National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Chronic Myelogenous Leukemia

NCCN Evidence Blocks™

Version 1.2016

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NCCN Guidelines Version 1.2016 Panel Members
Chronic Myelogenous Leukemia
NCCN Evidence Blocks™

NCCN Guidelines Index
CML Table of Contents
Discussion

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Continue

NCCN Guidelines Panel Disclosures

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NCCN Guidelines Version 1.2016 Table of Contents
Chronic Myelogenous Leukemia
NCCN Evidence Blocks™

NCCN Guidelines Index
CML Table of Contents
Discussion

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

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

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

NCCN Categories of Evidence and Consensus.

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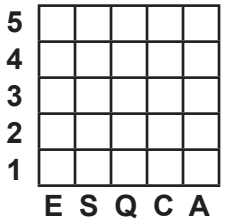
Chronic Myelogenous Leukemia
NCCN Evidence Blocks™

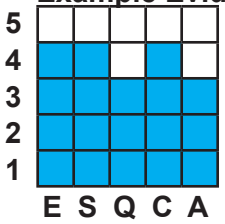
NCCN Guidelines Index
CML Table of Contents
Discussion

NCCN EVIDENCE BLOCKS CATEGORIES AND DEFINITIONS



E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

Example Evidence Block



E = 4
S = 4
Q = 3
C = 4
A = 3

Efficacy of Regimen/Agent

5	**Highly effective:** Often provides long-term survival advantage or has curative potential
4	**Very effective:** Sometimes provides long-term survival advantage or has curative potential
3	**Moderately effective:** Modest, no, or unknown impact on survival but often provides control of disease
2	**Minimally effective:** Modest, no, or unknown impact on survival and sometimes provides control of disease
1	**Palliative:** Provides symptomatic benefit only

Safety of Regimen/Agent

5	**Usually no meaningful toxicity:** Uncommon or minimal side effects. No interference with activities of daily living (ADLs)
4	**Occasionally toxic:** Rare significant toxicities or low-grade toxicities only. Little interference with ADLs
3	**Mildly toxic:** Mild toxicity that interferes with ADLs is common
2	**Moderately toxic:** Significant toxicities often occur; life threatening/fatal toxicity is uncommon. Interference with ADLs is usual
1	**Highly toxic:** Usually severe, significant toxicities or life threatening/fatal toxicity often observed. Interference with ADLs is usual and/or severe

Quality of Evidence

5	**High quality:** Multiple well-designed randomized trials and/or meta-analyses
4	**Good quality:** Several well-designed randomized trials
3	**Average quality:** Low quality randomized trials or well-designed non-randomized trials
2	**Low quality:** Case reports or clinical experience only
1	**Poor quality:** Little or no evidence

Consistency of Evidence

5	**Highly consistent:** Multiple trials with similar outcomes
4	**Mainly consistent:** Multiple trials with some variability in outcome
3	**May be consistent:** Few trials or only trials with few patients; lower quality trials whether randomized or not
2	**Inconsistent:** Meaningful differences in direction of outcome between quality trials
1	**Anecdotal evidence only:** Evidence in humans based upon anecdotal experience

Affordability of Regimen/Agent (includes drug cost, supportive care, infusions, toxicity monitoring, management of toxicity)

5	**Very inexpensive**
4	**Inexpensive**
3	**Moderately expensive**
2	**Expensive**
1	**Very expensive**

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Chronic Myelogenous Leukemia
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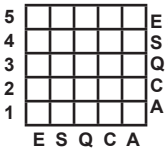

NCCN Guidelines Index
CML Table of Contents
Discussion

WORKUP[a]

- H&P, including spleen size by palpation (cm below costal margin)
- CBC with differential, platelets
- Chemistry profile
- Bone marrow aspirate and biopsy[b]
  - Morphologic review
    - ◊ Percent blasts
    - ◊ Percent basophils
  - Cytogenetics
    - ◊ FISH[c,d]
- Quantitative RT-PCR (QPCR) using International Scale (IS)[c] (blood or bone marrow)
- Determine risk score (See Risk Calculation Table CML-B)
- Human leukocyte antigen (HLA) testing, if considering allogeneic HCT[e]

PRIMARY TREATMENT

Ph positive or *BCR-ABL1* positive

- **Chronic phase CML** → **Discussion of treatment options[f] including:**
  - Tyrosine kinase inhibitor (TKI)[g]
  - Role of HCT[e]
  - Clinical trial

  → **Imatinib 400 mg QD (category 1)[h]** or **Nilotinib 300 mg BID (category 1)[i]** or **Dasatinib 100 mg QD (category 1)[j]** → **See 3-Month Evaluation (CML-2)**
- **Advanced phase CML** → See Treatment (CML-5)

Ph negative and *BCR-ABL1* negative → **Evaluate for diseases other than CML (See Discussion)**

[a] See Monitoring Response to TKI Therapy and Mutational Analysis (CML-A).
[b] Bone marrow should be done for the initial workup, not only to provide morphologic review, but also to detect chromosomal abnormalities that are not detectable on peripheral blood FISH.
[c] See Discussion for further details.
[d] FISH on peripheral blood, if collection of bone marrow is not feasible
[e] HCT = hematopoietic cell transplantation. Indications and outcomes of allogeneic HCT are dependent on age and comorbidities, donor type, and transplant center.
[f] For patients with symptomatic leukocytosis or thrombocytosis, see Supportive Care Strategies for Leukocytosis and Thrombocytosis (CML-C).
[g] There are 60-month follow-up data for dasatinib (DASISION study) and nilotinib (ENESTnd study) demonstrating superior cytogenetic and molecular response rates at certain time points and lower rates of progression to accelerated or blast phase compared to imatinib. Long-term survival benefit has not been established. Preliminary data from these studies also suggest that patients with an intermediate- or high-risk Sokal or Hasford score may preferentially benefit from dasatinib or nilotinib. See Discussion for additional information.
[h] See Management of Imatinib Toxicity (CML-D).
[i] See Management of Nilotinib Toxicity (CML-E).
[j] See Management of Dasatinib Toxicity (CML-F)

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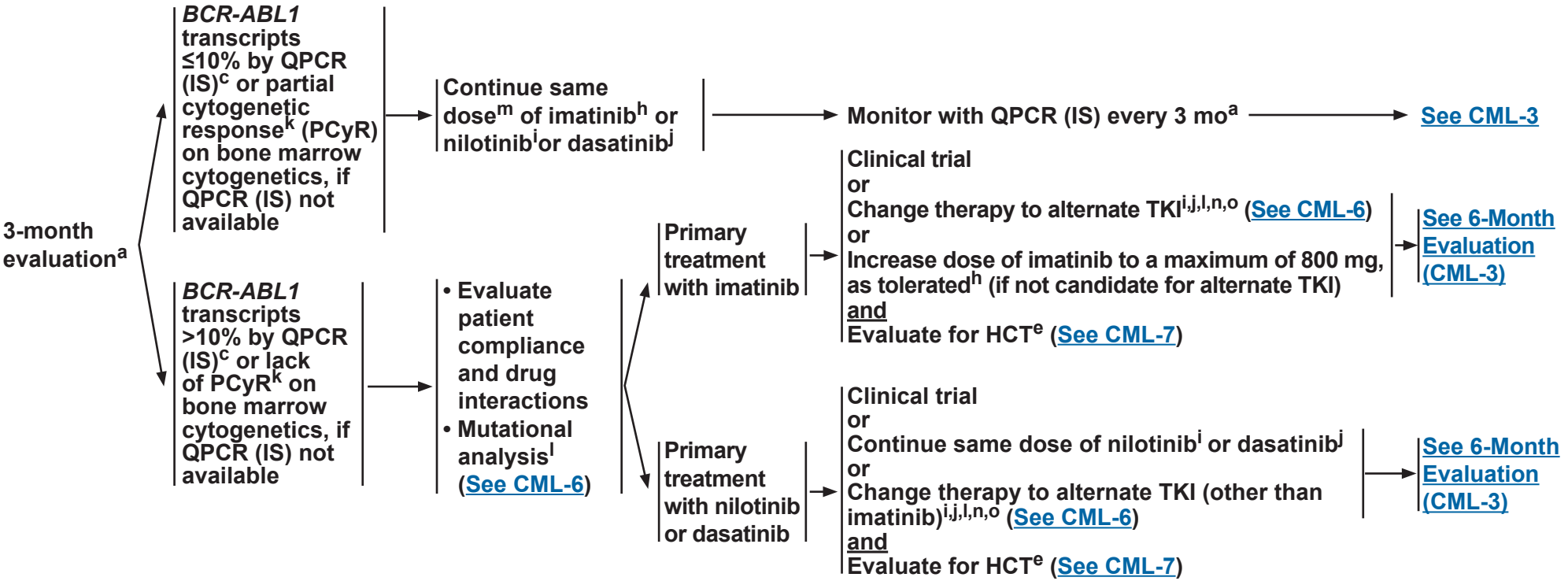
3-MONTH FOLLOW-UP THERAPY[a]



[a] See Monitoring Response to TKI Therapy and Mutational Analysis (CML-A).
[c] See Discussion for further details.
[e] HCT = hematopoietic stem cell transplantation. Indications and outcomes of allogeneic HCT are dependent on age and comorbidities, donor type, and transplant center.
[h] See Management of Imatinib Toxicity (CML-D).
[i] See Management of Nilotinib Toxicity (CML-E).
[j] See Management of Dasatinib Toxicity (CML-F).
[k] See Criteria for Hematologic, Cytogenetic, and Molecular Response and Relapse (CML-J).
[l] The selection of TKI is based on prior therapy and/or mutational testing. There are some data regarding the efficacy of second-generation TKIs against specific mutations. See Management of Cytogenetic or Hematologic Resistance to TKIs (CML-6).
[m] Same dose of TKI should be continued indefinitely. Discontinuation of TKI should only be done in the setting of a clinical trial. See Discussion for details.
[n] Consider IFN/PEG-IFN, allogeneic HCT, omacetaxine, or clinical trial for rare patients unable to tolerate TKI therapy.
[o] See Management of Bosutinib Toxicity (CML-G).

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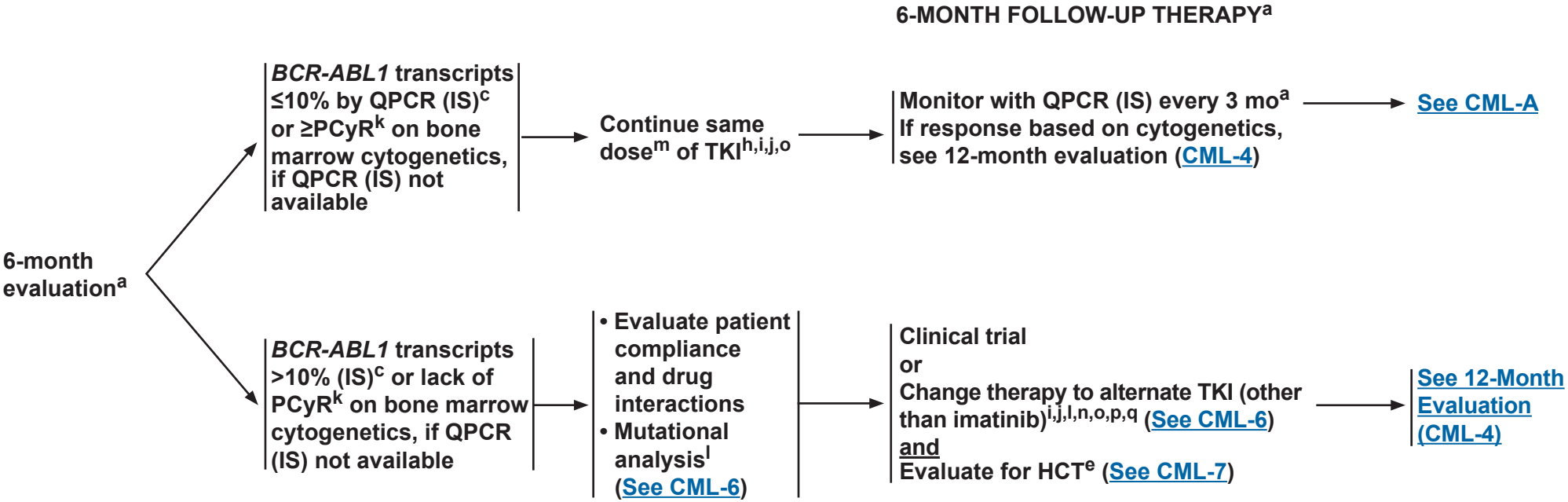

[a] See Monitoring Response to TKI Therapy and Mutational Analysis (CML-A).
[c] See Discussion for further details.
[e] HCT = hematopoietic stem cell transplantation. Indications and outcomes of allogeneic HCT are dependent on age and comorbidities, donor type, and transplant center.
[h] See Management of Imatinib Toxicity (CML-D).
[i] See Management of Nilotinib Toxicity (CML-E).
[j] See Management of Dasatinib Toxicity (CML-F).
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[m] Same dose of TKI should be continued indefinitely. Discontinuation of TKI should only be done in the setting of a clinical trial. See Discussion for details.
[n] Consider IFN/PEG-IFN, allogeneic HCT, omacetaxine, or clinical trial for rare patients unable to tolerate TKI therapy.
[o] See Management of Bosutinib Toxicity (CML-G).
[p] Omacetaxine is a treatment option for patients with disease that is resistant and/or intolerant to two or more TKIs. See Management of Omacetaxine Toxicity (CML-H).
[q] Ponatinib is a treatment option for patients with a T315I mutation or for patients with disease that has not responded to 2 or more TKI therapies. See Management of Ponatinib Toxicity (CML-I).

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12-MONTH FOLLOW-UP THERAPY AND BEYOND[a]

12-mo evaluation and beyond[a] with bone marrow cytogenetics if neither CCyR nor MMR[r] has been previously achieved

- **Complete cytogenetic response[k] or *BCR-ABL1* transcripts ≤1% but >0.1% by QPCR (IS)** → **Continue same dose[m] of TKI[h,i,j,o]** → **See CML-A**
- **PCyR[k] or *BCR-ABL1* transcripts ≤10% but >1% by QPCR (IS)** → • Evaluate patient compliance and drug interactions • Consider mutational analysis[l] (See CML-6) → **Change therapy to alternate TKI (preferred) (other than imatinib)[i,j,l,n,o,p,q] (See CML-6)** or **Continue same dose of TKI[h,i,j,o]** or **Increase dose of imatinib to a maximum of 800 mg, as tolerated[j] (if not candidate for alternate TKI or omacetaxine[p])**
- **Less than PCyR[k] or *BCR-ABL1* transcripts >10% by QPCR (IS)** → • Evaluate patient compliance and drug interactions • Mutational analysis[l] (See CML-6) → **Change therapy to alternate TKI (other than imatinib)[i,j,l,n,o,p,q] (See CML-6) and Evaluate for HCT[e] (See CML-7) or Clinical trial**
- **Cytogenetic relapse[k]** → • Evaluate patient compliance and drug interactions • Mutational analysis[l] (See CML-6) → **Change therapy to alternate TKI (preferred) (other than imatinib)[i,j,l,n,o,p,q] (See CML-6) or Increase dose of imatinib to a maximum of 800 mg, as tolerated[i] (if not candidate for alternate TKI or omacetaxine[p]) and Evaluate for HCT[e] (See CML-7) or Clinical trial**

All of the above → **Repeat bone marrow evaluation at 3 months to document CCyR, if <CCyR, treat as per <PCyR on this page**

[a] See Monitoring Response to TKI Therapy and Mutational Analysis (CML-A).
[e] HCT = hematopoietic stem cell transplantation. Indications and outcomes of allogeneic HCT are dependent on age and comorbidities, donor type, and transplant center.
[h] See Management of Imatinib Toxicity (CML-D).
[i] See Management of Nilotinib Toxicity (CML-E).
[j] See Management of Dasatinib Toxicity (CML-F).
[k] See Criteria for Hematologic, Cytogenetic, and Molecular Response and Relapse (CML-J).
[l] The selection of TKI is based on prior therapy and/or mutational testing. There are some data regarding the efficacy of second-generation TKIs against specific mutations. See Management of Cytogenetic or Hematologic Resistance to TKIs (CML-6).
[m] Same dose of TKI should be continued indefinitely. Discontinuation of TKI should only be done in the setting of a clinical trial. See Discussion for details.
[n] Consider IFN/PEG-IFN, allogeneic HCT, omacetaxine, or clinical trial for rare patients unable to tolerate TKI therapy.
[o] See Management of Bosutinib Toxicity (CML-G).
[p] Omacetaxine is a treatment option for patients with disease that is resistant and/or intolerant to two or more TKIs. See Management of Omacetaxine Toxicity (CML-H).
[q] Ponatinib is a treatment option for patients with a T315I mutation or for patients with disease that has not responded to 2 or more TKI therapies. See Management of Ponatinib Toxicity (CML-I).
[r] Absence of MMR in the presence of a CCyR is not considered a treatment failure.

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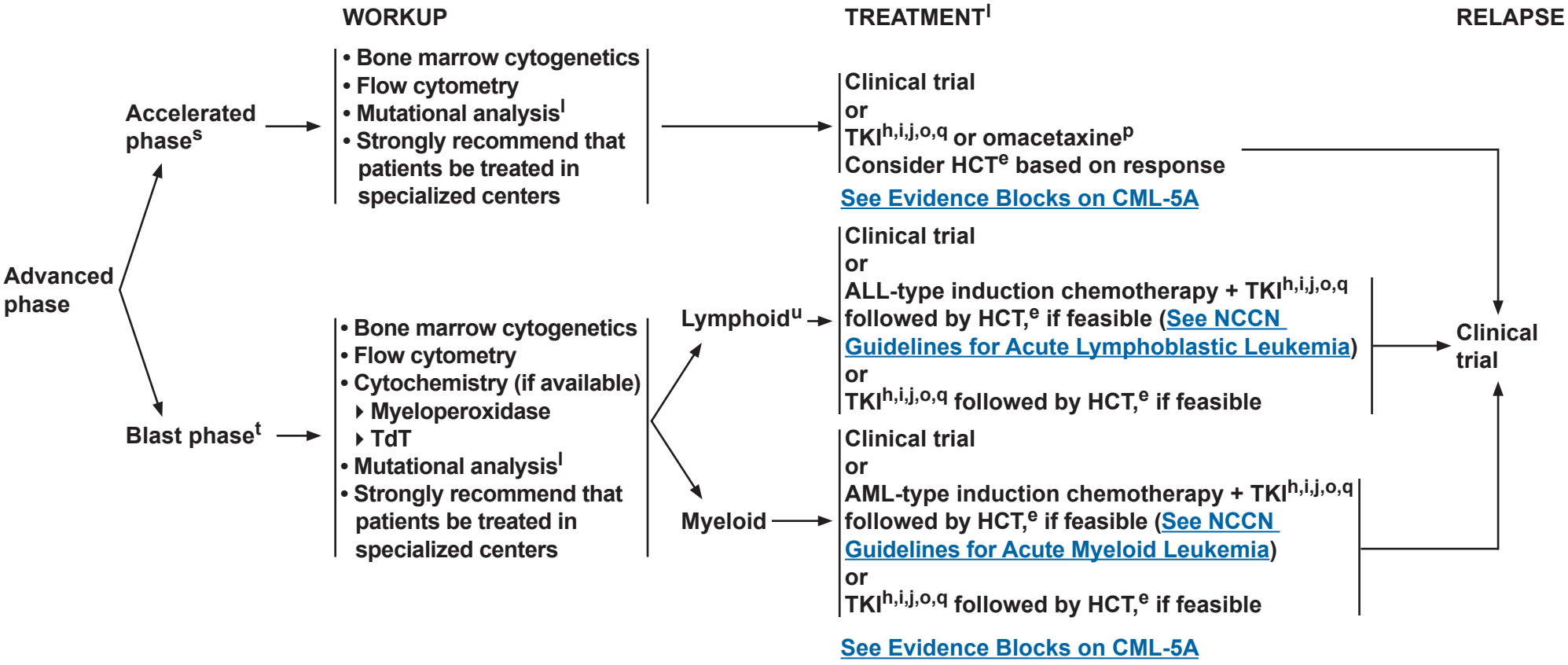

[e]HCT = hematopoietic stem cell transplantation. Indications and outcomes of allogeneic HCT are dependent on age and comorbidities, donor type, and transplant center.
[h]See Management of Imatinib Toxicity (CML-D).
[i]See Management of Nilotinib Toxicity (CML-E).
[j]See Management of Dasatinib Toxicity (CML-F).
[l]The selection of TKI is based on prior therapy and/or mutational testing. There are some data regarding the efficacy of second-generation TKIs against specific mutations. See Management of Cytogenetic or Hematologic Resistance to TKIs (CML-6).
[o]See Management of Bosutinib Toxicity (CML-G).
[p]Omacetaxine is a treatment option for patients with disease that is resistant and/or intolerant to two or more TKIs. See Management of Omacetaxine Toxicity (CML-H).
[q]Ponatinib is a treatment option for patients with a T315I mutation or for patients with disease that has not responded to 2 or more TKI therapies. See Management of Ponatinib Toxicity (CML-I).
[s]See Definitions of Accelerated Phase (CML-K).
[t]See Definitions of Blast Crisis (CML-L).
[u]Consider CNS prophylaxis/treatment.

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EVIDENCE BLOCKS FOR TKI THERAPY FOR ADVANCED PHASE

	ACCELERATED PHASE	BLAST PHASE
Bosutinib		
Dasatinib		
Imatinib		
Nilotinib		
Ponatinib		
Omacetaxine		N/A

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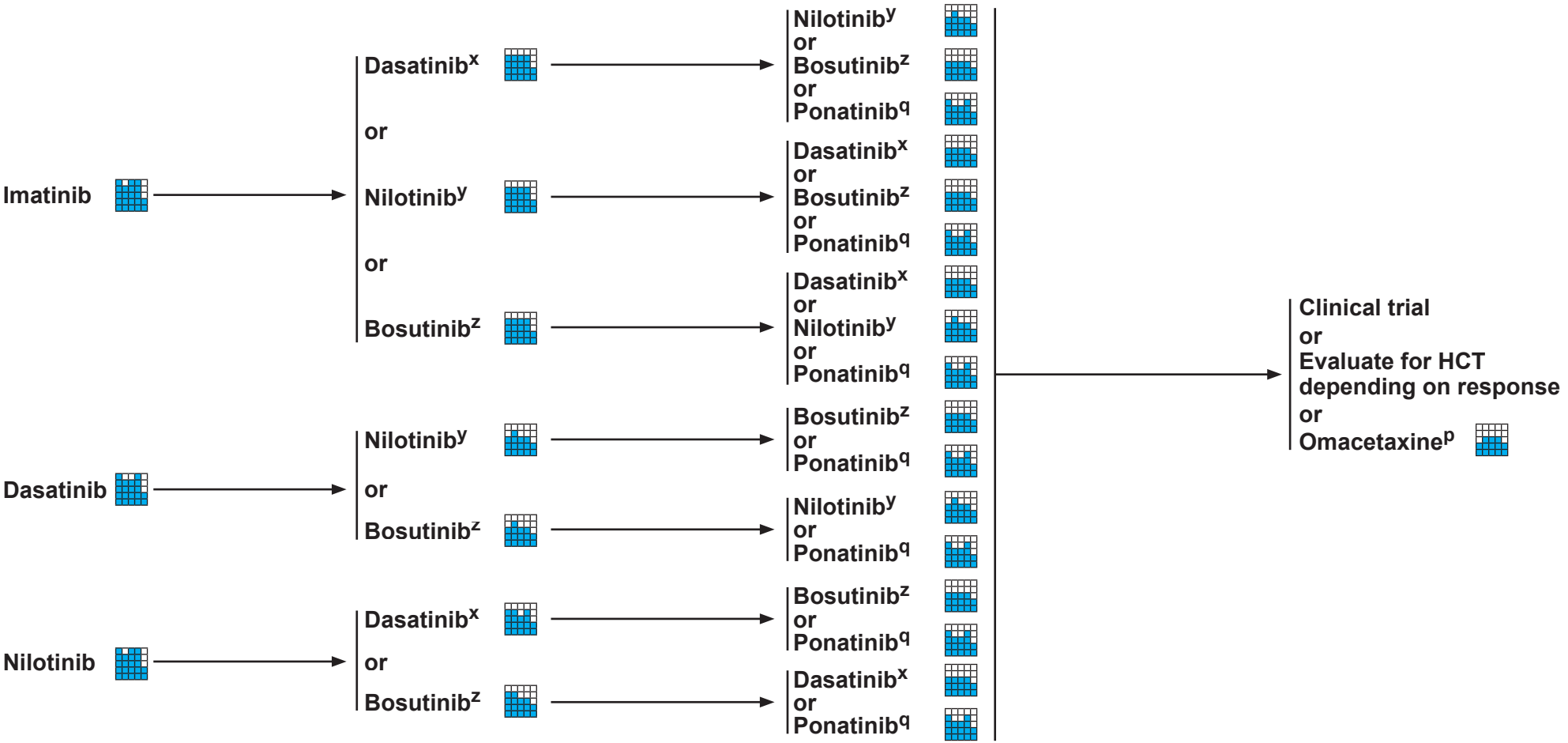
MANAGEMENT OF CYTOGENETIC OR HEMATOLOGIC RESISTANCE TO TKIs[v]

PRIMARY TREATMENT

SECOND-LINE AND SUBSEQUENT THERAPY[w]



[p]Omacetaxine is a treatment option for patients with disease that is resistant and/or intolerant to two or more TKIs. See Management of Omacetaxine Toxicity (CML-H).

