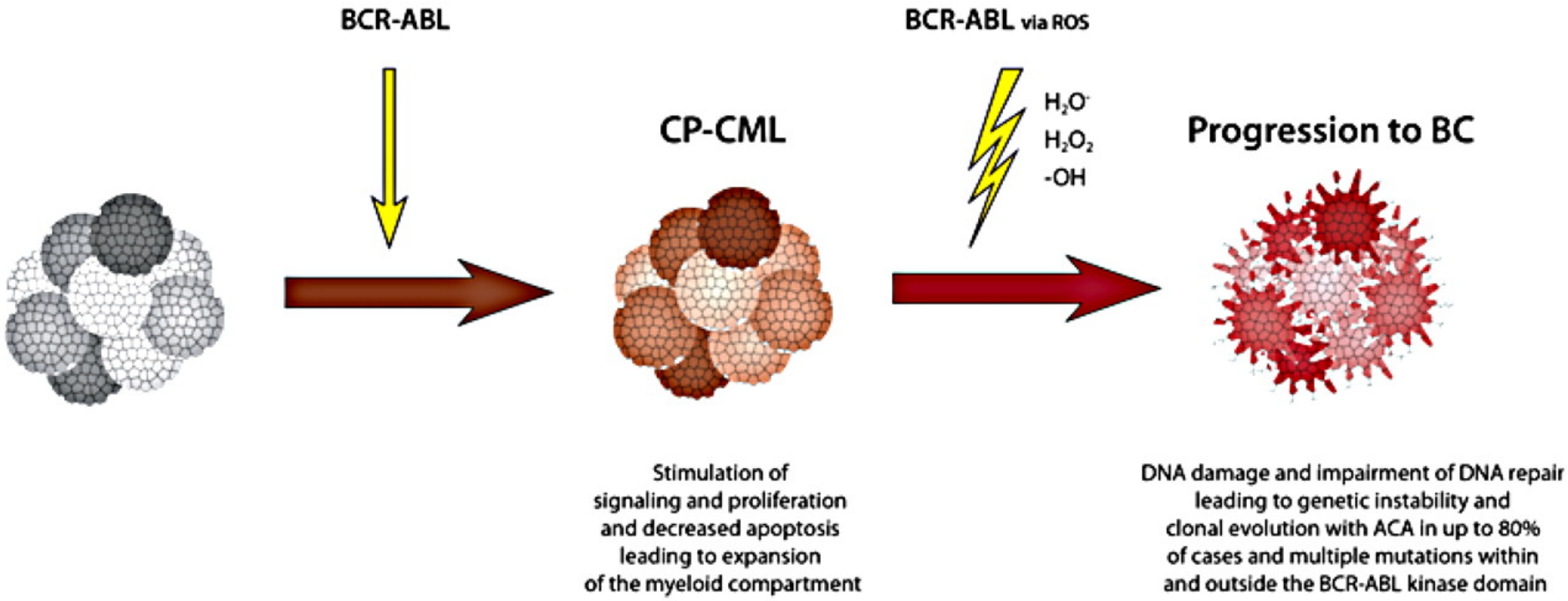
CML Diagnosis and Management

Lymphoma Tumor Board

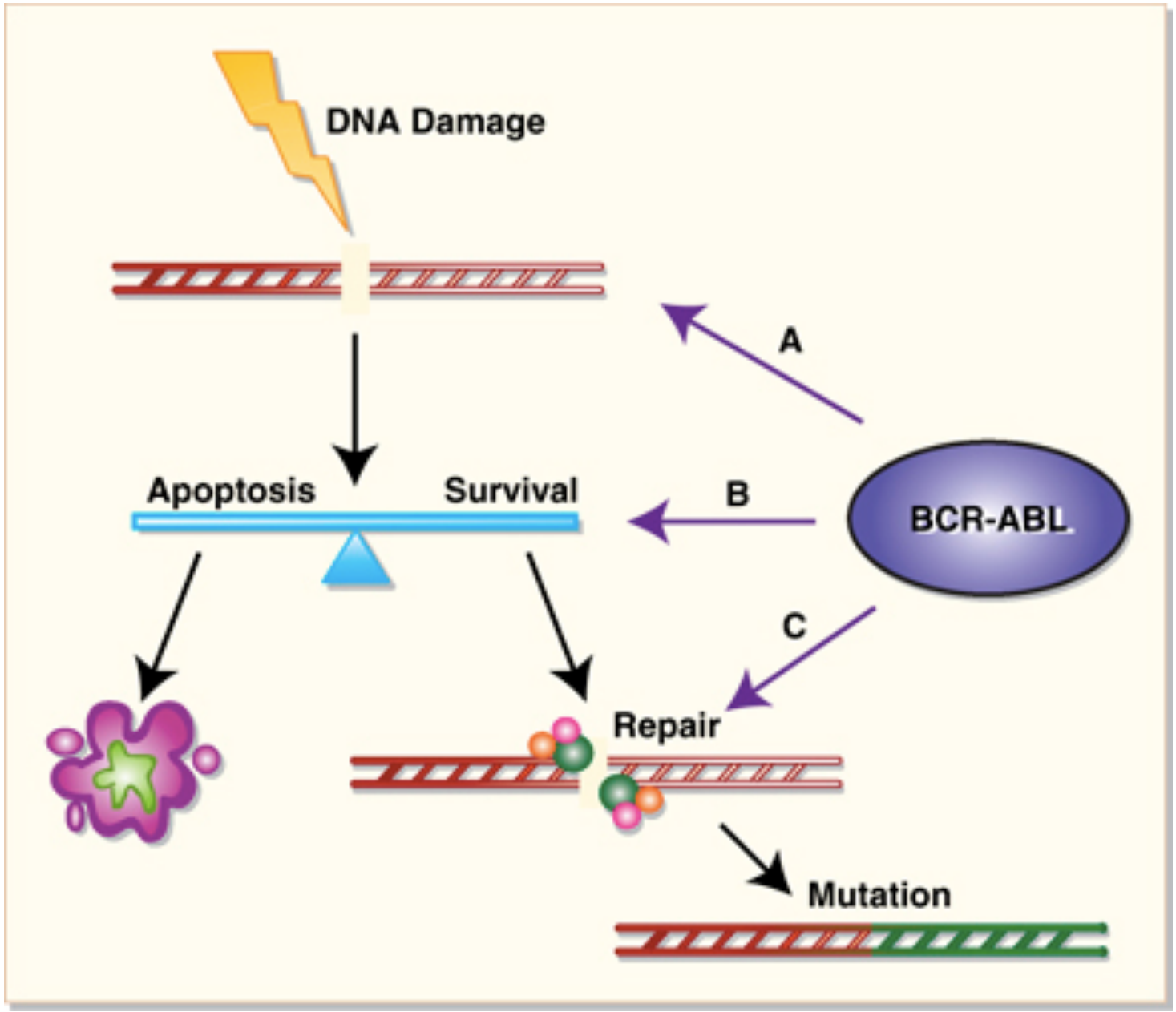
September 15, 2017

