Optimizing treatment of CML in the first-line setting and beyond: Insights from EHA 2024 and ESH-iCMLf 2024

Prof. Gianantonio Rosti
IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy

Dr Carla Boquimpani
Fundação Saúde, Rio de Janeiro, Brazil

Prof. Dr. med. Susanne Saussele
University of Mannheim, Mannheim, Germany

Recorded following EHA 2024 Hybrid Congress, Madrid, Spain, 13–16 June and ESH-iCMLf 2024, Prague, Czech Republic, 27–29 September

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What do the latest efficacy data for TKIs tell us about the evolving treatment paradigm for patients with CML in the first line?

Prof. Gianantonio Rosti
IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy

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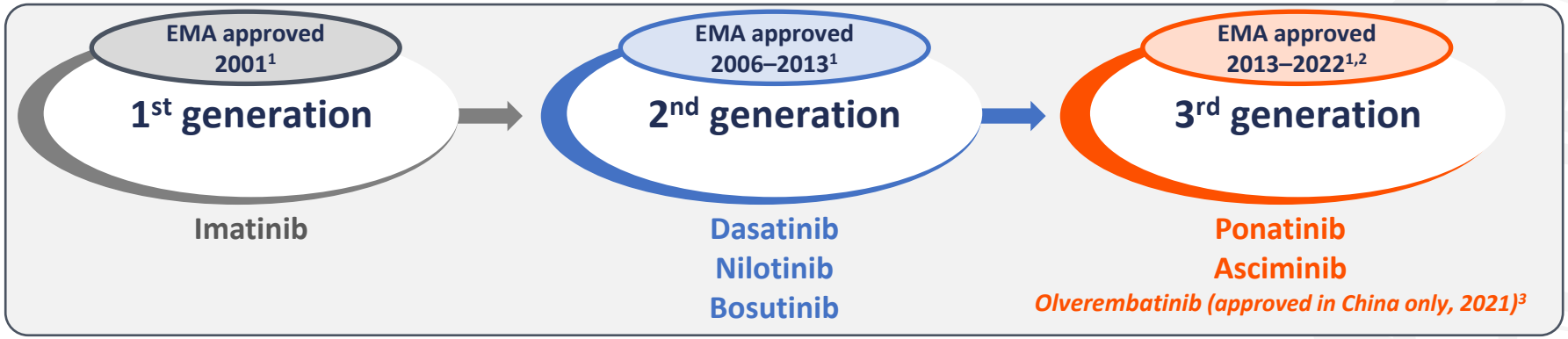
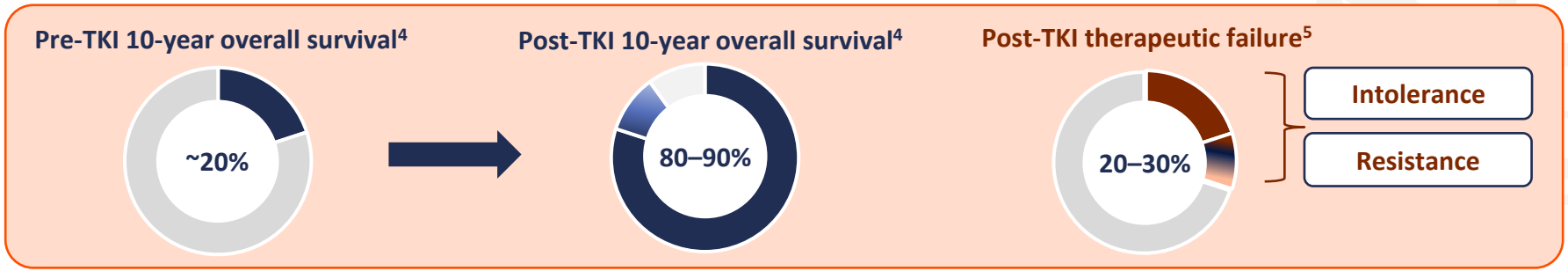
The approval of TKI treatment in CML has changed the fate of many patients with the disease





CML, chronic myeloid leukaemia; EMA, European Medicines Agency; TKI, tyrosine kinase inhibitor.

1. Vener C, et al. *Blood Adv.* 2020;4:2723–35; 2. Tesileanu CMS, et al. *Oncologist.* 2023;28:628–32; 3. Dhillon S. *Drugs.* 2022;82:469–75; 4. Jabbour E, Kantarjian H. *Am J Hematol.* 2020;95:691–709; 5. Yeung DT, et al. *Blood.* 2022;139:3474–9.

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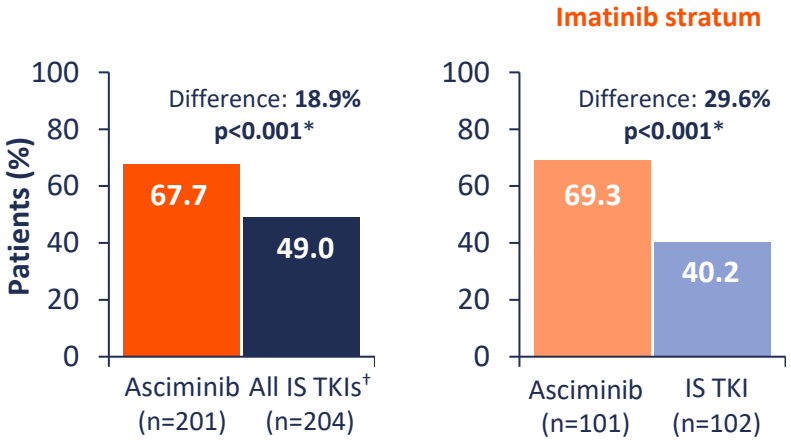
S103: Asciminib provides superior efficacy and excellent safety and tolerability vs TKIs in newly diagnosed CML in the pivotal ASC4FIRST study

Hochhaus A, et al.

