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CHRONIC MYELOID LEUKEMIAS (MJ MAURO AND G SAGLIO, SECTION EDITORS)

# Future Directions in Chronic Phase CML Treatment

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## Abstract

**Purpose of Review** This review will focus on recent and emerging treatment paradigms in chronic phase CML. The discussion of each novel treatment or drug combination will include a brief overview of scientific rational and pre-clinical data, followed by recently published or ongoing clinical trial efforts. The review will be divided into three focus areas in CML treatment: new frontline approaches and approaches to deepen remission, second treatment-free remission studies, and the treatment of refractory disease.

**Recent Findings** The section on new frontline approaches will highlight several strategies of combination therapy. These can be grouped into immunomodulatory approaches with interferons and immune checkpoint inhibitors, targeting of leukemia stem cells with compounds such as venetoclax and pioglitazone, and BCR-ABL1-intrinsic combination therapy with asciminib. The chance at a second treatment-free remission is an important emerging clinical trial concept, and again combination approaches are under investigation. Lastly, in advanced disease, the development of novel tyrosine kinase inhibitors remains a major focus.

**Summary** This review will provide an overview and perspective of treatment strategies on the horizon for chronic phase CML. Despite the already excellent clinical outcomes for most patients, challenges remain with regard to deepening initial responses, prolonging treatment-free remission, and providing efficacious and tolerable options for patients with refractory disease and resistance mutations.

**Keywords** Chronic myeloid leukemia · Tyrosine kinase inhibitor · Treatment-free remission · Leukemia stem cell · Interferon · BH3 mimetics · Immune checkpoint inhibitor · PPAR ligand

## Introduction

Tyrosine kinase inhibitors (TKIs) are the mainstay of current chronic myeloid leukemia (CML) treatment, and have produced high remission rates, fewer side effects, and vastly improved patient survival compared to the prior standard of care [1]. However, clinical challenges in the treatment of CML remain. New treatment approaches are needed to improve the depth and durability of response, avoid the development of TKI resistance, provide treatment that limits TKI toxicity, and provide the chance of successfully remaining in treatment-free remission. The initial goal of frontline treatment previously was to achieve a cytogenetic remission accompanied by a molecular remission to improve overall survival [2]. With the recent acceptance of treatment-free remission (TFR), the goal of frontline treatment now also includes the goal of achieving a deep molecular response, meaning a BCR-ABL1 transcript level at or below 0.01% on the international scale (also referred to as MR4, or a 4 logs reduction from baseline). This enables TKI discontinuation in approximately half of all patients. TFR has become an important goal because it improves patients' quality of life, frees patients from chronic TKI toxicities, and saves drug cost. However, even during treatment-free remission, it is understood that quiescent leukemia stem cells remain. These stem cells remain an important focus of many treatment approaches described here, as they represent a barrier to cure. We have limited the scope of this review to chronic phase CML as accelerated and blast phase CML are clinically and biologically very distinct disease entities.

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## New Frontline Approaches and Approaches to Deepen Remission

Treatment efforts in the frontline setting are aimed primarily at achieving a cytogenetic and molecular response, which correlates with overall survival, and at accelerating the time to deep molecular response, which can enable TKI discontinuation. Currently, it is estimated that 30–40% of patients treated with imatinib and 40–50% of patients treated with second-generation TKIs meet the discontinuation criteria; however, there are no predictive models to determine who is at risk of not achieving a deep remission. As TFR is a relatively new concept and goal in CML therapy, there are currently no approved treatments that can be selected to increase the chance of achieving a deep molecular response, or treatment adjuncts that could be added if a patient is not on track to achieve the desired response. Ultimately, the goal is to increase the percentage of patients eligible for discontinuation, prolong time off treatment, and eventually even achieve a cure in most patients. Several approaches to achieve these goals are under investigation. It should be noted that the primary endpoint for most studies in the following section is the proportion of patients who achieve a deep molecular response, but that the treatment-free remission period is not included in any of the study designs. While these studies will therefore answer our first objective, finding therapies to maximize the number of patients eligible for TFR, they will not directly inform which treatments provide the best chance of a sustained treatment-free remission.

