Tackling unmet needs in chronic myeloid leukemia: What's next in the treatment algorithm?

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Expert faculty

Prof. Massimo Breccia

Sapienza University of Rome
Azienda Policlinico Umberto I
Rome, Italy

Prof. Susanne Saussele

University Clinic
Mannheim, Germany

Prof. Valentín García Gutiérrez

Ramón y Cajal University Hospital
Madrid, Spain

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Tackling safety considerations when treating patients with CML

Prof. Valentín García Gutiérrez
Ramón y Cajal University Hospital
Madrid, Spain

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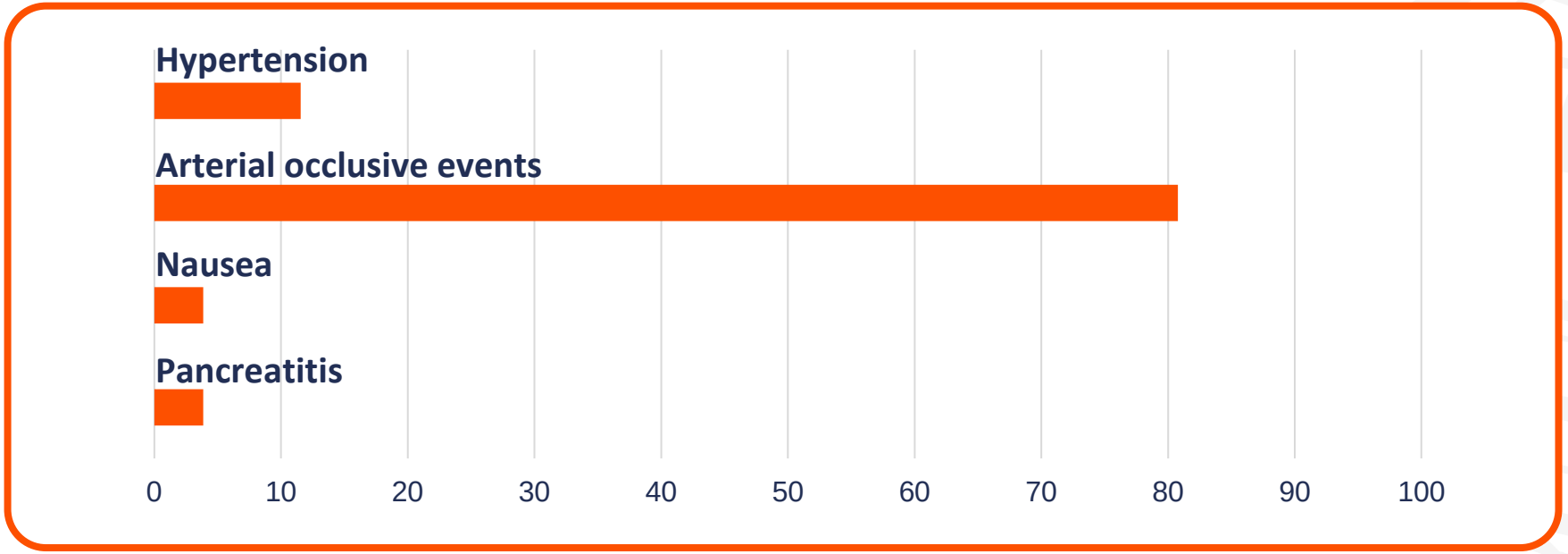
Poll question 1

What do you consider to be the most important safety concern when treating patients with CML in the later-line setting?

a. Hypertension
b. Arterial occlusive events
c. Nausea
d. Pancreatitis

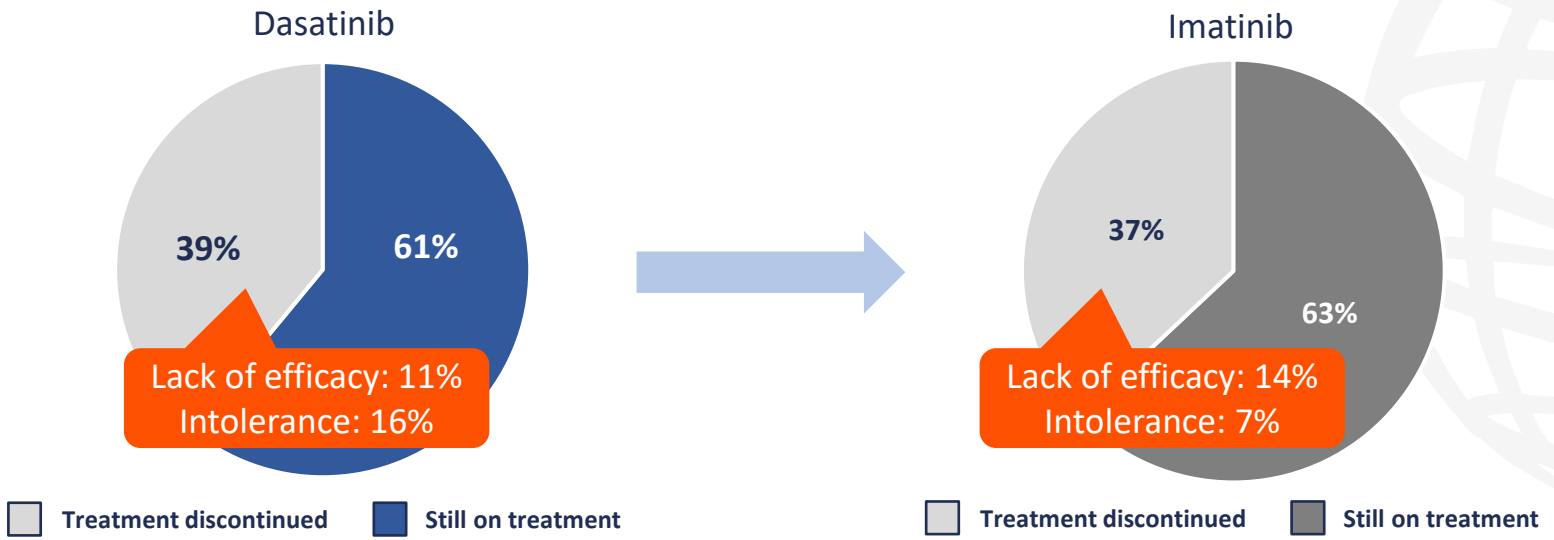
CML, chronic myeloid leukemia.

Poll question 1: Responses



What are the reasons for treatment discontinuation in the first-line setting for patients with CML?

DASISION trial: Patient status at the 5-year follow-up



CML, chronic myeloid leukemia.
Cortes JE, et al. *J Clin Oncol.* 2016;34:2333–40.

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TKIs have different toxicity profiles

	Imatinib		Dasatinib		Nilotinib		Bosutinib		Ponatinib	
Adverse events*	**All gr**	**Gr 3/4**	**All gr**	**Gr 3/4**	**All gr**	**Gr 3/4**	**All gr**	**Gr 3/4**	**All gr**	**Gr 3/4**
Fatigue	++++	+	+++	+	++++	-	NR	NR	++++	++
Rash	++++	++	+++	+	++++	-	++++	++	++++	++
Headache	+++	-	++++	-	++++	-	++++	++	++++	++
Myalgia	+++++	-	++++	-	NR	NR	++	-	++++	++
Bone pain	+++	++	NR	NR	NR	NR	++	-	NR	NR
Diarrhea	++++	++	++++	+	+++	+	+++++	++++	NR	NR
Nausea	++++	-	++++	-	+++	+	++++	++	++++	+
Vomiting	+++	-	+++	-	++	-	++++	++	NR	NR
Abdominal pain	++	-	NR	NR	NR	NR	++++	++	++++	+++
Pancreatitis	+	+	NR	NR	++	++	NR	NR	+++	+++
Peripheral edema	++++	++	++++	++	+++	+	+++	++	NR	NR
Pleural effusion	++	+	++++	++	++	+	NR	NR	NR	NR
Elevated lipase	++++	+++	NG	-	++++	+++	++++	+++	++++	++++
Hepatotoxicity	++++	++	NG	+	+++++	+++	+++++	++++	+++	++
Arterial occlusive events	+	+	++	++	+++	+++	++	++	++++	++++
Hyperglycemia	+	+	+	+	++++	+++	++	++	+++	+++
Hypercholesterolemia	+	+	+	+	++++	+++	++	++	+++	+++
Anemia	+++++	+++	+++++	++++	++++	++	+++++	+++	++++	++++
Thrombocytopenia	+++++	++++	+++++	++++	++++	+++	+++++	++++	++++	++++
Neutropenia	+++++	++++	+++++	++++	++++	+++	++++	++++	++++	++++

Key (% pts)

-, absent†
+, <1%
++, 1–5%
+++, 5–10%
++++, 10–50%
+++++, 50–100%

*Data derived from studies of first-line use, except for ponatinib (currently used in second-line or later-line settings); †specifically reported as absent.
Gr, grade; NG, data not given; NR, not reported; pts, patients; TKI, tyrosine kinase inhibitor.
Adapted from: Apperley JF. *Lancet.* 2015;11:385:1447–59 and data from personal communication (Prof. García Gutiérrez).