Patients with MMR at week 48 (%)



Safety and tolerability

Adverse events, %	Asciminib (n=200)	Imatinib (n=99)	2G TKIs (n=102)
Grade ≥3	38.0	44.4	54.9
Leading to discontinuation	4.5	11.1	9.8
Leading to dose adjustment/ interruption	30.0	39.4	52.9

Asciminib demonstrated superior efficacy vs imatinib and 2G TKIs and acceptable safety and tolerability in patients with newly diagnosed CML

*Estimated using the Mantel-Haenszel method after stratifying for prerandomization-selected TKI and baseline ELTS risk groups (both IRT data). Adjusted 1-sided p value calculated based on the graphical gatekeeping procedure. The null hypothesis is rejected if the adjusted p value is ≤0.025. †All IS-TKIs: Imatinib (n=102) + 2G-TKI (n=102; nilotinib, 48%; dasatinib, 41%; bosutinib, 11%). 2G, second generation; CI, confidence interval; CML, chronic myeloid leukaemia; ELTS, European Treatment and Outcome Study long-term survival score; IRT, interactive response technology; IS, investigator-selected; MMR, major molecular response; TKI, tyrosine kinase inhibitor.

Hochhaus A, et al. Presented at: EHA 2024 Hybrid Congress, Madrid, Spain. 13–16 June 2024. Oral presentation S103.

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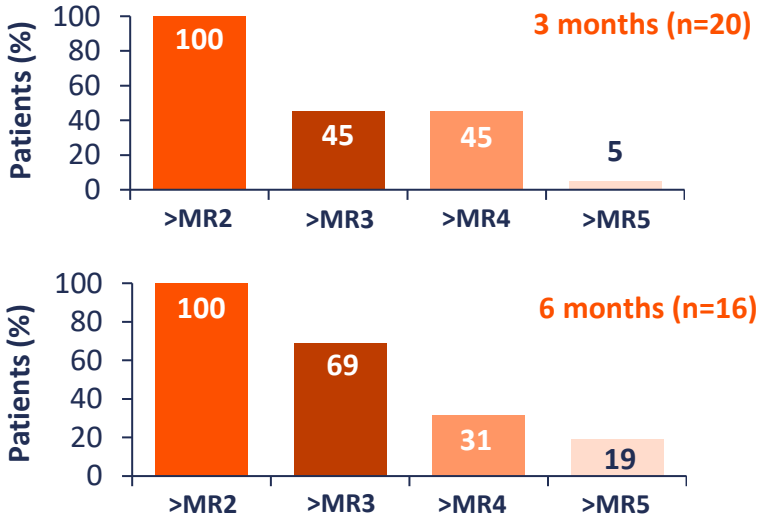
P730: Asciminib as initial therapy with addition of lower dose TKIs for patients with CML who do not achieve a deep molecular remission (ALERTCML)

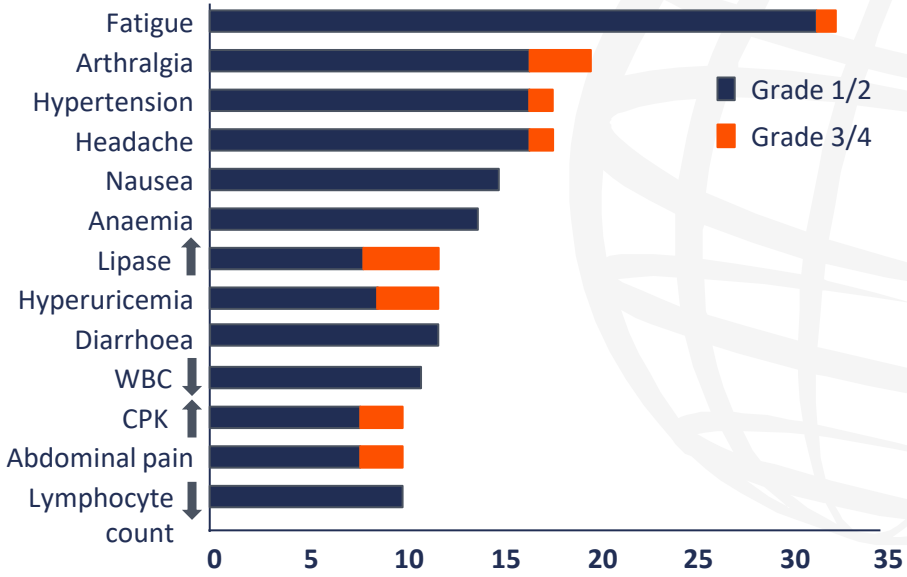
Atallah E, et al.

