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STAMP inhibitors and their future in CML therapy: a critical analysis

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Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm marked by the presence of the Philadelphia chromosome, which results in the BCR::ABL1 oncogenic fusion protein driving uncontrolled clonal expansion of myeloid cells [1]. Over the past two decades, prognosis of CML has improved significantly, primarily due to the development of ATP-competitive tyrosine kinase inhibitors (TKIs) targeting the BCR::ABL1 fusion protein [2, 3]. Imatinib and second-generation TKIs (2G-TKIs) (bosutinib, dasatinib, and nilotinib) function by binding to the ATP-binding site of kinases, preventing ATP from accessing the site and activating the kinase. These agents are utilized as first-line and later-line strategies in patients with CML in chronic phase (CML-CP).

In clinical practice, choice of frontline TKI is shaped by patient risk profile, comorbidities, and treatment goals. Imatinib is the most widely used frontline agent due to its well-established efficacy, tolerability, and cost-effectiveness, while 2G-TKIs are generally reserved for patients with high-risk features or when a more rapid and profound molecular response (MR) is desired. Ponatinib, a third-generation TKI (3G-TKI), can be used in CML-CP patients who have failed at least one 2G-TKI or who carry the T315I gatekeeper mutation, which confers resistance to all other approved TKIs. However, despite these advancements, a considerable proportion of patients experience resistance or intolerance, requiring a switch to alternative treatments [2].

To address these limitations, novel strategies, including allosteric inhibitors such as asciminib (initially ABL001) have been developed. Asciminib represents a new class of therapy, functioning as an allosteric inhibitor that specifically targets the ABL Myristoyl Pocket (STAMP), distinguishing it from conventional ATP-competitive TKIs [3].

The CABL001X2101 trial (NCT02081378), a first-in-human phase I study, established the safety and efficacy of asciminib in patients with CML-CP resistant or intolerant to ≥2 TKIs, including patients pretreated with ponatinib and those with the T315I mutation [4]. The trial also identified 40 mg twice daily (BID) as the recommended dose (primary endpoint). Notably, final results published by Hochhaus et al. confirmed the long-term efficacy and tolerability of asciminib, with continued improvements in MR over time and no new safety concerns, supporting asciminib as a potential long-term treatment option in heavily pretreated CML-CP [5]. While these results are highly promising, the lack of a comparator arm limits conclusions about the place of asciminib among other third-line options, and long-term benefit and safety at higher doses for T315I-positive patients remain under evaluation.

A subsequent phase III ASCEMBL trial (NCT03106779) compared asciminib to bosutinib in CML-CP patients who had failed ≥2 prior TKIs, showing superior major molecular response (MMR) at 24 weeks (25.5% vs. 13.2%) and sustained efficacy at 96 weeks (MMR 37.6% vs. 15.8%) [6]. Despite these encouraging results, some caveats should be highlighted. The treatment arms were not entirely balanced: more patients in the bosutinib arm had discontinued their prior TKI due to resistance (71.1% vs. 60.5%) rather than intolerance (28.9% vs. 37.6%), and a greater proportion had received ≥3 prior TKIs (60.5% vs. 47.8%) [7]. These differences may have contributed to the inferior outcomes in the bosutinib arm, amplifying the apparent efficacy of asciminib. In terms of safety, asciminib was associated with fewer overall adverse events (AEs) and discontinuations; however, arterial-occlusive events (AOEs) were more frequent with asciminib than bosutinib (5.1% vs. 1.3%) [6], although the longer median exposure to asciminib (23.7 vs. 7 months) may partially explain this imbalance. Importantly, the lack of stratification by baseline cardiovascular risk limits definitive safety conclusions, highlighting the need for careful long-term evaluation. Furthermore, the relatively limited real-world use of bosutinib—primarily due to gastrointestinal and hepatic toxicities—reduces the direct clinical applicability of this trial. Without a head-to-head comparison with ponatinib, the other major third-line option, the optimal sequencing of these agents remains uncertain.

Based on favorable outcomes from the phase I and ASCEMBL trials, asciminib was initially approved for third-line CML therapy and for patients with T315I mutation [2]. More recently, in October 2024, asciminib received approval from the US Food and Drug Administration for newly diagnosed CML-CP based on the ASC4FIRST trial (NCT04971226), demonstrating superior efficacy in the frontline setting compared to the investigator's choice TKI [8]. Nevertheless, interpretation of ASC4FIRST warrants caution. Within the investigator choice arm, patients allocated to imatinib were generally older (median age 54.5 years vs. 43.0 years in the 2G-TKI stratum; 31.4% vs. 16.7% aged ≥65 years) and had a higher comorbidity burden [Charlson comorbidity index score (CCI) ≥ 5: 30.4% vs. 12.8%, high Framingham-estimated 10-year cardiovascular risk: 32.4% vs. 14.7%] than those assigned to 2G-TKIs, reflecting physician preference in clinical practice. However, this design created an imbalance between the imatinib and overall asciminib groups, including a lower proportion of younger patients (18 to <65 years: 68.6% vs. 77.1%), a higher prevalence of significant comorbidities (CCI ≥ 5: 30.4% vs. 21.9%), and a greater proportion with intermediate or high Framingham-estimated cardiovascular risk (60.8% vs. 45.8%). These differences may have favored asciminib in safety comparisons when evaluated against imatinib. Importantly, despite this imbalance, AOEs occurred with asciminib (1%) but not with imatinib, underscoring the need for longer follow-up to clarify cardiovascular safety. In our opinion, asciminib should not yet be adopted as a preferred-choice frontline agent without meeting key benchmarks: higher rates of durable deep molecular response (DMR), a confirmed long-term (8–10 year) safety advantage—