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Fatigue	++++	+	+++	+	++++	-	NR	NR	++++	++
Rash	++++	++	+++	+	++++	-	++++	++	++++	++
Headache	+++	-	++++	-	++++	-	++++	++	++++	++
Myalgia	+++++	-	++++	-	NR	NR	++	-	++++	++
Bone pain	+++	++	NR	NR	NR	NR	++	-	NR	NR
Diarrhea	++++	++	++++	+	+++	+	+++++	++++	NR	NR
Nausea	+	-	++++	-	+++	+	++++	++	++++	+
Vomiting	+++		+++	-	++	-	++++	++	NR	NR
Abdominal pain	++			NR	NR	NR	++++	++	++++	+++
Pancreatitis	+							NR	+++	+++
Peripheral edema	+							++	NR	NR
Pleural effusion	+							NR	NR	NR
Elevated lipase	+							+++	++++	++++
Hepatotoxicity	+							++++	+++	++
Arterial occlusive events	+							++	++++	++++
Hyperglycemia	+							++	+++	+++
Hypercholesterolemia	+							++	+++	+++
Anemia	+++++	+++	+++++	++++	++++	++	+++++	+++	++++	++++
Thrombocytopenia	+++++	++++	+++++	++++	++++	+++	+++++	++++	++++	++++
Neutropenia	+++++	++++	+++++	++++	++++	+++	++++	++++	++++	++++

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"Grade 1/2 side effects that begin early during treatment can persist and become chronic. In principle, they are manageable and tolerable, but they negatively affect QoL and can cause a decrease in compliance, which is a major cause of failure"

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Treatment options for ‘low-grade’ side effects

Key early symptomatic management strategies[1–3]

Symptom	Strategy
Gastrointestinal	Antidiarrheal Antiemetic
Dermatologic	Antihistamines
Pulmonary	Diuretics
Muscle spasms	Potassium/calcium supplements
Pain	Analgesics

Dose reduction/treatment discontinuation (when possible)[4]

DESTINY

(N=174; imatinib, dasatinib, nilotinib)

- De-escalate (50% of standard dose): 12 mo
- Discontinue: 12–36 mo
- Diarize: new or evolving symptoms

Main symptoms at baseline

- Lethargy
- Diarrhea
- Nausea
- Hair thinning

Symptoms decreased rapidly in the first 3 mo following dose reduction

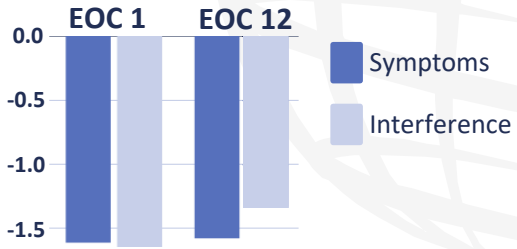
Treatment switching[5]

ENRICH

(N=52; imatinib → nilotinib)

- Impact on QoL of treatment switching for patients with chronic imatinib-related AEs
- Symptom burden assessed by MDASI-CML

Reduction in symptoms from BL



AE, adverse event; BL, baseline; EOC, end of cycle; MDASI-CML, MD Anderson Symptom Inventory–Chronic Myeloid Leukemia; mo, month; QoL, quality of life.

1. Lipton JH, et al. *Blood Rev*. 2022:100968; 2. Berman E. *Blood*. 2022;139:3138–47; 3. Steegmann JL, et al. *Leukemia*. 2016;30:1648–71; 4. Clark RE et al. *Lancet Haematol.* 2019;6:e375–83; 5. Cortes JE, et al. *Clin Lymphoma Myeloma Leuk*. 2016;16:286–96.

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Headache	+++								++++	++
Myalgia	+++++								++++	++
Bone pain	+++								NR	NR
Diarrhea	++++								NR	NR
Nausea	++++								++++	+
Vomiting	+++								NR	NR
Abdominal pain	++	-			NR	NR	++++	++	++++	+++
Pancreatitis	+	+		NR	++	++	NR	NR	+++	+++
Peripheral edema	++++		++++	++	+++	+	+++	++	NR	NR
Pleural effusion	++	+	++++	++	++	+	NR	NR	NR	NR
Elevated lipase	++++	+++	NG	-	++++	+++	++++	+++	++++	++++
Hepatotoxicity	++++	++	NG	+	+++++	+++	+++++	++++	+++	++
Arterial occlusive events	+	+	++	++	+++	+++	++	++	++++	++++
Hyperglycemia	+	+	+	+	++++	+++	++	++	+++	+++
Hypercholesterolemia	+	+	+	+	++++	+++	++	++	+++	+++
Anemia	+++++	+++	+++++	++++	++++	++	+++++	+++	++++	++++
Thrombocytopenia	+++++	++++	+++++	++++	++++	+++	+++++	++++	++++	++++
Neutropenia	+++++	++++	+++++	++++	++++	+++	++++	++++	++++	++++

> *"So-called 'off-target' complications can affect the cardiovascular, respiratory and immune systems; the liver; the pancreas; calcium, glucose, and lipid metabolism; and secondary malignancies, etc."*

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Adapted from: Apperley JF. *Lancet.* 2015;11:385:1447–59 and data from personal communication (Prof. García Gutiérrez).

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Why are some adverse events more frequent with specific TKIs?

	Targets	Adverse events
Imatinib (type 2 inhibitor)	*ABL1/2, KIT, PDGFRA/B, LCK, DDR1/2, NQ02*	Edema, nausea, vomiting, muscle cramps, musculoskeletal pain, diarrhea, rash, fatigue, abdominal pain
Dasatinib (type 1 inhibitor)	*ABL1/2, KIT, PDGFRA/B, CSK, BLK, FGR, TXK, EFGR, LCK, YES, BTK, SRC, TEC, SIK1/2, BMX, FRK, CSF1R, SRM, HCK, PTK6, TNK, BRAF, LIMK1, WEE1, TNIK, EPHA1/2/3/4/5/8, EPHB1/2/3/4, MAPK14, DDR1/2, MAP2K5, MAP3K3, ERBB4*	Myelosuppression, fluid retention events, diarrhea, headache, skin rash, hemorrhage, dyspnea, fatigue, nausea, musculoskeletal pain
Nilotinib (type 2 inhibitor)	*ABL1/2, KIT, PDGFRA/B, EPHA2/3/4/5/8, EPHB3/4, LCK, MAPK11/14, MAP2K3/6, CLK1, NQO2*	Rash, pruritus, headache, nausea, fatigue, myalgia, nasopharyngitis, constipation, diarrhea, abdominal pain, vomiting, arthralgia, pyrexia, upper urinary tract infection, back pain, cough, asthenia, myelosuppression

TKI, tyrosine kinase inhibitor.
Lee H, et al. *Int J Hematol.* 2021;113:632–41.

Why are some adverse events more frequent with specific TKIs?

