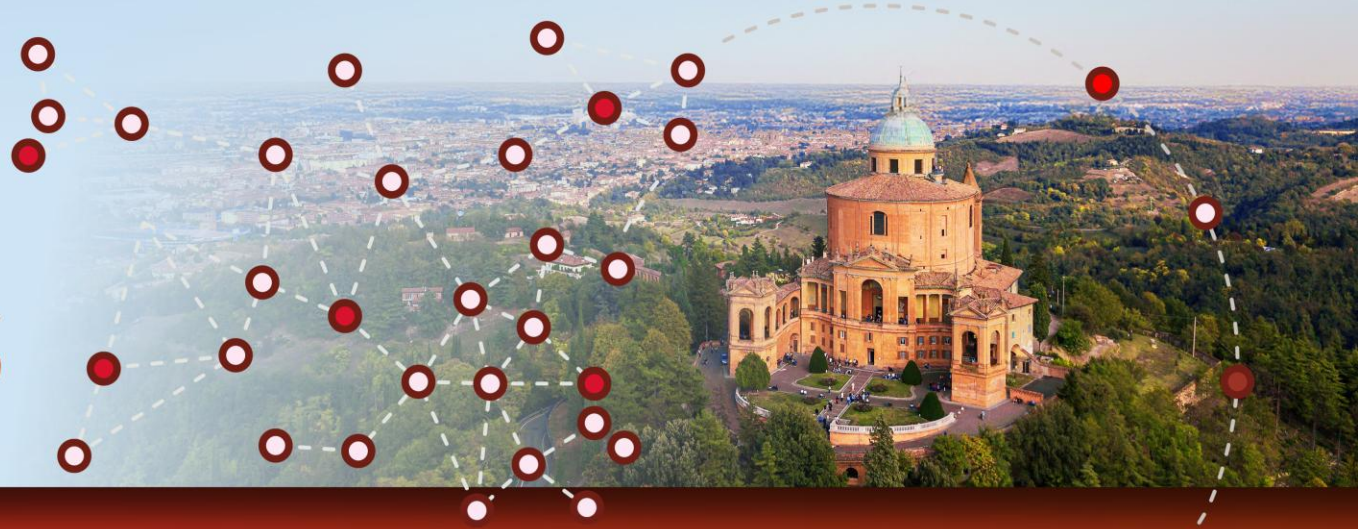
1ST INTERNATIONAL CONFERENCE ON

Ph+Leukemias



Bologna, Royal Hotel Carlton

September 29-30, 2025

New drugs in first-line CML treatment

Massimo Breccia

Sapienza University

Roma

Disclosures Massimo Breccia

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Novartis			x		x	x	
Incyte					x	x	
BMS						x	
Pfizer					x		
GSK					x	x	
AOP					x	x	
Abbvie					x		
Servier					x		
Otsuka					x		

Asciminib 1st line: ongoing trials

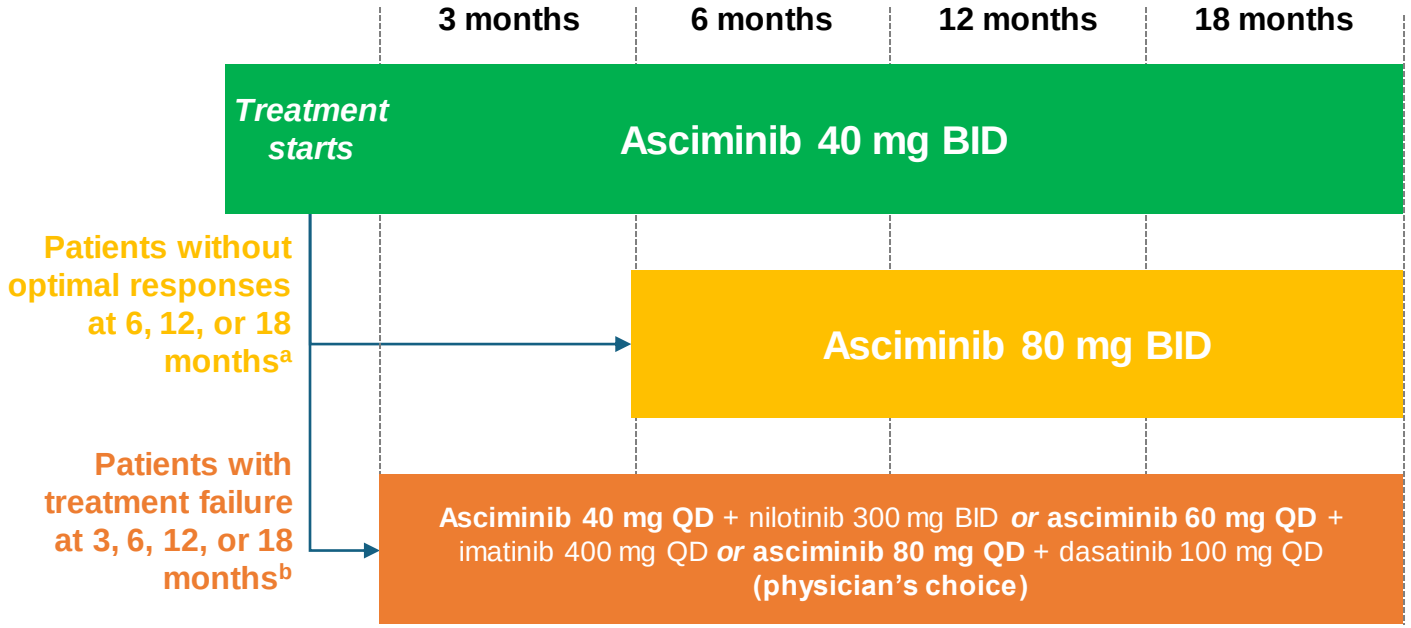
1	**Asciminib 1L treatment (monotherapy or combination upfront) short-term and long-term outcomes**	• *ASC4FIRST, ASC4START, ASC2ESCALATE* *RCs: EUTOS* *IIT: ALERTCML (US CML Consortium, CABL001AUS06T), FASCINATION, ASCEND, ASCENDANCE, US 1L MDACC, **PEARL***	• *Subanalysis / pooled analysis across 1L studies* *Support potential in scope IIT proposals* *US CML Registry*
2	**Real world use of asciminib in 1L: populations, factors/drivers for treatment choice, and outcomes**	• *CML Consortium*	• *Prospective observational studies/registries upon 1L approval* *US CML Registry*
3	**Asciminib vs dasatinib (including lower dose) in 1L**		• *ASC4FIRST (dasatinib cohort sub-analysis)* *US CML registry (indirect comparison)*

ASCEND is an ongoing, prospective, phase II IIT of frontline asciminib in patients with CML-CP

Study purpose: Assess efficacy of asciminib in newly diagnosed patients with CML-CP

Key inclusion criteria

- Newly diagnosed patients with CML-CP
- ≥18 years of age



Co-primary endpoints

- EMR or *BCR::ABL1*^{IS} ≤10% at 3 months (**final analysis**)
- MMR by 12 months (**interim analysis**)

ALLG, Australasian Leukaemia Lymphoma Group; BID, twice daily; CML, chronic myeloid leukemia; CP, chronic phase; DMR, deep molecular response (MR^4, *BCR::ABL1*^{IS} ≤0.01%; MR$^{4.5}$, *BCR::ABL1*^{IS} ≤0.0032%); EMR, early molecular response (*BCR::ABL1*^{IS} ≤10% at 3 months); IIT, investigator-initiated trial; IS, International Scale; MMR, major molecular response (*BCR::ABL1*^{IS} ≤0.1); QD, once daily; PRO, patient reported outcomes.

[a] *BCR::ABL1*^{IS} >1%, 0.1%, and 0.01% at 6, 12, and 18 months, respectively. [b] *BCR::ABL1*^{IS} >10% at 3 or 6 months, and *BCR::ABL1*^{IS} >1% at 12 or 18 months.

[c] ASCEND has completed enrolment at 14 Australian sites and 1 New Zealand site.

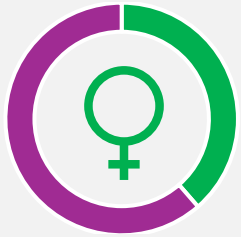
1. Yeung DT, et al. Presented at: ASH 2022; December 10-13, 2022; New Orleans, LA, and virtual. Abstract 79. 2. Yeung DT, et al. Presented at: ASH 2023; December 9-12, 2023; San Diego, CA, and virtual. Abstract 865. 3. Yeung DT, et al. *Blood*. 2024;7(144):1993-2001.

Patient demographics

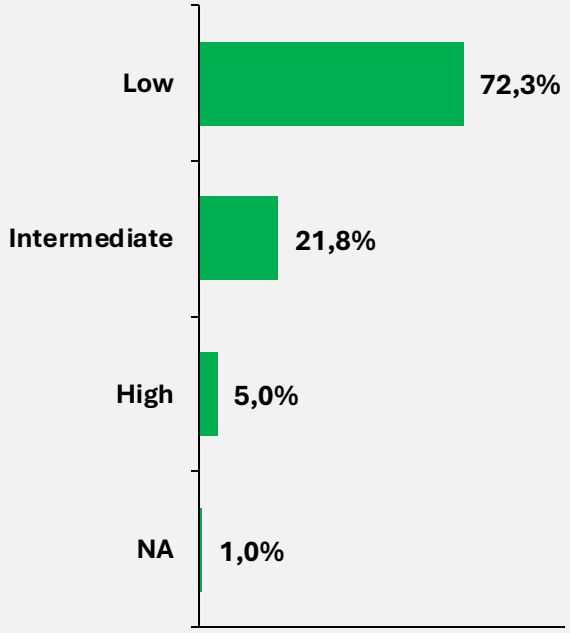
N=101

Age, median, years

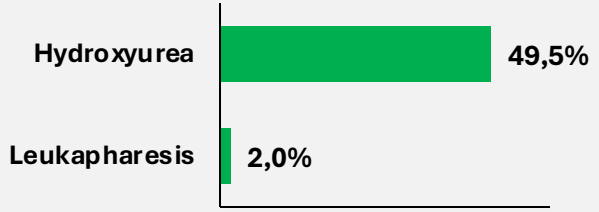
Female



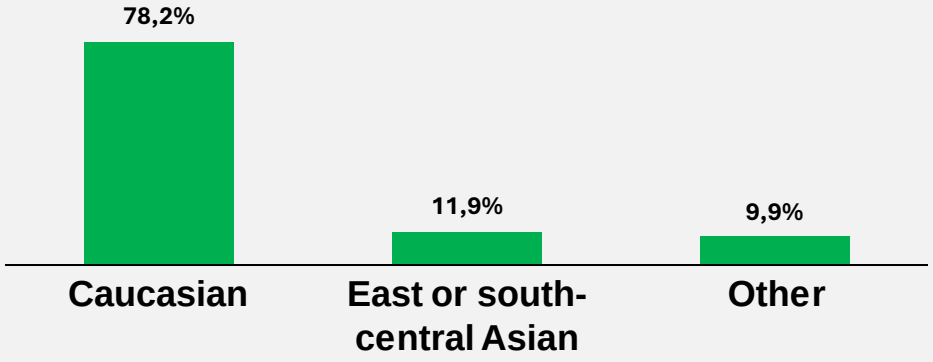
ELTS score



Prior therapies



Race



ELTS, EUTOS long-term survival; EUTOS, European Treatment and Outcome Study; IIT, investigator-initiated trial; NA, not applicable.
Yeung DT, et al. *Blood*. 2024;7(144):1993-2001.

