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Review

Mechanisms of Resistance in CML and the Emerging Role of Asciminib and Other Next-Generation Inhibitors

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Abstract

Chronic myeloid leukemia (CML) is a myeloproliferative disorder driven by the BCR-ABL1 fusion gene that confers constitutive tyrosine kinase activity. Although tyrosine kinase inhibitors (TKIs) have revolutionized CML therapy, resistance remains a major clinical challenge, primarily due to kinase domain mutations, leukemic stem cell persistence, and compensatory signalling pathways. Asciminib, a novel allosteric STAMP inhibitor targeting the ABL myristoyl pocket, introduces a distinct mechanism to overcome resistance associated with ATP-site mutations such as T315I. This review highlights the molecular basis of TKI resistance, mechanisms of BCR-ABL1–dependent and –independent resistance, and emerging strategies including combination therapy, degraders, and immunotherapeutic approaches. Real-world data and clinical trials demonstrate asciminib's efficacy and favorable safety in multi-resistant CML. The future of CML management lies in precision-driven multimodal therapy aimed at eradicating leukemic stem cells and achieving treatment-free remission.

1. INTRODUCTION

Chronic myeloid leukemia (CML) treatment has been significantly advanced by the development of tyrosine kinase inhibitors (TKIs), yet resistance remains a critical challenge, primarily due to mutations in the BCR-ABL1 gene, such as the T315I mutation, which confers resistance to first- and second-generation TKIs (1,2). Ponatinib, a third-generation TKI, has shown efficacy against the T315I mutation but is limited by its toxicity profile (3). Asciminib, a novel allosteric inhibitor targeting the myristoyl pocket of BCR-ABL1, offers a distinct mechanism of action that circumvents resistance associated with ATP-binding site mutations (4,5). Clinical trials have demonstrated asciminib's efficacy in patients who have failed multiple TKI therapies, including those with the T315I mutation, and it is associated with a favorable toxicity profile (5,6). However, resistance to asciminib can still occur, as seen with mutations like Y139D and T315I, which necessitate alternative treatments such as ponatinib and omacetaxine (6). The combination of asciminib with other TKIs, such as imatinib, has shown synergistic effects, potentially enhanced therapeutic efficacy and preventing resistance

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development (7). Despite these advancements, novel resistance mechanisms, such as the BCR::ABL1b6a3 rearrangement, continue to emerge, underscoring the need for ongoing research and development of new therapeutic strategies (8). Asciminib's role in frontline therapy is being explored, with promising early results suggesting it may facilitate treatment-free remission attempts by achieving rapid and deep molecular responses (4). Overall, asciminib and other next-generation inhibitors represent a significant step forward in overcoming resistance in CML, but continuous monitoring and innovation are essential to address emerging resistance mechanisms (9,10).

2. METHODS

This review was developed through a systematic literature search across PubMed, Scopus, and Google Scholar databases for publications between 2020 and 2025. Keywords included *"CML," "BCR-ABL1," "asciminib," "T315I mutation," "TKI resistance,"* and *"next-generation inhibitors."* Only peer-reviewed English articles, clinical trials, and relevant preclinical studies were included. Priority was given to original research and high-impact review articles addressing molecular mechanisms of resistance, clinical outcomes of asciminib, and emerging therapeutic strategies. In total, approximately 70 peer-reviewed journal articles and 2 online clinical updates were reviewed; few books were included.