Patients achieving a molecular response (N=36)*

Median follow-up: 24 weeks



Adverse events occurring ≥10 times

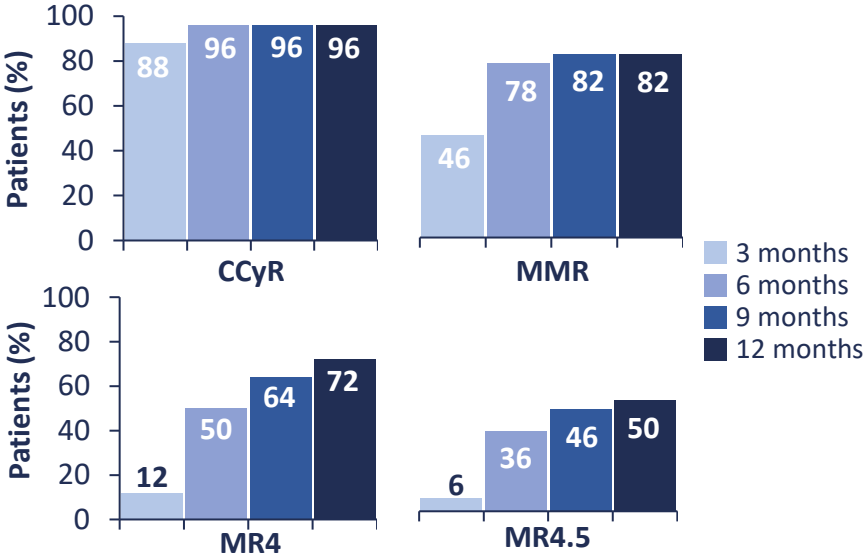


Asciminib as first-line therapy is effective and well tolerated

*MR2, BCR::ABL ≤1%; MR3, BCR::ABL ≤0.1%; MR4, BCR::ABL ≤0.01%; MR5, BCR::ABL ≤0.001%. CML, chronic myeloid leukaemia; CPK, creatine phosphokinase; MR, molecular response; WBC, white blood cell. Atallah E, et al. Presented at: EHA 2024 Hybrid Congress, Madrid, Spain. 13–16 June 2024. Poster presentation P730.

P718: Results of ponatinib as frontline therapy for CML in chronic phase
Haddad F, et al.

Patients achieving a response over time (N=51)
Median time on therapy: 13 months



Safety*

16%

CV SAEs:
Eight, in six patients

16%

Dose reduction due to CV AEs:
Eight patients

10%

Permanent discontinuations due to CV AEs:
Five patients

In newly diagnosed CML-CP, ponatinib was associated with high rates of cytogenetic and molecular responses. However, CV toxicity posed a challenge for its use in the first-line setting

*59% of patients (n=30) had ≥1 CV comorbidity at baseline. AE, adverse event; CCyR, complete cytogenetic response; CML, chronic myeloid leukaemia; CP, chronic phase; CV, cardiovascular; MMR, major molecular response; MR, molecular response; MR4.0, BCR::ABL ≤0.01%; MR4.5, BCR::ABL ≤0.0032%; SAE, serious AE.

Haddad F, et al. Presented at: EHA 2024 Hybrid Congress, Madrid, Spain. 13–16 June 2024. Poster presentation P718.

What do the latest efficacy data for TKIs tell us about the evolving treatment paradigm for patients with CML in the second- and later-line settings?

Prof. Gianantonio Rosti
IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy

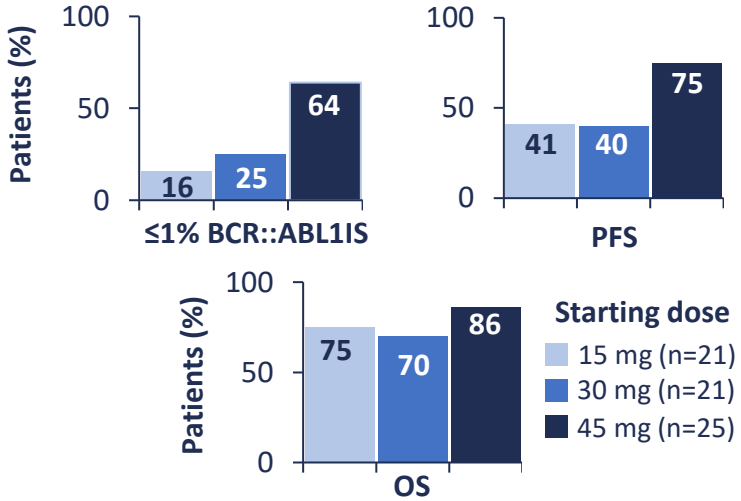
Recorded following EHA 2024 Hybrid Congress, Madrid, Spain, 13–16 June and ESH-iCMLf 2024, Prague, Czech Republic, 27–29 September

S173: Outcomes with ponatinib in patients with chronic-phase chronic myeloid leukemia and the *T315I* mutation: 4-year results from the OPTIC trial

Apperley J, et al.

Efficacy in patients with the *T315I* mutation (N=67)

Median follow-up 60.6–63.5 months[1]



Safety and tolerability, according to starting dose[2]

Adverse events, %	15 mg (n=21)	30 mg (n=21)	45 mg (n=25)
Grade ≥3 TEAE	38	38	60
TEAEs leading to discontinuation	5	14	8
TE-AOE	5	14	8
Exposure-adjusted TE-AOE	2.8	7.3	2.4

Ponatinib demonstrated long-term efficacy and manageable safety. A ponatinib 45 mg starting dose with reduction to 15 mg upon attainment of ≤1% BCR::ABL1IS provided the optimal benefit:risk ratio

IS, International Scale; OS, overall survival; PFS, progression-free survival; TE-AOE, treatment-emergent arterial occlusive events; TEAE, treatment-emergent adverse event.

