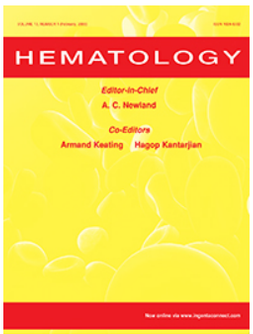

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REVIEW ARTICLE

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Treatment of chronic myeloid leukemia chronic phase patients in third-line setting and beyond: recommendations from a Belgian expert panel in 2025

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ABSTRACT

Introduction: Tyrosine kinase inhibitors (TKIs) have revolutionized the therapy of chronic myeloid leukemia (CML) in chronic phase, opening up the perspective of a normal life expectancy for most patients and of treatment-free remission for some of them. However, intolerance or resistance may necessitate treatment modifications.

Methods: A panel of five Belgian experts reviewed the treatment options in Belgium in 2025 for patients with chronic phase CML with resistance or intolerance to at least two lines of therapy.

Discussion: In contrast to the early years of TKI therapy, several options are available as third-line therapy or beyond for CML patients resistant or intolerant to at least two prior TKIs. These include the third generation TKI ponatinib, the allosteric BCR::ABL1 inhibitor asciminib, allogeneic hematopoietic stem cell transplantation, continuation of ongoing second-line TKI therapy with or without dose modification, or switching to alternative second generation TKIs. Careful consideration of the potency and safety profiles of these options, the clinical context, and treatment goal is needed. Ponatinib is currently reimbursed in Belgium for patients with CML showing resistance or intolerance to at least two prior TKIs, or with the BCR::ABL1 T315I mutation, regardless of the number of previous TKIs. Asciminib is currently reimbursed for patients with resistance or intolerance to at least two prior TKIs, excluding those with the BCR::ABL1 T315I mutation. This review provides guidance to weigh available safety and efficacy data in a setting of resistance or intolerance to second-line therapy with the goal of selecting the best available personalized treatment.

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BCR::ABL1 mutation; chronic myeloid leukemia; chronic phase; intolerance; personalized medicine; resistance; third-line setting; tyrosine kinase inhibitors

Plain language summary

Chronic myeloid leukemia, a cancer of the bone marrow, is typically caused by the acquisition of a specific genetic alteration, known as the t(9;22) translocation, and will be fatal if untreated. Currently, targeted therapies can control the disease and offer the patient a life expectancy comparable to the general population. However, intolerance or resistance to treatment may require adjustment of their treatment.

Experts reviewed data available on therapeutic options for patients who have undergone at least two prior treatments. Newly developed drugs, such as ponatinib or asciminib can be used, as well as allogeneic hematopoietic stem cell transplantation, continuation of ongoing treatment with or without dose adjustment or switching to alternative drugs.

To provide the best possible care for their patients, physicians need to choose and adapt treatment of chronic myeloid leukemia by carefully considering the benefits, possible side effects and the patient's response to previous treatments. This review aims to provide guidance to weigh the available safety and efficacy data to help physicians with this choice.

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Introduction

Chronic myeloid leukemia (CML) is typically diagnosed in chronic phase (CP). Unless treated with tyrosine kinase inhibitors (TKIs) or allogeneic stem cell transplantation (SCT), it will evolve to an aggressive and rapidly fatal blast phase after several years [1,2]. The defining driver mutation is the balanced translocation t(9;22)(q34;q11), creating the *BCR::ABL1* fusion gene on the derivative chromosome 22, also known as the Philadelphia chromosome. The encoded BCR::ABL1 fusion protein has constitutive tyrosine kinase activity.

The pivotal role of the kinase activity of BCR::ABL1 in the pathogenesis of CML has been exemplified by the response of CML to TKIs [2–4]. In most cases, TKIs prevent the evolution of CML to blast phase and most patients treated with TKIs enjoy a life expectancy comparable to the general population [5,6]. However, an estimated 25% of patients will develop intolerance or resistance and need treatment modification or adjustment [7,8].

Imatinib was the first generation (1G) TKI approved for frontline treatment of newly diagnosed CML-CP [9]. Second generation TKIs (2G-TKIs), such as dasatinib, nilotinib, and bosutinib, were subsequently developed to tackle imatinib intolerance and resistance mediated by several *BCR::ABL1* kinase domain (KD) point mutations. In addition, they also showed improved antileukemic activity [5]. In Belgium, these 2G-TKIs can currently be used as first-line treatment in patients with CML with an intermediate- or high-risk European Treatment Outcome Study (EUTOS) long-term survival score (ELTS) or Sokal score, or as an option to improve the probability of treatment-free remission (TFR), irrespective of the ELTS score. In case of treatment failure of one 2G-TKI, switching among 2G-TKIs is rarely successful, unless specific underlying KD mutations explain resistance to a specific TKI and predict sensitivity to another. Furthermore, the gatekeeper BCR::ABL1 T315I mutation is panresistant to all 2G-TKIs [5,10]. The context of resistance requires treatment options that can halt disease progression, improve survival prospects, and maintain quality of life [5,11,12].