Mechanisms of BCR-ABL activity in CML and blast crisis

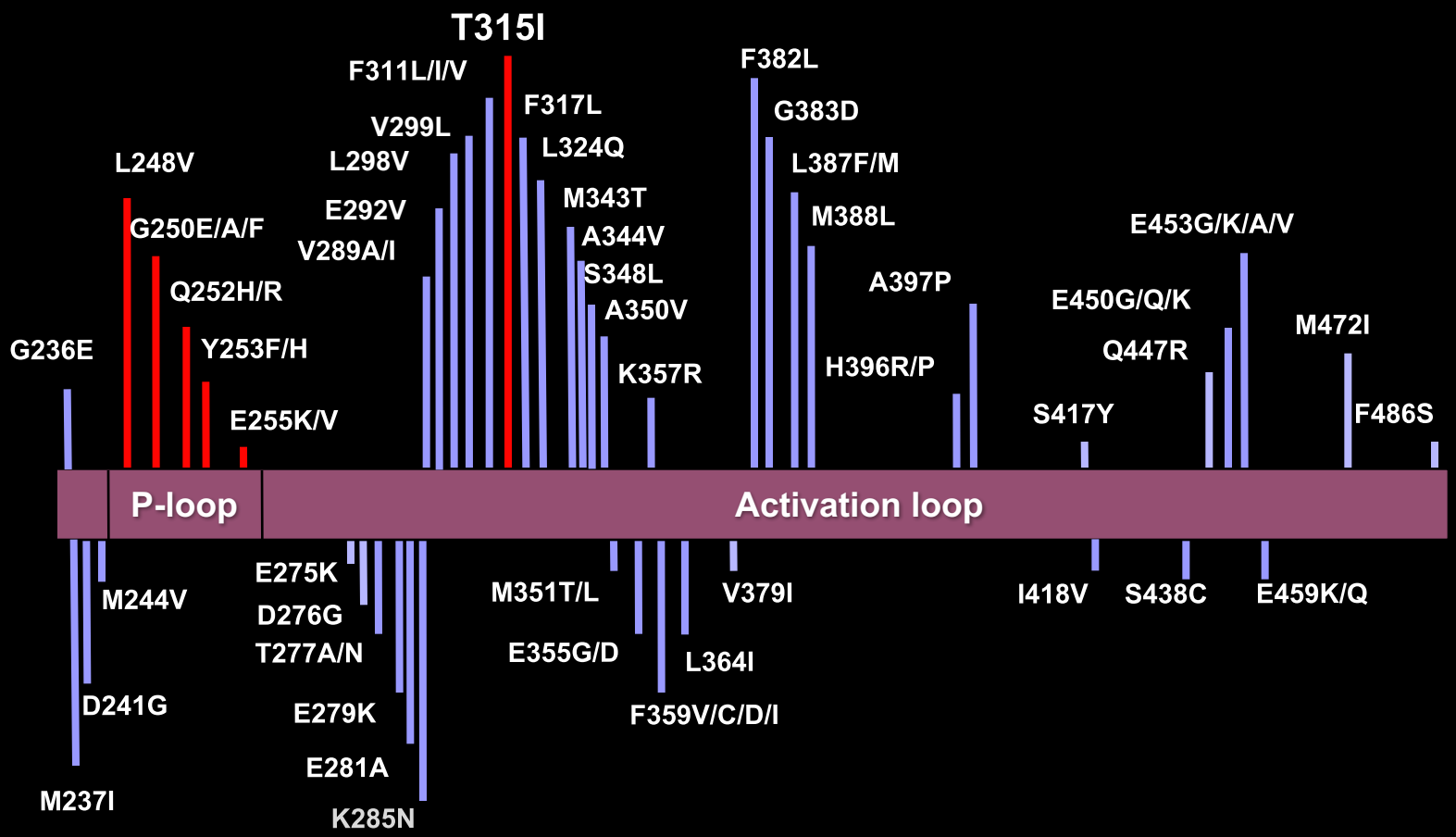


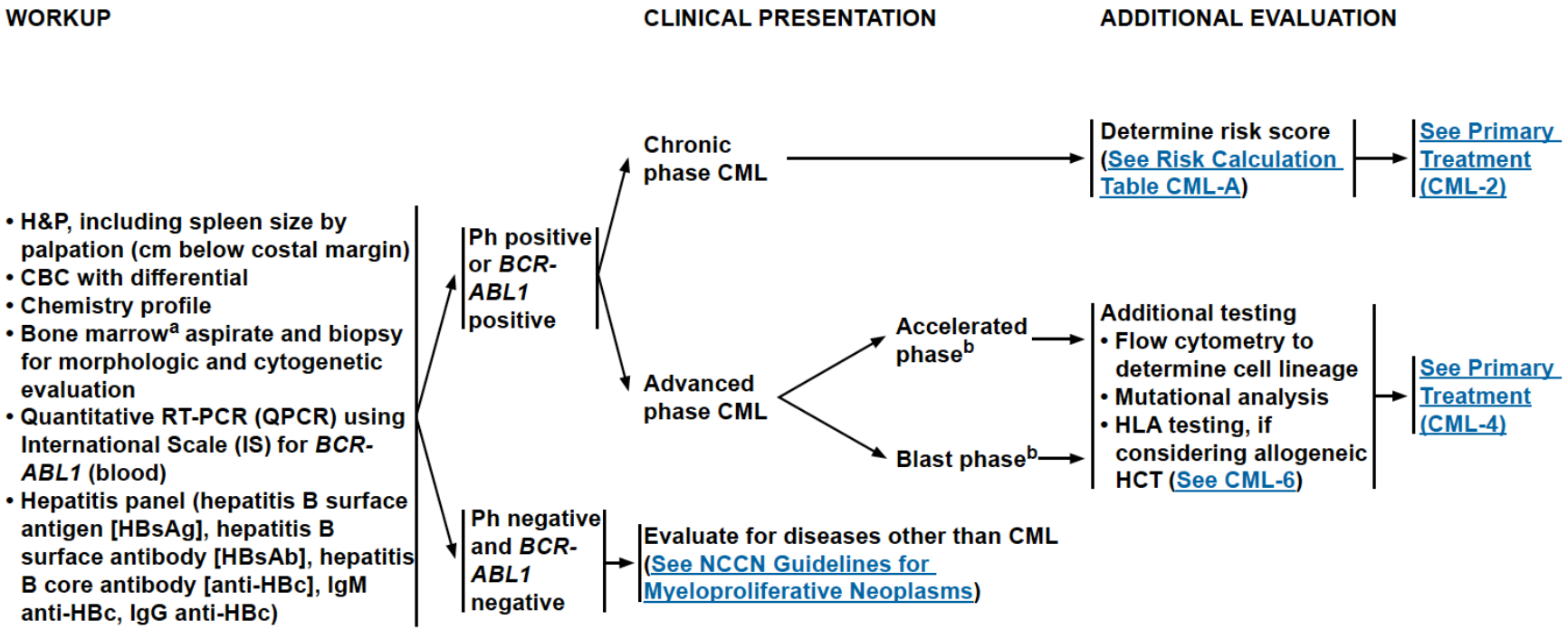
Rüdiger Hehlmann Blood 2012;120:737-747

