Current and emerging treatments for chronic myeloid leukaemia: What have we learnt from the EHA Hybrid Conference 2022?

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EHA Congress 2022

New data for emerging treatments in CML

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Efficacy results from ASCEMBL: 96-week update

Rea D, et al.

A phase III study of asciminib vs bosutinib in patients with chronic myeloid leukaemia in chronic phase at 96 weeks (secondary objective)

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%

Discontinued due to adverse events
Asciminib: 7.0%
Bosutinib: 25.0%

Week 96 efficacy, n (%)	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 (10.53–32.95) p=0.001
BCR::ABL1^{IS} ≤1%, cumulative incidence	45.1 (53.7)	19.4 (33.7)	26.0 (13.48–38.56) p<0.001
MR4, %	17.2	10.5	NR
MR4.5, %	10.8	5.3	NR

*Treatment difference after adjusting for baseline MCyR status

BID, twice daily; CI, confidence interval; MMR, major molecular response; MR, molecular response; NR, not reported; QD, once daily; TKI, tyrosine kinase inhibitor.

Rea D, et al. Presented at: EHA Hybrid Conference, Vienna. 9–12 June 2022. Abstr S155.

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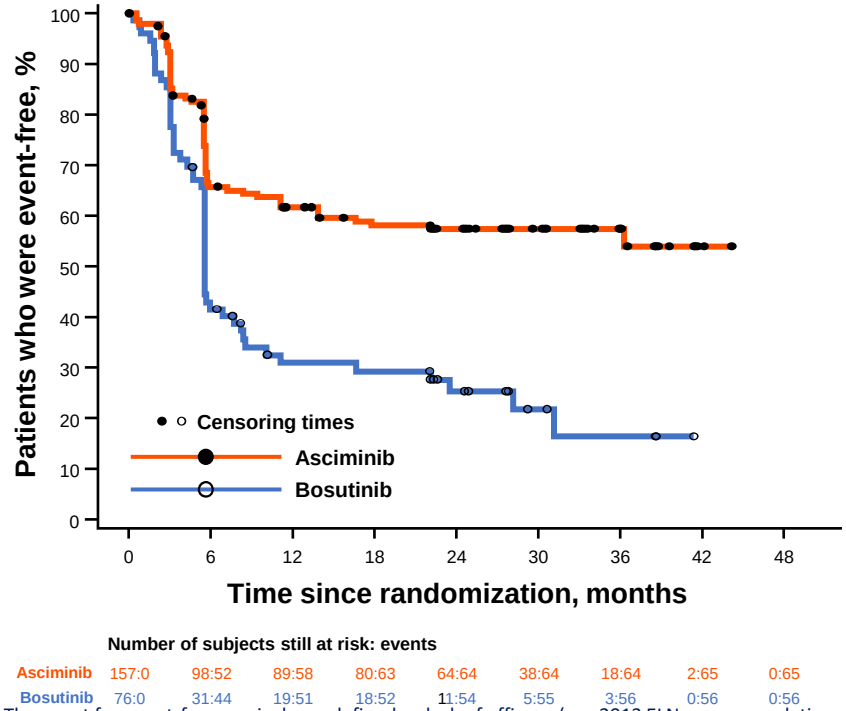
Efficacy results from ASCEMBL: 96-week update

Rea D, et al.



Event-free survival

The proportion of patients who were event-free by 2 years was **57.4%** (95% CI 49.0–64.8) with asciminib vs **25.2%** (95% CI 15.4–36.2) with bosutinib

Median time to event was not reached with asciminib, and was 5.6 months with bosutinib

	Asciminib	Bosutinib
No. of events/N (%)	65/157 (41.4)	56/76 (73.7)
Hazard ratio (95% CI)	0.42 (029–0.60), p<0.0001	

The event for event-free survival was defined as lack of efficacy (per 2013 ELN recommendations for second-line patients), disease progression (CML-AP/BP, CML death) or discontinuation due to AEs. AE, adverse event; AP, accelerated phase; BP, blast phase; CI, confidence interval; CML, chronic myeloid leukaemia; ELN, European LeukemiaNet.

