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Chronic Myeloid Leukemia, Version 1.2019

Clinical Practice Guidelines in Oncology

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Abstract

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

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NCCN Categories of Evidence and Consensus

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

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

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

Overview

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

CML is defined by the presence of Philadelphia chromosome (Ph) in a patient with a myeloproliferative neoplasm (MPN). Ph results from a reciprocal translocation between chromosomes 9 and 22

Please Note

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Disclosures for the NCCN Chronic Myeloid Leukemia Panel

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

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

These guidelines are also available on the Internet. For the latest update, visit NCCN.org.

[t(9;22] that gives rise to a *BCR-ABL1* fusion gene; the product of this fusion gene is a protein with deregulated tyrosine kinase activity (p210) that plays a central role in the pathogenesis of CML.[2] Another fusion protein, p190, is also produced, usually in the setting of Ph-positive acute lymphoblastic leukemia. p190 is detected only in 1% of patients with CML.[3]

CML occurs in 3 different phases (chronic, accelerated, and blast phases) and is usually diagnosed in the chronic phase. Untreated chronic phase CML (CP-CML) will eventually progress to advanced phase in 3 to 5 years.[4] Gene expression profiling has shown a close correlation of gene expression between accelerated phase CML (AP-CML) and blast phase CML (BP-CML). The bulk of the genetic changes in progression occur in the transition from CP-CML to AP-CML.[5] The activation of beta-catenin signaling pathway in CML granulocyte-macrophage progenitors (which enhances the self-renewal activity and leukemic potential of these cells) may also be a key pathobiologic event in the evolution to BP-CML.[6]

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

Diagnosis and Workup

Initial evaluation should consist of a history and physical exam, including palpation of spleen,

Text cont. on page 1117.

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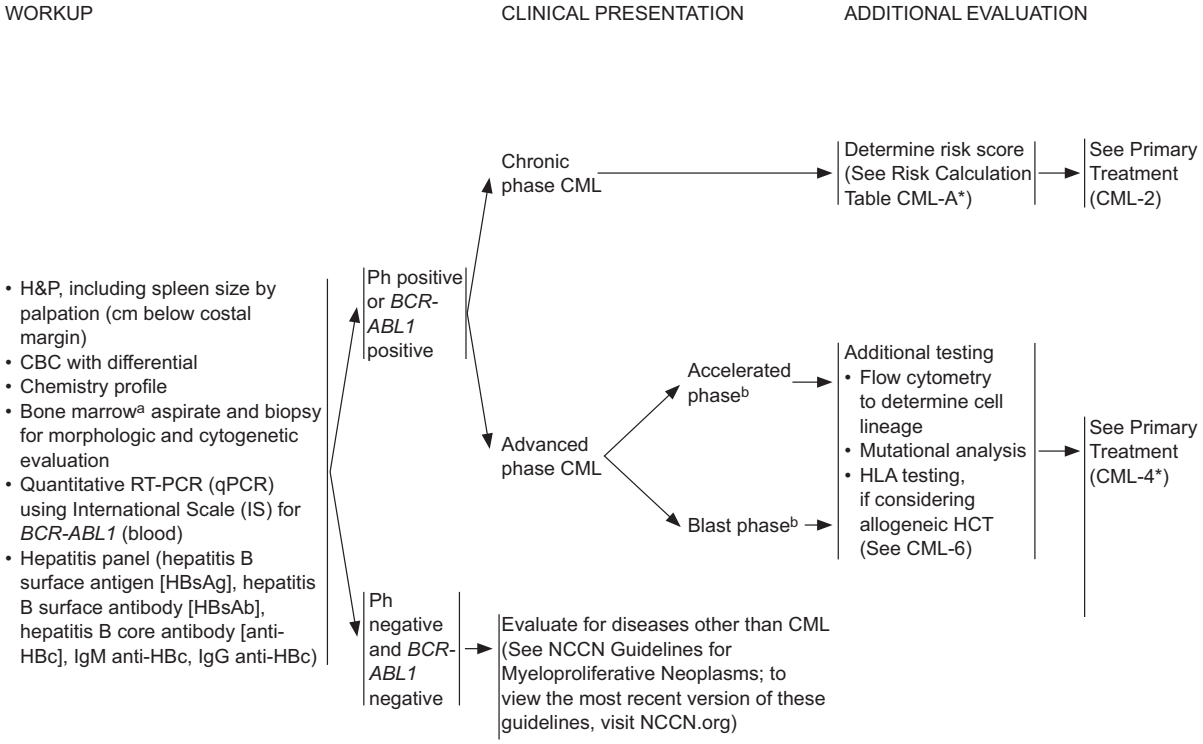

*Available online, in these guidelines, at NCCN.org

[a]Bone marrow evaluation should be done for the initial workup, to provide morphologic review, and also to detect other chromosomal abnormalities in addition to Ph chromosome. Fluorescence in situ hybridization (FISH) can be used if cytogenetic evaluation is not possible.
[b]See Definitions of Accelerated Phase and Blast Phase (CML-B, available online, in these guidelines, at NCCN.org).

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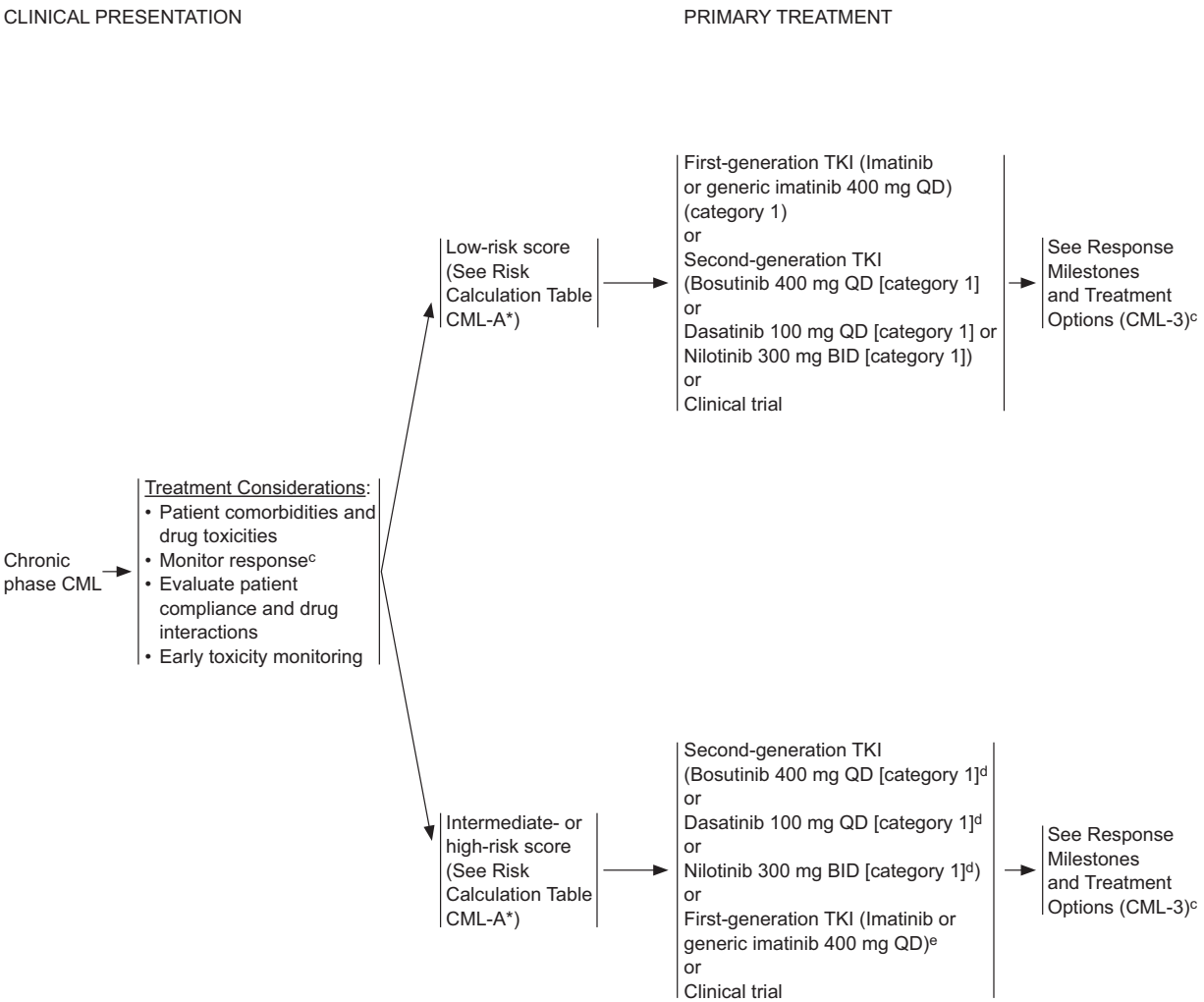

