Andreas Hochhaus
Andreas.Hochhaus@med.uni-jena.de

Asciminib Shows Superior Tolerability vs Nilotinib in Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase: Primary Endpoint Results of the Phase 3b ASC4START Trial

Andreas Hochhaus, Tim H. Brümmendorf, Francois Xavier Mahon, Delphine Rea, David J. Andorsky, Susanne Saussele, Stephen Strickland, Thomas Cluzeau, Francoise Huguet, Jiri Mayer, Viviane Dubruille, Dong-Wook Kim, Ilina Micheva, Gabrielle Roth-Guepin, Virginia Pilipovic, Jacqueline Ryan, Aoife Smyth, Nabil A. Angelozzi, Ennan Gu, Himanshu Pokhriyal, Philipp le Coutre

Scan to obtain

- Supplementary slides

https://tinyurl.com/HochhausS166

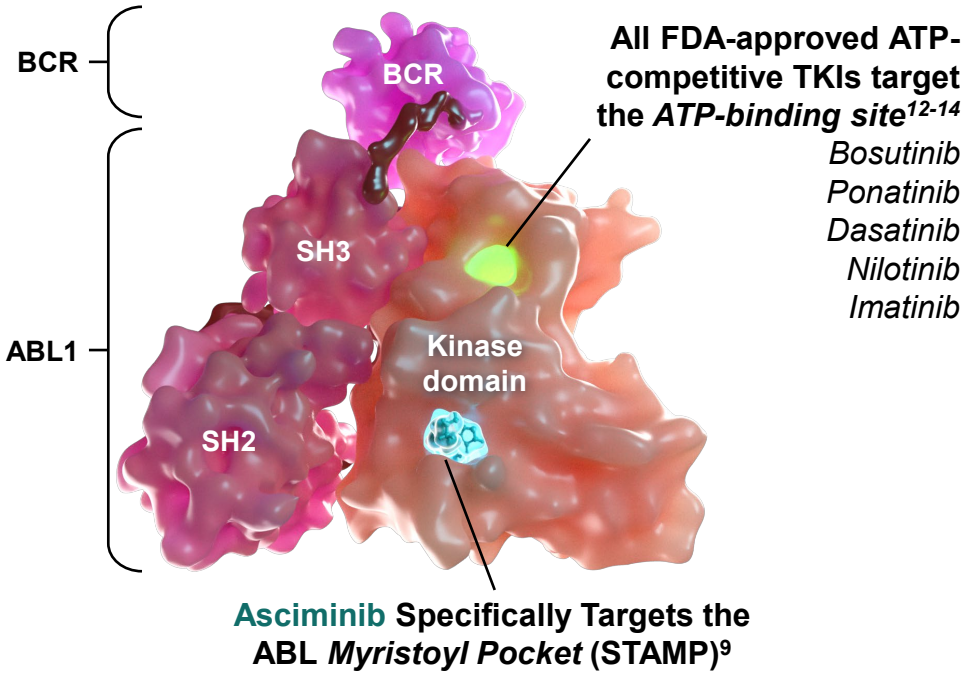
This study is sponsored by Novartis Pharma AG. For more information, please refer to https://clinicaltrials.gov/study/NCT05456191.

Oral presentation at: EHA2025 Congress; June 12-15, 2025; Milan, Italy.

Introduction

- CML requires prolonged treatment; therefore, an agent that is both highly efficacious and well tolerated is needed[1-2]
- Asciminib demonstrated superior efficacy and favorable safety and tolerability vs all IS-TKIs in newly diagnosed Ph+ CML-CP in the ASC4FIRST trial[3-4]
- Asciminib[a] is approved[b] for newly diagnosed Ph+ CML-CP in the US, China, Japan, Switzerland and other countries worldwide, and is currently under review by the EMA[5-6]
- Compared with 2G TKIs, the high specificity of asciminib for BCR::ABL1 may reduce off-target effects and improve tolerability while maintaining efficacy[7-11]
- **Here, we present the first results from the phase 3b ASC4START trial assessing the tolerability and efficacy of asciminib vs nilotinib in patients with newly diagnosed CML in chronic phase**

Asciminib: designed to improve efficacy and reduce off-target effects vs current ATP-competitive TKIs[9-11]