	Targets	Adverse events
Bosutinib (type 1 inhibitor)	*ABL1/2, PDGFRB, SRC, TINK, KDR, LCK, STK10/24/26, SIK2, MINK1, SIK1, SLK, SYK, WEE1, MST1, TNK, DDR1/2, CSK, CSNK1D/E, YES, BTK, RET, FER, FES, FRK, FYN, HCK, FLT1/4, BMX, BLK, PRKCQ, PTK2B, NTRK1, NEK2/4, NUAK1/2, HIPK4, CHEK1/2, AXL, PAK2, EGFR, ERBB2/4, EPHA2/4/5/6/8, EPHB1/2/4, FGFR2/3, MAP2K1/2, MAP3K2/3/4/9/11, MAP4K2/4, CAMK1D*	Diarrhea, nausea, thrombocytopenia, rash, vomiting, abdominal pain, respiratory tract infections, anemia, pyrexia, liver test abnormalities, fatigue, cough, headache
Ponatinib (type 2 inhibitor)	*ABL1/2, KIT, PDGFRA/B, LCK, SRC, RET, SRM, CSK, RPS6KB1, DDR1/2, BMX, YES1, FLT1/3/4, TEK, STK10, FYN, CSF1R, FGR, MUSK, FRK, TNK1, PTK2B, JAK1, TNK1, NEK4, JAK2/3, HCK, TXK, MKNK2, PTK6, BLK, SIK1, RAF1, TNIK, PRKACG, CHEK2, HIPK4, SLK, BTK, KDR, CLK1, BRAF, FER, MELK, ITK, LTK, FES, DLK1, PRKACA/B/G, MINK1, EPHA1/2/3/4/5/6/7/8, EPHB1/2/3/4, EGFR, ERBB2/4, FGFR1/2/3/4, MAPK11/12/13, MAP2K3/6, MAP3K3, MAP4K2/4, NTRK1/2/3*	Hypertension, rash, abdominal pain, fatigue, headache, dry skin, constipation, arthralgia, nausea, and pyrexia, thrombocytopenia, myelosuppression

TKI, tyrosine kinase inhibitor.

Lee H, et al. *Int J Hematol.* 2021;113:632–41.

How to avoid potential off-target effects of TKIs

Comorbidities	TKI recommendations
Cardiovascular	• Imatinib and bosutinib are generally preferred • Treat existing comorbidities in line with current guidelines for that condition; consider potential drug–drug interactions • Introduce lifestyle changes,* manage risk factors, correct serum electrolytes prior to initiating TKI and monitor throughout • Consider baseline ECG • Additional monitoring (e.g. ECG and blood pressure) is necessary throughout treatment with certain TKIs (i.e. bosutinib, dasatinib, nilotinib, and ponatinib)
Pulmonary	• Imatinib, nilotinib, and bosutinib are generally preferred
Diabetes	• Imatinib, dasatinib, and bosutinib are generally preferred
Gastrointestinal	• Dasatinib and nilotinib are generally preferred
Renal	
Hepatic	• Imatinib and dasatinib are generally preferred

*For example, smoking cessation; weight loss; exercise; or control of hypercholesterolemia, hypertension, or diabetes.
ECG, electrocardiogram; TKI, tyrosine kinase inhibitor.
Lipton JH et al. *Blood Rev.* 2022;56:100968.

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Conclusions

- Side effects are frequent with all current TKIs and a common reason for treatment discontinuation
- While some AEs are common to all TKIs, there are specific side effects that are related to individual TKIs
- Patient comorbidities can play a role in the onset and type side effects observed in individual patients

AE, adverse event; TKI, tyrosine kinase inhibitor.

Considering later lines of treatment for patients with CML: The unmet need

Prof. Massimo Breccia
Sapienza University of Rome
Azienda Policlinico Umberto I
Rome, Italy

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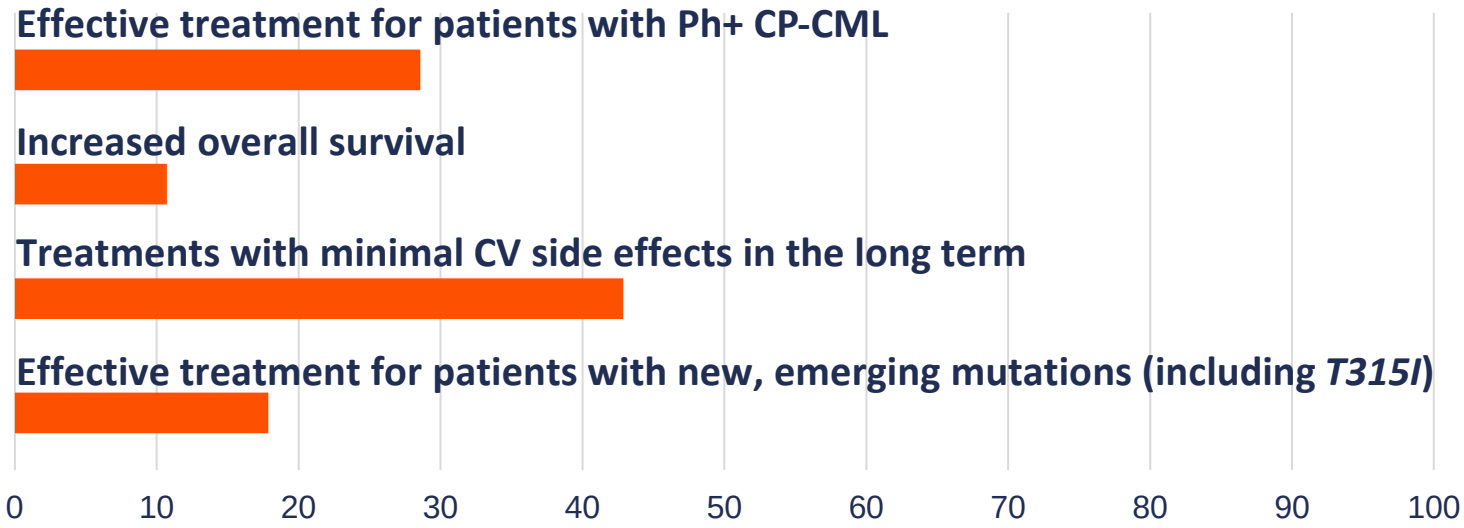
Poll question 2

What do you consider to be the primary unmet need in patients with CP-CML in the later-line setting?

a. Effective treatment for patients with Ph+ CP-CML
b. Increased overall survival
c. Treatments with minimal CV side effects in the long term
d. Effective treatment for patients with new, emerging mutations (including *T315I*)

CML, chronic myeloid leukemia; CP, chronic phase; CV, cardiovascular; Ph+, Philadelphia chromosome-positive.

Poll question 2: Responses



CP-CML, chronic phase chronic myeloid leukemia; CV, cardiovascular; Ph+, Philadelphia chromosome-positive.

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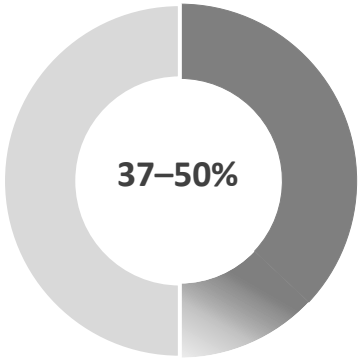
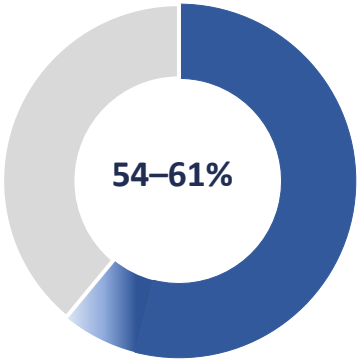
Sequential TKI use is associated with a decreased probability of response and reduced overall survival

Imatinib in the first-line setting:
Rate of discontinuation at 5 years



- **5–7%** discontinued due to toxicities
- **15–20%** did not respond

Nilotinib, dasatinib, bosutinib in the second-line setting: Rate of discontinuation at study cut-off



- **50–56%** fail to achieve CCyR
- **60–70%** fail to achieve MMR

Patients with treatment failure/resistance to second-line therapy have limited options

CCyR, complete cytogenetic response; MMR, major molecular response; TKI, tyrosine kinase inhibitor.
Cortes J, Lang F. *J Hematol Oncol*. 2021;14:44.