3. Molecular Pathophysiology of Chronic Myeloid Leukemia

The BCR-ABL fusion protein is a pivotal driver in the pathogenesis of Chronic Myeloid Leukemia (CML), primarily due to its constitutive tyrosine kinase activity, which disrupts normal cellular signaling and promotes leukemogenesis. This fusion protein results from a chromosomal translocation between chromosomes 9 and 22, forming the Philadelphia chromosome, which is a hallmark of CML (11,12). The BCR-ABL oncoprotein leads to aberrant cell proliferation and impaired apoptosis by continuously activating signaling pathways that regulate the cell cycle (12,13). This persistent activation is resistant to normal deactivation mechanisms, contributing to the uncontrolled growth of leukemic cells (12). Additionally, the BCR-ABL fusion gene can produce atypical isoforms, which may influence disease progression and therapeutic response, with some variants showing increased resistance to tyrosine kinase inhibitors (TKIs) like imatinib (14). The introduction of TKIs has significantly improved CML management by targeting the BCR-ABL tyrosine kinase activity, although resistance remains a challenge, often necessitating the development of second- and third-generation inhibitors (11,15). Moreover, novel insights into the role of BCR-ABL in CML pathogenesis include its impact on circular RNAs, such as F-circBA1, which further contribute to leukemogenesis by modulating gene expression and cell cycle progression (16,17). The BCR-ABL fusion protein also upregulates proteins like ENOX2, which are involved in redox regulation and may serve as potential biomarkers for CML (17). Overall, the BCR-ABL fusion protein is central to CML pathogenesis, driving both the disease's molecular mechanisms and therapeutic strategies (12,15) (**Figure 1**).

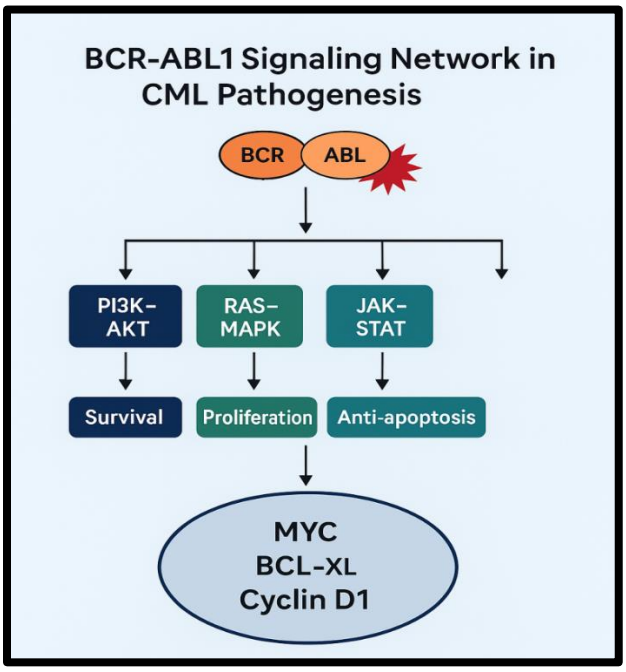

Figure 1. Constitutive activation of BCR-ABL1 signaling drives leukemogenesis through multiple oncogenic pathways.

4. Mechanisms of Resistance to Tyrosine Kinase Inhibitors

Resistance to tyrosine kinase inhibitors (TKIs) in cancer treatment is a multifaceted issue involving various molecular mechanisms. One primary mechanism is the mutation within the kinase domain, which prevents TKIs from effectively inactivating the target protein kinase, as seen in chronic myeloid leukemia (CML) with the BCR-ABL1 fusion gene (18,19). Gene amplification and increased protein expression also contribute to resistance by enhancing downstream signaling pathways, bypassing the inhibited kinase (20). In renal cell carcinoma (RCC), resistance mechanisms include the upregulation of alternative proangiogenic pathways, epithelial-

Table 1. Key Oncogenic Pathways Activated by BCR-ABL1 in CML.

Pathway	Key Components	Cellular Outcome	Therapeutic Implication
PI3K–AKT	PI3K, AKT, mTOR	Promotes cell survival and proliferation	Targeted inhibition (mTOR inhibitors, AKT blockers)
RAS–MAPK	RAS, RAF, MEK, ERK	Stimulates cell cycle progression	MEK/ERK inhibitors under evaluation
JAK–STAT	JAK2, STAT3/5	Anti-apoptotic signaling	JAK inhibitors may enhance TKI response
NF-κB	IKK complex, p65	Upregulation of pro-survival genes	Synergistic inhibition improves apoptosis
β-Catenin	GSK3β, Wnt ligands	Maintains leukemic stem cells	Potential target for LSC eradication

Table 2. General Mechanisms of TKI Resistance Across Cancer Types.