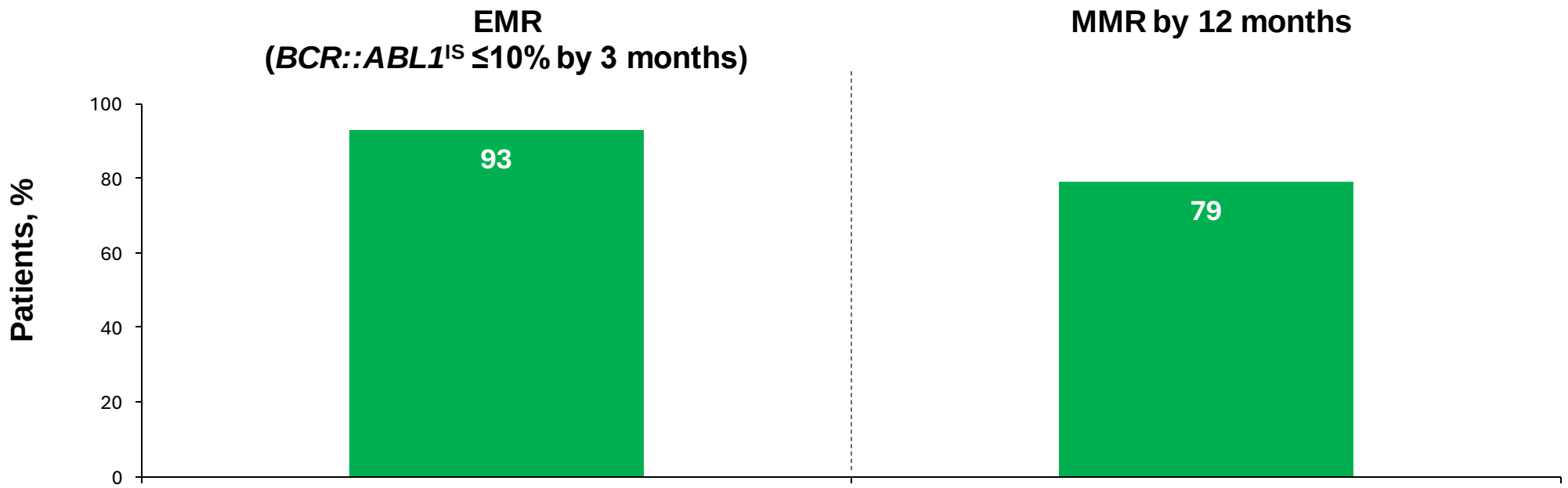
Patient disposition

Patients, n	Asciminib (n=101)
Continuing treatment	81
Discontinued treatment	20
Reason for discontinuation	
Intolerance[a]	6
Resistance	8
Failure to achieve EMR	2
Loss of response	5
Progression to AP/BC[b]	1
Loss to follow-up/withdrawn consent	5
Enrolled but never started	1

- With a median follow-up of 28 months (range, 0-42 months), 20 patients discontinued asciminib treatment

AP, accelerated phase; BC, blast crisis; EMR, early molecular response (*BCR::ABL1*^{IS} ≤10% at 3 months); IIT, investigator-initiated trial.
[a] Including lipase elevations (n=3), pancreatitis (n=1), and cytopenia (n=2). [b] Lymphoid BC.
Yeung DT, et al. Oral presentation at: 66th ASH Annual Meeting & Exposition; December 7-10, 2024; San Diego, CA. Oral 476.

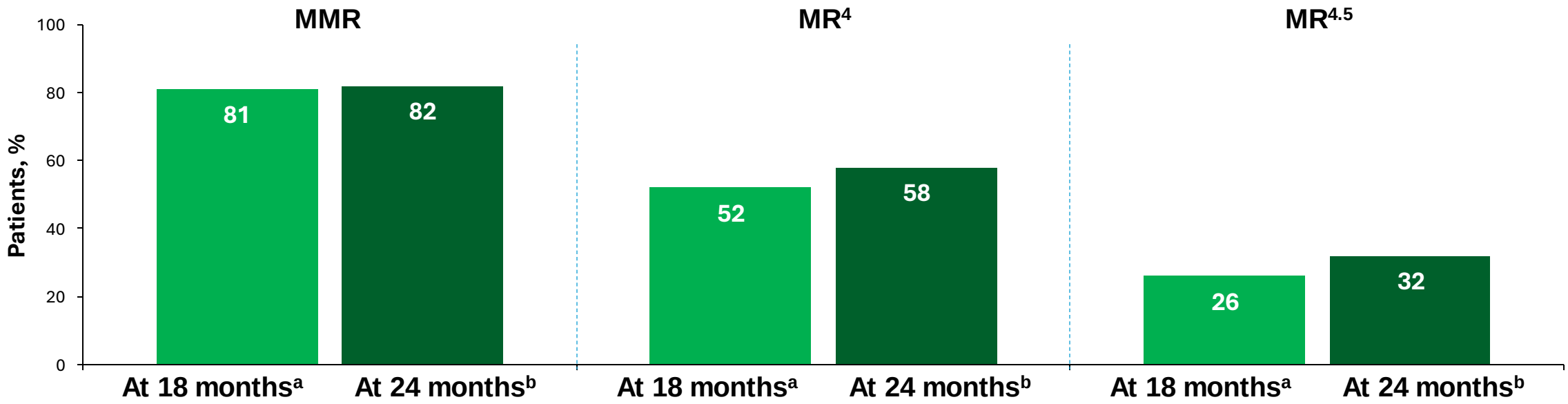
Co-primary endpoints



- Almost all patients achieved EMR, supporting the early responses associated with asciminib
- The second co-primary endpoint, MMR by 12 months, was achieved by 79% of patients

EMR, early molecular response, *BCR::ABL1*^{IS} ≤10% at 3 months; IIT, investigator-initiated trial; IS, International Scale; MMR, major molecular response (*BCR::ABL1*^{IS} ≤0.1%).
Yeung DT, et al. Oral presentation at: 66th ASH Annual Meeting & Exposition; December 7-10, 2024; San Diego, CA. Oral 476.

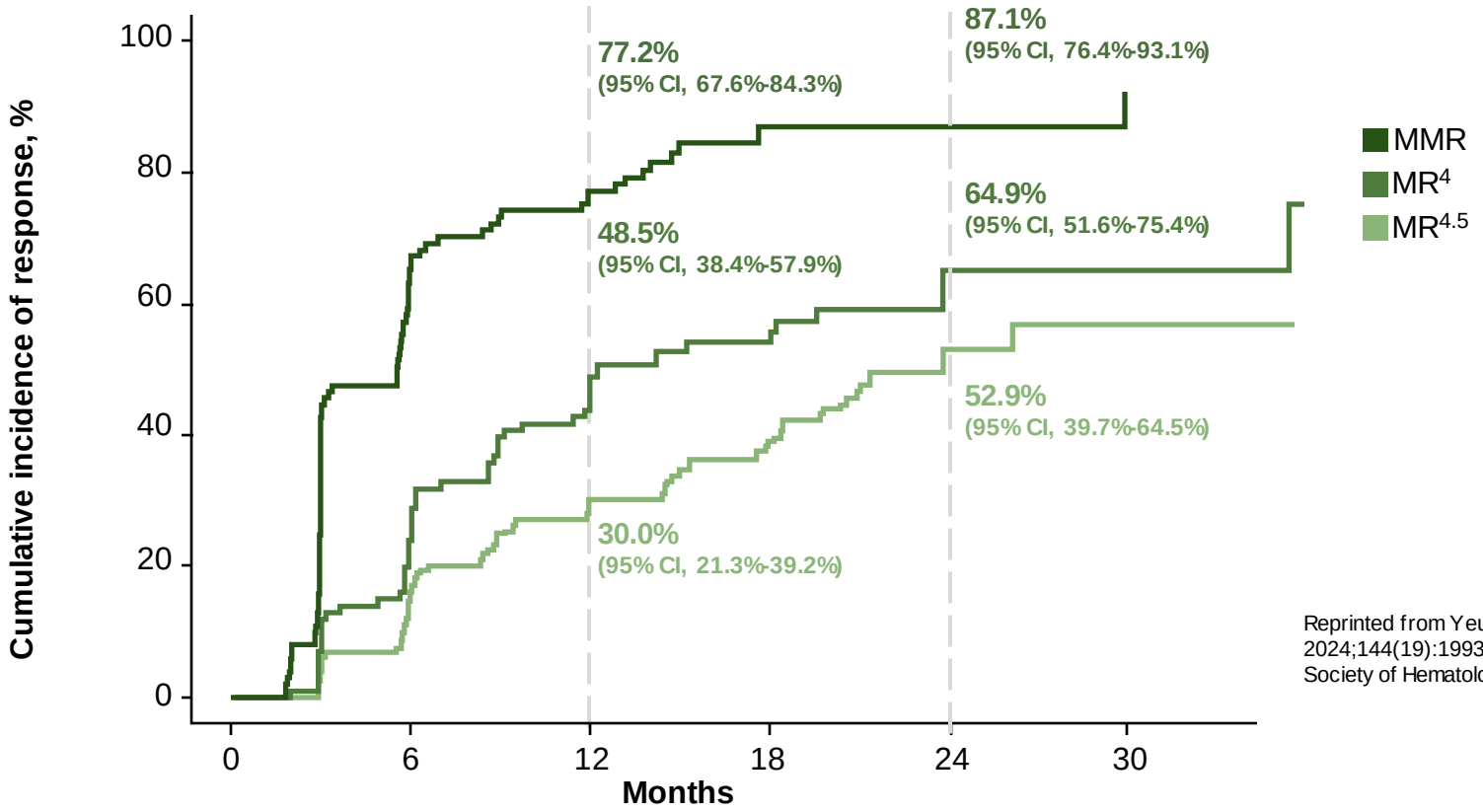
Molecular responses at time points



- Of 5 patients with high ELTS risk, 3 had MMR at 12 months and 0 had MR^4 at 18 months

ELTS, EUTOS long-term survival score; EMR, early molecular response, *BCR::ABL1*^{IS} ≤10% at 3 months; EUTOS, European Treatment and Outcome Study; IIT, investigator-initiated trial; 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%.
[a] Of 95 eligible patients. [b] Of 76 eligible patients.
Yeung DT, et al. Oral presentation at: 66th ASH Annual Meeting & Exposition; December 7-10, 2024; San Diego, CA. Oral 476.

Cumulative molecular responses by specific timepoints



- The cumulative incidences of MMR, MR^4, and $MR^{4.5}$ increased from 12 to 24 months

IIT, investigator-initiated trial; 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%.
Yeung DT, et al. *Blood*. 2024;7(144):1993-2001.