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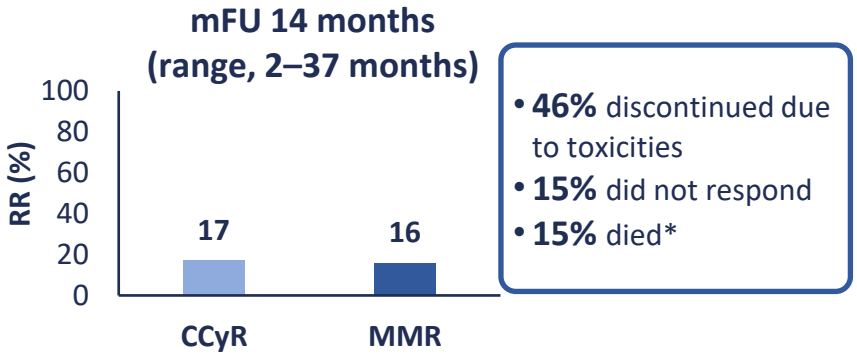
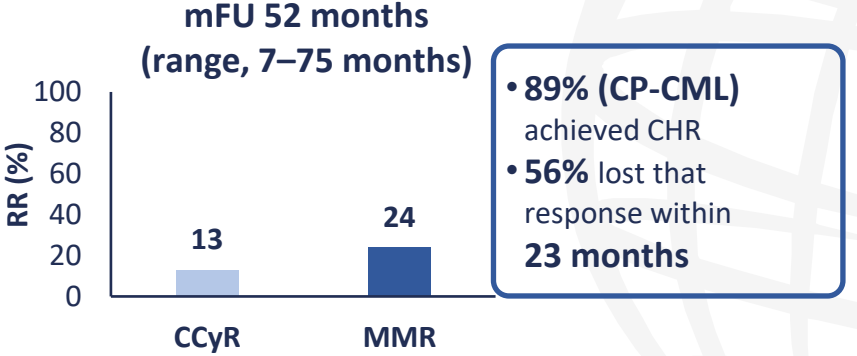
Reductions in likelihood of response and overall survival are particularly marked in ≥3rd-line settings

Results for 82 patients with CML (CP, n=68), treated with either dasatinib or nilotinib[1]



- **46%** discontinued due to toxicities
- **15%** did not respond
- **15%** died*

Results for 25 patients with CML (CP, n=18) treated with either dasatinib or nilotinib[2]



- **89% (CP-CML)** achieved CHR
- **56%** lost that response within **23 months**

The data suggest little clinical benefit of treatment with a ≥third-line, second-generation TKI after failure of a first-generation TKI and a second-generation TKI[3]

*Disease progression associated with *T315I*.
CCyR, complete cytogenetic response; CHR, complete hematological response; CML, chronic myeloid leukemia; CP, chronic phase; mFU, median follow-up; MMR, major molecular response; RR, response rate; TKI, tyrosine kinase inhibitor.
1. Rossi A, et al. *Haematologica.* 2013;98:399–403; 2. Ribeiro BF, et al. *Clinics*. 2015;70:550–5; 3. Cortes J, Lang F. *J Hematol Oncol*. 2021;14:44.

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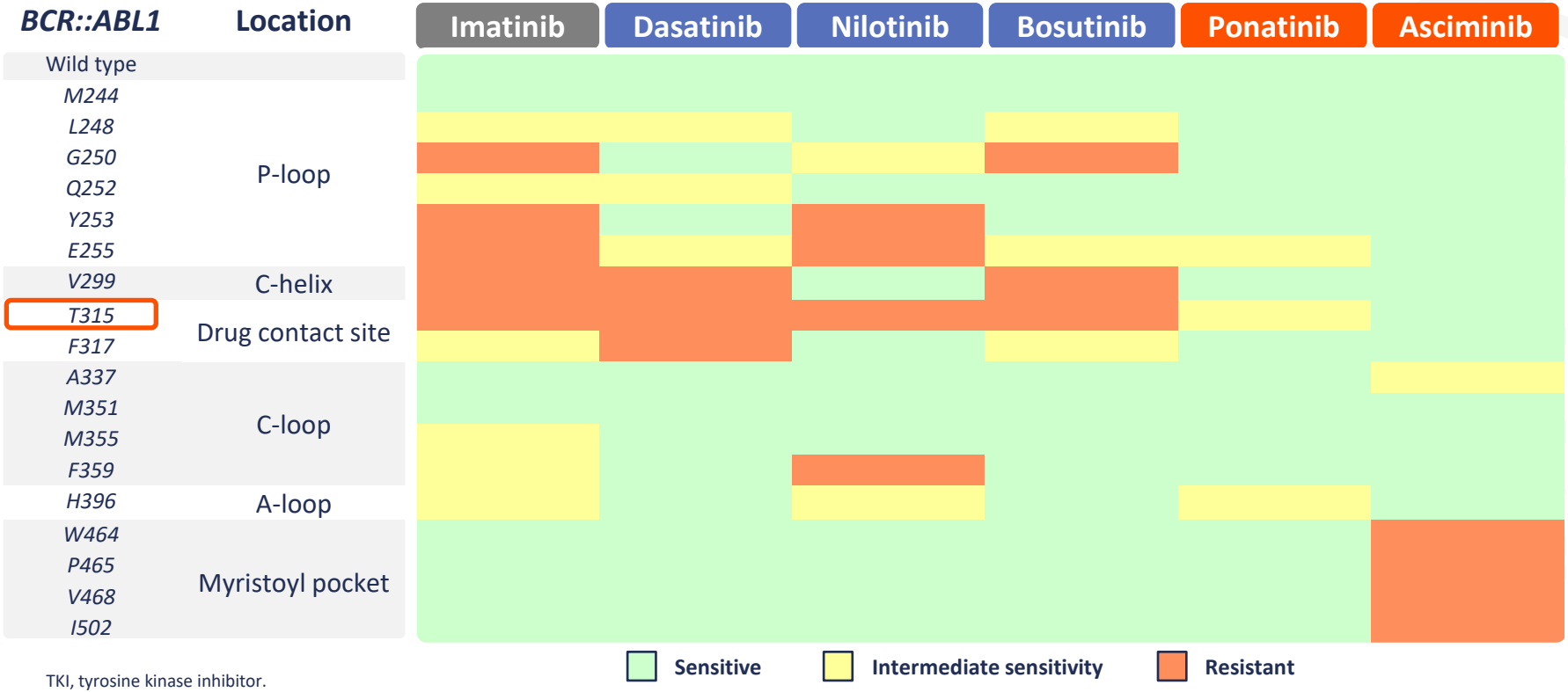
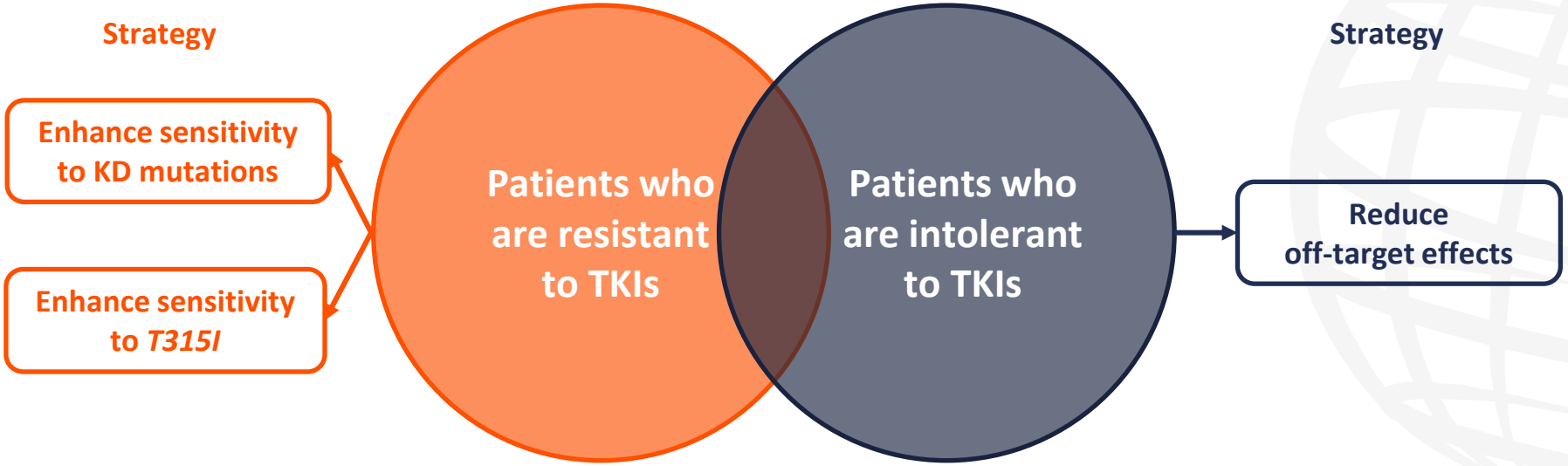
BCR::ABL1 mutations associated with resistance vary in their sensitivity to approved TKIs[1,2]



TKI, tyrosine kinase inhibitor.
Alves R, et al. *Cancers.* 2021;13:4820.

