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REVIEW ARTICLE

Three generations of targeted therapies in chronic myeloid leukemia: Molecular advances, adverse effects, therapeutic challenges, and future perspectives

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Abstract

Introduction: The therapeutic landscape of chronic myeloid leukemia (CML) represents a paradigm of precision oncology, evolving across multiple generations of targeted breakpoint cluster region–Abelson murine leukemia viral oncogene homolog 1 tyrosine kinase inhibitors. As survival approaches that of the general population, long-term care requires balancing drug efficacy with safety, sequencing optimization, and survivorship considerations.

Objectives: This review aims to evaluate modern CML management strategies, including drug mechanisms, resistance mutations, toxicity profiles, treatment sequencing, and criteria for treatment discontinuation.

Methods: Literature was retrieved up to June 2026 using databases indexing landmark phase I–III trials, European LeukemiaNet guidelines, and regulatory data. Evidence was synthesized thematically across adult chronic-phase CML management strategies to evaluate drug mechanisms, resistance mutations, organ-specific toxicities, and treatment discontinuation criteria.

Results: First-generation imatinib provides a well-characterized safety profile but is associated with slower response kinetics. Second-generation agents (e.g., dasatinib, nilotinib, bosutinib) achieve deeper molecular responses but present distinct, non-overlapping toxicities—including pleural, vascular, metabolic, and gastrointestinal complications—and remain vulnerable to the T315I gatekeeper mutation. Third-generation ponatinib and the newly approved allosteric inhibitor asciminib, which specifically targets the ABL myristoyl pocket, provide effective options for salvage-resistant disease, though they necessitate proactive cardiovascular and metabolic risk mitigation. Standardized molecular monitoring remains essential to distinguish true resistance from nonadherence and to guide mutation-directed sequencing.

Conclusion: Modern CML management has transitioned from uniform kinase

inhibition toward highly individualized survivorship. Optimizing long-term quality of life relies on aligning tyrosine kinase inhibitor selection with patient-specific comorbidities, implementing response-adjusted dosing, and utilizing well-defined clinical parameters to safely evaluate candidates for treatment-free remission.

Keywords: Chronic myeloid leukemia; Philadelphia chromosome; Breakpoint cluster region–Abelson murine leukemia viral oncogene homolog 1 fusion protein; Tyrosine kinase inhibitors; Imatinib

1. Introduction

Chronic myeloid leukemia (CML) is a clonal myeloproliferative neoplasm driven in almost all cases by the Philadelphia chromosome (Ph-chromosome), a reciprocal translocation between chromosomes 9 and 22 that generates the breakpoint cluster region–Abelson murine leukemia viral oncogene homolog 1 (*BCR::ABL1*) fusion gene.[1,2] The discovery of this cytogenetic abnormality and its molecular consequence established one of the clearest links between a cancer-defining lesion and a therapeutically actionable target.[1,2] The BCR::ABL1 fusion protein exhibits constitutive tyrosine kinase activity, activating downstream proliferative, anti-apoptotic, adhesive, and genomic instability pathways, including RAS/mitogen-activated protein kinase, phosphoinositide 3-kinase/protein kinase B, and Janus kinase and signal transducer and activator of transcription signaling networks.[3,4]

Clinically, CML is most often diagnosed in chronic phase, when patients may present with leukocytosis, thrombocytosis, basophilia, splenomegaly, fatigue, weight loss, night sweats, abdominal fullness, or incidental abnormalities on complete blood count. Without effective therapy, the disease progresses to accelerated and blast phases, marked by additional genetic and epigenetic changes, reduced dependence on BCR::ABL1 kinase activity, and poorer outcomes. This biology underscores the importance of early recognition, accurate molecular diagnosis, and timely initiation of therapy.[5-7]

The Ph-chromosome established CML as having a unique place in cancer biology as one of the first reproducible chromosomal abnormalities linked to a specific malignancy. Identification of BCR::ABL1 established the link between cytogenetics, molecular pathogenesis, and targeted pharmacology in a single disease model, making CML a proof-of-principle disorder for cancer cytogenetics, oncogene addiction, rational kinase inhibition, and molecular monitoring. Before targeted therapy, treatment relied on busulfan, hydroxyurea, interferon (IFN)-α, cytarabine, and transplantation, which improved hematologic parameters but rarely prevented progression. The advent of BCR::ABL1 tyrosine kinase inhibitors (TKIs) transformed outcomes, shifting goals from survival alone to rapid molecular response, avoidance of progression, minimization of toxicity, preservation of quality of life, pregnancy planning, and treatment-free remission (TFR).[7]

Population-based studies show survival in chronic-phase CML approaching that of the general population in high-resource settings, contingent on early diagnosis, continuous therapy, standardized monitoring, and access to salvage options.[8-10] CML thus represents both a landmark achievement in targeted oncology and a paradigm for the longterm management challenges that arise when a oncefatal malignancy is transformed into a chronic disease.

Although survival outcomes have improved, management remains complex. Patients often require longterm or lifelong exposure to TKIs, which makes chronic adverse effects, adherence, drug–drug interactions, comorbidities, insurance coverage, and access to laboratory monitoring critical determinants of prognosis. A patient achieving deep molecular remission may still experience clinically significant harm if persistent edema, diarrhea, fatigue, pleural effusion, vascular complications, or unaffordable copayments undermine quality of life. Conversely, individuals receiving older or less potent TKIs can fare well provided the therapy is tolerable, affordable, and consistently administered with reliable molecular followup. These realworld factors are especially relevant in a setting where multiple effective agents exist but differ markedly in toxicity profiles, cost, dosing schedules, and monitoring requirements.[11-14]

The therapeutic landscape now spans three generations: imatinib as the first adenosine triphosphate (ATP)-competitive inhibitor, dasatinib, nilotinib, and bosutinib as second-generation agents, and ponatinib and asciminib as third-generation and next-generation therapies.[15,16] Each generation expanded the clinical vocabulary of CML management, from durable disease suppression to

rapid molecular responses, resistance coverage, and novel mechanisms.[17-22]

Modern CML care is therefore defined not only by drug efficacy but by dynamic sequencing, patient-centered goals, and survivorship considerations. This review examines molecular advances, adverse effects, therapeutic challenges, and future perspectives, emphasizing that effective management requires balancing biology, toxicity, patient preference, comorbidities, affordability, and long-term management optimization. In this context, the present review adopts a sequential clinical framework to capture the evolution of CML therapy. It begins with the molecular foundations of the disease and the monitoring milestones that shape contemporary management, then traces the progression of first-, second-, and third-generation TKIs, highlighting how resistance mechanisms have driven the development of newer agents. Finally, it synthesizes the practical challenges of modern care, emphasizing personalized toxicity risk mitigation, barriers to implementation, and the criteria for safe TFR. By bridging laboratory discovery with long-term survivorship strategies, this structure reflects the dynamic, lifelong sequencing decisions that define clinical practice today.

2. Methods

This review provides a comprehensive narrative synthesis of targeted therapies for adult patients with Ph-chromosome–positive chronicphase CML. A narrative synthesis was deliberately chosen because the therapeutic evolution of CML spans laboratory discovery, randomized clinical trials, longterm observational followup, regulatory decisions, survivorship research, and expert recommendations. Unlike a purely statistical metaanalysis, this format allows nuanced discussion of complex clinical dilemmas—such as balancing modest early molecular gains against cumulative vascular risks, counseling patients who prioritize TFR, or selecting therapy when cost and monitoring access are limiting.

To ensure objective coverage, literature was retrieved using search concepts including "chronic myeloid leukemia," "BCR::ABL1," "imatinib," "dasatinib," "nilotinib," "bosutinib," "ponatinib," "asciminib," "T315I," "treatmentfree remission," "toxicity," and "European LeukemiaNet (ELN)," supplemented by terms related to monitoring, response depth, adverse events, adherence, quality of life, pregnancy, generic imatinib, and access to care. Evidence was incorporated from landmark phase I–III trials, longterm followup studies, ELN recommendations, regulatory approval summaries, prescribing information, and contemporary reviews addressing resistance, mutation biology, TFR, and emerging strategies.

The review synthesized data thematically to chart sequential clinical decisionmaking from diagnosis to survivorship, with particular focus on firstline selection and laterline sequencing, *T315I*mutated disease, intolerance, cardiovascular risk, and discontinuation. Guideline sources anchored response milestones, monitoring schedules, mutationdirected therapy, adverseevent management, and TFR eligibility, while mechanistic and translational studies explained resistance pathways, stemcell persistence, and the rationale for allosteric inhibition.

Eligibility criteria included adult CML biology, monitoring, TKI efficacy and toxicity, resistance, TFR, and sequencing. Pediatric CML, Ph-chromosome–positive acute lymphoblastic leukemia, nonBCR::ABL1 neoplasms, and supportive care were excluded unless mechanistically relevant. Foundational discoveries since 1960 onward were retained for historical context, while major clinical and regulatory developments through June 2026, including the 2025 ELN recommendations and frontline asciminib trials, were prioritized for treatment selection, toxicity prevention, dose optimization, and nextgeneration therapy. Conflicting or incomplete evidence was highlighted as uncertainty rather than resolved into a single preferred approach, particularly for newer agents, dosereduction strategies, and combinations lacking longterm comparative data.