Rea D, et al. Presented at: EHA Hybrid Conference, Vienna. 9–12 June 2022. Abstr S155.

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Safety results from ASCEMBL: 96-week update

Rea D, et al.

Median duration of exposure:
23.7 months (range 0.0–46.2 months) for asciminib, 7.0 months (range 0.2–43.3 months) for bosutinib

Week 96 AEs, %	Asciminib (n=156[a])		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

Most frequent grade ≥3 AEs (asciminib vs bosutinib):

- Thrombocytopenia (22.4% vs 9.2%)
- Neutropenia (19.9% vs 15.8%)
- Diarrhoea (0% vs 10.5%)
- Increased ALT (0.6% vs 14.5%)

- Most haematologic AEs with asciminib initially presented within the first 6 months of treatment
- Recurring haematologic AEs were manageable
- Rates of thrombocytopenia (3.2%) and neutropenia (2.6%) leading to discontinuation of asciminib were the same as the primary analysis

[a]1 patient on asciminib developed cytopenia after randomization and was not treated per investigator's decision. AE, adverse event; ALT, alanine aminotransferase.

Rea D, et al. Presented at: EHA Hybrid Conference, Vienna. 9–12 June 2022. Abstr S155.

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Asciminib in a real-world setting (UK)

Innes A, et al.

Real-world experience of asciminib in the UK

National survey (N=44, 43 in CP-CML)

Median prior lines of therapy was 4 (range 2–5)

44% of prior lines stopped due to resistance
56% for intolerance
5 patients had received allogeneic stem cell transplant

Response with asciminib, n (%)	N=44
No response	11 (25)
≥MR3	23 (53)
≥MR4	14 (32)

Non-T315I mutations associated with lower incidence of MR3 (1 of 6 evaluable patients) compared with no T315I or T315I detected (22 of 31 patients)

No worsening of baseline vascular or renal dysfunction was reported with asciminib

- 17 patients (38%) had haematological toxicity
- 19 patients (43%) had non-haematological toxicity (most commonly fatigue [n=4], insomnia [n=3], bone pain [n=2], nausea [n=2], and fluid retention [n=2])

Asciminib is well tolerated and effective in a real-world setting in patients who are resistant or intolerant to multiple TKIs

CP-CML, chronic phase chronic myeloid leukaemia; MR, molecular response; TKI, tyrosine kinase inhibitor.

Innes A, et al. Presented at: EHA Hybrid Conference, Vienna. 9–12 June 2022. Abstr P706.

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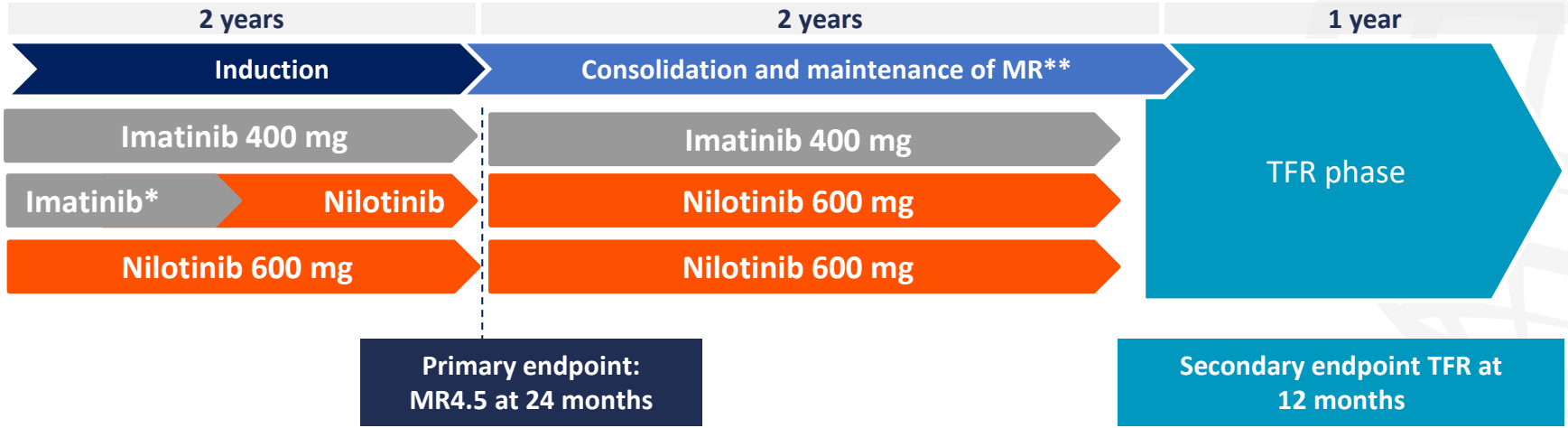
New data for established treatments in CML