There are two key unmet needs motivating the search for additional TKIs to manage CML



CML, chronic myeloid leukemia; KD, kinase domain; TKI, tyrosine kinase inhibitor.
Breccia M. *Adv Ther*. 2022;39:1101–6.

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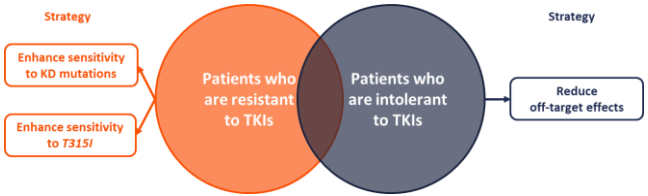
To address these needs, TKIs with alternative MoAs or higher *BCR::ABL1* specificity are now approved or under investigation



Asciminib[1]

MoA: Allosteric inhibition of *BCR::ABL1* kinase activity through targeting of the ABL1 myristoyl pocket

Olverembatinib[2]

MoA: Potent in vitro inhibitor of WT and mutant *BCR::ABL1* with enhanced cell cycle arrest and apoptosis in CML cells

Vodobatinib[3]

MoA: In vitro activity against most *BCR::ABL1* mutations, **but not *T315I***

PF-114[3]

Structurally similar to ponatinib; modified to avoid CV toxicity due to off-target inhibition of VEGFR

New and emerging agents aim to increase sensitivity to kinase domain mutations and reduce off-target activity; asciminib is unique in targeting the myristoyl pocket

CML, chronic myeloid leukemia; CV, cardiovascular; KD, kinase domain; MoA, mechanism of action; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor; WT, wild type.

1. Breccia M, et al. *Expert Opin Investig Drugs*. 2021;30:803–11; 2. Jiang Q, et al. *J Hematol Oncol*. 2022;15:113; 3. Cortes J, Lang F. *J Hematol Oncol*. 2021;14:44.

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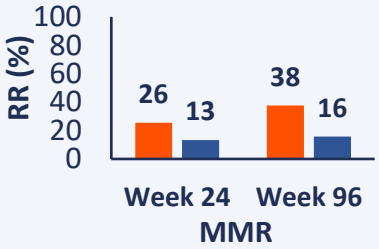
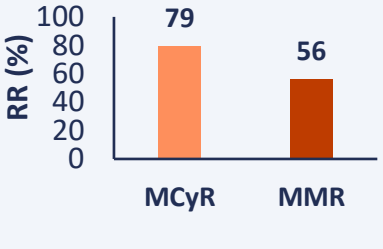
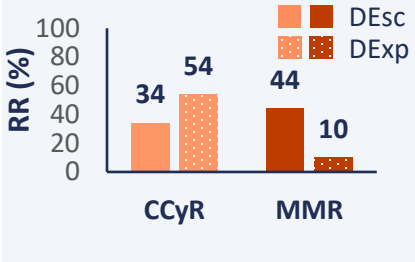
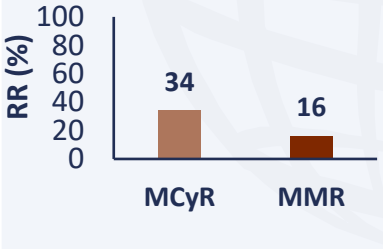
New and emerging agents show efficacy in patients who showed resistance to earlier lines of TKI*

Asciminib[1,2] ASCEMBL, Ph III (N=233)	**Olverembatinib**[3] Ph I/II (N=165)	**Vodobatinib**[4] Ph I (N=52)	**PF-114**[5] Ph I (N=51)
Asciminib vs **bosutinib**	mFU: 34 weeks Single arm	mDur: 23 mo; 16 mo Single arm (DEsc n=51; DExp n=11)	mFU: ≥31 weeks Single arm
Prior TKIs, 2–≥5	**Prior TKIs, 1–≥3**	**Prior TKIs, DEsc 1–6; DExp 1–3**	**Prior TKIs, ≥3**









*Clinical trials with olverembatinib and vodobatinib included patients who had been treated with only one prior line of TKI.
CCyR, complete cytogenetic response; DEsc, dose escalation; DExp, dose expansion; mFU, median follow-up; MCyR, major cytogenetic response; mDur, median duration; MMR, major molecular response; mo, months; Ph, phase; RR, response rate; TKI, tyrosine kinase inhibitor.
1. Réa D, et al. *Blood.* 2021;138:2031–41; 2. Réa D, et al. *HemaSphere.* 2022;6:56–7; 3. Jiang Q, et al. *J Hematol Oncol*. 2022;15:113;
4. Cortes JE, et al. *Blood*. 2021;138(Suppl. 1):309; 5. Turkina AG, et al. *Blood*. 2021;138(Suppl. 1):1482.

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New and emerging agents have fewer short-term AEs in patients treated with ≥2 lines of TKI therapy

Asciminib[1,2] ASCEMBL, Ph III (N=233)	Olverembatinib[3] Ph I/II (N=165)	Vodobatinib[4] Ph I (N=52)	PF-114[5] Ph I (N=51)
Asciminib vs **bosutinib**	Single arm	Single arm	Single arm
Response to prior TKI Refractory, 61% vs 71% Intolerant, 38% vs 29%	**Response to prior TKI** Not available	**Response to prior TKI** Refractory, 60% Intolerant, 40%	**Response to prior TKI** Not available
Grade ≥3 AEs (>10%) • Thrombocytopenia, 22% vs 9% • Neutropenia, 18% vs 15% • Diarrhea, 0% vs 11% • Increased ALT, 1% vs 15%	**Key grade ≥3 AEs** • Thrombocytopenia, 49% • Anemia, 20% • Hypertriglyceridemia, 9%	**Common grade ≥3 AEs** • Thrombocytopenia, 15% • Neutropenia/anemia, 12% • Increased amylase and lipase, 8% each	**Dose-limiting toxicity** • Gr 3 psoriasis-like skin AE **Common AEs, all grades** • Gastrointestinal, 33%
• AOEs, 3% vs 1%	• Skin pigmentation, 85%* • Hypertension, 6% • CV AEs, 32% • AOEs and VOEs, 5%	• CV TRAEs (grades 1–3), 19%	• No VOEs or deviations of ankle-brachial index

*Any grade. AE, adverse event; ALT, alanine amino-transferase; AOE, arterial occlusive event; CV, cardiovascular; Gr, grade; Ph, phase; TKI, tyrosine kinase inhibitor; TRAE, treatment-related AE; VOE, vascular occlusive event.

1. Réa D, et al. *Blood.* 2021;138:2031–41; 2. Réa D, et al. *HemaSphere.* 2022;6:56–7; 3. Jiang Q, et al. *J Hematol Oncol.* 2022;15:113; 4. Cortes JE, et al. *Blood.* 2021;138(Suppl. 1):309; 5. Turkina AG, et al. *Blood.* 2021;138(Suppl. 1):1482.

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Where do new and emerging agents fit into the treatment pathway for CML?