### Asciminib TKI Combinations

In February 2021, asciminib was granted breakthrough therapy designation by the FDA for the treatment of patients with CML previously treated with two or more TKIs. Asciminib was also granted breakthrough status for the treatment of patients with CML harboring the T315I mutation. Currently, asciminib has been evaluated in patients who have not responded to > 2 TKIs [3]. However, the efficacy and safety of asciminib raises the possibility that it could be used earlier, perhaps even as first-line therapy, to enhance the speed and depth of response. The combination of an ATP-pocket targeting TKI with asciminib also has the potential to prevent the development of resistance due to point mutations in one of the binding sites. An ongoing non-randomized Phase 2 study in Germany is testing these hypotheses across four arms with various doses of asciminib combined with imatinib, nilotinib, or dasatinib. The primary outcome measure is rate of deep molecular response (MR4), with a projected completion date in November 2022. Secondary outcome measures will be molecular response at 6, 12, 18, and 24 months, adverse events, progression free survival, and overall survival at month 24 (NCT03906292). A Novartis-initiated international study currently in the pre-recruitment phase will randomize patients who have been treated with imatinib first line for at least one year without achieving a deep molecular response to continued imatinib with or without two different doses of asciminib versus a switch to nilotinib (NCT03578367). A similar study will be conducted at MD Anderson, where patients currently treated with nilotinib or dasatinib who have achieved a complete cytogenetic response but who have never achieved, or plateaued after achieving a major molecular response, will receive asciminib for up to 36 months (NCT04216563). Together, these studies will help delineate the role of asciminib in the early treatment stages of CML.

### TKI Ruxolitinib Combination

Activation of the JAK-STAT3 pathway can contribute to BCR-ABL-independent CML cell survival during exposure to TKIs. Pre-clinical studies have demonstrated that inhibition of this pathway can re-sensitize cells to BCR-ABL inhibition while they are exposed to protective cytokines [4, 5]. In addition, the pan-JAK inhibitor ruxolitinib may decrease production of various protective cytokines, as demonstrated in myelofibrosis [6]. A phase I clinical trial investigated the tolerability and safety of adding ruxolitinib in CML patients treated with nilotinib who had molecular evidence of disease as defined by a detectable BCR-ABL1 transcript using qRT-PCR with a sensitivity of 4.5 logs [7]. Of eleven patients, one patient experienced a grade 3/4 adverse event (hypophosphatemia) and 4 patients experienced grade 1/2 anemia. Of 10 patients who were evaluable for responses, 4 had undetectable BCR-ABL transcripts at 6 months. A subsequent phase 2 SWOG study is currently in process and will evaluate the addition of ruxolitinib in patients who have received at least one year of treatment with bosutinib, dasatinib, or nilotinib and have molecularly detectable disease (NCT03654768).

### Dasatinib Venetoclax Combination

The anti-apoptotic BH3-only family member BCL-2 is upregulated in quiescent CML leukemia stem cells that contribute to therapeutic resistance [8]. In pre-clinical models, the combination of venetoclax and TKI eradicated CML leukemia stem cells and prolonged survival in a murine CML model [9]. A retrospective study at the University of Texas MD Anderson Cancer Center on the use of venetoclax combined with TKIs in patients with advanced CML showed encouraging results in a heavily pretreated population. In

particular, patients with CML in myeloid blast crisis had a response rate of 75% and had a median OS of 10.9 months, which compares favorably to response durations from other studies with single-agent dasatinib [10•]. Based on these encouraging data in advanced phase CML, a phase 2 clinical trial for upfront use of dasatinib compared with dasatinib with venetoclax in chronic phase CML is now under way. This is a non-randomized study in which patients were recruited either to a dasatinib-only arm, or to an arm that started with dasatinib alone and then added venetoclax after 3 months (NCT02689440). The primary objective is to estimate the proportion of patients who achieve major molecular response by 12 months of treatment.

### TKI Interferon Combination

Prior to the advent of imatinib, interferon-alpha was the treatment of choice for CML. Interferon-based therapy has experienced a resurgence in other myeloproliferative neoplasms thanks to improved tolerability of new pegylated formulations and the potential for disease-modifying activity [11]. In early clinical trials of imatinib combined with interferon, such as the exploratory GIMEMA studies, the French SPIRIT trial in 2010, the Nordic CML trial in 2011, and an arm of the German CML IV trial in 2017, significantly higher molecular response rates were initially observed with the combination, but the discontinuation rate for interferon was high, and where long-term follow-up is available, no difference in remission rate or overall survival was reported [12–16]. Second-generation TKIs are now being explored in combination with pegylated interferons in phase 3 trials. The BosuPeg trial compares bosutinib alone to bosutinib combined with ropeginterferon, which is administered every two weeks and is well-tolerated in polycythemia vera (NCT03831776). Two trials are ongoing to test the addition of interferons to nilotinib, in the case of the German TIGER study in the form on peginterferon alpha-2b (NCT01657604), where the combination arm will stop nilotinib after confirmation of a major molecular response, but will continue interferon for the study duration, up to 5 years. In the case of the French PETALs study, nilotinib is combined with peginterferon alpha-2a (NCT02201459). The interferon will be administered at 30 µg/week the first month prior to nilotinib initiation, then at 30 µg/every other week the first month of combination to nilotinib, and then at 45 µg/week thereafter until month 24 after nilotinib initiation.

