National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Chronic Myeloid Leukemia

Version 4.2018 — January 24, 2018

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NCCN Guidelines Version 4.2018 Panel Members
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NCCN Guidelines Panel Disclosures

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

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/physician.html.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

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Updates in Version 4.2018 of the NCCN Guidelines for Chronic Myeloid Leukemia from Version 3.2018 include:

CML-E

- **Bullet removed: No history of resistance to any TKI.**
- **Bullet 6 modified: Access to a reliable qPCR test with a sensitivity of detection *at least MR4.5 (BCR-ABL1 ≤ 0.0032% IS)* ~~of ≥4.5 logs that reports results on the IS~~ and provides results within 2 weeks.**
- **Bullet 7 modified: Monthly molecular monitoring for *one year, then every 6 weeks for the second year, and every 12 weeks thereafter* ~~the first six months following discontinuation, bimonthly during months 7–24, and quarterly thereafter~~ (indefinitely) *is recommended* for patients who remain in MMR (MR3; *BCR-ABL1* ≤0.1% IS) *after discontinuation of TKI therapy.***
- **Bullet 8 modified: Prompt resumption of TKI *within 4 weeks of a loss of MMR* with ~~a monthly~~ molecular monitoring *every 4 weeks until MMR is re-established, then every 12 weeks thereafter* ~~for the first six months following resumption of TKI and every 3 months thereafter~~ is recommended indefinitely for patients *who have reinitiated TKI therapy after a* loss of MMR. For those who fail to achieve MMR after *three* ~~six~~ months of TKI resumption, BCR-ABL1 kinase domain mutation testing should be performed, and monthly molecular monitoring should be continued for another six months.**

MS-1

- **The Discussion section has been updated to reflect the changes in the algorithm.**

Updates in Version 3.2018 of the NCCN Guidelines for Chronic Myeloid Leukemia from Version 2.2018 include:

CML-2

- **Primary Treatment**
  - **Bosutinib added as a treatment option for any risk score. This is a category 1 recommendation.**
  - **Intermediate- or high-risk score: Nilotinib recommendation changed from a category 2A to category 1.**
  - **Intermediate- or high-risk score: Dasatinib recommendation changed from a category 2A to category 1.**
- **Footnote d modified: Long-term follow-up data *from the DASISION and ENESTnd trials and preliminary data from the BFORE trial* suggest that patients with an intermediate- or high-risk Sokal or Hasford score may preferentially benefit from *second generation TKI* (dasatinib, nilotinib, *or bosutinib*). See Discussion for additional information.**

MS-1

- **The Discussion section has been updated to reflect the changes in the algorithm.**

Updates in Version 2.2018 of the NCCN Guidelines for Chronic Myeloid Leukemia from Version 1.2018 include:

CML-3

- ***BCR-ABL1* (IS) category changed from 0.1%–<1% to >0.1%–1% and <0.1% to ≤0.1%. (also applies to CML-D)**

CML-C

- **Quantitative RT-PCR (qPCR) using IS; bullet 2 modified with the addition of ≤1% after *BCR-ABL1* (IS) and > *before* 0.1%–1%.**

CML-D

- **Bullet 4 modified: Complete molecular response (CMR) ~~– no detectable *BCR-ABL1* mRNA using a qPCR assay with a sensitivity of at least 4.5 logs below the standardized baseline. CMR~~ is variably described, and is best defined by the assay's level of sensitivity (eg, MR4.5).**

MS-1

- **The Discussion section has been updated to reflect the changes in the algorithm.**

UPDATES

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Updates in Version 1.2018 of the NCCN Guidelines for Chronic Myeloid Leukemia from Version 2.2017 include:

CML-1

- **Workup**
  - **Bullet 2: "Platelets" removed**
  - **Bullet 4 modified and combined with sub-bullet: "Bone marrow ~~evaluation~~ aspirate and biopsy for morphologic ~~review~~ *and cytogenetic evaluation*"**
  - **Bullet 5 and sub-bullet removed: "Cytogenetics > FISH (blood, if bone marrow not available)"**
  - **Bullet 6 removed: "Molecular"**
  - **Sub-bullet to bullet 6 is the new bullet 6: "Quantitative RT-PCR (qPCR) using International Scale (IS) for *BCR-ABL1* (blood)"**
  - **Bullet 7 removed: "ECG for prolonged QTc"**
  - **Bullet 10 modified with the specification of test for the hepatitis panel: "hepatitis B surface antigen [HBsAg], hepatitis B surface antibody [HBsAb], hepatitis B core antibody [anti-HBc], IgM anti-HBc, IgG anti-HBc"**
- **Footnote a modified: "Bone marrow evaluation should be done for the initial workup, ~~not only~~ to provide morphologic review~~, but~~ *and* also to detect *other* chromosomal abnormalities *in addition to Ph chromosome* ~~that are not detectable on peripheral blood FISH~~. *FISH can be used if cytogenetic evaluation is not possible*."**

CML-2

- **Treatment Considerations moved to second column.**
- **Primary Treatment; Intermediate- or high-risk score**
  - **Nilotinib and Dasatinib: preferred designation removed.**
- **Footnote d modified: "~~Preliminary~~*Long-term follow-up* data suggest that patients with an intermediate- or high-risk Sokal or Hasford score may preferentially benefit from dasatinib or nilotinib. See Discussion for additional information."**

CML-3

- ***BCR-ABL1* (IS) category changed from 1%–10% to >1%–10% and 0.1%–<1% to 0.1%–1%. (also applies to CML-D)**

CML-4

- **Treatment Considerations moved to second column.**
  - **Bullet 1 modified: "*Evaluate for* ~~Role of~~ allogeneic HCT ~~should be discussed based on response.~~"**

CML-6

- **Footnote p moved into the algorithm: "Consider TKI therapy for at least one year in patients with prior accelerated or blast phase CML"**
- **Previous footnote p (now footnote n) replaced with "See Discussion."**

CML-B

- **Modified Criteria Used at MD Anderson Cancer Center**
  - **Bullet 5 modified: "~~Clonal evolution~~ *Additional clonal cytogenetic abnormalities in Ph+ cells*"**
- **World Health Organization (WHO) Criteria removed.**

CML-D 2 OF 2

- **Cytogenetic Assessment of Response to TKI Therapy removed.**

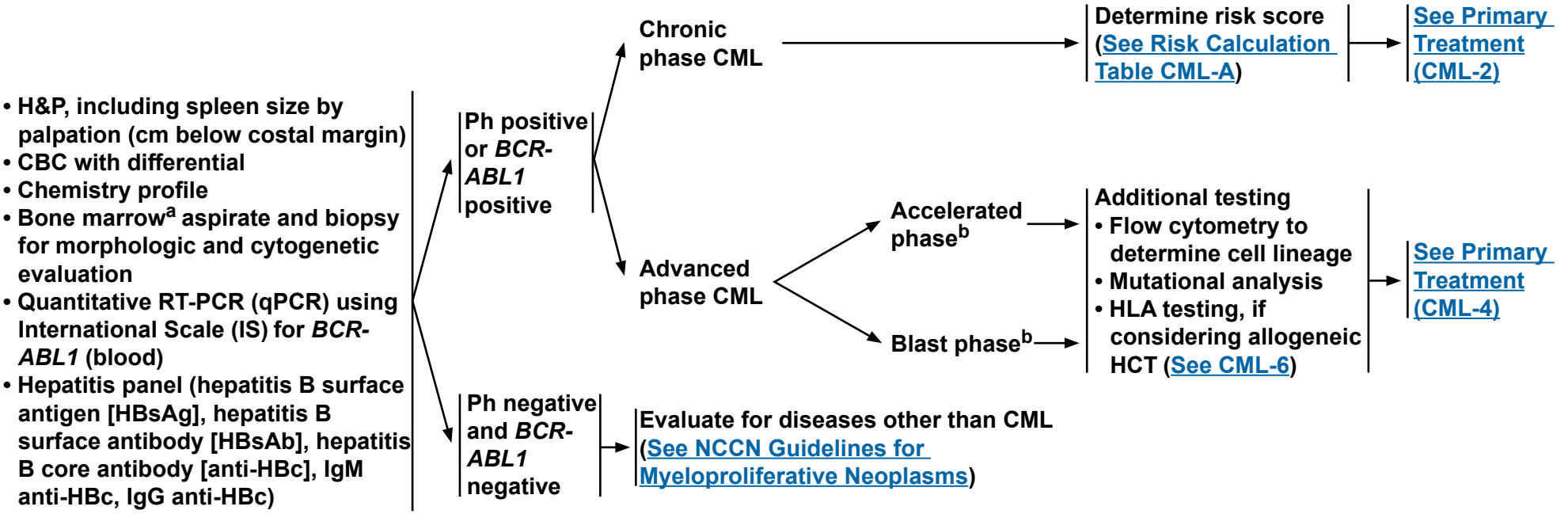
CML-D

- **Relapse, bullet 2 clarified: "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 cytogentic relapse)*"**
- **Footnote 4 added: "CCyR typically correlates with *BCR-ABL1*(IS) 0.1%–1%."**

CML-E

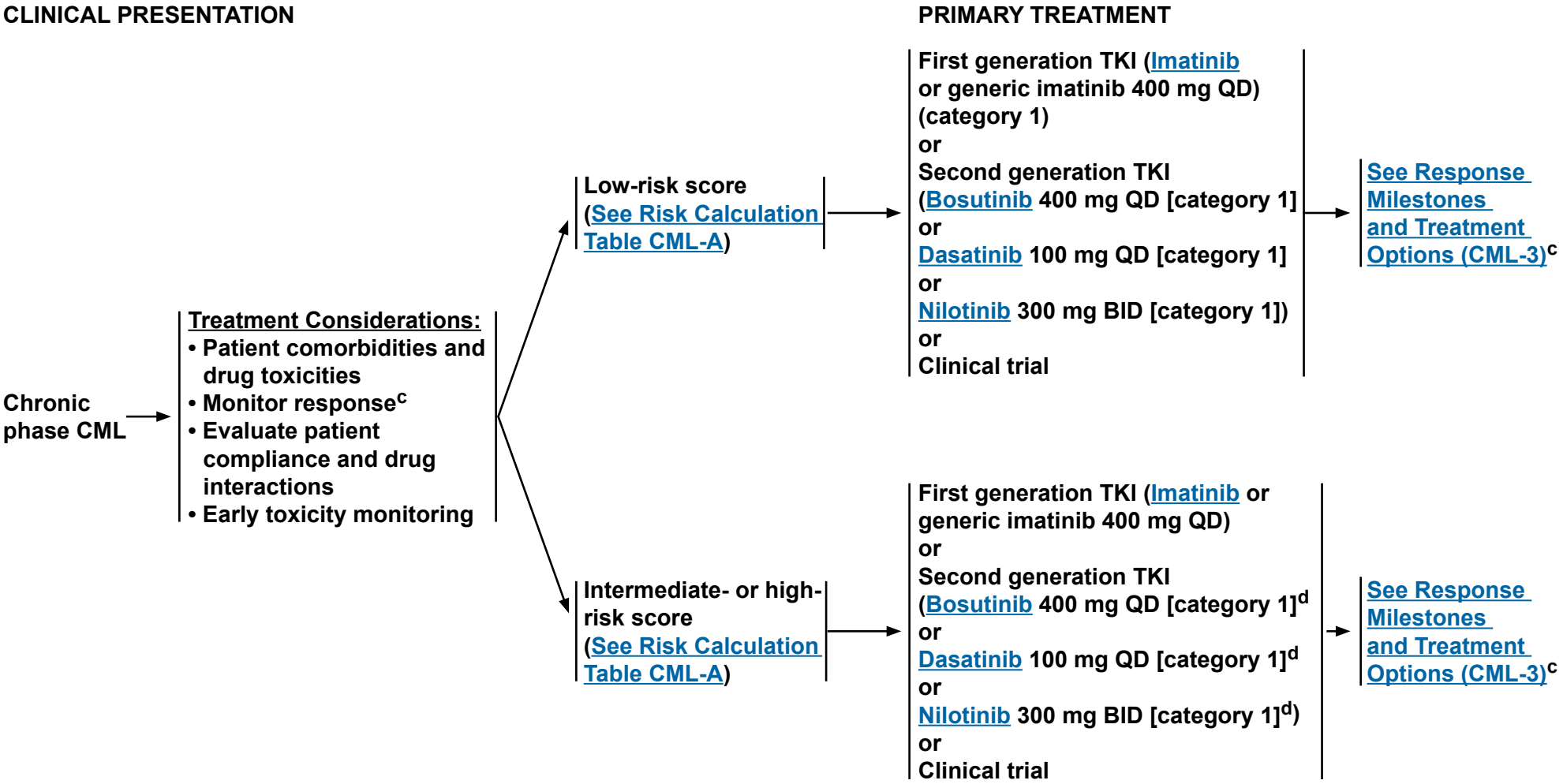
- **Last bullet, sub-bullet 3 added: "Failure to regain MMR after three months following treatment reinitiation."**

UPDATES



[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. FISH can be used if cytogenetic evaluation is not possible.
[b]See Definitions of Accelerated Phase and Blast Phase (CML-B).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



[c]See Monitoring Response to TKI Therapy and Mutational Analysis (CML-C).
[d]Long-term follow-up data from the DASISION and ENESTnd trials and preliminary data from the BFORE trial suggest that patients with an intermediate- or high-risk Sokal or Hasford score may preferentially benefit from second generation TKI (dasatinib, nilotinib, or bosutinib). See Discussion for additional information.

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RESPONSE MILESTONES[c,e]

BCR-ABL1 (IS)	3 months	6 months	12 months	>12 months
>10%[f]	YELLOW	RED		
>1%–10%	GREEN		YELLOW	RED
>0.1%–1%	GREEN			YELLOW
≤0.1%	GREEN			

	CLINICAL CONSIDERATIONS	SECOND-LINE AND SUBSEQUENT TREATMENT OPTIONS
RED	• Evaluate patient compliance and drug interactions • Mutational analysis	Switch to alternate TKI (CML-5) and Evaluate for HCT (CML-6)
YELLOW	• Evaluate patient compliance and drug interactions • Mutational analysis	Switch to alternate TKI (CML-5) or Continue same TKI (CML-F)[g] or Dose escalation of imatinib (to a max of 800 mg) and Evaluate for HCT (CML-6)
GREEN	• Monitor response (CML-F) and side effects	Continue same TKI (CML-F)[h]

[c] See Monitoring Response to TKI Therapy and Mutational Analysis (CML-C).
[e] See Criteria for Hematologic, Cytogenetic, and Molecular Response and Relapse (CML-D).
[f] 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.
[g] 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.
[h] Discontinuation of TKI with careful monitoring is feasible in selected patients. See Discontinuation of TKI Therapy (CML-E).

