National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Chronic Myeloid Leukemia

Version 1.2026 — July 16, 2025

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NCCN Guidelines Panel Disclosures

NCCN Chronic Myeloid Leukemia Panel Members
Summary of the Guidelines Updates

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Advanced Phase CML (CML-4)
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Abbreviations (ABBR-1)

Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

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

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

Updates in Version 1.2026 of the NCCN Guidelines for Chronic Myeloid Leukemia from Version 3.2025 include:

CML-1
- Workup
  - Bullet added: Assess for distress
  - Footnote d added: Refer to the NCCN Distress Management Thermometer and Problem List, which includes social determinants of health. See NCCN Guidelines for Distress Management (DIS-A).
- Additional Evaluation; Chronic phase CML
  - Bullet 2 modified: Consider myeloid mutational analysis ~~(category 2B)~~

CML-2
- Treatment considerations independent of risk score
  - Bullet 1 added: *BCR::ABL1* transcript type
  - Bullet 5 added: TKI dosing schedule
  - Bullet 7 added: Treatment goal
  - Bullet 8 added: Medication cost

CML-2A
- Footnote g added: Asciminib is contraindicated in patients with CML lacking ABL1 exon 2 (eg, b2(e13)a3, b3(e14)a3 isoforms) as it has no clinical activity in these cases (Leske IB, Hantschel O. Leukemia 2024;38:2041-2045; Leyte-Vidal A, et al. Leukemia 2024;38:2046-2050). (Also applies to CML-4A)
- Footnote h added: The cost of generic TKIs can be substantially less than that of brand name TKIs. The cost of treatment to both the patient and to society can be considered.
- Footnote i modified: If treatment is needed during pregnancy, it is preferable to initiate treatment with interferon. ~~alfa-2a.; in~~ In the United States~~.~~, peginterferon alfa-2a and *ropeginterferon alfa-2b are* ~~is the only interferon~~ available for clinical use. *There are very limited data for the use of ropeginterferon alfa-2b in CML during pregnancy.* TKI therapy, particularly during the first trimester, should be avoided because of teratogenic risk. See Management of CML During Pregnancy (CML-E). (Also applies to CML-4A)
- Footnote l modified: TKIs ~~(e.g. nilotinib)~~ are available in different formulations, dosage forms, and strengths that are subject to different administration instructions. These products are not interchangeable. Refer to package insert for full prescribing information for specific TKIs: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm. (Also applies to CML-3A, CML-4A, CML-6)
- Footnote m modified: FDA-approved generic ~~versions~~ *drugs* are appropriate substitutes for ~~innovator~~ *brand name* drugs (Kantarjian H, et al. Lancet Haematol 2022;9:e854-e861; Haddad FG, Kantarjian H. J Natl Compr Canc Netw 2024;22:e237116). ~~Innovator~~ *Brand name* and generic drugs approved by the regulatory authorities based on pharmacokinetic equivalence can be used interchangeably. *Clinicians should be aware of the potential pharmacokinetic variability and monitor patients closely during transitions, particularly for drugs with narrow therapeutic windows such as nilotinib and bosutinib.* (Also applies to CML-4A, CML-6; added to CML-3A)

CML-3A
- Footnote w modified: Switching from imatinib to a 2G TKI *or* allosteric TKI may improve~~s~~ response. The side effect profile of alternative TKIs may differ.

CML-4
- Treatment Considerations
  - Bullet 1 added: *BCR::ABL1* transcript type

CML-5
- Treatment Recommendations Based on *BCR::ABL1* Mutation*/Variant* Profile
  - Bullet 3 modified with addition of sentence: Select *BCR::ABL1* kinase domain mutations may be more sensitive to certain TKIs based on the IC_{50} values. See Discussion.
- Table: Contraindicated Mutations changed to Contraindicated Mutations*/Variants*
  - Asciminib; Contraindicated Mutations/Variants: Added b2(e13)a3, b3(e14)a3

Continued

Updates in Version 1.2026 of the NCCN Guidelines for Chronic Myeloid Leukemia from Version 3.2025 include:

CML-5 (continued)
- Footnote dd added: Initiation of ponatinib at lower doses and dose reduction (with close monitoring) in patients who achieve optimal responses are appropriate strategies to reduce the risk of cardiovascular toxicities. See the Discussion section for Dose Modifications of TKI Therapy.

CML-6
- Footnote hh modified: Indications for allogeneic HCT: CP-CML with resistance and/or intolerance to all available TKIs; ~~advanced phase CML at presentation or disease progression to BP-CML or~~ *disease progression to AP-CML during TKI therapy; BP-CML in patients who achieve morphologic remission*. Outcomes of allogeneic HCT are dependent on age, comorbidities, donor type, *pretransplant disease status,* and transplant center.

CML-B
- BP-CML
  - ▸ Added: Myeloid BP-CML
  - ▸ Added: Lymphoid BP-CML
    - ◊ Any increase in lymphoblasts in peripheral blood or bone marrow
- Footnote removed: Any increase in lymphoblasts is concerning for (nascent) blast phase.

CML-C 1 of 4
- Footnote e modified: *Consider bone marrow evaluation to rule out disease progression to AP-CML or BP-CML or the emergence of other myeloid neoplasms after TKI therapy.* Refer to package insert for monitoring hematologic toxicities: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

CML-C 3 of 4
- Pancreatitis
  - ▸ Symptom monitoring modified: Patients should *monitor and* report abdominal pain

CML-C 4 of 4
- Adverse Event modified
  - ▸ Hepatic symptoms, and/or LFT abnormalities ~~(eg, elevated AST, ALT, or total bilirubin)~~

CML-D 1 of 3
- Drug interactions of TKIs with the most commonly used medications, ~~and~~ supplements, *and fruits/fruit juices* are listed in the table below. (Also applies to CML-D 2 of 3, CML-D 3 of 3)
  - ▸ Histamine 2 Receptor Antagonists (H2RAs)
    - ◊ Bosutinib modified (see new footnote)
      - – Decrease in exposure~~; AVOID; If absolutely necessary consider once-daily H2RA ≥2 hours after taking bosutinib~~
    - ◊ Dasatinib modified (see new footnote)
      - – Decrease in exposure~~; AVOID; If absolutely necessary consider once-daily H2RA ≥2 hours after taking dasatinib~~
    - ◊ Nilotinib modified (see new footnote)
      - – Decrease in exposure~~; AVOID; If absolutely necessary consider once-daily H2RA ≥2 hours after or ≥10 hours before taking nilotinib~~
  - ▸ Antacids
    - ◊ Bosutinib modified (see new footnote)
      - – Decrease in exposure ~~if concomitant; Use antacids at least 2 hours before or at least 2 hours after taking bosutinib~~
    - ◊ Dasatinib modified (see new footnote)
      - – Decrease in exposure ~~if concomitant; Use antacids at least 2 hours before or at least 2 hours after taking dasatinib~~
    - ◊ Nilotinib modified (see new footnote)
      - – Decrease in exposure ~~if concomitant; Use antacids at least 2 hours before or at least 2 hours after taking nilotinib~~

Continued

Updates in Version 1.2026 of the NCCN Guidelines for Chronic Myeloid Leukemia from Version 3.2025 include:

CML-D 1 of 3 (continued)
- Footnote a added: Coadministration of bosutinib with PPIs and H2RAs should be avoided. If absolutely necessary, consider once daily H2RA ≥2 hours after taking bosutinib.
- Footnote b added: pH-independent version of dasatinib that allows for concomitant use with PPIs or H2RAs has been approved by the FDA as an alternative treatment option for adults with CML.
- Footnote c added: Coadministration of nilotinib with PPIs and H2RAs should be avoided. If absolutely necessary consider once-daily H2RA ≥2 hours after or ≥10 hours before taking nilotinib.
- Footnote d added: Coadministration with antacids should be avoided. Use antacids at least 2 hours before or at least 2 hours after taking bosutinib, dasatinib or nilotinib.

CML-D 2 of 3
- Cardiovascular Medications
  - Atorvastatin added

CML-D 3 of 3
- Added: Fruits/Fruit juices (listed in order of their propensity to inhibit the activity of CYP3A4 enzyme)
  - Grapefruit; Star fruit; Black mulberry or raspberry; Wild grape; Pomegranate
    - ◊ Added to all TKIs: Increase in exposure, AVOID

CML-E 1 of 2
- Treatment and Monitoring During Pregnancy
  - Bullet 3 modified: If treatment is needed during pregnancy, it is preferable to initiate treatment with interferon ~~alfa-2a~~. Most of the data using interferons during pregnancy have been reported in patients with essential thrombocythemia. *In the United States, peginterferon alfa-2a and ropeginterferon alfa-2b are available for clinical use*. If introduced earlier, the use of peginterferon alfa-2a can preserve molecular remission after discontinuation of TKI. ~~Ropeginterferon alfa-2b is also available for clinical use but~~ There are very limited data for ~~its~~ *the* use *of ropeginterferon alfa-2b* in CML during pregnancy.

CML-E 2 of 2
- Reference 19 added: Okikiolu J, Woodley C, Cadman-Davies L, et al. Real world experience with ropeginterferon alpha-2b (Besremi) in essential thrombocythaemia and polycythaemia vera following exposure to pegylated interferon alfa-2a (Pegasys). Leuk Res Rep 2022;19:100360.
- Reference 20 updated: Chelysheva E, Apperley J, Turkina A, et al. Chronic myeloid leukemia diagnosed in pregnancy: management and outcome of 87 patients reported to the European LeukemiaNet international registry. Leukemia 2024;38:788-795.

CML-H
- Criteria for TKI Discontinuation
  - Bullet removed: Age ≥18 years
- Footnote b modified: ~~Data from the EURO-SKI study suggest that MR4.0 (BCR::ABL1 ≤0.01% IS) for ≥3 years was the most significant predictor for successful discontinuation of imatinib. Total duration of imatinib therapy for at least 6 years was also predictive of successful discontinuation (Saussele S, et al. Lancet Oncol 2018;19:747-757).~~ *Disease characteristics at diagnosis, blast cell and platelet count in peripheral blood, a higher Sokal risk score, female gender, lower natural killer cell counts, suboptimal response or resistance to imatinib, duration of TKI therapy and DMR prior to TKI discontinuation have been identified as independent factors predictive of recurrence after TKI discontinuation. In the EURO-SKI study, only the duration of TKI therapy prior to discontinuation was significantly associated with the maintenance of MMR at 36 months after TKI discontinuation (Mahon FX, et al. J Clin Oncol 2024;42:1875-1880). Lack of MR4.0 at 36 months after discontinuation of TKI was highly predictive of subsequent loss of MMR (Richter J, et al. Leukemia 2021;35:2416-2418).*

MS-1
- The discussion section has been updated to reflect the changes in the algorithm.

WORKUP | **CLINICAL PRESENTATION** | **ADDITIONAL EVALUATION**

Workup:
- **H&P, including spleen size by palpation (cm below costal margin)**
- **CBC with differential[a]**
- **Chemistry profile, including uric acid**
- **Bone marrow aspirate and biopsy for morphologic review and cytogenetic evaluation[b]**
- **Quantitative RT-PCR (qPCR) using International Scale (IS) for *BCR::ABL1* (blood)**
- **Hepatitis B panel[c]**
- **Assess for distress[d]**

→ **Ph-positive or *BCR::ABL1* positive**
- → **Chronic phase CML (CP-CML)** → **Additional evaluation:**
  - **Determine risk score (Risk Calculation Table CML-A)**
  - **Consider myeloid mutational analysis**

  → **CML-2**
- → **Advanced phase CML**
  - → **Accelerated phase CML (AP-CML)[f]**
  - → **Blast phase CML (BP-CML)[f]**

  → **Additional evaluation:**
  - **Flow cytometry to determine cell lineage**
  - **Consider myeloid mutational analysis**
  - **Human leukocyte antigen (HLA) testing, if considering allogeneic hematopoietic cell transplant (HCT) (CML-6)**

  → **CML-4**

→ **Ph-negative and *BCR::ABL1* negative** → **Evaluate for atypical *BCR::ABL1* transcripts or for diseases other than CML[e] (See NCCN Guidelines for Myeloproliferative Neoplasms)**

[a] Hydroxyurea is the preferred option (until the initiation of TKI therapy) to lower very high white blood cell (WBC) counts. Leukapheresis is rarely indicated, except for high-risk indications (eg, persistent priapism, shortness of breath, transient ischemic attack).

[b] Bone marrow cytogenetics with a minimum of 20 metaphases is useful to detect chromosomal abnormalities in addition to the Ph chromosome. The presence of major route additional chromosomal abnormalities (ACAs) in Ph-positive cells (trisomy 8, isochromosome 17q, second Ph, trisomy 19, and chromosome 3 abnormalities) may have a negative prognostic impact on survival in patients with accelerated phase. Fluorescence in situ hybridization (FISH) on the bone marrow or peripheral blood (with a minimum of 100 interphase nuclei evaluated) can be used if bone marrow cytogenetic evaluation is not possible.

[c] Hepatitis B virus reactivation has been reported in patients receiving tyrosine kinase inhibitor (TKI) therapy. However, it is not always possible to reliably estimate the frequency or establish a relationship to drug exposure because these incidences are reported voluntarily from a population of uncertain size.

[d] Refer to the NCCN Distress Thermometer and Problem List, which includes social determinants of health. See NCCN Guidelines for Distress Management (DIS-A).

[e] Consider dual fusion FISH (D-FISH) or qualitative reverse transcription polymerase chain reaction (RT-PCR) for the detection of atypical *BCR::ABL1* transcripts. See Discussion. Referral to centers with expertise in the management of rare hematologic malignancies is recommended for patients with atypical *BCR::ABL1* transcripts.

[f] Definitions of Advanced Phase CML (CML-B).

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

CLINICAL PRESENTATION | **PRIMARY TREATMENT[i,j,k,l,m]**

CP-CML →

Treatment considerations independent of risk score
- *BCR*::*ABL1* transcript type[g]
- Age
- Comorbidities
- Toxicity profile of tyrosine kinase inhibitor (TKI) (CML-C)
- TKI dosing schedule
- Possible drug interactions
- Treatment goal
- Medication cost[h]
- Patient preference

→ **Low-risk score** (Risk Calculation Table CML-A) →

Preferred
First-generation (1G) TKI (Imatinib [category 1])
or
Second-generation (2G) TKI (alphabetical order) (Bosutinib [category 1] or (Dasatinib [category 1] or Nilotinib [category 1])
or
Allosteric TKI (Asciminib[g] [category 1])
or
Clinical trial

→ Response Milestones and Treatment Options (CML-3)[o,p]

→ **Intermediate- or high-risk score** (Risk Calculation Table CML-A) →

Preferred
2G TKI (alphabetical order) (Bosutinib [category 1] or Dasatinib [category 1] or Nilotinib [category 1])
or
Allosteric TKI (Asciminib;[g] category 1)
or
Other recommended
1G TKI (Imatinib)[n]
or
Clinical trial

→ Response Milestones and Treatment Options (CML-3)[o,p]

Footnotes on CML-2A

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

FOOTNOTES FOR CHRONIC PHASE CML

[g] Asciminib is contraindicated in patients with CML lacking ABL1 exon 2 (eg, b2(e13)a3, b3(e14)a3 isoforms) as it has no clinical activity in these cases (Leske IB, Hantschel O. Leukemia 2024;38:2041-2045; Leyte-Vidal A, et al. Leukemia 2024;38:2046-2050).

[h] The cost of generic TKIs can be substantially less than that of brand name TKIs. The cost of treatment to both the patient and to society can be considered.

[i] If treatment is needed during pregnancy, it is preferable to initiate treatment with interferon. In the United States, peginterferon alfa-2a and ropeginterferon alfa-2b are available for clinical use. There are very limited data for the use of ropeginterferon alfa-2b in CML during pregnancy. TKI therapy, particularly during the first trimester, should be avoided because of teratogenic risk. See Management of CML During Pregnancy (CML-E).

[j] Based on follow-up data from the BFORE, DASISION, ENESTnd, and ASC4FIRST trials, 2G TKIs (bosutinib, dasatinib, or nilotinib) and allosteric TKIs (asciminib) are preferred for patients with an intermediate- or high-risk score. 2G and allosteric TKIs should also be considered for specific subgroups (based on the assessment of treatment goals and benefit/risks), for example, younger patients who are interested in ultimately discontinuing treatment and especially young patients assigned female at birth whose goal is to achieve a deep and rapid molecular response and eventual discontinuation of TKI therapy for family planning purposes.

[k] Limited available evidence from small cohort studies suggests that initiation of first-line TKIs (bosutinib, dasatinib, or nilotinib) at lower doses (to minimize treatment-related adverse events) and dose reduction (with close monitoring) in patients who achieve optimal responses are appropriate strategies to reduce the risk of long-term toxicities. However, the minimum effective dose or optimal de-escalation of TKI (bosutinib, dasatinib, or nilotinib) has not yet been established in prospective randomized clinical trials. See the Discussion section for Dose Modifications of TKI Therapy.

[l] TKIs are available in different formulations, dosage forms, and strengths that are subject to different administration instructions. These products are not interchangeable. Refer to package insert for full prescribing information for specific TKIs: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.

[m] FDA-approved generic drugs are appropriate substitutes for brand name drugs (Kantarjian H, et al. Lancet Haematol 2022;9:e854-e861; Haddad FG, Kantarjian H. J Natl Compr Canc Netw 2024;22:e237116). Brand name and generic drugs approved by the regulatory authorities based on pharmacokinetic equivalence can be used interchangeably. Clinicians should be aware of the potential pharmacokinetic variability and monitor patients closely during transitions, particularly for drugs with narrow therapeutic windows such as nilotinib and bosutinib.

[n] Imatinib may be preferred for patients who are older with comorbidities such as cardiovascular disease.

[o] Criteria for Response and Relapse (CML-F).

[p] Monitoring Response to TKI Therapy and Mutational Analysis (CML-G).

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

EARLY TREATMENT RESPONSE MILESTONES

CRITERIA FOR RESPONSE AND RELAPSE

BCR::ABL1 (IS)	3 months	6 months	12 months[q]
>10%[r]	YELLOW	RED	RED
>1%–10%[s]	GREEN	GREEN	ORANGE
>0.1%–1%	GREEN	GREEN	LIGHT GREEN
≤0.1%	GREEN	GREEN	GREEN

COLOR	CONCERN	CLINICAL CONSIDERATIONS[u]	RECOMMENDATIONS[l,m,u]
RED	TKI-resistant disease[t]	• Evaluate patient adherence and drug interactions • Consider *BCR::ABL1* kinase domain mutational analysis[v] • Consider bone marrow cytogenetic analysis to assess additional chromosomal abnormalities (ACAs)	Switch to alternate TKI (CML-5) (other than imatinib) and evaluate for allogeneic HCT
YELLOW	Possible TKI resistance[t]	• Evaluate patient adherence and drug interactions • Consider *BCR::ABL1* kinase domain mutational analysis[v]	Switch to alternate TKI (CML-5) or Continue same TKI[r]
ORANGE	Possible TKI resistance[t]	• Evaluate patient adherence and drug interactions • Consider *BCR::ABL1* kinase domain mutational analysis[v] • Consider bone marrow cytogenetic analysis to assess for complete cytogenetic response (CCyR) at 12 mo	Consider switch to alternate TKI[s] (CML-5) or Continue the same TKI if CCyR is achieved
LIGHT GREEN	TKI-sensitive disease	• Evaluate patient adherence and drug interactions • If treatment goal is long-term survival: ≤1% optimal • If treatment goal is treatment-free remission: ≤0.1% optimal	• If optimal: continue same TKI • If not optimal: shared decision-making with patient[t,w]
GREEN	TKI-sensitive disease	• Evaluate patient adherence and drug interactions • Monitor response (CML-G)	Continue same TKI[x]

Footnotes on CML-3A

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

FOOTNOTES FOR EARLY TREATMENT RESPONSE MILESTONES

[l] TKIs are available in different formulations, dosage forms, and strengths that are subject to different administration instructions. These products are not interchangeable. Refer to package insert for full prescribing information for specific TKIs: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.

[m] FDA-approved generic drugs are appropriate substitutes for brand name drugs (Kantarjian H, et al. Lancet Haematol 2022;9:e854-e861; Haddad FG, Kantarjian H. J Natl Compr Canc Netw 2024;22:e237116). Brand name and generic drugs approved by the regulatory authorities based on pharmacokinetic equivalence can be used interchangeably. Clinicians should be aware of the potential pharmacokinetic variability and monitor patients closely during transitions, particularly for drugs with narrow therapeutic windows such as nilotinib and bosutinib.

[q] *BCR::ABL1* IS ≤0.1% at 12 months is associated with a very low probability of subsequent loss of response and a high likelihood of achieving a subsequent deep molecular response (DMR MR4.0; *BCR::ABL1* IS ≤0.01%), which is a prerequisite for a trial of treatment-free remission (TFR).

[r] Achievement of response milestones must be interpreted within the clinical context. 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. Same dose of TKI can be continued for another 3 months but imatinib is associated with slower molecular responses.

[s] Achievement of response milestones must be interpreted within the clinical context. Patients achieving MCyR (*BCR::ABL1* IS ≤10%) at 12 months have good long-term survival. Patients with more than 50% reduction compared to baseline or minimally above the 10% cutoff can continue the same dose of TKI for another 3 months. Consider switching to alternate 2G TKI or 3G TKI or allosteric TKI in the absence of continuing decline in *BCR::ABL1* transcript levels.

[t] Consider referral to a specialized CML center and/or enrollment in a clinical trial.

[u] Switching to an alternate TKI for intolerance is appropriate for patients with disease responding to TKI therapy. See Special Considerations for the use of TKI Therapy (CML-C).

[v] Consider myeloid mutation panel to identify *BCR::ABL1*–independent resistance mutations in patients with no *BCR::ABL1* kinase domain mutations.

[w] Switching from imatinib to a 2G TKI or allosteric TKI may improve response. The side effect profile of alternative TKIs may differ.

[x] Discontinuation of TKI with careful monitoring is feasible in selected patients. See Discontinuation of TKI Therapy (CML-H).

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

CLINICAL PRESENTATION

Advanced phase CML →

Treatment considerations
- *BCR*::*ABL1* transcript type[g]
- Disease progression to advanced phase while on TKI therapy has worse prognosis than de novo advanced phase CML.
- Selection of TKI is based on prior therapy and/or *BCR*::*ABL1* mutation/variant profile.
- Evaluation for allogeneic HCT as indicated.
- Central nervous system (CNS) involvement has been described in BP-CML. Lumbar puncture and CNS prophylaxis is recommended for lymphoid BP-CML.

TREATMENT[i,l,m,aa]

AP-CML[f,y] →

Clinical trial
or
Preferred
- 2G TKI (alphabetical order) (Bosutinib or Dasatinib or Nilotinib) or third-generation (3G) TKI (Ponatinib)

Useful in certain circumstances
- 1G TKI (Imatinib; if 2G or 3G TKI is contraindicated)[bb]
- Allosteric TKI (Asciminib)[g]

→ Lack of response or Disease progression → Allogeneic HCT (CML-6)

BP-CML[f,z]

Lymphoid →

Clinical trial
or
Preferred
- ALL-type induction chemotherapy (See NCCN Guidelines for ALL) + TKI[cc]

Useful in certain circumstances
- TKI[cc] + steroids (if not a candidate for induction chemotherapy)

Myeloid →

Clinical trial
or
Preferred
- AML-type induction chemotherapy (See NCCN Guidelines for AML) + TKI[cc]

Useful in certain circumstances
- TKI[cc] (if not a candidate for induction chemotherapy)

→ For patients in remission:
- Allogeneic HCT (CML-6)
- Consolidation chemotherapy and TKI[m,cc] maintenance for non-candidates for allogeneic HCT

Footnotes on CML-4A

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

FOOTNOTES FOR ADVANCED PHASE CML

[f] Definitions of Advanced Phase CML (CML-B).

[g] Asciminib is contraindicated in patients with CML lacking ABL1 exon 2 (eg, b2(e13)a3, b3(e14)a3 isoforms) as it has no clinical activity in these cases (Leske IB, Hantschel O. Leukemia. 2024;38:2041-2045; Leyte-Vidal A, et al. Leukemia 2024;38:2046-2050).

[i] If treatment is needed during pregnancy, it is preferable to initiate treatment with interferon. In the United States, peginterferon alfa-2a and ropeginterferon alfa-2b are available for clinical use. There are very limited data for the use of ropeginterferon alfa-2b in CML during pregnancy. TKI therapy, particularly during the first trimester, should be avoided because of teratogenic risk. See Management of CML During Pregnancy (CML-E).

[l] TKIs are available in different formulations, dosage forms, and strengths that are subject to different administration instructions. These products are not interchangeable. Refer to package insert for full prescribing information for specific TKIs: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.

[m] FDA-approved generic drugs are appropriate substitutes for brand name drugs (Kantarjian H, et al. Lancet Haematol 2022;9:e854-e861; Haddad FG, Kantarjian H. J Natl Compr Canc Netw 2024;22:e237116). Brand name and generic drugs approved by the regulatory authorities based on pharmacokinetic equivalence can be used interchangeably. Clinicians should be aware of the potential pharmacokinetic variability and monitor patients closely during transitions, particularly for drugs with narrow therapeutic windows such as nilotinib and bosutinib.

[y] The presence of major route ACAs in Ph-positive cells (trisomy 8, isochromosome 17q, second Ph, trisomy 19, and chromosome 3 abnormalities) may have a negative prognostic impact on survival. Patients who present with accelerated phase at diagnosis should be treated with a TKI at the FDA-approved dose for accelerated phase, followed by evaluation for allogeneic HCT, based on response to therapy. Consider evaluation for allogeneic HCT if response milestones are not achieved at 3, 6, and 12 months as outlined on CML-3.

[z] TKI (alone or in combination with minimal chemotherapy or steroids) is less effective in BP-CML compared to Ph-positive ALL. Interphase FISH for the detection of BCR::ABL1 transcript on blood granulocytes is recommended to differentiate between de novo BP-CML and de novo Ph-positive ALL.

[aa] TKI dose for advanced phase CML may differ from CP-CML. TKIs (eg, nilotinib) are available in different formulations, dosage forms, and strengths that are subject to different administration instructions. These products are not interchangeable. Refer to package insert for full prescribing information for specific TKIs: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.

[bb] Imatinib is not recommended for patients with disease progression on prior TKI therapy.

[cc] 2G or 3G TKI is preferred. Consider imatinib for patients with contraindications to 2G or 3G TKI.

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

TREATMENT RECOMMENDATIONS BASED ON *BCR::ABL1* MUTATION/VARIANT PROFILE

- **Patients with disease resistant to primary treatment with imatinib should be treated with an alternate TKI, taking into account *BCR::ABL1* kinase domain mutation status.**
- **Patients with disease resistant to primary treatment with asciminib, bosutinib, dasatinib, or nilotinib can be treated with an alternate TKI (other than imatinib), taking into account *BCR::ABL1* kinase domain mutation status. Subsequent therapy with an alternate TKI would be effective only in patients with identifiable *BCR::ABL1* mutations that confer resistance to TKI therapy. Ponatinib is preferred for patients with no identifiable *BCR::ABL1* mutations.**
  - **Asciminib is a treatment option for patients with CP-CML and AP-CML having the T315I mutation and/or previously treated CP-CML and AP-CML.**
  - **Ponatinib[dd] is a treatment option for patients with a T315I mutation in any phase (preferred for AP-CML or BP-CML). It is also a treatment option for CP-CML with resistance or intolerance to at least two prior TKIs or for patients with AP-CML or BP-CML for whom no other TKI is indicated.**
- **Select *BCR::ABL1* kinase domain mutations may be more sensitive to certain TKIs based on the IC_{50} values. See Discussion. *BCR::ABL1* kinase domain mutations that should NOT be treated with asciminib, bosutinib, dasatinib, or nilotinib are listed in the table below.**

THERAPY	CONTRAINDICATED MUTATIONS/VARIANTS[ee]
Asciminib	A337T, P465S, M244V, or F359V/I/C; b2(e13)a3, b3(e14)a3
Bosutinib	T315I, V299L, G250E, or F317L[ff]
Dasatinib	T315I/A, F317L/V/I/C, or V299L
Nilotinib	T315I, Y253H, E255K/V, or F359V/C/I
Ponatinib or allogeneic HCT	None[gg]

[dd] Initiation of ponatinib at lower doses and dose reduction (with close monitoring) in patients who achieve optimal responses are appropriate strategies to reduce the risk of cardiovascular toxicities. See the Discussion section for Dose Modifications of TKI Therapy.
[ee] Mutations contraindicated for imatinib are too numerous to include. *BCR::ABL35$_{INS}$* has been reported in patients with disease not responding to imatinib; however, there are not enough data to confirm that 2G TKIs could overcome this resistance (Berman E, et al. Leuk Res 2016;49:108-112). See Discussion.
[ff] Bosutinib has minimal activity against F317L mutation. Nilotinib may be preferred over bosutinib in patients with F317L mutation.
[gg] There are compound mutations (defined as harboring ≥2 mutations in the same *BCR::ABL1* allele) that can cause resistance to ponatinib, but those are uncommon following treatment with bosutinib, dasatinib, or nilotinib.

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ADDITIONAL THERAPY[l]

Allogeneic HCT[hh]

- **CCyR[o]** → **Monitor with qPCR (peripheral blood) every 3 mo for 2 y, then every 3–6 mo thereafter**
  - **Negative** (→ continue monitoring) → **Consider TKI[m,ii,jj] therapy for at least 1 y in patients with prior AP-CML or BP-CML[kk]**
  - **Positive** → **Discuss options with transplant team: TKI[m,ii,jj] ± donor lymphocyte infusion (DLI) (selection of TKI is based on prior therapy, *BCR*::*ABL1* mutation/variant profile, and post-HCT morbidities) or Clinical trial**
- **Less than CCyR or in relapse[o]** → **Discuss options with transplant team: TKI[m,ii,jj] ± donor lymphocyte infusion (DLI) (selection of TKI is based on prior therapy, *BCR*::*ABL1* mutation/variant profile, and post-HCT morbidities) or Clinical trial**

[l] TKIs are available in different formulations, dosage forms, and strengths that are subject to different administration instructions. These products are not interchangeable. Refer to package insert for full prescribing information for specific TKIs: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.
[m] FDA-approved generic drugs are appropriate substitutes for brand name drugs (Kantarjian H, et al. Lancet Haematol 2022;9:e854-e861; Haddad FG, Kantarjian H. J Natl Compr Canc Netw 2024;22:e237116). Brand name and generic drugs approved by the regulatory authorities based on pharmacokinetic equivalence can be used interchangeably. Clinicians should be aware of the potential pharmacokinetic variability and monitor patients closely during transitions, particularly for drugs with narrow therapeutic windows such as nilotinib and bosutinib.
[o] Criteria for Response and Relapse (CML-F).
[hh] Indications for allogeneic HCT: CP-CML with resistance and/or intolerance to all available TKIs; disease progression to AP-CML during TKI therapy; BP-CML in patients who achieve morphologic remission. Outcomes of allogeneic HCT are dependent on age, comorbidities, donor type, pretransplant disease status, and transplant center.
[ii] Ponatinib is a treatment option for patients with a T315I mutation in any phase (preferred for AP-CML or BP-CML). It is also a treatment option for CP-CML with resistance or intolerance to at least two prior TKIs or for patients with AP-CML or BP-CML for whom no other TKI is indicated. There are compound mutations (defined as harboring ≥2 mutations in the same *BCR::ABL* allele) that can cause resistance to ponatinib, but those are uncommon following treatment with bosutinib, dasatinib, or nilotinib.
[jj] Asciminib is a treatment option for patients with CP-CML and AP-CML having the T315I mutation and/or previously treated CP-CML and AP-CML.
[kk] Carpenter PA, et al. Blood 2007;109:2791-2793; Olavarria E, et al. Blood 2007;110:4614-4617; DeFilipp Z, et al. Clin Lymphoma Myeloma Leuk 2016;16:466-471.e1.

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

RISK CALCULATION TABLE

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

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

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

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

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DEFINITIONS OF ADVANCED PHASE CML

Clinical trials in the TKI era have mostly utilized the modified MD Anderson Cancer Center (MDACC) criteria[1,2] or the International Bone Marrow Transplant Registry (IBMTR) criteria.[3] The use of the International Consensus Classification (ICC)[4] or the World Health Organization (WHO) criteria[5] for the diagnosis of AP-CML and BP-CML is not recommended.

AP-CML[a]	BP-CML
Modified MDACC Criteria[1,2] • Peripheral blood myeloblasts ≥15% and <30% • Peripheral blood myeloblasts and promyelocytes combined ≥30% • Peripheral blood basophils ≥20% • Platelet count ≤100 x 10^9/L unrelated to therapy • Additional clonal cytogenetic abnormalities in Ph+ cells[b]	**IBMTR criteria[3]** **Myeloid BP-CML** • ≥30% blasts in the blood, marrow, or both • Extramedullary infiltrates of leukemic cells **Lymphoid BP-CML** • Any increase in lymphoblasts in peripheral blood or bone marrow

[1] Kantarjian HM, Deisseroth A, Kurzrock R, et al. Chronic myelogenous leukemia: A concise update. Blood 1993;82:691-703.
[2] 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.
[3] Gambacorti-Passerini C, le Coutre P. Chronic myelogenous leukemia. In: DeVita VT, Lawrence TS, Rosenburg SA, eds. DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology. 12th ed. Wolters Kluwer; 2022:1773-1784.
[4] Arber DA, Orazi A, Hasserjian RP, et al. International consensus classification of myeloid neoplasms and acute leukemias: Integrating morphologic, clinical, and genomic data. Blood 2022;140:1200-1228.
[5] Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: Myeloid and histiocytic/dendritic neoplasms. Leukemia 2022;36:1703-1719.
[6] Sokal JE, Baccarani M, Russo D, Tura S. Staging and prognosis in chronic myelogenous leukemia. Semin Hematol 1988;25:49-61.
[7] 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.

[a] Sokal criteria and IBMTR criteria are historically used when allogeneic HCT is the recommended treatment option.[6,7]
[b] The prognostic significance of ACAs in Ph-positive cells (ACA/Ph+) is related to the specific chromosomal abnormality and often other features of accelerated phase. The presence of "major route" ACA/Ph+ (trisomy 8, isochromosome 17q, second Ph, trisomy 19, and chromosome 3 abnormalities) at diagnosis may have a negative prognostic impact on survival.

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

SPECIAL CONSIDERATIONS FOR THE USE OF TKI THERAPY

- **Switching to an alternate TKI should be considered for the following non-hematologic adverse events[a,b,c]:**
  - **Arterial and vascular adverse events (more common with nilotinib and ponatinib)**
  - **Severe hypertension not responsive to antihypertensive medications (ponatinib and asciminib)**
  - **Pulmonary hypertension (dasatinib)**
  - **Recurrent pleural or pericardial effusions despite dose reduction (dasatinib; less common with bosutinib)**
  - **Recurrent pancreatitis despite dose reduction (most common with nilotinib, ponatinib, and asciminib)**
  - **Hyperglycemia (most common with nilotinib)**
  - **Persistent moderate to severe nephrotoxicity (all TKIs)**
  - **Liver function test (LFT) abnormalities (more common with bosutinib and imatinib)**
  - **Gastrointestinal bleeding (dasatinib)**
  - **Immune-mediated adverse events (all TKIs; eg, colitis, pneumonitis, hepatitis, myocarditis, pericarditis, or nephritis)**
  - **Neurotoxicity (rarely seen with imatinib and dasatinib; eg, dementia-like condition, parkinsonism, and intracranial hypertension)**
- **Patients should be counseled on the potential risk factors for cardiovascular disease (CVD), increased risk of CVD associated with long-term TKI therapy (based on comorbidity or risk factors), and on the ABCDEs of prevention of CVD.[d] See the Principles of Cardiovascular Disease Risk Assessment in the NCCN Guidelines for Survivorship.**
- **Recommendations for monitoring and management of non-hematologic adverse events are outlined in Table 1.[a]**
- **Hematologic toxicities (anemia, neutropenia, and thrombocytopenia) may persist after switching to alternate TKI. Growth factor support can be considered for persistent cytopenias.[e]**

[a] Lipton JH, et al. Blood Rev 2022;56:100968.
[b] Haddad FG, Kantarjian H. J Natl Compr Canc Netw 2024;22:e237116.
[c] Oehler VG, et al. J Natl Compr Canc Netw 2024;22:e247044.
[d] Barber MC, et al. Hematology Am Soc Hematol Educ Program 2017;2017:110-114.
[e] Consider bone marrow evaluation to rule out disease progression to AP-CML or BP-CML or the emergence of other myeloid neoplasms after TKI therapy. Refer to package insert for monitoring hematologic toxicities: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.

