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Abstract

Asciminib is a novel tyrosine kinase inhibitor that specifically targets the myristoyl pocket. It has increased selectivity and potent activity against BCR-ABL1 and the mutants that most frequently prevent the activity of the ATP-binding competitive inhibitors. Results for clinical trials in patients with chronic myeloid leukemia that have received 2 or more tyrosine kinase inhibitors (randomized against bosutinib) or who have a T315I mutation (single arm study) have shown high levels of activity and a favorable toxicity profile. Its approval has offered new options for patients with these disease features. There are however a number of unanswered questions that remain to be defined including the optimal dose, understanding the mechanisms of resistance and, importantly, how it compares to ponatinib in these patient populations where we now have these two options available. Ultimately, a randomized trial is needed to answer questions to which we currently offer speculative informed guesses. The novelty of its mechanism of action and the exciting early data offers the potential for asciminib to address some of the remaining needs in the management of patients with chronic myeloid leukemia, including second line therapy after resistance to a frontline second generation tyrosine kinase inhibitors and improving in the success of treatment free remission. Multiple studies are ongoing in these areas and one can only hope that the desired randomized trial comparing to ponatinib will occur soon.

Article summary: Asciminib is a tyrosine kinase inhibitor specifically targeting the ABL myristoyl pocket (STAMP) with clinical efficacy in patients with chronic myeloid leukemia with failure of multiple prior tyrosine kinase inhibitors or with the T315I mutation. The results offer great promise for these patients and open opportunities for the future in areas of need, but many questions remain to be answered before we understand its role in the overall spectrum of treatment for chronic myeloid leukemia.

It was a relatively short time in drug development terms from the initial description of the in vitro efficacy of a novel tyrosine kinase inhibitor (TKI), CGP 57I4S (now imatinib)(1) to the initial clinical demonstration of its clinical activity in chronic myeloid leukemia (CML)(2). Shortly thereafter, imatinib became standard therapy for patients with CML(3). Second generation TKIs (2G-TKIs; dasatinib, nilotinib and bosutinib) were a new leap forward, providing new options for patients in whom imatinib had failed, and eventually in the frontline setting. Ponatinib was a later breakthrough providing a needed option for patients with T315I mutation or with resistance to multiple prior TKIs. Through these innovations, life expectancy for patients with CML has nearly reached that of the general population(4) and some patient may even do what was initially unimaginable, stop therapy. Despite all this progress, only approximately 50% of patients treated with 2G-TKIs achieve sustained MR4.5 by 10 years and half of patients who stop therapy, relapse.(5) Upon failure, response rates and overall survival decrease as patients progress through subsequent TKIs. Safety concerns have also evolved, with arterio-occlusive events (AOEs) now recognized with most available TKIs, particularly affecting the wider use of ponatinib.(6) This has triggered continued development of new TKIs.

Asciminib (ABL001) is a first-in-class TKI that, unlike all other available TKIs that inhibit ABL kianse activity in an ATP-competitive manner, binds to the mirystoyl pocket of ABL1, inducing an inactive conformation of the kinase (Specifically Targeting the ABL Myristoyl Pocket or STAMP inhibitor).(7) Asciminib offers several distinct features with potential clinical implications that makes it unique and valuable. Among them are the activity against T315I, and a distinct pattern of resistant mutations, different from that of the ATP-competitive agents. Myristoyl pockets are present in only a limited number of kinases, offering the potential for greater selectivity.(7) The distinct binding site and complementary mechanism of resistance also offers the possibility of combination therapy which, in animal models, has led to complete, durable remissions.(7) These properties made asciminib an excting new agent to bring to the clinic. The results have not disapointed but challenges remain and opportunities exist for further development.