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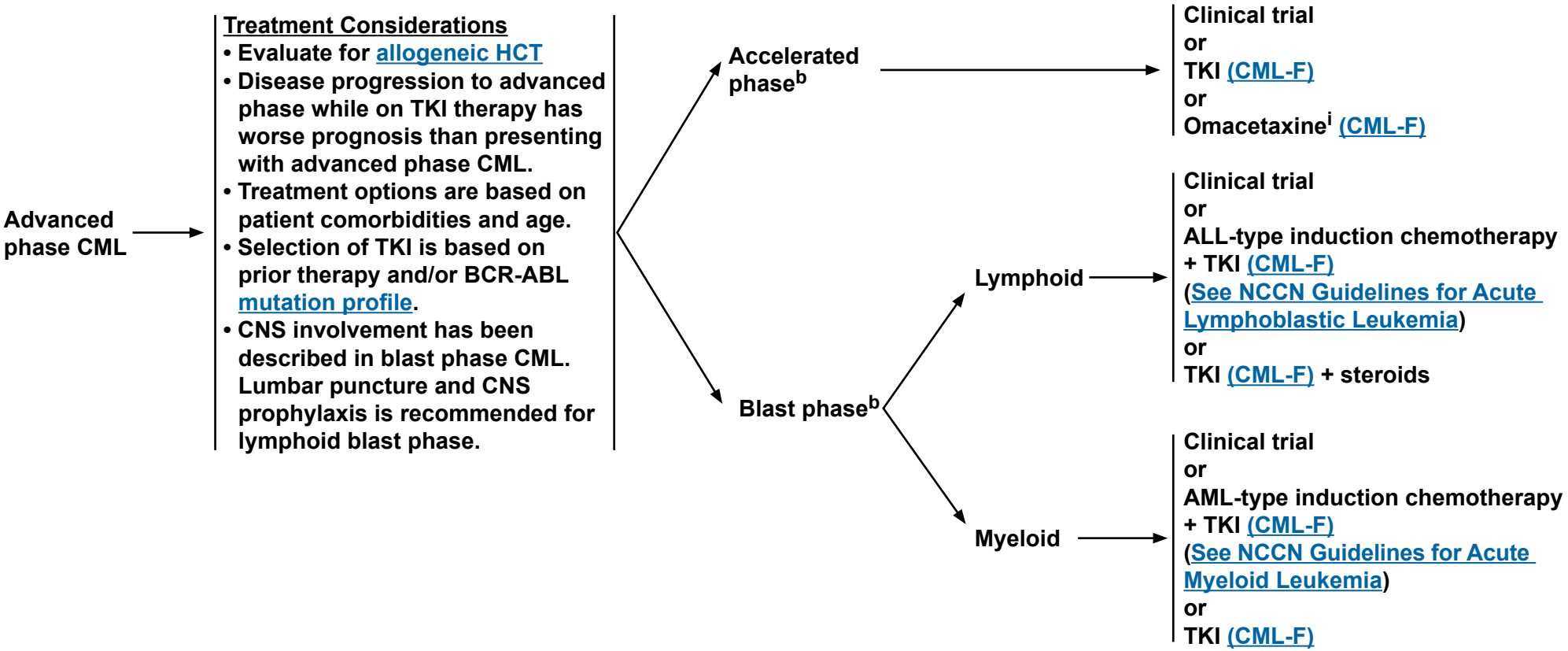
CLINICAL PRESENTATION | **TREATMENT**



[b] See Definitions of Accelerated Phase and Blast Phase (CML-B).
[i] Omacetaxine is a treatment option for patients with disease progression to accelerated phase CML. Omacetaxine is not a treatment option for patients who present with accelerated phase CML.

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TREATMENT OPTIONS BASED ON BCR-ABL1 MUTATION PROFILE

Mutation	Treatment Recommendation[j]
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,[k] Omacetaxine,[l] allogeneic HCT (CML-6), or clinical trial

[j]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.
[k]Ponatinib is a treatment option for patients with a T315I mutation or for patients for whom no other TKI is indicated
[l]Omacetaxine is a treatment option for patients with disease that is resistant and/or intolerant to 2 or more TKIs.

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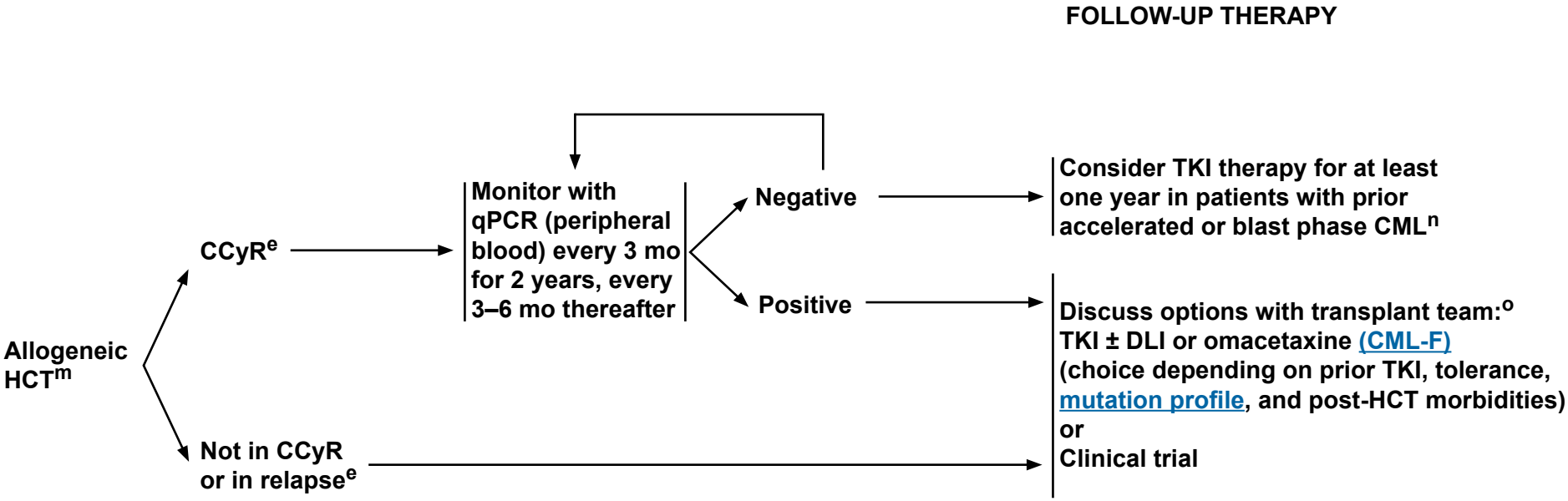

[e] See Criteria for Hematologic, Cytogenetic, and Molecular Response and Relapse (CML-D).
[m] Indications for allogeneic HCT: Advanced phase CML at presentation or disease progression to blast phase. Outcomes of allogeneic HCT are dependent on age and comorbidities, donor type, and transplant center.
[n] See Discussion.
[o] In patients who have disease that has failed prior TKI therapy, see CML-5 for the selection of post-HCT TKI.

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RISK CALCULATION TABLE

Study	Calculation	Risk Definition by Calculation	
Sokal et al, 1984[1]	**Exp 0.0116 x (age in years - 43.4) + (spleen - 7.51) + 0.188 x [(platelet count ÷ 700)^2 - 0.563] + 0.0887 x (blast cells - 2.10)**	**Low** **Intermediate** **High**	**<0.8** **0.8 - 1.2** **>1.2**
Hasford et al, 1998[2]	**0.666 when age ≥ 50 years + (0.042 x spleen) + 1.0956 when platelet count > 1500 x 10^9/L + (0.0584 x blast cells) + 0.20399 when basophils > 3% + (0.0413 x eosinophils) x 100**	**Low** **Intermediate** **High**	**≤780** **781 - 1480** **>1480**

Calculation of relative risk found at http://www.icsg.unibo.it/rrcalc.asp. Age is in years. Spleen is in centimeter below the costal margin (maximum distance). Blast cells, eosinophils, and basophils are in percents of peripheral blood differential. All factors must be collected prior to any treatment.

 Baccarani M, Cortes J, Pane F, Niederwieser D, et al. European LeukemiaNet. Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet. J Clin Oncol 2009;27(35):6041-6051.

[1]Sokal J, Cox E, Baccarani M, et al. Prognostic discrimination in "good-risk" chronic granulocytic leukemia. Blood 1984;63:789-799. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6584184.

[2]Hasford J, Pfirrmann M, Hehlmann R, et al. A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alfa. Writing Committee for the Collaborative CML Prognostic Factors Project Group. J Natl Cancer Inst 1998;90:850-858. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9625174.

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DEFINITION OF ACCELERATED PHASE[1,2]

Modified Criteria Used at MD Anderson Cancer Center[3,4] (most commonly used in clinical trials)
• Peripheral blood blasts ≥15% and <30% • Peripheral blood blasts and promyelocytes combined ≥30% • Peripheral blood basophils ≥20% • Platelet count ≤100 x 10^9/L unrelated to therapy • Additional clonal cytogenetic abnormalities in Ph+ cells

DEFINITIONS OF BLAST PHASE[1]

World Health Organization (WHO) Criteria[5]	International Bone Marrow Transplant Registry[6]
• Blasts ≥20% of peripheral white blood cells or of nucleated bone marrow cells • Extramedullary blast proliferation • Large foci or clusters of blasts in the bone marrow biopsy	• ≥30% blasts in the blood, marrow, or both • Extramedullary infiltrates of leukemic cells

[1]The table refers to myeloblasts. Any increase in lymphoblasts is concerning for (nascent) blast phase.
[2]Sokal criteria (Sokal JE, Baccarani M, Russo D, et al. Staging and prognosis in chronic myelogenous leukemia. Semin Hematol 1988;25:49-61) and IBMTR criteria (Savage DG, Szydlo RM, Chase A, et al. Bone marrow transplantation for chronic myeloid leukemia: The effects of differing criteria for defining chronic phase on probabilities of survival and relapse. Br J Haematol 1997;99:30-35) are historically used when HCT is the recommended treatment option.
[3]Kantarjian HM, Deisseroth A, Kurzrock R, et al. Chronic myelogenous leukemia: A concise update. Blood 1993;82:691-703.
[4]Talpaz M, Silver RT, Druker BJ, et al. Imatinib induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: results of a phase 2 study. Blood 2002;99:1928-1937.
[5]From Jaffe ES, Harris NL, Stein H, et al. WHO Classification of Tumours, Pathology, and Genetics of Tumours of Haematopoietic and Lymphoid Tissues, IARC, Lyon, 2001.
[6]Druker BJ. Chronic Myelogenous Leukemia In: DeVita VT, Lawrence TS, Rosenburg SA, eds. DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology. Vol. 2 (ed 8): Lippincott, Williams and Wilkins; 2007:2267-2304.

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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)
Quantitative RT-PCR (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.

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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]
- **Partial cytogenetic response (PCyR) - 1%–35% Ph-positive metaphases**
- **Major cytogenetic response - 0%–35% Ph-positive metaphases**
- **Minor cytogenetic response - >35% 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 et al: Chronic myelogenous leukemia: Biology and therapy. Ann Intern Med 1999;131:207-219. The American College of Physicians-American Society of Internal Medicine is not responsible for the accuracy of the translation.
[2]A minimum of 20 metaphases should be examined.
[3]O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 2003;348:994-1004.
[4]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.

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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.**
- **Outside of a clinical trial, TKI discontinuation should be considered only if ALL of the criteria included in the list below are met.**

Criteria for TKI Discontinuation

- **Age ≥18 years.**
- **Chronic phase CML. No prior history of accelerated or blast phase CML.**
- **On approved TKI therapy (imatinib, dasatinib, nilotinib, bosutinib, or ponatinib) for at least three years.**
- **Prior evidence of quantifiable *BCR-ABL1* transcript.**
- **Stable molecular response (MR4; *BCR-ABL1* ≤0.01% IS) for ≥2 years, as documented on at least four tests, performed at least three months apart.**
- **Access to a reliable qPCR test with a sensitivity of detection at least MR4.5 (BCR-ABL1 ≤ 0.0032% IS) and 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 three months of TKI resumption, BCR-ABL1 kinase domain mutation testing should be performed, and monthly molecular monitoring should be continued for another six 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 a member of the NCCN CML panel 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 three months following treatment reinitiation.**

[1]See full prescribing information for nilotinib: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022068s026lbl.pdf

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MANAGEMENT OF TOXICITIES

BOSUTINIB (CML-F 1 of 6)

DASATINIB (CML-F 2 of 6)

IMATINIB (CML-F 3 of 6)

NILOTINIB (CML-F 4 of 6)

OMACETAXINE (CML-F 5 of 6)

PONATINIB (CML-F 6 of 6)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

MANAGEMENT OF BOSUTINIB TOXICITY[1]

Dose Adjustments:

Hematologic Toxicities

- **ANC <1.0 x 10^9/L or platelets <50 x 10^9/L: Hold bosutinib until ANC ≥1.0 x 10^9/L and platelets ≥50 x 10^9/L. Resume treatment with bosutinib at the same dose if recovery occurs within 2 weeks. If blood counts remain low for greater than 2 weeks, upon recovery reduce dose by 100 mg and resume treatment. If cytopenia recurs, reduce dose by an additional 100 mg upon recovery and resume treatment. Doses less than 300 mg/d have not been evaluated.**
- **Growth factors can be used in combination with bosutinib for patients with resistant neutropenia and thrombocytopenia.**
- **Grade 3-4 anemia:[2] Check reticulocyte count, ferritin, iron saturation, B12, folate, and correct nutritional deficiencies if present. Transfusion support should be used if patient is symptomatic.**

Non-Hematologic Toxicities

- **Liver transaminases >5 x IULN: Hold bosutinib until recovery to ≤2.5 x IULN and resume dose at 400 mg once daily thereafter. If recovery takes longer than 4 weeks, discontinue bosutinib. If transaminase elevations ≥3 x IULN occur concurrently with bilirubin elevations >2 x IULN and alkaline phosphatase <2 x IULN (Hy's law case definition), discontinue bosutinib.**
- **Diarrhea: For NCI CTCAE Grade 3-4 diarrhea (increase of ≥7 stools/day over baseline/pretreatment), withhold bosutinib until recovery to Grade ≤1. Bosutinib may be resumed at 400 mg once daily.**
- **For other clinically significant, moderate, or severe non-hematologic toxicity, withhold bosutinib until the toxicity has resolved, then consider resuming bosutinib at 400 mg once daily. If clinically appropriate, consider re-escalating the dose of bosutinib to 500 mg once daily.**

Special Populations

- **In patients with pre-existing mild, moderate, and severe hepatic impairment, the recommended dose of bosutinib is 200 mg daily. A daily dose of 200 mg in patients with hepatic impairment is predicted to result in an area under the curve (AUC) similar to the AUC seen in patients with normal hepatic function receiving 500 mg daily. However, there are no clinical data for efficacy at the dose of 200 mg once daily in patients with hepatic impairment and CML.**

Specific Interventions

- **Fluid retention events (ie, pulmonary and/or peripheral edema; pleural and pericardial effusion): diuretics, supportive care.**
- **GI upset: take medication with a meal and large glass of water.**
- **Rash: topical or systemic steroids, dose reduction, interruption, or discontinuation.**

[1]Please refer to package insert for full prescribing information and monitoring of hematologic or biochemical abnormalities, available at www.fda.gov.
[2]Although erythropoietin is effective, recent guidelines from the Centers for Medicare & Medicaid Services (CMS) and the U.S. Food and Drug Administration (FDA) do not support the use of erythropoiesis-stimulating agents (ESAs) in myeloid malignancies.