### TKI Immune Checkpoint Inhibitor Combination

In addition to immunomodulation with interferons, treatment with immune checkpoint inhibitors is of interest based on preclinical data and is being explored in a small number of clinical trials.

PD-1 is upregulated on CD8 + T cells in CML patients [17], and blocking the PD-1/ligand interaction prolonged survival in a murine model [18]. Dasatinib in particular has been postulated to have synergy with immune checkpoint inhibitors based on the observation that a high proportion of patients treated with dasatinib develop a persistent large granular lymphocytosis with clonal TCR rearrangement, which is associated with higher response rates and prolonged survival [19]. The combination of dasatinib and nivolumab was tested in a phase 1b study in patients who had received two or more prior TKIs and had intolerance, progression, resistance, or suboptimal response. The combination was safe but showed a low overall response rate and recruitment into the dose-expansion phase was stopped [20]. One arm of the French ACTIW study will test the addition of avelumab to TKI with the aim to deepen complete cytogenetic response to a deep molecular response (NCT02767063). Another ongoing trial with similar design was initiated by the Eastern Cooperative Oncology Group with the primary objective of assessing the proportion of CML patients on a stable TKI regimen who convert to undetectable minimal residual disease (defined as MR4.5) within 2 years of adding pembrolizumab to their treatment (NCT03516279). Allowable TKIs in this study are imatinib, dasatinib, and nilotinib. Patients receive 18 courses of pembrolizumab every 21 days. If MR4.5 is achieved, the study continues for another 18 cycles with daily TKI treatment alone. If MR4.5 is not achieved, but disease progression or unacceptable toxicity have not occurred, pembrolizumab is continued for another 18 cycles.

### TKI Pioglitazone Combination

Laboratory data published in 2015 and 2016 demonstrated that pioglitazone, a PPAR $\gamma$ ligand, can stimulate the proliferation of quiescent CML leukemia stem cells and thereby deplete the stem cell pool [21]. In combination with various TKIs, pioglitazone reduced the colony-forming potential of a CML cell line and patient samples [22]. Another arm of the ACTIW study now investigates the combination of TKIs with pioglitazone (NCT02767063). Results of the phase II ACTIM clinical trial which investigated pioglitazone added to imatinib with the aim of deepening molecular responses showed that patients who received the combination achieved MR4.5 at 12 months in 56% of cases, compared to an estimated 23% with imatinib alone [23].

## Second Treatment-Free Remission

According to NCCN criteria [24], patients who achieve a response of MR4 or deeper become eligible for treatment discontinuation once they have received treatment with a

TKI for at least 3 years and have maintained the response for the last 2 years of treatment. In the previous section, we discussed approaches to deepen remission with the goal of increasing the percentage of patients eligible for TKI discontinuation. Treatment-free remission has recently become an important goal in CML treatment, as it frees patients from the financial and health consequences, including systemic and reproductive side effects, of chronic TKI therapy. Current treatment guidelines extend as far as the first discontinuation attempt, and resumption of TKI therapy in the event of relapse. A recent systematic review and meta-analysis of TKI discontinuation trials estimated the mean incidence of molecular relapse at one year at 39%, and at two years at 41%. Of all relapses, 82% occurred within the first 6 months. Thus, a prolonged treatment-free remission appears feasible in 59% of patients [25•]. While virtually all patients who relapse remain sensitive to TKI treatment, little data exists thus far on a second attempt at TKI cessation. Two of the reviewed approaches for optimizing frontline therapy, namely the combinations of TKI with ruxolitinib or asciminib, are now under investigation in second treatment-free remission studies.

