SPOTLIGHT REVIEW ARTICLE

Asciminib in chronic myeloid leukemia: a STAMP for expedited delivery?

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Abstract

Asciminib is a novel tyrosine kinase inhibitor (TKI) 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 two or more TKI (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 for whom 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 offer 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 front-line second-generation TKI and improving successful treatment-free remission. Multiple studies are ongoing in these areas, and one can only hope that the desired randomized trial comparing asciminib to ponatinib will be conducted soon.

Essential thrombocythemia in the realm of myeloproliferative neoplasms

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), CGP5714S (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 TKI (2G-TKI; dasatinib, nilotinib and bosutinib) were a new leap forward, providing new options for patients in whom imatinib had failed, and eventually in the front-line setting. Ponatinib was a later breakthrough providing a much needed option for patients with T315I mutation or with resistance to multiple prior TKI. Through these innovations, life expectancy for patients with CML has nearly reached that of the general population,[4] and some patients may even do what was initially considered unimaginable, stop therapy. Despite all this progress, only approximately 50% of patients treated with 2G-TKI achieve sustained MR4.5 by ten years, and approximately half the patients who stop therapy relapse.[5] Upon failure, response rates and overall survival decrease as patients progress through subsequent TKI. Safety concerns have also evolved, with arterio-occlusive events (AOE) now recognized with most available TKI, particularly affecting the wider use of ponatinib.[6] This has triggered continued development of new TKI.

Asciminib (ABL001) is a first-in-class TKI that, unlike all other available TKI that inhibit ABL kinase activity in an ATP-competitive manner, binds to the myristoyl 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 its 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 with traditional TKI which, in animal models, has led to complete, durable remissions.[7] These properties made asciminib an exciting new agent to bring to the clinic. The results have not disapointed, but challenges remain and there are opportunities for further development.

The data

The phase I study of monotherapy asciminib suggested its efficacy in patients with resistance or intolerance to multiple TKI. A dose range of from 10 to 200 mg, once (QD) or twice (BID) daily 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)-CML with resistance or intolerance to ≥2 TKI without T315I or V299L. Patients were randomized to asciminib (40 mg BID) or bosutinib (500 mg 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 (AE) compared to bosutinib after a 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 200 mg BID, has also induced high response rates in patients with CP-CML 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 TKI in many parts of the world; approval for patients with T315I has also been granted in some countries.

The analysis

ASCEMBL demonstrated the benefit of asciminib for patients with CP-CML with resistance or intolerance to ≥2 TKI. 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 AOE with ponatinib in the pivotal phase II 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 TKI, or were resistant *vs*. intolerant in the bosutinib cohort). Bosutinib is, among the 2G-TKI, the only one 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, remain limited (n=52 patients) and have not been controlled. The dose of bosutinib used in ASCEMBL is the standard beyond first-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., 200-300 mg), 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 the BYOND trial, the MMR rate with bosutinib by one 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 TKI, asciminib is a more effective agent than bosutinib. The approval for patients with T315I is welcome and the outcomes have been excellent, but it is based on a yet unpublished small cohort of patients. We can only hope that a randomized study against ponatinib will soon be 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 40 mg BID; yet the dose approved in the US for patients treated with ≥2 prior TKI includes 80 mg 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 200 mg BID, based on the fact that in the phase I study, 3 of the 4 patients with T315I who responded received >150 mg. In the phase I study, the MMR rates were numerically higher with QD dosing compared to BID in patients without

T315I, 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 maximum tolerated dose was identified, but pancreatitis, although infrequent (3% of all patients) occurred only at doses >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 as to whether better outcomes could be achieved with higher doses and/or a QD schedule. With the safety reported in the T315I cohort similar to that with lower doses, it is reasonable to consider exploring higher doses in non-T315I patients 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 the formulations currently available (20 mg and 40 mg tablets) require ten tablets to administer the full dose. The financial implications of these higher dose schedules cannot been ignored. Identifying the optimal dose and improving the available formulations are important aspects of the optimal use of asciminib.

Safety

The safety profile of asciminib has been consistent through the studies that have been reported. Not surprisingly for a heavily-treated patient population, myelosuppression is the most common AE, particularly thrombocytopenia (22.4% grade ≥3 in ASCEMBL). Among the non-hematologic AE, 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 I study (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 TKI. In ASCEMBL, it occurred in 6.6% with bosutinib (5.3% grade ≥3). It clearly deserves attention when using asciminib (and other TKI), 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 myristoyl pocket.

