CML-466

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Asciminib Provides Durable Molecular Responses in Patients With Chronic Myeloid Leukemia in Chronic Phase (CML-CP) With the T315I Mutation: Updated Efficacy and Safety Data From a Phase I Trial

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CONCLUSIONS

After approximately 9 months' additional exposure (median duration of exposure, >2 years), asciminib 200 mg BID continued to show **clinical efficacy** in patients with CML-CP with the T315I mutation—a subset of patients with typically poor prognosis

- **62.2%** of evaluable patients **achieved *BCR::ABL1*[IS] ≤1%**, including **47.6% of ponatinib-pretreated** patients, a response representative of a high level of activity in patients with very limited treatment options[8]
- **Nearly half of patients** (22 [48.9%]) **achieved MMR**. The **response was durable,** and 19 of 22 maintained MMR or improved to a deeper level of response up to the cutoff date
- **≥50% of patients** who achieved MMR **improved to a deeper molecular response level** (MR[4] and MR[4.5]) by the data cutoff

After approximately 9 months' additional exposure (median duration of exposure, >2 years), asciminib continued to demonstrate a **favorable safety profile** in patients with CML-CP with the T315I mutation, with limited increases in AEs over time

- Few patients (5 [10.4%]) experienced AEs leading to discontinuation at a dose of 200 mg BID

Remarkably, after a median exposure of >2 years, **56.3%** of these difficult-to-treat patients **remained on asciminib therapy**, reinforcing the efficacy and tolerability of asciminib as a **new treatment option for patients with CML-CP with the T315I mutation**, including those who have been previously treated with ponatinib

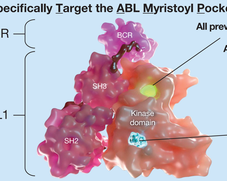
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INTRODUCTION

- In CML-CP, the *BCR::ABL1* T315I mutation confers **resistance** to previously approved adenosine triphosphate (ATP)–competitive tyrosine kinase inhibitor (TKIs), except ponatinib and olverembatinib[1-3]
- Asciminib was recently **approved** for the treatment of adults with:
  - Philadelphia chromosome–positive (Ph+) CML-CP previously treated with ≥2 TKIs and Ph+ CML-CP with the T315I mutation in the United States[4]
- A previous analysis of the X2101 study (median exposure of 68.4 weeks) demonstrated **meaningful clinical efficacy** and a **favorable safety profile of asciminib** in heavily pretreated patients with CML-CP or CML in accelerated phase (CML-AP) with the T315I mutation receiving a starting dose of 200 mg twice daily (BID)[5]

Asciminib is the first BCR::ABL1 inhibitor to Specifically Target the ABL Myristoyl Pocket (STAMP)[6]

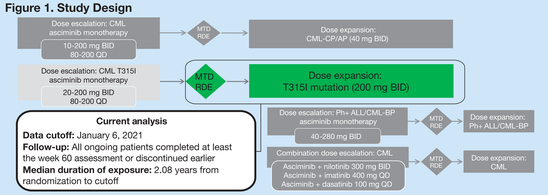


[a]Approved in China.

METHODS

- This is a phase I, multicenter, open-label, dose-finding study of asciminib in adult patients with CML-CP/AP or Ph+ acute lymphoblastic leukemia (ALL) who have been treated with ≥2 prior TKIs (**Figure 1**). Patients harboring the T315I mutation were included if previously treated with ≥1 TKI, provided no other treatments were available[7]
- The primary objective of this study was to determine the maximum tolerated dose (MTD) or recommended dose for expansion (RDE) of asciminib[7]
- Here we report updated efficacy and safety results from the expansion cohort in patients with T315I-mutated CML-CP treated with asciminib 200 mg BID