[q]Ponatinib is a treatment option for patients with a T315I mutation or for patients with disease that has not responded to 2 or more TKI therapies. See Management of Ponatinib Toxicity (CML-I).

[v]Patients with disease that is resistant to first-line imatinib should be treated with nilotinib, dasatinib, or bosutinib in the second-line setting. Patients with disease that is resistant to first-line nilotinib or dasatinib could be treated with an alternate TKI (other than imatinib) in the second-line setting.

[w]Consider clinical trial, ponatinib, omacetaxine, or HCT for patients with a T315I mutation.

[x]For patients with mutations Y253H, E255K/V or F359V/C/I.

[y]For patients with mutations F317L/V/I/C, T315A or V299L.

[z]For patients with mutations E255K/V, F317L/V/I/C, F359V/C/I, T315A or Y253H.

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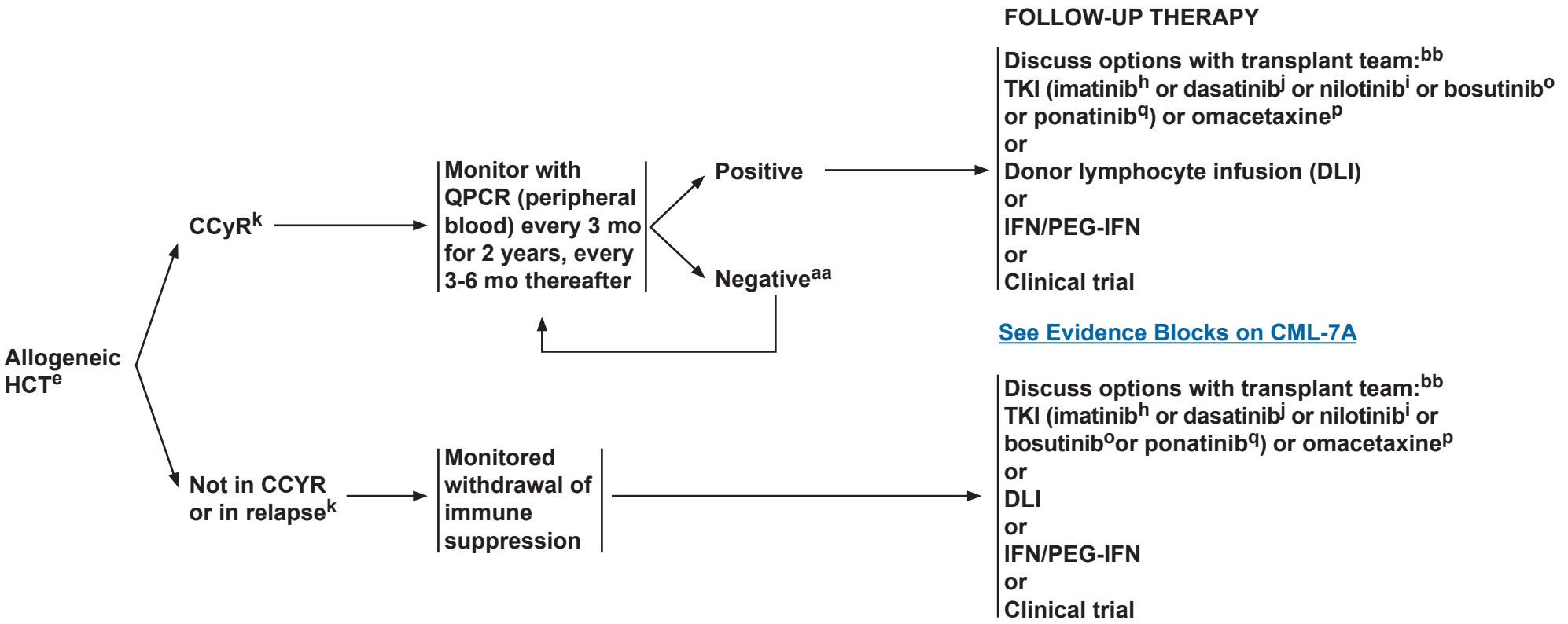

[e]HCT = hematopoietic stem cell transplantation. Indications and outcomes of allogeneic HCT are dependent on age and comorbidities, donor type, and transplant center.
[h]See Management of Imatinib Toxicity (CML-D).
[i]See Management of Nilotinib Toxicity (CML-E).
[j]See Management of Dasatinib Toxicity (CML-F).
[k]See Criteria for Hematologic, Cytogenetic, and Molecular Response and Relapse (CML-J).
[o]See Management of Bosutinib Toxicity (CML-G).
[p]Omacetaxine is a treatment option for patients with disease that is resistant and/or intolerant to two or more TKIs. See Management of Omacetaxine Toxicity (CML-H).
[q]Ponatinib is a treatment option for patients with a T315I mutation or for patients with disease that has not responded to 2 or more TKI therapies. See Management of Ponatinib Toxicity (CML-I).
[aa]In patients with prior accelerated or blast phase, consider TKI therapy post HCT for at least one year.
[bb]There are data to support the use of posttransplant imatinib but not in patients who have disease that previously failed imatinib. Other TKIs may be more appropriate. Very limited data are available on the use of dasatinib and nilotinib in a small number of patients with posttransplant relapse. There are no data for the use of bosutinib, or omacetaxine for patients posttransplant. In patients who have disease that has failed prior TKI therapy, see CML-6 for the selection of posttransplant TKI.

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EVIDENCE BLOCKS FOR RELAPSE OR FAILURE TO ACHIEVE CCyR FOLLOWING ALLOGENEIC HCT

	CHRONIC PHASE	ACCELERATED PHASE	BLAST PHASE
Bosutinib			
Dasatinib			
Imatinib			
Nilotinib			
Ponatinib			
Omacetaxine			
IFN alfa 2a			
IFN alfa 2b			
PEG IFN 2a			
PEG IFN 2b			

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MONITORING RESPONSE TO TKI THERAPY AND MUTATIONAL ANALYSIS[1]

Test	Recommendation
Bone marrow cytogenetics[2]	• At diagnosis to establish the disease phase. If collection of bone marrow is not feasible, FISH on a peripheral blood specimen using dual probes for the *BCR* and *ABL* genes is an acceptable method of confirming the diagnosis of CML. • At 3 and 6 months from initiation of therapy if QPCR using IS is not available to assess response to TKI therapy. • At 12 months from initiation of therapy, if CCyR or MMR is not achieved. Absence of MMR in the presence of a CCyR is not considered a treatment failure. • 1-log increase in *BCR-ABL1* transcript levels without MMR.
Quantitative RT-PCR (QPCR) using IS	• At diagnosis • Every 3 months after initiating treatment. After CCyR 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 analysis should be repeated in 1–3 months.
BCR-ABL kinase domain mutation analysis	• Chronic phase ▸ Inadequate initial response to TKI therapy (lack of PCyR or *BCR-ABL1* transcripts >10% (IS) at 3 and 6 months or less than a CCyR or *BCR-ABL1* transcripts >1% (IS) at 12 months). ▸ 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.

See CML-5 for Disease progression to accelerated or blast phase CML

[1]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(1):28-37.
[2]FISH has been inadequately studied for monitoring response to treatment.

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RISK CALCULATION TABLE

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

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

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

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

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

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SUPPORTIVE CARE STRATEGIES FOR LEUKOCYTOSIS AND THROMBOCYTOSIS

Factors to consider when choosing treatment include: patient's age, risk factors for thromboembolic disease, and degree of thrombocytosis.

Symptomatic leukocytosis:

- **Treatment options include hydroxyurea, apheresis, imatinib, dasatinib, nilotinib, or clinical trial**

Symptomatic thrombocytosis:

- **Treatment options include hydroxyurea, antiaggregants, anagrelide, or apheresis**

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MANAGEMENT OF IMATINIB TOXICITY[1,2]

Dose Adjustments:

Hematologic Toxicities

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

Non-Hematologic Toxicities

- **Bilirubin >3 x institutional upper limit of normal (IULN) or liver transaminases >5 x IULN: hold imatinib until bilirubin <1.5 x IULN and transaminase levels <2.5 x IULN. Resume imatinib at a reduced daily dose (400 mg to 300 mg, 600 mg to 400 mg, or 800 mg to 600 mg).**
- **Severe hepatotoxicity or severe fluid retention: hold imatinib until the event has resolved. Treatment can be resumed as appropriate depending on the severity of the event.**
- **Patients with moderate renal impairment (CrCL = 20–39 mL/min) should receive 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 (pleural effusion, pericardial effusion, edema, and ascites): diuretics, supportive care, dose reduction, interruption, or discontinuation. Consider echocardiogram to check LVEF.**
- **GI upset: Take medication with a meal and large glass of water.**
- **Muscle cramps: calcium supplement, tonic water**
- **Rash: topical or systemic steroids, dose reduction, interruption, or discontinuation**

[1]Please refer to package insert for full prescribing information and monitoring of hematologic or biochemical abnormalities, available at www.fda.gov.
[2]Many toxicities are self-limiting; consider re-escalating dose at a later time.
[3]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.
[4]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 NILOTINIB TOXICITY[1]

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

QT Interval Prolongation

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

Dose Adjustments:

Hematologic Toxicities

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

Non-Hematologic Toxicities

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

Hepatic impairment:

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

Glucose:

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

Rare But Serious Toxicities

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

Specific Interventions

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

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

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MANAGEMENT OF DASATINIB TOXICITY[1]

Dose Adjustments:

Hematologic Toxicities

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

Non-Hematologic Toxicities

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

Rare But Serious Toxicities

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

Specific Interventions

- **Fluid retention events (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/day x 3-4 days, may taper with 20 mg/day x 3-4 days); when resolved, reduce one dose level.**
- **GI upset: Take medication with a meal and large glass of water.**
- **Rash: topical or systemic steroids, dose reduction, interruption, or discontinuation**

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

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MANAGEMENT OF BOSUTINIB TOXICITY[1]

Dose Adjustments:

Hematologic Toxicities

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

Non-Hematologic Toxicities

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

Special Populations

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

Specific Interventions

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

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

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MANAGEMENT OF OMACETAXINE TOXICITY[1]

Dose Adjustments:

Hematologic Toxicities

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

Non-Hematologic Toxicities

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

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

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MANAGEMENT OF PONATINIB TOXICITY[1]

- **Vascular occlusion: Arterial and venous thrombosis and occlusions, including fatal myocardial infarction and stroke have occurred in patients treated with ponatinib. Monitor for evidence of thromboembolism and vascular occlusion. Interrupt or stop ponatinib immediately for vascular occlusion.**
- **Heart failure has occurred in patients treated with ponatinib. Monitor cardiac function. Interrupt or stop ponatinib for new or worsening heart failure.**
- **Hepatotoxicity: Hepatotoxicity, liver failure, and death have occurred in patients treated with ponatinib. Monitor hepatic function prior to and during treatment. Interrupt ponatinib if hepatotoxicity is suspected.**
- **Cardiovascular risk: Identify and control traditional risk factors for atherosclerosis (e.g. diabetes mellitus [DM], hypertension, hyperlipidemia, smoking, estrogen use) before starting ponatinib. Patients with cardiovascular risk factors should be referred to a cardiologist.**
- **Ponatinib is also associated with grade ≥3 skin rash and pancreatitis leading to dose modifications (dose delays or dose reductions).**

Dosing

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

Dose Adjustments:

Hematologic Toxicities

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

Non-Hematologic Toxicities

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

Rare But Serious Toxicities

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

Specific Interventions

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

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

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

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CRITERIA FOR HEMATOLOGIC, CYTOGENETIC, AND MOLECULAR RESPONSE AND RELAPSE

Complete hematologic response[1]

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

Cytogenetic response[2,3]

- Complete Cytogenetic Response (CCyR) - No Ph-positive metaphases
- Partial Cytogenetic Response (PCyR) - 1%–35% Ph-positive metaphases
- Major Cytogenetic Response - 0%–35% Ph-positive metaphases (complete + partial)
- Minor Cytogenetic Response - >35% Ph-positive metaphases

Molecular response[4,5]

- Early molecular response (EMR) - *BCR-ABL1* transcripts ≤10% by QPCR (IS) at 3 and 6 months.
- Major molecular response (MMR) - *BCR-ABL1* transcripts 0.1% by QPCR (IS) or ≥3-log reduction in *BCR-ABL1* mRNA from the standardized baseline, if QPCR (IS) is not available.
- Complete molecular response (CMR) - no detectable BCR-ABL mRNA by QPCR (IS) using an assay with a sensitivity of at least 4.5 logs below the standardized baseline. CMR is variably described, and is best defined by the the assay's level of sensitivity (eg. MR 4.5).

Relapse

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

[1]Faderl S et al: Chronic myelogenous leukemia: Biology and therapy. Ann Intern Med 1999;131:207-219. The American College of Physicians-American Society of Internal Medicine is not responsible for the accuracy of the translation.
[2]A minimum of 20 metaphases should be examined.
[3]O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 2003;348:994-1004.
[4]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.
[5]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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DEFINITIONS OF ACCELERATED PHASE[1,2]

Modified Criteria Used at MD Anderson Cancer Center[3,4] (most commonly used in clinical trials)	World Health Organization (WHO) Criteria[5] (most commonly used by pathologists)
• Peripheral blood blasts ≥15% and <30% • Peripheral blood blasts and promyelocytes combined ≥30% • Peripheral blood basophils ≥20% • Platelet count ≤100 x 10^9/L unrelated to therapy • Clonal evolution	• Blasts 10%–19% of WBCs in peripheral and/or nucleated bone marrow cells • Peripheral blood basophils ≥20% • Persistent thrombocytopenia (<100 x 10^9/L) unrelated to therapy, or persistent thrombocytosis (>1000 x 10^9/L) unresponsive to therapy • Increasing spleen size and increasing WBC count unresponsive to therapy • Cytogenetic evidence of clonal evolution

[1]The table refers to myeloblasts. Any increase in lymphoblasts is concerning for (nascent) blast crisis.
[2]Sokal criteria (Sokal JE, Baccarani M, Russo D, et al. Staging and prognosis in chronic myelogenous leukemia. Semin Hematol 1988;25:49-61) and IBMTR criteria (Savage DG, Szydlo RM, Chase A, et al. Bone marrow transplantation for chronic myeloid leukemia: The effects of differing criteria for defining chronic phase on probabilities of survival and relapse. Br J Haematol 1997;99:30-35) are historically used when HCT is the recommended treatment option.
[3]Kantarjian HM, Deisseroth A, Kurzrock R, et al. Chronic myelogenous leukemia: A concise update. Blood 1993;82:691-703.
[4]Talpaz M, Silver RT, Druker BJ, et al. Imatinib induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: results of a phase 2 study. Blood 2002;99:1928-1937.
[5]Adapted from Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW (Eds.): World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC Press: Lyon 2008.

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DEFINITIONS OF BLAST CRISIS

World Health Organization (WHO) Criteria[1]	International Bone Marrow Transplant Registry[2]
• Blasts ≥20% of peripheral white blood cells or of nucleated bone marrow cells • Extramedullary blast proliferation • Large foci or clusters of blasts in the bone marrow biopsy	• ≥30% blasts in the blood, marrow, or both • Extramedullary infiltrates of leukemic cells

[1]Adapted from Swerdlow SH, Campo E, Harris NL, et al. WHO classification of Tumours of Haematopoietic and Lymphoid Tissues, IARC, Lyon, 2008.
[2]Druker BJ. Chronic Myelogenous Leukemia In: DeVita VT, Lawrence TS, Rosenburg SA, eds. DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology. Vol. 2 (ed 8): Lippincott, Williams and Wilkins; 2007:2267-2304.

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Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

Table of Contents

Overview

Chronic myelogenous 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 2015, an estimated 6.660 people will be diagnosed with CML in the United States, and 1,140 people will die from the disease.[1]

CML is characterized by the presence of Philadelphia chromosome (Ph) resulting from a reciprocal translocation between chromosomes 9 and 22 [t(9;22]. This translocation t(9;22) results in the head-to-tail fusion of the breakpoint cluster region (*BCR)* gene on chromosome 22 at band q11 and the Abelson murine leukemia (*ABL1*) gene located on chromosome 9 at band q34.[2] The product of the *BCR-ABL1* fusion gene (p210), a fusion protein with deregulated tyrosine kinase activity, plays a central role in the pathogenesis of CML. Another fusion protein, p190, is also produced, usually in the setting of Ph-positive acute lymphoblastic leukemia (ALL). p190 is detected only in 1% of patients with CML.[3]

The oncogenic potential of the BCR-ABL1 fusion proteins has been validated by their ability to transform hematopoietic progenitor cells *in vitro* and *in vivo*. The mechanisms by which p210 promotes the transition from a benign state to a malignant state are not entirely understood. However, attachment of the *BCR* sequences to *ABL1* results in three critical functional changes: 1) the ABL1 protein becomes constitutively active as a protein tyrosine kinase enzyme; 2) the DNA protein binding activity of ABL1 is attenuated; and 3) the binding of ABL1 to cytoskeletal actin microfilaments is enhanced. These effects increase proliferation, affect differentiation, and block apoptosis.

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

The NCCN Guidelines for CML discuss the clinical management of CML in all three phases (chronic, accelerated or blast phase).

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for Chronic Myelogenous Leukemia, an electronic search of the PubMed database was performed to obtain key literature in Chronic Myelogenous Leukemia published between July 2014 and July 2015 using the following search terms: chronic myeloid (or myelogenous) leukemia, chronic phase, accelerated phase, blast phase, advanced phase, tyrosine kinase inhibitors, BCR-ABL1 mutations, response, monitoring, adherence and discontinuation. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[7]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial,

Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 28 citations and their potential relevance was examined. The data from key PubMed articles selected by the panel for review during the Guidelines update meeting as well as articles from additional sources deemed as relevant to these Guidelines have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

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

Tyrosine Kinase Inhibitor Therapy

Imatinib

Imatinib is a selective inhibitor of the BCR-ABL1 tyrosine kinase.[8,9] Initial clinical trials evaluated the efficacy of imatinib as second-line therapy for patients with CP-CML that had not responded to interferon or those with AP-CML or BP-CML.[10] At 5-year follow-up, complete cytogenetic response (CCyR) was seen in 41% of patients and 44% of patients remained on imatinib. Estimated rates of freedom from progression (FFP) to accelerated or blast phase and overall survival (OS) at 6 years were 61% and 76%, respectively.[11]

Newly diagnosed patients were evaluated in the IRIS trial. In this trial, 1106 patients were randomized to receive initial therapy with either imatinib 400 mg or interferon-alpha plus low-dose cytarabine.[12] Crossover was allowed for treatment failure or intolerance. With a median follow-up of 19 months, the best observed major cytogenetic response (MCyR) rate was 85.2% in the imatinib group compared to 22.1% in the interferon plus cytarabine group ($P < .001$).The CCyR rate was 73.8% and 8.5%, respectively ($P < .001$). The estimated rate of FFP was significantly higher in the imatinib than in the interferon plus cytarabine arm (96.7% and 91.5%, respectively; $P < .001$). Imatinib was also much better tolerated than the combination of interferon plus cytarabine.

In May 2001, the U.S. Food and Drug Administration (FDA) first approved imatinib mesylate for the advanced stages of CML. In December 2002, based on the results of the IRIS study, imatinib was approved for the first-line treatment of patients with CML.

Long-term follow-up data of the IRIS trial are now available.[13,14] With a median follow-up of 60 months, the best observed MCyR and CCyR rates were 89% and 82%, respectively. Only 7% of patients had progressed to accelerated or blast phase and the OS rate was 89%.[13] The estimated 8-year event-free survival (EFS), FFP to accelerated or blast phase, and OS were 81%, 92%, and 85%, respectively.[14] Major molecular response (MMR) rate increased from 24% at 6 months to 39% at 12 months, and the best observed MMR rate was 86% with 8-year follow-up. None of the patients with documented MMR at 12 months progressed to accelerated or blast phase. These results demonstrate that imatinib induces high durable responses with a decreasing rate of relapse in a large proportion of patients with CP-CML. However, due to the high rate of crossover (90%) from interferon-alpha to imatinib within a year of study, survival benefit for imatinib vs. interferon could not be demonstrated in the IRIS trial. In historical comparisons, survival benefit was significantly better for imatinib compared to interferon.[15,16] Recently, Guilhot and colleagues reported the safety and efficacy of imatinib in 359 patients who crossed over from interferon-alpha plus cytarabine to imatinib in the IRIS study.[17] After a median follow-up of 54 months on imatinib, 93%

achieved complete hematologic response (CHR); MCyR and CCyR were observed in 86% and 81% of patients, respectively. Estimated rates of FFP to accelerated or blast phase and OS were 91% and 89%, respectively, at 48 months after starting imatinib.

Toxicity

Imatinib is generally well tolerated. Frequently reported grade 3 or 4 hematologic toxicities include neutropenia and thrombocytopenia. Most frequently reported non-hematologic adverse events include gastrointestinal disturbances, edema, rash, and musculoskeletal complaints, but none of these led to discontinuation of treatment.[18] Skin hypopigmentation has also been reported to be a benign side effect of imatinib and is reversible upon discontinuation or dose reduction.[19,20] In a recent report, chronic fatigue (mostly correlated with musculoskeletal pain and muscular cramps) was identified as a major factor limiting health-related quality of life in patients with CML treated with imatinib.[21] Hypophosphatemia (with associated changes in bone and mineral metabolism) and decrease in bone mineral density has been noted in a small group of patients, suggesting that ongoing management of patients taking imatinib should include monitoring bone health.[22,23]

In a recent trial, long-term treatment with imatinib was associated with congestive heart failure (CHF) and cardiotoxicity.[24] However, this appears to be very rare, as shown by the recent analysis of 1276 patients treated with imatinib at MD Anderson Cancer Center.[25] After a median follow-up of 47 months, 22 (1.7%) patients were found to have CHF during imatinib therapy. Out of these patients, 13 had received prior treatment with cardiotoxic drugs. The authors concluded that CHF is uncommon among patients receiving imatinib, and its incidence rates are similar to those that occur in the general population. Patients with previous cardiac history should be monitored carefully. Aggressive medical therapy is recommended for symptomatic patients. Electrocardiogram (ECG) should be considered for patients taking QT interval-prolonging medication.

