeutic implications. Clin Cancer Res 2008;14:3881–3888.
174. Davies A, Jordanides NE, Giannoudis A, et al. Nilotinib concentration in cell lines and primary CD34(+) chronic myeloid leukemia cells is not mediated by active uptake or efflux by major drug transporters. Leukemia 2009;23:1999–2006.
175. White DL, Saunders VA, Dang P, et al. OCT-1-mediated influx is a key determinant of the intracellular uptake of imatinib but not nilotinib (AMN107): reduced OCT-1 activity is the cause of low in vitro sensitivity to imatinib. Blood 2006;108:697–704.
176. Branford S, Rudzki Z, Walsh S, et al. Detection of BCR-ABL mutations in patients with CML treated with imatinib is virtually always accompanied by clinical resistance, and mutations in the ATP phosphate-binding loop (P-loop) are associated with a poor prognosis. Blood 2003;102:276–283.
177. Soverini S, Martinelli G, Rosti G, et al. ABL mutations in late chronic phase chronic myeloid leukemia patients with up-front cytogenetic resistance to imatinib are associated with a greater likelihood of progression to blast crisis and shorter survival: a study by the GIMEMA Working Party on Chronic Myeloid Leukemia. J Clin Oncol 2005;23: 4100–4109.
178. Nicolini FE, Corm S, Lê QH, et al. Mutation status and clinical outcome of 89 imatinib mesylate-resistant chronic myelogenous leukemia patients: a retrospective analysis from the French intergroup of CML (Fi(phi)-LMC GROUP). Leukemia 2006;20:1061–1066.
179. Soverini S, Colarossi S, Gnani A, et al. Contribution of ABL kinase domain mutations to imatinib resistance in different subsets of Philadelphia-positive patients: by the GIMEMA Working Party on Chronic Myeloid Leukemia. Clin Cancer Res 2006;12:7374–7379.
180. Khorashad JS, de Lavallade H, Apperley JF, et al. Finding of kinase domain mutations in patients with chronic phase chronic myeloid leukemia responding to imatinib may identify those at high risk of disease progression. J Clin Oncol 2008;26:4806–4813.
181. Soverini S, Gnani A, Colarossi S, et al. Philadelphia-positive patients who already harbor imatinib-resistant Bcr-Abl kinase domain mutations have a higher likelihood of developing additional mutations associated with resistance to second- or third-line tyrosine kinase inhibitors. Blood 2009; 114:2168–2171.
182. Nicolini FE, Hayette S, Corm S, et al. Clinical outcome of 27 imatinib mesylate-resistant chronic myelogenous leukemia patients harboring a T315I BCR-ABL mutation. Haematologica 2007;92:1238–1241.
183. Jabbour E, Kantarjian H, Jones D, et al. Characteristics and outcomes of patients with chronic myeloid leukemia and T315I mutation following failure of imatinib mesylate therapy. Blood 2008; 112:53–55.
184. Soverini S, Colarossi S, Gnani A, et al. Resistance to dasatinib in Philadelphia-positive leukemia patients and the presence or the selection of mutations at residues 315 and 317 in the BCR-ABL kinase domain. Haematologica 2007;92:401–404.
185. Jabbour E, Kantarjian HM, Jones D, et al. Characteristics and outcome of chronic myeloid leukemia patients with F317L BCR-ABL kinase domain mutation after therapy with tyrosine kinase inhibitors. Blood 2008;112: 4839–4842.
186. Müller MC, Cortes JE, Kim D-W, et al. Dasatinib treatment of chronic-phase chronic myeloid leukemia: analysis of responses according to preexisting BCR-ABL mutations. Blood 2009;114:4944–4953.
187. Hughes T, Saglio G, Branford S, et al. Impact of baseline BCR-ABL mutations on response to nilotinib in patients with chronic myeloid leukemia in chronic phase. J Clin Oncol 2009;27:4204–4210.
188. Naqvi K, Cortes JE, Luthra R, et al. Characteristics and outcome of chronic myeloid leukemia patients with E255K/V BCR-ABL kinase domain mutations. Int J Hematol 2018;107:689–695.
189. Khoury HJ, Cortes JE, Kantarjian HM, et al. Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib and/or nilotinib therapy failure. Blood 2012;119:3403–3412.
190. Khorashad JS, Kelley TW, Szankasi P, et al. BCR-ABL1 compound mutations in tyrosine kinase inhibitor-resistant CML: frequency and clonal relationships. Blood 2013;121:489–498.
