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Poster ALL-724

First-in-Human Study of Asciminib Monotherapy in Adults With Relapsed/Refractory Philadelphia-Positive Acute Lymphoblastic Leukemia (Ph+ ALL)

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KEY FINDINGS & CONCLUSIONS

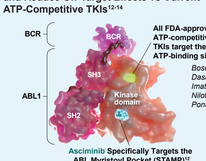
- In heavily pretreated patients with R/R Ph+ ALL—a small subset in the last cohort of the first-in-human phase 1 study that was initiated in 2014—asciminib monotherapy showed antileukemic activity and was generally safe and well tolerated
- Most patients discontinued therapy prematurely, primarily due to progressive disease
  - MTD was not reached, RDE was not determined but an enrichment cohort was opened at 200 mg BID, and no expansion cohort was initiated
  - This is the first study to show efficacy in the p190 Ph+ ALL population, the predominant subtype in our dataset
  - Most patients were heavily pretreated, and more than half had previously received ponatinib; 4 remained on therapy for ≥144 weeks and had sustained or deepening molecular responses
    - Over 2.5 years later, 2 patients are continuing asciminib monotherapy in rollover studies
  - All dose levels (40-280 mg BID) were tolerated and safe with no dose-dependent AEs observed
- The current analysis showed antileukemic activity of asciminib monotherapy in patients with Ph+ ALL, with a few patients showing long-term disease control
- Further exploration of asciminib in combination therapy regimens for Ph+ ALL is ongoing[1,2]

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INTRODUCTION

- OS in patients with Ph+ ALL has improved with the approval of chemotherapy or blinatumomab in combination with ATP-competitive TKIs and allogeneic stem cell transplant, resulting in 5-year OS rates up to 71%[3-7]
- Approximately 43% of patients experience relapse, most commonly due to BCR::ABL1 KD point mutations (eg, T315I)[4,8-10]; patients with TKI resistance may have limited treatment options and poor outcomes[4,11]
- There is an unmet need for efficacious treatment options with favorable safety and tolerability for patients with R/R Ph+ ALL
- Asciminib, the first BCR::ABL1 inhibitor to Specifically Target the ABL Myristoyl Pocket (STAMP), does not bind to the ATP-binding site of BCR::ABL1 and has a nonoverlapping resistance profile with ATP-competitive TKIs[12,13] (**Figure 1**)
- This primary and secondary endpoint analysis of asciminib monotherapy in patients with R/R Ph+ ALL was done in a small subgroup in the last cohort of the first-in-human phase 1 study (NCT02081378) conducted from April 24, 2014, to March 14, 2023

Figure 1. Asciminib: Designed to Improve Efficacy and Reduce Off-Target Effects vs Current ATP-Competitive TKIs[12-14]

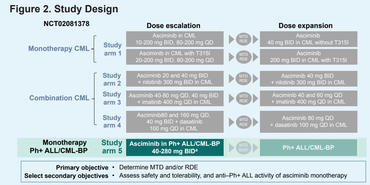


Adapted from Manley PW, et al. *Leuk Res*. 2020;98:106458. Copyright © 2020 Elsevier Ltd.[12]

METHODS

- This was a phase 1, open-label, dose-finding study of asciminib monotherapy or in combination therapy in patients with CML or Ph+ ALL (**Figure 2**)
- We present primary and secondary endpoint results from study arm 5 (the final cohort to report in the trial) from patients with R/R Ph+ ALL treated with ≥1 prior TKI, including patients with posttransplant relapse (data cutoff: March 14, 2023)
- The primary objective of the current analysis was to determine the MTD and/or the RDE

Figure 2. Study Design



From Hughes TP, et al. *New Engl J Med*. 2019;381:2315-2326. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.
*The current analysis only included patients with Ph+ ALL. † The MTD was not reached; based on 2 DLTs observed with 280 mg BID, an enrichment cohort at 200 mg BID was opened. No further dose levels were assessed, and RDE has not been determined.