Ponatinib is a highly potent third generation TKI (3G-TKI). Its development as a first-line treatment for CML-CP was halted due to excess cardiovascular toxicity [13]. Yet, it remains an effective therapeutic option for patients showing resistance or intolerance to at least two prior TKIs and for those with the BCR::ABL1 T315I mutation [14–17]. Its potential cardiovascular toxicity and dose-dependent rates of arterial occlusive events (AOEs) mandate careful selection of patients and monitoring of toxicity, as well as dose adjustments once a *BCR::ABL1* transcript level <1.0% on the international scale (*BCR::ABL1*^{IS}) has been reached [5].

1G-, 2G- and 3G-TKI are adenosine triphosphate (ATP)-competitive: they inhibit the constitutive BCR::ABL1 kinase activity by preventing access of ATP to its kinase groove. By contrast, asciminib is a first-in-class allosteric BCR::ABL1 inhibitor acting by a distinct mechanism: it specifically targets the ABL1 myristoyl pocket (STAMP), coercing BCR::ABL1 into its inactive, autoinhibited conformation [18]. Although infrequent (<1% of CML cases), *BCR::ABL1* transcript variants e13a3 and e14a3, which lack exon 2 of ABL1, lead to a lack of a functional SH3 domain required for asciminib action as evidenced in *in vitro* experiments. Therefore, CML patients in whom the e13a3 or e14a3 transcripts are identified, are predicted to be resistant to asciminib treatment [19]. In a phase 1 trial, asciminib was shown to be active in heavily pretreated, resistant or intolerant patients, with an acceptable safety profile [20]. The phase 3 ASCEMBL registration trial demonstrated superior efficacy and a better tolerability profile of asciminib over bosutinib in adult patients with CML-CP and intolerance or resistance to at least two prior lines of TKI therapy, with fewer adverse events (AEs) [21–23]. Asciminib was approved in Europe in 2022 for patients with CML-CP without the T315I mutation in third-line setting and beyond. The findings of the ASCEMBL study have recently been confirmed by real-world data from Canada, the United States, Spain, and the Netherlands [24–27].

According to data from the Belgian Cancer Registry, incidence rates of CML during 2013–2023 ranged between 1.3 and 1.7 cases per 100,000 person-years, corresponding to approximately 150–200 cases every year [28]. During that same period, 2–11 allogeneic stem cell transplantations were performed per year (median 5 per year), illustrating that in the era of multiple, potent TKIs, indications for transplants are rare. In Belgium, typical indications are persistent cytopenias on multiple TKIs, lack of achieving complete cytogenetic remission (CCyR) on all available TKIs, evolution to accelerated phase during TKI therapy, or blast phase of CML. The preferred stem cell source is peripheral blood stem cells, either from a sibling donor, or from an HLA-matched unrelated donor.

A panel of five Belgian experts in the field of CML convened to leverage their collective expertise on the management of CML in patients resistant or intolerant to at least two lines of therapy in Belgium, in the context of the current (2025) national reimbursement criteria. The goal of the panel is to support hematologists in choosing optimal treatment for their patients, in the best personalized way taking into account each patient's treatment history and clinical context.

General considerations on third-line treatment in CML-CP

Treatment goals in CML-CP

TKI therapy of CML requires careful three-monthly monitoring of disease response along with therapy-associated toxicities. Additionally, the treatment goals set for each individual patient need to be taken into account. In the 2020 European LeukemiaNet (ELN) guidelines [5], achieving TFR is an important treatment goal, in particular for young patients. To maximize the chance of achieving TFR with first- or second-line therapy, the ELN recommendations categorize responses into 'optimal', 'warning', or 'failure' by defining maximal levels of leukemic burden allowed at given milestones in time. For CML needing third- or higher-line therapy, the aim of TFR is often abandoned in favor of securing long-term survival. Here, ELN guidelines recommend aiming for a leukemic burden with *BCR::ABL1*^{IS} <1% or for CCyR, the proverbial safe haven in CML associated with optimal survival. Easing the pressure from maximal reduction of the leukemic burden to *BCR::ABL1*^{IS} <1% or at least CCyR also implies that in addition to escalation to allogeneic SCT or to more potent TKIs such as asciminib or ponatinib, continuation or dose adjustment of 2G-TKI, or switching to another 2G-TKI can also be considered as treatment options.