Figure 1. Study Design



RESULTS

Table 1. Baseline Characteristics

Variable	All patients, N=48
Age, median (range), years	56.5 (26-86)
Sex, n (%)	
Male	37 (77.1)
No. of prior TKIs, n (%)	
1	8 (16.7)
2	15 (31.3)
3	17 (35.4)
≥4	8 (16.7)
Individual prior TKIs, n (%)	
Bosutinib	3 (6.3)
Dasatinib	33 (68.8)
Imatinib	27 (56.3)
Nilotinib	26 (54.2)
Ponatinib	29 (60.4)
Radotinib	4 (8.3)
Mutations at screening, n (%)	
T315I alone	46 (95.8)
T315I and E255K	1 (2.1)
T315I and E355G	1 (2.1)
***BCR::ABL1*[IS] at screening, n (%)**	
>0.01% to 0.1%	0
>0.1% to 1%	8 (16.7)
>1% to 10%	11 (22.9)
>10%	26 (54.2)
Atypical/e1a2/unknown transcripts	3 (6.3)

- Of the 60.4% of patients with prior ponatinib treatment (**Table 1**), the last ponatinib dose was discontinued due to intolerance (n=9), resistance (n=14), and other reasons (n=6). Ponatinib was the immediate prior TKI in the majority of ponatinib-pretreated patients
- No patients were in major molecular response (MMR) at screening

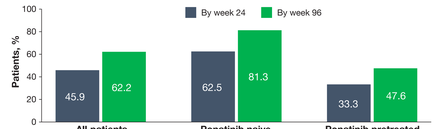
Table 2. Patient Disposition

Disposition reason	All patients, N=48
Patients treated, n (%)	
Treatment ongoing[a]	27 (56.3)
End of treatment	21 (43.8)
Primary reason for end of treatment, n (%)	
Physician decision	11 (22.9)
AE	4 (8.3)
Progressive disease	2 (4.2)
Death	2 (4.2)
Technical problems	1 (2.1)
Protocol deviation	1 (2.1)

[a] Ongoing at the time of cutoff: January 6, 2021.

- After a median of >2 years' exposure, few patients (8.3%) discontinued due to adverse events (AEs) and no new discontinuations due to AEs were reported since the previous April 2, 2020, data cutoff (**Table 2**)
- 2 new deaths were reported since last cutoff, both due to COVID-19. These were the only study deaths reported in this T315I patient population

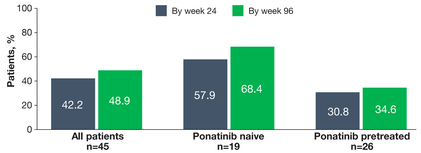
Figure 2. Cumulative *BCR::ABL1*[IS] ≤1%[a]



[a] In patients with *BCR::ABL1*[IS] ≥1% at baseline.

- *BCR::ABL1*[IS] ≤1% was achieved by a high proportion (62.2%) of patients without this response at baseline (n=37), including almost 50% of ponatinib-pretreated patients (**Figure 2**)

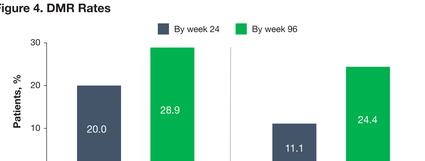
Figure 3. Cumulative MMR Rates



The KM-estimated **probability of maintaining MMR for ≥96 weeks** was:
- **84%** (95% CI, 68.1%-100.0%) in **all patients**
- **91%** (95% CI, 73.9%-100.0%) in **ponatinib-naive patients**
- **76%** (95% CI, 50.6%-100.0%) in **ponatinib-pretreated patients**

- 45 of 48 patients were evaluable (*BCR::ABL1*[IS] >0.1% at baseline) for MMR and deep molecular response (DMR); 3 were excluded for *BCR::ABL1* atypical/unknown transcripts (**Figure 3**)
- Almost half of patients (22 of 45 [48.9%]) achieved MMR by week 96, and responses were durable regardless of prior ponatinib treatment
- 19 of 22 patients maintained MMR or improved to a deeper level of response up to the cutoff date