RESULTS

- Most patients with Ph+ ALL were heavily pretreated at baseline; 53.6% had prior treatment with ponatinib (**Table 1**)

Table 1. Baseline Characteristics and Demographics

Variable	Ph+ ALL (N=28)
Age, median (range), years	60 (31-77)
Age category, n (%)	
18 to <65 years	16 (57.1)
≥65 to <75 years	8 (28.6)
≥75 years	4 (14.3)
Male, n (%)	16 (57.1)
ECOG performance status, n (%)	
0 to 1	25 (89.3)
≥2	3 (10.7)
Prior TKIs, n (%)	
1	3 (10.7)
2	13 (46.4)
≥3	12 (42.9)
Prior ponatinib, n (%)	15 (53.6)
Prior HSCT, n (%)	13 (46.4)
Bone marrow blasts at screening, median (range), %	4 (0-92)
***BCR::ABL1* transcript, n (%)**	
Atypical/p190/Unknown[a]	23 (82.1)
p210	5 (17.9)
Mutations at screening, n[b]	
Isolated T315I	5
Isolated Y253H	1
Compound mutations[c]	3

[a] A total of 18 patients had a p190 transcript, and 8 had unknown transcripts. [b] Twenty patients had mutational analysis at screening, 9 of whom had detectable mutations. [c] Compound mutations were Y253H/T315I, Y253H/F317L, and Q252H/T315I.

- At the data cutoff, all patients discontinued treatment, primarily due to progressive disease (**Table 2**)
- Of the 6 patients who discontinued treatment based on physician decision:
  - Two patients enrolled in the asciminib rollover study
  - One patient each discontinued to undergo HSCT, to receive alternative therapy, due to molecular progression with suspected chloroma, and due to refractory disease
- Of the 3 patients who discontinued treatment based on patient/guardian decision:
  - One patient started treatment with dasatinib and had a protocol deviation
  - One patient transitioned to palliative care
  - One patient with persistent disease changed to alternative therapy

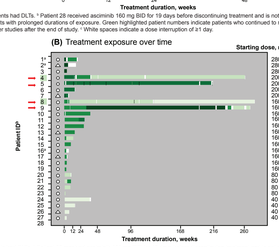
Table 2. Patient Disposition

Patients, n (%)	Ph+ ALL (N=28)
Primary reason for end of treatment	
AE	4 (14.3)
Death	2 (7.1)
Physician decision	6 (21.4)
Progressive disease	13 (46.4)
Patient/guardian decision	3 (10.7)

- Asciminib was evaluated at doses ranging from 40 to 280 mg BID
- A total of 3 patients had DLTs in the first 28 days (**Figure 3A**)
  - Asciminib 160 mg BID: 1 patient experienced grade 4 increased lipase and grade 2 pancreatitis
  - Asciminib 280 mg BID: 1 patient had grade 4 increased ALT, grade 4 increased AST, and grade 4 increased GGT, and 1 patient had grade 3 cerebrovascular accident
- The RDE was not determined, and a dose-expansion cohort was not opened for enrollment
- The median duration of exposure was 9.5 weeks (range: 1-275 weeks)
- Of 28 patients, 8 (28.6%) received asciminib for ≥24 weeks and 4 (14.3%) for ≥144 weeks (**Figure 3B**)
- The longest duration of exposure was in the asciminib 200-mg BID cohort at 114.6 weeks

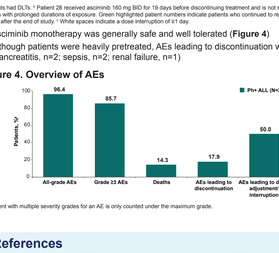
Figure 3. Treatment Duration and Exposure

(A) Treatment duration up to week 48



[a] Patients had DLTs. [b] Patient 28 received asciminib 160 mg BID for 19 days before discontinuing treatment and is not shown here. Red arrows indicate patients with prolonged durations of exposure. Green highlighted patient numbers indicate patients who continued to receive asciminib monotherapy in rollover studies after the end of study. * White spaces indicate a dose interruption of ≥1 day.