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[c]See Monitoring Response to TKI Therapy and Mutational Analysis (CML-C).
[d]Based on long-term follow-up data from the DASISION and ENESTnd trials and preliminary data from the BFORE trial, second-generation TKIs (dasatinib, nilotinib, or bosutinib) are preferred for patients with an intermediate- or high-risk Sokal or Hasford score, especially for young women whose goal is to achieve a deep and rapid molecular response and eventual drug discontinuation of TKI therapy for fertility purposes.
[e]Imatinib may be preferred for older patients with comorbidities such as cardiovascular disease.

EARLY TREATMENT RESPONSE MILESTONES[c,f]

BCR-ABL1 (IS)	3 months	6 months	12 months[g]	>15 months
>10%[h]	YELLOW	RED		
>1%–10%	GREEN		YELLOW	RED
≤1%	GREEN			

COLOR	CONCERN	CLINICAL CONSIDERATIONS	SECOND-LINE TREATMENT
RED	TKI-resistant disease	• Evaluate patient compliance and drug interactions • Consider mutational analysis	Switch to alternate TKI (CML-5) and evaluate for allogeneic HCT (CML-6*)
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-F*)[i] or Dose escalation of imatinib (to a max of 800 mg) and Consider evaluation for allogeneic HCT (CML-6*)
GREEN	TKI-sensitive disease	• Monitor response (CML-F*) and side effects	Continue same TKI (CML-F*)[j]

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

[c]See Monitoring Response to TKI Therapy and Mutational Analysis (CML-C).
[f]See Criteria for Hematologic, Cytogenetic, and Molecular Response and Relapse (CML-D).
[g]*BCR-ABL1* 0.1% at 12 months is associated with a very low probability of subsequent disease progression and a high likelihood of achieving a subsequent MR4.0, which may facilitate discontinuation of TKI therapy.
[h]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.
[i]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.
[j]Discontinuation of TKI with careful monitoring is feasible in selected patients. See Discontinuation of TKI Therapy (CML-E).

TREATMENT OPTIONS BASED ON BCR-ABL1 MUTATION PROFILE

Mutation	Treatment Recommendation[m]
Y253H, E255K/V, or *F359V/C/I*	Dasatinib
F317L/V/I/C, T315A, or *V299L*	Nilotinib
E255K/V, F317L/V/I/C, F359V/C/I, T315A, or *Y253H*	Bosutinib
T315I	Ponatinib,[n] Omacetaxine,[o] allogeneic HCT (CML-6*), or clinical trial

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[m]Patients with disease that is resistant to primary treatment with imatinib should be treated with bosutinib, dasatinib, or nilotinib in the second-line setting. Patients with disease that is resistant to primary treatment with bosutinib, dasatinib, or nilotinib could be treated with an alternate TKI (other than imatinib) in the second-line setting.
[n]Ponatinib is a treatment option for patients with a *T315I* mutation or for patients for whom no other TKI is indicated.
[o]Omacetaxine is a treatment option for patients with disease that is resistant and/or intolerant to 2 or more TKIs.

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% (>0.1%–1%) has been achieved, every 3 months for 2 years and every 3–6 months thereafter • If there is 1-log increase in *BCR-ABL1* transcript levels with MMR, qPCR should be repeated in 1–3 months
BCR-ABL kinase domain mutation analysis	• Chronic phase ▸ Failure to reach response milestones ▸ Any sign of loss of response (defined as hematologic or cytogenetic relapse) ▸ 1-log increase in *BCR-ABL1* transcript levels and loss of MMR • Disease progression to accelerated or blast phase

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

CML-C

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 disappearance of palpable splenomegaly

Cytogenetic response[2,3]
- Complete cytogenetic response (CCyR) - No Ph-positive metaphases[4]
- Major cytogenetic response (MCyR) mostly approves for this version - 0%–35% Ph-positive metaphases
- Partial cytogenetic response (PCyR) - 1%–35% Ph-positive metaphases
- Minor cytogenetic response - >35%–65% Ph-positive metaphases

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

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

[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 typically correlates with BCR-ABL1 (IS) ≤1% (>0.1%–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.

DISCONTINUATION OF TKI THERAPY[1]

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

Criteria for TKI Discontinuation (Outside of a clinical trial, TKI discontinuation should be considered only if ALL of the criteria included in the list below are met)

- Age ≥18 years.
- Chronic phase CML. No prior history of accelerated or blast phase CML.
- On approved TKI therapy for at least 3 years.[1,2]
- Prior evidence of quantifiable *BCR-ABL1* transcript.
- Stable molecular response (MR4; *BCR-ABL1* ≤0.01% IS) for ≥2 years, as documented on at least 4 tests, performed at least 3 months apart.[2]
- Access to a reliable qPCR test with a sensitivity of detection of at least MR4.5 (*BCR-ABL1* ≤0.0032% IS) and that provides results within 2 weeks.
- Monthly molecular monitoring for one year, then every 6 weeks for the second year, and every 12 weeks thereafter (indefinitely) is recommended for patients who remain in MMR (MR3; *BCR-ABL1* ≤0.1% IS) after discontinuation of TKI therapy.
- Prompt resumption of TKI within 4 weeks of a loss of MMR with molecular monitoring every 4 weeks until MMR is re-established, then every 12 weeks thereafter 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.
- Consultation with a CML Specialty Center to review the appropriateness for TKI discontinuation and potential risks and benefits of treatment discontinuation, including TKI withdrawal syndrome.
- Reporting of the following to an NCCN CML Panel Member is strongly encouraged:
  - Any significant adverse event believed to be related to treatment discontinuation.
  - Progression to accelerated or blast phase CML at any time.
  - Failure to regain MMR after 3 months following treatment reinitiation.

[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).

Cont. from page 1109.

CBC with differential, chemistry profile, and hepatitis panel. Bone marrow aspirate and biopsy for morphologic and cytogenetic evaluation and quantitative reverse transcriptase polymerase chain reaction (RT-PCR) to establish the presence of quantifiable *BCR-ABL1* mRNA transcripts at baseline are recommended to confirm the diagnosis of CML (see CML-1; page 1110).