An AE category of special interest is AOE. AOE were reported with asciminib in 5.1% of patients in ASCEMBL. The overall incidence of AOE is influenced by the breadth 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 front-line ENESTnd study, the reported cumulative incidence of such events was 7.5% by five years[19] and 16.5% by ten 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 TKI, AOE 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 AOE with asciminib, including assessment and management of co-morbidities, and risk factors at baseline and during therapy.

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] However, at least half of the patients still experienced treatment failure.[10] Being such a heavily-treated patient population this might be expected, but it still begs the question as to 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, six of the ten 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 IC_{50} in cellular assays (Ba/F3 cells) of some of these emerging mutations (e.g., E355G, F359V) are significantly higher than for the wild-type, being 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::ABL1* 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 Philadelphia translocation occur in a sizeable percentage of patients with CP-CML 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: comparison with ponatinib

In the absence of a randomized trial of ponatinib and asciminib for patients with resistance or intolerance to ≥2 TKI 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 which drug to use for a given patient who meets the criteria for the use of either. 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 patients' characteristics and outcomes are also reported differently. A summary of these trials is presented in Table 1. Patients are younger in the OPTIC trial and more patients with resistance (*vs.* 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 50% 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 an alternative option with a realistic expectation of a better outcome (e.g., stem cell transplantation), 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 AE such as myelosuppression. A major safety concern are AOE; these are reported with both ponatinib and asciminib. With most TKI there seems to be a dose effect for AOE. In ENESTnd, for example, cardiovascular events occurred in 16.5% of patients with 300 mg BID and 23.5% with 400 mg BID.[5] In OPTIC, the exposure-adjusted rates are 4.5 per 100 patient-years at 45 mg and 3.0 at 30 mg.[12] The most salient message is the need to assess, monitor, and manage co-morbidities and risk factors for AOE in all patients treated with TKI. Ultimately, having the added option of asciminib for patients with resistance to ≥2 TKI or with T315I is a very welcome development. This allows the patient's and the disease characteristics to be carefully reviewed in the context of the available information for each drug and for carefully weighted decisions to be made as to the most appropriate treatment for each patient. Drawing general conclusions for all patients in these scenarios, with one drug or the other being regarded as superior, would deny many of them of options that may offer efficacy or safety benefits for individual cases.

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 the one with the greatest needs is second-line therapy after resistance to front-line 2G-TKI. There is limited experience with prospective studies in this setting, but considering that the rate of complete cytogenetic response with 2G-TKI after resistance to only front-line 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 non-clinical 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 yet available. The hope is that this strategy may make successful treatment-free remission (TFR) achievable by more patients. The magnitude of any observed improvement will need to be balanced against safety, financial issues, convenience, and other implications to determine the ultimate value of this strategy. An intriguing possibility is to use asciminib as front-line 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 months), 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 an 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. Its current indication addresses some ongoing needs, and its mechanism of action

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

Characteristic	Subcategory	PACE[22,25]	OPTIC[j12,26]	ASCEMBL[10,27]	Asciminib T315I[11]
Patients' characteristics					
N	-	270	94	157	52
Median age, yrs (range)	-	60 (18-94)	46 (19-81)	52 (24-83)	54 (26-86)
CV risk factors, %	HTN Diabetes mellitus Hyperlipidemia BMI — kg/m^2	53 16 51 Obesity 24[a]	28 5 20 27[a]	NR NR NR NR	NR NR NR NR
Prior TKI, %	1 2 ≥3	7 36 57	1 46 53	0 52 48	17[b] 31[b] 52[b]
Resistance, %	-	84	98	61	NR
BCR-ABL1 mutation, %	No mutation T315I	51 24	54 27	87 0	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% ≤1%	60[c] 54[c]	44	43	-
When assessed	-	Median 57 mths[h]	At 12 mths	At 48 wks	-
Last report, % patients with response (time)	≤1% ≤0.1% (total) ≤0.1% (12 mths)	40 (overall) 37 (by 12 mths)	60 (by 36 mths) 34 (overall)	54 (by 96 wks) 41 (by 96 wks) 33 (by 48 wks)	47 (by 96 wks) 43 (by 48 wks)
Median follow-up	-	57 mths	32 mths	2.3 yrs	-
Median duration of exposure	-	32 mths	72% >12 mths	24 mths	68 wks
PFS, %[l]	-	53 (5-yrs)	79.99 (2-yrs)	94.4 (2-yrs)	-
OS, %	-	73 (5-yrs)	91.28 (2-yrs)	97.3 (2-yrs)	-
Safety					
AOE	Overall, % Per 100 patient-years	31[i] 14.1[i]	10 4.5[f]	5[d] 3.0[d]	5.8[e]
HTN, %	Grade ≥3	14	9	6.4	5.7
Lipase elevation, %	-	13	11	3.8	15.4
Thrombocytopenia, %	-	35	30	22.4	17.3