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SPECIAL CONSIDERATIONS FOR THE USE OF TKI THERAPY

Table 1: Monitoring and Management of Non-Hematologic Adverse Events of TKI Therapy

Adverse Event	Symptom Monitoring	Supportive Care Interventions	TKI Therapy Recommendations
Cardiovascular	• Patients should monitor and report symptoms suggestive of alterations in heart rate (eg, chest pain, palpitations, dizziness, fainting, or numbness). • Patients should monitor and report symptoms of vascular disease (eg, chest pain or heaviness; leg pain, cramping or heaviness; or weakness of the face, arm, or leg, vision changes, loss of balance, or confusion).	• Identify and control potential risk factors (eg, diabetes, hypertension, hyperlipidemia, smoking, estrogen use). • Identify drug interactions of TKIs with cardiovascular medications. • Referral to a cardiologist is recommended for patients with cardiovascular risk factors for additional monitoring and/or assessments. • Hold TKI.	• Switch to alternate TKI whenever possible for the onset of new arterial and/or vascular adverse events (more frequently seen with nilotinib or ponatinib)
QT Interval prolongation		• Monitor for hypokalemia or hypomagnesemia. • Correct deficiencies, prior to initiation of TKI therapy and periodically thereafter. • Avoid concomitant use of drugs known to prolong the QT interval (Drug Interactions of TKIs). • Electrocardiograms (ECGs) to monitor the QT interval at baseline, 7 days after initiation of treatment, and periodically thereafter, as well as following any dose modifications.	• Switch to alternate TKI if symptoms are persistent despite adequate supportive care interventions (more frequently seen with nilotinib)
Hypertension		• Monitor blood pressure. • Manage with anti-hypertensive medications. • Referral to a cardiologist is recommended.	• Switch to alternate TKI, if possible, for severe hypertension not responsive to antihypertensive medications (more frequently seen with ponatinib and asciminib)
Pulmonary arterial hypertension	• Patients should monitor and report symptoms (eg, shortness of breath, fainting, or fatigue).	• Hold TKI. • Consider oral corticosteroids and/or sildenafil. • Referral to a cardiologist or pulmonary vascular specialist is recommended.	• Switch to alternate TKI (more frequently seen with dasatinib)

[1] Adapted with permission from Lipton J, Brümmendorf TH, Gambacorti-Passerini C, et al. Long-term safety review of tyrosine kinase inhibitors in chronic myeloid leukemia - What to look for when treatment-free remission is not an option. Blood Rev 2022;56:100968.

Continued

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

SPECIAL CONSIDERATIONS FOR THE USE OF TKI THERAPY

Table 1: Monitoring and Management of Non-Hematologic Adverse Events of TKI Therapy[1] (*continued*)

Adverse Event	Symptom Monitoring	Supportive Care Interventions	TKI Therapy Recommendations
Pneumonitis	• Patients should monitor and report symptoms of pneumonitis (eg, cough, shortness of breath, or fever).	• Monitor for hypoxemia. • Hold TKI. • Consider oral corticosteroids.	• Switch to alternate TKI
Pleural or pericardial effusion	• Patients should monitor and report symptoms (eg, chest pain or discomfort, cough, or shortness of breath).	• Hold TKI. • Consider diuretics and/or oral corticosteroids for pleural effusion. • Consider echocardiogram to check left ventricular ejection fraction (LVEF).	• Consider dose reduction (with close monitoring) if not controlled by adequate supportive care interventions • Switch to alternate TKI if persistent despite dose reduction
Fluid retention and superficial edema	• Patients should monitor and report symptoms of weight gain, peripheral and periorbital edema, or bloating.	• Consider compression stockings for lower extremity peripheral edema. • May consider diuretics	
Hyperglycemia		• Monitor blood glucose levels before initiating treatment and periodically thereafter. • Referral to primary care physician or endocrinologist is recommended	
Pancreatitis	• Patients should monitor and report abdominal pain.	• Hold TKI. • Assess amylase and lipase levels. • Consider imaging by contrast-enhanced CT or MRI.	
Other laboratory or biochemical abnormalities		• Consider lifestyle modifications. • Identify potential risk factors or drug interactions of TKI with concomitant medications. • Hypophosphatemia, hypocalcemia, hypothyroidism or hypovitaminosis D should be corrected prior to initiating treatment and during TKI treatment. • Additional monitoring and/or assessments may be necessary.	
Muscle spasms, cramps, or musculoskeletal pain	• Patients should monitor and report symptoms.	• Evaluate levels of potassium, calcium, and phosphate. • Correct serum electrolyte abnormalities. Consider potassium and calcium supplements. • Consider non-pharmacologic interventions (eg, adequate hydration, stretching/gentle exercise, and tonic water). • Assess serum creatine kinase (CK) levels.	

[1] Adapted with permission from Lipton J, Brümmendorf TH, Gambacorti-Passerini C, et al. Long-term safety review of tyrosine kinase inhibitors in chronic myeloid leukemia - What to look for when treatment-free remission is not an option. Blood Rev 2022;56:100968.

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

SPECIAL CONSIDERATIONS FOR THE USE OF TKI THERAPY

Table 1: Monitoring and Management of Non-Hematologic Adverse Events of TKI Therapy[1] (*continued*)

Adverse Event	Symptom Monitoring	Supportive Care Interventions	TKI Therapy Recommendations
Osteopenia/ osteoporosis	• Monitor baseline bone mineral density.	• Consider lifestyle modifications. • Identify potential risk factors other than TKI therapy. • Check vitamin D levels before initiating treatment and periodically thereafter.	• None
Dermatologic: Rash or dry skin	• Patients should monitor and report symptoms.	• Consider lifestyle modifications (eg, avoid prolonged bathing, hot water when washing/showering, and tight clothing). • Manage with appropriate supportive care interventions (eg, moisturizers, antihistamines, or topical steroids, systemic antibiotics, and/or short-term systemic steroids). • Consultation with a dermatologist is recommended for patients with severe rash, and/or dry skin.	• Consider dose reduction (with close monitoring) if not controlled by adequate supportive care interventions. • Rash that requires cessation of treatment: switch to alternate TKI if the rash recurs after re-starting treatment.
Gastrointestinal (GI): Diarrhea, nausea and vomiting	• Patients should monitor and report symptoms.	• Take medication (except nilotinib [capsule formulation only] and asciminib) with a meal and large glass of water to avoid GI upset. • Consider the use of anti-diarrheal medications and/or fluid replacement, either prophylactically or after the onset of diarrhea. • Nausea and vomiting should be treated in accordance with the NCCN Guidelines for Antiemesis. • Consultation with gastroenterologist or dietician regarding specific food choices and management in severe cases.	• Consider dose reduction (with close monitoring) if not controlled by adequate supportive care interventions. • Switch to alternate TKI if persistent despite dose reduction.
Nephrotoxicity	• Patients should monitor and report changes in urinary output or frequency.	• Identify potential risk factors or drug interactions of TKI with concomitant medications. • Assess for alternative etiologies • Consultation with nephrologist is recommended.	
Hepatic symptoms, and/or LFT abnormalities	• Patients should monitor and report symptoms of jaundice, or tea colored urine. • Limit alcohol consumption.	• Monitor hepatic function panel. • Identify potential risk factors or drug interactions of TKI with concomitant medications. • Hold TKI for grade 3 LFT abnormalities. Monitor serum levels and resume TKI when levels return to grade ≤1. • No specific supportive care of proven efficacy. • Asymptomatic elevation of indirect bilirubin may not need intervention.	

[1] Adapted with permission from Lipton J, Brümmendorf TH, Gambacorti-Passerini C, et al. Long-term safety review of tyrosine kinase inhibitors in chronic myeloid leukemia - What to look for when treatment-free remission is not an option. Blood Rev 2022;56:100968.

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DRUG INTERACTIONS OF TKIs[1,2]

Drug interactions of TKIs with the most commonly used medications, supplements, and fruits/fruit juices are listed in the table below.
It is always important to take a detailed medication history (including herbal supplements) at every visit.

Drugs/Food/Drink/ Supplements	Change in TKI Level					
	Asciminib	**Bosutinib**	**Dasatinib**	**Imatinib**	**Nilotinib**	**Ponatinib**
Proton Pump Inhibitors (PPIs) • Lansoprazole • Rabeprazole • Esomeprazole • Omeprazole • Pantoprazole	No major interaction	Decrease in exposure[a]	Decrease in exposure[b]	No major interaction	Decrease in exposure[c]	Minor decrease in exposure
Histamine 2 Receptor Antagonists (H2RAs) • Famotidine • Ranitidine • Nizatidine	No major interaction	Decrease in exposure[a]	Decrease in exposure[b]	No major interaction	Decrease in exposure[c]	No major interaction
Antacids	No major interaction	Decrease in exposure[d]	Decrease in exposure[d]	No major interaction	Decrease in exposure[d]	No major interaction
Antidepressants • Fluoxetine • Bupropion • Citalopram	No major interaction	Minor increase in exposure; QTc monitoring	Minor increase in exposure; QTc monitoring	Minor increase in exposure; QTc monitoring	AVOID if possible due to cumulative QTc prolongation risk	Minor increase in exposure; QTc monitoring

[a] Coadministration of bosutinib with PPIs and H2RAs should be avoided. If absolutely necessary, consider once daily H2RA ≥2 hours after taking bosutinib.
[b] pH-independent version of dasatinib that allows for concomitant use with PPIs or H2RAs has been approved by the FDA as an alternative treatment option for adult patients with CML.
[c] Coadministration of nilotinib with PPIs and H2RAs should be avoided. If absolutely necessary consider once-daily H2RA ≥2 hours after or ≥10 hours before taking nilotinib.
[d] Coadministration with antacids should be avoided. Use antacids at least 2 hours before or at least 2 hours after taking bosutinib, dasatinib, or nilotinib.
[1] Refer to package insert for full prescribing information and drug interactions: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.
[2] van Leeuwen RW, van Gelder T, Mathijssen RH, et al. Drug-drug interactions with tyrosine-kinase inhibitors: a clinical perspective. Lancet Oncol 2014;15:e315-e326.

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DRUG INTERACTIONS OF TKIs[1,2]

Drug interactions of TKIs with the most commonly used medications, supplements, and fruits/fruit juices are listed in the table below.
It is always important to take a detailed medication history (including herbal supplements) at every visit.

Drugs/Food/Drink/ Supplements	Change in TKI Level					
	Asciminib	**Bosutinib**	**Dasatinib**	**Imatinib**	**Nilotinib**	**Ponatinib**
Cardiovascular Medications • Amiodarone • Diltiazem • Verapamil • Simvastatin • Atorvastatin	No major interaction	Increase in exposure and arrhythmia risk; Strongly consider alternative cardiac medication or TKI dose adjustment	Increase in exposure and arrhythmia risk; Strongly consider alternative cardiac medication or TKI dose adjustment	Increase in exposure; Strongly consider alternative cardiac medication or TKI dose adjustment	Increase in exposure and arrhythmia risk; AVOID	Increase in exposure; Strongly consider alternative cardiac medication or TKI dose adjustment
Anti-infectives • Azole Antifungals ‣ Fluconazole ≥200 mg ‣ Voriconazole ‣ Itraconazole ‣ Posaconazole ‣ Isavuconazole • Clarithromycin • Telithromycin • Ritonavir	Increase in exposure; Strongly consider alternative anti-infective or TKI dose adjustment	Increase in exposure; Strongly consider alternative anti-infective or TKI dose adjustment	Increase in exposure; Strongly consider alternative anti-infective or TKI dose adjustment	Increase in exposure; Strongly consider alternative anti-infective or TKI dose adjustment	Increase in exposure; Strongly consider alternative anti-infective or TKI dose adjustment	Increase in exposure; Strongly consider alternative anti-infective or TKI dose adjustment
Anti-infectives • Fluoroquinolones ‣ Levofloxacin ‣ Moxifloxacin ‣ Ciprofloxacin	No major interaction	QTc monitoring	QTc monitoring	No major interaction	Use with caution	No major interaction

[1] Refer to package insert for full prescribing information and drug interactions: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.
[2] van Leeuwen RW, van Gelder T, Mathijssen RH, et al. Drug-drug interactions with tyrosine-kinase inhibitors: a clinical perspective. Lancet Oncol 2014;15:e315-e326.

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DRUG INTERACTIONS OF TKIs[1,2]

Drug interactions of TKIs with the most commonly used medications, supplements, and fruits/fruit juices are listed in the table below.
It is always important to take a detailed medication history (including herbal supplements) at every visit.

Drugs/Food/Drink/ Supplements	Change in TKI Level					
	Asciminib	**Bosutinib**	**Dasatinib**	**Imatinib**	**Nilotinib**	**Ponatinib**
Herbal Supplements[3,4] • Curcumin (Turmeric) • Ginkgo Biloba • Green Tea Extract	Increase in exposure; Strongly consider supplement discontinuation	Increase in exposure; Strongly consider supplement discontinuation	Increase in exposure; Strongly consider supplement discontinuation	Increase in exposure; Strongly consider supplement discontinuation	Increase in exposure; Strongly consider supplement discontinuation	Increase in exposure; Strongly consider supplement discontinuation
Herbal Supplements[3,4] • St. John's Wort	Decrease in exposure; AVOID	Decrease in exposure; AVOID	Decrease in exposure; AVOID	Decrease in exposure; AVOID	Decrease in exposure; AVOID	Decrease in exposure; AVOID
Fruits/Fruit Juices (listed in order of their propensity to inhibit the activity of CYP3A4 enzyme) • Grapefruit • Star fruit • Black mulberry or raspberry • Wild grape • Pomegranate	Increase in exposure; AVOID	Increase in exposure; AVOID	Increase in exposure; AVOID	Increase in exposure; AVOID	Increase in exposure; AVOID	Increase in exposure; AVOID

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

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

MANAGEMENT OF CML DURING PREGNANCY

TKI Therapy and Conception

- TKI therapy appears to affect some male hormones at least transiently, but does not appear to have a deleterious effect on male fertility; miscarriage or fetal abnormality rate is not elevated in female partners of male patients on TKI therapy.[1-5]
- TKI therapy during pregnancy has been associated with both a higher rate of miscarriage and fetal abnormalities. A prolonged washout period prior to pregnancy, prompt consideration of holding TKI therapy (if pregnancy occurs while on TKI therapy), and close monitoring should be considered.[6-10] There are no data regarding how long a patient should be off therapy before trying to become pregnant.
- Discontinuation of TKI therapy because of pregnancy in patients who are not in DMR (≤0.01% *BCR::ABL1* IS) has only been reported in a small series of patients.[11-14] Conception while on active TKI therapy is strongly discouraged due to the risk of fetal abnormalities. There are no published guidelines regarding the optimal depth of molecular response that is considered "safe" to stop TKI therapy before attempting pregnancy, and the literature regarding this consists of case reports.[15]
- Prior to attempting pregnancy, patients of childbearing age and their partners should be counseled about the potential risks and benefits of discontinuation of TKI therapy, possible resumption of TKI therapy, and treatment options during pregnancy, should the CML recur. Referral to a CML specialty center and consultation with a high-risk obstetrician is recommended.
- Fertility preservation should be discussed with all patients of childbearing age prior to the initiation of TKI therapy. Referral to an in vitro fertilization (IVF) center is recommended in coordination with the patient's obstetrician. TKI should be stopped prior to attempting oocyte retrieval, but the optimal timing of discontinuation is unknown. There are no data to recommend how long a patient should be off therapy before oocyte retrieval, although usually at least 1 month off therapy is recommended. Sperm banking can also be performed prior to starting TKI therapy, although there are no data regarding the quality of sperm in patients with untreated CML.

Treatment and Monitoring During Pregnancy

- As noted above, in patients assigned male at birth, TKI therapy need not be discontinued if a pregnancy is planned.
- In patients assigned female at birth, TKI therapy should be stopped prior to natural conception, and patients should remain off therapy during pregnancy.[6-8]
- If treatment is needed during pregnancy, it is preferable to initiate treatment with interferon.[16] Most of the data using interferons during pregnancy have been reported in patients with essential thrombocythemia.[17,18,19] In the United States, peginterferon alfa-2a and ropeginterferon alfa-2b are available for clinical use. If introduced earlier, the use of peginterferon alfa-2a can preserve molecular remission after discontinuation of TKI.[20] There are very limited data for the use of ropeginterferon alfa-2b in CML during pregnancy.[19]
- TKI therapy, particularly during the first trimester, should be avoided because of teratogenic risk. If TKI therapy is considered during pregnancy, the potential risks and benefits must be carefully evaluated in terms of maternal health and fetal risk on an individual basis.
- The Panel recommends against the use of hydroxyurea during pregnancy, especially in the first trimester.[21-23]
- Leukapheresis can be used for a rising white blood cell (WBC) count and/or platelet count, although there are no data that recommend at what levels leukapheresis and/or platelet pheresis should be initiated.[24-27]
- Low-dose aspirin or low-molecular-weight heparin can be considered for patients with thrombocytosis.[28,29]
- Monthly monitoring of CBC with differential and frequent monitoring with qPCR (every 1–3 mo) would be helpful to guide the timing for initiation of TKI therapy.

Breastfeeding

- TKI therapy can be restarted after delivery. However, patients should be advised not to breastfeed while on TKI therapy, as TKIs pass into human breast milk.[30-33]
- Breastfeeding without TKI therapy may be safe with molecular monitoring, but preferably in those patients with CML who have achieved durable DMR. It may be acceptable to avoid TKIs for the short period of the first 2–5 days after labor to give the child colostrum.[33,34]
- Close molecular monitoring is recommended for patients who extend the treatment-free period for breastfeeding. If the loss of MMR after treatment cessation is confirmed, breastfeeding needs to be terminated and TKI therapy should be restarted.[33]

References on (CML-E 2 of 2)

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

MANAGEMENT OF CML DURING PREGNANCY – REFERENCES

[1] Ramasamy K, Hayden J, Lim Z, et al. Successful pregnancies involving men with chronic myeloid leukaemia on imatinib therapy. Br J Haematol 2007;137:374-375.
[2] Breccia M, Cannella L, Montefusco E, et al. Male patients with chronic myeloid leukemia treated with imatinib involved in healthy pregnancies: report of five cases. Leuk Res 2008;32:519-520.
[3] Oweini H, Otrock ZK, Mahfouz RAR, Bazarbachi A. Successful pregnancy involving a man with chronic myeloid leukemia on dasatinib. Arch Gynecol Obstet 2011;283:133-134.
[4] Ghalaut VS, Prakash G, Bansal P, et al. Effect of imatinib on male reproductive hormones in BCR-ABL positive CML patients: A preliminary report. J Oncol Pharm Pract 2014;20:243-248.
[5] Alizadeh H, Jaafar H, Rajnics P, et al. Outcome of pregnancy in chronic myeloid leukaemia patients treated with tyrosine kinase inhibitors: short report from a single centre. Leuk Res 2015;39:47-51.
[6] Pye SM, Cortes J, Ault P, et al. The effects of imatinib on pregnancy outcome. Blood 2008;111:5505-5508.
[7] Cortes JE, Abruzzese E, Chelysheva E, et al. The impact of dasatinib on pregnancy outcomes. Am J Hematol 2015;90:1111-1115.
[8] Barkoulas T, Hall PD. Experience with dasatinib and nilotinib use in pregnancy. J Oncol Pharm Pract 2018;24:121-128.
[9] Salem W, Li K, Krapp C, et al. Imatinib treatments have long-term impact on placentation and embryo survival. Sci Rep 2019;9:2535.
[10] Madabhavi I, Sarkar M, Modi M, Kadakol N. Pregnancy outcomes in chronic myeloid leukemia: A single center experience. J Glob Oncol 2019;5:1-11.
[11] Ault P, Kantarjian H, O'Brien S, et al. Pregnancy among patients with chronic myeloid leukemia treated with imatinib. J Clin Oncol 2006;24:1204-1208.
[12] Kuwabara A, Babb A, Ibrahim A, et al. Poor outcome after reintroduction of imatinib in patients with chronic myeloid leukemia who interrupt therapy on account of pregnancy without having achieved an optimal response. Blood 2010;116:1014-1016.
[13] Lasica M, Willcox A, Burbury K, et al. The effect of tyrosine kinase inhibitor interruption and interferon use on pregnancy outcomes and long-term disease control in chronic myeloid leukemia. Leuk Lymphoma 2019;60:1796-1802.
[14] Stella S, Tirro E, Massimino M, et al. Successful management of a pregnant patient with chronic myeloid leukemia receiving standard dose imatinib. In Vivo 2019;33:1593-1598.
[15] Berman E. Family planning and pregnancy in patients with chronic myeloid leukemia. Curr Hematol Malig Rep 2023;18:33-39.
[16] Balsat M, Etienne M, Elhamri M, et al. Successful pregnancies in patients with BCR-ABL-positive leukemias treated with interferon-alpha therapy during the tyrosine kinase inhibitors era. Eur J Haematol 2018;101:774-780.
[17] Schrickel L, Heidel FH, Sadjadian P, et al. Interferon alpha for essential thrombocythemia during 34 high-risk pregnancies: outcome and safety. J Cancer Res and Clin Oncol 2021: 147;1481-1491.
[18] Beauverd Y, Radia D, Cargo C, et al. Pegylated interferon alpha-2a for essential thrombocythemia during pregnancy: outcome and safety. A case series. Haematologica 2016;101:e182-184.
[19] Okikiolu J, Woodley C, Cadman-Davies L, et al. Real world experience with ropeginterferon alpha-2b (Besremi) in essential thrombocythaemia and polycythaemia vera following exposure to pegylated interferon alfa-2a (Pegasys). Leuk Res Rep 2022;19:100360.
[20] Chelysheva E, Apperley J, Turkina A, et al. Chronic myeloid leukemia diagnosed in pregnancy: management and outcome of 87 patients reported to the European LeukemiaNet international registry. Leukemia 2024;38:788-795.
[21] Baykal C, Zengin N, Coskun F, et al. Use of hydroxyurea and alpha-interferon in chronic myeloid leukemia during pregnancy: a case report. Eur J Gynaecol Oncol 2000;21:89-90.
[22] Thauvin-Robinet C, Maingueneau C, Robert E, et al. Exposure to hydroxyurea during pregnancy: a case series. Leukemia 2001;15:1309-1311.
[23] Fadilah SA, Ahmad-Zailani H, Soon-Keng C, Norlaila M. Successful treatment of chronic myeloid leukemia during pregnancy with hydroxyurea. Leukemia 2002;16:1202-1203.
[24] Koh LP, Kanagalingam D. Pregnancies in patients with chronic myeloid leukemia in the era of imatinib. Int J Hematol 2006;84:459-462.
[25] Ali R, Ozkalemkas F, Ozkocaman V, et al. Successful pregnancy and delivery in a patient with chronic myelogenous leukemia (CML), and management of CML with leukapheresis during pregnancy: a case report and review of the literature. Jpn J Clin Oncol 2004;34:215-217.
[26] Palani R, Milojkovic D, Apperley JF. Managing pregnancy in chronic myeloid leukaemia. Ann Hematol 2015;94 Suppl 2:S167-176.
[27] Staley EM, Simmons SC, Feldman AZ, et al. Management of chronic myeloid leukemia in the setting of pregnancy: when is leukocytapheresis appropriate? A case report and review of the literature. Transfusion 2018;58:456-460.
[28] James AH, Brancazio LR, Price T. Aspirin and reproductive outcomes. Obstet Gynecol Surv 2008;63:49-57.
[29] Deruelle P, Coulon C. The use of low-molecular-weight heparins in pregnancy--how safe are they? Curr Opin Obstet Gynecol 2007;19:573-577.
[30] Russell MA, Carpenter MW, Akhtar MS, et al. Imatinib mesylate and metabolite concentrations in maternal blood, umbilical cord blood, placenta and breast milk. J Perinatol 2007;27:241-243.
[31] Ali R, Ozkalemkas F, Kimya Y, et al. Imatinib use during pregnancy and breast feeding: a case report and review of the literature. Arch Gynecol Obstet 2009;280:169-175.
[32] Drugs and Lactation Database (LactMed) [Internet]. Bethesda (MD): National Library of Medicine (US); 2006.
[33] Chelysheva E, Aleshin S, Polushkina E, et al. Breastfeeding in patients with chronic myeloid leukaemia: Case series with measurements of drug concentrations in maternal milk and literature review. Mediterr J Hematol Infect Dis 2018;10:e2018027.
[34] Abruzzese E, Trawinska MM, Perrotti AP, De Fabritiis P. Tyrosine kinase inhibitors and pregnancy. Mediterr J Hematol Infect Dis 2014;6:e2014028.

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

CRITERIA FOR RESPONSE AND RELAPSE

Response/Relapse	Definition
Complete hematologic response (CHR)[1]	• Complete normalization of peripheral blood counts with leukocyte count <10 x 10^9/L • Platelet count <450 x 10^9/L • No immature cells, such as myelocytes, promyelocytes, or blasts in peripheral blood • No signs and symptoms of disease with resolution of palpable splenomegaly
Cytogenetic response[2,3,4]	• **Complete cytogenetic response (CCyR):** No Ph-positive metaphases • **Major cytogenetic response (MCyR):** 0%–35% Ph-positive metaphases • **Partial cytogenetic response (PCyR):** 1%–35% Ph-positive metaphases • **Minor cytogenetic response:** >35% to 65% Ph-positive metaphases
Molecular response[5,6,7]	• **Early molecular response (EMR):** *BCR::ABL1* (IS) ≤10% at 3 and 6 months • **Major molecular response (MMR):** *BCR::ABL1* (IS) ≤0.1% or ≥3-log reduction in *BCR::ABL1* transcripts from the standardized baseline, if qPCR (IS) is not available • **Deep molecular response (DMR): MR4.0:** *BCR::ABL1* (IS) ≤0.01% or **MR4.5:** *BCR::ABL1* (IS) ≤0.0032%
Relapse	• Any sign of loss of hematologic response • Any sign of loss of CCyR or its molecular response correlate (**MR2.0:** *BCR::ABL1* [IS] ≤1%) – defined as an increase in *BCR::ABL1* transcript to >1% • 1-log increase in *BCR::ABL1* transcript levels with loss of MMR[8]

[1] Faderl S, Talpaz M, Estrov Z, Kantarjian HM. Chronic myelogenous leukemia: biology and therapy. Ann Intern Med 1999;131:207-219. The American College of Physicians-American Society of Internal Medicine is not responsible for the accuracy of the translation.
[2] A minimum of 20 metaphases should be examined.
[3] O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 2003;348:994-1004.
[4] CCyR correlates with *BCR::ABL1* (IS) ≤1% (MR2.0).
[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.
[7] Cross NC, White HE, Müller MC, et al. Standardized definitions of molecular response in chronic myeloid leukemia. Leukemia 2012;26:2172-2175.
[8] The loss of MMR in the presence of a CCyR does not necessarily indicate inadequate response to treatment.

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

MONITORING RESPONSE TO TKI THERAPY AND MUTATIONAL ANALYSIS

Test	Recommendation
Hematologic	• CBC every 1–2 weeks for the first 1–2 months (or until stable normalization of blood counts) and thereafter as indicated based on the persistence of cytopenias
Bone marrow cytogenetics[1]	• At diagnosis • Response milestones not reached • Any sign of loss of hematologic response • Any sign of loss of CCyR or its molecular response correlate (MR2.0: *BCR::ABL1* [IS] ≤1%) – defined as an increase in *BCR::ABL1* transcript to >1%
qPCR using IS	• At diagnosis • Every 3 months after initiating treatment. After *BCR::ABL1* (IS) ≤1% (MR2.0)[2] has been achieved, every 3 months for 2 years and every 3–6 months thereafter • If there is a 1-log increase in *BCR::ABL1* transcript levels with MMR, qPCR should be repeated in 1–3 months
***BCR::ABL1* kinase domain mutation analysis**[3]	• CP-CML ‣ Response milestones not reached ◊ Any sign of loss of hematologic response ◊ Any sign of loss of CCyR or its molecular response correlate (MR2.0: *BCR::ABL1* [IS] ≤1%) – defined as an increase in *BCR::ABL1* transcript to >1% ◊ 1-log increase in *BCR::ABL1* transcript levels and loss of MMR • Disease progression to AP-CML or BP-CML[3]

[1] FISH has been inadequately studied for monitoring response to treatment.
[2] CCyR correlates with *BCR::ABL1* (IS) ≤1% (MR2.0).
[3] Consider myeloid mutation panel to identify *BCR::ABL1*–independent resistance mutations in patients with no *BCR::ABL1* kinase domain mutations.

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

DISCONTINUATION OF TKI THERAPY

General Considerations

- **Discontinuation of TKI therapy appears to be safe in select patients with CML.**
- **Consult with a CML specialist to review the appropriateness for TKI discontinuation and potential risks and benefits of treatment discontinuation, including TKI withdrawal syndrome.**
- **Clinical studies that have evaluated the safety and efficacy of TKI discontinuation have used strict eligibility criteria and have mandated more frequent molecular monitoring than typically recommended for patients on TKI therapy.**
- **Some patients have experienced significant adverse events that are believed to be due to TKI discontinuation.**
- **Discontinuation of TKI therapy should only be performed in patients who give consent after a thorough discussion of the potential risks and benefits.**
- **Consultation with an NCCN Panel Member or center of expertise is recommended in the following circumstances:**
  - **Any significant adverse event believed to be related to treatment discontinuation.**
  - **There is progression to AP-CML or BP-CML at any time.**
  - **MMR is not regained after 3 months following treatment reinitiation.**
- **Outside of a clinical trial, discontinuation of TKI therapy should be considered only if *all* of the criteria included in the list below are met.**

Criteria for TKI Discontinuation

- **CP-CML. No prior history of AP-CML or BP-CML.**
- **On approved TKI therapy for at least 3 years.[a,b]**
- **Prior evidence of quantifiable *BCR::ABL1* transcript.**
- **Stable molecular response (MR4; *BCR::ABL1* ≤0.01% IS) for ≥2 years, as documented on at least 4 tests, performed at least 3 months apart.[b]**
- **Access to a reliable qPCR test with a sensitivity of detection of at least MR4.5 (*BCR::ABL1* ≤0.0032% IS) and that provides results within 2 weeks.**
- **Molecular monitoring every 1–2 months for the first 6 months following discontinuation, bimonthly during months 7–12, and quarterly thereafter (indefinitely) for patients who remain in MMR (MR3; *BCR::ABL1* ≤0.1% IS).**
- **Prompt resumption of TKI within 4 weeks of a loss of MMR with monthly molecular monitoring until MMR is re-established, then every 3 months thereafter is recommended indefinitely for patients who have reinitiated TKI therapy after a loss of MMR. If MMR is not achieved after 3 months of TKI resumption, *BCR::ABL1* kinase domain mutation testing should be performed, and monthly molecular monitoring should be continued for another 6 months.**

[a] The feasibility of TFR following discontinuation of TKIs other than dasatinib, imatinib, or nilotinib has not yet been evaluated in clinical studies. It is reasonable to assume that the likelihood of TFR following discontinuation would be similar irrespective of TKI in patients who have achieved and maintained DMR (MR4.0; ≤0.01% *BCR::ABL1* IS) for ≥2 years, based on the extrapolation of findings from the studies that have evaluated TFR following discontinuation of imatinib, dasatinib, or nilotinib.

[b] Disease characteristics at diagnosis, blast cell and platelet count in peripheral blood, a higher Sokal risk score, female gender, lower natural killer (NK) cell counts, suboptimal response or resistance to imatinib, duration of TKI therapy and DMR prior to TKI discontinuation have been identified as independent factors predictive of recurrence after TKI discontinuation. In the EURO-SKI study, only the duration of TKI therapy prior to discontinuation was significantly associated with the maintenance of MMR at 36 months after TKI discontinuation (Mahon FX, et al. J Clin Oncol 2024;42:1875-1880). Lack of MR4.0 at 36 months after discontinuation of TKI was highly predictive of subsequent loss of MMR (Richter J, et al. Leukemia 2021;35:2416-2418).

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

ABBREVIATIONS

1G	first-generation
2G	second-generation
3G	third-generation
ACAs	additional chromosomal abnormalities
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AP-CML	accelerated phase CML
AST	aspartate aminotransferase
BP-CML	blast phase chronic myeloid leukemia
CBC	complete blood count
CCyR	complete cytogenetic response
CHR	complete hematologic response
CK	creatine kinase
CML	chronic myeloid leukemia
CNS	central nervous system
CP-CML	chronic phase CML
CVD	cardiovascular disease
D-FISH	dual fusion FISH
DLI	donor lymphocyte infusion
DMR	deep molecular response
ECG	electrocardiogram
ELTS	EUTOS long-term survival
EMR	early molecular response
EUTOS	European Treatment and Outcome Study
FISH	fluorescence in situ hybridization
GI	gastrointestinal
H&P	history and physical
H2RA	histamine 2 receptor antagonist
HCT	hematopoietic cell transplant
HLA	human leukocyte antigen
IBMTR	International Bone Marrow Transplant Registry
ICC	International Consensus Classification
IS	International Scale
IVF	in vitro fertilization
LFT	liver function test
LVEF	left ventricular ejection fraction
MCyR	major cytogenetic response
MDACC	MD Anderson Cancer Center
MMR	major molecular response
PCyR	partial cytogenetic response
Ph	Philadelphia chromosome
PPI	proton pump inhibitor
qPCR	quantitative RT-PCR
QTc	corrected QT interval
RT-PCR	reverse transcriptase polymerase chain reaction
TFR	treatment-free remission
TKI	tyrosine kinase inhibitor
WBC	white blood cell

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

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

All recommendations are considered appropriate.

Discussion

This discussion corresponds to the NCCN Guidelines for Chronic Myeloid Leukemia. Last updated: July 16, 2025

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Overview

Chronic myeloid leukemia (CML) accounts for 15% of adult leukemias. The median age of disease onset is 67 years; however, CML occurs in all age groups (SEER statistics). In 2025, an estimated 9560 people will be diagnosed with CML in the United States, and 1290 people will die from the disease.[1]

CML is defined by the presence of the Philadelphia chromosome (Ph) in a patient with a myeloproliferative neoplasm (MPN). Ph results from a reciprocal translocation between chromosomes 9 and 22 [t(9;22] that gives rise to a *BCR::ABL1* fusion gene.[2] In most patients, the chromosomal breakpoints are located in intron 13 or 14 of the *BCR* gene on chromosome 22 (major breakpoint cluster region; *M-BCR*). In the *ABL1* gene they are located between the two alternative *ABL1* exons Ib and Ia, or between *ABL1* exons 1 and 2.[3,4] Irrespective of the precise *ABL1* breakpoint, splicing almost invariably fuses *ABL1* exon 2 with *BCR* exons 13 or 14, resulting in e13a2 and e14a2 transcripts that code for a protein, p210, with deregulated tyrosine kinase activity, which causes CML.

Unusual *BCR::ABL1* transcripts, e1a2 encoding for p190 (involving the minor breakpoint cluster region; *m-BCR*), or e19a2 encoding for p230 (involving the micro breakpoint cluster region; µ-*BCR*), are found infrequently.[3,4] p190 is usually produced in the setting of Ph-positive acute lymphoblastic leukemia (ALL), and p230 is associated with enhanced neutrophil differentiation. Atypical *BCR::ABL1* transcripts (eg, e13a3, e14a3, e6a2) have also been detected in about 1% to 2% of patients with CML. The proportion of different *BCR::ABL1* transcripts and the impact of *BCR::ABL1* transcript type on response to tyrosine kinase inhibitor (TKI) therapy are discussed in the section *BCR::ABL1 Transcript Variants in CML*.

CML occurs in three different phases (chronic, accelerated, and blast phase) and is usually diagnosed in the chronic phase in developed countries. Untreated chronic phase CML (CP-CML) will eventually progress to accelerated phase CML (AP-CML) or blast phase CML (BP-CML) in 3 to 5 years on average.[5] Progression to AP-CML and BP-CML bridges a continuum of clinical features (ie, fever, bone pain, spleen size), cytogenetic changes, and blast count. Gene expression profiling has shown a close correlation of gene expression between AP-CML and BP-CML indicating that the bulk of the genetic changes in progression occur in the transition from CP-CML to AP-CML.[6] The activation of the beta-catenin signaling pathway in CML granulocyte-macrophage progenitors (which enhances the self-renewal activity and leukemic potential of these cells) may be a key pathobiologic event in the evolution to BP-CML.[7]

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Myeloid Leukemia discuss the clinical management of CML in all three phases (chronic, accelerated, or blast phase). Evaluation for diseases other than CML as outlined in the NCCN Guidelines® for Myeloproliferative Neoplasms is recommended for all patients with *BCR::ABL1*–negative MPN.

Guidelines Update Methodology

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Literature Search Criteria

Prior to the update of this version of the NCCN Guidelines for Chronic Myeloid Leukemia, an electronic search of the PubMed database was performed to obtain key literature in Chronic Myeloid Leukemia since the last guideline update using the following search terms: chronic myeloid leukemia or chronic myelogenous leukemia. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[8]

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

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

Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation. NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

Diagnosis and Workup

Initial evaluation should consist of a history and physical exam, including palpation of the spleen, complete blood count (CBC) with differential, chemistry profile, and hepatitis B panel. Bone marrow aspirate and biopsy for morphologic and cytogenetic evaluation and quantitative reverse transcriptase polymerase chain reaction (RT-PCR) to establish the presence of quantifiable *BCR::ABL1* mRNA transcripts at baseline are recommended to confirm the diagnosis of CML (CML-1).