BCR::ABL1 kinetics in patients with suboptimal response at 12 and 18 months

Patients with *BCR::ABL1*^{IS} ≤1% but not in MMR at 12 months (n=13)

7 patients increased dose to asciminib 80 mg BID

↓

5 of these patients achieved MMR after 3 to 18 months

5 patients continued asciminib at 40 mg QD

↓

2 of these patients achieved MMR after 6 months

Patients not in MR^4 at 18 months (n=33)[a]

21 patients had a follow-up at 24 months

3 of 12 patients who had a dose increase to asciminib 80 mg BID achieved MR^4

1 of 9 patients who remained on asciminib 80 mg QD achieved MR^4

- *BCR::ABL1* kinetics were assessed in patients with suboptimal response at 12 and 18 months

BID, twice daily; IS, International Scale; MMR, major molecular response (*BCR::ABL1*^{IS} ≤0.1%); MR^4, *BCR::ABL1*^{IS} ≤0.01%; QD, once daily.
[a] Including 3 patients without MMR, with *BCR::ABL1* 0.12%, 0.28%, and 0.31%.
Yeung DT, et al. Oral presentation at: 66th ASH Annual Meeting & Exposition; December 7-10, 2024; San Diego, CA. Oral 476.

PFS and EFS at specific time points

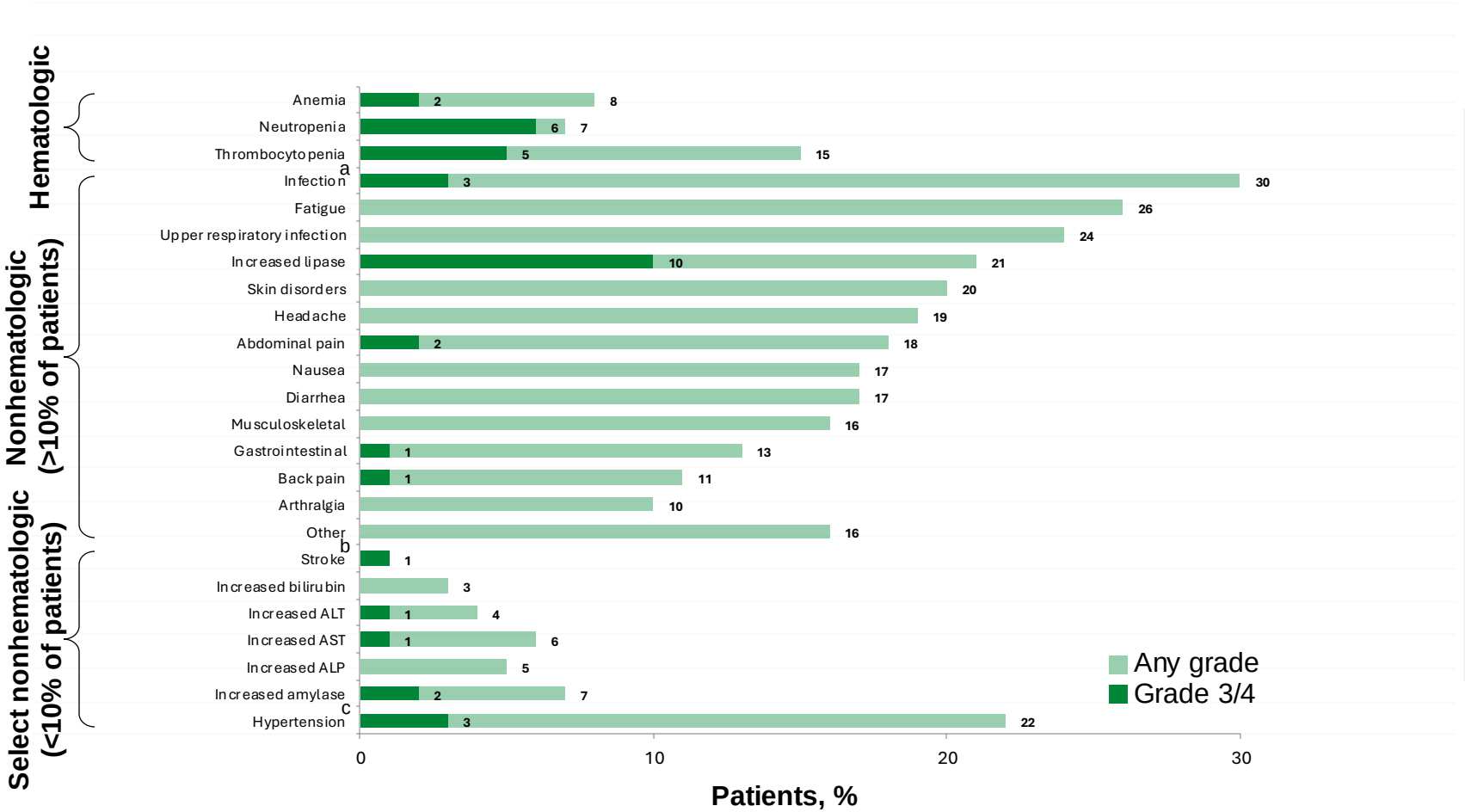
Event, % (95% CI)	PFS	EFS
At 12 months	–	90 (82.1-94.4)
At 24 months	99 (96.8-100)	85 (75.7-91.4)

- No deaths were reported on study
- 4 patients received allogeneic stem cell transplants after discontinuation, including:
  - 1 patient whose disease progressed to lymphoid BC
  - 2 patients who discontinued due to prolonged treatment-emergent cytopenias
  - 1 patient with EMR failure

BC, blast crisis; EFS, event-free survival; EMR, early molecular response (*BCR::ABL1*^{IS} ≤10% at 3 months); IIT, investigator-initiated trial; IS, International Scale; PFS, progression-free survival.

Yeung DT, et al. *Blood*. 2024;7(144):1993-2001.

Treatment-emergent AEs



- Most TEAEs manifested within the first 3 months of treatment
- Hematologic TEAEs contributed to treatment discontinuation in 3 patients
- Most nonhematologic AEs were grade 1/2 and resolved without leading to treatment discontinuation
- Hypertension was reported as a clinically significant AE in 5% of patients

AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AOE, arterial occlusive event; AST; aspartate transferase; BMI, body mass index; CTCAE, Common Terminology Criteria for Adverse Events; DBP, diastolic blood pressure; IIT, investigator-initiated trial; SBP, systolic blood pressure; TIA, transient ischemic attack.
[a] The 3 grade 3 infective episodes were hospitalizations in 3 patients for pneumonia, skin infection from cat scratch, and septic arthritis. [b] A 73-year-old woman with pre-existing type 2 diabetes, hypertension, and high BMI had a lacunar infarct 20 months into treatment presenting as a TIA, with a second TIA affecting the same territory 28 months into treatment. There was complete neurological recovery after each episode. No other treatment-emergent AOE was reported. [c] Defined as 2 consecutive measurements meeting the CTCAE criteria, without a prior history of hypertension at study entry. The relevant parameters are: SBP ≥140-159 mm Hg and/or DBP ≥90-99 mm Hg for all grades and SBP ≥160 mm Hg and/or DBP ≥100 mm Hg for grade ≥3.
Yeung DT, et al. *Blood*. 2024;7(144):1993-2001.

Mutations

Mutations[a]	Patients who discontinued asciminib due to resistance (n=8)	Reason
Patients with ≥1 mutation, n	5	
A337T	1	Loss of MMR at 6 months
A337T	1	Loss of MR^4 at 18 months
V506L	1	Loss of MR^2 at 6 months
T315I/M244V	1	Loss of MMR at 12 months
A337T/A337V/P465S	1	Lymphoid blast crisis at 6 months

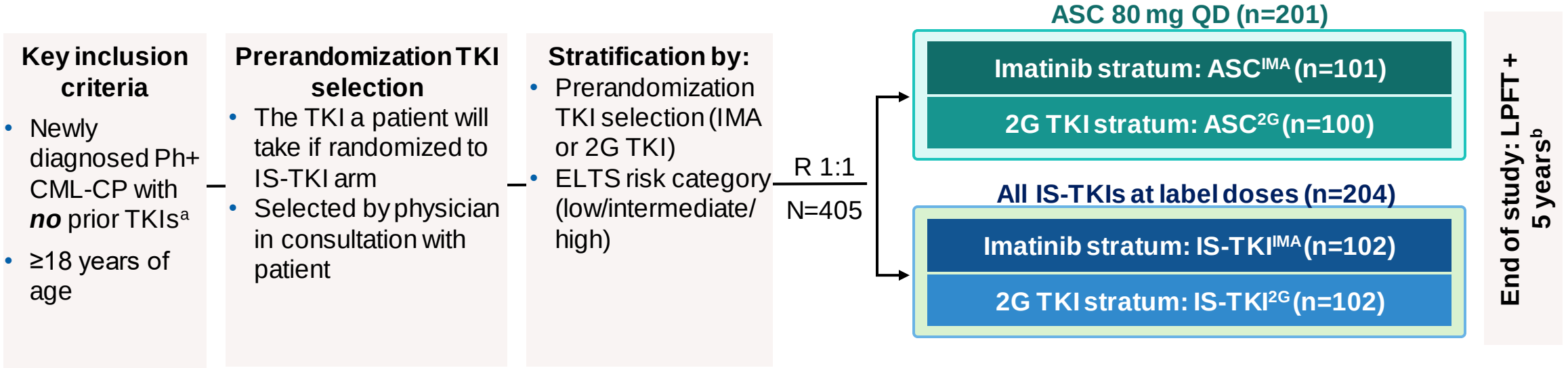
- Of the 20 patients who discontinued asciminib, 8 discontinued due to resistance, with 5 patients developing mutations leading to loss of response or disease progression[1]

IIT, investigator-initiated trial; IS, International Scale; MMR, major molecular response (*BCR::ABL1*^{IS} ≤0.1%); MR^2, *BCR::ABL1*^{IS} ≤1%; MR^4, *BCR::ABL1*^{IS} ≤0.01%; $MR^{4.5}$, *BCR::ABL1*^{IS} ≤0.0032%; TMC, trial management committee.

[a] *BCR::ABL1* kinase domain testing was conducted if 1 of the following criteria was met: (1) *BCR::ABL1*^{IS} >10% at 3 months, >1% at 6 months, and >1% at 12, 18, and/or 24 months; (2) any events classified as acquired or primary resistance or disease progression; (3) study discontinuation because of treatment failure or loss of response; (4) a >2-fold rise in *BCR::ABL1* transcript levels at the first occurrence, from a nadir of ≤0.1% to a level of >0.1%; or (5) a specific request for mutation testing from the treating clinician or the TMC.[2]

1. Yeung DT, et al. Oral presentation at: 66th ASH Annual Meeting & Exposition; December 7-10, 2024; San Diego, CA. Oral 476. 2. Data on file. ASCEND-CML Study Protocol V2.0. Australasian Leukaemia and Lymphoma Group; 2021.

ASC4FIRST: Study design



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.

Primary endpoints
- MMR at week 48 with **ASC** vs all **IS-TKIs**
- MMR at week 48 with **ASC^{IMA}** vs **IS-TKI^{IMA}** (**imatinib stratum**)

Data cutoff: Nov 28, 2023

Key secondary endpoints
- MMR at week 96 with **ASC** vs all **IS-TKIs**
- MMR at week 96 with **ASC^{IMA}** vs **IS-TKI^{IMA}** (**imatinib stratum**)

Data cutoff: Oct 22, 2024

2G, 2nd generation; ASC, asciminib; CML-CP, chronic myeloid leukemia in chronic phase; ELTS, EUTOS long-term survival score; EUTOS, European Treatment and Outcome Study; IMA, imatinib; IS, investigator selected; LPFT, last person 1st treatment; MMR, major molecular response; Ph, Philadelphia chromosome; QD, once daily; R, randomized; TKI, tyrosine kinase inhibitor.

