Poster CML-918

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Asciminib in Chronic Myeloid Leukemia in Chronic Phase: Interim Analysis Efficacy and Safety Results of the Phase 2 ASC2ESCALATE Trial in the Cohort of Newly Diagnosed Patients

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Conclusions

- This preliminary analysis of ASC2ESCALATE continues to demonstrate the clinical efficacy and favorable safety and tolerability of asciminib in patients with 1L CML-CP
- A majority of 91 evaluable patients at week 12 (91.2%) achieved an early molecular response, a response level associated with higher rates of subsequent deeper molecular responses, improved OS, and lower rates of disease progression[25]
- In 93 evaluable patients at week 24, a majority (78.5%) achieved *BCR::ABL1*^{IS} ≤1%
- In 75 evaluable patients at week 48, asciminib demonstrated high molecular response rates with 53.3% of the patients having achieved MMR and 24.0% having achieved MR^4 or better
- Of all 95 patients, 16 (16.8%) had dose escalations per protocol because they did not achieve optimal response milestones at 6 and 12 months per ELN 2020 recommendations
  – The outcomes in patients with asciminib dose escalations continue to be explored, with analyses planned for future presentations
- In 95 enrolled patients who received ≥1 dose, asciminib demonstrated a favorable safety and tolerability profile
  – Asciminib was well tolerated by most patients; 11 discontinued due to AEs
  – Overall, the safety profile of asciminib was consistent with the previously established profile in frontline and later-line (3L+) studies[8-11,26]
- These interim results further support asciminib as a standard-of-care treatment option in 1L CML-CP

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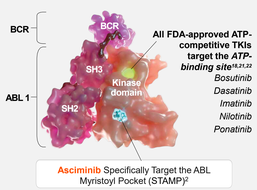
Introduction

- In 1L CML-CP, 18% to 49% of patients switch to 2L treatment,[1-3] often within the first year of treatment[1,3]
- Treatment switch is frequently due to a lack of treatment efficacy or intolerance[2,3] and may lead to worse survival outcomes and limited subsequent treatment options[4-6]
- Asciminib is the first approved *BCR::ABL1* inhibitor to Specifically Target the ABL Myristoyl Pocket (STAMP)[7] **(Figure 1)**
- Asciminib has demonstrated efficacy, safety, and tolerability in 1L and 2L+ CML-CP,[8-14] with consistent safety across a wide dose range of 10 to 200 mg bid in 2L+ CML-CP[8,9,10,15]
- Asciminib is approved in the United States (at doses of 80 mg qd and 40 mg bid) for patients with 1L CML-CP (under accelerated approval) and 2L+ CML-CP[16]
  – Accelerated approval is based on MMR rate. Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial(s)[16]
- The ASC2ESCALATE trial explores the safety and efficacy of 1L and 2L asciminib at 80 mg qd and after dose escalation in patients not achieving optimal response milestones at 6 and 12 months per ELN 2020 recommendations[17]

Objective

- Here, we present interim analysis results from the ASC2ESCALATE trial (NCT05384587) in the 1L CML-CP cohort of patients, including safety (n = 95) and week 48 efficacy (n = 75)

Figure 1. Asciminib: Designed to Improve Efficacy and Reduce Off-Target Effects vs Current ATP-Competitive TKIs[7,18,19]

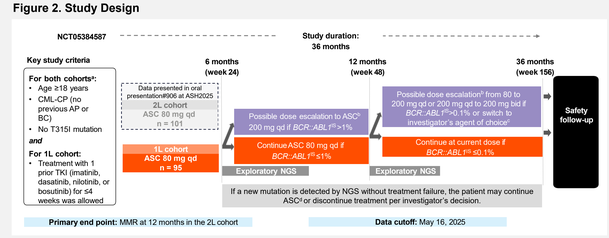


Adapted from Manley PW et al with permission.[19]