(B) Treatment exposure over time



[a] Patients had DLTs. [b] Patient 28 received asciminib 160 mg BID for 19 days before discontinuing treatment and is not shown here. Red arrows indicate patients with prolonged durations of exposure. Green highlighted patient numbers indicate patients who continued to receive asciminib monotherapy in rollover studies after the end of study. * White spaces indicate a dose interruption of ≥1 day.

- Asciminib monotherapy was generally safe and well tolerated (**Figure 4**)
- Although patients were heavily pretreated, AEs leading to discontinuation were infrequent (pancreatitis, n=2; sepsis, n=2; renal failure, n=1)

Figure 4. Overview of AEs

[a] A patient with multiple severity grades for an AE is only counted under the maximum grade.

- Observed AEs were not dose dependent (**Table 3**)
- The most frequent (in ≥15% of all patients) grade ≥3 AEs were anemia (32.1%), neutropenia (32.1%), thrombocytopenia (32.1%), GGT increased (21.4%), ALT increased (17.9%), lipase increased (17.9%), and pneumonia (17.9%)

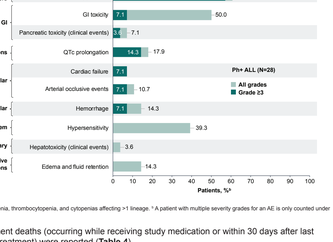
Table 3. Observed AEs in ≥20% of All Patients

Patients, %[a]	Asciminib 40 mg BID (n=4)		Asciminib 80 mg BID (n=4)		Asciminib 160 mg BID (n=13)		Asciminib 200 mg BID (n=4)		Asciminib 280 mg BID (n=3)		All patients (N=28)	
	All grade	Grade ≥3	All grade	Grade ≥3	All grade	Grade ≥3	All grade	Grade ≥3	All grade	Grade ≥3	All grade	Grade ≥3
Anemia[a]	50	25	25	25	39	23	100	75	33	33	46	32
Headache	–	–	25	–	46	8	50	–	33	–	36	4
Fatigue	25	25	–	–	23	–	50	–	100	–	32	4
GGT increased	–	–	–	–	46	23	50	50	33	33	32	21
Neutropenia[a]	50	50	–	–	31	31	50	50	33	33	32	32
Thrombocytopenia[a]	50	50	25	25	31	31	25	25	33	33	32	32
ALT increased	–	–	–	–	31	23	75	25	33	33	29	18
Lipase increased	25	25	–	–	23	23	50	25	67	–	29	18
Nausea	25	–	–	–	31	–	50	–	33	–	29	–
ALP increased	25	–	–	–	39	8	25	–	–	–	25	4
Dyspnea	50	–	–	–	15	–	50	–	33	–	25	–
Leukopenia[a]	50	50	–	–	23	23	25	25	33	33	25	25
Pyrexia	25	–	–	–	39	–	–	–	33	–	25	–
Vomiting	–	–	25	–	15	–	75	25	33	–	25	4
AST increased	–	–	–	–	31	15	25	–	33	33	21	11

[a] A patient with multiple severity grades for an AE is only counted under the maximum grade. All values were rounded to the nearest whole number. A dash indicates 0% of patients. [b] Includes hemoglobin decreased and anemia. [c] Includes neutrophil count decreased and neutropenia. [d] Includes platelet count decreased and thrombocytopenia. [e] Includes white blood cell count decreased and leukopenia.

- The most frequent all-grade AE of special interest was myelosuppression in 60.7% of patients (**Figure 5**)

Figure 5. Overview of AEs of Special Interest



[a] Includes anemia, leukopenia, thrombocytopenia, and cytopenias affecting >1 lineage. [b] A patient with multiple severity grades for an AE is only counted under the maximum grade.

