National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Chronic Myeloid Leukemia

Version 3.2020 — January 30, 2020

NCCN.org

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National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2020
Chronic Myeloid Leukemia

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

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

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

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Updates in Version 3.2020 of the NCCN Guidelines for Chronic Myeloid Leukemia from Version 2.2020 include:

MS-1
- **Discussion section updated based on the changes in the algorithm.**

Updates in Version 2.2020 of the NCCN Guidelines for Chronic Myeloid Leukemia from Version 1.2020 include:

CML-5
- **Treatment Options Based on *BCR-ABL1* Mutation Profile:**
  - **The table has been revised to list "CONTRAINDICATED mutations" to TKIs used in the second-line setting.**
- **The following footnotes are new to this page:**
  - **Footnote o: Mutations contraindicated for imatinib are too numerous to include. There are compound mutations that can cause resistance to ponatinib, but those are uncommon following treatment with bosutinib, dasatinib or nilotinib.**
  - **Footnote p: Bosutinib has minimal activity against *F317L* mutation. Nilotinib may be preferred over bosutinib in patients with *F317L* mutation.**

Updates in Version 1.2020 of the NCCN Guidelines for Chronic Myeloid Leukemia from Version 1.2019 include:

CML-1
- **Advanced phase CML; Additional evaluation: *Consider* mutational analysis**
- **Footnote a modified: Bone marrow evaluation should be done for the initial workup, to provide morphologic review, and also to detect ~~other~~ chromosomal abnormalities in addition to *the* Ph chromosome. Fluorescence in situ hybridization (FISH) can be used if cytogenetic evaluation is not possible.**
- **Footnote c added: For patients with progression to accelerated phase or blast phase, consider myeloid mutation panel to identify BCR-ABL1–independent resistance mutations in patients with no BCR-ABL1 kinase domain mutations.**

CML-2
- **Pre-treatment evaluation modified.**
  - **The following were removed:**
    - **Treatment Considerations:**
      - **Patient comorbidities and drug toxicities**
      - **Monitor response**
      - **Evaluate patient compliance and drug interactions**
      - **Early toxicity monitoring**
  - **The following were added:**
    - **Treatment considerations independent of risk score**
    - **Comorbidities**
    - **Toxicity profile of TKI**
    - **Possible drug interactions**
    - **Patient preference**

Continued

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Updates in Version 1.2020 of the NCCN Guidelines for Chronic Myeloid Leukemia from Version 1.2019 include:

CML-2
- Primary treatment: preference stratification added.
- The regimens are noted as listed in alphabetical order.
- Footnote e modified: Based on preliminary data from the BFORE trial and long-term follow-up data from the DASISION and ENESTnd trials, second-generation TKIs (dasatinib, nilotinib, or bosutinib) are preferred for patients with an intermediate- or high-risk ~~Sokal or Hasford~~ score, especially for young women whose goal is to achieve a deep and rapid molecular response and eventual drug discontinuation of TKI therapy for ~~fertility~~ *family planning* purposes.

CML-3
- Early Treatment Response Milestones: >15 months changed to ≥15 months.
- Secondline treatment for possible TKI resistance (yellow): ~~Dose escalation of~~ Increase imatinib dose to a max of 800 mg
- Footnote h modified: BCR-ABL1 0.1% at 12 months is associated with a very low probability of subsequent disease progression and a high likelihood of achieving a subsequent MR4.0, which ~~may facilitate discontinuation of TKI therapy~~ *is a prerequisite for a trial of treatment-free remission.*

CML-4
- Treatment considerations
  - Bullet 1 modified with change of Disease progressioning to advanced phase while on TKI therapy has worse prognosis than ~~presenting with advanced phase CML~~ *de novo advanced phase CML.*
  - Bullet 2 modified with change of "Evaluate for allogeneic HCT" to "Evaluation for allogeneic HCT as indicated"
- Treatment: preference stratification added.
- The regimens are noted as listed in alphabetical order.
- Footnote m added: Imatinib is not recommended for patients with disease progression on prior TKI therapy.

CML-5
- Footnote o modified: Patients with disease that is resistant to primary treatment with bosutinib, dasatinib, or nilotinib can be treated with an alternate TKI (other than imatinib) in the second-line setting, *taking into account BCR-ABL1 mutation status. The durability of these responses is frequently limited.*

CML-6
- Footnote removed: In patients who have disease that has failed prior TKI therapy, see CML-5 for the selection of post-HCT TKI.

CML-A
- The EUTOS long-term survival (ELTS) score has been added with the following reference: Pfirrman M, Baccarani M, Saussele S, et al. Prognosis of long-term survival considering disease-specific death in patients with chronic myeloid leukemia. Leukemia 2016;30:48-56.

CML-B
- Footnote 5 added: The prognostic significance of additional chromosomal abnormalities in Ph-positive cells (ACA/Ph+) is related to the specific chromosomal abnormality and often other features of accelerated phase. The presence of “major route” ACA/Ph+ (trisomy 8, isochromosome 17q, second Ph, and trisomy 19) at diagnosis may have a negative prognostic impact on survival.
- Footnote 7 modifed: However, it should be noted that ~~IBMTR~~ *modified MDACC* criteria were used in most clinical trials leading to the approval of TKIs.

CML-D
- Complete hematologic response; bullet 4 modified: No signs and symptoms of disease with ~~disappearance~~ *resolution* of palpable splenomegaly

Continued

UPDATES

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Updates in Version 1.2020 of the NCCN Guidelines for Chronic Myeloid Leukemia from Version 1.2019 include:

CML-E

- **General Considerations added as a sub-heading and the following bullets were moved to this section from the Criteria for TKI discontinuation**
  - **reporting recommendations**
  - **consultation**
- **Criteria for TKI Discontinuation**
  - **Bullet 7 modified: Monthly molecular monitoring for one year, then every ~~6 weeks~~ *2 months* for the second year, and every ~~12 weeks~~ *3 months* 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 *monthly* molecular monitoring ~~every 4 weeks~~ until MMR is re-established, then every ~~12 weeks~~ *3 months* thereafter is recommended indefinitely for patients who have reinitiated TKI therapy after a loss of MMR.**

CML-F (applies to CML-F 1 of 8 through CML-F 6 of 8)

- **"...resistent netropenia..." changed to "...persistent neutropenia..."**

CML-F 2 of 8

- **Rare but Serious Toxicities; bullet modified: Pulmonary arterial hypertension (PAH): Dasatinib ~~may increase the risk of developing~~ *can cause* PAH, which may occur any time after initiation, including after more than one year of treatment.**

CML-F 6 of 8

- **Bullet 1 modified: Vascular occlusion: Arterial and venous thrombosis and occlusions, including fatal myocardial infarction and stroke, have occurred *at a considerable rate* in patients treated with ponatinib. Monitor for evidence of thromboembolism and vascular occlusion. Interrupt or stop ponatinib immediately for vascular occlusion.**

CML-F 7 of 8

- **A new table titled "Drug Interactions of TKIs with the Most Commonly Used Drugs and Supplements" was added.**

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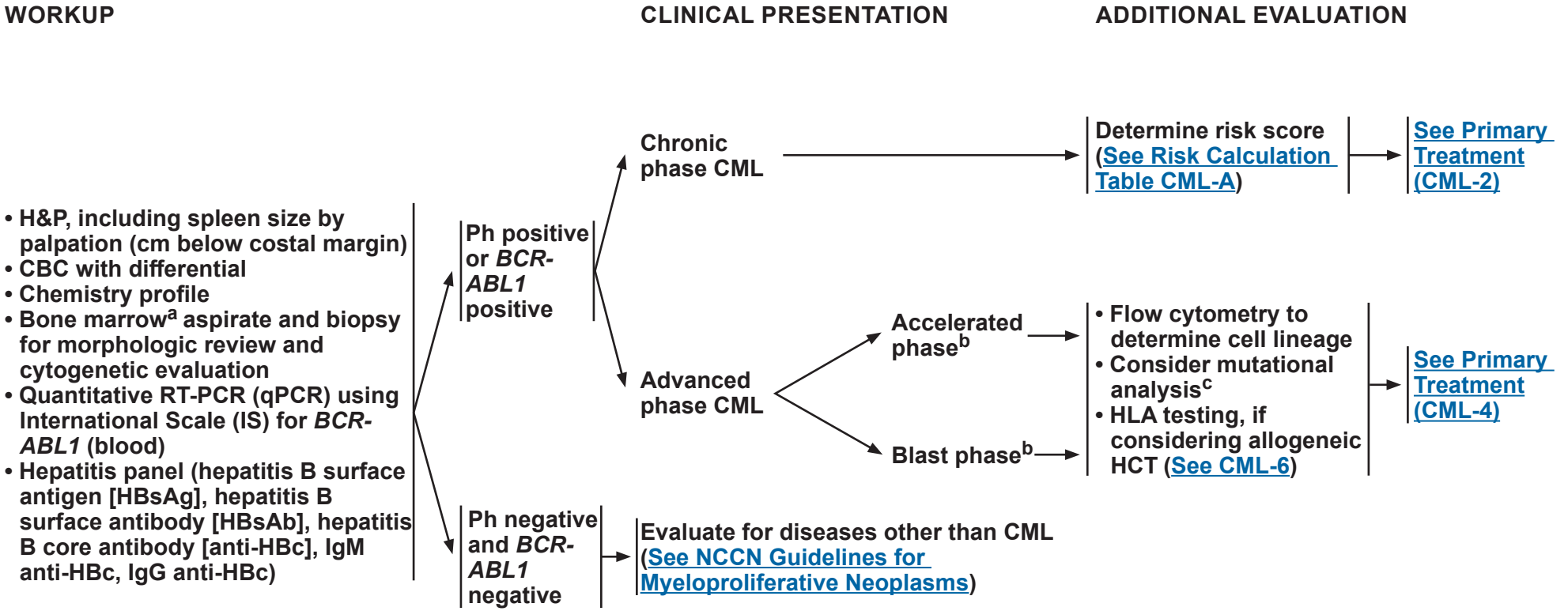

[a] Bone marrow evaluation should be done for the initial workup, to provide morphologic review, and also to detect chromosomal abnormalities in addition to the Ph chromosome. Fluorescence in situ hybridization (FISH) can be used if cytogenetic evaluation is not possible.

[b] See Definitions of Accelerated Phase and Blast Phase (CML-B).

[c] For patients with progression to accelerated phase or blast phase, consider myeloid mutation panel to identify BCR-ABL1–independent resistance mutations in patients with no BCR-ABL1 kinase domain mutations.

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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.

