Selecting the optimal treatment for patients with chronic myeloid leukaemia after two prior lines of therapy

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Agenda

How can we best use the current treatment options to optimize outcomes for patients with CML after two prior lines of therapy?

What are the new and emerging therapies for the treatment of patients with CML after two prior lines of therapy and what are the latest clinical trial data?

How could new and emerging treatments impact the management of CML after two prior lines of therapy?

CML, chronic myeloid leukeamia.

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How can we best use the current treatment options to optimize outcomes for patients with chronic myeloid leukaemia after two prior lines of therapy?

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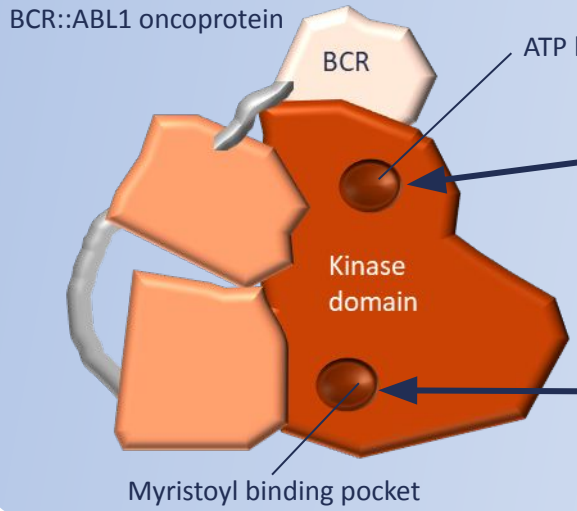
Current TKI treatment options approved in CML

- First-generation: imatinib[1]
- **Second-generation: nilotinib, dasatinib** and **bosutinib**[1]
- Third-generation: ponatinib[2]
- **Inhibitors specifically targeting the ABL myristoyl pocket (STAMP): asciminib**[3]

TKI mechanisms of action[4]



Imatinib, nilotinib, dasatinib, bosutinib and ponatinib inhibit BCR::ABL1 activity by competitively binding to its ATP binding site.

Asciminib specifically targets the ABL myristoyl pocket. It binds to the myristoyl binding pocket and restores the allosteric inhibition of BCR::ABL1 kinase activity.

ABL, Abelson tyrosine kinase; ATP, adenosine triphosphate; BCR, breakpoint cluster region; CML, chronic myeloid leukaemia; TKI, tyrosine kinase inhibitor.

1. Jabbour E, Kantarjian H. *Am J Hematol*. 2020;95:691–709; 2. EMA. Ponatinib SmPC. Available at: www.medicines.org.uk/emc/product/1212 (accessed 22 September 2022);
3. EMA. Asciminib SmPC. Available at: www.medicines.org.uk/emc/product/13817 (accessed 22 September 2022); 4. Réa D, Hughes TP. *Crit Rev Oncol Hematol.* 2022;171:103580.

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Challenges of CML treatment after two prior lines of therapy

- Increasing probability of failure with each line and decreased overall survival[1]
- Comorbidities and adverse-event accumulation limit the availability of appropriate TKIs[2]
- Absence of well-defined guidelines[1]
- Increased risk of resistant mutation acquisition[3]

CML, chronic myeloid leukaemia; TKI, tyrosine kinase inhibitor.

1. Cortes J, Long F. *J Hematol Oncol.* 2021;14:44; 2. Cortes J. *Blood*. 2020;136:2507–12; 3. Soverini S, et al. *Blood*. 2009;114:2168–71.

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Question 1

What is the best treatment sequence for patients with CML? Could you summarize the current recommendations from the guidelines?

Question 2

What factors can help guide treatment selection after two prior lines of therapy?

Question 3

What are the mechanisms of resistance to therapies in the second line and beyond? What molecular characteristics or biomarkers can help us recognize treatment failure?

What are the new and emerging therapies for the treatment of patients with chronic myeloid leukaemia after two prior lines of therapy and what are the latest clinical trial data?