In this manuscript, the panel of experts discusses the management of failure and/or intolerance of TKI treatment beyond second-line treatment. The experts have identified four major clinical scenarios including (i) primary refractory disease with failure to meet ELN treatment milestones [5], (ii) failure to achieve optimal time-dependent molecular targets despite TKI-responsive disease, (iii) acquired secondary resistance with or without *BCR::ABL1* KD mutations, and (iv) intolerance to previous 2G-TKIs.

Clinical studies

In Belgium, ponatinib and asciminib are reimbursed for CML resistant or intolerant to at least two prior TKIs. Ponatinib is also reimbursed for CML with the BCR::ABL1 T315I mutation, regardless of the number of prior treatment lines. This reimbursement is based on separate clinical trials: PACE and OPTIC for ponatinib [14–16], and ASCEMBL for asciminib [21,22]. In the absence of a direct comparative study, insight in the study designs and patient populations is required to make an educated choice between ponatinib and asciminib for individual patients (Table 1).

PACE was a phase 2 trial of ponatinib in adult patients with CML or Philadelphia chromosome positive (Ph^+) acute lymphoblastic leukemia (ALL), resistant or intolerant to dasatinib or nilotinib, or with the BCR::ABL1 T315I mutation [14]. In this study, 270 patients had CML-CP, including 64 (24%) with the BCR::ABL1 T315I mutation. The ponatinib starting dose was 45 mg once daily, with a median treatment duration of 32.1 months and a median follow-up of 56.8 months. Among 267 evaluable patients, 159 (60%) patients achieved a major cytogenetic response (MCyR) at any time during the study, 108 (40%) patients achieved a major molecular response (MMR), and 64 (24%) patients achieved a 4.5-log molecular response ($MR^{4.5}$: *BCR::ABL1*^{IS} ≤0.0032% or undetectable) [15]. Following the high incidence of serious AOEs in about 25% of patients, the follow-up OPTIC study demonstrated that reduction of the ponatinib dose to 15 mg daily after achieving *BCR::ABL1*^{IS} ≤1% mitigated this risk, with improved survival rates [16,17].

The ASCEMBL trial was an open-label, randomized, phase 3 study, in which patients with CML-CP (N = 233) previously treated with at least two TKIs were randomized to either 40 mg asciminib twice daily (N = 157) or 500 mg bosutinib once daily (N = 76) [21]. Patients with the BCR::ABL1 T315I or V299L mutations were excluded due to their resistance to bosutinib. After a median follow-up of 14.9 months, the study met its primary endpoint with an MMR rate of 25.5% at 24 weeks with asciminib, compared to a 13.2% MMR rate with bosutinib [21]. Its key secondary endpoints were also met with improved MMR rate at 96 weeks (37.6% versus 15.8%) and improved CCyR rates at 24 weeks (40.8% versus 24.2%) and 96 weeks (39.8%

Table 1. Details of the PACE, OPTIC, and ASCEMBL trials.

PACE trial [14,15]	
Study Design	Phase 2, open-label
Dosage	Starting dose: 45 mg ponatinib once daily (Dose reduction during study allowed for SAE)
Treatment duration	Median 32.1 months (CML-CP cohort)
Follow-up	Median 56.8 months (CML-CP cohort)
Main eligibility criteria	CML or Ph^+ ALL Resistant or intolerant to dasatinib or nilotinib or T315I mutation present
Participants (CML-CP cohort)	203 (resistant or intolerant) of which 39 (14%) intolerant-only; 64 (with T315I mutation)
Response at study entry	Ph^+ <35%: 53 (20%)
Fraction *BCR::ABL1*^{IS} between 0.1% and 1%	Not eligible
Study definitions	
Resistance definition	- No complete hematological response or no cytogenetic response (>95% Ph^+) after three months - Less than minor cytogenetic response (>65% Ph^+) after six months - Less than PCyR (>35% Ph^+) after twelve months - New cytogenetic abnormalities in the absence of CCyR - Loss of any cytogenetic response - Disease progression
Intolerance definition	Unresponsive grade 3 or grade 4 toxicity in the absence of CCyR
Results	
Efficacy (at any time during treatment)	MCyR: 159 (60%) CCyR: 144 (54%) MMR: 108 (40%) $MR^{4.5}$: 64 (24%)
SAE	Pancreatitis (7%) Atrial fibrillation (6%) Pneumonia (6%) Angina pectoris (5%) Note: 84 AOEs occurred in 46 patients
Study discontinuation due to AE	57 (21%)
OPTIC trial [16]	
Study Design	Phase 2, open-label
Dosage	Starting dose: 45, 30, or 15 mg ponatinib once daily (Dose reduction to 15 mg upon CCyR)
Treatment duration	Ongoing in 47.5% of participants
Follow-up	Median 32 months
Main eligibility criteria	CML-CP Resistant or intolerant to ≥2 TKIs or T315I mutation present *BCR::ABL*^{IS} >1%
Participants	283 of which 280 resistant 67 with T315I mutation
Response at study entry	CHR or worse: 61 (65%)
Fraction *BCR::ABL1*^{IS} between 0.1% and 1%	Not eligible
Study definitions	
Resistance definition	Not reported
Intolerance definition	Not reported
Results	
Efficacy	*BCR::ABL1*^{IS} ≤1% at 12 months: 45 mg cohort: 44.1% 30 mg cohort: 29.0% 15 mg cohort: 23.1%
SAE (% of participants)	45 mg cohort: 34.0% 30 mg cohort: 25.5% 15 mg cohort: 33.0% 17 patients experienced AOEs
Study discontinuation due to AE	45 (15.9%)
ASCEMBL trial [21,22]	
Study Design	Phase 3, open-label
Dosage	Asciminib 40 mg twice daily or bosutinib 500 mg once daily
Treatment duration	Ongoing in 97 (61.8%) of participants in asciminib arm
Follow-up	Median 14.9 months
Main eligibility criteria	CML-CP, previously treated with ≥2 TKIs Treatment failure according to ELN 2013 guidelines or intolerance *BCR::ABL1*^{IS} ≥1% (*BCR::ABL1*^{IS} >0.1% for intolerant patients after protocol amendment) No known T315I or V299L mutations
Participants	233 (157 in asciminib arm)
Response at study entry	MCyR: 46 (29.3%) in asciminib arm
Fraction *BCR::ABL1*^{IS} between 0.1% and 1%	15 (9.6%) in asciminib arm