[a] Either imatinib, bosutinib, dasatinib, or nilotinib is allowed for ≤2 weeks prior to randomization. Treatment with other TKIs prior to randomization was not permitted. [b] Patients will remain on study for 5 years after the last patient 1st dose, unless they have discontinued early due to treatment failure, disease progression, intolerance, or investigator or patient decision.

Hochhaus A, et al. *N Engl J Med*. 2024;391(10):885-898.

Demographics and baseline disease characteristics

Variable	Asciminib			IS-TKI		
	All asciminib (n=201)	Imatinib stratum (n=101)	2G TKI stratum (n=100)	All comparators (n=204)	Imatinib stratum (n=102)	2G TKI stratum (n=102)
Age, median (range), years	52.0 (18.0-79.0)	56.0 (21.0-79.0)	43.0 (18.0-76.0)	50.5 (19.0-86.0)	54.5 (20.0-86.0)	43.0 (19.0-83.0)
Age group, %						
18 to <65 years	77.1	68.3	86.0	76.0	68.6	83.3
65 to <75 years	17.9	23.8	12.0	16.7	21.6	11.8
≥75 years	5.0	7.9	2.0	7.4	9.8	4.9
Male, %	65.2	61.4	69.0	61.3	63.7	58.8
Framingham 10-year cardiovascular disease risk, %						
Low (<10%)	54.2	40.6	68.0	54.9	39.2	70.6
Intermediate (10%-20%)	15.9	20.8	11.0	21.6	28.4	14.7
High (≥20%)	29.9	38.6	21.0	23.5	32.4	14.7
ELTS risk, %[a]						
Low	60.7	61.4	60.0	61.3	62.7	59.8
Intermediate	27.9	29.7	26.0	27.9	29.4	26.5
High	11.4	8.9	14.0	10.8	7.8	13.7

From Hochhaus A, et al. *N Engl J Med*. 2024;391(10):885-898.

- More patients in the IMA stratum were >65 years old, with higher cardiovascular disease risk and lower ELTS risk, which may reflect physician preference for IMA in these subgroups

2G, 2nd generation; ELTS, EUTOS long-term survival score; EUTOS, European Treatment and Outcome Study; IMA, imatinib; IS, investigator selected; TKI, tyrosine kinase inhibitor.
[a] Based on randomization data.
Hochhaus A, et al. *N Engl J Med*. 2024;391(10):885-898.

Patient disposition at data cutoff

Patients randomized, %	Asciminib			IS-TKI		
	All asciminib (n=201)	Imatinib stratum (n=101)	2G TKI stratum (n=100)	All IS-TKI (n=204)	Imatinib stratum (n=102)	2G TKI stratum (n=102)
Treatment ongoing[a,b]	81.6	82.2	81.0	60.3	52.0	68.6
Discontinued treatment	17.9	16.8	19.0	38.2	46.1	30.4
Unsatisfactory therapeutic effect	9.5	7.9	11.0	20.6	28.4	12.7
Treatment failure per ELN	5.0	5.9	4.0	13.7	18.6	8.8
Confirmed loss of MMR	2.0	2.0	2.0	1.5	2.0	1.0
Other	2.5	0	5.0	5.4	7.8	2.9
Adverse event	6.0	5.9	6.0	12.7	12.7	12.7
Progressive disease	1.0	2.0	0	2.0	2.9	1.0
Physician decision	0.5	0	1.0	0	0	0
Protocol deviation	0.5	1.0	0	1.0	1.0	1.0
Patient deviation	0.5	0	1.0	1.5	1.0	2.0

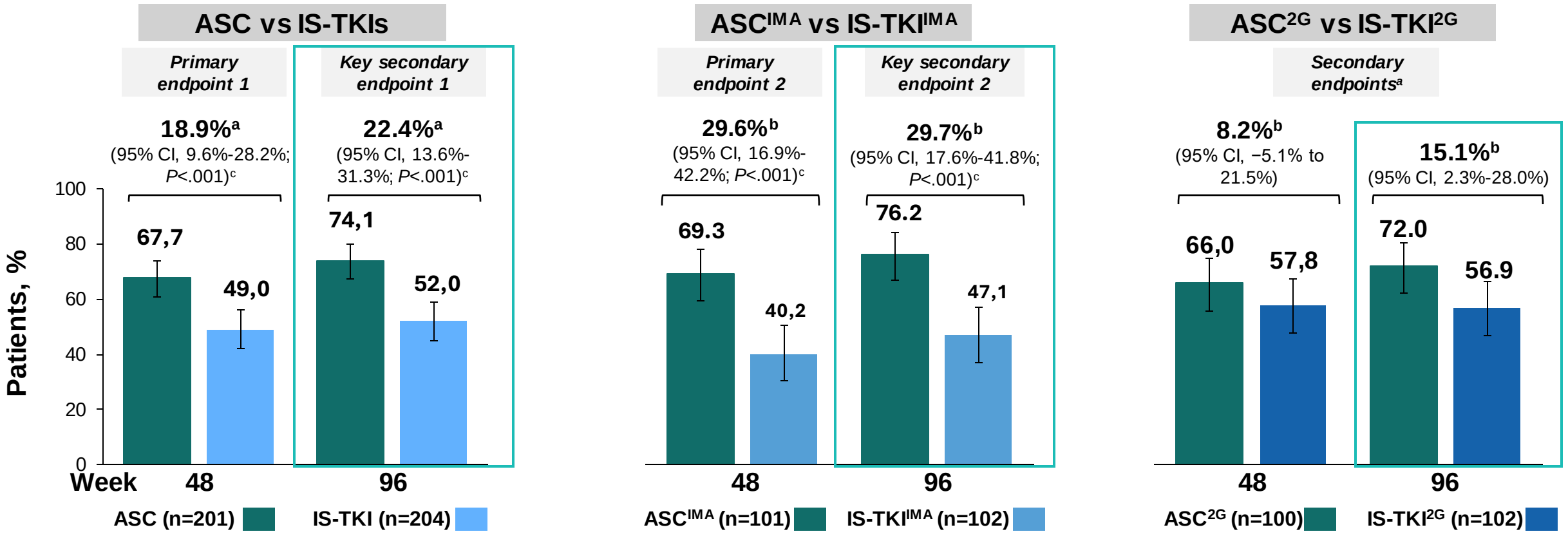
- More patients were ongoing treatment with asciminib than all IS-TKIs
- The discontinuation rate was twice as high with all IS-TKIs compared with asciminib

2G, 2nd generation; ELN, European LeukemiaNet; IS, International Scale; IS-TKI, investigator-selected tyrosine kinase inhibitor; MMR, major molecular response (*BCR::ABL1*^{IS} ≤0.1%); TKI, tyrosine kinase inhibitor.

[a] At data cutoff: October 22, 2024. [b] A patient stratified to imatinib as prerandomization selection of TKI received nilotinib as actual treatment. Hence, this patient is considered in the imatinib stratum for efficacy analysis and in the 2G TKI stratum for safety analysis.

Cortes JE, et al. Oral presentation at: 66th ASH Annual Meeting & Exposition; December 7-10, 2024; San Diego, CA. Oral presentation 475.

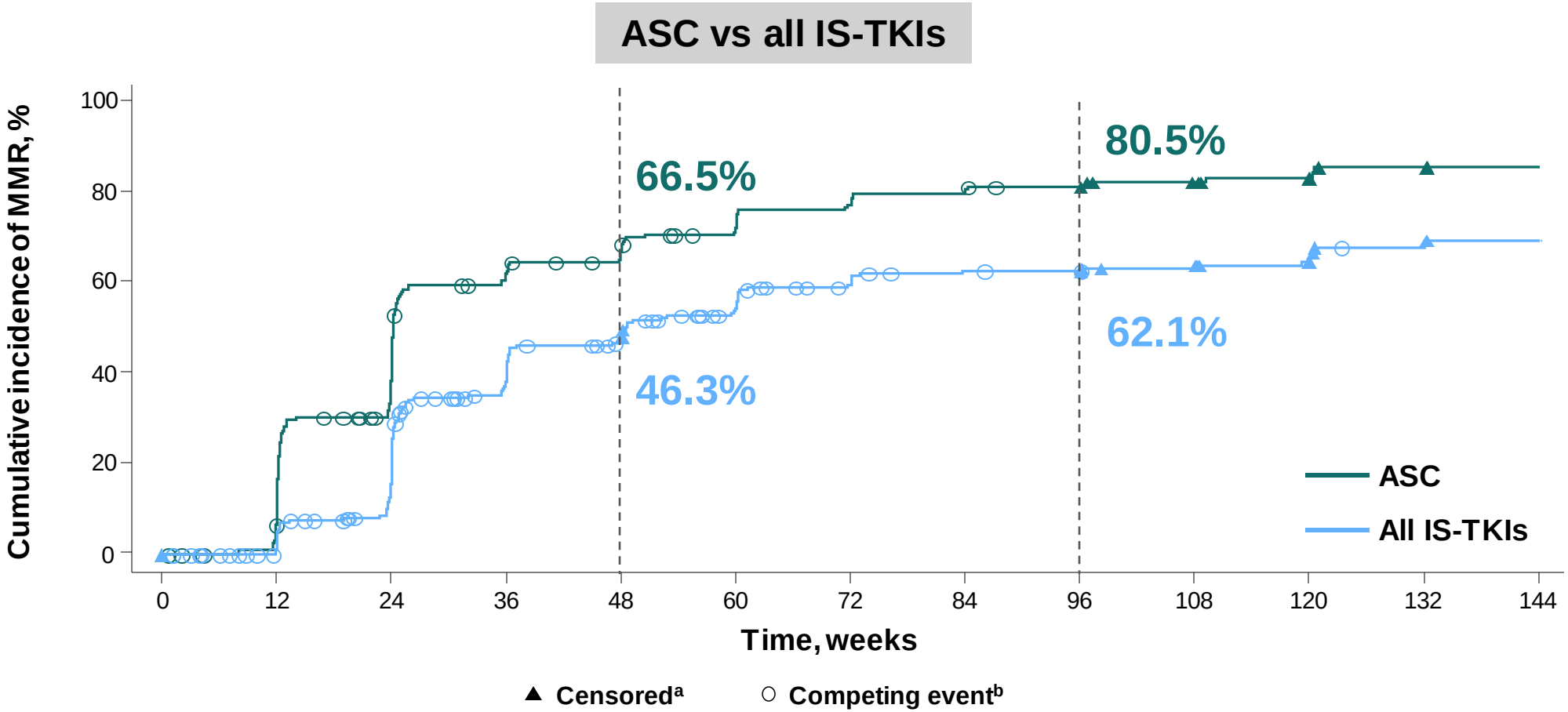
MMR rates at time points



- MMR rate at week 96 continued to be superior with ASC vs all IS-TKIs, meeting the 1st key secondary endpoint
- MMR rate at week 96 continued to be superior with ASC^{IMA} vs IS-TKI^{IMA}, meeting the 2nd key secondary endpoint
- Treatment difference for the MMR rate at week 96 between ASC^{2G} and IS-TKI^{2G} increased
- MMR rates at week 96 were consistently higher with ASC overall and across strata

2G, 2nd generation; ASC, asciminib; ELTS, EUTOS long-term survival score; EUTOS, European Treatment and Outcome Study; IMA, imatinib; IRT, interactive response technology; IS, International Scale; IS-TKI, investigator-selected tyrosine kinase inhibitor; MMR, major molecular response (*BCR::ABL1*^{IS} ≤0.1%); TKI, tyrosine kinase inhibitor.
Error bars represent 95% CIs. The common treatment difference and its 95% CI were estimated using the Mantel-Haenszel method after stratifying for [a] prerandomization-selected TKI and baseline ELTS risk groups (both IRT data) or [b] baseline ELTS risk groups (IRT data). [c] Adjusted 1-sided *P* value was calculated based on the graphical gatekeeping procedure. The null hypothesis is rejected if the adjusted *P* value is ≤.025.
Cortes JE, et al. Oral presentation at: 66th ASH Annual Meeting & Exposition; December 7-10, 2024; San Diego, CA. Oral presentation 475.