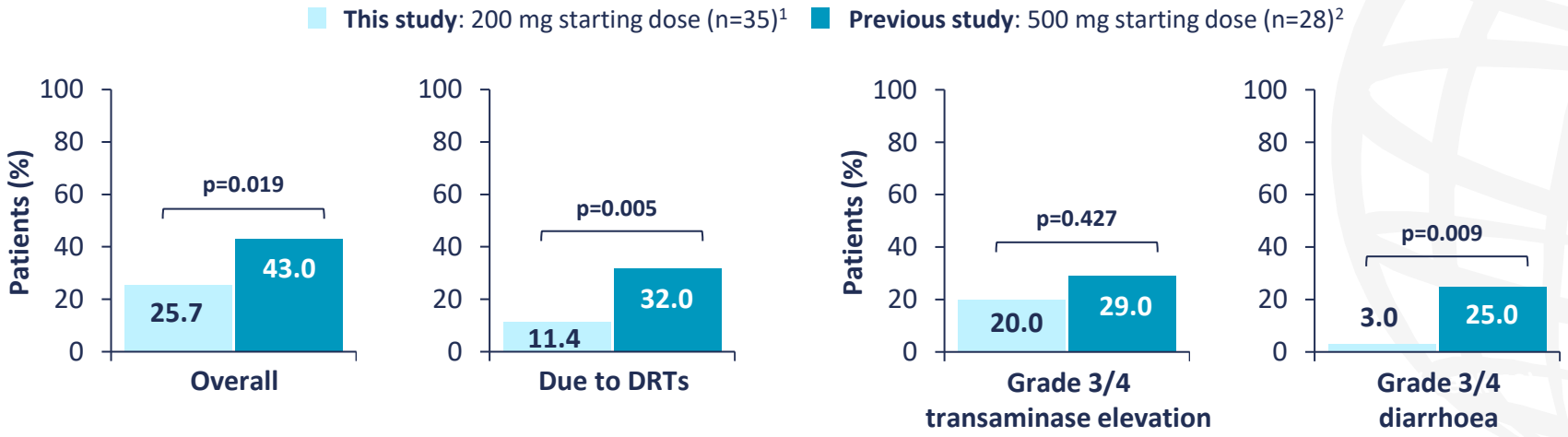
1. Deininger M, et al. *J Clin Oncol.* 2024;42 (Suppl. 16):6501; 2. Apperley J, et al. Presented at: EHA 2024 Hybrid Congress, Madrid, Spain. 13–16 June 2024. Oral presentation S173.

P719: Lower-dose initiating bosutinib is safe and effective for resistant or intolerant to prior therapy CML patients (BOGI trial): A single-arm, multicenter, phase II trial

Kimura S, et al.

Bosutinib discontinuation rate at 12 months

Selected safety data



The lower initiating bosutinib dose reduced the drug discontinuation rate due to severe DRTs, especially diarrhoea, while maintaining clinical efficacy

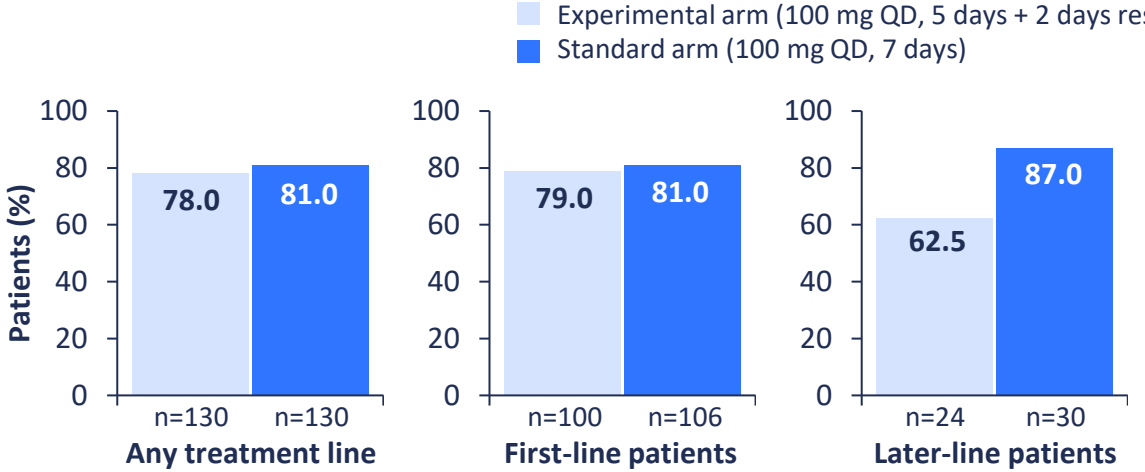
CML, chronic myeloid leukaemia; DRT, drug-related toxicities.

1. Kimura S, et al. Presented at: EHA 2024 Hybrid Congress, Madrid, Spain. 13–16 June 2024. Poster presentation P719; 2. Nakaseko C, et al. *Int J Hematol*. 2015;101:154–64.