Figure 4. DMR Rates



- ≥50% of patients who achieved MMR improved to a deeper molecular response level (MR[4] or MR[4.5]), with most achieving deeper responses by week 60 (**Figure 4**)

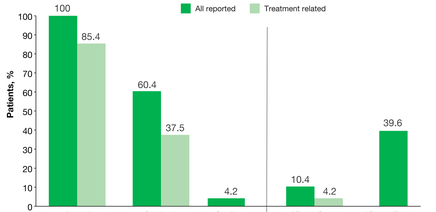
Table 3. Additional *BCR::ABL1* Mutations[a]

Patients who did not achieve MMR	n=23
Mutations at baseline	
Isolated T315I, n	21
Additional mutations, n	2
T315I/E255K	1
T315I/E355G	1
Mutations acquired during the study	
None, n	18
Mutations,[b] n	5
T315I/M244V	1
T315I/M351T	1
F359I, T315I/F359I	1, 1
A337T[c]/F359V	1
Patients who lost MMR	**n=3**
Mutations at baseline	
Isolated T315I, n	3
Additional mutations, n	0
Mutations acquired during the study	
None, n	2
Mutations,[b] n	1
F359V[c]	1

[a] Mutation status based on Sanger sequencing at central laboratory (measuring mutations between amino acids 35 and 510). Per protocol, mutational analysis was performed when there was unconfirmed loss of response or as needed; when a mutation was detected, additional mutational analyses were to be performed every 3 cycles. [b] Among patients with the T315I mutation alone at baseline. [c] Patient had T315I alone at screening, but follow-up assessment detected only the newly reported mutation. [d] Myristoyl pocket mutation.

- Only a few patients acquired additional *BCR::ABL1* mutations during the study (**Table 3**)
  - All patients with additional mutations lost or did not achieve MMR
- Only 1 of 6 mutations acquired during the study (A337T) was in the myristoyl pocket

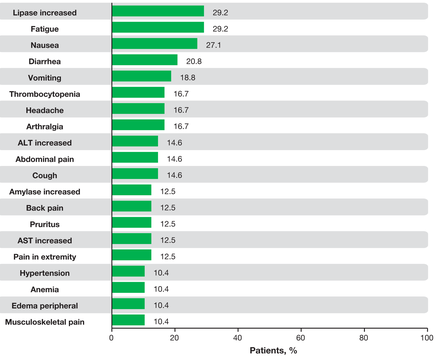
Figure 5. Overview of AEs in All Patients (N=48)



[a] Treatment-related AEs not reported.

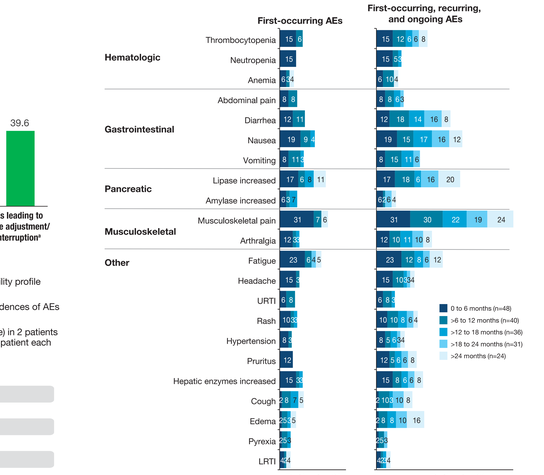
- Even after >2 years of median exposure, asciminib maintained a favorable safety/tolerability profile (**Figure 5**)
  - After approximately 9 months of added exposure, there was <5% difference in incidences of AEs compared with the previous cutoff
- AEs leading to discontinuation included COVID-19 pneumonia (grade 4 with fatal outcome) in 2 patients and pancytopenia (grade 4), thrombocytosis (grade 2), and lipase increased (grade 3) in 1 patient each

Figure 6. Most Frequent All-Grade AEs (in ≥10% of Patients)