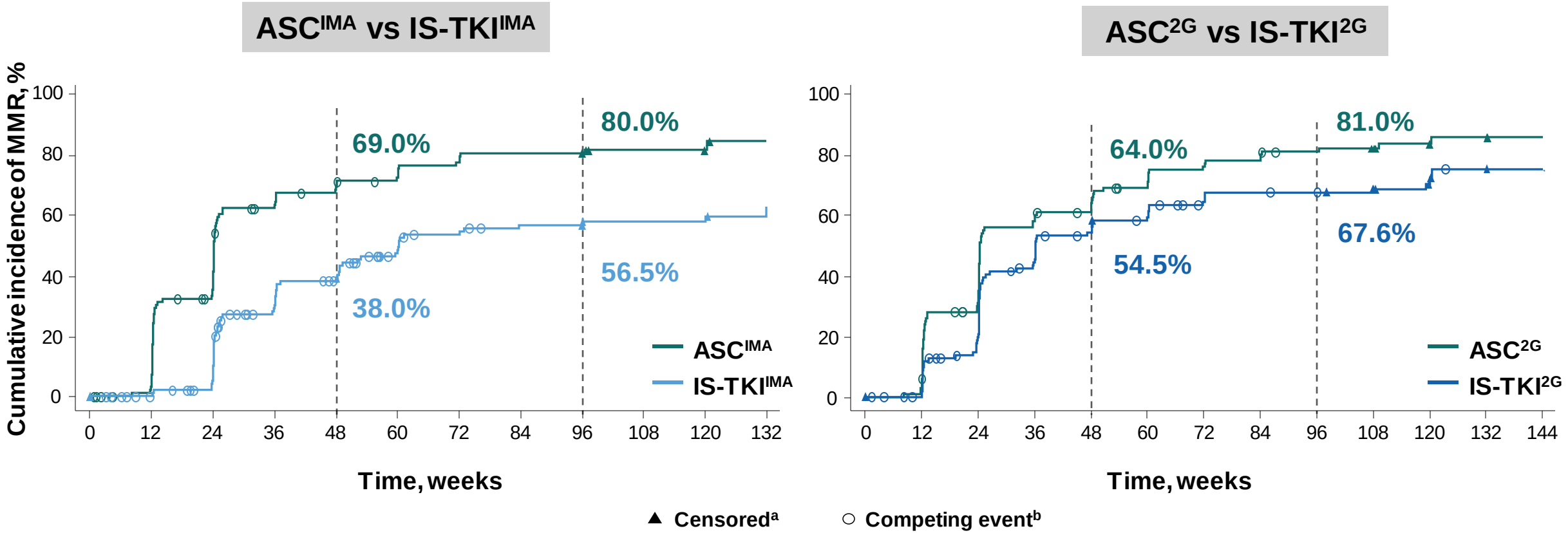
Cumulative incidence of MMR with ASC vs all IS-TKIs



- Cumulative incidence of MMR[c] continued to be higher with ASC than all IS-TKIs

ASC, asciminib; IS, International Scale; IS-TKI, investigator-selected tyrosine kinase inhibitor; MMR, major molecular response (*BCR::ABL1*^{IS} ≤0.1%).
[a] Nonresponders were censored at their last molecular assessment date. [b] Discontinuation from treatment for any reason without prior achievement of MMR was considered a competing event. [c] Defined as the proportion of patients who achieved MMR at or before specific times.
Cortes JE, et al. Oral presentation at: 66th ASH Annual Meeting & Exposition; December 7-10, 2024; San Diego, CA. Oral presentation 475.

Cumulative incidence of MMR with ASC^{IMA} vs IS-TKI^{IMA} and ASC^{2G} vs IS-TKI^{2G}



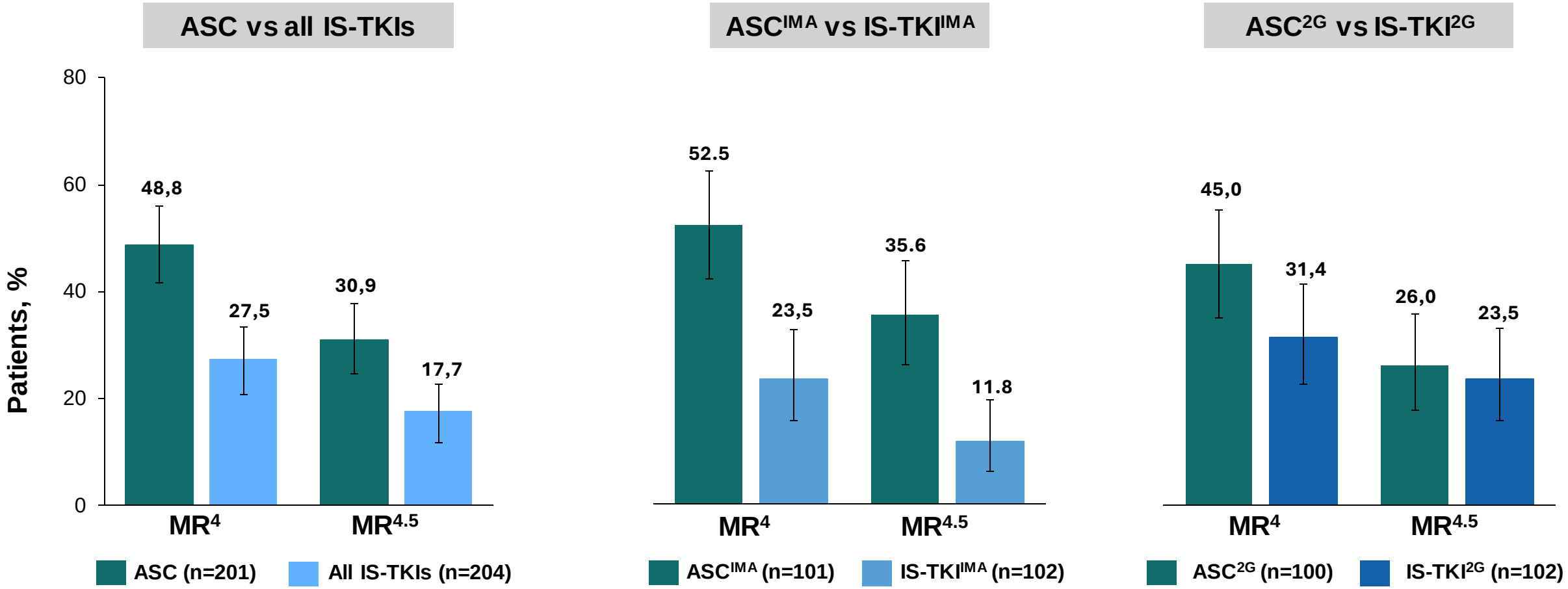
- Cumulative incidence of MMR[c] continued to be higher with ASC than IS-TKIs across imatinib and 2G TKI strata

2G, 2nd generation; ASC, asciminib; IMA, imatinib; IS, International Scale; IS-TKI, investigator-selected tyrosine kinase inhibitor; MMR, major molecular response (*BCR::ABL1*^{IS} ≤0.1%); TKI, tyrosine kinase inhibitor.

[a] Nonresponders were censored at their last molecular assessment date. [b] Discontinuation from treatment for any reason without prior achievement of MMR was considered a competing event. [c] Defined as the proportion of patients who achieved MMR at or before specific times.

Cortes JE, et al. Oral presentation at: 66th ASH Annual Meeting & Exposition; December 7-10, 2024; San Diego, CA. Oral presentation 475.

DMR at week 96 overall and across strata

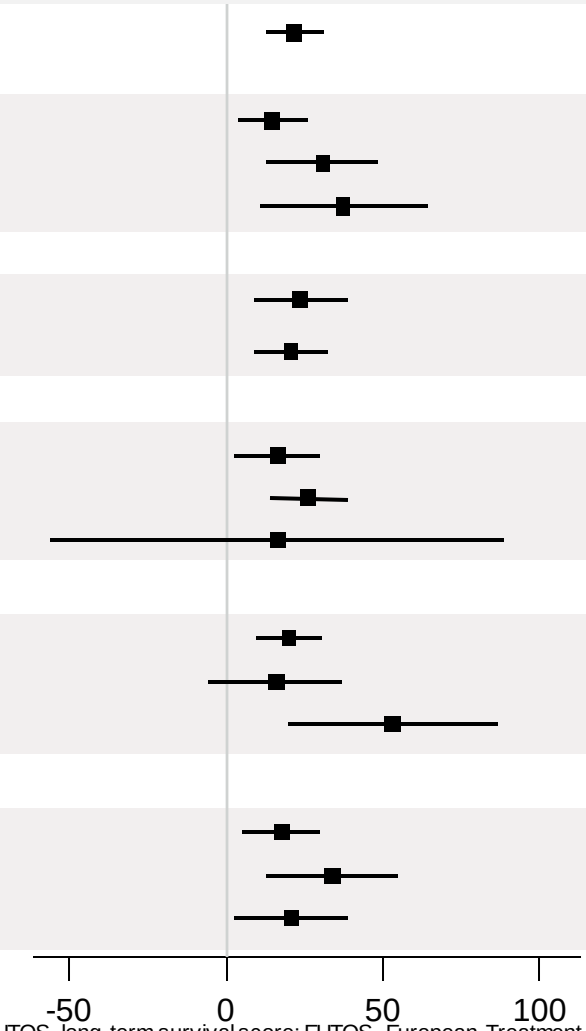


- DMR rates at week 96 continued to be higher with ASC overall and across strata

2G, 2nd generation; ASC, asciminib; DMR, deep molecular response; IMA, imatinib; IS, International Scale; IS-TKI, investigator-selected tyrosine kinase inhibitor; MR^4, *BCR::ABL1*^{IS} ≤0.01%; $MR^{4.5}$, *BCR::ABL1*^{IS} ≤0.0032%.
Error bars represent 95% CIs.
Cortes JE, et al. Oral presentation at: 66th ASH Annual Meeting & Exposition; December 7-10, 2024; San Diego, CA. Oral presentation 475.

