Innovations and advances in CML: A focus on navigating early-line options and maintaining quality of life

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Quality of life and the unmet needs of patients with CML in early-line settings

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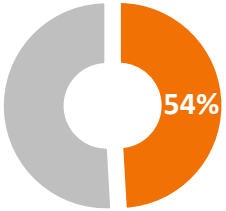
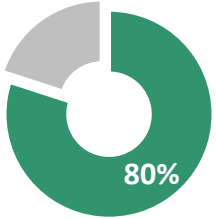
The current treatment landscape for CML-CP

5-year relative survival rate 1994–2000*[1]



0.54 (95% CI 0.50–0.58)

5-year relative survival rate 2001–2008[1]



0.80 (95% CI 0.75–0.83)

Agent Approval (EMA)	Imatinib[2] Nov. 2001	Dasatinib[2] Nov. 2006	Nilotinib[2] Nov. 2007	Bosutinib[2] Mar. 2013†	Ponatinib[2] Jul. 2013	Asciminib[2] Aug. 2022
MoA[3]	Bind to ATP binding site of ABL1 with differences in potency and off-target effect profile[3]					STAMPi[4]
Generation[3]	1st	2nd			3rd	1st
Indication[2]	1L	1L/≥2L‡			≥2L§/*T315I*	≥3L

CHMP positive opinion (17 October 2025) for the treatment of adult patients with Ph+ CML-CP[2]

*Survival rates in this period reflect use of allogeneic SCTs, the introduction of IFN-α and better supportive care.[1] †Conditional. Bosutinib received full marketing authorization in April 2022.[2] ‡The 2G TKIs are also approved for use following resistance or intolerance to prior therapy, including to imatinib. §Resistant/intolerant to dasatinib or nilotinib for whom subsequent treatment with imatinib is not clinically appropriate.

ATP, adenosine triphosphate; CHMP, Committee for Medicinal Products for Human Use; CI, confidence interval; CML-CP, chronic myeloid leukaemia-chronic phase; EMA, European Medicines Agency; IFN, interferon; L, line; MoA, mechanism of action; Ph+, Philadelphia chromosome-positive; SCT, stem cell transplant; STAMPi, Specifically Targeting the ABL Myristoyl Pocket inhibitor; TKI, tyrosine kinase inhibitor.

1. Björkholm M, et al. *J Clin Oncol*. 2011;29:2514–20; 2. All information about approval dates, indications and CHMP is available at: www.ema.europa.eu/ according to the product name (accessed 20 November 2025); 3. Lee H, et al. *Int J Hematol*. 2021;113:632–41; 4. Cortes J, Lang F. *J Hematol Oncol*. 2021;14:44.

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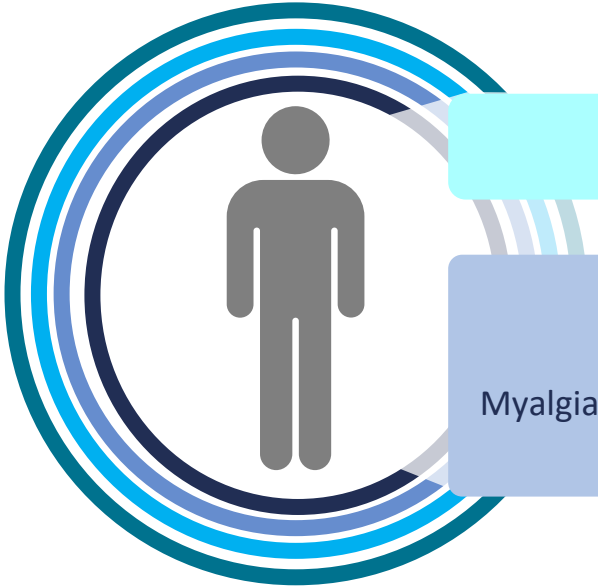
Key low-grade TKI-related side effects



Fatigue

Rash, peripheral oedema

Pain

Headache

Myalgia/muscle cramp/arthralgia

Bone pain

Gastrointestinal

Diarrhoea

Nausea

Vomiting

Grade 2 side effects can negatively affect QoL leading to a decrease in compliance; this is a major cause of treatment failure

QoL, quality of life; TKI, tyrosine kinase inhibitor.
Apperley JF. *Lancet*. 2015;385:1447–59.