Study definitions	
Resistance definition	ELN 2013 guidelines
Intolerance definition	Unresponsive grade 3 or grade 4 toxicity
Results	
Efficacy	At 24 weeks: CCyR: 40.8% MMR: 25.5% *BCR::ABL1*^{IS} ≤1%: 49% MR$^{4.5}$: 8.9%
SAE	not reported
Study discontinuation due to AE	4.5% in asciminib arm, 14.5% in bosutinib arm

AE, adverse event; ALL, acute lymphoblastic leukemia; AOE, arterial occlusion event; *BCR::ABL1*^{IS}, *BCR::ABL1* transcript levels, expressed on the international scale; CCyR, complete cytogenetic response; CML, chronic myeloid leukemia; CP, chronic phase; ELN, European LeukemiaNet; MCyR, major cytogenetic response; MMR, major molecular response; MR$^{4.5}$, 4.5-log molecular response; PCyR, partial cytogenetic response; Ph^{+}, Philadelphia chromosome positive; SAE, serious adverse event.

versus 16.1%), across major demographic and prognostic patient subgroups [21,22]. The gain in MMR rate between asciminib and bosutinib was more pronounced in the subgroup with an MCyR at baseline (40.7%) than in the subgroup without (14%). The safety profile of asciminib was favorable, with neutropenia and thrombocytopenia occurring as most frequent grade 3/4 events in about 20% of patients [21,22].

Of note, these three trials enrolled patients with TKI resistance, intolerance, or both, but with differing inclusion criteria. In the resistant population, the eligible leukemic burden at study entry was significantly higher and the previous response kinetics slower in PACE than in ASCEMBL. Intolerant patients qualified if dose interruptions or dose adjustments for grade 3/4 or persistent grade 2 AEs led to suboptimal responses, i.e. less than a CCyR in the PACE study contrasting with *BCR::ABL1*^{IS} >0.1% in the ASCEMBL study; therefore, also for intolerant patients, the eligible minimal leukemic load was about 1 logarithm higher in PACE than in ASCEMBL. Moreover, the ASCEMBL study had a higher proportion of intolerant-only patients and fewer patients with KD mutations [15,21].

Both asciminib and ponatinib induced MMR in a substantial fraction of patients beyond two lines of therapy. Overall, the effectiveness of ponatinib was demonstrated in a population with a higher leukemic burden, more resistant disease, and higher frequency of KD mutations than asciminib. Over time, the beneficial effect of ponatinib was partly offset however by a disturbingly high rate of dose-dependent AOEs (cumulative incidence of 31%), leading to its discontinuation in 13% to 17% of patients [14–17]. Asciminib had a favorable safety profile in the ASCEMBL trial with an AOE frequency of 3.2%, and a discontinuation rate of 4.5% due to AEs, mainly thrombocytopenia and neutropenia [21]. Asciminib therefore has an attractive safety profile for patients with significant vascular risk factors or serial intolerance to the class of ATP-competitive TKIs [21,22].