### TKI Ruxolitinib Combination

As described above in the section on new frontline approaches, ruxolitinib has been postulated to undercut BCR-ABL-independent resistance mechanisms by inhibiting protective cytokine signaling in the bone marrow niche. Given the favorable risk profile of the combination in a phase I trial, this is an attractive strategy in the setting of relapse after treatment discontinuation as well. A trial sponsored by the H. Jean Khoury Cure CML Consortium (HJKC3) consortium and the H. Lee Moffitt Cancer Center is currently investigating whether the addition of ruxolitinib to TKI therapy can help patients achieve eligibility for a second treatment discontinuation, and whether the combination treatment will lead to prolonged treatment free remission (NCT03610971).

### Asciminib Imatinib Combination

Another study in collaboration between the HJKC3 consortium and the Medical College of Wisconsin currently in the pre-recruitment phase will investigate the combination of imatinib and asciminib in patients who relapsed after a prior attempt at TKI discontinuation (NCT04838041). The trial will involve treatment with the combination for all participants for one year, followed by evaluation for treatment discontinuation. Those who are eligible will discontinue both drugs, while those who are ineligible will continue imatinib alone. Response monitoring will continue for three additional years.

## Refractory Disease

The trial landscape in treatment refractory chronic phase CML remains the domain of novel TKIs. Refinement of BCR-ABL1 targeting strategies remains essential to increase the portfolio of agents available to heavily pretreated patients. In addition to targeting resistance mutations, increased specificity and tolerability are the main foci in drug development. Important forays into combination treatments are under way in this setting as well, although no successes can be reported thus far.

## New TKIs

A major focus of novel TKI development is targeting of the gatekeeper mutation T315I. Currently, only ponatinib is approved for the treatment of CML with this mutation, and in some countries, no approved third-generation TKI is available. In addition, motivations driving TKI development are the quest for increased kinase selectivity and the limitation of side effects, in particular the cardiovascular complications associated with ponatinib. Table 1 summarizes ongoing trials of novel TKIs in the USA.

#### Asciminib (ABL001)

Asciminib is the most advanced in clinical trials and at the same time the most novel in terms of inhibitor mechanism of the new TKIs currently under investigation. Rather than competing with ATP for a binding site in the active conformation of ABL, it specifically targets the myristoyl pocket and effects allosteric inhibition by trapping ABL in the inactive conformation. Asciminib has been discussed previously as an adjunct to ATP-competitive TKIs both in the frontline and in the second treatment-free remission setting. The initial dose escalation study included patients who had resistance or intolerance to at least two previous TKIs. Forty-eight percent of patients who could be evaluated achieved a major molecular response. A major molecular response was also achieved in patients who had been exposed to ponatinib, and in 28% of patients with T315I mutation. Common AEs included fatigue, headache, arthralgia, hypertension, and thrombocytopenia. Dose-limiting effects included asymptomatic elevations in the lipase level and clinical pancreatitis [26•]. Several phase 2 and 3 trials are currently ongoing to evaluate the efficacy of asciminib in previously treated patients with CML. Data from the phase 3 ASCEMBL trial, where asciminib was compared to bosutinib in patients with CML previously treated with two or more TKIs (NCT03106779), was presented at the 2020 ASH Annual Meeting. Data showed that, at 24 weeks, more patients achieved a complete cytogenetic response in the asciminib arm (40.8%) than in the bosutinib arm (24.2%),

**Table 1** Ongoing international and US clinical trials of novel tyrosine kinase inhibitors in CML. MMR, major molecular response; Cmax, maximal plasma concentration; AUC, area under the curve; DLTs, dose-limiting toxicities; MTD, maximum tolerated dose; MCyR, major cytogenetic response; MHR, major hematologic response; AEs, adverse events; CP, chronic phase; AP, accelerated phase; BP, blast phase