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Selected serious off-target TKI-related side effects*

	Imatinib[1]	Nilotinib[2]	Dasatinib[3]	Bosutinib[4]	Ponatinib[5]	Asciminib[6]
Pancreatitis						
Pleural effusion						
PAH/PH	†	†		†	†	–
↑Hepatic enzymes			–			
AOE	–		–	–	‡	–

Patients (%)
- – Absent
- ≥0.01–<0.1%
- ≥0.1–<1%
- ≥1–<10%
- ≥10%

Although many AEs occur mostly during the first few weeks or months of therapy and frequently improve over time, some AEs (notably pleural effusions and AOEs) may appear for the first time after many years of therapy[7]

*Comparison of AEs (all grade and grade 3/4) across studies are hampered by the different study designs, eligibility criteria/patient populations and inconsistencies in the AEs reported.[7] †PAH not reported. ‡Dose-related.[5]
AE, adverse event; AOE, arterial occlusive events; PAH, pulmonary arterial hypertension, PH, pulmonary hypertension; TKI, tyrosine kinase inhibitor.
1. EMA. Imatinib SmPC; 2. EMA. Nilotinib SmPC; 3. EMA. Dasatinib SmPC; 4. EMA. Bosutinib SmPC; 5. EMA. Ponatinib SmPC; 6. EMA. Asciminib SmPC; All available at: www.ema.europa.eu/ according to the product name (accessed 20 November 2025); 7. Lipton JH, et al. *Blood Rev*. 2022;56:100968.

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Recent clinical data on TKIs in CML and their impact on quality of life

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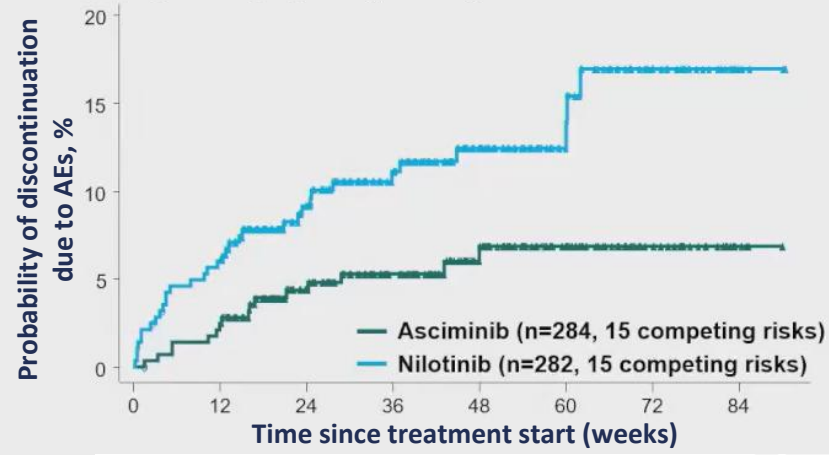
Improving TKI tolerability in the first-line setting

ASC4START (NCT05456191), phase IIIb
asciminib vs nilotinib in the first line (N=568): interim analysis (median follow-up: 9.7 months)[1]

The primary endpoint was met showing a statistically significant difference in TTDAE in favour of asciminib;
TTDAE was defined as time from first dose of study treatment to discontinuation due to AEs (including death due to AE)

Events of interest (discontinuations or deaths due to AEs)			
	Events n/N (%)	**HR (95% CI)**	**P value**
Asciminib	16/284 (6)	0.45 (0.25–0.81)	0.004
Nilotinib	34/282 (12)		

The primary analysis supported the interim data in showing a tolerability benefit for asciminib vs nilotinib[2]
HR (95% CI): 0.46 (0.27–0.76), p=0.001



Preliminary PRO data from ASC4FIRST for three PROMs also favour asciminib vs IS-TKI, indicating better QoL and reduced symptom burden[3]

Figure from Hochhaus A, et al. ASCO 2025, reproduced with permission.
AE, adverse event; CI, confidence interval; HR, hazard ratio; IS-TKI, investigator-selected TKI; MMR, major molecular response; PRO, patient-reported outcome; PROM, PRO measure; QoL, quality of life; TKI, tyrosine kinase inhibitor; TTDAE, time to treatment discontinuation due to AEs.
1. Hochhaus A, et al. Presented at: The American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago, IL, USA, 30 May–3 June 2025. #6501; 2. Mahon F-X, et al. Presented at: The 27th Annual John Goldman Conference on CML in Estoril, Portugal, 10–12 October 2025; 3. Hochhaus A, et al. Presented at: EHA 2025, Milan, Italy. 12–15 June 2025. #PS1588.