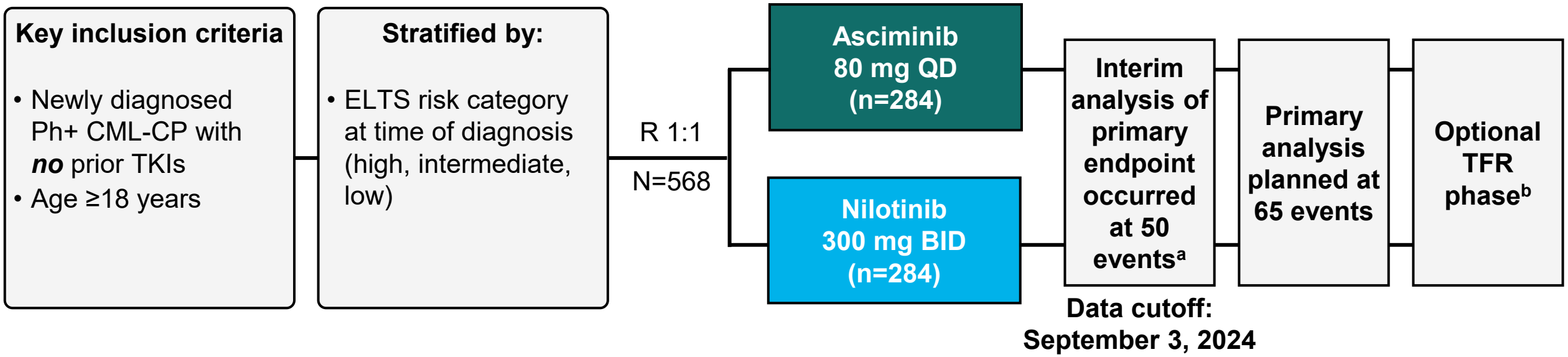


Adapted from Manley PW, et al. *Leuk Res*. 2020;98:106458. Copyright © 2020 Elsevier Ltd.[11]

2G, second-generation; ATP, adenosine triphosphate; BID, twice daily; CML, chromic myeloid leukemia; CP, chronic phase; IS-TKI, investigator-selected TKI; Ph, Philadelphia chromosome; QD, once daily; TKI, tyrosine kinase inhibitor.
[a] At doses of 80 mg QD and 40 mg BID. [b] Based on major molecular response rate. Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial(s).

ASC4START is a study comparing the tolerability of asciminib vs nilotinib in newly diagnosed patients with CML

NCT05456191



Primary endpoint:	time to treatment discontinuation due to adverse events (TTDAE), defined as time from first dose of study treatment to discontinuation due to AEs (including death due to AE)
Secondary safety endpoints:	type, frequency and severity of AEs, dose modification due to AEs
Secondary efficacy endpoints:	MMR, MR^4, $MR^{4.5}$, CHR, and *BCR::ABL1*^{IS} ≤1% rates ***at*** and ***by*** all scheduled time points

CHR, complete hematologic response; ELTS, EUTOS long-term survival; EUTOS, European Treatment and Outcome Study; MR^4, *BCR::ABL1*^{IS} ≤0.01%; $MR^{4.5}$, *BCR::ABL1*^{IS} ≤0.0032%; TFR, treatment-free remission.

[a] To allow early assessment of the tolerability of asciminib, one formal interim analysis was planned when approximately 46 discontinuations due to AEs occurred.

[b] Exploratory analysis for TFR will include TFR eligibility by 3, 4, and 5 years and TFR success rates by weeks 48 and 96 in all patients who enter the optional TFR phase.

Oral presentation at: EHA2025 Congress; June 12-15, 2025; Milan, Italy.

Baseline characteristics were well balanced between asciminib and nilotinib arms

Variable	Asciminib n=284	Nilotinib n=284	All patients N=568
Age, median (range), years	49.0 (19-82)	50.0 (18-84)	50.0 (18-84)
Age group, n (%)			
18 to <65 years	237 (83.5)	247 (87.0)	484 (85.2)
65 to <75 years	38 (13.4)	24 (8.5)	62 (10.9)
≥75 years	9 (3.2)	13 (4.6)	22 (3.9)
Male, n (%)	177 (62.3)	158 (55.6)	335 (59.0)
ELTS, n (%)[a]			
Low	171 (60.2)	172 (60.6)	343 (60.4)
Intermediate	75 (26.4)	75 (26.4)	150 (26.4)
High	38 (13.4)	37 (13.0)	75 (13.2)
Race, n (%)			
White	227 (79.9)	217 (76.4)	444 (78.2)
Asian	40 (14.1)	45 (15.8)	85 (15.0)
Black or African American	12 (4.2)	10 (3.5)	22 (3.9)
Other[b]	5 (1.8)	12 (4.2)	17 (3.0)
ECOG PS, n (%)			
0	226 (79.6)	235 (82.7)	461 (81.2)
1	57 (20.1)	49 (17.3)	106 (18.7)
2	1 (0.4)	0	1 (0.2)

ECOG PS, Eastern Cooperative Oncology Group performance status.
[a] Based on randomization data. [b] American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, unknown, and not reported.

Oral presentation at: EHA2025 Congress; June 12-15, 2025; Milan, Italy.

More patients were continuing treatment with asciminib than with nilotinib at data cutoff

Randomized patients, n (%)	Asciminib n=284	Nilotinib n=284	All Patients N=568
Treatment ongoing	**253 (89.1)**	**233 (82.0)**	**486 (85.6)**
Discontinued from treatment	**31 (10.9)**	**49 (17.3)**	**80 (14.1)**
Adverse events	14 (4.9)	33 (11.6)	47 (8.3)
Unsatisfactory therapeutic effect	7 (2.5)	8 (2.8)	15 (2.6)
Progressive disease	3 (1.1)	1 (0.4)	4 (0.7)
Physician decision	2 (0.7)	2 (0.7)	4 (0.7)
Patient decision	2 (0.7)	2 (0.7)	4 (0.7)
Death[a]	2 (0.7)	1 (0.4)	3 (0.5)
Protocol deviation	1 (0.4)	1 (0.4)	2 (0.4)
Pregnancy	0	1 (0.4)	1 (0.2)

- **By interim analysis data cutoff (September 3, 2024), 50 events were observed and the boundary for statistical significance was recalculated as .0062**
- **The median duration of follow-up was 9.7 months (range, 0-20.8) from randomization to data cutoff**
- **Time to treatment discontinuation due to adverse events (primary endpoint):**
  - **Events of interest were discontinuation due to AEs (n=47) and death due to AEs (n=3)**

AE, adverse event.