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MANAGEMENT OF DASATINIB TOXICITY[1]

Dose Adjustments:

Hematologic Toxicities

- **Chronic phase, ANC <0.5 x 10^9/L or platelets <50 x 10^9/L: Hold dasatinib until ANC ≥1.0 x 10^9/L and platelets ≥50 x 10^9/L, then resume dasatinib at the starting dose if recovery occurs in ≤7 days. If platelets <25 x 10^9/L or recurrence of ANC <0.5 x 10^9/L for >7 days, hold drug until ANC ≥1.0 x 10^9/L and platelets ≥50 x 10^9/L, then resume dasatinib at reduced dose of 80 mg once daily for second episode. For third episode, further reduce dose to 50 mg once daily (for newly diagnosed patients) or discontinue dasatinib (for patients with disease that is resistant or intolerant to prior therapy including imatinib).**
- **Accelerated phase and blast phase, ANC <0.5 x 10^9/L and/or platelets <10 x 10^9/L: Patients may have cytopenias related to disease. If cytopenia is unrelated to disease, hold dasatinib until ANC ≥1.0 x 10^9/L and platelets ≥20 x 10^9/L, and resume at original starting dose. If recurrence, hold dasatinib until ANC ≥1.0 x 10^9/L and platelets ≥20 x 10^9/L, and resume dasatinib at reduced dose of 100 mg once daily (second episode) or 80 mg once daily (third episode).**
- **Growth factors can be used in combination with dasatinib for patients with resistant neutropenia and thrombocytopenia.**
- **Grade 3-4 anemia:[2] Check reticulocyte count, ferritin, iron saturation, B12, folate, and correct nutritional deficiencies if present. Transfusion support should be used if patient is symptomatic.**

Non-Hematologic Toxicities

- **If a severe, non-hematologic, adverse reaction develops with dasatinib, treatment must be held until the event has resolved or improved. Thereafter, treatment can be resumed as appropriate at a reduced dose depending on the initial severity of the event.**

Rare But Serious Toxicities

- **Pulmonary arterial hypertension (PAH): Dasatinib may increase the risk of developing PAH, which may occur anytime after initiation, including after more than one year of treatment. PAH may be reversible on discontinuation of dasatinib. Evaluate patients for signs and symptoms of underlying cardiopulmonary disease prior to initiating dasatinib and during treatment. If PAH is confirmed, dasatinib should be permanently discontinued.**

Specific Interventions

- **Fluid retention events (ie, ascites, edema, pleural and pericardial effusion): diuretics, supportive care.**
- **Pleural/pericardial effusion: diuretics, dose interruption. If patient has significant symptoms, consider short course of steroids (prednisone 20–50 mg/d x 3–4 days, may taper with 20 mg/d x 3–4 days); when resolved, reduce one dose level.**
- **GI upset: Take medication with a meal and large glass of water.**
- **Rash: topical or systemic steroids, dose reduction, interruption, or discontinuation.**

[1]Please refer to package insert for full prescribing information and monitoring of hematologic or biochemical abnormalities, available at www.fda.gov.
[2]Although erythropoietin is effective, recent guidelines from the Centers for Medicare & Medicaid Services (CMS) and the U.S. Food and Drug Administration (FDA) do not support the use of erythropoiesis-stimulating agents (ESAs) in myeloid malignancies.

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MANAGEMENT OF IMATINIB TOXICITY[1,3]

Dose Adjustments:

Hematologic Toxicities

- **Chronic phase, absolute neutrophil count (ANC) <1.0 x 10^9/L, and/or platelets <50 x 10^9/L: Hold imatinib until ANC ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L, then resume imatinib at the starting dose of 400 mg. If recurrence of ANC <1.0 x 10^9/L and/or platelets <50 x 10^9/L, hold drug until ANC ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L, then resume imatinib at reduced dose of 300 mg.**
- **Accelerated phase and blast phase, ANC <0.5 x 10^9/L and/or platelets <10 x 10^9/L: Patients may have cytopenias related to disease. If cytopenia is unrelated to disease, reduce dose to 400 mg. If cytopenia persists for 2 weeks, reduce dose further to 300 mg. If cytopenia persists for 4 weeks, stop imatinib until ANC ≥1.0 x 10^9/L and platelet count ≥20 x 10^9/L and then resume treatment at 300 mg.**
- **Growth factors can be used in combination with imatinib for patients with resistant neutropenia.[4]**
- **Grade 3-4 anemia:[2] Check reticulocyte count, ferritin, iron saturation, B12, folate, and correct nutritional deficiencies if present. Transfusion support should be used if patient is symptomatic.**

Non-Hematologic Toxicities

- **Bilirubin >3 x institutional upper limit of normal (IULN) or liver transaminases >5 x IULN: hold imatinib until bilirubin <1.5 x IULN and transaminase levels <2.5 x IULN. Resume imatinib at a reduced daily dose (400 mg to 300 mg, 600 mg to 400 mg, or 800 mg to 600 mg).**
- **Severe hepatotoxicity or severe fluid retention: hold imatinib until the event has resolved. Treatment can be resumed as appropriate depending on the severity of the event.**
- **Patients with moderate renal impairment (CrCl = 20–39 mL/min) should receive a 50% decrease in the recommended starting dose and future doses can be increased as tolerated. Doses greater than 600 mg are not recommended in patients with mild renal impairment (CrCl = 40–59 mL/min). For patients with moderate renal impairment, doses greater than 400 mg are not recommended. Imatinib should be used with caution in patients with severe renal impairment.**

Specific Interventions

- **Fluid retention (ie, pleural effusion, pericardial effusion, edema, ascites): diuretics, supportive care, dose reduction, interruption, or discontinuation. Consider echocardiogram to check LVEF.**
- **GI upset: Take medication with a meal and large glass of water.**
- **Muscle cramps: calcium supplement, tonic water.**
- **Rash: topical or systemic steroids, dose reduction, interruption, or discontinuation.**

[1]Please refer to package insert for full prescribing information and monitoring of hematologic or biochemical abnormalities, available at www.fda.gov.
[3]Many toxicities are self-limiting; consider re-escalating dose at a later time.
[2]Although erythropoietin is effective, guidelines from the Centers for Medicare & Medicaid Services (CMS) and the U.S. Food and Drug Administration (FDA) do not support the use of erythropoiesis-stimulating agents (ESAs) in myeloid malignancies.
[4]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(12):2592-2597.

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

MANAGEMENT OF NILOTINIB TOXICITY[1]

- **Nilotinib prolongs the QT interval. Prior to administration of nilotinib and periodically, monitor for hypokalemia or hypomagnesemia and correct deficiencies. ECGs should be obtained to monitor the QTc at baseline, seven days after initiation, and periodically thereafter, as well as following any dose adjustments.**
- **Sudden deaths have been reported in patients receiving nilotinib.**
- **Avoid use of concomitant drugs known to prolong the QT interval and strong CYP3A4 inhibitors.**
- **Patients should avoid food 2 hours before and 1 hour after taking dose.**

QT Interval Prolongation

- **ECGs with a QTc >480 msec: Hold drug. If serum potassium and magnesium levels are below lower limit of normal, correct with supplements to within normal limits. Review concomitant medication usage. Resume within 2 weeks at prior dose if QTcF is <450 msec and within 20 msec of baseline. If QTcF is between 450 and 480 msec after 2 weeks, resume at reduced dose (400 mg once daily). Following dose reduction, if QTcF returns to >480 msec, nilotinib should be discontinued. ECG should be obtained 7 days after any dose adjustment to monitor QTc.**

Dose Adjustments:

Hematologic Toxicities

- **Chronic or accelerated phase, ANC <1.0 x 10^9/L, and/or platelets <50 x 10^9/L: Hold nilotinib and monitor blood counts. Resume within 2 weeks at prior dose if ANC >1.0 x 10^9/L and platelets >50 x 10^9/L. If blood counts remain low for >2 weeks, reduce dose to 400 mg once daily.**
- **Growth factors can be used in combination with nilotinib for patients with resistant neutropenia and thrombocytopenia.**
- **Grade 3–4 anemia:[2] Check reticulocyte count, ferritin, iron saturation, B12, folate, and correct nutritional deficiencies if present. Transfusion support should be used if patient is symptomatic.**

Non-Hematologic Toxicities

- **Elevated serum lipase, amylase, bilirubin, or hepatic transaminases grade ≥3: hold nilotinib and monitor serum levels. Resume nilotinib at 400 mg once daily if serum levels return to grade ≤1.**

Hepatic Impairment:

- **Consider alternate therapies. See prescribing information for dose adjustments related to hepatic impairment.**

Glucose:

- **Assess glucose levels before initiating treatment and monitor treatment as clinically indicated.**

Rare But Serious Toxicities

- **Peripheral arterial occlusive disease (PAOD): Nilotinib is associated with an increased risk of vascular adverse events, including PAOD, and should be used with caution in patients with cardiovascular risk factors or a history of PAOD. Evaluate patients for a history of PAOD and for vascular risk factors prior to initiating nilotinib and during treatment. If PAOD is confirmed, nilotinib should be permanently discontinued.**

Specific Interventions

- **Rash: topical or systemic steroids, dose reduction, interruption, or discontinuation.**

[1]Please refer to package insert for full prescribing information and monitoring of hematologic or biochemical abnormalities, available at www.fda.gov.
[2]Although erythropoietin is effective, recent guidelines from the Centers for Medicare & Medicaid Services (CMS) and the U.S. Food and Drug Administration (FDA) do not support the use of erythropoiesis-stimulating agents (ESAs) in myeloid malignancies.

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MANAGEMENT OF OMACETAXINE TOXICITY[1]

Dose Adjustments:

Hematologic Toxicities

- **Complete blood counts (CBCs) should be performed weekly during induction and initial maintenance cycles. After initial maintenance cycles, monitor CBCs every two weeks or as clinically indicated. ANC <0.5 x 10^9/L or platelet count <50 x 10^9/L: Delay starting the next cycle until ANC ≥1.0 x 10^9/L and platelet count ≥50 x 10^9/L and reduce the number of dosing days by 2 days for the next cycle.**

Non-Hematologic Toxicities

- **Grade 3 or 4 hyperglycemia: Monitor blood glucose levels frequently, especially in patients with diabetes or risk factors for diabetes. Avoid omacetaxine in patients with poorly controlled diabetes mellitus until good glycemic control has been established.**
- **Manage other clinically significant non-hematologic toxicity symptomatically. Interrupt and/or delay omacetaxine until toxicity is resolved.**

[1]Please refer to package insert for full prescribing information and monitoring of hematologic or biochemical abnormalities, available at www.fda.gov.

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MANAGEMENT OF PONATINIB TOXICITY[1]

- **Vascular occlusion: Arterial and venous thrombosis and occlusions, including fatal myocardial infarction and stroke, have occurred in patients treated with ponatinib. Monitor for evidence of thromboembolism and vascular occlusion. Interrupt or stop ponatinib immediately for vascular occlusion.**
- **Heart failure has occurred in patients treated with ponatinib. Monitor cardiac function. Interrupt or stop ponatinib for new or worsening heart failure.**
- **Hepatotoxicity: Hepatotoxicity, liver failure, and death have occurred in patients treated with ponatinib. Monitor hepatic function prior to and during treatment. Interrupt ponatinib if hepatotoxicity is suspected.**
- **Cardiovascular risk: Identify and control traditional risk factors for atherosclerosis (eg, diabetes mellitus [DM], hypertension, hyperlipidemia, smoking, estrogen use) before starting ponatinib. Patients with cardiovascular risk factors should be referred to a cardiologist. Consider the use of low-dose aspirin if there is no contraindication.**
- **Ponatinib is also associated with grade ≥3 skin rash and pancreatitis leading to dose modifications (dose delays or dose reductions).**

Dosing

- **The recommended initial dose of ponatinib is 45 mg once daily. However, an initial starting dose of 30 mg may be a safer and effective dose for patients with risk factors. Safety and efficacy of ponatinib at initial doses lower than 45 mg is being evaluated in a randomized clinical trial.**

Dose Adjustments:

Hematologic Toxicities

- **ANC <1.0 x 10^9/L or platelets <50 x 10^9/L**
  - **First occurrence: Hold ponatinib until ANC ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L and resume at initial dose of 45 mg.**
  - **Second occurrence: Hold ponatinib until ANC ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L and resume at 30 mg.**
  - **Third occurrence: Hold ponatinib until ANC ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L and resume at 15 mg.**
- **Growth factors can be used in combination with ponatinib for patients with resistant neutropenia and thrombocytopenia.**
- **Grade 3-4 anemia:[2] Check reticulocyte count, ferritin, iron saturation, B12, folate, and correct nutritional deficiencies if present. Transfusion support should be used if patient is symptomatic.**

Non-Hematologic Toxicities

- **Liver transaminase >3 x ULN (grade ≥2): Monitor hepatic function. Hold drug until serum levels are <3 x IULN. Resume at lower dose after recovery (30 mg if patient receiving 45 mg; 15 mg if patient receiving 30 mg). Discontinue ponatinib if patient receiving 15 mg.**
- **AST or ALT ≥3 x ULN concurrent with bilirubin >2 x ULN and alkaline phosphatase <2 x ULN: Discontinue ponatinib.**
- **Serum lipase elevation, grade 1 or 2 (asymptomatic): Consider dose interruption or reduction. Serum lipase elevation, grade 3 or 4 (>2 x IULN) (asymptomatic) or asymptomatic radiologic pancreatitis: Hold drug until serum levels are <1.5 x ULN. Resume at lower dose after recovery (30 mg if patient receiving 45 mg; 15 mg if patient receiving 30 mg). Discontinue ponatinib if patient receiving 15 mg.**
- **Pancreatitis (symptomatic), grade 3: Hold drug until serum lipase levels are ≤grade 1. Resume at lower dose after recovery (30 mg if patient receiving 45 mg; 15 mg if patient receiving 30 mg). Discontinue ponatinib if patient receiving 15 mg. Grade 4: Discontinue ponatinib.**

Rare But Serious Toxicities

- **Hemorrhage: Hemorrhagic events were reported in clinical trials. Cerebral and gastrointestinal hemorrhage were the most commonly reported serious bleeding events. Serious hemorrhage should be managed with dose interruption.**
- **Cardiac arrhythmias: Advise patients to report signs and symptoms suggestive of alterations in heart rate (fainting, dizziness, chest pain, or palpitations).**
- **Tumor lysis syndrome: Ensure adequate hydration and correct high uric acid levels prior to initiating therapy with ponatinib in patients with advanced-phase CML.**

Specific Interventions

- **Fluid retention events (ie, edema, ascites, pleural and pericardial effusion) are managed with dose interruption, dose reduction, or discontinuation of ponatinib as clinically indicated.**
- **Hypertension: Monitor and manage blood pressure elevations.**
- **Rash: topical or systemic steroids, dose reduction, interruption, or discontinuation.**

[1]Please refer to package insert for full prescribing information and monitoring of hematologic or biochemical abnormalities, available at www.fda.gov.