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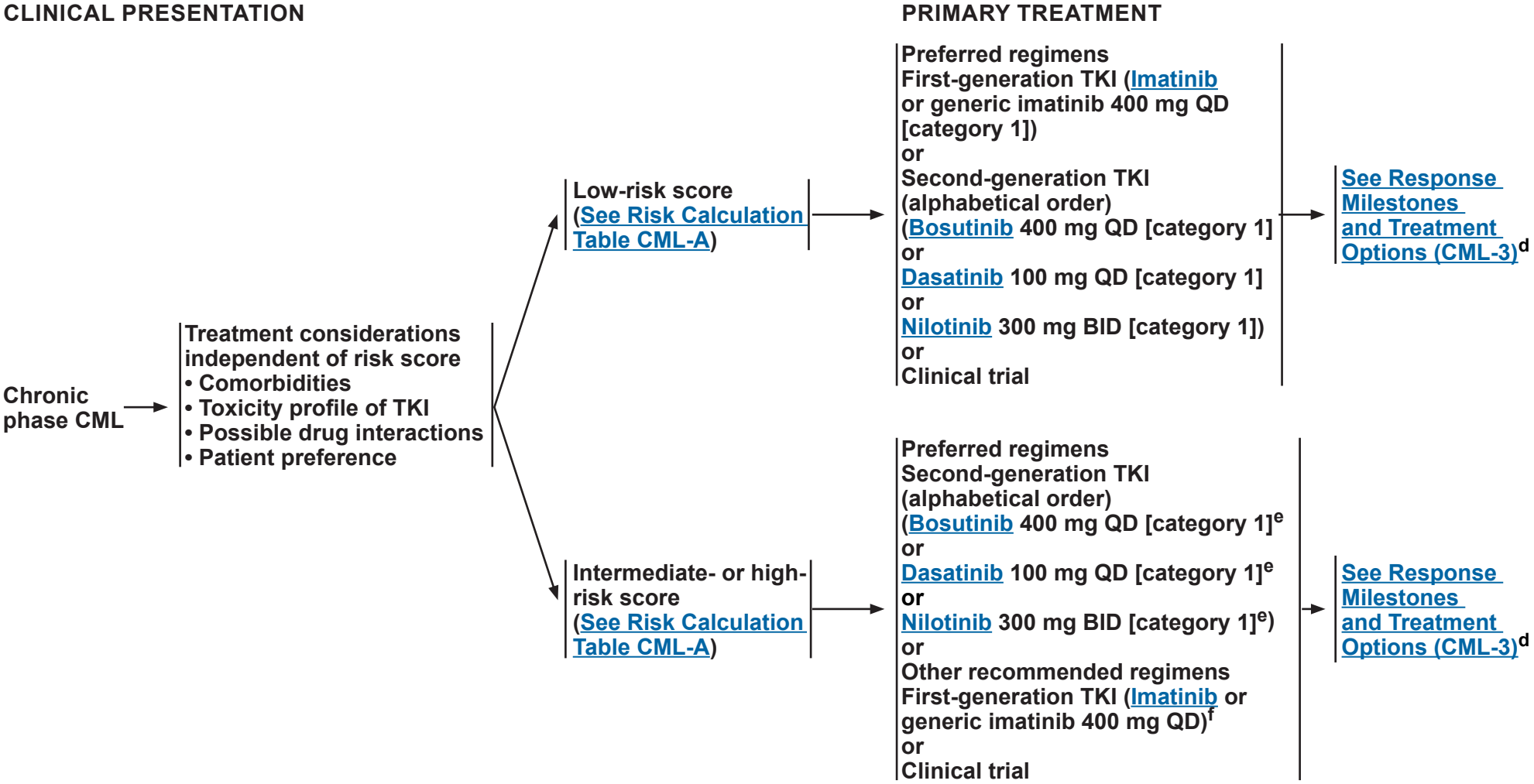

[d] See Monitoring Response to TKI Therapy and Mutational Analysis (CML-C).
[e] Based on preliminary data from the BFORE trial and long-term follow-up data from the DASISION and ENESTnd trials, second-generation TKIs (bosutinib, dasatinib, or nilotinib) are preferred for patients with an intermediate-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

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EARLY TREATMENT RESPONSE MILESTONES[d,g]

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

COLOR	CONCERN	CLINICAL CONSIDERATIONS	SECOND-LINE TREATMENT
RED	TKI-resistant disease	• Evaluate patient compliance and drug interactions • Consider mutational analysis	Switch to alternate TKI (CML-5) and evaluate for allogeneic HCT
YELLOW	Possible TKI resistance	• Evaluate patient compliance and drug interactions • Consider mutational analysis • Consider bone marrow cytogenetic analysis to assess for MCyR at 3 mo or CCyR at 12 mo	Switch to alternate TKI (CML-5) or Continue same TKI (other than imatinib) (CML-F)[j] or Increase imatinib dose to a max of 800 mg and Consider evaluation for allogeneic HCT
GREEN	TKI-sensitive disease	• Monitor response (CML-C) and side effects	Continue same TKI (CML-F)[k]

[d] See Monitoring Response to TKI Therapy and Mutational Analysis (CML-C).
[g] See Criteria for Hematologic, Cytogenetic, and Molecular Response and Relapse (CML-D).
[h] *BCR-ABL1* 0.1% at 12 months is associated with a very low probability of subsequent disease progression and a high likelihood of achieving a subsequent MR4.0, which is a prerequisite for a trial of treatment-free remission.
[i] 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.
[j] Achievement of response milestones must be interpreted within the clinical context. Patients with more than 50% reduction compared to baseline or minimally above the 10% cutoff can continue the same dose of dasatinib, nilotinib, or bosutinib for another 3 months. Continuation of imatinib 400 mg is not recommended.
[k] Discontinuation of TKI with careful monitoring is feasible in selected patients. See Discontinuation of TKI Therapy (CML-E).

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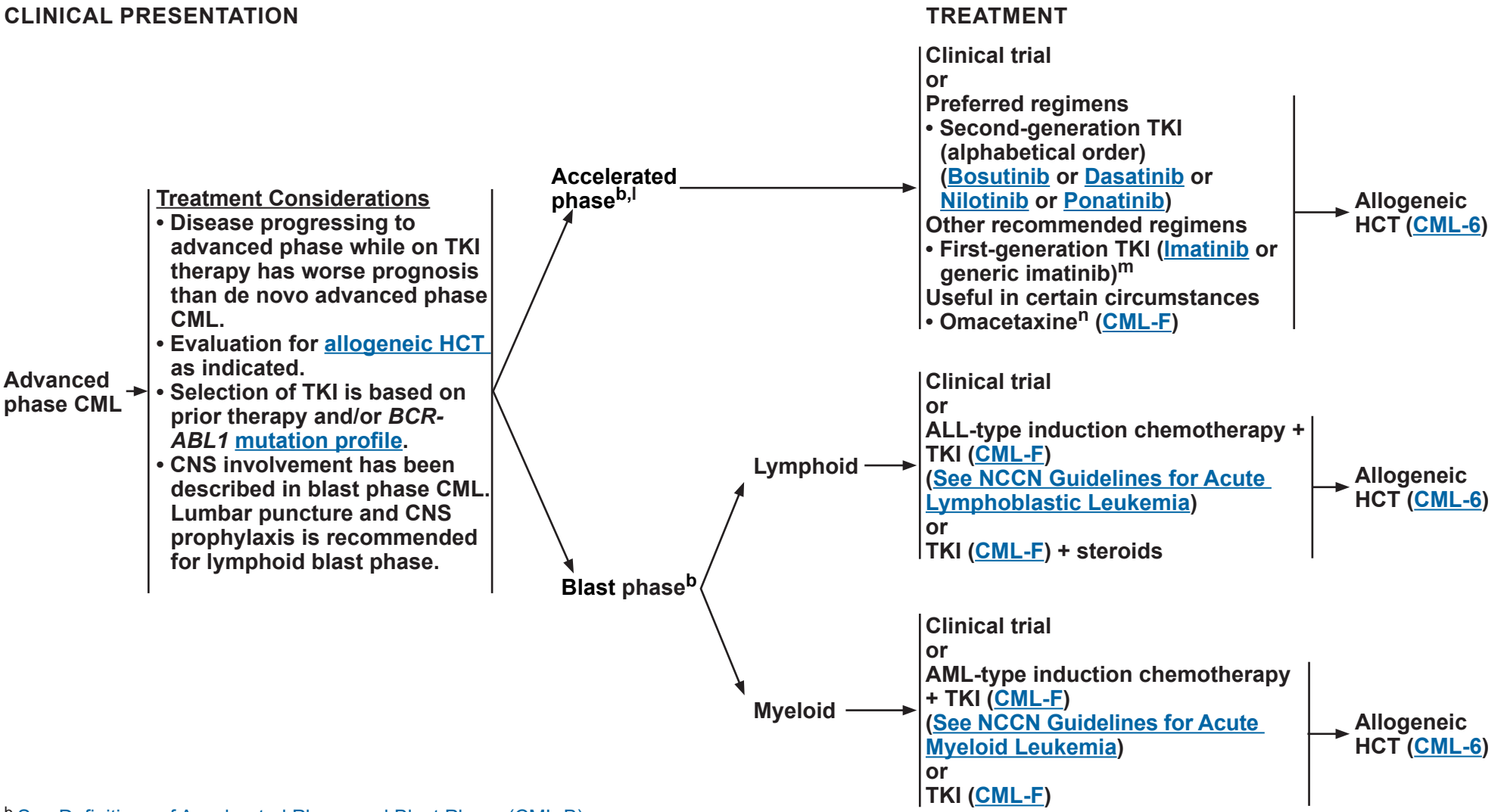

[b] See Definitions of Accelerated Phase and Blast Phase (CML-B).
[l] Patients who present with accelerated phase at diagnosis should be treated with a TKI, followed by evaluation for allogeneic HCT.
[m] Imatinib is not recommended for patients with disease progression on prior TKI therapy.
[n] Omacetaxine 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 RECOMMENDATIONS BASED ON *BCR-ABL1* MUTATION PROFILE

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

THERAPY	CONTRAINDICATED mutations[o]
Bosutinib	*T315I, V299L, G250E or F317L*[p]
Dasatinib	*T315I/A, F317L/V/I/C* or *V299L*
Nilotinib	*T315I, Y253H, E255K/V*, or *F359V/C/I or G250E*
Ponatinib,[q] Omacetaxine,[r] allogeneic HCT (CML-6), or clinical trial	None

[o] Mutations contraindicated for imatinib are too numerous to include. There are compound mutations that can cause resistance to ponatinib, but those are uncommon following treatment with bosutinib, dasatinib or nilotinib.
[p] Bosutinib has minimal activity against *F317L* mutation. Nilotinib may be preferred over bosutinib in patients with *F317L* mutation.
[q] Ponatinib is a treatment option for patients with a *T315I* mutation and/or for patients for whom no other TKI is indicated.
[r] Omacetaxine is a treatment option for patients with disease that is resistant and/or intolerant to 2 or more TKIs.

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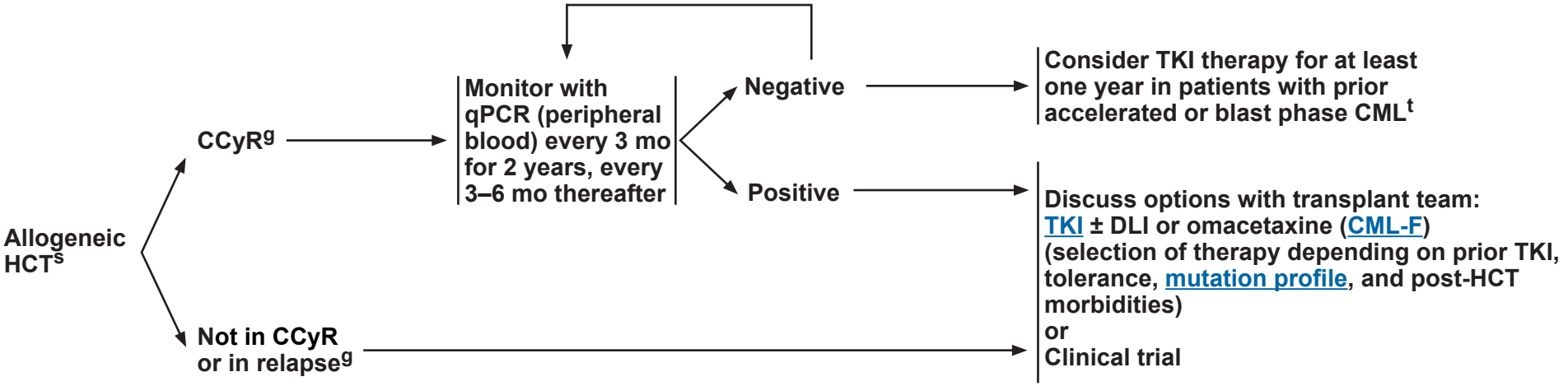
FOLLOW-UP THERAPY



[g] See Criteria for Hematologic, Cytogenetic, and Molecular Response and Relapse (CML-D).
[s] 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.
[t] See Discussion.