S172: Improved tolerability with dasatinib 5 days compared to 7 days per week in patients with CML in chronic phase. Final results of the DasaHIT trial

La Rosée P, et al.

Molecular efficacy (MMR) at 24 months



Safety

Median cTS=2
for both the experimental and standard arms

Pleural- and pericardial effusions occurred **significantly less frequently** in the experimental arm vs the standard arm:
8.0% vs **16.2%** (p=0.0468)

There was a favourable effect of dose modification of dasatinib to reduce pleural/cardiac effusions while maintaining efficacy in patients with CML in the first-line;
patients in the later line seemed to derive more benefit from continuous dosing

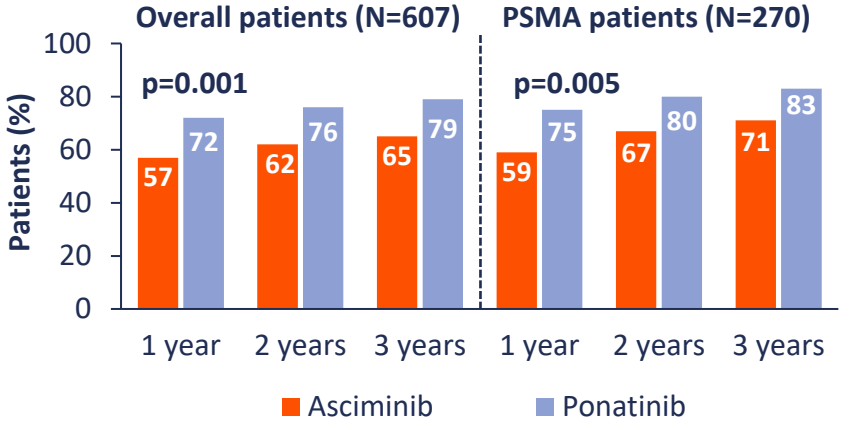
CML, chronic myeloid leukaemia; cTS, cumulative toxicity score; MMR, major molecular response; QD, once daily.

La Rosée P, et al. Presented at: EHA 2024 Hybrid Congress, Madrid, Spain. 13–16 June 2024. Oral presentation S172.

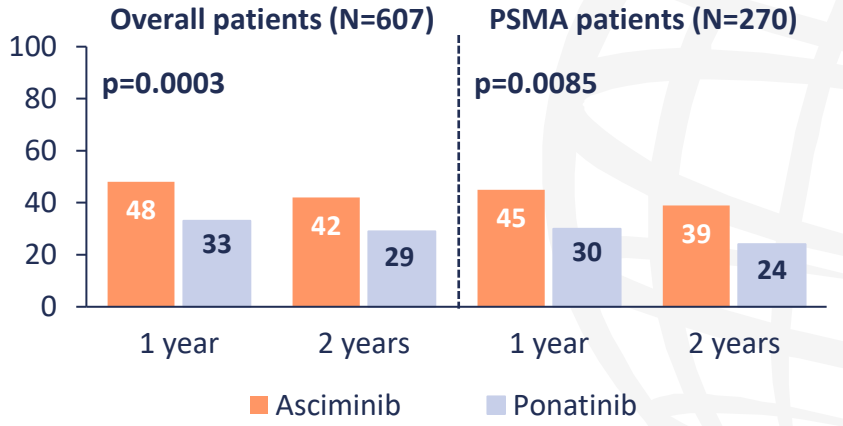
ESH-iCMLf oral presentation: Propensity-score matching analysis comparing treatment outcomes of asciminib with ponatinib in later line treatment for chronic myeloid leukemia patients

Kim D, et al.

Event rate over time



Failure-free survival at 12 months



At 1 year in overall cohort: Improved EFS with asciminib in patients with no T315I mutation (p=0.0002) *but not* in those with T315I-mutated disease (p=0.575)

Asciminib had at least equal efficacy to ponatinib, provided there was no asciminib-resistant ABL1 KD mutation. Asciminib was associated with a superior event-free and failure-free survival rate vs ponatinib overall, and in the PSMA-selected subgroup

KD, kinase domain; PSMA, propensity-score matching analysis.

Kim D, et al. Presented at: ESH-iCMLf 2024, Prague, Czech Republic, 27–29 September. Oral presentation.

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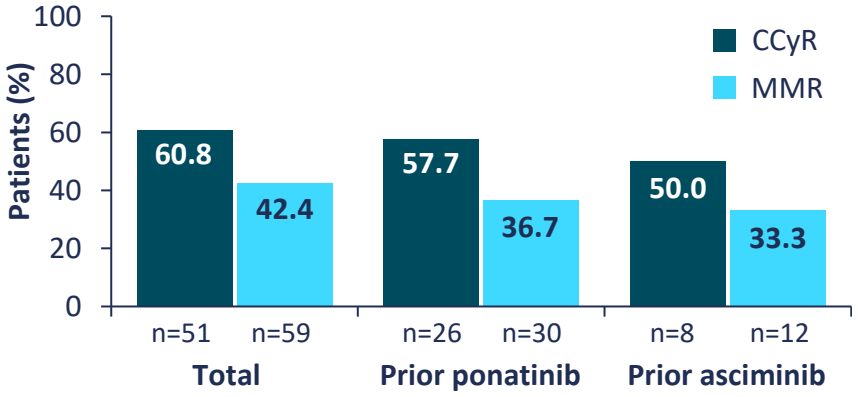
P722: Olverembatinib overcomes ponatinib and asciminib resistance in patients with heavily pretreated CML and Philadelphia+ ALL

Jabbour E, et al.