Efficacy of early switch from imatinib to nilotinib

Pane F, et al.

A prospective, interventional, randomized (1:1) study to evaluate efficacy of nilotinib or imatinib followed by a switch to nilotinib*



*In absence of optimal response defined according to the ELN 2013 criteria. Early switch at 3, 6 or 12 months.
**One and all subsequent tests ≥MR4.0. Quarterly Q-PCR analysis of minimal residual disease.
ELN, European LeukemiaNet; MR, molecular response; Q-PCR, quantitative polymerase chain reaction; TFR, treatment-free remission.
Pane F, et al. Presented at: EHA Hybrid Conference, Vienna. 9–12 June 2022. Abstr S156.

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Efficacy of early switch from imatinib to nilotinib

Pane F, et al.

Efficacy	Imatinib (n=161)	Nilotinib (n=177)	Total (N=339)
MR4.5, n (%)	29 (18.0)	52 (29.4)	81 (23.9)
Chi square	p=0.0156		
MR4.5 by ELTS score, n/N Low Intermediate High	 23/95 5/48 1/18	 43/118 7/44 2/15	NR

Early vs late switch to nilotinib does not impact the probability of MR4.5 at 24 months

Imatinib arm, n (%)	<MR4.5	MR4.5	Chi square
Early switch (n=48)	41 (85.4)	7 (14.6)	p=0.4452
Late switch (n=16)	12 (75.0)	4 (25.0)	

ELTS, EUTOS long-term survival score; MR, molecular response.

Pane F, et al. Presented at: EHA Hybrid Conference, Vienna. 9–12 June 2022. Abstr S156.

Meta-analysis: identifying patients suitable for early TKI discontinuation with BCR::ABL1

Kockerols C, et al.

To assess the prognostic value of BCR::ABL1 digital PCR in relation to prior TKI treatment duration

Patient-level meta-analysis with data from different study cohorts (N=483)

Eligibility: Adult CP-CML patients, discontinued TKI, prior BCR::ABL1 digital PCR

Studies: 5 published and 1 unpublished

Pooled patient-level data: Digital PCR results

Data analysis: One-stage approach*

Univariable regression analysis	Hazard ratio	95% CI	p-value
BCR::ABL1 below cut-off	0.54	0.41–0.72	<0.001
Age	0.99	0.98–1.00	0.275
Male sex	0.92	0.70–1.21	0.530
Low Sokal score	0.94	0.70–1.26	0.685
Imatinib treatment	0.69	0.45–1.04	0.077
Treatment duration	0.92	0.88–0.97	0.001
DMR duration	0.96	0.90–1.02	0.142

- 205 patients experienced molecular relapse, (median time to relapse 3 months)
- The probability of molecular relapse at 24 months was 38% for BCR::ABL1 below cut-off vs 58% above (p<0.001)**
- TKI duration <6 years and BCR::ABL1 below cut-off resulted in clinically acceptable molecular relapse rate (48%)

*Kaplan–Meier estimates and cox regression analysis for between study heterogeneity with confounding variables including age, gender, Sokal score, TKI generation, BCR::ABL1 transcript type.
**BCR::ABL1 >0.1%[IS] or a 1-log BCR::ABL1 increase in two consecutive analyses.
CI, confidence interval; CP-CML, chronic phase chronic myeloid leukaemia; PCR, polymerase chain reaction; TKI, tyrosine kinase inhibitor.
Kockerols C, et al. Presented at: EHA Hybrid Conference, Vienna. 9–12 June 2022. Abstr S157.