Bone marrow cytogenetics should be done at initial workup to detect additional chromosomal abnormalities in Ph-positive cells (ACA/Ph$^+$), also known as clonal cytogenetic evolution.[7] The prognostic significance of ACA/Ph$^+$ is related to the specific chromosomal abnormality and often other features of accelerated phase.[8–12] The presence of "major route" ACA/Ph$^+$ (trisomy 8, isochromosome 17q, second Ph, and trisomy 19) at diagnosis may have a negative prognostic impact on survival and disease progression to accelerated or blast phase.[13–15] However, in a more recent analysis that evaluated the outcomes of patients with CP-CML (with or without ACA) treated with tyrosine kinase inhibitors (TKIs) in prospective studies, the presence of ACA/Ph$^+$ at the time of diagnosis was not associated with worse prognosis.[16] Patients with ACA/Ph$^+$ at diagnosis should be watched carefully for evidence of therapy failure. Clonal cytogenetic evolution in Ph-negative cells has also been reported in a small subset of patients during the course of imatinib therapy.[17–22] The most common abnormalities include trisomy 8 and loss of Y chromosome. Previous work suggested that the overall prognosis of Ph-negative CML with clonal evolution is good and is dependent on response to imatinib therapy.[21] Recently, however, the presence of chromosome abnormalities other than loss of Y chromosome has been associated with decreased survival in patients with CP-CML treated with various TKIs, suggesting that closer follow-up is indicated until definitive data are available.[23] Progression to myelodysplastic syndromes (MDS) and acute myeloid leukemia have been reported in patients with monosomy 7.[24,25]

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

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

BCR-ABL1 transcripts in the peripheral blood at very low levels (1–10 of 10^8 peripheral blood leukocytes) can also be detected in approximately 30% of normal individuals, and the incidence of *BCR-ABL1* transcripts increases with advancing age in healthy individuals.[31,32] TKI therapy is not indicated, as the risk of developing CML for these individuals is extremely low.

Management of Chronic Phase CML

Risk Stratification

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

European Treatment and Outcome Study (EUTOS) score is based only on the percentage of ba-

sophils in the blood and spleen size. The predictive value of EUTOS score was validated in a cohort of 2,060 patients enrolled in studies of first-line treatment with imatinib-based regimens.[35] EUTOS score was better than Sokal and Euro score in predicting the probability of achieving a complete cytogenetic response (CCyR) at 18 months and 5-year progression-free survival (PFS). However, the predictive value of EUTOS score has not been confirmed in subsequent studies by other investigators, and additional studies are needed to validate the EUTOS score.[36–38]

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

Primary Treatment

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

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

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

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

Trial	Study Arms	N	Median Follow-Up	CCyR[a]	MMR[b]	Disease Progression, n (%)	PFS Rate[c]	OS Rate[c]
IRIS[d,39]	Imatinib (400 mg qd)	553	11 y	83%	—	38 (7%)	92%	83%
	Interferon-alpha plus low-dose cytarabine	553		—	—	71 (13%)	—	79%[e]
DASISION[40]	Dasatinib (100 mg qd)	259	5 y	—	76% (*P*=.002)	12 (5%)	85%	91%
	Imatinib (400 mg qd)	260		—	64%	19 (7%)	86%	90%
ENESTnd[41]	Nilotinib (300 mg bid)	282	5 y	—	77% (*P* vs imatinib <.0001)	10 (4%)	92%	94%
	Nilotinib (400 mg bid)	281		—	77% (*P* vs imatinib <.0001)	6 (2%)	96%	96%
	Imatinib (400 mg qd)	283		—	60%	21 (7%)	91%	92%
BFORE[f,42]	Bosutinib (400 mg qd)	268	12 mo	77% (*P*=.0075)	47% (*P*=.02)	4 (2%)	—	—
	Imatinib (400 mg qd)	268		66%	37%	6 (3%)	—	—

Abbreviations: CCyR, complete cytogenetic response; CP-CML, chronic phase chronic myeloid leukemia; IS, International Scale; MMR, major molecular response (*BCR-ABL1* ≤0.1% IS); OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.
[a]Primary end point of DASISION study: confirmed CCyR rate at 12 mo.
[b]Primary end point of ENESTnd and BFORE studies: MMR (*BCR-ABL1* ≤0.1%) rate at 12 mo.
[c]Long-term primary end point 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 plus 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 of 12 months; long term follow up is ongoing.

Table 2. High-Dose Imatinib as First-Line Therapy for CP-CML: Long-Term Follow-Up Data From Phase III Studies

Trial	Study Arms	N	Median Follow-Up	MMR	MR4.5	PFS Rate	OS Rate
TOPS[a,43]	Imatinib (800 mg qd)	319	42 mo	79%	—	96% at 48 mo	93% at 48 mo
	Imatinib (400 mg qd)	157		76%	—	94% at 48 mo	94% at 48 mo
CML IV[b,45]	Imatinib (800 mg qd)	420	10 y	89%	71%	77%	79%
	Imatinib (400 mg qd)	400		92%	67%	80%	80%
SWOG[c,44]	Imatinib (800 mg qd)	73	12 mo	53%	19%	92% (4-y PFS)	95% (4-y OS)
	Imatinib (400 mg qd)	72		36%	9%	80% (4-y PFS)	90% (4-y OS)

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

[a]Primary end point: MMR rate at 12 mo (≤0.1% *BCR-ABL1*), which corresponds to a 3-log reduction in *BCR-ABL1* transcripts compared with the standardized baseline established in IRIS study.

[b]Primary end point: impact of MMR on survival at 12 mo. This study had 5 treatment arms (imatinib, 400 mg qd alone; imatinib, 800 mg bid; imatinib, 400 mg qd with interferon or cytarabine; imatinib after interferon failure). Only the data for imatinib at 400 mg qd alone vs imatinib at 800 mg bid are included in this table.

[c]Primary end point: MR4.0 (≥4-log reduction in *BCR-ABL1* transcripts from baseline) at 12 mo. These are results from the first part of SWOG S0325 study; follow-up after 12 mo was not required for this study.

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

The prospective studies evaluating imatinib, 800 mg, daily found that increased toxicity of that dose forced decreasing dose to approximately 600 mg, daily when considering the actually administered dose intensity.[43–45] Additionally, the French SPIRIT trial reported superior major molecular response (MMR) rates in patients treated with imatinib, 600 mg daily compared with 400 mg daily.[46] These data suggest that imatinib, 600 mg, daily may be closer to the optimal dose than 400 mg.

Clinical Considerations for The Selection of First-Line Therapy

Risk Stratification: Imatinib (400 mg daily) and second-generation TKIs (dasatinib, 100 mg once daily; nilotinib, 300 mg twice daily; and bosutinib, 400 mg daily) are all appropriate options for first-line TKI therapy for patients with CP-CML across all risk scores (see CML-2; page 1112).[39–42]

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

Second-generation TKIs also result in quicker molecular responses and higher rates of deep molecular responses (MMR [*BCR-ABL1* ≤0.1% IS] and MR4.5 [≥4.5-log reduction in *BCR-ABL1* transcripts from baseline]) in patients with CP-CML across all risk scores (Table 3), which may facilitate subsequent discontinuation of TKI therapy in selected patients.[40–42] Therefore, second-generation TKIs may be preferred over imatinib for younger patients, particularly women, because the achievement of a deep and rapid molecular response may allow eventual discontinuation of TKI therapy for fertility purposes. Imatinib may be preferred for older patients with comorbidities, especially cardiovascular.