High-dose Imatinib

Several studies have evaluated the efficacy of high-dose imatinib in newly diagnosed patients.[26-30] Imatinib 600 or 800 mg daily was well tolerated and was also associated with significantly better cytogenetic and molecular response rates.[26]

The investigators of the TIDEL trial also reported superior response rates (MMR at 12 and 24 months were 55% and 77%, respectively) in patients receiving imatinib 600 mg as the initial dose compared to those receiving less than 600 mg (MMR at 12 and 24 months were 32% and 53%, respectively).[27]

In a phase II multicenter study, newly diagnosed patients (n = 115; 70% Sokal low-risk) treated with imatinib 400 mg twice daily achieved rapid and deep responses.[28] CHR at 6, 12, and 18 months was achieved and maintained in 93%, 94%, and 93% of evaluable patients, respectively. The rate of MCyR at 12 and 18 months was 90% and 96%, respectively, and the corresponding CCyR rates were 85% and 83%, respectively. MMR rates were 48% and 54% at 6 months and 12 months, respectively. The response rates were also higher in this trial compared to historic controls that received 400 mg daily in the IRIS trial. At 12 months, MMR was 54% for patients in the RIGHT trial compared with an estimated 39% for the historical control group. At 18 months, MCyR and CCyR rates were 90% and 85%, respectively, in the RIGHT trial compared with 85% and 74%, respectively, in the historical control group in the IRIS trial.

The TOPS trial is an open-label, phase III, randomized trial comparing the efficacy of higher-dose imatinib and standard-dose imatinib in patients with newly diagnosed CP-CML.[29] This trial randomized 476 patients to receive either high-dose imatinib (800 mg; 400 mg twice daily) or standard-dose imatinib (400 mg once daily). High-dose imatinib was well tolerated in most patients and was also associated with more rapid responses than the standard dose. However, MMR and CCyR at 12 months were comparable between arms (MMR: 46% vs. 40%, respectively; CCyR: 70% vs. 66%, respectively). In patients with high Sokal risk scores, MMR rates at 12 months were 51% for high-dose imatinib compared to 31% for standard-dose imatinib. The MMR rate also correlated with average dose intensity. At 12 months, MMR was observed in 83 (62%) of 134 patients with an average dose intensity of 600 to 799 mg/day, and it was observed in 26 (38%) of 69 patients with an average dose intensity of 400 to 599 mg/day. At a medium follow-up of 42 months, MMR rates were similar in both treatment arms (51.6% and 50.2 % for 400 mg and 800 mg, respectively; *P* = .77). High-dose imatinib (in patients who were able to tolerate ≥600 mg/day) resulted in faster and higher response rates. However, there were no differences in OS, EFS or PFS rates between treatment arms but adverse events were more frequent with high-dose imatinib.[31]

The German CML IV study (1,551 patients) also reported significantly faster response rates with imatinib 800 mg as compared to imatinib 400 mg with or without interferon.[30] The incidence of MMR at 12 months was also significantly higher with imatinib 800 mg/day (59% vs. 44% and 46% for imatinib 800 mg, imatinib 400 mg, and imatinib 400 mg with interferon, respectively). More rapid achievement of MMR with imatinib 800 mg was observed in low- and intermediate-risk patients, but not in high-risk patients. At 3 years, the OS (95%) and progression-free survival (PFS) (94%) rates for all patients were not different between treatment arms. After a median follow-up of 67.5 months, the 5-year OS and PFS rates were 90% and 87.5% respectively. Deeper molecular response (MR 4.5; ≥ 4.5 log reduction of *BCR-ABL1* (IS) as determined by quantitative reverse transcriptase polymerase chain reaction [QPCR] in 2 consecutive analyses) was reached more quickly with optimized high-dose imatinib than with imatinib 400 mg/day (*P* = .016). Independent of treatment approach, confirmed MR4.5 (*BCR-ABL1* ≤0.0032% [IS]) at 4 years was a predictor of significantly higher survival probabilities than a response of 0.1% to 1% IS (8-year OS rates were 92% v 83% respectively; *P* = .047).[32]

The results of another randomized intergroup phase II study (SWOG S0325) that compared imatinib 800 mg and imatinib 400 mg in newly diagnosed patients with CP-CML also reported similar findings. More patients in the imatinib 800 mg arm achieved deeper molecular responses at 12 months (4-log reduction of BCR-ABL1 mRNA: 25% vs. 10% respectively, *P* = .038; 3-log reduction: 53% vs. 35%, respectively; *P* = .049). CCyR rates were also higher in patients treated with imatinib 800 mg (85% vs. 67% respectively; *P* =.040). However, as reported in previous studies, grade 3-4 toxicities were more common with imatinib 800 mg (58% vs. 31%; *P* = .0007).[33]

The efficacy of imatinib 800 mg as front-line therapy in intermediate and high Sokal risk patients with CP-CML was evaluated by the GIMEMA CML Working Party and the European LeukemiaNet (ELN) Study Group, respectively.[34,35] The results of the phase II trial by the GIMEMA CML Working Party indicated that high-dose imatinib is effective in inducing rapid cytogenetic and molecular responses in intermediate Sokal risk patients.[34] The response rates at 12 months were better than

those documented in the IRIS study for intermediate-risk patients treated with 400 mg imatinib. The ELN Study, which randomized high Sokal risk patients to receive 800 mg or 400 mg of imatinib, did not show a significant benefit for high-dose imatinib.[35] The CCyR at one year was 64% and 58% for high- and standard-dose imatinib, respectively. No differences were detectable in CCyR rates at 3 and 6 months or in the molecular response rates at any time.

In newly diagnosed patients, high-dose imatinib induces higher and faster CCyR and MMR compared to standard-dose imatinib early on, but there is no difference in response rates between the two arms at 12 months. Imatinib 800 mg has not been shown to have lower rates of disease progression than standard-dose imatinib in any of the studies, despite improved early responses. High-dose imatinib is associated with higher rates of dose interruption, reduction, or discontinuation in a substantial number of patients due to grade 3 or 4 adverse events. However, the data suggest that patients who can actually tolerate the higher dose of imatinib do achieve better response rates than those receiving standard-dose imatinib.

Dasatinib

Dasatinib is a potent, orally available small-molecule dual inhibitor of ABL1 and SRC family of kinases. Dasatinib has an added advantage in that it can bind to both the active and inactive conformation of the ABL1 kinase domain. As a result, dasatinib is active against nearly all *BCR-ABL1* mutations resistant to imatinib, except T315I.[36]

First-line Therapy

The efficacy and safety of dasatinib as first-line therapy for newly diagnosed patients with CP-CML was first confirmed in a phase II trial.[37] Fifty patients with newly diagnosed CP-CML were randomly assigned to dasatinib 100 mg once daily or 50 mg twice daily. With a median follow-up of 24 months, 98% of evaluable patients had achieved CCyR and 82% had achieved MMR. In historical comparison, the CCyR rates at 3, 6, and 12 months were comparable to those achieved with high-dose imatinib and better than those achieved with standard-dose imatinib.[37] There were no significant differences in response rate and toxicity between the two arms, and the median dose at 12 months was 100 mg.

The efficacy and safety of dasatinib (100 mg once daily) and imatinib (400 mg once daily) among patients with newly diagnosed CP-CML were compared in a multinational randomized study (DASISION trial). In this study, 519 patients with newly diagnosed CP-CML were randomized to receive dasatinib (100 mg once daily; 259 patients) or imatinib (400 mg once daily; 260 patients).[38] After a minimum follow-up of 12 months, the confirmed CCyR (77% vs. 66%, respectively) and MMR (46% vs. 28%) rates were higher for dasatinib than for imatinib. Responses were achieved in a shorter time with dasatinib. The CCyR rates at 3, 6, and 9 months after initiation of therapy were 54%, 73%, and 78%, respectively, for dasatinib, and the corresponding response rates were 31%, 59%, and 67%, respectively, for imatinib. The rates of MMR at 3, 6, and 9 months after dasatinib treatment were 8%, 27%, and 39%, respectively, and the corresponding rates for imatinib were 0.4%, 8%, and 18%, respectively.[38] Although there was a trend in favor of dasatinib, progression to the accelerated or blast phase was not statistically different between the two groups; 5 patients on dasatinib (2%) and 9 patients who were receiving imatinib (3.5%) met the definition of progression (transformation to accelerated or blast phase, death as a result of any cause or loss of CHR or MCyR).The safety profiles were similar in both treatment arms.

In October 2010, based on the results of the DASISION trial, the FDA approved dasatinib (100 mg once daily) for the treatment of adult patients with newly diagnosed Ph-positive CP-CML.

Long-term follow-up data confirmed that dasatinib induces faster and deeper cytogenetic and molecular responses in newly diagnosed patients with CP-CML with fewer progressions to accelerated or blast phase.[39,40] In the final 5-year analysis, the rates of CCyR (83% vs 78; *P* =.187), MMR (*BCR-ABL1* ≤0.1% [IS]; 76% vs 64%; *P* =.002) and MR4.5 (42% vs 33%; *P* =.025) were higher with dasatinib than with imatinib.[40] The proportion of patients achieving *BCR-ABL1* ≤10% (IS) at 3 months was also higher in the dasatinib arm (84% vs. 64%). Fewer patients transformed to accelerated or blast phase on dasatinib (12 patients; 4.6%) than on imatinib (19 patients; 7.3%). The 5-year PFS (85% and 86%, respectively for dasatinib and imatinib) and OS (91% and 90%, respectively for dasatinib and imatinib) rates were not different between the treatment groups. MMR rates were also higher with dasatinib across all the risk groups (as determined by Hasford score).[39] MMR rates for dasatinib were 73%, 61%, and 57% for patients with low, intermediate, and high risk scores. The corresponding MMR rates for imatinib were 56%, 50%, and 38%, respectively.

In the Intergroup phase II randomized trial (S0325; n = 250), dasatinib (100 mg once daily) induced more complete cytogenetic and deeper molecular responses, compared with imatinib (400 mg once daily) in patients with newly diagnosed CP-CML.[41] The molecular response rates (3-log reductions in *BCR-ABL1* transcript level) at 12 months were 59% and 44%, respectively, for dasatinib and imatinib (*P* = .059); and with a median follow-up of 3 years, the OS and PFS were similar in both arms.

Second-line Therapy

In a phase I dose escalation study, dasatinib induced hematologic and cytogenetic responses in patients with CML or Ph-positive ALL intolerant to imatinib or those with resistant disease.[42] This result led to the initiation of several phase II studies (START trial) of dasatinib in imatinib-resistant Ph-positive leukemias. Resistance to imatinib was defined as an absence of a CHR within 3 to 6 months, an absence of a MCyR at 12 months, or disease progression following prior response to imatinib. Dasatinib was administered at 70 mg twice daily on a continuous basis. Interruption of treatment and dose modifications were allowed for the management of disease progression or toxicity after one cycle of treatment.

The START-C trial evaluated dasatinib (70 mg twice daily) in 387 patients with CP-CML intolerant to imatinib or those with resistant disease.[43,44] After a median follow-up of 15.2 months, CHR, MCyR, and CCyR were observed in 91%, 59%, and 49% of patients, respectively; only 3% of patients experienced disease progression after achieving MCyR. The 15-month PFS and OS rates were 90% and 96%, respectively.[44]

In the dose-optimization randomized study (CA180-034), dasatinib dosed at 100 mg once daily was equally as effective as 70 mg twice daily in patients (n = 167) with CP-CML intolerant to imatinib or those with resistant disease.[45,46] At 24 months, the CCyR (50% vs. 54%), MCyR (63% vs.61%), PFS (80% vs. 76%), and OS (91% and 88%) rates for patients who received dasatinib 100 mg once daily were comparable to those seen in patients who received dasatinib at 70 mg twice daily.[46] The incidences of grade 3/4 toxicities (pleural effusion [2% vs. 5%] and thrombocytopenia [23% vs. 38%]) were also lower with 100 mg daily dose, and fewer patients required dose interruption (62% vs.

77%), dose reduction (39% vs. 62%), and toxicity-related discontinuation (16% vs. 23%). Long-term follow-up data confirmed the safety and durability of cytogenetic responses in patients with CP-CML intolerant to imatinib or those with resistant disease treated with dasatinib 100 mg once daily.[47,48] At 7-year follow-up, the MMR, PFS, and OS rates were 46%, 42%, and 65%, respectively.[48] The rate of progression to accelerated or blast phase was 6% (n =10) and the estimated 6-year survival rate without transformation was 76%.[47]

Based on the results of this study, the FDA has approved 100 mg once daily as the recommended starting dose of dasatinib for patients with CP-CML intolerant to imatinib or those with resistant disease.

Dasatinib is associated with higher response rates and EFS when administered early after imatinib failure.[49] In the retrospective analysis of data from phase II studies of dasatinib in patients with CP-CML intolerant to imatinib or those with resistant disease, EFS was higher for those who went on dasatinib after the loss of MCyR on imatinib than those who received dasatinib after the loss of both MCyR and CHR (89% and 29%, respectively).[49]

The efficacy of high-dose imatinib and dasatinib was evaluated in a phase II trial (START-R) in which 150 patients with CP-CML resistant to imatinib were randomized to receive 140 mg (70 mg twice a day) of dasatinib or 800 mg of imatinib.[50,51] In the initial report from the START-R trial, dasatinib was clearly superior to 800 mg of imatinib in patients with CP-CML that had not responded to treatment with 600 mg of imatinib, whereas response rates were equivalent for high-dose imatinib and dasatinib in patients with CP-CML that had failed treatment with 400 mg of imatinib.[50] However, the 2-year follow-up data suggested that dasatinib is clearly superior to imatinib 800 mg in patients with CP-CML that is resistant to imatinib at doses of 400 or 600 mg daily.[51] At a minimum follow-up of 2 years, dasatinib demonstrated higher rates of CHR (93% vs. 82%), MCyR (53% vs. 33%), and CCyR (44% vs. 18%) compared to high-dose imatinib. MMR was also more frequent with dasatinib than with high-dose imatinib (29% vs. 12%) and the estimated PFS also favored dasatinib, indicating that dasatinib is an effective treatment for patients with CP-CML resistant to standard-dose as well as high-dose imatinib.

The START-A trial evaluated the safety and efficacy of dasatinib (70 mg twice daily) in patients with AP-CML intolerant to imatinib or those with resistant disease.[52] At 8-month follow-up (for the first 107 patients enrolled in the study), major hematologic response (MaHR) was achieved in 64% of patients, MCyR was achieved in 33% of the treated population, and 76% of patients remained progression-free. Follow-up data from the full patient cohort of 174 patients have confirmed the efficacy and safety of dasatinib in patients with AP-CML intolerant to imatinib or those with resistant disease.[53] The 12-month PFS and OS rates were 66% and 82%, respectively.

The efficacy of dasatinib in patients with CML in myeloid blast crisis (MBC) or in lymphoid blast crisis (LBC) intolerant to imatinib or those with resistant disease was evaluated in START-B and START-L trials, respectively.[54] In patients with MBC-CML, 32% had achieved MaHR at 6-month follow-up, which increased to 34% at 8-month follow-up and was maintained at 12-month follow-up.[55] MCyR was achieved in 31% of patients. In the LBC-CML group, 31% achieved MaHR at 6-month follow-up, and this rate increased to 35% at 12-month follow-up.[55] After a minimum follow-up of 12 months, MCyR was achieved in 33% (MBC-CML) and 52% (LBC-CML) of patients and CCyR was achieved in 26 and 46% of patients, respectively. Median PFS and OS for

patients with MBC were 6.7 and 11.8 months, respectively. In patients with LBC, the corresponding survival rates were 3.0 and 5.3 months, respectively.[55]

Kantarjian et al recently reported that once-daily dosing of dasatinib at 140 mg has similar efficacy to 70 mg twice-daily dosing with an improved safety profile in patients with AP-CML.[56] Recently, 2-year follow-up data from a phase III trial showed that dasatinib 140 mg once daily demonstrates equivalent efficacy and improved safety compared with 70 mg twice daily in patients with BP-CML.[57]

Toxicity

Dasatinib is also well tolerated. Nonhematologic adverse events are mild to moderate and cytopenias, although more common, are manageable with dose modification. ECG should be considered for patients taking QT interval-prolonging medications. See “Management of Dasatinib Toxicity” in the guidelines. Dasatinib, however, is associated with significant but reversible inhibition of platelet aggregation that may contribute to bleeding in some patients receiving the drug.[58]

Pleural effusion can be an adverse effect of dasatinib.[59,60] In an analysis of 138 patients with CML treated with varying doses of dasatinib in phase I and phase II studies, pleural effusion occurred in 29% of patients with CP-CML, 50% of patients with AP-CML, and 33% of patients with BP-CML.[59] Pleural effusion led to dose interruption in 83% of patients and dose reduction was necessary in 71% patients. Patients with prior cardiac history, patients with hypertension, and those receiving twice-daily dosing of dasatinib at 70 mg are at increased risk of developing pleural effusion. In the dose-optimization study (CA180-034), the occurrence of pleural effusion was significantly minimized with dasatinib 100 mg once daily compared with 70 mg twice daily.[60] Close monitoring and timely intervention are necessary for patients at risk of developing pleural effusion.

Reversible pulmonary arterial hypertension has been reported as a rare but serious side effect associated with dasatinib.[61-66] 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 should be permanently discontinued.

Lymphocytosis from the clonal expansion of NK/T-cells has been reported during dasatinib treatment in patients with all stages of CML intolerant to imatinib or those with resistant disease, and it has been associated with increased incidence of pleural effusion and improved cytogenetic response rates.[67-70] Further studies are needed to confirm these preliminary findings.

The recommended starting dose of dasatinib is 100 mg once daily for patients with CP-CML and 140 mg once daily for patients with AP-CML or BP-CML. However, the minimum effective dose has not been established in randomized clinical trials. Data from case reports and retrospective analysis suggest that lower doses of dasatinib may potentially have similar efficacy as the standard dose.[71,72] In one report, among patients with intolerance to standard dose dasatinib, initiation of treatment at a reduced daily dose induced CCyR in a similar time frame compared to the standard dose dasatinib.[71] The median dose of dasatinib until achievement of CCyR was 60 mg daily (range = 20 to 120 mg). In a retrospectively analysis of 280 patients with all phases of CML, among patients that had a dose reduction, the median lowest daily dose of dasatinib was 60mg (range 20–80mg) in patients with

CP-CML and 80mg (range 20–100mg) in patients in advanced phase CML.[72] In another small study, treatment interruption of dasatinib at standard dose and reintroduction of dasatinib at a lower dose of 40 mg twice daily resolved all pulmonary complications without recurrence.[73] These data suggest that initiation of dasatinib at 50 mg (20 mg with careful monitoring in selected patients) should be considered for patients with clinically significant intolerance to high-dose dasatinib to avoid serious adverse events (eg. pleural effusion and myelosuppression) necessitating the discontinuation of dasatinib.

Nilotinib

Nilotinib is a highly selective inhibitor of BCR-ABL1 tyrosine kinase that is more potent than imatinib (20–50 times more potent in imatinib-resistant cell lines and 3–7 times more potent in imatinib-sensitive cell lines).

First-line Therapy

The efficacy and safety of nilotinib as first-line therapy in early chronic phase patients were initially evaluated in 2 separate phase II studies.[74,75] Nilotinib at 400 mg twice daily induced high rates of CCyR and MMR, with most patients reaching these responses early during their therapy.

In a phase III, randomized, open-label, multicenter trial (ENESTnd trial), the efficacy and safety of nilotinib (300 mg twice daily; n = 282 or 400 mg twice daily; n = 281) was compared with that of imatinib (400 mg once daily; n = 283) in patients with newly diagnosed CP-CML.[76] At 12 months, the MMR (the primary endpoint) rates were 44%, 43%, and 22%, respectively, for nilotinib (300 mg and 400 mg) and imatinib. The CCyR rates by 12 months (80% for the 300 mg dose and 78% for the 400 mg dose vs. 65% for imatinib) were also higher for nilotinib than for imatinib. Patients receiving nilotinib at either of the two dose levels had a significant improvement in the time to progression to the accelerated or blast phase, as compared with those receiving imatinib. The rate of progression to accelerated or blast phase was 4% with imatinib and less than 1% with nilotinib (P = .01 for the 300 mg and P = .004 for the 400 mg). Progression was defined as transformation to accelerated or blast phase or CML-related death. Superior rates of CCyR and MMR were observed in both nilotinib arms compared with the imatinib arm across all Sokal risk groups. Among patients with a high Sokal risk, CCyR rates by 12 months were 74%, 63%, and 49% among patients receiving 300 mg of nilotinib, 400 mg of nilotinib, and 400 mg of imatinib, respectively.[76] MMR at 12 months in these patients was 41%, 32%, and 17% for patients receiving 300 mg of nilotinib, 400 mg of nilotinib, and 400 mg of imatinib, respectively. The 300 mg dose of nilotinib had the lowest rate of discontinuation due to adverse events or laboratory abnormalities among the 3 study groups.

In June 2010, based on the results of the ENESTnd trial, FDA approved nilotinib (300 mg twice daily) for the treatment of adult patients with newly diagnosed Ph-positive CP-CML.

Long-term follow-up data confirmed that nilotinib induces superior molecular responses in patients with newly diagnosed CML, with significantly fewer progressions to accelerated or blast phase.[77-80] At 5 years, significantly more patients in the nilotinib arms achieved MMR (77% for nilotinib 300 mg and 400 mg twice daily vs. 60% for imatinib 400 mg once daily; P < .0001) and MR4.5 (54% for nilotinib 300 mg twice daily, 52% for nilotinib 400 mg twice daily vs. 31% for imatinib 400 mg once daily; P < .0001).[80] Fewer patients progressed to accelerated or blast phase in the nilotinib arm (10 patients treated with nilotinib 300 mg twice daily and 6 patients treated with nilotinib 400 mg twice daily)

than in the imatinib arm (21 patients). The 4-year OS rates were 94.3%, 96.7%, and 93.3%, respectively. The corresponding 4-year PFS rates were 92.7%, 96.3% and 92%, respectively.[79] The rates of early molecular response (EMR) and MR4.5 at 5 years were significantly higher for nilotinib across all the Sokal risk groups.[80] The EMR rates for nilotinib 300 mg were 93%, 92%, and 86% for patients with low-, intermediate-, and high-risk scores.[78] The corresponding EMR rates for imatinib were 79%, 70%, and 44%, respectively. MR4.5 rates were 53%, 60% and 45% for nilotinib 300 mg for patients with low-, intermediate-, and high-risk scores. The corresponding rates for imatinib were 37%, 33% and 27% respectively.

Second-line Therapy

In a phase I study, nilotinib was found to be active in imatinib-resistant CML with a favorable safety profile.[81] Following this study, a phase II open-label trial evaluated the safety and efficacy of nilotinib (400 mg twice daily) in patients with CP-CML (n = 280) and AP-CML (n = 119) intolerant to imatinib or those with resistant disease.[82,83] The efficacy endpoint for CP-CML was MCyR and the endpoint for AP-CML was MaHR.