Resistance Mechanism	Molecular Basis	Example Cancer	Representative TKI	Reference
Kinase domain mutation	Alters drug binding	CML	Imatinib	(18,19)
Gene amplification	Overexpression of target	RCC	Sunitinib	(20,21)
EMT transition	Phenotypic plasticity	HCC	Sorafenib	(22,23)
Drug efflux	ABC transporter activation	NSCLC	Erlotinib	(24)
Microenvironment-mediated	Stromal cytokines, hypoxia	Breast cancer	Lapatinib	(25)

mesenchymal transition (EMT), and decreased intracellular drug concentrations due to efflux pumps and lysosomal sequestration (21,22). Similarly, in hepatocellular carcinoma (HCC), EMT, ATP-binding cassette (ABC) transporters, and hypoxia are implicated in TKI resistance (23). Intratumoral heterogeneity, particularly in EGFR-mutated non-small-cell lung cancer (NSCLC), also plays a crucial role, with drug-tolerant persister cells and extrachromosomal DNA contributing to resistance (24). In HER2+ metastatic breast cancer, genomic alterations such as mutations in PIK3CA and ERBB2, as well as clonal evolution, have been identified as resistance mechanisms (25). Additionally, the tumor microenvironment, including tumor-associated fibroblasts and bone marrow-derived cells, influences resistance by altering drug metabolism and promoting survival pathways (21). Understanding these diverse mechanisms is essential for developing next-generation TKIs and combination therapies to overcome resistance and improve patient outcomes (18).

5. BCR-ABL1–Dependent Resistance Mechanisms

In chronic myeloid leukemia (CML), BCR-ABL1–dependent resistance mechanisms significantly contribute to the failure of tyrosine kinase inhibitors (TKIs). The most extensively studied mechanism involves mutations in the kinase domain of the BCR-ABL1 gene, which alter the binding affinity of TKIs, thereby reducing their efficacy. These mutations, such as the T315I mutation, are known to confer high resistance to several first-line TKIs like imatinib, dasatinib, and nilotinib (26,27). Additionally, novel isoforms of BCR-ABL1, such as BCR/ABL1ΔE7-8-9, have been identified, which exhibit reduced sensitivity to TKIs due to altered binding sites, further complicating treatment strategies (28). The presence of secondary mutations in the BCR-ABL1 kinase domain, particularly in the N-lobe, can also confer resistance to newer agents like asciminib, which targets an allosteric site distinct from the ATP-binding pocket (10). Furthermore, the activation of downstream signaling pathways, such as PI3K/AKT, MAPK, and JAK/STAT, driven by BCR-ABL1, contributes to the survival and proliferation of leukemic cells, thereby promoting resistance (29,30). These pathways, along with the persistence of leukemic stem cells (LSCs) that are less responsive to TKIs, underscore the complexity of resistance mechanisms (31). The integration of advanced molecular techniques, such as next-generation sequencing, is crucial for identifying these mutations and tailoring treatment strategies to overcome resistance and improve patient outcomes (19,32).