- Four on-treatment deaths (occurring while receiving study medication or within 30 days after last dose of study treatment) were reported (**Table 4**)
- In these patients, 2 deaths occurred after discontinuation of asciminib

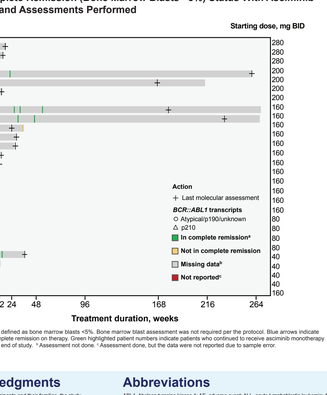
Table 4. Patient Narratives for On-Treatment Deaths[a]

Patient ID	Cause of death	Age, years	Sex	Last dose of asciminib	Key events prior to death
5	Cardiac arrest	75	Male	200 mg BID (day 1499)	Known cardiac history. Patient entered the study in MMR and later achieved MR⁴. The patient died 7 days after the last dose of asciminib, in week 215
22	Sepsis[b]	47	Male	80 mg BID (day 56)	Developed severe sepsis with hypotension and fever, asciminib was discontinued on study day 56. The patient died 3 days after the last dose of asciminib, in week 9
23	Pneumonia and sepsis	73	Male	80 mg BID (day 6)	Developed pneumonia on day 7 and sepsis on day 9. The patient died 5 days after the last dose of asciminib, in week 2
27	Study indication[b]	65	Male	40 mg BID (day 15)	Asciminib permanently discontinued due to disease progression, thereafter patient received prednisolone and dasatinib. The patient died 25 days after the last dose of asciminib, in week 6

[a] On-treatment deaths were defined as deaths occurring while receiving study medication or within 30 days after last dose of study treatment. [b] Deaths occurred after discontinuation of asciminib.

- At screening, 14 patients were in complete remission (**Figure 6**)
- Between days 1 and 30, 3 patients maintained complete remission (patients 4, 14, and 20), and 2 (patients 17 and 18) had progressive disease
- A total of 4 patients with complete remission at screening (and no assessments at days 1-30) had assessments after day 30
  - One patient had progressive disease (patient 7)
  - Three remained in complete remission (patients 8, 9, and 24)

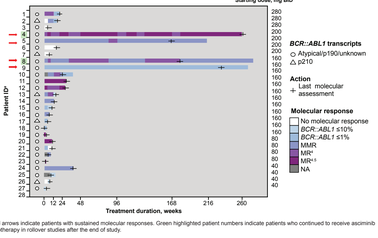
Figure 6. Complete Remission (Bone Marrow Blasts <5%) Status With Asciminib Monotherapy and Assessments Performed



[a] Complete remission was defined as bone marrow blasts <5%. Bone marrow blast assessment was not required per the protocol. Blue arrows indicate patients who achieved complete remission on therapy. Green highlighted patient numbers indicate patients who continued to receive asciminib monotherapy in rollover studies after the end of study. * Assessment not done. ^ Assessment done, but the data were not reported due to sample error.

- Four patients had sustained molecular responses (**Figure 7**)

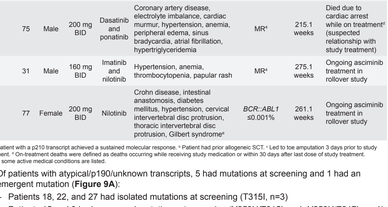
Figure 7. Molecular Response Assessments by Peripheral Blood



[a] Red arrows indicate patients with sustained molecular responses. Green highlighted patient numbers indicate patients who continued to receive asciminib monotherapy in rollover studies after the end of study.

- In this heavily pretreated population, patients 9, 5, 8, and 4 had sustained molecular responses (**Figure 8** and **Table 5**)

Figure 8. *BCR::ABL1* Levels Over Time in Patients With Sustained Responses[a]



[a] Patients had atypical/p190/unknown transcript. No patient with a p210 transcript achieved a sustained molecular response. [b] Patients had prior allogeneic SCT.