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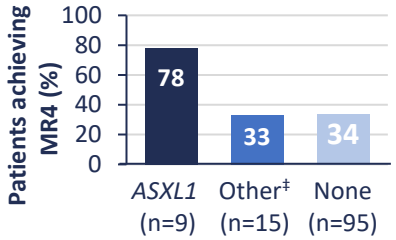
Novel strategies for managing resistance/intolerance

Combination therapy

FASCINATION (NCT03906292)
phase II, 1L[1,2]

- Asciminib in combination with 1G or 2G TKI*
- **Primary endpoint** (MR4† at 12 months): 38%
- Primary endpoint correlated with mutation status

MR4 according to mutation profile



Selected emerging agents

ELVN-001 (ENABLE, NCT05304377) phase I, ≥2L[3,4]

- Highly selective, active-site TKI of *BCR::ABL1* with broad pre-clinical activity against native and mutant *BCR::ABL1*, including the *T315I* mutation[5]

Olverembatinib (ChiCTR2200061655), phase II, 2L[6]

- Targets *BCR::ABL1* and a spectrum of *BCR::ABL1* mutations including *T315I*[7]

TERN-701 (CARDINAL NCT06163430) phase I, ≥2L[8]

- Potent selective allosteric TKI, specifically targeting the ABL1 myristoyl pocket, with activity against the *T315I* mutation
- Preliminary PK data support QD dosing without regard to food intake

*Imatinib, nilotinib or dasatinib. †*BCR::ABL1*IS transcripts ≤0.01% on the International Scale. ‡The other mutations were: *ATRX*, *BCOR*, *BCORL1*, *CBLB*, *CEBPA*, *CUX1*, *DNMT3A*, *ETV6*, *IKZF1*, *KDM6A*, *RAD21*, *STAG2*, *TET2* and *ZRSR2*.
AE, adverse event; G, generation; L, line; MR4, molecular response 4; PK, pharmacokinetic; QD, once daily; TEAE, treatment-emergent AE; TKI, tyrosine kinase inhibitor.

1. Ernst T, et al. *HemaSphere*. 2023;7(Suppl. 3):131; 2. Ernst T, et al. *Blood*. 2024;144(Suppl. 1):1774–5; 3. Lang F, et al. Presented at: The 27th Annual John Goldman Conference on CML in Estoril, Portugal, 10–12 October 2025; 4. ClinicalTrials.gov. NCT05304377. Available at: http://bit.ly/4o6SeTW (accessed 20 November 2025);
5. Mauro M, et al. *Clin Lymphoma Myeloma Leuk*. 2025;25(Suppl. 1):S568; 6. Li W, et al. Presented at: The 27th Annual John Goldman Conference on CML in Estoril, Portugal, 10–12 October 2025; 7. Kantarjian H, et al. *Cancer*. 2025;131:e35832; 8. Jabbour E, et al. *Blood*. 2024;144:6594–5.

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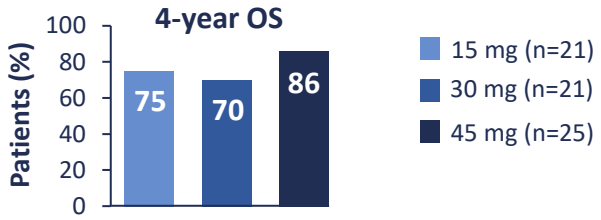
Dosing strategies to optimize TKI outcomes/QoL

OPTIC (NCT02467270), phase II, patients (≥3L) with the *T315I* mutation[1]



A ponatinib 45 mg starting dose with reduction to 15 mg upon attainment of ≤1% *BCR::ABL1*IS provided the optimal benefit:risk ratio

Studies investigating dosing strategies with dasatinib

Dose reduction (NCT02689440): 50 mg QD[2]

- Follow-up 24 months: no patient transformed to AP or BP
- 2-year event-free and overall survival rates: 100%
- 6% of patients developed pleural effusion, with 80% requiring a dose reduction