The data

The phase 1 study of monotherapy asciminib suggested its efficacy in patients with resistance or intolerance to multiple TKIs. A dose range of 10 mg to 200 mg, once (QD) or twice-daily (BID), was investigated. By 12 months, a major cytogenetic response (MCyR) was achieved in 60% of patients without T315I and 55% with T315I. Corresponding figures for major molecular response (MMR) were 36% and 24%.(8) These encouraging results led to a pivotal randomized trial (ASCEMBL) for patients in chronic phase (CP) with resistance or intolerance to ≥2 TKIs without T315I or V299L. Patients were randomized to asciminib (40mg BID) or bosutinib (500mg daily). The primary endpoint of MMR at 24 weeks was met: 25.5% with asciminib and 13.2% with bosutinib.(9) Additional follow-up shows MMR rates of 37.6% and 15.8%, respectively, at 96 weeks. Also important is the rate of *BCR::ABL1 ≤1%* which for patients with resistance and/or intolerance to multiple prior therapies should be considered an adequate response. The rates at 96 weeks were 45.1% and 19.4%, respectively. The safety profile generally favored asciminib with fewer patients treated with asciminib discontinuing therapy due to adverse events compared to bosutinib after median follow-up of 2.3 years (7.7% and 26.3%, respectively). Overall, 45.9% of patients treated with asciminib discontinued therapy, most frequently due to lack of efficacy.(10) Asciminib, at a dose of 200mg BID, has also induced high response rates in patients with CML-CP with T315I. Among 52 patients, 46.9% achieved MMR.(11) The results of these studies constituted the basis for the approval of asciminib for the treatment of patients with resistance or intolerance to ≥2 TKIs in many parts of the world; approval for patients with T315I has been granted in some countries.

The analysis

ASCEMBL demonstrated the benefit of asciminib for patients with CML-CP with resistance or intolerance to ≥2 TKIs. The design and the results however have not been without controversy. A central question has been the selection of bosutinib for the control arm. Undoubtedly, a direct comparison with ponatinib would have been ideal to better define the role of these two drugs, both effective in this patient population. The counter-argument is that, at the time ASCEMBL was designed, there were major concerns about the risk of AOEs with ponatinib in the pivotal phase 2 trial (PACE), and a study to define the optimal ponatinib dose was ongoing (OPTIC).(12) This made ponatinib a desirable but questionable control that could challenge completion of the study if these concerns dissuaded investigators and/or patients from enrolling. There were also imbalances in the two cohorts (e.g., a numerical trend for more patients that had received ponatinib and more TKIs, or were resistant vs intolerant in the bosutinib cohort). Bosutinib is, among the 2G-TKIs, the only with prospective data in third-line (13, 14) which made it a next-best alternative. This choice precluded the enrollment of patients with T315I and V299L. As a result, the data for T315I patients, although encouraging, remains limited (52 patients) and uncontrolled. The dose of bosutinib used in ASCEMBL is the standard beyond 1st line, and in this regard it cannot be questioned. However, current practice and recent studies have suggested that starting at a lower dose (e.g., 200-300mg) and escalating as tolerated and as needed, allows better tolerability.(15, 16) There was a very high rate of early treatment discontinuation (71.1%) after a median follow-up of only 14.9 months.(9) Bosutinib may have also underperformed (MMR in ASCEMBL 19% by 48 weeks) compared to other series. In BYOND, the MMR rate with bosutinib by 1-year was 74.5% in third-line and 56.3% in fourth-line. With a median follow-up of 30.4 months, 54.1%, and 49.0% of patients, respectively, remained on therapy.(14) Studies using a lower starting dose and escalation based on tolerance and efficacy have also yielded far better tolerability with excellent responses even in older patients.(15) Still, there is perhaps little doubt that for patients with resistance to ≥2 prior TKIs, asciminib is a more effective agent than bosutinib. The approval for patients with T315I is welcome and the outcomes have been excellent, but is based on a yet unpublished small cohort of patients. We can only hope that a randomized study against ponatinib will be soon conducted to help us better understand the relative role of these two valuable agents for these patients.

The dose

The dose of asciminib in ASCEMBL was 40mg BID; yet the dose approved in the US for patients treated with ≥2 prior TKIs includes 80mg daily. In either case, no food should be consumed at least two hours prior and one hour after administration. For patients with T315I, the approved dose is 200mg BID. This is based on the fact that in the phase 1 study, 3 of the 4 patients with T315I who responded received >150mg. In the phase 1, the MMR rates were numerically higher with QD dosing compared to BID, both by 6 months (47% and 38%, respectively) and 12 months (69% and 53%). With smaller numbers, the opposite was seen in patients with T315I.(8) No maximally tolerated dose was identified, but pancreatitis, although infrequent (3% of all patients) occurred only at doses greater than 40 mg. A response by dose was not reported for non-T315I patients. It is thus not evident that the optimal dose has been identified. The higher dose required for patients with T315I is explained by a 10-fold lower anti-proliferative activity of asciminib in Ba/F3 cells expressing T315I compared to cells expressing the wild-type variant.(17) Despite the encouraging clinical activity reported in ASCEMBL, one can speculate whether better outcomes could be achieved with higher doses and/or QD schedule. With the safety reported in the T315I cohort similar to that with lower doses, it is reasonable to consider exploring