3. Molecular basis and evolution of targeted therapy

3.1. BCR::ABL1 as the founding target

Chronic myeloid leukemia originates from the transformation of a hematopoietic stem or progenitor cell that acquires the *BCR::ABL1* fusion gene. The resulting protein retains ABL1 kinase activity but loses normal regulatory constraints, producing persistent proliferative and survival signaling that explains the clinical phenotype of leukocytosis, myeloid expansion, splenomegaly, and progression risk if the disease is not controlled. Experimental models established that BCR::ABL1 is not merely associated with CML but can initiate a CML-like myeloproliferative disease, supporting the development of selective ABL kinase inhibition and providing a biological rationale for using molecular response as a surrogate for disease control. Early preclinical work demonstrated that inhibition of BCR::ABL1-positive cells could be achieved without broadly suppressing hematopoiesis, creating a therapeutic window later validated clinically.[23,24]

The molecular clarity of CML enabled the development of therapies that directly suppress the driver lesion, providing proof that a rationally designed small molecule could durably control a human malignancy by inhibiting

a dominant oncogenic kinase. The success of BCR::ABL1 inhibition subsequently influenced targeted drug development across oncology. Nevertheless, BCR::ABL1 operates within a complex cellular ecosystem, where disease behavior reflects not only kinase activity but also stem cell biology, immune surveillance, clonal evolution, pharmacokinetics, adherence, and the bone marrow microenvironment. These factors explain why the same molecular lesion can produce different response kinetics and why treatment decisions must account for patient and disease heterogeneity rather than assuming all chronic-phase CML is biologically identical.

3.2. Molecular monitoring and response milestones

The clinical application of TKIs in CML depends on accurate molecular monitoring. Quantitative reverse transcription polymerase chain reaction (RT-qPCR), standardized to the International Scale (IS), measures BCR::ABL1 transcript burden and guides response assessment. Clinically relevant categories include early molecular response, major molecular response (MMR), defined as BCR::ABL1^{IS} ≤ 0.1%, and deep molecular responses (DMR) such as MR4 and MR4.5.[7] The value of molecular monitoring depends on both analytic quality and clinical interpretation. Laboratories must control pre-analytic variables, transcript type, assay sensitivity, conversion to the IS, reporting of control gene copy number, and turnaround time. Inconsistent testing can lead to unnecessary anxiety, inappropriate drug switching, or delayed recognition of treatment failure, making harmonization efforts and laboratory recommendations as important for modern CML care as drug development itself.[25-27]

Response milestones help identify patients who can continue therapy safely, those requiring closer observation, and those who may need mutation testing or a treatment change. A confirmed BCR::ABL1^{IS} > 10% at three months, failure to achieve lower transcript thresholds over time, loss of MMR, or the emergence of kinase-domain mutations should prompt careful assessment of adherence, drug interactions, intolerance, laboratory quality, disease phase, and alternative therapy.[6,7] Milestones should be interpreted as decision aids rather than rigid substitutes for clinical judgment. A single unexpected polymerase chain reaction (PCR) increase may reflect assay variation or adherence interruption, whereas a confirmed trend is more clinically meaningful. Mutation testing is particularly useful after treatment failure because it distinguishes TKI-resistant clones from nonadherence or intolerance and identifies mutations that favor or discourage specific TKIs (Table 1).[28,29]

3.3. Resistance mechanisms

Resistance to TKIs in CML can be either BCR::ABL1-dependent or BCR::ABL1-independent. BCR::ABL1-dependent resistance includes kinase-domain point

Table 1. Practical molecular monitoring concepts used to interpret response during chronic-phase chronic myeloid leukemia treatment

Time point or status	Typical response concept	Clinical interpretation and action
Baseline	Confirm transcript type and disease phase	Establish the measurable BCR::ABL1 transcript, document chronic phase, calculate risk, and create a reference point for future PCR interpretation[6,7]
3 months	Early molecular response, commonly BCR::ABL1^{IS} ≤ 10%	Failure to reach this level should prompt adherence review, interaction assessment, repeat testing, and consideration of closer follow-up or treatment change if confirmed[6,7]
6–12 months	Continued decline toward cytogenetic and molecular response targets	Persistent high transcript levels or plateauing response may indicate suboptimal exposure, intolerance-related nonadherence, or emerging resistance[6,7]
Any time after response	Sustained deep response, maintenance of MMR and trend stability, MR4 or MR4.5 over time	Loss of MMR, confirmed rising PCR values, or new cytopenias should trigger repeat testing, mutation analysis, and reassessment of disease phase.[28,29] Durable deep response may support discussion of TFR only when monitoring access, patient readiness, and restart plans are reliable[25-27]

Abbreviations: ABL1: Abelson murine leukemia viral oncogene homolog 1; BCR: Breakpoint cluster region; IS: International Scale; MMR: Major molecular response; MR4: Molecular response with log reductions of ≤0.01% BCR::ABL1^{IS}; MR4.5: Molecular response with log reductions of ≤0.0032%; PCR: Polymerase chain reaction; TFR: Treatment-free remission.

mutations, gene amplification, and altered kinase conformation. The T315I gatekeeper mutation is particularly significant because it prevents binding of most first- and second-generation ATP-competitive TKI agents, while compound mutations may further restrict therapeutic options. The clinical importance of kinase-domain mutations became evident during early imatinib treatment, when relapse was linked to *BCR::ABL1* amplification and point mutations that interfered with drug binding. Subsequent mutation catalogs demonstrated that resistance is often polyclonal and dynamic, especially after sequential TKI exposure, making mutation status interpretation dependent on treatment history, disease burden, and the sensitivity of the testing platform.[30-32]

Furthermore, BCR::ABL1-independent mechanisms include altered drug influx or efflux, activation of parallel signaling pathways, clonal evolution, epigenetic changes, bone marrow microenvironmental protection, immune escape, and persistence of quiescent leukemic stem cells.[33,34] These mechanisms explain why kinase inhibition controls CML in most patients but does not eradicate all leukemic clones. Leukemic stem cell persistence is particularly important for future cure strategies, as primitive CML cells may survive despite effective inhibition of bulk BCR::ABL1 signaling. Quiescence, niche interactions, anti-apoptotic pathways, and metabolic adaptation protect these cells from kinase inhibition, creating a residual disease reservoir that necessitates continuous therapy for many patients and explains why TFR is successful only in a subset with sustained deep molecular response.[35,36]

4. First-generation targeted therapy: Imatinib

4.1. Mechanism and clinical impact

Imatinib inhibits the ATP-binding site of BCR::ABL1 when the kinase is in its inactive conformation and also targets KIT (a type III transmembrane receptor tyrosine kinase) and platelet-derived growth factor receptors, contributing to both therapeutic efficacy and adverse-effect profiles. Early clinical studies demonstrated activity in IFN-resistant CML and advanced Ph-chromosome–positive leukemias, followed by the International Randomized Study of IFN and STI571 (IRIS) trial that compared imatinib with IFN-α plus cytarabine in newly diagnosed chronic-phase CML.[37,38] The impact of imatinib extended beyond response rates, transforming patient and clinician expectations by replacing frequent injections, transplantation referral, and high progression anxiety with a daily oral therapy capable of producing durable cytogenetic responses. The IRIS trial also established enduring principles for CML trials, including the importance of molecular response depth, progression to advanced phases, tolerability, crossover, and long-term follow-up in interpreting comparative efficacy.[39,40]

Long-term follow-up of IRIS confirmed imatinib as a foundational therapy, demonstrating durable cytogenetic and molecular responses and an estimated overall survival rate of 83.3% at 10 years among patients initially assigned to imatinib.[17] Clinically, imatinib remains important because it is effective, extensively characterized, widely available as a generic formulation of imatinib, and often preferable to more potent TKIs in patients with substantial vascular risk. The availability of generic imatinib has also reshaped the economics of CML care, as lower-cost therapy with mature safety data can preserve adherence and widen access more effectively than newer agents that may be difficult to obtain. For patients with low-risk disease and no urgent need for rapid deep molecular response, this practical advantage is clinically meaningful rather than merely administrative.[14,41]

4.2. Adverse effects

Common adverse effects of imatinib include fluid retention, periorbital edema, muscle cramps, nausea, diarrhea, rash, fatigue, myelosuppression, and mild elevations in hepatic enzymes. Most of these are manageable with supportive care, dose adjustment, or temporary interruption. Serious toxicities are less frequent but may involve clinically significant cytopenias, hepatotoxicity, heart failure in susceptible patients, and decline in renal function with long-term therapy. Chronic low-grade toxicity requires particular attention because patients may remain on therapy for decades. Symptoms such as muscle cramps, fatigue, edema, gastrointestinal disturbances, and cognitive or mood effects can reduce adherence even when not classified as severe in clinical trials. Management strategies include taking imatinib with food and water, the use of antiemetics or antidiarrheals, diuretics for selected patients, assessment of magnesium or calcium levels for cramps, dose interruption for cytopenias, and periodic evaluation of renal and hepatic function.[13,42]

The main limitation of imatinib is not its safety profile but rather slower molecular responses and incomplete activity against several clinically important resistance mutations. For patients prioritizing TFR and with lower comorbidity burden, second-generation TKIs or asciminib-based strategies may achieve faster deep responses. However, imatinib remains an appropriate first-line therapy for many patients because long-term survival is excellent and toxicity is predictable.[7] Imatinib also retains an important role in treatment de-escalation discussions. Patients experiencing chronic toxicity on more potent TKIs but maintaining stable molecular control may benefit from switching to imatinib or adopting dose-adjusted

strategies under careful monitoring. Such approaches must be individualized and should not compromise response milestones, but they highlight that therapeutic success in CML is measured over years rather than by the earliest molecular response time point alone.