Response to olverembatinib according to treatment history



Median follow-up: 48.9 weeks

Safety (N=80)

75% TRAEs (mostly grade 1/2 and clinically manageable)

40% Grade 3/4 treatment-related AEs

15% Treatment-related SAEs

Olverembatinib was efficacious and well tolerated at doses up to 50 mg QOD in pts with heavily pretreated CML-CP and advanced leukaemia, including ponatinib- or asciminib-resistant/intolerant disease

AE, adverse event; ALL, acute lymphoblastic leukaemia; CCyR, complete cytogenetic response; CML, chronic myeloid leukaemia; CP, chronic phase; MMR, major molecular response; QOD, every other day; SAE, serious AE; TRAE, treatment-related AE.

Jabbour E, et al. Presented at: EHA 2024 Hybrid Congress, Madrid, Spain. 13–16 June 2024. Poster presentation P722.

How might the emerging data for current and investigational TKIs for CML influence the treatment of patients now and in the future?

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P712: Update of the French Stop Imatinib Study (STIM1) extended long-term follow-up

Mahon F, et al.

Durability of disease remission following imatinib discontinuation (N=100)

Median molecular follow-up after imatinib discontinuation	153 months (range 9–180) → None had CML progression
Confirmed molecular recurrence	62%
Molecular recurrence-free survival at 120 months	37% (95% CI 28–48)
Molecular recurrence-free survival at 156 months	35% (95% CI 26–46)

Overall survival

- 10 years: 97% (95% CI 94–100)
- 20 years: 88% (95% CI 81–96)

Results contribute significantly to understanding treatment-free remission in CML and its long-term survival implications

CI, confidence interval; CML, chronic myeloid leukaemia.

Mahon F, et al. Presented at: EHA 2024 Hybrid Congress, Madrid, Spain. 13–16 June 2024. Poster presentation P712.

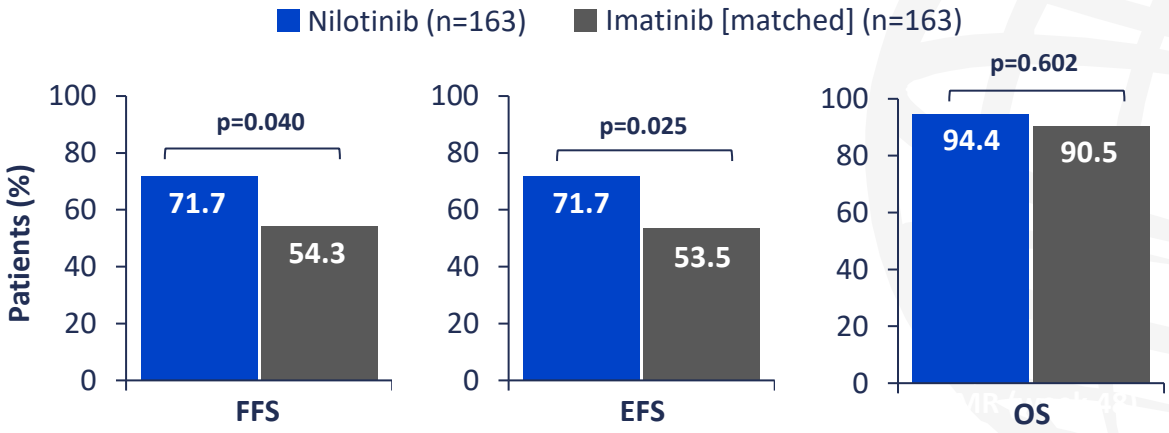
P721: Clinical efficacy of first-line nilotinib or imatinib therapy in patients with CML – nationwide real-life data

Belohlavkova P, et al.

Comparison of TKI efficacy in matched treatment groups

Patients treated with nilotinib achieved CCyR and MMR faster than imatinib-treated matched patients (both p<0.001)

No difference in disease-specific survival between matched groups or all four groups, due to older age and comorbidities in imatinib-unmatched groups



In this real-world analysis with long-term follow-up, first-line nilotinib demonstrated faster achievement of CCyR and MMR, and a higher FFS and EFS, but did not show any benefit for OS. Imatinib is still an effective choice for first-line treatment of CML-CP, especially for older patients with comorbidities

CCyR, complete cytogenetic response; CML, chronic myeloid leukaemia; EFS, event-free survival; FFS, failure-free survival; MMR, major molecular response; OS, overall survival.