Subgroup analysis with ASC vs all IS-TKIs

Subgroup	ASC n/N (%)	All IS-TKIs n/N (%)	Risk difference (95% CI)
All patients	149/201 (74.1)	106/204 (52.0)	22.2 (13.0 to 31.3)
ELTS risk based on randomization data			
Low	98/122 (80.3)	81/125 (64.8)	15.5 (4.6 to 26.5)
Intermediate	37/56 (66.1)	20/57 (35.1)	31.0 (13.5 to 48.5)
High	14/23 (60.9)	5/22 (22.7)	38.1 (11.6 to 64.7)
Sex			
Female	54/70 (77.1)	42/79 (53.2)	24.0 (9.2 to 38.7)
Male	95/131 (72.5)	64/125 (51.2)	21.3 (9.7 to 32.9)
Race and ethnicity			
Asian	66/90 (73.3)	51/90 (56.7)	16.7 (2.9 to 30.4)
White	81/108 (75.0)	53/110 (48.2)	26.8 (14.4 to 39.2)
Other	2/3 (66.7)	2/4 (50.0)	16.7 (−55.8 to 89.1)
Age category			
18 to <65 years	113/155 (72.9)	81/155 (52.3)	20.6 (10.1 to 31.2)
65 to <75 years	28/36 (77.8)	21/34 (61.8)	16.0 (−5.2 to 37.3)
≥75 years	8/10 (80.0)	4/15 (26.7)	53.3 (19.9 to 86.7)
Framingham 10-year CV disease risk			
Low	80/109 (73.4)	62/112 (55.4)	18.0 (5.6 to 30.4)
Intermediate	24/32 (75.0)	18/44 (40.9)	34.1 (13.2 to 55.0)
High	45/60 (75.0)	26/48 (54.2)	20.8 (3.0 to 38.7)



- MMR rates at week 96 were higher with ASC than all IS-TKIs across demographic and prognostic subgroups

ASC, asciminib; CV, cardiovascular; ELTS, EUTOS long-term survival score; EUTOS, European Treatment and Outcome Study; IS-TKI, investigator-selected tyrosine kinase inhibitor; MMR, major molecular response.

Cortes JE, et al. Oral presentation at: 66th ASH Annual Meeting & Exposition; December 7-10, 2024; San Diego, CA. Oral presentation 475.

21

Postbaseline treatment-emergent *BCR::ABL1* mutations (by NGS)

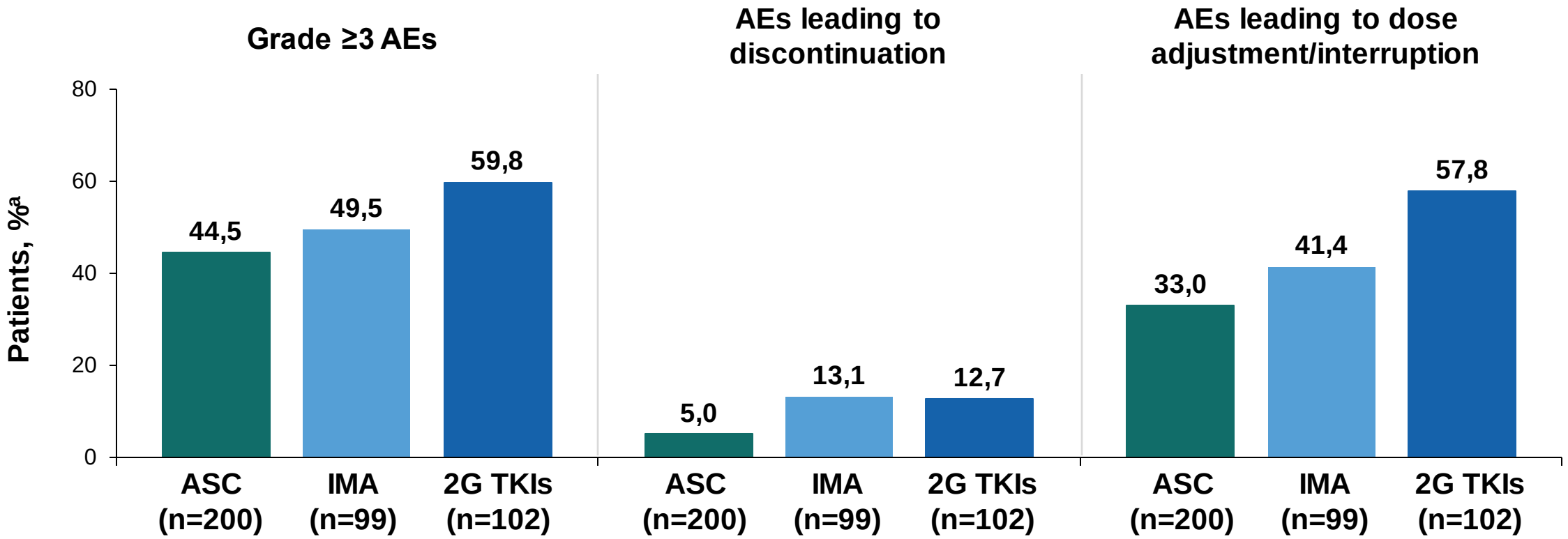
Patients	Postbaseline mutations[a]	Discontinuation reason	Postprotocol therapy (2L+)	Current disease/survival status
Asciminib	**Myristoyl pocket**			
1	A433D	Treatment failure per ELN	Bosutinib, dasatinib	CP/alive
2	A337V, V506M[b]		Dasatinib	CP/alive
3	A337T, A344P,[b] P465Q,[b] I502N[b]		Dasatinib	AP/alive
4	A433D		Dasatinib, olverembatinib	AP/alive
5	A337T, V506M[b]		Ponatinib	Discontinued study
6	L340Q		Not available	Discontinued study
7[c]	A337T	Confirmed loss of MMR	Dasatinib	Discontinued study
8	A337T, L340Q	Unsatisfactory therapeutic effect (other)	Dasatinib	CP/alive
9	A337T,[b] F497L[b]	Progressive disease	Ponatinib	BP/death post HSCT
10[c]	A337V	Ongoing on study	Not applicable	
Imatinib	**ATP-binding domain**			
1	L248V, E255V,[b] G250E[b]	Treatment failure per ELN	Flumatinib, olverembatinib	BP/death post HSCT
2[c]	F317L[b]		Imatinib	CP/alive
3	L248V, E450G[b]		Nilotinib	CP/alive
4[c]	E459K	Confirmed loss of MMR	Dasatinib	CP/alive
Nilotinib	**ATP-binding domain**			
5[c]	Y253H	Treatment failure per ELN	Dasatinib	CP/alive
6	Y253H	Treatment failure per ELN	Dasatinib, ponatinib	CP/alive
7	Y253H[b]	Ongoing on study	Not applicable	

2L, 2nd line; AP, accelerated phase; ATP, adenosine triphosphate; BP, blast phase; CP, chronic phase; ELN, European LeukemiaNet; HSCT, hematopoietic stem cell transplant; MMR, major molecular response; NGS, next-generation sequencing.

[a] A patient with multiple mutations is only counted once. [b] Variant allele frequency was <20%. [c] Patients with new mutations since the week 48 data cutoff (November 28, 2023).

Cortes JE, et al. Oral presentation at: 66th ASH Annual Meeting & Exposition; December 7-10, 2024; San Diego, CA. Oral presentation 475.

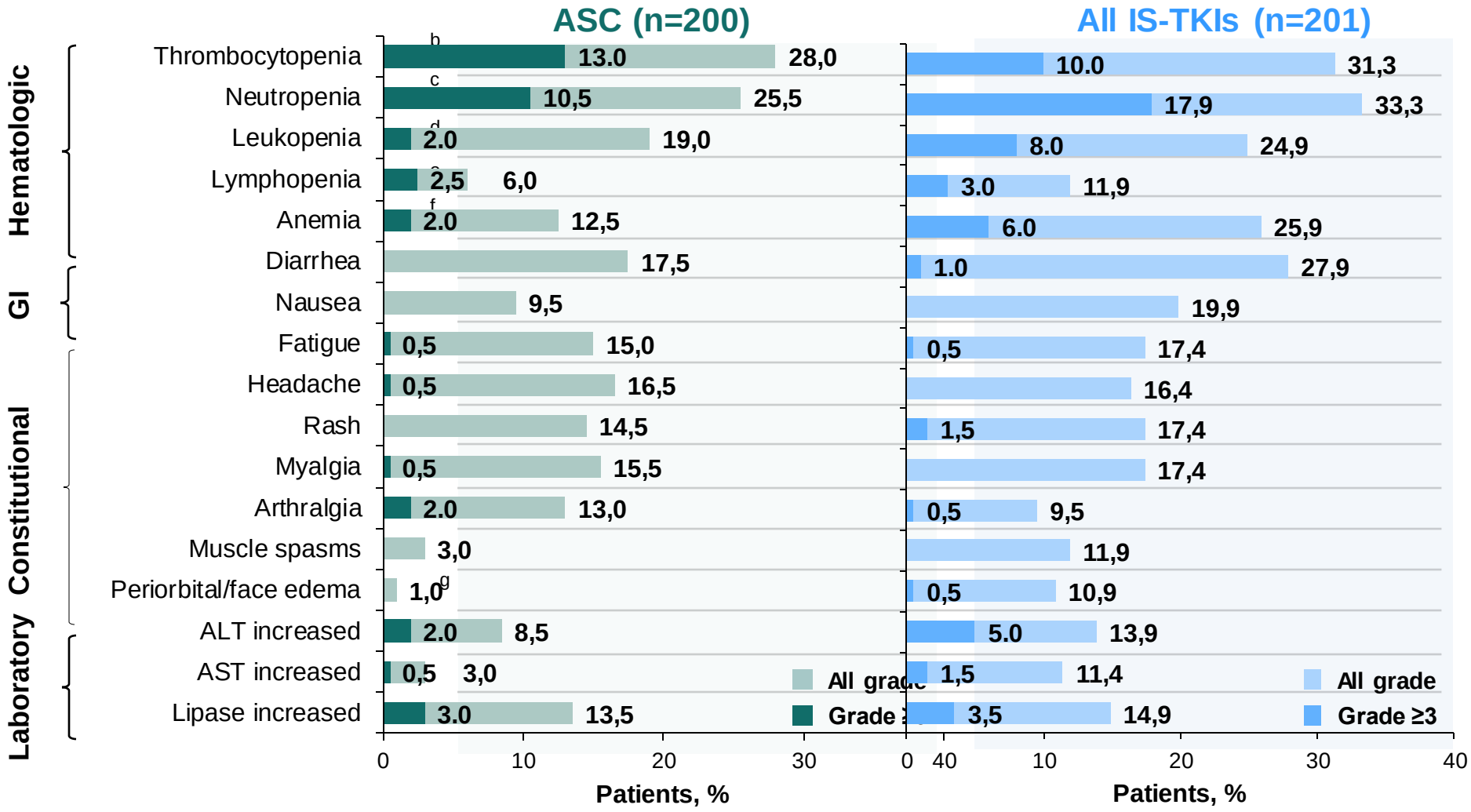
Overview of AEs



- The median average daily dose was 80 mg/day with ASC, 400 mg/day with IMA, 600 mg/day with NIL, 100 mg/day with DAS, and 316 mg/day with BOS
- The hazard ratio for time to treatment discontinuation due to AEs with ASC vs 2G TKIs was 0.46 (95% CI, 0.215-0.997)
  - Risk of discontinuation due to AEs[b] was 54% lower with asciminib than 2G TKIs

2G, 2nd generation; AE, adverse event; ASC, asciminib; BOS, bosutinib; DAS, dasatinib; IMA, imatinib; NIL, nilotinib; TKI, tyrosine kinase inhibitor.
[a] Safety analyses were done in patients who received ≥1 dose of study drug. Patients were analyzed according to the study treatment received. A patient with multiple severity grades for an AE is only counted under the maximum grade. [b] Discontinuation for other reasons was a competing event.
Cortes JE, et al. Oral presentation at: 66th ASH Annual Meeting & Exposition; December 7-10, 2024; San Diego, CA. Oral presentation 475.