General considerations about patient adherence and ease-of-use

Poor therapy adherence is frequent. A recent review of medical records from 1,194 Belgian patients with CML treated with imatinib (diagnosed between 2004 and 2016) showed that only 60.3% of patients were truly adherent after six months of treatment, dropping further to just 30.1% at 24 months [29]. Transplants and deaths occurred mainly in patients who were non-adherent at 24 months. Addressing adherence is therefore essential.

According to the European label, the dosage of asciminib is 40 mg twice daily, on an empty stomach. Food consumption should be avoided for at least two hours before and one hour after taking the dose [30]. This may be challenging for patients with an irregular lifestyle, and it is practically impossible to monitor whether patients comply with these dietary restrictions. An alternative posology of 80 mg once daily is equally efficacious and tolerable, and endorsed by the United States Food and Drug Administration [31] but not yet included in the European label. Ponatinib is taken as one dose (starting at 45 mg) daily, with or without a meal [32], possibly leading to better adherence by the patient.

The most common grade 3/4 AEs for both ponatinib and asciminib are thrombocytopenia and neutropenia, occurring in 35% and 17% of patients using ponatinib and 21.8% and 17.9% of patients using asciminib [15,21]. In the clinical trials for both drugs, the recommendation was to maintain the dose in case of grade

1/2 cytopenia, but to interrupt the TKI in case of grade 3/4 cytopenia. The TKI was resumed at the original dose if the cytopenia recovered to grade 1/2 within two weeks or resumed at a lower dose if recovery took longer. For grade 3/4 cytopenias not recovering after TKI interruption, hematopoietic growth factors were administered [14,21].

TKI dose reductions or interruptions may lead to suboptimal disease responses or even therapy failure. In case of grade 3/4 anemia or thrombocytopenia, blood transfusion and use of erythropoietin stimulating agents or thrombopoietin receptor agonist can allow to maintain the TKI dose and reduce the risk of therapy failure. The safety of hematopoietic growth factors as a strategy to maintain dose intensity in a setting of hematological toxicity has not been thoroughly explored but older evidence does not indicate that the myeloid growth factors selects or favors the outgrowth of CML hematopoietic progenitors over normal hematopoietic progenitors [33].

Treating patients with primary refractory disease

The definition of refractory disease is based on the treatment milestones outlined in the ELN guidelines. 'Failure' signals, associated with a higher risk of disease progression, are identified as *BCR::ABL1*^{IS} >10% at three months (if confirmed within one to three months), *BCR::ABL1*^{IS} >10% at six months, and *BCR::ABL1*^{IS} >1% at 12 months [5]. A rapid reduction of the CML disease burden is desirable to reach the safe haven of CCyR and preferentially MMR. However, treatment responses must be interpreted carefully, also considering the patient's treatment goals, the rate of BCR::ABL1 decline, the degree of deviation from the targeted leukemic burden, and previous therapies [34,35].

A common mechanism of resistance in CML is the acquisition of mutations in the *BCR::ABL1* KD, or clonal evolution. Therefore, in case of resistance, a comprehensive re-evaluation is essential, including bone marrow examination with cytogenetic analysis to identify any additional chromosomal abnormalities, and with analysis of KD mutations. Drug interactions and treatment adherence should be thoroughly reviewed. When a *BCR::ABL1* KD mutation is identified, switching to alternative 2G-TKIs can be considered; however, randomly switching is rarely effective.

In patients who fail second-line treatment and in the absence of *BCR::ABL1* KD mutations, switching to ponatinib or asciminib is essential. At this stage, it is also critical to consider allogeneic SCT with prompt initiation of a search for a compatible donor to ensure timely transplantation if treatment failure persists after the third-line therapy. The PACE and OPTIC trials included a higher proportion of resistant patients (84% and 98%) in the 45 mg ponatinib arm than the ASCEMBL trial (60.5%) in the asciminib arm [15,16,21]. In addition, resistant patients also had a significantly higher leukemic disease burden in the PACE study compared to the ASCEMBL study. Given the broader experience with ponatinib in this setting, ponatinib is preferred in patients with primary refractory disease, especially with persisting high leukemic burden (*BCR::ABL1*^{IS} >10%). However, patient-specific factors – in particular the cardiovascular risk – must be carefully factored in and asciminib may be a more suitable option for some patients.