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RISK CALCULATION TABLE

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

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

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

[1] Sokal J, Cox EB, Baccarani M, et al. Prognostic discrimination in "good-risk" chronic granulocytic leukemia. Blood 1984;63:789-799.
[2] Hasford J, Pfirrmann M, Hehlmann R, et al. A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alfa. Writing Committee for the Collaborative CML Prognostic Factors Project Group. J Natl Cancer Inst 1998;90:850-858.
[3] Pfirrman M, Baccarani M, Saussele S, et al. Prognosis of long-term survival considering disease-specific death in patients with chronic myeloid leukemia. Leukemia 2016;30:48-56.

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DEFINITIONS OF ACCELERATED PHASE[1,2]

Modified MD Anderson Cancer Center (MDACC) Criteria[3,4] (most commonly used in clinical trials)
• Peripheral blood myeloblasts ≥15% and <30% • Peripheral blood myeloblasts 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[5]

DEFINITIONS OF BLAST PHASE[1]

International Bone Marrow Transplant Registry[6,7]
• ≥30% blasts in the blood, marrow, or both • Extramedullary infiltrates of leukemic cells

[1] Any increase in lymphoblasts is concerning for (nascent) blast phase.
[2] Sokal criteria (Sokal JE, Baccarani M, Russo D, Tura S. 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] The prognostic significance of additional chromosomal abnormalities in Ph-positive cells (ACA/Ph+) is related to the specific chromosomal abnormality and often other features of accelerated phase. The presence of “major route” ACA/Ph+ (trisomy 8, isochromosome 17q, second Ph, and trisomy 19) at diagnosis may have a negative prognostic impact on survival.
[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.
[7] World Health Organization (WHO) criteria may be included in some reports (Swerdlow SH, Harris NL, Jaffe ES, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Revised 4th ed. Lyon, France: IARC; 2017): blasts ≥20% of peripheral white blood cells or of nucleated bone marrow cells; extramedullary blast proliferation; and large foci or clusters of blasts in the bone marrow biopsy. However, it should be noted that modified MDACC criteria were used in most clinical trials leading to the approval of TKIs.

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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)
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-ABL1 kinase domain mutation analysis	• Chronic phase ▸ Failure to reach response milestones ▸ Any sign of loss of response (defined as hematologic or cytogenetic relapse) ▸ 1-log increase in *BCR-ABL1* transcript levels and loss of MMR • Disease progression to accelerated or blast phase[2]

[1] FISH has been inadequately studied for monitoring response to treatment.
[2] Consider myeloid mutation panel to identify BCR-ABL1–independent resistance mutations in patients with no BCR-ABL1 kinase domain mutations.

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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 resolution of palpable splenomegaly

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

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

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

[1]Faderl S, Talpaz M, Estrov Z, Kantarjian HM. Chronic myelogenous leukemia: biology and therapy. Ann Intern Med 1999;131:207-219. The American College of Physicians-American Society of Internal Medicine is not responsible for the accuracy of the translation.
[2]A minimum of 20 metaphases should be examined.
[3]O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 2003;348:994-1004.
[4]CCyR typically correlates with *BCR-ABL1* (IS) ≤1% (>0.1%–1%).
[5]Hughes TP, Kaeda J, Branford S, et al. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. N Engl J Med 2003;349:1423-1432.
[6]Hughes T, Deininger M, Hochhaus A, et al. Monitoring CML patients responding to treatment with tyrosine kinase inhibitors: review and recommendations for harmonizing current methodology for detecting BCR-ABL transcripts and kinase domain mutations and for expressing results. Blood 2006;108:28-37.

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DISCONTINUATION OF TKI THERAPY

General Considerations

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

Criteria for TKI Discontinuation

- **Age ≥18 years.**
- **Chronic phase CML. No prior history of accelerated or blast phase CML.**
- **On approved TKI therapy for at least 3 years.[1,2]**
- **Prior evidence of quantifiable *BCR-ABL1* transcript.**
- **Stable molecular response (MR4; *BCR-ABL1* ≤0.01% IS) for ≥2 years, as documented on at least 4 tests, performed at least 3 months apart.[2]**
- **Access to a reliable qPCR test with a sensitivity of detection of at least MR4.5 (*BCR-ABL1* ≤0.0032% IS) and that provides results within 2 weeks.**
- **Monthly molecular monitoring for one year, then every 2 months for the second year, and every 3 months 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 monthly molecular monitoring until MMR is re-established, then every 3 months thereafter is recommended indefinitely for patients who have reinitiated TKI therapy after a loss of MMR. For those who fail to achieve MMR after 3 months of TKI resumption, BCR-ABL1 kinase domain mutation testing should be performed, and monthly molecular monitoring should be continued for another 6 months.**

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

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

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MANAGEMENT OF TOXICITIES AND DRUG INTERACTIONS

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MANAGEMENT OF BOSUTINIB TOXICITY[1]

Dose Adjustments:

Hematologic Toxicities

- **Absolute neutrophil count (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 persistent 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 institutional upper limit of normal (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 Common Terminology Criteria for Adverse Events (CTCAE) grade 3–4 diarrhea (increase of ≥7 stools/d 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: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.

[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.

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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 persistent 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 can cause PAH, which may occur any time 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: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.

[2]Although erythropoietin is effective, guidelines from CMS and the FDA do not support the use of ESAs in myeloid malignancies.

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MANAGEMENT OF IMATINIB TOXICITY[1,3]

Dose Adjustments:

Hematologic Toxicities

- **Chronic phase 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 persistent 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 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 (400–300 mg, 600–400 mg, or 800–600 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 (creatinine clearance [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 left ventricular ejection fraction (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: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.
[2]Although erythropoietin is effective, guidelines from CMS and the FDA do not support the use of ESAs in myeloid malignancies.
[3]Many toxicities are self-limiting; consider re-escalating dose at a later time.
[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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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. Electrocardiograms (ECGs) should be obtained to monitor the QTc at baseline, 7 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 persistent 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: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.

[2]Although erythropoietin is effective, guidelines from CMS and the FDA do not support the use of 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 2 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 (DM) 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: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.

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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 at a considerable rate 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, 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 persistent 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: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.
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DRUG INTERACTIONS OF TKIs WITH MOST COMMONLY USED DRUGS AND SUPPLEMENTS[1,2]

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

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

Continued on next page

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.

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Drug Class/ Medications	Change in TKI Level				
	Bosutinib	Dasatinib	Imatinib	Nilotinib	Ponatinib
Anti-infectives • Azole Antifungals ▸ Fluconazole ≥200 mg ▸ Voriconazole ▸ Itraconazole ▸ Posaconazole ▸ Isavuconazole • Clarithromycin • Telithromycin • Ritonavir	Increase in exposure; Strongly consider alternative anti-infective or TKI dose adjustment	Increase in exposure; Strongly consider alternative anti-infective or TKI dose adjustment	Increase in exposure; Strongly consider alternative anti-infective or TKI dose adjustment	Increase in exposure; Strongly consider alternative anti-infective or TKI dose adjustment	Increase in exposure; Strongly consider alternative anti-infective or TKI dose adjustment
Anti-infectives • Fluoroquinolones ▸ Levofloxacin ▸ Moxifloxacin ▸ Ciprofloxacin	QTc monitoring	QTc monitoring	No major interaction	CONTRAINDICATED	No major interaction
Herbal Supplements[3,4] • Curcumin (Turmeric) • Ginkgo Biloba • Green Tea Extract	Increase in exposure; Strongly consider supplement discontinuation	Increase in exposure; Strongly consider supplement discontinuation	Increase in exposure; Strongly consider supplement discontinuation	Increase in exposure; Strongly consider supplement discontinuation	Increase in exposure; Strongly consider supplement discontinuation
Herbal Supplements[3,4] • St. John's Wort	Decrease in exposure; AVOID	Decrease in exposure; AVOID	Decrease in exposure; AVOID	Decrease in exposure; AVOID	Decrease in exposure; AVOID

[1] Please refer to package insert for full prescribing information and drug interactions: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.
[2] van Leeuwen RW, van Gelder T, Mathijssen RH, et al. Drug-drug interactions with tyrosine-kinase inhibitors: a clinical perspective. Lancet Oncol 2014;15:e315-e326.
[3] Zhang W, Lim LY. Effects of spice constituents on P-glycoprotein-mediated transport and CYP3A4-mediated metabolism in vitro. Drug Metab Dispos 2008;36:1283-1290.
[4] Scott GN, Elmer GW. Update on natural product–drug interactions. Am J Health Syst Pharm 2002;59:339-347.

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NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

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NCCN Guidelines Version 3.2020
Chronic Myeloid Leukemia

Discussion

This discussion corresponds to the NCCN Guidelines for Chronic Myeloid Leukemia. Last updated on 01/30/2020.

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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 2020, an estimated 8,450 people will be diagnosed with CML in the United States, and 1,130 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 less than 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 accelerated phase CML (AP-CML) or blast phase CML (BP-CML) in 3 to 5 years on average.[4] Progression to AP-CML and BP-CML bridges a continuum of clinical features (ie, fever, bone pain, spleen size), cytogenetic changes, and blast count. Gene expression profiling has shown a close correlation of gene expression between AP-CML and BP-CML indicating that the bulk of the genetic changes in progression occur in the transition from CP-CML to AP-CML.[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 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 Myeloid Leukemia, an electronic search of the PubMed database was performed to obtain key literature in Chronic Myeloid Leukemia since the last guideline update using the following search terms: chronic myeloid leukemia or chronic myelogenous leukemia. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes 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 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 at www.NCCN.org.

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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 (RT-PCR) to establish the presence of quantifiable *BCR-ABL1* mRNA transcripts at baseline are recommended to confirm the diagnosis of CML.

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

Quantitative RT-PCR (qPCR) should be done at initial workup to establish the presence of quantifiable *BCR-ABL1* mRNA transcripts. qPCR, usually done on peripheral blood, is the most sensitive assay available for the measurement of *BCR-ABL1* mRNA and it can detect one CML cell in a background of ≥100,000 normal cells. qPCR results can be expressed in various ways, for instance as the ratio of *BCR-ABL1* transcript numbers to the number of control gene transcripts.[12] An International Scale (IS) has been established to standardize molecular monitoring with qPCR across different laboratories with the use of 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 monitoring with qPCR using IS are provided on MS-9.

BCR-ABL1 transcripts in the peripheral blood at very low levels (1–10 out of 10^8 peripheral blood leukocytes) can be detected in approximately 30% of normal individuals, and the incidence of this increases with age. The risk of developing CML for these individuals is extremely low, and neither continued monitoring nor therapy are indicated.[14,15]

Clonal Cytogenetic Evolution

The prognostic significance of ACA/Ph$^+$ is related to the specific chromosomal abnormality and other features of accelerated phase.[16-20] The presence of “major route” ACA/Ph$^+$ (trisomy 8, isochromosome 17q, second Ph, and trisomy 19) at diagnosis may have a negative prognostic impact on survival and disease progression to accelerated or blast phase.[21-23] However, in a more recent analysis that evaluated the outcomes of patients with CP-CML (with or without ACA) treated with tyrosine kinase inhibitor (TKI) therapy in prospective studies, the presence of ACA/Ph$^+$ at the time of diagnosis was not associated with worse prognosis.[24] Survival outcomes were not statistically significant different among patients with ACA/Ph$^+$ based on TKI therapy (imatinib vs. second generation TKIs) or imatinib dose (400 mg vs. 800 mg). It remains uncertain if second generation TKIs or high dose imatinib would be more beneficial for patients with ACA/Ph$^+$. Patients with ACA/Ph$^+$ at diagnosis should be watched carefully for evidence of therapy failure.