higher doses to improve outcomes. A QD schedule is more practical for patients considering the need for fasting conditions. In contrast to nilotinib, which also requires fasting conditions, plasma concentration of asciminib decreases when administered with food, particularly if it is a high-fat meal.(18) The dosing schedule for patients with T315I is also inconvenient because of the formulations currently available, in 20mg and 40mg tablets, requiring 10 tablets to administer the full dose. The financial implications of these higher dose cannot been ignored. Identifying the optimal dose and improving the available formulations are important aspects of the optimal use of asciminib.

The safety

The safety profile of asciminib has been consistent through the studies that have been reported. Unsurprisingly for a heavily treated patient population, myelosuppression is the most common adverse event (AE), particularly thrombocytopenia (grade ≥3 in 22.4% in ASCEMBL). Among the non-hematologic AEs, the only grade ≥3 event occurring in >5% was hypertension. Lipase elevation is also frequently observed, reported in 26.7% of patients in the phase 1 (10% grade ≥3) and 5.1% in ASCEMBL (3.8% grade ≥3).(8, 10) Lipase elevation is a class effect AE, reported at similar rates with other TKIs. In ASCEMBL, it occurred in 6.6% with bosutinib (5.3% grade ≥3). It clearly deserves attention when using asciminib (and other TKIs), but it is seldom associated with clinical pancreatitis. So far, the favorable toxicity profile is in keeping with the selectivity of the binding to the mirystoil pocket.

An AE category of special interest is arterio-occlusive events (AOEs). AOEs were reported with asciminib in 5.1% of patients in ASCEMBL. The overall incidence of AOEs is influenced by the breath of the search (i.e., what specific MedDRA terms are included, not described in ASCEMBL). It is also influenced by the duration of follow-up as the incidence increases over time. For example, with nilotinib in the frontline ENESTnd study, the reported cumulative incidence of such events was 7.5% by 5 years(19) and 16.5% by 10 years(5). The overall incidence reported with asciminib is low (5.1%), but still higher than with bosutinib (1.3%), even when adjusting for exposure (3.0 vs 1.4 per 100 patient-years).(10) At least two patients were reported to have died of such events.(9) As is the case with other TKIs, AOEs occur predominantly among patients with risk features for such events and those with a higher Framingham score. It is thus important to consider the potential risk of AOEs with asciminib, including assessment and management of co-morbidities and risk factors at baseline and during therapy.

The resistance

The response rate to asciminib has been encouragingly high, and responses have been durable (97% maintained MMR and 95% maintained *BCR::ABL1* ≤1% at the time of last report)(10). Still, at least half of the patients experienced treatment failure(10). Being such a heavily treated patient population, this might be expected, but it still begs the question of why patients may not respond to treatment with such an active drug with a novel mechanism of kinase inhibition. Furthermore, among patients who have had sequencing after failure of asciminib, 25.6% of patients treated with asciminib and 6.7% of those treated with bosutinib had newly emerging mutations.(10) Remarkably, 6 of the 10 newly emerging mutations were in the ATP-binding site, including M244V, E355G, F359V, and T315I; four others were in the myristoyl pocket. Six other patients had mutations at baseline that persisted at the end of treatment, including F317L (n=2), F359C/V (n=3), and Y253H (n=1). The growth inhibitory IC50 in cellular assays (Ba/F3 cells) of some of these emerging mutations (e.g., E355G, F359V) are significantly higher than for the wild-type, in the same range or higher than for T315I. Whether a dose escalation would overcome resistance in such instances deserves clinical investigation. It is also important to

recognize that focusing on BCR-ABL mutations as the sole mechanism of resistance is an oversimplification of the complexity of the disease and the patients. Asciminib may be subject to ABCG2 efflux.(20) We now also know that mutations in other cancer related genes, such as ASXL1, and other gene fusions not associated with the Ph translocation occur in a sizeable percentage of patients with CML-CP at the time of diagnosis and they confer a poor prognosis, with lower probability of achieving deep molecular response (DMR) and higher risk of progression.(21) The frequency of these events among patients enrolled in asciminib trials has not been reported. These events, particularly those involving other genes, may not be responsive to ABL kinase inhibition and may require alternative approaches.