Bone marrow cytogenetics with a minimum of 20 metaphases is useful to detect additional chromosomal abnormalities (ACAs) in Ph-positive cells, also known as clonal cytogenetic evolution (discussed below).[9-13] If bone marrow evaluation is not feasible, fluorescence in situ hybridization (FISH) on the bone marrow or a peripheral blood specimen with dual probes for *BCR* and *ABL1* genes can be used to confirm the diagnosis of CML. Interphase FISH is performed on peripheral blood but can be associated with a false-positive rate of 1% to 5% depending on the specific probe used in the assay.[14] Hypermetaphase FISH is more sensitive and can analyze up to 500 metaphases at a time, but it is applicable only to dividing cells in the bone marrow.[15] Double-fusion FISH (D-FISH) is associated with low false-positive rates and can detect all variant translocations of the Ph-chromosome.[16]

Quantitative RT-PCR (qPCR) should be done at initial workup to establish the presence of quantifiable *BCR::ABL1* mRNA transcripts. qPCR, usually done on peripheral blood, is the most sensitive assay available for the measurement of *BCR::ABL1* mRNA and it can detect one CML cell in a background of ≥100,000 normal cells. qPCR results can be expressed in various ways, such as the ratio of *BCR::ABL1* transcript numbers to the number of control gene transcripts.[17] An International Scale (IS) has been established to standardize molecular monitoring with qPCR across different laboratories with the use of one of three control genes (*BCR*, *ABL1*, or *GUSB*) and a qPCR assay with a sensitivity of at least 4-log reduction from the standardized baseline.[18] IS has become the gold standard of expressing qPCR values. More details on monitoring with qPCR using IS are provided on MS-10. Qualitative RT-PCR or D-FISH should be considered for detecting atypical *BCR::ABL1* transcripts if there is discordance between FISH and qPCR results. See the section on *BCR::ABL1 Transcript Variants in CML* below.

BCR::ABL1 transcripts in the peripheral blood at very low levels (1–10 out of 10^8 peripheral blood leukocytes) can be detected in approximately 30% of individuals without CML, and the incidence of this increases with age. The risk of developing CML for these individuals is extremely low, and neither continued monitoring nor therapy is indicated.[19,20]

BCR::ABL1 Transcript Variants in CML

e13a2 and e14a2 transcripts (both encoding for p210) were the most common *BCR::ABL1* transcript variants identified in about 39% and 62% of patients, respectively; e13a2 was more frequent in males and the proportion decreased with age in both sexes.[21,22] Unusual or atypical transcripts were identified in about 2% of patients, with e1a2, e19a2, e13a3, and e14a3 being the most frequently identified transcripts.[21] The incidence of these atypical transcripts was higher in females and the proportion decreased with age in both genders. The presence of e14a2 at baseline was associated with higher molecular response rates to imatinib.[23-29] While some studies have demonstrated a trend towards better survival outcomes with e14a2 transcript,[25,26] in other studies the type of transcript did not have any significant impact on long-term survival outcomes.[24,27,30]

Limited available data from studies that evaluated the impact of *BCR::ABL1* transcript variants on response to second-generation (2G) TKI therapy suggest that nilotinib may be associated with inferior molecular response rates in patients with e13a2 as well as e14a2 transcripts compared to imatinib 800 mg or dasatinib.[25,31] The results of other studies indicate that difference in the amplification characteristics between the e13a2 and e14a2 transcripts can affect the measurement of residual disease, thus emphasizing the need to consider sequential measurement of minimal residual disease in addition to the achievement of response milestones at specific timepoints.[32-34]

The presence of e1a2 transcript (encoding for p190) is associated with a higher risk of disease progression, inferior cytogenetic and molecular responses to TKI therapy, and the presence of frequent mutations in epigenetic modifiers genes.[35-41] In a multivariate analysis, the e1a2 transcript was also identified as an independent predictor of inferior survival outcomes.[37] It is important to be aware that these data refer to the presence of dominant e1a2 transcript, not to the presence of low-level e1a2 transcripts in patients with dominant e13a2 or e14a2 transcripts. The presence of e19a2 transcript (encoding for p230) is associated with lower rates of cytogenetic and molecular response to TKIs and inferior survival outcomes, despite previous reports of an indolent disease course in the pre-TKI era.[38,39,42] Referral to centers with expertise in the management of CML is recommended.

Qualitative RT-PCR, nested RT-PCR, or Sanger sequencing are useful for identifying atypical *BCR::ABL1* transcripts.[43,44] qPCR using log-reduction from standardized baseline can be used to monitor e1a2 transcripts, and monitoring e19a2 transcripts is usually performed using qualitative RT-PCR or nested RT-PCR. However, there are no standardized qPCR assays for monitoring molecular response to TKI therapy in patients with atypical *BCR::ABL1* transcripts.[45,46] The utility of multiplex PCR assays and patient-specific genomic quantitative DNA PCR assays for monitoring atypical *BCR::ABL1* transcripts has been demonstrated in some reports.[47-51]

Clonal Cytogenetic Evolution

The prognostic significance of ACAs in Ph-positive cells is related to the specific chromosomal abnormality and other features of the accelerated phase.[9-13] The presence of "major route" ACAs in Ph-positive cells (trisomy 8, isochromosome 17q, second Ph, trisomy 19, and chromosome 3 abnormalities) at diagnosis may have a negative prognostic impact on survival and disease progression to accelerated or blast phase.[52-55] However, in another analysis that evaluated the outcomes of patients with CP-CML (with or without ACAs) treated with TKI therapy in prospective studies, the presence of ACAs in Ph-positive cells at the time of diagnosis was not associated with worse prognosis.[56] Survival outcomes were not significantly different among patients with ACAs in Ph-positive cells based on TKI therapy (imatinib vs. 2G TKIs) or imatinib dose (400 vs. 800 mg). It remains uncertain if 2G TKIs or high-dose imatinib would be more beneficial for patients with ACAs in Ph-positive cells. Patients with ACAs in Ph-positive cells at diagnosis should be monitored carefully for evidence of resistance to TKI therapy and follow-up metaphase karyotype analysis should be performed if resistance is evident.

Clonal cytogenetic evolution in Ph-negative cells has also been reported in a small subset of patients treated with TKI therapy.[57-68] The most common abnormalities include trisomy 8 and loss of the Y chromosome. Previous work suggested that the overall prognosis of Ph-negative clonal evolution is good and depends on response to imatinib therapy.[61] However, the presence of chromosome abnormalities other than loss of the Y chromosome has been associated with decreased survival in patients with CP-CML treated with various TKIs, suggesting that closer follow-up is indicated.[69] Progression to myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) has been reported in patients with monosomy 7 (del 7q).[70-72]

Additional Evaluation

Chronic Phase CML: Risk Stratification

Sokal and Hasford (Euro) scoring systems have been used for the risk stratification of patients into three risk groups (low, intermediate, and high) in clinical trials evaluating TKIs.[73,74] The Sokal score is based on the patient's age, spleen size on clinical examination, platelet count, and percentage of blasts in the peripheral blood.[73] The Euro score includes eosinophils and basophils in the peripheral blood in addition to the same clinical variables used in the Sokal score.[74]

The European Treatment and Outcome Study long-term survival (ELTS) score is based on the same variables as the Sokol score and provides the most useful predictor of CML-related death in patients treated with first-line imatinib.[75] The ELTS score has been validated in a cohort of 1120 patients with CP-CML treated with imatinib in six clinical trials. Older age, higher peripheral blasts, bigger spleen, and low platelet counts were significantly associated with increased probabilities of dying of CML. Patients in the intermediate- and the high-risk groups had significantly higher probabilities of dying of CML than those in the low-risk group, and the probabilities were also significantly different between the intermediate- and high-risk groups. Unlike other scoring systems, the ELTS score is focused on CML-specific overall survival (OS). This is important, as many patients with CML die from non-CML causes, reflecting the efficacy of TKI therapy.

Determination of risk score using either the Sokal or Euro or ELTS scoring systems (CML-A) prior to initiation of TKI therapy is recommended for patients diagnosed with CP-CML.[73-75]

Advanced Phase CML: Diagnostic Criteria

The modified MD Anderson Cancer Center (MDACC) criteria for AP-CML (15% and 29% peripheral blood or bone marrow myeloblasts; ≥30% of peripheral blood myeloblasts and promyelocytes; ≥20% of peripheral blood or bone marrow basophils; platelet count ≤100 x 10^9/L unrelated to therapy; and clonal cytogenetic evolution in Ph+ cells) are used in many clinical trials that have evaluated the efficacy of TKIs (CML-B).[76] AP-CML defined only by clonal cytogenetic evolution on imatinib therapy is associated with a better prognosis than AP-CML defined by clonal cytogenetic evolution and additional features of progression.[52,77]

The 2022 International Consensus Classification (ICC) includes a lower threshold (10%–19%) of bone marrow or peripheral blasts and the presence of ACA/Ph+ for the diagnosis of AP-CML, whereas AP-CML is not included in the updated 2022 World Health Organization (WHO) classification.[78,79] The updated WHO classification emphasizes the high-risk features associated with the progression of CP-CML to BP-CML.[79]

The International Bone Marrow Transplant Registry (IBMTR) criteria define blast phase as the presence of ≥30% myeloblasts in the blood, bone marrow, or both, or as the presence of extramedullary disease (CML-B).[80] Any increase in lymphoblasts should be concerning for nascent lymphoid blast phase disease. IBMTR criteria were used in most of the clinical trials leading to the approval of TKIs and is best aligned with prognostication systems derived from these studies. The 2022 ICC and WHO classification require the presence of ≥20% blast cells in the peripheral blood or bone marrow, the presence of extramedullary blast proliferation, and the presence of increased lymphoblasts in peripheral blood or bone marrow to confirm the diagnosis of BP-CML.[78,79]

Clinical trials in the TKI era have almost uniformly utilized the modified MDACC or the IBMTR criteria. The use of ICC or WHO criteria for the diagnosis of AP-CML and BP-CML is not recommended.

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

Myeloid Mutational Analysis

Mutations in epigenetic modifier genes (eg, *ASXL1, IKZF1, BCOR*, *TET1/2, IDH1/2, DNMT3A/3B, EZH2*) have been described in patients with CML and the presence of epigenetic gene mutations at diagnosis has been associated with lower rates of molecular or cytogenetic responses and lower rates of progression-free survival (PFS)/event-free survival (EFS).[81-97]

Mutations in the *ASXL1* gene are the most commonly described secondary alterations in patients with CP-CML and are an independent predictor of inferior molecular/cytogenetic responses and EFS rates following TKI therapy (including 2G-TKI therapy).[94,95] In an analysis of 222 patients with CP-CML (prospectively enrolled in the CML-V study), an *ASXL1* mutation was detected in 20 patients at the time of diagnosis. All patients had received nilotinib-based TKI therapy. The probability of achieving major molecular response (MMR) or better at 12 months was significantly lower for patients with an *ASXL1* mutation (55%; P = .0036) compared to 85% for patients with no mutations and 82% for patients with other non-*ASXL1* mutations.[95] However, in another study of 124 patients with newly diagnosed CP-CML, mutations in epigenetic modifier genes (including *ASXL1* mutation) were predictive of response rates only in patients treated with imatinib but did not have any impact on the outcomes in patients treated with 2G TKIs.[89]

IKZF1 exon deletions and mutations in *ASXL1, RUNX1,* and *BCOR* genes were the most frequently described secondary alterations in advanced phase CML, while *IDH1/2* mutations were detected at a markedly lower frequency.[82,87,90,92,93] *IKZF1*, *RUNX1,* and *DNMT3A* alterations were identified as important markers of disease progression to advanced phase CML and risk of relapse after discontinuation of TKI.[81,83,87,96] Mutations at diagnosis in *ASXL1*, *DNMT3A,* JAK2, and *TET2* genes have been associated with increased risk of cardiovascular events associated with TKI therapy.[97]

Next-generation sequencing (NGS) allows for the detection of low-level *BCR::ABL1* kinase domain mutations and mutations in genes other than *BCR::ABL1* that may confer resistance to TKIs or portend disease progression.[98,99] In a prospective, multicenter study (NEXT-in-CML) that assessed the feasibility of NGS to detect low-level mutations in 236 consecutive patients with CML and an inadequate response to TKI therapy, NGS was more effective than conventional Sanger sequencing in the detection of low-level mutations.[99] Prospective monitoring of mutation kinetics demonstrated that TKI-resistant low-level mutations are invariably selected if the patients are not switched to another TKI or if they are switched to an inappropriate TKI or TKI dose.[99] NGS with myeloid mutation panel should be considered for patients with no identifiable *BCR::ABL1* mutations.

Testing for *BCR::ABL1*–independent mutations using NGS with myeloid mutation panel may be useful for patients with CP-CML who do not achieve optimal response milestones due to the presence of cytopenias, for those patients with TKI-resistant disease and for patients with advanced phase CML.[88,91] However, there are very limited data on the impact of *BCR::ABL1*–independent mutations in patients with newly diagnosed CP-CML. Additionally, *BCR::ABL1*–independent gene mutations have also been frequently described in Ph-negative clones.[100] The impact of mutations is also variable depending on whether they occur in Ph-positive or Ph-negative clones.

Myeloid mutational analysis using NGS can be considered for patients with CP-CML and advanced phase CML at diagnosis.

Management of Chronic Phase CML

Primary Treatment

Long-term efficacy data from randomized phase III studies for first-line TKI therapy in patients with newly diagnosed CP-CML are summarized in Table 1.[101-105] In summary, 1) all TKIs are highly effective as primary treatment for patients with newly diagnosed CP-CML, with long-term OS expected to be similar to that of aged-matched controls; 2) 2G TKIs (bosutinib, dasatinib, and nilotinib) and asciminib (allosteric TKI; STAMP inhibitor) generally result in faster cytogenetic and molecular responses with less progression to advanced phase CML compared to imatinib; and 3) in randomized clinical trials, as of yet, there are no significant differences in OS between imatinib and a 2G TKI or asciminib.

Clinical Considerations for the Selection of First-Line Therapy

The selection of first-line TKI therapy (asciminib, bosutinib, dasatinib, imatinib, or nilotinib) in a given patient should be based on the risk score, toxicity profile and dosing schedule of TKI, patient's age, ability to tolerate therapy, and the presence of comorbid conditions, patient preference, treatment goals, and medication costs (CML-2).

***BCR::ABL1* Transcript Type**

BCR::ABL1 variants lacking ABL1 exon 2 (referred to as *BCR::ABL1*/ b2a3 or *BCR::ABL1*/b3a3 isoforms) are present in a minority of patients with CML and these isoforms confer a high degree of resistance to asciminib (allosteric TKI; specially targeting the ABL1 myristoyl pocket [STAMP]) that cannot be overcome with higher doses of aciminib.[21,106,107] Therefore, asciminib is contraindicated for CML with *BCR::ABL1*/ b2a3 or *BCR::ABL1*/b3a3 isoforms.

Risk Score

Asciminib, bosutinib, dasatinib, imatinib, or nilotinib are all appropriate options for first-line TKI therapy for patients with CP-CML across all risk scores.[101-105]

Disease progression is more frequent in patients with intermediate- or high-risk score, and prevention of disease progression to AP-CML or BP-CML is the primary goal of TKI therapy in patients with CP-CML. 2G TKIs and asciminib are associated with a lower risk of disease progression than imatinib and are preferred for patients with an intermediate- or high-risk Sokal or Euro score. 2G TKIs result in quicker molecular responses and higher rates of MMR (≤0.1% *BCR::ABL1* IS) and deep molecular response (DMR) (MR4.0 [≤0.01% *BCR::ABL1* IS] or MR4.5 [≤0.0032% *BCR::ABL1* IS]) in patients with CP-CML across all risk scores (Table 2), which may facilitate subsequent discontinuation of TKI therapy in selected patients.[102-104] In the ASC4FIRST study, asciminib also resulted in higher rates of MMR compared to investigator-selected TKI (imatinib or 2G TKIs) in patients across all risk scores. There was a significant difference versus imatinib ($P < .001$), but there was no statistically significant difference in MMR rates versus 2G TKI. Therefore, 2G TKIs and asciminib are preferred for patients with an intermediate-risk or high-risk score.[105]

2G TKIs and asciminib should also be considered for specific subgroups (based on the assessment of treatment goals and benefit/risks), for example in younger patients who are interested in ultimately discontinuing treatment, particularly in young patients assigned female at birth with a goal of achieving a deep and rapid molecular response which may allow for eventual discontinuation of TKI therapy for family planning purposes. Imatinib may be preferred for older patients with comorbidities, especially cardiovascular comorbidities.

Toxicity Profile of TKI

All the TKIs are generally well tolerated. Since asciminib, bosutinib, dasatinib, and nilotinib have very good efficacy in the treatment of newly diagnosed CP-CML, differences in their potential toxicity profiles may inform the selection of a specific TKI as initial therapy. Adverse events of first-line TKI therapy in patients with CP-CML reported in phase III randomized studies are discussed below and are summarized in Table 3.

See also the section on *Special Considerations for the Use of TKI Therapy* in the algorithm (CML-C).

Asciminib, bosutinib, or nilotinib may be preferred for patients with a history of lung disease or deemed to be at risk of developing pleural effusions. Bosutinib or dasatinib may be preferred in patients with a history of arrhythmias, cardiovascular disease (CVD), hypertension, pancreatitis, or hyperglycemia.

Asciminib

In the ASC4FIRST study, rash, headache, edema, muscle spasms, gastrointestinal toxicities (diarrhea, constipation, and vomiting), and biochemical abnormalities (elevated aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) were less common with asciminib than with imatinib and 2G TKIs.[105] Headache, rash, and elevated AST/ALT were more common with 2G TKIs, whereas muscle spasms, vomiting, and edema were more common with imatinib. The incidences of arterial adverse events were low across all 3 treatment groups occurring in 1% and 2% of patients treated with asciminib and 2G TKIs, respectively, with no such adverse event reported with imatinib. The incidence of adverse events leading to discontinuation of treatment was also lower with asciminib. However, longer term side effects are not evaluable because of the short median follow-up of 16 months.

Bosutinib

In the BFORE study, diarrhea, increased ALT and AST levels were more common with bosutinib whereas muscle spasms and peripheral edema were more common with imatinib.[104] Grade 3/4 thrombocytopenia was higher with bosutinib, and grade 3/4 neutropenia was higher with imatinib. Grade 3/4 anemia was similar in both groups. Discontinuation of therapy due to drug-related adverse events occurred in 14% of patients in the bosutinib group compared to 11% in the imatinib group. Increased ALT (5%) and increased AST (2%) were the most common adverse events leading to discontinuation of bosutinib. However, there were no hepatotoxicity-related fatalities during the study.

Dasatinib

In the DASISION study, the incidences of grade 3/4 hematologic toxicities (anemia, neutropenia, and thrombocytopenia) were higher for dasatinib than imatinib.[102] Nonhematologic adverse events such as muscle spasms, peripheral edema, and hypophosphatemia were more frequent with imatinib. Discontinuation of therapy because of drug-related adverse events occurred in 16% and 7% of patients in the dasatinib and imatinib arms, respectively. Dasatinib is associated with significant but reversible inhibition of platelet aggregation that may contribute to bleeding in some patients, especially if accompanied by thrombocytopenia.[108]

Pleural effusion was also more common with dasatinib (28% in the DASISION study compared to <1% with imatinib and 33% in a dose optimization study) and age has been identified as a significant risk factor for the development of pleural effusion.[109] The occurrence of pleural effusion is significantly reduced with dasatinib 100 mg once daily compared with 70 mg twice daily. Patients with prior cardiac history, with hypertension, and receiving dasatinib 70 mg twice daily are at increased risk of developing pleural effusions.[110]

Largely reversible pulmonary arterial hypertension (PAH) has been reported as a rare but serious side effect of dasatinib.[111-113] In the DASISION study, pulmonary hypertension was reported in 5% of patients treated with dasatinib compared to <1% of patients treated with imatinib.[102]

Evaluation for signs and symptoms of underlying cardiopulmonary disease prior to initiating and close monitoring during treatment with dasatinib is recommended. Dose reduction (with close monitoring) should be considered for patients at risk of developing pleural effusions. Switching to alternate TKI is recommended for persistent pleural effusion or PAH despite adequate supportive care interventions and dose reduction.

A pH-independent formulation of dasatinib that can be administered concomitantly with proton pump inhibitors (PPIs), or histamine 2 receptor antagonists (H2RAs) has been approved by the FDA as an alternative treatment option for adult patients with CML. Dasatinib products are available in different formulations, dosage forms, and strengths. These products are not interchangeable. Refer to package insert for full prescribing information: https://www.accessdata.fda.gov/.

Imatinib

Chronic fatigue (often correlated with musculoskeletal pain and muscular cramps) is a major factor in reducing quality of life in patients who take imatinib.[114] Hypophosphatemia and decrease in bone mineral density have been noted in a small group of patients, suggesting that monitoring bone health should be considered for patients taking imatinib.[115,116] Skin hypopigmentation has also been reported as a side effect of imatinib and is reversible upon discontinuation or dose reduction.[117,118] Reversible renal dysfunction with prolonged use of imatinib has also been reported.[119]

Nilotinib

In the ENESTnd study, rates of nonhematologic adverse events such as nausea, diarrhea, vomiting, muscle spasm, and peripheral edema of any grade were higher for patients receiving imatinib. Conversely, rash and headache were more common with nilotinib.[103] Grade 3 or 4 neutropenia was more frequently observed in the imatinib group, whereas thrombocytopenia and anemia were similar in both groups. Electrolyte abnormalities and elevations in lipase, glucose, and bilirubin were more frequent with nilotinib than with imatinib. Patients with a previous history of pancreatitis may be at greater risk of elevated serum lipase. The overall incidences of adverse events leading to discontinuation of therapy were comparable in the nilotinib 300 mg twice-daily and imatinib arms (12% and 14%, respectively) and slightly higher in the nilotinib 400 mg twice-daily arm (20%).

Nilotinib labeling contains a black box warning regarding the risk of QT interval prolongation, and sudden cardiac death has been reported in patients receiving nilotinib.[113] Electrolyte abnormalities should be corrected prior to initiation of treatment with nilotinib, and electrolytes should be monitored periodically. Drugs that prolong QT interval should be avoided. Electrocardiogram (ECG) should be obtained to monitor the QT interval at baseline, 7 days after initiation of nilotinib, and periodically thereafter, as well as following any dose adjustments. Nilotinib is associated with an increased risk of ischemic heart disease, ischemic cerebrovascular disease, and peripheral arterial occlusive disease (PAOD).[103] The 10-year follow-up data from the ENESTnd study showed a higher rate of adverse cardiovascular events with nilotinib (17% and 24%, respectively, for nilotinib 300 mg twice daily and nilotinib 400 mg twice daily) versus imatinib (4%).[103]

Evaluation for pre-existing cardiovascular risk factors prior to initiating treatment with nilotinib and close monitoring for any adverse cardiovascular events during treatment with nilotinib is recommended for all patients. Referral to a cardiologist is recommended for patients with cardiovascular risk factors for additional monitoring and/or assessments. QT interval prolongation could be managed with dose reduction. Switching to alternate TKI is recommended if persistent despite dose reduction and adequate supportive care interventions.

Nilotinib tablets with improved bioavailability that allows for administration at a lower dose without mealtime restrictions has been approved by the FDA. Nilotinib products are available in different formulations, dosage forms, and strengths. These products are not interchangeable. Refer to package insert for full prescribing information: https://www.accessdata.fda.gov.

TKI Dose

TKIs are available in different formulations, dosage forms, and strengths that are subject to different administration instructions. These products are not interchangeable. Refer to package insert of specific TKIs for full prescribing information: https://www.accessdata.fda.gov.

Data from randomized phase III studies that have evaluated high-dose imatinib as first-line therapy for CP-CML suggest that imatinib 800 mg was not associated with lower rates of disease progression than imatinib 400 mg, despite improved early responses (Table 4).[120-122] Imatinib 800 mg was also associated with higher rates of dose interruption, reduction, or discontinuation due to grade 3 or 4 adverse events in all of the studies. However, patients who could tolerate the higher dose of imatinib achieved higher response rates than those receiving standard-dose imatinib.[123] Imatinib 800 mg is not recommended as initial therapy, given the data showing superior efficacy of 2G TKIs in newly diagnosed CP-CML.

Limited available evidence from small cohort studies suggests that initiation of select first-line TKIs (bosutinib, dasatinib, or nilotinib) at lower doses (to minimize treatment-related adverse events) and dose reduction (with close monitoring) in patients who achieve optimal responses are appropriate strategies to reduce the risk of long-term toxicities.[124,125] See the section on *Dose Modifications of TKI Therapy*. However, the minimum effective dose or optimal de-escalation of TKIs (bosutinib, dasatinib, or nilotinib) has not yet been established in prospective randomized clinical trials.

Management of Toxicities of TKI Therapy

Hematologic Toxicities

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

Assessment of reticulocyte count, ferritin, iron saturation, vitamin B12, and folate and correction of nutritional deficiencies if present is recommended for patients with grade 3–4 anemia. Red blood cell transfusions are indicated in symptomatic patients. Growth factor support can be used in combination with TKI therapy for the management of persistent cytopenias.[126,127] Bone marrow evaluation should be considered to rule out disease progression to AP-CML or BP-CML or the emergence of other myeloid neoplasms after TKI therapy.

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.[128] The 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.

Nonhematologic Toxicities

Recommendations for monitoring and supportive care interventions for the management of nonhematologic adverse events are outlined in the section *Special Considerations for the Use of TKI Therapy* in the algorithm.

Dose reduction (with close monitoring) should be considered if nonhematologic adverse events are not controlled by adequate supportive care interventions. Switching to an alternate TKI is recommended for persistent adverse events despite dose reduction.

Patients should be counseled on the potential risk factors for CVD and the increased risk of CVD associated with long-term TKI therapy.[129] Cardiovascular risk factors (eg, diabetes, hypertension, hyperlipidemia, smoking, estrogen use) should be identified and controlled prior to initiating TKI therapy. Patients with a history of cardiovascular risk factors or cardiovascular signs and symptoms should be carefully monitored for high blood pressure; evidence of arterial, vascular, or thromboembolic events; and reduced cardiac function.[130] Switching to an alternate TKI is recommended for the onset of new arterial and vascular events, new or worsening heart failure, and severe hypertension not responsive to antihypertensive medications. Referral to a cardiologist is recommended for patients with cardiovascular risk factors for additional monitoring and/or assessments.

Treatment Goal

See the section on *Response Milestones After First-Line TKI Therapy*.

Medication Cost

The cost of the treatment is an important factor to consider, especially for patients in whom TKI therapy should be continued indefinitely. High cost TKIs can limit their long-term use and could potentially be a barrier to adherence to therapy.[131] The cost of generic TKIs can be substantially less than that of brand name TKIs, and the cost of treatment to both the patient and to society should be considered while selecting TKI therapy in an individual patient. Generic drugs have been shown to be noninferior to brand name drugs in terms of efficacy with an acceptable toxicity profile.[132-136] Therefore, FDA-approved generic drugs are appropriate substitutes for brand name drugs.[125,137]

Imatinib and dasatinib are currently available as generic TKIs. Brand name and generic drugs approved by the regulatory authorities based on pharmacokinetic equivalence can be used interchangeably. In some instances, the safety profile of the generic drug may be different than that of the brand name drug (likely due to differences in formulation) and effective management of adverse effects associated with generic drugs is essential to prevent treatment interruption.[138] Clinicians should be aware of the potential pharmacokinetic variability and monitor patients closely during transitions, particularly for drugs with narrow therapeutic windows such as nilotinib and bosutinib.

Monitoring Response to TKI Therapy

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

Conventional bone marrow cytogenetics is the standard method for monitoring cytogenetic responses, and many clinical trial response analyses have been based on conventional bone marrow cytogenetics. With the advent of qPCR, bone marrow cytogenetic analyses to assess response are rarely performed. If conventional bone marrow cytogenetics yield no analyzable metaphases, cytogenetic response can be evaluated by FISH, preferably with a dual color probe to minimize false-positive rates. FISH and cytogenetic results are correlated, but are not superimposable.[139-141] Although some investigators have reported that interphase FISH can be used to monitor complete cytogenetic response (CCyR), inadequate response to TKI therapy has not been defined on the basis of FISH analysis.[142,143] The Panel feels that FISH has been inadequately studied for monitoring response to TKI therapy and is not generally recommended for monitoring response if conventional cytogenetics or qPCR are available.

qPCR is the only tool capable of monitoring responses after the patient has achieved CCyR, since *BCR::ABL1* transcripts typically remain detectable after CCyR is achieved. A major advantage of qPCR is the strong correlation between the results obtained from the peripheral blood and the bone marrow, allowing for molecular monitoring without bone marrow aspirations.[144,145]

Standardization of Molecular Monitoring Using the International Scale

In the IS, the standardized baseline (defined as the median expression of *BCR::ABL1* transcripts in 30 patients with untreated CML enrolled in the IRIS trial) is set to 100%. Molecular response is expressed as log-reduction from 100%. For example, a ≥2-log reduction (≤1% *BCR::ABL1* IS; MR2.0) generally correlates with CCyR and a ≥3-log reduction (≤0.1% *BCR::ABL1* IS) is referred to as MMR or MR3.0.[18,146,147]

DMR is defined by the assay's level of sensitivity [≤0.01% *BCR::ABL1* (IS), MR4.0; ≤0.0032% *BCR::ABL1* (IS), MR4.5].[148] The sensitivity of a qPCR assay depends not only on the performance of the assay, but also on the quality of a given sample.

As such, the term “complete molecular response” to denote undetectable *BCR::ABL1* transcripts (a negative qPCR test) should be abandoned, as it may refer to very different levels of response, dependent on the quality of the sample and sensitivity of the test. Laboratories can use their individual assays, but the *BCR::ABL1* transcripts obtained in a given laboratory should be converted to the IS by applying a laboratory-specific conversion factor (CF).[18,149]

Recommendations for Monitoring Response to TKI Therapy

qPCR (IS) is the preferred method to monitor response to TKI therapy. qPCR assays with a sensitivity of ≥4.5-log reduction from the standardized baseline are recommended to measure *BCR::ABL1* transcripts (CML-G). In patients with prolonged myelosuppression who may not be in complete hematologic response (CHR) due to persistent cytopenias or an unexplained drop in blood counts during therapy, bone marrow cytogenetics is indicated to confirm response to TKI therapy and exclude other pathology, such as MDS or the presence of chromosomal abnormalities other than Ph. Given the risk for transient myelosuppression that can occur during early disease responses, TKI therapy should not be held while bone marrow evaluation is pending.

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

Frequent molecular monitoring with qPCR (IS) can help to identify non-adherence to TKI therapy early in the treatment course.[150] Since adherence to TKI therapy is associated with better clinical outcomes, frequent molecular monitoring is essential if there are concerns about the patient's adherence to TKI therapy. In patients with deeper molecular responses (MMR and better) and adherence to TKI therapy, the frequency of molecular monitoring can be reduced, though the optimal frequency is unknown. Molecular monitoring of response to TKI therapy more frequently than every 3 months is not presently recommended.

Prognostic Significance of Cytogenetic and Molecular Response

Early molecular response (EMR; ≤10% *BCR::ABL1* IS at 3 and 6 months) after first-line TKI therapy has emerged as an effective prognosticator of favorable long-term PFS and OS (Table 5).[102,122,151,152] Some reports suggest that EMR at 3 months has a superior prognostic value and supports early intervention strategies based on the *BCR::ABL1* transcript level at 3 months.[153,154] However, other studies yielded partially conflicting results regarding the predictive value of *BCR::ABL1* transcripts at 3 months.[155] From a practical perspective, it is important to consider these data points within the clinical context. For instance, if *BCR::ABL1* transcript level is minimally above the 10% cutoff (eg, 11%–15% at 3 months), it is reasonable to reassess at 6 months before considering major changes to the treatment strategy.

Some studies have suggested that the rate of decline in *BCR::ABL1* transcripts correlates with longer-term response.[156-158] Among patients with >10% *BCR::ABL1* IS after 3 months of treatment with imatinib, those with a faster decline in *BCR::ABL1* (*BCR::ABL1* halving time <76 days) had a superior outcome compared to those with a slower decline (4-year PFS rate was 92% vs. 63%, respectively).[156] 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.[157] The results of the D-First study also showed that in patients treated with dasatinib, *BCR::ABL1* halving time of ≤14 days was a significant predictor of MMR by 12 months and DMR (MR4.0; ≤0.01% *BCR::ABL1* IS) by 18 months.[158]

Achievement of CCyR or ≤1% *BCR::ABL1* IS within 12 months after first-line TKI therapy is an established prognostic indicator of long-term survival.[159,160] In the IRIS study, the estimated 6-year PFS rate was 97%

for patients achieving a CCyR at 6 months compared to 80% for patients with no cytogenetic response at 6 months.[159] In an analysis of patients with newly diagnosed CP-CML treated with imatinib or 2G TKIs, the 3-year EFS and OS rates were 98% and 99% for patients who achieved CCyR at 12 months compared to 67% and 94% in patients who did not achieve a CCyR.[160]

MMR (≤0.1% *BCR::ABL1* IS) as a predictor of PFS and OS has also been evaluated in several studies.[144,161-167] In all of these studies, the analyses were done for different outcomes measures at multiple time points, but did not adjust for multiple comparisons, thereby reducing the validity of the conclusions. The general conclusion from these studies is that the achievement of MMR is associated with durable long-term cytogenetic remission and lower rate of disease progression, but MMR is not a significant predictor of superior OS in patients with a stable CCyR. Importantly, with longer follow-up, CCyR becomes an ever-stronger indicator of MMR, reducing the added prognostic value of MMR. Although the CML IV study showed that MR4.5 (≤0.0032% *BCR::ABL1* IS) at 4 years was associated with a significantly higher OS (independent of therapy) than MR2.0 (≤1% *BCR::ABL1* IS, which corresponds to CCyR), this study demonstrated no significant differences in OS in patients who achieved MMR (≤0.1% *BCR::ABL1* IS) and those who achieved MR2.0 (≤1% *BCR::ABL1* IS).[166]

The absence of MMR in the presence of a CCyR is therefore not considered as an inadequate response to treatment. While some investigators have reported that dose escalation of imatinib might benefit patients in CCyR with no MMR,[168] there are no randomized studies to show that a change of therapy would improve survival, PFS, or EFS in this group of patients.[169] However, the achievement of MMR (≤0.1% *BCR::ABL1* IS) at 12 months is associated with a very low probability of subsequent loss of response and a high likelihood of achieving a subsequent DMR (MR4.0; ≤0.01% *BCR::ABL1* IS), which may facilitate discontinuation of TKI therapy.[46,167] In view of the ongoing evolution of treatment goals (OS vs. treatment-free remission [TFR]), expert Panels have emphasized the importance of joint decision-making between patient and provider, particularly in ambiguous situations.[170]

Response Milestones After First-Line TKI Therapy

The most important goals of TKI therapy are to prevent disease progression to AP-CML or BP-CML and to achieve either MR2.0 (≤1% *BCR::ABL1* IS, which corresponds to CCyR) or MMR (≤0.1% *BCR::ABL1* IS) within 12 months after first-line TKI therapy. The guidelines emphasize that achievement of response milestones must be interpreted within the clinical context, before making drastic changes to the treatment strategy, especially in ambiguous situations.

The Panel has included ≤10% *BCR::ABL1* IS at 3 and 6 months after initiation of first-line TKI therapy as a response milestone since the achievement of EMR after first-line TKI therapy is an effective prognosticator of favorable long-term PFS (CML-3). Achievement of >0.1% to 1% *BCR::ABL1* IS (≤1% *BCR::ABL1* IS, which correlates with CCyR) is considered the optimal response milestone at 12 months if the goal of therapy in an individual patient is long-term survival, whereas the achievement of MMR (≤0.1% *BCR::ABL1* IS) at 12 months should be considered as the optimal response milestone if the treatment goal in an individual patient is TFR. Patients who achieve these response milestones are considered to have TKI-sensitive disease, and continuation of the same dose of TKI and assessment of *BCR::ABL1* transcripts with qPCR (IS) every 3 months is recommended for this group of patients.

Inability to achieve ≤10% *BCR::ABL1* IS at 3 months or ≤1% *BCR::ABL1* IS at 12 months is associated with a higher risk for disease progression. Clinical judgment should be used in patients with a >10% *BCR::ABL1* IS at 3 months and >1% *BCR::ABL1* IS at 12 months, considering problems with adherence (which can be common given drug toxicity at the initiation of therapy), rate of decline in *BCR::ABL1*, and how far from the cutoff the *BCR::ABL1* value falls.