In patients with CP-CML, at 6-month follow-up, MCyR was observed in 48% of patients and CCyR was observed in 31% of patients.[82] Long-term follow-up results from this study confirmed that these responses are durable with no change in safety profile.[84,85] At the 2-year follow-up, the overall MMR, MCyR, and CCyR rates were 28%, 59%, and 44% of patients, respectively, and the responses were durable with 84% maintaining CCyR and 77% maintaining MCyR at 24 months.[84] MCyR, MMR, and PFS rates were higher in patients with CHR at study entry (73%, 38%, and 77%, respectively) compared to 52%, 22%, and 56%, respectively, among patients without CHR at study entry. At 48 months, patients with baseline CHR had a significantly higher PFS rate than those without baseline CHR (71% vs. 49%, respectively; *P* = .001) and the estimated PFS and OS rates at 48 months were 57% and 78%, respectively.[85]

In patients with AP-CML, hematologic response was observed in 47% of patients and MCyR was observed in 29% of patients.[83] OS rate among the 119 patients after 12 months of follow-up was 79%. Non-hematologic adverse events were mostly mild to moderate. Grade 3 or higher bilirubin and lipase elevations occurred in 9% and 18% of patients. Long-term follow-up results confirmed that nilotinib induces rapid and durable responses with a favorable risk/benefit profile in patients with AP-CML who were intolerant or resistant to prior imatinib.[86] Among patients with at least 24-month follow-up (n = 137), confirmed hematologic response was observed in 55% of patients and 31% had CHR (30% of patients with AP-CML resistant to imatinib and 37% of patients intolerant to imatinib achieved CHR). MCyR and CCyR were achieved in 32% and 20% of patients, respectively. Cytogenetic and molecular responses were also durable, with 66% of patients maintaining MCyR at 24 months and 83% of patients maintaining CCyR at 12 months. The estimated PFS and OS rates at 24 months were 70% and 33%, respectively.[86]

Nilotinib has also been evaluated in patients with BP-CML. In a phase II study of 136 patients (MBC, n = 105; LBC, n = 31), after a minimum follow-up of 24 months, MaHR was observed in 60% of patients with MBC and 59% of patients with LBC.[87] MCyR was achieved in 38% of patients with MBC and 52% of patients with LBC. CCyR was seen in 30% of patients with MBC and 32% of patients with LBC. The OS rate was 42% at 12 months and 27% at 24 months. However, the responses

were not durable. The duration of MCyR was 11 months for patients with MBC and 3 months for those with LBC.

Nilotinib (400 mg twice daily) is approved for the treatment of patients with CP-CML and AP-CML intolerant to imatinib or those with resistant disease. However, it is not yet approved for the treatment of patients with BP-CML.

Toxicity

Nilotinib was rarely associated with fluid retention, edema, or muscle cramps. Neutropenia and thrombocytopenia (grade 3-4) were reported only in 29% of patients with CP-CML. Grade 3 or 4 elevations in lipase and bilirubin, hypophosphatemia, and hyperglycemia were observed in 17%, 8%, 16%, and 12% of patients with CP-CML, respectively. Patients with a previous history of pancreatitis may be at greater risk of elevated serum lipase. However, these abnormalities were transient and clinically asymptomatic. See *Management of Nilotinib Toxicity* in the guidelines.

QT interval prolongation is a nonhematologic adverse reaction associated with nilotinib, which could be managed with dose reduction. 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. Electrolyte abnormalities should be corrected prior to initiation of treatment with nilotinib and should be monitored periodically. Drugs that prolong QT interval should be avoided. ECG should be obtained to monitor the QT interval at baseline, 7 days after initiation of nilotinib and periodically thereafter, as well as following any dose adjustments.

Nilotinib may be associated with an increased risk of vascular adverse events, including peripheral arterial occlusive disease (PAOD).[88-90] 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.

Bosutinib

Bosutinib, a member of the dual ABL1/SRC family of kinases, has demonstrated activity against many of the BCR-ABL1 kinase domain mutations resistant to imatinib, dasatinib, and nilotinib, except T315I, with minimal inhibition of KIT and PDGFR.[91,92]

First-line Therapy

The phase III randomized trial (BELA trial) compared the efficacy of bosutinib (n = 250; 500 mg once daily) with imatinib (n = 252; 400 mg once daily) in newly diagnosed patients with CP-CML.[93,94] At 24 months, bosutinib was associated with a higher MMR rate (47% vs. 41% for imatinib; $P < .001$; cumulative MMR rates were 59% and 49% respectively), fewer transformations to AP-CML or BP-CML (2% vs. 4% on imatinib), and faster times to CCyR and MMR. However, this trial did not meet its primary endpoint of CCyR at 12 months. The CCyR rates at 12 months were 70% and 68%, respectively, for bosutinib and imatinib ($P = .601$). Bosutinib is currently not recommended as first-line therapy for newly diagnosed patients with CP-CML.

Second-line Therapy

The safety and efficacy of bosutinib (500 mg once daily) was evaluated in a single-arm multicenter phase I-II trial, in a total of 570 patients with CML intolerant to prior TKI therapy or those with resistant disease (288 patients with CP-CML following prior imatinib only; 118 patients with CP-CML pretreated with imatinib followed by dasatinib and/or nilotinib;

164 patients with AP-CML, BP-CML and ALL).[95-99] The primary endpoint was MCyR at 24 weeks for patients with CP-CML and CHR by 8 weeks for patients with advanced phase CML and ALL.

An open-label phase I-II study evaluated bosutinib as second-line therapy in 288 patients with CP-CML treated with imatinib alone (196 patients with CP-CML resistant to imatinib and 90 patients intolerant to imatinib).[97] After a median follow-up of 48 months, CHR, MCyR, and CCyR were achieved in 86%, 59%, and 49% of patients, respectively and the 2-year OS rate was 91% (88% for patients with CP-CML resistant to imatinib and 98% for patients intolerant to imatinib). At 4 years, the cumulative incidence of disease progression (transformation to AP-CML or BP-CML, increasing white blood cell count or loss of confirmed CHR or unconfirmed MCyR) was 22% for patients with CP-CML resistant to imatinib and 10% for patients intolerant to imatinib. The 36-month follow-up data confirmed the durable efficacy and tolerability of bosutinib in patients with CP-CML resistant to more than one TKI therapy.

In the cohort of 119 patients with CP-CML pretreated with more than one TKI (imatinib followed by dasatinib and/or nilotinib), with a median follow-up of 28.5 months, CHR, MCyR, and CCyR were achieved in 73%, 32%, and 24% of patients, respectively.[96] In a subgroup analysis of 33 patients who were in CCyR, MMR, and CMR were observed in 49% (16 of 33) and 36% (12 of 33) of patients, respectively. The median duration of MCyR and CHR has not been reached at the time of median follow-up. Patients intolerant to dasatinib had a trend towards higher rates of CHR (67% vs. 50%), CCyR (28% vs. 14%), and MMR (25% vs. 3%) compared to those with CP-CML resistant to dasatinib. The rate of disease progression to AP-CML and BP-CML was 4% and 0%, respectively. The estimated PFS and OS rates at 2 years were 73% and 83%, respectively. The 48-month follow-up data also confirmed the efficacy and safety of bosutinib as third-line therapy in patients with CP-CML resistant to prior TKI therapy (imatinib followed by dasatinib and/or nilotinib).[100]

Long-term efficacy and safety data (≥4 years follow-up) showed that bosutinib induces hematologic and MCyR in the cohort of patients with advanced phase CML (AP-CML, n = 79 and BP-CML, n = 64) with and without *BCR-ABL1* mutations.[99] Among patients with AP-CML evaluable for response, overall hematologic response and MCyR were attained or maintained in 57% and 40% of patients, respectively.[99] The corresponding response rates in patients with BP-CML evaluable for response were 28% and 37%, respectively. Responses were durable in approximately 50% of patients with AP-CML at 4 years; approximately 25% of patients with BP-CML responded at one year.

Based on the results of this study, the FDA approved bosutinib (500 mg once daily) for the treatment of patients in all three phases of CML intolerant to prior TKI therapy or those with resistant disease.

Toxicity

Bosutinib has a favorable toxicity profile. Diarrhea, nausea, vomiting, and rash were the most common non-hematologic grade 1 or 2 adverse events.[95,96,99,101] Grade 3 or 4 diarrhea and rash were reported in 10% and 9% of patients, respectively. Thrombocytopenia (25%), neutropenia (18%), and anemia (14%) were the most common grade 3 or 4 hematologic toxicities. Bosutinib was also associated with minimal effects on QTc interval prolongation and a low incidence of pleural effusions, muscle cramps, musculoskeletal events, and cardiac toxicities that may be seen with other TKIs. See *Management of Bosutinib Toxicity* in the guidelines for specific interventions.

Ponatinib

Ponatinib is a potent, orally available multitargeted kinase inhibitor active against many of the BCR-ABL1 kinase domain mutations including T315I.[102]

A single-arm, multicenter, phase II trial (PACE trial) evaluated the safety and efficacy of ponatinib (45 mg once daily) in a total of 449 patients with CML intolerant to prior TKI therapy or those with resistant disease (dasatinib or nilotinib) or with the T315I mutation (270 patients with CP-CML; 85 patients with AP-CML; 62 patients with BP-CML; 32 patients with Ph-positive ALL).[103] The primary endpoint was MCyR at any time within 12 months after initiation of treatment in patients with CP-CML and MaHR at any time within 6 months after initiation of treatment for patients with advanced phase CML. The median follow-up was 15 months.

In the cohort of patients with CP-CML, ponatinib induced durable MCyR, CCyR, and MMR in 56%, 46%, and 34% of patients respectively.[103] Among patients who achieved MCyR, responses were durable in 91% of patients at 12 months. The estimated PFS and OS rates at 12 months were 80% and 94%, respectively. The response rates were higher in patients with T315I mutation (MCyR, CCyR, and MMR rates were 70%,66%, and 56% in patients with T315I mutation; the corresponding response rates were 51%, 40%, and 27%, respectively, in patients intolerant to prior TKI and for those with CP-CML resistant to prior TKI).[103]In a post hoc analysis, younger age in patients with T315I mutation, exposure to fewer prior TKIs, and shorter duration of leukemia were identified as predictors of response. Response rates were higher in patients who were exposed to fewer prior TKIs (MCyR, CCyR, and MMR rates were 84%, 79%, and 53%, respectively, for patients treated with one prior TKI compared to 46%, 38%, and 29%, respectively, for those treated with 3 prior TKIs).[103] The difference in MCyR rates were statistically significant between the groups (P = .003), whereas the differences in MMR rates were not statistically significant (P = .062). At a median follow-up of 27.9 months, the overall MCyR, CCyR, and MMR rates were 59%, 53%, and 38% respectively.[104] The 2-year MCyR duration, PFS and OS rates were 87%, 67% and 86%, respectively.

Among patients with AP-CML intolerant to dasatinib or nilotinib or those with resistant disease, MaHR by 6 months was observed in 57% of patients. MCyR, CCyR, and MMR rates were 34%, 22%, and 14%, respectively.[103] The corresponding response rates were 50%, 56%, 33%, and 22%, respectively, for patients with T315I mutation. The estimated PFS and OS rates at 12 months were 55% and 84%, respectively. Among patients with BP-CML intolerant to dasatinib or nilotinib or those with resistant disease, MaHR, MCyR, and CCyR were observed in 32%, 18%, and 16% of patients, respectively.[103] The corresponding response rates were 29%, 29%, and 21%, respectively, for patients with T315I mutation. The estimated PFS and OS rates at 12 months were 19% and 29%, respectively. Longer term follow-up data also confirmed the activity of ponatinib in patients with AP-CML and BP- CML.[104] The estimated 2-year OS rates were 72% and 18%, respectively, for patients with AP-CML and BP-CML.

Toxicity

The most common non-hematologic adverse events were rash (34%), dry skin (32%) and abdominal pain (22%).[103] Thrombocytopenia (37%), neutropenia (19%), and anemia (13%) were the most common grade 3-4 hematologic toxicities. Clinical pancreatitis resulting in discontinuation of treatment has been reported in patients treated with ponatinib. Routine monitoring of serum lipase (every 2 weeks for the

first 2 months and then monthly thereafter or as clinically indicated) is recommended. Dose reduction or interruption may be required. Thrombocytopenia, neutropenia, and pancreatitis were typically reported early in treatment and were managed with dose modification. Ponatinib was also associated with fluid retention events (edema, ascites, pleural and pericardial effusion), which could be managed with dose interruption, dose reduction, or discontinuation of ponatinib as clinically indicated.

Hepatotoxicity, liver failure, and death have been rarely reported in patients treated with ponatinib. Liver function tests should be done at baseline, and at least monthly or as clinically indicated during treatment. Dose interruption and dose reductions or discontinuation of ponatinib should be considered for hepatotoxicity. Serious arterial thrombotic events were observed in 9% of patients (cardiovascular events 5.1%, cerebrovascular events 2.4%, and peripheral vascular events 2.0%) and these events were considered to be treatment-related in 3% of patients (cardiovascular, cerebrovascular, and peripheral vascular events occurred in 2.0%, 0.4%, and 0.4% of patients, respectively).[103]

Based on the results of the PACE trial, the FDA approved ponatinib for the treatment of patients in all three phases of CML intolerant to prior TKI therapy or those with resistant disease. However, the recent Drug Safety Communication issued by the FDA on October 31st, 2013 has revealed an increase in the cumulative incidence of serious arterial thrombotic events.[105] Serious arterial and venous thrombosis and occlusions occurred in approximately 27% of patients: cardiovascular occlusion, cerebrovascular occlusion and peripheral arterial occlusive events occurred in 12%, 6% and 8% of patients respectively. Heart failure, including fatalities, occurred in 8% of patients. These adverse events were seen in patients with and without cardiovascular risk factors (such as history of ischemia, hypertension, diabetes, or hyperlipidemia).[106]

Ponatinib is now indicated only for the treatment of patients with T315I mutation and for the treatment patients for whom no other TKI therapy is indicated in all three phases of CML. Ponatinib labeling also contains a black box warning regarding vascular occlusion, heart failure and hepatotoxicity. Cardiovascular risk factors (eg. diabetes mellitus, hypertension, hyperlipidemia, smoking, estrogen use) should be identified and controlled before starting ponatinib. Patients should be monitored for evidence of thromboembolism and vascular occlusion. Ponatinib should be interrupted or stopped immediately for vascular occlusion and for new or worsening heart failure. Patients with cardiovascular risk factors should be referred to a cardiologist.

The guidelines recommend consideration of ponatinib for patients with a T315I mutation and for patients with disease that has not responded to two or more TKIs. See “Management of Cytogenetic and Hematologic Resistance to TKIs” in the guidelines.

The recommended initial dose of ponatinib is 45 mg once daily. Dose intensity of ponatinib is significantly associated with increased risk of adverse events.[107] Therefore, dose modifications may be necessary for the management of adverse events. In the post hoc analysis that assessed the clinical impact of dose modification and dose intensity on outcomes of patients treated with ponatinib in the PACE study, dose intensity was also the most significant predictor of MCyR by 12 months.[108] However substantial responses were observed at lower dose levels. The estimated MCyR rates were approximately 75% at 45 mg, 60% at 30 mg, and 30% at 15 mg. Thus, an initial dose of 30 mg

may be a safer and effective dose for patients with cardiovascular risk factors. Safety and efficacy of ponatinib at initial doses lower than 45 mg are being evaluated in a randomized clinical trial.

Management of Hematologic Toxicities of TKI therapy

Cytopenias (anemia, neutropenia and thrombocytopenia) are the most common hematologic toxicities associated with TKI therapy. These complications should be managed with transient interruptions of TKI therapy and dose modifications. Please refer to the package insert for full prescribing information available at www.fda.gov, for the recommended dose modifications of specific TKI therapy.

The use of growth factor support has been shown to be effective for the management of TKI-induced cytopenias.[109-111] In a recent report, 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.[112]

Routine monitoring of reticulocyte count, ferritin, iron saturation, B12 and folate and correction of nutritional deficiencies if present, is recommended for patients with grade 3-4 anemia. Transfusion support should be used in symptomatic patients. Growth factor support can be used in combination with TKI therapy for the management of neutropenia and thrombocytopenia.[110,111] 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.

TKI Therapy and Conception

Imatinib, dasatinib and nilotinib have been shown to be teratogenic and are known to cause embryonic or fetal toxicities in animal studies. There are some reports in the literature regarding the outcome of pregnancy in patients receiving TKI therapy at the time of conception.[113-124] Rare instances of congenital malformations and spontaneous abortions remain a cause of concern. [118,119]

In the report by Ault and colleagues, of the 10 women who discontinued imatinib due to pregnancy, 6 had an increase in Ph-positive metaphases. Only 3 women had CCyR at 18 months after resuming therapy.[116] Pye and colleagues reported the outcome of pregnancies in 180 women exposed to imatinib during pregnancy. Fifty percent of pregnancies with known outcome were normal and 10% of pregnancies with known outcome had fetal abnormalities.[118] Eighteen pregnancies ended in spontaneous abortion. In a report from Cortes and colleagues involving 16 patients, among the 8 female patients who became pregnant while on dasatinib, induced or spontaneous abortion was reported in 3 and 2 patients, respectively.[119] The outcome and pregnancy course in the other 3 patients was normal. Among the 8 male patients treated with dasatinib whose partners became pregnant while on treatment, normal pregnancy was reported for 7 cases and the outcome was unknown in one case.[119]

At the present time, enough evidence is not available to favor the continuation of TKI therapy during pregnancy. Potential benefit of TKI therapy for the mother and the potential risk to the fetus of continuing TKI therapy vs. the risk of treatment interruption leading to the loss of optimal disease response must be carefully evaluated on an individual basis prior to initiation of TKI therapy in pregnant women. Consultation with high-risk obstetrician is recommended. Fertility preservation should be discussed with all patients of childbearing age prior to the initiation of TKI therapy.

Drug Interactions

Imatinib, dasatinib, nilotinib, bosutinib, and ponatinib are extensively metabolized in the liver by cytochrome P450 (CYP) enzymes. Drugs that induce or inhibit CYP3A4 or CYP3A5 enzymes may alter the therapeutic effect of TKIs.[125] Drug interactions between TKIs and some of the concomitantly prescribed drugs are summarized below. Please refer to the package insert for full prescribing information and drug interactions, available at www.fda.gov.

Imatinib

CYP3A4 or CYP3A5 inducers such as anticonvulsants and steroids may decrease the therapeutic plasma concentration of imatinib. Conversely, CYP3A4 inhibitors enzyme activity and drugs that are metabolized by the CYP3A4 or CYP3A5 enzyme might result in increased plasma levels of imatinib. Imatinib is also a weak inhibitor of the CYP2D6 and CYP2C9 isoenzymes; therefore, drugs metabolized by these enzymes should be used with caution in patients receiving imatinib, and appropriate alternatives should be explored to maximize treatment outcome.

Dasatinib

CYP3A4 inducers may decrease plasma concentration of dasatinib. CYP3A4 inhibitors and drugs that are metabolized by this enzyme may increase the concentration of dasatinib. Therefore, concomitant administration with CYP3A4 inhibitors or inducers should be avoided. If coadministration cannot be avoided, a dose adjustment and close monitoring for toxicity should be considered. In addition, the solubility of dasatinib is pH-dependent, and long-term suppression of gastric acid secretion reduces dasatinib exposure. Concomitant use with H2 blockers or proton pump inhibitors (PPIs) is not recommended.

Nilotinib

CYP3A4 inducers may decrease nilotinib plasma concentrations. If nilotinib needs to be administered with a CYP3A4 inducer, dose increase should be considered. Concomitant administration of strong inhibitors of CYP3A4 may increase the plasma concentration of nilotinib. If coadministration cannot be avoided, nilotinib should be interrupted or dose reduction should be considered. In addition, nilotinib is a competitive inhibitor of CYP2C8, CYP2C9, CYP2D6, and UGT1A1, potentially increasing the plasma concentrations of drugs eliminated by these enzymes.

Bosutinib

CYP3A4 inducers and PPIs may decrease bosutinib plasma concentrations. Concomitant administration of strong or moderate CYP3A inducers with bosutinib should be avoided. The use of short-acting antacids or H2 blockers instead of PPIs should be considered to avoid reduction in bosutinib plasma concentrations. Concomitant use of strong or moderate inhibitors of CYP3A4 should also be avoided since these drugs may increase the plasma concentration of bosutinib.

Ponatinib

CYP3A4 inducers may decrease ponatinib plasma concentrations. Coadministration of strong CYP3A inducers with ponatinib should be avoided unless the benefit outweighs the possible risk of ponatinib underexposure. CYP3A4 inhibitors may increase the plasma concentration of ponatinib. Dose reduction to 30 mg is recommended when ponatinib has to be coadministered with strong CYP3A inhibitors. Elevated gastric pH may reduce the bioavailability of ponatinib. Coadministration of ponatinib with drugs that could elevate the gastric

pH (PPIs, H2 blockers, or antacids) should be avoided unless the benefit outweighs the possible risk of ponatinib underexposure.

Workup

Initial evaluation of patients with CML should include a history and physical (H&P), including palpation of spleen, complete blood count (CBC) with differential, chemistry profile, bone marrow aspirate, and biopsy.

Bone marrow cytogenetics and measurement of *BCR-ABL1* transcript levels by QPCR is recommended before initiation of treatment as well as for monitoring response to therapy.[126] Bone marrow cytogenetics not only provides morphologic review, but also detects chromosomal abnormalities other than Ph chromosome that are not detectable using peripheral blood.

The guidelines emphasize that conventional bone marrow cytogenetics should be done to confirm the diagnosis of Ph-positive CML at initial workup. If collection of bone marrow 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 for confirming the diagnosis of CML.

BCR-ABL1 transcripts in the peripheral blood at very low levels (1–10 out of 10^8 peripheral blood leukocytes) can also be detected in approximately 30% of normal individuals.[127,128] In addition, it has also been demonstrated that the incidence of *BCR-ABL1* transcripts in healthy individuals increases with advancing age.[127] TKI therapy would not be warranted, since the vast majority of these individuals would not develop CML.

The guidelines recommend determination of risk score and human leukocyte antigen (HLA) testing as part of initial workup.

Sokal and Hasford are the two prognostic scoring systems available for the risk stratification of patients with CML.[129,130] Both of these scoring systems stratify patients into three risk groups (low, intermediate, and high) and have been used for the risk stratifications of patients in clinical trials evaluating tyrosine kinase inhibitors (TKIs). The Sokal score is based on the patient's age, spleen size, platelet count, and percentage of blasts in the peripheral blood.[129] The Hasford model includes eosinophils and basophils in the peripheral blood in addition to the same clinical variables used in the Sokal model.[130]

In 2011, the European Treatment and Outcome Study (EUTOS) score (based only on the percentage of basophils in the blood and on spleen size) was developed and its predictive value was confirmed in a validation study of 2060 patients enrolled in studies of first-line treatment with imatinib-based regimens.[131] In this study, EUTOS score was better than Sokal and Hasford score in predicting the probability of achieving CCyR at 18 months and 5-year PFS. However, the predictive value of EUTOS score has not been confirmed in subsequent studies by other investigators.[132-134] Additional studies are necessary to confirm the importance of EUTOS score in predicting clinical outcomes of patients receiving TKI therapy.