Methods

- ASC2ESCALATE is a phase 2, single-arm, open-label trial of asciminib with dose escalation in adults with 1L or 2L CML-CP without the T315I mutation in the United States **(Figure 2)**
- The trial is fully enrolled as of September 17, 2024, and includes 85 trial sites
- For patients with newly diagnosed CML-CP (1L cohort), treatment with 1 prior TKI (imatinib, dasatinib, nilotinib, or bosutinib) for ≤4 weeks was allowed
- The primary end point is MMR at week 48 in the 2L cohort; this measure is a secondary end point for the 1L cohort
- Secondary end points include the assessment of molecular response rates at and by scheduled timepoints; time to and duration of MMR; TTF; PFS; OS; and the type, frequency, and severity of AEs
- Interim safety analyses included all 95 patients in the 1L cohort
- Interim week 48 efficacy analyses included 75 patients with adequate follow-up, defined as having completed RQ-PCR assessments or having discontinued prior to data cutoff, and disease measurable on the International Scale; these analyses included applicable patients with dose escalation

Figure 2. Study Design



Adapted from Sasaki K et al and Atallah EL et al with permission.[22,23]
[a]For patients with CML-CP after 1 prior TKI (2L cohort), patients must have had warning or failure (per ELN 2020) with their first TKI or intolerance and *BCR::ABL*^{IS} >0.1% with their first TKI at screening. [b]For any grade 3 or 4 toxicity or persistent grade 2 toxicity unresponsive to optimal management, the dose escalation did not apply, and patients were continued on the current ASC dosage. [c]Patients switching to the investigator's agent of choice were taken off study. [d]At the same dose, unless meeting dose-escalation criteria.

Results

- Of 95 total patients, 22 (23.2%) were ≥65 years old **(Table 1)**

Table 1. Demographics and Baseline Characteristics

Variable	All patients (n = 95)
Age, median (range), years	51.0 (21-90)
Female, n (%)	34 (35.8)
Male, n (%)	61 (64.2)
Race, n (%)	
American Indian or Alaska Native	2 (2.1)
Asian	3 (3.2)
Black or African American	11 (11.6)
White	75 (78.9)
Unknown	4 (4.2)
Ethnicity, n (%)	
Hispanic or Latino	15 (15.8)
Not Hispanic or Latino	76 (80.0)
Unknown	3 (3.2)
Not reported	1 (1.1)
ECOG performance status	
0	60 (63.2)
1	33 (34.7)
2	2 (2.1)
Time since initial diagnosis, median (range), weeks	5.4 (2-38)

- Most patients (73.7%) remained on treatment at the data cutoff **(Table 2)**
  – Twenty-five patients (26.3%) discontinued asciminib, most frequently due to AEs (10.5%) and unsatisfactory therapeutic effect (9.5%)
    ○ Of 9 patients who discontinued due to unsatisfactory therapeutic effect, 5 did not have dose escalation and reasons for discontinuation were treatment failure per ELN (n = 3) and confirmed loss of MMR (n = 2)
  – Of 75 patients included in molecular response sensitivity analyses at week 48, 51 (68.0%) continued treatment at the data cutoff
    ○ Of these 51 patients, 8 had dose escalation

Table 2. Disposition (Median Follow-Up; 11.0 Months [Range, 1.2-19.4 Months][a])

Patients, n (%)	All patients (n = 95)
Treated	95 (100.0)
Treatment ongoing	70 (73.7)
Discontinued from treatment	25 (26.3)
<week 48	16 (16.8)
≥week 48 and <week 96	9 (9.5)
Reason for discontinuation	
AE	10 (10.5)
Unsatisfactory therapeutic effect	9 (9.5)
Patient decision	3 (3.2)
Physician decision	2 (2.1)
Death	1 (1.1)

[a]Defined as the duration from the date of treatment start until that of last contact or data cutoff, whichever comes first.