4.3. Therapeutic role

Imatinib is particularly attractive for patients with low-risk chronic-phase CML, older patients with cardiovascular comorbidities, those for whom cost or access is a major concern, and patients who prefer a therapy with a well-established safety record. Conversely, it may be less suitable for patients with high-risk disease, early warning features, or those strongly motivated to achieve deep molecular responses within a shorter timeframe. Risk scores such as Sokal, Hasford, European Treatment and Outcome Study, and European Treatment and Outcome Study Long-Term Survival (ELTS) score can support treatment decisions, but they should always be interpreted alongside comorbidities and patient goals. ELTS is especially valuable because it was developed in the TKI era to predict CML-related death rather than overall survival, which can be influenced by age and non-CML comorbidities. For example, a patient with low ELTS risk but significant vascular disease may reasonably begin therapy with imatinib, whereas a patient with high ELTS risk and minimal comorbidities may benefit from a more potent first-line option.[43-46]

4.4. Molecular mechanisms of imatinib resistance

Despite its transformative clinical impact, the durability of imatinib therapy can be undermined by the development of resistance.[30] Mechanistically, resistance in CML is broadly divided into BCR::ABL1dependent and BCR::ABL1independent pathways, with the former most commonly driven by point mutations within the BCR::ABL1 kinase domain.[31] These mutations disrupt the structural conformation of the protein, preventing imatinib from binding to its favored inactive state. Among the recurrent alterations, mutations in the ATPbinding Ploop (e.g., Y253H, E255K/V) destabilize the binding region and markedly diminish drug affinity, while changes in the activation loop and Chelix (e.g., F317L and F359V/I/C) remodel the kinase pocket and impair inhibition.[32] The most formidable barrier, however, is the T315I "gatekeeper" mutation, in which substitution of threonine with a bulky isoleucine residue at position 315 causes substantial steric hindrance. This structural alteration substantially restricts access to the binding pocket, rendering the leukemic clone resistant to imatinib and posing a major therapeutic challenge (Figure 1).[30-32]

5. Second-generation targeted therapies

5.1. Rationale for second-generation tyrosine kinase inhibitors

Secondgeneration TKIs, including dasatinib, nilotinib, and bosutinib, were designed to overcome imatinib resistance and accelerate molecular response kinetics through greater potency and structural flexibility.[47,48] Unlike imatinib, dasatinib demonstrates conformational adaptability, binding both active and inactive kinase states, thereby circumventing many singlepoint mutations. Dasatinib and bosutinib also inhibit Srcfamily kinases, suppressing parallel BCR::ABL1independent signaling pathways that often mediate escape from singletarget inhibition. Importantly, the resistance profiles of these agents are distinct, making mutationspecific sequencing clinically valuable: dasatinib or bosutinib are preferred for Y253H, E255K/V, or F359V/I/C mutations, whereas nilotinib is favored in the presence of F317L.

Bosutinib occupies a unique role as salvage therapy, particularly when systemic toxicities or mutation patterns preclude the use of other secondgeneration options. Despite these expanded mechanisms, none of these agents can reliably overcome the steric hindrance imposed by the T315I gatekeeper mutation. Their introduction broadened both frontline and laterline strategies, but also created therapeutic dilemmas: while faster molecular responses reduce early progression risk and increase the likelihood of deep remission, longterm survival differences remain modest because effective salvage therapy is available. Thus, frontline use of secondgeneration TKIs depends on the relative importance assigned to early depth of response, ambition for TFR, disease risk, and susceptibility to toxicity rather than potency alone.[47,48]

Across pivotal trials, these agents consistently achieved faster and deeper molecular responses than imatinib, yet overall survival in chronicphase disease remains comparable due to low CMLrelated mortality and the availability of sequential therapy. The central tradeoff therefore lies between maximizing rapid molecular responses and potential TFR eligibility versus managing drugspecific toxicities. Notably, dasatinib, nilotinib, and bosutinib differ in offtarget kinase activity, dosing requirements, food effects, drug–drug interactions, and organspecific toxicities, underscoring the need for careful baseline assessment to avoid unnecessary switches, preserve quality of life, and maintain laterline options for

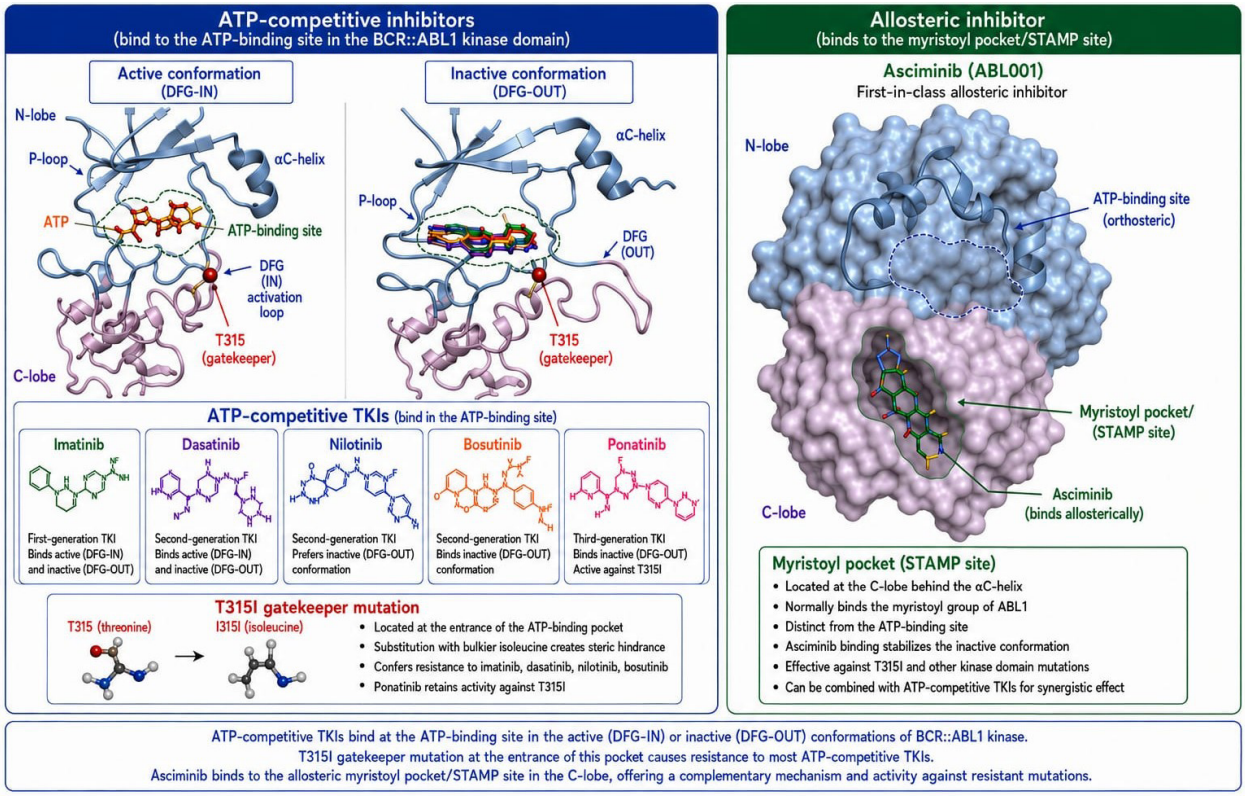


Figure 1. Structural evolution, conformational binding modes, and target pockets of TKIs in chronic myeloid leukemia. Image created by the authors. Abbreviations: ABL1: Abelson murine leukemia viral oncogene homolog 1; ATP: Adenosine triphosphate; BCR: Breakpoint cluster region; DFG: Aspartate–phenylalanine–glycine motif; STAMP: Specifically targeting the ABL myristoyl pocket; TKI: Tyrosine kinase inhibitor.

true resistance.[47,48]

5.2. Dasatinib

Dasatinib is a highly potent secondgeneration TKI that inhibits both BCR::ABL1 and Srcfamily kinases.[18] Structurally, it demonstrates notable conformational flexibility, binding to the ABL kinase domain in both active and inactive states. This dualbinding capability enables broad activity against a wide spectrum of imatinibresistant mutations, making dasatinib effective after initial treatment failure, although its offtarget kinase profile contributes to distinctive systemic toxicities.[49-51]

In the landmark phase III DASISION trial, which compared dasatinib with imatinib sin treatmentnaïve patients with CML, frontline dasatinib achieved superior therapeutic efficacy compared with imatinib.[18] Longterm followup confirmed significantly higher and faster rates of MMR and DMR, translating into durable disease control and reduced risk of early progression to advanced phases.[18]