- Frequent all-grade AEs occurring in ≥10% of patients were consistent (differences of <5%) with the rates of the previous cutoff, with the exception of lipase increase in 4 (+8.4%) new patients (**Figure 6**)
  - All cases of lipase increase were asymptomatic elevations with no clinical impact
- The most common grade ≥3 AEs were occurring in ≥5% of patients
  - Lipase increase (18.8%, all asymptomatic elevations)
  - Thrombocytopenia (14.6%)
  - Vomiting, ALT increase, abdominal pain, hypertension, anemia, neutropenia, and neutrophil count decrease (6.3% each)

Figure 7. Adverse Reactions Over Time[a,b,c]



[a] Includes reported AEs and ADRs. [b] Includes first-occurring AEs reported in ≥10% of patients. [c] Proportions are calculated based on the number of patients at risk of an event (ie, left side: patients ongoing treatment and event free at the start of the interval; right-side: patients ongoing treatment at the start of the interval). A patient with multiple occurrences of an event within the same time interval is counted only once in that time interval. The safety topics correspond to either single PTs or groups of PTs according to the ADR definitions.

- The majority of AEs occurred within the first 6 months of treatment, and incidence rates decreased over time (**Figure 7**)

Table 4: Adverse Events of Special Interest

	All patients, N=48	
Safety topic, n (%)	**All grade**	**Grade ≥3**
GI toxicity	23 (47.9)	5 (10.4)
Hypersensitivity[a]	13 (27.1)	0
Hepatotoxicity (including laboratory terms)[b]	13 (27.1)	5 (10.4)
Myelosuppression[c]	12 (25.0)	10 (20.8)
Pancreatic toxicity (including laboratory terms)	15 (31.3)	11 (22.9)
Pancreatic toxicity (clinical events)	1 (2.1)	0
Edema and fluid retention	8 (16.7)	3 (6.3)
Hemorrhage	9 (18.8)	1 (2.1)
Arterial occlusive events	4 (8.3)[d]	2 (4.2)
Phototoxicity	1 (2.1)	0
QTc prolongation	1 (2.1)	1 (2.1)

[a] Mainly mild dermatologic events. [b] Mainly enzyme elevations. [c] Myelosuppression includes anemia, leukopenia, thrombocytopenia, cytopenias affecting >1 lineage. [d] PT terms include cerebrovascular accident (n=2 [4.2%]), carotid artery disease (n=1 [2.1%]), and coronary artery disease (n=1 [2.1%]), and peripheral artery occlusion (n=1 [2.1%]). None led to adjustment, interruption, or discontinuation of asciminib or death. Only coronary artery disease was treatment-related. Coronary artery disease, peripheral arterial occlusive disease, and peripheral artery occlusion were reported in the same patient. PTs peripheral arterial occlusive disease and peripheral artery occlusion describe the same event in the same patient.

Abbreviations

ABL1, Abelson tyrosine kinase 1; **ADR**, adverse drug reaction; **AE**, adverse event; **ALL**, acute lymphoblastic leukemia; **ALT**, alanine aminotransferase; **AP**, accelerated phase; **AST**, aspartate aminotransferase; **ATP**, adenosine triphosphate; **BCR**, breakpoint cluster region; **BID**, twice daily; **BP**, blast phase; **CML-CP**, chronic myeloid leukemia in chronic phase; **DMR**, deep molecular response; **GI**, gastrointestinal; **IS**, International Scale; **KM**, Kaplan-Meier; **LRTI**, lower respiratory tract infection; **MMR**, major molecular response; **MTD**, maximum tolerated dose; **MR[4]**, (*BCR::ABL1*[IS] ≤0.1%); **MR[4.5]**, (*BCR::ABL1*[IS] ≤0.032%); **PFL**, Philadelphia chromosome; **PT**, preferred term; **QD**, once daily; **QTcI**, corrected QT interval; **RDE**, recommended dose for expansion; **SH**, Src homology; **TKI**, tyrosine kinase inhibitor; **URTI**, upper respiratory tract infection.

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