[2]Although erythropoietin is effective, recent guidelines from the Centers for Medicare & Medicaid Services (CMS) and the U.S. Food and Drug Administration (FDA) do not support the use of erythropoiesis-stimulating agents (ESAs) in myeloid malignancies.

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Discussion

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 indicated.

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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 2017, an estimated 8,950 people will be diagnosed with CML in the United States, and 1080 people will die from the disease.[1]

CML is defined by the presence of Philadelphia chromosome (Ph) in a patient with a myeloproliferative neoplasm (MPN). Ph results from a reciprocal translocation between chromosomes 9 and 22 [t(9;22] that gives rise to a *BCR-ABL1* fusion gene; 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 (ALL). p190 is detected only in 1% of patients with CML.[3]

CML occurs in three different phases (chronic, accelerated, and blast phase) 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 the 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 three phases (chronic, accelerated, or blast phase). Evaluation for diseases other than CML as outlined in the NCCN Guidelines for MPN is recommended for all patients with *BCR-ABL1*-negative MPN.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for Chronic Myelogenous Leukemia, an electronic search of the PubMed database was performed to obtain key literature in Chronic Myelogenous Leukemia published between April 2016 and March 2017 using the following search terms: chronic myeloid (or myelogenous) leukemia, chronic phase, accelerated phase, blast phase, advanced phase, tyrosine kinase inhibitors (TKIs), BCR-ABL1 mutations, response, monitoring, adherence, and discontinuation. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[7]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 118 citations and their potential relevance was examined. The data from key PubMed articles selected by the panel for review during the Guidelines update meeting as well as articles from additional sources deemed as relevant to these Guidelines have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN website.

Diagnosis and Workup (CML-1)

Initial evaluation should consist of a history and physical exam, including palpation of spleen, complete blood count (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 (QPCR) to establish the presence of quantifiable *BCR-ABL1* mRNA transcripts at baseline are recommended to confirm the diagnosis of CML.

Bone marrow cytogenetics should be done at initial workup to detect additional chromosomal abnormalities in Ph-positive cells (ACA/Ph$^+$), also known as clonal cytogenetic evolution.[8] If bone marrow evaluation is not feasible, fluorescence in situ hybridization (FISH) on a peripheral blood specimen with dual probes for *BCR* and *ABL1* genes is an acceptable method to confirm the diagnosis of CML. Interphase FISH is performed on peripheral blood but is associated with a background level of 1%–5% depending on the specific probe used in the assay.[9] Hypermetaphase FISH is more sensitive and can analyze up to 500 metaphases at a time, but it is applicable only to dividing cells in the bone marrow.[10] Double-fusion FISH is also associated with low false-positive rates and can detect all variant translocations of the Ph-chromosome.[11]

Quantitative reverse transcriptase polymerase chain reaction (qPCR), should be done at initial workup to establish the presence of quantifiable *BCR-ABL1* mRNA transcripts at baseline. qPCR, usually done on peripheral blood is the most sensitive assay available for the measurement of *BCR-ABL1* mRNA and it can detect one CML cell in a background of ≥100,000 normal cells. qPCR results can be expressed in various ways, for instance as the ratio of *BCR-ABL1* transcript numbers to the number of control gene transcripts.[12] An International Scale (IS) has been proposed to standardize molecular monitoring with qPCR across different laboratories with the use of one of three control genes (*BCR*, *ABL1*, or *GUSB*) and a qPCR assay with a sensitivity of at least 4-log reduction from the standardized baseline.[13] In recent years, IS has become the gold standard of expressing qPCR values. More details on qPCR monitoring using IS are provided on MS-10.

BCR-ABL1 transcripts in the peripheral blood at very low levels (1–10 out 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.[14,15] TKI therapy is not indicated, as the risk of developing CML for these individuals is extremely low.

Clonal Cytogenetic Evolution

The prognostic significance of ACA/Ph$^+$ is related to the specific chromosomal abnormality and the presence of other features of accelerated phase.[16-23] The presence of major route ACA/Ph$^+$ (trisomy 8, isochromosome 17q, second Ph, and trisomy 19) at diagnosis is generally associated with negative prognostic impact on survival and disease progression to accelerated or blast phase.[18-20] In the German CML IV study, patients with major route ACA/Ph+ at the time of diagnosis had longer times to cytogenetic and molecular responses and shorter progression-free survival (PFS) and overall survival (OS) than patients with t(9;22), t(v;22), loss of Y chromosome, or other minor ACA/Ph+.[19,20] The 5-year survival rates were 91%, 87%, 89%, 92%, and 52%, respectively, for patients with t(9;22), t(v; 22), loss of Y chromosome, minor route ACA/Ph+, and major route ACA/Ph+.[20] Other studies have reported that some of the minor route ACA/Ph+ such as 11q23 and 3q26 rearrangements are also associated with

poor prognosis.[21,22] In a more recent study that evaluated the prognostic impact of individual chromosomal abnormalities, the presence of trisomy 8, second Ph, or loss of Y chromosome, or had no adverse impact on treatment response and survival, whereas the presence of isochromosome 17q, del7q, or 3q26.2 rearrangements was associated with lower response rates and inferior survival.[23] The concurrent presence of 2 or more ACA/Ph+ was associated with a poor prognosis.

Clonal cytogenetic evolution in Ph-negative cells has also been reported in a small subset of patients during the course of imatinib therapy.[24-29] The most common abnormalities include trisomy 8 and loss of Y chromosome. The overall prognosis of Ph-negative CML with clonal evolution seems to be good and is dependent on response to imatinib therapy.[28] Progression to myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) have been reported in patients with monosomy 7.[30,31]

Additional Evaluation (CML-1)

Chronic Phase CML

Determination of risk score (using either the Sokal or Hasford scoring systems) prior to initiation of TKI therapy is recommended for patients diagnosed with CP-CML. Sokal and Hasford (Euro) scoring systems stratify patients into three risk groups (low, intermediate, and high) and have been used for the risk stratifications of patients in clinical trials evaluating TKIs.[32,33] The Sokal score is based on the patient's age, spleen size, platelet count, and percentage of blasts in the peripheral blood.[32] The Euro score includes eosinophils and basophils in the peripheral blood in addition to the same clinical variables used in the Sokal score.[33]

European Treatment and Outcome Study (EUTOS) score is based only on the percentage of basophils in the blood and spleen size. The predictive value of EUTOS score was validated in a cohort of 2060 patients enrolled in studies of first-line treatment with imatinib-based regimens.[34] EUTOS score was better than Sokal and Hasford score in predicting the probability of achieving CCyR at 18 months and 5-year 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.[35-37]

Advanced Phase CML

Flow cytometry to determine cell lineage, mutational analysis, and human leukocyte antigen (HLA) testing, if considering allogeneic hematopoietic cell transplantation (HCT), are recommended for patients with advanced-phase CML.

The revised 2016 WHO diagnostic criteria for AP-CML include a "provisional" response to TKI criteria in addition to hematologic and cytogenetic criteria.[38] These diagnostic criteria require validation in prospective clinical trials. It should be noted that clinical trials of TKIs have largely reported efficacy data using the modified MD Anderson Cancer Center accelerated phase criteria (15% and <30% peripheral blood or bone marrow blasts, ≥30% or more of peripheral blood blasts and promyelocytes, ≥20% peripheral blood or bone marrow basophils, platelet count ≤100 x 10^9/L unrelated to therapy, and clonal cytogenetic evolution in Ph+ cells).[39] AP-CML defined only by clonal cytogenetic evolution is associated with a better prognosis than AP-CML defined by clonal cytogenetic evolution and additional features of progression.[18,40]

The WHO diagnostic criteria define blast phase as the presence of ≥20% blast cells in the peripheral blood or bone marrow, the presence of extramedullary blast proliferation, and large foci or clusters of blasts

in the bone marrow biopsy.[38] The International Bone Marrow Transplant Registry (IBMTR) criteria define blast phase as the presence of ≥30% blasts in the blood, bone marrow, or both, or as the presence of extramedullary disease.[41] This same definition was used in most of the clinical trials leading to the approval of TKIs, and is best aligned with prognostication systems derived from these studies.

Management of Chronic Phase CML

Primary Treatment (CML-2)

Imatinib

In the IRIS trial 1106 patients with newly diagnosed CP-CML were randomized to receive either imatinib 400 mg or interferon-alpha plus low-dose cytarabine. After a median follow-up of 60 months, the estimated 5-year OS rate and the best observed major cytogenetic response (MCyR) and complete cytogenetic response (CCyR) rates were 89%, 89%, and 82%, respectively.[42] The final analysis (after 11 years of follow-up) confirmed the long-term safety and efficacy of imatinib.[43] The cumulative rates of MCyR and CCyR at the end of the trial were 89.0% and 82.8%, respectively. Among patients who could be evaluated for cytogenetic (n = 134) or molecular response (n = 204) at 10 years, the rates of CCyR and major molecular response (MMR; 3-log reduction in the BCR-ABL1 from the standardized baseline level) were 92% and 93%, respectively. The estimated rates of freedom-from-progression (FFP) to accelerated or blast phase, the 10-year event-free survival (EFS), and OS were 92%, 80%, and 83%, respectively. Among the patients who had been randomly assigned to interferon alpha plus low-dose cytarabine, 363 patients crossed over to imatinib due to disease progression, lack of response, or intolerance. In an analysis that evaluated the safety and efficacy of imatinib in 359 patients who crossed over from interferon-alpha plus cytarabine to imatinib in the IRIS study, after a median follow-up of 54 months on imatinib, MCyR and CCyR were observed in 86% and 81% of patients, respectively. Estimated rates of FFP to accelerated or blast phase and OS at 48 months were 91% and 89%, respectively.[44]

Imatinib 800 mg daily has also been evaluated in newly diagnosed patients.[45-52] In the TOPS study, although imatinib 800 mg induced higher and faster CCyR and MMR compared to imatinib 400 mg early on, there is no difference in response rates between the two arms at 12 months and beyond.[50] After a minimum follow-up of 42 months, the MMR rates were 76% and 79.0% for 400 mg and 800 mg respectively (P = .4807). Other studies have reported higher MMR rates at 12 months for imatinib 800 mg.[51,52] In the CML IV study, after a median follow-up of 7 years, the cumulative incidence of deep molecular response (MR4.0 or better) was higher for imatinib 800 mg (66% vs. 56% for imatinib 400 mg).[51] The SWOG study (S0325) also reported higher rates of MR4.0 with imatinib 800 mg at 12 months (25% vs. 10%, respectively, P = .038).[52] However, imatinib 800 mg was not associated with lower rates of disease progression than imatinib 400 mg in any of the studies, despite improved early responses. Imatinib 800 mg was associated with higher rates of dose interruption, reduction, or discontinuation due to grade 3 or 4 adverse events in all of the studies. However, patients who can actually tolerate the higher dose of imatinib achieve better response rates than those receiving standard-dose imatinib.

Given the recent data showing superior efficacy of nilotinib and dasatinib in newly diagnosed CML, imatinib 800 mg is not recommended as initial therapy. Several prospective studies evaluating imatinib 800 mg daily coalesced at approximately 600 mg daily when considering the actually administered dose intensity.[50-52] The French SPIRIT trial reported superior MMR rates in patients treated with imatinib 600 mg daily compared to 400 mg daily.[49] These data suggest

that imatinib 600 mg daily may be closer to the optimal dose than 400 mg, and should be used as a comparator in prospective efficacy trials.

Dasatinib

In the DASISION study, 519 patients with newly diagnosed CP-CML were randomized to receive dasatinib (100 mg once daily; 259 patients) or imatinib (400 mg once daily; 260 patients). In the final 5-year analysis, the rates of CCyR (83% vs. 78%; *P* = .187), MMR (≤0.1% *BCR-ABL1* IS; 76% vs. 64%; *P* = .002), and MR4.5 (42% vs. 33%; *P* = .025) were significantly higher with dasatinib than with imatinib.[53] The proportion of patients achieving ≤10% *BCR-ABL1* IS at 3 months was also higher with dasatinib **(**84% vs. 64%) and fewer patients transformed to AP-CML or BP-CML on dasatinib (12 patients; 5%) than on imatinib (19 patients; 7%). The estimated 5-year PFS (85% vs. 86%) and OS (91% vs. 90%) rates were similar for dasatinib and imatinib.[53]

The 3-year follow-up results of the Intergroup phase II randomized trial (S0325; n = 250) also confirmed that dasatinib (100 mg once daily) induced more CCyR and deeper molecular responses, compared with imatinib (400 mg once daily) in patients with newly diagnosed CP-CML.[54] The molecular response rates (3-log reductions in *BCR-ABL1* transcript level) at 12 months were 59% and 44%, respectively, for dasatinib and imatinib (*P* = .059) and the estimated 3-year OS (97% for both dasatinib and imatinib) and PFS (93% for dasatinib and 90% for imatinib) rates were similar in both arms.

Nilotinib

The ENESTnd study compared the safety and efficacy of nilotinib at two different dose levels (300 mg twice daily; n = 282 or 400 mg twice daily; n = 281) with that of imatinib (400 mg once daily; n = 283) in patients with newly diagnosed CP-CML. At 5 years, significantly more patients in the nilotinib arms had achieved MMR (77% for nilotinib 300 mg and 400 mg twice daily vs. 60% for imatinib 400 mg once daily; *P* < .0001) and MR4.5 (54% for nilotinib 300 mg twice daily, 52% for nilotinib 400 mg twice daily vs. 31% for imatinib 400 mg once daily; *P* < .0001).[55] Fewer patients progressed to AP-CML or BP-CML in the nilotinib arm (10 patients treated with nilotinib 300 mg twice daily and 6 patients treated with nilotinib 400 mg twice daily) than in the imatinib arm (21 patients). The estimated 5-year OS rates were 93.7%, 96%, and 92%, respectively. The corresponding 5-year PFS rates were 92%, 96%, and 91%, respectively.