The signature adverse effect of dasatinib is pleural effusion, which often develops late and recurs upon rechallenge.[52,53] Other notable toxicities include pulmonary arterial hypertension, pericardial effusion, cytopenias, and mild bleeding tendencies related to platelet dysfunction. Clinically, dasatinib is particularly valuable for patients requiring rapid cytoreduction or those harboring nilotinibresistant clones (e.g., Y253H, E255K/V, F359V/I/C), but it should be avoided or used cautiously in individuals with preexisting pulmonary or pleural disease.[52,53]

5.3. Nilotinib

Nilotinib was rationally engineered as a structurally modified derivative of imatinib, sharing a similar topological blueprint but optimized to possess significantly higher binding affinity and selectivity for the ATPbinding site.[19,47,48] Like imatinib, nilotinib binds strictly to the inactive conformation of the BCR::ABL1 kinase, utilizing its lipophilic trifluoromethyl and imidazole groups to fit deep within the hydrophobic pocket.[47,48] This design confers approximately 20 to 50fold greater potency than imatinib, accommodating mild structural changes in the pocket while remaining vulnerable to mutations that prevent the kinase from adopting its inactive state.[47,48] Compared with imatinib, this selectivity reduces certain offtarget toxicities,

though clinical use requires strict twicedaily fasting administration to avoid foodrelated absorption variability and the risk of QT prolongation.[54,55]

In the pivotal ENESTnd trial, which evaluated nilotinib efficacy and safety in patients with newly diagnosed CML, nilotinib demonstrated faster, deeper, and more durable molecular responses compared with imatinib, including superior rates of MR4 and MR4.5.[19] Longterm analyses confirmed a significant reduction in progression to accelerated and blast phases relative to imatinib.[19]

Nilotinib's safety profile is dominated by metabolic and vascular toxicities, particularly arterial occlusive events involving peripheral, coronary, and cerebrovascular systems.[56-58] Additional adverse effects include hyperglycemia, hyperlipidemia, bilirubin elevations, pruritus, and pancreatitis. Consequently, nilotinib is best suited for younger, highrisk patients motivated to achieve rapid achievement of deep molecular responses for potential TFR, but it is generally avoided in those with diabetes, metabolic syndrome, or cardiovascular disease.[56-58]

5.4. Bosutinib

Bosutinib acts as a dual inhibitor of BCR::ABL1 and Srcfamily kinases, but uniquely targets the enzyme in a conformationinsensitive manner.[20,47,48] Unlike imatinib and nilotinib, which require the kinase domain to be tightly locked in its inactive state, bosutinib can bind to both the active and intermediate inactive conformations of the ATPbinding pocket.[20,47,48] This versatile binding mechanism, combined with its distinctive structural feature of sparing offtarget kinases such as KIT and plateletderived growth factor receptor, reduces fluid retention, edema, and myelosuppressive toxicities commonly observed with other TKIs, while maintaining broad efficacy against a diverse array of imatinibresistant clones.[20,47,48,56]

In the frontline setting, the phase III BFORE trial, which compared bosutinib with imatinib in patients with newly diagnosed chronic phase CML, demonstrated that bosutinib achieves significantly superior and faster MMR rates compared to imatinib.[20] The five-year final results confirmed high, comparable overall survival rates between the treatment arms, with 73.9% of bosutinib-treated patients achieving cumulative MMR compared to 64.6% in the imatinib cohort.[20] Furthermore, substantial long-term data from historical phase I/II trials validate bosutinib's efficacy as a durable second-line salvage therapy for patients who have experienced treatment failure or intolerance with imatinib.[59,60]

The main limitations of bosutinib are gastrointestinal and hepatic toxicities, particularly transient diarrhea during early therapy and reversible elevations in liver enzymes.[59-61] Because it lacks the vascular risks of nilotinib and the pleural effusion risk of dasatinib, bosutinib represents a safe compromise for older patients or those with multiorgan comorbidities, provided early gastrointestinal and hepatic monitoring is implemented.[59-61]

5.5. Clinical positioning

Second-generation TKIs are frequently selected for patients with intermediate- or high-risk chronic-phase CML, those requiring rapid cytoreduction, patients with suboptimal imatinib response or intolerance, and patients strongly motivated to achieve deep molecular responses. Drug selection should be tailored to comorbidities: dasatinib is generally avoided in pulmonary or pleural disease, nilotinib in vascular, metabolic, or QT-risk conditions, and bosutinib in patients with active gastrointestinal or hepatic vulnerability. Mutation profile becomes decisive after treatment resistance; for example, F317L reduces dasatinib activity, while Y253H, E255K/V, and F359V/I/C are clinically relevant for nilotinib selection.[7]

In practice, the distinction between first-line and second-line therapy is becoming increasingly nuanced. Some patients begin with a second-generation TKI to maximize early molecular response, later considering dose reduction, discontinuation, or switching due to chronic toxicity. Others start with imatinib and switch only if milestones are not achieved. Both strategies are reasonable when accompanied by transparent counseling, reliable molecular monitoring, and timely intervention for warning or failure responses.

6. Third-generation and next-generation targeted therapies

6.1. Ponatinib

Ponatinib is a potent, thirdgeneration ATPcompetitive panBCR::ABL1 inhibitor, rationally designed using structureguided drug templates to overcome the T315I mutation, a mutation that confers resistance to most first and secondgeneration TKIs.[15,20,62,63] Biochemically, ponatinib binds to the inactive conformation of the ABL kinase domain, utilizing an elongated carbon–carbon triple bond (an ethynyl linker). This linear ethynyl linkage is crucial because it physically spans the mutated residue, completely avoiding the steric clash caused by the bulky isoleucine side chain at position 315 that disables earlier TKIs.[15,20]

The PACE trial, which evaluated ponatinib in patients with CML and Ph-chromosome–positive acute lymphoblastic leukemia, demonstrated clinically meaningful efficacy in heavily pretreated Ph-chromosome–

positive leukemias, including CML with T315I mutation or resistance/intolerance to dasatinib or nilotinib.[15] Ponatinib therefore filled a critical therapeutic gap for patients with otherwise limited kinaseinhibitor options. Its development also highlighted the importance of structureguided drug design, as the molecule was engineered to avoid steric interference from the isoleucine substitution at residue 315, a major cause of resistance to earlier TKIs.[20,62]

This broad activity is clinically valuable but necessitates deliberate use, with careful consideration of whether the patient's mutation profile or clinical scenario justifies its vascular risk profile, as ponatinib has been associated with arterial occlusive events, hypertension, and other cardiovascular toxicities.[62,63]

The principal challenge with ponatinib is vascular toxicity. Arterial occlusive events, hypertension, venous thromboembolism, pancreatitis, hepatotoxicity, rash, and myelosuppression require vigilant monitoring and proactive risk mitigation. The OPTIC trial, which evaluated optimized ponatinib dosing in chronic-phase CML, supported a response-adapted dosing strategy, particularly initiating therapy at 45 mg daily and reducing to 15 mg once *BCR::ABL1*^{IS} ≤ 1% is achieved, to preserve efficacy while reducing toxicity.[21] In practice, ponatinib is most compelling for patients with T315I-mutated disease, multi-TKI resistance, or selected high-risk cases, but it should always be paired with aggressive cardiovascular risk assessment and management. Dose intensity should be reconsidered once a meaningful molecular response is achieved, especially in chronic-phase disease, with the clinical goal being durable disease control at the lowest acceptable cumulative toxicity. Collaboration with cardiology or cardio-oncology is appropriate for patients with prior arterial events, uncontrolled hypertension, diabetes, dyslipidemia, smoking history, or multiple risk factors.[58,64]

6.2. Asciminib

Asciminib represents a mechanistic shift in CML therapy. Unlike ATP-competitive TKIs, it binds the ABL myristoyl pocket and restores an autoinhibited kinase conformation, a strategy termed "STAMP" (specifically targeting the ABL myristoyl pocket) inhibition.[16] Because its binding site differs from that of ATP-competitive TKIs, asciminib has a distinct resistance profile and may retain activity after multiple prior TKIs. In the ASCEMBL trial, which compared asciminib with bosutinib in patients with CML previously treated with at least two TKIs, asciminib produced superior rates of MMR and better tolerability compared with bosutinib.[65,66]

Allosteric inhibition is conceptually important because it separates target specificity from the crowded ATP-binding site used by many kinases. This distinction may help explain asciminib's favorable tolerability profile and creates opportunities for sequential or combination strategies. At the same time, myristoyl pocket mutations, compound mutations, and transcript-specific considerations highlight that allosteric therapy is not immune to resistance.[67-69]

Asciminib has also advanced into frontline therapy. In the ASC4FIRST trial, which evaluated asciminib in patients with newly diagnosed CML, asciminib improved MMR at week 48 compared with investigator-selected TKIs and with imatinib, leading to the accelerated approval in the United States in October 2024 for newly diagnosed Ph-chromosome–positive chronic-phase CML.[22,70] Ongoing follow-up continues to define durability, long-term safety, resistance mechanisms, sequencing strategies, and implications for TFR.

