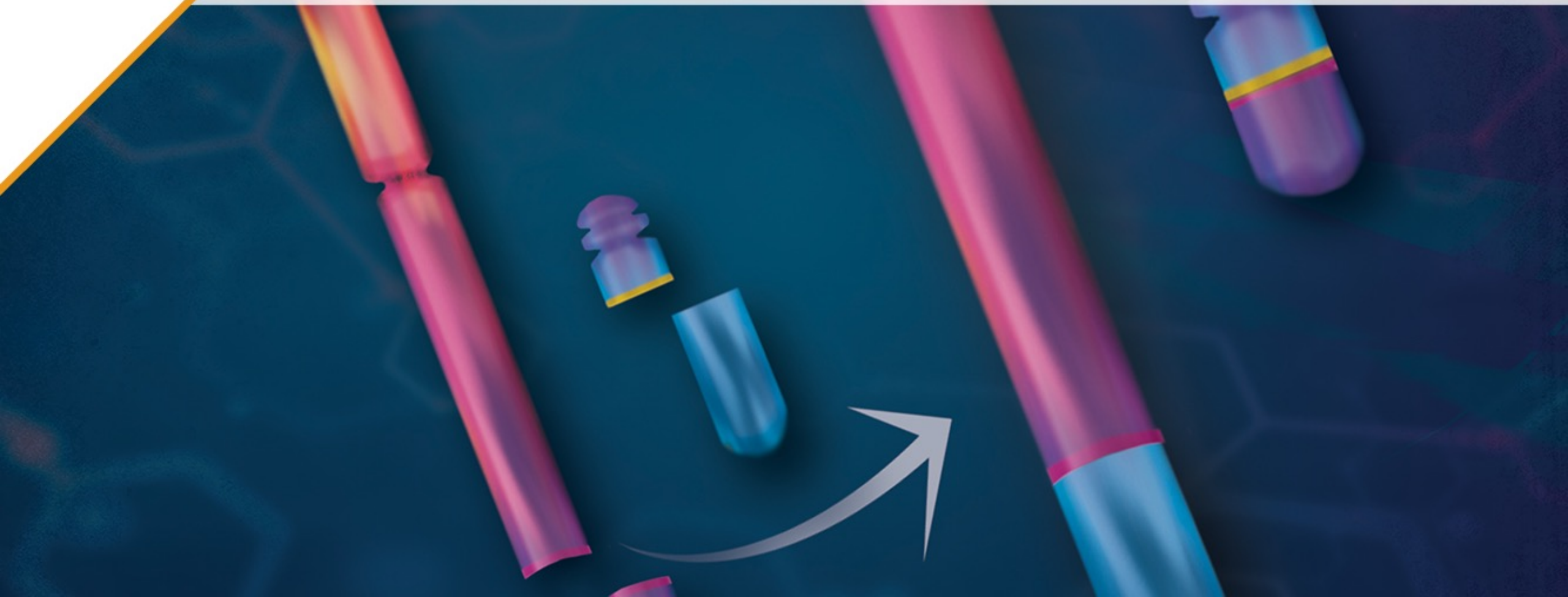
AXIS Medical Education

Response Matters:

Transforming the Standard of Care in CML by Mastering Response-Guided Treatment



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Learning Objectives

Upon completion of this activity, participants should be better able to:

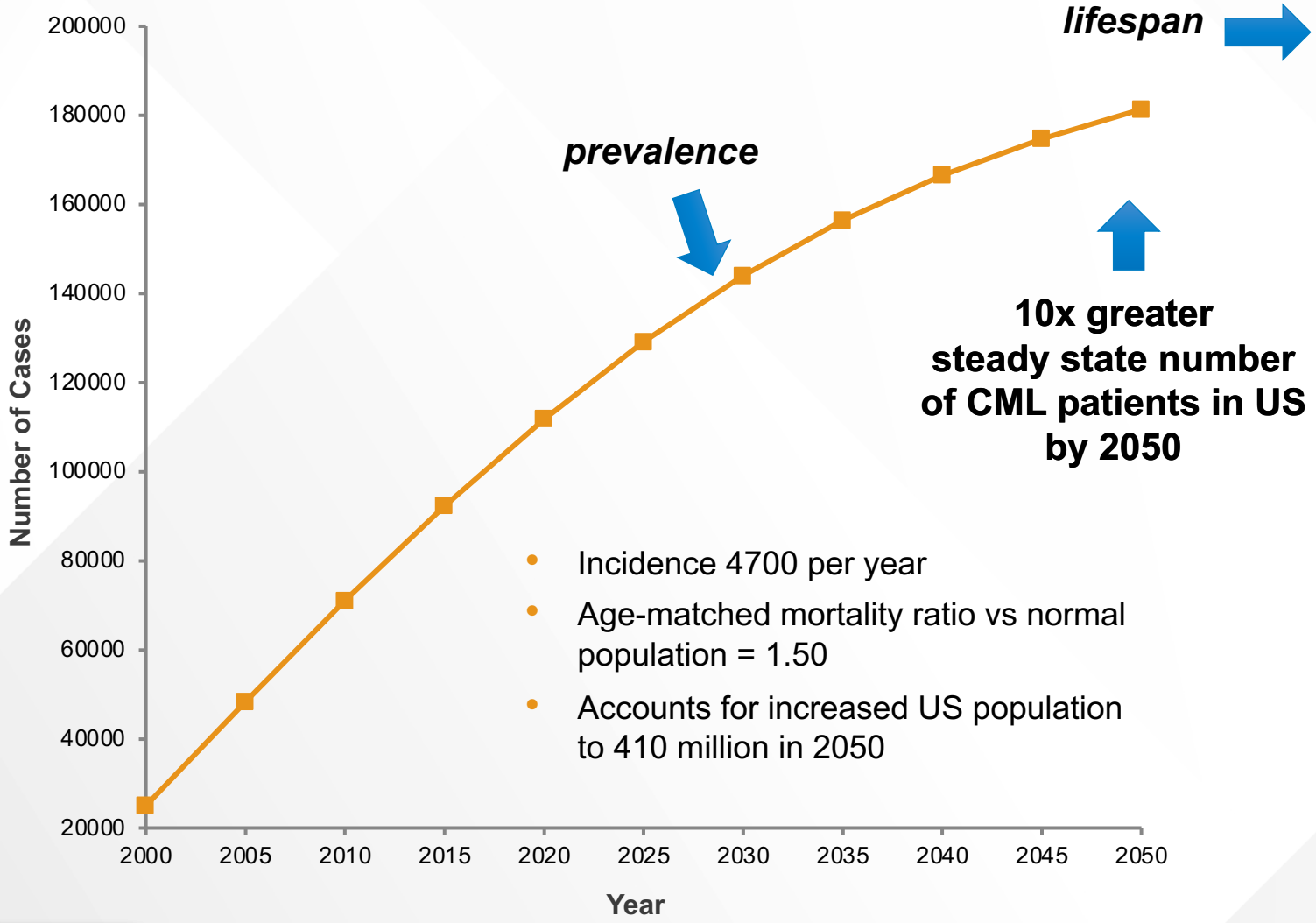
- Formulate strategies to individualize molecular testing in CML patients to drive appropriate treatment selection based on guideline recommendations, risk stratification, and treatment response.
- Apply updated guidelines, clinical trial data, and real-world evidence of 2nd and 3rd generation TKIs and BCR-ABL inhibitors to develop personalized treatment regimens for CML patients.
- Propose effective CML mitigation and management strategies for potential AEs and drug resistance.