Patients with *BCR::ABL1* that is slightly >10% at 3 months (with a steep decline from baseline level) may achieve <10% *BCR::ABL1* IS at 6 months and have favorable outcomes.[155-158] Therefore, many patients with >10% *BCR::ABL1* at 3 months can continue the same dose of TKI (asciminib, bosutinib, dasatinib, imatinib, or nilotinib) for another 3 months (but imatinib is associated with slower molecular responses) or switch to alternate TKI. *BCR::ABL1* mutational analysis should be considered.

Achievement of ≤10% *BCR::ABL1* IS (which correlates with MCyR) within 2 years is associated with favorable long-term OS, even if deeper molecular response is not achieved.[171] These data suggest that patients with >1% to 10% *BCR::ABL1* at 12 months have favorable outcomes. Patients with a >50% reduction in *BCR::ABL1* levels compared to baseline or if *BCR::ABL1* is minimally above the 10% cutoff at 12 months can continue the same dose of TKI for another 3 months. Bone marrow cytogenetics should be considered to assess for CCyR at 12 months in cases where the *BCR::ABL1* transcript level is between 1% and 10%. The same dose of TKI can be continued if CCyR is achieved. Switching to alternate 2G TKI or asciminib or 3G TKI should be considered if CCyR is not achieved or in the absence of continuing decline in *BCR::ABL1* transcript levels. *BCR::ABL1* mutational analysis should be considered.

In patients with >0.1% to 1% *BCR::ABL1* IS at 12 months, shared decision-making is recommended depending on the goal of therapy in individual patients (longer-term survival vs. TFR). As discussed before, although not associated with increased OS, MMR at 12 months is associated with a lower rate of disease progression and a higher likelihood of achieving DMR, which is a prerequisite for TFR.[46,167] Switching from imatinib to a 2G TKI or asciminib may increase the probability of achieving MMR (≤0.1% *BCR::ABL1* IS) at 12 months. However, the side effect profile of alternative TKIs may differ. Referral to specialized CML centers and/or enrollment in a clinical trial should be considered.

Patients with >10% *BCR::ABL1* IS at 6 and 12 months are considered to have TKI-resistant disease. Evaluation for allogeneic HCT (discussion with a transplant specialist, which might include HLA testing) is recommended. Bone marrow cytogenetic analysis to assess ACAs should be considered. Alternative treatment options should be considered as described below.

Second-Line Therapy

Dose escalation of imatinib up to 800 mg daily has been shown to overcome some cases of primary resistance and is particularly effective for cytogenetic relapse in patients who had achieved cytogenetic response with imatinib 400 mg daily, although the duration of responses has typically been short.[172-175] However, it is unlikely to benefit patients who do not achieve hematologic response or those who never had a cytogenetic response with imatinib 400 mg daily.

In patients with >10% *BCR::ABL1* IS at 3 months after imatinib 400 mg, switching to nilotinib or dasatinib has been shown to result in higher rates of MMR at 12 months than dose escalation of imatinib.[176-178] Although dose escalation of imatinib has been shown to be beneficial for patients in CCyR without MMR, no randomized studies have shown that a change of therapy would improve PFS or EFS in this group of patients.[168,169]

Dasatinib and nilotinib retain activity against many of the imatinib-resistant BCR::ABL1 kinase domain mutants except T315I and are effective treatment options for CP-CML that is resistant to imatinib and also for patients who are intolerant to imatinib.[179,180] Bosutinib also has demonstrated activity in CP-CML that is resistant to multiple TKIs (imatinib, dasatinib, and nilotinib).[181-183] Ponatinib and asciminib are active against most of the resistant BCR::ABL1 kinase domain mutants, including T315I.[184-187]

Long-term efficacy data from clinical trials on second-line and subsequent TKI therapy for CP-CML are summarized in Table 6.

Ponatinib was initially approved as a treatment option for patients with a T315I mutation and/or for patients for whom no other TKI is indicated based on the results of the PACE trial.[184] Ponatinib, at the recommended initial dose of 45 mg once daily, was associated with increased risk of arterial and vascular adverse events. The incidence of cardiovascular adverse events was highest among patients with preexisting cardiovascular risk factors.[184,188-190] In the PACE trial, serious arterial and vascular adverse events (cardiovascular, cerebrovascular, and peripheral vascular) and venous thromboembolic events occurred in 31% and 6% of patients, respectively.[184] Cardiovascular, cerebrovascular, and peripheral vascular adverse events were reported in 16%, 13%, and 14% of patients, respectively.

See *Special Considerations for the Use of TKI Therapy* in the algorithm for the supportive care interventions and treatment recommendations for the management of arterial and cardiovascular adverse events associated with ponatinib.

In the OPTIC trial that evaluated the safety and efficacy of response-adjusted dosing regimen, patients were randomized to ponatinib starting doses of 45 mg, 30 mg, and 15 mg, with dose reduction to 15 mg with achievement of ≤1% *BCR::ABL1* (IS) in the 45 mg and 30 mg cohorts.[185] Ponatinib was effective at all 3 dose levels (45 mg, 30 mg, and 15 mg) and the maximum benefit was observed with 45 mg. After a median follow-up of 32 months, *BCR::ABL1* (IS) ≤1% at 12 months was achieved in 44% of patients in the 45 mg cohort compared to 29% and 23% in the 30 mg and 15 mg cohorts, respectively. After response-based dose reduction to 15 mg, responses were maintained in 73% and 79% of patients in the 45 mg and 30 mg cohorts, respectively. The rate of any arterial and vascular adverse events reported in the OPTIC trial (10% in the 45 mg cohort; 5% and 3% in the 30 mg and 15 mg cohorts, respectively) was lower than that reported for ponatinib 45 mg in the PACE trial. Based on the results of the OPTIC trial, the FDA has approved a response-adjusted dosing regimen for ponatinib [starting dose of 45 mg once daily with a reduction to 15 mg upon achievement of *BCR::ABL1* (IS) ≤1%] for patients with CP-CML with resistance or intolerance to at least two prior kinase inhibitors.

Asciminib is approved for CP-CML with T315I mutation and/or previously treated CP-CML. In the phase III randomized study (ASCEMBL), asciminib 40 mg twice daily achieved higher molecular response rates (MMR, MR4.0, and MR4.5) than bosutinib 500 mg once daily in patients with CP-CML previously treated with ≥2 prior TKIs.[186] Gastrointestinal toxicities (diarrhea, nausea, and vomiting) and biochemical abnormalities (increased ALT and AST levels) were notably higher with bosutinib. Arterial and vascular adverse events were reported in 3% and 1% of patients treated with asciminib and bosutinib, respectively. The incidence of adverse events leading to treatment discontinuation were also lower with asciminib (8% vs. 28%).[186] Patients with detectable bosutinib-resistant *BCR::ABL1* mutations (T315I or V299L) were ineligible to participate in the ASCEMBL trial. The results of the phase I dose escalation study confirmed the efficacy of asciminib in patients with previously treated CP-CML with a T315I mutation.[187] The recommended initial dose of asciminib is 80 mg once daily or 40 mg twice daily in patients without a T315I mutation and 200 mg twice daily in patients with a T315I mutation.

Clinical Considerations for the Selection of Second-Line TKI Therapy

EMR (≤10% *BCR::ABL1* IS at 3 and 6 months) after second-line TKI therapy with dasatinib or nilotinib has also been reported to be a prognosticator of OS and PFS (Table 7).[179,180] Patients who do not achieve cytogenetic or molecular responses at 3, 6, or 12 months after second-line and subsequent TKI therapy should be considered for alternative therapies or allogeneic HCT if deemed eligible.

BCR::ABL1 kinase domain mutation analysis (see below), evaluation of drug interactions, and adherence to therapy are recommended prior to the initiation of second-line TKI therapy. As discussed earlier, myeloid mutational analysis using NGS to identify *BCR::ABL1*–independent mutations may also be useful for patients with CP-CML who do not achieve optimal response milestones due to the presence of cytopenias and for those with TKI-resistant disease.

Drug Interactions

All TKIs are metabolized in the liver by cytochrome P450 (CYP) enzymes and concomitant use of drugs/food/fruits/fruit juices/supplements metabolized by CYP enzymes alter the therapeutic effect of TKIs.[191-193]

Drugs that are CYP3A4 or CYP3A5 inducers may decrease the therapeutic plasma concentration of TKIs, whereas CYP3A4 inhibitors and drugs that are metabolized by the CYP3A4 or CYP3A5 enzyme might result in increased plasma levels of TKIs. In addition, imatinib is also a weak inhibitor of the CYP2D6 and CYP2C9 isoenzymes and nilotinib is a competitive inhibitor of CYP2C8, CYP2C9, CYP2D6, and UGT1A1, potentially increasing the plasma concentrations of drugs eliminated by these enzymes. Asciminib is also a CYP2C9 inhibitor and concomitant use of asciminib increases the plasma concentration of other drugs that are CYP2C9 substrates.

Fruits/fruit juices that inhibit the activity of CYP3A4 enzyme (eg, grapefruit, star fruit, black mulberry, black raspberry, wild grape, pomegranate) should be avoided since they increase the therapeutic plasma concentration of TKIs.[191] If coadministration of medications and supplements that are metabolized by CYP enzymes cannot be avoided, dose modification should be considered, and appropriate alternatives should be explored to minimize toxicity. Alternative acid-reducing strategies such as the use of H2RAs or spacing out PPI use from TKI administration may be preferable if coadministration of TKIs with PPIs cannot be avoided. A pH-independent formulation of dasatinib that can be administered concomitantly with PPIs or H2RAs has been approved by the FDA as an alternative treatment option for adult patients with CML.

See *Drug Interactions of TKIs* in the algorithm (CML-D) for specific interactions of TKIs with the most commonly used medications, supplements, and fruits/fruit juices.

Adherence to Therapy

Treatment interruptions and non-adherence to therapy may lead to undesirable clinical outcomes.[194-196] In the ADAGIO study, non-adherence to imatinib was associated with poorer response. Patients with suboptimal response missed significantly more imatinib doses (23%) than did those with optimal response (7%).[194] Adherence to imatinib therapy has been identified as the only independent predictor for achieving complete molecular response (CMR) on standard-dose imatinib.[195] The 6-year probability of achieving CMR was significantly higher for patients with a >90% adherence rate (44% compared to 0% for patients with ≤90% adherence rate; *P* = .002).[195] Poor adherence to imatinib therapy has also been identified as the most important factor contributing to cytogenetic relapse and inadequate response to imatinib.[196] Patients with adherence of ≤85% had a higher probability of losing CCyR at 2 years than those with adherence of >85% (27% and 2%, respectively). Poor adherence to therapy has also been reported in patients receiving dasatinib and nilotinib following inadequate response to imatinib.[197,198]

Patient education on adherence to therapy and close monitoring of each patient's adherence is critical to achieving optimal responses. In a significant proportion of patients with TKI-induced toxicities, responses have been observed with doses well below their determined maximum tolerated doses.[199] Short interruptions or dose reductions, when medically necessary, may not have a negative impact on disease control or other outcomes. Adequate and appropriate management of side effects and scheduling appropriate follow-up visits to review side effects may be helpful to improve patient adherence to therapy.[200]

Switching to an alternate TKI because of intolerance is appropriate for patients with disease responding to TKI therapy and it might be beneficial for selected patients with acute grade ≥3 nonhematologic toxicities or in those with chronic, low-grade nonhematologic toxicities that are not manageable with adequate supportive care interventions.[201,202] Asciminib and ponatinib are appropriate treatment options for CP-CML with intolerance to prior 2G TKIs.

Adverse events of second-line and subsequent TKI therapy in patients with CP-CML are summarized in Table 8.

Resistance to TKI Therapy

Aberrant expressions of drug transporters[203-205] and plasma protein binding of TKI[206-208] could contribute to primary resistance by altering the intracellular and plasma concentration of TKI.

Pretreatment levels of organic cation transporter 1 (OCT1) have been reported as the most powerful predictor of response to imatinib.[209] On the other hand, cellular uptake of dasatinib or nilotinib seems to be independent of OCT1 expression, suggesting that patients with low OCT1 expression might have better outcomes with dasatinib or nilotinib than with imatinib.[210-213]

Monitoring imatinib plasma levels may be useful in determining patient adherence to therapy. However, there are no data to support that change of therapy based on plasma imatinib levels will affect treatment outcomes, and assays that measure plasma levels of imatinib are not widely available.

BCR::ABL1 Kinase Domain Mutation Analysis

Point mutations in the *BCR::ABL1* kinase domain are a frequent mechanism of secondary resistance to TKI therapy.[214-219] The efficacy of a TKI against *BCR::ABL1* kinase domain mutations varies based on the IC_{50} values (concentration of TKI required for 50% inhibition), with select mutations conferring a lesser degree of resistance to a given TKI and other mutations conferring a stronger degree of resistance to the same TKI.[220]

T315I confers complete resistance to imatinib, dasatinib, nilotinib, and bosutinib.[221,222] T315A, F317L/I/V/C, and V299L mutants are resistant to dasatinib and the E255K/V, F359V/C, and Y253H mutants are resistant to nilotinib.[223-226] The G250E and V299L mutants are resistant to bosutinib.[227] E255K/V, F359C/V, Y253H, and T315I mutants are most commonly associated with disease progression and relapse.[226,228] There are limited data available regarding the impact of new myristoyl-pocket mutations detected during asciminib treatment on the efficacy of asciminib, and patients with detectable bosutinib-resistant *BCR::ABL1* mutations (T315I or V299L) were ineligible to participate in the ASCEMBL trial.[186] A337T, P465S, F359V/I/C, and M244V are considered as contraindicated mutations to asciminib.[229,230]

Dasatinib and bosutinib have demonstrated activity in patients with *BCR::ABL1* mutants resistant to nilotinib (Y253H, E255K/V, and

F359C/I/V).[181,182,225] Bosutinib has minimal activity against the F317L mutation (which is resistant to dasatinib) and nilotinib may be preferred over bosutinib in patients with the F317L mutation.[224,226,231] Ponatinib is active against *BCR::ABL1* mutants resistant to dasatinib or nilotinib, including E255V, Y253H, F359V, and T315I.[184] Asciminib is active against select *BCR::ABL1* mutants resistant to bosutinib, dasatinib, or nilotinib (G250E, Y253H, E255V, and T315I).[186]

A 35-bp insertion in the *BCR::ABL1* gene *(BCR::ABL1*[35INS]) has been associated with resistance to imatinib.[232,233] In one study, *BCR::ABL1*[35INS] was detected in 23% of patients (64 out of the 284 patients; 45 patients with CP-CML).[233] Among the 34 patients with CP-CML treated with imatinib, primary refractory disease, disease progression while on imatinib, and disease progression after dose interruption were reported in 24% (n = 8), 32% (n = 11), and 12% (n = 4) of patients, respectively. *BCR::ABL1*[35INS] was also associated with grade 3 or 4 hematologic toxicity. This study, however, was not powered to determine the efficacy of 2G TKI against *BCR-ABL1*[35INS] since very few patients with this mutation received either dasatinib or nilotinib.

BCR::ABL1 compound mutations (variants containing ≥2 mutations within the same *BCR::ABL1* allele that presumably arise sequentially) confer different levels of resistance to TKI therapy, and compound mutants involving T315I confer the highest level of resistance to all TKIs, including ponatinib.[220,234,235] In another study that used NGS to detect low-level and *BCR::ABL1* compound mutations in 267 patients with heavily pretreated CP-CML from the PACE trial, no compound mutation was identified that consistently conferred resistance to ponatinib, suggesting that such compound mutations are uncommon following treatment with bosutinib, dasatinib, or nilotinib for CP-CML.[236]

BCR::ABL1 kinase domain mutational analysis is helpful in the selection of subsequent TKI therapy for patients with inadequate initial response to first-line or second-line TKI therapy.[237] The guidelines recommend *BCR::ABL1* kinase domain mutational analysis for patients who do not achieve response milestones, for those with any sign of loss of response (hematologic or cytogenetic relapse), and if there is a 1-log increase in *BCR::ABL1* level with loss of MMR. *BCR::ABL1* kinase domain mutational analysis provides additional guidance for selecting subsequent TKI therapy only in patients with identifiable mutations. Treatment recommendations based on BCR::ABL1 kinase domain mutation status are outlined on CML-5.

Switching to an alternate TKI (based on the BCR::ABL1 kinase domain mutation status) is recommended for patients with disease that is resistant to primary treatment with imatinib. Patients with disease that is resistant to primary treatment with asciminib, bosutinib, dasatinib, or nilotinib could be switched to an alternate TKI (based on the BCR::ABL1 kinase domain mutation status). However, there is no clear evidence to support that switching to an alternate TKI would improve long-term clinical outcome for this group of patients.[238] Ponatinib is a treatment option for patients with a T315I mutation in any phase (preferred for AP-CML or BP-CML) and asciminib is a treatment option for patients with CP-CML having a T315I mutation.

Subsequent therapy with an alternate TKI is expected to be effective only in patients with identifiable *BCR::ABL1* mutations that confer resistance to TKI therapy. In patients with no identifiable mutations, the selection of subsequent TKI therapy should be based on the patient's age, ability to tolerate therapy, presence of comorbid conditions, and toxicity profile of the TKI. Ponatinib is preferred for patients with no identifiable *BCR::ABL1* mutations. Evaluation of allogeneic HCT or enrollment in a clinical trial should be considered for this group of patients.

Rising BCR::ABL1 Transcripts

Rising *BCR::ABL1* transcripts are associated with an increased likelihood of detecting BCR::ABL1 kinase domain mutations and cytogenetic relapse.[239-243] In patients who had achieved very low levels of *BCR::ABL1* transcripts, emergence of BCR::ABL1 kinase domain mutations was more frequent in those who had a >2-fold increase in *BCR::ABL1* transcripts compared to those with stable or decreasing *BCR::ABL1* transcripts.[239] A serial rise has been reported to be more reliable than a single ≥2-fold increase in *BCR::ABL1* transcripts.[240,241] Among patients in CCyR with a ≥0.5-log increase in *BCR::ABL1* transcripts on at least two occasions, the highest risk of disease progression was associated with loss of MMR and >1-log increase in *BCR::ABL1* transcripts.[241]

Rising transcript levels should prompt an investigation of treatment adherence and reassessment of coadministered medications. The precise increase in *BCR::ABL1* transcripts that warrants a mutation analysis depends on the performance characteristics of the qPCR assay.[243] Some laboratories have advocated a 2- to 3-fold range,[164,242,243] while others have taken a more conservative approach (5- to 10-fold).[241] Obviously, some common sense must prevail, since the amount of change in absolute terms depends on the level of molecular response. For example, a finding of any *BCR::ABL1* after achieving a DMR (MR4.5; ≤0.0032% *BCR::ABL1* IS) is an infinite increase in *BCR::ABL1* transcripts. However, a change in *BCR::ABL1* transcripts from a barely detectable level to MR4.5 is clearly different from a 5-fold increase in *BCR::ABL1* transcripts after achieving MMR.

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

Discontinuation of TKI Therapy

The feasibility of discontinuation of TKI therapy (dasatinib, imatinib, or nilotinib) with close monitoring in carefully selected patients who have achieved and maintained DMR (≥MR4.0; ≤0.01% *BCR::ABL1* IS) for ≥2 years has been evaluated in several clinical studies.[244-258] Longer-term follow-up data from the TKI discontinuation trials are summarized in Table 9.

The results of the RE-STIM study demonstrated the safety of a second TKI discontinuation after a first unsuccessful attempt.[259] The rate of molecular relapse after the first TKI discontinuation attempt was the only factor significantly associated with outcome. The TFR rate 24 months after the second TKI discontinuation was higher for patients who remained in DMR within the first 3 months after the first TKI discontinuation (72% vs. 32% for other patients).

Approximately 40% to 60% of patients who discontinue TKI therapy after achieving DMR experience recurrence within 12 months of treatment cessation, in some cases as early as 1 month after discontinuation of TKI therapy. Disease characteristics at diagnosis, blast cell and platelet count in peripheral blood, a higher Sokal risk score, female gender, lower natural killer (NK) cell counts, suboptimal response or resistance to imatinib, duration of TKI therapy, and DMR prior to TKI discontinuation have been identified as independent factors predictive of risk of recurrence after TKI discontinuation.[244,249,253,258] The duration of TKI therapy prior to discontinuation was significantly associated with the maintenance of MMR between 6 and 36 months after TKI discontinuation in the EURO-SKI study.[258] The EURO-SKI study also reported that the presence of transcript type e13a2 together with e14a2 was associated with a higher probability of maintaining MMR over 36 months compared to the presence of e13a2 alone.[258]

Lack of MR4.0 at 36 months after discontinuation of TKI therapy was highly predictive of subsequent loss of MMR in the AFTER-SKI study.[260] A rapid initial decline in *BCR::ABL1* transcripts after initiation of first-line TKI therapy has also been shown to be an independent predictor of TFR eligibility and sustained TFR.[261]

Resumption of TKI therapy immediately after recurrence results in the achievement of DMR in almost all patients. In the STIM study, molecular relapse (trigger to resume TKI therapy) was defined as positivity for *BCR::ABL1* transcripts by qPCR confirmed by a 1-log increase in *BCR::ABL1* transcripts between two successive assessments or loss of MMR at one point.[244,245] The results of the A-STIM study showed that loss of MMR (≤0.1% *BCR::ABL1* IS) could be used as a practical criterion for restarting TKI therapy. The estimated probability of MMR loss was 35% at 12 months and 36% at 24 months after discontinuation of imatinib.[247]

TKI withdrawal syndrome (aggravation or new development of musculoskeletal pain and/or pruritus after discontinuation of TKI therapy) has been reported during the TFR period in some TKI discontinuation studies.[249,253,255,256] The occurrence of imatinib withdrawal syndrome was associated with a lower rate of molecular relapse in the KID study.[249]

TFR after discontinuation of ponatinib in patients achieving DMR (MR4.5 for at least 2 years) has been reported in a small cohort of patients.[262] The feasibility of TFR following discontinuation of TKIs other than dasatinib, imatinib, or nilotinib has not yet been evaluated in prospective clinical studies. In the EURO-SKI study that evaluated TFR after discontinuation of any first-line TKI therapy (imatinib, dasatinib, or nilotinib) in eligible patients, the type of first-line TKI therapy did not significantly affect molecular relapse-free survival.[258] Therefore, it is reasonable to assume that the likelihood of TFR following discontinuation would be similar irrespective of TKI in patients who have achieved and maintained DMR (MR4.0; ≤0.01% *BCR::ABL1* IS) for ≥2 years.

Clinical studies that have evaluated the safety and efficacy of discontinuation of TKI have used strict eligibility criteria and have mandated more frequent molecular monitoring than typically recommended for patients on TKI therapy. Access to a reliable qPCR (IS) with a sensitivity of detection of at least MR4.5 (*BCR::ABL1* ≤0.0032% IS) and the availability of test results within 2 weeks is one of the key requirements to monitor patients after discontinuation of TKI therapy and ascertain their safety.

Based on available evidence from clinical studies that have evaluated the feasibility of TFR, the Panel members feel that discontinuation of TKI therapy (with close monitoring) is feasible in carefully selected, consenting patients (in early CP-CML) who have achieved and maintained a DMR (≥MR4.0) for ≥2 years. The Panel acknowledges that more frequent molecular monitoring is essential following discontinuation of TKI therapy for the early identification of loss of MMR. Frequency of molecular monitoring has varied substantially among different studies, and the optimal frequency of molecular monitoring in patients with a loss of MMR after discontinuation of TKI therapy has not been established.

The criteria for the selection of patients suitable for discontinuation of TKI therapy and recommendations for molecular monitoring in TFR phase are outlined on CML-H. The Panel emphasizes that discontinuation of TKI therapy outside of a clinical trial should be considered only if *ALL* the criteria included on the list are met.

Limited available data (mainly from case reports) suggest that stable and well-controlled chronic CML (≥MR2.0) is not an absolute contraindication to solid organ transplant.[263-265] The Panel acknowledges that the management of TKI along with antirejection therapy (in patients who undergo transplant) will require close coordination between the patient's oncologist and the transplant team.

Dose Modifications of TKI Therapy

Limited available evidence (mostly from non-randomized studies and retrospective analysis) suggests that initiation of TKIs (ie, bosutinib, dasatinib, nilotinib) at lower doses and/or de-escalation for all TKIs (with close monitoring) in patients who achieve optimal responses are appropriate strategies for the prevention and management of treatment-related adverse events and to avoid long-term toxicities. However, except for ponatinib (OPTIC trial), the minimum effective dose or optimal de-escalation of TKI has not yet been established in prospective phase III randomized clinical trials. Initiation of TKIs at Lower Dose Low-dose TKIs for first-line or dose modifications for intolerance or resistance have been evaluated mostly in non-randomized studies and retrospective analyses.

Data from selected studies are outlined in Table 10 and Table 11.

Bosutinib

The recommended starting dose of bosutinib is 400 mg daily for patients with newly diagnosed CP-CML (which is better tolerated than the 500-mg daily dose that was used in the initial randomized phase III trial) and 500 mg once daily for intolerant or resistant CP-CML.

In patients with newly diagnosed CP-CML, recommendations from an expert Panel suggest initiating bosutinib at 200 to 300 mg once daily (with dose escalation as clinically indicated) in most patients, and initiation at 400 mg daily is recommended only for patients with high-risk disease.[266] Treatment with lower dose bosutinib (≤400) has also been shown to reduce the incidences of drug-related adverse events without compromising efficacy in patients with CP-CML–resistant imatinib, dasatinib, and/or nilotinib.[267,268]

Dasatinib

The recommended starting dose of dasatinib is 100 mg once daily for patients with CP-CML.

Long-term follow-up of a single-arm study (81 evaluable patients) suggests that dasatinib 50 mg once daily may have similar efficacy in patients with low- or intermediate-risk CP-CML.[269,270] Dasatinib 20 mg once daily has also been shown to be an appropriate starting dose for patients ≥65 years with newly diagnosed CP-CML.[271,272] Intermittent dosing (on/off treatment with a drug holiday) or dose reduction to 50 mg once daily has also been shown to be effective as second-line and subsequent therapy in patients with CP-CML resistant/intolerant to imatinib.[273-276]

Dasatinib at 50 mg (20 mg with careful monitoring in selected patients) should be considered for patients with clinically significant intolerance to dasatinib 100 mg once daily to avoid serious adverse events (eg, pleural effusion, myelosuppression), necessitating the discontinuation of dasatinib.

Imatinib

The recommended starting dose of imatinib is 400 mg once daily for patients with CP-CML.

In a phase II study that evaluated imatinib 400 mg in 481 patients with newly diagnosed CML, dose reduction was required in 46% of patients due to intolerance, and excessive dose reductions to <300 mg was associated with inferior response rates and survival outcomes.[277]

Nilotinib

The recommended starting dose of nilotinib is 300 mg twice daily for patients with newly diagnosed CP-CML and 400 mg twice daily for patients with resistant or intolerant CP-CML.

In a retrospective analysis of 70 patients with newly diagnosed CP-CML, early dose reduction of nilotinib to <600 mg/day resulted in a lower rate of adverse events and better therapeutic efficacy.[278] One-year MMR and overall MR4.5 rates were 90% and 60%, respectively, for the 10 patients treated with 600 mg/day of nilotinib throughout the study, with no disease progression to advanced phase.

The ENESTswift study showed that switching to nilotinib 300 mg twice daily (which is lower than the recommended dose of 400 mg daily in the second-line setting) was effective and well-tolerated in most patients with CP-CML with intolerance to imatinib or dasatinib in the first-line setting.[279]

Nilotinib tablets with improved bioavailability (without compromise in efficacy) that allows for administration at lower doses without mealtime restrictions has been approved by the FDA. Refer to package insert for full prescribing information: https://www.accessdata.fda.gov.

Ponatinib

The recommended initial dose of ponatinib is 45 mg once daily.

In the OPTIC trial, the optimal benefit was observed with 45 mg once daily for all patients including those with the T315I mutation. Ponatinib at lower dose levels (30 mg once daily and 15 mg once daily) resulted in clinical benefit in patients without theT315I mutation (Table 6). These data support initiation of ponatinib at 45 mg once daily for patients with the T315I mutation followed by dose reduction to 15 mg once daily upon achievement of *BCR::ABL1* (IS) ≤1%.[185]

The results of a retrospective analysis showed that ponatinib 15 mg daily was associated with a lower incidence of drug-related adverse events with no impact on efficacy.[280]

De-escalation or Intermittent Dosing of TKI

TKI de-escalation has been shown to be feasible in patients, primarily those without prior TKI resistance, who had received TKI therapy for ≥2 years with durable MMR or DMR for ≥12 months.[281-288]

Data from selected clinical trials that have evaluated this approach are summarized in Table 12.

The phase II INTERIM study first established that intermittent dosing of imatinib is feasible in patients ≥65 years in stable MMR or MR4, after ≥2 years of treatment.[281] The results of the phase III OPTkIMA study demonstrated that this approach is also feasible for patients treated with dasatinib or nilotinib.[289] OPTkIMA is an ongoing study that is evaluating the potential de-escalation of all TKIs after achieving a stable DMR.

The DESTINY trial showed the feasibility of de-escalating TKIs (imatinib, dasatinib, or nilotinib) to half the standard dose for 12 months (imatinib 200 mg once daily; dasatinib 50 mg once daily, or nilotinib 200 mg twice daily) in patients achieving MMR or MR4 followed by discontinuation for 24 months (with frequent monitoring).[284,285]

The NILO-RED study (published only as an abstract) demonstrated the feasibility of maintenance therapy with reduced-dose nilotinib (once daily) in patients achieving MMR on standard-dose nilotinib (twice daily).

Management of Advanced Phase CML

Imatinib has induced favorable hematologic and cytogenetic response rates in patients with AP-CML or BP-CML.[290-294] Dasatinib,[295-297] nilotinib,[298,299] bosutinib,[300] and ponatinib[184] have demonstrated activity in imatinib-resistant or imatinib-intolerant AP-CML and/or BP-CML. Ponatinib is a treatment option for patients with a T315I mutation or patients for whom no other TKI is indicated.

The efficacy of imatinib in combination with decitabine or cytarabine-based chemotherapy in AP-CML and myeloid BP-CML has been demonstrated in several small studies.[301-304] Hyper-CVAD in combination with imatinib or dasatinib is also effective for patients with lymphoid BP-CML, particularly when followed by allogeneic HCT.[305,306] Treatment with TKI in combination with intensive chemotherapy resulted in better outcomes (higher response rates, lower risk of relapse, and improved OS and EFS rates) compared to treatment with TKI alone in patients with myeloid BP-CML.[307]

Long-term follow-up data from clinical trials of TKI therapy for disease progression to AP-CML and BP-CML are summarized in Table 13 and Table 14, respectively.

Treatment Considerations

Participation in clinical trials and evaluation for allogeneic HCT is recommended for all patients with AP-CML and BP-CML. Disease progression to AP-CML or BP-CML while on TKI therapy has a worse prognosis than de novo AP-CML or BP-CML. Patients with disease progression from CP-CML to AP-CML while on a TKI therapy have a high rate of progression to BP-CML, with predictably poor survival. These patients should be considered for a clinical trial and/or allogeneic HCT.

De novo AP-CML can often be initially managed like CP-CML with single-agent TKI followed by evaluation for allogeneic HCT.[308,309] Treatment with a course of alternate 2G or 3G TKI (not received before) can be beneficial as a “bridge” to allogeneic HCT in patients with disease progression to AP-CML. In patients with disease progression to AP-CML or BP-CML, the selection of TKI therapy is based on prior therapy and/or BCR::ABL1 kinase domain mutational analysis. Imatinib is not recommended for patients with disease progression on prior TKI therapy. However, imatinib may be an appropriate option for patients with disease progression to AP-CML on TKI therapy with a contraindication to 2G or 3G TKI.[310] Asciminib has also demonstrated activity in a small series of patients with AP-CML and is included as an option for patients with AP-CML.[311] Asciminib is contraindicated for CML with *BCR::ABL1*/ b2a3 or *BCR::ABL1*/b3a3 isoforms.[106,107]

A significant proportion of patients with advanced phase CML treated with TKI therapy achieve a MCyR but not a concomitant CHR because of persistent cytopenias, which in turn is associated with an inferior outcome.[312] There is a lack of evidence for the definition of optimal response milestones on TKI therapy. Evaluation for allogeneic HCT should be considered if response milestones (recommended for CP-CML) are not achieved at 3, 6, and 12 months.

Induction therapy followed by consolidation with allogeneic HCT is the preferred treatment approach for de novo BP-CML and disease progression to BP-CML.[307,313] TKI in combination with induction chemotherapy (ALL type chemotherapy for lymphoid BP-CML and AML type chemotherapy for myeloid BP-CML) is the recommended treatment option. TKI + steroids is appropriate for patients with lymphoid BP-CML and TKI alone is an option for those with myeloid BP-CML, who are not candidates for induction chemotherapy. Consolidation chemotherapy and TKI maintenance is recommended for patients who are not candidates for allogeneic HCT. Since TKI (alone or in combination with minimal chemotherapy or steroids) is less effective in BP-CML compared to Ph-positive ALL, interphase FISH for the detection of *BCR::ABL1* transcript on blood granulocytes is recommended to differentiate between de novo BP-CML and de novo Ph-positive ALL.

Central nervous system (CNS) involvement has been described in case reports of BP-CML.[314-317] Lumbar puncture and CNS prophylaxis is recommended for lymphoid BP-CML. Documented CNS involvement in patients with lymphoid BP-CML should be managed according to the standard of care for AML or ALL. Dasatinib has been reported to cross the blood brain barrier and may represent the best TKI option for patients with CNS disease.[318] TKI therapy has not been optimized for patients with CNS involvement.

Allogeneic Hematopoietic Cell Transplant

Allogeneic HCT is a potentially curative treatment for patients with CML. Several studies have confirmed that prior TKI therapy does not compromise the outcome following allogeneic HCT or increase transplant-related toxicity.[319-325] Ongoing advances in alternative donor sources (such as unrelated donors and cord blood), more accurate HLA testing for a stringent selection of unrelated matched donors, and the use of reduced-intensity conditioning regimens have improved outcomes following allogeneic HCT.[326-332]

Allogeneic HCT is an appropriate treatment option for patients with CP-CML that is resistant and/or intolerant to all available TKIs, patients with disease progression to AP-CML during TKI therapy or patients with BP-CML who achieve morphologic remission.[333-336]

Age and sex of the donor and recipient, pretransplant disease phase, HLA matching, and time from diagnosis to transplant have been identified as pretransplant risk factors.[337] A low HCT comorbidity index is a prognostic indicator of lower non-relapse mortality and improved survival.[338] The disease phase at the time of transplant remains an important prognostic factor, and the survival outcomes following transplant are clearly better for patients in second chronic CP-CML compared to patients with AP-CML or BP-CML.[339-344] Therefore, the potential use of allogeneic HCT must be tied to faithful monitoring of disease, since the major potential pitfall in delaying transplantation is “missing” the chronic phase interval.

Monitoring Response After Allogeneic HCT ***(CML-6)***

BCR::ABL1 transcripts may persist for many years in patients after allogeneic HCT. The prognostic significance of *BCR::ABL1* positivity is influenced by the time of testing after allogeneic HCT. A positive qPCR assay for *BCR::ABL1* at ≥18 months after allogeneic HCT is associated with a lower risk of relapse than a positive qPCR assay for *BCR::ABL1* at 6 to 12 months after allogeneic HCT.[345-352] Early detection of *BCR::ABL1* transcripts after allogeneic HCT may be useful to identify patients who may need alternative therapies before overt relapse occurs.

Management of Post-transplant Relapse ***(CML-6)***

Donor lymphocyte infusion (DLI) is effective in inducing durable molecular remissions in the majority of patients with relapsed CML following allogeneic HCT, although it is more effective in patients with chronic phase relapse than advanced phase relapse.[353-359] However, DLI is associated with complications such as graft-versus-host disease (GVHD), susceptibility to infections, and immunosuppression.[353] Improvements in the methods of detecting *BCR::ABL1* transcripts to predict relapse, the development of reduced-intensity conditioning regimens, modified delivery of lymphocytes with the depletion of CD8+ cells, and the use of escalating cell dosage regimens have reduced the incidence of GVHD associated with DLI.[360-364]

Imatinib induces durable cytogenetic and molecular responses in the majority of patients relapsing with chronic and advanced phase CML following allogeneic HCT, and the response rates are higher in patients with chronic phase relapse than advanced phase relapse.[365-372] Very limited data are available on the use of dasatinib and nilotinib in patients with post-transplant relapse.[373-376] There are also data suggesting that the use of DLI in combination with imatinib may be more effective at inducing rapid molecular remissions than either modality alone.[377] Retrospective studies have shown that TKIs are superior to DLI alone or in combination with TKI for post-transplant relapse.[378,379] However, these observations are yet to be confirmed in randomized trials.

Patients who are in CCyR (qPCR-negative) should undergo regular qPCR monitoring (every 3 months for 2 years, then every 3–6 months thereafter). Post-transplant TKI therapy is also effective in preventing relapse following allogeneic HCT in patients at high-risk for disease relapse.[380-382] 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 1 year in this cohort of patients who are in remission following allogeneic HCT.