Clonal cytogenetic evolution in Ph-negative cells has also been reported in a small subset of patients treated with TKI therapy.[25-36] The most common abnormalities include trisomy 8 and loss of Y chromosome. Previous work suggested that the overall prognosis of Ph-negative CML with clonal

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evolution is good and is dependent on response to imatinib therapy.[29] Recently, however, the presence of chromosome abnormalities other than loss of Y chromosome has been associated with decreased survival in patients with CP-CML treated with various TKIs, suggesting that closer follow-up is indicated.[37] Progression to myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) have been reported in patients with monosomy 7 (del 7q).[38-40]

Additional Evaluation

Chronic Phase CML (CML-1)

Sokal and Hasford (Euro) scoring systems have been used for the risk stratification of patients into three risk groups (low, intermediate, and high) in clinical trials evaluating TKIs (CML-A).[41,42] The Sokal score is based on the patient's age, spleen size, platelet count, and percentage of blasts in the peripheral blood.[41] The Euro score includes eosinophils and basophils in the peripheral blood in addition to the same clinical variables used in the Sokal score.[42]

The European Treatment and Outcome Study long-term survival (ELTS) score is based on the same variables as the Sokol score and provides the most useful predictor of CML-related death in patients treated with first-line imatinib.[43] The ELTS score has been validated in a cohort of 1120 patients with CP-CML treated with imatinib in six clinical trials. Higher age, higher peripheral blasts, bigger spleen, and low platelet counts were significantly associated with increased probabilities of dying of CML. Patients in the intermediate- and the high-risk group had significantly higher probabilities of dying of CML than those in the low-risk group and the probabilities were also significantly different between the intermediate- and high-risk groups. Unlike other scoring systems, the ELTS score is focused on CML-specific overall survival (OS). This is important, as many patients with CML die from non-CML causes, reflecting the efficacy of TKI therapy.

Determination of risk score using either the Sokal or Euro or ELTS scoring systems prior to initiation of TKI therapy is recommended for patients diagnosed with CP-CML.[41-43]

Advanced Phase CML (CML-1)

The modified MD Anderson Cancer Center criteria for AP-CML (15% and 29% peripheral blood or bone marrow myeloblasts; ≥30% or more of peripheral blood myeloblasts and promyelocytes; ≥20% of peripheral blood or bone marrow basophils; platelet count ≤100 x 10^9/L unrelated to therapy; and clonal cytogenetic evolution in Ph+ cells) are used in many clinical trials that have evaluated the efficacy of TKIs (CML-B).[44] The revised 2017 WHO diagnostic criteria for AP-CML include a "provisional" response to TKI criteria in addition to hematologic and cytogenetic criteria.[45] These diagnostic criteria require validation in prospective clinical trials. AP-CML defined only by clonal cytogenetic evolution on imatinib therapy is associated with a better prognosis than AP-CML defined by clonal cytogenetic evolution and additional features of progression.[21,46]

The International Bone Marrow Transplant Registry (IBMTR) criteria define blast phase as the presence of ≥30% myeloblasts in the blood, bone marrow, or both, or as the presence of extramedullary disease (CML-B).[47] Any increase in lymphoblasts should be concerning for nascent lymphoid blast phase disease. IBMTR criteria were used in most of the clinical trials leading to the approval of TKIs, and is best aligned with prognostication systems derived from these studies. The WHO diagnostic criteria (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) were included in some reports.[45]

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

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CML. Next-generation sequencing (NGS) of genes associated with myeloid malignancies allows for the detection of low-level BCR-ABL1 kinase domain mutations as well as resistance mutations in genes other than *BCR-ABL1* that would not be detected by mutational analysis using Sanger sequencing.[48-50] A myeloid mutation panel should be considered for patients with progression to advanced phase CML with no BCR-ABL1 kinase domain mutations.

Management of Chronic Phase CML

Primary Treatment (CML-2)

Long-term efficacy data from randomized phase III studies for first-line TKI therapy in patients with newly diagnosed CP-CML are summarized in Table 1.[51-54] In summary, 1) all TKIs are highly effective in newly diagnosed CP-CML, with long-term OS approaching that of aged-matched controls; 2) second-generation TKIs, compared to imatinib, generally result in faster cytogenetic and molecular responses, with less progression to advanced phase CML; and 3) as of yet, in randomized clinical trials, there are no differences in OS between imatinib and second-generation TKIs (dasatinib, nilotinib, and bosutinib).

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

Imatinib 800 mg is not recommended as initial therapy, given the recent data showing superior efficacy of second-generation TKIs in newly diagnosed CP-CML. Data from randomized phase III studies that have evaluated high-dose imatinib as first-line therapy for CP-CML suggest that imatinib 800 mg was not associated with lower rates of disease progression than imatinib 400 mg in any of these studies, despite improved early responses (Table 2).[55-57] Imatinib 800 mg was also associated with higher rates of dose interruption, reduction, or discontinuation due to grade 3 or 4 adverse events in all of the studies. However, patients who were able to tolerate the higher dose of imatinib achieved higher response rates than those receiving standard-dose imatinib.[58]

In prospective studies, the increased toxicity of imatinib 800 mg daily forced a dose reduction to an effectively administered dose of approximately 600 mg daily.[55-57] Additionally, the French SPIRIT trial reported superior major molecular response (MMR) rates in patients treated with imatinib 600 mg daily compared to 400 mg daily.[59] These data suggest that imatinib 600 mg daily may be closer to the optimal dose than 400 mg daily.

Clinical Considerations for the Selection of First-Line Therapy

Risk Stratification

Imatinib (400 mg daily) and second-generation TKIs (dasatinib [100 mg once daily], nilotinib [300 mg twice daily], and bosutinib [400 mg daily]) are all appropriate options for first-line TKI therapy for patients with CP-CML across all risk scores.[51-54]

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

Second-generation TKIs also result in quicker molecular responses and higher rates of deep molecular responses (MMR [≤0.1% *BCR-ABL1* IS] and MR4.5 [≤0.0032% *BCR-ABL1* IS]) in patients with CP-CML across all risk scores (Table 3), which may facilitate subsequent discontinuation of

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TKI therapy in selected patients.[52-54] Therefore, second-generation TKIs may be preferred over imatinib for younger patients, particularly women since the achievement of a deep and rapid molecular response may allow eventual discontinuation of TKI therapy for fertility purposes. Imatinib may be preferred for older patients with comorbidities, especially cardiovascular comorbidities.

Toxicity Profile

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

Adverse events of first-line TKI therapy in patients with CP-CML reported in phase III randomized studies are discussed below and are also summarized in Table 4. See CML-F for the management of toxicities associated with TKI therapy.

Imatinib

Chronic fatigue (often correlated with musculoskeletal pain and muscular cramps) is a major factor reducing quality of life.[60] Hypophosphatemia and decrease in bone mineral density have been noted in a small group of patients, suggesting that monitoring bone health should be considered for patients taking imatinib.[61,62] Skin hypopigmentation has also been reported as a side effect of imatinib and is reversible upon discontinuation or dose reduction.[63,64]

Dasatinib

In the DASISION study, the incidences of grade 3/4 hematologic toxicities (anemia, neutropenia, and thrombocytopenia) were higher for dasatinib than imatinib.[52] Nonhematologic adverse events such as muscle spasms, peripheral edema, and hypophosphatemia were more frequent with imatinib. Discontinuation of therapy because of drug-related adverse events occurred in 16% and 7% of patients in the dasatinib and imatinib arms, respectively. Dasatinib is associated with significant but reversible inhibition of platelet aggregation that may contribute to bleeding in some patients, especially if accompanied by thrombocytopenia.[65]

Pleural effusion was also more common with dasatinib (28% in the DASISION study compared to <1% with imatinib and 33% in a dose optimization study) and age has been identified as a significant risk factor for the development of pleural effusion.[66] The occurrence of pleural effusion is significantly reduced with dasatinib 100 mg once daily compared with 70 mg twice daily. Patients with prior cardiac history, hypertension, and those receiving dasatinib 70 mg twice-daily are at increased risk of developing pleural effusions.[67] Close monitoring and timely intervention are necessary for patients at risk of developing pleural effusions.

Reversible pulmonary arterial hypertension has been reported as a rare but serious side effect of dasatinib.[68,69] In the DASISION study, pulmonary hypertension was reported in 5% of patients treated with dasatinib compared to <1% of patients treated with imatinib.[52] 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 newly diagnosed CP-CML. Long-term follow-up results of a study in a small cohort of patients suggest that dasatinib 50 mg once daily may have similar efficacy.[70] Treatment interruption of dasatinib at 100 mg once daily and reintroduction at a lower dose (40 mg twice daily or 60 mg

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once daily) has been shown to be effective for patients with intolerance to dasatinib at 100 mg once daily.[71,72] Dasatinib at 50 mg (20 mg with careful monitoring in selected patients) should be considered for patients with clinically significant intolerance to dasatinib 100 mg once daily to avoid serious adverse events necessitating the discontinuation of dasatinib (eg, pleural effusion, myelosuppression). However, the minimum effective dasatinib dose has not been established in randomized clinical trials.

Nilotinib

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

Nilotinib labeling contains a black box warning regarding the risk of QT interval prolongation, and sudden cardiac death has been reported in patients receiving nilotinib. QT interval prolongation could be managed with dose reduction. Electrolyte abnormalities should be corrected 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. Patients with cardiovascular risk factors should be referred to a cardiologist.

Nilotinib is associated with an increased risk of peripheral arterial occlusive disease (PAOD).[73-76] 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.

The recommended starting dose of nilotinib is 300 mg twice daily for patients with newly diagnosed CP-CML. Limited data from small cohorts of patients suggest that lower doses of nilotinib (<600 mg per day) may be associated with better safety and efficacy than nilotinib 300 mg twice daily.[77] However, as with dasatinib, the minimum effective dose of nilotinib has not been established in randomized clinical trials.

Bosutinib

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

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.

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Assessment of reticulocyte count, ferritin, iron saturation, vitamin B12, and folate and correction of nutritional deficiencies if present is recommended for patients with grade 3–4 anemia. Red blood cell transfusions are indicated in symptomatic patients. Myeloid growth factor support can be used in combination with TKI therapy for the management of neutropenia.[78,79] 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.[80] 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.

Monitoring Response to TKI Therapy

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

Conventional bone marrow cytogenetics is the standard method for monitoring cytogenetic responses, and many clinical trial response analyses were based on conventional bone marrow cytogenetics. If conventional bone marrow cytogenetics yields no analyzable metaphases, cytogenetic response can be evaluated by FISH, preferably with a dual color probe to minimize false-positive rates; FISH and cytogenetic results are correlated, but not superimposable.[81-83] 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.[84,85] The panel feels that FISH has been inadequately studied for monitoring response to TKI therapy and is not generally recommended for monitoring response if conventional cytogenetics or qPCR are available.

qPCR is the only tool capable of monitoring responses after the patient has achieved CCyR, since *BCR-ABL1* transcripts typically remain detectable after CCyR is achieved. A major advantage of qPCR is the strong correlation between the results obtained from the peripheral blood and the bone marrow, allowing molecular monitoring without bone marrow aspirations.[86,87]

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 with untreated CML enrolled in 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).[13,88,89] A 2-log reduction generally correlates with CCyR (≤1% *BCR-ABL1* IS).

The sensitivity of a qPCR assay depends not only on the performance of the assay, but also on the quality of a given sample. As such, the term “complete molecular response” to denote undetectable *BCR-ABL1* transcripts (a negative qPCR test) should be abandoned, as it may refer to very different levels of response, dependent on the quality of the sample. Laboratories can use their individual assays, but the *BCR-ABL1* transcripts obtained in a given laboratory should be converted to the IS by applying a laboratory-specific conversion factor (CF).[13,90]

Recommendations for Monitoring Response to TKI Therapy

qPCR (IS) is the preferred method to monitor response to TKI therapy. qPCR assays with a sensitivity of ≥4.5-log reduction from the standardized baseline are recommended for the measurement of *BCR-ABL1* transcripts (CML-C). 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

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other pathology, such as MDS or the presence of chromosomal abnormalities other than Ph.

