SPOTLIGHT REVIEW ARTICLE

Asciminib for Philadelphia chromosome-positive leukemias

Timothy P. Hughes,[1-3] Deborah L. White[1,2] and David T. Yeung[1-3]

[1]Precision Cancer Medicine Theme, South Australian Health and Medical Research Institute; [2]Adelaide Medical School, University of Adelaide and [3]Department of Haematology, Royal Adelaide Hospital and SA Pathology, Adelaide, Australia

Correspondence: T.P. Hughes
tim.hughes@sahmri.com

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Abstract

Twenty-five years after the introduction of imatinib, we have entered a new era of therapy for chronic myeloid leukemia (CML). Despite the development of second- and third-generation tyrosine kinase inhibitors (TKI), their impact has been incremental in improving outcomes for CML patients. While frontline use of second-generation TKI has improved molecular response rates and reduced progression to blast phase, there has been no improvement in overall survival compared to that achieved with imatinib, likely due to the higher toxicity and consequent higher non-CML-related mortality. Imatinib remains the most prescribed therapy for CML worldwide, despite it being the least potent TKI and most prone to resistance and progression. Asciminib, the first STAMP (specifically targeting the ABL myristoyl pocket) inhibitor, binds to the myristoyl pocket of BCR::ABL1. Its specificity minimizes off-target toxicity which enabes asciminib to finally break this frustrating link between potency and toxicity. After a decade of clinical trials, both in patients with resistance and intolerance to two or more TKI, and more recently in the frontline setting, asciminib is fulfilling its early promise of a more rapid and reliable pathway to long-term disease control with minimal toxicity. There are, however, some unexpected challenges when using asciminib that require further investigation. In this Spotlight Review we examine the key studies and outline the potential impact and current limitations of this first STAMP inhibitor in the CML setting and in other leukemias in which ABL1 or ABL2 is the key target.

Introduction

Clinical outcomes for patients with chronic phase chronic myeloid leukemia (CP-CML) have improved dramatically in the era of tyrosine kinase inhibitors (TKI). Imatinib remains the TKI of choice as frontline therapy for many clinicians. Second-generation TKI are more potent than imatinib and induce a more rapid and deeper molecular response overall. They are also more effective at preventing resistance and disease progression. However, the higher potency of second- and third-generation TKI has always been linked to greater toxicity, which has limited the advantage of these drugs over imatinib. This has led to a reluctance, on the part of many clinicians, to universally adopt second-generation TKI upfront, instead reserving these more potent drugs either for patients with high-risk features, or for patients with intolerance or resistance to imatinib. Ponatinib, the only third-generation TKI approved in most countries, has similar limitations in terms of greater potency but even greater toxicity when used at the approved dose.

The current outlook for CML patients is mixed – most will achieve good disease control and can expect a near normal survival, but many experience significant side effects and toxicities which impact quality of life, and may lead to organ damage in some cases. The fortunate few go on to achieve treatment-free remission but, even in these 20-30% of patients, treatment-free remission is only successful after many years of TKI therapy. Meanwhile, around 10-20% have poor responses to several lines of therapy and among this cohort, around half will die due to progressive CML, or due to the complications of an allogeneic transplant.

Canonically, BCR::ABL1 kinase activity is inhibited using small molecules that competitively bind to its ATP pocket. In the early 2000s, Hantschel and colleagues identified a unique myristoyl site through which inhibition of BCR::ABL1 kinase activity is also possible.[1] The first agent in a new class of inhibitors specifically targeting the ABL1 myristoyl pocket (STAMP) to undergo clinical development was asciminib. Pre-clinical studies demonstrated activity in leukemia models with *BCR::ABL1*, and in models with commonly encountered

kinase domain mutations including T315I,[2] a "gatekeeper" mutation that confers resistance to all ATP-pocket-binding TKI except for ponatinib. The differences in BCR::ABL1 binding sites between asciminib and other TKI also suggests the possibility of additive or synergistic BCR::ABL1 inhibition utilizing STAMP and ATP-pocket-binding TKI.[3]

Studies have demonstrated the safety and efficacy of asciminib in patients with resistance or intolerance to two or more lines of prior therapy and, more recently, in newly diagnosed CP-CML patients. For the first time, a more potent TKI does not appear to induce extra toxicity when compared to imatinib. After a decade of clinical trials, we can now appreciate the potential for asciminib and other STAMP inhibitors to revolutionize CML therapy but debate about its role is ongoing (Table 1).