[a] Deaths on treatment: asciminib, cardiac arrest (n=1) and suicide (n=1); nilotinib, cardiac arrest (n=1).

Oral presentation at: EHA2025 Congress; June 12-15, 2025; Milan, Italy.

Asciminib demonstrated significantly superior tolerability vs nilotinib based on time to treatment discontinuation due to AEs (TTDAE)

Events of interest (Discontinuations due to AEs and deaths due to AEs)[a]			
Treatment	**Events n/N, (%)[b]**	**Hazard ratio (95% CI)[c]**	***P*-value[d]**
Asciminib	16/284 (**5.6**)	0.45 (0.25, 0.81)	**0.004**
Nilotinib	34/282 (**12.1**)		

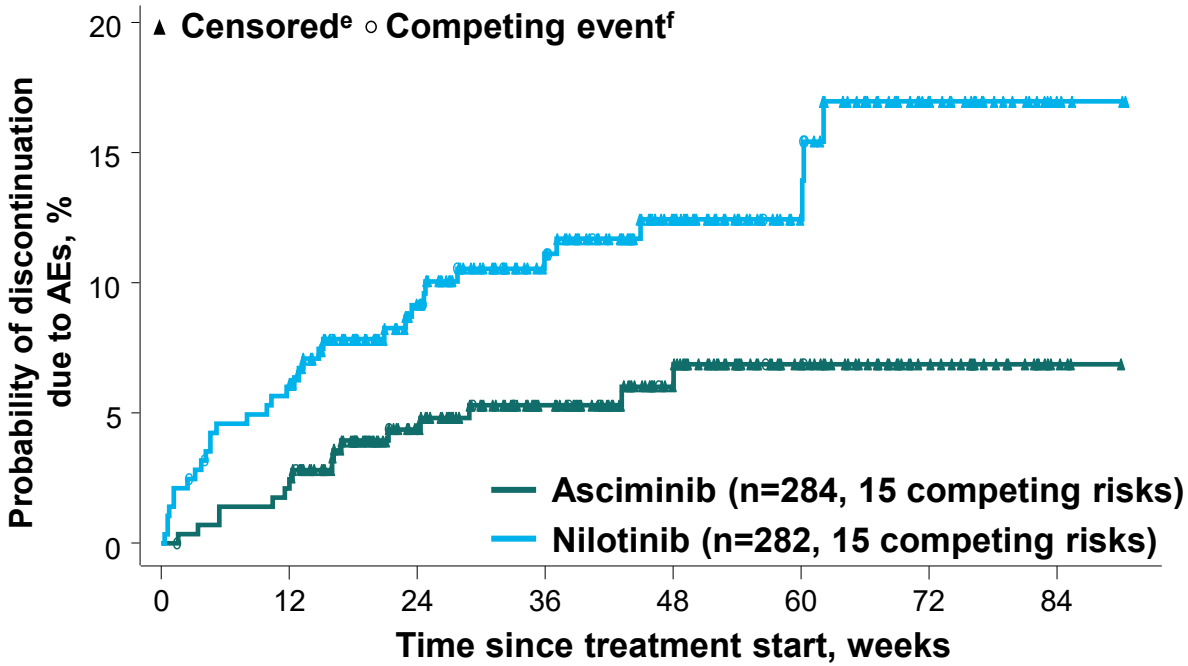
- The **primary endpoint was met,** showing a **statistically significant difference** in time to treatment discontinuation due to AEs (TTDAE) **in favor of asciminib** with a cause specific hazard ratio of 0.45 (95% CI, 0.25-0.81; *P*=.004)

[a] Events counting towards primary endpoint from disposition: asciminib, 14 discontinuations due to AEs and 2 deaths due to AEs; nilotinib, 33 discontinuations due to AEs and 1 death due to an AE. [b] The safety set comprised 566 patients as 2 patients in the nilotinib arm were randomized but not treated due to AEs (grade 2 thrombocytopenia, n=1) and patient decision (n=1). [c] Hazard ratio of asciminib vs nilotinib. The cause-specific hazard model is stratified by ELTS risk score. [d] Wald test p-value.

Oral presentation at: EHA2025 Congress; June 12-15, 2025; Milan, Italy.