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

Frequent molecular monitoring with qPCR (IS) can help to identify non-adherence to TKI therapy early in the treatment course.[91] Since adherence to TKI therapy is associated with better clinical outcomes, frequent molecular monitoring is essential if there are concerns about the patient's adherence to TKI therapy. In patients with deeper molecular responses (MMR and better) and who are compliant with TKI therapy, the frequency of molecular monitoring can be reduced, though the optimal frequency is unknown. Molecular monitoring of response to TKI therapy more frequently than every 3 months is not presently recommended.

Prognostic Significance of Cytogenetic and Molecular Response

Early molecular response (EMR; ≤10% *BCR-ABL1* IS at 3 and 6 months) after first-line TKI therapy has emerged as an effective prognosticator of favorable long-term PFS and OS (Table 5).[52,53,57,92] Some reports suggest that EMR at 3 months has a superior prognostic value and support the use of early intervention strategies based on the *BCR-ABL1* transcript level at 3 months.[93,94] However, other studies yielded partially conflicting results regarding the predictive value of *BCR-ABL1* transcripts at 3 months.[95] From a practical perspective, it is important to consider these data points within the clinical context. For instance, if *BCR-ABL1* transcript level is minimally above the 10% cutoff (11% at 3 months), it is reasonable to re-assess at 6 months before considering major changes to the treatment strategy.

Quite recently, studies have suggested that the rate of decline in *BCR-ABL1* transcripts correlates with longer-term response.[96-98] 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).[96] 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.[97] 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.[98]

Achievement of CCyR (≤1% *BCR-ABL1* IS) within 12 months after first-line TKI therapy is an established prognostic indicator of long-term survival.[99,100] 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.[99] In an analysis of patients with newly diagnosed CP-CML treated with imatinib or second-generation TKIs, the 3-year event-free survival (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.[100]

The prognostic significance of MMR (≤0.1% *BCR-ABL1* IS) after first-line imatinib has also been evaluated in several studies.[86,101-105] In all of these studies, the analyses were done for different outcomes measures at multiple time points, but failed to adjust for multiple comparisons, thereby reducing the validity of the conclusions. The synoptic conclusion from these studies is that MMR is moderately superior to CCyR in predicting long-term PFS and OS. Importantly, with longer follow-up, CCyR

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becomes an ever-stronger indicator of MMR, reducing the added prognostic value of MMR. Consistent with this, 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 and.[106,107] The absence of MMR in the presence of a CCyR is not considered a treatment failure. However, the achievement of MMR (0.1% *BCR-ABL1* IS) at 12 months is associated with a very low probability of subsequent disease progression and a high likelihood of achieving a subsequent deep molecular response (MR4.0; ≤0.01% *BCR-ABL1* IS), which may facilitate discontinuation of TKI therapy. De-escalation of TKI therapy has also been shown to be feasible in patients who had received TKI therapy for ≥3 years with either a stable MMR or MR4.0 for ≥12 months.[108]

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

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

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

In patients with a >10% *BCR-ABL1* IS at 3 months and >1% *BCR-ABL1* IS at 12 months, clinical judgment should be used, considering problems with adherence (which can be common given drug toxicity at initiation of therapy), rate of decline in *BCR-ABL1* (the faster, the better), and how far from the cutoff the *BCR-ABL1* value falls. That being said, failure to achieve ≤10% *BCR-ABL1* IS at 3 months or ≤1% *BCR-ABL1* IS at 12 months is associated with a higher risk for disease progression. Patients with >10% *BCR-ABL1* at 3 months or >1% *BCR-ABL1* at 12 months can continue the same dose of dasatinib or nilotinib or bosutinib for another 3 months. *BCR-ABL1* mutational analysis and evaluation for allogeneic HCT should be considered. Bone marrow cytogenetics should be considered to assess for major cytogenetic response (MCyR) at 3 months or CCyR at 12 months.

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

Second-line Therapy

Long-term efficacy data from phase II/III studies on second-line TKI therapy for CP-CML are summarized in Table 6.[109-112]

Early molecular response (≤10% *BCR-ABL1* IS at 3 and 6 months) after second-line TKI therapy with dasatinib or nilotinib has also been reported to be a prognosticator of OS and PFS (Table 7). Patients who do not 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.

Management of Patients with Inadequate Response to Imatinib

Switching to an alternate TKI is recommended for patients with disease that is resistant to imatinib 400 mg daily. Dasatinib, nilotinib, and bosutinib are active against many of the imatinib-resistant BCR-ABL1 kinase domain mutants, except T315I, and are effective treatment options for patients with CP-CML intolerant or resistant to imatinib.[109-111]

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Dose escalation of imatinib up to 800 mg daily has been shown to overcome some of the primary resistance and is particularly effective for cytogenetic relapse in patients who had achieved cytogenetic response with imatinib 400 mg daily, although the duration of responses has typically been short.[113-116] However, it is unlikely to benefit patients with hematologic failure or those who never had a cytogenetic response with imatinib 400 mg daily. In patients with inadequate response to imatinib 400 mg, switching to nilotinib has been shown to result in higher rates of cytogenetic and molecular response than dose escalation of imatinib.[117,118] In the TIDEL-II study, the cohort of patients with >10% *BCR-ABL1* IS at 3 months after imatinib 400 mg who were switched directly to nilotinib had higher rates of MMR and complete molecular response (CMR) at 12 months (but not at 24 months) than the cohort of patients who received dose escalation of imatinib before switching to nilotinib.[117] Although dose escalation of imatinib has been shown to be beneficial for patients in CCyR with no MMR, no randomized studies have shown that a change of therapy would improve PFS or EFS in this group of patients.[119,120]

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

Switching to an alternate TKI (other than imatinib) in the second-line setting could be considered for patients with disease that is resistant to dasatinib, nilotinib, or bosutinib. Bosutinib has demonstrated activity in patients with CP-CML resistant/intolerant to multiple TKIs (imatinib, dasatinib, and nilotinib).[121] However, there is no clear evidence to support that switching to alternate TKI therapy would improve long-term clinical outcome for this group of patients.

Ponatinib is an option for patients with T315I mutation and for those with disease that has not responded to several TKIs.[112] Long-term efficacy data from phase II/III studies evaluating bosutinib or ponatinib in patients with pretreated CP-CML are summarized in Table 6.

In the PACE trial, serious arterial occlusive events (cardiovascular, cerebrovascular, and peripheral vascular) and venous thromboembolic events occurred in 31% and 6% of patients, respectively.[112] Cardiovascular, cerebrovascular, and peripheral arterial occlusive events were reported in 16%, 13%, and 14% of patients, respectively. In an analysis of cardiovascular, arterial and thrombotic adverse events associated with front-line TKI therapy in prospective clinical trials, the incidence of cardiovascular adverse events were highest among patients treated with ponatinib and those with preexisting cardiovascular risk factors.[122] The increased incidences of arterial occlusive events among patients treated with ponatinib were also confirmed in another multicenter real-life study.[123]

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

According to the package insert, the recommended initial dose of ponatinib is 45 mg once daily, the maximum tolerated dose determined in phase 1 dose-escalation study.[124] As high dose intensity of ponatinib is associated with increased risk of adverse events, dose modifications may be necessary to prevent or manage adverse events.[125] Recent reports suggest that substantial responses can be observed at lower dose levels (30 mg or 15 mg) with decreased incidence of cardiovascular events; the rates at which MCyR and MMR were maintained were independent of the dose-reductions.[112,126] Thus, an initial dose of 15 mg or 30 mg may be a

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safer and effective dose for patients with cardiovascular risk factors. The safety and efficacy of ponatinib at initial doses lower than 45 mg are under study in a randomized clinical trial, with results expected in the near future.

Omacetaxine is an option for patients with CP-CML resistant or intolerant to ≥2 TKIs including those with T315I mutation.[127,128] In the CML 202 study, among 62 evaluable patients with CP-CML resistant to prior TKI therapy and T315I mutation, after a median follow-up of 19 months, MCyR, CCyR, and MMR rates were 23%, 16%, and 17% respectively and the T315I clone declined to below detection limits in 61% of patients.[127] The median PFS was 8 months and the median OS had not yet been reached. In the cohort of 46 patients with CP-CML resistant or intolerant to ≥2 TKIs (CML 203 study), after a median follow-up of 19 months, the MCyR and CCyR rates were 22% and 4%, respectively. The median PFS and OS were 7 months and 30 months, respectively.[128] The response rates and survival outcomes, however, are lower than that observed with ponatinib in the PACE trial in this patient population (Table 6; the estimated 5-year PFS rate was 52% for patients with CP-CML resistant or intolerant to ≥2 TKIs and 50% for those with T315I mutation).[112] Omacetaxine had an acceptable toxicity profile and the most common grade 3/4 adverse events were thrombocytopenia (67%), neutropenia (47%), and anemia (37%).

Clinical Considerations for the Selection of Second-Line Therapy

BCR-ABL kinase domain mutation analysis (see below), evaluation of drug interactions and compliance to therapy are recommended prior to the initiation of second-line TKI therapy.

Drug Interactions

Bosutinib, dasatinib, imatinib, nilotinib, and ponatinib are metabolized in the liver by cytochrome P450 (CYP) enzymes and concomitant use of drugs that induce or inhibit CYP3A4 or CYP3A5 enzymes may alter the therapeutic effect of TKIs.[129,130] Drugs that are CYP3A4 or CYP3A5 inducers may decrease the therapeutic plasma concentration of TKIs, whereas CYP3A4 inhibitors and drugs that are metabolized by the CYP3A4 or CYP3A5 enzyme might result in increased plasma levels of TKIs. In addition, imatinib is also a weak inhibitor of the CYP2D6 and CYP2C9 isoenzymes and nilotinib is a competitive inhibitor of CYP2C8, CYP2C9, CYP2D6, and UGT1A1, potentially increasing the plasma concentrations of drugs eliminated by these enzymes.

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

Adherence to Therapy

Treatment interruptions and non-adherence to therapy may lead to undesirable clinical outcomes.[131-133] 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%).[131] Adherence to imatinib therapy has been identified as the only independent predictor for achieving CMR on standard-dose imatinib.[132] Poor adherence to imatinib therapy has also been identified as the most important factor contributing to cytogenetic relapse and imatinib failure.[133] Patients with adherence of ≤85% had a higher probability of losing CCyR at 2 years than those with adherence of >85% (27% and 2%, respectively). Poor adherence to therapy has also been reported in patients receiving dasatinib and nilotinib following imatinib failure.[134,135]

Patient education on adherence to therapy and close monitoring of patient's adherence is critical to achieving optimal responses. In a

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significant proportion of patients with TKI-induced toxicities, responses have been observed with doses well below their determined maximum tolerated doses.[136] 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.[137] Switching to an alternate TKI because of intolerance might be beneficial for selected patients with acute grade 3/4 non-hematologic toxicities or in those with chronic, low-grade nonhematologic toxicities that are not manageable with adequate supportive care measures.[138-140]

Resistance to TKI Therapy

Aberrant expressions of drug transporters[141-143] and plasma protein binding of TKI[144-146] could contribute to primary resistance by altering the intracellular and plasma concentration of TKI.

Pretreatment levels of organic cation transporter 1 (OCT1) have been reported as the most powerful predictor of response to imatinib.[147] On the other hand, cellular uptake of dasatinib or nilotinib seems to be independent of OCT1 expression, suggesting that patients with low OCT1 expression might have better outcomes with dasatinib or nilotinib than with imatinib.[148-151]

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.

BCR-ABL1 Kinase Domain Mutation Analysis

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.