Activity Agenda

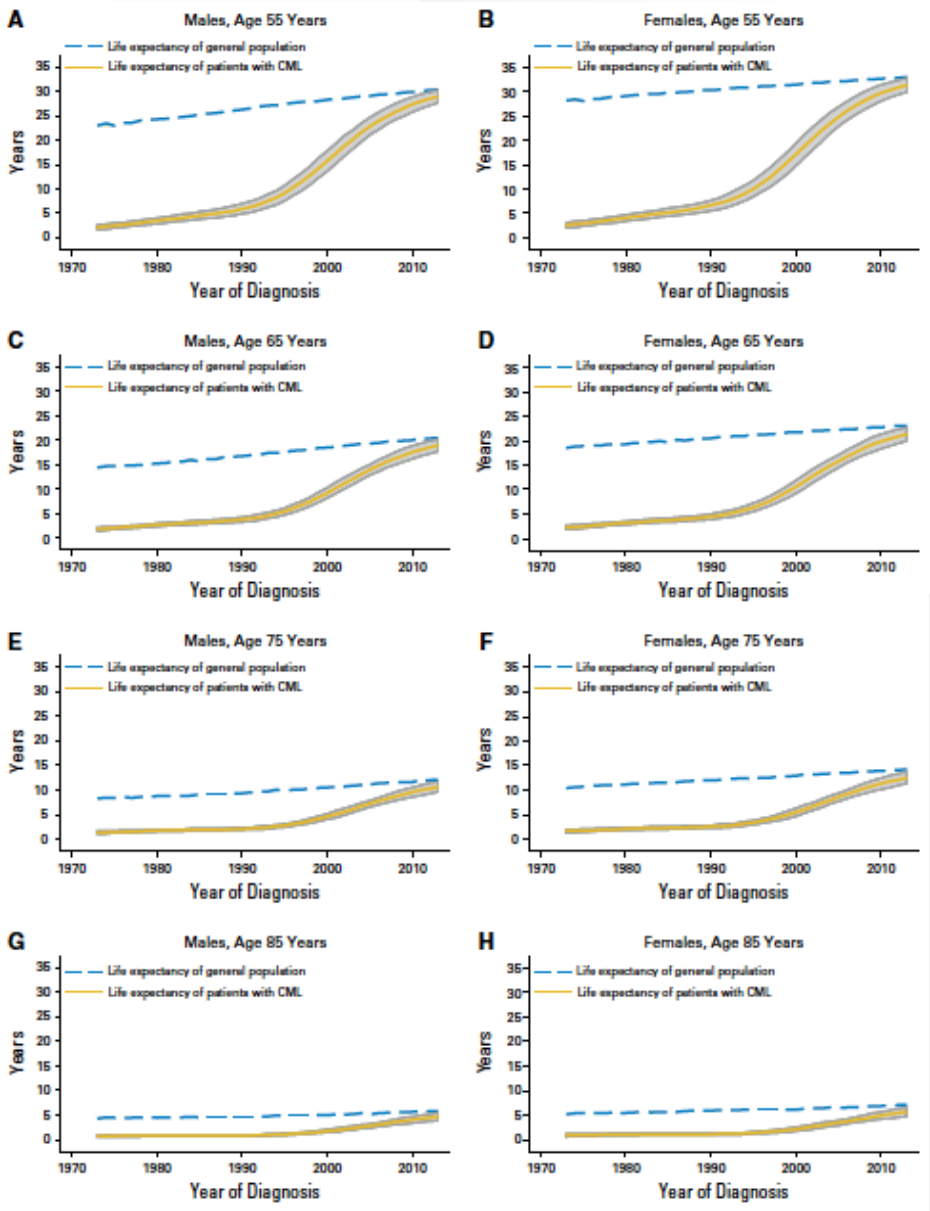
- Current and emerging detection methods
- Unmet needs in CML treatment
- Expanding treatment options for CML
- Future directions
- Case study and key takeaways

Current and Emerging Detection Methods

CML Is an Increasingly Prevalent and Survivable Cancer

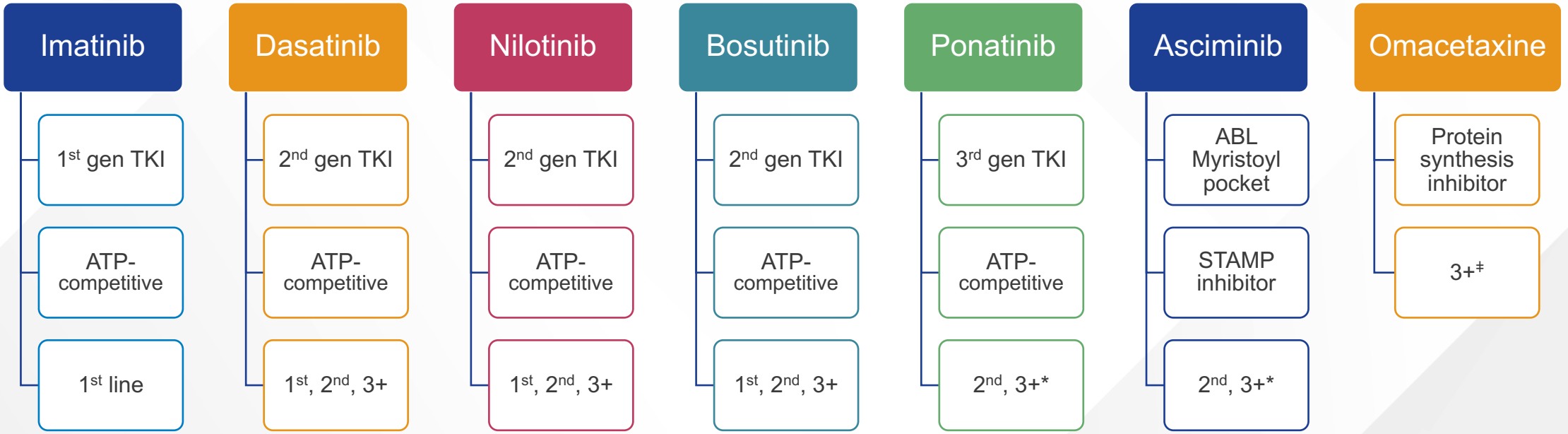


- Incidence 4700 per year
- Age-matched mortality ratio vs normal population = 1.50
- Accounts for increased US population to 410 million in 2050



Huang X, et al. *Cancer.* 2012;118(12):3123-3127. Bower H, et al. *J Clin Oncol.* 2016;34:2851-2857.