Bosutinib

In the phase III randomized trial (BELA trial; n = 500), although bosutinib (500 mg daily) resulted in higher MMR rate (47% vs. 41% for imatinib; *P* < .001) and fewer transformations to AP-CML or BP-CML at 24 months (2% vs. 4% on imatinib) than imatinib 400 mg in newly diagnosed patients with CP-CML, there was no difference in CCyR rate at 12 months between the 2 treatment arms (70% and 68%, respectively, for bosutinib and imatinib; *P* = .601).[56] In a subsequent phase III randomized study (BFORE trial), bosutinib at a lower starting dose of 400 mg daily resulted in higher response rates than imatinib in newly diagnosed patients with CP-CML.[57] In this trial, 536 patients were randomized to receive bosutinib (400 mg once daily; n = 268) or imatinib (400 mg once daily; n = 268). MMR (47% vs 37%; *P* = .02) and CCyR (77% vs 66%; *P* = .0075) at 12 months were significantly higher with bosutinib than with imatinib. The proportion of patients achieving ≤10% *BCR-ABL1* IS at 3 months was also higher with bosutinib **(**75% vs. 57%). Disease progression to AP-CML or BP-CML was reported in 4 patients (2%) receiving bosutinib and 6 patients (3%) receiving imatinib. After a minimum follow-up was 12 months, there was no difference in EFS or OS between the two treatment cohorts and

long-term follow-up is ongoing. Bosutinib is now approved for the treatment of patients with newly diagnosed CP-CML.

Treatment Considerations (CML-2)

The selection of first-line TKI therapy 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 HCT is no longer recommended as a first-line treatment option for patients with CP-CML.

Treatment Recommendations Based on Risk Stratification

Dasatinib, nilotinib and bosutinib are associated with higher rates of molecular response and lower risk of disease progression than imatinib in intermediate- and high-risk patients.[53,55,57] In the DASISION study, the MMR rates were higher for dasatinib than for imatinib in patients with intermediate (71% and 65%, respectively) and high (67% and 54%, respectively) Hasford (Euro) risk scores, and achievement of MMR after first-line dasatinib is associated with reduced risk of progression to AP-CML or BP-CML.[53,58] In the ENESTnd study, fewer patients with intermediate and high Sokal risk score progressed to AP-CML or BP-CML in the nilotinib arm (2 patients with intermediate-risk score and 7 patients with high-risk score) than in the imatinib arm (10 patients with intermediate-risk score and 11 patients with high-risk score).[55] The estimated 5-year PFS rates were 93% and 86% for patients with intermediate- and high-risk scores, respectively, in the nilotinib arm. The corresponding PFS rates for imatinib were 88% and 83%, respectively. In the BFORE trial, MMR rates at 12 months were higher for bosutinib than imatinib in all Sokal risk groups (high risk, 34% vs. 17%; intermediate risk, 45% vs 39%; and low risk, (58% vs 46%).[57] In the IRIS trial, the estimated 10-year OS rates were higher for patients with a low or intermediate Sokal score than for patients with a high Sokal score (90%, 80%, and 69%, respectively).[43]

Imatinib (400 mg daily) and second generation TKIs (dasatinib [100 mg once daily], nilotinib [300 mg twice daily] and bosutinib [400 mg daily]) are included as options for primary treatment (category 1 for patients with low-risk score). Long-term follow-up data from DASISION and ENESTnd trials and preliminary data from the BEFORE trial suggest that patients with an intermediate- or high-risk Sokal or Hasford score may preferentially benefit from second generation TKI therapy (bosutinib, dasatinib or nilotinib).[53,55,57]Therefore, imatinib is included with category 2A recommendation and second generation TKIs are included with a category 1 recommendation for patients with intermediate- or high-risk score.

Toxicity Profile

Since bosutinib, dasatinib and nilotinib have very good efficacy in the upfront setting, differences in their potential toxicity profiles may inform the selection of either one of these TKIs over imatinib in patients with a low-risk score. Dasatinib or bosutinib may be preferred in patients with a history of arrhythmias, heart disease, pancreatitis, or hyperglycemia. 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

Nonhematologic adverse events are mild to moderate and most of the adverse events are manageable with dose modification. The incidences of grade 3 or 4 cytopenias (neutropenia, 29% vs. 24%; anemia, 13% vs. 9%; and thrombocytopenia, 22% vs. 14%) were higher with dasatinib compared to imatinib.

Pleural effusion is an adverse effect of dasatinib. In the DASISION study, drug-related pleural effusion was more common with dasatinib (28%) than with imatinib (0.8%).[53] The incidences of pleural effusion are higher in patients with advanced phase CML (occurring in 50% of

patients with AP-CML and 33% of patients with BP-CML compared to 29% of patients with CP-CML).[59] The occurrence of pleural effusion is significantly reduced with dasatinib 100 mg once daily compared with 70 mg twice daily.[60] Lymphocytosis related to dasatinib treatment has been associated with increased incidences of pleural effusion and improved cytogenetic response rates.[61] 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. 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.[62]

Reversible pulmonary arterial hypertension has been reported as a rare but serious side effect of dasatinib.[63,64] In the DASISION study, pulmonary hypertension was reported in 5% of patients compared to 0.4% of patients treated with imatinib.[53] Evaluation for signs and symptoms of underlying cardiopulmonary disease prior to initiating and during treatment with dasatinib is recommended. If pulmonary arterial hypertension is confirmed, dasatinib must be permanently discontinued.

The recommended starting dose of dasatinib is 100 mg once daily for patients with CP-CML. Limited data available from small cohorts of patients suggest that lower doses of dasatinib (20 mg–120 mg) may potentially have similar efficacy.[65,66] 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.[67] However, the minimum effective dose has not been established in randomized clinical trials. Initiation 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).

Imatinib

Imatinib (400 mg daily) is generally well-tolerated. Most frequently reported non-hematologic adverse events include gastrointestinal disturbances, edema, rash, and musculoskeletal complaints. Skin hypopigmentation has also been reported as a side effect of imatinib and is reversible upon discontinuation or dose reduction.[68,69] Chronic fatigue (mostly correlated with musculoskeletal pain and muscular cramps) is a major factor reducing quality of life.[70] 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.[71,72]

Nilotinib

Fluid retention, pleural effusion, pericardial effusion, pulmonary edema, or muscle cramps were less common with nilotinib than with imatinib. Neutropenia and thrombocytopenia (grade 3-4) were reported only in 12% and 10% of patients treated with nilotinib 300 mg twice daily. Grade 3 or 4 elevations in lipase and bilirubin, hypophosphatemia, and hyperglycemia were observed in 9%, 4%, 8%, and 7% of patients, respectively. Patients with a previous history of pancreatitis may be at greater risk of elevated serum lipase. However, these abnormalities were typically transient and clinically asymptomatic.

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 prior to initiation of treatment with nilotinib and electrolytes should be monitored periodically. Drugs that prolong QT interval should be

avoided. Electrocardiogram (ECG) should be obtained to monitor the QT interval at baseline, 7 days after initiation of nilotinib and periodically thereafter, as well as following any dose adjustments.

Nilotinib is associated with an increased risk of peripheral arterial occlusive disease (PAOD).[73-75] Patients should be evaluated for pre-existing PAOD and vascular risk factors prior to initiating and during treatment with nilotinib. If PAOD is confirmed, nilotinib should be permanently discontinued. Patients with cardiovascular risk factors should be referred to a cardiologist.

Bosutinib

Diarrhea (70%), nausea (35%), thrombocytopenia (35%), increased alanine aminotransferase (ALT; 31%), and increased aspartate aminotransferase (AST; 23%) were the most common adverse events associated with bosutinib.[57] Grade ≥3 diarrhea (8% vs 1%), increased ALT (19% vs. 2%) and AST (10% vs 2%) levels were more common with bosutinib. Liver function abnormalities (increased ALT [5%] and increased AST increase [2%]) were the most common adverse events leading to discontinuation of bosutinib. However, there were no hepatotoxicity-related fatalities during the study.

Drug Interactions

Bosutinib, dasatinib, imatinib and nilotinib are metabolized in the liver by cytochrome P450 (CYP) enzymes. Drugs that induce or inhibit CYP3A4 or CYP3A5 enzymes may alter the therapeutic effect of TKIs.[76] CYP3A4 or CYP3A5 inducers may decrease the therapeutic plasma concentration of TKIs, whereas CYP3A4 inhibitors and drugs that are metabolized by the CYP3A4 or CYP3A5 enzyme might result in increased plasma levels of TKIs. In addition, imatinib is also a weak inhibitor of the CYP2D6 and CYP2C9 isoenzymes and nilotinib is a competitive inhibitor of CYP2C8, CYP2C9, CYP2D6, and UGT1A1, potentially increasing the plasma concentrations of drugs eliminated by these enzymes. Concomitant use of drugs that are metabolized by these enzymes should be used with 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 prior to 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.

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, B12, and folate and correction of nutritional deficiencies if present, is recommended for patients with grade 3-4 anemia. Red blood cell transfusions are indicated in symptomatic patients. Myeloid growth factor support can be used in combination with TKI therapy for the management of neutropenia.[77,78] 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.[79] Recent guidelines from the U.S. Centers for Medicare & Medicaid Services (CMS) and the FDA do not support the use of ESAs in patients with myeloid malignancies.

Adherence to Therapy

Treatment interruptions and non-adherence to therapy may lead to undesirable clinical outcomes.[80-82] 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%).[80] Marin and colleagues identified adherence as the only independent predictor for achieving complete molecular response (CMR) on standard-dose imatinib.[81] Patients whose imatinib doses were increased had poor adherence (86%), and in these patients adherence was the only independent predictor for inability to achieve an MMR. Poor adherence to imatinib therapy has also been identified as the most important factor contributing to cytogenetic relapse and imatinib failure.[82] Patients with adherence of 85% or less had a higher probability of losing CCyR at 2 years than those with adherence of more than 85% (27% and 2%, respectively).

Poor adherence to therapy has also been reported in patients receiving dasatinib and nilotinib following imatinib failure.[83,84] However, the impact of non-adherence to bosutinib, dasatinib or nilotinib on treatment efficacy has not yet been reported. In the absence of such data, findings from the studies involving patients treated with imatinib should be extrapolated to patients receiving second-generation TKI therapy.

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.[85] 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.[86]

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 goal of TKI therapy is to achieve a CCyR (≤1% *BCR-ABL1 IS*) within 12 months of initiation of therapy and to prevent disease progression to accelerated or blast phase.

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%.[87,88] Although some investigators have reported that interphase FISH can be used to monitor CCyR, endpoints for TKI failure have not been defined on the basis of FISH analysis.[89,90] 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 achieved CCyR, since *BCR-ABL1* transcripts typically remain detectable after CCyR is achieved. A major advantage of the qPCR is the strong correlation between the results obtained from the peripheral blood and the bone marrow, allowing molecular monitoring without the necessity of obtaining bone marrow aspirations.[91,92]

Standardization of Molecular Monitoring Using the International Scale

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).[13,93,94] A 2-log reduction generally correlates with CCyR (≤1% *BCR-ABL1* IS). The level of molecular response is best defined by the assay's level of sensitivity. Importantly, the sensitivity of a qPCR assay depends not only on the performance of the assay, but also on the quality of a given sample. As such the term 'complete molecular response' to denote undetectable *BCR-ABL1* transcripts (a negative qPCR test) should be abandoned, as it may refer to very different levels of response, dependent on the quality of the sample. Laboratories can use their individual assays, but the *BCR-ABL1* transcripts obtained in a given laboratory must be converted to the IS by applying a laboratory-specific conversion factor (CF).[13,95] Typically each laboratory has to exchange 20 to 30 pre-treatment samples with a reference laboratory to obtain a laboratory-specific CF. Both laboratories analyze the samples and the results are plotted on a log scale for comparison. The antilog of the estimated mean bias between the methods is designated as the CF.[95] Once a laboratory-specific CF is established, it is validated again through a second sample exchange with the reference laboratory.

Recommendations for Monitoring Response to TKI Therapy (CML-D)

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 (CHR) due to persistent cytopenias or unexplained drop in blood counts during therapy, bone marrow cytogenetics is indicated to confirm response to TKI therapy and exclude other pathology, such as MDS or the presence of chromosomal abnormalities other than Ph.

qPCR (IS) is still not available in many laboratories because the process is relatively cumbersome, time consuming, and is not seen as practical if the laboratory does not have a high volume of assays to perform, or if the prescribing physicians do not demand it. If qPCR (IS) is not available, it is acceptable to use the log-reduction from the laboratory-specific standardized baseline to monitor molecular response. This is an effective method, and was used in the IRIS trial to establish the 3-log reduction in the *BCR-ABL1* transcripts from the standardized baseline (not a reduction from the actual baseline level in an individual patient) as the MMR.[96] In addition, this technique was recently used in the U.S. Intergroup CML trial and the findings from the post hoc analyses of the RIGHT study also confirmed the feasibility of this technique.[54,92] Laboratories with no access to qPCR (IS) may establish their own standardized baseline, based on a large number of pre-treatment samples. Molecular response to TKI therapy is then measured as the log-reduction of *BCR-ABL1* transcripts from the standardized baseline (not a reduction from the actual baseline level in an individual patient).

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

Frequent molecular monitoring with qPCR (IS) can help to identify non-adherence to TKI therapy early in the treatment course.[97] Since adherence to TKI therapy is associated with better clinical outcomes, frequent molecular monitoring is essential if there are concerns about the patient's adherence to TKI therapy after CCyR has been achieved. In patients with deeper molecular responses (MMR and better) and who are compliant with TKI therapy, the frequency of molecular monitoring can be reduced, though the optimal frequency is unknown.