Clinical studies in chronic phase chronic myeloid leukemia

Early studies in CP-CML patients with prior resistance or intolerance to several lines of TKI therapy demonstrated that asciminib was indeed very well tolerated, and often efficacious. The phase I study of asciminib (ClinicalTrials.gov number NCT02081378, referred to hereafter as the X2101 study) enrolled patients with chronic and accelerated phase CML, as well as Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL), who had resistance or intolerance to two or more lines of treatment. Patients received doses between 10 mg and 200 mg once or twice a day. No dose-limiting toxicities were reported at any dose. The most recent update reported on 115 patients with CP-CML without the T315I mutation.[4] With a median exposure of 4 years, a major molecular response (MMR; *BCR::ABL1* ≤0.1%) was achieved by 62%; and a 4-log reduction in transcripts (MR4, *BCR::ABL1* ≤0.01%) by 34%. Event-free survival (events included discontinuation because of adverse events, progression to accelerated or blast phase, or death on treatment) was 87% and 81% at 24 and 48 months respectively. Supported by additional pharmacokinetic studies, the dose of 80 mg QD was determined to be optimal in patients without T315I.[5] *In vitro* data suggested that targeting T315I required a higher dose, and 200 mg twice a day was selected for a separate T315I cohort within the X2101 study.[6] The latest data showed that 56% of this group of 48 patients remain on therapy, and 62% achieved a ≥2-log reduction in transcripts (MR2, *BCR::ABL1* ≤1%). Ponatinib-naïve patients had an MR2 rate of 81%, *versus* 48% in patients resistant or intolerant to ponatinib. After a median follow-up of 2 years, grade 3-4 lipase elevation was observed in 19%, with 8% of patients reporting arterial occlusive events. These findings have been supported by small, real-world datasets (Table 2).[7-14] One such cohort comprised 31 patients with T315I mutations from eight countries.[15] Twenty-eight had prior resistance or intolerance to ponatinib; MMR was achieved by 42% of those who were not in MMR at commencement of asciminib treatment. In patients who entered the study in MMR, six of 12 lost the MMR during the study. The safety data looked less favorable than those in the X2101 report; 26% experienced serious adverse events leading to hospitalization. Thus, asciminib is a reasonable option for patients with the T315I mutation, but more data are needed to determine the safety of this higher dose, especially in heavily pre-treated patients who may be particularly vulnerable to toxicity.

The key later-line study in chronic phase chronic myeloid leukemia

The phase III ASCEMBL study tested the safety and efficacy of asciminib in CP-CML patients with resistance or intolerance to two or more lines of therapy. The comparator was bosutinib, contemporaneously used commonly after failure of nilotinib or dasatinib. Patients with T315I or V299L, which

Table 1. Possible arguments for and against asciminib as frontline therapy for chronic phase chronic myeloid leukemia.

In favor of frontline asciminib	Arguments made against frontline asciminib
Best tolerated tyrosine kinase inhibitor with lowest discontinuation rates as monotherapy in the ASC4FIRST study	Safety profile not yet fully defined with regards to infrequent and late adverse events, such as arterial occlusive events
Low rates of organ toxicity	Increased cost compared to generic tyrosine kinase inhibitors
Low rate of transformation to blast phase + Low rate of non CML-related mortality = Expected survival advantage	Survival advantage yet to be proven
Superior rates of MMR and MR4 compared to those with all other tyrosine kinase inhibitors at 2 years of therapy	Some clinicians may prefer to reserve more potent drugs for imatinib-resistant or intolerant patients
Predicted higher rate of treatment-free remission based on molecular response data	Treatment-free remission data not yet available
-	Some rare *BCR::ABL1* transcripts will confer resistance to asciminib (those missing *ABL1* exon 2) may be a trap for the unwary

CML: chronic myeloid leukemia; MMR: major molecular response; MR4: 4-log reduction in transcripts.