DasaHIT (NCT02890784): 100 mg QD vs 100 mg QD for 5 days + 2 days' holiday[3]

- Reduced pleural/cardiac effusions, while maintaining efficacy in patients with CML in the first line

HALF (NCT04147533), phase II, N=207[4,5]

Efficacy and safety of TKI discontinuation following a two-step reduction in dosing (median follow-up: 35.9 months)*

- MMR was maintained in >60% of patients
- TKI withdrawal syndrome was observed in 12% of patients; most patients experienced musculoskeletal pain

ASC4OPT (NCT0494833), phase III, N=165[6]

Efficacy and safety of asciminib 80 mg QD vs 40 mg BID

- Regardless of dosing schedule
  - Patients maintained MMR at week 96
  - Low rates of AEs were observed

*Half of the standard during the first 6 months, followed by the same dose given alternatively (every other day) during the next 6 months.

AE, adverse event; AP, advanced phase; BID, twice a day; BP, blast phase; CML, chronic myeloid leukaemia; IS, international scale; MMR, major molecular response; OS, overall survival; QD, every day; QoL, quality of life; TKI, tyrosine kinase inhibitor.

1. Deininger M, et al. *J Clin Oncol*. 2024;42(Suppl. 16):6501; 2. Naqvi K, et al. *Cancer*. 2020;26:67–75; 3. La Rosée P, et al. *HemaSphere*. 2024;8(Suppl. 1):172; 4. ClinicalTrials.gov. NCT04147533. Available at: http://bit.ly/49sCwhl (accessed 20 November 2025); 5. Žáčková D, et al. Presented at: The 27th Annual John Goldman Conference on CML in Estoril, Portugal, 10–12 October 2025; 6. Boquimpani CM, et al. Presented at: The 27th Annual John Goldman Conference on CML in Estoril, Portugal, 10–12 October 2025.

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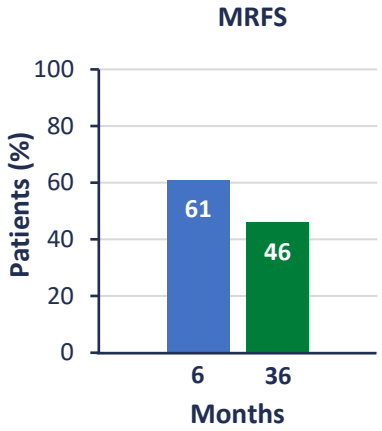
Understanding factors influencing TFR

EURO-SKI (NCT01596114), open label, N=728[1,2]

Persistence of molecular remission in patients with CML after stopping TKI treatment



Prognostic factors for MMR maintenance over 36 months

- Duration of TKI treatment
- Duration of on-treatment DMR
- PB blast cells at diagnosis
- Transcript type
  - e14a2 (+e13a2) had a higher probability of MMR over 36 months vs e13a2 alone

CML, chronic myeloid leukaemia; DMR, deep molecular response; MMR, major molecular response; MRFS, molecular recurrence-free survival; PB, peripheral blood; TFR, treatment-free remission; TKI, tyrosine kinase inhibitor.

1. ClinicalTrials.gov. NCT01596114. Available at: http://bit.ly/4quBhEA (accessed 20 November 2025); 2. Mahon F-X, et al. *J Clin Oncol*. 2024;42:1875–80.

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Approaches for working with patients with CML to optimize their quality of life and treatment outcomes

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Perspectives on treatment and quality of life in CML

Patient perspective

Treatment goal

- First line: stop/slow disease progression
- Switching therapy:
  normal life expectancy, tolerability and maintaining or improving QoL

Unmet needs

- Information on treatment options, side-effect management and strategies for treatment transitions
- Involvement in treatment decision-making

Clinician perspective

Treatment goal

- First line: achieving MMR/DMR
  - More important than impact of side effects on patient QoL
- Switching therapy: long-term survival and manageable side effects

Addressing information needs

- Provide patients with required information on treatment options and side-effect management

The nuances of patient–physician communication and treatment satisfaction are often overlooked, despite playing a fundamental role in adherence, QoL and long-term treatment success

CML, chronic myeloid leukaemia; DMR, deep molecular response; MMR, major molecular response; QoL, quality of life; SDM, shared decision-making.
Lang F, et al. *Haematologica*. 2025:doi:10.3324/haematol.2025.287772.

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