Ehab Atallah; Eatallah@MCW.edu

Poster PF595

Interim Analysis Results From ASC2ESCALATE Support Asciminib as a Treatment Option in Chronic-Phase Chronic Myeloid Leukemia After 1 Tyrosine Kinase Inhibitor

Ehab L. Atallah,[1] David Andorsky,[2] Marlise R. Luskin,[3] Srinivas K. Tantravahi,[4] Koji Sasaki,[5] James Dugan,[6] Celeste Bremer,[7] Vivian G. Oehler, [8] Joshua F. Zeidner,[9] Moshe Y. Levy,[10] Camille N. Abboud,[11] Paul Koller,[12] Bonnie Kiner-Strachan,[13] Habte Yimer,[14] Islam Sadek,[15] Daisy Yang,[15] Dramane Laine,[15] John Sabo,[15] Amanda Hall,[15] Dheeraj Gianchandani,[16] Michael J. Mauro,[17] Jorge E. Cortes[18]

[1]Medical College of Wisconsin, Milwaukee, WI, USA; [2]Sarah Cannon Research Institute and Rocky Mountain Cancer Centers, Boulder, CO, USA; [3]Dana-Farber Cancer Institute, Boston, MA, USA; [4]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA; [5]The University of Texas MD Anderson Cancer Center, Houston, TX, USA ; [6]Novant Health Cancer Institute, Winston-Salem, NC, USA; [7]Virginia Oncology Associates, Virginia Beach, VA, USA; [8]Fred Hutchinson Cancer Center Hematology Clinic, Seattle, WA, USA ; [9]University of North Carolina, Lineberger Comprehensive Cancer Center, Chapel Hill, NC, USA; [10]Baylor Scott & White Health, Dallas, TX, USA; [11]Washington University School of Medicine, St Louis, MO, USA; [12]City of Hope National Medical Center, Duarte, CA, USA; [13]PerImutter Cancer Center, NYU Langone-New York, NY, USA; [14]Christus Trinity Mother Frances Hospital Texas Oncology, Tyler, TX, USA; [15]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [16]Novartis Healthcare Private Limited, Hyderabad, India; [17]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [18]Georgia Cancer Center, Augusta, GA, USA

KEY FINDINGS & CONCLUSIONS

- ASC2ESCALATE is the first prospective trial of asciminib in 2L CML-CP with dose escalation in patients not achieving response milestones
- At week 24, asciminib demonstrated high molecular response rates in 63 patients with adequate follow-up
  - MMR was achieved by 44.4% of patients, and 25.4% achieved MR[4] or better
  - Of 63 patients, 7 (11.1%) had dose escalations per protocol because they did not achieve response milestones
- In 101 enrolled patients who received ≥1 dose, asciminib demonstrated a favorable safety and tolerability profile
  - Asciminib was well tolerated by most patients; 4 discontinued due to AEs
  - Overall, the safety profile of asciminib was consistent with the previously established profile in frontline and later-line (3L+) studies,[6-9,19] and no new or worsening safety findings were observed
- These interim results further support asciminib as a treatment option in 2L CML-CP
- The outcomes in patients with asciminib dose escalations continue to be explored, with analyses planned for future presentations

Scan to obtain:
- Poster

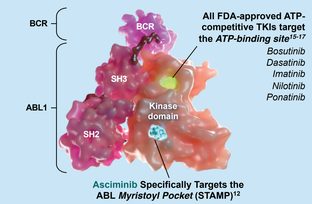
https://tinyurl.com/AtallahPF595

This study is sponsored by Novartis Pharma AG.
Poster presentation at: EHA2025 Congress; June 12-15, 2025; Milan, Italy.