Response Milestones after First-Line TKI Therapy

Early molecular response (≤10% *BCR-ABL1* IS after 3 and 6 months) after first-line TKI therapy has emerged as an effective prognosticator of favorable long-term outcomes (Table 1).[53,55,98]

While some investigators suggest that early molecular response at 3 months has a superior prognostic value,[99,100] others have reported that of early molecular response at 6 months is a better discriminator of patients with poor outcome.[101] In an analysis that included 274 patients treated with imatinib 400 mg daily as first-line therapy, the 8-year probability of OS for patients with low *BCR-ABL1* transcripts at 3 months (<9.8%) and high *BCR-ABL1* transcripts at 6 months (>1.67%) was similar to that of patients who had low *BCR-ABL1* transcripts at both time points (92.4% and 93.5%, respectively; $P = .78$).[100] Similarly, among patients treated with dasatinib 100 mg once daily as first-line therapy, 6-month response assessment did not improve the predictive power of the 3-month response assessment.[100] These findings support the use of early intervention strategies based on the *BCR-ABL1* transcript level at 3 months. However, in another analysis of 456 patients with CP-CML treated with first-line TKI therapy (imatinib, dasatinib, or nilotinib), patients with >10% *BCR-ABL1* IS at 3 months who subsequently achieved <10% *BCR-ABL1* IS at 6 months had survival outcomes very similar to that of patients who initially achieved <10% *BCR-ABL1* IS at 3 months, suggesting that response assessment at 6 months may be a better prognosticator of long-term outcome.[101]

Achievement of CCyR within 12 months after first-line TKI therapy is an established prognostic indicator of long-term survival.[102,103] In the IRIS study, the estimated 6-year PFS rate was 97% for patients achieving a CCyR at 6 months compared to 80% for patients with no cytogenetic response at 6 months.[102] In an analysis of patients with newly diagnosed CP-CML treated with imatinib or second-generation TKIs, the 3-year EFS and OS rates were 98% and 99% for patients who achieved CCyR at 12 months compared to 67% and 94% in patients who did not achieve a CCyR.[103]

The prognostic significance MMR after first-line imatinib has also been evaluated in several studies.[42,91,104-107] The synoptic conclusion from these studies is that MMR is moderately superior to CCyR in predicting long-term PFS and OS. However, with longer 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.[108,109] These findings suggest that MMR may not be of prognostic significance in patients who have achieved CCyR. Furthermore, 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.

Resistance to TKI Therapy and BCR-ABL1 Kinase Domain Mutational Analysis

Primary Resistance

Aberrant expressions of drug transporters[110-112] and plasma protein binding of TKI[113-115] 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.[116] On the other hand, 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.[117-120]

Secondary Resistance

Point mutations in the BCR-ABL1 kinase domain are the most frequent mechanism of secondary resistance to TKI therapy and are associated with poor prognosis and higher risk of disease progression.[121-125] Among the BCR-ABL1 kinase domain mutations, theT315I mutation confers the complete resistance to imatinib, dasatinib, nilotinib, and bosutinib.[126,127] In addition to T315I, F317L and V299L mutants are resistant to dasatinib and Y253H, E255K/V, and F359V/C mutants are resistant to nilotinib.[128-132]

In an analysis of 1043 patients with imatinib-resistant CP-CML treated with dasatinib, the presence of T315I and F317L mutants at baseline was associated with less favorable responses.[130] F317L was associated with a high rate of CHR (93%) but low rates of MCyR and CCyR (14% and 7%, respectively), whereas favorable CCyR rates were achieved in patients with highly imatinib-resistant mutants such as E255K/V (38%) and L248V (40%). Several patients with the T315I mutation achieved CHR and MCyR, but no CCyRs were seen. In another analysis that assessed the occurrence and impact of baseline BCR-ABL1 mutations in patients with imatinib-resistant CP-CML treated with nilotinib, Y253H, E255V/K, and F359V/C mutants were associated with less favorable MCyR rates (13%, 43%, and 9%, respectively) and none of the patients with these mutations achieved CCyR within 12 months of therapy.[131] E255K/V, F359C/V, Y253H, and T315I mutants were most commonly associated with disease progression and relapse.

Bosutinib has demonstrated activity in patients with BCR-ABL1 mutants resistant to dasatinib (F317L) and nilotinib (Y253H, E255K/V, and F359C/I/V).[133] The most common baseline mutations were T315I, F359C/I/S/V, F317L, G250E, Y253F/H, and M351T. T315I and V299L mutants are resistant to bosutinib. Ponatinib was also active against other *BCR-ABL1* mutants resistant to dasatinib or nilotinib, including E255V, Y253H, and F359V, in addition to T315I.[134]

Rising Levels of BCR-ABL1 Transcripts

Rising levels of *BCR-ABL1* transcripts are associated with an increased likelihood of detecting BCR-ABL1 mutations and cytogenetic relapse.[135-139] 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 to those with stable or decreasing *BCR-ABL1*.[135] A serial rise has been reported to be more reliable than a single ≥2-fold increase in *BCR-ABL1* transcripts.[136,137] Among patients in CCyR with a ≥0.5-log increase in *BCR-ABL1* transcripts on at least two occasions, those with the highest risk were those who lost MMR with a more than 1-log increase in *BCR-ABL1* transcripts and had the highest risk of

disease progression compared to those who never achieved an MMR and had 1-log increase in *BCR-ABL1* transcripts.[137]

The precise increase in *BCR-ABL1* transcripts that warrants a mutation analysis depends on the performance characteristics of the qPCR assay.[139] Some labs have advocated a 2- to 3-fold range,[106,138,139] while others have taken a more conservative approach (0.5-log to 1-log).[137] Obviously, some common sense must prevail, since the amount of change in absolute terms depends on the level of molecular response. For example, a finding of any *BCR-ABL1* after achieving a deep molecular response (MR4.5; ≤0.0032% *BCR-ABL*1 IS) is an infinite increase in *BCR-ABL1* transcripts; however, a change in *BCR-ABL1* transcripts from MR4.5 to a barely detectable level is clearly different from a 5-fold increase in *BCR-ABL1* transcripts after achieving MMR.

Second-Line and Subsequent Therapy (CML-3)

Based on data demonstrating the prognostic significance of early molecular response at 3 and 6 months, the panel has included ≤10% and >1%–10% *BCR-ABL1* IS as the response milestone at 3 and 6 months. >0.1%–1% *BCR-ABL1* IS and ≤0.1% *BCR-ABL1* IS are included as response milestones at 12 months and >12 months, respectively**.**

Continuation of the same dose of TKI therapy (ie, imatinib, dasatinib, nilotinib) and assessment of *BCR-ABL1* transcripts with qPCR (IS) every 3 months is recommended for patients who meet response milestones. If the 3-month response milestone is not achieved after first-line TKI therapy, patients are considered to be at high risk for disease progression and alternate treatment options should be considered. Evaluation for allogeneic HCT (that is, a discussion with a transplant specialist, which might include initiating HLA testing) is recommended if the response milestones are not achieved at 3, 6, and 12 months.

Quite recently, studies have suggested that the rate of decline in *BCR-ABL1* transcripts correlates with longer-term response.[140-143] 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 to those with a slower decline (4-year PFS rate was 92% vs. 63%, respectively).[140] 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.[141] 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.[142] 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.[143]

The guidelines emphasize that achievement of response milestones months must be interpreted within the clinical context, before making drastic changes to the treatment strategy. Evaluation of compliance to therapy and mutational analysis are recommended prior to changing therapy. Mutational analysis is helpful in the selection of subsequent TKI therapy for patients with inadequate initial response to first-line or second-line TKI therapy.[144] Treatment options based on BCR-ABL1 mutation status are outlined on CML-5. The guidelines recommend BCR-ABL1 mutational analysis for patients who do not achieve response milestones, for those with any sign of loss of response

(hematologic or cytogenetic relapse), and if there is a 1-log increase in *BCR-ABL1* level with loss of MMR. 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.

Management of Patients with Inadequate Response to Imatinib

Switching to an alternate TKI or dose escalation of imatinib (up to 800 mg daily) is recommended for patients with >10% *BCR-ABL1* IS after initial treatment with imatinib.

Dasatinib, nilotinib, and bosutinib are active against many of the imatinib-resistant BCR-ABL1 kinase domain mutants, except T315I, and are effective second-line treatment options for patients with CP-CML intolerant to imatinib or those with CP-CML resistant to imatinib.[145-148]

In the START-R trial, at a minimum follow-up of 2 years, dasatinib (70 mg twice a day) demonstrated higher rates of MCyR (53% vs. 33%), CCyR (44% vs. 18%), and MMR (29% vs. 12%) compared to high-dose imatinib and the estimated PFS also favored dasatinib.[145] In the dose-optimization study (CA180-034) after 7-year follow-up, the MMR, PFS, and OS rates were 46%, 42%, and 65%, respectively, for dasatinib 100 mg once daily and the corresponding rates were 46%, 44%, and 68% for dasatinib 70 mg twice daily.[146] Severe grade 3 or 4 adverse events including pleural effusion were less frequent with dasatinib 100 mg once daily compared to dasatinib 70 mg twice daily.

In a phase II study, nilotinib (400 mg twice daily) resulted in MCyR and CCyR rates of 59% and 45%, respectively, in patients with CP-CML (n = 280) intolerant or resistant to imatinib. The estimated PFS and OS rates at 48 months were 57% and 78%, respectively.[147] The estimated PFS rate at 48 months was 89% for patients with CCyR at 12 months, compared to 56% for those with no CCyR at 12 months.

In a phase I-II study of 288 patients (196 patients with CP-CML resistant to imatinib and 90 patients intolerant to imatinib), after a median follow-up of 44 months, bosutinib resulted in MCyR and CCyR rates of 59% and 49%, respectively.[148] The estimated 2-year OS rate was 88% for patients with resistance to imatinib and 98% for patients with intolerance to imatinib. At 4 years, the cumulative incidence of disease progression to AP-CML or BP-CML was 22% for patients with resistance to imatinib and 10% for patients with intolerance to imatinib. Diarrhea (86%), nausea (46%), rash (36%), and vomiting (37%) were the most common adverse events.

Dose escalation of imatinib up to 800 mg daily has been shown to overcome some of the primary resistance, but the duration of responses has typically been short.[149-152] Dose escalation was particularly effective in patients with cytogenetic relapse who had achieved cytogenetic response with imatinib 400 mg daily.[151] However, it is unlikely to benefit those with hematologic failure or those who never had a cytogenetic response with standard-dose imatinib. In patients with inadequate response to imatinib 400 mg, switching to nilotinib has been shown to result in higher rates of cytogenetic and molecular response than dose escalation of imatinib.[153,154] 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.[153] Although dose escalation of imatinib has been shown to be beneficial for patients in CCyR with no MMR,[155] there are no randomized studies to show that a change of therapy would improve PFS or EFS in this group of patients.[156]

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 as well as for patients with intolerance to first-line dasatinib, nilotinib or bosutinib. Although failure to achieve ≤10% *BCR-ABL1* IS at 3 months after first-line therapy with dasatinib, nilotinib or bosutinib is associated with a high risk for disease progression, there is no clear evidence to support that switching to alternate TKI therapy would improve long-term clinical outcome for this group of patients. 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.[101] Therefore, it is important to interpret the value at 3 months in this context, before making drastic changes to the treatment strategy. Patients with >50% reduction in *BCR-ABL1* compared to baseline or minimally >10% *BCR-ABL1* can continue the same dose of dasatinib or nilotinib for another 3 months, if response milestones are not achieved at 3 months after first-line dasatinib or nilotinib.

Bosutinib is an effective treatment option for patients with CP-CML pretreated with dasatinib or nilotinib. In the cohort of 119 patients with CP-CML pretreated with more than one TKI (imatinib followed by dasatinib and/or nilotinib), at 40 months of follow-up, CHR, MCyR, and estimated 4-year OS rates were 74%, 40%, 32%, and 78%, respectively.[157] Diarrhea (83%), nausea (48%), vomiting (38%), and thrombocytopenia (39%) were the most common adverse events.

Ponatinib is an option for patients with T315I mutation and for those with disease that has not responded to multiple TKIs.[134,158] In the PACE trial, after a minimum follow-up of 52 months, in the cohort of 267 patients with CP-CML refractory ≥3 prior TKIs or those with T315I mutation (51% of patients had disease that is resistant to prior TKI or intolerant dasatinib or nilotinib and 70% of patients had T315I mutation), ponatinib induced durable MCyR, CCyR, MMR, and MR4.5 in 60%, 54%, 40%, and 24% of patients, respectively.[158] The estimated 5-year PFS and OS rates were 49% and 77%, respectively. In a post hoc analysis, exposure to fewer prior TKIs and shorter duration of CML were identified as predictors of response.[134] Response rates were higher in patients who were exposed to fewer prior TKIs: MCyR, CCyR, and MMR rates were 84%, 79%, and 53%, respectively, for patients treated with one prior TKI compared to 46%, 38%, and 29%, respectively, for those treated with 3 prior TKIs.

Hepatotoxicity, liver failure, and death have been rarely reported in patients treated with ponatinib. Liver function tests should be done at baseline, and at least monthly or as clinically indicated during treatment. Dose interruption and dose reductions or discontinuation of ponatinib should be considered for hepatotoxicity. Serious arterial and venous thrombosis and occlusions occurred in approximately 27% of patients: cardiovascular occlusion, cerebrovascular occlusion, and peripheral arterial occlusive events occurred in 12%, 6%, and 8% of patients, respectively. Heart failure, including fatalities, occurred in 8% of patients.[159] These adverse events were seen in patients with and without cardiovascular risk factors (such as history of ischemia, hypertension, diabetes, or hyperlipidemia). Ponatinib labeling contains a black box warning regarding vascular occlusion, heart failure, and hepatotoxicity. Cardiovascular risk factors (eg, diabetes mellitus, hypertension, hyperlipidemia, smoking, estrogen use) should be identified and controlled before starting ponatinib. Patients should be monitored for evidence of thromboembolism and vascular occlusion. 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.