TKI with or without DLI can be considered for patients who are not in remission or in cytogenetic relapse or those with an increasing level of molecular relapse. The selection of TKI depends on prior TKI therapy, the side effect profile of the TKI under consideration, the presence of comorbidities, and *BCR::ABL1* mutation status. Pre-existing mutations in the *BCR::ABL1* kinase domain, frequently associated with resistance to TKIs, are detectable in the majority of patients who relapse after allogeneic HCT.[383] *BCR::ABL1* mutational analysis is therefore essential prior to the selection of TKI for the treatment of post-transplant relapse.

In patients with CML that has not responded to previous imatinib, there are no data to support the use of post-transplant imatinib. Dasatinib, nilotinib, bosutinib, ponatinib, or asciminib may be more appropriate options. However, there are no data to support the use of post-transplant bosutinib, ponatinib or asciminib. CNS relapse of CML following allogeneic HCT has been described in few case reports.[384,385] Participation in a clinical trial is highly desirable. Dasatinib may also be an effective treatment for extramedullary relapse following allogeneic HCT.[318,386,387]

Emerging Treatment Options

Novel BCR::ABL1 inhibitors are being evaluated in ongoing clinical trials in all three phases of CML. Results from selected published phase II/III studies are outlined in Table 15.

The use of pegylated interferons in combination with 2G TKIs is also being explored as a potential strategy to improve TFR in ongoing clinical trials.[388-390] Immunotherapy approaches such as the use of *BCR::ABL1* immune peptides, immune checkpoint blockade, leukemia-associated antigens, and dendritic cell vaccines are also being evaluated to improve molecular response.[391]

Management of CML During Pregnancy and Breastfeeding

The median age of disease onset is 65 years, but CML occurs in all age groups. The EUTOS population-based registry has reported that approximately 37% of patients at the time of diagnosis are of reproductive age.[392] Clinical care teams should be prepared to address issues relating to fertility and pregnancy as well as counsel these patients about the potential risks and benefits of treatment discontinuation and possible resumption of TKI therapy should CML recur during pregnancy.

TKI Therapy and Conception (CML-E)

TKI therapy appears to affect some male hormones at least transiently but does not appear to have a deleterious effect on male fertility. Furthermore, the miscarriage or fetal abnormality rate is not elevated in female partners of males on TKI therapy.[393-397]

TKI therapy during pregnancy has been associated with both a higher rate of miscarriage and fetal abnormalities.[398-403] In one report on the outcome of pregnancies in 180 patients exposed to imatinib during pregnancy, 50% of pregnancies with known outcome were normal and 10% of pregnancies with known outcome had fetal abnormalities.[398] Eighteen pregnancies ended in spontaneous abortion. In another report on the outcomes of pregnancy and conception during treatment with dasatinib, among 46 patients treated with dasatinib, 15 patients (33%) delivered a normal infant.[399] Elective or spontaneous abortions were reported in 18 (39%) and 8 patients (17%), respectively, and 5 patients (11%) had an abnormal pregnancy. Fetal abnormalities were reported in 7 cases. Among 33 patients who conceived with males who had received treatment with dasatinib, 30 (91%) delivered infants who were normal at birth. In a report of 16 pregnancy cases among patients assigned female at birth treated with bosutinib, there were six live births, four abortions, and six unknown outcomes.[404]

Although there is paucity of data regarding the outcome of pregnancy in patients receiving bosutinib, ponatinib or asciminib at the time of conception, all TKIs also must be considered unsafe for use during pregnancy. Conception while on active TKI therapy is strongly discouraged due to the risk of fetal abnormalities. Close monitoring, and prompt consideration of holding TKI therapy (if pregnancy occurs while on TKI therapy) should be considered.

Depending on other factors such as age, a natural pregnancy may occur months after stopping TKI therapy.[405,406] A prolonged washout period prior to pregnancy should be considered, although there are no data regarding how long a patient should be off TKI therapy before trying to become pregnant. There are no published guidelines regarding the optimal depth of molecular response that is considered “safe” to stop TKI therapy before attempting pregnancy.[407,408]

Discontinuation of TKI therapy because of pregnancy in patients assigned female at birth who were not in DMR (≤0.01% *BCR::ABL1* IS) has only been reported in a small series of patients.[405,406,409,410] In one series, among 10 patients who stopped imatinib because of pregnancy after a median of 8 months of therapy, five of the nine patients who had achieved a CHR lost the response after stopping therapy, and six had an increase in Ph-positive metaphases.[405] At 18 months after resuming therapy, all nine patients had achieved a CHR but only three females achieved a CCyR and none had achieved an MMR. In another series that reported the outcomes of seven patients who were not in DMR at the time imatinib was stopped because of pregnancy, three were in an MMR.[406] All seven patients had disease relapse. The three who had an MMR at the time imatinib was stopped could regain the same response once the drug was restarted, whereas the remaining four patients did not.

Planning a Pregnancy

In patients assigned male at birth, the general recommendation is that TKI therapy need not be discontinued if a pregnancy is planned. However, experience is limited. Sperm banking can also be performed prior to starting TKI therapy, but there are no data regarding quality of sperm in males with untreated CML.

In patients assigned female at birth, due to the risk of miscarriage and fetal abnormalities during pregnancy, TKI therapy should be stopped prior to natural conception and patients should remain off therapy during pregnancy.[398-400]

Fertility preservation should be discussed with all patients of childbearing age prior to the initiation of TKI therapy. Referral to an in vitro fertilization (IVF) center is recommended in coordination with the patient’s obstetrician. TKI should be stopped prior to attempting oocyte retrieval, but the optimal timing of discontinuation is unknown. There are no data to recommend how long a patient should be off therapy before oocyte retrieval, although usually at least 1 month off therapy is recommended.

In addition to the high incidence of disease recurrence off TKI therapy, patients should also be made aware of the significant obstacles related to IVF (eg, lack of access to centers that perform the procedure, high costs associated with drugs, surgical procedures and embryo/oocyte storage that may not be covered by insurance, variable access to surrogate programs, the need to take family medical leave from work to attend IVF appointments).

Prior to attempting pregnancy, patients and their partners should be counseled that no guidelines exist regarding how best to monitor CML during pregnancy, nor how best to manage progressive disease should it occur during pregnancy. Referral to a CML specialty center and consultation with a high-risk obstetrician is recommended.

Treatment and Monitoring During Pregnancy (CML-E)

Most of the literature regarding treatment during pregnancy consists of case reports. TKI therapy, particularly during the first trimester, should be avoided because of teratogenic risk. If TKI therapy is considered during pregnancy, the potential benefit for the mother and the potential risk to the fetus of continuing TKI therapy versus the risk of treatment interruption leading to the loss of optimal disease response must be carefully evaluated on an individual basis.

Leukapheresis can be used for a rising white blood cell (WBC) count and/or platelet count, although there are no data that recommend at what level leukapheresis and/or platelet pheresis should be initiated.[411-414] Low-dose aspirin or low-molecular-weight heparin can be considered for patients with thrombocytosis.[415,416]

The Panel also recommends against the use of hydroxyurea during pregnancy, especially in the first trimester.[417-419] Most of the data using interferons during pregnancy have been reported in patients with essential thrombocythemia; if treatment is needed during pregnancy, it is preferable to initiate treatment with interferon alfa-2a.[408,420-422] Peginterferon alfa-2a and ropeginterferon alfa-2b are available for clinical use in the United States. If introduced earlier, the use of peginterferon alfa-2a can preserve molecular remission after discontinuation of TKI.[423,424] There are very limited data for the use of ropeginterferon alfa-2b in patients with CML during pregnancy.

Monthly monitoring of CBC with differential and frequent monitoring with qPCR (every 1–3 months) would be helpful to guide the timing for initiation of TKI therapy, although specific thresholds for treatment reinitiation have not been defined.

Breastfeeding (CML-E)

TKI therapy can be restarted after delivery. However, patients on TKI therapy should be advised not to breastfeed, as TKIs pass into human breast milk.[425-428] Breastfeeding without TKI therapy may be safe with molecular monitoring, preferably in those patients with CML who have durable DMR. It may be acceptable to avoid TKIs for the short period of the first 2 to 5 days after labor to give the child colostrum.[428,429]

Close molecular monitoring is recommended for females who extend the treatment-free period for breastfeeding. If the loss of MMR after treatment cessation is confirmed, breastfeeding needs to be terminated and TKI should be restarted.[428]

Specific Considerations for Children with CML

CML accounts for <3% of all pediatric leukemias. In general, children are diagnosed at a median age of 11 to 12 years, with approximately 10% presenting in advanced phase; favorable outcome has been reported in pediatric patients presenting with de novo advanced phase CML treated with TKI therapy.[430]

Due to its rarity, there are no evidence-based recommendations for the management of CML in the pediatric population. Many pediatric oncologists follow treatment guidelines that are designed for adult patients. However, clinical presentations and host factors are different between children and adults, and several factors should be considered when treating pediatric patients with CML.[431]

Selection of TKI

Bosutinib, dasatinib, imatinib, and nilotinib (capsules) are approved for treatment of CML in children.[432-434] Bosutinib is approved based on the results of the BCHILD trial (published only as an abstract). Higher dose imatinib (340 mg/m²) has also been shown to be effective and well tolerated in children.[435-437] There are very little data on the safety and efficacy of ponatinib and asciminib in children.[438]

The validity of prognostic scores (eg, Sokal, Euro) for risk assessment or to make treatment decisions has not been established in the pediatric population.[439] The ELTS score has demonstrated better differentiation of PFS than Sokal and Euro scores in children treated with imatinib.[440]

Monitoring for Long-Term Side Effects

Children have a much longer life expectancy than adults, and TKI therapy may be needed for many decades; therefore, there are potential long-term side effects (such as delayed growth, changes in bone metabolism, thyroid abnormalities, and effects on puberty and fertility) that may not be seen in adults.[441]

A number of studies have reported impaired longitudinal growth in children with CML treated with TKI therapy, and the effect is more significant when treatment was initiated during prepubertal age.[442-448] Growth should be monitored closely, and a bone age x-ray should be obtained if longitudinal growth is delayed. A dual-energy x-ray absorptiometry (DEXA) scan should be obtained if bone mineral density is decreased on plain radiograph or if there is unprovoked fracture. Further evaluation and referral to an endocrinologist is also warranted.

The feasibility of discontinuation of imatinib in children in sustained DMR for ≥2 years has been demonstrated in small studies.[449-451] Further studies in a larger cohort of patients are needed to identify the criteria for discontinuation of TKI therapy in children. Therefore, discontinuation of TKI therapy in children is not recommended outside the context of a clinical trial.

Immunizations

There are little data regarding the long-term impact of TKIs on the immune function of patients with CML receiving TKI therapy. Available evidence suggests that TKI therapy could potentially hinder routine immunization with some vaccines in adults and children with CML.[452-454] A study that evaluated the safety and efficacy of H1N1 influenza vaccine in patients with hematologic malignancies showed a higher seroconversion rate in adult patients with CML compared to patients with B-cell malignancies or recipients of HCT.[452] The findings from another study that evaluated the impact of TKI therapy on B-cell responses to vaccination in patients with CML suggest that TKI therapy with dasatinib, imatinib, or nilotinib is associated with impaired B-cell response to polysaccharide pneumococcal (PPS) vaccine due to the off-target inhibition of kinases involved in B-cell signaling pathway.[453]

In general, the use of inactivated killed vaccines for children on TKI therapy is safe, although it is unknown whether responses are comparable to those seen in healthy children. Administration of live vaccines during TKI therapy is not recommended in general, although preliminary findings from a few case reports have shown that MMR and varicella vaccine could be safely given to some children with immune deficiency.[454,455] Live attenuated annual influenza vaccine (nasal spray) should be avoided, and the inactivated killed vaccine (flu shot) should be used for children receiving TKI therapy. Live vaccines could be considered after stopping TKI therapy for several weeks in patients with a DMR.[456] In the United States, all required live vaccines are completed by age 4 to 6 years (http://www.cdc.gov/vaccines). As CML is rarely seen in children younger than this age, few patients face this issue.

The mRNA-based vaccines have shown safety and efficacy against the SARS-CoV-2 infection (COVID-19) among immunocompetent individuals.[457] Studies that have evaluated the efficacy of these vaccines in patients with hematologic malignancies have reported higher seroconversion rate and robust memory T-cell responses in patients with CML in contrast to patients with solid tumors or other hematologic malignancies.[458-461] The mRNA-based vaccines are considered inactivated vaccines.

The FDA has given full approval for the use of mRNA-based vaccines in individuals ≥16 years and emergency use authorization (EUA) for use in children beginning at 6 months of age. See the CDC COVID-19 Vaccination Clinical & Professional Resources for dosage and administration of the COVID-19 vaccine in for specific populations.

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

Trial	Study Arms	No. of Patients	Median Follow-up	CCyR[a]	MMR[b]	Disease Progression n (%)	PFS[c]	OS
IRIS[101,d]	**Imatinib (400 mg once daily)**	553	11 years	83%	—	38 (7)	92%	83%
	Interferon alpha plus low-dose cytarabine	553		—	—	71 (13)	—	79%[e]
DASISION[102]	**Dasatinib (100 mg once daily)**	259	5 years	—	76% (*P* = .002)	12 (5)	85%	91%
	Imatinib (400 mg once daily)	260		—	64%	19 (7)	86%	90%
ENESTnd[103]	**Nilotinib (300 mg twice daily)**	282	10 years	—	78% (*P* < .0001)	11 (4)	86%	88%
	Imatinib (400 mg once daily)	283		—	63%	24 (8.5)	87%	88%
BFORE[104]	**Bosutinib (400 mg once daily)**	268	60 months	83%	74%	6 (2)	—	95%
	Imatinib (400 mg once daily)	268		77%	65%	7 (3)	—	95%
ASC4FIRST[105]	**Asciminib**	101	16 months (16.3)	84%	69%	—	—	—
	Imatinib	102		62%	40%	—	—	—
	Asciminib	100	16 months (15.7)	90%	66%	—	—	—
	Investigator-selected 2G TKI	102		83%	58%	—	—	—

CCyR, complete cytogenetic response (≤1% *BCR::ABL1* IS); MMR, major molecular response (≤0.1% *BCR::ABL1* IS); OS, overall survival; PFS, progression-free survival

a. Confirmed CCyR rate at 12 months was the primary endpoint of DASISION study.
b. MMR (≤0.1% *BCR::ABL1* IS) rate at 12 months (48 weeks) was the primary endpoint of ENESTnd, BFORE, and ASC4FIRST studies.
c. Primary endpoint of IRIS trial in the imatinib group.
d. Due to the high rate of crossover to imatinib (66%) and the short duration of therapy (<1 year) before crossover among patients who had been randomly assigned to interferon alfa plus cytarabine, the long-term follow-up data focused on patients who had been randomly assigned to receive imatinib.
e. Data include survival among the 363 patients who crossed over to imatinib.

Table 2: First-Line TKI Therapy for CP-CML: Outcomes According to Risk Score

Trial	Study Arms	Low-Risk			Intermediate-Risk			High-Risk		
		MMR	MR4.5	PFS/OS[a]	MMR	MR4.5	PFS/OS[a]	MMR	MR4.5	PFS/OS[a]
DASISION[102] (Euro risk score)	**Dasatinib (100 mg once daily)**	90%	55%	—	71%	43%	—	67%	31%	—
	Imatinib (400 mg once daily)	69%	44%	—	65%	28%	—	54%	30%	—
ENESTnd[103] (Sokal risk score)	**Nilotinib (300 mg twice daily)**	—	51%	94%/95%	—	55%	87%/88%	—	40%	74%/77%
	Imatinib (400 mg once daily)	—	39%	98%/99%	—	30%	84%/84%	—	23%	78%/79%
BFORE[104] (Sokal risk score)	**Bosutinib (400 mg once daily)**	76%	54%	—	74%	43%	—	70%	46%	—
	Imatinib (400 mg once daily)	73%	43%	—	64%	37%	—	51%	25%	—

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

a. 10-year outcomes according to Sokal risk score.

Table 3. Adverse Events of First-Line TKI Therapy in CP-CML

Toxicity	DASISION[102]		ENESTnd[103]		BFORE[104]		ASC4FIRST[105]		
	Dasatinib 100 mg QD	Imatinib 400 mg QD	**Nilotinib 300 mg BID**	Imatinib 400 mg QD	**Bosutinib 400 mg QD**	Imatinib 400 mg QD	**Asciminib 80 mg QD or 40 mg BID**	Imatinib 400 mg QD	2G TKI
Biochemical abnormalities (Grade 3 or 4; *any grade)									
Increased glucose	NR	NR	9%	<1%	4%*	6%*	NR	NR	NR
Increased ALT	NR	NR	4%	3%	34%*	6%*	2%	2%	8%
Increased AST	NR	NR	NR	NR	26%*	7%*	<1%	1%	3%
Nonhematologic toxicities (any grade)[a]									
Rash	13%	18%	39%	21%	23%	15%	13%	10%	22%
Headache	13%	11%	34%	25%	19%	13%	14%	8%	22%
Fatigue	9%	11%	25%	20%	19%	18%	14%	8%	22%
Diarrhea	21%	22%	21%	48%	75%	40%	16%	26%	26%
Constipation	NR	NR	23%	9%	NR	NR	10%	4%	13%
Nausea	10%	24%	22%	42%	37%	42%	9%	21%	18%
Vomiting	5%	11%	17%	28%	21%	20%	6%	12%	6%
Muscle spasms	23%	41%	14%	35%	4%	31%	2%	19%	5%
Peripheral or Periorbital edema	13%	37%	12%	23%	2%	17%	1%	10%	1%
Pleural effusion	28%	<1%	NR	NR	5%	2%	NR	NR	NR
Hypertension	NR	NR	16%	6%	10%	11%	NR	NR	NR
Pulmonary hypertension	5%	<1%	NR	NR	NR	NR	NR	NR	NR

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; NR, not reported; QD, once daily; TKI, tyrosine kinase inhibitor.
a. Non-hematologic toxicities from the DASISION study (except pleural effusion) are from the 3-year follow-up. No new adverse events were observed with 5-year follow-up.

Table 4: High-Dose Imatinib as First-Line Therapy for CP-CML: Long-Term Follow-up Data from Phase III Studies

Trial	Study Arms	No. of Patients	Median Follow-up	MMR	MR4.5	PFS	OS
TOPS study[120,a]	Imatinib (800 mg once daily)	319	42 months	79%	—	96% at 48 months	93% at 48 months
	Imatinib (400 mg once daily)	157		76%	—	94% at 48 months	94% at 48 months
SWOG study[121,c]	Imatinib (800 mg once daily)	73	12 months	53%	19%	92% (4-year PFS)	95% (4-year OS)
	Imatinib (400 mg once daily)	72		36%	9%	80% (4-year PFS)	90% (4-year OS)
CML IV study[122,b]	Imatinib (800 mg once daily)	420	10 years	89%	71%	77%	79%
	Imatinib (400 mg once daily)	400		92%	67%	80%	80%

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

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

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

Trial	Study Arms	5-Year PFS		5-Year OS	
		BCR::ABL1 ≤10%	*BCR::ABL1* >10%	*BCR::ABL1* ≤10%	*BCR::ABL1* >10%
DASISION[102]	Dasatinib (100 mg once daily)	89%	72%	94%	81%
	Imatinib (400 mg once daily)	93%	72%	95%	81%
CML IV Study[151]	Imatinib (400 mg once daily)	92%	87%	94%	87%
ENESTnd[152]	Nilotinib (300 mg twice daily)	95%	78%	98%	82%
	Nilotinib (400 mg twice daily)	96%	89%	96%	93%
	Imatinib (400 mg once daily)	98%	79%	99%	79%

OS, overall survival; PFS, progression-free survival

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

TKI/Trial	Study Arms (No. of patients)	Median Follow-up	MCyR	CCyR	MMR	PFS	OS
Dasatinib[179,a] (100 mg once daily)	Imatinib-R (n = 124)	7 years	—	—	43%	39%	63%
	Imatinib-I (n = 43)		—	—	55%	51%	70%
Nilotinib[180,b] (400 mg twice daily)	Imatinib-R (n = 226) Imatinib-I (n = 95)	4 years	59%	45%	—	57%	78%
Bosutinib (BYOND) (500 mg once daily)[182]	Imatinib-R (n = 53)	≥3 years	86%	84%	73%	—	—
	Dasatinib and/or nilotinib-R (n = 29)		69%	62%	41%	—	—
	TKI intolerant (n = 74)		88%	87%	82%	—	—
Ponatinib (PACE)[184,c] (45 mg once daily)	Dasatinib or nilotinib-R or I (n = 203)	57 months	56%	49%	35%	52% at 5 years	76% at 5 years
	T315I mutation (n = 64)		72%	70%	58%	50% at 5 years	66% at 5 years
Ponatinib (OPTIC)[185]	45 mg (n = 93)	32 months	51%	44%	34%	73% at 3 years	89% at 3 years
	30 mg (n = 93)		33%	29%	25%	66% at 3 years	89% at 3 years
	15 mg (n = 91)		44%	23%	23%	70% at 3 years	92% at 3 years
Asciminib (ASCEMBL) (40 mg twice daily)[186,d]	Asciminib (40 mg twice daily; n = 157)	4 years	—	54%[e] at 156 weeks	45% at 156 weeks	85% at 3 years	92% at 3 years
	Bosutinib (500 mg once daily; n = 76)		—	Not evaluable at 156 weeks	24% at 156 weeks	84% at 3 years	97% at 3 years

CCyR, complete cytogenetic response; I, Intolerant; MCyR, major cytogenetic response; MMR, major molecular response (≤0.1% *BCR::ABL1* IS); OS, overall survival; PFS, progression-free survival; R, resistant; TKI, tyrosine kinase inhibitor

a. Primary endpoint: MCyR rate at 6 months when administered 100 mg once daily versus 70 mg twice daily.
b. Primary endpoint: MCyR rate in patients with imatinib intolerance or imatinib-resistant disease.
c. Primary endpoint: MCyR at any time within the first 12 months.
d. Primary endpoint: MMR rate at 24 weeks; Secondary endpoint: MMR rate at 96 weeks.
e. CCyR rate in patients who were not in CCyR at baseline.

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

TKI	Median Follow-up	PFS				OS			
		BCR::ABL1 ≤10%		*BCR::ABL1* >10%		*BCR::ABL1* ≤10%		*BCR::ABL1* >10%	
		3 months	6 months	3 months	6 months	3 months	6 months	3 months	6 months
Dasatinib[179] **(100 mg once daily)**	7 years	56%	57%	21%	4%	72%	74%	56%	50%
Nilotinib[180] **(400 mg twice daily)**	4 years	67%	58%	42%	39%	81%	82%	71%	73%

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

Table 8. Adverse Events of Second-Line and Subsequent TKI Therapy in CP-CML

Toxicity (any grade)	Dasatinib[179] (100 mg once daily)	Nilotinib[180] (400 mg twice daily)	Bosutinib[181] (500 mg once daily)	Ponatinib[184] (45 mg once daily)	Asciminib[186] (40 mg twice daily)
Rash	33%	31%	15%	47%	10%
Headache	—	18%	28%	43%	19%
Fatigue	37%	21%	24%	30%	15%
Myalgias/Arthralgias	38%	11%	14%	24%/33%	6%/15%
Pleural effusion	28%	—	17%	—	1%
Hypertension	—	—	—	37%	15%
Hemorrhage	26%	—	—	—	—
Diarrhea	42%	12%	88%	20%	13%
Constipation	—	13%	17%	41%	—
Nausea	27%	25%	40%	29%	12%
Vomiting		13%	33%	19%	8%
Increased blood creatinine	—	—	15%	—	—
Increased lipase	—	—	—	27%	—
Increased ALT/AST	—	—	20% (AST) 26% (ALT)	—	6% (AST) 5% (ALT)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TKI, tyrosine kinase inhibitor.

Table 9. Summary of Longer-Term Follow-up Data from the TKI Discontinuation Trials

Trial	Treatment Prior to Discontinuation	No. of Patients	Depth and Duration of MR Required for Discontinuation	Trigger to Resume TKI Therapy	Median Follow-up	Treatment-Free Remission (TFR) Rate
STIM1[245]	Imatinib ± interferon	100	MR5.0 for at least 2 years	Loss of MR5.0	77 months	38% at 60 months
TWISTER[250]	Imatinib ± interferon	40	MR4.5 for at least 2 years	Loss of MR5.0	103 months	45% (molecular relapse-free survival at 8 years: 45%)
HOVON[246]	Imatinib + cytarabine	15	MR4.5 for at least 2 years	Loss of MR4.5	36 months	33% at 24 months
A-STIM[247]	Imatinib ± interferon	80	MR5.0 for at least 2 years	Loss of MMR	31 months	61% at 36 months
ISAV study[248]	Imatinib (after prior treatment with interferon or hydroxyurea)	108	CMR for at least 18 months	Loss of MMR	36 months	52% at 36 months
KID study[249]	Imatinib ± interferon	90	MR4.5 for at least 2 years	Loss of MMR	27 months	59% at 24 months
Stop 2G-TKI[251]	Dasatinib/Nilotinib (first- or second-line)	60	MR4.5 for at least 24 months	Loss of MMR	47 months	54% at 48 months
DASFREE[253]	Dasatinib (first- or second-line)	84	MR4.5 for 12 months	Loss of MMR	2 years	46% at 24 months
ENESTFreedom[255]	Nilotinib (first-line)	190	MR4.5 for 12 months	Loss of MMR	5 years	43% at 5 years
ENESTop study[256]	Nilotinib (second-line)	126	MR4.5 for 12 months	Loss of MMR	5 years	43% at 5 years
DADI[254]	Dasatinib (first-line)	68	MR4.5 for at least 24 months	Loss of MMR	23 months	55% at 6 months
DADI[252]	Dasatinib (second-line)	63	MR4.0 for at least 12 months	Loss of MR4.0	44 months	44% at 36 months
EURO-SKI[258]	Any TKI	728	MR4.0 for at least 1 year	Loss of MMR	36 months	46% at 36 months

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

Table 10. Initiating Lower Dose First-Line TKI Therapy

TKI	Study	Patient Characteristics	TKI Dose	Study Findings
Dasatinib	**Single center Pilot Study**[269]	81 evaluable patients [majority of patients had low-risk (n = 55; 66%) or intermediate-risk (n = 21; 25%) disease by Sokol score] Minimum follow-up: 12 months	50 mg/day	The cumulative rates for MMR, MR4, and MR4.5 at 12 months were achieved in 81%, 55%, and 49% of patients, respectively.
	DAVLEC (Phase II study)[272]	52 patients; aged >70 years; Median follow-up of 366 days	20 mg/day	MMR at 12 months was achieved in 60% of patients.

MMR, major molecular response; MR, molecular response; MR4.0, ≤0.01% *BCR::ABL1* IS; MR4.5, ≤0.0032% *BCR::ABL1* IS; TKI, tyrosine kinase inhibitor

Table 11. Dose Modifications for Intolerance or Resistance

TKI	Study	Patient Characteristics	TKI Dose	Study Findings
Dasatinib	**NordCML006 (Phase II study)**[275]	Newly diagnosed CP-CML; dasatinib (n = 22) vs. imatinib (n = 24)	Dose reduction due to intolerance in 27% of patients (50 mg/day; mean dose was 50 mg at 36 months)	MR4.5 rates were comparable for the dose-reduced group and the standard-dose group (100 mg once daily)
	Japanese LD-CML study[276]	CP-CML resistant to imatinib ≤200 mg/day (n = 9)	Starting dose 50 mg/day	5 patients attained MMR by 12 months, and 3 patients achieved a DMR by 18 months
Imatinib	**JALSG CML202 (Phase II study)**[277]	481 patients with newly diagnosed CP-CML	Dose reduction due to intolerance (n = 90; 300 mg group); (n = 67; 200 mg group)	Response rates and survival were significantly inferior in the 200-mg group compared to the 300-mg group
Nilotinib	**ENESTswift (Phase IIIb study)**[279]	CP-CML intolerant to imatinib (n = 16) or dasatinib (n = 4)	Starting dose 300 mg BID	MR4.5 at any time point (up to 24 months) was achieved in 10 of 20 patients (50%)
Ponatinib	**OPTIC (Phase II dose ranging study)**[185]	CP-CML resistant to or intolerant of at least 2 prior TKIs or with T315I mutation	271 patients randomized to 45 mg, 30 mg, and 15 mg; Dose reduction to 15 mg in the 45 mg and 30 mg cohorts after achievement of *BCR::ABL1* (IS) ≤1%	Results demonstrated the safety and efficacy of response-adjusted dosing regimen for ponatinib (Table 6)

DMR, deep molecular response; MMR, major molecular response; MR, molecular response; MR4.5, ≤0.0032% *BCR::ABL1* IS; TKI, tyrosine kinase inhibitor.

Table 12. De-escalation or Intermittent Dosing of TKI

TKI	Study	Patient Characteristics	TKI Dose	Study Findings
Imatinib	**INTERIM**[281]	76 patients (≥65 years) on imatinib for ≥2 years with a stable CCyR and MMR; Minimum follow-up: 6 years	Intermittent imatinib (1 month ON/OFF)	21% of patients lost CCyR and MMR; All patients regained CCyR and MMR after resumption of imatinib
Imatinib, Dasatinib, or Nilotinib	**DESTINY**[284,285]	174 patients with chronic phase CML on TKI therapy for a median of 7 years (imatinib, n = 148; dasatinib, n = 10; nilotinib, n = 16)	De-escalation to half the standard dose for 12 months after achieving MMR (n = 49) or MR4.0 (n = 125), then stop for a further 24 months	During the dose reduction phase, loss of molecular response occurred in 3 (2%) patients with MR4.0 and 9 (19%) patients with MMR. At 36 months, the RFS rates were 72% and 36% for patients with MR4.0 and MMR group, respectively. All recurrences regained MMR within 5 months of resumption of TKI therapy.
	OPTkIMA (Phase III study)[289]	Patients with CP-CML (≥60 years) in stable MMR or MR4.0 after ≥2 years of TKI therapy (imatinib, dasatinib, nilotinib) randomized to receive "fixed" (n = 111) or "progressive" (n = 104) intermittent dosing of TKI until loss of MMR	Intermittent dosing of TKI; "fixed" (1 month ON/1 month OFF for 3 years) vs. "progressive de-escalation of TKI dose" (1 month ON/OFF for the 1st year; 1 month ON/2 months OFF for the 2nd year; 1 month ON/3 months OFF for the 3rd year)	Progressive de-escalation of TKI dose was associated with higher incidences of loss of MMR compared to fixed intermittent dosing (46% vs. 27%; *P* = .005) and the 3-year probability of maintaining the MR3.0 was 53% and 59%, respectively, for the 2 groups (*P* = .13)

CCyR, complete cytogenetic response; MMR, major molecular response; MR, molecular response; MR4.0, ≤0.01% *BCR::ABL1* IS; RFS, relapse-free survival; TKI, tyrosine kinase inhibitor.

Table 13. TKI Therapy for Disease Progression to accelerated phase CML: Long-Term Follow-up Data from Phase II/III Studies

TKI	No. of Patients	Median Follow-up	MCyR	CCyR	OS	PFS
Dasatinib[295,a] (140 mg once daily)	Imatinib-R (n = 117)	24 months	36%	29%	63%	51%
	Imatinib-I (n = 41)		46%	41%		
Nilotinib[298,b] (400 mg twice daily)	Imatinib-R (n = 109)	24 months	30%	19%	70%	33%
	Imatinib-I (n = 27)		41%	30%		
Bosutinib[300,c] (500 mg once daily)	Prior imatinib only (n = 49)	48 months	48%	35%	66%	—
	Imatinib followed by dasatinib or nilotinib (n = 30)		27%	23%	45%	—
Ponatinib[184,d] (45 mg once daily)	Dasatinib or nilotinib-R or I (n = 65)	32 months	45%	28%	48% at 5 years	19% at 5 years
	T315I mutation (n = 18)		67%	44%	52% at 5 years	29% at 5 years

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

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

Table 14. TKI Therapy for Disease Progression to blast phase CML: Long-Term Follow-up Data from Phase II/III Studies

<table>
<tr><th>TKI</th><th>No. of Patients</th><th>Median Follow-up</th><th>MCyR</th><th>CCyR</th><th>OS</th></tr>
<tr><td rowspan="2">Dasatinib[297,a] (140 mg once daily)</td><td>Lymphoid blast phase (n = 33)</td><td rowspan="2">24 months</td><td>50%</td><td>38%</td><td>21%</td></tr>
<tr><td>Myeloid blast phase (n = 75)</td><td>25%</td><td>14%</td><td>24%</td></tr>
<tr><td rowspan="2">Nilotinib[299,b] (400 mg twice daily)</td><td>Lymphoid blast phase (n = 31)</td><td rowspan="2">24 months</td><td>52%</td><td>32%</td><td>10%</td></tr>
<tr><td>Myeloid blast phase (n = 105)</td><td>38%</td><td>30%</td><td>32%</td></tr>
<tr><td rowspan="2">Bosutinib[300,c] (500 mg once daily)</td><td>Prior imatinib only (n = 36)</td><td rowspan="2">48 months</td><td>50%</td><td>37%</td><td>28%</td></tr>
<tr><td>Imatinib followed by dasatinib or nilotinib (n = 28)</td><td>21%</td><td>17%</td><td>17%</td></tr>
<tr><td rowspan="2">Ponatinib[184,d] (45 mg once daily)</td><td>Dasatinib or nilotinib-R or -I (n = 38)</td><td rowspan="2">6 months</td><td>18%</td><td>16%</td><td rowspan="2">9% at 3 years</td></tr>
<tr><td>T315I mutation (n = 24)</td><td>29%</td><td>21%</td></tr>
</table>

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

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

Table 15: Results from Selected Published Clinical Trials Evaluating Novel *BCR::ABL1* Inhibitors

Clinical Trial	TKI	No. of Patients	Median Follow-up	Response Rates
Phase III (REPRISE study)[462] Newly diagnosed CP-CML	**Radotinib** (300 mg twice daily)	n = 79	≥48 months	MMR: 85%; MR4.5: 58%
	Radotinib (400 mg twice daily)	n = 81		MMR: 83%; MR4.5: 56%
	Imatinib (400 mg once daily)	n = 81		MMR: 75%; MR4.5: 49%
Phase III (FESTnd study)[463] Newly diagnosed CP-CML	**Flumatinib** (600 mg once daily)	n = 196	12 months	EMR: 82%; MMR at 12 months: 53%
	Imatinib (400 mg once daily)	n = 198		EMR: 53%; MMR at 12 months: 40%
Phase II[464] CP-CML with resistance or intolerance to imatinib	**Radotinib** (400 mg twice daily)	n = 77	23 months	MCyR: 65%; CCyR: 47%; MMR: 14%
Phase I/II[465] CP-CML or AP-CML with resistance to TKI	**Olverembatinib** (40 mg on alternate days for 28-day cycles)	CP-CML (n = 127)	34 months	MCyR: 79%; CCyR: 69%; MMR: 56%
		AP-CML (n = 38)		MCyR: 47%; CCyR: 47%; MMR: 45%
Phase I/II[466] CP-CML or AP-CML or BP-CML with resistance to TKI	**Vodobatinib** (240 mg)	CP-CML (n = 66)	22 months	MCyR: 70%
		AP-CML (n = 8)		MHR: 86%
		BP-CML (n = 4)		MHR: 50%

EMR, early molecular response; MCyR, major cytogenetic response; MHR, major hematologic response; MMR, major molecular response; TKI, tyrosine kinase inhibitor

References

1. Siegel RL, Kratzer TB, Giaquinto AN, et al. Cancer statistics, 2025. CA Cancer J Clin 2025;75:10-45. Available at: https://www.ncbi.nlm.nih.gov/pubmed/39817679.

2. Faderl S, Talpaz M, Estrov Z, et al. The biology of chronic myeloid leukemia. N Engl J Med 1999;341:164-172. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10403855.

3. Melo JV. The diversity of BCR-ABL fusion proteins and their relationship to leukemia phenotype. Blood 1996;88:2375-2384. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8839828.

4. Melo JV. BCR-ABL gene variants. Baillieres Clin Haematol 1997;10:203-222. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9376660.

5. Sawyers CL. Chronic myeloid leukemia. N Engl J Med 1999;340:1330-1340. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10219069.

6. Radich JP, Dai H, Mao M, et al. Gene expression changes associated with progression and response in chronic myeloid leukemia. Proc Natl Acad Sci U S A 2006;103:2794-2799. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16477019.

7. Jamieson CHM, Ailles LE, Dylla SJ, et al. Granulocyte-macrophage progenitors as candidate leukemic stem cells in blast-crisis CML. N Engl J Med 2004;351:657-667. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15306667.

8. PubMed Overview. Available at: https://pubmed.ncbi.nlm.nih.gov/about/. Accessed July 14, 2025.

9. Cortes JE, Talpaz M, Giles F, et al. Prognostic significance of cytogenetic clonal evolution in patients with chronic myelogenous leukemia on imatinib mesylate therapy. Blood 2003;101:3794-3800. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12560227.