Table 2. Real-world data on asciminib in the later-line setting in chronic phase chronic myeloid leukemia patients.

Cohort origin	N	Proportion with resistance, N (%)	Overall MMR	Prior ponatinib treatment, N (%)	Response in ponatinib-exposed patients
Australian[7]	24	10 (42)	56% MMR	6 (25)	33% MMR
British[8]	49	17 (35)	59% MMR	29 (59)	56% CCyR
Canadian[9]	41	28 (68)	46% MMR at 12 months	14 (34)	20% MMR at 12 months
Dutch[10]	53	44 (83)	45% MMR	38 (72)	Primary ponatinib failure - 0% MMR
Italian[11]	77	44 (57)	53% MMR	43 (56)	35% MMR
Russian[12]	68	-	68% MMR at 24 months, 40 mg BID 56% MMR at 24 months, 200 mg BID	26 (38)	12% MMR
Spanish[13]	77	28 (36)	60% MMR	26 (34)	-
USA[14]	97	-	50% MMR by 24 weeks	15 (15.5)	-

The table shows a summary of observational studies reporting outcomes for chronic phase chronic myeloid leukemia patients who received asciminib treatment after being intolerant or resistant to at least two prior lines of therapy, including patients treated on managed access programs. Listed response rates are indicative and not intended to be comparisons. Some studies reported overall response rates, while others reported rates of response in patients without the specified response at the start of treatment. MMR: major molecular response; CCyR: complete cytogenetic response; BID: twice daily.

confer resistance to bosutinib, were excluded. There was a higher discontinuation rate in the bosutinib arm, due to both inefficacy and adverse events. Of note, gastrointestinal toxicity and liver enzyme increases were more frequently encountered with bosutinib. At last publication, with a median follow up of 2.3 years, 53.5% of patients assigned to asciminib remained on therapy, as opposed to 19.7% on the bosutinib arm. Rates of MMR (41.2% *vs*. 22.6%) and MR2 (53.7% *vs*. 33.7%) remained clearly in favor of asciminib.[16] However, asciminib monotherapy could not be regarded as a major step forward in this challenging setting, as a significant proportion of patients could not achieve MR2 or MMR on study. Ponatinib may provide a better prospect of response when there is high-level resistance. The choice between ponatinib and asciminib is often a difficult one. Where ponatinib is preferred, the OPTIC study provides evidence for an effective and safer dosing schedule. In this study, patients commenced ponatinib at 45 mg, 30 mg, or 15 mg daily; the two higher doses were subsequently reduced to 15 mg daily as soon as MR2 was achieved.[17] The higher doses produced better response rates, but also an increase in adverse events. Figure 1 presents the authors' recommendations regarding when to use asciminib and when ponatinib might be preferred in CP-CML in the third line and beyond.