Asciminib demonstrated significantly superior tolerability vs nilotinib based on time to treatment discontinuation due to AEs (TTDAE)

Events of interest (Discontinuations due to AEs and deaths due to AEs)[a]			
Treatment	**Events n/N, (%)[b]**	**Hazard ratio (95% CI)[c]**	***P*-value[d]**
Asciminib	16/284 (**5.6**)	0.45 (0.25, 0.81)	**0.004**
Nilotinib	34/282 (**12.1**)		



- The **primary endpoint was met,** showing a **statistically significant difference** in time to treatment discontinuation due to AEs (TTDAE) **in favor of asciminib** with a cause specific hazard ratio of 0.45 (95% CI, 0.25-0.81; *P*=.004)
- There was a **55% lower risk** of **discontinuation due to AEs with asciminib** compared with nilotinib at cutoff

[a] Events counting towards primary endpoint from disposition: asciminib, 14 discontinuations due to AEs and 2 deaths due to AEs; nilotinib, 33 discontinuations due to AEs and 1 death due to an AE. [b] The safety set comprised 566 patients as 2 patients in the nilotinib arm were randomized but not treated due to AEs (grade 2 thrombocytopenia, n=1) and patient decision (n=1). [c] Hazard ratio of asciminib vs nilotinib. The cause-specific hazard model is stratified by ELTS risk score. [d] Wald test p-value. [e] Patients who did not discontinue treatment were censored at the analysis cutoff. [f] Discontinuation of study treatment due to any other reason was a competing risk event.

Oral presentation at: EHA2025 Congress; June 12-15, 2025; Milan, Italy.

AEs leading to treatment discontinuation were less frequent with asciminib vs nilotinib

Adverse events leading to discontinuation[a]	Asciminib[b] n=284		Nilotinib[c] n=282	
	All grades	Grade ≥3	All grades	Grade ≥3
	Patients, n (%)[a]			
Patients with ≥1 AE leading to discontinuation	**15 (5.3)**	**12 (4.2)**	**33 (11.7)**	**23 (8.2)**
AEs leading to discontinuation (≥2 patients in either arm):				
Thrombocytopenia[d]	4 (1.4)	4 (1.4)	1 (0.4)	1 (0.4)
Lipase increased[e]	2 (0.7)	0	6 (2.1)	4 (1.4)
ALT increased	1 (0.4)	1 (0.4)	2 (0.7)	2 (0.7)
Pancreatitis[e,f]	1 (0.4)	1 (0.4)	4 (1.4)	4 (1.4)
Amylase increased[e]	0	0	3 (1.1)	1 (0.4)
Asthenia	0	0	2 (0.7)	0
Atrial fibrillation	0	0	2 (0.7)	0
Blood bilirubin increased	0	0	3 (1.1)	1 (0.4)
Drug-induced liver injury	0	0	2 (0.7)	2 (0.7)

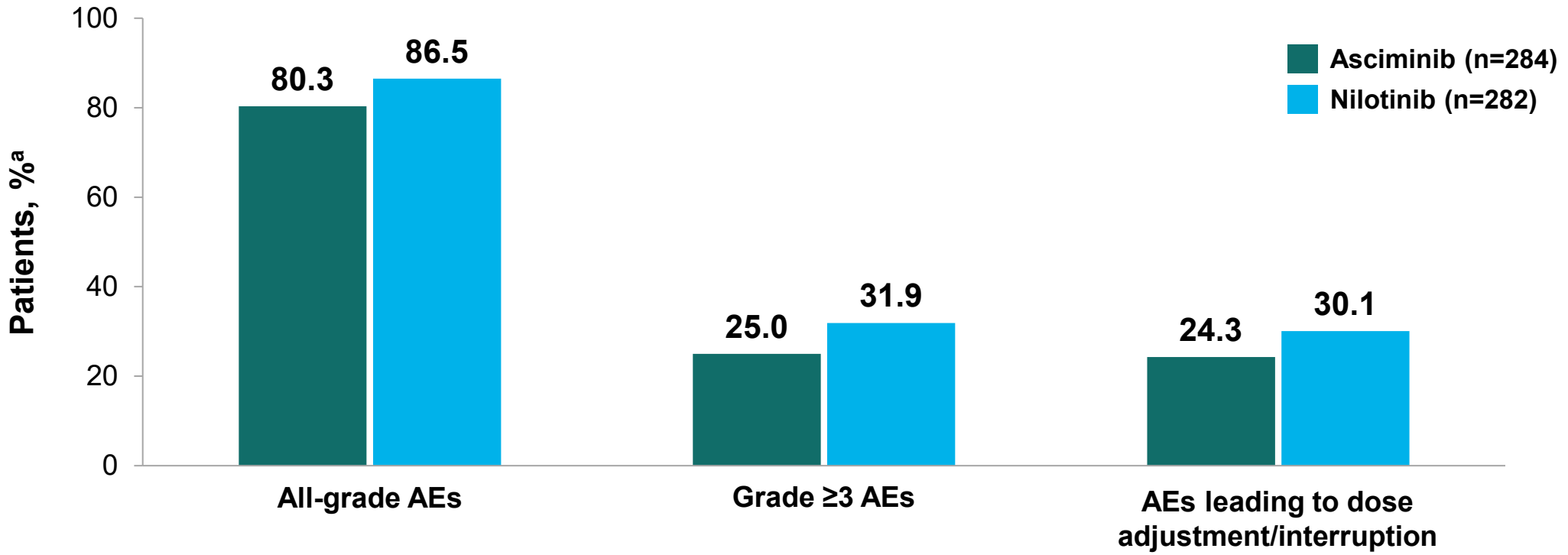
ALT, alanine aminotransferase; disc, discontinuation.