Prof. Susanne Saussele
University Clinic
Mannheim, Germany

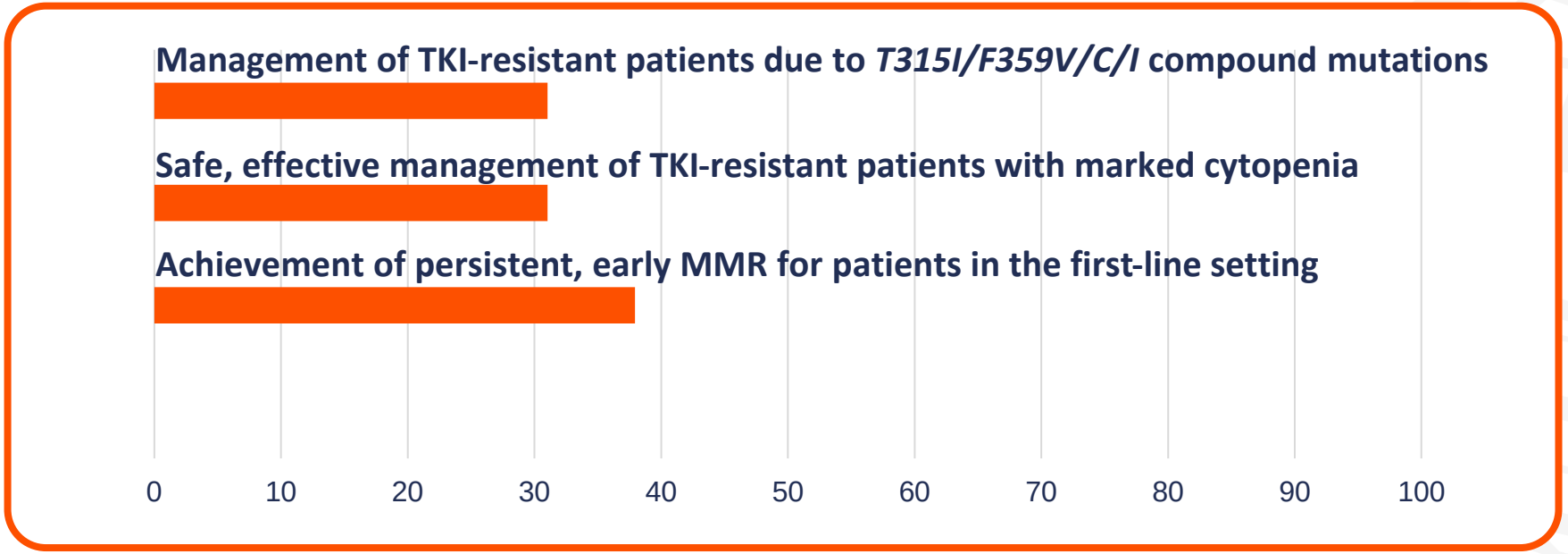
Poll question 3

Which of these aspects of the management of CML is the most important for future therapies to address?

a. Management of TKI-resistant patients due to *T315I/F359V/C/I* compound mutations
b. Safe, effective management of TKI-resistant patients with marked cytopenia
c. Achievement of persistent, early MMR for patients in the first-line setting

CML, chronic myeloid leukemia; MMR, major molecular response; TKI, tyrosine kinase inhibitor.

Poll question 3: Responses



MMR, major molecular response; TKI, tyrosine kinase inhibitor.

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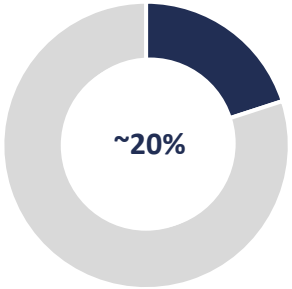
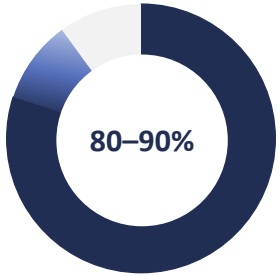
TKIs have changed the fate of many, but not all, patients with CML

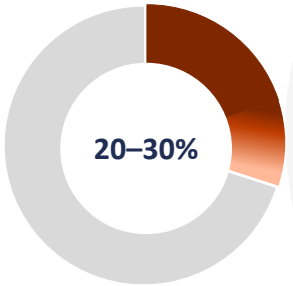
Pre-TKI
10-year overall survival[1]



Post-TKI
10-year overall survival[1]



Post-TKI
therapeutic failure[2]



- Intolerance
- Resistance

Significant overlap often exists between treatment resistance and intolerance;[2]
compliance and drug–drug interactions should be assessed before defining a patient as having TKI resistance[1]

CML, chronic myeloid leukemia; TKI, tyrosine kinase inhibitor.
1. Jabbour E, Kantarjian H. *Am J Hematol*. 2020;95:691–709; 2. Yeung DT, et al. *Blood*. 2022;139:3474–9.

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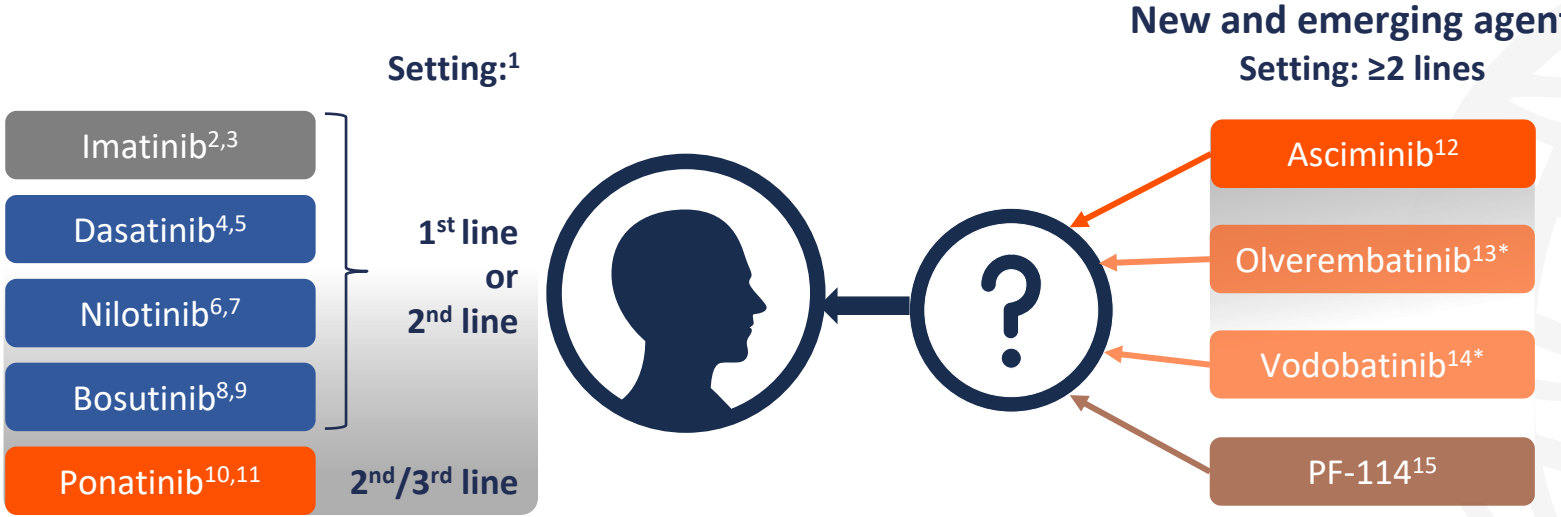
New and emerging TKIs may contribute to improving patient outcomes in later-line settings



Key concerns for effective management of patients with CML include adherence and tolerance to chronic treatment, onset of late and unexpected side effects, worsening of QoL, and high costs of TKI therapy[6]

*Trials with olverembatinib and vodobatinib included patients who had been treated with only one prior TKI.

CML, chronic myeloid leukemia; QoL, quality of life; TKI, tyrosine kinase inhibitor. 1. Hochhaus A, et al. *Leukemia*. 2020;34:966–84; 2. FDA. Imatinib PI; 3. EMA. Imatinib SmPC; 4. FDA. Dasatinib PI; 5. EMA. Dasatinib SmPC; 6. FDA. Nilotinib PI; 7. EMA. Nilotinib SmPC; 8. FDA. Bosutinib PI; 9. EMA. Bosutinib SmPC; 10. FDA. Ponatinib PI; 11. EMA. Ponatinib SmPC; 12. Réa D, et al. *Blood.* 2021;138:2031–41; 13. Jiang Q, et al. *J Hematol Oncol*. 2022;15:113; 14. Cortes JE, et al. *Blood*. 2021;138(Suppl. 1):309; 15. Turkina AG, et al. *Blood*. 2021; 138(Suppl. 1):1482; 16. Russo D, et al. *J Clin Med*. 2020;9:1709. All PIs are available at: Available at: www.fda.gov/drugs; All SmPCs are available at: www.ema.europa.eu (accessed 21 October 2022).