BCR/ABL influences DNA mutation in multiple ways



BCR-ABL Imatinib-Resistance Mutations





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

Note: All recommendations are category 2A unless otherwise indicated.
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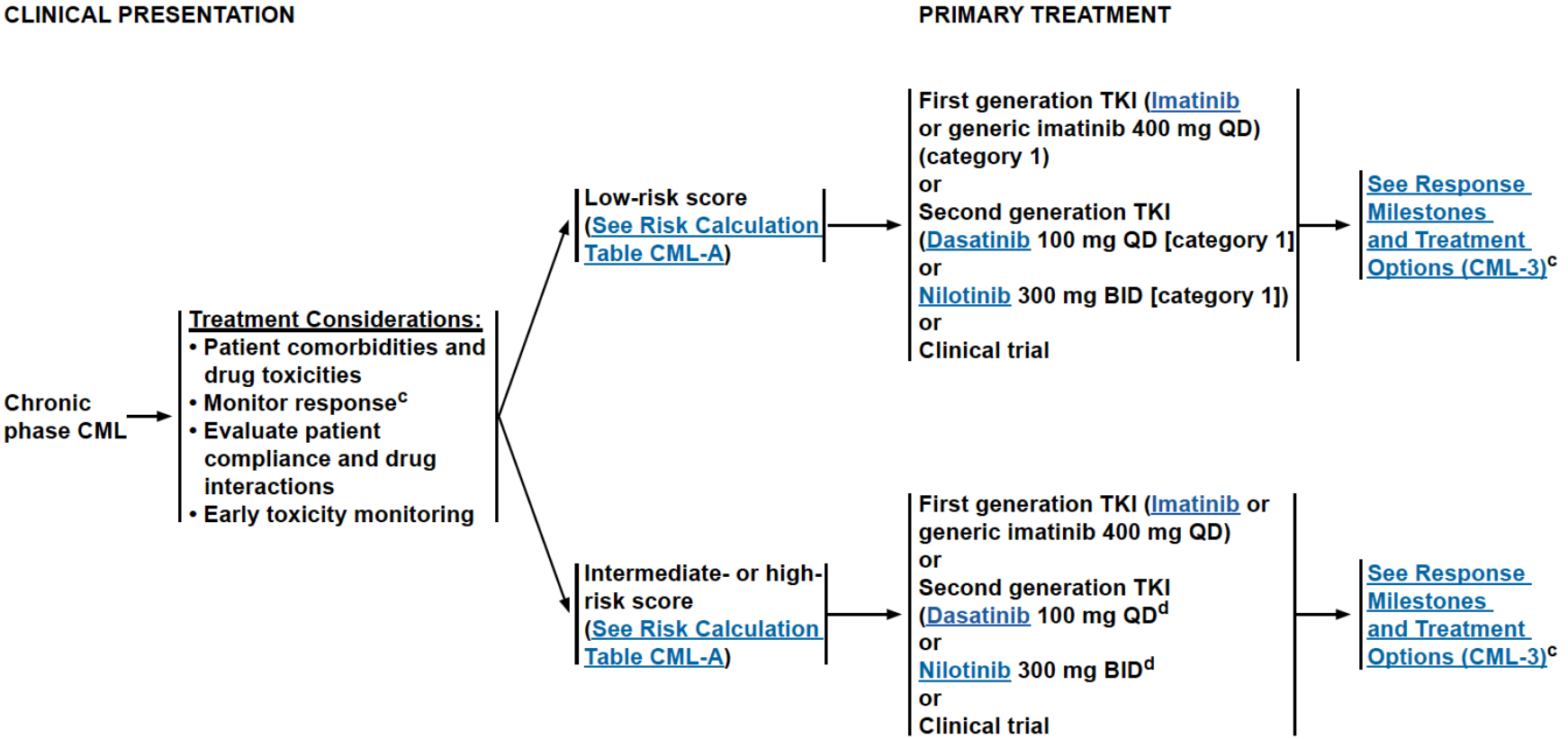