[a] Included AEs occurring during treatment or within 30 days of the last study treatment. A patient may have multiple AEs leading to treatment disc. Events counting towards primary endpoint included 14 patients who disc due to AEs and 2 deaths 16/284 (5.6%) on asciminib; 33 patients disc due to AEs and 1 death 34/282 (12.1%) on nilotinib. [b] One patient on asciminib had AE blast cell crisis and treatment disc due to progressive disease (not contributing to primary endpoint). [c] One patient on nilotinib had death recorded as AE and treatment disc due to death (contributed to primary endpoint). One patient on nilotinib had treatment disc due to an AE, but the AE (thrombocytopenia) leading to disc occurred after 30 days of last dose (contributed to primary endpoint).

[d] Thrombocytopenia included platelet count decreased and thrombocytopenia. [e] In the nilotinib arm, 1 patient discontinued due to increased amylase and pancreatitis, and 1 patient discontinued due to increased amylase and increased lipase. [f] Pancreatitis included acute pancreatitis and pancreatitis.

Oral presentation at: EHA2025 Congress; June 12-15, 2025; Milan, Italy.

Asciminib showed a favorable safety profile vs nilotinib with lower rates of AEs leading to dose modifications

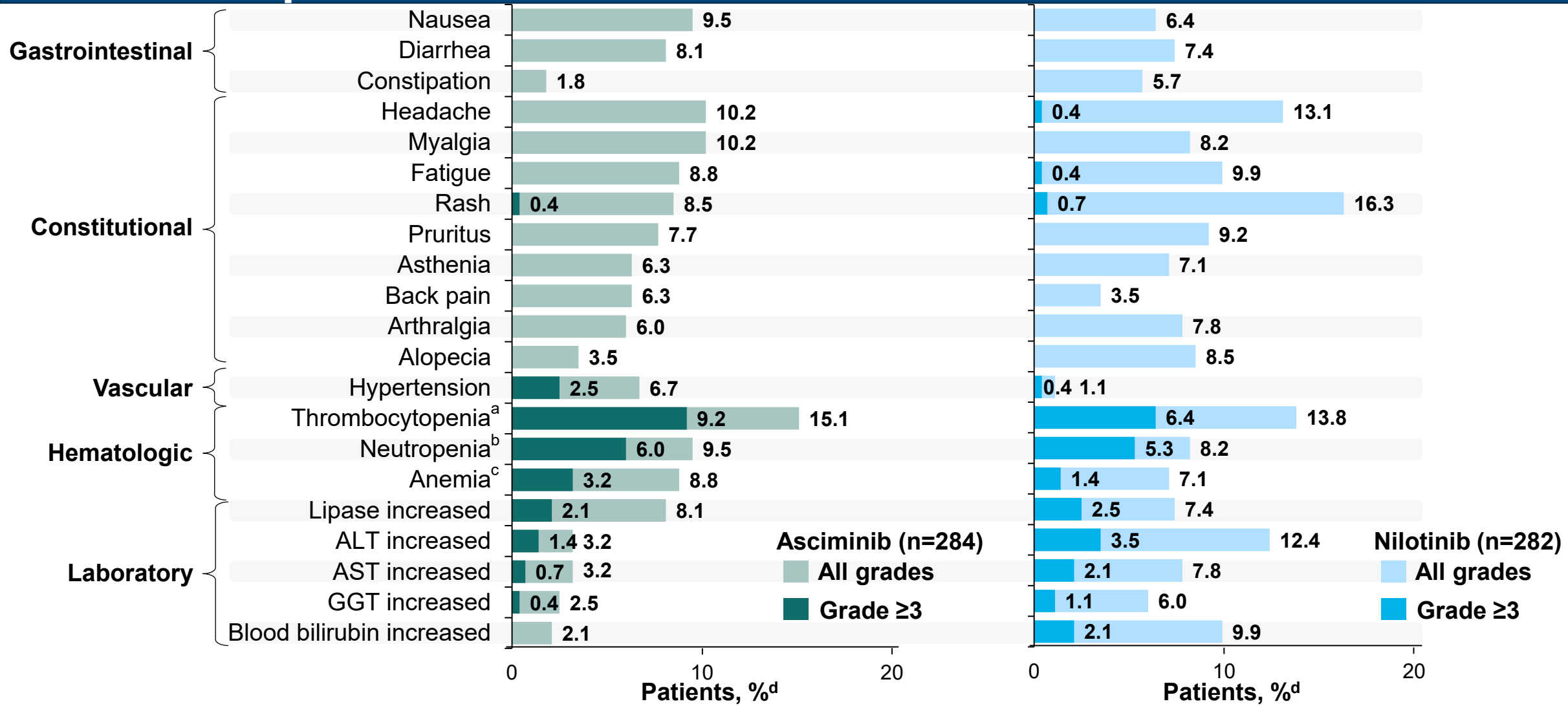


- Median duration of exposure was 39.1 weeks with asciminib vs 38.0 weeks with nilotinib
- Mean relative dose intensity was 94.8% with asciminib vs 92.6% with nilotinib

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

Oral presentation at: EHA2025 Congress; June 12-15, 2025; Milan, Italy.