191. Zabriskie MS, Eide CA, Tantravahi SK, et al. BCR-ABL1 compound mutations combining key kinase domain positions confer clinical resistance to ponatinib in Ph chromosome-positive leukemia. Cancer Cell 2014;26:428–442.
192. Deininger MW, Hodgson JG, Shah NP, et al. Compound mutations in BCR-ABL1 are not major drivers of primary or secondary resistance to ponatinib in CP-CML patients. Blood 2016;127:703–712.

193. Soverini S, Branford S, Nicolini FE, et al. Implications of BCR-ABL1 kinase domain-mediated resistance in chronic myeloid leukemia. Leuk Res 2014;38:10–20.
194. Grossmann V, Kohlmann A, Zenger M, et al. A deep-sequencing study of chronic myeloid leukemia patients in blast crisis (BC-CML) detects mutations in 76.9% of cases. Leukemia 2011;25:557–560.
195. Schmidt M, Rinke J, Schäfer V, et al. Molecular-defined clonal evolution in patients with chronic myeloid leukemia independent of the BCR-ABL status. Leukemia 2014;28:2292–2299.
196. Soverini S, de Benedittis C, Mancini M, et al. Mutations in the BCR-ABL1 Kinase Domain and Elsewhere in Chronic Myeloid Leukemia. Clin Lymphoma Myeloma Leuk 2015;15(Suppl):S120–S128.
197. Kim T, Tyndel MS, Kim HJ, et al. Spectrum of somatic mutation dynamics in chronic myeloid leukemia following tyrosine kinase inhibitor therapy. Blood 2017;129:38–47.
198. Togasaki E, Takeda J, Yoshida K, et al. Frequent somatic mutations in epigenetic regulators in newly diagnosed chronic myeloid leukemia. Blood Cancer J 2017;7:e559.
199. Branford S, Wang P, Yeung DT, et al. Integrative genomic analysis reveals cancer-associated mutations at diagnosis of CML in patients with high-risk disease. Blood 2018;132:948–961.
200. Branford S, Kim DDH, Apperley JF, et al. Laying the foundation for genomically-based risk assessment in chronic myeloid leukemia. Leukemia 2019;33:1835–1850.
201. Adnan Awad S, Kankainen M, Ojala T, et al. Mutation accumulation in cancer genes relates to nonoptimal outcome in chronic myeloid leukemia. Blood Adv 2020;4:546–559.
202. Branford S, Rudzki Z, Parkinson I, et al. Real-time quantitative PCR analysis can be used as a primary screen to identify patients with CML treated with imatinib who have BCR-ABL kinase domain mutations. Blood 2004;104:2926–2932.
203. Wang L, Knight K, Lucas C, et al. The role of serial BCR-ABL transcript monitoring in predicting the emergence of BCR-ABL kinase mutations in imatinib-treated patients with chronic myeloid leukemia. Haematologica 2006;91:235–239.
204. Kantarjian HM, Shan J, Jones D, et al. Significance of increasing levels of minimal residual disease in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in complete cytogenetic response. J Clin Oncol 2009;27:3659–3663.
205. Marin D, Khorashad JS, Foroni L, et al. Does a rise in the BCR-ABL1 transcript level identify chronic phase CML patients responding to imatinib who have a high risk of cytogenetic relapse? Br J Haematol 2009;145:373–375.
206. Press RD, Willis SG, Laudadio J, et al. Determining the rise in BCR-ABL RNA that optimally predicts a kinase domain mutation in patients with chronic myeloid leukemia on imatinib. Blood 2009;114:2598–2605.
207. Mahon FX, Réa D, Guilhot J, et al. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. Lancet Oncol 2010;11:1029–1035.
208. Etienne G, Guilhot J, Rea D, et al. Long-term follow-up of the french stop imatinib (STIM1) study in patients with chronic myeloid leukemia. J Clin Oncol 2017;35:298–305.
209. Thielen N, van der Holt B, Cornelissen JJ, et al. Imatinib discontinuation in chronic phase myeloid leukaemia patients in sustained complete molecular response: a randomised trial of the Dutch-Belgian Cooperative Trial for Haemato-Oncology (HOVON). Eur J Cancer 2013;49:3242–3246.
210. Rousselot P, Charbonnier A, Cony-Makhoul P, et al. Loss of major molecular response as a trigger for restarting tyrosine kinase inhibitor therapy in patients with chronic-phase chronic myelogenous leukemia who have stopped imatinib after durable undetectable disease. J Clin Oncol 2014;32:424–430.