Table 5. Patient Narratives for Patients With Sustained Molecular Responses[a]

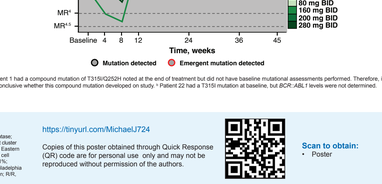
Patient ID	Age, years	Sex	Starting dose	Prior TKIs	Relevant active medical conditions at screening	Best response on treatment	Duration on treatment	Status
9[b]	70	Male	160 mg BID	Imatinib, dasatinib, and nilotinib	Hypertension, chronic kidney disease, increased brain natriuretic peptide, peripheral arterial occlusive disease,[c] anemia, prostatomegaly	*BCR::ABL1* ≤1%	268.9 weeks	Died due to cardiac failure 67 days after the last dose (unrelated to disease)
5	75	Male	200 mg BID	Dasatinib and ponatinib	Coronary artery disease, electrolyte imbalance, cardiac murmur, hypertension, anemia, peripheral edema, sinus bradycardia, atrial fibrillation, hypertriglyceridemia	MR⁴	215.1 weeks	Died due to cardiac arrest while on treatment[d] (suspected relationship with study treatment)
8[b]	31	Male	160 mg BID	Imatinib and nilotinib	Hypertension, anemia, thrombocytopenia, papular rash	MR⁴	275.1 weeks	Ongoing asciminib treatment in rollover study
4	77	Female	200 mg BID	Nilotinib	Crohn disease, intestinal anastomosis, diabetes mellitus, hypertension, cervical intervertebral disc protrusion, thoracic intervertebral disc protrusion, Gilbert syndrome[e]	*BCR::ABL1* ≤0.001%	261.1 weeks	Ongoing asciminib treatment in rollover study

[a] No patient with a p210 transcript achieved a sustained molecular response. [b] Patient had prior allogeneic SCT. [c] Led to toe amputation 3 days prior to study treatment. [d] On-treatment deaths were defined as deaths occurring while receiving study medication or within 30 days after last dose of study treatment. [e] Only some active medical conditions are listed.

- Of patients with atypical/p190/unknown transcripts, 5 had mutations at screening and 1 had an emergent mutation (**Figure 9A**):
  - Patients 18, 22, and 27 had isolated mutations at screening (T315I, n=3)
  - Patients 15 and 3 had compound mutations at screening (Y253H/T315I, n=1; Y253H/F317L, n=1)
  - Patient 3 with the Y253H/F317L compound mutation had F486S identified on study day 32
- Of patients with p210 transcripts, 4 had mutations at screening and 1 had an emergent mutation (**Figure 9B**):
  - Patients 13, 26, and 2 had isolated mutations at screening (T315I, n=2; Y253H, n=1)
  - Patient 17 had a compound mutation at screening (Q252H/T315I, n=1)
  - Patient 13 with the T315I mutation had S501I identified on study day 100

Figure 9. Detection of Mutations in Patients Over Time

(A) MMR over time in patients with atypical/p190/unknown transcripts



(B) MMR over time in patients with p210 transcripts

[a] Patient 1 had a compound mutation of T315I/Q252H noted at the end of treatment but did not have baseline mutational assessments performed. Therefore, it is inconclusive whether this compound mutation developed on study. [b] Patient 22 had a T315I mutation at baseline, but *BCR::ABL1* levels were not determined.

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Abbreviations

ABL1, Abelson tyrosine kinase 1; AE, adverse event; ALL, acute lymphoblastic leukemia; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATP, adenosine triphosphate; BCR, breakpoint cluster region; BID, twice daily; BP, blast phase; CML, chronic myeloid leukemia; DLT, dose-limiting toxicity; ECOG, Eastern Cooperative Oncology Group; EHA, European Hematology Association; GGT, gamma-glutamyltransferase; HSCT, hematopoietic stem cell transplant; KD, kinase domain; MMR, major molecular response (*BCR::ABL1* ≤0.1%); MR⁴, *BCR::ABL1* ≤0.0032%; MTD, maximum tolerated dose; NA, not applicable; OS, overall survival; Ph, Philadelphia chromosome; PI, patient; QD, once daily; QTc, corrected QT interval; RDE, recommended dose for expansion; R/R, relapsed/refractory; SCT, stem cell transplant; TKI, tyrosine kinase inhibitor.

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