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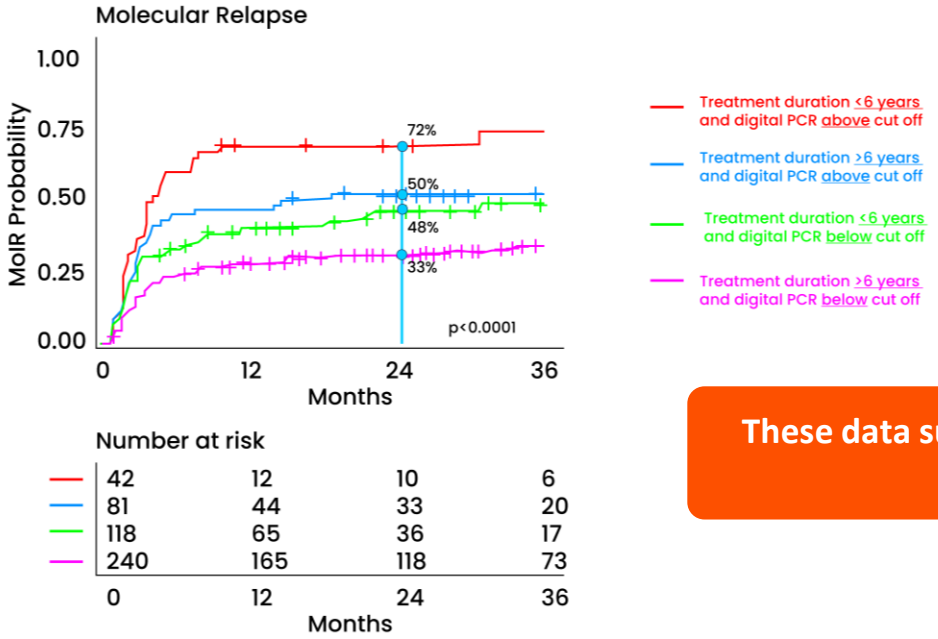
Meta-analysis: identifying patients suitable for early TKI discontinuation with BCR::ABL1

Kockerols C, et al.



Median TFR:
3 months (IQR 2–6 months)

Median follow-up:
27 months (IQR 24–56 months)

These data support the independent prognostic value of BCR::ABL1 digital PCR for TFR

IQR, interquartile range; PCR, polymerase chain reaction; TFR, treatment-free remission; TKI, tyrosine kinase inhibitor.

Kockerols C, et al. Presented at: EHA Hybrid Conference, Vienna. 9–12 June 2022. Abstr S157.

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Second attempt at TFR after dasatinib discontinuation

Kim D, et al.

To assess if dasatinib therapy can lead to a second TFR after failing imatinib discontinuation

Imatinib ≥3 years → Discontinuation → Dasatinib *At molecular relapse* → Discontinuation

Patient eligibility: CP-CML diagnosis, and total duration of MR4.5 or deeper response over 2 years

35 patients discontinued dasatinib for second TFR attempt

- All 35 patients attained ≥MR4 for ≥12 months
- 11.4% maintained MR at last follow-up (n=4)
- 31 (88.6%) patients lost MR, median onset of relapse 3.65 months

Second TFR rate after dasatinib discontinuation

6 months	22.9% (95% CI 10.8–37.6%)
12 months	10.0% (95% CI 2.7–23.1%)

Rechallenge with dasatinib after imatinib discontinuation for 12 months does not improve second TFR rate

CI, confidence interval; CP-CML, chronic phase chronic myeloid leukaemia; MR, molecular response; TFR, treatment-free remission.

Kim D, et al. Presented at: EHA Hybrid Conference, Vienna. 9–12 June 2022. Abstr S158.

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Safety of established treatments in CML

Proactive dasatinib dose reduction study

Yeung D, et al.