211. Mori S, Vagge E, le Coutre P, et al. Age and dPCR can predict relapse in CML patients who discontinued imatinib: the ISAV study. Am J Hematol 2015;90:910–914.
212. Lee SE, Choi SY, Song HY, et al. Imatinib withdrawal syndrome and longer duration of imatinib have a close association with a lower molecular relapse after treatment discontinuation: the KID study. Haematologica 2016;101:717–723.
213. Ross DM, Pagani IS, Shanmuganathan N, et al. Long-term treatment-free remission of chronic myeloid leukemia with falling levels of residual leukemic cells. Leukemia 2018;32:2572–2579.
214. Rea D, Nicolini FE, Tulliez M, et al. Discontinuation of dasatinib or nilotinib in chronic myeloid leukemia: interim analysis of the STOP 2G-TKI study. Blood 2017;129:846–854.
215. Ross DM, Masszi T, Gómez Casares MT, et al. Durable treatment-free remission in patients with chronic myeloid leukemia in chronic phase following frontline nilotinib: 96-week update of the ENESTfreedom study. J Cancer Res Clin Oncol 2018;144:945–954.
216. Mahon FX, Boquimpani C, Kim DW, et al. Treatment-free remission after second-line nilotinib treatment in patients with chronic myeloid leukemia in chronic phase: results from a single-group, phase 2, open-label study. Ann Intern Med 2018;168:461–470.
217. Okada M, Imagawa J, Tanaka H, et al. Final 3-year results of the dasatinib discontinuation trial in patients with chronic myeloid leukemia who received dasatinib as a second-line treatment. Clin Lymphoma Myeloma Leuk 2018;18:353–360, e351.
218. Saussele S, Richter J, Guilhot J, et al. Discontinuation of tyrosine kinase inhibitor therapy in chronic myeloid leukaemia (EURO-SKI): a prespecified interim analysis of a prospective, multicentre, non-randomised, trial. Lancet Oncol 2018;19:747–757.
219. Shah NP, García-Gutiérrez V, Jiménez-Velasco A, et al. Dasatinib discontinuation in patients with chronic-phase chronic myeloid leukemia and stable deep molecular response: the DASFREE study. Leuk Lymphoma 2020;61:650–659.
220. Kimura S, Imagawa J, Murai K, et al. Treatment-free remission after first-line dasatinib discontinuation in patients with chronic myeloid leukaemia (first-line DADI trial): a single-arm, multicentre, phase 2 trial. Lancet Haematol 2020;7:e218–e225.
221. Legros L, Nicolini FE, Etienne G, et al. Second tyrosine kinase inhibitor discontinuation attempt in patients with chronic myeloid leukemia. Cancer 2017;123:4403–4410.
222. Ilander M, Olsson-Strömberg U, Schlums H, et al. Increased proportion of mature NK cells is associated with successful imatinib discontinuation in chronic myeloid leukemia. Leukemia 2017;31:1108–1116.
223. Massimino M, Stella S, Tirrò E, et al. Non ABL-directed inhibitors as alternative treatment strategies for chronic myeloid leukemia. Mol Cancer 2018;17:56.
224. Annunziata M, Bonifacio M, Breccia M, et al. Current strategies and future directions to achieve deep molecular response and treatment-free remission in chronic myeloid leukemia. Front Oncol 2020;10:883.
225. Clark RE, Polydoros F, Apperley JF, et al. De-escalation of tyrosine kinase inhibitor therapy before complete treatment discontinuation in patients with chronic myeloid leukaemia (DESTINY): a non-randomised, phase 2 trial. Lancet Haematol 2019;6:e375–e383.
226. Westerweel PE, Te Boekhorst PAW, Levin MD, et al. New approaches and treatment combinations for the management of chronic myeloid leukemia. Front Oncol 2019;9:665.
227. Hoffmann VS, Baccarani M, Hasford J, et al. The EUTOS population-based registry: incidence and clinical characteristics of 2904 CML patients in 20 European Countries. Leukemia 2015;29:1336–1343.
228. Ramasamy K, Hayden J, Lim Z, et al. Successful pregnancies involving men with chronic myeloid leukaemia on imatinib therapy. Br J Haematol 2007;137:374–375.
229. Breccia M, Cannella L, Montefusco E, et al. Male patients with chronic myeloid leukemia treated with imatinib involved in healthy pregnancies: report of five cases. Leuk Res 2008;32:519–520.
230. Oweini H, Otrock ZK, Mahfouz RAR, et al. Successful pregnancy involving a man with chronic myeloid leukemia on dasatinib. Arch Gynecol Obstet 2010;283:133–134.