Rates of adverse events (>5% in either arm) regardless of relationship to treatment

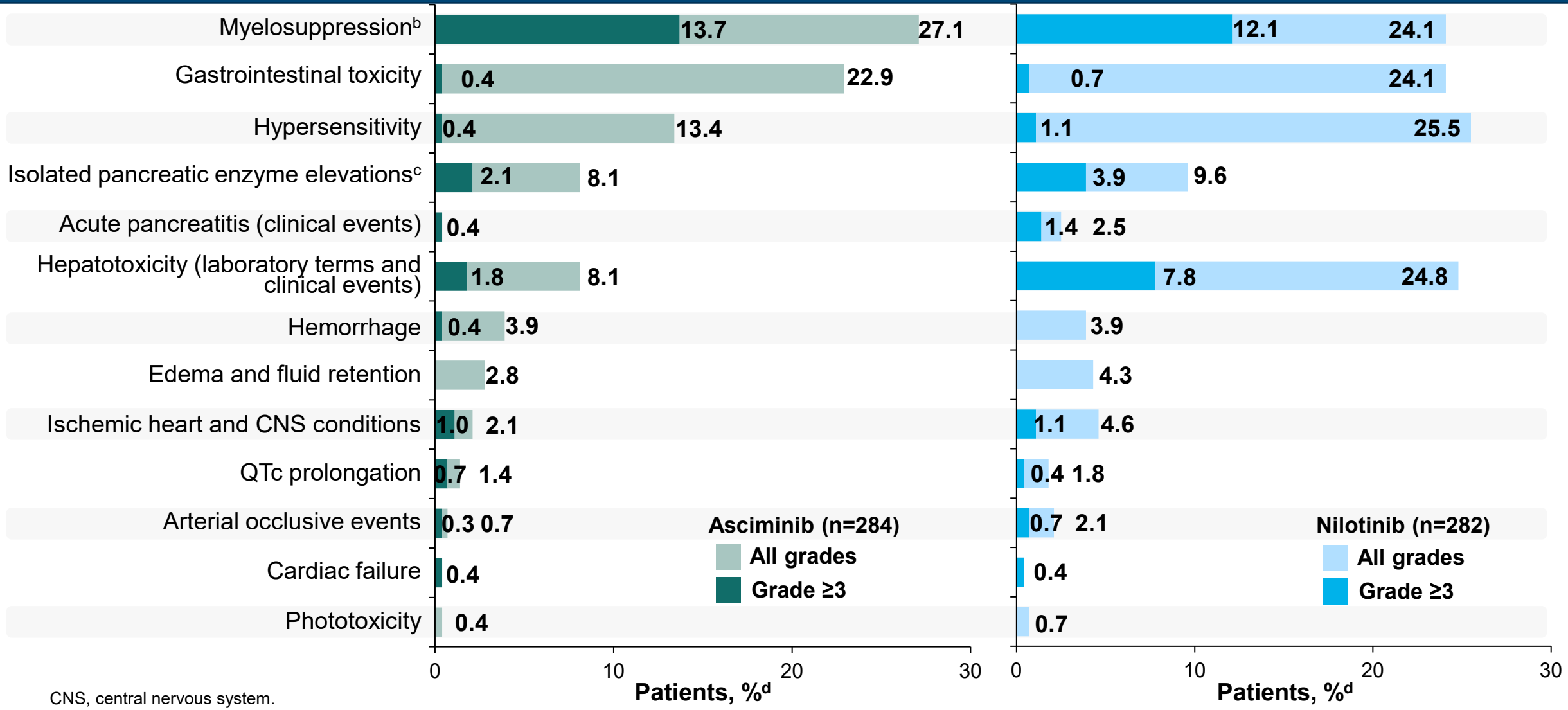


ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase.

[a] Thrombocytopenia included platelet count decreased and thrombocytopenia. [b] Neutropenia included neutrophil count decreased and neutropenia. [c] Anemia included anemia, red blood cell count decreased, and hematocrit decreased. [d] AEs occurring during treatment or within 30 days of the last study treatment are presented. A patient with multiple severity grades for an AE was only counted under the maximum grade.

Oral presentation at: EHA2025 Congress; June 12-15, 2025; Milan, Italy.

AEs of special interest[a] were generally less frequent with asciminib than with nilotinib