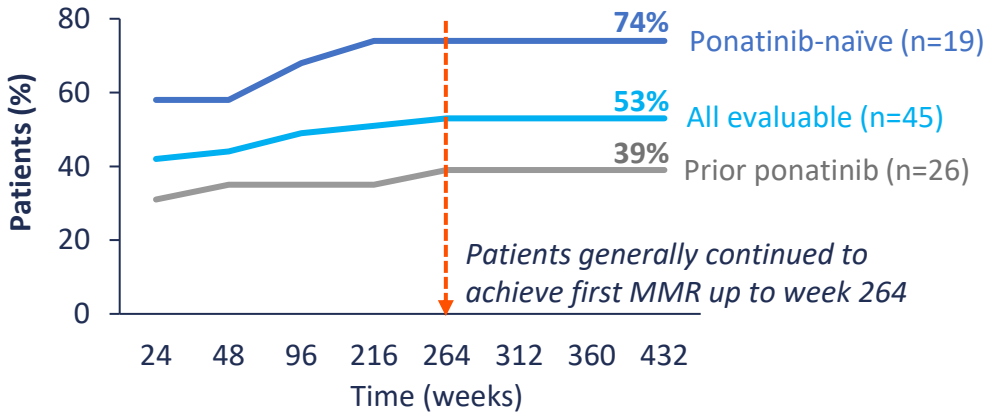
Belohlavkova P, et al. Presented at: EHA 2024 Hybrid Congress, Madrid, Spain. 13–16 June 2024. Poster presentation P721.

ESH-iCMLf oral presentation: Asciminib provides long-term, durable molecular responses and a consistent safety profile in patients with T315I-mutated CML-CP with up to approximately 6 years' exposure: final analysis from a phase 1 trial

Cortes J, et al.

Cumulative MMR over time with asciminib 200 mg BID (n=45)

Median exposure, 3.5 years



Safety*

Adverse events (%)	All patients (N=48)
All grade	100
Grade ≥3	60
Leading to dose adj./ interrupt.	44
Leading to discontinuation	10
Requiring additional therapy	81
Deaths	6
Arterial occlusive events, All/Gr ≥3	12.5†/6.3

This final analysis confirms asciminib as a treatment option in T315I-mutated CML-CP, with potential to provide durable MMR regardless of prior ponatinib treatment status, with sustained efficacy and tolerability

*After 1.4 years' added exposure compared with the previous data cutoff (2.1 years of median exposure), the rate of grade ≥3 AEs (60.4%) did not increase, and no new AEs leading to discontinuation occurred. Rates of AEs of special interest were consistent with the previous analysis. †Most (5 of 6) patients had prior exposure to ≥3 TKIs and all had ≥1 past or active cardiovascular risk factor at baseline. No arterial occlusive events led to dose adjustment/interruption/discontinuation.

Adj./interrupt., adjustment or interruption; AE, adverse event; BID, twice daily; CML-CP, chronic-phase chronic myeloid leukaemia; Gr, grade, MMR, major molecular response.

Cortes J, et al. Presented at: ESH-iCMLf 2024, Prague, Czech Republic, 27–29 September. Oral presentation.

ESH-iCMLf oral presentation: Investigation of resistance mechanisms of the allosteric BCR::ABL1 inhibitor asciminib

Leske IB, et al.

To investigate the structural basis and molecular mechanisms of asciminib-resistant mutations

Hypothesis: The mechanism of action of asciminib-resistant mutations differs with their location on BCR::ABL1

Design:

- Analysis of BCR::ABL1 mutations from asciminib-treated patients
- Structural analysis of four clusters:
    1. Vicinity of myristoyl pocket
    2. KD, ATP-binding pocket
    3. Kinase N-lobe (top)
    4. SH3-domain/SH2-KD-linker
- Pure, homogeneous Abl protein produced in *E. coli* to study asciminib binding/resistance

ATP, adenosine trisphosphate; KD, kinase domain; SH, SRC homology.

Leske IB, et al. Presented at: ESH-iCMLf 2024, Prague, Czech Republic, 27–29 September.

ESH-iCMLf oral presentation: Investigation of resistance mechanisms of the allosteric BCR::ABL1 inhibitor asciminib

Leske IB, et al.

	Mutation (Location)				
	None (Wild-type)	A337T/G463D (myristoyl pocket)	M244V (KD, N-lobe)	F359I (KD, C-lobe/ATP)	Y115N (SH3 domain)
Abl construct	**Binding/K_D (nM)**				
KD only	4.4	151/360	3.0	4.3	--
SH2-KD	3.5	287/101	40.0	14.7	--
SH3-SH2-KD	5.3	178/93	10.8	6.3	6.1

Two mechanisms of asciminib resistance?

Mutations with *strongly decreased* binding affinity: **myristoyl pocket mutations**

Mutations with *unchanged* binding affinity: **outside of myristoyl pocket**, but still confer medium-to-strong resistance in cells

KD, kinase domain; K_D, dissociation constant; SH, SRC homology.

Leske IB, et al. Presented at: ESH-iCMLf 2024, Prague, Czech Republic, 27–29 September. Oral presentation.

ESHi-CMLf oral presentation: Investigation of resistance mechanisms of the allosteric BCR::ABL1 inhibitor asciminib

Leske IB, et al.