Most relevant AEs[a] with asciminib vs all IS-TKIs



- Most relevant AEs were lower with ASC than all IS-TKIs by the week 96 cutoff

AE, adverse event; ALT, alanine aminotransferase; ASC, asciminib; AST, aspartate aminotransferase; GI, gastrointestinal; IS-TKI, investigator-selected tyrosine kinase inhibitor.
[a] A patient with multiple severity grades for an AE is only counted under the maximum grade. COVID-19 is not listed. [b] Includes platelet count decreased and thrombocytopenia. [c] Includes neutrophil count decreased and neutropenia. [d] Includes decreased white blood cell count and leukopenia. [e] Includes decreased lymphocyte count and lymphopenia. [f] Includes anemia and red blood cell count decreased and hematocrit decreased. [g] Includes periorbital edema and face edema.
Cortes JE, et al. Oral presentation at: 66th ASH Annual Meeting & Exposition; December 7-10, 2024; San Diego, CA. Oral presentation 475.

AOEs

Patients, n (%)	All ASC (n=200)[a]		IMA (n=99)[a]		2G TKIs (n=102)[a]	
	All grade	Grade ≥3	All grade	Grade ≥3	All grade	Grade ≥3
Patients with ≥1 AOE	**4 (2.0)**	**1 (0.5)**	**0**	**0**	**3 (2.9)**	**1 (1.0)**
Angina pectoris	1 (0.5)	0	0	0	0	0
Peripheral arterial occlusive disease	1 (0.5)[b]	0	0	0	0	0
Arteriosclerosis coronary artery	2 (1.0)[b]	0	0	0	0	0
Cerebrovascular accident	1 (0.5)	1 (0.5)	0	0	0	0
Cerebral infarction	0	0	0	0	1 (1.0)	0
Myocardial infarction	0	0	0	0	1 (1.0)[c]	1 (1.0)[c]
Myocardial ischemia	0	0	0	0	1 (1.0)[c]	0
Vertebral artery arteriosclerosis	0	0	0	0	1 (1.0)	0

- Since the week 48 cutoff, 2 additional patients had AOEs with ASC (angina pectoris and peripheral arterial occlusive disease [in the patient who had arteriosclerosis coronary artery in the week 48 analysis] and arteriosclerosis coronary artery), and 1 additional patient had an AOE with bosutinib (cerebral infarction)
- AOEs occurred in 2 patients with ASC^{IMA} stratum and 2 with ASC^{2G}

2G, 2nd generation; AOE, arterial-occlusive event; ASC, asciminib; IMA, imatinib; TKI, tyrosine kinase inhibitor.
[a] Safety analyses were done in patients who received ≥1 dose of study drug. Patients were analyzed according to the study treatment received. [b] 1 patient who had arteriosclerosis coronary artery at the week 48 analysis presented with new peripheral arterial occlusive disease. [c] Myocardial infarction and myocardial ischemia occurred in the same patient with 2G TKIs.
Cortes JE, et al. Oral presentation at: 66th ASH Annual Meeting & Exposition; December 7-10, 2024; San Diego, CA. Oral presentation 475.

ASC4FIRST: Week 48 PROs in ND CP-CML

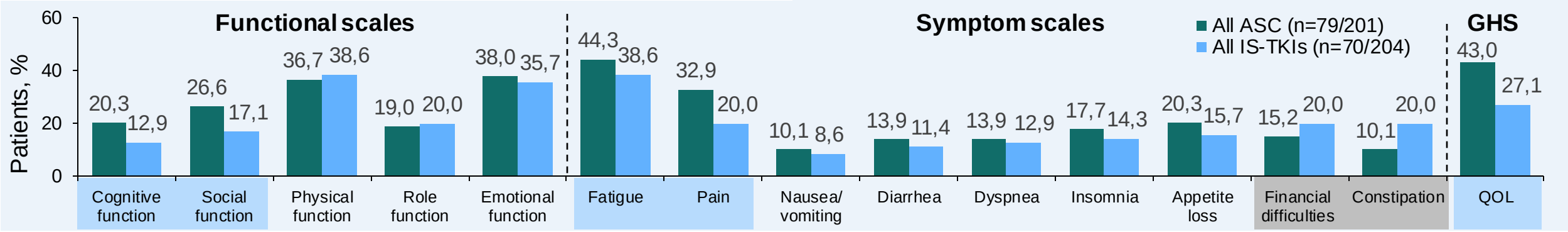
Poster presented at EHA 2025:
Prof. Andreas Hochhaus
Poster Presentation #PS1588

Methods

- ≥1 PRO assessment: ASC (n=194), IS-TKIs (n=195)
- Completion rates in pts (with PRO assessments at baseline and ≥1 post baseline) receiving ASC vs IS-TKI were balanced for QLQ-C30 and QLQ-CML24

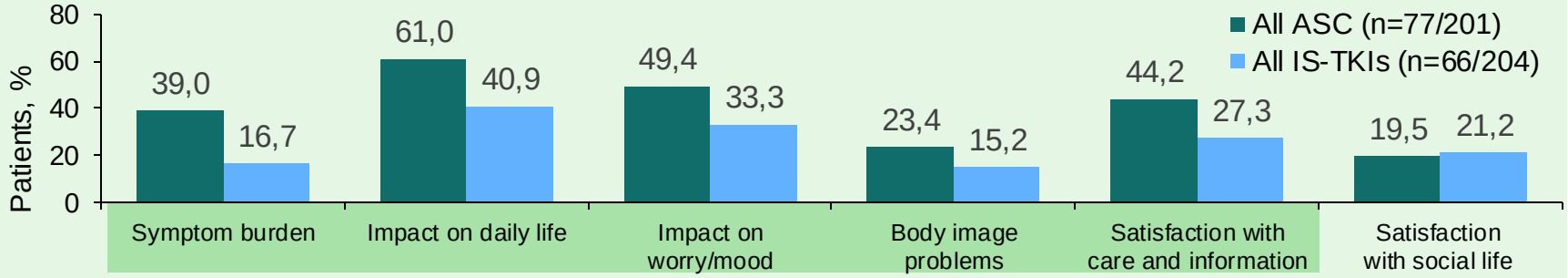
EORTC QLQ-C30*

- **More patients receiving ASC** vs IS-TKIs had improvements in:
  - **Fatigue, pain, HRQOL, and cognitive and social functioning**
- **Fewer patients receiving ASC** vs IS-TKIs had improvements in:
  - **Financial difficulties and constipation**



EORTC QLQ-CML24*

- **More patients receiving ASC** vs IS-TKIs had improvements in:
  - **Symptom burden, impact on daily life, worry/mood, body image, and satisfaction with care and information**



*Improvements[a] in EORTC QLQ-C30 and EORTC QLQ-CML24 scores from baseline to wk 48 in pts with both baseline and wk 48 assessments in ASC4FIRST. a Improvements were defined as an increase in functional scales and GHS/QOL and decrease for symptom scales.
AE=Adverse Event. ASC=Asciminib. EORTC=European Organization for Research and Treatment of Cancer. GHS=Global Health Status. GI=Gastrointestinal.
IS-TKI=Investigator-Selected Tyrosine Kinase Inhibitor. PRO=Patient Reported Outcomes. QLQ-C30=Quality of Life Questionnaire.
Hochhaus et al, Poster #PS1588. 2025 EHA Congress. June 12–15, 2025, Milan, Italy.

ASC4FIRST: Week 48 PROs in ND CP-CML

EHA2025 30th Congress
Poster presented at EHA 2025:
Prof. Andreas Hochhaus
Poster Presentation #PS1588

Methods

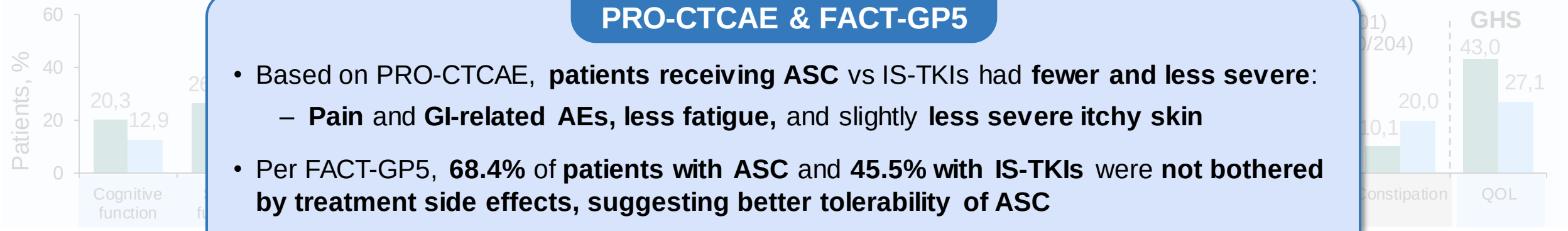
- ≥1 PRO assessment: ASC (n=194), IS-TKIs (n=195)
- Completion rates in pts (with PRO assessments at baseline and ≥1 post baseline) receiving ASC vs IS-TKI were balanced for QLQ-C30 and QLQ-CML24

EORTC QLQ-C30*

- **More patients receiving ASC** vs IS-TKIs had improvements in:
  - **Fatigue, pain, HRQOL, and cognitive and social functioning**
- **Fewer patients receiving ASC** vs IS-TKIs had improvements in:
  - **Financial difficulties and constipation**

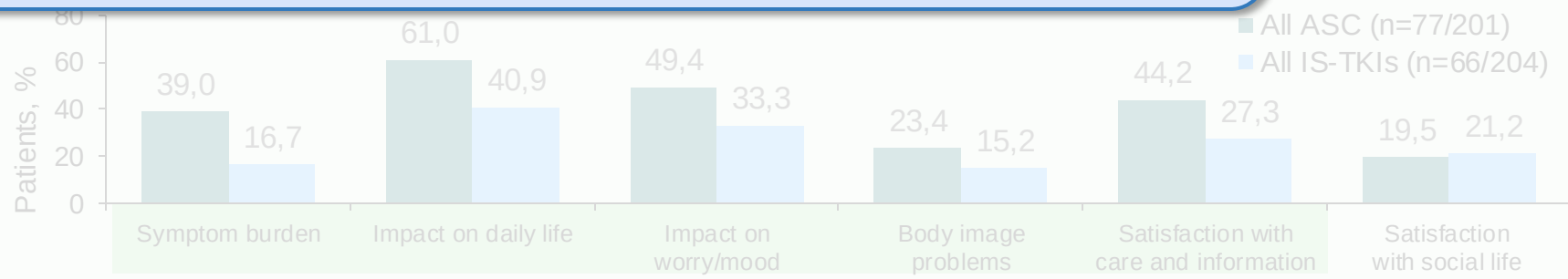
PRO-CTCAE & FACT-GP5

- Based on PRO-CTCAE, **patients receiving ASC** vs IS-TKIs had **fewer and less severe**:
  - **Pain** and **GI-related AEs, less fatigue,** and slightly **less severe itchy skin**
- Per FACT-GP5, **68.4%** of **patients with ASC** and **45.5% with IS-TKIs** were **not bothered by treatment side effects, suggesting better tolerability of ASC**



EORTC QLQ-CML24*

- **More patients receiving ASC** vs IS-TKIs had improvements in:
  - **Symptom burden, impact on daily life, worry/mood, body image, and satisfaction with care and information**



*Improvements[a] in EORTC QLQ-C30 and EORTC QLQ-CML24 scores from baseline to wk 48 in pts with both baseline and wk 48 assessments in ASC4FIRST. a Improvements were defined as an increase in functional scales and GHS/QOL and decrease for symptom scales.
AE=Adverse Event. ASC=Asciminib. EORTC=European Organization for Research and Treatment of Cancer. GHS=Global Health Status. GI=Gastrointestinal.
IS-TKI=Investigator-Selected Tyrosine Kinase Inhibitor. PRO=Patient Reported Outcomes. QLQ-C30=Quality of Life Questionnaire.
Hochhaus et al, Poster #PS1588. 2025 EHA Congress. June 12–15, 2025, Milan, Italy.