Frontline studies in chronic phase chronic myeloid leukemia

Encouraging data about asciminib's effectiveness and tolerability in patients exposed to multiple prior TKI provided momentum for frontline studies, which commenced in 2019. The first was FASCINATION from the German CML study group, in which asciminib was used in combination with either imatinib (400 mg daily, with asciminib 60 mg daily), dasatinib (100 mg daily, with asciminib 80 mg daily) or nilotinib (300 mg twice a day, with asciminib at either 20 mg twice a day, or 40 mg daily).[18] MR4 at 12 months was reached by 38% of patients overall, without notable differences in either toxicity or response across the fours arms. Shortly after, the Australasian Leukaemia and Lymphoma Group conducted the first frontline monotherapy study - ASCEND-CML. In this 100-patient study, the rates of MMR and a 4.5-log reduction in transcript levels (MR4.5) at 12 months were 79% and 33%, respectively.[19] The definitive phase III study, ASC4FIRST, randomized asciminib against the investigator's choice of TKI in a study of 400 patients.[20] These three studies led to the following (tentative) conclusions about frontline asciminib. (i) The rate of treatment discontinuation due to toxicity appears to be lower with asciminib than with other TKI. With follow-up approaching 24 months, only 6% of patients discontinued therapy due to adverse events in both the ASCEND-CML and ASC4FIRST studies, which is significantly lower than the rate seen with other TKI on ASC4FIRST.[19,20] (ii) In ASC4FIRST, in which asciminib was compared to imatinib and second-generation TKI, asciminib led to superior MMR and MR4 rates at 96 weeks (although the comparison of molecular response for asciminib *versus* second-generation TKI was not statistically significant).[21] (iii) High specificity does not mean no toxicity. Targeting ABL1 and possibly ABL2 is presumably the reason that rates of adverse events such as fatigue,