Patients with *BCR-ABL1*-positive CML (by bone marrow cytogenetics, FISH, or QPCR) are the focus of the NCCN Guidelines for CML. Patients who are *BCR-ABL1*-negative do not have CML. Patients who clearly do not have a myeloproliferative neoplasm (MPN; polycythemia vera, essential thrombocythemia and primary myelofibrosis), have clinical features suggestive of CML, but do not have *BCR-ABL1* may

have a so-called “Ph-negative” or “atypical CML”, and these patients have a significantly worse prognosis than those with *BCR-ABL1*-positive CML.[135]

In ambiguous cases of *BCR-ABL1*-negative MPNs, further mutational analysis may help document clonality and define the entity. For example, mutations involving multiple genes such as *JAK2*, *MPL*, *CALR, TET2*, *ASXL1*, *CBL*, *EZH2*, *IDH*, *DNMT3A, LNK, RAS* and *IKZF1* have been described in *BCR-ABL1*-negative MPNs.[136-140] *TET2*, *ASXL1*, *CBL*, *IDH, RAS, LNK* and *IKZF1* mutations are more common in chronic myelomonocytic leukemia, myelodysplastic syndromes (MDS) and blast phase MPNs.[136,137,141] *JAK2, CALR* and *MPL* mutations are the most frequent mutations detected in *BCR-ABL1*-negative MPNs including polycythemia vera, essential thrombocythemia and primary myelofibrosis.[140,141] *EZH2* mutations have been detected more frequently in patients with MDS and primary myelofibrosis.[142] More recently, activating mutations in the *CSF3R* and *SETBP1* genes have been identified in chronic neutrophilic leukemia and atypical CML (Ph-negative).[143,144] Abnormalities in fibroblast growth factor receptor 1 (*FGFR1*) and platelet-derived growth factor receptor (*PDGFRA* and *PDGFRB*) genes have been reported in a subset of patients with atypical MPNs that are usually associated with eosinophilia.[145]

Chronic Phase CML

Primary Treatment

Imatinib (400 mg once daily) is still recommended as a reasonable first-line therapy (category 1) for newly diagnosed patients with CP-CML. Based on the recent FDA approval of nilotinib (300 mg twice daily) and dasatinib (100 mg once daily), the guidelines have also included nilotinib or dasatinib as first-line therapy options (category 1) for newly diagnosed patients. This recommendation is based on the long-term data from randomized trials demonstrating that dasatinib and nilotinib are associated with superior cytogenetic and molecular response rates at certain time points and lower rates of disease progression compared to imatinib.[39,40,78,80]

Preliminary data from DASISION and ENESTnd studies also suggest that intermediate- and high-risk patients (as determined by Sokal or Hasford scores) may preferentially benefit from dasatinib or nilotinib since they are associated with lower risk of disease progression in this patient population.[39,78] Longer-term follow-up is needed to determine whether dasatinib and nilotinib should be implemented as standard first-line therapy in such a risk-adapted fashion.

In general, the choice of first-line therapy in a given patient may depend on the risk score, physician’s experience, age, ability to tolerate therapy, and the presence of comorbid conditions. Since both dasatinib and nilotinib have very good efficacy in the upfront setting, differences in their potential toxicity profiles may be helpful in the selection of a second-generation TKI over imatinib as first-line therapy. For example, nilotinib may be preferred for patients with a history of lung disease or deemed to be at risk of developing pleural effusions. Alternatively, dasatinib may be preferred in patients with a history of arrhythmias, heart disease, pancreatitis, or hyperglycemia.

Given the recent data showing superior efficacy of nilotinib and dasatinib in newly diagnosed patients, high-dose imatinib is currently not recommended as initial therapy for patients with newly diagnosed CML. The NCCN Member Institutions believe that interferon should no longer be considered as initial therapy for patients with newly diagnosed CML. In patients treated with interferon, CCyR is achieved in

10% to 15% of patients with a median survival of more than 10 years and some of these patients may actually be cured.[146,147] However, EFS benefit is seen mainly in low-risk patients with a CCyR.[148] In phase II/III studies, pegylated interferon-alpha 2a and alpha 2b have been shown to be active as initial treatment in patients with CP-CML.[149,150] Most of the panel believed that these data for interferon do not outweigh the significant benefits seen with TKI therapy. Participation in a clinical trial or allogeneic hematopoietic cell transplant (HCT) or ponatinib is a reasonable treatment option for patients with T315I mutation.

Monitoring Response to TKI Therapy

Monitoring response to TKI therapy is one of the key management strategies of CML.[151-153] Response to TKI therapy is determined by the measurement of hematologic, cytogenetic, and molecular responses. The goal of TKI therapy is to achieve a CCyR within 12 months of initiation of therapy and to prevent disease progression to accelerated or blast phase.

Hematologic Response

CHR is defined as complete normalization of peripheral blood counts with no immature blood cells, leukocyte count less than 10 x 10^9/L, and platelet count less than 450 x 10^9/L. The patient is free of signs and symptoms of the disease with the disappearance of splenomegaly. Partial hematologic response indicates the presence of immature blood cells and/or platelet count less than 50% of pretreatment count but more than 450 x 10^9/L and/or persistent splenomegaly (but less than 50% of pretreatment). The majority of patients in CP-CML will achieve a CHR with TKI therapy.

Cytogenetic Response

Cytogenetic response is determined by the decrease in the number of Ph-positive metaphases, as determined by bone marrow aspirate and cytogenetics. CCyR indicates that there are no Ph-positive metaphases. MCyR indicates that 0% to 35% of the cells still have Ph-positive metaphases, and in the case of partial cytogenetic response (PCyR) 1% to 34% of the cells have Ph-positive metaphases.

Cytogenetic monitoring is the most widely used technique for monitoring response in patients with CML. Conventional bone marrow cytogenetics for Ph-positive metaphases is the standard for monitoring cytogenetic responses in CML, and clinical trial response analyses are most often based on conventional bone marrow cytogenetics. It is widely available and reliable. However, the sensitivity is approximately 5% if only 20 metaphases are examined. If conventional bone marrow cytogenetics showed no analyzable metaphases, cytogenetic response can be further evaluated by more sensitive techniques such as FISH;[154,155] however, endpoints for imatinib failure have not been defined on the basis of FISH analysis. FISH uses 5'-*BCR* and 3'-*ABL1* probes and has a false-positive rate of 1% to 10%. Interphase or hypermetaphase FISH can be performed on peripheral blood or bone marrow aspirates, respectively. Interphase FISH does not require cell division. It is applicable to a larger number of cells but is associated with a background level of 1% to 5% (depending on the specific probe used in the assay).[156] Hypermetaphase FISH is applicable only to dividing cells in the bone marrow. Hypermetaphase FISH is more sensitive and can analyze up to 500 metaphases at a time.[157] Techniques such as double-fusion FISH can detect all variant translocations of the Ph-chromosome and are also associated with low false-positive rates.[158] FISH can be used complementary to

conventional cytogenetics until FISH levels are less than 5% to 10%. This technique is no longer useful for monitoring further reduction in Ph-positive metaphases. At this point, more sensitive techniques are required.

Prognostic Significance of Cytogenetic Response to First-line TKI Therapy

Achievement of cytogenetic response is an important prognostic indicator of long-term survival in patients treated with imatinib.[13,14,159] In the IRIS study, PFS was significantly better for patients who achieved any cytogenetic response at 6 months and a MCyR at 12 months, compared to those with no cytogenetic response at 6 months or less than a MCyR at 12 months. At the median follow-up of 60 months, PFS rate was better for patients who achieved a CCyR or PCyR at 12 months compared to those who did not have a MCyR at 12 months (97%, 93%, and 81%, respectively).[13] At 8 year follow-up, of the 456 patients who achieved CCyR on imatinib, only 15 patients (3%) had progressed to accelerated or blast phase during study treatment.[14] The updated results of the IRIS trial also confirmed that patients with minor cytogenetic response at 3 months, PCyR at 6 and 12 months, and CCyR at 18 months were associated with stable CCyR over the observation period. Patients with minor to PCyR at 3 months and those with PCyR at 6 and 12 months were more likely to achieve a stable CCyR than have an event.[14] de Lavallade and colleagues also identified cytogenetic response after 1 year of imatinib therapy as the major prognostic factor for OS and PFS.[159] In the German CML IV study, an absence of a PCyR at 3 months and an absence of a CCyR at 6 months on imatinib correlated with lower rates of OS. The 5-year OS rates were 95% and 97%, respectively, for patients with a PCyR at 3 months and CCyR at 6 months. The corresponding survival rates were 87% and 91%, respectively, for those with no PCyR or CCyR at these time points.[160]

Early cytogenetic response to initial therapy with second-generation TKIs is also predictive of long-term survival in newly diagnosed patients with CP-CML.[161,162] Jabbour et al reported that the achievement of a CCyR at 3, 6, and 12 months remains a major prognostic factor for outcome in patients with early CP-CML regardless of the TKI (imatinib 400 mg, imatinib 800 mg, or second-generation TKI).[161] Patients with CCyR at 3, 6, and 12 months had significantly better 3-year EFS (98%, 97%, and 98%) and OS rates (99%, 99%, and 99%) compared to 83%, 72%, and 67% and 95%, 90%, and 94% in patients who did not achieve a CCyR at these time points.[161] Landmark analysis from the DASISION study also demonstrated that MCyR at 3 and 6 months after first-line therapy with dasatinib is a significant predictor of PFS in newly diagnosed patients with CP-CML.[162] The 3-year PFS rate was 94% for patients with MCyR at 3 and 6 months after initial therapy with dasatinib. The corresponding 3-year PFS rates were 71% and 84% respectively for patients without a MCyR at 3 and 6 months.

Prognostic Significance of Cytogenetic Response to Second-line TKI Therapy

Early cytogenetic response to second-line TKIs can predict survival and guide subsequent therapy.[47,85,163-165] Tam and colleagues reported that in patients receiving dasatinib or nilotinib, patients achieving MCyR after 12 months of treatment had a significant advantage over those achieving minor cytogenetic response or CHR.[163] Milojkovic and colleagues also reported that among patients with CP-CML resistant to imatinib and who were treated with dasatinib or nilotinib, patients with a CCyR at 12 months had significantly superior event-free (97% vs. 80%) and overall (100% vs. 85%) survival probabilities compared to those

who had failed to achieve a CCyR. There were no significant differences in PFS.[164] In another report, lack of CCyR at 3-months was identified as the only poor predictor of EFS and OS in patients treated with second-line TKI therapy after imatinib failure.[165] Giles et al also reported that, among patients treated with nilotinib for CP-CML that is resistant to imatinib, the estimated PFS rate at 48 months was significantly higher for patients who were in CCyR at 12 months than for those who were not in CCyR (89% and 56%, respectively; $P < .001$).[85] Shah et al also reported that achievement of CCyR to dasatinib 100 mg once daily (with or without MMR) at 3 and 6 months was predictive of PFS; the 6-year PFS rate was 68% and 72% respectively for those with a CCyR at 3 and 6 months compared to 30% and 24%, respectively, for those with no CCyR at 3 and 6 months.[47]

Molecular Response

Molecular response is determined by the decrease in the amount of *BCR-ABL1* chimeric mRNA. Reverse transcriptase polymerase chain reaction (RT-PCR) is the most sensitive assay available for the detection of *BCR-ABL1* chimeric mRNA. This assay measures the levels of *BCR-ABL1* transcripts in the peripheral blood or in the bone marrow, and it can detect one CML cell in a background of ≥100,000 normal cells. Qualitative RT-PCR assay is reported as either positive or negative; it is rarely used in the context of monitoring patients. In contrast, a QPCR assay reports the actual percentage of *BCR-ABL1* mRNA transcripts.[166]

QPCR is the most sensitive assay available for the measurement of *BCR-ABL1* chimeric mRNA. A major advantage of the QPCR assay is the strong correlation between the results obtained from the peripheral blood and the bone marrow, allowing molecular monitoring without the necessity of obtaining bone marrow aspirations. The post hoc analyses of the RIGHT study reported strong and significant correlations between the results obtained by QPCR using peripheral blood vs bone marrow, suggesting that molecular monitoring by QPCR using peripheral blood might obviate the need for invasive bone marrow testing.[167]

QPCR with either peripheral blood or bone marrow should be done before initiation of TKI therapy to establish the presence of quantifiable *BCR-ABL1* mRNA transcripts at baseline. The *BCR-ABL1* mRNA transcripts typically remain detectable after CCyR is achieved. Therefore, QPCR assay is the only tool capable of monitoring responses after the patient has achieved CCyR.

In the QPCR assay, results are expressed as the ratio of *BCR-ABL1* transcript numbers to the number of control gene transcripts.[168] Alternatively, this ratio is also expressed as a percentage whereby equal copy numbers of the *BCR-ABL1* gene and the control gene at diagnosis would be expressed as 100%.[168] Thus, the choice of an appropriate control gene is important for generating reliable and reproducible data. *BCR, ABL1,* beta-glucuronidase (*GUSB*), and beta-2-microglobilin (*B2M*) have been widely studied for *BCR-ABL1* quantification.[169-171] *BCR* was used as the control gene in the IRIS trial.[169]

Standardization Using the International Scale

A substantial effort has been made to standardize *BCR-ABL1* testing and reporting across academic and private laboratories.[168,172,173] In 2006, the National Institutes of Health Consensus Group proposed the use of an International Scale (IS) to standardize molecular monitoring with QPCR across different laboratories.[168] This group recommended 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.

In the IS, the standardized baseline (defined as the median value of *BCR-ABL1* mRNA at the time of diagnosis in 30 CML patients as established in the IRIS study) is taken to represent 100%. MMR, 3-log reduction in the *BCR-ABL1* transcripts from this standardized baseline, is fixed at 0.1%.[168,172] A 2-log reduction (*BCR-ABL1* transcripts 1% IS) from the standardized baseline generally correlates with CCyR. CMR is defined as undetectable *BCR-ABL1* transcripts as assessed by QPCR with a sensitivity of 4.5-log reduction or more from the standardized baseline. CMR is variably described, and is best defined by the assay's level of sensitivity.

The *BCR-ABL1* transcript levels obtained in a given laboratory are converted to the IS by applying a laboratory-specific conversion factor (CF).[168,174] To obtain a laboratory-specific CF, typically each laboratory has to exchange 20 to 30 pre-treatment samples with a reference laboratory. Both laboratories analyze the samples and the results are plotted on a log scale for comparison. The antilog of the estimated mean bias between the methods is designated as the CF.[174] Once a laboratory-specific CF is established, it is validated again through a second sample exchange with the reference laboratory.

QPCR (IS) is still not available in many laboratories because the process is relatively cumbersome, time consuming, and is not seen as practical if the laboratory does not have a high volume of assays to perform, or if the prescribing physicians do not demand it. Alternatively, laboratories with no access to QPCR (IS) may establish their own standardized baseline, based on a large number of pre-treatment samples. Molecular response to TKI therapy is then measured as the log-reduction of *BCR-ABL1* mRNA from the standardized baseline (not a reduction from the actual baseline level in an individual patient). This is an effective method, and was used in the IRIS trial to establish the 3-log reduction in the *BCR-ABL1* transcript levels from the standardized baseline (not a reduction from the actual baseline level in an individual patient) as the MMR.[169] In addition, this technique was recently used in the U.S. Intergroup CML trial.[41] The findings from the post hoc analyses of the RIGHT study also confirmed the feasibility of this technique.[167] The probability of achieving MMR at 18 months was higher in patients with > 2-log reduction in *BCR-ABL1* levels at 3, 6, and 9 months than those with ≤2-log reduction.[167]

Prognostic Significance of Molecular Response to First-line TKI Therapy

Several studies have reported that achievement of MMR after treatment with imatinib is associated with durable long-term cytogenetic remission[171,175-177] and a lower rate of disease progression.[13,177-179]

Cortes et al reported that a significantly lower portion of patients (5% with MMR and 4% with CMR) lost their CCyR compared to 37% who did not reach these levels of molecular response.[171] In the 7-year follow-up of the IRIS study, the probability of loss of CCyR by 7 years was only 3% for patients in MMR at 18 months compared to 26% for those with CCyR but not MMR.[177] The GIMEMA study group reported similar findings.[175,176] Patients with a stable MMR have a significantly lower risk of losing the CCyR than patients with unstable MMR (4% vs. 21%, respectively; $P = .03$) and those with no MMR (4% vs. 33%, respectively, $P < .0001$).[176]

The 5-year follow-up of the IRIS trial showed that no patient who had a CCyR and a MMR at 12 months had progressed to the accelerated or

blast phase.[13] The estimated PFS rate at 24 months was 100% for patients with a CCyR and at least a 3-log reduction in the *BCR-ABL1* transcript level at 12 months, compared to 95% for those with CCyR and a less than 3-log reduction in *BCR-ABL1* transcript level at 12 months. The 7-year follow-up of the IRIS study also showed that progression is very rare in patients who achieved MMR (*BCR-ABL1* ≤ 0.1% IS) at any time point during imatinib therapy.[177] The estimated EFS rate at 84 months was 95% for patients who had a MMR at 18 months compared to 86% in those with less than MMR at this time point (86% for those with *BCR-ABL1* > 0.1% to ≤ 1.0%; *P* = .01 and 65% for those with *BCR-ABL1* >1.0%).[177] Press and colleagues also reported that absence of at least a 2-log reduction in *BCR-ABL1* mRNA at the time of CCyR or a 3-log reduction any time thereafter is associated with a significantly shorter PFS,[178] and a minimal half-log increase in the *BCR-ABL1* or a loss of MMR predicts shorter relapse-free survival in patients who were in CCyR on imatinib.[179]

Although some investigators have reported that dose escalation of imatinib might benefit patients in CCyR with no MMR,[180] no randomized studies have shown that a change of therapy would improve survival, PFS, or EFS in this group of patients.[181] Some investigators have also suggested that MMR may not be of prognostic significance in patients who have achieved CCyR at 12 months with imatinib.[30,159,182] de Lavallade et al reported that in patients achieving CCyR at 12 months or 18 months, achievement of molecular response at these time points did not affect PFS or OS.[159] Marin et al also confirmed that among patients with CCyR, even though patients who did not have a MMR at 18 months had a higher chance of losing CCyR, this did not translate into difference in PFS.[182] Recently, Hehlman et al from a German CML study group reported that independent of the treatment approach, MMR at 12 months was associated with a better PFS (99% vs. 94%; *P* = .0023) and OS (99% vs. 93%; *P* = .0011) at 3 years when compared with *BCR-ABL1* >1% (IS) or no MMR.[30] However, there was no difference in PFS and OS when compared with the *BCR-ABL1* (IS) 0.1% to 1% group (which closely correlates with CCyR). The 3-year survival rates for MMR at 12 months and *BCR-ABL1* (IS) 0.1% to 1% at 12 months were 99% and 98%, respectively, implying that MMR is not of prognostic significance in patients who have achieved CCyR at 12 months. Jabbour et al also reported that achievement of MMR may not be a significant prognostic indicator of outcome in patients who are in stable CCyR after treatment with second-generation TKIs.[183]

The prognostic significance of early molecular response to imatinib was first established in a subset analysis of the IRIS study.[184] The incidence of disease progression was significantly higher in patients who failed to achieve a 1-log reduction in *BCR-ABL1* transcript levels by 3 months or a 2-log reduction in *BCR-ABL1* transcript levels by 6 months. In a subsequent report, Quintas-Cardama et al also showed that patients with a *BCR-ABL1* >10% had a significantly lower probability of achieving a CCyR or MMR and higher probability of disease progression compared to those with transcript levels lower than or equal to 10% at the same time point.[185] More recent studies have demonstrated that achievement of *BCR-ABL1* transcript levels ≤10% after 3 months, or ≤1% at 6 months after treatment with imatinib 400 mg, is an effective prognostic indicator for long-term outcomes.[160,186]

In the CML IV study (1,303 newly diagnosed patients treated with imatinib), Hanfstein et al showed that *BCR-ABL1* >10% (IS) at 3 months and *BCR-ABL1* >1% (IS) at 6 months after imatinib treatment correlated with significantly lower OS and PFS rates at 5 years. At 3 months, the 5-year OS rate was 87% for patients with a *BCR-ABL1* >10% (IS) compared to 95% for those who achieved BCR-*ABL1* ≤ 10%

at 3 months (P < .0001).[160] The 5-year PFS rates were 87% and 92%, respectively (P = .037). Similarly, at 6 months, the 5-year OS rate was 89% for those with a *BCR-ABL1* > 1% (IS) compared to 97% for patients with *BCR-ABL1* ≤ 1% (IS) (P < .0001). The corresponding 5-year PFS rates were 89% and 96%, respectively (P = .006).

In an analysis of 282 patients with CP-CML treated with imatinib 400 mg as first-line therapy, Marin et al reported that patients with *BCR-ABL1* ≤ 9.84% (IS) at 3 months had significantly higher rates of OS, PFS and EFS at 8-years than patients with *BCR-ABL1* >9.84% (IS) at 3 months (P < .001).[186] The rates of OS, PFS, and EFS rates were 93.3%, 92.8%, and 65%, respectively, for patients with *BCR-ABL1* ≤ 9.84% (IS) at 3 months compared to 56.9%, 57%, and 6.9%, respectively, for those with *BCR-ABL1* >9.84% (IS). In a more recent report, the same investigators also established the superior prognostic value of molecular response assessment at 3 months over molecular response assessment at 6 months.[187] The 8-year probability of OS for those with low *BCR-ABL1* transcript levels at 3 months and high *BCR-ABL1* transcript levels at 6 months following imatinib therapy was similar to that of patients who had low *BCR-ABL1* transcript levels at both time points (92.4% and 93.5%, respectively; P = .78).

Landmark analyses from the DASISION and ENESTnd studies have also demonstrated the prognostic significance of early molecular response to first-line therapy with dasatinib or nilotinib in newly diagnosed patients with CP-CML.[40,79,162]

In the DASISION study, *BCR-ABL1* ≤10% (IS) at 3 months was predictive of PFS in both treatment arms.[162] The 3-year PFS rates for patients with *BCR-ABL1* (IS) ≤10% and >10% at 3 months were 93% and 68%, respectively for dasatinib (P = .0003) and 96% and 75%, respectively for imatinib (P < .0001).[162] The corresponding 3-year OS rates were 96% and 86% respectively for dasatinib (P = .0348) and 96% and 88%, respectively for imatinib (P = .0036). The rate of transformation to accelerated or blast phase was also less for patients with *BCR-ABL1* ≤ 10% at 3 months (3% for both dasatinib and imatinib) compared to 13% for those who did not reach this response milestone at 3 months). The 6-month landmark analysis also showed that *BCR-ABL1* ≤10% (IS) or ≤1% at 6 months is associated with significantly higher 3-year PFS and OS rates.[162] In the dasatinib arm, the 3-year PFS rates were 94% and 95% respectively for patients achieving *BCR-ABL1* ≤10% or ≤1% at 6 months compared to 66% and 85% for those achieving *BCR-ABL1* >10% or >1% at 6 months. The rate of transformation was 2% (3 of 164 patients) for patients with *BCR-ABL1* ≤ 1% at 6 months compared to 9.7% for patients with *BCR-ABL1* >1%. The 5-year follow-up data of DASISION study also confirmed that *BCR-ABL1* ≤10% at 3 months is associated with improved PFS and OS rates for dasatinib (PFS: 89% vs 72%, P=.0014; OS: 94% vs 81%, P=.0028) and imatinib (PFS: 93% vs 72%, P<.0001; OS: 95% vs 81%, P=.0003).[40] The rates of transformation to accelerated or blast phase was also lower among patients who achieved *BCR-ABL1* ≤10% at 3 months (3% for dasatinib and imatinib) vs. *BCR-ABL1* > 10% at 3 months (14% for dasatinib and 15% for imatinib) in both treatment arms.

In the ENESTnd study, *BCR-ABL1* >10% at 3 months was associated with lower rates of molecular response, an increased risk of progression, and lower OS.[79] Patients who achieved *BCR-ABL1* ≤10% at 3 months were more likely to achieve MMR by 2 years than those with *BCR-ABL1* >10% at 3 months (80% vs. 29% on nilotinib 300 mg twice daily, P <.0001; 75% vs 29% on nilotinib 400 mg twice daily, P < .0001 and 58% vs 20% on imatinib, P <.0001). The estimated 3-year

PFS rates were also significantly higher for patients with *BCR-ABL1* ≤10% than those with *BCR-ABL1* >10% at 3 months (95.2% vs. 82.9% for nilotinib 300 mg twice daily, *P* = .0061; 96.9% vs. 89.0% for nilotinib 400 mg twice daily, *P* = .0399; 97.7% vs. 82.6% for imatinib, *P* < .0001). The estimated 4-year OS rates were also higher for patients who achieved *BCR-ABL1* ≤10% at 3 months than those who failed to achieve this milestone at 3 months (96.7% and 86.7%, respectively for nilotinib 300 mg twice daily; *P* =.0116; 96.9% and 92.7%, respectively for nilotinib 400 mg twice daily; *P* = .2483 and 98.9% and 83.6%, respectively for imatinib; *P* < .0001). The results of 6-month landmark analysis were similar to those obtained at 3 months.[79]

Jain et al also reported the importance of achieving molecular response at 3 months in patients with CP-CML treated with imatinib (800 mg), dasatinib, or nilotinib as first-line therapy.[188] The 3-year EFS probability was significantly lower for patients with *BCR-ABL1* >10% (IS) at 3 months than those with lower transcript levels (61% compared to 95% and 98% for those with *BCR-ABL1* (IS) <1%, or >1% to 10% at 3 months, respectively; *P* < .001).