Ponatinib is presently indicated in all phases of CML only for the treatment of patients with the T315I mutation and for the treatment of patients for whom no other TKI therapy is indicated. 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.[160] Therefore, dose modifications may be necessary for the management of adverse events. In a post hoc analysis that assessed the clinical impact of dose modification and dose intensity on outcomes of patients treated with ponatinib in the PACE trial, dose intensity was also the most significant predictor of MCyR by 12 months.[161] However substantial responses were observed at lower dose levels. The estimated MCyR rates were approximately 75% at 45 mg, 60% at 30 mg, and 30% at 15 mg. 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 has demonstrated safety and efficacy in patients with the T315I mutation and in those with CML that is resistant to ≥2 TKIs.[162-164] In a phase II study (CML 202 study), among 62 evaluable patients with T315I and CP-CML resistant to prior TKI therapy, CHR, MCyR, and CCyR were seen in 77%, 23%, and 16% of patients, respectively.[162] MMR was achieved in 17% of patients and the T315I clone declined to below detection limits in 61% of patients. Median duration of CHR and MCyR was 9 and 7 months, respectively. After a median follow-up of 19 months, 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), hematologic response was achieved or maintained in 67% of patients, with median response duration of 7 months; MCyR and CCyR were achieved in 22% and 4% of patients, respectively. Median PFS and OS were 7 months and 30 months, respectively.[163] Omacetaxine had an acceptable toxicity profile and the most common grade 3/4 adverse events were thrombocytopenia (67%), neutropenia (47%), and anemia (37%).[164]

Response Milestones after Second-Line TKI Therapy

Early molecular response to second-line TKI therapy has also been reported to be a prognosticator of OS and PFS. The achievement of early molecular response to second-line dasatinib was associated with improved PFS and OS.[146] The estimated 7-year PFS rates were 56% and 57% respectively, for patients with *BCR-ABL1* ≤10% (IS) at 3 and 6 months compared to 21% and 4%, respectively, for those with *BCR-ABL1* >10% (IS) at 3 and 6 months. The estimated 7-year OS rates were 72% and 74% respectively, for patients with *BCR-ABL1* ≤10% (IS) at 3 and 6 months compared to 56% and 50% respectively for those with *BCR-ABL1* >10% (IS) at 3 and 6 months. Early molecular response to second-line nilotinib was associated with higher PFS and OS rates in patients with CP-CML (n = 280) intolerant of or resistant to imatinib.[147] The estimated PFS rates at 48 months were 85% for patients with ≤1% *BCR-ABL1* at 3 months compared to 67% and 42%, respectively, for those with >1% to 10% *BCR-ABL1* and >10% *BCR-ABL1* at 3 months. The estimated OS rates at 48 months were 95% for patients with ≤1% *BCR-ABL1* at 3 months compared to 81% and 71%, respectively, for those with >1% to 10% *BCR-ABL1* and >10% *BCR-ABL1* at 3 months.

Based on the available data, patients who do not achieve 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. The use of an alternate second

generation TKI after treatment failure with two prior TKIs, including a second generation TKI is not associated with durable responses, except in occasional patients in chronic phase.[165] BCR-ABL1 mutational analysis may identify a subgroup of patients who require careful monitoring (as these patients are at a higher risk of progression) and the subset of patients who will be eligible for allogeneic HCT.

Discontinuation of TKI Therapy

TKI therapy has significantly reduced the annual mortality rate among patients with CML and it is the standard first-line therapy for patients with newly diagnosed CP-CML. In the majority of patients achieving CCyR, CML is now managed like a chronic disease, requiring long-term treatment and supportive care. Despite this efficacy, residual CML remains detectable in many patients, and it is thought that even the majority of patients who achieve negativity for *BCR-ABL1* transcripts by the most sensitive qPCR assay continue to harbor minimal residual disease. Several clinical studies have evaluated the feasibility of discontinuation of TKI therapy (with close monitoring) in carefully selected patients who have achieved and maintained deep molecular response (≥MR4.0; ≤0.01% *BCR-ABL1* IS) for 2 or more years.[166-177]

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 reduction in *BCR-ABL1* levels and undetectable minimal residual disease on qPCR with a sensitivity of ≥4.5-log reduction from the standardized baseline).[166,167] 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.[167] Other subsequent TKI discontinuation trials have also reported similar findings.[168-176] Limited longer-term follow-up data from the TKI discontinuation trials are summarized in Table 2.[178]

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 one month after discontinuation of TKI therapy. 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 two successive assessments or loss of MMR at one point.[166,167] 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.[170] Resumption of TKI therapy immediately after recurrence results in the achievement of undetectable disease in almost all patients.[166-176] Some patients may experience significant adverse events that are believed to be due to TKI discontinuation. An imatinib withdrawal syndrome (aggravation or new development of musculoskeletal pain and/or pruritus after discontinuation of imatinib) has been reported in 25% to 42% of patients during the TFR period.[174,176]

Several factors may help predict relapse after discontinuation of TKI therapy (eg, a higher Sokal risk score, female gender, lower natural killer cell counts, suboptimal response or resistance to imatinib, duration of TKI therapy and deep molecular response prior to TKI discontinuation).[166,167,171-173,175,179] In the KID study, the occurrence of imatinib withdrawal syndrome was associated with a lower rate of molecular relapse.[174] However, only the duration of TKI therapy and deep molecular response prior to TKI discontinuation therapy have been associated with TFR with a high level of consistency.[166,172]

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

Management of Advanced Phase CML

TKI Therapy

Imatinib has induced favorable hematologic and cytogenetic response rates in patients with AP-CML or BP-CML.[180-185] Dasatinib,[186,187] nilotinib,[188,189] bosutinib,[190] and ponatinib[134] have demonstrated activity in imatinib-resistant or imatinib-intolerant AP-CML or BP-CML.

Dasatinib 140 mg once daily has similar efficacy to 70 mg twice-daily dosing with an improved safety profile in patients with AP-CML and BP-CML.[186,187] In a phase III study of patients with AP-CML that were randomized to 140 mg once daily (n = 158) or 70 mg twice-daily (n = 159), the MCyR rates and the estimated PFS and OS rates at 24 months were comparable in the 2 treatment groups (MCyR, 39% vs. 43%; PFS, 51% vs. 55%; OS, 63% vs. 72%).[186] In a phase III study of patients with BP-CML, dasatinib 140 mg once daily and 70 mg twice-daily resulted in similar rates of MCyR (25% vs. 28%) and OS rates at 24 months (24% vs. 28%) in patients with myeloid BP-CML.[187] In patients with lymphoid BP-CML, dasatinib 140 mg once daily resulted in higher rates of MCyR compared to 70 mg twice daily (50% vs. 40%), and the OS rates at 24 months were 21% and 16%, respectively.

In patients with imatinib-resistant or imatinib-intolerant AP-CML, after a median follow-up of 24 months (n = 137), nilotinib resulted in MCyR and CCyR in 32% and 21% of patients, respectively; MCyR was durable in 66% of patients at 24 months.[188] The estimated OS and PFS rates at 24 months were 70% and 33%, respectively. In a phase II study of 136 patients (105 patients with myeloid BP-CML; 31 patients with lymphoid BP-CML), after a minimum follow-up of 24 months, MCyR was achieved in 38% of patients with myeloid BP-CML and 52% of patients with lymphoid BP-CML.[189] CCyR was seen in 30% of patients with myeloid BP-CML and 32% of patients with lymphoid BP-CML. The OS rate was 42% at 12 months and 27% at 24 months. The duration of MCyR was 11 months for patients with myeloid BP-CML and 3 months for those with lymphoid BP-CML.

Long-term efficacy and safety data (≥4 years of follow-up) showed that bosutinib induces hematologic response and MCyR in patients with advanced-phase CML with and without *BCR-ABL1* mutations.[190] In the

cohort of patients with AP-CML (n = 79), MCyR was attained or maintained in 40% of patients.[190] Among patients with BP-CML (n = 64), the corresponding response rates in evaluable patients were 28% and 37%, respectively. Responses were durable in approximately 50% of patients with AP-CML at 4 years; approximately 25% of patients with BP-CML responded at one year.

The PACE trial confirmed the efficacy of ponatinib in patients with advanced phase CML (83 patients with AP-CML and 62 patients with BP-CML) intolerant to ≥3 TKIs or those with resistant disease.[134] After a median follow-up of 15 months, major hematologic response (MaHR) and the estimated 1-year PFS and OS rates were 55%, 55% and 72%, respectively, for patients with AP-CML. The corresponding MaHR and the estimated 1-year PFS and OS rates were 31%,19% and 29% respectively, for patients with BP-CML. Among patients with T315I mutation, MaHR rates were 50% and 29%, respectively, for patients with AP-CML and BP-CML.

The efficacy of imatinib in combination with decitabine or cytarabine-based chemotherapy in AP-CML and myeloid BP-CML has been demonstrated in several small studies.[191-194] HyperCVAD in combination with imatinib or dasatinib is also effective for patients with lymphoid BP-CML, particularly when followed by allogeneic HCT.[195,196] Among 42 patients with BP-CML, CCyR and CMR were achieved in 58% and 25% of patients, respectively. The median remission duration and median OS were 14 months and 17 months, respectively. In multivariate analysis, remission duration ($P = .01$) and OS were longer among HCT recipients ($P < .001$).[196]

Omacetaxine is a treatment option for advanced phase CML that is resistant to multiple TKIs as well as for patients with T315I mutation.[197] Among the 51 patients with AP-CML, after a median follow-up of 16 months, major hematologic response, CHR, and minor cytogenetic response were achieved or maintained in 37%, 29%, and 11% of patients, respectively.[197] The MaHR rates were 55% and 58%, respectively, for patients with a history of a T315I mutation and for those with confirmed T315I mutation at baseline. The median PFS and OS were 4.8 months and 17.6 months, respectively. The most common grade 3/4 hematologic adverse events were thrombocytopenia (51%), anemia (39%), neutropenia (20%), and febrile neutropenia (14%).

Allogeneic Hematopoietic Cell Transplant

Allogeneic HCT is a potentially curative treatment for patients with CML, but the excellent results with TKI therapy have challenged the role of allogeneic HCT as a first-line therapy for patients with CP-CML. Allogeneic HCT is no longer recommended as a first-line treatment option for CP-CML. Allogeneic HCT is an appropriate first-line treatment option for the very rare patients presenting with blast phase at diagnosis, patients with T315I and other BCR-ABL1 mutations that are resistant to all TKIs, and for the rare patients intolerant to all TKIs.[198-201]

Ongoing advances in alternative donor sources (such as unrelated donors and cord blood), more accurate HLA testing for a stringent selection of unrelated matched donors,[202,203] and the use of reduced-intensity conditioning regimens[204-208] have improved outcomes following allogeneic HCT. Several studies have confirmed that TKI therapy prior to allogeneic HCT does not compromise the outcome following allogeneic HCT or increase transplant-related toxicity.[209-215]

Disease phase, HLA matching, age and sex of the donor and recipient, and time from diagnosis to transplant have been identified as pretransplant risk factors.[216] Low HCT comorbidity index has been identified as prognostic indicators of lower non-relapsed mortality and a

somewhat improved survival.[217] The disease phase at the time of transplant remains an important prognostic factor and the survival outcomes following transplant are clearly better for patients in CP-CML compared to patients with AP-CML or BP-CML.[218-223] Therefore, the potential use of transplantation must be tied to faithful monitoring of disease, since the major potential pitfall in delaying transplantation is "missing" the chronic phase interval.

Treatment Considerations (CML-4)

Disease progression to advanced phase while on TKI therapy has worse prognosis than de novo advanced phase CML. Evaluation for allogeneic HCT (that is, a discussion with a transplant specialist, which might include initiating HLA testing) and participation in clinical trials (evaluating TKI in combination with chemotherapy or other novel treatment options) is recommended for all patients with AP-CML or BP-CML. Treatment options are based on patient's age and comorbidities. In patients with disease progression to AP-CML or BP-CML, the selection of TKI therapy is based on prior therapy and/or mutational analysis. Mutational analysis is recommended for all patients with AP-CML and BP-CML prior to initiation of TKI therapy. A significant portion of patients with AP-CML or BP-CML treated with TKI therapy achieve a MCyR but not a concomitant CHR because of persistent cytopenias, which in turn is associated with an inferior outcome.[224]

Accelerated Phase CML

TKI therapy is recommended as first-line treatment for patients with newly diagnosed AP-CML. Allogeneic HCT can be considered based on response to TKI therapy. In patients with disease progression to AP-CML on prior TKI therapy, treatment with a course of alternate TKI (not received before) will be beneficial as a "bridge" to allogeneic HCT. Omacetaxine is an option for patients with disease progression to AP-CML on TKI therapy.[197]

Blast Phase CML

Allogeneic HCT is an appropriate first-line treatment option for the very rare patients presenting with BP-CML at diagnosis. In patients with disease progression to BP-CML on prior TKI therapy, treatment with a course of alternate TKI (not received before) will be beneficial as a "bridge" to allogeneic HCT. TKI in combination with ALL-type chemotherapy or steroids is recommended for patients with myeloid or lymphoid BP-CML and AML-type chemotherapy is recommended for those with myeloid BP-CML.

Central nervous system (CNS) involvement has been described in case reports of BP-CML.[225-228] Lumbar puncture and CNS prophylaxis is recommended for lymphoid blast phase. Documented CNS involvement in patients with lymphoid BP-CML should be managed according to the standard of care for AML or ALL. TKI therapy has not been optimized for patients with CNS involvement. Dasatinib has been reported to cross the blood brain barrier and may represent the best TKI option for patients with CNS disease.[229]

Monitoring Response after Allogeneic HCT (CML-6)

BCR-ABL1 transcripts may persist after many years in most patients after allogeneic HCT. The prognostic significance of *BCR-ABL1* positivity is influenced by the time of testing after allogeneic HCT. While a qPCR assay positive for *BCR-ABL1* at 6 to 12 months after transplant is associated with a high risk of relapse, a positive qPCR assay at a much later time point after transplant is associated with a lower risk of relapse.[230-237] Early detection of *BCR-ABL1* transcripts after transplant may be useful to identify patients who may be in need of alternative therapies before the onset of a complete relapse.

Management of Post-transplant Relapse (CML-6)

Donor lymphocyte infusion (DLI) is effective in inducing durable molecular remissions in the majority of patients with relapsed CML following allogeneic HCT, though it is more effective in patients with chronic phase relapse than advanced phase relapse.[238-243] However, DLI is associated with complications such as graft-vs-host disease (GVHD), susceptibility to infections, and immunosuppression.[238] Improvements in the methods of detecting *BCR-ABL1* transcripts to predict relapse, the development of reduced-intensity conditioning regimens, modified delivery of lymphocytes with the depletion of CD8+ cells, and the use of escalating cell dosage regimens have reduced the incidence of GVHD associated with DLI.[244-248]

Imatinib induces durable cytogenetic and molecular responses in the majority of patients relapsing with chronic and advanced phase CML following allogeneic HCT, and the response rates are higher in patients with chronic phase relapse than advanced phase relapse.[249-256] Very limited data are available on the use of dasatinib and nilotinib in patients with post-transplant relapse.[257-260] There are also data suggesting that the use of DLI in combination with imatinib may be more effective at inducing rapid molecular remissions than either modality alone.[261] Recent retrospective studies have shown that TKIs are superior to DLI alone or in combination with TKI for post-transplant relapse.[262,263] However, these observations are yet to be confirmed in randomized trials. Post-transplant TKI therapy is also effective to prevent relapse following allogeneic HCT in high-risk patients.[264-266]

Patients who are in CCyR (qPCR-negative) should undergo regular qPCR monitoring (every 3 months for 2 years, then every 3–6 months thereafter). Given the high risk for hematologic relapse in patients with prior accelerated or blast phase, post-transplant TKI therapy should be considered for at least one year in this cohort of patients who are in remission following allogeneic HCT.[264-266]

TKI with or without DLI or omacetaxine can be considered for patients who are not in remission or in cytogenetic relapse or those with an increasing level of molecular relapse. The selection of TKI depends on prior TKI, the side effect profile of the TKI under consideration, the presence of comorbidities, and BCR-ABL1 mutational status. Pre-existing mutations in the BCR-ABL1 kinase domain, frequently associated with resistance to TKIs are detectable in the majority of patients who relapse after allogeneic HCT.[267] Mutational analysis is therefore essential prior to the selection of TKI for the treatment of post-transplant relapse.