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TKI efficacy after two previous lines of therapy

- Results from a study evaluating the comparative efficacy of ponatinib and second-generation TKIs after failure of at least one previous second-generation TKI in patients with CP-CML

Synthesized treatment-specific probabilities of CCyR after two previous lines of therapy

Treatment*	Probability of CCyR (95% CI)
All studies, all patients	
Bosutinib	0.22 (0.15–0.29)
Dasatinib	0.24 (0.09–0.45)
Nilotinib	0.26 (0.21–0.32)
Bafetinib, bosutinib, dasatinib or nilotinib	0.24 (0.10–0.41)
Dasatinib or nilotinib	0.25 (0.18–0.32)
Ponatinib	**0.60 (0.52–0.68)**

- Compared with second-generation TKIs, ponatinib has superior efficacy

*Studies using the same treatment/choice of treatments were pooled, and all CP patients were included regardless of T315I status.
CCyR, complete cytogenetic response; CI, confidence interval; CML, chronic myeloid leukaemia; CP, chronic phase; TKI, tyrosine kinase inhibitor.
Lipton JH, et al. *Leuk Res.* 2015;39:58–64.

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Third-generation TKI: Ponatinib

Results from PACE and OPTIC

PACE: phase II trial evaluating efficacy and safety of ponatinib in adult patients with CML or Ph+ ALL who were resistant/intolerant to dasatinib or nilotinib, or with the BCR::ABL1^{T315I} mutation regardless of prior TKI use (N=449)[1]

Ponatinib efficacy in CP-CML (n=267)*[1]	n (%)
MMR	108 (40)

Cumulative and exposure-adjusted incidences of TEAOEs[1]	CP-CML (n=270)	
	AE	SAE
AOEs, n (%)	84 (31)†	69 (26)‡
Exposure-adjusted AOEs, no. of patients with events per 100 patient-years	14.1	10.9

OPTIC: randomized phase II trial with a novel response-based dosing regimen of ponatinib in patients with CP-CML resistant/intolerant to ≥2 TKIs or with BCR::ABL1^{T315I} mutation (N=283)[2]

OPTIC primary analysis demonstrates the optimal ponatinib benefit-risk profile is a 45 mg/day starting dose reduced to 15 mg/day upon achieving ≤1% BCR::ABL1^{IS} [2]

45 mg/day starting dose reduced to 15 mg/day cohort[2]	CP-CML (n=94)	
	AE	SAE
AOEs, %	10	4

*3 patients were not evaluable for efficacy as they did not have T315I confirmed at baseline; †46 patients had >1 AOE; ‡31 patients had >1 serious AOE.
AE, adverse event; AOE, arterial occlusive event; BCR::ABL, breakpoint cluster region–Abelson; CP-CML, chronic phase chronic myeloid leukaemia; MMR, major molecular response; Ph+ ALL, Philadelphia chromosome–positive acute lymphoblastic leukaemia; SAE, serious AE; TEAOE, treatment-emergent AOE; TKI, tyrosine kinase inhibitor.

1. Cortes J, et al. *Blood*. 2018;132:393–404; 2. Cortes J*, et al. J Clin Oncol.* 2021;39(Suppl.):7000.

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STAMP inhibitor: Asciminib

Results from ASCEMBL (96-week update)

A phase III study of asciminib vs bosutinib in patients with CP-CML at 96 weeks (secondary objective)

233 patients randomized 2:1 to asciminib or bosutinib

- Intolerance or lack of efficacy to ≥2 prior TKIs
- 40 mg asciminib BID
- 500 mg bosutinib QD

After 96 weeks, 53.5% (n=84) of patients on asciminib continued treatment, compared with 19.7% (n=15) of patients continuing bosutinib

Discontinued due to lack of efficacy
Asciminib: 24.2%
Bosutinib: 35.5%

Week 96 efficacy %	Asciminib (n=157)	Bosutinib (n=76)	Between group treatment difference* % (95% CI)
MMR (cumulative incidence)	37.6 (41.2)	15.8 (22.6)	21.7 (10.5–33.0) p=0.001
BCR::ABL1^{IS} ≤1% (cumulative incidence)	45.1 (53.7)	19.4 (33.7)	26.0 (13.5–38.6) p<0.001

Week 96 AEs, %	Asciminib (n=156†)		Bosutinib (n=76)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any	91.0	56.4	97.4	68.4
Leading to discontinuation	7.7	7.7	26.3	19.7
Leading to dose adjustment or interruption	42.3	36.5	64.5	51.3

*Treatment difference after adjusting for baseline MCyR status; †1 patient on asciminib developed cytopenia after randomization and was not treated per investigator's decision.
AE, adverse event; BCR::ABL, breakpoint cluster region–Abelson; BID, twice daily; CI, confidence interval; CML, chronic myeloid leukaemia; MMR, major molecular response; QD, once daily; TKI, tyrosine kinase inhibitor.