N: number; NR: not reported; yrs: years; mths: months; wks: weeks; CV: cardiovascular disease; HTN: hypertension; TKI: tyrosine kinase inhibitor; MCyR: major cytogenetic response; PFS: progression-free survival; OS: overall survival; AOE: arterio-occlusive events. [a]Obesity: Body Mass Index (BMI) ≥30. Overweight: BMI 25-29.9. [b]60% prior ponatinib. [c]Reflects MCyR and complete cytogenetic response (CCyR) by 12 mth. [d]96-week report. [e]Median duration of exposure 68.4 wk. [f]With 45 mg (3.0 with 30 mg). [g]Most recent dasatinib or nilotinib treatment. [h]By 12 mth, MCyR 56%, CCyR 46%, major molecular response 34%. [i]17% and 10.4% per 100 patient-years after adjudication.[28] [j]Presented for 45 mg cohort. [k]Better than complete hematologic response (CHR). [l]In OPTIC, defined as the interval between the first dose and disease progression (progression to accelerated-phase chronic myeloid leukemia [CML] or blast-phase CML, loss of CHR or MCyR, or doubling of white blood cell count to 20x10^9/L on 2 occasions at least 4 weeks apart in patients without CHR); in ASCEMBL, no definition was provided in the manuscript.

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.

Disclosures

SP has no conflicts of interest to disclose. JC has been a consultant for Novartis, Pfizer, Takeda, Sun Pharma, and has received research support (to his institution) from Novartis, Pfizer, Takeda, Incyte, Sun Pharma and Ascentage.

Contributions

SP reviewed the literature. JC conceived the study and designed the outline of the manuscript, reviewed and analyzed the literature, and wrote the manuscript. Both authors edited the manuscript and approved the final version for publication.

