Poster PF593

✉ Timothy Hughes | Tim.Hughes@sahmri.com

Exploratory Analysis of Prevalent Additional Genomic Alterations at Baseline in Patients With Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase From ASC4FIRST

Susan Branford,[1] Jorge E. Cortes,[2] Naoto Takahashi,[3] Richard A. Larson,[4] Ghayas C. Issa,[5] Felice Bombaci,[6] Jianxiang Wang,[7] Dong-Wook Kim,[8] Dennis Dong Hwan Kim,[9] Jiri Mayer,[10] Yeow-Tee Goh,[11] Philipp Le Coutre,[12] Inho Kim,[13] Gabriel Etienne,[14] Shruti Kapoor,[15] Rajendra Jinwal,[16] Kamel Malek,[16] Amila Sarac,[15] Andreas Brüderle,[16] Pablo Serrano-Fernández,[16] Andreas Hochhaus,[17] **Timothy P. Hughes**[18]

[1]Genetics and Molecular Pathology, SA Pathology, Adelaide, Australia; [2]Georgia Cancer Center at Augusta University, Augusta, GA, USA; [3]Akita University, Akita City, Japan; [4]The University of Chicago, Chicago, IL, USA; [5]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [6]CML Patients Group, CML Advocates Network, Turin, Italy; [7]State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin, China; [8]Ujeongbu Eulji Medical Center, Geumo-dong, Ujeongbu-si, South Korea; [9]Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, Canada; [10]Hematology and Oncology, University Hospital Brno, Brno, Czech Republic; [11]Singapore General Hospital, Singapore, Singapore; [12]Charité-Universitätsmedizin Berlin, Berlin; [13]Seoul National University Hospital, Biomedical Research Institute, Cancer Research Institute, Seoul National University College of Medicine, Seoul, South Korea; [14]Institut Bergonié, Bordeaux, France; [15]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [16]Novartis Pharma AG, Basel, Switzerland; [17]Hematology and Medical Oncology, Universitätsklinikum Jena, Jena, Germany; [18]South Australian Health and Medical Research Institute and University of Adelaide, Adelaide, SA, Australia

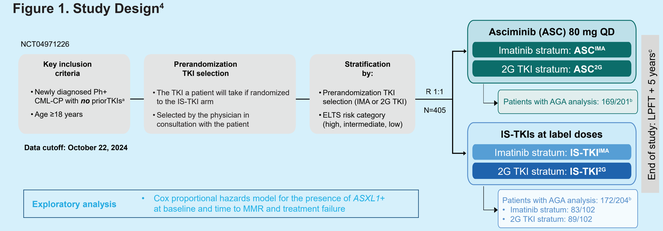
INTRODUCTION

- Approximately 20%-33% of patients with newly diagnosed CML-CP harbor AGAs, most often identified in epigenetic modifiers such as *ASXL1*, *DNMT3A*, and *TET2*[1-2]
- The *ASXL1* mutation (*ASXL1+*), which has been associated with inferior clinical outcomes, was the most frequently observed AGA occurring in about 9% to 15% of patients[2-7]
- High VAF of *ASXL1+* is associated with adverse outcomes[2,8] such as disease progression in CML[9] and is part of prognostic scoring in other diseases such as MPN and AML[10-11]
- Asciminib is a BCR::ABL1 inhibitor that works by Specifically Targeting the ABL Myristoyl Pocket (STAMP)[12-13]
- In primary (week 48) and key secondary (week 96) analyses from ASC4FIRST, a phase 3 study of asciminib vs all standard-of-care TKIs in newly diagnosed CML-CP, asciminib demonstrated statistically superior efficacy and improved safety and tolerability compared with IS-TKIs;[14-15] asciminib's safety profile in ASC4FIRST[14] remained consistent with its known safety profile[16-17]
- Asciminib is approved for the treatment of adults with newly diagnosed Ph+ CML-CP in the US,[18] China, Japan, Switzerland, and other countries worldwide and is currently under review by the EMA
- **Here we present an exploratory analysis from ASC4FIRST on the effect of prevalent AGAs at baseline in patients from ASC4FIRST on treatment outcomes (MMR and treatment failure) until week 96**

STUDY DESIGN AND METHODS

- ASC4FIRST (NCT04971226) is a phase 3, randomized, multicenter, open-label, head-to-head study comparing asciminib vs IS-TKIs in newly diagnosed patients with CML-CP (**Figure 1**)
- The primary objective of the current exploratory analysis was to determine the prevalence of baseline AGAs (including *ASXL1+*) in ASC4FIRST and explore their potential association with achievement of MMR and treatment failure until week 96; treatment failure was defined as discontinuation of study treatment due to intolerance, lack of efficacy, or confirmed loss of MMR
- The prevalence of AGAs was determined using a next-generation sequencing panel of 89 genes from diagnostic blood samples collected at baseline, with a VAF ≥0.5%
- A multivariable Cox proportional hazards regression model adjusted for age, sex, treatment, and baseline *BCR::ABL1*[IS] was used to determine the prognostic value of baseline AGAs
- For the predictive model of treatment failure, an interaction term between baseline AGAs and treatment was added