The context (vs ponatinib)

In the absence of a randomized trial of ponatinib and asciminib for patients with resistance or intolerance to ≥2 TKIs and/or with T315I, an analysis of the results of the recent trials may shed some light on their value in this setting. This is important as a physician is faced with the question of what drug to use for a given patient who meets the criteria for the use of either drug. A formal comparison of these separate trials is not possible or appropriate since, despite the similarities in the target population, not only are these independent trials, but many aspects of the trial design and selection of the patients differ or are not clearly described. The patient characteristics and outcomes are also reported differently. A summary of these trials is presented in Table 1. Patients are youngest in the OPTIC trial and more patients with resistance (versus intolerance) are enrolled in the PACE and OPTIC trials. This summary shows good levels of response with both agents, but many patients have not responded to either drug. *BCR::ABL1* levels of ≤1% are achieved in approximately half of patients with both ponatinib and asciminib. The follow-up is short in these studies but the probability of response seems to plateau at around 48 weeks. For example, in ASCEMBL the rate of *BCR::ABL1* ≤1% was 50.6% by 48 weeks and 53.7% by 96 weeks.(10) Still, some patients may achieve DMR. With asciminib the rate of MR4 at 96 weeks was 17.2% and of MR4.5 10.8%.(10) With ponatinib, with median follow-up of 56.8 months, they occur in 30% and 24%, respectively.(22) Thus, unless the patient has alternative option with realistic expectation for a better outcome (e.g., SCT), treatment can be continued in patients who achieve *BCR::ABL1* ≤1%. Excellent survival rates are reported with both agents.

The safety profile is generally adequate with both drugs, with some shared AEs such as myelosuppression. A major safety concern are AOEs. These are reported with both ponatinib and asciminib. With most TKIs there seems to be a dose effect for AOEs. In ENESTnd for example, cardiovascular events occurred in 16.5% of patients with 300mg BID and 23.5% with 400mg BID.(5) In OPTIC, the exposure-adjusted rates are 4.5 per 100 patient-years at 45mg and 3.0 at 30mg.(12) The most salient message is the need to assess, monitor, and manage co-morbidities and risk factors for AOEs in all patients treated TKIs. Ultimately, having the added option of asciminib for patients with resistance to ≥2 TKIs or with T315I is a very welcome development. This allows to carefully review the patient and disease characteristics in the context of the available information for each drug and make carefully weighted decisions on the treatment that might be most appropriate for each patient. Drawing blanket conclusions for all patients in these scenarios with one drug or the other being regarded as superior would negate many patients options that may offer efficacy or safety benefits for individual scenarios.

The future

The high efficacy and favorable safety profile with asciminib in settings where poor outcomes have historically been observed have triggered interest in exploring its use in other areas. Perhaps one with the greatest need is second line therapy after resistance to frontline 2G-TKI. There is limited experience with prospective studies in this setting, but considering that the rate of CCyR with 2G-TKIs after resistance to frontline imatinib is only 45-50%, treatment options with better outcomes are needed. Ongoing studies are exploring asciminib in this setting. There is also interest in combining asciminib in patients who have not reached a DMR. A recent analysis of the ASC4MORE trial reported, in small cohorts, a higher probability of achieving MR4.5 in this setting with adding asciminib at either 40 mg or 60 mg to imatinib compared to switching to nilotinib or continuing with imatinib.(23) The preclinical data suggesting synergy in preventing the emergence of resistant clones makes this approach attractive. It is also possible that switching to asciminib instead of adding it to imatinib could achieve similar results with less toxicity, cost and inconvenience. A cohort using this approach has been added to the study but results are not available. The hope is that this strategy may make successful TFR achievable by more patients. The magnitude of any observed improved arte will need to balanced against safety, financial, convenience and other implications to determine the ultimate value of this strategy. An intriguing possibility is to use asciminib as frontline therapy. Several studies are ongoing in this context. Early results of the first of these studies to report data show encouraging rates of early molecular response (92% *BCR::ABL1* ≤10% at 3 month), although 9 of 63 patients had discontinued therapy for various reasons.(24) The main benefit of this approach would be to increase the probability of TFR. Considering the generally favorable results achieved in most patients with current therapy, such improvement would have to be sizeable to trigger a shift in treatment standards in a significant number of patients. Other intriguing possibilities would be to use asciminib in advanced phase CML, and the use of combinations, particularly for patients in blast phase or Philadelphia-chromosome positive acute lymphoblastic leukemia.