Phase II study of dose adaptation guided by dasatinib trough levels to minimize toxicity

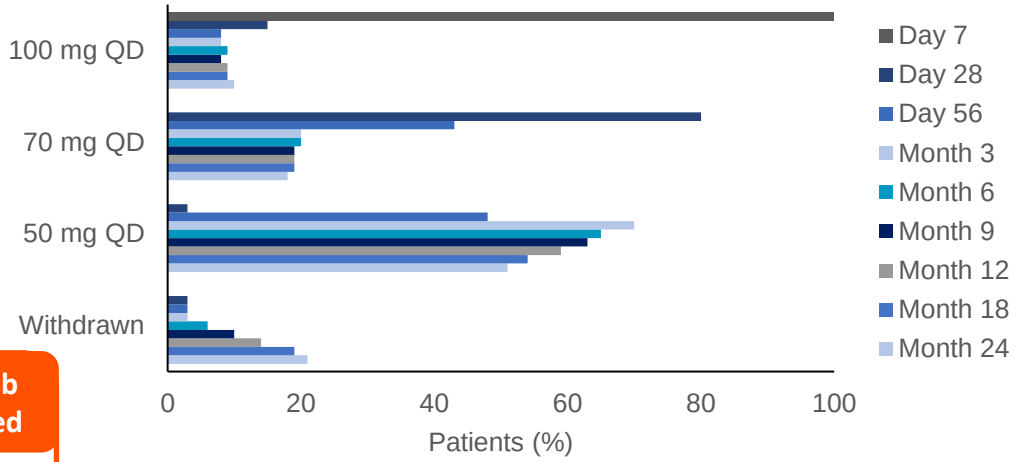
Primary endpoint: cumulative incidence of pleural effusion at 24 months

Newly diagnosed CP-CML patients (N=80)

At 24 months 74% of patients remained on dasatinib (n=59), and high rates of MMR/MR4.5 were achieved

- 15 pleural events occurred (cumulative incidence: 15%, 95% CI 8–25%)
- AEs leading to discontinuation were pleural effusion (n=6), pulmonary hypertension (n=4), pericardial effusion (n=2) and cardiac failure (n=2)

Assigned doses of dasatinib prior to specified timepoints



Reduced dosage of dasatinib maintained efficacy with acceptable toxicity; however, adaptive dasatinib dosing has limited capacity to influence early development of pleural effusion

AE, adverse event; CI, confidence interval; CP-CML, chronic phase chronic myeloid leukaemia; MMR, major molecular response; MR, molecular response; QD, once daily.

Yeung D, et al. Presented at: EHA Hybrid Conference, Vienna. 9–12 June 2022. Abstr P720.

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Safety characterization of bosutinib (BFORE trial)

Cortes J, et al.

To characterize the safety profile of bosutinib after 5 years of follow-up

Patients who received ≥1 dose of bosutinib (n=268) or imatinib (n=265) from the BFORE trial

TEAEs, %	Bosutinib (n=268)					Imatinib (n=265)				
	Year					Year				
	1	2	3	4	5+	1	2	3	4	5+
Gastrointestinal	76.5	78.0	79.5	79.5	79.9	52.8	56.6	58.5	61.1	61.5
Liver	39.2	41.4	42.2	42.9	44.0	11.7	13.6	14.0	14.3	15.5
Effusion	2.2	3.0	4.5	6.0	6.0	1.5	1.5	1.5	1.5	2.3
Renal	6.0	7.8	8.2	9.7	10.4	6.0	8.3	8.7	8.7	9.8

Most commonly occurring TEAEs:

- Diarrhoea (bosutinib 75.0%, imatinib 40.4%)
- Nausea (bosutinib 37.3%, imatinib 42.3%)
- ↑ AST and/or ALT (bosutinib 34.0%, imatinib 8.3%)
- ↑ creatinine (bosutinib 6.7%, imatinib 8.3%)
- Pleural effusion (bosutinib 5.2%, imatinib 1.9%)

After 5 years of follow-up, no new safety signals reported with bosutinib or imatinib; onset of gastrointestinal and liver TEAEs primarily in year 1, and effusion and renal TEAEs occurring in later years

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse events.

Cortes J, et al. Presented at: EHA Hybrid Conference, Vienna. 9–12 June 2022. Abstr P717.