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particularly with respect to AOEs—, and cost-effectiveness (ideally < US$20,000–30,000/year). These requirements are crucial given the availability of highly effective, low-cost TKIs such as imatinib (~US$500/year) and dasatinib (~US$5000–10,000/year) that already normalise survival and achieve high DMR and treatment-free remission rates. Similar caution has been expressed by Jabbour et al. as well [2].

The distinct mechanism of asciminib has prompted investigations into its combinations with conventional TKIs to enhance BCR::ABL1 inhibition and overcome resistance. Supported by strong preclinical evidence of synergy in both in vitro and in vivo models, several trials are exploring the efficacy and safety of asciminib in various combination settings [2, 9]. Among these approaches, perhaps the most promising potential application of asciminib lies in its combination with ATP-competitive TKIs, particularly ponatinib, for the treatment of advanced or refractory CML. This dual targeting of the ATP-binding and myristoyl pockets may prove particularly valuable in patients with advanced disease or compound mutations, where treatment options are limited. Although of little commercial interest given the rarity of advanced-phase CML in the TKI era, such combinations may ultimately represent the setting in which asciminib delivers its greatest therapeutic value.

Building on the success of asciminib, TGRX-678 has emerged as an allosteric inhibitor with considerable therapeutic promise (Table 1). In a recent publication, Shi et al. detailed the preclinical characterization of TGRX-678, highlighting its high selectivity, potent BCR::ABL1 inhibition, and unique pharmacological properties, including brain penetrance and resistance to ABCB1/ABCG2-mediated efflux [10]. The study also demonstrated in vivo efficacy in a CNS blast crisis model and showed that TGRX-678, when combined with ponatinib, more effectively suppressed resistant compound mutants than asciminib, underscoring its potential role in addressing advanced or refractory CML. These features may offer advantages in managing CNS involvement and complex resistance profiles; however, translation from preclinical models to sustained clinical benefit is yet to be studied. Moreover, head-to-head trials against ponatinib and/or asciminib will be needed to confirm any incremental benefit.

Preliminary results from a phase Ia/Ib trial (NCT05434312) presented at ASH 2023 and 2024 evaluated TGRX-678 in patients with CML-CP and CML in accelerated phase (CML-AP) resistant or intolerant to ≥3 TKIs [10]. Dose escalation included 10–80 mg BID or 40–240 mg once daily (QD), with no maximum tolerated dose (MTD) reached.

In phase Ib, 158 patients were enrolled into three cohorts: CML-CP without T315I and ≥2 TKI failures; CML-CP with T315I and ≥1 TKI failure; CML-AP with ≥1 TKI failure [11]. As of the data cut-off in November 2024, with the median treatment duration of 17 months, TGRX-678 was well tolerated and demonstrated clinical activity across all groups, including in those pretreated with 3G-TKIs or STAMP inhibitors.

Among 107 CML-CP patients, cumulative complete hematologic response (CHR), major cytogenetic response (MCyR), complete cytogenetic response (CCyR), and MMR rates were 88%, 59%, 48%, and 28%, respectively. Among 51 patients with CML-AP, rates of major hematologic response (MHR), MCyR, CCyR, and MMR were 90%, 44%, 35%, and 23%, respectively. Higher doses correlated with improved responses in CML-AP, though mutation-specific patterns were not definitive. Notably, MR outcomes were stronger in patients without prior exposure to 3G-TKIs or asciminib. At 24 months, progression-free survival (PFS) and overall survival (OS) were 95% (CML-CP) and 81% and 77%, respectively (CML-AP).

Treatment discontinuations occurred due to progression ($n = 12$), AEs ($n = 7$), consent withdrawal ($n = 9$), or other reasons ($n = 22$). One death occurred but was not treatment-related. Grade ≥ 3 hematologic treatment-related adverse

Table 1. Ongoing clinical trials of TGRX-678 and TERN-701.