References

1. Druker BJ, Tamura S, Buchdunger E, et al. Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. Nat Med. 1996;2(5):561-566.
2. Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med. 2001;344(14):1031-1037.
3. O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2003;348(11):994-1004.
4. Sasaki K, Strom SS, O'Brien S, et al. Relative survival in patients with chronic-phase chronic myeloid leukaemia in the tyrosine-kinase inhibitor era: analysis of patient data from six prospective clinical trials. Lancet Haematol. 2015;2(5):e186-193.
5. Kantarjian HM, Hughes TP, Larson RA, et al. Long-term outcomes with frontline nilotinib versus imatinib in newly diagnosed chronic myeloid leukemia in chronic phase: ENESTnd 10-year analysis. Leukemia. 2021;35(2):440-453.
6. Lipton JH, Brummendorf TH, Gambacorti-Passerini C, et al. Long-term safety review of tyrosine kinase inhibitors in chronic myeloid leukemia - What to look for when treatment-free remission is not an option. Blood Rev. 2022;56:100968.
7. Wylie AA, Schoepfer J, Jahnke W, et al. The allosteric inhibitor ABL001 enables dual targeting of BCR-ABL1. Nature. 2017;543(7647):733-737.
8. Hughes TP, Mauro MJ, Cortes JE, et al. Asciminib in chronic myeloid leukemia after ABL kinase inhibitor failure. N Engl J Med. 2019;381(24):2315-2326.
9. Rea D, Mauro MJ, Boquimpani C, et al. A phase 3, open-label, randomized study of asciminib, a STAMP inhibitor, vs bosutinib in CML after 2 or more prior TKIs. Blood. 2021;138(21):2031-2041.
10. Hochhaus A, Rea D, Boquimpani C, et al. Asciminib vs bosutinib in chronic-phase chronic myeloid leukemia previously treated with at least two tyrosine kinase inhibitors: longer-term follow-up of ASCEMBL. Leukemia. 2023;37(3):617-626.
11. Cortes J, Hughes T, Mauro M, et al. Asciminib, a first-in-class STAMP inhibitor, provides durable molecular response in patients (pts) with chronic myeloid leukemia (CML) harboring the T315I mutation: primary efficacy and safety results from a phase 1 trial. Blood. 2020;136(Suppl 1):47-50.
12. Cortes J, Apperley J, Lomaia E, et al. Ponatinib dose-ranging study in chronic-phase chronic myeloid leukemia: a randomized, open-label phase 2 clinical trial. Blood. 2021;138(21):2042-2050.
13. Cortes JE, Khoury HJ, Kantarjian HM, et al. Long-term bosutinib for chronic phase chronic myeloid leukemia after failure of imatinib plus dasatinib and/or nilotinib. Am J Hematol. 2016;91(12):1206-1214.
14. Hochhaus A, Gambacorti-Passerini C, Abboud C, et al. Bosutinib for pretreated patients with chronic phase chronic myeloid leukemia: primary results of the phase 4 BYOND study. Leukemia. 2020;34(8):2125-2137.
15. Castagnetti F, Bocchia M, Abruzzese E, et al. Bosutinib dose optimization in the second-line treatment of elderly CML patients: extended 3-year follow-up and final results of the best study. Hemasphere. 2022;6:593-594.
16. Cortes JE, Apperley JF, DeAngelo DJ, et al. Management of adverse events associated with bosutinib treatment of chronic-phase chronic myeloid leukemia: expert panel review. J Hematol Oncol. 2018;11(1):143.
17. Manley PW, Barys L, Cowan-Jacob SW. The specificity of asciminib, a potential treatment for chronic myeloid leukemia, as a myristate-pocket binding ABL inhibitor and analysis of its interactions with mutant forms of BCR-ABL1 kinase. Leuk Res. 2020;98:106458.
18. Hoch M, Zack J, Quinlan M, et al. Pharmacokinetics of asciminib when taken with imatinib or with food. Clin Pharmacol Drug Dev. 2022;11(2):207-219.
19. Hochhaus A, Saglio G, Hughes TP, et al. Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. Leukemia. 2016;30(5):1044-1054.
20. Qiang W, Antelope O, Zabriskie MS, et al. Mechanisms of resistance to the BCR-ABL1 allosteric inhibitor asciminib. Leukemia. 2017;31(12):2844-2847.
21. Branford S, Wang P, Yeung DT, et al. Integrative genomic analysis reveals cancer-associated mutations at diagnosis of CML in patients with high-risk disease. Blood. 2018;132(9):948-961.
22. Cortes JE, Kim DW, Pinilla-Ibarz J, et al. Ponatinib efficacy and safety in Philadelphia chromosome-positive leukemia: final 5-year results of the phase 2 PACE trial. Blood. 2018;132(4):393-404.
23. Cortes J, Hughes T, Geissler J, et al. Efficacy and safety results from ASC4MORE, a randomized study of asciminib (ASC) add-on to imatinib (IMA), continued IMA, or switch to nilotinib (NIL) in patients (Pts) with chronic-phase chronic myeloid leukemia (CML-CP) not achieving deep molecular responses (DMRs) with ≥1 year of IMA. Blood. 2022;140(Suppl 1):195-197.
24. Yeung DT, Shanmuganathan N, Reynolds J, et al. Early and deep molecular responses achieved with frontline asciminib in chronic phase CML - interim results from ALLG CML13 Ascend-CML. Blood. 2022;140(Suppl 1):192-194.
25. Cortes JE, Kim DW, Pinilla-Ibarz J, et al. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. N Engl J Med. 2013;369(19):1783-1796.
26. Cortes J, Deininger M, Lomaia E, et al. Three-year update from the Optic trial: a dose-optimization study of 3 starting doses of ponatinib. Blood. 2022;140(Suppl 1):1495-1497.
27. Mauro M, Minami Y, Rea D, et al. Efficacy and safety results from ASCEMBL, a multicenter, open-label, phase 3 study of asciminib, a first-in-class STAMP inhibitor, vs bosutinib in patients with chronic myeloid leukemia in chronic phase after ≥2 prior tyrosine kinase inhibitors: update after 48 weeks. Blood. 2021;138(Suppl 1):310.
28. Januzzi JL, Garasic JM, Kasner SE, et al. Retrospective analysis of arterial occlusive events in the PACE trial by an independent adjudication committee. J Hematol Oncol. 2022;15(1):1.