ASC4START: Phase 3b – Study Schema

Presented at ASCO/EHA 2025:
Prof. Andreas Hochhaus
ASCO #6501, EHA #S166

ASC4START (N=568)

Inclusion:
- Newly diagnosed Ph+ CML-CP within 3 months of diagnosis
- No prior TKIs
- ≥18 years of age

R 1:1

Asciminib 80 mg QD (n=284)

Nilotinib 300 mg BID (n=284)*

Methods
- Recruited from 120 participating sites across 24 countries
- 2 patients who did not receive nilotinib were excluded from safety analysis.

Stratification
- ELTS risk category

Primary endpoint:
- TTDAE (AEs leading to treatment discontinuation and deaths due to AE)

Secondary endpoints:
- Molecular response
- Safety

AE=Adverse Event. BID=Twice A Day. CP-CML=Chronic Phase CML. ELTS=EUTOS Long-Term Survival Score. ND=Newly Diagnosed. QD=Daily. TTDAE=Time to Treatment Discontinuation Due to Adverse Events.

1. Clinicaltrials.gov. NCT05456191. Available at: https://clinicaltrials.gov/study/NCT05456191. 2. Hochhaus et al, Abstract 6501. 2025 ASCO Annual Meeting. May 30 – June 3, 2025.
3. Hochhaus et al, Abstract S166. EHA 2025 Congress. June 12-15, 2025.

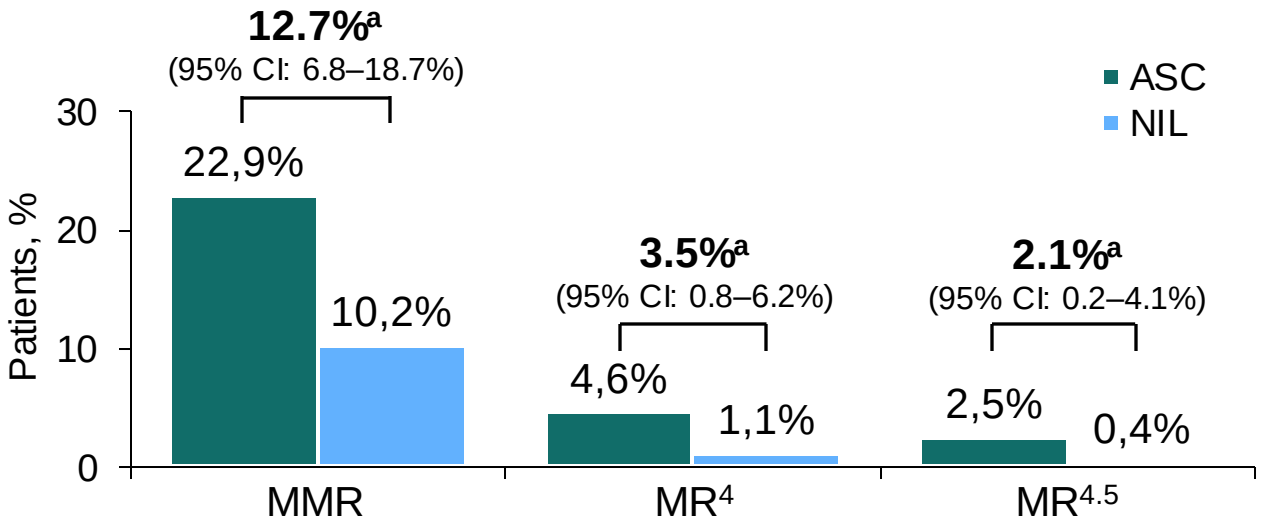
ASC4START: Phase 3b ND CP-CML – Efficacy

2025 ASCO ANNUAL MEETING
EHA2025 30th Congress
Presented at ASCO/EHA 2025:
Prof. Andreas Hochhaus
ASCO #6501, EHA #S166

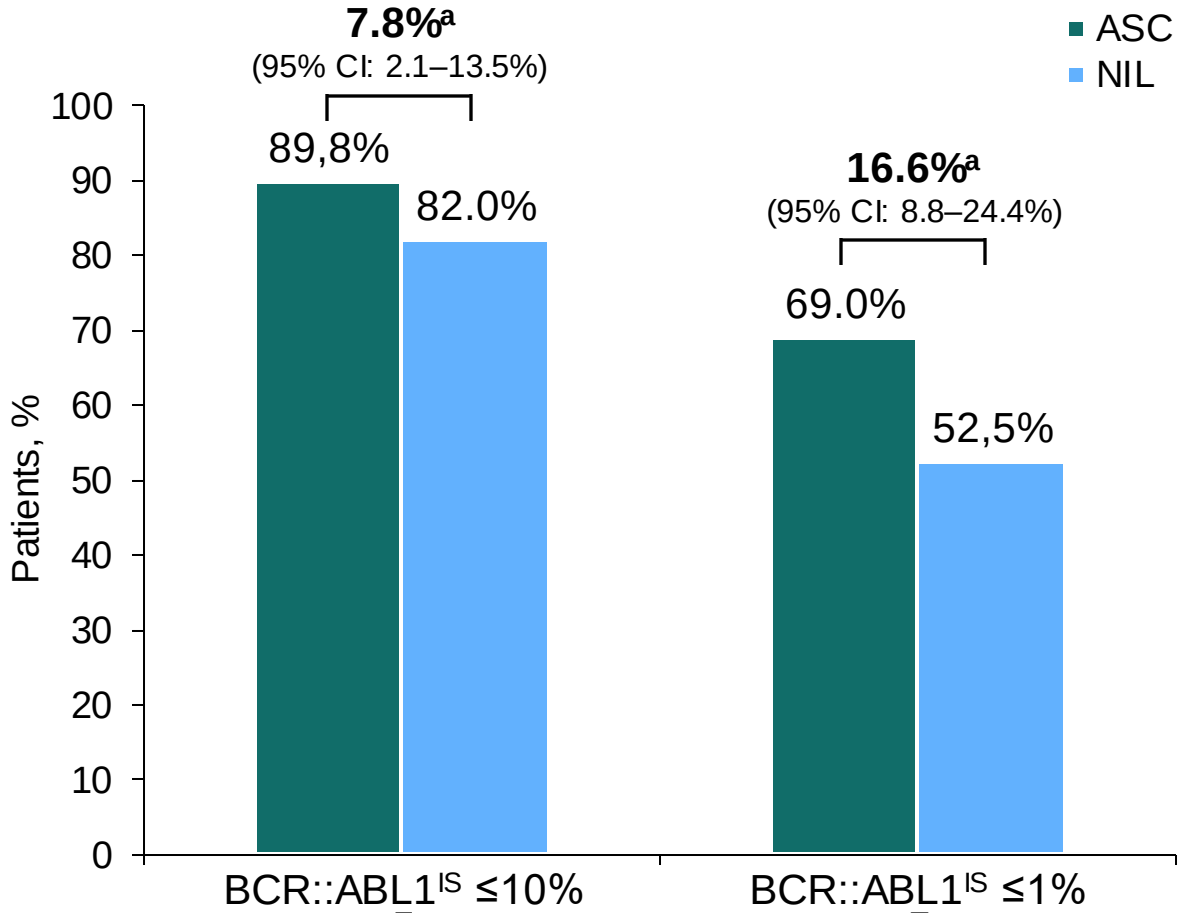
Patient Characteristics

- Data cutoff: Sep 3, 2024
- Median follow-up: 9.7 months

Molecular Response Rates by 12 Weeks



BCR::ABL1^{IS} Response Rates by 12 Weeks



a The common risk difference and its 95% CI were estimated using the Mantel-Haenszel method after adjusting for stratum: ELT scores at baseline.
ASC=Asciminib. CP-CML=Chronic-Phase Chronic Myeloid Leukemia. ND=Newly Diagnosed. NIL=Nilotinib. HR=Hazard Ratio. MMR=Major Molecular Response. MR=Molecular Response. TTDAE=Time to Treatment Discontinuation Due to Adverse Events.

1. Hochhaus et al, Abstract 6501. 2025 ASCO Annual Meeting. May 30 – June 3, 2025.
2. Hochhaus et al, Abstract S166. EHA 2025 Congress. June 12-15, 2025.

ASC4START: Phase 3b ND CP-CML – Safety

Presented at ASCO/EHA 2025:
Prof. Andreas Hochhaus
ASCO #6501, EHA #S166

Safety

- Primary Endpoint: **Statistically significant difference in TTDAE in favor of ASC** –
  Cause-specific HR 0.45 (95% CI: 0.25-0.81; *P*=0.004)
- **Fewer treatment discontinuations due to AEs (including deaths due to AEs):**
  ASC (5.6%) vs NIL (12.1%)
- 3 deaths due to AEs:
  - ASC: cardiac arrest, suicide, n=1 each
  - NIL: cardiac arrest, n=1

Summary

The study met the primary endpoint with asciminib showing significantly superior tolerability vs nilotinib based on TTDAE

Responses, %	Asciminib N=284	Nilotinib N=284
Tx discontinuation at cutoff	**10.9**	**17.3**
Due to AE	4.9	11.6
Unsatisfactory therapeutic effect	2.5	2.8
Median duration of exposure, weeks	39.1	38.0
Mean relative dose intensity	94.8	92.6
Any-grade AE	80.3	86.5
Grade ≥3	25.0	31.9
AEs leading to dose adjustment/interruptions	24.3	30.1
Most frequent any-grade AEs (≥10%)		
Thrombocytopenia	15.1	13.8
Headache	10.2	13.1
Myalgia	10.2	8.2
Rash	8.5	16.3
Increased ALT	3.2	12.4
AEs of special interest		
Arterial occlusive events	0.7	2.1
Acute pancreatitis	0.4	2.5
Hepatotoxicity	8.1	24.8

AE=Adverse Event. ALT=Alanine Aminotransferase. ASC=Asciminib. CP-CML=Chronic-Phase Chronic Myeloid Leukemia. ND=Newly Diagnosed. NIL=Nilotinib. TTDAE=Time to Treatment Discontinuation Due to Adverse Events.

1. Hochhaus et al, Abstract 6501. 2025 ASCO Annual Meeting. May 30 – June 3, 2025.
2. Hochhaus et al, Abstract S166. EHA 2025 Congress. June 12-15, 2025.

Conclusions

- Asciminib, first example of allosteric TKI, is a manageable and effective option in first line.
- The current trials showed higher rates of MR compared to imatinib and 2gen TKIs
- The most common side effects reported are fatigue, myalgia, thrombocytopenia.
- The first QoL study showed improvements in several PROs compared to available TKIs.
- Longer follow-up is needed to determine the impact of the drug as 1st line and its role for TFR.