6. BCR-ABL1–Independent Resistance Mechanisms

In chronic myeloid leukemia (CML), BCR-ABL1–independent resistance mechanisms significantly contribute to the failure of tyrosine kinase inhibitors (TKIs). One key mechanism involves the persistence of leukemic stem cells (LSCs), which are not effectively targeted by TKIs and can survive in the bone marrow niche, receiving oncogene-independent survival signals such as those from the bone-morphogenetic pathway (BMP) (33). Additionally, secondary fusion proteins, such as RUNX1::MECOM, have been identified as contributors to TKI resistance by promoting proliferation and differentiation changes that evade TKI effects (34). Phosphoproteomics studies have revealed that acquired FLT3-dependency is another resistance mechanism, suggesting that FLT3 could be a therapeutic target in TKI-resistant CML (35). Furthermore, the deregulation of serine-threonine kinases like Aurora kinase A and Polo-like kinase 1 (PLK1) has been implicated in resistance, as they maintain genomic stability and promote additional genomic alterations (36). Adaptive phenotypic modulations, such as changes in cell surface markers and gene expression profiles, also contribute to resistance by allowing cells to become oncogene-independent (37). Moreover, the emergence of novel BCR-ABL1 rearrangements, such as BCR::ABL1b6a3, can confer resistance to multiple TKIs, including ponatinib and asciminib, highlighting the complexity of resistance mechanisms (8). These findings underscore the need for combinatorial therapeutic strategies targeting multiple pathways to effectively overcome TKI resistance in CML (38,39) (**Figure 2**).

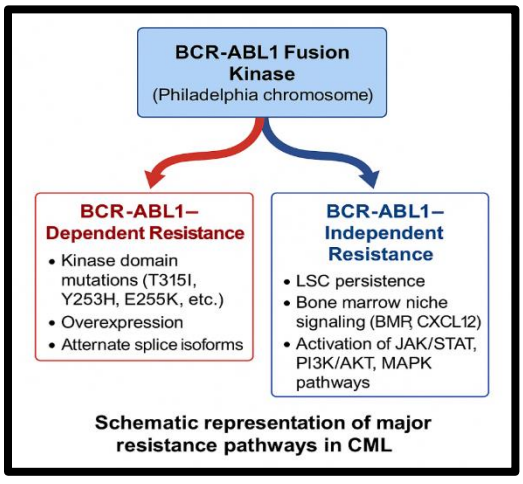

Figure 2. Schematic representation of major resistance pathways to TKIs in CML.

7. Evolution of Second- and Third-Generation TKIs

The evolution of second- and third-generation Tyrosine Kinase Inhibitors (TKIs) in cancer therapy has been driven by structural modifications aimed at overcoming resistance mutations and improving selectivity and safety profiles. First-generation TKIs, such as gefitinib and erlotinib, initially showed efficacy against EGFR mutations in non-small cell lung cancer (NSCLC) but were limited by resistance due to secondary mutations like T790M (40,41). Second-generation TKIs, including afatinib and dacomitinib, introduced irreversible binding to target the T790M mutation but suffered from lack of selectivity, leading to adverse effects due to inhibition of wild-type EGFR (40,42). Third-generation TKIs, such as osimertinib and lazertinib, were developed to selectively target both the T790M mutation and the original activating mutations while sparing wild-type EGFR, thus offering a better safety profile and therapeutic windows (42). Structural insights reveal that these inhibitors utilize van der Waals interactions and hydrogen bonds to enhance binding affinity and selectivity, as seen in lazertinib's improved properties over osimertinib. Additionally, the emergence of resistance mutations like C797S has prompted the exploration of non-irreversible mechanisms and bivalent inhibitors that can target multiple sites on EGFR (43). In chronic myeloid leukemia (CML), the development of second- and third-generation TKIs, such as dasatinib, nilotinib, and ponatinib, has been crucial in addressing resistance mutations like T315I, with ponatinib specifically designed to overcome this challenge (44,45). These advancements underscore the importance of structural modifications in enhancing the efficacy and safety of TKIs, addressing resistance, and expanding their therapeutic applications in oncology (46,47).