Prognostic Significance of Molecular Response to Second-line TKI Therapy

The 3-month molecular response after initiation of second-line TKI therapy has also been reported to be a predictor of OS and EFS in patients who are still in chronic phase resistant to imatinib.[47,189,190] In an analysis of 119 patients treated with dasatinib or nilotinib for imatinib-resistant disease, Milojkovic et al reported significantly superior OS (91.3% vs. 72.1%, *P* = .02) and EFS (49.3% vs. 13.0%, *P* < .001) rates for patients with a *BCR-ABL1* ≤ 10% (IS) at 3 months compared to those with *BCR-ABL1* >10% (IS).[189] Branford et al also reported that molecular response at 3 months after second-line nilotinib was predictive of EFS in patients with CP-CML intolerant to imatinib or those with resistant disease.[190] The estimated 24-month EFS rates were 82% and 48% respectively, for patients with *BCR-ABL1* ≤ 1% (IS) and *BCR-ABL1* of >10% (IS) at 3 months after second-line therapy with nilotinib. Exploratory analyses of the dasatinib dose-optimization study also suggest that achievement of *BCR-ABL1* ≤10% at 1 or 3 months after initiation of dasatinib 100 mg is associated with a higher 6-year PFS rate; the estimated 6-year PFS rates 68%, 58%, and 26%, respectively, for patients with ≤1%, >1% to 10%, and >10% *BCR-ABL* transcripts at 3 months.[47] Recently, in an analysis of 112 patients with CP-CML treated with dasatinib or nilotinib for imatinib-resistant disease, Kim et al reported that *BCR-ABL1* transcript levels at 3 months provide a better prediction of long-term survival than *BCR-ABL1* transcript levels at 6 months after second-line TKI therapy.[191] Among patients intolerant to imatinib or those with resistant disease, *BCR-ABL1* transcript levels at 3 and 6 months after nilotinib therapy correlated with higher PFS and OS at 48 months.[85] The 4-year PFS and OS rates were 85% and 95%, respectively, for patients with *BCR-ABL1* ≤ 1% at 3 months compared to 42% and 71%, respectively, for those with *BCR-ABL1* >10% at 3 months.

Rising BCR-ABL1 Levels

Several studies have shown that rising *BCR-ABL1* transcripts may be associated with an increased likelihood of detecting *BCR-ABL1* mutations and cytogenetic relapse.[192-196] Branford and colleagues reported that in patients who had achieved very low levels of *BCR-ABL1* transcripts, emergence of *BCR-ABL1* mutations was more frequent in those who had more than a 2-fold increase in *BCR-ABL1* levels compared to those with stable or decreasing *BCR-ABL1*.[192] In contrast, Wang reported that a serial rise is more reliable than a single

2-fold or greater rise in *BCR-ABL1* transcript levels.[193] In an analysis of 258 patients with CP-CML on imatinib therapy, Kantarjian et al studied 116 patients in CCyR and who experienced an increase in *BCR-ABL1* transcript levels of half-log or more on at least two occasions.[194] Eleven of 116 (9%) patients had CML progression. The patients with the highest risk were those who lost MMR with more than 1-log increase in *BCR-ABL1*, or those who never achieved a MMR and had 1-log rise in *BCR-ABL1*.

The precise increase in *BCR-ABL1* transcripts that warrants a mutation analysis depends on the performance characteristics of QPCR assay in the laboratory.[196] Some labs have advocated a 2 to 3 fold range,[182,195,196] while others have taken a more conservative approach (half-log to 1-log).[194] Obviously, some common sense must prevail, since the amount of change in absolute terms depends on the MMR level. For example, a finding of any *BCR-ABL1* compared to CMR is an infinite increase in *BCR-ABL1* level, though a change from CMR to a barely detectable level is clearly different than a 5-fold increase in a case hovering at the MMR level.

Currently there are no specific guidelines for changing therapy based on rising *BCR-ABL1* transcripts as detected by QPCR. Changes of therapy based solely on rising *BCR-ABL1* transcripts should be done only in the context of a clinical trial. The guidelines recommend mutational analysis for patients with a 1-log increase in *BCR-ABL1* transcripts with loss of MMR (Table 1).

Rate of Decline in BCR-ABL1 Levels

Quite recently, studies have suggested that the rate of *BCR-ABL1* decline is also related to longer-term response. Among patients with BCR-*ABL1* (IS) >10% after 3 months of treatment with imatinib, those with a faster decline in *BCR-ABL1* transcript levels (*BCR-ABL1* halving time < 76 days) had a superior outcome compared to those patients with a slower decline of tumor burden (4-year PFS rate was 92% vs. 63%, respectively).[197] The results of the D-First study showed that in patients treated with dasatinib, a shorter halving time of *BCR-ABL1* transcripts (≤14 days) was a significant predictor of MMR by 12 months and deep molecular response (*BCR-ABL1* <0.01% IS) by 18 months.[198] 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.[199]

Branford et al recently reported that a rapid initial *BCR-ABL1* decline also identifies a subgroup of high-Sokal risk patients with outcomes similar to those of low-Sokal risk patients.[200] The 4-year FFS rate was 79% for high-risk patients with ≤11 days halving time and 84% for low-risk patients (*P* = .39). The MMR rate at 12 months was 57% for high-risk patients with ≤11 days halving time vs 59% for low-risk patients (*P* = .95). The corresponding MR4.5 rate at 4 years was 36% and 40%, respectively (*P* = .82). Among high-Sokal risk patients, *BCR-ABL1* halving time of ≤11 days at 1 month was also associated with significantly improved outcomes (4- year FFS rate was 79% for patients with ≤11 days halving time vs. 53% for those with > 11 days halving time; *P* = .03).

Suboptimal Response

Suboptimal response to imatinib, first introduced in the ELN guidelines, was defined as no cytogenetic response at 3 months, less than PCyR at 6 months, PCyR at 12 months, and less than MMR at 18 months.[201] However, these definitions are not applicable to patients with newly diagnosed CML treated with second-generation TKIs in the first-line setting. Jabbour et al have recently proposed that for this group of

patients, CCyR and PCyR at 3 months should be considered as optimal and suboptimal responses, respectively.[183] In the recently updated ELN Guidelines, suboptimal response is designated as "warning." Warning implies that the characteristics of the disease and the response to treatment require more frequent monitoring, so as to permit timely changes in therapy, in case of treatment failure.[202]

Suboptimal response to TKI therapy could result from many factors, including poor compliance to TKI therapy; individual variation in drug metabolism; aberrant expression of drug transporters; differences in the intrinsic biology of the disease, which might result in clonal competition between clones highly sensitive to a particular TKI and those resistant.[203] The prognostic implications of suboptimal response may also be different depending on the time point of suboptimal response. Thus, the outcomes of patients with suboptimal response at 6 and 12 months are more similar to those of patients who met the criteria for treatment failure, and the outcomes of patients with a suboptimal response at 18 months are very similar to those of patients with an optimal response.[182] However, other investigators suggest that suboptimal responders at 12 months have an outcome closer to that of patients with an optimal response, with a similar transformation-free survival but with worse EFS.[204]

A few early reports have suggested that dose escalation of imatinib to 800 mg as tolerated,[204-206] or switching to dasatinib[46,207] or nilotinib,[208-210] are effective in patients with suboptimal response to imatinib 400 mg. Dose escalation of nilotinib (400 mg twice daily) has also been shown to improve responses in patients with suboptimal response or disease that is resistant to imatinib 400 mg or nilotinib 300 mg twice daily.[211]

Resistance to TKIs

Primary Resistance

Primary hematologic resistance to TKI therapy (no hematologic remission within 3 to 6 months of initiation of treatment) is very rare in newly diagnosed patients with Ph-positive CP-CML, whereas primary cytogenetic resistance to imatinib (absence of any level of cytogenetic response at 6 months, MCyR at 12 months, or CCyR at 18 months) is evident in 15% to 25% of patients.

Plasma Protein Binding

Imatinib, dasatinib, and nilotinib are all more than 90% bound to the plasma proteins, albumin as well as alpha-1 acid glycoprotein (AGP).[212] Available data indicate that inadequate plasma concentration of imatinib may be one of the causes for primary resistance.[213-215] Excessive binding of imatinib to AGP has been reported to reduce the therapeutic effect of imatinib.[213] In a subanalysis of the IRIS study, plasma levels of imatinib following the first month of treatment proved to be a significant prognostic factor for long-term clinical response.[214] Picard and colleagues also observed that trough plasma levels of imatinib were significantly higher in patients achieving CCyR and MMR at 12 months.[215] An imatinib trough plasma concentration of > 1000 ng/mL has also been significantly associated with major and complete molecular responses.[216] However, other investigators have suggested that plasma levels of imatinib in patients receiving different dose schedules had no correlation with response to therapy.[217,218]

The clinical value of monitoring plasma levels of imatinib remains to be defined. Monitoring imatinib plasma levels may be useful in determining patient adherence to therapy. However, at the present time, there is no data to support that change of therapy based on plasma imatinib levels

will affect treatment outcomes. Therefore, the panel does not recommend routine imatinib plasma level testing.

Intracellular Concentration of TKIs

Aberrant expressions of drug transporters such as multidrug resistance ATP-binding cassette (ABC) transporters (MDR1 or ABCB1 and ABCG2) and human organic cation transporter-1 (hOCT1) also contribute to resistance by altering the intracellular concentration of TKIs.[212] Imatinib, dasatinib, and nilotinib have been identified as substrates for ABCB1 and ABCG2.[219] Overexpression of the multidrug resistance (*MDR1)* gene has been associated with decreased intracellular concentration of imatinib, which may confer resistance to imatinib.[220] Recent reports also suggest that ABCB1 and ABCG2 can confer resistance to dasatinib and nilotinib.[221,222] Further clinical studies are needed to confirm these preliminary findings.

Pretreatment levels of hOCT1 have been reported as the most powerful predictor of response to imatinib.[223] White and colleagues recently reported that most patients with suboptimal response to imatinib have low hOCT1 activity.[224] In the updated analysis of patients enrolled in the TIDEL trial, MMR rate at 60 months was higher for patients with high hOCT1 activity compared to those with low hOCT1 activity (89% vs. 55%, respectively). Low hOCT1 activity was also associated with a significantly lower OS (87% vs. 96%) and EFS (48% vs. 74%) as well as a higher kinase domain mutation rate (21% vs. 4%).[225] These differences were highly significant in patients who averaged less than 600 mg/day of imatinib. Similar findings were also reported in the subset analysis of the TOPS trial.[226] Among patients receiving 400 mg of imatinib daily, MMR rates at 24 months were significantly higher for patients with high hOCT1 activity than those with low hOCT1 activity (100% and 57%, respectively; $P < .001$), but this difference was not significant in patients receiving 800 mg of imatinib. The corresponding MMR rates were 95% and 68%, respectively ($P = .073$). On the other hand, cellular uptake of dasatinib or nilotinib seems to be independent of hOCT1 expression, suggesting that patients with low hOCT1 expression might have better outcomes with dasatinib or nilotinib.[227-230]

Secondary Resistance

The most common mechanism for secondary resistance is the reactivation of *BCR-ABL1* activity.[212] This occurs most often by mutations in the ABL1 tyrosine kinase domain of the *BCR-ABL1* gene (resulting in conformational changes in the fusion protein that affect the binding site of imatinib on the tyrosine kinase), and less frequently by *BCR-ABL1* gene amplification or increased *BCR-ABL1* expression.[231-233] In the START-C study, 46% of patients with imatinib-resistant CP-CML did not carry *BCR-ABL1* mutations, thus confirming that resistance to imatinib is multifactorial. Other mechanisms that are independent of *BCR-ABL1* include activation of the SRC family of kinases or cytogenetic clonal evolutions characterized by additional chromosomal abnormalities in the Ph-positive cells.[212,232]

ABL1 Kinase Domain Mutations

Point mutations in the *BCR-ABL1* kinase domain are emerging as the most frequent mechanism of resistance to TKI therapy.[234]

In a large study of 319 chronic-phase patients, Khorashad et al found that kinase domain mutations were the only independent predictor for the loss of CCyR and a higher risk progression (3.8- and 3.7-fold, respectively) when compared to patients without a mutation.[235] Patients with P-loop mutations were associated with a particularly high risk of progression. Other studies have also reported that mutations in the ATP phosphate-binding loop (P-loop) are associated with a poor

prognosis and high risk of progression among patients treated with imatinib.[236-239] However, Jabbour and colleagues could not confirm these findings.[240] In the START trials, dasatinib induced similar rates of major hematologic and cytogenetic responses irrespective of the presence of P-loop or other mutations resistant to imatinib in patients with AP-CML or BP-CML.[52,54] Branford and colleagues observed that although there was a higher incidence of P-loop mutations in the accelerated phase, the difference in the frequency of mutation was significant between early chronic phase and accelerated phase, compared to that between accelerated phase and late chronic phase.[236]

Among the mutations in the ABL1 kinase domain, the presence of T315I mutation confers the highest resistance to imatinib, dasatinib, and nilotinib. Some reports have suggested that T315I is associated with disease progression and poor survival.[241,242] Jabbour and colleagues reported that survival of patients with T315I is dependent on the stage of the disease, with many chronic phase patients having an indolent course.[242] Patients in the chronic phase had a 2-year survival rate of 87%. In patients in the accelerated phase and blast phase, survival rates were similarly poor irrespective of their T315I mutational status. Available clinical evidence indicates that in addition to T315I, mutations F317 and V299 are resistant to dasatinib and mutations Y253H, E255, and F359 are resistant to nilotinib.[243-245] Among patients with *BCR-ABL1* mutations resistant to imatinib, clinically relevant mutations less sensitive to nilotinib (Y253H, E255K/V, and F359V/C) or dasatinib (F317L and V299L) or both (T315I) occurred in 43% of cases including 14% with T315I.[243]

Muller et al recently reported the results of the largest analysis of clinical response to dasatinib in 1043 patients with imatinib-resistant CP-CML according to the pre-existing *BCR-ABL1* mutations.[246] The presence of T315I and F317L mutations at baseline was associated with less favorable responses. A few responses (CHR and MCyR) were observed in patients with a T315I mutation but no CCyRs. Patients with an F317L mutation had a high rate of CHR (93%) but low rates of MCyR and CCyR (14% and 7%, respectively), whereas favorable CCyR rates were achieved in patients with highly imatinib-resistant mutations such as E255K/V (38%) and L248V (40%). Other studies have also reported similar findings in patients with F317 mutations at baseline.[247,248] In one study, F315 and/or F317 mutations were associated with resistance to dasatinib.[248] In another study, patients with a F317L mutation had a similar survival compared with patients with other mutations with an outcome dependent on the CML phase; this mutation was sensitive to other TKIs.[247]

Hughes et al assessed the occurrence and impact of baseline *BCR-ABL1* mutations on nilotinib therapy in patients with imatinib-resistant CP-CML.[249] Patients with Y253H, E255V/K, and F359V/C mutations achieved less favorable MCyR rates (13%, 43%, and 9%, respectively) and none of them achieved CCyR within 12 months of therapy. E255K/V, F359C/V, Y253H, and T315I mutations were most commonly associated with disease progression. Consistent with these findings, F359V, Y253H, and E255K/V mutations were associated with relapse to nilotinib in the study reported by Soverini et al.[250]

In the phase I/II study that evaluated the efficacy of bosutinib in patients with CP-CML, AP-CML, and BP-CML intolerant to prior TKI therapy or those with resistant disease, bosutinib was active in patients with *BCR-ABL1* mutations.[96] The most common baseline mutations were T315I, F359C/I/S/V, F317L, G250E, Y253F/H, and M351T. T315I and V299L were the most common emergent mutations, both of which are resistant to bosutinib. Among patients with baseline mutations, CHR

and MCyR were observed in those with mutations resistant to dasatinib (F317L) and nilotinib (Y253H, E255K/V, and F359C/I/V).[96]

In the PACE trial, in addition to T315I, ponatinib was also active against other *BCR-ABL1* mutations resistant to dasatinib or nilotinib, including F317L, E255K/V, Y253H, F359V, and G250E.[251] In patients with CP-CML, MMR rates were 41%, 50%, 31%, and 38%, respectively, for patients with F317L, E255K, F359V, and G250E mutations.[251]

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.[244,245] Mutational analysis would also be helpful to identify a subgroup of patients who demand careful monitoring (as these patients are at a higher risk of progression) and the subset of patients who will be eligible for allogeneic HCT.

Clonal Evolution

Clonal evolution is defined by the presence of additional chromosomal abnormalities (ACAs) besides the Ph-chromosome and is considered to be a feature of AP-CML.[252] In an analysis of patients who developed cytogenetic clonal evolution on interferon therapy (prior to the use of imatinib), Majlis and colleagues from MD Anderson Cancer Center concluded that the prognostic significance of clonal evolution is not uniform, but it is related to the specific chromosomal abnormality and the presence of other features of accelerated phase.[253] In this study, presence of chromosome 17 abnormality, predominance of abnormal metaphases (≥36%), and the other accelerated features were identified as the worst prognostic factors.

In patients with accelerated phase treated with imatinib, clonal evolution resulted in lower response rates and a shorter time to treatment failure. However, in a subset of patients, clonal evolution was associated with a better prognosis when it was considered as the only criteria for accelerated phase disease.[254] With a median follow-up of 12 months, the MCyR and CCyR rates were 73% (11 of 15) and 60% (9 of 15), respectively. In a subsequent report, of 141 patients treated with imatinib after interferon therapy, O'Dwyer and colleagues identified clonal evolution, an elevated platelet count, and absence of a MCyR by 6 months as adverse prognostic factors for hematologic relapse.[255] In a large trial of 498 patients in chronic or accelerated phase, cytogenetic clonal evolution was not an important factor for achieving MCyR or CCyR with imatinib, but it was an independent poor prognostic factor for survival in both CP-CML and AP-CML.[256]

In the German CML IV study, patients with cytogenetic abnormalities including trisomy 8, second Ph-chromosome, and isochromosome 17q at the time of diagnosis had longer times to cytogenetic and molecular responses and shorter PFS and OS than in patients with t(9;22) [major-route ACA].[257] After a median observation follow-up of 5 years, the PFS and OS rates were 90% and 92%, respectively, for patients with t(9;22), and the corresponding survival rates were 50% and 53%, respectively, for those with major-route ACA.

Among patients intolerant to imatinib or those with resistant disease, the hematologic and cytogenetic response rates, OS, and EFS after treatment with alternate TKIs were not different between patients in the chronic phase with clonal evolution and those with no clonal evolution.[258] However, clonal evolution had a significant adverse impact when associated with other features of accelerated phase. Patients with cytogenetic abnormalities including trisomy 8, chromosome 17, and complex abnormalities had the worst outcome, regardless of the number of metaphases involved.

Clonal cytogenetic abnormalities in Ph-negative cells have also been reported in a small subset of patients during the course of imatinib therapy.[259-262] The significance of these chromosomal abnormalities is unclear, but the most common abnormalities include trisomy 8, an abnormality frequently seen in patients with myelodysplastic syndrome (MDS). Only rare cases of MDS or acute myeloid leukemia (AML) have been reported in patients with these abnormalities, usually in those who had received interferon as well as prior chemotherapy. Some of these abnormalities may persist only in a small percentage of metaphases or may be transient and disappear with continued therapy in patients who have achieved CCyR. In a recent report, Deininger and colleagues concluded that the overall prognosis for patients with Ph-negative CML and clonal cytogenetic evolution was good and was dependent on patients' response to imatinib therapy.[263] In newly diagnosed patients with CP-CML treated with imatinib, chromosomal abnormalities in Ph-negative cells appeared in 9% of the patients.[264] Loss of Y chromosome was most common. The significance of loss of Y chromosome in this setting is unclear. It has been reported that this phenomenon is a common occurrence among aging males.

Management of Resistance

Dose escalation of imatinib up to 800 mg daily has been shown to overcome some of the primary resistance, but the duration of responses has typically been short.[265-269] Jabbour and colleagues assessed the long-term efficacy of imatinib dose escalation after hematologic or cytogenetic failure in 84 patients with CP-CML.[268] After a median follow-up of 61 months, the estimated 2- and 3-year EFS and OS rates were 57% and 47% and 84% and 76%, respectively. Responses were also durable; 88% of patients with MCyR sustained their response beyond 2 years. Dose escalation was particularly effective in patients with cytogenetic relapse who had achieved cytogenetic response with standard-dose imatinib. In this group of patients, CCyR and MCyR rates were 73% and 87%, respectively, compared to 52% and 60% for the overall group of patients with cytogenetic failure. In a retrospective analysis of 106 patients with newly diagnosed CP-CML from the IRIS trial who received imatinib at a dose of 400 mg daily, and subsequently underwent dose escalation to either 600 mg or 800 mg daily, the rates of FFP to accelerated or blast phase and OS were 89% and 84% at 3 years after dose increase, respectively.[269] These results indicate that dose escalation of imatinib is unlikely to benefit those with hematologic failure or those who never had a cytogenetic response with standard-dose imatinib; dose escalation of imatinib might be beneficial for patients with cytogenetic relapse or suboptimal cytogenetic response to imatinib 400 mg daily (See *Suboptimal Response*).

Dasatinib, nilotinib, and bosutinib are active against many of the imatinib-resistant BCR-ABL1 kinase domain mutations, except T315I, and are effective treatment options for patients with CP-CML resistant to standard-dose imatinib.[43,46,84,95] The results of the START-R trial demonstrated that dasatinib is also effective for patients with CP-CML resistant to high-dose imatinib.[51] Bosutinib has shown potent activity in patients with *BCR-ABL1* mutations resistant to dasatinib (F317L) and nilotinib (Y253H and F359C/I/V).[96] Ponatinib has demonstrated activity in patients with E255K/V, F317L, F359V, G250E, M351T, T315I and Y253H mutations.[251,270]

Omacetaxine (Homoharringtonine, a cephalotoxic alkaloid) is a protein synthesis inhibitor with demonstrated activity against CML lines including those harboring the T315I mutation. The safety and efficacy of omacetaxine in patients with CML that is resistant to prior

TKI therapy was evaluated in two phase II studies (CML-202 study involving patients with a T315I mutation and those CML that had failed treatment with one or more TKIs and CML 203 study involving patients with CML that had failed treatment with 2 or more TKIs). [271-274]

In the subset analysis of 46 patients with CP-CML enrolled in the CML 203 study, hematologic response was achieved or maintained in 67% of patients, with median response duration of 7.0 months; MCyR and CCyR were achieved in 22% and 4% of patients, respectively. Median PFS and OS were 7.0 months and 30 months respectively.[272] Omacetaxine was also effective in the treatment for patients with T315I mutation and with disease resistant to prior TKI therapy. Among 62 evaluable patients with CP-CML enrolled in the CML 202 study, CHR, MCyR, and CCyR were seen in 77%, 23%, and 16% of patients, respectively.[271] MMR was achieved in 17% of patients and the T315I clone was reduced to below detection limits in 61% of patients. Median duration of CHR and MCyR was 9 and 7 months, respectively. After a median follow-up of 19 months, median PFS was 7.7 months and the median OS had not yet been reached. Omacetaxine had an acceptable toxicity profile among patients with CP-CML. In the pooled analysis of 82 patients with CP-CML enrolled in the two phase II studies (CML-202 and CML-203), the most common grade 3/4 adverse events were thrombocytopenia (67%), neutropenia (47%), and anemia (37%).[273]

The results of a pooled analysis of 51 patients with AP-CML and 44 patients with BP-CML enrolled in the two phase II studies (CML-202 and CML-203) demonstrated that omacetaxine is a feasible treatment option for patients with advanced phase CML that had failed treatment with multiple TKIs as well as those with a T315I mutation.[274] The median follow-up was 16 months for patients with AP-CML and 3.5 months for patients with BP-CML. Among the 51 patients with AP-CML, MaHR, CHR and minor cytogenetic response were achieved or maintained in 37%, 29% and 11% of patients, respectively. The median duration of MaHR was 5.6 months.[274] MaHR rates were 55% and 58%, respectively, for patients with a history of T315I mutation and for those with confirmed T315I mutation at baseline. The overall median PFS and OS were 4.8 months and 17.6 months, respectively. Among patients with a history of T315I mutation, the median PFS and OS were 5.9 months and 18.7 months respectively. Among the 44 patients with BP-CML, MaHR and CHR were achieved in 9% and 7% of patients, respectively.[274] The median duration of overall hematologic response was 1.7 months. The overall median PFS and OS in patients were 2.2 months and 3.5 months. Among the subgroup of patients with a history of T315I mutation (n=21), the median PFS and OS were 1.9 months and 3.5 months, respectively. The most common grade 3/4 hematologic adverse events were thrombocytopenia (51% and 30%, respectively for patients with AP-CML and BP-CML), anemia (39% and 21%), neutropenia (20% and 21%) and febrile neutropenia (14% and 18%).