| Agent | Aim | Phase of development | Trial number | Primary endpoints | Preliminary results |
|---|---|---|---|---|---|
| Asciminib (ABL001) | Dose optimization in the 3rd and subsequent line | IIIb | NCT04948333 | MMR at 48 weeks | |
| | Efficacy and safety of asciminib versus best available therapy in patients previously treated with 2 or more tyrosine kinase inhibitors | III | NCT04795427 | MMR at 24 weeks | |
| | Asciminib versus bosutinib in patients previously treated with 2 or more tyrosine kinase inhibitors | III | NCT03106779 | MMR at 24 weeks | |
| Olverembatinib (HQP1351) | Pharmacokinetics, safety and efficacy in refractory CML and and Ph + acute lymphoblastic leukemia | Ib | NCT04260022 | Cmax, AUC | |
| PF-114 | Tolerability, safety, pharmacokinetics and preliminary efficacy in patients with resistance to 2nd generation Bcr-Abl inhibitors or T315I mutation | I | NCT02885766 | DLTs; MTD | Complete hematologic response 42% (8 of 19 evaluable patients), major cytogenetic response 29% (6 of 21 evaluable patints) [30] |
| Radotinib (IY5511) | Efficacy and safety in patients with failure or intolerance to previous tyrosine kinase inhibitors | III | NCT03459534 | MCyR at 6 months | |
| Vodobatinib (K0706) | Safety and anti-leukemic activity for patients intolerant to or failing ≥ 3 prior CML therapies | I/II | NCT02629692 | MTD; treatment-emergent AEs; proportion of CP subjects achieving MCyR; proportion of AP and BP subjects achieving MHR | Response rate 50% in ponatinib-treated, 67% in ponatinib-naïve CP patients [33] |

and deep molecular response rates were higher for patients in the asciminib arm than in the bosutinib arm — with 10.8% and 8.9% patients achieving MR4 and MR4.5 on asciminib, respectively, vs. 5.3% and 1.3% on bosutinib [3].The FDA granted breakthrough therapy designation to asciminib in February 2021. Another study will focus on dose optimization in heavily pre-treated patients (NCT04948333), while a Chinese phase 2 trial will randomize patients to asciminib vs best available therapy (NCT04795427).

#### Olverembatinib (HQP1351)

Olverembatinib is a novel third-generation TKI designed to effectively target BCR-ABL mutants, including T315I, and the first third-generation TKI developed in China, where currently no third-generation TKIs are available. In May 2020, olverembatinib was granted an Orphan Drug Designation and a Fast Track Designation by the FDA. In December 2020, clinical trial results of olverembatinib were selected for oral presentation at the ASH Annual Meeting. These data demonstrated a favorable safety and efficacy profile and promising efficacy readouts [27]: Data on a single-arm, multicenter, open-label study of olverembatinib in 41 patients with chronic-phase CML carrying the T315I mutation at a median 7.9 months follow-up showed a 3-month PFS of 100% and a 6-month PFS of 96.7%. None of the patients had a complete cytogenetic response at baseline, and 65.9% achieved a complete cytogenetic response, including 48.8% who achieved a major molecular response. The first phase 1b clinical trial in the USA is currently under way (NCT04260022). Eligibility includes patients who are resistant or intolerant to at least 3 TKIs, or those who carry the T315I mutation and are resistant or intolerant to ponatinib. For patients with cardiovascular risk factors, intolerance to ponatinib can be listed based on investigators' discretion. Given the risk for arterial occlusive disease and cardiovascular adverse events associated with ponatinib that first emerged in the phase II PACE trial [28], olverembatinib may fill an important niche in the US as well.

#### PF-114

PF-114 is a novel third-generation TKI that blocks native and mutated BCR-ABL1 isoforms including T315I. In preclinical studies, PF-114 showed improved selectivity for BCR-ABL1 compared to ponatinib [29]. A phase I clinical trial for patients who are resistant or intolerant to at least one second-generation TKI and imatinib or who carry the T315I mutation has been completed in Russia (NCT02885766). The interim analysis at the ASH annual meeting in 2018 reported a complete hematologic response in 8 of 19 evaluable patients including 3 out of 8 carrying the T315I mutation. Major cytogenetic response was achieved in 6 of 21 evaluable subjects including 3 of 7 with T315I. Major molecular response was achieved in 2 of 18 subjects who had completed at least 13 cycles. Dose-limiting toxicity was a psoriasis-like skin rash [30].

#### Radotinib (IY5511)

Radotinib is a novel second-generation inhibitor that inhibits common BCR-ABL1 mutations but not T315I. Radotinib is approved in South Korea, and the recent RERISE study found that it may yield similar long-term OS and progression-free survival and higher MMR rates compared with imatinib in patients with newly diagnosed CML, as well as lower rates of treatment failure and grade 3/4 neutropenia and hypophosphatemia [31]. A multinational single-arm phase 3 trial of radotinib is now under way in Russia, Turkey, and Ukraine for patients with CML who have experienced failure or intolerance to previous TKI therapy including imatinib. Patients with the T315I mutation are excluded from this trial (NCT03459534).