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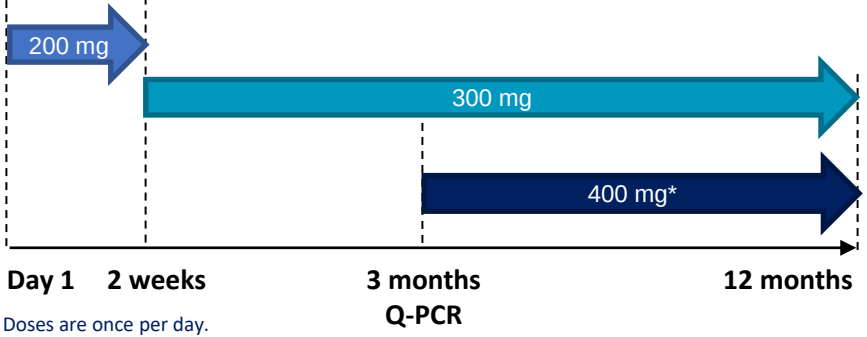
Dose optimization study of bosutinib (BEST trial)

Castagnetti F, et al.

To evaluate the efficacy of low-dose bosutinib in the second-line treatment of elderly patients with CML

Prospective, Phase II, single-arm study (BEST; N=63)
3-year follow-up
Dose increases in patients without an optimal MR

Q-PCR every 4 weeks until the achievement of stable MMR, dose maintained in responsive patients



Bosutinib dose escalation
(36 patients still on bosutinib at last contact)

200 mg	Maximum dose: 6% (n=4), 44% of patients still on 200 mg dose bosutinib at last contact
300 mg	Maximum dose: 73% (n=46), 50% of patients still on 300 mg dose bosutinib at last contact
400 mg	Maximum dose: 21% (n=13), 6% of patients still on 400mg dose bosutinib at last contact

Doses are once per day.
*In patients where Q-PCR transcript >1%.
CML, chronic myeloid leukaemia; MMR, major molecular response; MR, molecular response; Q-PCR, quantitative polymerase chain reaction.
Castagnetti F, et al. Presented at: EHA Hybrid Conference, Vienna. 9–12 June 2022. Abstr P698.

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Dose optimization study of bosutinib (BEST trial)

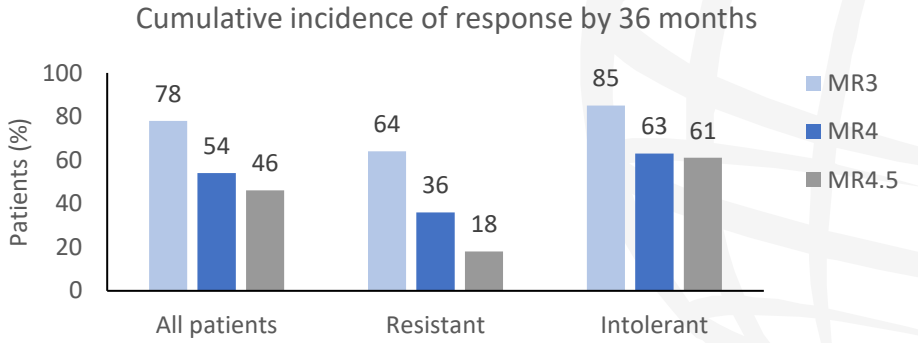
Castagnetti F, et al.

Safety findings

	No. patients
AEs leading to discontinuation	
Increase in transaminases	5
Skin rash	1
Myalgia	1
GI toxicity	1
Renal failure	1

	No. patients
Patients with CV AEs	
Acute coronary symptoms	6
Pericarditis	2
Peripheral arterial thrombosis	1

68% of patients → **Molecular improvement from baseline to 36 months**



A progressive dose increase of second-line bosutinib based on MR in elderly patients resulted in high response rates, and was well tolerated

AE, adverse event; CV, cardiovascular; GI, gastrointestinal; MR, molecular response.

Castagnetti F, et al. Presented at: EHA Hybrid Conference, Vienna. 9–12 June 2022. Abstr P698.

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Ponatinib in a real-world setting (Italy)

Breccia M, et al.