In patients with CML that has previously failed imatinib, there are no data to support the use of post-transplant imatinib, and dasatinib, nilotinib, bosutinib, ponatinib, or omacetaxine may be more appropriate options. However, there are no data to support the use of post-transplant bosutinib, ponatinib, or omacetaxine. CNS relapse of CML following allogeneic HCT has been described in few case reports.[268,269] Dasatinib may also be an effective treatment for extramedullary relapse following allogeneic HCT.[229,270,271] Participation in a clinical trial is highly desirable.

Management of CML During Pregnancy

The median age of disease onset is 67 years, but CML occurs in all age groups. The EUTOS population-based registry has reported that approximately 36.5% of patients at the time of diagnosis are of reproductive age.[272] Clinical care teams should be prepared to address issues relating to fertility and pregnancy as well as counsel these patients about the potential risks and benefits of treatment discontinuation and possible resumption of TKI therapy should CML

recur during pregnancy. Referral to a CML specialty center is recommended.

TKI Therapy and Conception

Imatinib, dasatinib, and nilotinib have been shown to be teratogenic and are known to cause embryonic or fetal toxicities in animal studies. TKI therapy appears to affect some male hormones at least transiently, but these drugs do not appear to have an effect on fertility in men. Furthermore, the miscarriage or fetal abnormality rate is not higher in female partners of men on TKI therapy.[273-277]

The situation is more complex for women as TKI therapy during pregnancy has been associated with both a higher rate of miscarriage and fetal abnormalities.[278,279] Pye and colleagues reported the outcome of pregnancies in 180 women exposed to imatinib during pregnancy. Fifty percent of pregnancies with known outcome were normal and 10% of pregnancies with known outcome had fetal abnormalities.[278] Eighteen pregnancies ended in spontaneous abortion. Cortes and colleagues reported the outcomes of pregnancy and conception during treatment with dasatinib.[279] Among 46 women treated with dasatinib, 15 women (33%) delivered a normal infant. Elective or spontaneous abortions were reported in 18 women (39%) and 8 women (17%), respectively, and 5 women (11%) had an abnormal pregnancy. Fetal abnormalities were reported in 7 cases. Among 33 women fathered by dasatinib-treated men, 30 (91%) delivered infants who were normal at birth. Although there are no data regarding the outcome of pregnancy in patients receiving bosutinib and ponatinib at the time of conception, these agents must be considered unsafe to use in pregnant women.

Discontinuation of TKI therapy because of pregnancy in women who were not in a CMR has only been reported in two small series.[280,281] Ault and colleagues have reported 10 women who stopped imatinib because of pregnancy after a median of 8 months of therapy.[280] Five of the nine women who had achieved a CHR lost the response after stopping therapy, and six had an increase in Ph-positive metaphases. At 18 months after resuming therapy, all nine patients had achieved a CHR but only three women achieved a CCyR and none had achieved an MMR. Kuwabara and colleagues reported outcomes of seven women who were not in a CMR at the time imatinib was stopped because of pregnancy, three of whom were in an MMR.[281] All seven women had disease progression. The three women who had an MMR at the time imatinib was stopped were able to regain the same response once the drug was restarted, whereas the remaining four patients were not.

Depending on other factors such as age, a natural pregnancy may occur months after stopping TKI therapy. Assuming the earliest time a woman could conceive and give birth naturally, without any wash out period, is 10 months after stopping TKI, the likelihood is about 60% that her PCR will become positive if she was in a CMR at the time of getting pregnant. It is even higher if she was not in a CMR when she became pregnant.[280,281]

Planning a Pregnancy

Prior to attempting pregnancy, women and their partners should be counseled that no guidelines exist regarding how best to monitor CML during pregnancy, nor how best to manage progressive disease should it occur during pregnancy. Conception while on active TKI therapy is strongly discouraged due to the risk of fetal abnormalities. Fertility preservation should be discussed with all patients of childbearing age prior to the initiation of TKI therapy.

TKI therapy does not appear to have a deleterious effect on male sperm, and the general recommendation is that men who take TKIs do

not need to stop therapy if a pregnancy is planned. However, experience is limited. Sperm banking can also be performed prior to starting TKI therapy, although there are no data regarding quality of sperm in untreated men with CML.

In women, due to the risk of miscarriage and fetal abnormalities during pregnancy, TKI therapy should be stopped prior to natural conception and the patient should remain off therapy during pregnancy.[278,279] Consultation with a high-risk obstetrician is recommended. Referral to an IVF center is recommended in coordination with the patient's obstetrician. TKI should be stopped prior to attempting a natural pregnancy or oocyte retrieval, but is unknown how long before. Compounding the high incidence of disease recurrence off TKI therapy are the significant obstacles that exist for women who choose one of the above forms of IVF, chief among which is the lack of access to centers that perform the procedure, high costs associated with the drugs and surgical procedures that may not be covered by insurance, costs of embryo/oocyte storage, and access to surrogate programs. Some women may require more than one IVF cycle to obtain enough potentially viable embryos for implantation. In addition, women may need a family medical leave from work to attend IVF appointments. It is also important to note that not all states allow surrogacy.

TKI therapy can be restarted after delivery. If TKI therapy is considered during pregnancy, the potential benefit for the mother and the potential risk to the fetus of continuing TKI therapy vs. the risk of treatment interruption leading to the loss of optimal disease response must be carefully evaluated on an individual basis prior to initiation of TKI therapy. Women on TKI therapy should also be advised not to breast feed, as TKIs pass into human breast milk.[282,283]

Monitoring and Treatment During Pregnancy

It is recommended to check monthly blood qPCR, and initiate treatment if the *BCR-ABL1* increases to >1.0% IS. Most of the literature regarding treatment during pregnancy consists of case reports. Leukapheresis can be initiated for a rising WBC, although there are no data that recommend at what level WBC this should be started.[284-286] Low-dose aspirin or low-molecular-weight heparin can also be considered for patients with thrombocytosis.[287,288] Interferon alpha (in wide range of doses: 3–6 million units every other day to 5–8 million units daily) has been shown to be safe during pregnancy, although it has a low rate of molecular response.[285,289-292] Hydroxyurea is also considered safe during pregnancy.[285,293-295] The potential risks and benefits should be carefully evaluated in terms of maternal health and fetal risk prior to initiation of treatment during pregnancy, especially during the first trimester.

Specific Considerations for Children with CML

CML accounts for less than 3% of all pediatric leukemias. In general, children are diagnosed at a median age of 11 to 12 years, with approximately 10% presenting in advanced phase. As a consequence of its rarity, there are no evidence-based recommendations for the management of CML in the pediatric population. Many pediatric oncologists follow treatment guidelines that are designed for adult patients. However, clinical presentations and host factors are different between children and adults, and some factors should be considered when treating pediatric patients with CML.[296-298]

Selection of TKI

Imatinib and dasatinib are the only 2 TKIs that are currently approved as first-line treatment for children with CML by the U.S. Food and Drug Administration. The efficacy and safety of nilotinib in pediatric patients

with newly diagnosed CML is being evaluated in an ongoing phase II trial. There are very little data on the safety and efficacy of bosutinib and ponatinib in children.[299]

The validity of prognostic scores (eg, Sokal, Hasford [Euro], and EUTOS scores) has not been established in the pediatric population. In an analysis that attempted to validate the three prognostic scoring systems in a cohort of 90 children (median age 12 years), there was a high discordance among the scoring methods.[300] Therefore, it is not recommended to use these scoring systems for risk assessment or to make treatment decisions for children with CML.

Imatinib

Imatinib has been evaluated in pediatric patients with newly diagnosed CP-CML in clinical studies.[301-303] In the French National phase IV study, 44 patients from age 10 months to 17 years with newly diagnosed CP-CML were treated with imatinib (260 mg/m^2).[302] At a median follow-up of 31 months, a CHR was achieved in 98% of the patients and the estimated PFS rate at 36 months was 98%. At 12 months, the rates of CCyR and MMR were 61% and 31%, respectively. The updated results of this trial showed that early molecular response at 3 months (≤10% *BCR-ABL1* IS) correlated with better PFS and higher rates of CCyR and MMR at 12 months.[303]

Higher dose imatinib (340 mg/m²) has also been shown to be effective and well tolerated in children, inducing a high rate of hematologic, cytogenetic, and molecular responses.[304,305] Long-term results of an Italian multicenter study (47 patients with CP-CML) showed that higher dose imatinib (340 mg/m²) induced CCyR in 92% of the evaluable patients at a median time of 6 months.[305] At 12 months, MMR (≤ 0.1% *BCR-ABL1*) and MR *(*≤0.01% *BCR-ABL1*) were observed in 67% and 33% of patients, respectively. Imatinib has also been effective in children with late chronic phase and advanced phase CML as well as for disease relapse following allogeneic HCT.[306]

Dasatinib

Dasatinib was evaluated in phase I/II studies in the pediatric population with newly diagnosed as well as relapsed or refractory CP-CML.[307] In a dose escalation study that evaluated dasatinib (60 mg/m^2 to 120 mg/m^2) in 58 children with relapsed or refractory leukemia (17 patients had CP-CML), CCyR and MMR were achieved in 82% and 47% of patients with imatinib-pretreated CP-CML.[307] After 24 months of follow-up, median CHR and MCyR durations were not reached. Another prospective study (CA180-226), so far only published as an abstract, also confirmed the efficacy of dasatinib in children with newly diagnosed (n= 84) as well as relapsed or refractory (n = 29) CP-CML. Dasatinib was recently approved for the treatment of CML in pediatric patients based on the results of this study.

Monitoring for Long-Term Side Effects

Children have a much longer life expectancy than adults and TKI therapy may be needed for many decades; therefore, there are potential long-term side effects (such as delayed growth, changes in bone metabolism, thyroid abnormalities, and effects on puberty and fertility) that may not be seen in adults.[308] A number of studies have reported impaired longitudinal growth in children treated with TKIs.[309-312] It appears that prepubertal children are affected more significantly.[310,313]

Growth should be monitored closely and a bone age x-ray should be obtained if longitudinal growth is delayed. A DEXA scan should be obtained if bone mineral density is decreased on plain radiograph or if there is unprovoked fracture. Further evaluation and referral to an endocrinologist is also warranted. There are no data available on the cessation of TKI therapy in the pediatric population and

discontinuation of TKI therapy in children is not recommended outside the context of a clinical trial.[314]

Immunizations

There are little data on immune function with patients on TKI therapy, and it potentially hinders routine vaccination for children with CML.[315] In general, the use of inactivated killed vaccines to children on TKI therapy is safe, although it is unknown whether responses are comparable to those seen in healthy children. A study showed a higher seroconversion rate to H1N1 influenza vaccine in adult CML patients compared to patients with B-cell malignancies or HCT recipients.[316] Administration of live vaccines during TKI therapy is not recommended in general, although one study showed that varicella vaccine could be safely given to some children with immune deficiency.[317] Live vaccines could be considered after stopping TKI therapy for several weeks in patients with a deep molecular response. In the United States, all required live vaccines are completed by the age of 4 to 6 years (http://www.cdc.gov/vaccines/). As CML is rarely seen in children younger than this age, few patients face this issue. For the annual influenza vaccine, the live attenuated vaccine (nasal spray) should be avoided, and the inactivated killed vaccine (flu shot) should be used for children receiving TKI.

Table 1. Early Molecular Response (BCR-ABL1 IS ≤10% at 3 months) after First-line TKI Therapy and Survival Outcomes

Survival Rates	CML IV Study[98]		DASISION[53]				ENESTnd[55]			
	Imatinib (n = 692) (400 mg once daily)		Dasatinib (n = 259) (100 mg once daily)		Imatinib (n = 260) (400 mg once daily)		Nilotinib (n = 258) (300 mg BID)		Imatinib (n = 264) (400 mg once daily)	
	≤10%	>10%	≤10%	>10%	≤10%	>10%	≤10%	>10%	≤10%	>10%
5-year PFS	92%	87%	89%	72%	93%	72%	95%	78%	98%	79%
5-yrear OS	94%	87%	94%	81%	95%	81%	98%	82%	99%	79%

Table 2. Summary of Limited Longer-term Follow-up Data from the TKI Discontinuation Trials

Study	Treatment prior to discontinuation	No. of patients	Depth and duration of molecular response (MR) required for discontinuation	Trigger to resume TKI therapy	Median duration of follow-up	Treatment-free remission (TFR) rate
STIM1[166,167]	Imatinib ± interferon	100	MR5.0 for at least 2 years	Loss of MR5.0	77 months	43% at 6 months; 38% at 60 months
TWISTER[168]	Imatinib ± interferon	40	MR4.5 for at least 2 years	Loss of MR5.0	42 months	47% at 24 months
HOVON[169]	Imatinib + cytarabine	15	MR4.5 for at least 2 years	Loss of MR4.5	36 months	33% at 24 months
A-STIM[170]	Imatinib ± interferon	80	MR5.0 for at least 2 years	Loss of MMR	31 months	64% at 24 months; 61% at 36 months
KIDS[174]	Imatinib ± interferon	90	MR4.5 for at least 2 years	Loss of MMR	27 months	62% at 12 months; 59% at 24 months
Stop 2G-TKI[175]	Dasatinib/Nilotinib (first-line or second-line)	60	MR4.5 for at least 24 months	Loss of MMR	47 months	63% at 12 months; 54% at 48 months
DADI[172,173]	Dasatinib (second-line)	63	MR4.0 for at least 12 months	Loss of MR4.0	36 months	44% at 36 months
ENESTFreedom[176,177]	Nilotinib (first-line)	190	MR4.5 for 12 months	Loss of MMR	96 weeks	52% at 48 weeks 49% at 96 weeks

MR5.0: 5-log reduction in *BCR ABL1* levels and undetectable minimal residual disease on qPCR with a sensitivity of ≥4.5-log reduction;
MR4.5: ≤0.0032% *BCR-ABL1* IS or >4.5-log reduction of *BCR-ABL1* and undetectable minimal residual disease on qPCR with a sensitivity of ≥4.5-log reduction;
MR4.0: <0.01% *BCR-ABL1* IS; **Major molecular response (MMR):** ≤0.1% *BCR-ABL1* IS;

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