- In all patients, the median duration of exposure was 50.4 weeks (range, 1-94 weeks) **(Table 3)**
  – Dose escalation per protocol occurred in 16 patients
  – In the 75 patients included in molecular response sensitivity analyses at week 48, the median duration of exposure was 54.3 weeks (range, 1-94 weeks)

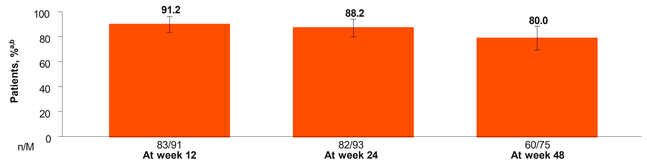
Table 3. Asciminib Exposure

Variable	All patients (n = 95)
Duration of exposure, median (range), weeks	50.4 (1-94)
Dose intensity, median (range), mg/day	80.0 (31-232)
Relative dose intensity, median (range), %[a]	100.0 (33-100)
Relative dose intensity categories, n (%)[b]	
>90% to 110%	75 (78.9)
>75% to 90%	8 (8.4)
≤75%	12 (12.6)
≥1 Dose escalation, n (%)[c]	16 (16.8)
From 80 to 200 mg qd	16 (16.8)
At week 24	8 (8.4)
At week 48	8 (8.4)
From 200 mg qd to 200 mg bid	3 (3.2)

[a]In 79 patients without dose escalation, the median relative dose intensity was 100% (range, 33%-100%). [b]In 79 patients without dose escalation, the relative dose intensity categories included >90% to 110% (n = 60 [75.9%]), >75% to 90% (n = 7 [8.9%]), and ≤75% (n = 12 [15.2%]). [c]Per the study protocol, dose escalation was only considered in patients not achieving response milestones at 24 and 48 weeks.

- A majority of patients (91.2%) achieved an early molecular response (*BCR::ABL1*^{IS} <10% at week 12; **Figure 3**)

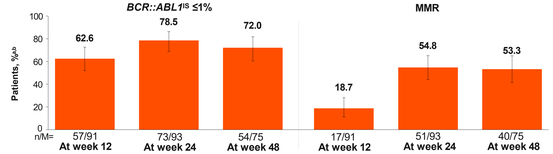
Figure 3. Rate of *BCR::ABL1*^{IS} ≤10% in Patients With Adequate Follow-Up



[a]Included patients with adequate follow-up (M), defined as those with assessments in the corresponding analysis time interval or who discontinued early. One patient had nonmeasurable disease on the International Scale due to the expression of p190/atypical/unknown transcripts at screening; they were excluded from molecular response sensitivity analyses. [b]Error bars represent 95% CIs calculated using the Clopper-Pearson 2-sided method.

- Many patients were in *BCR::ABL1*^{IS} ≤1% at week 24, which was the first dose-escalation cutoff, and/or MMR at week 48, which was the second dose-escalation cutoff **(Figure 4)**
  – Of 35 patients without MMR at week 48, fourteen had *BCR::ABL1*^{IS} ≤1%
  – Of 51 patients with MMR at week 24, forty-eight remained on treatment; 11 of those 48 did not have week 48 follow-up

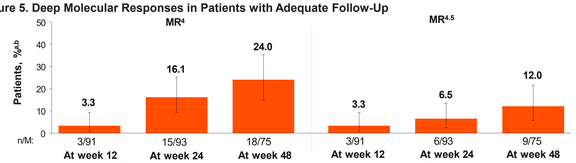
Figure 4. Molecular Response Rates in Patients with Adequate Follow-Up



[a]Included patients with adequate follow-up (M), defined as those with assessments in the corresponding analysis time interval or who discontinued early. One patient had non-measurable disease on the International Scale due to the expression of p190/atypical/unknown transcripts at screening; they were excluded from molecular response sensitivity analyses. [b]Error bars represent 95% CIs calculated using the Clopper-Pearson 2-sided method.