10. O'Dwyer ME, Mauro MJ, Blasdel C, et al. Clonal evolution and lack of cytogenetic response are adverse prognostic factors for hematologic relapse of chronic phase CML patients treated with imatinib mesylate. Blood 2004;103:451-455. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14512312.

11. Wang W, Cortes JE, Lin P, et al. Clinical and prognostic significance of 3q26.2 and other chromosome 3 abnormalities in CML in the era of tyrosine kinase inhibitors. Blood 2015;126:1699-1706. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26243778.

12. Wang W, Tang G, Cortes JE, et al. Chromosomal rearrangement involving 11q23 locus in chronic myelogenous leukemia: a rare phenomenon frequently associated with disease progression and poor prognosis. J Hematol Oncol 2015;8:32. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25888368.

13. Wang W, Cortes JE, Tang G, et al. Risk stratification of chromosomal abnormalities in chronic myelogenous leukemia in the era of tyrosine kinase inhibitor therapy. Blood 2016;127:2742-2750. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27006386.

14. Douet-Guilbert N, Morel F, Le Charpentier T, et al. Interphase FISH for follow-up of Philadelphia chromosome-positive chronic myeloid leukemia treatment. Anticancer Res 2004;24:2535-2539. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15330210.

15. Seong DC, Kantarjian HM, Ro JY, et al. Hypermetaphase fluorescence in situ hybridization for quantitative monitoring of Philadelphia chromosome-positive cells in patients with chronic myelogenous leukemia during treatment. Blood 1995;86:2343-2349. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7662980.

16. Dewald GW, Wyatt WA, Juneau AL, et al. Highly sensitive fluorescence in situ hybridization method to detect double BCR/ABL fusion and monitor response to therapy in chronic myeloid leukemia. Blood 1998;91:3357-3365. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9558393.

17. Kantarjian HM, Talpaz M, Cortes J, et al. Quantitative polymerase chain reaction monitoring of BCR-ABL during therapy with imatinib mesylate (STI571; gleevec) in chronic-phase chronic myelogenous leukemia. Clin Cancer Res 2003;9:160-166. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12538464.

18. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16522812.

19. Biernaux C, Loos M, Sels A, et al. Detection of major bcr-abl gene expression at a very low level in blood cells of some healthy individuals. Blood 1995;86:3118-3122. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7579406.

20. Bose S, Deininger M, Gora-Tybor J, et al. The presence of typical and atypical BCR-ABL fusion genes in leukocytes of normal individuals: biologic significance and implications for the assessment of minimal residual disease. Blood 1998;92:3362-3367. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9787174.

21. Baccarani M, Castagnetti F, Gugliotta G, et al. The proportion of different BCR-ABL1 transcript types in chronic myeloid leukemia. An international overview. Leukemia 2019;33:1173-1183. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30675008.

22. Ghalesardi OK, Khosravi A, Azizi E, et al. The prognostic importance of BCR-ABL transcripts in Chronic Myeloid Leukemia: A systematic review and meta-analysis. Leuk Res 2021;101:106512. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33524640.

23. Lucas CM, Harris RJ, Giannoudis A, et al. Chronic myeloid leukemia patients with the e13a2 BCR-ABL fusion transcript have inferior responses to imatinib compared to patients with the e14a2 transcript. Haematologica 2009;94:1362-1367. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19713230.

24. Hanfstein B, Lauseker M, Hehlmann R, et al. Distinct characteristics of e13a2 versus e14a2 BCR-ABL1 driven chronic myeloid leukemia under first-line therapy with imatinib. Haematologica 2014;99:1441-1447. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24837466.

25. Jain P, Kantarjian H, Patel KP, et al. Impact of BCR-ABL transcript type on outcome in patients with chronic-phase CML treated with tyrosine kinase inhibitors. Blood 2016;127:1269-1275. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26729897.

26. Castagnetti F, Gugliotta G, Breccia M, et al. The BCR-ABL1 transcript type influences response and outcome in Philadelphia chromosome-positive chronic myeloid leukemia patients treated frontline with imatinib. Am J Hematol 2017;92:797-805. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28466557.

27. Pagnano KBB, Miranda EC, Delamain MT, et al. Influence of BCR-ABL Transcript Type on Outcome in Patients With Chronic-Phase Chronic Myeloid Leukemia Treated With Imatinib. Clin Lymphoma Myeloma Leuk 2017;17:728-733. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28822797.

28. Lee SE, Choi SY, Kim SH, et al. Baseline BCR-ABL1 transcript type of e13a2 and large spleen size are predictors of poor long-term outcomes in chronic phase chronic myeloid leukemia patients who failed to achieve an early molecular response after 3 months of imatinib therapy. Leuk Lymphoma 2018;59:105-113. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28540759.

29. Ercaliskan A, Eskazan AE. The impact of BCR-ABL1 transcript type on tyrosine kinase inhibitor responses and outcomes in patients with chronic myeloid leukemia. Cancer 2018;124:3806-3818. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29694669.

30. Pfirrmann M, Evtimova D, Saussele S, et al. No influence of BCR-ABL1 transcript types e13a2 and e14a2 on long-term survival: results in 1494 patients with chronic myeloid leukemia treated with imatinib. J Cancer Res Clin Oncol 2017;143:843-850. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28083711.

31. Genthon A, Nicolini FE, Huguet F, et al. Influence of major BCR-ABL1 transcript subtype on outcome in patients with chronic myeloid leukemia in chronic phase treated frontline with nilotinib. Oncotarget 2020;11:2560-2570. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32655840.

32. Dominy KM, Claudiani S, O'Hare M, et al. Assessment of quantitative polymerase chain reaction for BCR-ABL1 transcripts in chronic myeloid leukaemia: Are improved outcomes in patients with e14a2 transcripts an

artefact of technology? Br J Haematol 2022;197:52-62. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34997766.

33. Salmon M, White HE, Zizkova H, et al. Impact of BCR::ABL1 transcript type on RT-qPCR amplification performance and molecular response to therapy. Leukemia 2022;36:1879-1886. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35676453.

34. Cross NCP, Ernst T, Branford S, et al. European LeukemiaNet laboratory recommendations for the diagnosis and management of chronic myeloid leukemia. Leukemia 2023;37:2150-2167. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37794101.

35. Verma D, Kantarjian HM, Jones D, et al. Chronic myeloid leukemia (CML) with P190 BCR-ABL: analysis of characteristics, outcomes, and prognostic significance. Blood 2009;114:2232-2235. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19531657.

36. Arun AK, Senthamizhselvi A, Mani S, et al. Frequency of rare BCR-ABL1 fusion transcripts in chronic myeloid leukemia patients. Int J Lab Hematol 2017;39:235-242. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28035733.

37. Gong Z, Medeiros LJ, Cortes JE, et al. Clinical and prognostic significance of e1a2 BCR-ABL1 transcript subtype in chronic myeloid leukemia. Blood Cancer J 2017;7:e583. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28708130.

38. Qin YZ, Jiang Q, Jiang H, et al. Prevalence and outcomes of uncommon BCR-ABL1 fusion transcripts in patients with chronic myeloid leukaemia: data from a single centre. Br J Haematol 2018;182:693-700. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29974949.

39. Xue M, Wang Q, Huo L, et al. Clinical characteristics and prognostic significance of chronic myeloid leukemia with rare BCR-ABL1 transcripts. Leuk Lymphoma 2019;60:3051-3057. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31258010.

40. Adnan-Awad S, Kim D, Hohtari H, et al. Characterization of p190-Bcr-Abl chronic myeloid leukemia reveals specific signaling pathways and therapeutic targets. Leukemia 2021;35:1964-1975. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33168949.

41. Abdelmagid MG, Litzow MR, McCullough KB, et al. Chronic phase CML with sole P190 (e1a2) BCR::ABL1: long-term outcome among ten consecutive cases. Blood Cancer J 2022;12:103. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35794090.

42. Verstovsek S, Lin H, Kantarjian H, et al. Neutrophilic-chronic myeloid leukemia: low levels of p230 BCR/ABL mRNA and undetectable BCR/ABL protein may predict an indolent course. Cancer 2002;94:2416-2425. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12015767.

43. Langabeer SE, McCarron SL, Kelly J, et al. Chronic Myeloid Leukemia with e19a2 BCR-ABL1 Transcripts and Marked Thrombocytosis: The Role of Molecular Monitoring. Case Rep Hematol 2012;2012:458716. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22937329.

44. Crampe M, Haslam K, Kelly J, et al. Characterization of a novel variant BCR-ABL1 fusion transcript in a patient with chronic myeloid leukemia: Implications for molecular monitoring. Hematol Oncol Stem Cell Ther 2017;10:85-88. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27013275.

45. Langabeer SE. Standardized Molecular Monitoring for Variant BCR-ABL1 Transcripts in Chronic Myeloid Leukemia. Arch Pathol Lab Med 2015;139:969. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26230589.

46. Shanmuganathan N, Hughes TP. Molecular monitoring in CML: how deep? How often? How should it influence therapy? Hematology Am Soc Hematol Educ Program 2018;2018:168-176. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30504306.

47. Burmeister T, Reinhardt R. A multiplex PCR for improved detection of typical and atypical BCR-ABL fusion transcripts. Leuk Res 2008;32:579-585. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17928051.

48. Bennour A, Ouahchi I, Moez M, et al. Comprehensive analysis of BCR/ABL variants in chronic myeloid leukemia patients using multiplex RT-PCR. Clin Lab 2012;58:433-439. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22783572.

49. Mir R, Ahmad I, Javid J, et al. Simple multiplex RT-PCR for identifying common fusion BCR-ABL transcript types and evaluation of molecular

response of the a2b2 and a2b3 transcripts to Imatinib resistance in north Indian chronic myeloid leukemia patients. Indian J Cancer 2015;52:314-318. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26905124.

50. Pagani IS, Dang P, Saunders VA, et al. Clinical utility of genomic DNA Q-PCR for the monitoring of a patient with atypical e19a2 BCR-ABL1 transcripts in chronic myeloid leukemia. Leuk Lymphoma 2020;61:2527-2529. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32508223.

51. Petiti J, Lo Iacono M, Dragani M, et al. Novel Multiplex Droplet Digital PCR Assays to Monitor Minimal Residual Disease in Chronic Myeloid Leukemia Patients Showing Atypical BCR-ABL1 Transcripts. J Clin Med 2020;9:1457. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32414125.

52. Verma D, Kantarjian H, Shan J, et al. Survival outcomes for clonal evolution in chronic myeloid leukemia patients on second generation tyrosine kinase inhibitor therapy. Cancer 2010;116:2673-2681. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20499401.

53. Fabarius A, Kalmanti L, Dietz CT, et al. Impact of unbalanced minor route versus major route karyotypes at diagnosis on prognosis of CML. Ann Hematol 2015;94:2015-2024. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26385387.

54. Fabarius A, Leitner A, Hochhaus A, et al. Impact of additional cytogenetic aberrations at diagnosis on prognosis of CML: long-term observation of 1151 patients from the randomized CML Study IV. Blood 2011;118:6760-6768. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22039253.

55. Hehlmann R, Voskanyan A, Lauseker M, et al. High-risk additional chromosomal abnormalities at low blast counts herald death by CML. Leukemia 2020;34:2074-2086. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32382082.

56. Alhuraiji A, Kantarjian H, Boddu P, et al. Prognostic significance of additional chromosomal abnormalities at the time of diagnosis in patients with chronic myeloid leukemia treated with frontline tyrosine kinase inhibitors. Am J Hematol 2018;93:84-90. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29027261.

57. Bumm T, Muller C, Al-Ali H-K, et al. Emergence of clonal cytogenetic abnormalities in Ph- cells in some CML patients in cytogenetic remission to imatinib but restoration of polyclonal hematopoiesis in the majority. Blood 2003;101:1941-1949. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12411298.

58. Feldman E, Najfeld V, Schuster M, et al. The emergence of Ph-, trisomy -8+ cells in patients with chronic myeloid leukemia treated with imatinib mesylate. Exp Hematol 2003;31:702-707. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12901975.

59. Medina J, Kantarjian H, Talpaz M, et al. Chromosomal abnormalities in Philadelphia chromosome-negative metaphases appearing during imatinib mesylate therapy in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase. Cancer 2003;98:1905-1911. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14584073.

60. Terre C, Eclache V, Rousselot P, et al. Report of 34 patients with clonal chromosomal abnormalities in Philadelphia-negative cells during imatinib treatment of Philadelphia-positive chronic myeloid leukemia. Leukemia 2004;18:1340-1346. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15190256.

61. Deininger MW, Cortes J, Paquette R, et al. The prognosis for patients with chronic myeloid leukemia who have clonal cytogenetic abnormalities in philadelphia chromosome-negative cells. Cancer 2007;110:1509-1519. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17702093.

62. Jabbour E, Kantarjian HM, Abruzzo LV, et al. Chromosomal abnormalities in Philadelphia chromosome negative metaphases appearing during imatinib mesylate therapy in patients with newly diagnosed chronic myeloid leukemia in chronic phase. Blood 2007;110:2991-2995. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17625066.

63. Vignetti M, Fazi P, Cimino G, et al. Imatinib plus steroids induces complete remissions and prolonged survival in elderly Philadelphia chromosome-positive patients with acute lymphoblastic leukemia without additional chemotherapy: results of the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) LAL0201-B protocol. Blood

2007;109:3676-3678. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17213285.

64. Fabarius A, Haferlach C, Muller MC, et al. Dynamics of cytogenetic aberrations in Philadelphia chromosome positive and negative hematopoiesis during dasatinib therapy of chronic myeloid leukemia patients after imatinib failure. Haematologica 2007;92:834-837. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17550857.

65. Baldazzi C, Luatti S, Marzocchi G, et al. Emergence of clonal chromosomal abnormalities in Philadelphia negative hematopoiesis in chronic myeloid leukemia patients treated with nilotinib after failure of imatinib therapy. Leuk Res 2009;33:e218-220. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19525008.

66. Wang H, Jin J, Wang Y, et al. Clonal chromosomal abnormalities in Philadelphia-negative cells in chronic myeloid leukemia patients treated with nilotinib used in first-line therapy. Ann Hematol 2013;92:1625-1632. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23793947.

67. Ni H, Sun X, Xu Y, et al. Clinical implications of clonal chromosomal abnormalities in Philadelphia negative cells in CML patients after treated with tyrosine kinase inhibitors. Cancer Genet 2019;238:44-49. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31425925.

68. Sheng G, Xue M, Wang Q, et al. Occurrence of chromosomal abnormalities in Philadelphia chromosome-negative metaphases in patients with chronic-phase chronic myeloid leukemia undergoing TKI treatments. Leuk Lymphoma 2019;60:3503-3511. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31282805.

69. Issa GC, Kantarjian HM, Gonzalez GN, et al. Clonal chromosomal abnormalities appearing in Philadelphia chromosome-negative metaphases during CML treatment. Blood 2017;130:2084-2091. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28835440.

70. Karimata K, Masuko M, Ushiki T, et al. Myelodysplastic syndrome with Ph negative monosomy 7 chromosome following transient bone marrow dysplasia during imatinib treatment for chronic myeloid leukemia. Intern Med 2011;50:481-485. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21372464.

71. Navarro JT, Feliu E, Grau J, et al. Monosomy 7 with severe myelodysplasia developing during imatinib treatment of Philadelphia-positive chronic myeloid leukemia: two cases with a different outcome. Am J Hematol 2007;82:849-851. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17563075.

72. Bidet A, Dulucq S, Smol T, et al. Poor prognosis of chromosome 7 clonal aberrations in Philadelphia-negative metaphases and relevance of potential underlying myelodysplastic features in chronic myeloid leukemia. Haematologica 2019;104:1150-1155. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30573507.

73. 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.

74. 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.

75. Pfirrmann M, Baccarani M, Saussele S, et al. Prognosis of long-term survival considering disease-specific death in patients with chronic myeloid leukemia. Leukemia 2016;30:48-56. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26416462.

76. Cortes JE, Talpaz M, O'Brien S, et al. Staging of chronic myeloid leukemia in the imatinib era: an evaluation of the World Health Organization proposal. Cancer 2006;106:1306-1315. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16463391.

77. O'Dwyer ME, Mauro MJ, Kurilik G, et al. The impact of clonal evolution on response to imatinib mesylate (STI571) in accelerated phase CML. Blood 2002;100:1628-1633. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12176881.

78. Arber DA, Orazi A, Hasserjian RP, et al. International consensus classification of myeloid neoplasms and acute leukemias: Integrating morphologic, clinical, and genomic data. Blood 2022;140:1200-1228. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35767897.

79. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: Myeloid and histiocytic/dendritic neoplasms. Leukemia 2022;36:1703-1719. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35732831.

80. 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.

81. Grossmann V, Kohlmann A, Zenger M, et al. A deep-sequencing study of chronic myeloid leukemia patients in blast crisis (BC-CML) detects mutations in 76.9% of cases. Leukemia 2011;25:557-560. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21274004.

82. Makishima H, Jankowska AM, McDevitt MA, et al. CBL, CBLB, TET2, ASXL1, and IDH1/2 mutations and additional chromosomal aberrations constitute molecular events in chronic myelogenous leukemia. Blood 2011;117:e198-206. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21346257.

83. Kim T, Tyndel MS, Zhang Z, et al. Exome sequencing reveals DNMT3A and ASXL1 variants associate with progression of chronic myeloid leukemia after tyrosine kinase inhibitor therapy. Leuk Res 2017;59:142-148. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28667884.

84. Kim T, Tyndel MS, Kim HJ, et al. Spectrum of somatic mutation dynamics in chronic myeloid leukemia following tyrosine kinase inhibitor therapy. Blood 2017;129:38-47. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27733357.

85. Mologni L, Piazza R, Khandelwal P, et al. Somatic mutations identified at diagnosis by exome sequencing can predict response to imatinib in chronic phase chronic myeloid leukemia (CML) patients. Am J Hematol 2017;92:E623-E625. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28718956.

86. Togasaki E, Takeda J, Yoshida K, et al. Frequent somatic mutations in epigenetic regulators in newly diagnosed chronic myeloid leukemia. Blood Cancer J 2017;7:e559. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28452984.

87. Branford S, Wang P, Yeung DT, et al. Integrative genomic analysis reveals cancer-associated mutations at diagnosis of CML in patients with high-risk disease. Blood 2018;132:948-961. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29967129.

88. Erbilgin Y, Eskazan AE, Hatirnaz Ng O, et al. Deep sequencing of BCR-ABL1 kinase domain mutations in chronic myeloid leukemia patients with resistance to tyrosine kinase inhibitors. Leuk Lymphoma 2019;60:200-207. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29965782.

89. Nteliopoulos G, Bazeos A, Claudiani S, et al. Somatic variants in epigenetic modifiers can predict failure of response to imatinib but not to second-generation tyrosine kinase inhibitors. Haematologica 2019;104:2400-2409. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31073075.

90. Adnan Awad S, Kankainen M, Ojala T, et al. Mutation accumulation in cancer genes relates to nonoptimal outcome in chronic myeloid leukemia. Blood Adv 2020;4:546-559. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32045476.

91. Wu W, Xu N, Zhou X, et al. Integrative Genomic Analysis Reveals Cancer-Associated Gene Mutations in Chronic Myeloid Leukemia Patients with Resistance or Intolerance to Tyrosine Kinase Inhibitor. Onco Targets Ther 2020;13:8581-8591. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32943879.

92. Adnan Awad S, Dufva O, Ianevski A, et al. RUNX1 mutations in blast-phase chronic myeloid leukemia associate with distinct phenotypes, transcriptional profiles, and drug responses. Leukemia 2021;35:1087-1099. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32782381.

93. Ochi Y, Yoshida K, Huang YJ, et al. Clonal evolution and clinical implications of genetic abnormalities in blastic transformation of chronic myeloid leukaemia. Nat Commun 2021;12:2833. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33990592.

94. Bidikian A, Kantarjian H, Jabbour E, et al. Prognostic impact of ASXL1 mutations in chronic phase chronic myeloid leukemia. Blood Cancer J 2022;12:144. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36307398.

95. Schonfeld L, Rinke J, Hinze A, et al. ASXL1 mutations predict inferior molecular response to nilotinib treatment in chronic myeloid leukemia. Leukemia 2022;36:2242-2249. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35902731.

96. Adnan Awad S, Bruck O, Shanmuganathan N, et al. Epigenetic modifier gene mutations in chronic myeloid leukemia (CML) at diagnosis are associated with risk of relapse upon treatment discontinuation. Blood Cancer J 2022;12:69. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35443743.

97. Stuckey R, Segura-Diaz A, Saez Perdomo MN, et al. Presence of Myeloid Mutations in Patients with Chronic Myeloid Leukemia Increases Risk of Cardiovascular Event on Tyrosine Kinase Inhibitor Treatment. Cancers (Basel) 2023;15:3384. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37444494.

98. Kizilors A, Crisa E, Lea N, et al. Effect of low-level BCR-ABL1 kinase domain mutations identified by next-generation sequencing in patients with chronic myeloid leukaemia: a population-based study. Lancet Haematol 2019;6:e276-e284. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31036317.

99. Soverini S, Bavaro L, De Benedittis C, et al. Prospective assessment of NGS-detectable mutations in CML patients with nonoptimal response: the NEXT-in-CML study. Blood 2020;135:534-541. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31877211.

100. Schmidt M, Rinke J, Schafer V, et al. Molecular-defined clonal evolution in patients with chronic myeloid leukemia independent of the BCR-ABL status. Leukemia 2014;28:2292-2299. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25212276.

101. Hochhaus A, Larson RA, Guilhot F, et al. Long-term outcomes of imatinib treatment for chronic myeloid leukemia. N Engl J Med 2017;376:917-927. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28273028.

102. Cortes JE, Saglio G, Kantarjian HM, et al. Final 5-year study results of DASISION: the dasatinib versus imatinib study in treatment-naive chronic myeloid leukemia patients trial. J Clin Oncol 2016;34:2333-2340. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27217448.

103. Kantarjian HM, Hughes TP, Larson RA, et al. Long-term outcomes with frontline nilotinib versus imatinib in newly diagnosed chronic myeloid leukemia in chronic phase: ENESTnd 10-year analysis. Leukemia 2021;35:440-453. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33414482.

104. Brummendorf TH, Cortes JE, Milojkovic D, et al. Bosutinib versus imatinib for newly diagnosed chronic phase chronic myeloid leukemia: final results from the BFORE trial. Leukemia 2022;36:1825-1833. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35643868.

105. Hochhaus A, Wang J, Kim DW, et al. Asciminib in Newly Diagnosed Chronic Myeloid Leukemia. N Engl J Med 2024;391:885-898. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38820078.

106. Leske IB, Hantschel O. The e13a3 (b2a3) and e14a3 (b3a3) BCR::ABL1 isoforms are resistant to asciminib. Leukemia 2024;38:2041-2045. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38879610.

107. Leyte-Vidal A, DeFilippis R, Outhwaite IR, et al. Absence of ABL1 exon 2-encoded SH3 residues in BCR::ABL1 destabilizes the autoinhibited kinase conformation and confers resistance to asciminib. Leukemia 2024;38:2046-2050. Available at: https://www.ncbi.nlm.nih.gov/pubmed/39085402.

108. Quintas-Cardama A, Han X, Kantarjian H, Cortes J. Tyrosine kinase inhibitor-induced platelet dysfunction in patients with chronic myeloid leukemia. Blood 2009;114:261-263. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19414863.

109. Hughes TP, Laneuville P, Rousselot P, et al. Incidence, outcomes, and risk factors of pleural effusion in patients receiving dasatinib therapy for Philadelphia chromosome-positive leukemia. Haematologica 2019;104:93-101. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30093398.

110. Porkka K, Khoury HJ, Paquette RL, et al. Dasatinib 100 mg once daily minimizes the occurrence of pleural effusion in patients with chronic myeloid leukemia in chronic phase and efficacy is unaffected in patients who develop pleural effusion. Cancer 2010;116:377-386. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19924787.

111. Montani D, Bergot E, Gunther S, et al. Pulmonary arterial hypertension in patients treated by dasatinib. Circulation 2012;125:2128-2137. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22451584.

112. Orlandi EM, Rocca B, Pazzano AS, Ghio S. Reversible pulmonary arterial hypertension likely related to long-term, low-dose dasatinib treatment for chronic myeloid leukaemia. Leuk Res 2012;36:e4-6. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21890201.

113. Cirmi S, El Abd A, Letinier L, et al. Cardiovascular toxicity of tyrosine kinase inhibitors used in chronic myeloid leukemia: An analysis of the FDA Adverse Event Reporting System Database (FAERS). Cancers (Basel) 2020;12:826. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32235443.

114. Efficace F, Baccarani M, Breccia M, et al. Chronic fatigue is the most important factor limiting health-related quality of life of chronic myeloid leukemia patients treated with imatinib. Leukemia 2013;27:1511-1519. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23417029.

115. Berman E, Nicolaides M, Maki RG, et al. Altered bone and mineral metabolism in patients receiving imatinib mesylate. N Engl J Med 2006;354:2006-2013. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16687713.

116. Berman E, Girotra M, Cheng C, et al. Effect of long term imatinib on bone in adults with chronic myelogenous leukemia and gastrointestinal stromal tumors. Leuk Res 2013;37:790-794. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23473999.

117. Tsao AS, Kantarjian H, Cortes J, et al. Imatinib mesylate causes hypopigmentation in the skin. Cancer 2003;98:2483-2487. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14635084.

118. Aleem A. Hypopigmentation of the skin due to imatinib mesylate in patients with chronic myeloid leukemia. Hematol Oncol Stem Cell Ther 2009;2:358-361. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20118061.

119. Sakurai M, Kikuchi T, Karigane D, et al. Renal dysfunction and anemia associated with long-term imatinib treatment in patients with chronic myelogenous leukemia. Int J Hematol 2019;109:292-298. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30680668.

120. Baccarani M, Druker BJ, Branford S, et al. Long-term response to imatinib is not affected by the initial dose in patients with Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase: final update from the Tyrosine Kinase Inhibitor Optimization and Selectivity (TOPS) study. Int J Hematol 2014;99:616-624. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24658916.

121. Deininger MW, Kopecky KJ, Radich JP, et al. Imatinib 800 mg daily induces deeper molecular responses than imatinib 400 mg daily: results of SWOG S0325, an intergroup randomized PHASE II trial in newly diagnosed chronic phase chronic myeloid leukaemia. Br J Haematol 2014;164:223-232. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24383843.

122. Hehlmann R, Lauseker M, Saussele S, et al. Assessment of imatinib as first-line treatment of chronic myeloid leukemia: 10-year survival results of the randomized CML study IV and impact of non-CML determinants. Leukemia 2017;31:2398-2406. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28804124.

123. Hoffmann VS, Hasford J, Deininger M, et al. Systematic review and meta-analysis of standard-dose imatinib vs. high-dose imatinib and second generation tyrosine kinase inhibitors for chronic myeloid leukemia. J Cancer Res Clin Oncol 2017;143:1311-1318. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28275866.

124. Lipton JH, Brummendorf TH, Gambacorti-Passerini C, et al. Long-term safety review of tyrosine kinase inhibitors in chronic myeloid leukemia - What to look for when treatment-free remission is not an option. Blood Rev 2022;56:100968. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35570071.

125. Haddad FG, Kantarjian H. Navigating the Management of Chronic Phase CML in the Era of Generic BCR::ABL1 Tyrosine Kinase Inhibitors. J Natl Compr Canc Netw 2024;22. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38394773.

126. Quintas-Cardama A, Kantarjian H, O'Brien S, et al. Granulocyte-colony-stimulating factor (filgrastim) may overcome imatinib-induced

neutropenia in patients with chronic-phase chronic myelogenous leukemia. Cancer 2004;100:2592-2597. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15197801.

127. Quintas-Cardama A, De Souza Santos FP, Kantarjian H, et al. Dynamics and management of cytopenias associated with dasatinib therapy in patients with chronic myeloid leukemia in chronic phase after imatinib failure. Cancer 2009;115:3935-3943. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19517473.

128. Santos FP, Alvarado Y, Kantarjian H, et al. Long-term prognostic impact of the use of erythropoietic-stimulating agents in patients with chronic myeloid leukemia in chronic phase treated with imatinib. Cancer 2011;117:982-991. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20960502.

129. Barber MC, Mauro MJ, Moslehi J. Cardiovascular care of patients with chronic myeloid leukemia (CML) on tyrosine kinase inhibitor (TKI) therapy. Hematology Am Soc Hematol Educ Program 2017;2017:110-114. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29222244.

130. Casavecchia G, Galderisi M, Novo G, et al. Early diagnosis, clinical management, and follow-up of cardiovascular events with ponatinib. Heart Fail Rev 2020;25:447-456. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32026180.

131. Dusetzina SB, Winn AN, Abel GA, et al. Cost sharing and adherence to tyrosine kinase inhibitors for patients with chronic myeloid leukemia. J Clin Oncol 2014;32:306-311. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24366936.

132. Chen LF, Yuan GL, Zhong ZD, et al. Efficacy and Safety of Generic Dasatinib as a Second-line Treatment for Patients with Chronic Myeloid Leukemia: a Multicenter Retrospective Study in Hubei Province, China. Curr Med Sci 2018;38:1005-1011. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30536062.

133. Gemelli M, Elli EM, Elena C, et al. Use of generic imatinib as first-line treatment in patients with chronic myeloid leukemia (CML): the GIMS (Glivec to Imatinib Switch) study. Blood Res 2020;55:139-145. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32792470.

134. Scalzulli E, Colafigli G, Latagliata R, et al. Switch from branded to generic imatinib: impact on molecular responses and safety in chronic-phase chronic myeloid leukemia patients. Ann Hematol 2020;99:2773-2777. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32462330.

135. Ercaliskan A, Seyhan Erdogan D, Eskazan AE. Current evidence on the efficacy and safety of generic imatinib in CML and the impact of generics on health care costs. Blood Adv 2021;5:3344-3353. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34477815.

136. Yu W, Du X, Wang W, et al. Efficacy and Safety of Generic Dasatinib in Patients With Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase: A Multicenter Prospective Study in China. Clin Lymphoma Myeloma Leuk 2022;22:e867-e873. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35842355.

137. Kantarjian H, Paul S, Thakkar J, Jabbour E. The influence of drug prices, new availability of inexpensive generic imatinib, new approvals, and post-marketing research on the treatment of chronic myeloid leukaemia in the USA. Lancet Haematol 2022;9:e854-e861. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36174582.

138. Klil-Drori AJ, Yin H, Azoulay L, et al. Persistence with generic imatinib for chronic myeloid leukemia: a matched cohort study. Haematologica 2019;104:e293-e295. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30630987.

139. Reinhold U, Hennig E, Leiblein S, et al. FISH for BCR-ABL on interphases of peripheral blood neutrophils but not of unselected white cells correlates with bone marrow cytogenetics in CML patients treated with imatinib. Leukemia 2003;17:1925-1929. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14513039.

140. Fugazza G, Miglino M, Bruzzone R, et al. Cytogenetic and fluorescence in situ hybridization monitoring in Ph+ Chronic Myeloid Leukemia patients treated with imatinib mesylate. J Exp Clin Cancer Res 2004;23:295-299. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15354415.

141. Landstrom AP, Ketterling RP, Knudson RA, Tefferi A. Utility of peripheral blood dual color, double fusion fluorescent in situ hybridization for BCR/ABL fusion to assess cytogenetic remission status in chronic

myeloid leukemia. Leuk Lymphoma 2006;47:2055-2061. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17071476.

142. Testoni N, Marzocchi G, Luatti S, et al. Chronic myeloid leukemia: a prospective comparison of interphase fluorescence in situ hybridization and chromosome banding analysis for the definition of complete cytogenetic response: a study of the GIMEMA CML WP. Blood 2009;114:4939-4943. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19797518.

143. Lima L, Bernal-Mizrachi L, Saxe D, et al. Peripheral blood monitoring of chronic myeloid leukemia during treatment with imatinib, second-line agents, and beyond. Cancer 2011;117:1245-1252. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21381013.

144. Hughes T, Hochhaus A, Branford S, et al. Long-term prognostic significance of early molecular response to imatinib in newly diagnosed chronic myeloid leukemia: an analysis from the International Randomized Study of Interferon and STI571 (IRIS). Blood 2010;116:3758-3765. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20679528.

145. Akard LP, Cortes JE, Albitar M, et al. Correlations between cytogenetic and molecular monitoring among patients with newly diagnosed chronic myeloid leukemia in chronic phase: post hoc analyses of the rationale and insight for gleevec high-dose therapy study. Arch Pathol Lab Med 2014;138:1186-1192. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24308645.

146. Branford S, Cross NCP, Hochhaus A, et al. Rationale for the recommendations for harmonizing current methodology for detecting BCR-ABL transcripts in patients with chronic myeloid leukaemia. Leukemia 2006;20:1925-1930. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16990771.

147. Cross NC. Standardisation of molecular monitoring for chronic myeloid leukaemia. Best Pract Res Clin Haematol 2009;22:355-365. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19959086.

148. Cross NC, White HE, Muller MC, et al. Standardized definitions of molecular response in chronic myeloid leukemia. Leukemia 2012;26:2172-2175. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22504141.

149. Branford S, Fletcher L, Cross NC, et al. Desirable performance characteristics for BCR-ABL measurement on an international reporting scale to allow consistent interpretation of individual patient response and comparison of response rates between clinical trials. Blood 2008;112:3330-3338. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18684859.

150. Guerin A, Chen L, Dea K, et al. Association between regular molecular monitoring and tyrosine kinase inhibitor therapy adherence in chronic myelogenous leukemia in the chronic phase. Curr Med Res Opin 2014;30:1345-1352. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24640967.

151. Hanfstein B, Muller MC, Hehlmann R, et al. Early molecular and cytogenetic response is predictive for long-term progression-free and overall survival in chronic myeloid leukemia (CML). Leukemia 2012;26:2096-2102. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22446502.

152. Hochhaus A, Saglio G, Hughes TP, et al. Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. Leukemia 2016;30:1044-1054. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26837842

153. Marin D, Ibrahim AR, Lucas C, et al. Assessment of BCR-ABL1 transcript levels at 3 months is the only requirement for predicting outcome for patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors. J Clin Oncol 2012;30:232-238. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22067393.

154. Neelakantan P, Gerrard G, Lucas C, et al. Combining BCR-ABL1 transcript levels at 3 and 6 months in chronic myeloid leukemia: implications for early intervention strategies. Blood 2013;121:2739-2742. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23380743.

155. Nazha A, Kantarjian H, Jain P, et al. Assessment at 6 months may be warranted for patients with chronic myeloid leukemia with no major cytogenetic response at 3 months. Haematologica 2013;98:1686-1688. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23812943.

156. Branford S, Yeung DT, Parker WT, et al. Prognosis for patients with CML and >10% BCR-ABL1 after 3 months of imatinib depends on the rate of BCR-ABL1 decline. Blood 2014;124:511-518. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24859364.

157. Hanfstein B, Shlyakhto V, Lauseker M, et al. Velocity of early BCR-ABL transcript elimination as an optimized predictor of outcome in chronic myeloid leukemia (CML) patients in chronic phase on treatment with imatinib. Leukemia 2014;28:1988-1992. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24798484.

158. Iriyama N, Fujisawa S, Yoshida C, et al. Shorter halving time of BCR-ABL1 transcripts is a novel predictor for achievement of molecular responses in newly diagnosed chronic-phase chronic myeloid leukemia treated with dasatinib: Results of the D-first study of Kanto CML study group. Am J Hematol 2015;90:282-287. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25530131.

159. Hochhaus A, O'Brien SG, Guilhot F, et al. Six-year follow-up of patients receiving imatinib for the first-line treatment of chronic myeloid leukemia. Leukemia 2009;23:1054-1061. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19282833.

160. Jabbour E, Kantarjian H, O'Brien S, et al. The achievement of an early complete cytogenetic response is a major determinant for outcome in patients with early chronic phase chronic myeloid leukemia treated with tyrosine kinase inhibitors. Blood 2011;118:4541-4546. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21803854.

161. Druker BJ, Guilhot F, O'Brien SG, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. N Engl J Med 2006;355:2408-2417. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17151364.

162. Press RD, Galderisi C, Yang R, et al. A half-log increase in BCR-ABL RNA predicts a higher risk of relapse in patients with chronic myeloid leukemia with an imatinib-induced complete cytogenetic response. Clin Cancer Res 2007;13:6136-6143. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17947479.

163. de Lavallade H, Apperley JF, Khorashad JS, et al. Imatinib for newly diagnosed patients with chronic myeloid leukemia: incidence of sustained responses in an intention-to-treat analysis. J Clin Oncol 2008;26:3358-3363. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18519952.

164. Marin D, Milojkovic D, Olavarria E, et al. European LeukemiaNet criteria for failure or suboptimal response reliably identify patients with CML in early chronic phase treated with imatinib whose eventual outcome is poor. Blood 2008;112:4437-4444. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18716134.