Frontline asciminib raises several clinical considerations requiring longer-term observation. First, the durability of its early molecular advantage must be confirmed beyond the first year. Second, comparative safety must be assessed over decades rather than months, given the chronic nature of CML therapy. Third, optimal sequencing after asciminib failure remains incompletely defined. Finally, payers and health systems must determine how to balance drug costs against potential gains in tolerability, adherence, response depth, and discontinuation eligibility.[22]

Adverse effects include myelosuppression, hypertension, pancreatic enzyme elevation or pancreatitis, fatigue, nausea, headache, arthralgia, and hypersensitivity. Although asciminib appears favorable in many patients, cardiovascular and pancreatic monitoring remain important. Specific myristoyl pocket mutations may confer resistance, and uncommon BCR::ABL1 transcript structures can influence drug activity. These issues reinforce the importance of molecular characterization and careful follow-up. Asciminib may be particularly useful for patients who discontinued prior TKIs due to chronic intolerance rather than overt resistance, where the therapeutic goal is restoration of quality of life while maintaining molecular control. Clinicians should avoid assuming that a favorable trial profile eliminates the need for monitoring; blood pressure, pancreatic enzyme levels when clinically indicated, cytopenias, adherence, and molecular response remain central.

6.3. Combining adenosine triphosphate-competitive and allosteric inhibition

Because ponatinib and asciminib bind distinct sites, combined ATP-binding site and myristoyl pocket inhibition is biologically attractive. The rationale is to

suppress a broader mutational spectrum, reduce the outgrowth of resistant clones, and potentially deepen molecular responses. However, combination therapy may increase cost and toxicity, and requires clinical trials to define optimal dose, patient populations, treatment duration, and safety. At present, such approaches should be considered investigational or reserved for highly selected cases under expert guidance.[67,69]

Combination therapy is most compelling in scenarios where monotherapy is unlikely to provide durable control, such as compound mutations, advanced-phase disease, or repeated emergence of resistant subclones. In contrast, chronic-phase CML sets a high therapeutic bar because most patients already achieve excellent outcomes with single-agent therapy. Any combination strategy must therefore demonstrate not only deeper molecular responses but also acceptable long-term tolerability, clear stopping rules, and a convincing rationale for added cost and monitoring burden.[67,69]

7. Adverse effects and long-term survivorship

7.1. Toxicity as a determinant of first-line choice

As survival in CML has improved, adverse effects have become central to treatment success. Even low-grade chronic toxicities can impair adherence, employment, mental health, physical activity, and overall quality of life. Treatment selection should therefore begin with a structured assessment of cardiovascular disease, pulmonary disease, diabetes, dyslipidemia, hepatic dysfunction, renal function, pancreatitis history, pregnancy plans, concomitant medications, and patient priorities. Survivorship assessment must be repeated over time because risk profiles evolve. A patient who is healthy at diagnosis may later develop hypertension, diabetes, renal disease, plan a pregnancy, depression, or require new medications that interact with TKIs. Conversely, a patient who initially requires a potent TKI for disease control may later achieve a stable deep response and become a candidate for dose reduction, switching, or discontinuation. Longitudinal care should therefore be proactive rather than reactive.[13,71,72]

Table 2 provides a practical overview and should not be considered a substitute for prescribing information or individualized assessment. Within each drug class, toxicity probability is influenced by dose, age, baseline comorbidity, concomitant therapies, prior TKI exposure, disease phase, and duration of therapy. Patient-reported symptoms should be taken seriously even when laboratory values and molecular response appear reassuring.

Table 2. Selected features of targeted therapies for chronic-phase chronic myeloid leukemia

Agent	Generation/class	Key strengths	Adverse-effect considerations
Imatinib	First-generation ATP-competitive TKI	Longest follow-up; generic availability; favorable vascular profile; durable survival[17,37-41]	Edema, cramps, nausea, diarrhea, fatigue, rash, cytopenias, hepatic enzyme elevation, and renal function decline[13,42]
Dasatinib	Second-generation ATP-competitive TKI	Rapid molecular responses; activity against many imatinib-resistant mutations[18,47-51]	Pleural effusion, pulmonary arterial hypertension, cytopenias, bleeding tendency, diarrhea, and rash[49-53]
Nilotinib	Second-generation ATP-competitive TKI	Deep molecular responses; strong efficacy in frontline therapy[19,54,55]	Arterial occlusive events, hyperglycemia, dyslipidemia, pancreatitis, QT prolongation, and hepatobiliary toxicity[56-58]
Bosutinib	Second-generation ATP-competitive TKI	Effective frontline and later-line option; useful when vascular or pulmonary risks limit alternatives[20,59-61]	Diarrhea, nausea, vomiting, hepatic enzyme elevation, rash, and cytopenias[59,60]
Ponatinib	Third-generation ATP-competitive TKI	Activity against T315I; potent option after multiple TKI failures[15,21,62-64]	Arterial occlusive events, hypertension, pancreatitis, hepatotoxicity, and rash, myelosuppression; requires vascular risk mitigation[58,64]
Asciminib	Allosteric STAMP inhibitor	Distinct binding site; activity after multiple TKIs; favorable efficacy and tolerability in trials; frontline option in some jurisdictions[16,22,65-70]	Cytopenias, hypertension, pancreatic enzyme elevation or pancreatitis, fatigue, and nausea; emerging resistance considerations[67-69]

Abbreviations: ATP: Adenosine triphosphate; STAMP: Specifically targeting the ABL myristoyl pocket; TKI: Tyrosine kinase inhibitor.

7.2. Cardiovascular and metabolic risk

Cardiovascular risk is one of the most important differentiators among TKIs. Nilotinib and ponatinib carry particular concern for arterial occlusive events, with ponatinib requiring especially rigorous risk management. Baseline evaluation should include blood pressure, lipid profile, blood glucose or hemoglobin A1c, smoking status, family history, prior vascular events, body mass index, and concomitant therapies. Preventive strategies encompass treatment of hypertension, lipid-lowering therapy where indicated, diabetes optimization, smoking cessation, weight management, and coordination with cardiology for high-risk patients.[73-75]

The mechanisms of vascular toxicity remain incompletely understood and may involve endothelial dysfunction, platelet activation, metabolic changes, vascular inflammation, and off-target kinase effects. Regardless of mechanism, the practical implication is clear: cardiovascular prevention is integral to TKI prescribing. Baseline risk tools can help structure assessment, but they should not replace clinical judgment in patients with prior myocardial infarction, stroke, peripheral arterial disease, or multiple uncontrolled risk factors.[73-75]

The goal is not simply to avoid certain TKIs but to select the agent whose risk profile best aligns with the patient's disease risk and comorbidity profile. For example, in a patient with T315I-mutated CML, ponatinib or asciminib may be necessary despite vascular risk; in such cases, dose optimization, close monitoring, and aggressive risk-factor modification are essential.[73-75]

Clinical documentation should explicitly state why a vascular-risk TKI is being used when alternatives exist. This provides a shared reference point for future clinicians, helps patients understand the rationale, and supports timely reassessment if toxicity emerges or molecular response allows de-escalation. Preventive care should also include coordination with primary care, since CML visits alone may not address all modifiable risks.[73-75]

7.3. Pulmonary, hepatic, pancreatic, and renal issues

Pulmonary toxicity is most relevant to dasatinib. New symptoms such as dyspnea, cough, chest discomfort, or reduced exercise tolerance should prompt evaluation for pleural effusion and pulmonary hypertension.[76,77] Hepatic enzyme elevations occur with several TKIs but are of particular concern with bosutinib and nilotinib. Pancreatitis or pancreatic enzyme elevations are notable with nilotinib, ponatinib, and asciminib. Renal function should be monitored longitudinally, especially with imatinib and in patients with pre-existing kidney disease.[76,77]

Organ-specific monitoring should be tailored to the selected TKI. For dasatinib, respiratory symptoms should not be dismissed as aging or infection without considering pleural effusion. For nilotinib, fasting glucose, lipid profile, electrocardiographic abnormalities, and pancreatic symptoms require close attention. For bosutinib, early hepatic and gastrointestinal monitoring is essential. For ponatinib, systematic surveillance of vascular status, blood pressure, pancreatic enzymes, and hepatic function is critical. For asciminib, cytopenias, blood pressure, and pancreatic toxicity remain relevant even when overall tolerability appears favorable.[76,77]

7.4. Adherence and quality of life

Because CML treatment often continues for years or decades, adherence is a major determinant of treatment effectiveness and molecular response. Barriers include chronic low-grade adverse effects, complex dosing instructions, fasting requirements, drug–drug interactions, high out-of-pocket costs, depression, health literacy, and limited access to molecular testing. Management should encourage open discussions about missed doses, simplify regimens where possible, treat adverse effects proactively, and involve pharmacists, nurses, financial counselors, and primary care clinicians.[11,12,78]

Adherence assessment should adopt a patient-centered and nonjudgmental approach. Many patients miss doses due to side effects, work schedules, travel, cost, pharmacy delays, or misunderstanding of instructions. Objective pharmacy refill data, patient diaries, digital reminders, and open communication can identify problems before molecular relapse occurs. The ADAGIO study and related adherence research demonstrated that nonadherence is common and clinically consequential, reinforcing that even a potent TKI cannot be effective if it is not taken consistently.[11,12,78]