Trial name	NCT	Agent	Phase	Population	Primary endpoint	Key results
TGRX-678–1001	NCT05434312	TGRX-678	Ia/Ib	CML-CP/AP, ≥3 TKIs	MTD	Well tolerated; CHR 88%, MMR 28% in CML-CP; activity in T315I and compound mutants; CNS activity confirmed
–	NCT06088888	TGRX-678	I	CML-CP/AP	MTD or recommended dose	Ongoing; results not yet reported
–	NCT06453902	TGRX-678	II	CML-AP, prior 3G-TKI	Undisclosed	Ongoing; results not yet reported
–	NCT05367700	TERN-701	I	CML-CP/AP, TKI-resistant	MTD in escalation; efficacy in expansion (undisclosed)	Ongoing; results not yet reported
CARDINAL	NCT06163430	TERN-701	I	CML-CP, ≥1 prior 2G-TKI (± asciminib)	DLTs in escalation; MMR at 6 mo in expansion	No DLTs; well tolerated up to 500 mg; 6-month MMR data pending

2G-TKI second-generation tyrosine kinase inhibitor, *CHR* complete hematological response, *CML-AP* chronic myeloid leukemia in accelerated phase, *CML-CP* chronic myeloid leukemia in chronic phase, *CNS* central nervous system, *DLT* dose-limiting toxicity, *MMR* major molecular response, *MTD* maximum tolerated dose, *NCT* National Clinical Trial.

events (TRAEs) included thrombocytopenia (47%), neutropenia (46%), leukopenia (30%), and anemia (27%). Most non-hematologic TRAEs were mild and included hypertriglyceridemia, hyperuricemia, hypercholesterolemia, and hyperglycemia. As of the cutoff, the trial remained active in 76% of CML-CP and 51% of CML-AP patients. While the response rates are encouraging in heavily pretreated cohorts, the depth of response, particularly for MMR, remains limited. Extended follow-up data will be needed to assess the durability of these remissions and their impact on PFS. Additional phase II (NCT06453902) and phase I (NCT06088888) trials of TGRX-678 are underway in China and the U.S, respectively [11].

TERN-701 (HS-10382) is another investigational allosteric BCR::ABL1 inhibitor (Table 1). Preclinical data presented at the 2023 ASH meeting and 2025 European Hematology Association (EHA) meeting demonstrated stronger BCR::ABL1 selectivity, comparable or greater potency than asciminib, and synergy with ATP-competitive TKIs, including activity against T315I [12, 13].

The ongoing CARDINAL trial (NCT06163430) is a global, open-label phase I study evaluating safety, pharmacokinetics, and efficacy in CML-CP patients previously treated with ≥1 2G-TKI, including those pretreated with asciminib [14]. Interim results from Terns Pharmaceuticals (Foster City, California) reported no dose-limiting toxicities up to 500 mg QD [15]. No discontinuations or dose reductions occurred due to AEs.

A dose-expansion phase launched in April 2025 will randomize patients to 320 mg or 500 mg QD (up to 40 patients per arm), with 6-month MMR results anticipated in late 2025. A separate phase I study (NCT05367700) is ongoing in China to evaluate TERN-701 in CML-CP and CML-AP patients resistant or intolerant to TKIs [16].

Collectively, the CML treatment landscape is evolving toward multiple agents targeting BCR::ABL1 through distinct mechanisms. The central challenge is no longer the lack of effective therapies, but rather how to optimally sequence them to maximise efficacy, minimise toxicity, and preserve future treatment options. Direct comparative trials are lacking, leaving uncertainty in resistant disease management. Moreover, the potential benefits of newer agents such as TGRX-678 and TERN-701 must be weighed against their cost and availability in the future. Integrating these novel agents into treatment algorithms will require both robust long-term follow-up and head-to-head evidence to define their true clinical and economic value.

In conclusion, despite encouraging early data and growing interest in STAMP inhibitors, imatinib still remains the preferred choice in frontline therapy in most regions. While asciminib has demonstrated superior efficacy over investigator-selected TKIs in the first-line setting, its adoption should await long-term safety data and confirmation in real-world studies.

In our opinion, the current positioning of asciminib appears strongest in second- and later-line settings, particularly for patients with intolerance to prior TKIs or those harbouring specific mutations, and studies comparing it directly with ponatinib are warranted. Looking ahead, the greatest added value of asciminib to the CML armamentarium may lie not in monotherapy but in rational combination strategies. For next-generation STAMP inhibitors, including TGRX-678 and TERN-701, available early evidence supports their development in heavily pretreated or T315I-positive populations, but broader use is premature.

Cost is another critical consideration influencing treatment decisions. The availability of generic imatinib has significantly expanded global access to CML treatment. In contrast, novel agents are likely to be significantly more expensive, raising concerns about equity and sustainability, particularly in low- and middle-income countries.

While STAMP inhibitors represent an exciting mechanistic shift in CML therapy, their role must be defined carefully, integrating efficacy, safety, access, and health economics. Only with further follow-up and validation will it be clear whether these agents can truly reshape the CML therapy paradigm or will remain niche options for selected patients.

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COMPETING INTERESTS

The authors declare no competing interests.