INTRODUCTION

- Approximately 30% of patients with CML-CP discontinue or switch 2L treatment within 1 year,[1] which may lead to worse survival outcomes and limited subsequent treatment options[2-4]
- Asciminib is a BCR::ABL1 inhibitor that specifically targets the ABL myristoyl pocket (**Figure 1**) and has demonstrated efficacy, safety, and tolerability in 1L and 3L+ CML-CP[5-9]
- Asciminib 80 mg QD and 40 mg BID received accelerated FDA approval for 1L CML-CP and full approval for 2L+ CML-CP[10]
  - 1L approval of asciminib is based on MMR rate. Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial(s)
- In 2L, asciminib demonstrated favorable safety in 71 patients and week 24 efficacy in 28 patients in a previous interim analysis of the ASC2ESCALATE trial (NCT05384587; data cutoff: June 28, 2024)[11]
- Here, we present results of updated interim analyses (data cutoff: November 15, 2024) from ASC2ESCALATE in the 2L CML-CP cohort of patients, including safety (n=101) and week 24 efficacy (n=63)

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

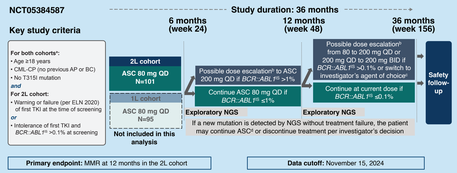


Adapted from Manley PW, et al. *Leuk Res*. 2020;98:106458. Copyright © 2020 Elsevier Ltd.[14]

METHODS

- ASC2ESCALATE is a phase 2, single-arm, open-label US study of 1L and 2L asciminib in adults with CML-CP without the T315I mutation (**Figure 2**)
  - The study is fully enrolled (as of September 17, 2024) and includes 85 trial sites
- Patients in the 2L cohort must have discontinued their prior TKI due to:
  - Warning response (*BCR::ABL1*[IS] >1%-10% after 6 month or >0.1%-1% after 12 month of 1L treatment)
  - Resistance (*BCR::ABL1*[IS] >10% during 6-12 months, or >1% or loss of MMR after >12 months of 1L treatment)
  - Intolerance with *BCR::ABL1*[IS] >0.1% at screening
- The primary endpoint is the rate of MMR at week 48 in the 2L cohort
- Secondary endpoints include the assessment of molecular response rates at and by scheduled time points, time to and duration of MMR, TTF, PFS, OS, and the type, frequency, and severity of AEs
  - All primary and secondary endpoints for the 2L cohort will be repeated for the 1L cohort as secondary endpoints

Figure 2. Study Design



[a] For patients with newly diagnosed CML-CP (1L cohort), treatment with 1 prior TKI (imatinib, dasatinib, nilotinib, or bosutinib) for ≤4 weeks was allowed. [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 asciminib dosage. Per the study protocol, dose escalation was only considered in patients not achieving response milestones at 24 and 48 weeks. [c] Patients switching to investigator's agent of choice were taken off study. [d] At the same dose unless meeting dose escalation criteria.

RESULTS

- This interim analysis included all 101 patients with CML-CP in 2L (**Table 1**)
  - Safety analyses included all 101 patients who received ≥1 asciminib dose
  - Efficacy analyses included patients with adequate follow-up, defined as having completed RQ-PCR assessments or discontinued prior to data cutoff
- Of 101 total patients, 27 (26.7%) were ≥65 years old

Table 1. Demographics and Baseline Characteristics

Variable	All patients (n=101)
Age, median (range), years	50.0 (18-89)
Male, n (%)	57 (56.4)
Race, n (%)	
American Indian or Alaska Native	1 (1.0)
Asian	4 (4.0)
Black or African American	9 (8.9)
White	83 (82.2)
Unknown	4 (4.0)
Ethnicity, n (%)	
Hispanic or Latino	12 (11.9)
Not Hispanic or Latino	88 (87.1)
Unknown	1 (1.0)
≥1 mutation detected at baseline, n (%)[a]	
E450Q/M244V	1 (1.0)
E459G	1 (1.0)
V299L	1 (1.0)
Prior TKIs, n (%)[b]	
Dasatinib	45 (44.6)
Imatinib	43 (42.6)
Nilotinib	10 (9.9)
Bosutinib	5 (5.0)
Duration of prior TKI, n (%)	
≥12 months	67 (66.3)
≥6 to <12 months	16 (15.8)
<6 months	18 (17.8)

[a] Analyzed by Sanger sequencing. [b] In this analysis, 2 patients had received 2 prior TKIs: 1 received dasatinib for 5 months and imatinib for 7 days; the other (included in the efficacy analysis set) received dasatinib for 41 months and imatinib for 1 month. This was identified by the sponsor after the patients were enrolled in the trial and was documented as a protocol deviation.