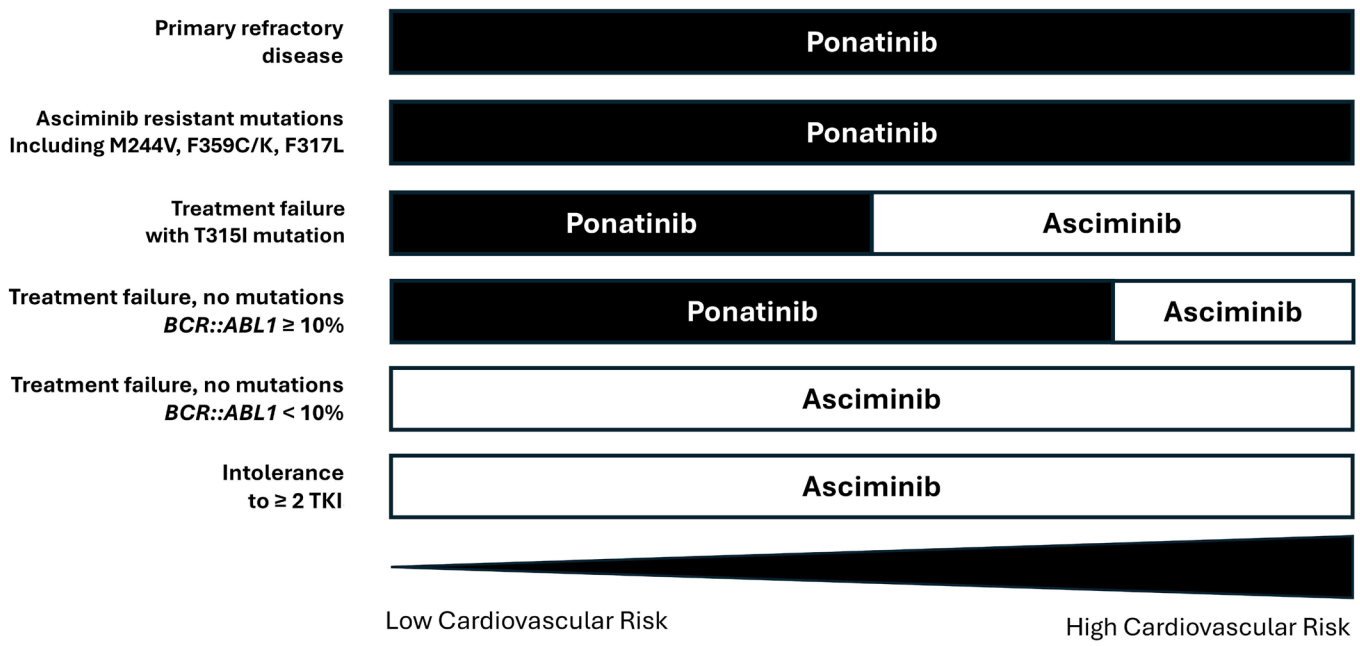

Figure 1. Recommended treatment matrix for resistance or intolerance. Asciminib and ponatinib are both registered in multiple jurisdictions for the treatment of chronic phase chronic myeloid leukemia in patients who have experienced resistance or intolerance to two or more prior tyrosine kinase inhibitors, or who have acquired the T315I mutation. There are no phase III trial data comparing these two drugs. This diagram sets out the authors' recommended approach to individualizing treatment based on the risk of ongoing disease resistance/progression, *versus* risk of toxicity. In particular, given the known association between the increased risk of arterial occlusive disease and ponatinib use, this agent should be used with caution in patients with cardiovascular risk factors. The profile of *BCR::ABL1* mutations, if present, should also be factored into the decision. TKI: tyrosine kinase inhibitors.

myalgia, lipase elevation, and arterial occlusive events are not significantly different from the rates observed with the second-generation TKI. (iv) Notwithstanding high response rates documented in the frontline studies, an increasing number of cases of resistance have been reported with asciminib, almost all mediated by *BCR::ABL1* mutations. The most common are myrisotyl pocket mutations, but some ATP pocket mutations may also confer resistance to asciminib (Table 3). As noted above, T315I also confer resistance to asciminib at standard doses. On the positive side, resistance due to less well-defined causes is quite rare in asciminib-treated patients; the majority are mediated by *BCR::ABL1* mutations which are likely sensitive to dasatinib and nilotinib. (vi) Combining asciminib with an ATP-competitive TKI is possible, as demonstrated in the FASCINATION study, but toxicity is significant. More than 20% of subjects withdrew from the study because of adverse events. Despite this, there were very few discontinuations due to emergent kinase domain mutations, suggesting that this approach may address one of the key challenges of asciminib monotherapy. Emerging data suggest that CP-CML patients with *ASXL1* mutations at diagnosis may be at higher risk of treatment failure mediated through *BCR::ABL1* mutations, and may benefit from combination approaches, although such approaches remain to be tested.[22,23]

Recent second-line studies

Studies of asciminib in the second-line setting have lagged behind those on later-line treatment and the frontline studies. The ASC4MORE study enrolled imatinib-treated patients who had achieved an initial response of MR2, but failed to achieve MR4.5 (*BCR::ABL1* ≤0.0032%). Patients were randomized to one of four treatment arms: either staying on imatinib, switching to nilotinib, or adding asciminib to ongoing imatinib at either 40 mg or 60 mg daily.[24] The primary endpoint, MR4.5 after 48 weeks of treatment, was achieved by 19.0% and 28.6% of the patients who added 40 mg and 60 mg of ascimimib, respectively, to imatinib therapy, as compared with 4.8% in the nilotinib arm. With continuing imatinib monotherapy, no patient achieved MR4.5 at week 48. The benefit of alternative strategies in this setting – either substituting asciminib for imatinib, or adding asciminib to more potent second-generation TKI – also remains to be determined.

ASC2ESCALATE is a US-only study in which patients not in MMR are switched to asciminib. In an interim analysis of 71 patients (resistant N=40, intolerant N=31), rates of MR2 and MMR at 24 weeks were 86% and 43%, respectively.[25]

Questions regarding asciminib in chronic phase chronic myeloid leukemia

Is quality of life substantially better for patients on asciminib?

In ASCEMBL, patients on asciminib had a general trend to decreased severity of CML and treatment-related symptoms,

and improved quality of life, compared to that of patients on bosutinib. Assessment of quality of life in ASC4FIRST will be critical as comparisons can be made with imatinib and the second-generation TKI.[26]

How does the risk of arterial occlusive events with asciminib compare with the risk with other tyrosine kinase inhibitors?