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Treatment can now be personalized to patients' specific needs and treatment goals

Patients with a life expectancy >5 years

Treatment goal
Treatment-free remission

Approach
A potent TKI that can potentially achieve DMR more quickly

Patients with a life expectancy <5 years, or with comorbidities

Treatment goals
Reduced toxicities; improved QoL; reduced costs over the long term

Approaches
Minimal effective dose
TKIs with fewer off-target effects

The main goal in CML treatment is to avoid potential progression to advanced phases; treatment strategies should be personalized according to the age and needs of individual patients

CML, chronic myeloid leukemia; DMR, deep molecular response; QoL, quality of life; TKI, tyrosine kinase inhibitor.
Russo D, et al. *J Clin Med*. 2020;9:1709.

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ELN 2020 guidelines recommend ponatinib following resistance to second-generation TKIs[1,2]

Considerations for benefit

Patient need
- Resistant/intolerant to 2G TKIs following ≥1 line of treatment

Mutation profile
- *T315I*
- Compound mutations

Disease risk
- Latency of molecular response
- Progression

Ponatinib[3]

Considerations for risk

Toxicities
- Comorbidities
- Lifestyle factors

Target effects
- Broad;[4] includes VEGFR 1–3 and PDGFR α/β

Mitigation strategies
- Dose reductions
- Prophylaxis
- Monitoring

Treatment with ponatinib represents a balance between a potentially higher response rate versus a higher probability of suffering serious side effects;[2] **asciminib, which was approved following the publication of the ELN 2020 guidelines, may have a role to play in this setting[5]**

2G, second generation; CV, cardiovascular; ELN, European LeukemiaNet; PDGFR, platelet-derived growth factor receptor; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

1. Hochhaus A, et al. *Leukemia*. 2020:966–84; 2. Russo D et al. *J Clin Med.* 2020;9:1709 3. EMA. Ponatinib SmPC. Available at: www.ema.europa.eu (accessed 21 October 2022); 4. Lee H, et al. *Int J Hematol*. 2021;113:632–41; 5. EMA. Asciminib SmPC. Available at: www.ema.europa.eu (accessed 21 October 2022).

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New and emerging TKIs enable further personalization of care for patients with CML in later-line settings

Asciminib[1] Approved (US,[2] EU[3])	Olverembatinib[5] Investigational	Vodobatinib[6] Investigational	PF-114[7] Investigational
Target: Myristoyl pocket	**Target:** ATP-binding site	**Target:** ATP-binding site	**Target:** ATP-binding site
Activity: Against most *ABL1* KD mutations[1] (incl. *T315I*)[2,4]	**Activity**: Against WT and mutant *BCR::ABL1* (incl. *T315I*)	**Activity:** Against WT and mutant *BCR::ABL1* (excl. *T315I*)	**Activity:** Against WT and mutant *BCR::ABL1* (incl. *T315I*)
Ph III (MMR, 24 wks) 26% vs 13% (bosutinib)	**Ph I/II (MMR, 34 mo*)** 56% (CP); 45% (AP)	**Ph I (MMR, 23 mo*)** 44%	**Ph I (MMR, ≥31 mo*)** 16%
Gr ≥3 AEs 51% vs 61% (bosutinib)	**Gr ≥3 AEs** 79%	**Gr ≥3 AEs** 60%	**AEs** No VOEs or deviations of ankle-brachial index

New and emerging agents have different safety profiles and sensitivities to specific mutations versus ponatinib

*Median follow-up. AE, adverse event; AP, advanced phase; ATP, adenosine triphosphate; CML, chronic myeloid leukemia; CP, chronic phase; Gr, grade; KD, kinase domain; MMR, major molecular response; mo, months; Ph, phase; TKI, tyrosine kinase inhibitor; VOE, vascular occlusive event; wk, week; WT, wild type.

1. Réa D, et al. *Blood.* 2021;138:2031–41; 2. FDA. Asciminib PI. Available at: accessdata.fda.gov/drugsatfda_docs/label/2021/215358s000Orig2lbl.pdf (accessed 21 October 2022); 3. EMA. Asciminib SmPC. Available at: www.ema.europa.eu (accessed 21 October 2022); 4. Hughes TP, *N Engl J Med*. 2019;381:2315–26; 5. Jiang Q, et al. *J Hematol Oncol*. 2022;15:113; 6. Cortes JE, et al. *Blood*. 2021;138(Suppl. 1):309; 7. Turkina AG, et al. *Blood*. 2021;138(Suppl. 1):1482.

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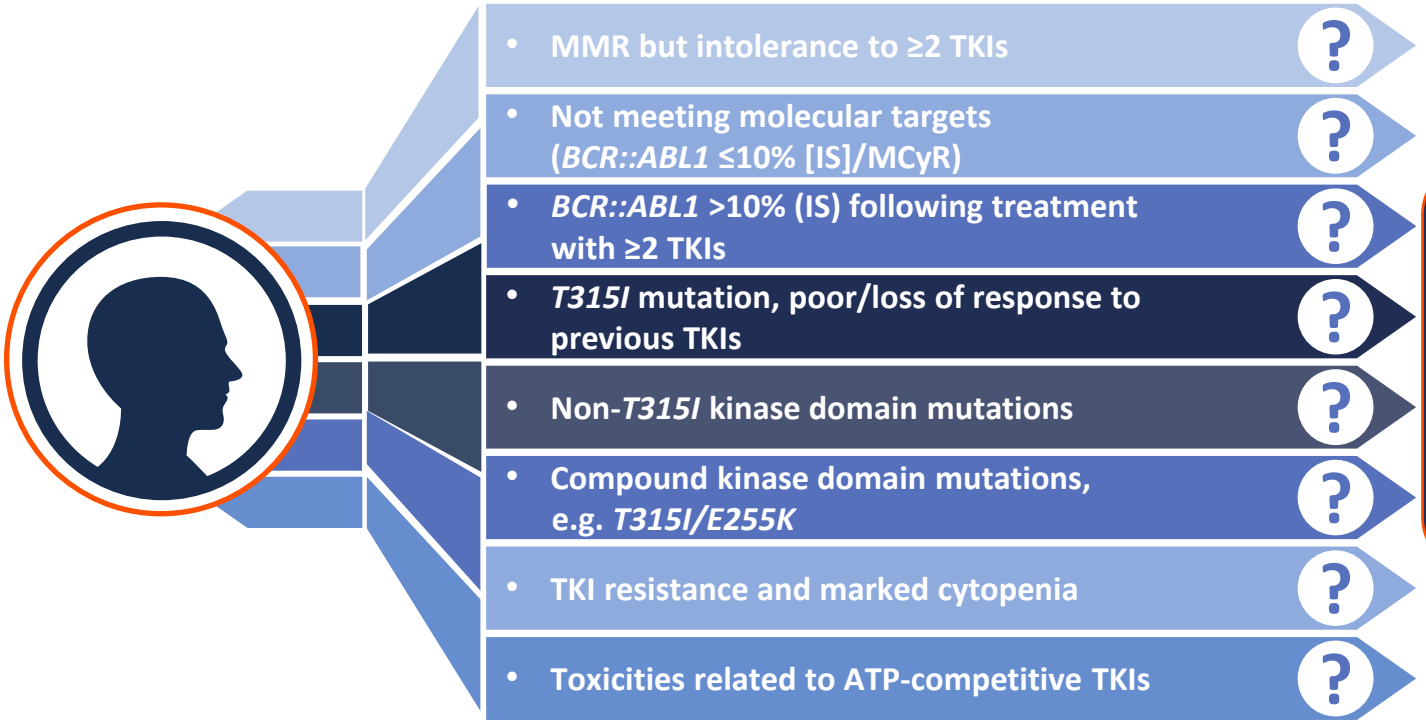
Decision making is challenging without head-to-head trials of new/emerging agents versus ponatinib



ATP, adenosine triphosphate; IS, International Scale; MCyR, major cytogenetic response; MMR, major molecular response; TKI, tyrosine kinase inhibitor.

Yeung DT, et al. *Blood*. 2022;139:3474–9.