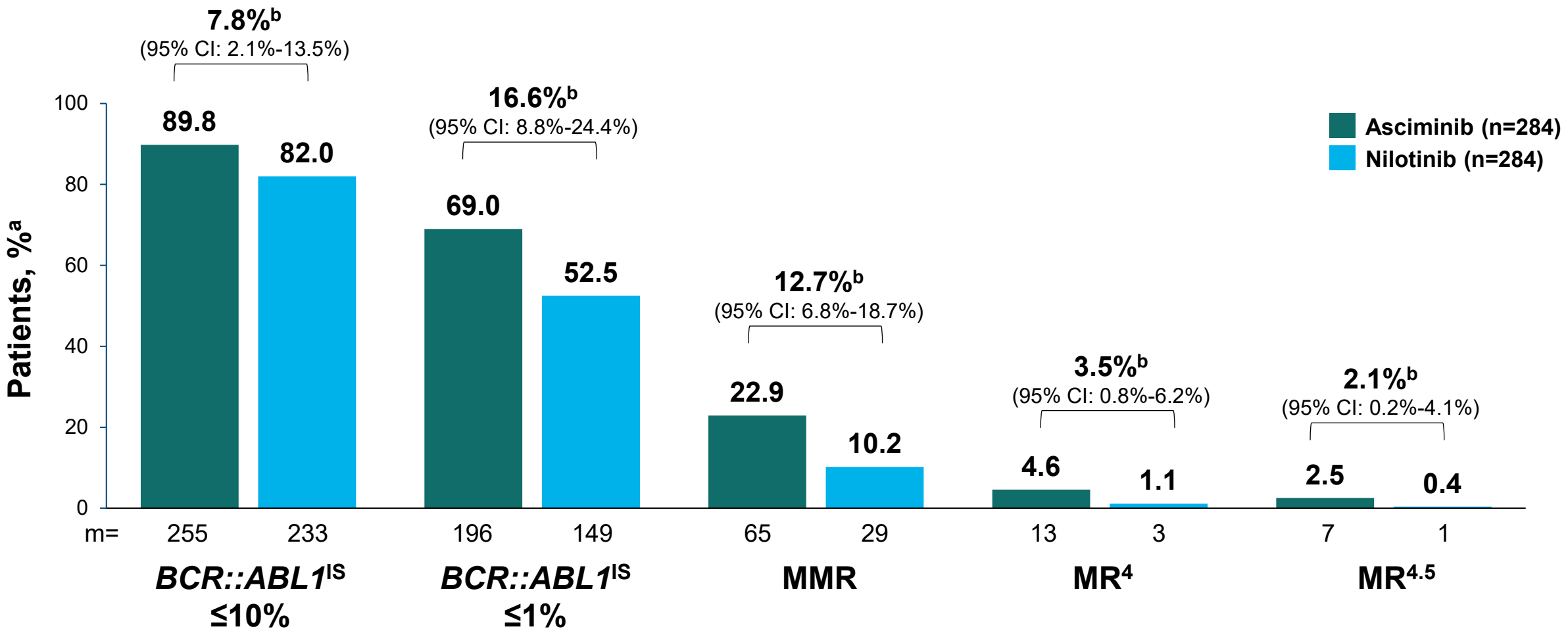


CNS, central nervous system.

[a] Other AEs of special interest in the asciminib vs nilotinib arms were hepatotoxicity (clinical events; all-grade, 2.1% vs 4.6%; grade ≥3, 1.1% vs 1.1%) and reproductive toxicity (all-grade, 0.4% vs 1.1%). [b] Included erythropenia, leukopenia, thrombocytopenia, and cytopenias affecting >1 lineage. [c] Isolated enzyme elevations in the asciminib vs nilotinib arms were increased lipase (all-grade, 8.1% vs 7.4; grade ≥3, 2.1% vs 2.5%), increased amylase (all-grade, 1.8% vs 4.6%; grade ≥3, 0.4% vs 2.1%), and increased pancreatic enzymes (all-grade, 0% vs 0.4%; grade ≥3, 0% vs 0.4%). [d] AEs occurring during treatment or within 30 days of the last study treatment are summarized. A patient with multiple severity grades for an AE was only counted under the maximum grade.

Oral presentation at: EHA2025 Congress; June 12-15, 2025; Milan, Italy.

A higher proportion of patients achieved early and deep molecular responses with asciminib vs nilotinib by week 12



m, number of patients within each subgroup with response.

[a] Patients with no evidence of typical transcript [e14a2 and/or e13a2] were considered as nonresponders. [b] The common risk difference and its 95% CI were estimated using the Mantel-Haenszel method after adjusting for stratum: ELTS scores at baseline.

Oral presentation at: EHA2025 Congress; June 12-15, 2025; Milan, Italy.

Conclusions

- **The ASC4START trial met its primary endpoint** and **asciminib demonstrated significantly superior tolerability** vs nilotinib based on TTDAE with a cause-specific hazard ratio of 0.45 (95% CI, 0.25-0.81; *P*=.004)
- **Significantly fewer patients discontinued treatment due to AEs** (including deaths due to AEs) with asciminib (16/284, 5.6%) vs nilotinib (34/282, 12.1%)[a]
- **The safety profile of asciminib remained consistent** with earlier trials[3-4,15-16] and no new safety signals were identified
- Rates of *BCR::ABL1*^{IS} ≤10%, *BCR::ABL1*^{IS} ≤1%, and MMR by week 12 **were higher with asciminib** than nilotinib
- **The study is ongoing** with analyses planned for longer term tolerability, quality of life, efficacy, and TFR
- These findings, along with data from ASC4FIRST, further support the **potential for asciminib to be standard of care** for patients with newly diagnosed CML-CP allowing **more patients to meet their treatment goals** without requiring treatment switch

[a] Asciminib: 14 discontinuations due to AEs and 2 deaths due to AEs (cardiac arrest and suicide, n=1 each); nilotinib: 33 discontinuations due to AEs and 1 death due to AEs (cardiac arrest).

Oral presentation at: EHA2025 Congress; June 12-15, 2025; Milan, Italy.