Quality of life is also an outcome in its own right. Patients may experience fear of progression, treatment fatigue, sexual dysfunction, fertility concerns, body-image changes related to edema or rash, financial stress, and uncertainty about stopping therapy. Incorporating patient-reported outcomes into routine care can help clinicians detect burdens that remain invisible in PCR values.[71,72]

8. Therapeutic challenges

8.1. Choosing initial therapy

Initial therapy should be guided by disease risk, molecular features, patient comorbidities, and treatment goals. Imatinib remains appropriate for low-risk patients, those with elevated cardiovascular risk, or individuals for whom affordability is critical. A second-generation TKI

may be favored in intermediate- or high-risk disease, when rapid cytoreduction is needed, or when patients strongly prioritize achieving deep molecular responses. Asciminib is increasingly relevant as a frontline option where approved and available, particularly if its favorable tolerability is confirmed with longer-term follow-up.[6,7,79]

The initial visit should extend beyond prescribing a drug. Clinicians should confirm chronic-phase status, document transcript type for future PCR monitoring, calculate a risk score, assess spleen size and blood counts, review cardiovascular and pulmonary history, reconcile medications for CYP3A4 interactions and QT risk, discuss pregnancy plans, and explain response milestones. This baseline work prevents later ambiguity when interpreting molecular response or toxicity.[6,7,79]

No single agent is optimal for every patient. A high-risk young patient seeking eventual TFR may reasonably prioritize a drug associated with rapid deep responses. Conversely, an older patient with coronary artery disease and stable low-risk CML may prioritize safety and cost. Shared decision-making is therefore not an adjunct to CML care but a central component of precision therapy. This personalized framework integrates baseline patient characteristics, organ-specific risks, and TKI safety profiles to guide initial treatment selection, as summarized in the organ-mapping clinical matrix (Figure 2).

Shared decision-making should explicitly address trade-offs. Patients should understand that a more rapid early molecular response may increase the probability of later deep response but may also expose them to drug-specific risks. They should also recognize that switching therapy is possible, although each switch introduces additional toxicity risks, costs, monitoring requirements, and uncertainty. Transparent discussions at diagnosis can improve trust and adherence when adjustments become necessary.[6,7,79] Table 3 outlines common factors that influence initial TKI selection in chronic-phase CML.

8.2. Managing resistance and intolerance

Treatment failure should trigger a systematic evaluation. The first step is to determine whether apparent resistance reflects nonadherence, drug interactions, poor absorption, incorrect dosing, or laboratory variability. If resistance is confirmed, mutation testing guides the choice of the next TKI. A comprehensive, three-tiered decision matrix mapping mutational branches and subsequent TKI sensitivities to guide salvage sequencing is visually outlined in Figure 3.

An inadequate response after multiple TKIs, the presence of T315I, compound mutations, clonal evolution, or progression to accelerated phase should prompt referral to a CML specialist and consideration of ponatinib, asciminib, clinical trial enrollment, or allogeneic transplantation in appropriate candidates.[7]

The distinction between warning and failure is

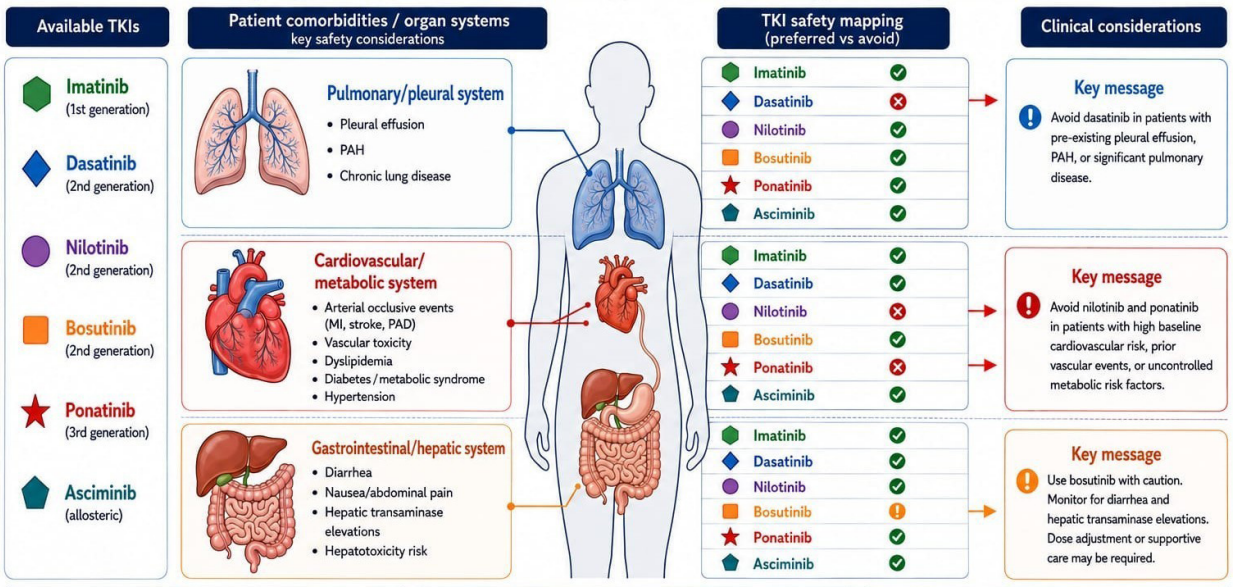


Figure 2. Comorbidity-driven TKI selection framework mapping patient-specific organ system vulnerabilities to TKI safety profiles. Image created by the authors.
Abbreviations: MI: Myocardial infarction; PAD: Peripheral arterial disease; PAH: Pulmonary arterial hypertension; TKI: tyrosine kinase inhibitor.

Table 3. Clinical factors influencing initial tyrosine kinase inhibitor selection

Clinical factor	Clinical relevance	Potential treatment implication
Disease risk and response urgency	Higher-risk disease or need for rapid cytoreduction may justify prioritizing faster molecular response[6,7,79]	Consider a second-generation TKI or asciminib where appropriate, while balancing toxicity and access[6,7,79]
Cardiovascular and metabolic profile	Arterial events, diabetes, dyslipidemia, smoking, or uncontrolled hypertension increase concern with vascular-risk TKIs[73-75]	Imatinib, dasatinib, bosutinib, or asciminib may be preferable to nilotinib or ponatinib unless mutation profile requires otherwise[73-75]
Pulmonary or pleural history	Prior pleural effusion, pulmonary hypertension, or substantial lung disease increases risk with dasatinib[49-53,76,77]	Avoid or use dasatinib cautiously; consider alternative agents with non-overlapping pulmonary toxicity[49-53,76,77]
Hepatic, gastrointestinal, or pancreatic vulnerability	Baseline organ dysfunction can amplify drug-specific adverse effects[56-61,67-69]	Match agent and monitoring plan to organ risk; bosutinib may require early diarrhea and liver-enzyme management[59,60]
Cost, access, and adherence feasibility	Long-term treatment fails if medication or PCR monitoring is unreliable[11,12,78]	Generic imatinib may be the most sustainable first-line option when affordability and access dominate decision-making[11,12,78]
Reproductive considerations	TKIs may require interruption or avoidance during pregnancy planning and gestation[6,7,79]	Discuss timing, alternatives, specialist consultation, and individualized risk before selecting therapy[6,7,79]

Abbreviations: PCR: Polymerase chain reaction; TKI: Tyrosine kinase inhibitor.