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

Adverse events of first-line TKI therapy in patients with CP-CML reported in phase III random-

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

		Low-Risk[a,b]		Intermediate-Risk[a,b]		High-Risk[a,b]	
Trial	Study Arms	MMR	MR4.5	MMR	MR4.5	MMR	MR4.5
DASISION[40]	Dasatinib (100 mg qd)	90%	55%	71%	43%	67%	31%
	Imatinib (400 mg qd)	69%	44%	65%	28%	54%	30%
ENESTnd[41]	Nilotinib (300 mg bid)	—	53%	—	60%	—	45%
	Nilotinib (400 mg bid)	—	62%	—	50%	—	42%
	Imatinib (400 mg qd)	—	38%	—	33%	—	23%
BFORE[42]	Bosutinib (400 mg qd)	58%	—	45%	—	34%	—
	Imatinib (400 mg qd)	46%	—	39%	—	17%	—

Abbreviations: CP-CML, chronic phase chronic myeloid leukemia; IS, International Scale; MMR, major molecular response (≤0.1% *BCR-ABL1* IS); MR, molecular response; MR4.5: 4.5-log reduction in *BCR-ABL1* transcripts from baseline; TKI, tyrosine kinase inhibitor.
[a]DASISION study: Risk stratification by Hasford (Euro) risk score.
[b]ENESTnd and BFORE trial: Risk stratification by Sokal risk score.

ized studies are discussed subsequently and are also summarized in Table 4. See CML-F (available online, in these guidelines, at NCCN.org) for the management of toxicities associated with TKI therapy.

Imatinib: Chronic fatigue (mostly correlated with musculoskeletal pain and muscular cramps) is a major factor reducing quality of life.[47] Hypophosphatemia and decrease in bone mineral density has been noted in a small group of patients, suggesting that monitoring bone health should be considered for patients taking imatinib.[48,49] Skin hypopigmentation has also been reported as a side effect of imatinib and is reversible on discontinuation or dose reduction.[50,51]

Dasatinib: In the DASISION study, the incidences of grade 3/4 hematologic toxicities (anemia, neutropenia, and thrombocytopenia) were higher for dasatinib than imatinib. Nonhematologic adverse events such as muscle spasms, peripheral edema, and hypophosphatemia were more frequent with imatinib. Discontinuation of therapy because of drug-related adverse events occurred in 16% and 7% of patients in the dasatinib and imatinib arms, respectively.[40] Dasatinib is also associated with significant but reversible inhibition of platelet aggregation that may contribute to bleeding in some patients, especially if accompanied by thrombocytopenia.[52]

Pleural effusion was more common with dasatinib (28%) than with imatinib (<1%).[40] The occurrence of pleural effusion is significantly reduced with dasatinib, 100 mg once daily compared with 70 mg twice daily.[53] Patients with prior cardiac history, hypertension, and those receiving twice-daily dosing of dasatinib at 70 mg are at increased risk of developing pleural effusions. Close monitoring and timely intervention are necessary for patients at risk of developing pleural effusions.

Reversible pulmonary arterial hypertension has been reported as a rare but serious side effect of dasatinib.[54,55] In the DASISION study, pulmonary hypertension was reported in 5% of patients compared with 0.4% of patients treated with imatinib.[40] Evaluation for signs and symptoms of underlying cardiopulmonary disease before starting and during treatment with dasatinib is recommended. If pulmonary arterial hypertension is confirmed, dasatinib must be permanently discontinued.

The recommended starting dose of dasatinib is 100 mg once daily for patients with CP-CML. Limited data available from small cohorts of patients suggest that lower doses of dasatinib may potentially have similar efficacy.[56,57] Treatment interruption of dasatinib at standard dose and reintroduction of dasatinib at a lower dose of 40 mg twice daily also resolved all pulmonary complications without recurrence.[58] However, the minimum effective dose has not been established in randomized clinical trials. Reintroduction of dasatinib at 50 mg (20 mg with careful monitoring in selected patients) should be considered for patients with clinically significant intolerance to dasatinib at 100 mg once daily to avoid serious adverse events necessitating the discontinuation of dasatinib (eg, pleural effusion, myelosuppression).

Table 4. Adverse Events of First-Line TKI Therapy in CP-CML

Toxicity	DASISION[40]		ENESTnd[41]		BFORE[42]	
	Dasatinib, 100 mg qd	Imatinib, 400 mg qd	Nilotinib, 300 mg bid	Imatinib, 400 mg qd	Bosutinib, 400 mg qd	Imatinib, 400 mg qd
Hematologic toxicities (grade 3/4)						
Anemia	13%	9%	4%	6%	3%	5%
Neutropenia	29%	24%	12%	22%	7%	12%
Thrombocytopenia	22%	14%	10%	9%	14%	6%
Biochemical abnormalities (grade 3/4)						
Increased lipase	NR	NR	9%	4%	13%	6%
Increased glucose	NR	NR	7%	<1%	2%	2%
Decreased phosphate	7%	28%	8%	10%	5%	17%
Increased ALT	NR	NR	4%	2%	23%	3%
Increased AST	NR	NR	NR	NR	12%	3%
Nonhematologic toxicities (any grade)[a]						
Rash	13%	18%	38%	19%	20%	13%
Headache	13%	11%	32%	23%	19%	13%
Fatigue	9%	11%	23%	20%	19%	18%
Muscle spasms	23%	41%	12%	34%	2%	26%
Peripheral edema	13%	37%	9%	20%	4%	14%
Pleural effusion	28%	<1%	2%	1%	NR	NR
Hypertension	NR	NR	10%	4%	NR	NR
Pulmonary hypertension	5%	<1%	0%	0%	NR	NR
Diarrhea	21%	22%	19%	46%	70%	34%
Constipation	NR	NR	20%	8%	NR	NR
Nausea	10%	24%	22%	41%	35%	39%
Vomiting	5%	11%	15%	27%	18%	16%

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

[a]Nonhematologic toxicities reported for the DASISION study (except pleural effusion) are from the 3-y follow-up. No new adverse events were observed with 5-y follow-up.

Nilotinib: In the ENESTnd study, nonhematologic adverse events such as nausea, diarrhea, vomiting, muscle spasm, and peripheral edema of any grade were higher for patients receiving imatinib.[41] Conversely, rash and headache were higher with nilotinib. Grade 3 or 4 neutropenia was more frequent in the imatinib group, whereas thrombocytopenia and anemia were similar in both groups. Electrolyte abnormalities and elevations in lipase, glucose, and bilirubin were more frequent with nilotinib than with imatinib. Patients with a previous history of pancreatitis may be at greater risk of elevated serum lipase levels. The overall incidences of adverse events leading to discontinuation of therapy were comparable in the nilotinib, 300 mg, twice daily arm and imatinib arms (12% and 14%, respectively) and slightly higher in the nilotinib, 400 mg, twice daily arm (20%).

Nilotinib labeling contains a black box warning regarding the risk of QT interval prolongation, and sudden cardiac death has been reported in patients receiving nilotinib. QT interval prolongation could be managed with dose reduction. Electrolyte abnormalities should be corrected before start of treatment with nilotinib, and electrolytes should be monitored periodically. Drugs that prolong QT interval should be avoided. Electrocardiogram should be obtained to monitor the QT interval at baseline, 7 days after start of nilotinib, and periodically thereafter, and after any dose adjustments. Patients with cardiovascular risk factors should be referred to a cardiologist.

Nilotinib is associated with an increased risk of peripheral arterial occlusive disease (PAOD).[59–61] Patients should be evaluated for pre-existing PAOD and vascular risk factors before starting and during

treatment with nilotinib. If PAOD is confirmed, nilotinib should be permanently discontinued.

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

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

Assessment of reticulocyte count, ferritin, iron saturation, vitamin B_{12}, and folate and correction of nutritional deficiencies if present is recommended for patients with grade 3/4 anemia. Red blood cell transfusions are indicated in symptomatic patients. Myeloid growth factor support can be used in combination with TKI therapy for the management of neutropenia.[62,63] The use of erythropoiesis-stimulating agents (ESAs) did not impact survival or cytogenetic response rate, but was associated with a higher thrombosis rate in patients with CP-CML.[64] Recent guidelines from the Centers for Medicare & Medicaid Services (CMS) and the FDA do not support the use of ESAs in patients with myeloid malignancies.