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Available evidence from clinical trials can guide treatment decisions (1)

Clinical context	Treatment considerations
MMR, but intolerant to previous TKI	Data for new and emerging TKIs are positive[1–8]
Not meeting molecular targets (*BCR::ABL1* ≤10% [IS]/MCyR)	Data for new and emerging TKIs are positive;[1–9] more data are needed to determine their comparative efficacy
BCR::ABL1 >10% (IS) following treatment with ≥2 TKIs	Ponatinib (OPTIC trial subgroup analysis[10]); asciminib, ASCEMBL trial, patients with *BCR::ABL1* >10% at week 24 did not continue treatment;[8] TKI combinations may be effective in this context
Non-*T315I* kinase domain mutations	Ponatinib, or new and emerging TKIs, may be acceptable; more data on individual mutations are needed

IS, International Scale; MCyR, major cytogenetic response; MMR, major molecular response; TKI, tyrosine kinase inhibitor.

1. Yeung DT, et al. *Blood*. 2022;139:3474–9; 2. Réa D, et al. *Blood.* 2021;138:2031–41; 3. Hughes TP, *N Engl J Med*. 2019;381:2315–26; 4. NCT03106779; 5. NCT04126681; 6. Cortes JE, et al. *Blood*. 2021;138(Suppl. 1):309; 7. Turkina AG, et al. *Blood*. 2021;138(Suppl. 1):1482; 8. NCT02885766; 9. Jiang Q, et al. *J Hematol Oncol*. 2022;15:113; 10. Deininger M, et al. *Clin Lymphoma Myeloma Leuk*. 2022;22(Suppl. 2):S285–6; All clinical trials available at: ClinicalTrials.gov (accessed 21 October 2022).

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Available evidence from clinical trials can guide treatment decisions (2)

Clinical context	Treatment considerations
T315I mutation with consequent poor response/loss of response to previous TKIs	Ponatinib, asciminib, olverembatinib and PF-114 show efficacy;[1–5] longer follow-up data are needed for new and emerging agents and head-to-head trials to determine their comparative efficacy
Toxicities related to ATP-competitive TKIs	Asciminib may be preferred and may offer benefits where patients show features of both intolerance and resistance;[1,6] a low discontinuation rate vs bosutinib was observed in ASCEMBL[6]
Compound kinase domain mutations, e.g. *T315I/E255K*	Allograft is currently the preferred option; there are conflicting data for combinations of TKIs in this setting; clinical trials are required[1]
TKI resistance and marked cytopenia	Allograft may be the only effective therapy[1]

ATP, adenosine triphosphate; TKI, tyrosine kinase inhibitor.

1. Yeung DT, et al. *Blood*. 2022;139:3474–9. 2. EMA. Ponatinib SmPC. Available at: www.ema.europa.eu (accessed 21 October 2022); 3. Hughes TP, *N Engl J Med*. 2019;381:2315–26; 4. Jiang Q, et al. *J Hematol Oncol*. 2022;15:113; 5. Turkina AG, et al. *Blood*. 2021;138(Suppl. 1):1482; 6. Réa D, et al. *Blood.* 2021;138:2031–41.

A number of trials are in progress to address further unmet needs (1)

Asciminib, first-line setting[1]	Asciminib, first-line setting[2]	Olverembatinib + chemotherapy[3]
Trial ASC4FIRST (NCT04971226); Ph III Primary completion: Sept 2024	**Trial** ASC4START (NCT05456191); Ph III Primary completion: Feb 2027	**Trial** NCT05376852; Ph II Primary completion: Dec 2024
Patients ND with Ph+ CP-CML (N=402) Asciminib vs physician's choice*	**Patients** ND with Ph+ CP-CML (N=541) Asciminib vs nilotinib	**Patients** AP-CML or BP-CML (N=40)
Primary endpoint MMR at week 48	**Primary endpoint** Time to discontinuation of study treatment due to AE (TTDAE)	**Primary endpoint** ORR: CR or CRi after two cycles

A range of trials are in progress to address gaps in understanding of how to optimize potential benefits offered by new and emerging therapies

*Imatinib, dasatinib, nilotinib, or bosutinib.
AE, adverse event; AP, acute phase; BP, blast phase; CML, chronic myeloid leukemia; CP, chronic phase; CR, complete remission; CRi, CR with incomplete count recovery; MMR, major molecular response; ND, newly diagnosed; ORR, overall response rate; Ph, phase; Ph+, Philadelphia chromosome-positive.
All references available at ClinicalTrials.gov (accessed 21 October 2022). 1. NCT04971226; 2. NCT05456191; 3. NCT05376852.

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A number of trials are in progress to address further unmet needs (2)

TKIs + IFN-α[1]	TKI + ruxolitinib[2]	TKI + venetoclax[3]
Trial TIGER (NCT01657604); Ph III Primary completion: May 2022	**Trial** NCT03654768; Ph II Primary completion: Jan 2024	**Trial** NCT02689440; Ph II Primary completion: Dec 2040
Patients ND with Ph+ CP-CML (N=717) Nilotinib vs nilotinib + IFN-α	**Patients** CP-CML (≥12 months' TKI; no progression to AP or BP; N=84)	**Patients** CP-CML or Ph+ CP-CML (N=140)
Primary endpoint MMR at 18 months	**Primary endpoint** MR[4.5] TKI + ruxolitinib vs TKI at 12 months	**Primary endpoint** MMR up to 12 months

A range of trials are in progress to optimize patient outcomes through novel drug combinations involving TKIs

AP, accelerated phase; BP, blast phase; CML, chronic myeloid leukemia; CP, chronic phase; IFN, interferon; MMR, major molecular response; MR, molecular response; ND, newly diagnosed; Ph, phase; Ph+, Philadelphia chromosome-positive; TKI, tyrosine kinase inhibitor.
All references available at ClinicalTrials.gov (accessed 21 October 2022). 1. NCT01657604; 2. NCT03654768; 3. NCT02689440.

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Case-based panel discussion

Prof. Massimo Breccia

Sapienza University of Rome
Azienda Policlinico Umberto I
Rome, Italy

Prof. Susanne Saussele

University Clinic
Mannheim, Germany

Prof. Valentín García Gutiérrez

Ramón y Cajal University Hospital
Madrid, Spain

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Patient case study 1

Case history

- 74-year-old man
- Ph+ CP-CML
- Hypertension (good control)

TKI treatment history

- First line: Nilotinib (600 mg/d)
  - Severe exanthem (grade 3)
- Second line: Dasatinib (100 mg)
  - Hypertensive crisis (grade 3)
  - Dose reduction (100 mg→80 mg)
    - Pleural effusion still apparent
- Third line: Bosutinib (400 mg/d)
  - Diarrhea (persisted for 3 weeks)
  - Liver enzymes elevated following reduction to 300 mg/d

What therapeutic strategy should be employed next in this patient?

CP-CML, chronic phase-chronic myeloid leukemia; Ph+, Philadelphia chromosome-positive; TKI, tyrosine kinase inhibitor.

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Patient case study 2

Case history

- 44-year-old man
- ELTS score: high-risk
- Not using medication for any comorbidities

TKI treatment history

- First line: Nilotinib (600 mg/d)
  - Fast response; MMR achieved within 6 months; no severe AEs
  - Month 12: loss of MMR (confirmed with second PCR [0.02–0.2])
  - ACAs were diagnosed; no mutation
- Second line: Dasatinib (100 mg/d)
  - *BCR::ABL* (PCR) increased within 8 weeks

What therapeutic strategy should be employed next in this patient?

ACA, additional chromosome abnormalities; AE, adverse event; ELTS, EUTOS long-term survival score; MMR, major molecular response; PCR, polymerase chain reaction; TKI, tyrosine kinase inhibitor.

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Patient case study 3

Case history

- 31-year-old woman
- Recently diagnosed with Ph+ CP-CML and an isochromosome 17q
- WBC: 125,000

Prior treatment with TKIs

- Newly diagnosed

QoL needs

- She was planning to start a family prior to her diagnosis

What therapeutic strategy should be employed in this patient?

CP-CML, chronic phase-chronic myeloid leukemia; Ph+, Philadelphia chromosome-positive; QoL, quality of life; TKI, tyrosine kinase inhibitor; WBC, white blood cell count.