- All patients (n=101) discontinued prior treatment due to lack of efficacy (56.4%) or intolerance (43.6%) (**Table 2**)

Table 2. Baseline Molecular Response Level

BCR::ABL1[IS] level at baseline, n (%)	All patients	Discontinued prior TKI due to:	
		Lack of efficacy	Lack of tolerability
All patients	**n=101**	**n=57**	**n=44**
>0.1% to ≤1%	40 (39.6)	27 (47.4)	13 (29.5)
>1% to ≤10%	31 (30.7)	19 (33.3)	12 (27.3)
>10%	30 (29.7)	11 (19.3)	19 (43.2)
Week 24 efficacy-evaluable	**n=63**	**n=37**	**n=26**
>0.1% to ≤1%	22 (34.9)	15 (40.5)	7 (26.9)
>1% to ≤10%	21 (33.3)	15 (40.5)	6 (23.1)
>10%	20 (31.7)	7 (18.9)	13 (50.0)

- As of data cutoff, 91.1% of patients remained on treatment (**Table 3**):
  - The median duration of exposure was 26.1 weeks (range, 6-100 weeks)
  - The median asciminib dose intensity was 80.0 mg/day (range, 30-140 mg/day)
  - The median relative dose intensity was 100% (range, 38%-100%) with intensity ranges including >90% to 110% (n=80 [79.2%]), >75% to 90% (n=4 [4.0%]), and ≤75% (n=17 [16.8%])
- Of 101 total patients, 63 were evaluable for week 24 efficacy analyses:
  - The median duration of exposure was 40.4 weeks (range, 6-100 weeks)

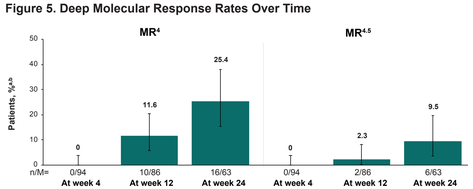
Table 3. Patient Disposition as of Data Cutoff

Patients, n (%)	All patients (n=101)	Week 24 efficacy-evaluable patients (n=63)
Treated	101 (100)	63 (100)
Treatment ongoing	92 (91.1)	55 (87.3)
Discontinued from treatment	9 (8.9)	8 (12.7)
Adverse events	4 (4.0)[a]	4 (6.3)[a]
Patient decision	3 (3.0)	2 (3.2)
Loss to follow-up	1 (1.0)	1 (1.6)
Physician decision	1 (1.0)	1 (1.6)

[a] One of these adverse events occurred off treatment, defined as >30 days after the last dose of asciminib.

- Most patients had *BCR::ABL1*[IS] ≤1% at week 24, which was the first dose escalation cutoff (**Figure 3**)
- MMR was achieved at week 24 in 44.4% of patients

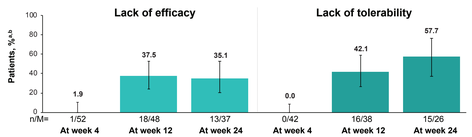
Figure 3. Molecular Response Over Time in Evaluable Patients



[a] Included patients with this response at baseline. [b] Included patients with adequate follow-up (M), defined as those with assessments within the corresponding analysis time interval or who discontinued early. [c] Error bars represent 95% CIs calculated using the Pearson-Clopper 2-sided method.

- MMR rates at week 24 were higher in patients who discontinued their prior TKI due to lack of tolerability vs efficacy (**Figure 4**)

Figure 4. MMR Rate by Reason for Discontinuation of Previous TKI



[a] Included patients with adequate follow-up (M), defined as those with assessments within the corresponding analysis time interval or who discontinued early. [b] Error bars represent 95% CIs calculated using the Pearson-Clopper 2-sided method.

- The rate of deep molecular responses increased over time (**Figure 5**)

Figure 5. Deep Molecular Response Rates Over Time

[a] Included patients with adequate follow-up (M), defined as those with assessments within the corresponding analysis time interval or who discontinued early. [b] Error bars represent 95% CIs calculated using the Pearson-Clopper 2-sided method.