Point mutations in the BCR-ABL1 kinase domain are a frequent mechanism of secondary resistance to TKI therapy and are associated with poor prognosis and higher risk of disease progression.[152-157] Among the BCR-ABL1 kinase domain mutations, the T315I mutation confers complete resistance to imatinib, dasatinib, nilotinib, and bosutinib.[158,159] The T315A, F317L/I/V/C, and V299L mutants are resistant to dasatinib and E255K/V, F359V/C, and Y253H mutants are resistant to nilotinib.[160-163] E255K/V, F359C/V, Y253H, and T315I mutants are most commonly associated with disease progression and relapse.[163,164] Bosutinib has demonstrated activity in patients with BCR-ABL1 mutants resistant to dasatinib (F317L) and nilotinib (Y253H, E255K/V, and F359C/I/V).[121] However, bosutinib has minimal activity against F317L mutant while *in vitro* studies suggest that F317L is highly sensitive to nilotinib.[161,163,165] Nilotinib may be preferred over bosutinib in patients with F317L mutation. T315I, G250E, and V299L mutants are resistant to bosutinib.[121] Ponatinib is active against *BCR-ABL1* mutants resistant to dasatinib or nilotinib, including E255V, Y253H, and F359V, in addition to T315I.[112]

Response rates to TKI therapy based on BCR-ABL mutation status are listed in Table 8.

BCR-ABL1 compound mutations (variants containing ≥2 mutations within the same *BCR-ABL1* allele that presumably arise sequentially) confer different levels of resistance to TKI therapy and T315I-inclusive compound mutants confer the highest level of resistance to all TKIs, including ponatinib.[166,167] In a more recent study that used NGS to detect low-level and *BCR-ABL1* compound mutations in 267 patients with heavily pretreated CP-CML from the PACE trial, no compound mutation was identified that consistently conferred resistance to ponatinib, suggesting

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that such compound mutations are uncommon following treatment with bosutinib, dasatinib, or nilotinib for chronic phase CML.[168]

BCR-ABL1 kinase domain mutational analysis is helpful in the selection of subsequent TKI therapy for patients with inadequate initial response to first-line or second-line TKI therapy.[169] Treatment options based on BCR-ABL1 kinase domain mutation status are outlined on CML-5. *BCR-ABL1* mutational analysis provides additional guidance in the selection of subsequent TKI therapy only in patients with identifiable mutations. In patients with no identifiable mutations, the selection of subsequent TKI therapy should be based on the toxicity profile of TKI, patient's age, ability to tolerate therapy, and the presence of comorbid conditions. Adverse events of second-line TKI therapy in patients with CP-CML are summarized in Table 9. NGS (myeloid mutation panel) can detect mutations in genes other than *BCR-ABL1* that may confer resistance to TKIs or portend disease progression (such as *RUNX1* mutations) and should be considered for patients with no identifiable *BCR-ABL1* mutations.[48-50]

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 with CP-CML.[170]

Rising BCR-ABL1 Transcripts

Rising *BCR-ABL1* transcripts are associated with an increased likelihood of detecting BCR-ABL1 kinase domain mutations and cytogenetic relapse.[171-175] In patients who had achieved very low levels of *BCR-ABL1* transcripts, emergence of BCR-ABL1 kinase domain mutations was more frequent in those who had >2-fold increase in *BCR-ABL1* transcripts compared to those with stable or decreasing *BCR-ABL1* transcripts.[171] A serial rise has been reported to be more reliable than a single ≥2-fold increase in *BCR-ABL1* transcripts.[172,173] Among patients in CCyR with a ≥0.5-log increase in *BCR-ABL1* transcripts on at least two occasions, the highest risk of disease progression was associated with loss of MMR and >1-log increase in *BCR-ABL1* transcripts.[173]

The precise increase in *BCR-ABL1* transcripts that warrants a mutation analysis depends on the performance characteristics of the qPCR assay.[175] Some labs have advocated a 2- to 3-fold range,[104,174,175] while others have taken a more conservative approach (5 – 10-fold).[173] 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 a barely detectable level to MR4.5 is clearly different from a 5-fold increase in *BCR-ABL1* transcripts after achieving MMR.

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

Discontinuation of TKI Therapy (CML-E)

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 has been evaluated in several clinical studies. Limited longer-term follow-up data from the TKI discontinuation trials are summarized in Table 10.

The possibility of treatment-free remission (TFR) after discontinuation of imatinib was first evaluated in the Stop Imatinib (STIM1) study in 100 patients with undetectable *BCR-ABL1* transcripts for at least 2 years (5-log reduction in *BCR-ABL1* transcripts and undetectable minimal residual disease on qPCR with a sensitivity of ≥4.5-log reduction from the standardized baseline).[176,177] With a median follow-up of 77 months

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after discontinuation of imatinib, the molecular recurrence-free survival was 43% at 6 months and 38% at 60 months.[177] Other subsequent studies that have evaluated the discontinuation of imatinib have also reported similar findings.[178-182]

More recent studies have also confirmed the feasibility of TFR after discontinuation of dasatinib or nilotinib in patients with CP-CML who have achieved and maintained MR4.5 for 12 months after ≥2 years of TKI therapy in the first-line or second-line setting (TFR rates ranging from 44% to 54%; Table 10).[183-188] The feasibility of TFR following discontinuation of bosutinib or ponatinib has not yet been evaluated in clinical studies. In the EURO-SKI study that evaluated TFR after discontinuation of any first-line TKI therapy (imatinib, dasatinib, or nilotinib) in eligible patients, the type of first-line TKI therapy did not significantly affect molecular relapse-free survival.[187] Therefore, it is reasonable to assume that the likelihood of TFR following discontinuation would be similar irrespective of TKI in patients who have achieved and maintained deep molecular response (MR4.0; ≤0.01% *BCR-ABL1* IS) for ≥2 years.

The results of the RE-STIM study demonstrated the safety of a second TKI discontinuation after a first unsuccessful attempt.[189] The rate of molecular relapse after the first TKI discontinuation attempt was the only factor significantly associated with outcome. The TFR rate at 24 months after second TKI discontinuation was higher for patients who remained in deep molecular response within the first 3 months after the first TKI discontinuation (72% vs. 32% for other patients). De-escalation of TKI therapy before complete discontinuation has been shown to improve the success of TFR in patients with deep molecular response.[190]

Approximately 40% to 60% of patients who discontinue TKI therapy after achieving deep molecular response experience recurrence within 12 months of treatment cessation, in some cases as early as one month after discontinuation of TKI therapy. Resumption of TKI therapy immediately after recurrence results in the achievement of undetectable disease in almost all patients.[176-188] TKI withdrawal syndrome (aggravation or new development of musculoskeletal pain and/or pruritus after discontinuation of TKI therapy) has been reported during the TFR period in some TKI discontinuation studies,[181,184,185,188] and the occurrence of imatinib withdrawal syndrome was associated with a lower rate of molecular relapse in the KID study.[181]

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.[176,177] 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.[179] Several factors may help predict the risk of recurrence after discontinuation of TKI therapy (eg, a higher Sokal risk score, female gender, lower natural killer cell counts, suboptimal response or resistance to imatinib, duration of TKI therapy, and deep molecular response prior to TKI discontinuation).[176,177,181,183-188,191] 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.[176,181,187,188] In the EURO-SKI study, duration of treatment with imatinib (≥ 6 years) and deep molecular response duration (MR4.0 for 3 years) were significantly associated with MMR maintenance at 6 months after discontinuation of imatinib.[187]

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

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

Management of Advanced Phase CML

Imatinib has induced favorable hematologic and cytogenetic response rates in patients with AP-CML or BP-CML.[192-196] Dasatinib,[197-199] nilotinib,[200,201] bosutinib,[202] and ponatinib[112] have demonstrated activity in imatinib-resistant or imatinib-intolerant AP-CML or BP-CML. Long-term follow-up data from phase II/III studies evaluating TKI therapy for disease progression to AP-CML and BP-CML are summarized in Table 11 and Table 12, respectively.

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.[203-206] Hyper-CVAD in combination with imatinib or dasatinib is also effective for patients with lymphoid BP-CML, particularly when followed by allogeneic HCT.[207,208]

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.[209] Omacetaxine has shown efficacy in patients with AP-CML that is resistant to multiple TKIs as well as for patients with T315I mutation.[210] Among the 51 patients with AP-CML, after a median follow-up of 16 months, major hematologic response (MaHR), CHR, and minor cytogenetic response were achieved or maintained in 37%, 29%, and 11% of patients, respectively.[210] 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 5 months and 18 months, respectively. As with CP-CML, the response rates and survival outcomes were lower than that observed with ponatinib in the PACE trial for patients with AP-CML (Table 11; the estimated 5-year PFS rates were 19% for patients with CP-CML resistant or intolerant to ≥2 TKIs and 29% for those with T315I mutation. The corresponding 5-year OS rates were 48% and 52%, respectively).[112] The most common grade 3/4 hematologic adverse events were thrombocytopenia (51%), anemia (39%), neutropenia (20%), and febrile neutropenia (14%).

Treatment Considerations (CML-4)

Disease progression to AP-CML or BP-CML while on TKI therapy has worse prognosis than de novo AP-CML or BP-CML. Participation in clinical trials and evaluation for allogeneic HCT is recommended for all patients with AP-CML and BP-CML. In patients with disease progression to AP-CML or BP-CML, the selection of TKI therapy is based on prior therapy and/or BCR-ABL1 kinase domain mutational analysis.

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De-*novo* AP-CML can often be initially managed like CP-CML with single-agent TKI followed by evaluation for allogeneic HCT.[211,212] However, patients with disease progression from CP-CML to AP-CML while on a TKI therapy have a high rate of progression to BP-CML, with predictably poor survival. These patients should be considered for a clinical trial and/or allogeneic HCT. Treatment with a course of alternate TKI (not received before) can be beneficial as a "bridge" to allogeneic HCT in patients with disease progression. Omacetaxine is also an option for patients with disease progression to AP-CML on TKI therapy.[210]

TKI in combination with chemotherapy (ALL-type chemotherapy for lymphoid BP-CML and AML-type chemotherapy for myeloid BP-CML) or steroids followed by allogeneic HCT is recommended for *de-novo* BP-CML and disease progression to BP-CML.[213]

Central nervous system (CNS) involvement has been described in case reports of BP-CML.[214-217] Lumbar puncture and CNS prophylaxis is recommended for lymphoid BP-CML. Documented CNS involvement in patients with lymphoid BP-CML should be managed according to the standard of care for AML or ALL. Dasatinib has been reported to cross the blood brain barrier and may represent the best TKI option for patients with CNS disease.[218] TKI therapy has not been optimized for patients with CNS involvement.

Allogeneic Hematopoietic Cell Transplant

Allogeneic HCT is a potentially curative treatment for patients with CML. 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, and the use of reduced-intensity conditioning regimens have improved outcomes following allogeneic HCT.[219-225]

Allogeneic HCT is an appropriate treatment option for the very rare patients presenting with BP-CML at diagnosis, patients with disease that is resistant to TKIs, patients with progression to AP-CML or BP-CML while on TKI therapy, and for patients with CML resistant and/or intolerant to all TKIs.[226-229] Several studies have confirmed that prior TKI therapy does not compromise the outcome following allogeneic HCT or increase transplant-related toxicity.[230-236]

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.[237] A low HCT comorbidity index is a prognostic indicator of lower non-relapse mortality and improved survival.[238] 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.[239-244] Therefore, the potential use of allogeneic HCT must be tied to faithful monitoring of disease, since the major potential pitfall in delaying transplantation is "missing" the chronic phase interval.

Monitoring Response after Allogeneic HCT (CML-6)

BCR-ABL1 transcripts may persist for many years in patients after allogeneic HCT. The prognostic significance of *BCR-ABL1* positivity is influenced by the time of testing after allogeneic HCT. A positive qPCR assay for *BCR-ABL1* at ≥18 months after allogeneic HCT is associated with a lower risk of relapse than a positive qPCR assay for *BCR-ABL1* at 6 to 12 months after allogeneic HCT.[245-252] Early detection of *BCR-ABL1* transcripts after allogeneic HCT may be useful to identify patients who may be in need of alternative therapies before overt relapse occurs.