Treating patients who fail to achieve optimal time-dependent molecular targets, despite TKI-responsive disease

Patients who respond to treatment, yet do not achieve the optimal time-dependent milestones after at least two lines of TKI therapy because of a lack of efficacy, are usually confronted with a more aggressive disease state. As a result, they are less likely to respond to any additional 2G-TKI treatment unless specific *BCR::ABL1* KD mutations are present. These patients highlight the need for more potent treatments, such as ponatinib or asciminib [5]. In a first- or second-line setting, the ELN 2020 guidelines identify the optimal treatment goals. In third-line or later settings, the strict definitions of time-dependent molecular target thresholds in terms of *BCR::ABL1*^{IS} may be too restrictive. Hence, continuing the same TKI could be a valid option, especially in the absence of suitable alternatives. For example, a stable suboptimal *BCR::ABL1*^{IS} <1% from month 12 onwards could be considered acceptable for some patients even if this means that the patient will never qualify for TFR. The dynamics of *BCR::ABL1*^{IS} levels over time are critical, whereby increasing trends are conducive to treatment modification, while treatment continuation is acceptable with stable or decreasing trends.

The different mechanism of action of asciminib can affect the physician's decision to modify the treatment for patients failing to achieve satisfactory response with conventional ATP-competitive TKIs. The toxicity profile of asciminib could also favor a TKI shift in patients for whom an incomplete molecular response would have been accepted in the past due to lack of therapeutic alternatives compatible with the patient's comorbidities. However, some BCR::ABL1 mutations (such as M244 V, L248V, Y253F, F359C/I/V) are *in vitro* refractory to asciminib [36], favoring the use of ponatinib (Figure 1). The BCR::ABL1 T315I mutation is sensitive to both drugs, but currently ponatinib is the only drug approved and reimbursed in this setting in Europe.

In patients presenting with a persistent low disease burden (*BCR::ABL1*^{IS} between 1% and 10%), asciminib could be preferred over ponatinib [37]. By contrast, ponatinib could be indicated in the presence of adverse CML features, such as any suspicion of a disease evolution toward an accelerated phase, for which only ponatinib has undergone efficacy evaluation [15].

Treating patients with secondary resistance (with or without *BCR::ABL1* mutations)

Secondary or acquired resistance is defined as the loss of complete hematological response, CCyR or MMR [5]. As in every patient with less-than-optimal response, treatment adherence and interactions with other drugs must be re-evaluated. In secondary resistance, ABL1-dependent pathways such as *BCR::ABL1* mutations or gene amplification are commonly involved [38]. The work-up in these patients should therefore include a bone marrow aspirate to assess cytogenetic clonal evolution and testing for mutations in the *BCR::ABL1* KD [5,35]. Next generation sequencing for other myeloid mutations is currently not standard of care.

If a KD mutation is identified, the treatment choice needs to be adapted according to the sensitivity of the available TKIs to the specific mutation (Figure 1). In the absence of KD mutations, rotating among other 2G-TKIs has only a small chance of achieving a good response and is therefore not recommended. In these cases, ponatinib or asciminib are the preferred treatment options; however, in the absence of direct comparisons between both drugs, no evidence-based guidance on specific drug selection can be provided. Comparing the outcomes of the PACE, OPTIC, and ASCEMBL trials is hampered by the differing patient populations and inclusion criteria regarding disease burden. The choice between ponatinib and asciminib in third-line setting for patients with secondary resistance and without a documented KD mutation should, therefore, be guided by patient and disease characteristics. In patients with a high cardiovascular risk, asciminib tends to be favored based on the safety profile; however, strict management of cardiovascular risk factors remains important, since no data is yet available on long-term therapy using asciminib. In patients with a high disease burden, ponatinib may be preferred. In the absence of evidence-based guidelines, a thorough evaluation of the characteristics of each agent with regards to ease-of-use, toxicity profile, and patient preferences can help decide on the best third-line treatment plan.

Treating patients with intolerance to at least two previous TKIs

TKI intolerance usually refers to the inability to continue a TKI due to persistent side effects that impact tolerability and quality of life, or due to – sometimes life-threatening – complications that affect patient health [34]. In clinical trials, dose interruptions and failure to meet optimal milestones are also usually included in the definition. The choice between the available treatment options in third-line therapy depends on patient age, comorbidities, cardiovascular risk factors, previous TKI intolerances, baseline CML prognostic factors, and treatment goals (Table 2). In this setting, it is key to prioritize between competing treatment goals: avoid toxicity or cross-intolerance (Table 3) with third-line therapy, safeguard the patient from CML-related death (e.g. in elderly patients), or achieve criteria for TFR (e.g. in young patients).