Molecular mechanisms of asciminib resistance, by point mutation:	Rational actions for therapeutic decisions, based on the data
A337V/T, G463D: Sterically block asciminib binding	**Switch** to ATP-competitive TKI; myristoyl-pocket mutations are ATP-competitive TKI sensitive
M244V, Y115N: Allosterically shift BCR::ABL1 to its active conformation, that cannot reassemble	**Dose escalation**, or **switch** to ATP-competitive TKI
F359V/I: Induce a more active conformation of KD that is overactive, although assembled	**Dose escalation** or **potential combination** **Do not** switch to nilotinib or imatinib; F359 mutation is resistant to these agents

Asciminib resistance is more diverse than ATP-competitive TKI resistance
The asciminib resistance mechanism is complex, e.g. resistance despite unaltered binding affinity

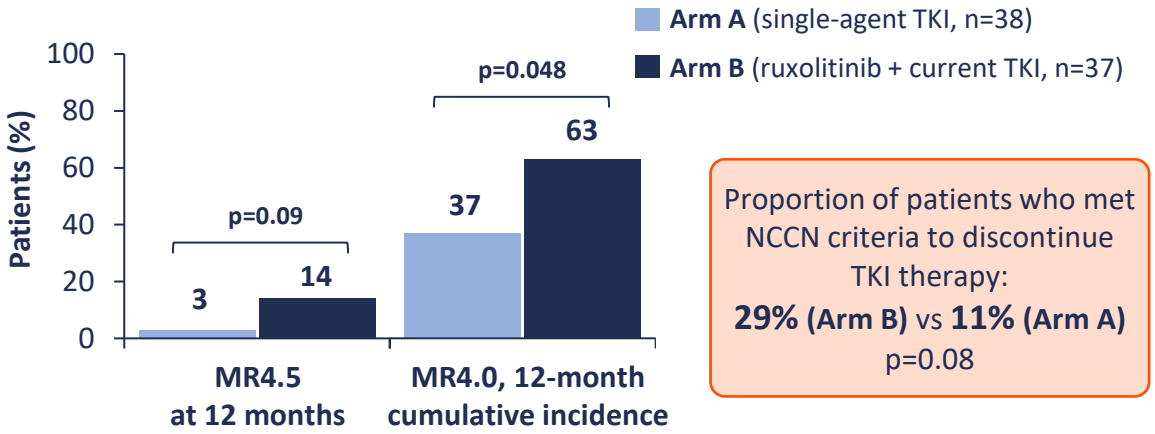
ATP, adenosine trisphosphate; KD, kinase domain; TKI, tyrosine kinase inhibitor.
Leske IB, et al. Presented at: ESH-iCMLf 2024, Prague, Czech Republic, 27–29 September. Oral presentation.

S174: A phase 2, randomized trial of ruxolitinib in addition to BCR::ABL1 TKIs in CML patients with molecular evidence of disease (SWOG TRIAL S1712)

Sweet K, et al.

Molecular response at 12 months (N=75)

Median time on TKI prior to enrolment: 3.2 years



Proportion of patients who met NCCN criteria to discontinue TKI therapy:

29% (Arm B) vs **11% (Arm A)**

p=0.08

Grade 3 related AEs

Arm A, n=2

Arm B, n=3

The combination of ruxolitinib plus TKIs warrants further investigation in a larger study to determine if it could lead to higher treatment-free remission rates

AE, adverse event; CML, chronic myeloid leukaemia; MR, molecular response; MR4.0, BCR::ABL ≤0.01%; MR4.5, BCR::ABL ≤0.0032%; NCCN, National Comprehensive Cancer Network; TKI, tyrosine kinase inhibitor.

Sweet K, et al. Presented at: EHA 2024 Hybrid Congress, Madrid, Spain. 13–16 June 2024. Poster presentation S174.

ESH iCMLf oral presentation: Preliminary safety and efficacy of ELVN-001, a selective active site inhibitor of BCR::ABL1 in CML

Lang F, et al.

TEAEs in phase Ia

Median (range) duration of exposure 20 weeks (0.1–80)

	Preferred term, n (%)	All patients (N=37) Any grade	All patients (N=37) Grade 3/4
Haematologic	Neutropenia†	4 (10.8)	4 (10.8)
	Thrombocytopenia‡	4 (10.8)	2 (5.4)
	Leukopenia§	1 (2.7)	0
	Pancytopenia	1 (2.7)	1 (2.7)
	Anaemia	2 (5.4)	0
Non-haematologic*	Headache	5 (13.5)	0
	Lipase increased	5 (13.5)	0
	Arthralgia	4 (10.8)	0
	Diarrhoea	4 (10.8)	0
	Nausea	4 (10.8)	0

Cumulative MMR¶ in patients without T315I mutation

At 24 weeks

	MMR, % (n/N)
All evaluable patients	44.4 (8/18)
Achieved MMR	23.1 (3/13)
Maintained MMR	100 (5/5)
TKI-resistant	41.7 (5/12)
TKI-intolerant	50 (3/6)
Post-asciminib	40 (4/10)

ELVN-001 had a low incidence of AEs, consistent with a selective kinase profile, with no exposure–toxicity relationship identified to date.
There was early evidence of anti-CML activity, including in those who received prior asciminib

*Non-haematologic TEAEs in ≥10% of patients. †Grouped term for neutropenia includes neutrophil count decreased. ‡Grouped term for thrombocytopenia includes platelet count decreased. §Grouped term for leukopenia includes white blood cell count decreased. ¶Molecular response was assessed by central qPCR measured every 4 weeks x6, then every 12 weeks. MMR is defined as BCR::ABL1 <0.1%. AE, adverse event; CML, chronic myeloid leukaemia, MMR, major molecular response; qPCR, quantitative polymerase chain reaction; TEAE, treatment-emergent AE. Lang F, et al. Presented at: ESH-iCMLf 2024, Prague, Czech Republic, 27–29 September. Oral presentation.