231. Ghalaut VS, Prakash G, Bansal P, et al. Effect of imatinib on male reproductive hormones in BCR-ABL positive CML patients: A preliminary report. J Oncol Pharm Pract 2014;20:243–248.
232. Alizadeh H, Jaafar H, Rajnics P, et al. Outcome of pregnancy in chronic myeloid leukaemia patients treated with tyrosine kinase inhibitors: short report from a single centre. Leuk Res 2015;39:47–51.
233. Pye SM, Cortes J, Ault P, et al. The effects of imatinib on pregnancy outcome. Blood 2008;111:5505–5508.
234. Cortes JE, Abruzzese E, Chelysheva E, et al. The impact of dasatinib on pregnancy outcomes. Am J Hematol 2015;90:1111–1115.
235. Barkoulas T, Hall PD. Experience with dasatinib and nilotinib use in pregnancy. J Oncol Pharm Pract 2018;24:121–128.
236. Salem W, Li K, Krapp C, et al. Imatinib treatments have long-term impact on placentation and embryo survival. Sci Rep 2019;9:2535.
237. Madabhavi I, Sarkar M, Modi M, et al. Pregnancy outcomes in chronic myeloid leukemia: a single center experience. J Glob Oncol 2019;5:1–11.
238. Ault P, Kantarjian H, O'Brien S, et al. Pregnancy among patients with chronic myeloid leukemia treated with imatinib. J Clin Oncol 2006;24:1204–1208.

239. Kuwabara A, Babb A, Ibrahim A, et al. Poor outcome after reintroduction of imatinib in patients with chronic myeloid leukemia who interrupt therapy on account of pregnancy without having achieved an optimal response. Blood 2010;116:1014–1016.
240. Lasica M, Willcox A, Burbury K, et al. The effect of tyrosine kinase inhibitor interruption and interferon use on pregnancy outcomes and long-term disease control in chronic myeloid leukemia. Leuk Lymphoma 2019; 60:1796–1802.
241. Stella S, Tirró E, Massimino M, et al. Successful management of a pregnant patient with chronic myeloid leukemia receiving standard dose imatinib. In Vivo 2019;33:1593–1598.
242. Haggstrom J, Adriansson M, Hybbinette T, et al. Two cases of CML treated with alpha-interferon during second and third trimester of pregnancy with analysis of the drug in the new-born immediately postpartum. Eur J Haematol 1996;57:101–102.
243. Kuroiwa M, Gondo H, Ashida K, et al. Interferon-alpha therapy for chronic myelogenous leukemia during pregnancy. Am J Hematol 1998; 59:101–102.
244. Lipton JH, Derzko CM, Curtis J. Alpha-interferon and pregnancy in a patient with CML. Hematol Oncol 1996;14:119–122.
245. Baykal C, Zengin N, Coşkun F, et al. Use of hydroxyurea and alpha-interferon in chronic myeloid leukemia during pregnancy: a case report. Eur J Gynaecol Oncol 2000;21:89–90.
246. Thauvin-Robinet C, Maingueneau C, Robert E, et al. Exposure to hydroxyurea during pregnancy: a case series. Leukemia 2001;15: 1309–1311.
247. Fadilah SA, Ahmad-Zailani H, Soon-Keng C, et al. Successful treatment of chronic myeloid leukemia during pregnancy with hydroxyurea. Leukemia 2002;16:1202–1203.
248. Al Bahar S, Pandita R, Nath SV. Pregnancy in chronic myeloid leukemia patients treated with alpha interferon. Int J Gynaecol Obstet 2004;85: 281–282.
249. Koh LP, Kanagalingam D. Pregnancies in patients with chronic myeloid leukemia in the era of imatinib. Int J Hematol 2006;84:459–462.
250. Balsat M, Etienne M, Elhamri M, et al. Successful pregnancies in patients with BCR-ABL-positive leukemias treated with interferon-alpha therapy during the tyrosine kinase inhibitors era. Eur J Haematol 2018;101: 774–780.
251. Burchert A, Müller MC, Kostrewa P, et al. Sustained molecular response with interferon alfa maintenance after induction therapy with imatinib plus interferon alfa in patients with chronic myeloid leukemia. J Clin Oncol 2010;28:1429–1435.
252. Abruzzese E, Turkina AG, Apperley JF, et al. Pregnancy management in CML patients: to teat or not to treat? Report of 224 outcomes of the European Leukemia Net (ELN) Database. Blood 2019;134-(Supplement_1):498–498.