Dose adjustments and supportive care

Dose reduction of the TKI may alleviate certain non-prohibitive side effects [34]. Close monitoring of the *BCR::ABL1* transcript is recommended every three months. Failure to maintain an acceptable response beyond second-line (*BCR::ABL1*^{IS} >1% or less than CCyR [$Ph^+ > 0\%$]) will constitute an indication for switching to a

Mutated region	Mutation	Asciminib	Ponatinib	Imatinib	Nilotinib	Dasatinib
Wild-type	-	31±4	11	565±656	31±4	10±3
SH2 contact region	M351T	47±34	13±1	1298±542	37±4	8±4
Substrate binding region	F359V	6066±355	466±73	>10000	1710±635	598±624
P loop	E255K	10	49±4	8222±484	648±395	14±1
	Y253H	28±13	37±4	8936±1774	497±122	11±2
	E255V	24±4	56±1	7565±3268	587±151	29±15
	M244V	5223±4899	75±42	2963±83	236±152	40±1
Gate keeper	T315I	148±14	33±11	>10000	3425±650	2525±322
Hinge region	F317L	6±3	7±1	526±56	89±8	11±1
	F311I	107±1	30±8	3547±223	226±122	13±0
SH3 contact region	V299L	562±552	10±4	1987±1237	103±6	118±2
T315I + Other compound mutation	T315I/E255V	93±86	244±125	>10000	6467±4431	3571±1385
	T315I/F359V	6631±1201	101±22	>10000	4586±1397	3392±211
	T315I/G250E	7451±3057	130±16	>10000	8511±5599	5001±2939
	T315I/E255K	8944±748	339±12	>10000	>10000	4706±803
	T315I/E453K	2931±74	130±5	8466±1628	>10000	4724±155
	T315I/M351T	>10000	127±5	7603±1498	>10000	7683±3645
	T315I/F311I	7061±1423	438±88	7144±2459	>10000	4789±1739
	T315I/H396R	>10000	211±134	8953±5314	>10000	9286±3386
	T315I/Y253H	6981±2481	889±100	>10000	>10000	7080±3233
	T315I/F317L	860±96	688±412	>10000	>10000	>10000
	T315M	996±405	1987±1414	>10000	>10000	>10000
Other compound mutation	G250E/V299L	2601±2903	12±3	6486±2622	641±368	570±599
	F317L/F359V	5214±810	24±12	7195±1729	926±24	50±12
	Y253H/E255V	5014±2920	772±220	>10000	7026±2183	231±92
	T253H/F359V	>10000	432±23	>10000	>10000	110±1

Sensitive (IC_{50} value ≤100 nM)
Intermediate sensitive (100 nM < IC_{50} value ≤ 1000 nM)
Insensitive (IC_{50} value >1000 nM)

Figure 1. *In vitro* comparison of growth inhibition by tyrosine kinase inhibitors on Ba/F3 cells expressing *BCR::ABL1* mutants (growth inhibition expressed as IC_{50} values, nM).

Note: This table is based on *in vitro* cell-line data. Translating this into the clinic should also consider drug exposure, especially plasma through levels at the recommended prescribed dose. Adapted from table 2 from [39] with modifications (CC-BY 4.0, http://creativecommons.org/licenses/by/4.0). Some discrepancies in the color coding, present in the original version, are reproduced here.

different TKI [5]. Temporary short interruptions of TKI before restarting at a lower dose and supportive care (such as growth factors in the case of cytopenia, typically occurring within the first weeks of treatment) may be beneficial in intolerant patients with an acceptable molecular response.

Table 2. Key considerations for third-line treatment of chronic phase (CP) chronic myeloid leukemia (CML).

	First-line	Second-line	Treatment goals	Key considerations	Third-line and beyond
Resistance	Imatinib or 2G-TKI	2G-TKI	Avoid resistance Obtain response Avoid toxicity	*BCR::ABL1* mutations Age Comorbidities CV risk factors CML prognostic factors	Ponatinib Asciminib Prepare transplant (Clinical study) (Continue 2G-TKI if no failure criteria)
Intolerance	Imatinib or 2G-TKI	2G-TKI	Avoid cross-intolerance Keep response Improve response Avoid toxicity	Age Comorbidities CV risk factors Previous intolerance CML prognostic factors	Asciminib Other 2G-TKI Ponatinib

2G-TKI, second generation tyrosine kinase inhibitor; CML, chronic myeloid leukemia; CV, cardiovascular.

Table 3. Common toxicities associated with tyrosine kinase inhibitors (TKI).