Figure 1. Study Design[4]

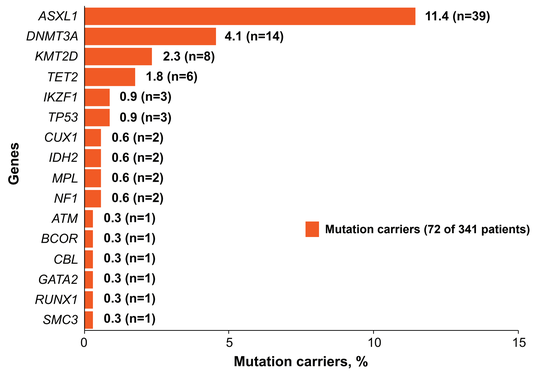


From Hochhaus A, et al. *N Engl J Med*. 2024;391(10):885-898. Copyright © 2024 Massachusetts Medical Society. Adapted with permission from Massachusetts Medical Society. [a]Either imatinib, bosutinib, dasatinib, or nilotinib is allowed for up to 2 weeks prior to randomization. Treatment with other TKIs prior to randomization was not permitted. [b]Of 405 enrolled patients, AGA analysis was not performed in 60 patients in China and 4 patients who did not receive treatment. [c]Patients will remain on study for 5 years after the last patient first dose, unless they have discontinued early due to treatment failure, disease progression, pregnancy, intolerance, or investigator or patient decision.

RESULTS

- Of the 405 patients randomized to receive treatment in ASC4FIRST, 341 patients had AGA analysis performed at baseline; 169 were in the asciminib arm and 172 were in the IS-TKIs arm (imatinib, n=83; 2G TKIs, n=89) (**Figure 1**)
- AGAs were detected in 21% (72/341) of all patients at baseline; *ASXL1+* was the most prevalent AGA, occurring in 11% (39/341) of all patients, followed by *DNMT3A* (4% [14/341]) and *KMT2D* (2% [8/341]) (**Figure 2**)

Figure 2. Patients With Detectable AGAs at Baseline



- The distribution of overall AGAs was balanced between treatment arms at 19% (32/169) in the asciminib arm and 23% (40/172) in the IS-TKI arm (**Table 1**)
  - The distribution of *ASXL1+* was balanced between treatment arms with 11% (18/169) in the asciminib arm and 12% (21/172) in the IS-TKI arm
  - *ASXL1+* was the only AGA with a high enough frequency to allow robust statistical analysis

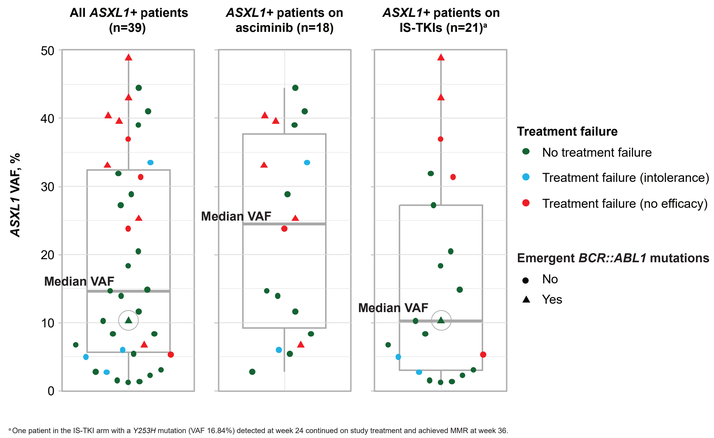
Table 1. Patient Characteristics

Characteristics (among those with genetic data)	Asciminib (n=169)	IS-TKIs (n=172)[a]
Male, n (%)	106 (63)	103 (60)
Mean age at diagnosis, years (range)	52 (18-79)	50.5 (19-86)
Transcript, n (%)		
e13a2 only	58 (35)	58 (34)
e14a2 only	109 (65)	111 (65)
e19a2 only	0	1 (0.6)
e13a2 and *e14a2*	1 (0.6)	0
e13a2 and *e14a3*	0	1 (0.6)
Other	1 (0.6)	1 (0.6)
Patients with AGAs, n (%)	32 (19)	40 (23)
ASXL1+	18 (11)	21 (12)
Other AGAs	14 (8)	19 (11)

[a]Comprised 83 patients receiving imatinib and 89 patients receiving 2G TKIs.