Acknowledgments

Country	Patients, n
France	127
Germany	125
Czechia	28
Bulgaria	27
Argentina	24
Italy	24
India	23
United States	21
Romania	20
Republic of Korea	19
Singapore	19
Greece	16

Country	Patients, n
Malaysia	16
South Africa	16
Canada	11
Hungary	11
United Kingdom	10
Oman	8
Jordan	5
Turkey	5
Slovakia	4
Switzerland	4
Netherlands	3
United Arab Emirates	2

- We thank all study participants and their families, the study investigators, the staff at the 120 participating study sites spanning 24 countries, and the study steering committee
- Medical writing support was provided by Kenneth Maus, PhD, and Rohini Roy, PhD, of Nucleus Global and was funded by Novartis Pharma AG

Oral presentation at: EHA2025 Congress; June 12-15, 2025; Milan, Italy.

References

1. Efficace F and Cannella L. *Hematology Am Soc Hematol Educ Program.* 2016;1:170-179.
2. Garcia-Horton A and Lipton, JH. *J Natl Compr Canc Netw.* 2020;18:1421-1428.
3. Hochhaus A, et al. *N Engl J Med*. 2024;391:885-898.
4. Cortes JE, et al. Oral presentation at: 66th ASH Annual Meeting & Exposition; December 7-10, 2024; San Diego, CA. Abstract 475.
5. Scemblix (asciminib). Prescribing information. Novartis Pharmaceuticals Corp; 2024.
6. Scemblix (asciminib). EMA Summary of Product Characteristics. Novartis Europharm Limited; 2022.
7. Wylie AA, et al. *Nature.* 2017;543:733-737.
8. Lee H, et al. *Int J Hematol.* 2021;113:632-641.
9. Rea D, et al. *Blood*. 2021;138:2031-2041.
10. Mauro MJ, et al. Oral presentation at: 63rd ASH Annual Meeting & Exposition; December 11-14, 2021; Atlanta, GA. Abstract 310.
11. Manley PW, et al. *Leuk Res*. 2020;98:106458.
12. Schoepfer J, et al. *J Med Chem*. 2018;61:8120-8135.
13. Westerweel PE, et al. *Front Oncol*. 2019;9:665.
14. Hochhaus A, et al. *Leukemia*. 2020;34:966-984.
15. Mauro MJ, et al. *Blood Advances.* 2025. Online ahead of print. https://doi.org/10.1182/bloodadvances.2025016042
16. Hochhaus A, et al. *Leukemia.*2025;39:1114-1123.

Disclosures

A.H. received institutional research support from Bristol Myers Squibb, Pfizer, TERNS, and Enliven, and honoraria and institutional research support from Novartis and Incyte. **T.H.B.** received honoraria from Janssen, Merck, AstraZeneca, Pfizer, Incyte, SCOR, Roche, Synlab, and Novartis, consulting fees from Pfizer, Novartis, and Gilead; and research funding from Pfizer, Novartis, and GSK, and has patents, royalties, or other IP with Novartis. **F.X.M.** received support for attending meetings from Novartis and Incyte. **D.R.** received honoraria from and is a member of the Board of Directors or an advisory committee for Novartis, Incyte, and Pfizer and provided consultancy for Novartis. **D.J.A.** received research funding from Novartis and AstraZeneca, and research funding and consulting fees from AbbVie and Celgene. **S. Saussele.** received honoraria from Roche and Pfizer, research funding from Bristol Myers Squibb and honoraria and research funding from Incyte and Novartis. **S. Strickland** has received consulting fees from AbbVie, Kura Oncology, Novartis, SentiBio, Sumitomo, Sobi, and TERNS, received research funding from Beam Therapeutics, Blossom Hill, Caribou, Cellectis, Daiichi-Sankyo, Janssen, Kumquat Biosciences, Kura Oncology, Novartis, Oryzon, Schrodinger, SentiBio, Stemline, Sumitomo, Systimmune, Syros, Takeda, TERNS, Vincerx, Vironexis, and Zentalis, and participated in a speakers' bureau for GSK. **T.C.** received consulting fees from Celgene/BMS, AbbVie, Jazz Pharmaceuticals, Servier, and Novartis, honoraria from Novartis, Syros, Celgene/BMS, Takeda, Servier, and Keros; and support for attending meetings from Pfizer, Celgene/BMS, Novartis, AbbVie, and Gilead, and participated on a Data Safety Monitoring Board for Novartis and Celgene/BMS. **F.H.** received honoraria from Amgen, Incyte, Novartis, Pfizer, Clinigen, Servier, and Amgen and support for attending meetings from Amgen, Novartis, and Incyte. **J.M.** received research funding from BeiGene and Novartis. **V.D.** received support for attending meetings from Novartis and Pfizer, and honoraria from Novartis. **D.-W.K.** received honoraria and research funding and is a member of speaker's bureaus with Novartis, Bristol Myers Squibb, Korea Otsuka, and Il-Yang and received research funding and honoraria for Enliven, and research funding from Pharmaessencia. **I.M.** received honoraria, consulting fees, and travel, accommodation, and expenses reimbursement from Novartis. **G.R.-G.** reports no conflicts of interest. **V.P., J.R., A.S., N.A.A., E.G.,** and **H.P.** are employed by Novartis. **P.L.C.** received honoraria from Novartis, Blueprint, Incyte, Pfizer, AOP, and Bristol Myers Squibb.

Oral presentation at: EHA2025 Congress; June 12-15, 2025; Milan, Italy.