#### Vodobatinib (K0706)

Vodobatinib is a novel TKI that has activity against a large spectrum of clinically relevant mutations, but in pre-clinical studies showed decreased activity against T315I compared to ponatinib [32]. The agent has recently undergone a multicenter, open-label, dose escalation and expansion study to evaluate its safety and antileukemic activity and to determine the maximum therapeutic dose (NCT02629692). In an interim analysis presented at the ASH annual meeting in December 2020, vodobatinib demonstrated activity in patients who had previously undergone treatment with three other TKIs, or were ineligible for a third approved TKI, including activity against all mutations except T315I: Vodobatinib was evaluated in a 3 + 3 study design over 9 escalating doses. Exploratory analyses were conducted in two groups, one for patients previously treated with ponatinib (PT), and one for ponatinib-naïve patients (PN). Overall, efficacy was noted on both groups, with 50% of PT patients achieving a complete cytogenetic response, and 67% of PN patients achieving a complete cytogenetic response. However, there was only one patient with a T315I mutation (in the PN group), who had progression at an early dose, and several patients with baseline double (E225V + F317L; E225V + F359V) or single mutations (Y253H, F317L, and E255V) who also progressed. Early trial experience suggests excellent tolerability [33].

### Ponatinib Dose Range (OPTIC) Trial

Ponatinib remains an essential drug for heavily pre-treated CML patients and those with the T315I mutation. However,

the high rate of adverse cardiovascular events has raised the question whether the approved starting dose of 45 mg daily could be altered without loss of efficacy. The phase 2 OPTIC trial was designed to determine the optimal dose of ponatinib for safety and efficacy. An interim analysis of the trial was presented at the ASCO20 Virtual Scientific Program in July 2020. The trial has three cohorts with daily starting doses of 45, 30, and 15 mg (cohorts A, B, and C). The higher dose cohorts were reduced to 15 mg when patients achieved less than 1% BCR-ABL1 on the international scale or had an adverse event. At the interim analysis, discontinuation, dose reductions, or dose interruptions as a result of treatment-emergent adverse events had occurred in 69.1%, 57.4%, and 55.3% of cohorts A, B, and C respectively. Between the three cohorts, discontinuations were reported at 18.1%, 14.9%, and 13.8%, respectively. BCR-ABL1 less than 1% was achieved in 38.7, 27.4, and 26.5% of patients in cohorts A, B, and C respectively. However, the percentage of major molecular responses was not significantly different with a trend to a higher percentage in the lowest dose group [34]. Data from longer follow-up of this trial may support reduced ponatinib dosing.

### Dasatinib Nivolumab Combination

The rationale for the combination of TKIs, and in particular dasatinib, with immune checkpoint inhibitors is discussed above in a section on new frontline approaches. The safety and tolerability of the combination of dasatinib and nivolumab was investigated in a phase 1b dose-escalation study in patients with CML in chronic or accelerated phase. Eligible patients had received at least two prior TKIs with resistance or intolerance and were progressing, resistant to, or had a suboptimal response to their most recent therapy. The combination was shown to be safe, but unfortunately yielded no meaningful activity. No drug limiting toxicities were observed even with the maximum dose of both drugs. The overall response rate was low with none being durable [20]. The promise of controlling CML progression by blocking the PD1/PDL1 interaction and restoring the function of CML-specific cytotoxic T cells remains to be realized, hopefully in the described ongoing trials in the frontline setting.

## Conclusion

The development of new TKIs and combination treatments stand out as central themes across all areas of CML treatment discussed in this review. Many combination strategies are unified by the goal of achieving immune modulation to achieve leukemia stem cell clearance. To this end, the addition of immune checkpoint inhibitors and new interferon formulations to TKIs are being explored. This is an intriguing concept because it harkens back to earlier CML treatment history which documented a small percentage of durable remissions with interferon. The CML leukemia stem cell is also the target of combinations such as TKI plus venetoclax, ruxolitinib, and pioglitazone. The ongoing prolific development of TKIs highlights the enduring motivation to optimize the silver bullet. This will hopefully result in not only a wider armamentarium for the treatment of advanced disease, but will make third-generation TKIs more tolerable and accessible worldwide. Lastly, asciminib continues to stand out as a truly novel approach to targeting BCR-ABL1. There is enormous promise in the combination of asciminib with ATP-competitive TKIs, currently explored mainly in the frontline setting.

## Declarations

**Conflict of Interest** The authors declare no competing interests.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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