- A higher *ASXL1+* allelic burden (measured by VAF) at baseline was associated with an increased risk of treatment-emergent *BCR::ABL1* kinase domain mutations and treatment failure in all patients (**Figure 3**)
- The median VAF for *ASXL1+* was higher in patients receiving asciminib (24.5%; 95% CI, 15.9-30.5) vs IS-TKIs (10.2%; 95 CI, 8.9-22.5), indicating a higher *ASXL1+* allelic burden at baseline in patients receiving asciminib
  - *ASXL1+* VAF was <5% in 1 patient in the asciminib arm and 7 patients in the IS-TKI arm
  - *ASXL1+* VAF was >25% in 4 of 5 patients with emergent *BCR::ABL1* mutations in the asciminib arm and 2 of 3 patients with emergent *BCR::ABL1* mutations in the IS-TKI arm

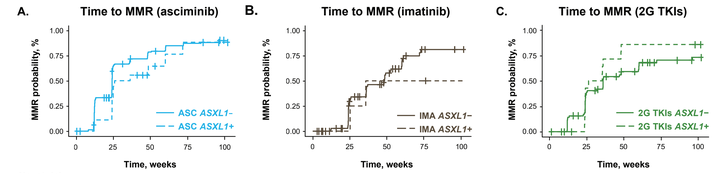
Figure 3. Impact of Baseline *ASXL1+* Allelic Burden on Treatment-Emergent *BCR::ABL1* Mutations and Treatment Failure



[a]One patient in the IS-TKI arm with a *Y253H* mutation (VAF 16.84%) detected at week 24 continued on study treatment and achieved MMR at week 36.

- There was no association between *ASXL1+* at baseline and probability of achieving MMR (**Figure 4**)
  - *ASXL1+* at baseline could not be confirmed as negative prognostic risk factor for MMR in ASC4FIRST

Figure 4. Time to MMR



- In the overall study population, regardless of baseline *ASXL1* status, the treatment failure rate was 15% (26/169) in the asciminib arm vs 38% (66/172) in the IS-TKI arm (**Figure 5**)
  - In patients with *ASXL1−* at baseline, the treatment failure rate was 12% (18/151) in the asciminib arm vs 39% (59/151) in the IS-TKI arm
  - In patients with *ASXL1+* at baseline, the treatment failure rate in the asciminib arm was comparable to that in the IS-TKI arm irrespective of *ASXL1* status (44% [8/18] vs 38% [66/172])
  - Sensitivity analyses that excluded patients who experienced treatment failure due to intolerance or VAF <5% did not change the conclusions (data not shown)
- **Figure 6** illustrates the impact of baseline *ASXL1+* on treatment failure rate by treatment arm (asciminib vs imatinib vs 2G TKIs)
  - The risk of treatment failure in *ASXL1+* patients receiving asciminib was comparable to that in *ASXL1−* patients receiving IS-TKIs
  - The risk of treatment failure was higher in *ASXL1+* vs *ASXL1−* patients receiving asciminib (**Figure 6A**) and imatinib (**Figure 6B**)
  - Conversely, the risk of treatment failure was lower in *ASXL1+* vs *ASXL1−* patients receiving 2G TKIs, which may be attributed to a small sample size and a lower median VAF for *ASXL1+* (ie, a lower allelic burden) (**Figure 6C**)

Figure 5. Association of Baseline *ASXL1+/−* With the Probability of Treatment Failure in Patients Receiving Asciminib vs IS-TKIs

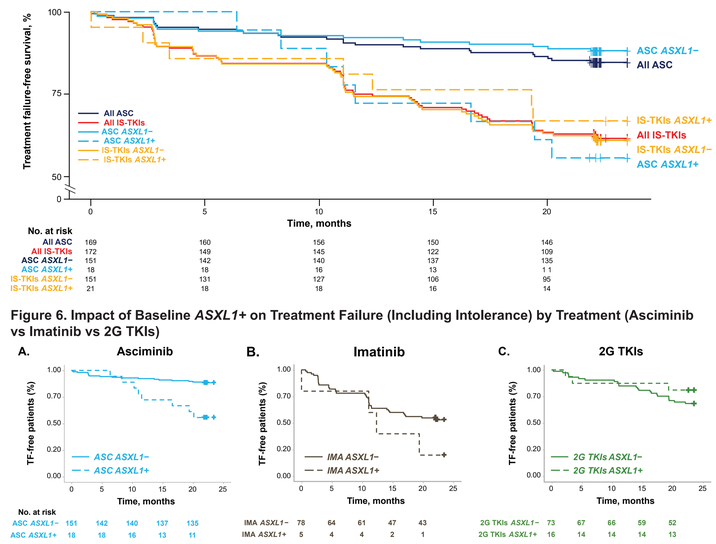
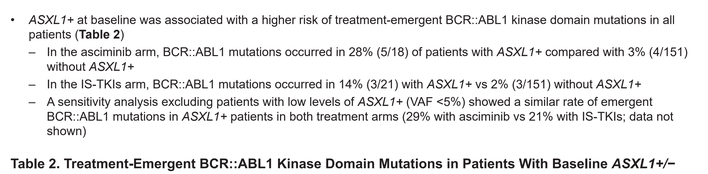