Monitoring Response to TKI Therapy

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

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

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

Standardization of Molecular Monitoring Using the IS: In the IS, the standardized baseline (defined as the average expression of *BCR-ABL1* transcripts in 30 patients treated on the IRIS trial) is set to 100%. Molecular response is expressed as log-reduction from 100%. For example, ≥3-log reduction (≤0.1% *BCR-ABL1* IS) is referred to as MMR or MR3.0).[30,71,72] A 2-log reduction generally correlates with CCyR (≤1% *BCR-ABL1* IS).

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

Recommendations for Monitoring Response to TKI Therapy: qPCR (IS) is the preferred method to

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

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

Frequent molecular monitoring with qPCR (IS) can help to identify nonadherence to TKI therapy early in the treatment course.[74] Because adherence to TKI therapy is associated with better clinical outcomes, frequent molecular monitoring is essential if there are concerns about the patient's adherence to TKI therapy after CCyR has been achieved. In patients with deeper molecular responses (MMR and better) and who are adherent with TKI therapy, the frequency of molecular monitoring can be reduced, though the optimal frequency is unknown.

Prognostic Significance of Cytogenetic and Molecular Response

Early molecular response (≤10% *BCR-ABL1* IS at 3 and 6 months) after first-line TKI therapy has emerged as an effective prognosticator of favorable long-term PFS and OS, regardless of TKI used (Table 5).[40,41,45,75] Some reports suggest that early molecular response at 3 months has a superior prognostic value and support the use of early intervention strategies based on the *BCR-ABL1* transcript level at 3 months.[76,77] However other studies yielded partially conflicting results regarding the predictive value of *BCR-ABL1* transcript levels at 3-months.[78] From a practical perspective, it is important to consider these data points within the clinical context. For instance, if *BCR-ABL1* transcript level is minimally above the 10% cutoff (11% at 3 months), it is reasonable to reassess at 6 months before considering major changes to the treatment strategy.

Recently, studies have suggested that the rate of decline in *BCR-ABL1* transcripts correlates with longer-term response.[79–82] 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).[79] A rapid initial *BCR-ABL1* decline also identifies a subgroup of Sokal high-risk patients with outcomes similar to those of Sokal low-risk patients.[80] Among Sokal high-risk patients, a *BCR-ABL1* halving time of ≤11 days was associated with significantly improved FFS (4-year FFS rate was 79% for patients with halving time of ≤11 days vs 53% for those with halving time of >11 days; *P*=.03). In the German CML IV study, lack of a half-log reduction of *BCR-ABL1* transcripts at 3 months was associated with a higher risk of disease progression on imatinib therapy.[81] The results of the D-First study also showed that in patients treated with dasatinib, *BCR-ABL1* halving time of ≤14 days was a significant predictor of MMR by 12 months and deep molecular response (*BCR-ABL1* <0.01% IS) by 18 months.[82]

Achievement of CCyR (≤1% *BCR-ABL1* IS) within 12 months after first-line TKI therapy is an established prognostic indicator of long-term survival.[83,84] 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.[83] 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.[84]

The prognostic significance of MMR (0.1% *BCR-ABL1* IS) after first-line imatinib has also been evaluated in several studies.[69,85–89] In all of these studies, the analyses were done for different outcomes measures at multiple time points, but failed to adjust for multiple comparisons, thereby reducing the validity of the conclusions. The synoptic conclusion from these studies is that MMR is moderately superior to CCyR in predicting long-term PFS and OS. However, with longer

Table 5. 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	*BCRABL1* ≤10%	*BCRABL1* >10%	*BCRABL1* ≤10%	*BCRABL1* >10%
DASISION[40]	Dasatinib (100 mg qd)	89%	72%	94%	81%
	Imatinib (400 mg qd)	93%	72%	95%	81%
ENESTnd[41]	Nilotinib (300 mg bid)	95%	78%	98%	82%
	Nilotinib (400 mg bid)	96%	89%	96%	93%
	Imatinib (400 mg qd)	98%	79%	99%	79%
CML IV[75]	Imatinib (400 mg qd)	92%	87%	94%	87%

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

follow-up, CCyR becomes an ever stronger indicator of MMR. The achievement of MMR is also not a significant prognosticator of long-term outcome in patients who are in stable CCyR after first-line treatment with dasatinib or nilotinib.[90,91] These findings suggest that MMR may not be of prognostic significance in patients who have achieved CCyR and absence of MMR in the presence of a CCyR is not considered a treatment failure. Achievement of MMR (0.1% *BCR-ABL1* IS) at 12 months, however, is associated with a very low probability of subsequent disease progression and a high likelihood of achieving a subsequent deep molecular response (MR4.0; ≤0.01% *BCR-ABL1* IS) which may facilitate discontinuation of TKI therapy. TKI de-escalation has also been shown to be feasible in patients who had received TKI therapy for ≥3 years with either a stable MMR or MR4.0 for ≥12 months.[92]

Response Milestones after First-Line TKI Therapy

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

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

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

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

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

Second-Line Therapy

Long-term efficacy data from phase II/III studies on second-line TKI therapy for CP-CML are summarized in Table 6.[93–96]

Early molecular response (≤10% *BCR-ABL1* IS at 3 and 6 months) after second-line TKI therapy with dasatinib or nilotinib has also been reported to be a prognosticator of OS and PFS (Table 7). Patients who do not experience cytogenetic or molecular responses at 3, 6, or 12 months after second-line and subsequent TKI therapy should be considered for alternative therapies or allogeneic HCT if deemed eligible.

Table 6. Second-line and Subsequent TKI Therapy for CP-CML: Long-Term Follow-Up Data From Phase II/III Studies

TKI	N	Median Follow-Up	MCyR	CCyR	MMR	PFS	OS
Dasatinib[a,93]	Imatinib-R (n=124)	7 y	—	—	43%	39%	63%
(100 mg qd)	Imatinib-I (n=43)		—	—	55%	51%	70%
Nilotinib[b,94]	325	4 y	59%	45%	—	57%	78%
(400 mg bid)	(Imatinib-R, n=226; Imatinib-I, n=95)						
Bosutinib[b,95]	Imatinib and dasatinib-R (n=38)	4 y	39%	22%	—	—	67%
(400 mg qd)	Imatinib and dasatinib-I (n=50)		42%	40%	—	—	80%
	Imatinib and nilotinib-R (n=26)		38%	31%	—	—	87%
Ponatinib[c,96]	Dasatinib- or nilotinib-R or I (n=203)	57 mo	56%	49%	35%	52% at 5 y	76% at 5 y
(45 mg qd)	*T315I* mutation (n=64)		72%	70%	58%	50% at 5 y	66% at 5 y

Abbreviations: CCyR, complete cytogenetic response; I, intolerant; IS, International Scale; MCyR, major cytogenetic response; MMR, major molecular response (≤ 0.1% *BCR-ABL1* IS); R, resistant; OS, overall survival; PFS, progression-free survival.
[a]Primary end point: MCyR rate at 6 mo when administered 100 mg qd vs 70 mg bid.
[b]Primary end point: MCyR rate in patients with imatinib-I or imatinib-R disease.
[c]Primary end point: MCyR at any time within the first 12 mo.

Management of Patients With Inadequate Response to Imatinib: Switching to an alternate TKI is recommended for patients with disease that is resistant to imatinib 400 mg daily. Dasatinib, nilotinib, and bosutinib are active against many of the imatinib-resistant BCR-ABL1 kinase domain mutants, except T315I, and are effective treatment options for patients with CP-CML intolerant to imatinib or those with CP-CML resistant to imatinib.[93-95]

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

Management of Patients with Inadequate Response to Dasatinib, Nilotinib or Bosutinib: Switching to an alternate TKI (other than imatinib) in the second-line setting could be considered for patients with disease that is resistant to dasatinib, nilotinib, or bosutinib. However, no clear evidence supports that switching to alternate TKI therapy would improve long-term clinical outcome for this group of patients.