165. Jabbour E, Kantarjian HM, O'Brien S, et al. Front-line therapy with second-generation tyrosine kinase inhibitors in patients with early chronic phase chronic myeloid leukemia: what is the optimal response? J Clin Oncol 2011;29:4260-4265. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21990394.

166. Hehlmann R, Muller MC, Lauseker M, et al. Deep molecular response is reached by the majority of patients treated with imatinib, predicts survival, and is achieved more quickly by optimized high-dose imatinib: results from the randomized CML-study IV. J Clin Oncol 2014;32:415-423. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24297946.

167. Saussele S, Hehlmann R, Fabarius A, et al. Defining therapy goals for major molecular remission in chronic myeloid leukemia: results of the randomized CML Study IV. Leukemia 2018;32:1222-1228. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29479070.

168. Cervantes F, López-Garrido P, Montero MI, et al. Early intervention during imatinib therapy in patients with newly diagnosed chronic-phase chronic myeloid leukemia: a study of the Spanish PETHEMA group. Haematologica 2010;95:1317-1324. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20220063.

169. Kantarjian H, Cortes J. Considerations in the management of patients with Philadelphia chromosome-positive chronic myeloid leukemia receiving tyrosine kinase inhibitor therapy. J Clin Oncol 2011;29:1512-1516. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21422414.

170. Hochhaus A, Baccarani M, Silver RT, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia 2020;34:966-984. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32127639.

171. Bidikian A, Jabbour E, Issa GC, et al. Chronic myeloid leukemia without major molecular response after 2 years of treatment with tyrosine kinase inhibitor. Am J Hematol 2023;98:639-644. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36606715.

172. Kantarjian HM, Talpaz M, O'Brien S, et al. Dose escalation of imatinib mesylate can overcome resistance to standard-dose therapy in patients with chronic myelogenous leukemia. Blood 2003;101:473-475. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12393385.

173. Marin D, Goldman JM, Olavarria E, Apperley JF. Transient benefit only from increasing the imatinib dose in CML patients who do not achieve complete cytogenetic remissions on conventional doses. Blood 2003;102:2702-2704. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14504074.

174. Jabbour E, Kantarjian HM, Jones D, et al. Imatinib mesylate dose escalation is associated with durable responses in patients with chronic myeloid leukemia after cytogenetic failure on standard-dose imatinib therapy. Blood 2009;113:2154-2160. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19060245.

175. Kantarjian HM, Larson RA, Guilhot F, et al. Efficacy of imatinib dose escalation in patients with chronic myeloid leukemia in chronic phase. Cancer 2009;115:551-560. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19117345.

176. Yeung DT, Osborn MP, White DL, et al. TIDEL-II: first-line use of imatinib in CML with early switch to nilotinib for failure to achieve time-dependent molecular targets. Blood 2015;125:915-923. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25519749.

177. Cortes JE, De Souza CA, Ayala M, et al. Switching to nilotinib versus imatinib dose escalation in patients with chronic myeloid leukaemia in chronic phase with suboptimal response to imatinib (LASOR): a randomised, open-label trial. Lancet Haematol 2016;3:e581-e591. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27890073.

178. Cortes JE, Jiang Q, Wang J, et al. Treatment of chronic-phase chronic myeloid leukemia in patients randomized to dasatinib or imatinib after suboptimal responses to 3 months of imatinib therapy: final 5-year results from DASCERN. Haematologica 2024;109:3251-3260. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38695123.

179. Shah NP, Rousselot P, Schiffer C, et al. Dasatinib in imatinib-resistant or -intolerant chronic-phase, chronic myeloid leukemia patients: 7-year follow-up of study CA180-034. Am J Hematol 2016;91:869-874. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27192969.

180. Giles FJ, le Coutre PD, Pinilla-Ibarz J, et al. Nilotinib in imatinib-resistant or imatinib-intolerant patients with chronic myeloid leukemia in chronic phase: 48-month follow-up results of a phase II study. Leukemia 2013;27:107-112. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22763385.

181. Hochhaus A, Gambacorti-Passerini C, Abboud C, et al. Bosutinib for pretreated patients with chronic phase chronic myeloid leukemia: primary results of the phase 4 BYOND study. Leukemia 2020;34:2125-2137. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32572189.

182. Smith BD, Brümmendorf TH, Roboz GJ, et al. Efficacy and safety of bosutinib in patients treated with prior imatinib and/or dasatinib and/or nilotinib: Subgroup analyses from the phase 4 BYOND study. Leukemia Research 2024;139:107481. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38484432.

183. Gambacorti-Passerini C, Brummendorf TH, Abruzzese E, et al. Efficacy and safety of bosutinib in previously treated patients with chronic myeloid leukemia: final results from the BYOND trial. Leukemia 2024;38:2162-2170. Available at: https://www.ncbi.nlm.nih.gov/pubmed/39164407.

184. Cortes JE, Kim D-W, Pinilla-Ibarz J, et al. Ponatinib efficacy and safety in Philadelphia chromosome–positive leukemia: final 5-year results of the phase 2 PACE trial. Blood 2018;132:393-404. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29567798.

185. Cortes J, Apperley J, Lomaia E, et al. Ponatinib dose-ranging study in chronic-phase chronic myeloid leukemia: a randomized, open-label phase 2 clinical trial. Blood 2021;138:2042-2050. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34407543.

186. Mauro MM, Minami Y, Hochhaus A, et al. Asciminib remained superior vs bosutinib in late-line CML-CP after nearly 4 years of follow-up in ASCEMBL. Blood Adv 2025:Online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/40334072.

187. Cortes JE, Sasaki K, Kim DW, et al. Asciminib monotherapy in patients with chronic-phase chronic myeloid leukemia with the T315I mutation after >/=1 prior tyrosine kinase inhibitor: 2-year follow-up results. Leukemia 2024;38:1522-1533. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38755421.

188. Dorer DJ, Knickerbocker RK, Baccarani M, et al. Impact of dose intensity of ponatinib on selected adverse events: Multivariate analyses from a pooled population of clinical trial patients. Leuk Res 2016;48:84-91. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27505637.

189. Jain P, Kantarjian H, Boddu PC, et al. Analysis of cardiovascular and arteriothrombotic adverse events in chronic-phase CML patients after frontline TKIs. Blood Adv 2019;3:851-861. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30885996.

190. Caocci G, Mulas O, Abruzzese E, et al. Arterial occlusive events in chronic myeloid leukemia patients treated with ponatinib in the real-life practice are predicted by the Systematic Coronary Risk Evaluation (SCORE) chart. Hematol Oncol 2019;37:296-302. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30892724.

191. Kim H, Yoon YJ, Shon JH, et al. Inhibitory effects of fruit juices on CYP3A activity. Drug Metab Dispos 2006;34:521-523. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16415112.

192. van Leeuwen RW, van Gelder T, Mathijssen RH, Jansman FG. Drug-drug interactions with tyrosine-kinase inhibitors: a clinical perspective. Lancet Oncol 2014;15:e315-326. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24988935.

193. Osorio S, Escudero-Vilaplana V, Gomez-Centurion I, et al. Drug-to-drug interactions of tyrosine kinase inhibitors in chronic myeloid leukemia patients. Is it a real problem? Ann Hematol 2018;97:2089-2098. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29955943.

194. Noens L, van Lierde M-A, De Bock R, et al. Prevalence, determinants, and outcomes of nonadherence to imatinib therapy in patients with chronic myeloid leukemia: the ADAGIO study. Blood 2009;113:5401-5411. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19349618.

195. Marin D, Bazeos A, Mahon F-X, et al. Adherence is the critical factor for achieving molecular responses in patients with chronic myeloid leukemia who achieve complete cytogenetic responses on imatinib. J Clin Oncol 2010;28:2381-2388. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20385986.

196. Ibrahim AR, Eliasson L, Apperley JF, et al. Poor adherence is the main reason for loss of CCyR and imatinib failure for chronic myeloid leukemia patients on long-term therapy. Blood 2011;117:3733-3736. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21346253.

197. Wu EQ, Guerin A, Yu AP, et al. Retrospective real-world comparison of medical visits, costs, and adherence between nilotinib and dasatinib in chronic myeloid leukemia. Curr Med Res Opin 2010;26:2861-2869. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21062136.

198. Yood MU, Oliveria SA, Cziraky M, et al. Adherence to treatment with second-line therapies, dasatinib and nilotinib, in patients with chronic myeloid leukemia. Curr Med Res Opin 2012;28:213-219. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22168217.

199. Quintas-Cardama A, Cortes JE, Kantarjian H. Practical management of toxicities associated with tyrosine kinase inhibitors in chronic myeloid leukemia. Clin Lymphoma Myeloma 2008;8 Suppl 3:S82-88. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19254885.

200. Cornelison M, Jabbour EJ, Welch MA. Managing side effects of tyrosine kinase inhibitor therapy to optimize adherence in patients with chronic myeloid leukemia: the role of the midlevel practitioner. J Support Oncol 2012;10:14-24. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22244674.

201. Cortes JE, Lipton JH, Miller CB, et al. Evaluating the impact of a switch to nilotinib on imatinib-related chronic low-grade adverse events in patients with CML-CP: The ENRICH study. Clin Lymphoma Myeloma Leuk

2016;16:286-296. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26993758.

202. Kim DW, Saussele S, Williams LA, et al. Outcomes of switching to dasatinib after imatinib-related low-grade adverse events in patients with chronic myeloid leukemia in chronic phase: the DASPERSE study. Ann Hematol 2018;97:1357-1367. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29556695.

203. Thomas J, Wang L, Clark RE, Pirmohamed M. Active transport of imatinib into and out of cells: implications for drug resistance. Blood 2004;104:3739-3745. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15315971.

204. Mahon FX, Hayette S, Lagarde V, et al. Evidence that resistance to nilotinib may be due to BCR-ABL, Pgp, or Src kinase overexpression. Cancer Res 2008;68:9809-9816. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19047160.

205. Hegedus C, Ozvegy-Laczka C, Apati A, et al. Interaction of nilotinib, dasatinib and bosutinib with ABCB1 and ABCG2: implications for altered anti-cancer effects and pharmacological properties. Br J Pharmacol 2009;158:1153-1164. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19785662.

206. Picard S, Titier K, Etienne G, et al. Trough imatinib plasma levels are associated with both cytogenetic and molecular responses to standard-dose imatinib in chronic myeloid leukemia. Blood 2007;109:3496-3499. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17192396.

207. Larson RA, Druker BJ, Guilhot F, et al. Imatinib pharmacokinetics and its correlation with response and safety in chronic-phase chronic myeloid leukemia: a subanalysis of the IRIS study. Blood 2008;111:4022-4028. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18256322.

208. Bouchet S, Titier K, Moore N, et al. Therapeutic drug monitoring of imatinib in chronic myeloid leukemia: experience from 1216 patients at a centralized laboratory. Fundam Clin Pharmacol 2013;27:690-697. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23113675.

209. White DL, Radich J, Soverini S, et al. Chronic phase chronic myeloid leukemia patients with low OCT-1 activity randomised to high-dose imatinib achieve better responses, and lower failure rates, than those randomized to standard-dose. Haematologica 2012;97:907-914. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22207690.

210. Giannoudis A, Davies A, Lucas CM, et al. Effective dasatinib uptake may occur without human organic cation transporter 1 (hOCT1): implications for the treatment of imatinib-resistant chronic myeloid leukemia. Blood 2008;112:3348-3354. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18669873.

211. Hiwase DK, Saunders V, Hewett D, et al. Dasatinib cellular uptake and efflux in chronic myeloid leukemia cells: therapeutic implications. Clin Cancer Res 2008;14:3881-3888. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18559609.

212. Davies A, Jordanides NE, Giannoudis A, et al. Nilotinib concentration in cell lines and primary CD34(+) chronic myeloid leukemia cells is not mediated by active uptake or efflux by major drug transporters. Leukemia 2009;23:1999-2006. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19710702.

213. White DL, Saunders VA, Dang P, et al. OCT-1-mediated influx is a key determinant of the intracellular uptake of imatinib but not nilotinib (AMN107): reduced OCT-1 activity is the cause of low in vitro sensitivity to imatinib. Blood 2006;108:697-704. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16597591.

214. Branford S, Rudzki Z, Walsh S, et al. Detection of BCR-ABL mutations in patients with CML treated with imatinib is virtually always accompanied by clinical resistance, and mutations in the ATP phosphate-binding loop (P-loop) are associated with a poor prognosis. Blood 2003;102:276-283. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12623848.

215. Soverini S, Martinelli G, Rosti G, et al. ABL mutations in late chronic phase chronic myeloid leukemia patients with up-front cytogenetic resistance to imatinib are associated with a greater likelihood of progression to blast crisis and shorter survival: a study by the GIMEMA Working Party on Chronic Myeloid Leukemia. J Clin Oncol 2005;23:4100-4109. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15867198.

216. Nicolini FE, Corm S, Le QH, et al. Mutation status and clinical outcome of 89 imatinib mesylate-resistant chronic myelogenous leukemia patients: a retrospective analysis from the French intergroup of CML (Fi(phi)-LMC GROUP). Leukemia 2006;20:1061-1106. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16642048.

217. Soverini S, Colarossi S, Gnani A, et al. Contribution of ABL kinase domain mutations to imatinib resistance in different subsets of Philadelphia-positive patients: by the GIMEMA Working Party on Chronic Myeloid Leukemia. Clin Cancer Res 2006;12:7374-7379. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17189410.

218. Khorashad JS, de Lavallade H, Apperley JF, et al. Finding of kinase domain mutations in patients with chronic phase chronic myeloid leukemia responding to imatinib may identify those at high risk of disease progression. J Clin Oncol 2008;26:4806-4813. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18645191.

219. Soverini S, Gnani A, Colarossi S, et al. Philadelphia-positive patients who already harbor imatinib-resistant Bcr-Abl kinase domain mutations have a higher likelihood of developing additional mutations associated with resistance to second- or third-line tyrosine kinase inhibitors. Blood 2009;114:2168-2171. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19589924.

220. Braun TP, Eide CA, Druker BJ. Response and Resistance to BCR-ABL1-Targeted Therapies. Cancer Cell 2020;37:530-542. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32289275.

221. Nicolini FE, Hayette S, Corm S, et al. Clinical outcome of 27 imatinib mesylate-resistant chronic myelogenous leukemia patients harboring a T315I BCR-ABL mutation. Haematologica 2007;92:1238-1241. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17768119.

222. Jabbour E, Kantarjian H, Jones D, et al. Characteristics and outcomes of patients with chronic myeloid leukemia and T315I mutation following failure of imatinib mesylate therapy. Blood 2008;112:53-55. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18403620.

223. Soverini S, Colarossi S, Gnani A, et al. Resistance to dasatinib in Philadelphia-positive leukemia patients and the presence or the selection of mutations at residues 315 and 317 in the BCR-ABL kinase domain. Haematologica 2007;92:401-404. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17339191.

224. Jabbour E, Kantarjian HM, Jones D, et al. Characteristics and outcome of chronic myeloid leukemia patients with F317L BCR-ABL kinase domain mutation after therapy with tyrosine kinase inhibitors. Blood 2008;112:4839-4842. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18818391.

225. Muller MC, Cortes JE, Kim D-W, et al. Dasatinib treatment of chronic-phase chronic myeloid leukemia: analysis of responses according to preexisting BCR-ABL mutations. Blood 2009;114:4944-4953. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19779040.

226. Hughes T, Saglio G, Branford S, et al. Impact of baseline BCR-ABL mutations on response to nilotinib in patients with chronic myeloid leukemia in chronic phase. J Clin Oncol 2009;27:4204-4210. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19652056.

227. Cortes JE, Khoury HJ, Kantarjian HM, et al. Long-term bosutinib for chronic phase chronic myeloid leukemia after failure of imatinib plus dasatinib and/or nilotinib. Am J Hematol 2016;91:1206-1214. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27531525.

228. Naqvi K, Cortes JE, Luthra R, et al. Characteristics and outcome of chronic myeloid leukemia patients with E255K/V BCR-ABL kinase domain mutations. Int J Hematol 2018;107:689-695. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29464484.

229. Eide CA, Zabriskie MS, Savage Stevens SL, et al. Combining the Allosteric Inhibitor Asciminib with Ponatinib Suppresses Emergence of and Restores Efficacy against Highly Resistant BCR-ABL1 Mutants. Cancer Cell 2019;36:431-443 e435. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31543464.

230. Leyte-Vidal A, Garrido Ruiz D, DeFilippis R, et al. BCR::ABL1 kinase N-lobe mutants confer moderate to high degrees of resistance to asciminib. Blood 2024;144:639-645. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38643492.

231. Khoury HJ, Cortes JE, Kantarjian HM, et al. Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib

and/or nilotinib therapy failure. Blood 2012;119:3403-3412. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22371878.

232. Laudadio J, Deininger MW, Mauro MJ, et al. An intron-derived insertion/truncation mutation in the BCR-ABL kinase domain in chronic myeloid leukemia patients undergoing kinase inhibitor therapy. J Mol Diagn 2008;10:177-180. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18276770.

233. Berman E, Jhanwar S, Hedvat C, et al. Resistance to imatinib in patients with chronic myelogenous leukemia and the splice variant BCR-ABL1(35INS). Leuk Res 2016;49:108-112. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27658269.

234. Khorashad JS, Kelley TW, Szankasi P, et al. BCR-ABL1 compound mutations in tyrosine kinase inhibitor-resistant CML: frequency and clonal relationships. Blood 2013;121:489-498. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23223358.

235. Zabriskie MS, Eide CA, Tantravahi SK, et al. BCR-ABL1 compound mutations combining key kinase domain positions confer clinical resistance to ponatinib in Ph chromosome-positive leukemia. Cancer Cell 2014;26:428-442. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25132497.

236. Deininger MW, Hodgson JG, Shah NP, et al. Compound mutations in BCR-ABL1 are not major drivers of primary or secondary resistance to ponatinib in CP-CML patients. Blood 2016;127:703-712. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26603839.

237. Soverini S, Branford S, Nicolini FE, et al. Implications of BCR-ABL1 kinase domain-mediated resistance in chronic myeloid leukemia. Leuk Res 2014;38:10-20. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24131888.

238. Garg RJ, Kantarjian H, O'Brien S, et al. The use of nilotinib or dasatinib after failure to 2 prior tyrosine kinase inhibitors: long-term follow-up. Blood 2009;114:4361-4368. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19729517.

239. Branford S, Rudzki Z, Parkinson I, et al. Real-time quantitative PCR analysis can be used as a primary screen to identify patients with CML treated with imatinib who have BCR-ABL kinase domain mutations. Blood 2004;104:2926-2932. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15256429.

240. Wang L, Knight K, Lucas C, Clark R. The role of serial BCR-ABL transcript monitoring in predicting the emergence of BCR-ABL kinase mutations in imatinib-treated patients with chronic myeloid leukemia. Haematologica 2006;91:235-239. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16461309.

241. Kantarjian HM, Shan J, Jones D, et al. Significance of increasing levels of minimal residual disease in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in complete cytogenetic response. J Clin Oncol 2009;27:3659-3663. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19487383.

242. Marin D, Khorashad JS, Foroni L, et al. Does a rise in the BCR-ABL1 transcript level identify chronic phase CML patients responding to imatinib who have a high risk of cytogenetic relapse? Br J Haematol 2009;145:373-375. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19344397.

243. Press RD, Willis SG, Laudadio J, et al. Determining the rise in BCR-ABL RNA that optimally predicts a kinase domain mutation in patients with chronic myeloid leukemia on imatinib. Blood 2009;114:2598-2605. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19625707.

244. Mahon FX, Rea D, Guilhot J, et al. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. Lancet Oncol 2010;11:1029-1035. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20965785.

245. Etienne G, Guilhot J, Rea D, et al. Long-term follow-up of the french stop imatinib (STIM1) study in patients with chronic myeloid leukemia. J Clin Oncol 2017;35:298-305. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28095277.

246. Thielen N, van der Holt B, Cornelissen JJ, et al. Imatinib discontinuation in chronic phase myeloid leukaemia patients in sustained complete molecular response: a randomised trial of the Dutch-Belgian Cooperative Trial for Haemato-Oncology (HOVON). Eur J Cancer

2013;49:3242-3246. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23876833.

247. Rousselot P, Charbonnier A, Cony-Makhoul P, et al. Loss of major molecular response as a trigger for restarting tyrosine kinase inhibitor therapy in patients with chronic-phase chronic myelogenous leukemia who have stopped imatinib after durable undetectable disease. J Clin Oncol 2014;32:424-430. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24323036.

248. Mori S, Vagge E, le Coutre P, et al. Age and dPCR can predict relapse in CML patients who discontinued imatinib: the ISAV study. Am J Hematol 2015;90:910-914. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26178642.

249. Lee SE, Choi SY, Song HY, et al. Imatinib withdrawal syndrome and longer duration of imatinib have a close association with a lower molecular relapse after treatment discontinuation: the KID study. Haematologica 2016;101:717-723. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26888022.

250. Ross DM, Pagani IS, Shanmuganathan N, et al. Long-term treatment-free remission of chronic myeloid leukemia with falling levels of residual leukemic cells. Leukemia 2018;32:2572-2579. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30315232.

251. Rea D, Nicolini FE, Tulliez M, et al. Discontinuation of dasatinib or nilotinib in chronic myeloid leukemia: interim analysis of the STOP 2G-TKI study. Blood 2017;129:846-854. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27932374.

252. Okada M, Imagawa J, Tanaka H, et al. Final 3-year Results of the Dasatinib Discontinuation Trial in Patients With Chronic Myeloid Leukemia Who Received Dasatinib as a Second-line Treatment. Clin Lymphoma Myeloma Leuk 2018;18:353-360 e351. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29610029.

253. Shah NP, Garcia-Gutierrez V, Jimenez-Velasco A, et al. Dasatinib discontinuation in patients with chronic-phase chronic myeloid leukemia and stable deep molecular response: the DASFREE study. Leuk Lymphoma 2020;61:650-659. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31647335.

254. Kimura S, Imagawa J, Murai K, et al. Treatment-free remission after first-line dasatinib discontinuation in patients with chronic myeloid leukaemia (first-line DADI trial): a single-arm, multicentre, phase 2 trial. Lancet Haematol 2020;7:e218-e225. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31978329.

255. Radich JP, Hochhaus A, Masszi T, et al. Treatment-free remission following frontline nilotinib in patients with chronic phase chronic myeloid leukemia: 5-year update of the ENESTfreedom trial. Leukemia 2021;35:1344-1355. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33707652.

256. Hughes TP, Clementino NCD, Fominykh M, et al. Long-term treatment-free remission in patients with chronic myeloid leukemia after second-line nilotinib: ENESTop 5-year update. Leukemia 2021;35:1631-1642. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33980976.

257. Gugliotta G, Castagnetti F, Breccia M, et al. Treatment-free remission in chronic myeloid leukemia patients treated front-line with nilotinib: 10-year followup of the GIMEMA CML 0307 study. Haematologica 2022;107:2356-2364. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35385922.

258. Mahon FX, Pfirrmann M, Dulucq S, et al. European Stop Tyrosine Kinase Inhibitor Trial (EURO-SKI) in Chronic Myeloid Leukemia: Final Analysis and Novel Prognostic Factors for Treatment-Free Remission. J Clin Oncol 2024;42:1875-1880. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38471049.

259. Legros L, Nicolini FE, Etienne G, et al. Second tyrosine kinase inhibitor discontinuation attempt in patients with chronic myeloid leukemia. Cancer 2017;123:4403-4410. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28743166.

260. Richter J, Lubking A, Soderlund S, et al. Molecular status 36 months after TKI discontinuation in CML is highly predictive for subsequent loss of MMR-final report from AFTER-SKI. Leukemia 2021;35:2416-2418. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33589755.

261. Shanmuganathan N, Pagani IS, Ross DM, et al. Early BCR-ABL1 kinetics are predictive of subsequent achievement of treatment-free

remission in chronic myeloid leukemia. Blood 2021;137:1196-1207. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32871588.

262. Haddad FG, Sasaki K, Senapati J, et al. Successful Treatment-Free Remission After Ponatinib Discontinuation in Pretreated Patients with Chronic Myeloid Leukemia in Chronic Phase. Clin Lymphoma Myeloma Leuk 2025;25:254-257. Available at: https://www.ncbi.nlm.nih.gov/pubmed/39592322.

263. Etienne I, Benghiat FS, Knoop C. Chronic myeloid leukemia may no longer be a contraindication to lung transplantation. J Heart Lung Transplant 2020;39:987-988. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32312659.

264. Thiem U, Buxhofer-Ausch V, Kranewitter W, et al. Successful kidney transplantation in a patient with pre-existing chronic myeloid leukemia treated with imatinib. Am J Transplant 2021;21:405-409. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32654389.

265. Tokumoto T, Setoguchi K, Osaka A, et al. A Case Report of Successful Kidney Transplantation in a Patient With Chronic Myelogenous Leukemia (CML) Who Has Been in Remission for 15 Years on Imatinib. Transplant Proc 2023;55:1074-1077. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37147192.

266. Cortes JE, Apperley JF, DeAngelo DJ, et al. Management of adverse events associated with bosutinib treatment of chronic-phase chronic myeloid leukemia: expert panel review. J Hematol Oncol 2018;11:143. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30587215.

267. Kota V, Brummendorf TH, Gambacorti-Passerini C, et al. Efficacy and safety following bosutinib dose reduction in patients with Philadelphia chromosome–positive leukemias. Leuk Res 2021;111:106690. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34673442.

268. Ureshino H, Takahashi N, Ikezoe T, et al. A lower initial dose of bosutinib for patients with chronic myeloid leukemia patients resistant and/or intolerant to prior therapy: a single-arm, multicenter, phase 2 trial (BOGI trial). Int J Hematol 2024;120:492-500. Available at: https://www.ncbi.nlm.nih.gov/pubmed/39136895.

269. Naqvi K, Jabbour E, Skinner J, et al. Long-term follow-up of lower dose dasatinib (50 mg daily) as frontline therapy in newly diagnosed chronic-phase chronic myeloid leukemia. Cancer 2020;126:67-75. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31553487.

270. Jabbour E, Sasaki K, Haddad FG, et al. Low-dose dasatinib 50 mg/day versus standard-dose dasatinib 100 mg/day as frontline therapy in chronic myeloid leukemia in chronic phase: A propensity score analysis. Am J Hematol 2022;97:1413-1418. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36054032.

271. Itamura H, Kubota Y, Shindo T, et al. Elderly patients with chronic myeloid leukemia benefit from a dasatinib dose as low as 20 mg. Clin Lymphoma Myeloma Leuk 2017;17:370-374. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28396095.

272. Murai K, Ureshino H, Kumagai T, et al. Low-dose dasatinib in older patients with chronic myeloid leukaemia in chronic phase (DAVLEC): a single-arm, multicentre, phase 2 trial. Lancet Haematol 2021;8:e902-e911. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34826413.

273. Visani G, Breccia M, Gozzini A, et al. Dasatinib, even at low doses, is an effective second-line therapy for chronic myeloid leukemia patients resistant or intolerant to imatinib. Results from a real life-based Italian multicenter retrospective study on 114 patients. Am J Hematol 2010;85:960-963. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21069865.

274. La Rosee P, Martiat P, Leitner A, et al. Improved tolerability by a modified intermittent treatment schedule of dasatinib for patients with chronic myeloid leukemia resistant or intolerant to imatinib. Ann Hematol 2013;92:1345-1350. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23625298.

275. Hjorth-Hansen H, Stenke L, Soderlund S, et al. Dasatinib induces fast and deep responses in newly diagnosed chronic myeloid leukaemia patients in chronic phase: clinical results from a randomised phase-2 study (NordCML006). Eur J Haematol 2015;94:243-250. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25082346.

276. Iriyama N, Ohashi K, Hashino S, et al. The efficacy of reduced-dose dasatinib as a subsequent therapy in patients with chronic myeloid

leukemia in the chronic phase: The LD-CML study of the KANTO CML study group. Intern Med 2018;57:17-23. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29033428.

277. Ohnishi K, Nakaseko C, Takeuchi J, et al. Long-term outcome following imatinib therapy for chronic myelogenous leukemia, with assessment of dosage and blood levels: the JALSG CML202 study. Cancer Sci 2012;103:1071-1078. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22364419.

278. Tokuhira M, Kimura Y, Sugimoto K, et al. Efficacy and safety of nilotinib therapy in patients with newly diagnosed chronic myeloid leukemia in the chronic phase. Med Oncol 2018;35:38. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29442179.

279. Hiwase D, Tan P, D'Rozario J, et al. Efficacy and safety of nilotinib 300mg twice daily in patients with chronic myeloid leukemia in chronic phase who are intolerant to prior tyrosine kinase inhibitors: Results from the Phase IIIb ENESTswift study. Leuk Res 2018;67:109-115. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29494928.

280. Iurlo A, Cattaneo D, Malato A, et al. Low-dose ponatinib is a good option in chronic myeloid leukemia patients intolerant to previous TKIs. Am J Hematol 2020;95:E260-E263. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32557788.

281. Russo D, Malagola M, Skert C, et al. Managing chronic myeloid leukaemia in the elderly with intermittent imatinib treatment. Blood Cancer J 2015;5:e347. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26383820.

282. Faber E, Divoka M, Skoumalova I, et al. A lower dosage of imatinib is sufficient to maintain undetectable disease in patients with chronic myeloid leukemia with long-term low-grade toxicity of the treatment. Leuk Lymphoma 2016;57:370-375. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26022524.

283. Cervantes F, Correa JG, Perez I, et al. Imatinib dose reduction in patients with chronic myeloid leukemia in sustained deep molecular response. Ann Hematol 2017;96:81-85. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27717993.

284. Clark RE, Polydoros F, Apperley JF, et al. De-escalation of tyrosine kinase inhibitor dose in patients with chronic myeloid leukaemia with stable major molecular response (DESTINY): an interim analysis of a non-randomised, phase 2 trial. Lancet Haematol 2017;4:e310-e316. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28566209.

285. Clark RE, Polydoros F, Apperley JF, et al. De-escalation of tyrosine kinase inhibitor therapy before complete treatment discontinuation in patients with chronic myeloid leukaemia (DESTINY): a non-randomised, phase 2 trial. Lancet Haematol 2019;6:e375-e383. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31201085.

286. Cayssials E, Torregrosa-Diaz J, Gallego-Hernanz P, et al. Low-dose tyrosine kinase inhibitors before treatment discontinuation do not impair treatment-free remission in chronic myeloid leukemia patients: Results of a retrospective study. Cancer 2020;126:3438-3447. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32459375.

287. Claudiani S, Apperley JF, Szydlo R, et al. TKI dose reduction can effectively maintain major molecular remission in patients with chronic myeloid leukaemia. Br J Haematol 2021;193:346-355. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33368155.

288. Malagola M, Iurlo A, Abruzzese E, et al. Molecular response and quality of life in chronic myeloid leukemia patients treated with intermittent TKIs: First interim analysis of OPTkIMA study. Cancer Med 2021;10:1726-1737. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33594821.

289. Malagola M, Iurlo A, Bucelli C, et al. The Italian Multicentric Randomized OPTkIMA Trial on Fixed vs Progressive Intermittent TKI Therapy in CML Elderly Patients: 3-Years of Molecular Response and Quality of Life Monitoring After Completing the Treatment Plan. Clin Lymphoma Myeloma Leuk 2024;24:323-331. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38369436.

290. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11877262.

291. Kantarjian HM, Cortes J, O'Brien S, et al. Imatinib mesylate (STI571) therapy for Philadelphia chromosome-positive chronic myelogenous

leukemia in blast phase. Blood 2002;99:3547-3553. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11986206.

292. Sawyers CL, Hochhaus A, Feldman E, et al. Imatinib induces hematologic and cytogenetic responses in patients with chronic myelogenous leukemia in myeloid blast crisis: results of a phase II study. Blood 2002;99:3530-3539. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11986204.

293. Palandri F, Castagnetti F, Testoni N, et al. Chronic myeloid leukemia in blast crisis treated with imatinib 600 mg: outcome of the patients alive after a 6-year follow-up. Haematologica 2008;93:1792-1796. Available at: http://www.ncbi.nlm.nih.gov/pubmed18838477.

294. Palandri F, Castagnetti F, Alimena G, et al. The long-term durability of cytogenetic responses in patients with accelerated phase chronic myeloid leukemia treated with imatinib 600 mg: the GIMEMA CML Working Party experience after a 7-year follow-up. Haematologica 2009;94:205-212. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19144656.

295. Kantarjian H, Cortes J, Kim DW, et al. Phase 3 study of dasatinib 140 mg once daily versus 70 mg twice daily in patients with chronic myeloid leukemia in accelerated phase resistant or intolerant to imatinib: 15-month median follow-up. Blood 2009;113:6322-6329. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19369231.

296. Ottmann O, Saglio G, Apperley JF, et al. Long-term efficacy and safety of dasatinib in patients with chronic myeloid leukemia in accelerated phase who are resistant to or intolerant of imatinib. Blood Cancer J 2018;8:88. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30190469.

297. Saglio G, Hochhaus A, Goh YT, et al. Dasatinib in imatinib-resistant or imatinib-intolerant chronic myeloid leukemia in blast phase after 2 years of follow-up in a phase 3 study: efficacy and tolerability of 140 milligrams once daily and 70 milligrams twice daily. Cancer 2010;116:3852-3861. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20564086.

298. le Coutre PD, Giles FJ, Hochhaus A, et al. Nilotinib in patients with Ph+ chronic myeloid leukemia in accelerated phase following imatinib resistance or intolerance: 24-month follow-up results. Leukemia 2012;26:1189-1194. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22076466.

299. Giles FJ, Kantarjian HM, le Coutre PD, et al. Nilotinib is effective in imatinib-resistant or -intolerant patients with chronic myeloid leukemia in blastic phase. Leukemia 2012;26:959-962. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22157807.

300. Gambacorti-Passerini C, Kantarjian HM, Kim DW, et al. Long-term efficacy and safety of bosutinib in patients with advanced leukemia following resistance/intolerance to imatinib and other tyrosine kinase inhibitors. Am J Hematol 2015;90:755-768. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26040495.

301. Oki Y, Kantarjian HM, Gharibyan V, et al. Phase II study of low-dose decitabine in combination with imatinib mesylate in patients with accelerated or myeloid blastic phase of chronic myelogenous leukemia. Cancer 2007;109:899-906. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17236224.

302. Quintas-Cardama A, Kantarjian H, Garcia-Manero G, et al. A pilot study of imatinib, low-dose cytarabine and idarubicin for patients with chronic myeloid leukemia in myeloid blast phase. Leuk Lymphoma 2007;48:283-289. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17325887.

303. Fruehauf S, Topaly J, Buss EC, et al. Imatinib combined with mitoxantrone/etoposide and cytarabine is an effective induction therapy for patients with chronic myeloid leukemia in myeloid blast crisis. Cancer 2007;109:1543-1549. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17340589.

304. Deau B, Nicolini FE, Guilhot J, et al. The addition of daunorubicin to imatinib mesylate in combination with cytarabine improves the response rate and the survival of patients with myeloid blast crisis chronic myelogenous leukemia (AFR01 study). Leuk Res 2011;35:777-782. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21145590.

305. Strati P, Kantarjian H, Thomas D, et al. HCVAD plus imatinib or dasatinib in lymphoid blastic phase chronic myeloid leukemia. Cancer 2014;120:373-380. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24151050.

306. Morita K, Kantarjian HM, Sasaki K, et al. Outcome of patients with chronic myeloid leukemia in lymphoid blastic phase and Philadelphia chromosome-positive acute lymphoblastic leukemia treated with hyper-CVAD and dasatinib. Cancer 2021;127:2641-2647. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33823073.

307. Saxena K, Jabbour E, Issa G, et al. Impact of frontline treatment approach on outcomes of myeloid blast phase CML. J Hematol Oncol 2021;14:94. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34130720.

308. Rea D, Etienne G, Nicolini F, et al. First-line imatinib mesylate in patients with newly diagnosed accelerated phase-chronic myeloid leukemia. Leukemia 2012;26:2254-2259. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22460758.

309. Ohanian M, Kantarjian HM, Quintas-Cardama A, et al. Tyrosine kinase inhibitors as initial therapy for patients with chronic myeloid leukemia in accelerated phase. Clin Lymphoma Myeloma Leuk 2014;14:155-162 e151. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24332214.

310. Khoury HJ, Cortes J, Baccarani M, et al. Omacetaxine mepesuccinate in patients with advanced chronic myeloid leukemia with resistance or intolerance to tyrosine kinase inhibitors. Leuk Lymphoma 2015;56:120-127. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24650054.

311. Hughes TP, Mauro MJ, Cortes JE, et al. Asciminib in chronic myeloid leukemia after ABL kinase inhibitor failure. N Engl J Med 2019;381:2315-2326. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31826340.

312. Fava C, Kantarjian HM, Jabbour E, et al. Failure to achieve a complete hematologic response at the time of a major cytogenetic response with second-generation tyrosine kinase inhibitors is associated with a poor prognosis among patients with chronic myeloid leukemia in accelerated or blast phase. Blood 2009;113:5058-5063. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19282457.