[c] See Monitoring Response to TKI Therapy and Mutational Analysis (CML-C).
[d] Long-term follow-up data suggest that patients with an intermediate- or high-risk Sokal or Hasford score may preferentially benefit from dasatinib or nilotinib. See Discussion for additional information.

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RESPONSE MILESTONES[c,e]

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

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

[c] See Monitoring Response to TKI Therapy and Mutational Analysis (CML-C).
[e] See Criteria for Hematologic, Cytogenetic, and Molecular Response and Relapse (CML-D).
[f] Patients with *BCR-ABL1* only slightly >10% at 3 months and/or with a steep decline from baseline, may achieve <10% at 6 months and have generally favorable outcomes. Therefore, it is important to interpret the value at 3 months in this context, before making drastic changes to the treatment strategy.
[g] Achievement of response milestones must be interpreted within the clinical context. Patients with more than 50% reduction compared to baseline or minimally above the 10% cutoff can continue the same dose of dasatinib or nilotinib for another 3 months.
[h] Discontinuation of TKI with careful monitoring is feasible in selected patients. See Discontinuation of TKI Therapy (CML-E).

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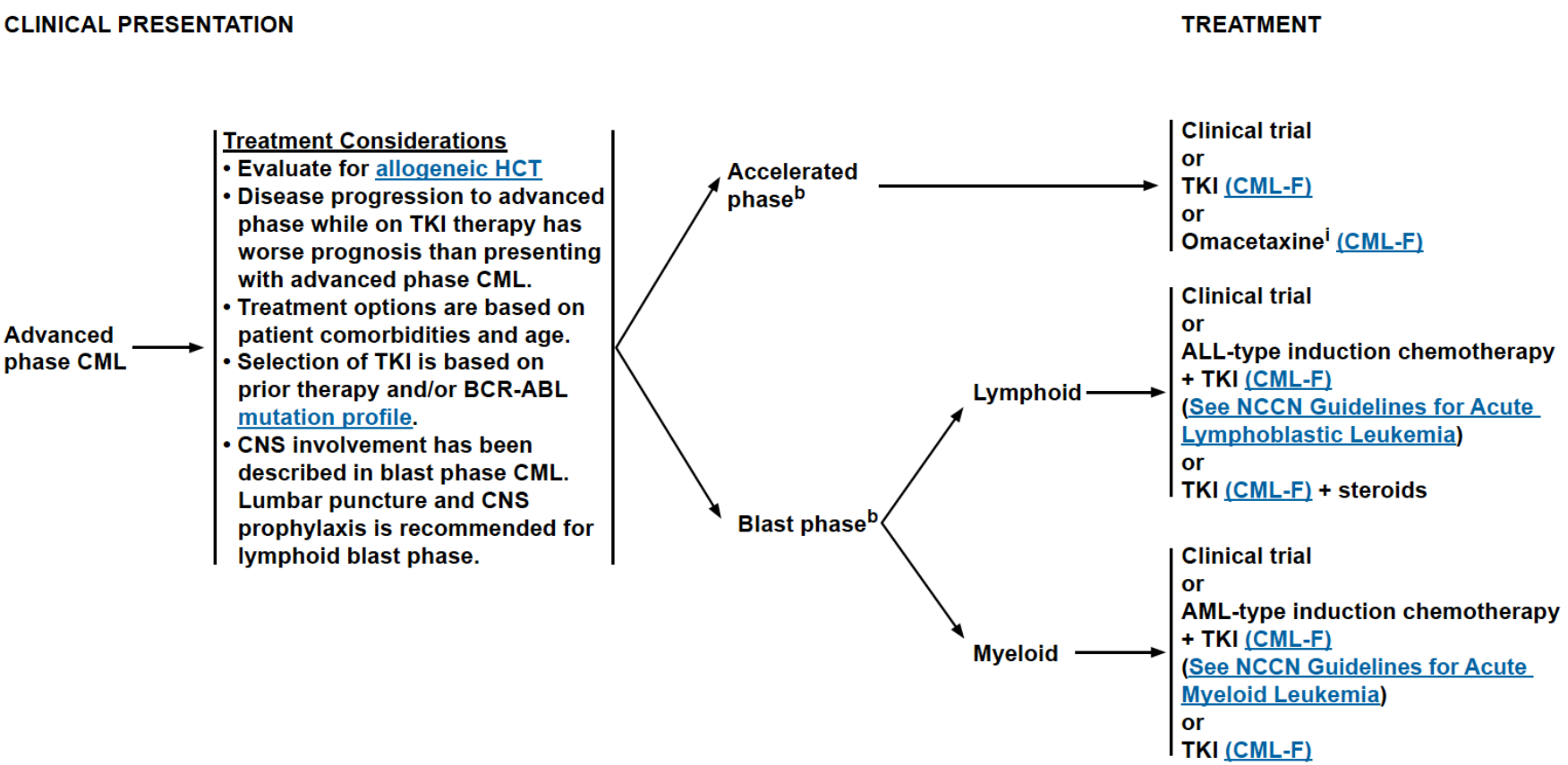

[b] See Definitions of Accelerated Phase and Blast Phase (CML-B).
[i] Omacetaxine is a treatment option for patients with disease progression to accelerated phase CML. Omacetaxine is not a treatment option for patients who present with accelerated phase CML.

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TREATMENT OPTIONS BASED ON BCR-ABL1 MUTATION PROFILE

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

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

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RISK CALCULATION TABLE

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

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

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

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

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

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DEFINITION OF ACCELERATED PHASE[1,2]

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

DEFINITIONS OF BLAST PHASE[1]

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

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

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MONITORING RESPONSE TO TKI THERAPY AND MUTATIONAL ANALYSIS

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

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

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CRITERIA FOR HEMATOLOGIC, CYTOGENETIC, AND MOLECULAR RESPONSE AND RELAPSE

Complete hematologic response[1]

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

Cytogenetic response[2,3]

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

Molecular response[5,6]

- Early molecular response (EMR) - *BCR-ABL1* ≤10% (IS) at 3 and 6 months
- Major molecular response (MMR) - *BCR-ABL1* <0.1% (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-ABL1* mRNA using a QPCR assay with a sensitivity of at least 4.5 logs below the standardized baseline. CMR is variably described, and is best defined by the 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-ABL1* transcript levels with loss of MMR should prompt bone marrow evaluation for loss of CCyR but is not itself defined as relapse (eg, hematologic or cytogenetic relapse)

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

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