In ASCEMBL, the exposure-adjusted incidence rate of arterial occlusive events with asciminib was 2.2 per 100 patient-years.[27] This is relatively low considering the prior exposure of most of these patients to second-generation TKI and, in some cases, ponatinib. The incidence of arterial occlusive events remains relatively low in the ASC4FIRST study, but is still numerically higher in patients treated with asciminib than in those treated with imatinib (2% *vs*. 0%, respectively). This suggests that potent inhibition of ABL1 and/or ABL2 may be an important driver of this specific toxicity. Key evidence supporting the link between arterial occlusive events and both nilotinib and ponatinib was convincing because of the close relationship between dose and incidence. The higher nilotinib dose of 400 mg BID led to a higher incidence of arterial occlusive events as compared to that with 300 mg BID in the phase III ENESTnd study.[28] Similarly, there was a stepwise increase in the incidence of arterial occlusive events at the higher commencement doses of 45 mg and 30 mg daily, as compared with the incidence in patients given the 15 mg daily dose.[17] Whether an increase of arterial occlusive events is associated with the higher doses of asciminib used in patients with T315I remains to be seen.

Is pancreatitis an issue of particular relevance for asciminib?

The evidence from ASC4FIRST is that pancreatitis and increases in lipase concentrations, without other clinical features, are observed with all TKI with similar frequency and severity. So the answer is no – it is an issue for all TKI, but rarely a clinically significant issue.

Is there a group of patients who may not be optimally treated with asciminib frontline?

In the frontline setting, asciminib represents a very attractive option for most patients. However, asciminib may not be the drug of choice over imatinib in elderly, frail patients, particularly when cardiovascular risk is high. Patients with *ASXL1*, accounting for 7-10% of patients at diagnosis, also appear to be at increased risk of treatment failure due to the acquisition of kinase domain mutations when treated with asciminib monotherapy.[23] However, this may equally apply to monotherapy with other TKI, and the scope of the problem needs confirmation in larger studies. Patients with the rare e13/14a3 *BCR::ABL1* transcripts, with a truncated SH3 domain, are intrinsically resistant to asciminib (and probably other STAMP inhibitors as well).[29,30]

Table 3. *ABL1* mutations asscociated with asciminib resistance.

Mutation	Third-line	Frontline	
	ASCEMBL	ASCEND	ASC4FIRST
Resistant mutations in the context of ATP-pocket binding TKI, but also reported after asciminib treatment			
M244V	X	X	
L248V	X		
G250E	X		
Y253H	X		
E255K	X		
E255V	X		
T315I		X	
F317L	X		
E355G	X		
F359C	X		
L387V		X	
Mutations which may only have significance in the context of treatment with asciminib			
A337T		X	
A337V		X	X
A340Q			X
A344P			X
A433D			X
E459K	X		
P456Q			X
P456S		X	
V486F	X		
F497L			X
I502N			X
V506L		X	
V506M			X

Emergent *ABL1* mutations associated with clinical resistance to asciminib, as reported in the ASCEMBL study[16] (in which chronic phase chronic myeloid leukemia patients had intolerance or failure of two other tyrosine kinase inhibitors) and the ASCEND/ASC4FIRST studies[19,20] (in which chronic phase chronic myeloid leukemia patients were treated in the frontline setting). Some mutations reported in ASCEMBL may have developed in response to prior therapy and re-emerged after exposure to asciminib. However, there is clinical evidence that T315I, F317L, F359C and M244V confer relative resistance to asciminib.

Is asciminib a good option in cases of intolerance?

Patients switching to another TKI because of intolerance to their frontline treatment will, in most cases, not develop cross-intolerance. For instance, patients with recurrent pleural effusions on dasatinib are unlikely to develop further pleural effusions on either imatinib or nilotinib. However, 5-10% of patients will switch several times without find-

ing a TKI that they can tolerate easily. Many patients with "pan-intolerance" were included in the phase I X2101 study, as well as the ASCEMBL study. The outcome for patients with intolerance to their last therapy, and who were assigned asciminib in ASCEMBL, was impressive, with 51% achieving MMR by 24 months.

How should emerging *ABL* mutations on current therapy influence the decision to use asciminib and the dose selected?