8. The T315I "Gatekeeper" Mutation

The T315I 'gatekeeper' mutation in the BCR-ABL1 kinase domain is a significant challenge in the treatment of chronic myeloid leukemia (CML) due to its role in conferring resistance to most tyrosine kinase inhibitors (TKIs). This mutation alters the kinase's conformation, preventing effective binding of ATP-competitive inhibitors, such as imatinib, nilotinib, and dasatinib, by blocking access to a critical hydrophobic pocket (48). The T315I mutation not only reduces drug efficacy but also increases the intrinsic kinase activity, leading to more aggressive

disease progression (48). Ponatinib, a third-generation TKI, has shown efficacy against T315I, but its use is limited by severe side effects, including thrombotic microangiopathy (49,50). Asciminib, an allosteric inhibitor targeting the myristoyl pocket, offers a distinct mechanism of action and has demonstrated effectiveness in patients with the T315I mutation, especially when combined with other TKIs like nilotinib, which shifts the kinase from an active to an inactive conformation (51,3). However, resistance can still develop, as seen with novel BCR-ABL1 rearrangements that maintain the T315I mutation, necessitating ongoing surveillance and novel therapeutic strategies (8). Additionally, the role of protein kinase CK2 in maintaining aberrant signaling in T315I-mutant cells suggests that its inhibition could sensitize these cells to TKIs, offering another potential therapeutic avenue (52). The development of new inhibitors, such as KF1601, which targets both wild-type and T315I-mutant BCR-ABL1 without severe side effects, represents a promising direction for overcoming this mutation's resistance (50). Overall, the T315I mutation exemplifies the complexity of drug resistance in CML, highlighting the need for innovative approaches combining orthosteric and allosteric inhibitors to effectively manage and overcome resistance (53).

9. Emergence of Asciminib: A Novel STAMP Inhibitor

The emergence of Asciminib as a novel STAMP inhibitor significantly impacts the landscape of targeted cancer therapies, particularly for chronic myeloid leukemia (CML). Asciminib represents a breakthrough as it specifically targets the ABL myristoyl pocket, offering a new mechanism distinct from traditional ATP-competitive tyrosine kinase inhibitors (TKIs) (54,55). This specificity allows Asciminib to overcome resistance issues associated with mutations like T315I, which are resistant to many existing TKI. Clinical trials have demonstrated its efficacy and favorable safety profile, especially in patients who have failed two or more lines of therapy or have the T315I mutation (5,56). Asciminib's reduced off-target effects translate into lower toxicity, addressing a critical need for therapies that maintain potency without compromising patient quality of life (54,57). Despite its promise, questions remain regarding its optimal positioning among existing TKIs, particularly in comparison to ponatinib, which is also used for similar indications (56). Asciminib's potential extends to combination therapies and its role in earlier treatment lines, which are currently under investigation (55,58). The drug's approval and integration into treatment protocols mark a significant advancement, offering hope for improved management of CML, especially for patients with limited options due to resistance or intolerance to previous therapies (59). As ongoing studies continue to explore its full potential, Asciminib is poised to become a cornerstone in the therapeutic armamentarium for CML, potentially setting a new standard for treatment efficacy and patient outcomes (58,60) (**Figure 3**).

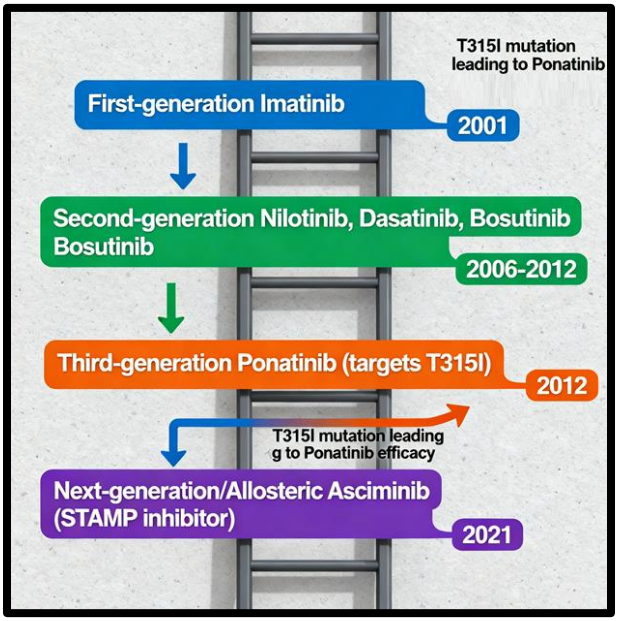

Figure 3. Chronological development of TKIs for CML and the progressive overcoming of resistance mutations