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.[253-258] However, DLI is associated

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with complications such as graft-versus-host disease (GVHD), susceptibility to infections, and immunosuppression.[253] 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.[259-263]

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.[264-271] Very limited data are available on the use of dasatinib and nilotinib in patients with post-transplant relapse.[272-275] 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.[276] Recent retrospective studies have shown that TKIs are superior to DLI alone or in combination with TKI for post-transplant relapse.[277,278] 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.[279-281]

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.[279-281]

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.[282] BCR-ABL1 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.[283,284] Dasatinib may also be an effective treatment for extramedullary relapse following allogeneic HCT.[218,285,286] Participation in a clinical trial is highly desirable.

Management of CML during Pregnancy

The median age of disease onset is 65 years, but CML occurs in all age groups. The EUTOS population-based registry has reported that approximately 37% of patients at the time of diagnosis are of reproductive age.[287] 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

TKI therapy appears to affect some male hormones at least transiently, but does not appear to have a deleterious effect on fertility in men. Furthermore, the miscarriage or fetal abnormality rate is not elevated in female partners of men on TKI therapy.[288-292]

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The situation is more complex for women as TKI therapy during pregnancy has been associated with both a higher rate of miscarriage and fetal abnormalities. Limited evidence from case reports on women with CML exposed to imatinib, dasatinib, or nilotinib during pregnancy indicate the need for close monitoring, a prolonged wash-out period prior to pregnancy, and prompt consideration of holding TKI therapy if pregnancy occurs while on imatinib, nilotinib, or dasatinib.[293-296]

In one report on the outcome of pregnancies in 180 women exposed to imatinib during pregnancy, 50% of pregnancies with known outcome were normal and 10% of pregnancies with known outcome had fetal abnormalities.[293] Eighteen pregnancies ended in spontaneous abortion. In another report on the outcomes of pregnancy and conception during treatment with dasatinib, among 46 women treated with dasatinib, 15 women (33%) delivered a normal infant.[294] 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 or 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 deep molecular response (≥MR4.0; ≤0.01% *BCR-ABL1* IS) has only been reported in small series of patients.[297-299] In one series, among 10 women who stopped imatinib because of pregnancy after a median of 8 months of therapy, 5 of the 9 women who had achieved a CHR lost the response after stopping therapy, and 6 had an increase in Ph-positive metaphases.[297] 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. In another series that reported the outcomes of seven women who were not in deep molecular response at the time imatinib was stopped because of pregnancy, three were in an MMR.[298] All seven women had disease relapse. 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 deep molecular response at the time of getting pregnant.[297,298]

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.

In men, the general recommendation is that TKI therapy need not be discontinued if a pregnancy is planned. However, experience is limited. Sperm banking can also be performed 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.[293-295] Consultation with a high-risk obstetrician is recommended. Referral to an in vitro fertilization (IVF) center is recommended in coordination with the patient's

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obstetrician. TKI should be stopped prior to attempting a natural pregnancy or oocyte retrieval, but the optimal timing of discontinuation is unknown. Compounding the high incidence of disease recurrence off TKI therapy are the significant obstacles that exist for women who choose one of the 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 versus the risk of treatment interruption leading to the loss of optimal disease response must be carefully evaluated on an individual basis prior to initiation of TKI therapy. The use of TKI therapy, particularly during the first trimester should be avoided. Women on TKI therapy should also be advised not to breastfeed, as TKIs pass into human breast milk.[300-302]

Monitoring and Treatment during Pregnancy

Most of the literature regarding treatment during pregnancy consists of case reports. It is recommended to check monthly blood qPCR, and initiate treatment if the *BCR-ABL1* increases to >1.0% IS. Leukapheresis can be used for a rising white blood cell (WBC) count, although there are no data that recommend at what level of WBC count leukapheresis should be initiated.[303-306] Low-dose aspirin or low-molecular-weight heparin can be considered for patients with thrombocytosis.[307,308]

Interferon alpha (in wide range of doses: 3–6 million units every other day to 5–8 million units daily) and hydroxyurea have been used during pregnancy.[304,309-316]

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. Due to 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 several factors should be considered when treating pediatric patients with CML.[317-319]

Selection of TKI

Imatinib, dasatinib, and nilotinib are currently approved for treatment of CML in children.[320-322] Higher dose imatinib (340 mg/m^2) has also been shown to be effective and well tolerated in children.[323-325] There are very little data on the safety and efficacy of bosutinib and ponatinib in children.[326]

The validity of prognostic scores (eg, Sokal, Euro) for risk assessment or to make treatment decisions has not been established in the pediatric population.[327] The ELTS score has demonstrated better differentiation of PFS than Sokal and Euro scores in children treated with imatinib.[328]

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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.[329] A number of studies have reported impaired longitudinal growth in children with CML treated with TKI therapy and the effect is more significant in prepubertal children.[330-334]

Growth should be monitored closely and a bone age x-ray should be obtained if longitudinal growth is delayed. A dual-energy x-ray absorptiometry (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.

In an international study (STOP IMAPED) that evaluated the discontinuation of imatinib in 14 children who were in sustained deep molecular remission, the overall probability of maintaining it at 6 months was 29%.[335] Further studies in a larger cohort of patients are needed to identify the criteria for discontinuation TKI therapy in the pediatric population. Therefore, discontinuation of TKI therapy in children at this time is not recommended outside the context of a clinical trial.[336]

Immunizations

There are little data on immune function with patients on TKI therapy, and it potentially hinders routine vaccination for children with CML.[337] 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.[338]

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.[339] Live attenuated annual influenza vaccine (nasal spray) should be avoided, and the inactivated killed vaccine (flu shot) should be used for children receiving TKI therapy. 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.

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Table 1: First-Line TKI Therapy for CP-CML: Long-Term Follow-up Data from Phase III Studies

Trial	Study Arms	No. of Patients	Median Follow-up	CCyR[a]	MMR[b]	Disease Progression n (%)	PFS[c]	OS[c]
IRIS[51,d]	Imatinib (400 mg once daily)	553	11 years	83%	—	38 (7%)	92%	83%
	Interferon alpha plus low-dose cytarabine	553		—	—	71 (13%)	—	79%[e]
DASISION[52]	Dasatinib (100 mg once daily)	259	5 years	—	76% (*P* = .002)	12 (5%)	85%	91%
	Imatinib (400 mg once daily)	260		—	64%	19 (7%)	86%	90%
ENESTnd[53]	Nilotinib (300 mg twice daily)	282	5 years	—	77% (*P* vs imatinib <.0001)	10 (4%)	92%	94%
	Nilotinib (400 mg twice daily)	281		—	77% (*P* vs imatinib <.0001)	6 (2%)	96%	96%
	Imatinib (400 mg once daily)	283		—	60%	21 (7%)	91%	92%
BFORE[54,f]	Bosutinib (400 mg once daily)	268	12 months	77% (*P* = .0075)	47% (*P* = .02)	4 (2%)	—	—
	Imatinib (400 mg once daily)	268		66%	37%	6 (3%)	—	—

CCyR, complete cytogenetic response; MMR, major molecular response (≤ 0.1% *BCR-ABL1* IS); OS, overall survival; PFS, progression-free survival

a. Primary endpoint of DASISION study: Confirmed CCyR rate at 12 months.
b. Primary endpoint of ENESTnd and BFORE studies: MMR (≤ 0.1% BCR-ABL1 IS) rate at 12 months.
c. Long-term primary endpoint of IRIS trial in the imatinib group.
d. Due to the high rate of crossover to imatinib (66%) and the short duration of therapy (<1 year) before crossover among patients who had been randomly assigned to interferon alfa plus cytarabine, the long-term follow-up data focused on patients who had been randomly assigned to receive imatinib.
e. Data include survival among the 363 patients who crossed over to imatinib.
f. There were no differences in survival rates between the two treatment arms after a minimum follow-up of 12 months; long-term follow-up is ongoing.

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

Trial	Study Arms	No. of Patients	Median Follow-up	MMR	MR4.5	PFS	OS
TOPS study[55,a]	Imatinib (800 mg once daily)	319	42 months	79%	—	96% at 48 months	93% at 48 months
	Imatinib (400 mg once daily)	157		76%	—	94% at 48 months	94% at 48 months
CML IV study[57,b]	Imatinib (800 mg once daily)	420	10 years	89%	71%	77%	79%
	Imatinib (400 mg once daily)	400		92%	67%	80%	80%
SWOG study[56,c]	Imatinib (800 mg once daily)	73	12 months	53%	19%	92% (4-year PFS)	95% (4-year OS)
	Imatinib (400 mg once daily)	72		36%	9%	80% (4-year PFS)	90% (4-year OS)

MMR, major molecular response (≤ 0.1% *BCR-ABL1* IS); MR, molecular response;
MR4.5: ≥4.5-log reduction in *BCR-ABL1* transcripts from baseline; OS, overall survival; PFS, progression-free survival

a. Primary endpoint: MMR rate at 12 months (≤ 0.1% BCR-ABL1), which corresponds to a 3-log reduction in BCR-ABL1 transcripts compared with the standardized baseline established in IRIS study.
b. Primary endpoint: The impact of MMR on survival at 12 months. This study had 5 [change to 4?] treatment arms (imatinib 400 mg once daily alone; imatinib 800 mg twice daily; imatinib 400 mg once daily with interferon or cytarabine; and imatinib after interferon failure). Only the data for imatinib 400 mg once daily alone vs. imatinib 800 mg twice daily are included in this table.
c. Primary endpoint: MR4.0 (≥4-log reduction in BCR-ABL1 transcripts from baseline) at 12 months. Results from the first part of SWOG S0325 study; follow-up after 12 months was not required for this study.

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

Trial	Study Arms	Low-risk[a,b]		Intermediate-risk[a,b]		High-risk[a,b]	
		MMR	MR4.5	MMR	MR4.5	MMR	MR4.5
DASISION[52]	Dasatinib (100 mg once daily)	90%	55%	71%	43%	67%	31%
	Imatinib (400 mg once daily)	69%	44%	65%	28%	54%	30%
ENESTnd[53]	Nilotinib (300 mg twice daily)	—	53%	—	60%	—	45%
	Nilotinib (400 mg twice daily)	—	62%	—	50%	—	42%
	Imatinib (400 mg once daily)	—	38%	—	33%	—	23%
BFORE[54]	Bosutinib (400 mg once daily)	58%	—	45%	—	34%	—
	Imatinib (400 mg once daily)	46%	—	39%	—	17%	—

MMR, major molecular response (≤ 0.1% *BCR-ABL1* IS); MR, molecular response;
MR4.5: 4.5-log reduction in *BCR-ABL1* transcripts from baseline

a. DASISION study: Risk stratification by Hasford (Euro) risk score.
b. ENESTnd and BFORE trial: Risk stratification by Sokal risk score.