Toxicity	Commonly associated with	Alternative TKI
Pleural effusions	**dasatinib**, **bosutinib**	nilotinib, imatinib, asciminib, ponatinib
Peripheral edema	**imatinib**, **dasatinib**, bosutinib, nilotinib	asciminib, ponatinib
Pancreatitis	**nilotinib**, **ponatinib**, asciminib	dasatinib, imatinib, bosutinib
Hepatotoxicity	**bosutinib**, **nilotinib**, **ponatinib**, asciminib, imatinib	dasatinib
Hypertension	**ponatinib**, nilotinib, bosutinib, dasatinib, asciminib	bosutinib
Cardiovascular events	**ponatinib**, **nilotinib**, dasatinib, asciminib, bosutinib	imatinib, bosutinib, asciminib
QT prolongation	**nilotinib**, **ponatinib**, bosutinib, asciminib	imatinib, dasatinib
Hematological toxicities	**ponatinib, asciminib**, **dasatinib**, imatinib, bosutinib, nilotinib	nilotinib, bosutinib
Diarrhea	**bosutinib**, **imatinib**, dasatinib, nilotinib, ponatinib, asciminib	asciminib, ponatinib
Rash	**bosutinib**, **ponatinib**, nilotinib, imatinib, dasatinib, asciminib	asciminib
Myalgia	**Imatinib**, nilotinib, ponatinib, dasatinib	asciminib, bosutinib

TKIs are ordered by the most frequent to less frequent. Bold TKIs are most frequently associated with each side effect. Alternative TKIs are shown in the order they are advised.

Note that some TKIs are listed in both columns. Although these TKIs are associated with a particular side effect, they may still be recommended when that side effect is less pronounced.

Switching to a different TKI

Switching to an alternative TKI is recommended in case of prohibitive toxicity or loss of response after dose adjustments.

Asciminib is a promising option for patients with poor tolerance to previous TKI, as its allosteric, non-ATP-competitive inhibition of BCR::ABL1 is highly specific and less subject to the side effects of ATP-competitive TKIs. Asciminib showed higher MMR rates at week 24 than bosutinib in intolerant patients treated with at least two prior TKIs, with fewer than 6% of patients on asciminib experiencing AEs leading to discontinuation [21]. Real-world data confirmed its efficacy in intolerant patients, with a low incidence of relevant toxicities, although cross-toxicity was significant for previous cytopenia, fatigue, vomiting, and pancreatitis [26]. Although cross-intolerance can occur, alternative 1G- or 2G-TKIs can also be considered (Table 3). The dose of the new TKI may be lower than the standard recommended dose when switching in a patient already responding (*BCR::ABL1*^{IS} <1%, level of CCyR) [34].

Ponatinib provided durable, deep responses in heavily pretreated, TKI-resistant or intolerant CML patients in the PACE trial, with a discontinuation rate due to AEs of 21% in the CML-CP cohort [15]. The median time to response was short (ranging from 2.8 months for MCyR to 5.5 months for MMR), indicating rapid efficacy. These results were confirmed in a 6-year analysis of the Belgian ponatinib registry [40]. Approximately half of the 54 patients with CML in the registry had received ≥3 previous TKIs and were switched to ponatinib due to intolerance. Although treatment was discontinued due to AEs in 37% of the patients with CML who stopped treatment over a median 545-day follow-up period, MMR was achieved in 65% of patients with CML as best response, and a progression-free survival of 83.8% was observed after 48 months.

However, the cardiovascular risks of ponatinib in this setting must also be considered. Adapting the dose according to molecular response as shown in the OPTIC trial can help improve tolerability while maintaining therapeutic efficacy. In patients with significant cardiovascular risk factors or a history of cardiovascular disease predictive for TKI-induced AOEs, asciminib is preferred, although the long-term cardiovascular outcomes of prolonged asciminib therapy remain to be clarified.

Finally, participation in a clinical study, if available, could also be a good option for intolerant CML patients.

Conclusion

The availability of TKIs has dramatically transformed CML management and treatment perspectives into an increasingly personalized, patient-tailored approach. Within this rapidly evolving clinical landscape, it is incumbent on physicians to maintain a critical attitude towards the different therapeutic options available and select the one optimal for each patient profile. Monitoring of the patient, identifying resistance, intolerance, and KD mutations, all contribute to guiding the treating physicians towards ponatinib, asciminib, alternative 2G-TKI, or allogeneic stem cell transplantation.

Ponatinib may be favored in a context where increased potency is needed, such as in patients with primary resistance, high leukemic burden and few comorbidities, or if the BCR::ABL1 T315I gatekeeper mutation is diagnosed.

Conversely, asciminib is a unique targeted therapy that offers an additional third-line and beyond option for different profiles of heavily pretreated patients. Important advantages of asciminib include its favorable tolerability profile, its novel mechanism of action, and its high inhibitory potency with demonstrated antileukemic activity against a wide spectrum of *BCR::ABL1* KD resistance mutations. Asciminib is an attractive option for patients who are intolerant to other TKIs, have already experienced cardiovascular events, or are at risk for cardiovascular events. Further clinical investigations, such as trials using asciminib in earlier treatment lines will assist clinicians treating patients with CML to harness this promising drug to its full therapeutic potential.

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