253. Beauverd Y, Radia D, Cargo C, et al. Pegylated interferon alpha-2a for essential thrombocythemia during pregnancy: outcome and safety. A case series. Haematologica 2016;101:e182–e184.
254. Ali R, Ozkalemkaş F, Ozkocaman V, et al. Successful pregnancy and delivery in a patient with chronic myelogenous leukemia (CML), and management of CML with leukapheresis during pregnancy: a case report and review of the literature. Jpn J Clin Oncol 2004;34: 215–217.
255. Palani R, Milojkovic D, Apperley JF. Managing pregnancy in chronic myeloid leukaemia. Ann Hematol 2015; 94(S2, Suppl 2)S167–S176.
256. Staley EM, Simmons SC, Feldman AZ, et al. Management of chronic myeloid leukemia in the setting of pregnancy: when is leukocytapheresis appropriate? A case report and review of the literature. Transfusion 2018; 58:456–460.
257. James AH, Brancazio LR, Price T. Aspirin and reproductive outcomes. Obstet Gynecol Surv 2008;63:49–57.
258. Deruelle P, Coulon C. The use of low-molecular-weight heparins in pregnancy--how safe are they? Curr Opin Obstet Gynecol 2007;19: 573–577.
259. Russell MA, Carpenter MW, Akhtar MS, et al. Imatinib mesylate and metabolite concentrations in maternal blood, umbilical cord blood, placenta and breast milk. J Perinatol 2007;27:241–243.
260. Ali R, Ozkalemkas F, Kimya Y, et al. Imatinib use during pregnancy and breast feeding: a case report and review of the literature. Arch Gynecol Obstet 2009;280:169–175.
261. National Library of Medicine. Drugs and Lactation Database (LactMed). Accessed August 21, 2020. Available at: https://www.ncbi.nlm.nih.gov/books/NBK501922/
262. Chelysheva E, Aleshin S, Polushkina E, et al. Breastfeeding in patients with chronic myeloid leukaemia: case series with measurements of drug concentrations in maternal milk and literature review. Mediterr J Hematol Infect Dis,10.4084/mjhid.2018.027
263. Abruzzese E, Trawinska MM, Perrotti AP, et al. Tyrosine kinase inhibitors and pregnancy. Mediterr J Hematol Infect Dis 2014;6:e2014028.
264. Hughes TP, Mauro MJ, Cortes JE, et al. Asciminib in chronic myeloid leukemia after ABL kinase inhibitor failure. N Engl J Med 2019;381: 2315–2326.
265. Do YR, Kwak JY, Kim JA, et al. Long-term data from a phase 3 study of radotinib versus imatinib in patients with newly diagnosed, chronic myeloid leukaemia in the chronic phase (RERISE). Br J Haematol 2020; 189:303–312.
266. Kim SH, Menon H, Jootar S, et al. Efficacy and safety of radotinib in chronic phase chronic myeloid leukemia patients with resistance or intolerance to BCR-ABL1 tyrosine kinase inhibitors. Haematologica 2014; 99:1191–1196.
267. Cortes J, Jabbour E, Daley GQ, et al. Phase 1 study of lonafarnib (SCH 66336) and imatinib mesylate in patients with chronic myeloid leukemia who have failed prior single-agent therapy with imatinib. Cancer 2007; 110:1295–1302.
268. Cortes J, Quintás-Cardama A, Garcia-Manero G, et al. Phase 1 study of tipifarnib in combination with imatinib for patients with chronic myelogenous leukemia in chronic phase after imatinib failure. Cancer 2007; 110:2000–2006.
269. Borthakur G, Dombret H, Schafhausen P, et al. A phase I study of danusertib (PHA-739358) in adult patients with accelerated or blastic phase chronic myeloid leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia resistant or intolerant to imatinib and/or other second generation c-ABL therapy. Haematologica 2015;100: 898–904.
270. Seymour JF, Kim DW, Rubin E, et al. A phase 2 study of MK-0457 in patients with BCR-ABL T315I mutant chronic myelogenous leukemia and philadelphia chromosome-positive acute lymphoblastic leukemia. Blood Cancer J 2014;4:e238.
271. Sweet K, Hazlehurst L, Sahakian E, et al. A phase I clinical trial of ruxolitinib in combination with nilotinib in chronic myeloid leukemia patients with molecular evidence of disease. Leuk Res 2018;74:89–96.

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The NCCN Guidelines Staff have no conflicts to disclose.