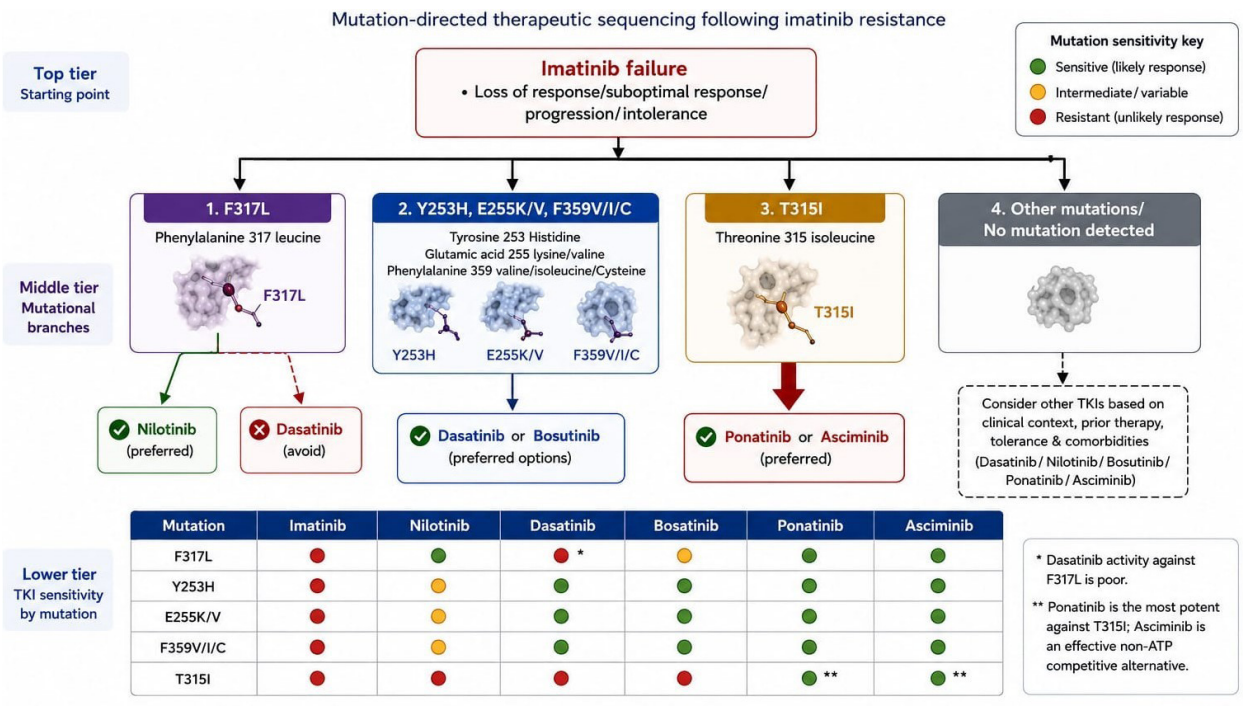


Figure 3. Mutation-directed salvage sequencing algorithm AFTER imatinib failure. Image created by the authors.
Abbreviations: ATP: Adenosine triphosphate; TKI: Tyrosine kinase inhibitor.

clinically important. Warning responses should prompt closer monitoring of adherence, repeat testing, and risk factor assessment, whereas confirmed failure generally requires a change in therapy. Bone marrow cytogenetics may still be useful when atypical transcripts, unusual blood-count changes, suspected clonal evolution, or accelerated-phase features are present. Next-generation sequencing can detect low-level mutations, though the clinical significance of very small mutant clones must be interpreted cautiously.[28,29]

Intolerance is distinct from resistance. Patients who maintain excellent molecular control but experience unacceptable chronic toxicity may benefit from dose reduction, supportive care, or switching to a better-tolerated agent. Because quality of life directly affects adherence and long-term outcomes, intolerance should be treated as a clinically meaningful endpoint rather than a minor inconvenience. This distinction has practical consequences: a patient with intolerance and deep molecular response may not require the same next therapy as a patient with rising BCR::ABL1 transcript levels and a resistant mutation. Switching due to intolerance should prioritize non-overlapping toxicity, dosing feasibility, and quality of life, whereas switching due to resistance should prioritize mutation coverage and potency. Failure to separate these scenarios risks overtreatment of intolerance or undertreatment of resistance.

8.3. Advanced-phase disease

Most contemporary patients are diagnosed in chronic phase, but accelerated, or blast-phase disease remains a major therapeutic challenge. Advanced-phase CML reflects additional genetic and epigenetic evolution beyond BCR::ABL1-driven disease biology. Management typically requires a potent TKI selected according to the mutation profile, disease-phase–appropriate chemotherapy where indicated, and early assessment for allogeneic transplantation in eligible patients. Outcomes remain inferior to those in chronic-phase disease, underscoring the importance of early diagnosis, molecular monitoring, and timely intervention for treatment failure.[5,80]

Advanced-phase disease underscores the limitations of kinase inhibition alone. Blast-phase CML may resemble acute myeloid or lymphoblastic leukemia and often requires induction-type therapy combined with a TKI, central nervous system evaluation in lymphoid presentations, and transplant planning once remission is achieved. Prevention of progression through early recognition of inadequate response remains more effective than treating disease after transformation.[5,80]

8.4. Treatment-free remission

Treatment-free remission is one of the most important achievements in modern CML care. Prospective discontinuation studies such as STIM and EURO-SKI have shown that a substantial proportion of carefully selected patients with sustained deep molecular response can stop TKI therapy under close molecular monitoring, although molecular recurrence is common and usually occurs within the first few months. Most patients who lose MMR regain response after restarting therapy.[81,82]

Discontinuation studies with imatinib, dasatinib, and nilotinib confirm that TFR is feasible across several TKI treatment histories when eligibility criteria and monitoring are rigorous. Predictors of success include longer TKI duration, longer deep molecular response duration, lower-risk disease, and possibly immune factors, though prediction remains imperfect. Patients should be counseled about TKI withdrawal syndrome, anxiety surrounding PCR testing, and the need for rapid restart if molecular relapse occurs.[83-86]

Successful TFR requires more than deep response. It depends on reliable access to standardized RT-qPCR, patient willingness to undergo frequent monitoring, rapid communication of results, and a clear plan for restarting therapy. TFR should not be attempted casually in patients without stable deep response or in settings where timely monitoring is unavailable. Future research must improve prediction of who can maintain remission after discontinuation.[6,7] The chronological progression from stable molecular suppression to formal evaluation within a standardized discontinuation algorithm is illustrated in the clinical framework map (Figure 4).

The ethical dimension of TFR is equally important. Stopping therapy can reduce adverse effects and cost, but it requires patients to actively participate in frequent testing and rapid response to results. Clinicians should ensure that discontinuation is a shared, informed decision rather than a cost-containment strategy imposed on patients or a milestone pursued without appropriate monitoring infrastructure.[6,7] Table 4 summarizes the practical domains that should be reviewed before attempting TFR.

9. Ethical, practical, and implementation considerations

9.1. Ethical considerations

Chronic myeloid leukemia illustrates both the promise and inequity of precision oncology. Highly effective oral targeted therapies can transform survival, yet their

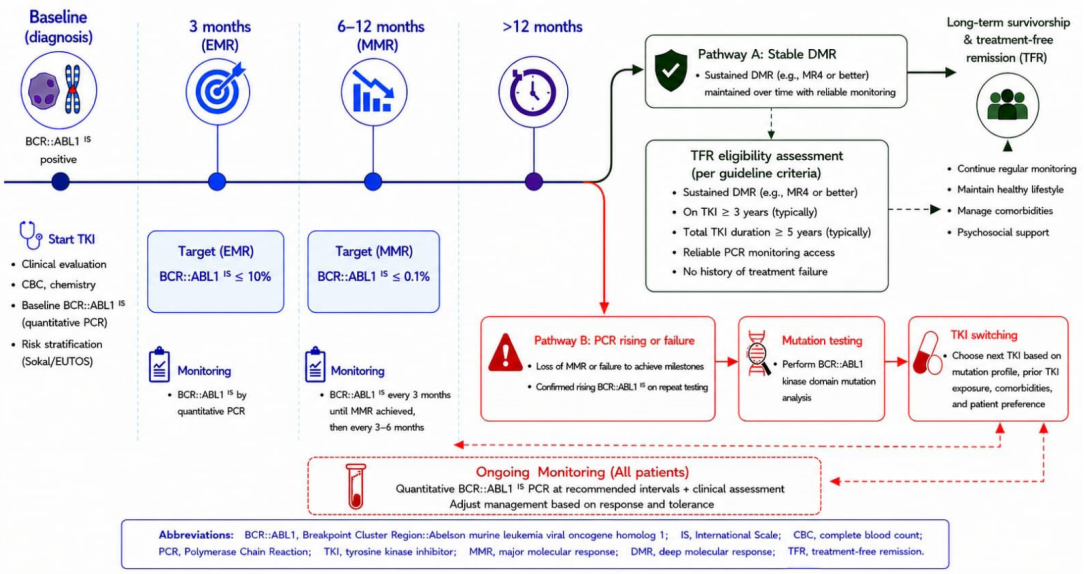


Figure 4. Chronological milestones, treatment pathways, and management algorithms for chronic-phase CML. Image created by the authors.
Abbreviations: ABL1: Abelson murine leukemia viral oncogene homolog 1; BCR: Breakpoint cluster region; CBC: Complete blood count; DMR: Deep molecular response; EMR: Early molecular response; EUTOS: European Treatment and Outcome Study; MMR: Major molecular response; MR4: Molecular response with log reductions of ≤ 0.01% BCR::ABL1[IS]; MR4.5: Molecular response with log reductions of ≤ 0.0032%; PCR: Polymerase chain reaction; TFR: Treatment-free remission; TKI: Tyrosine kinase inhibitor.