Rea D, et al. EHA Hybrid Conference, Vienna. 9–17 June 2022. Abstr S155 Oral presentation 4005.

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TKI treatment options in development in CML

TKI	Study/treatment	MMR	CCyR
Third-generation TKIs: *In patients treated with prior TKIs or with the T315I mutation*			
HQP1351 (Olverembatinib)	Single-arm phase II trial[1,2]	Median follow-up 13 months After ≥12 treatment cycles: **56%**	**68%** (in pts without CCyR at baseline)
Other TKIs in early clinical development*: In patients treated with prior TKIs or with the T315I mutation*			
PF-114 (targets T315I)	Phase I study*[3]	**16%**	**22%**
K0706 (vodobatinib, BCR::ABL1 TKI)	Phase I study[4]	Ponatinib-treated†: **27%** Ponatinib-naive†: **40%**	Ponatinib-treated†: **18%** Ponatinib-naive†: **30%**

*Includes a small number of patients with acute phase CML in the study population;†Patients continuing on treatment.
BCR::ABL, breakpoint cluster region–Abelson; CCyR, complete cytogenetic response; CML, chronic myeloid leukaemia; MMR, major molecular response; TKI, tyrosine kinase inhibitor.

1. Qian J, et al. *Blood.* 2020;136(Suppl. 1):50–1; 2. Qian J, et al. *Blood.* 2021;138(Suppl. 1):3598; 3. Turkina AG, et al. *Blood*. 2021;138(Suppl. 1):1482; 4. Cortes JE, et al. *Blood.* 2020;136(Suppl. 1):51–2.

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Question 1

What are the unmet needs for patients with CML after two prior lines of therapy?

Question 2

What are the newly approved treatments, and how will these address unmet needs? Are there any other agents currently in development?

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Question 3

Have new and emerging therapies shown a greater duration/depth of response? And how do the safety profiles of new and emerging therapies compare with previously available tyrosine kinase inhibitors?

How could new and emerging treatments impact the management of chronic myeloid leukaemia after two prior lines of therapy?

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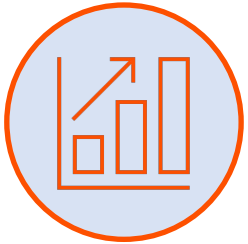
Management of CML after two prior lines of therapy



Strategies for use in clinical practice

Dose optimization using long-established TKIs, which may reduce toxicity associated with the most potent TKIs[1,2]

New agents in CML therapy

Development and use of new agents to address modest efficacy and safety concerns with ATP-competitive TKIs in this setting[3–5]

Future goals in CML management

- Improve first-line setting management[6,7]
- Target leukaemic stem cells with the aim to cure CML and to avoid the risk of toxicity associated with prolonged therapy[7]

ATP, adenosine triphosphate; CML, chronic myeloid leukaemia; STAMP, specifically targeting Abelson tyrosine kinase myristoyl pocket; TKI, tyrosine kinase inhibitor.

1. Apperley J, et al. EHA 2022. Abstract P707; 2. Yeung D, et al. EHA 2022. Abstract P720; 3. Réa D, et al. *Blood.* 2021;138:2031–41; 4. Atallah EL, et al. *Value in Health.* 2022;25(Suppl.):521; 5. Jiang Q, et al. *Blood.* 2020;136(Suppl. 1):50–1; 6. Hochhaus A, et al. *Leukemia.*2020;34:966–84; 7. Bhatia R. *Hematology Am Soc Hematol Educ Program*. 2017;2017:115–20.

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Question 1

How can we identify suitable patients for new and emerging therapies? And how do you think treatment pathways will incorporate new and emerging therapies?

Question 2

Are the mechanisms of action of the different TKIs significant in clinical practice?

Question 3

How could new and emerging treatments impact the management of CML after two prior lines of therapy? What is the role of the multidisciplinary team in incorporating these agents into the treatment paradigm?