Omacetaxine was approved by the FDA in October 2012 for the treatment of patients with CP-CML or AP-CML who are intolerant to 2 or more TKIs or those with resistant disease not responding to prior treatment with 2 or more TKIs.

Recommendations for Monitoring Response to TKI Therapy

Bone marrow cytogenetics and QPCR (IS) with a sensitivity of 4.5-log reduction or more from the standardized baseline are recommended to monitor cytogenetic and molecular responses to TKI therapy, respectively (Table 1). The guidelines emphasize that QPCR (IS) is the preferred method for the measurement of *BCR-ABL1* transcript levels. The panel members agreed that the goal is for all institutions to use

QPCR (IS) for molecular monitoring. If QPCR (IS) is not available, it is acceptable to use the log-reduction from the laboratory-specific standardized baseline to monitor molecular response. In patients with prolonged myelosuppression who may not be in CHR due to persistent cytopenias or unexplained drop in blood counts during therapy, bone marrow cytogenetics may be useful to confirm response to TKI therapy and to look for non-Ph clonal changes and evidence of myelodysplasia.

Routine monitoring of *BCR-ABL1* transcripts, in conjunction with cytogenetic evaluation, provides important information about long-term disease control in patients with CML.[177] Some investigators have reported that interphase FISH can be used to monitor CCyR.[275,276] However, the panel feels that FISH has been inadequately studied for monitoring response to TKI therapy. Therefore, FISH is not recommended for monitoring response.

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 (*BCR-ABL1* transcripts ≤10% (IS) at 3 and 6 months, CCyR or *BCR-ABL1* transcripts ≤1% IS at 12 months). After CCyR 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.[277] Since adherence to TKI therapy is associated with better clinical outcomes, frequent molecular monitoring is essential if there are concerns about the patient's adherence to TKI therapy after CCyR has been achieved. In patients with deeper molecular responses (MMR and below) and who are compliant to TKI therapy, the frequency of molecular monitoring could be reduced, though the optimal frequency is unknown.

Follow-up Therapy

Mutational analysis and evaluation of patient compliance to TKI therapy are recommended if the response milestones are not achieved with TKI therapy at 3, 6, and 12 months (Table 1).

Patients with imatinib-resistant disease or those with intolerance to first-line imatinib should be treated with dasatinib or nilotinib or bosutinib in the second-line setting. Patients with intolerance to first-line dasatinib or nilotinib or those with disease that is resistant to dasatinib or nilotinib could be treated with an alternate TKI (other than imatinib) in the second-line setting. In an analysis of 218 patients with CML treated with dasatinib (n = 101) or nilotinib (n = 117) as first-line therapy, Eghtedar et al reported that treatment failure after first-line therapy was mostly associated with toxicity or patient preference, and these patients had disease that responded to alternative TKIs.[278]

The panel believes that at the present time there are not enough data to recommend one TKI over the other as the preferred second line therapy. Mutational analysis may be helpful in selection of subsequent TKI therapy. See "*Management of Cytogenetic and Hematologic Resistance to TKIs*" in the guidelines for the selection of alternate TKI therapy based on mutational analysis. In very rare patients who are not

able to tolerate TKI therapy, interferon, or PEG-interferon, allogeneic HCT or participation in a clinical can be considered.

Recommendations for follow-up therapy based on response at 3, 6, and 12 months are outlined in Table 2.

Low Sokal risk score at diagnosis, best cytogenetic response on imatinib, neutropenia at any time during imatinib therapy requiring dose reduction despite growth factor support, and time from detection of imatinib failure to start of second-line TKI have been identified as predictive factors for achievement of cytogenetic response on second-line TKI therapy.[164] Recently, Jabbour et al identified a lack of any cytogenetic response to imatinib therapy and a poor performance status as independent poor predictive factors of outcome to second-line TKIs.[279] Based on the available data, patients receiving dasatinib or nilotinib with no cytogenetic or molecular response at 3, 6, or 12 months should be considered for alternative therapies or allogeneic HCT, if a suitable donor is available.

The use of an alternate TKIs after treatment failure with two prior TKIs may induce responses in some patients, but these are not durable except in occasional patients in chronic phase.[280] Investigational therapies or allogeneic HCT should be considered for this group of patients.

3-Month Evaluation

Based on the recent data demonstrating the prognostic significance of early molecular response at 3 months, the panel has included *BCR-ABL1* transcripts ≤10% (IS) as a response milestone at 3 months. If QPCR (IS) is not available, the guidelines have included PCyR on bone marrow cytogenetics as a response milestone at 3 months. In the German CML IV study, absence of a PCyR at 3 months and CCyR at 6 months on imatinib correlated with lower rates of OS.[160]

The NCCN Guidelines recommend continuation of the same dose of TKI therapy (imatinib, dasatinib, nilotinib) and assessment of *BCR-ABL1* transcript levels every 3 months for patients with *BCR-ABL1* transcripts ≤10% (IS) or PCyR on bone marrow cytogenetics. For patients with *BCR-ABL1* transcripts >10% (IS) or lack of PCyR, the second-line treatment options are based on the TKI they received as first-line therapy.

Management of patients with BCR-ABL1 transcripts >10% (IS) or lack of PCyR following first-line imatinib

The CML IV study group identified patients with *BCR-ABL1* (IS) >10% at 3 months as a high-risk group based on their prognosis and recommend switching TKI therapy for this group of patients.[160] In the TIDEL-II study, early switch to nilotinib if molecular response milestones at 3 and 6 months are not achieved after imatinib therapy was associated with higher rates of MMR and transformation-free survival.[210] The cohort of patients with *BCR-ABL1* (IS) >10% at 3 months after imatinib who were switched directly to nilotinib had higher rates of MMR and CMR at 12 months (but not at 24 months) than the cohort of patients who received dose escalation of imatinib before switching to nilotinib.[210] Long-term data from clinical studies that have evaluated dasatinib and nilotinib as second-line therapy have reported durable cytogenetic responses and high transformation-free survival rates in patients with CP-CML intolerant to imatinib or those with resistant disease.[46,47,85]

The panel consensus was to recommend change of therapy to an alternate TKI (dasatinib, nilotinib, or bosutinib) for patients with

BCR-ABL1 transcripts >10% (IS) after initial treatment with imatinib.[160,210] Given some of the serious side effects associated with newer TKIs (eg, pulmonary arterial hypertension with dasatinib,[65] PAOD with nilotinib,[90] cardiovascular side effects with ponatinib[281]), the guidelines have included dose escalation of imatinib as an option for patients who were not candidates for alternate TKI. Evaluation of patient compliance and drug interactions are recommended prior to changing therapy for patients with inadequate initial response.

Management of patients with BCR-ABL1 transcripts >10% (IS) or lack of PCyR following first-line dasatinib or nilotinib

Early landmark analyses from DASISION and ENESTnd studies suggest that if the 3-month response milestone (*BCR-ABL1* transcripts ≤10%) is not achieved after first-line therapy with dasatinib or nilotinib, patients could be considered for early intervention strategies with an alternate TKI.[40,79] In the DASISION and ENESTnd studies, 9% to 16% of patients treated with dasatinib or nilotinib failed to meet the 3-month response milestone (*BCR-ABL1* ≤10%).

Although the long-term PFS and OS rates were significantly better for patients with *BCR-ABL1* ≤10% at 3 months compared to those with *BCR-ABL1* >10% at 3 months after initial treatment with dasatinib and nilotinib, there was only a small difference in OS rates between the two groups (*BCR-ABL1* ≤10% vs. *BCR-ABL1* >10%). In the DASISION study, among patients treated with dasatinib, the 5-year OS rates were 94% vs. 81%, respectively, for patients with *BCR-ABL1* ≤10% and *BCR-ABL1* >10% at 3 months (*P* = .0028). The corresponding 5-year OS rates were 95% and 81% (*P* =.0003), respectively for patients treated with imatinib.[40] In the ENESTnd study, the corresponding 4-year OS rates were 97% and 87%, respectively, for patients treated with nilotinib 300 mg BID (*P* = .0116).[79] The difference in long-term OS rates between the two groups (*BCR-ABL1* ≤10% vs. *BCR-ABL1* >10%) was more significant in the imatinib arm in both the studies (99% vs. 84% in the ENESTnd study, *P* ≤ .0001; 95% and 81% (*P* =.0003) in the DASISION study).[40,79]

The panel members acknowledged that if the 3-month response milestone (*BCR-ABL1* transcripts ≤10% [IS]) is not achieved after first-line therapy with dasatinib or nilotinib, patients are considered to be at high risk for disease progression and should be considered for alternate treatment options or enrollment in a clinical trial. However, in the absence of clear evidence supporting an early intervention strategy, there was no uniform consensus among panel members to recommend a definite treatment option for this group of patients. While some panel members agreed that switching to an alternate TKI may be justified to prevent disease progression for patients with *BCR-ABL1* transcripts >10% (IS) at 3 months, other panel members, however, were not in favor of change of therapy based on a single measurement of *BCR-ABL1* transcripts at 3 months.

Therefore, the guidelines have included clinical trial, continuation of the same dose of dasatinib or nilotinib, or switching to an alternate TKI (after evaluation of patient compliance and drug interactions) as options for patients with *BCR-ABL1* >10% (IS) after initial treatment with dasatinib or nilotinib.

6-Month Evaluation

While some investigators suggest that response assessment at 3 months has a superior prognostic value over response assessment at 6 months,[187] other have reported that assessment of response at 6 months better discriminates patients with poor outcome.[282] In an analysis of 456 patients with CP-CML treated with first-line TKI therapy

(imatinib, dasatinib, or nilotinib), Nazha et al also reported that the outcome of patients who did not achieve MCyR (or *BCR-ABL1* [IS] <10%) at 3 months and subsequently achieved this response at 6 months was similar to that of patients who achieved a MCyR (or *BCR-ABL1* [IS] <10%) at 3 months and superior to that of patients who are not in MCyR (or *BCR-ABL1* <10% IS) at 6 months. At a median follow-up of 95 months, the 5-year OS rates were 100%, 93% and 81%, respectively for the 3 groups of patients. Available data from clinical studies that have evaluated dasatinib or nilotinib as second-line therapy suggest that achievement of molecular response at 3 months after initiation of second-line TKI therapy is predictive of long-term outcome.[47,189,190] Therefore, 6-month response evaluation would allow for timely intervention for those patients who had been switched to an alternate TKI at 3 months.

The guidelines recommend 6-month evaluation with QPCR (IS) for all patients, consistent with the recommendation to monitor with QPCR (IS) every 3 months after initiating TKI therapy. The panel has included *BCR-ABL1* transcripts ≤10% (IS) or ≥ PCyR on bone marrow cytogenetics, if QPCR (IS) is not available, as a response milestone at 6 months as well. Some investigators have suggested *BCR-ABL1* transcripts ≤1% as an optimal response milestone at 6 months.[160,162,186] But the panel members felt that there are not enough mature data to recommend this value. In a recent report, Kim et al also concluded that the *BCR-ABL1* 10% (IS) cut-off at 3 months following second-line TKI therapy provided better stratification than the *BCR-ABL1* 1% (IS) cut-off. The rates of PFS (98.7% vs. 73.2; $P = .001$) and OS (100% vs. 90.7%; $P < .001$) were significantly higher for those with *BCR-ABL1* transcripts <10% compared to those with *BCR-ABL1* >10% at 3 months.[191]

Continuation of the same dose of TKI therapy and assessment of *BCR-ABL1* transcripts every 3 months is recommended for patients with *BCR-ABL1* transcripts ≤10% (IS) or ≥ PCyR on bone marrow cytogenetics. Clinical trial or switching to an alternate TKI (after evaluation of patient compliance and drug interactions) are included as options for patients with *BCR-ABL1* transcripts >10% (IS) or lack of PCyR on bone marrow cytogenetics.

Although landmark analyses from the DASISION and ENESTnd trials have shown that *BCR-ABL1* transcripts >10% (IS) at 6 months is associated with inferior clinical outcomes, these analyses do not address the prognostic significance of 6-month molecular response based on the molecular response at 3 months.[79,162] Limited data available from a retrospective analysis suggest that a change of TKI therapy is not required for the group of patients with *BCR-ABL1* transcripts ≤10% (IS) at 3 months and *BCR-ABL1* transcripts >10% (IS) at 6 months.[187] In this analysis (275 patients treated with imatinib or dasatinib as first-line therapy), the outcomes of patients (11%; 30 of 274) who achieved the 3-month response milestone (*BCR-ABL1* transcripts ≤10% IS) but failed to achieve the 6-month response milestone (*BCR-ABL1* transcripts ≤1% IS) were similar to that of patients who met both response milestones.

The panel acknowledged that there are no data from prospective studies regarding the optimal management of patients with *BCR-ABL1* transcripts ≤10% (IS) at 3 months and *BCR-ABL1* transcripts >10% (IS) at 6 months. This is an unusual group, and attention towards patient adherence to therapy is warranted. However, given the poor prognostic significance of *BCR-ABL1* transcripts >10% (IS) at 6 months (as shown in the landmark analyses of DASISION and ENESTnd trials), the panel consensus was to recommend change of TKI therapy for all patients

with *BCR-ABL1* transcripts >10% (IS) or lack of PCyR at 6 months, regardless of their 3-month response.

12-months and beyond

CCyR (or *BCR-ABL1* transcripts ≤1% IS) is the optimal response milestone at 12 months and beyond. Bone marrow cytogenetics is recommended if CCyR or MMR is not achieved prior to these time points. Continuation of the same dose of TKI therapy is recommended for patients who are in CCyR at 12 months and beyond. For patients with less than CCyR, bone marrow evaluation at 3 months after change of therapy to alternate TKI is recommended to document CCyR. Recommendations for follow-up therapy based on response are outlined in Table 2.

Absence of MMR in the presence of a CCyR is not considered a treatment failure. Several studies have reported that MMR may not be of prognostic significance in patients who have achieved CCyR.[30,159,162,182,183] In the 12-month landmark analysis of the DASISION study, the achievement of CCyR at 12 months was predictive of OS in both treatment arms regardless of the achievement of MMR and there was no difference in outcome between patients who achieved MMR and those who achieved only CCyR.[162] In an analysis of 483 patients with CP-CML, Falchi et al also reported that deeper molecular response at 18 months was not associated with a survival benefit. Furthermore, achievement of sustained MR4·5 was also not associated with a reduced the risk of transformation.[283]

Adherence to TKI Therapy

Treatment interruptions and non-adherence to TKI therapy may lead to undesirable clinical outcomes.[284-286] In the ADAGIO study, which evaluated the outcomes of non-adherence to imatinib therapy in patients with CML, non-adherence was associated with poorer response to imatinib. Patients with suboptimal response had significantly higher mean percentages of imatinib not taken (23%) than did those with optimal response (7%).[286] Marin and colleagues recently identified adherence as the only independent predictor for achieving CMR on standard-dose imatinib.[285] Patients whose imatinib doses were increased had poor adherence (86%), and in these patients adherence was the only independent predictor for inability to achieve a MMR. Poor adherence to imatinib therapy has also been identified as the most important factor contributing to cytogenetic relapse and imatinib failure.[287] Patients with an adherence rate of 85% or less had a higher probability of losing their CCyR at 2 years than those with an adherence rate of more than 85% (27% and 1.5%, respectively). *BCR-ABL1* doubling time has been reported as a marker to identify non-adherence to TKI therapy in patients who are still in CP-CML.[288]

Poor adherence to TKI therapy has also been reported in patients receiving dasatinib and nilotinib following imatinib failure.[289,290] However, the impact of non-adherence to dasatinib and nilotinib on treatment efficacy has not yet been reported. In the absence of such data, findings from the studies involving patients treated with imatinib should be extrapolated to patients receiving second-generation TKI therapy.

Patient education on adherence to TKI therapy and close monitoring of patient's adherence is critical to achieve optimal responses.[291,292] In a significant proportion of patients with TKI-induced toxicities, responses have been observed with doses well below their determined maximum tolerated doses.[293] Short interruptions or dose reductions, when medically necessary, may not have a negative impact on the control of disease or other outcomes. Adequate and appropriate management of

side effects and scheduling appropriate follow-ups to review side effects could be helpful to improve patient adherence to therapy.[294]

Discontinuation of TKI Therapy

TKI therapy has become the standard of care for patients with CML. Imatinib has significantly reduced the annual mortality rate among patients with CML (less than 5% in the first 5–6 years of treatment compared to 10%–20% in the pre-imatinib era), and patients with imatinib-responsive disease are likely to maintain responses on long-term therapy.[14,295] CCyR can be achieved in most patients with CP-CML receiving imatinib, and CMR has been documented in 40% of patients after 7 years of first-line treatment with imatinib.[296] Dasatinib and nilotinib induce faster and deeper treatment responses than imatinib in the first-line setting.[39,40,78,80] However, the vast majority of patients who achieve a clinically undetectable level of *BCR-ABL1* transcripts by the most sensitive PCR measures remain with residual disease that may eventually lead to disease relapse.[297,298]

Results from recent studies suggest that discontinuation of imatinib (with close molecular monitoring and early rescue of molecular relapse) may be possible in selected patients with a stable CMR for 2 or more years.[299-304]

In the multicenter Stop Imatinib (STIM) study, Mahon et al evaluated the possibility of discontinuation of imatinib in 100 patients with a CMR (5-log reduction in *BCR-ABL1* and *ABL1* levels and undetectable transcripts on QPCR) for at least 2 years while on imatinib.[300] Among 69 patients with a follow-up of more than 12 months (median follow-up of 24 months), 39% of patients remained in CMR and 61% of patients relapsed, most within 6 months after discontinuation of imatinib. The molecular relapse-free survival was 41% and 38%, respectively, at 12 months and 2 years. In the updated analysis of the STIM study, the overall probability of maintaining CMR at 24 and 36 months was 39%, and it was significantly better for patients in the low Sokal risk group (55% at 24 months; $P < .001$) compared to those in the intermediate and high-risk groups.[305] Sokal risk score and the duration of imatinib therapy were identified as the independent prognostic factors for the prediction of molecular relapse after imatinib discontinuation. In a recent multicenter observational study (A-STIM study) that evaluated the persistence of MMR in patients with CML who had previously stopped imatinib after prolonged CMR, Rousselot et al reported that the estimated probability of losing MMR 4 months after discontinuation of imatinib was 36% and that loss of MMR could be used as a practical criterion for restarting therapy.[306]

In the Australasian CML8 (TWISTER) study, Ross et al evaluated discontinuation of imatinib in 40 patients (21 had received imatinib after prior interferon and 19 patients had received imatinib as first-line therapy) with CP-CML in CMR for 2 or more years.[303] At the median follow-up of 42 months, the estimated rate of treatment-free remission (free of molecular relapse without treatment for 24 months) at 2 years was 47.1% for all patients and 33.7% for patients treated with imatinib alone. Most relapses occurred within 4 months after discontinuation of imatinib with no relapses beyond 27 months. High Sokal risk score and shorter duration of interferon treatment were associated with increased risk of relapse.

Discontinuation of TKI therapy in patients treated with dasatinib or nilotinib following imatinib failure has been reported in only a small number of patients.[307,308] Ross et al reported that CMR was maintained for more than 12 months in 2 of 3 patients after discontinuation of dasatinib.[307] Rea et al from the French CML Study Group reported that

discontinuation of TKI therapy is possible in patients with stable undetectable *BCR-ABL1* transcripts after treatment with dasatinib or nilotinib following imatinib failure.[308] The majority of patients in this study were in the low Sokal risk group. The median duration of TKI therapy (dasatinib or nilotinib following imatinib failure) and the median duration of sustained undetectable *BCR-ABL1* transcripts prior to discontinuation were 39 months and 28 months, respectively. In a landmark analysis, for patients who were still in MMR without therapy at 6 months, the probability of 12-month and 24-month treatment-free survival without loss of MMR were 91.2% and 84.7%, respectively. Prior history of suboptimal response or resistance to imatinib was associated with a significantly lower chance of successful treatment discontinuation. The 12-month probability of treatment-free survival without loss of MMR was 41.7% for patients with suboptimal response or disease that is resistant to imatinib, compared to 67.3% in other patients (*P* =.04).

Additional prospective studies in larger cohorts with long-term follow-up are needed to determine the optimal duration of CMR, prior to discontinuation of TKI therapy. At the present time, the guidelines recommend continuation of TKI therapy at the prescribed dose indefinitely in patients with responsive disease. Discontinuation of TKI therapy should be considered only in the context of a clinical trial.

Advanced Phase CML

Accelerated Phase

Varying definitions have been used for AP-CML.[309-314] The most commonly used definition is the WHO criteria, which defines accelerated phase as the presence of any of the following features: 10% to 19% of blasts in the peripheral blood or bone marrow, 20% or more of basophils in the peripheral blood, persistent thrombocytopenia (less than 100 x 10^9/L) unrelated to therapy or persistent thrombocytosis (more than 1000 x 10^9/L) unresponsive to therapy, increasing spleen size, and increasing white blood cell (WBC) count unresponsive to therapy.[314] Cortes et al have suggested a modification to the WHO criteria (≥ 10% to 29% peripheral blood or bone marrow blasts, ≥ 30% or more of peripheral blood blasts and promyelocytes, ≥ 20% peripheral blood or bone marrow basophils, platelet count ≤ 100 x 10^9/L unrelated to therapy, and clonal evolution).[313] It should be noted that clinical trials of TKIs have largely reported efficacy data using the modified MD Anderson Cancer Center accelerated phase criteria (15% and < 30% peripheral blood or bone marrow blasts, ≥ 30% or more of peripheral blood blasts and promyelocytes, ≥ 20% peripheral blood or bone marrow basophils, platelet count ≤ 100 x 10^9/L unrelated to therapy, and clonal evolution).[312]

Blast Phase

Approximately 50% of all the blast phase cases are of the myeloid subtype, 25% are of the lymphoid subtype, and the rest are undifferentiated. According to the International Bone Marrow Transplant Registry (IBMTR), blast crisis is defined as 30% or greater blasts in the blood, bone marrow, or both, or as the presence of extramedullary disease.[315] In the WHO criteria, blast crisis is defined as 20% or greater 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.[314] See *Definitions for Blast Phase* in the guidelines.