- Patients achieved *BCR::ABL1*[IS] ≤1% and MMR regardless of baseline response level (**Table 4**)

Table 4. Categorical Response Shift From Baseline at Week 24 (Bolded Values Represent Improvement From Baseline Response)

	BCR::ABL1[IS] level at baseline, n (%)			
Molecular response at week 24, n (%)	**>0.1% to ≤1% (M=22)**	**>1% to ≤10% (M=21)**	**>10% (M=20)**	**All patients (M=63)**
≤0.1%	**9 (40.9)**	**12 (57.1)**	**7 (35.0)**	28 (44.4)
>0.1% to ≤1%	13 (59.1)	**6 (28.6)**	**5 (25.0)**	24 (38.1)
>1% to ≤10%	0	1 (4.8)	**4 (20.0)**	5 (7.9)
>10%	0	2 (9.5)	4 (20.0)	6 (9.5)

- Dose escalations from 80 to 200 mg QD occurred in 7 patients per their response levels at protocol-defined time points (3 at week 24 and 4 at week 48) (**Table 5**)

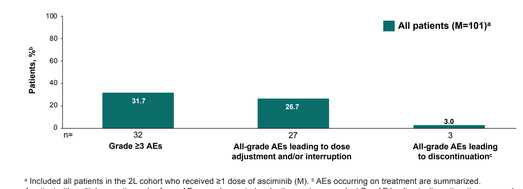
Table 5. Molecular Response Rates in Patients with Dose Escalation

Baseline characteristics (at screening)					Time point (week) of:		*BCR::ABL1*[IS] (%) at:			
Patient	**Prior TKI**	**Prior TKI duration, months**	**Discontinued prior TKI due to lack of:**	***BCR::ABL1*[IS], %**	**Dose escalation**	**Most recent follow-up**	**Dose escalation**	**Most recent follow-up**	**Duration of follow-up since dose escalation, days[a]**	**Disposition**
1	IMA	79.2	Efficacy	83.866	48	96	0.289	0.106	348	On treatment
2	IMA	103.5	Tolerability	50.001	24	48	7.24	9.073	149	Discontinued
3	DAS	18.9	Efficacy	1.173	48	60	0.674	0.368	109	On treatment
4	DAS	15.0	Efficacy	1.386	24	36	1.156	0.774	104	On treatment
5	DAS	3.9	Tolerability	38.987	24	36	1.193	1.102	70	On treatment
6	DAS	40.9	Efficacy	1.675	48	48	0.600	0.600	29	On treatment
7	DAS	17.2	Efficacy	0.369	48	48	0.113	0.113	7	On treatment

[a] Calculated as the time from the date of dose escalation to the end of follow-up, defined as the date of data cutoff, last contact, death, or withdrawal of consent, whichever occurs first.

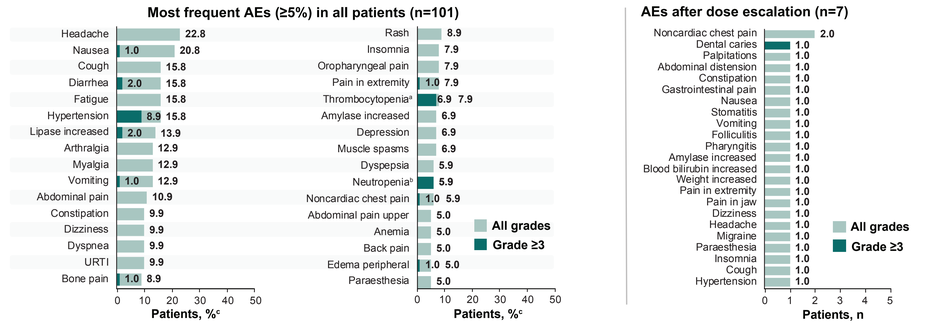
- All-grade AEs occurred in 96 patients (95.0%), with grade ≥3 events in 31.7% (**Figure 6**)
- Dose reduction due to AEs occurred in 16 patients (15.8%); dose interruption due to AEs occurred in 25 (24.8%)
- Four patients had AEs leading to discontinuation:
  - One AE leading to discontinuation occurred off treatment, defined as >30 days after the last dose of asciminib
  - 3 patients (3.0%) had on-treatment events including grade 3 nausea and vomiting, grade 2 dyspepsia, and grade 2 tremors (n=1 each)
- No deaths during treatment or within 30 days after the last asciminib dose were reported
- Most AEs (≥5% of patients) were grade 1/2 (**Figure 7**)
- In all patients, hematologic AEs (≥5%) included thrombocytopenia (7.9%), neutropenia (5.9%), and anemia (5.0%)
- No arterial occlusive events or clinical pancreatic events were reported