10. Clinical Evidence and Real-World Outcomes of Asciminib

The real-world outcomes of asciminib in treating chronic myeloid leukemia (CML) generally align with its clinical trial results, demonstrating comparable efficacy and safety profiles. In clinical trials, such as the ASCEMBL study, asciminib showed superior efficacy and tolerability compared to bosutinib, with a major molecular response (MMR) rate of 37.6% at 96 weeks (61). Real-world studies corroborate these findings, with MMR rates ranging from 39% to 52% across various cohorts, often achieved in shorter timeframes than in clinical trials (62,63). For instance, in a Canadian study, the MMR rate was 39% at 6 months and 42% at 12 months. Similarly, a global chart review of patients with the T315I mutation reported consistent effectiveness with clinical trials, with 40-41.7% achieving MMR by 6 to 12 months. Real-world data also highlight asciminib's tolerability, with lower discontinuation rates due to intolerance or resistance compared to clinical trials (63). Cardiovascular events, a

concern with other TKIs, were infrequent in real-world settings, with one study reporting a 2.4% incidence over 18 months. Additionally, real-world studies indicate that asciminib is effective even in heavily pre-treated, multi-resistant populations, maintaining or improving molecular responses in a significant proportion of patients (64,65). Overall, these findings suggest that asciminib's real-world performance is consistent with its clinical trial outcomes, supporting its role as a viable treatment option for CML patients who have failed multiple lines of TKI therapy (63) **(Figure 4)**.

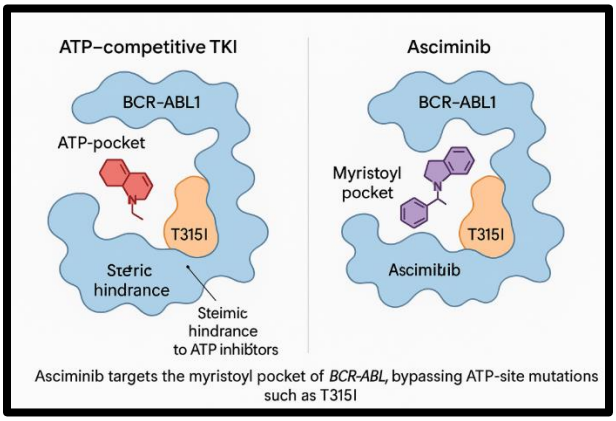

Figure 4. Asciminib targets the myristoyl pocket of BCR-ABL1, bypassing ATP-site mutations such as T315I.

11. Other Next-Generation Inhibitors in Development

The development of next-generation inhibitors across various oncogenic pathways is a rapidly evolving field, addressing the limitations of first-generation therapies, such as resistance and toxicity. In the context of Bruton's tyrosine kinase (BTK) inhibitors, new strategies include non-covalent inhibitors and BTK degraders, which are being developed to overcome resistance mutations like BTK C481S, a common issue with irreversible inhibitors (66,4). Similarly, in the realm of RET inhibitors, APS03118 has emerged as a potent next-generation option, demonstrating efficacy against resistant RET mutations and showing promising preclinical and early clinical trial results (67). For KRAS mutations, particularly the G12C variant, novel inhibitors are being explored alongside strategies like molecular shielding and targeted protein degradation to enhance efficacy and overcome resistance (68). In the case of TRK inhibitors, zurletrectinib has shown strong intracranial activity and effectiveness against TRK resistance mutations, outperforming other next-generation agents in preclinical models (69). Additionally, the development of next-generation androgen receptor inhibitors, such as apalutamide, darolutamide, and enzalutamide, has significantly improved outcomes in non-metastatic castration-resistant prostate cancer by delaying metastasis and improving survival (70). In the realm of JAK inhibitors, newer agents like fedratinib, momelotinib, and pacritinib are being evaluated for their roles in managing myeloproliferative neoplasms, particularly in patients who progress on ruxolitinib (71). Lastly, advancements in mTOR inhibitors, including dual PI3K/mTOR inhibitors and nanoparticle-based strategies, are being investigated to overcome resistance mechanisms in cancer treatment (72). These developments highlight the ongoing efforts to refine targeted therapies and address the challenges of resistance and toxicity in cancer treatment.