Treatment Options

Imatinib has induced favorable hematologic and cytogenetic response rates in patients with AP-CML or BP-CML.[312,316-323] Dasatinib,[53,55,56,323] nilotinib,[86,87,323] bosutinib,[99] and ponatinib[103,104] have demonstrated clinical activity in imatinib-resistant or imatinib-intolerant AP-CML or BP-CML. Omacetaxine has shown activity in patients with accelerated or blast phase CML resistant or intolerant to prior therapy with 2 or more TKIs.[274,324]

High-dose combination chemotherapy has been used in patients with AP-CML or BP-CML resulting in response rates of 25% to 60%.[325-329] In a study of 48 patients with AP-CML or BP-CML, intensive chemotherapy induced hematologic and cytogenetic responses in 29% and 23% of patients, respectively; CHR was observed in 25% of patients with AP-CML and 33% of patients with BP-CML.[325] Among patients with BP-CML, ALL-type chemotherapy regimens are associated with higher response rates in patients with lymphoid BP-CML (49% vs. less than 20% for other morphologies; $P < .001$); however, the responses are not durable.[326]

The addition of TKI to chemotherapy has been shown to improve outcome in patients with advanced phase CML.[330-340] The efficacy of imatinib in combination with chemotherapy in AP-CML and myeloid BP-CML has been demonstrated in several small studies.[333-335,337] In one study involving 18 patients with AP-CML and 10 patients with myeloid BP-CML, the combination of imatinib and decitabine induced CHR and MCyR in 32% and 18% of patients, respectively.[333] Partial hematologic response and minor cytogenetic response was observed in 4% and 11% of patients, respectively. The hematologic response rate was higher in patients without BCR-ABL1 kinase mutations (53% vs. 14% for those with mutations). The median duration of hematologic response was 18 weeks. In a pilot study of 19 patients with myeloid BP-CML, the combination of imatinib, low-dose Ara-C, and idarubicin-induced CHR in 47% of patients and 26% of patients returned to chronic phase.[334] In a more recent study of 36 patients with myeloid BP-CML, the addition of imatinib to daunorubicin and cytarabine resulted in a hematologic response rate of 78% (CHR rate of 55.5%) with a median follow-up of 6 years.[337] Median OS was 16 months, and the OS in patients with hematologic response was 35.4 months.

The use of imatinib or dasatinib in combination with hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) has been shown to be effective for the treatment of patients with lymphoid BP-CML.[339,340] In a study of 34 patients with lymphoid BP-CML or relapsed Ph-positive ALL, the addition of dasatinib to hyper-CVAD resulted in an overall response rate of 91% (71% achieving complete remission [CR] and 21% achieved CR with incomplete platelet recovery); 84% of patients achieved CCyR after one cycle of therapy.[339] The overall CMR rate was 42% (35% achieved MMR). Among patients with lymphoid BP-CML, at a median follow-up of 37.5 months, the 3-year OS rate was 70%, with 68% remaining in CR at 3 years.[339] The efficacy of hyper-CVAD used in combination with imatinib or dasatinib for patients with BP-CML, particularly when followed by allogeneic HCT, was also confirmed in a more recent report.[340] Among 42 patients with BP-CML, CHR, CCyR and CMR were achieved in 90%, 58% and 25% of patients respectively. The median remission duration and median OS were 14 months and 17 months respectively. In multivariate analysis, the median remission duration was longer among HCT recipients ($P = .01$); the median OS was longer among HCT recipients ($P < .001$) and in patients treated with dasatinib ($P = .07$).[340]

NCCN Recommendations

The guidelines strongly recommend that patients with advanced phase CML be treated in specialized centers. Participation in clinical trials (evaluating TKI in combination with chemotherapy or other novel treatment options) is recommended for all patients with AP-CML or BP-CML.

Imatinib (600 mg once daily), dasatinib (140 mg once daily) or nilotinib (400 mg twice daily) or bosutinib (500 mg once daily) are appropriate options for patients with de novo AP-CML. Allogeneic HCT can be considered based on response to TKI therapy. Omacetaxine is a treatment option for patients with resistant disease and/or intolerance to two or more TKIs.

TKI therapy alone or in combination with chemotherapy followed by allogeneic HCT (if feasible) is recommended for patients with myeloid or lymphoid BP-CML. ALL-type chemotherapy is recommended for patients with lymphoid BP-CML (See NCCN Guidelines for ALL). AML-type chemotherapy is recommended for those with myeloid BP-CML (See NCCN Guidelines for AML).

Central nervous system (CNS) involvement has been described in few case reports of BP-CML.[341-344] Documented CNS involvement in patients with myeloid or lymphoid BP-CML should be managed according to the standard of care for AML or ALL. CNS prophylaxis should be given for lymphoid BP-CML. TKI therapy has not been optimized for patients with CNS involvement. Dasatinib has been reported to cross the blood brain barrier and may represent the best TKI option for patients with CNS disease.[345]

Mutational analysis is recommended for all patients with AP-CML and BP-CML prior to initiation of TKI therapy. In patients with disease progression to AP-CML or BP-CML, the selection of TKI therapy is based on prior therapy and/or mutational analysis.[243-245] See "*Management of Cytogenetic and Hematologic Resistance to TKIs*" in the guidelines for the selection of alternate TKI therapy based on mutational analysis.

A significant portion of patients with AP-CML or BP-CML treated with dasatinib or nilotinib achieve a MCyR but not a concomitant CHR because of persistent cytopenias. Fava et al reported that absence of a CHR at the time of MCyR was associated with an inferior outcome. The 2-year survival rate was 37% compared to 77% for patients with MCyR and concomitant CHR, suggesting that patients with MCyR without a CHR should be considered for alternate treatment options.[346]

Allogeneic Hematopoietic Cell Transplant

Allogeneic HCT is a potentially curative treatment for patients with CML, but the excellent results with TKI therapy have challenged the role of allogeneic HCT as a first-line therapy.[347,348] The widespread application of allogeneic HCT is limited by donor availability and the high toxicity of the procedure in older patients, which limits the age of eligibility at many centers to younger than 65 years. Ongoing advances in alternative donor sources (such as unrelated donors and cord blood), more accurate HLA typing of unrelated donors, and less toxic regimens are broadening the use of allogeneic HCT. Transplants from unrelated matched donors can now be used for many patients with CML. The advent of molecular DNA assessment of HLA typing has enabled a rigorous and stringent selection of unrelated matched donors, and this improvement in typing has translated into greatly improved transplant

outcomes, so that results with unrelated, fully matched donors are comparable to those of related matched donors.[349-351]

Prognostic Factors

The outcome of allogeneic HCT is influenced by the disease phase, HLA matching, age, sex, and time from diagnosis to transplant.[352] Low HCT comorbidity index (HCT-CI) and low C-reactive protein were recently identified as prognostic indicators for lower non-relapsed mortality rate and a somewhat improved survival rate.[353] The disease phase at the time of transplant remains an important prognostic factor; outcomes following transplant are clearly better for patients in chronic phase compared to patients with advanced disease; 5-year survival rates after matched-related transplants are approximately 75%, 40%, and 10% for patients in chronic, accelerated, and blast phases, respectively.[351] Patients who receive allogeneic HCT for CML in first chronic phase and remain in remission for at least 5 years have favorable subsequent long-term survival.[354] Survival remains poor for patients transplanted in accelerated or blast phase compared to those transplanted in chronic phase.[355-357] Gratwohl et al reported improved survival across all the EBMT risk groups due to significant reduction in incidences of relapse and treatment-related mortality. However, survival was still poor for patients transplanted in accelerated or blast phase (40%–47% and 16%, respectively) compared to 70% for those transplanted in chronic phase.[355] In the subgroup analysis of the German CML IV study, among 84 patients who underwent allogeneic HCT because of a high-disease risk score at diagnosis, imatinib failure, or disease progression, the 3-year survival rates were 91% for patients with chronic phase and 59% for those with advanced phase, with a treatment-related mortality of 8%.[357] In a more recent report from the Center for International Blood and Marrow Transplant Research (CIBMTR) disease-free survival rates after allogeneic HCT were 35% to 40%, 26% to 27%, and 8% to 11% for patients transplanted in the second chronic phase, accelerated phase, and blast phase, respectively.[358] Multivariate analyses demonstrated that conventional prognostic indicators remain the strongest determinants of transplant outcomes. Therefore, the potential use of transplantation must be tied to faithful monitoring of disease, since the major potential pitfall in delaying transplantation is “missing” the chronic phase interval.

Effect of Prior TKI Therapy

There has been concern that previous treatment with TKIs might have a deleterious effect on subsequent allogeneic HCT outcomes, as previously implicated with busulfan and interferon.[359-361] However, results from several studies have confirmed that the use of TKIs prior to allogeneic HCT does not compromise the outcome of subsequent allogeneic HCT or increase transplant-related toxicity.[362-369] In fact, the IBMTR data on 409 patients treated with imatinib before transplant and 900 patients who did not receive imatinib showed that prior use of imatinib was associated with improved survival for patients transplanted in chronic phase, although this was limited to patients who underwent transplant because of intolerance rather than treatment failure with imatinib.[366] Such a survival benefit was not seen in patients transplanted in advanced phase. In a recent analysis of 97 patients with CP-CML who underwent allogeneic HCT in, Lee et al identified achievement of MMR at 1 month and MR4.5 at 3 months after allogeneic HCT as important predictors of favorable long-term outcomes. In multivariate analysis, prior TKI therapy was not associated with either treatment-related mortality or relapse.[370]

Indications for Allogeneic HCT

Allogeneic HCT is an appropriate first-line treatment option for the very rare patients presenting with blast phase at diagnosis, patients with T315I and other *BCR-ABL1* mutations that are resistant to all TKIs, and for rare patients intolerant to all TKIs.[201,347] A recent report from the MD Andersen Cancer Center indicated that allogeneic HCT is an effective strategy for patients with CML with T315I mutation, particularly in earlier stages; patients who underwent transplant in chronic phase had the best outcome.[371] In a more recent analysis of patients with CML resistant to imatinib (chronic phase, n = 34; accelerated phase, n = 9; and blast phase, n = 4) who underwent HCT at the MD Anderson Cancer Center, the overall response rate was 89% and 68% of patients had MMR.[372] The 2-year EFS rate was 36% for patients with *BCR-ABL1* mutations and 58% for those with no mutations, respectively. The corresponding 2-year OS rate was 44% and 76%, respectively. Nicolini et al also reported similar findings in 64 patients with T315I mutation.[373] At a median follow-up of 26 months, survival probabilities at 24 months after allogeneic HCT were 59%, 67%, and 30% for patients with chronic, accelerated, and blast phase, respectively. In multivariate analysis, blast phase at the time of transplant and transplants from unrelated donors were identified as adverse prognostic factors for OS.

NCCN Recommendations

Chronic Phase CML

Given the successful induction of durable responses with imatinib in the vast majority of patients and the recent results showing superior early efficacy of nilotinib and dasatinib in newly diagnosed patients, allogeneic HCT is no longer recommended as a first-line treatment option for patients with CP-CML. In a randomized study, primary HCT and drug treatment were compared in 621 newly diagnosed patients.[374] Among the 354 patients who were eligible for HCT based on the availability of a related donor, 123 patients received a HCT and 219 patients received the best possible drug treatment (interferon until imatinib became available later in the trial; imatinib was offered to patients with disease that failed interferon therapy). Survival with drug therapy was clearly superior for the first 5 years. Survival differences were significant in low-risk patients and no survival difference was observed in intermediate- or high-risk patients.[374]

Allogeneic HCT is recommended for patients with T315I mutation that is resistant to TKI therapy. Evaluation for allogeneic HCT (that is, a discussion with a transplant specialist, which might include initiating HLA typing) is recommended if the response milestones are not achieved at 3, 6, and 12 months, as indicated below:

- *BCR-ABL1* transcripts >10% by QPCR (IS) or lack of PCyR at 3 and 6 months
- Less than PCyR or *BCR-ABL1* transcripts >10% by QPCR (IS) at 12 months
- Cytogenetic relapse at 12 months

Nonmyeloablative allogeneic HCT is a well-tolerated treatment option for patients with a matched donor and the selection of patients is based on their age and the presence of comorbidities.[375-381]

Advanced Phase CML

Allogeneic HCT should be considered for patients with AP-CML or BP-CML. In patients with disease progression to accelerated or blast phase on prior TKI therapy, treatment with a course of alternate TKI (not received before) will be beneficial as a “bridge” to allogeneic HCT.

Monitoring Response after Allogeneic HCT

The *BCR-ABL1* transcripts persist after many years in most patients after allogeneic HCT. Several studies have investigated the clinical significance of monitoring *BCR-ABL1* transcript levels by QPCR following HCT.[382-387] Radich et al reported that PCR positivity 6 or 12 months after HCT is associated with a higher risk of disease relapse (42%) compared to only 3% in patients who tested PCR-negative. This study also showed that early PCR positivity is associated with more aggressive disease and high risk of relapse.[384] Olavarria et al reported similar findings. QPCR was performed at 3 to 5 months after allogeneic HCT. At 3 years after allogeneic HCT, the cumulative relapse rate was 17% for patients with no evidence of *BCR-ABL1* transcripts, 43% for those who had less than 100 *BCR-ABL1* transcripts, and 86% for those with more than 100 *BCR-ABL1* transcripts.[386] PCR positivity at 6 months or less was also highly predictive of relapse in patients who received T-cell–depleted transplant.[385] The prognostic significance of *BCR-ABL1* positivity is less evident after a longer period of time following transplantation. Costello et al reported that the relapse rate was only 8% in patients who were *BCR-ABL1* positive at more than 36 months after HCT.[388] Other investigators have reported that *BCR-ABL1* transcripts persist even in patients who are in CR for more than 10 years after HCT.[389] More recently, Radich et al analyzed 379 consecutive CML patients alive at 18 months or more after HCT to assess the relapse risk associated with *BCR-ABL1* detection in "late" CML survivors.[387] Ninety of 379 patients (24%) had at least one positive *BCR-ABL1* test 18 months after transplantation or later; 13 of 90 *BCR-ABL1*-positive patients (14%) and 3 of 289 *BCR-ABL1*-negative patients (1.0%) relapsed.

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

Management of Post-transplant Relapse

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.[390-394] The probability of survival at 3 years following DLI was significantly better for patients who achieved molecular remission than for those who did not achieve molecular remission (95% and 53%, respectively; P = .0001).[391] However, DLI is associated with complications such as graft-vs-host disease (GVHD), susceptibility to infections, and immunosuppression.[390] 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, the use of escalating cell dosage regimens, and very-low-dose DLI in combination with IFN alpha have reduced the incidence of GVHD associated with DLI.[395-399]

Imatinib has also been very effective in inducing durable remissions in the majority of patients relapsing in all phases of CML following allogeneic HCT.[400-405] CHR and CCyR rates with post-transplant imatinib are higher in patients with chronic phase relapse than advanced phase relapse. More recent studies have also reported durable molecular

responses with imatinib in patients relapsing with chronic and advanced phase disease.[406,407] Imatinib has also been shown to be effective in the prophylactic setting to prevent relapse following HCT in high-risk patients. In a prospective evaluation of patients with Ph-positive ALL (n = 15) or CML beyond first chronic phase (n = 7) in remission following myeloablative allogeneic HCT, Carpenter et al showed that imatinib can be safely administered during the first 90 days after myeloablative allogeneic HCT at a dose intensity comparable to that used in primary therapy.[408] Imatinib was administered for one year following HCT. At a median follow-up of 1.4 years, the majority of patients (5 patients with CML and 12 patients with ALL) were in molecular remission. Olavarria et al also reported similar findings in patients undergoing nonmyeloablative allogeneic HCT in first chronic phase.[409]

In a recent retrospective analysis, disease-free survival was significantly higher for patients receiving DLI than for those in the imatinib group.[410] There was also a trend towards higher rates of complete molecular remissions in the DLI group. Some investigators have suggested that the combination of DLI and imatinib may be more effective at inducing rapid molecular remissions than either modality alone.[411] These observations are yet to be confirmed in randomized trials.

NCCN Recommendations

Patients who are in CCyR (QPCR-negative) should undergo regular QPCR monitoring (every 3 months for 2 years, then every 3 to 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.[408]

Imatinib, dasatinib, nilotinib, bosutinib, ponatinib or omacetaxine, DLI, or interferon or PEG-interferon can be considered as options for patients who are not in remission or in cytogenetic relapse or those with an increasing level of molecular relapse. Monitored withdrawal of immune suppression is recommended prior to initiation of TKI therapy for post-transplant relapse.

In patients with CML that has previously failed imatinib, there are no data to support the use of post-transplant imatinib. Very limited data in a small number of patients are available on the use of dasatinib and nilotinib in patients with post-transplant relapse.[412-418] There are no data to support the use of post-transplant bosutinib, ponatinib, or omacetaxine. Dasatinib, nilotinib, bosutinib, ponatinib, or omacetaxine may be more appropriate for patients with CML that has previously failed imatinib. Participation in a clinical trial should be considered.

CNS relapse of CML following allogeneic HCT has been described in few case reports.[419,420] Dasatinib may also be an effective treatment for extramedullary relapse following allogeneic HCT.[345,421,422]

Summary

CML is characterized by the presence of Ph chromosome resulting from the reciprocal translocation t(9;22). The development of small molecule inhibitors of BCR-ABL1 tyrosine kinase has significantly improved the outcomes of patients with newly diagnosed CML.

The results of the IRIS trial established the safety, efficacy, and excellent survival benefit for imatinib in patients with newly diagnosed CML. Long-term data from DASISION and ENESTnd studies have demonstrated that dasatinib and nilotinib are associated with superior cytogenetic and molecular response rates and lower rates of

progression to accelerated or blast phase compared to imatinib in newly diagnosed patients with CML. Imatinib 400 mg daily is still considered a reasonable first-line treatment for newly diagnosed patients with CP-CML. Dasatinib and nilotinib are also included as first-line treatment options for patients with newly diagnosed CP-CML.

Early molecular response to first-line TKI therapy (*BCR-ABL1* transcripts ≤10% by QPCR (IS) at 3 and 6 months) is an effective predictor of long-term clinical outcomes. QPCR (IS) is the preferred method for monitoring response to TKI therapy. Bone marrow cytogenetics can be used if QPCR (IS) is not available. 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. After CCyR has been achieved, molecular monitoring is recommended every 3 months for 3 years and every 3 to 6 months thereafter.

Point mutations in the BCR-ABL1 kinase domain are a frequent mechanism of resistance to TKI therapy. Dasatinib and nilotinib are effective against a majority of mutations resistant to imatinib, except for the T315I mutation. Bosutinib has shown potent activity in patients with *BCR-ABL1* mutations resistant to dasatinib (F317L) and nilotinib (Y253H and F359). Ponatinib has demonstrated activity in patients with *BCR-ABL1* mutations resistant to imatinib, dasatinib, or nilotinib (F317L, E255K, F359V, and G250E) including patients with T315I. Mutational analysis is recommended if there is inadequate initial response, or any sign of loss of response or 1-log increase in *BCR-ABL1* transcripts with loss of MMR or disease progression. Evaluation for allogeneic HCT (a discussion with a transplant specialist, which might include initiating HLA typing) is recommended for all patients with CP-CML who do not meet response milestones to first-line TKI therapy.

Dasatinib, nilotinib, or bosutinib are effective treatment options for patients with CP-CML intolerant to imatinib or those with resistant disease as well as for patients with AP-CML. Allogeneic HCT should be considered based on response to therapy. TKI therapy either alone or in combination with chemotherapy followed by allogeneic HCT is recommended for patients with BP-CML. Ponatinib is an option for patients with T315I mutation and for those with disease that has not responded to multiple TKIs. Omacetaxine is an option for patients with intolerance to two or more TKIs or for those with CP-CML and AP-CML resistant to two or more TKIs and for those with T315I mutation.

Allogeneic HCT remains a potentially curative treatment for patients with CML and is recommended for patients with T315I mutation as well as for the rare patients who present with BP-CML at diagnosis. Post-transplant TKI therapy should be considered for at least one year for patients with prior accelerated or blast phase who are in remission following allogeneic HCT. Imatinib, dasatinib, nilotinib, bosutinib, omacetaxine, DLI, interferon, or PEG-interferon can be considered for patients with post-transplant relapse.

The selection of appropriate TKI is dependent on the disease phase, the agent's side effect profile, and its relative effectiveness against BCR-ABL1 mutations. Ongoing clinical trials are evaluating alternate treatment options for patients with BCR-ABL1 mutations resistant to currently approved TKIs. Consistent with NCCN philosophy, participation in clinical trials is encouraged

Table 1. Recommendations for Monitoring Response to TKI Therapy and Mutational Analysis[1,2]

Test	Recommendation
Bone marrow cytogenetics[2]	At diagnosis to establish the disease phase. If collection of bone marrow is not feasible, FISH on a peripheral blood specimen using dual probes for the *BCR* and *ABL1* genes is an acceptable method of confirming the diagnosis of CML. At 3 months and 6 months after the initiation of TKI therapy, if QPCR (IS) is not available. At 12 months and beyond from the initiation of TKI therapy, if there is no CCyR or MMR. Absence of MMR in the presence of a CCyR is not considered a treatment failure. For patients with less than CCyR at 12 months and beyond, bone marrow cytogenetics should be repeated at 3 months after change of therapy to alternate TKI to document CCyR. Rising levels of *BCR-ABL1* transcript (1-log increase) without a MMR.
QPCR (IS)	At diagnosis. Every 3 months after initiation of treatment. After CCyR has been achieved, every 3 months for 2 years and every 3–6 months thereafter. If there is a rising level of *BCR-ABL1* transcript (1-log increase) with a MMR, QPCR should be repeated in 1–3 months.
BCR-ABL1 kinase domain mutation analysis	Chronic phase ➢ Inadequate initial response to TKI therapy (*BCR-ABL1* transcripts >10% (IS) or lack of PCyR at 3 and 6 months or less than a CCyR or *BCR-ABL1* transcripts >1% (IS) at 12 months). ➢ 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.

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

Table 2. Recommendations for Follow-up Therapy

Follow-up	Response	Treatment Recommendations[1,2,3]
3 months	*BCR-ABL1* transcripts ≤10% (IS) or PCyR	Continue the same dose of TKI[4]
	BCR-ABL1 transcripts >10% (IS) or lack of PCyR[5,6]	***Primary treatment with imatinib*** Switch to alternate TKI or Dose escalation of imatinib to a maximum of 800 mg, as tolerated (if not a candidate for alternate TKI) ***Primary treatment with dasatinib or nilotinib*** Continue the same dose of TKI or Switch to alternate TKI (other than imatinib)
6 months	*BCR-ABL1* transcripts ≤10% (IS) or ≥ PCyR	Continue the same dose of TKI[4]
	BCR-ABL1 transcripts >10% (IS) or lack of PCyR[5,6]	Switch to alternate TKI (other than imatinib)
12 months	CCyR or *BCR-ABL1* transcripts ≤1% but >0.1% (IS)	Continue the same dose of TKI[4]
	PCyR or *BCR-ABL1* transcripts ≤10% but >1% (IS)	Continue the same dose of TKI[4] or Switch to alternate TKI (other than imatinib) (preferred) or Dose escalation of imatinib to a maximum of 800 mg, as tolerated (if not a candidate for alternate TKI or omacetaxine)
	Less than PCyR or *BCR-ABL1* transcripts >10% (IS)[5,6]	Switch to alternate TKI (other than imatinib)
	Cytogenetic relapse[5,6]	Switch to alternate TKI (other than imatinib) or Dose escalation of imatinib to a maximum of 800 mg, as tolerated (if not a candidate for alternate TKI or omacetaxine)

1. Mutational analysis and evaluation of patient compliance to TKI therapy are recommended if the response milestones are not achieved.
2. Ponatinib is a treatment option for patients with T315I mutation or for patients with disease that has not responded to two or more TKIs.
3. Omacetaxine is a treatment option for patients who are intolerant to two or more TKIs or for resistant disease not responding to two or more TKIs.
4. Same dose of TKI should be continued indefinitely. Discontinuation of TKI should only be done in the setting of a clinical trial.
5. Evaluation for allogeneic HCT (a discussion with a transplant specialist, which might include initiating HLA typing) is recommended.
6. Enrollment in clinical trial is an option for this group of patients.

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