Table 4. Key readiness domains for treatment-free remission attempts

Domain	Recommended review	Reason for inclusion
Disease eligibility	Chronic-phase history, no uncontrolled resistance, typical measurable transcript, and sustained deep molecular response[81,82]	TFR is safest in patients with stable disease biology and reliable molecular measurability[81,82]
Treatment history	Duration of TKI exposure, duration of MR4 or deeper response, prior resistance, and prior intolerance[83-86]	Longer and more stable deep response improves confidence, while prior resistance may alter risk assessment[83-86]
Monitoring infrastructure	Access to standardized RT-qPCR, rapid reporting, and frequent testing during the first months after stopping[6,7,79]	Most molecular recurrences occur early and require timely detection[6,7,79]
Patient readiness	Understanding of relapse thresholds, willingness for frequent testing, and acceptance of possible restart[83-86]	TFR is a shared management strategy rather than simply stopping medication[83-86]
Restart plan	Predefined threshold for restarting TKI, preferred agent, communication pathway, and follow-up schedule[6,7,79]	Clear plans reduce anxiety and prevent delayed re-treatment after molecular recurrence[6,7,79]
Symptom and quality-of-life plan	Counseling about withdrawal symptoms, anxiety, and patient-reported outcomes[71,72]	Discontinuation can improve daily life but may also create new physical or psychological burdens[71,72]

Abbreviations: MR4: Molecular response with log reductions of ≤ 0.01%; RTqPCR: Reverse transcription quantitative polymerase chain reaction; TFR: Treatmentfree remission; TKI: Tyrosine kinase inhibitor.

benefit depends on timely diagnosis, continuous access to medication, molecular monitoring, toxicity management, and specialist expertise. Ethical care requires transparent discussion of benefits, risks, alternatives, uncertainties, fertility and pregnancy issues, financial toxicity, and patient preferences.[87,88]

Ethical prescribing also demands humility about uncertainty. New agents may demonstrate impressive early response data but lack decades-long safety experience, while older agents may be less potent yet more predictable and accessible. Patients should not be directed toward one approach without understanding why it fits their clinical and personal context. This is particularly relevant when recommending a drug with known vascular risk, a high-cost agent, or attempting treatment discontinuation.[87,88]

Fertility and pregnancy require specific counseling. TKIs carry embryo–fetal risks and are generally avoided during pregnancy when possible, yet uncontrolled CML also poses substantial risk. Management may involve treatment interruption, IFN-α, leukapheresis in selected circumstances, timing therapy around conception, and individualized collaboration with maternal–fetal medicine specialists. These discussions should occur early for patients of reproductive potential rather than only after pregnancy is established.[87,88]

9.2. Equity and access

Global outcomes are shaped by the affordability of TKIs, availability of generics, insurance coverage, supply-chain reliability, and access to standardized BCR::ABL1 testing. A treatment plan that is molecularly ideal but financially unsustainable may lead to treatment interruptions and worse outcomes. In many settings, generic imatinib remains the most realistic and impactful targeted therapy. Expanding access to reliable molecular monitoring may be as important as expanding access to newer drugs.[9,14]

Equity challenges also exist within high-income countries. Rural patients may struggle to access specialist visits or PCR testing; underinsured patients may face delays due to prior authorization; language barriers can impair adherence counseling; and transportation or employment constraints may make frequent TFR monitoring unrealistic. Telemedicine, local laboratory partnerships, patient assistance programs, and simplified care pathways can help reduce these barriers when implemented thoughtfully.[9,14]

9.3. Practical implementation challenges

Implementation challenges include coordinating laboratory monitoring, recognizing late toxicities, managing drug interactions, supporting adherence, transitioning adolescents and young adults into adult care, counseling about pregnancy, and deciding when to switch therapy.

Oral therapy can create the false impression that CML care is simple. In reality, optimal outcomes require a longitudinal, multidisciplinary care model that integrates hematology, primary care, cardiology, pharmacy, laboratory medicine, and psychosocial support.[6,7,79]

Medication reconciliation is a recurring challenge because many TKIs interact with acid-suppressive therapy, CYP3A4 inhibitors or inducers, anticoagulants, antiplatelet agents, QT-prolonging drugs, and supplements. Pharmacist involvement can prevent avoidable loss of efficacy or the development of toxicity. Clear written care plans should specify when PCR testing is due, what results require action, which symptoms should prompt urgent contact, and how dose interruptions should be managed.[6,7,79]

10. Future directions and recommendations

10.1. Refining treatment sequencing

The expanding number of effective therapies makes sequencing increasingly complex. Future studies should compare not only response rates but also survival, TFR eligibility, patient-reported outcomes, cardiovascular events, cumulative cost, and quality-adjusted survival. The integration of asciminib into frontline therapy will require careful long-term comparison with imatinib and second-generation TKIs, particularly with respect to resistance patterns and the likelihood of successful treatment discontinuation.[77,89]

Sequencing research must also address real-world populations that remain underrepresented in clinical trials, including older adults, patients with multiple comorbidities, those with renal or hepatic impairment, individuals with prior vascular events, and patients with limited access to molecular monitoring. Pragmatic trials and registry studies can complement randomized trials by demonstrating how strategies perform when adherence, cost, and monitoring are suboptimal.[77,89]

10.2. Improving safety through personalized risk management

Risk-adapted dosing and monitoring should continue to evolve toward greater sophistication. Ponatinib already demonstrates the value of response-based dose reduction, and similar strategies may prove useful for other TKIs, particularly in patients with stable deep molecular response and chronic toxicity.[90,91] Biomarkers capable of predicting vascular events, pleural effusion, pancreatitis, and intolerance would further refine drug selection.

Therapeutic drug monitoring and pharmacogenomic

approaches remain underdeveloped in routine CML care. Interpatient variability in drug exposure may help explain why some patients experience toxicity at standard doses while others have inadequate response. Future studies should determine whether exposure-guided dosing can improve adherence, reduce toxicity, or preserve deep responses at lower doses.[90,91]

10.3. Targeting residual disease

Persistent leukemic stem cells remain a major biological barrier to achieving a definitive cure in CML. Future strategies may include combinations that target survival pathways, immune-based approaches, IFN-based regimens, metabolic vulnerabilities, epigenetic regulators, microenvironmental interactions, or dual-site BCR::ABL1 inhibition. The challenge is to deepen remission without compromising the safety that makes chronic-phase CML highly manageable.[92,93]

Immunologic research is particularly relevant to TFR. Natural killer-cell function, T-cell exhaustion, cytokine patterns, and immune reconstitution may influence whether residual leukemic cells remain controlled after therapy discontinuation. IFN-based approaches, vaccines, checkpoint modulation, and other immune strategies are biologically plausible, but they must be evaluated carefully given that patients with chronic-phase CML already achieve excellent outcomes with well-tolerated therapy.[92,93]

10.4. Optimizing treatment-free remission

Treatment-free remission research should prioritize predictive biomarkers, immune signatures, duration and depth of molecular response, patient-reported outcomes, and safe monitoring models. Digital reminders, decentralized phlebotomy, rapid PCR reporting, and patient education may expand access to TFR while maintaining safety.[94,95]

Future discontinuation trials should include diverse populations and report not only molecular recurrence but also anxiety, musculoskeletal withdrawal symptoms, financial impact, work productivity, and patient preference after treatment restart. TFR is meaningful because it changes daily life; its evaluation should therefore extend beyond the binary outcome of remaining off therapy.[94,95]

10.5. Recommendations for practice

Based on current evidence and clinical practice considerations, the following recommendations are proposed to optimize CML management:[6,7,79]

(i) Document disease phase, transcript type, baseline risk, comorbidities, and treatment goals before selecting therapy.
(ii) Align TKI choice with both disease risk and patient-specific toxicity vulnerability.
(iii) Employ standardized molecular monitoring and act promptly on confirmed milestone failures.
(iv) Distinguish resistance from intolerance and address adherence without stigma.
(v) Consider TFR only in carefully selected patients with sustained deep response and reliable monitoring.
(vi) Integrate survivorship care from diagnosis, as most patients will live for decades with CML.

Additional practical recommendations include documenting the rationale for every switch, repeating comorbidity assessment at least annually, proactively managing cardiovascular risk, involving pharmacists for interaction checks, discussing fertility and pregnancy early, and preparing patients for the possibility that treatment goals may evolve over time. A patient may initially prioritize disease control, later emphasize quality of life, and eventually consider discontinuation. Good CML care anticipates and adapts to this evolution.[6,7,79]

11. Conclusion

The evolution of CML therapy across three generations of TKIs illustrates the remarkable progress of precision oncology. Imatinib established the principle that targeted inhibition of a dominant oncogenic kinase could transform survival. Second-generation agents accelerated and deepened responses while introducing distinct toxicity considerations. Third- and next-generation therapies, particularly ponatinib and asciminib, now provide options for resistant disease and enable more individualized sequencing. This therapeutic progress has also reframed CML as a complex chronic-care model. Patients and clinicians must interpret molecular results, manage late toxicities, navigate access and insurance barriers, evaluate drug interactions, and balance treatment goals that may shift over time—from durable disease control to deeper response, reduced toxicity, or eventual discontinuation. These decisions are interconnected, requiring careful alignment of therapy choice with both clinical risk and patient priorities.

The central challenge today is not whether CML can be controlled, but how to achieve control safely, affordably, and in a way that sustains long-term quality of life. The next era of therapy should emphasize rational sequencing, proactive toxicity prevention, equitable access to monitoring, deeper understanding of residual disease, and more reliable pathways to TFR. Future advances may be less dramatic than the introduction of imatinib, yet they will be equally important: safer long-term dosing, improved prediction of resistance and intolerance, broader access to high-quality

molecular monitoring, more inclusive trial populations, and dependable strategies for discontinuation. Meeting these goals will shift the measure of success in CML from survival alone toward a fuller concept of functional cure, disease control, and quality of life.

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The authors declare no conflicts of interest related to this work.

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Writing–review & editing: All authors

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Consent for publication

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Further disclosure

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