313. Jain P, Kantarjian HM, Ghorab A, et al. Prognostic factors and survival outcomes in patients with chronic myeloid leukemia in blast phase in the tyrosine kinase inhibitor era: Cohort study of 477 patients. Cancer 2017;123:4391-4402. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28743165.

314. Rajappa S, Uppin SG, Raghunadharao D, et al. Isolated central nervous system blast crisis in chronic myeloid leukemia. Hematol Oncol 2004;22:179-181. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15995975.

315. Kim HJ, Jung CW, Kim K, et al. Isolated blast crisis in CNS in a patient with chronic myelogenous leukemia maintaining major cytogenetic response after imatinib. J Clin Oncol 2006;24:4028-4029. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16921058.

316. Altintas A, Cil T, Kilinc I, et al. Central nervous system blastic crisis in chronic myeloid leukemia on imatinib mesylate therapy: a case report. J Neurooncol 2007;84:103-105. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17318411.

317. Aftimos P, Nasr F. Isolated CNS lymphoid blast crisis in a patient with imatinib-resistant chronic myelogenous leukemia: case report and review of the literature. Leuk Res 2009;33:e178-180. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19446330.

318. Porkka K, Koskenvesa P, Lundan T, et al. Dasatinib crosses the blood-brain barrier and is an efficient therapy for central nervous system Philadelphia chromosome-positive leukemia. Blood 2008;112:1005-1012. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18477770.

319. Deininger M, Schleuning M, Greinix H, et al. The effect of prior exposure to imatinib on transplant-related mortality. Haematologica 2006;91:452-459. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16585011.

320. Oehler VG, Gooley T, Snyder DS, et al. The effects of imatinib mesylate treatment before allogeneic transplantation for chronic myeloid leukemia. Blood 2007;109:1782-1789. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17062727.

321. Jabbour E, Cortes J, Kantarjian H, et al. Novel tyrosine kinase inhibitor therapy before allogeneic stem cell transplantation in patients with chronic myeloid leukemia: no evidence for increased transplant-related

toxicity. Cancer 2007;110:340-344. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17559140.

322. Shimoni A, Leiba M, Schleuning M, et al. Prior treatment with the tyrosine kinase inhibitors dasatinib and nilotinib allows stem cell transplantation (SCT) in a less advanced disease phase and does not increase SCT Toxicity in patients with chronic myelogenous leukemia and philadelphia positive acute lymphoblastic leukemia. Leukemia 2009;23:190-194. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18596746.

323. Breccia M, Palandri F, Iori AP, et al. Second-generation tyrosine kinase inhibitors before allogeneic stem cell transplantation in patients with chronic myeloid leukemia resistant to imatinib. Leuk Res 2010;34:143-147. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19481800.

324. Lee SE, Choi SY, Kim SH, et al. Prognostic factors for outcomes of allogeneic stem cell transplantation in chronic phase chronic myeloid leukemia in the era of tyrosine kinase inhibitors. Hematology 2014;19:63-72. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23684143.

325. Piekarska A, Gil L, Prejzner W, et al. Pretransplantation use of the second-generation tyrosine kinase inhibitors has no negative impact on the HCT outcome. Ann Hematol 2015;94:1891-1897. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26220759.

326. Hansen JA, Gooley TA, Martin PJ, et al. Bone marrow transplants from unrelated donors for patients with chronic myeloid leukemia. N Engl J Med 1998;338:962-968. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9521984.

327. Davies SM, DeFor TE, McGlave PB, et al. Equivalent outcomes in patients with chronic myelogenous leukemia after early transplantation of phenotypically matched bone marrow from related or unrelated donors. Am J Med 2001;110:339-346. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11286947.

328. Crawley C, Szydlo R, Lalancette M, et al. Outcomes of reduced-intensity transplantation for chronic myeloid leukemia: an analysis of prognostic factors from the Chronic Leukemia Working Party of the EBMT. Blood 2005;106:2969-2976. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15998838.

329. Or R, Shapira MY, Resnick I, et al. Nonmyeloablative allogeneic stem cell transplantation for the treatment of chronic myeloid leukemia in first chronic phase. Blood 2003;101:441-445. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12393604.

330. Faber E, Koza V, Vitek A, et al. Reduced-intensity conditioning for allogeneic stem cell transplantation in patients with chronic myeloid leukemia is associated with better overall survival but inferior disease-free survival when compared with myeloablative conditioning - a retrospective study of the Czech National Hematopoietic Stem Cell Transplantation Registry. Neoplasma 2007;54:443-446. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17688375.

331. Kebriaei P, Detry MA, Giralt S, et al. Long-term follow-up of allogeneic hematopoietic stem-cell transplantation with reduced-intensity conditioning for patients with chronic myeloid leukemia. Blood 2007;110:3456-3462. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17652620.

332. Warlick E, Ahn KW, Pedersen TL, et al. Reduced intensity conditioning is superior to nonmyeloablative conditioning for older chronic myelogenous leukemia patients undergoing hematopoietic cell transplant during the tyrosine kinase inhibitor era. Blood 2012;119:4083-4090. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22408257.

333. Velev N, Cortes J, Champlin R, et al. Stem cell transplantation for patients with chronic myeloid leukemia resistant to tyrosine kinase inhibitors with BCR-ABL kinase domain mutation T315I. Cancer 2010;116:3631-3637. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20564073.

334. Jabbour E, Cortes J, Santos FP, et al. Results of allogeneic hematopoietic stem cell transplantation for chronic myelogenous leukemia patients who failed tyrosine kinase inhibitors after developing BCR-ABL1 kinase domain mutations. Blood 2011;117:3641-3647. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21156844.

335. Nicolini FE, Basak GW, Soverini S, et al. Allogeneic stem cell transplantation for patients harboring T315I BCR-ABL mutated leukemias. Blood 2011;118:5697-5700. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21926354.

336. Nair AP, Barnett MJ, Broady RC, et al. Allogeneic hematopoietic stem cell transplantation is an effective salvage therapy for patients with chronic myeloid leukemia presenting with advanced disease or failing treatment with tyrosine kinase inhibitors. Biol Blood Marrow Transplant 2015;21:1437-1444. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25865648.

337. Gratwohl A, Hermans J, Goldman JM, et al. Risk assessment for patients with chronic myeloid leukaemia before allogeneic blood or marrow transplantation. Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. Lancet 1998;352:1087-1092. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9798583.

338. Pavlu J, Kew AK, Taylor-Roberts B, et al. Optimizing patient selection for myeloablative allogeneic hematopoietic cell transplantation in chronic myeloid leukemia in chronic phase. Blood 2010;115:4018-4020. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20304808.

339. Horowitz MM, Rowlings PA, Passweg JR. Allogeneic bone marrow transplantation for CML: a report from the International Bone Marrow Transplant Registry. Bone Marrow Transplant 1996;17 Suppl 3:S5-6. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8769690.

340. Gratwohl A, Brand R, Apperley J, et al. Allogeneic hematopoietic stem cell transplantation for chronic myeloid leukemia in Europe 2006: transplant activity, long-term data and current results. An analysis by the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT). Haematologica 2006;91:513-521. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16533723.

341. Goldman JM, Majhail NS, Klein JP, et al. Relapse and late mortality in 5-year survivors of myeloablative allogeneic hematopoietic cell transplantation for chronic myeloid leukemia in first chronic phase. J Clin Oncol 2010;28:1888-1895. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20212247.

342. Saussele S, Lauseker M, Gratwohl A, et al. Allogeneic hematopoietic stem cell transplantation (allo SCT) for chronic myeloid leukemia in the imatinib era: evaluation of its impact within a subgroup of the randomized German CML Study IV. Blood 2010;115:1880-1885. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19965667.

343. Boehm A, Walcherberger B, Sperr WR, et al. Improved outcome in patients with chronic myeloid leukemia after allogeneic hematopoietic stem cell transplantation over the past 25 years: A single center experience. Biol Blood Marrow Transplant 2011 17:133-140. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20601032.

344. Khoury HJ, Kukreja M, Goldman JM, et al. Prognostic factors for outcomes in allogeneic transplantation for CML in the imatinib era: a CIBMTR analysis. Bone Marrow Transplant 2012;47:810-816. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21986636.

345. Delage R, Soiffer R, Dear K, Ritz J. Clinical significance of bcr-abl gene rearrangement detected by polymerase chain reaction after allogeneic bone marrow transplantation in chronic myelogenous leukemia. Blood 1991;78:2759-2767. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1824268.

346. Roth M, Antin J, Ash R, et al. Prognostic significance of Philadelphia chromosome-positive cells detected by the polymerase chain reaction after allogeneic bone marrow transplant for chronic myelogenous leukemia. Blood 1992;79:276-282. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1728316.

347. van Rhee F, Lin F, Cross NC, et al. Detection of residual leukaemia more than 10 years after allogeneic bone marrow transplantation for chronic myelogenous leukaemia. Bone Marrow Transplant 1994;14:609-612. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7858536.

348. Radich JP, Gehly G, Gooley T, et al. Polymerase chain reaction detection of the BCR-ABL fusion transcript after allogeneic marrow transplantation for chronic myeloid leukemia: results and implications in 346 patients. Blood 1995;85:2632-2638. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7727789.

349. Costello RT, Kirk J, Gabert J. Value of PCR analysis for long term survivors after allogeneic bone marrow transplant for chronic myelogenous leukemia: a comparative study. Leuk Lymphoma 1996;20:239-243. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8624462.

350. Mackinnon S, Barnett L, Heller G. Polymerase chain reaction is highly predictive of relapse in patients following T cell-depleted allogeneic bone marrow transplantation for chronic myeloid leukemia. Bone Marrow

Transplant 1996;17:643-647. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8722369.

351. Olavarria E, Kanfer E, Szydlo R, et al. Early detection of BCR-ABL transcripts by quantitative reverse transcriptase-polymerase chain reaction predicts outcome after allogeneic stem cell transplantation for chronic myeloid leukemia. Blood 2001;97:1560-1565. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11238091.

352. Radich JP, Gooley T, Bryant E, et al. The significance of bcr-abl molecular detection in chronic myeloid leukemia patients "late," 18 months or more after transplantation. Blood 2001;98:1701-1707. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11535500.

353. Kolb HJ, Schattenberg A, Goldman JM, et al. Graft-versus-leukemia effect of donor lymphocyte transfusions in marrow grafted patients. Blood 1995;86:2041-2050. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7655033.

354. Dazzi F, Szydlo RM, Cross NC, et al. Durability of responses following donor lymphocyte infusions for patients who relapse after allogeneic stem cell transplantation for chronic myeloid leukemia. Blood 2000;96:2712-2716. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11023502.

355. Luznik L, Fuchs EJ. Donor lymphocyte infusions to treat hematologic malignancies in relapse after allogeneic blood or marrow transplantation. Cancer Control 2002;9:123-137. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11965233.

356. Michallet AS, Nicolini F, Furst S, et al. Outcome and long-term follow-up of alloreactive donor lymphocyte infusions given for relapse after myeloablative allogeneic hematopoietic stem cell transplantations (HSCT). Bone Marrow Transplant 2005;35:601-608. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15756285.

357. Weisser M, Tischer J, Schnittger S, et al. A comparison of donor lymphocyte infusions or imatinib mesylate for patients with chronic myelogenous leukemia who have relapsed after allogeneic stem cell transplantation. Haematologica 2006;91:663-666. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16627251.

358. Chalandon Y, Passweg JR, Guglielmi C, et al. Early administration of donor lymphocyte infusions upon molecular relapse after allogeneic hematopoietic stem cell transplantation for chronic myeloid leukemia: a study by the Chronic Malignancies Working Party of the EBMT. Haematologica 2014;99:1492-1498. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24997146.

359. Schmidt S, Liu Y, Hu ZH, et al. The Role of Donor Lymphocyte Infusion (DLI) in Post-Hematopoietic Cell Transplant (HCT) Relapse for Chronic Myeloid Leukemia (CML) in the Tyrosine Kinase Inhibitor (TKI) Era. Biol Blood Marrow Transplant 2020;26:1137-1143. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32062061.

360. Dazzi F, Szydlo RM, Craddock C, et al. Comparison of single-dose and escalating-dose regimens of donor lymphocyte infusion for relapse after allografting for chronic myeloid leukemia. Blood 2000;95:67-71. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10607686.

361. Shimoni A, Gajewski JA, Donato M, et al. Long-Term follow-up of recipients of CD8-depleted donor lymphocyte infusions for the treatment of chronic myelogenous leukemia relapsing after allogeneic progenitor cell transplantation. Biol Blood Marrow Transplant 2001;7:568-575. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11760089.

362. Gilleece MH, Dazzi F. Donor lymphocyte infusions for patients who relapse after allogeneic stem cell transplantation for chronic myeloid leukaemia. Leuk Lymphoma 2003;44:23-28. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12691139.

363. Posthuma EFM, Marijt EWAF, Barge RMY, et al. Alpha-interferon with very-low-dose donor lymphocyte infusion for hematologic or cytogenetic relapse of chronic myeloid leukemia induces rapid and durable complete remissions and is associated with acceptable graft-versus-host disease. Biol Blood Marrow Transplant 2004;10:204-212. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14993886.

364. Simula MP, Marktel S, Fozza C, et al. Response to donor lymphocyte infusions for chronic myeloid leukemia is dose-dependent: the importance of escalating the cell dose to maximize therapeutic efficacy. Leukemia 2007;21:943-948. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17361226.

365. Kantarjian HM, O'Brien S, Cortes JE, et al. Imatinib mesylate therapy for relapse after allogeneic stem cell transplantation for chronic myelogenous leukemia. Blood 2002;100:1590-1595. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12176876.

366. Olavarria E, Ottmann OG, Deininger M, et al. Response to imatinib in patients who relapse after allogeneic stem cell transplantation for chronic myeloid leukemia. Leukemia 2003;17:1707-1712. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12970768.

367. Anderlini P, Sheth S, Hicks K, et al. Re: Imatinib mesylate administration in the first 100 days after stem cell transplantation. Biol Blood Marrow Transplant 2004;10:883-884. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15570257.

368. DeAngelo DJ, Hochberg EP, Alyea EP, et al. Extended follow-up of patients treated with imatinib mesylate (gleevec) for chronic myelogenous leukemia relapse after allogeneic transplantation: durable cytogenetic remission and conversion to complete donor chimerism without graft-versus-host disease. Clin Cancer Res 2004;10:5065-5071. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15297408.

369. Hess G, Bunjes D, Siegert W, et al. Sustained complete molecular remissions after treatment with imatinib-mesylate in patients with failure after allogeneic stem cell transplantation for chronic myelogenous leukemia: results of a prospective phase II open-label multicenter study. J Clin Oncol 2005;23:7583-7593. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16234522.

370. Palandri F, Amabile M, Rosti G, et al. Imatinib therapy for chronic myeloid leukemia patients who relapse after allogeneic stem cell transplantation: a molecular analysis. Bone Marrow Transplant 2007;39:189-191. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17211436.

371. Conchon M, Sanabani SS, Bendit I, et al. The use of imatinib mesylate as a lifesaving treatment of chronic myeloid leukemia relapse after bone marrow transplantation. J Transplant 2009;2009:357093-357093. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20107580.

372. Wright MP, Shepherd JD, Barnett MJ, et al. Response to tyrosine kinase inhibitor therapy in patients with chronic myelogenous leukemia relapsing in chronic and advanced phase following allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 2010;16:639-646. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20005967.

373. Breccia M, Cannella L, Stefanizzi C, et al. Efficacy of dasatinib in a chronic myeloid leukemia patient with disease molecular relapse and chronic GVHD after haploidentical BMT: an immunomodulatory effect? Bone Marrow Transplant 2009;44:331-332. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19219075.

374. Klyuchnikov E, Schafhausen P, Kroger N, et al. Second-generation tyrosine kinase inhibitors in the post-transplant period in patients with chronic myeloid leukemia or Philadelphia-positive acute lymphoblastic leukemia. Acta Haematol 2009;122:6-10. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19602874.

375. Reinwald M, Schleyer E, Kiewe P, et al. Efficacy and pharmacologic data of second-generation tyrosine kinase inhibitor nilotinib in BCR-ABL-positive leukemia patients with central nervous system relapse after allogeneic stem cell transplantation. Biomed Res Int 2014;2014:637059. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25025064.

376. Shimoni A, Volchek Y, Koren-Michowitz M, et al. Phase 1/2 study of nilotinib prophylaxis after allogeneic stem cell transplantation in patients with advanced chronic myeloid leukemia or Philadelphia chromosome-positive acute lymphoblastic leukemia. Cancer 2015;121:863-871. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25387866.

377. Savani BN, Montero A, Kurlander R, et al. Imatinib synergizes with donor lymphocyte infusions to achieve rapid molecular remission of CML relapsing after allogeneic stem cell transplantation. Bone Marrow Transplant 2005;36:1009-1015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16205732.

378. Shanavas M, Messner HA, Kamel-Reid S, et al. A comparison of long-term outcomes of donor lymphocyte infusions and tyrosine kinase inhibitors in patients with relapsed CML after allogeneic hematopoietic cell transplantation. Clin Lymphoma Myeloma Leuk 2014;14:87-92. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24252361.

379. Zeidner JF, Zahurak M, Rosner GL, et al. The evolution of treatment strategies for patients with chronic myeloid leukemia relapsing after allogeneic bone marrow transplant: can tyrosine kinase inhibitors replace donor lymphocyte infusions? Leuk Lymphoma 2015;56:128-134. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24712979.

380. Carpenter PA, Snyder DS, Flowers MED, et al. Prophylactic administration of imatinib after hematopoietic cell transplantation for high-risk Philadelphia chromosome-positive leukemia. Blood 2007;109:2791-2793. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17119111.

381. Olavarria E, Siddique S, Griffiths MJ, et al. Posttransplantation imatinib as a strategy to postpone the requirement for immunotherapy in patients undergoing reduced-intensity allografts for chronic myeloid leukemia. Blood 2007;110:4614-4617. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17881635.

382. DeFilipp Z, Langston AA, Chen Z, et al. Does post-transplant maintenance therapy with tyrosine kinase inhibitors improve outcomes of patients with high-risk Philadelphia chromosome-positive leukemia? Clin Lymphoma Myeloma Leuk 2016;16:466-471 e461. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27297665.

383. Egan DN, Beppu L, Radich JP. Patients with Philadelphia-positive leukemia with BCR-ABL kinase mutations before allogeneic transplantation predominantly relapse with the same mutation. Biol Blood Marrow Transplant 2015;21:184-189. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25300870.

384. Oshima K, Kanda Y, Yamashita T, et al. Central nervous system relapse of leukemia after allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 2008;14:1100-1107. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18804039.

385. Fuchs M, Reinhofer M, Ragoschke-Schumm A, et al. Isolated central nervous system relapse of chronic myeloid leukemia after allogeneic hematopoietic stem cell transplantation. BMC Blood Disord 2012;12:9. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22871019.

386. Ocheni S, Iwanski GB, Schafhausen P, et al. Characterisation of extramedullary relapse in patients with chronic myeloid leukemia in advanced disease after allogeneic stem cell transplantation. Leuk Lymphoma 2009;50:551-558. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19373652.

387. Nishimoto M, Nakamae H, Koh KR, et al. Dasatinib maintenance therapy after allogeneic hematopoietic stem cell transplantation for an isolated central nervous system blast crisis in chronic myelogenous leukemia. Acta Haematol 2013;130:111-114. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23548721.

388. Annunziata M, Bonifacio M, Breccia M, et al. Current strategies and future directions to achieve deep molecular response and treatment-free remission in chronic myeloid leukemia. Front Oncol 2020;10:883. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32582549.

389. Matsushita M. Novel Treatment Strategies Utilizing Immune Reactions against Chronic Myelogenous Leukemia Stem Cells. Cancers (Basel) 2021;13:5435. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34771599.

390. Flygt H, Soderlund S, Stentoft J, et al. Long-term tolerability and efficacy after initial PegIFN-alpha addition to dasatinib in CML-CP: Five-year follow-up of the NordCML007 study. Eur J Haematol 2021;107:617-623. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34418168.

391. Hsieh YC, Kirschner K, Copland M. Improving outcomes in chronic myeloid leukemia through harnessing the immunological landscape. Leukemia 2021;35:1229-1242. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33833387.

392. Hoffmann VS, Baccarani M, Hasford J, et al. The EUTOS population-based registry: incidence and clinical characteristics of 2904 CML patients in 20 European Countries. Leukemia 2015;29:1336-1343. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25783795.

393. Ramasamy K, Hayden J, Lim Z, et al. Successful pregnancies involving men with chronic myeloid leukaemia on imatinib therapy. Br J Haematol 2007;137:374-375. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17408403.

394. Breccia M, Cannella L, Montefusco E, et al. Male patients with chronic myeloid leukemia treated with imatinib involved in healthy

pregnancies: report of five cases. Leuk Res 2008;32:519-520. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17804066.

395. Oweini H, Otrock ZK, Mahfouz RAR, Bazarbachi A. Successful pregnancy involving a man with chronic myeloid leukemia on dasatinib. Arch Gynecol Obstet 2011;283:133-134. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20473616.

396. Ghalaut VS, Prakash G, Bansal P, et al. Effect of imatinib on male reproductive hormones in BCR-ABL positive CML patients: A preliminary report. J Oncol Pharm Pract 2014;20:243-248. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23966360.

397. Alizadeh H, Jaafar H, Rajnics P, et al. Outcome of pregnancy in chronic myeloid leukaemia patients treated with tyrosine kinase inhibitors: short report from a single centre. Leuk Res 2015;39:47-51. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25455655.

398. Pye SM, Cortes J, Ault P, et al. The effects of imatinib on pregnancy outcome. Blood 2008;111:5505-5508. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18322153.

399. Cortes JE, Abruzzese E, Chelysheva E, et al. The impact of dasatinib on pregnancy outcomes. Am J Hematol 2015;90:1111-1115. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26348106.

400. Barkoulas T, Hall PD. Experience with dasatinib and nilotinib use in pregnancy. J Oncol Pharm Pract 2018;24:121-128. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29284357.

401. Salem W, Li K, Krapp C, et al. Imatinib treatments have long-term impact on placentation and embryo survival. Sci Rep 2019;9:2535. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30796277.

402. Madabhavi I, Sarkar M, Modi M, Kadakol N. Pregnancy Outcomes in Chronic Myeloid Leukemia: A Single Center Experience. J Glob Oncol 2019;5:1-11. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31584851.

403. Cortes JE, Gambacorti-Passerini C, Deininger M, et al. Pregnancy outcomes in patients treated with bosutinib. Int J Hematol Oncol 2020;9:IJH26. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33005329.

404. Assi R, Kantarjian H, Keating M, et al. Management of chronic myeloid leukemia during pregnancy among patients treated with a tyrosine kinase inhibitor: a single-Center experience. Leuk Lymphoma 2021;62:909-917. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33283580.

405. Ault P, Kantarjian H, O'Brien S, et al. Pregnancy among patients with chronic myeloid leukemia treated with imatinib. J Clin Oncol 2006;24:1204-1208. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16446320.

406. Kuwabara A, Babb A, Ibrahim A, et al. Poor outcome after reintroduction of imatinib in patients with chronic myeloid leukemia who interrupt therapy on account of pregnancy without having achieved an optimal response. Blood 2010;116:1014-1016. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20705771.

407. Berman E. Family Planning and Pregnancy in Patients with Chronic Myeloid Leukemia. Curr Hematol Malig Rep 2023;18:33-39. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36763239.

408. Kondo T, Matsuki E, Takaku T, et al. Outcomes of pregnancy in patients with chronic myeloid leukemia in the era of tyrosine kinase inhibitors. Cancer 2025;131:e35611. Available at: https://www.ncbi.nlm.nih.gov/pubmed/39475400.

409. Lasica M, Willcox A, Burbury K, et al. The effect of tyrosine kinase inhibitor interruption and interferon use on pregnancy outcomes and long-term disease control in chronic myeloid leukemia. Leuk Lymphoma 2019;60:1796-1802. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30632843.

410. Stella S, Tirro E, Massimino M, et al. Successful Management of a Pregnant Patient With Chronic Myeloid Leukemia Receiving Standard Dose Imatinib. In Vivo 2019;33:1593-1598. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31471409.

411. Ali R, Ozkalemkas F, Ozkocaman V, et al. Successful pregnancy and delivery in a patient with chronic myelogenous leukemia (CML), and management of CML with leukapheresis during pregnancy: a case report and review of the literature. Jpn J Clin Oncol 2004;34:215-217. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15121759.

412. Koh LP, Kanagalingam D. Pregnancies in patients with chronic myeloid leukemia in the era of imatinib. Int J Hematol 2006;84:459-462. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17189230.

413. Palani R, Milojkovic D, Apperley JF. Managing pregnancy in chronic myeloid leukaemia. Ann Hematol 2015;94 Suppl 2:S167-176. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25814083.

414. Staley EM, Simmons SC, Feldman AZ, et al. Management of chronic myeloid leukemia in the setting of pregnancy: when is leukocytapheresis appropriate? A case report and review of the literature. Transfusion 2018;58:456-460. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29230832.

415. James AH, Brancazio LR, Price T. Aspirin and reproductive outcomes. Obstet Gynecol Surv 2008;63:49-57. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18081940.

416. Deruelle P, Coulon C. The use of low-molecular-weight heparins in pregnancy--how safe are they? Curr Opin Obstet Gynecol 2007;19:573-577. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18007136.

417. Baykal C, Zengin N, Coskun F, et al. Use of hydroxyurea and alpha-interferon in chronic myeloid leukemia during pregnancy: a case report. Eur J Gynaecol Oncol 2000;21:89-90. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10726630.

418. Thauvin-Robinet C, Maingueneau C, Robert E, et al. Exposure to hydroxyurea during pregnancy: a case series. Leukemia 2001;15:1309-1311. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11480579.

419. Fadilah SA, Ahmad-Zailani H, Soon-Keng C, Norlaila M. Successful treatment of chronic myeloid leukemia during pregnancy with hydroxyurea. Leukemia 2002;16:1202-1203. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12040456.

420. Beauverd Y, Radia D, Cargo C, et al. Pegylated interferon alpha-2a for essential thrombocythemia during pregnancy: outcome and safety. A case series. Haematologica 2016;101:e182-184. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26819057.

421. Balsat M, Etienne M, Elhamri M, et al. Successful pregnancies in patients with BCR-ABL-positive leukemias treated with interferon-alpha therapy during the tyrosine kinase inhibitors era. Eur J Haematol 2018;101:774-780. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30179268.

422. Schrickel L, Heidel FH, Sadjadian P, et al. Interferon alpha for essential thrombocythemia during 34 high-risk pregnancies: outcome and safety. J Cancer Res Clin Oncol 2021;147:1481-1491. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33140210.

423. Burchert A, Muller MC, Kostrewa P, et al. Sustained molecular response with interferon alfa maintenance after induction therapy with imatinib plus interferon alfa in patients with chronic myeloid leukemia. J Clin Oncol 2010;28:1429-1435. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20142590.

424. Chelysheva E, Apperley J, Turkina A, et al. Chronic myeloid leukemia diagnosed in pregnancy: management and outcome of 87 patients reported to the European LeukemiaNet international registry. Leukemia 2024;38:788-795. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38388649.

425. Russell MA, Carpenter MW, Akhtar MS, et al. Imatinib mesylate and metabolite concentrations in maternal blood, umbilical cord blood, placenta and breast milk. J Perinatol 2007;27:241-243. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17377606.

426. Ali R, Ozkalemkas F, Kimya Y, et al. Imatinib use during pregnancy and breast feeding: a case report and review of the literature. Arch Gynecol Obstet 2009;280:169-175. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19083009.

427. Drugs and Lactation Database (LactMed) [Internet]. Bethesda (MD): National Library of Medicine (US); 2006-. Available at: https://www.ncbi.nlm.nih.gov/books/NBK501922/.

428. Chelysheva E, Aleshin S, Polushkina E, et al. Breastfeeding in patients with chronic myeloid leukaemia: Case series with measurements of drug concentrations in maternal milk and literature review. Mediterr J Hematol Infect Dis 2018;10:e2018027. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29755704.

429. Abruzzese E, Trawinska MM, Perrotti AP, De Fabritiis P. Tyrosine kinase inhibitors and pregnancy. Mediterr J Hematol Infect Dis 2014;6:e2014028. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24804001.

430. Yoshikawa T, Ishida H, Watanabe A, et al. Favorable outcomes of de novo advanced phases of pediatric chronic myeloid leukemia in the tyrosine kinase inhibitor era. Int J Hematol 2025. Available at: https://www.ncbi.nlm.nih.gov/pubmed/40088374.

431. Hijiya N, Suttorp M. How I treat chronic myeloid leukemia in children and adolescents. Blood 2019;133:2374-2384. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30917954.

432. Gore L, Kearns PR, de Martino ML, et al. Dasatinib in pediatric patients with chronic myeloid leukemia in chronic phase: Results from a phase II trial. J Clin Oncol 2018;36:1330-1338. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29498925.

433. Suttorp M, Schulze P, Glauche I, et al. Front-line imatinib treatment in children and adolescents with chronic myeloid leukemia: results from a phase III trial. Leukemia 2018;32:1657-1669. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29925908.

434. Hijiya N, Maschan A, Rizzari C, et al. A phase 2 study of nilotinib in pediatric patients with CML: long-term update on growth retardation and safety. Blood Adv 2021;5:2925-2934. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34309636.

435. Millot F, Guilhot J, Nelken B, et al. Imatinib mesylate is effective in children with chronic myelogenous leukemia in late chronic and advanced phase and in relapse after stem cell transplantation. Leukemia 2006;20:187-192. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16341042.

436. Champagne MA, Fu CH, Chang M, et al. Higher dose imatinib for children with de novo chronic phase chronic myelogenous leukemia: a report from the Children's Oncology Group. Pediatr Blood Cancer 2011;57:56-62. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21465636.

437. Giona F, Putti MC, Micalizzi C, et al. Long-term results of high-dose imatinib in children and adolescents with chronic myeloid leukaemia in chronic phase: the Italian experience. Br J Haematol 2015;170:398-407. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25891192.

438. Nickel RS, Daves M, Keller F. Treatment of an adolescent with chronic myeloid leukemia and the T315I mutation with ponatinib. Pediatr Blood Cancer 2015;62:2050-2051. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25939962.

439. Gurrea Salas D, Glauche I, Tauer JT, et al. Can prognostic scoring systems for chronic myeloid leukemia as established in adults be applied to pediatric patients? Ann Hematol 2015;94:1363-1371. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25894600.

440. Millot F, Guilhot J, Suttorp M, et al. Prognostic discrimination based on the EUTOS long-term survival score within the International Registry for Chronic Myeloid Leukemia in children and adolescents. Haematologica 2017;102:1704-1708. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28838993.

441. Samis J, Lee P, Zimmerman D, et al. Recognizing endocrinopathies associated with tyrosine kinase inhibitor therapy in children with chronic myelogenous leukemia. Pediatr Blood Cancer 2016;63:1332-1338. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27100618.

442. Suttorp M, Millot F. Treatment of pediatric chronic myeloid leukemia in the year 2010: use of tyrosine kinase inhibitors and stem-cell transplantation. Hematology Am Soc Hematol Educ Program 2010;2010:368-376. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21239821.

443. Shima H, Tokuyama M, Tanizawa A, et al. Distinct impact of imatinib on growth at prepubertal and pubertal ages of children with chronic myeloid leukemia. J Pediatr 2011;159:676-681. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21592517.

444. Bansal D, Shava U, Varma N, et al. Imatinib has adverse effect on growth in children with chronic myeloid leukemia. Pediatr Blood Cancer 2012;59:481-484. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22052850.

445. Rastogi MV, Stork L, Druker B, et al. Imatinib mesylate causes growth deceleration in pediatric patients with chronic myelogenous leukemia. Pediatr Blood Cancer 2012;59:840-845. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22378641.

446. Narayanan KR, Bansal D, Walia R, et al. Growth failure in children with chronic myeloid leukemia receiving imatinib is due to disruption of GH/IGF-1 axis. Pediatr Blood Cancer 2013;60:1148-1153. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23322583.

447. Boddu D, Thankamony P, Guruprasad CS, et al. Effect of imatinib on growth in children with chronic myeloid leukemia. Pediatr Hematol Oncol 2019;36:189-197. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31298597.

448. Sabnis HS, Keenum C, Lewis RW, et al. Growth disturbances in children and adolescents receiving long-term tyrosine kinase inhibitor therapy for Chronic Myeloid Leukaemia or Philadelphia Chromosome-positive Acute Lymphoblastic Leukaemia. Br J Haematol 2019;185:795-799. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30407613.

449. de Bruijn CMA, Millot F, Suttorp M, et al. Discontinuation of imatinib in children with chronic myeloid leukaemia in sustained deep molecular remission: results of the STOP IMAPED study. Br J Haematol 2019;185:718-724. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30843196.

450. Millot F, Suttorp M, Ragot S, et al. Discontinuation of imatinib in children with chronic myeloid leukemia: A study from the international registry of childhood CML. Cancers (Basel) 2021;13:4102. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34439257.

451. Roy Moulik N, Keerthivasagam S, Chatterjee G, et al. Treatment-Free Remissions in Children With Chronic Myeloid Leukemia (CML): A Prospective Study From the Tata Memorial Hospital (TMH) Pediatric CML (pCML) Cohort. Am J Hematol 2025;100:210-217. Available at: https://www.ncbi.nlm.nih.gov/pubmed/39568222.

452. de Lavallade H, Garland P, Sekine T, et al. Repeated vaccination is required to optimize seroprotection against H1N1 in the immunocompromised host. Haematologica 2011;96:307-314. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20971824.

453. de Lavallade H, Khoder A, Hart M, et al. Tyrosine kinase inhibitors impair B-cell immune responses in CML through off-target inhibition of kinases important for cell signaling. Blood 2013;122:227-238. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23719297.

454. Suttorp M, Webster Carrion A, Hijiya N. Chronic Myeloid Leukemia in Children: Immune Function and Vaccinations. J Clin Med 2021;10:4056. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34575167.

455. Bettoni da Cunha-Riehm C, Hildebrand V, Nathrath M, et al. Vaccination with live attenuated vaccines in four children with chronic myeloid leukemia while on imatinib treatment. Front Immunol 2020;11:628. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32362894.

456. Hijiya N, Millot F, Suttorp M. Chronic myeloid leukemia in children: clinical findings, management, and unanswered questions. Pediatr Clin North Am 2015;62:107-119. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25435115.

457. Creech CB, Walker SC, Samuels RJ. SARS-CoV-2 Vaccines. JAMA 2021;325:1318-1320. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33635317.

458. Chowdhury O, Bruguier H, Mallett G, et al. Impaired antibody response to COVID-19 vaccination in patients with chronic myeloid neoplasms. Br J Haematol 2021;194:1010-1015. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34132395.

459. Greenberger LM, Saltzman LA, Senefeld JW, et al. Antibody response to SARS-CoV-2 vaccines in patients with hematologic malignancies. Cancer Cell 2021;39:1031-1033. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34331856.

460. Harrington P, Doores KJ, Radia D, et al. Single dose of BNT162b2 mRNA vaccine against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) induces neutralising antibody and polyfunctional T-cell responses in patients with chronic myeloid leukaemia. Br J Haematol 2021;194:999-1006. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34085278.

461. Harrington P, Harrison CN, Dillon R, et al. Evidence of robust memory T-cell responses in patients with chronic myeloproliferative

neoplasms following infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Br J Haematol 2021;193:692-696. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33719038.

462. Do YR, Kwak JY, Kim JA, et al. Long-term data from a phase 3 study of radotinib versus imatinib in patients with newly diagnosed, chronic myeloid leukaemia in the chronic phase (RERISE). Br J Haematol 2020;189:303-312. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32012231.

463. Zhang L, Meng L, Liu B, et al. Flumatinib versus Imatinib for Newly Diagnosed Chronic Phase Chronic Myeloid Leukemia: A Phase III, Randomized, Open-label, Multi-center FESTnd Study. Clin Cancer Res 2021;27:70-77. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32928796.

464. Kim SH, Menon H, Jootar S, et al. Efficacy and safety of radotinib in chronic phase chronic myeloid leukemia patients with resistance or intolerance to BCR-ABL1 tyrosine kinase inhibitors. Haematologica 2014;99:1191-1196. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24705186.

465. Jiang Q, Li Z, Qin Y, et al. Olverembatinib (HQP1351), a well-tolerated and effective tyrosine kinase inhibitor for patients with T315I-mutated chronic myeloid leukemia: results of an open-label, multicenter phase 1/2 trial. J Hematol Oncol 2022;15:113. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35982483.

466. Cortes JE, Kim DW, Saikia T, et al. Vodobatinib for patients with Philadelphia chromosome-positive chronic myeloid leukaemia resistant or intolerant to multiple lines of previous therapy: an open-label, multicentre, phase 1/2 trial. Lancet Haematol 2025;12:e201-e213. Available at: https://www.ncbi.nlm.nih.gov/pubmed/39929221.