- Three patients (3.3%) achieved deep molecular response (MR^4 or better) early in treatment (at week 12), with more patients achieving deeper responses over time **(Figure 5)**

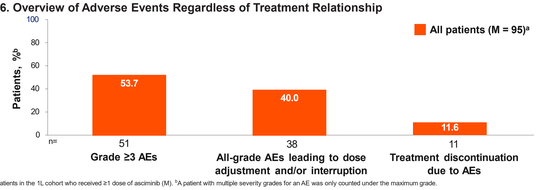
Figure 5. Deep Molecular Responses in Patients with Adequate Follow-Up



[a]Included patients with adequate follow-up (M), defined as those with assessments in the corresponding analysis time interval or who discontinued early. One patient had non-measurable disease on the International Scale due to the expression of p190/atypical/unknown transcripts at screening; they were excluded from molecular response sensitivity analyses. [b]Error bars represent 95% CIs calculated using the Clopper-Pearson 2-sided method.

- All-grade AEs occurred in 95 patients (100%), with fewer patients (53.7%) experiencing grade ≥3 events **(Figure 6)**
  – Dose reduction due to AEs occurred in 15 patients (15.8%); dose interruption due to AEs occurred in 41 (43.2%)
  – Eleven patients had AEs leading to discontinuation, including cerebrovascular accident and neutropenia (n = 2 each) and alopecia, fatigue, hypertension, multiple organ dysfunction syndrome, acute pancreatitis, headache and thrombocytosis, and thrombocytopenia (n = 1 each)
    ○ One of these 11 patients died due to multiple organ dysfunction syndrome; this was the only on-treatment (during treatment or ≤30 days after the last asciminib dose) death reported and was unrelated to asciminib per the investigator

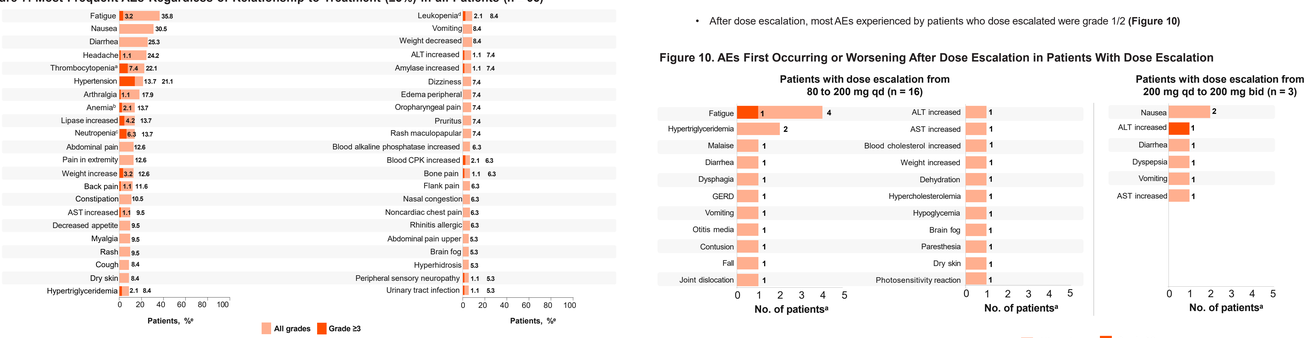
Figure 6. Overview of Adverse Events Regardless of Treatment Relationship



[a]Included all patients in the 1L cohort who received ≥1 dose of asciminib (M). [b]A patient with multiple severity grades for an AE was only counted under the maximum grade.

- Of the most frequent AEs (≥5%), most events were grade 1/2 (**Figure 7**)
  – Hematologic AEs (≥5%) included thrombocytopenia (22.1%), neutropenia (13.7%), anemia (13.7%), and leukopenia (8.4%)
  – Grades 1, 2, and 3 hypertension was experienced by 2 (2.1%), 5 (5.3%) and 13 (13.7%) patients, respectively

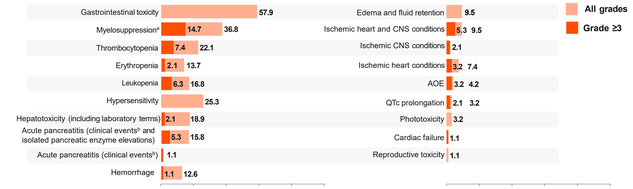
Figure 7. Most Frequent AEs Regardless of Relationship to Treatment (≥5%) in all Patients (n = 95)



[a]Included platelet count decreased and thrombocytopenia. [b]Included anemia, red blood cell decrease, and hematocrit decreased. [c]Included neutrophil count decreased and neutropenia. [a]Included white blood cell count decreased and leukopenia. [a]A patient with multiple severity grades for an AE was only counted under the maximum grade. The incidence of COVID-19 is not reported here.