Ponatinib is an option for patients with *T315I* mutation and for those with disease that has not responded to several TKIs.[96] Long-term efficacy data from phase II/III studies evaluating bosutinib or ponatinib in patients with pretreated CP-CML are summarized in Table 6.

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

Table 7. Early Molecular Response (≤10% *BCR-ABL1* IS) After Second-Line TKI Therapy and Survival Outcomes

		PFS				OS			
		BCRABL1 ≤10%		*BCRABL1* >10%		*BCRABL1* ≤10%		*BCRABL1* >10%	
TKI	Median Follow-Up	3 mo	6 mo	3 mo	6 mo	3 mo	6 mo	3 mo	6 mo
Dasatinib[93] (100 mg qd)	7 y	56%	57%	21%	4%	72%	74%	56%	50%
Nilotinib[94] (400 mg bid)	4 y	67%	58%	42%	39%	81%	82%	71%	73%

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

for high blood pressure, evidence of arterial occlusive or thromboembolic events, and reduced cardiac function. Ponatinib should be interrupted or stopped immediately for vascular occlusion and for new or worsening heart failure. Patients with cardiovascular risk factors should be referred to a cardiologist.

The recommended initial dose of ponatinib is 45 mg once daily. High dose intensity of ponatinib is significantly associated with increased risk of adverse events.[105] Therefore, dose modifications may be necessary for the management of adverse events. In a post hoc analysis of the PACE trial that assessed the clinical impact of dose modification and dose intensity on outcomes of patients with CP-CML, substantial responses were seen at lower dose levels and the rates of maintenance of MCyR and MMR were high irrespective of dose-reductions.[96] Thus, an initial dose of 30 mg may be a safer and effective dose for patients with cardiovascular risk factors. Safety and efficacy of ponatinib at initial doses lower than 45 mg are being evaluated in a randomized clinical trial.

Omacetaxine is an option for patients with the T315I mutation and in those with CML that is resistant to ≥2 TKIs.[106–108] In the CML 202 study, among 62 evaluable patients with T315I and CP-CML resistant to prior TKI therapy, MCyR, CCyR, and MMR were achieved in 23%, 16%, and 17% of patients, respectively, and the T315I clone declined to below detection limits in 61% of patients.[106] After a median follow-up of 19 months, the median PFS was 8 months and the median OS had not yet been reached. In the cohort of 46 patients with CP-CML that is resistant to ≥2 TKIs (CML 203 study), MCyR and CCyR were achieved in 22% and 4% of patients, respectively. Median PFS and OS were 7 months and 30 months, respectively.[107] Omacetaxine had an acceptable toxicity profile, and the most common grade 3/4 adverse events were thrombocytopenia (67%), neutropenia (47%), and anemia (37%).[108]

Clinical Considerations For The Selection Of Second-Line Therapy

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

Drug Interactions: Bosutinib, dasatinib, imatinib, and nilotinib are metabolized in the liver by cytochrome P450 (CYP) enzymes. Drugs that are CYP3A4 or CYP3A5 inducers may decrease the therapeutic plasma concentration of TKIs, whereas CYP3A4 inhibitors and drugs that are metabolized by the CYP3A4 or CYP3A5 enzyme might result in increased plasma levels of TKIs.[109] In addition, imatinib is also a weak inhibitor of the CYP2D6 and CYP2C9 isoenzymes and nilotinib is a competitive inhibitor of CYP2C8, CYP2C9, CYP2D6, and UGT1A1, potentially increasing the plasma concentrations of drugs eliminated by these enzymes.

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

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

Adherence to Therapy: Treatment interruptions and nonadherence to therapy may lead to undesirable clinical outcomes.[110–112] In the ADAGIO study, non-

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

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

Resistance to TKI Therapy: Aberrant expressions of drug transporters[118–120] and plasma protein binding of TKI[121–123] could contribute to primary resistance by altering the intracellular and plasma concentration of TKI. Monitoring imatinib plasma levels may be useful in determining patient adherence to therapy. However, there are no data to support that change of therapy based on plasma imatinib levels will affect treatment outcomes. Pretreatment levels of organic cation transporter 1 (OCT1) have been reported as the most powerful predictor of response to imatinib.[124] Conversely, cellular uptake of dasatinib or nilotinib seems to be independent of OCT1 expression, suggesting that patients with low hOCT1 expression might have better outcomes with dasatinib or nilotinib than with imatinib.[125–128]

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

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

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

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

Rising BCR-ABL1 Transcript Levels: Rising *BCR-ABL1* transcript levels are associated with an in-

Table 8. Responses Based on *BCR-ABL1* Mutations Status

Mutation	Major Cytogenetic Response, n/N (%)			
	Bosutinib[95]	Dasatinib[139]	Nilotinib[140]	Ponatinib[141]
E255K[a]	NR	9/16 (56%)	3/7 (43%)	8/13 (62%)
E255V[a]	NR	4/11 (36%)		1/4 (25%)
E459K	NR	NR	NR	3/7 (43%)
F317L[b]	1/7 (14%)	2/14 (14%)	NR	13/29 (45%)
F359C[a]	1/2 (50%)	3/5 (60%)	1/11 (9%)	1/7 (14%)
F359V[a]	2/3 (67%)	17/27 (63%)		11/20 (55%)
F359I[a]	2/2 (100%)	10/12 (83%)	NR	3/4 (75%)
G250E[c]	0/5 (0%)	29/60 (48%)	3/5 (60%)	8/12 (67%)
H396R	NR	17/33 (52%)	NR	1/5 (20%)
L248V	NR	10/15 (67%)	NR	1/2 (50%)
M244V	2/3 (67%)	27/26 (59%)	NR	4/9 (56%)
M351T	NR	28/54 (52%)	NR	1/2 (50%)
Y253H[a]	5/6 (83%)	15/23 (65%)	1/8 (13%)	1/2 (50%)
V299L[b,c]	0/2 (0%)	NR	NR	3/8 (38%)

Abbreviation: NR, not reported.
[a]*BCR-ABL1* mutations resistant to nilotinib.
[b]*BCR-ABL1* mutations resistant to dasatinib.
[c]*BCR-ABL1* mutations resistant to bosutinib.

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

Toxicity (Any grade)	Dasatinib[93] (100 mg qd)	Nilotinib[94] (300 mg bid)	Bosutinib[95] (400 mg qd)	Ponatinib[96] (45 mg qd)
Rash	33%	31%	28%	47%
Headache	—	18%	27%	43%
Fatigue	37%	21%	24%	30%
Myalgias/ Arthralgias	38%	11%	18%	24%/33%
Pleural effusion	28%	—	17%	—
Hypertension	—	—	8%	37%
Hemorrhage	26%	—	—	—
Diarrhea	42%	12%	83%	20%
Constipation	—	13%	13%	41%
Nausea	27%	25%	48%	29%
Vomiting		13%	38%	19%
Increased blood creatinine	—	—	13%	—
Increased lipase	—	—	—	27%
Increased ALT/AST	—	—	15%	—

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

creased likelihood of detecting BCR-ABL1 kinase domain mutations and cytogenetic relapse.[144–148] In patients who had achieved very low levels of *BCR-ABL1* transcripts, emergence of *BCR-ABL1* mutations was more frequent in those who had more than a 2-fold increase in *BCR-ABL1* levels compared with those with stable or decreasing *BCR-ABL1*.[144] A serial rise has been reported to be more reliable than a single ≥2-fold increase in *BCR-ABL1* transcripts.[145,146] Among patients in CCyR with a ≥0.5-log increase in *BCR-ABL1* transcripts on at least 2 occasions, the highest risk of disease progression was associated with loss of MMR and a more than 1-log increase in *BCR-ABL1* transcripts.[146]

The precise increase in *BCR-ABL1* transcripts that warrants a mutation analysis depends on the performance characteristics of the qPCR assay.[148] Some laboratories have advocated a 2- to 3-fold range,[88,147,148] whereas others have taken a more conservative approach (5- to 10-fold).[146] Obviously, some common sense must prevail, because 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 deep molecular response (MR4.5; ≤0.0032% *BCR-ABL1* IS) is an infinite increase in *BCR-ABL1* transcripts. However, a change in *BCR-ABL1* transcripts from a barely detectable level to MR4.5 is clearly different from a 5-fold increase in *BCR-ABL1* transcripts after achieving MMR.