12. Future Directions in Overcoming Resistance

Although the therapeutic landscape of chronic myeloid leukemia (CML) has evolved remarkably with successive generations of tyrosine kinase inhibitors (TKIs) and the advent of asciminib, resistance continues to emerge through multifaceted molecular pathways. Future strategies must therefore focus on precision-based, multi-modal approaches that can pre-empt and overcome such resistance mechanisms. One promising direction is the rational combination of orthosteric and allosteric inhibitors, such as asciminib with imatinib or nilotinib, which has demonstrated synergistic inhibition of BCR-ABL1 activity. This dual blockade could prevent the clonal evolution of resistant leukemic subpopulations and enhance molecular response rates.

Beyond kinase inhibition, targeting leukemic stem cells (LSCs) represents another frontier in CML management. LSCs persist as a reservoir of disease relapse because of their quiescent state and independence from BCR-ABL1 signaling. Novel agents that modulate survival pathways like Wnt/β-catenin, Hedgehog, JAK/STAT, and autophagy signaling are being explored to eradicate this resistant niche. Additionally, immunotherapeutic strategies, including CAR-T cells, bispecific antibodies, and immune checkpoint inhibitors, are being investigated to stimulate immune-mediated clearance of residual leukemic cells.

Technological advancements such as next-generation sequencing (NGS) and digital PCR will play a pivotal role in adaptive therapy by enabling early detection of emerging mutations and allowing real-time therapeutic modification. The integration of machine learning models for mutation trajectory prediction and outcome forecasting may further refine personalized treatment decisions. Moreover, the design of BCR-ABL1 degraders and multi-kinase inhibitors capable of simultaneously targeting key compensatory

pathways (e.g., FLT3, AURKA, and CK2) holds promise in addressing both BCR-ABL1–dependent and independent mechanisms.

Finally, as clinical trials evaluate asciminib in frontline settings, its potential to induce deep molecular responses early in treatment may pave the way for treatment-free remission (TFR) strategies. Combining genomic, proteomic, and metabolomic data to guide therapy selection will bring CML management closer to the paradigm of personalized and durable remission.

13. CONCLUSION

The introduction of tyrosine kinase inhibitors revolutionized CML therapy, converting it from a fatal disease to a largely manageable chronic condition. However, despite these advances, resistance remains a persistent obstacle that threatens sustained remission and long-term survival. Resistance arises from both BCR-ABL1–dependent mutations, such as T315I and Y139D, and BCR-ABL1–independent processes, including leukemic stem cell persistence and activation of compensatory survival pathways. The development of asciminib, a first-in-class STAMP inhibitor that selectively targets the myristoyl pocket of ABL1, marks a paradigm shift in overcoming traditional ATP-competitive resistance. Its superior tolerability, clinical efficacy in multi-resistant cases, and compatibility with combination regimens position it as a cornerstone of next-generation CML therapy. Nonetheless, the emergence of novel resistance mutations and complex rearrangements underscores the need for continuous surveillance and therapeutic innovation. Looking ahead, the future of CML treatment lies in multi-targeted precision medicine—integrating molecular monitoring, stem cell eradication, and immune-based therapies. Through a combination of cutting-edge pharmacologic design, adaptive treatment algorithms, and real-time genomic profiling, the goal of achieving deep, durable, and treatment-free remission in CML is transitioning from aspiration to achievable reality.

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Conflict of interest

The authors declare no potential conflict of interest.

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Ethical statement

Not applicable, as this article is based on a review of previously published studies and does not involve new human or animal research.

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