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

Toxicity	DASISION[52]		ENESTnd[53]		BFORE[54]	
	Dasatinib 100 mg QD	Imatinib 400 mg QD	Nilotinib 300 mg BID	Imatinib 400 mg QD	Bosutinib 400 mg QD	Imatinib 400 mg QD
Hematologic toxicities (Grade 3/4)						
Anemia	13%	9%	4%	6%	3%	5%
Neutropenia	29%	24%	12%	22%	7%	12%
Thrombocytopenia	22%	14%	10%	9%	14%	6%
Biochemical abnormalities (Grade 3/4)						
Increased lipase	NR	NR	9%	4%	13%	6%
Increased glucose	NR	NR	7%	<1%	2%	2%
Decreased phosphate	7%	28%	8%	10%	5%	17%
Increased ALT	NR	NR	4%	2%	23%	3%
Increased AST	NR	NR	NR	NR	12%	3%
Nonhematologic toxicities (any grade) *						
Rash	13%	18%	38%	19%	20%	13%
Headache	13%	11%	32%	23%	19%	13%
Fatigue	9%	11%	23%	20%	19%	18%
Muscle spasms	23%	41%	12%	34%	2%	26%
Peripheral edema	13%	37%	9%	20%	4%	14%
Pleural effusion	28%	<1%	2%	1%	NR	NR
Hypertension	NR	NR	10%	4%	NR	NR
Pulmonary hypertension	5%	<1%	0%	0%	NR	NR
Diarrhea	21%	22%	19%	46%	70%	34%
Constipation	NR	NR	20%	8%	NR	NR
Nausea	10%	24%	22%	41%	35%	39%
Vomiting	5%	11%	15%	27%	18%	16%

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; QD, once daily.
* Non-hematologic toxicities from the DASISION study (except pleural effusion) are from the 3-year follow-up. No new adverse events were observed with 5-year follow-up.

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Table 5. Early Molecular Response (≤10% *BCR-ABL1* IS at 3 months) After First-Line TKI Therapy and Survival Outcomes

Trial	Study Arms	5-year PFS		5-year OS	
		BCR-ABL1 ≤10%	*BCR-ABL1* >10%	*BCR-ABL1* ≤10%	*BCR-ABL1* >10%
DASISION[52]	Dasatinib (100 mg once daily)	89%	72%	94%	81%
	Imatinib (400 mg once daily)	93%	72%	95%	81%
ENESTnd[53]	Nilotinib (300 mg twice daily)	95%	78%	98%	82%
	Nilotinib (400 mg twice daily)	96%	89%	96%	93%
	Imatinib (400 mg once daily)	98%	79%	99%	79%
CML IV Study[92]	Imatinib (400 mg once daily)	92%	87%	94%	87%

OS, overall survival; PFS, progression-free survival

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Table 6. Second-Line and Subsequent TKI Therapy for CP-CML: Long-Term Follow-up Data from Phase II/III Studies

TKI	No. of Patients	Median Follow-up	MCyR	CCyR	MMR	PFS	OS
Dasatinib[109,a] (100 mg once daily)	Imatinib-R (n = 124)	7 years	—	—	43%	39%	63%
	Imatinib-I (n = 43)		—	—	55%	51%	70%
Nilotinib[110,b] (400 mg twice daily)	Imatinib-R (n = 226) Imatinib-I (n = 95)	4 years	59%	45%	—	57%	78%
Bosutinib[121,b] (400 mg once daily)	Imatinib and dasatinib-R (n = 38)	4 years	39%	22%	—	—	67%
	Imatinib and dasatinib-I (n = 50)		42%	40%	—	—	80%
	Imatinib and nilotinib-R (n = 26)		38%	31%	—	—	87%
Ponatinib[112,c] (45 mg once daily)	Dasatinib or nilotinib-R or I (n = 203)	57 months	56%	49%	35%	52% at 5 years	76% at 5 years
	T315I mutation (n = 64)		72%	70%	58%	50% at 5 years	66% at 5 years

R = Resistant; I = Intolerant; CCyR, complete cytogenetic response; MCyR, major cytogenetic response; MMR, major molecular response (≤ 0.1% *BCR-ABL1* IS); OS, overall survival; PFS, progression-free survival

a. Primary endpoint: MCyR rate at 6 months when administered 100 mg once daily vs. 70 mg twice daily.
b. Primary endpoint: MCyR rate in patients with imatinib intolerance or imatinib-resistant disease.
c. Primary endpoint: MCyR at any time within the first 12 months.

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

TKI	Median Follow-up	Progression-Free Survival (PFS)				Overall Survival (OS)			
		BCR-ABL1 ≤10%		*BCR-ABL1* >10%		*BCR-ABL1* ≤10%		*BCR-ABL1* >10%	
		3 months	6 months	3 months	6 months	3 months	6 months	3 months	6 months
Dasatinib[109] (100 mg once daily)	7 years	56%	57%	21%	4%	72%	74%	56%	50%
Nilotinib[110] (400 mg twice daily)	4 years	67%	58%	42%	39%	81%	82%	71%	73%

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Table 8. Responses Based on BCR-ABL1 Mutations Status[a]

Mutation	Major Cytogenetic Response (MCyR), n/N (%)			
	Bosutinib[121]	Dasatinib[162]	Nilotinib[163]	Ponatinib[168]
E255K[b]	—	9/16 (56%)	3/7 (43%)	8/13 (62%)
E255V[b]	—	4/11 (36%)		1/4 (25%)
E459K[b]	—	—	—	3/7 (43%)
F317L[c,d]	1/7 (14%)	2/14 (14%)	—	13/29 (45%)
F359C[b]	1/2 (50%)	3/5 (60%)	1/11 (9%)	1/7 (14%)
F359V[b]	2/3 (67%)	17/27 (63%)		11/20 (55%)
F359I[b]	2/2 (100%)	10/12 (83%)	—	3/4 (75%)
G250E[b,e]	0/5 (0%)	29/60 (48%)	3/5 (60%)	8/12 (67%)
H396R	—	17/33 (52%)	—	1/5 (20%)
L248V	—	10/15 (67%)	—	1/2 (50%)
M244V	2/3 (67%)	27/26 (59%)	—	4/9 (56%)
M351T	—	28/54 (52%)	—	1/2 (50%)
Y253H[b]	5/6 (83%)	15/23 (65%)	1/8 (13%)	1/2 (50%)
V299L[c,e]	0/2 (0%)	—	—	3/8 (38%)

a. Mutations contraindicated for imatinib are too numerous to include. There are compound mutations that can cause resistance to ponatinib, but those are uncommon following treatment with bosutinib, dasatinib, or nilotinib.
b. *BCR-ABL1* mutations resistant to nilotinib.
c. *BCR-ABL1* mutations resistant to dasatinib.
d. Bosutinib has minimal activity against F317L mutation and in-vitro studies suggest that F317L is highly sensitive to nilotinib.
e. *BCR-ABL1* mutations resistant to bosutinib.

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

Toxicity (any grade)	Dasatinib[109] (100 mg QD)	Nilotinib[110] (300 mg BID)	Bosutinib[121] (400 mg QD)	Ponatinib[112] (45 mg QD)
Rash	33%	31%	28%	47%
Headache	—	18%	27%	43%
Fatigue	37%	21%	24%	30%
Myalgias/Arthralgias	38%	11%	18%	24%/33%
Pleural effusion	28%	—	17%	—
Hypertension	—	—	8%	37%
Hemorrhage	26%	—	—	—
Diarrhea	42%	12%	83%	20%
Constipation	—	13%	13%	41%
Nausea	27%	25%	48%	29%
Vomiting		13%	38%	19%
Increased blood creatinine	—	—	13%	—
Increased lipase	—	—	—	27%
Increased ALT/AST	—	—	15%	—

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; QD, once daily.

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Table 10. 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 MR Required for Discontinuation	Trigger to Resume TKI Therapy	Median Follow-up	Treatment-free Remission (TFR) Rate
STIM1[177]	Imatinib ± interferon	100	MR5.0 for at least 2 years	Loss of MR5.0	77 months	38% at 60 months
TWISTER[182]	Imatinib ± interferon	40	MR4.5 for at least 2 years	Loss of MR5.0	103 months	45% (molecular relapse-free survival 45% at 8 years)
HOVON[178]	Imatinib + cytarabine	15	MR4.5 for at least 2 years	Loss of MR4.5	36 months	33% at 24 months
A-STIM[179]	Imatinib ± interferon	80	MR5.0 for at least 2 years	Loss of MMR	31 months	61% at 36 months
ISAV study[180]	Imatinib (after failure of interferon or hydroxyurea)	108	CMR for at least 18 months	Loss of MMR	36 months	52% at 36 months
KID study[181]	Imatinib ± interferon	90	MR4.5 for at least 2 years	Loss of MMR	27 months	59% at 24 months
Stop 2G-TKI[183]	Dasatinib/Nilotinib (first- or second-line)	60	MR4.5 for at least 24 months	Loss of MMR	47 months	54% at 48 months
DASFREE[188]	Dasatinib (first- or second-line)	84	MR4.5 for 12 months	Loss of MMR	2 years	46% at 24 months
ENESTFreedom[184]	Nilotinib (first-line)	190	MR4.5 for 12 months	Loss of MMR	96 weeks	49% at 96 weeks
ENESTop study[185]	Nilotinib (second-line)	126	MR4.5 for 12 months	Loss of MMR	96 weeks	53% at 96 weeks
DADI[186]	Dasatinib (second-line)	63	MR4.0 for at least 12 months	Loss of MR4.0	44 months	44% at 36 months
EURO-SKI[187]	Any TKI	758	MR4.0 for at least 1 year	Loss of MMR	27 months	50% at 24 months

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

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Table 11. TKI Therapy for Disease Progression to AP-CML: Long-Term Follow-up Data from Phase II/III Studies

TKI	No. of Patients	Median Follow-up	MCyR	CCyR	OS	PFS
Dasatinib[197,a] (140 mg once daily)	Imatinib-R (n = 117)	24 months	36%	29%	63%	51%
	Imatinib-I (n = 41)		46%	41%		
Nilotinib[200,b] (400 mg twice daily)	Imatinib-R (n = 109)	24 months	30%	19%	70%	33%
	Imatinib-I (n = 27)		41%	30%		
Bosutinib[202,c] (500 mg once daily)	Prior imatinib only (n = 49)	48 months	48%	35%	66%	—
	Imatinib followed by dasatinib or nilotinib (n = 30)		27%	23%	45%	—
Ponatinib[112,d] (45 mg once daily)	Dasatinib or nilotinib-R or I (n = 65)	32 months	45%	28%	48% at 5 years	19% at 5 years
	T315I mutation (n = 18)		67%	44%	52% at 5 years	29% at 5 years

R = Resistant; I = Intolerant; CCyR, Complete cytogenetic response; MCyR, major cytogenetic response; OS, overall survival; PFS, progression-free survival

a. Primary endpoint: Major hematologic response (MaHR). The rate of MaHR at 5 years was 67% for 140 mg once daily and 69% for 70 mg twice daily (Blood Cancer J 2018; 8:88).
b. Primary endpoint: Confirmed complete hematologic response rate, achieved in 30% of patients with imatinib-resistant disease and 37% of imatinib-intolerant patients.
c. Primary endpoint: Confirmed overall hematologic response by 48 weeks.
d. Primary endpoint: MaHR at any time within the first 6 months.

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Table 12. TKI Therapy for Disease Progression to BP-CML: Long-term Follow-up Data from Phase II/III Studies

TKI	No. of Patients	Median Follow-up	MCyR	CCyR	OS
Dasatinib[a,199] (140 mg once daily)	Lymphoid blast phase (n = 33)	24 months	50%	38%	21%
	Myeloid blast phase (n = 75)		25%	14%	24%
Nilotinib[b,201] (400 mg twice daily)	Lymphoid blast phase (n = 31)	24 months	52%	32%	10%
	Myeloid blast phase (n = 105)		38%	30%	32%
Bosutinib[c,202] (500 mg once daily)	Prior imatinib only (n = 36)	48 months	50%	37%	28%
	Imatinib followed by dasatinib or nilotinib (n = 28)		21%	17%	17%
Ponatinib[d,112] (45 mg once daily)	Dasatinib or nilotinib-R or I (n = 38)	6 months	18%	16%	9% at 3 years
	T315I mutation (n = 24)		29%	21%	

R = Resistant; I= Intolerant; CCyR, complete cytogenetic response; MCyR, major cytogenetic response; OS, overall survival

a. Primary endpoint: Major hematologic response (MaHR).
b. Endpoints: Duration of MaHR, MCyR, and OS.
c. Primary endpoint: Confirmed overall hematologic response by 48 weeks.
d. MaHR at any time within the first 6 months.

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