Currently there are no specific guidelines for changing therapy based on rising *BCR-ABL1* levels as detected by qPCR. Changes of therapy based solely on rising *BCR-ABL1* levels 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 experienced and maintained deep molecular response (≥MR4.0; ≤0.01% *BCR-ABL1* IS) for ≥2 or more years has been evaluated in several clinical studies. Limited longer-term follow-up data from the TKI discontinuation trials are summarized in Table 10.

The possibility of treatment-free remission (TFR) after discontinuation of imatinib was first evaluated in the Stop Imatinib (STIM1) study in 100 patients with a CMR for at least 2 years (5-log

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

Trial	Treatment Prior to Discontinuation	N	Depth and Duration of MR Required for Discontinuation	Trigger to Resume TKI Therapy	Median Follow-Up	Treatment-Free Remission Rate
STIM1[150]	**Imatinib ± interferon**	100	MR5.0 for at least 2 y	Loss of MR5.0	77 mo	38% at 60 mo
TWISTER[151]	**Imatinib ± interferon**	40	MR4.5 for at least 2 y	Loss of MR5.0	42 mo	47% at 24 mo
HOVON[152]	**Imatinib + cytarabine**	15	MR4.5 for at least 2 y	Loss of MR4.5	36 mo	33% at 24 mo
ASTIM[153]	**Imatinib ± interferon**	80	MR5.0 for at least 2 y	Loss of MMR	31 mo	61% at 36 mo
ISAV[154]	Imatinib (after failure of interferon or hydroxyurea)	108	CMR for at least 18 mo	Loss of MMR	36 mo	52% at 36 mo
KID[155]	**Imatinib ± interferon**	90	MR4.5 for at least 2 y	Loss of MMR	27 mo	59% at 24 mo
Stop 2GTKI[157]	**Dasatinib/Nilotinib (first or secondline)**	60	MR4.5 for at least 24 mo	Loss of MMR	47 mo	54% at 48 mo
ENESTfreedom[158]	**Nilotinib (firstline)**	190	MR4.5 for 12 mo	Loss of MMR	96 wk	49% at 96 wk
ENESTop[159]	**Nilotinib (secondline)**	126	MR4.5 for 12 mo	Loss of MMR	96 wk	53% at 96 wk
DADI[160]	**Dasatinib (secondline)**	63	MR4.0 for at least 12 mo	Loss of MR4.0	44 mo	44% at 36 mo
EUROSKI[156]	**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; IS, International Scale; MMR, major molecular response (≤0.1% *BCRABL1* IS); MR, molecular response; MR4.0, ≤0.01% *BCRABL1* IS; MR4.5, ≤0.0032% *BCRABL1* IS or >4.5log reduction of *BCRABL1* and undetectable minimal residual disease on qPCR with a sensitivity of ≥4.5log reduction; MR5.0, 5log reduction in *BCR ABL1* levels and undetectable minimal residual disease on qPCR with a sensitivity of ≥4.5log reduction; TKI, tyrosine kinase inhibitor.

reduction in *BCR-ABL1* levels and undetectable minimal residual disease on qPCR with a sensitivity of ≥4.5-log reduction from the standardized baseline).[149,150] 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.[150] Other subsequent studies that have evaluated discontinuation of imatinib have also reported similar findings.[151–156]

More recent studies have also confirmed the feasibility of TFR after discontinuation of dasatinib or nilotinib, in patients with CP-CML who have achieved and maintained MR4.5 for 12 months after ≥2 years of TKI therapy in the first-line or second-line setting (TFR rates ranging from 44% to 54%; Table 10).[156–160] 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.[156] Therefore, it is reasonable to assume that the likelihood of TFR after discontinuation would be similar irrespective of TKI in patients who have experienced and maintained deep molecular response (MR4.0; ≤0.01% *BCR-ABL1* IS) for ≥2 years.

The results of the RE-STIM study demonstrated the safety of a second TKI discontinuation after a first unsuccessful attempt.[161] The rate of molecular relapse after the first TKI discontinuation attempt was the only factor significantly associated with outcome. The TFR rate at 24 months after second TKI discontinuation was higher for patients who remained in deep molecular response within the first 3 months after the first TKI discontinuation (72% vs 32% for other patients).

Approximately 40% to 60% of patients who discontinue TKI therapy after achieving deep molecular response experience recurrence within 6 months of treatment cessation, in some cases as early as 1 month after discontinuation of TKI therapy. Resumption of TKI therapy immediately after recurrence results in the achievement of undetectable disease in almost all patients.[149–160] TKI withdrawal syndrome (aggravation or new development of musculoskeletal pain and/or pruritus after discontinuation of TKI therapy) has been reported during the TFR period in some TKI discontinuation studies,[155,158,159] and the occurrence of imatinib withdrawal syndrome was associated with a lower rate of molecular relapse in the KID study.[155]

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.[149,150] 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.[153] Several factors may help predict the risk of relapse after discontinuation of TKI therapy (eg, a higher Sokal risk score, female sex, lower natural killer cell counts, suboptimal response or resistance to imatinib, duration of TKI therapy, and deep molecular response prior to TKI discontinuation).[149,150,156–160,162] However, only the duration of TKI therapy and deep molecular response before TKI discontinuation therapy have been associated with TFR with a high level of consistency.[149,156] In the EURO-SKI study, duration of treatment with imatinib (≥ 6 years) and deep molecular response duration (MR4.0 for 3 years) were significantly associated with MMR maintenance at 6 months after discontinuation of imatinib.[156]

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

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

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7–30.
2. Faderl S, Talpaz M, Estrov Z, et al. The biology of chronic myeloid leukemia. N Engl J Med 1999;341:164–172.
3. 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.
4. Sawyers CL. Chronic myeloid leukemia. N Engl J Med 1999;340:1330–1340.
5. Radich JP, Dai H, Mao M, et al. Gene expression changes associated with progression and response in chronic myeloid leukemia. Proc Natl Acad Sci U S A 2006;103:2794–2799.
6. 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.
7. Mitelman F. The cytogenetic scenario of chronic myeloid leukemia. Leuk Lymphoma 1993;11 Suppl 1:11–15.
8. 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.
9. 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.
10. 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.
11. 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.
12. 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.
13. 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.
14. 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.
15. 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.
16. 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.
17. Bumm T, Muller 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.
18. 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.
19. 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.