In summary, asciminib is a new leap forward in the management of patients with CML, with a novel mechanism of action and increased selectivity. In its current indication addresses some ongoing needs, and its mechanism of action and non-clinical data open new possibilities in areas where current treatment is adequate but not optimal. The quest for cure for most patients with CML continues and new agents such as asciminib may get us closer to reaching this elusive goal for more patients.

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Table 1. Summary of the pivotal studies with ponatinib and asciminib

Characteristic	Subcategory	PACE(22, 25)	OPTIC[j](12, 26)	ASCEMBL(10, 27)	Asciminib T315I(11)
N		270	94	157	52
Patient characteristics					
Median age, y (range)		60 (18-94)	46 (19–81)	52 (24–83)	54 (26-86)
CV risk factors, %	HTN	53	28	NR	NR
	Diabetes mellitus	16	5	NR	NR
	Hyperlipidemia	51	20	NR	NR
	BMI — kg/m^2	Obesity 24%	27	NR	NR
Prior TKIs, %	1	7	1	0	17[b]
	2	36	46	52	31[b]
	≥3	57	53	48	52[b]
Resistance, %		84	98	61	NR
BCR-ABL1 mutation, %	No mutation	51	54	87	0
	T315I	24	27	0	100
Best response last TKI, %	≥MCyR	26[g]	30[k]	NR	NR
Baseline *BCR::ABL1*	>10%	NR	79	62	54
Efficacy					
BCR::ABL1, % patients with response	≤10%	60[c]			
	≤1%	54[c]	44	43	
When assessed		Median 57 months[h]	@12 months	@48 weeks	
Last report, % patients with response (time)	≤1%		60 (by 36 months)	54 (by 96 weeks)	
	≤0.1% (total)	40 (overall)	34 (overall)	41 (by 96 weeks)	47 (by 96 weeks)
	≤0.1% (12 months)	37 (by 12 months)		33 (by 48 weeks)	43 (by 48 weeks)
Median follow-up		57 months	32 months	2.3 years	
Median duration of exposure		32 months	72% >12 months	24 months	68 weeks
Progression-free survival, %[l]		53 (5-year)	79.99 (2-year)	94.4 (2-year)	
Overall survival, %		73 (5-year)	91.28 (2-year)	97.3 (2-year)	
Safety					
AOEs	Overall, %	31[i]	10	5[d]	5.8[e]
	Per 100 patient-years	14.1[i]	4.5[f]	3.0[d]	
Hypertension, %	Grade ≥3	14	9	6.4	5.7
Lipase elevation, %		13	11	3.8	15.4
Thrombocytopenia, %		35	30	22.4	17.3

[a] Obesity BMI ≥30, overweight BMI 25-29.9; [b] 60% prior ponatinib; [c] Reflects MCyR and CCyR by 12 mo; [d] 96 week report; [e] Median duration of exposure 68.4 weeks; [f] With 45 mg (3.0 with 30 mg); [g] Most recent dasatinib or nilotinib treatment; [h] By 12 months MCyR 56%, CCyR 46%, MMR 34%; [i] 17% and 10.4 per 100 patient-years after adjudication(28); [j] Presented for 45 mg cohort; [k] Better than CHR; [l] In OPTIC defined as the interval between the first dose and disease progression (progression to accelerated-phase CML or blast-phase CML, loss of CHR or MCyR, or doubling of white blood cell count to .20 000 on 2 occasions at least 4 weeks apart in patients without CHR; in ASCEMBL no definition provided in the manuscript.