Figure 6. Overview of Adverse Events Regardless of Treatment Relationship



[a] Included all patients in the 2L cohort who received ≥1 dose of asciminib (M). [b] AEs occurring on treatment are summarized. A patient with multiple severity grades for an AE was only counted under the maximum grade. [c] One AE leading to discontinuation occurred off treatment, defined as >30 days after the last dose of asciminib, and is not reported here.

Figure 7. Adverse Events Regardless of Treatment Relationship



[a] Included platelet count decreased and thrombocytopenia. [b] Included neutrophil count decreased and neutropenia. [c] 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.

Acknowledgments

We thank all study participants and their families, the study investigators, and staff participating at the study sites. Medical writing support was provided by Chris Hofmann, PhD, CMPP, of Nucleus Global and funded by Novartis Pharma AG.

Abbreviations

1L, first line; 2L, second line; 3L, third line; AE, adverse event; AP, accelerated phase; ASC, asciminib; ATP, adenosine triphosphate; BC, blast crisis; BID, twice daily; CML, chronic myeloid leukemia; CP, chronic phase; DAS, dasatinib; ELN, European LeukemiaNet; FDA, US Food and Drug Administration; IMA, imatinib; 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; RQ-PCR, real-time quantitative polymerase chain reaction; TTF, time to treatment failure; TKI, tyrosine kinase inhibitor; URTI, upper respiratory tract infection.

References

1. Kota V, et al. Presented at: 65th ASH Annual Meeting and Exposition; December 9-12, 2023; San Diego, CA. Abstract 5190.
2. Bosi GR, et al. *Hematol Transfus Cell Ther*. 2019;41(3):222-228.
3. Cortes J, Lang F. *J Hematol Oncol*. 2021;14(1):44.
4. Kong JH, et al. *J Clin Med*. 2020;9(5):1542.
5. Hughes TP, et al. *N Engl J Med*. 2019;381(24):2315-2326.
6. Mauro MJ, et al. *Leukemia*. 2023;37(5):1048-1059.
7. Hughes TP, et al. Presented at: 2024 ASCO Annual Meeting; May 31-June 4, 2024; Chicago, IL. Oral presentation 6500.
8. Hochhaus A, et al. *Leukemia*. 2023;37(3):617-626.
9. Hochhaus A, et al. *N Engl J Med*. 2024;391(10):885-898.
10. Scemblix (asciminib). Prescribing information. Novartis Pharmaceuticals Corporation; 2024.
11. Atallah EL, et al. Presented at: 66th ASH Annual Meeting and Exposition; December 7-10, 2024; San Diego, CA, and online. Oral presentation 479.
12. Rea D, et al. *Blood*. 2021;138(21):2031-2041.
13. Mauro MJ, et al. Oral presentation at: 63rd ASH Annual Meeting and Exposition; December 11-14, 2021; Atlanta, GA. Abstract 310.
14. Manley PW, et al. *Leuk Res*. 2020;98:106458.
15. Schoepfer J, et al. *J Med Chem*. 2018;61(18):8120-8135.
16. Westerweel PE, et al. *Front Oncol*. 2019;9:665.
17. Hochhaus A, et al. *Leukemia*. 2020;34(8):2125-2137.
18. Atallah EL, et al. *Future Oncol*. 2024;20(38):3065-3075.
19. Cortes JE, et al. *Leukemia*. 2024;38(7):1522-1533.