20. 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.
21. 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.
22. 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.
23. Issa GC, Kantarjian HM, Gonzalez GN, et al. Clonal chromosomal abnormalities appearing in Philadelphia chromosome–negative metaphases during CML treatment. Blood 2017;130:2084.
24. 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.
25. 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.
26. 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.
27. 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.
28. 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.
29. 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.
30. 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.
31. 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.
32. 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.
33. Sokal J, Cox E, Baccarani M, et al. Prognostic discrimination in "good-risk" chronic granulocytic leukemia. Blood 1984;63:789–799.
34. 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.
35. Hasford J, Baccarani M, Hoffmann V, et al. Predicting complete cytogenetic response and subsequent progression-free survival in 2060 patients with CML on imatinib treatment: the EUTOS score. Blood 2011;118:686–692.
36. Marin D, Ibrahim AR, Goldman JM. European Treatment and Outcome Study (EUTOS) score for chronic myeloid leukemia still requires more confirmation. J Clin Oncol 2011;29:3944–3945.
37. Jabbour E, Cortes J, Nazha A, et al. EUTOS score is not predictive for survival and outcome in patients with early chronic phase chronic myeloid leukemia treated with tyrosine kinase inhibitors: a single institution experience. Blood 2012;119:4524–4526.
38. Yamamoto E, Fujisawa S, Hagihara M, et al. European Treatment and Outcome Study score does not predict imatinib treatment response and outcome in chronic myeloid leukemia patients. Cancer Sci 2014;105:105–109.
39. Hochhaus A, Larson RA, Guilhot F, et al. Long-term outcomes of imatinib treatment for chronic myeloid leukemia. N Engl J Med 2017;376:917–927.
40. 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.
41. 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.
42. 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.
43. 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.
44. 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.
45. 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.
46. Preudhomme C, Guilhot J, Nicolini FE, et al. Imatinib plus peginterferon alfa-2a in chronic myeloid leukemia. N Engl J Med 2010;363:2511–2521.
47. 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.
48. 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.
49. 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.
50. Tsao AS, Kantarjian H, Cortes J, et al. Imatinib mesylate causes hypopigmentation in the skin. Cancer 2003;98:2483–2487.
51. 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.
52. Quintas-Cardama A, Han X, Kantarjian H, Cortes J. Tyrosine kinase inhibitor-induced platelet dysfunction in patients with chronic myeloid leukemia. Blood 2009;114:261–263.
53. 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.
54. Montani D, Bergot E, Gunther S, et al. Pulmonary arterial hypertension in patients treated by dasatinib. Circulation 2012;125:2128–2137.
55. Orlandi EM, Rocca B, Pazzano AS, Ghio S. Reversible pulmonary arterial hypertension likely related to long-term, low-dose dasatinib treatment for chronic myeloid leukaemia. Leuk Res 2012;36:e4–6.
56. 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.
57. Naqvi K, Jabbour E, Skinner J, et al. Early results of lower dose dasatinib (50 mg daily) as frontline therapy for newly diagnosed chronic-phase chronic myeloid leukemia. Cancer 2018;124:2740–2747.
58. Bergeron A, Rea 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.
59. 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.
60. 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.
61. 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.

62. 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.
63. Quintas-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.
64. 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.
65. Landstrom AP, Ketterling RP, Knudson RA, Tefferi A. 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.
66. Muhlmann J, Thaler J, Hilbe W, et al. Fluorescence in situ hybridization (FISH) on peripheral blood smears for monitoring Philadelphia chromosome-positive chronic myeloid leukemia (CML) during interferon treatment: a new strategy for remission assessment. Genes Chromosomes Cancer 1998;21:90–100.
67. 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.
68. 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.
69. Hughes T, 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.
70. 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.
71. 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.
72. Cross NC. Standardisation of molecular monitoring for chronic myeloid leukaemia. Best Pract Res Clin Haematol 2009;22:355–365.
73. 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.
74. Guerin 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.
75. Hanfstein B, Muller 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.
76. 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.
77. 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.
78. 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.
79. 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.
80. Branford S, Yeung DT, Ross DM, et al. The adverse effect of high sokal risk for first line imatinib treated patients is overcome by a rapid rate of BCR-ABL decline measured as early as 1 month of treatment [abstract]. Blood 2014;124:Abstract 816.
81. 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.
82. 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.
83. 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.
84. 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.
85. 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.
86. 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.
87. 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.
88. 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.
89. Hehlmann R, Lauseker M, Jung-Munkwitz S, et al. Tolerability-adapted imatinib 800 mg/d versus 400 mg/d versus 400 mg/d plus interferon-α in newly diagnosed chronic myeloid leukemia. J Clin Oncol 2011;29:1634–1642.
90. 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.
91. Jabbour E, Kantarjian HM, Saglio G, et al. Early response with dasatinib or imatinib in chronic myeloid leukemia: 3-year follow-up from a randomized phase 3 trial (DASISION). Blood 2014;123:494–500.
92. Clark RE, Polydoros F, Apperley JF, et al. De-escalation of tyrosine kinase inhibitor dose in patients with chronic myeloid leukaemia with stable major molecular response (DESTINY): an interim analysis of a non-randomised, phase 2 trial. Lancet Haematol 2017;4:e310–e316.
93. 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.
94. 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.
95. 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.
96. Cortes JE, Kim DW, 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.
97. 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.
98. Marin D, Goldman JM, Olavarria E, Apperley JF. Transient benefit only from increasing the imatinib dose in CML patients who do not achieve complete cytogenetic remissions on conventional doses. Blood 2003;102:2702–2704.
99. 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.
100. 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.
101. 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.

102. 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.

103. 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.

104. 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.

105. 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.

106. 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.

107. 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.

108. Cortes JE, Nicolini FE, Wetzler M, et al. Subcutaneous omacetaxine mepesuccinate in patients with chronic-phase chronic myeloid leukemia previously treated with 2 or more tyrosine kinase inhibitors including imatinib. Clin Lymphoma Myeloma Leuk 2013;13:584–591.

109. Haouala A, Widmer N, Duchosal MA, et al. Drug interactions with the tyrosine kinase inhibitors imatinib, dasatinib, and nilotinib. Blood 2011;117:e75–87.

110. 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.

111. 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.

112. 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.

113. 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.

114. 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.

115. Quintas-Cardama A, Cortes JE, Kantarjian H. Practical management of toxicities associated with tyrosine kinase inhibitors in chronic myeloid leukemia. Clin Lymphoma Myeloma 2008;8 Suppl 3:S82–88.

116. 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.

117. 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.

118. Thomas J, Wang L, Clark RE, Pirmohamed M. Active transport of imatinib into and out of cells: implications for drug resistance. Blood 2004;104:3739–3745.

119. 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.

120. Hegedus C, Ozvegy-Laczka C, Apati 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.

121. 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.

122. 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.

123. 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.

124. White DL, Radich J, Soverini S, et al. Chronic phase chronic myeloid leukemia patients with low OCT-1 activity randomised to high-dose imatinib achieve better responses, and lower failure rates, than those randomized to standard-dose. Haematologica 2012;97:907–914.

125. 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.

126. 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.

127. 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.

128. 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.

129. 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.

130. 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.

131. Nicolini FE, Corm S, Le 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;20:1061–1106.

132. 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.

133. 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.

134. 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.

135. 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.

136. 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.

137. 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.

138. 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.

139. Muller 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.

140. 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.

141. 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.

142. 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.

143. 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.

144. 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.
145. Wang L, Knight K, Lucas C, Clark R. 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.
146. 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.
147. 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.
148. 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.
149. Mahon FX, Rea 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 2010:1029–1035.
150. 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.
151. Ross DM, Branford S, Seymour JF, et al. Safety and efficacy of imatinib cessation for CML patients with stable undetectable minimal residual disease: results from the TWISTER study. Blood 2013;122:515–522.
152. 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.
153. 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.
154. 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.
155. 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.
156. 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.
157. 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.
158. Ross DM, Masszi T, Gomez 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.
159. 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, pPhase 2, open-label study. Ann Intern Med 2018;168:461–470.
160. 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.
161. 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.
162. Ilander M, Olsson-Stromberg 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.

Individual Disclosures for Chronic Myeloid Leukemia

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Camille N. Abboud, MD	None	Pfizer Inc.	Agios Pharmaceuticals, Inc.; Cardinal Health; and Jazz Pharmaceuticals	7/12/18
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