- AEs of special interest are reported in **Figure 8**
  – AOEs occurred in 4 patients (4.2%), including grade 3 cerebrovascular accident (n = 2), grade 3 angina pectoris (n = 1), and grade 2 transient blindness (n = 1)
    ○ Two of 4 patients, both with cerebrovascular accident, discontinued treatment; the remaining 2 patients continued asciminib treatment
    ○ All AOEs resolved by the data cutoff
  – One patient experienced clinical pancreatitis (grade 3) and discontinued asciminib treatment
    ○ The event had resolved by the data cutoff
  – No cases of hepatotoxicity (clinical events) were reported

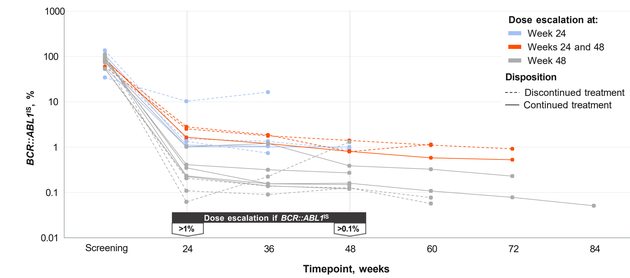
Figure 8. AEs of Special Interest in all Patients (n = 95)



[a]Included erythropenia, leukopenia, thrombocytopenia, cytopenias affecting >1 lineage. [b]Included the preferred terms pancreatitis and pancreatitis acute. [a]A patient with multiple severity grades for an AE was only counted under the maximum grade.

- Dose escalation from 80 to 200 mg qd occurred in 16 of 95 patients (16.8%) due to suboptimal response at weeks 24 (n = 8) and 48 (n = 8) **(Figure 9)**
  – Of 8 patients with dose escalation to 200 mg qd at week 24, 3 escalated to 200 mg bid at week 48
  – Overall, 9 of 16 with dose escalation remained on treatment

Figure 9. *BCR::ABL1*^{IS} Level at Time Points in Patients With Dose Escalation (n = 16)



- After dose escalation, most AEs experienced by patients who dose escalated were grade 1/2 **(Figure 10)**

Figure 10. AEs First Occurring or Worsening After Dose Escalation in Patients With Dose Escalation

[a]AEs occurring during treatment or within 30 days of the last study medication are summarized.

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Abbreviations

1L, first line; **2L**, second line; **3L**, third line; **AE**, adverse event; **ALT**, alanine aminotransferase; **AOE**, arterial-occlusive event; **AP**, accelerated phase; **ASC**, asciminib; **AST**, aspartate aminotransferase; **ATP**, adenosine triphosphate; **BC**, blast crisis; **bid**, twice daily; **CML**, chronic myeloid leukemia; **CNS**, central nervous system; **CP**, chronic phase; **CPK**, creatine phosphokinase; **ECOG**, Eastern Cooperative Oncology Group; **ELN**, European LeukemiaNet; **FDA**, US Food and Drug Administration; **GERD**, gastroesophageal reflux disease; **IS**, International Scale; **MMR**, major molecular response (*BCR::ABL1*^{IS} ≤0.1%); **MR^4**, *BCR::ABL1*^{IS} ≤0.01%; **MR$^{4.5}$**, *BCR::ABL1*^{IS} ≤0.0032%; **NGS**, next-generation sequencing; **OS**, overall survival; **PFS**, progression-free survival; **qd**, once daily; **QTc**, corrected QT interval; **RQ-PCR**, real-time quantitative polymerase chain reaction; **SH**, Src homology; **TKI**, tyrosine kinase inhibitor; **TTF**, time to treatment failure.

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