Retrospective analysis to provide data on daily practice and management of CML patients treated with ponatinib

Monitoring registries of the Italian Medicines Agency (N=666)
- 515 CP-CML and 50 AP-CML

2.35 years Median time from diagnosis to start of ponatinib

T315I mutations in 46 (6.9%) patients

38.9% (n=259) had received 2 treatment lines

39.0% (n=260) had received 3 treatment lines

22.1% (n=147) had received 4+ treatment lines

BCR::ABL1^{IS} efficacy outcomes, n (%)	AP/BP-CML (n=151)	CP-CML (n=515)	Overall (N=666)
1% to 10%	26	32	58 (8.7)
<1%	20	62	82 (12.3)
0.1% to 0.01%	12	116	128 (19.2)
<0.01%	44	222	266 (39.9)

Median follow-up of 14.4 months

- 136 patients required a dose reduction due to AEs
- 309 patients had dose decreased in absence of AEs
- 144 patients discontinued treatment (7.4% due to intolerance, 5.6% due to resistance)

Ponatinib dose reductions were mainly performed in the absence of reported toxicity

AE, adverse event; AP, accelerated phase; BP, blast phase; CML, chronic myeloid leukaemia; CP, chronic phase.

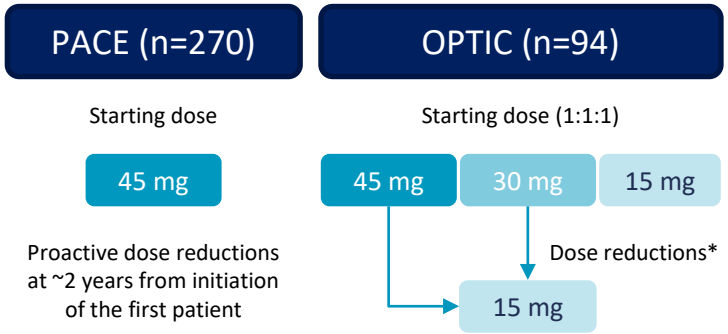
Breccia M, et al. Presented at: EHA Hybrid Conference, Vienna. 9–12 June 2022. Abstr P697.

Dose modification of ponatinib

Apperley J, et al.

In-depth analysis of dosing dynamics of ponatinib from the Phase II PACE and OPTIC studies

CP-CML patients, ≥1 prior second generation TKI or T315I mutation



Median follow-up was 57 months (PACE) and 32 months (OPTIC)

Efficacy outcomes	PACE (n=270)	OPTIC (n=94)
≤1 BCR::ABL1^{IS} response at 24 months, %	52	56
2-year PFS rate, %	68	80
2-year OS rate, %	86	91

Median time to dose reduction for AEs was 2.85 months in PACE and 3.64 months in OPTIC

- Dose reductions due to AEs occurred in 82% of patients in PACE and 46% in OPTIC
- Per 100-patient years, exposure-adjusted TEAOEs were 15.8 events in PACE and 7.6 events in OPTIC at 0 to <1 year

Response-based dose-reduction strategy used in the OPTIC study resulted in comparable efficacy outcomes, fewer dose reductions due to AEs and fewer TEAOEs than seen in PACE

*In patients ≤1% BCR::ABL1^{IS}.

AE, adverse event; CP-CML, chronic phase chronic myeloid leukaemia; OS, overall survival; PFS, progression-free survival; TEAOEs treatment-emergent arterial occlusive event; TKI, tyrosine kinase inhibitor.

Apperley J, et al. Presented at: EHA Hybrid Conference, Vienna. 9–12 June 2022. Abstr P707.

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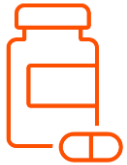
Conclusions based on the data presented at EHA 2022 congress



New agents in CML therapy

- New class of TKIs (STAMP inhibitor; e.g. asciminib) appear to be associated with a higher efficacy and a lower toxicity compared with earlier generation TKIs

Potent, next generation TKIs available

- Faster and deeper molecular responses in more CML patients compared with imatinib, with the possibility for successful TFR

Several strategies for use in clinical practice

- Progressive dose reduction in patients with good response, which may reduce toxicity associated with the most potent TKIs

CML, chronic myeloid leukaemia; STAMP, ABL Myristoyl Pocket; TFR, treatment-free remission; TKI, tyrosine kinase inhibitor.

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