This is becoming more complex with increasing understanding regarding the activity of asciminib against various *ABL1* mutations. Some mutations are clearly sensitive to higher doses of asciminib *in vitro*, but clinical experience with higher doses is largely restricted to cases of T315I. Additional mutations of concern when considering a switch to asciminib can be classified into two types: (i) kinase domain mutations that affect asciminib binding and/or increase ABL kinase activity: these reduce asciminib effectiveness, and include M244V, F359V/K, F317L and probably others not yet fully characterized; (ii) myristoyl site mutations emerging on treatment with asciminib or other STAMP inhibitors: these are not likely to respond to any achievable dose of asciminib. Examples include A337T/V, P465S and V506L.

The role of asciminib beyond chronic phase chronic myeloid leukemia

Given the excellent results demonstrated in CP-CML, an exploration of the role of asciminib in advanced phase disease would follow naturally. The initial phase I X2101 trial only enrolled small numbers of patients with accelerated phase disease, and results for accelerated phase CML have not been reported separately. Descriptions of asciminib's activity in blast phase is largely limited to pre-clinical models, without clinical reports of any sizeable cohort.[31]

In Ph+ ALL, pre-clinical data show excellent activity,[32] but ascimimib may be best used in combination with other agents. Animal studies suggest limited penetration of the blood-brain barrier,[33] and prior experience with ponatinib suggests that therapy resistance develops rapidly to monotherapy, especially when used as salvage.[34] Inhibiting both the ATP and the myristoyl pockets of BCR::ABL1 may circumvent resistance mediated by single mutations at either BCR::ABL1 site. A recent US study of 22 newly diagnosed Ph+ ALL patients combined dasatinib (140 mg daily) and prednisolone (60 mg/m^2 daily), together with escalating doses of asciminib in a chemotherapy-free induction regimen. At 3 months, the rate of negativity for minimal residual disease, determined by flow cytometry, was 89%, with a MMR of 74%.[35] These promising findings need to be confirmed in larger studies. This strategy also needs to be considered in the context of other increasingly common chemotherapy-free approaches for Ph+ ALL, such as GIMEMA ALL2820 in which ponatinib is combined with blinatumomab, leading to similarly high rates of molecular response.[36] Speculatively, adding a STAMP inhibitor to such combinations may further enhance efficacy, but this remains to be tested. The role of asciminib in *BCR::ABL1*-like ALL, a group of disorders mediated by variant *ABL1* and *ABL2* fusions is yet to be defined although, again, promising pre-clinical data exist.[37,38]

Other STAMP inhibitors

Other STAMP inhibitors are now in clinical development, two examples being TERNS-701 (formerly HS-10382) and TGRX-678.[39,40] Data are preliminary and limited, but efficacy and safety appear promising with both agents. The STAMP inhibitor era, which is in its infancy, may lead to more dramatic progress in treatments of Ph+ leukemias, as new agents come along, and we learn how best to use them.

Prospective

Asciminib, the first of the STAMP inhibitors, will have a major impact on the therapeutic pathway for many CML patients over the next decade. Will we finally see a new TKI that will improve overall survival of CML patients? Given the efficacy and safety profile of asciminib, this seems likely, but proving it will require a very large-scale study. Even without a demonstrated survival benefit, being able to take a STAMP inhibitor long-term with minimal impact on quality of life may be the most important advantage over ATP-competitive TKI. Improving the rate of treatment-free remission and/or reducing the duration of therapy needed to achieve treatment-free remission would also be a major step forward for CML patients. We will not know for several years whether asciminib can achieve this. The initial answers will come from the ASC4FIRST and ASC4START studies which both have embedded treatment-free remission extension studies. Given the superior rates of MMR and MR4 observed with asciminib in the 2-year report from ASC4FIRST, it would seem likely that the current 25-30% rate of achievement of treatment-free remission will be improved.[21]

However, there are issues emerging with asciminib therapy which still need further study. How can we address the higher rate of kinase domain mutations that emerge on frontline asciminib monotherapy? Can we clearly define the role of asciminib in cases in which *ABL* mutations are present? Finally, what role does asciminib play beyond CP-CML? Numerous studies are now proceeding to address these questions.

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