Figure 6. Impact of Baseline *ASXL1+* on Treatment Failure (Including Intolerance) by Treatment (Asciminib vs Imatinib vs 2G TKIs)



- *ASXL1+* at baseline was associated with a higher risk of treatment-emergent BCR::ABL1 kinase domain mutations in all patients (**Table 2**)
  - In the asciminib arm, BCR::ABL1 mutations occurred in 28% (5/18) of patients with *ASXL1+* compared with 3% (4/151) without *ASXL1+*
  - In the IS-TKIs arm, BCR::ABL1 mutations occurred in 14% (3/21) with *ASXL1+* vs 2% (3/151) without *ASXL1+*
  - A sensitivity analysis excluding patients with low levels of *ASXL1+* (VAF <5%) showed a similar rate of emergent BCR::ABL1 mutations in *ASXL1+* patients in both treatment arms (29% with asciminib vs 21% with IS-TKIs; data not shown)

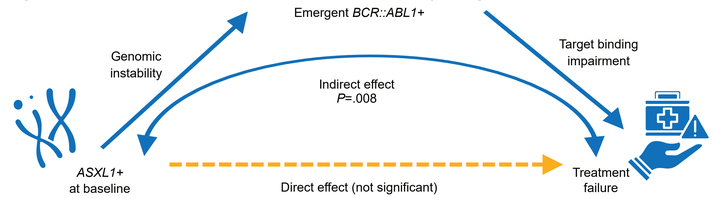
Table 2. Treatment-Emergent BCR::ABL1 Kinase Domain Mutations in Patients With Baseline *ASXL1+/−*

		Asciminib patients (n=169)		IS-TKI patients (n=172)[a]	
	Baseline *ASXL1+*	**No**	**Yes**	**No**	**Yes**
Emergent BCR::ABL1 mutations, n (%)	**No**	147 (97)	13 (72)	148 (98)	18 (86)
	Yes	4 (3)	**5 (28)**	3 (2)	**3 (14)**

[a]Comprised 83 patients receiving imatinib and 89 patients receiving 2G TKIs.

- A causal inference analysis suggested that the effect of *ASXL1+* on treatment failure risk may be indirectly mediated through the increased probability of on-treatment emergence of *BCR::ABL1* mutations (**Figure 7**)

Figure 7. Causal Inference Model of Treatment Failure Mediated by Emergent *BCR::ABL1* Mutations



CONCLUSIONS

- Consistent with reported literature,[1-3] *ASXL1+* was found to be the most prevalent AGA at baseline in the current analysis, occurring in 11% of all patients
- A higher baseline *ASXL1+* allelic burden was associated with poor outcomes (increased risk of *BCR::ABL1* mutations and treatment failure) in all patients; of note, the *ASXL1+* allelic burden at baseline was higher in patients receiving asciminib vs IS-TKIs, likely reflecting inherent variability
- The treatment failure rate by week 96 in *ASXL1+* patients treated with asciminib was comparable to that in patients treated with all IS-TKIs, irrespective of their *ASXL1* status
- *ASXL1+* at baseline was associated with a higher risk of developing *BCR::ABL1* kinase domain mutations in all patients
- Future studies are needed to further investigate association of *ASXL1+* with treatment failure and other outcomes in patients with newly diagnosed CML-CP, particularly given the known prognostic relevance of AGAs and their allelic burden in other malignancies[10-11]

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This study is sponsored by Novartis Pharma AG. For more information, please refer to https://clinicaltrials.gov/study/NCT04971226
Poster presentation at EHA2025 Congress; 12-15 June, 2025; Milan, Italy.

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Abbreviations

2G, second-generation; ABL1, Abelson tyrosine kinase 1; AGA, additional genomic alteration; AML, acute myeloid leukemia; ASC, asciminib; BCR, breakpoint cluster region; CML, chronic myeloid leukemia; CP, chronic phase; ELTS, European Treatment and Outcome Study long-term survival; EMA, European Medicines Agency; IMA, imatinib; IS, International Scale; IS-TKI, investigator-selected tyrosine kinase inhibitor; LPFD, last patient first dose; MMR, major molecular response (*BCR::ABL1*[IS] ≤0.1%); MPN, myeloproliferative neoplasm; Ph+, Philadelphia chromosome positive; QD, once daily; R, randomized; STAMP, Selectively Targeting the ABL Myristoyl Pocket; TKI, tyrosine kinase inhibitor; VAF, variant allele frequency.