Currently Available CML Therapies



Ex-US: Flumatinib (1st line, 2nd gen TKI) from China
Olverembatinib (3rd gen TKI with activity in TKI-resistant *T315I*-mutant CP-CML) from China
Radotinib (1st line, 2nd gen TKI) from South Korea

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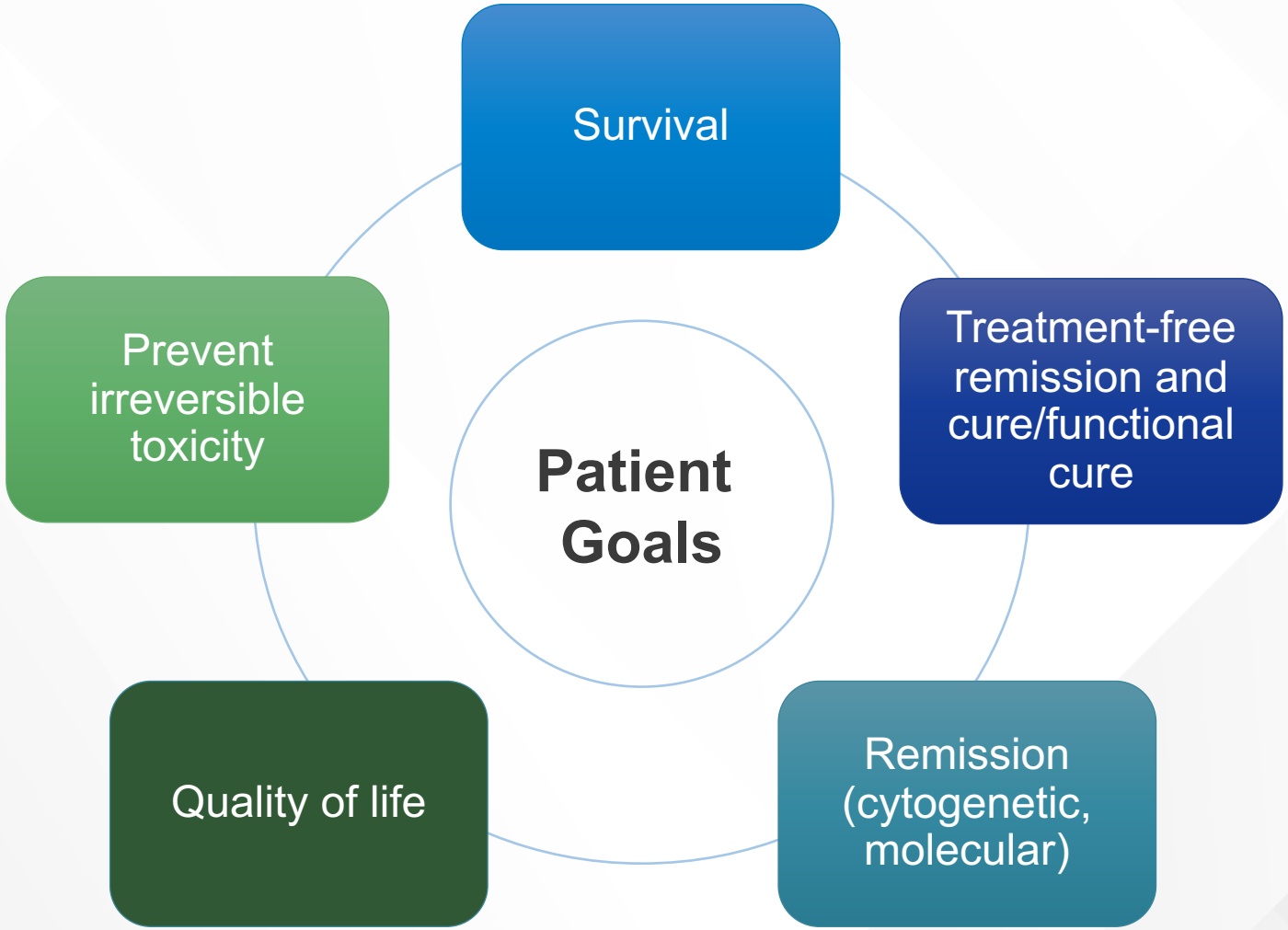
*Approved in US for a patients after ≥2 TKIs or for patients with T315I CP-CML in any line; ‡Only available in the US.

Hochhaus A, et al. *Leukemia* 2020;34: 966-984. Shah NP, et al. NCCN Guidelines. Chronic Myeloid Leukemia. V1.2024. Garcia-Gutierrez V, et al. *J Hematol Oncol.* 2022;15:90.

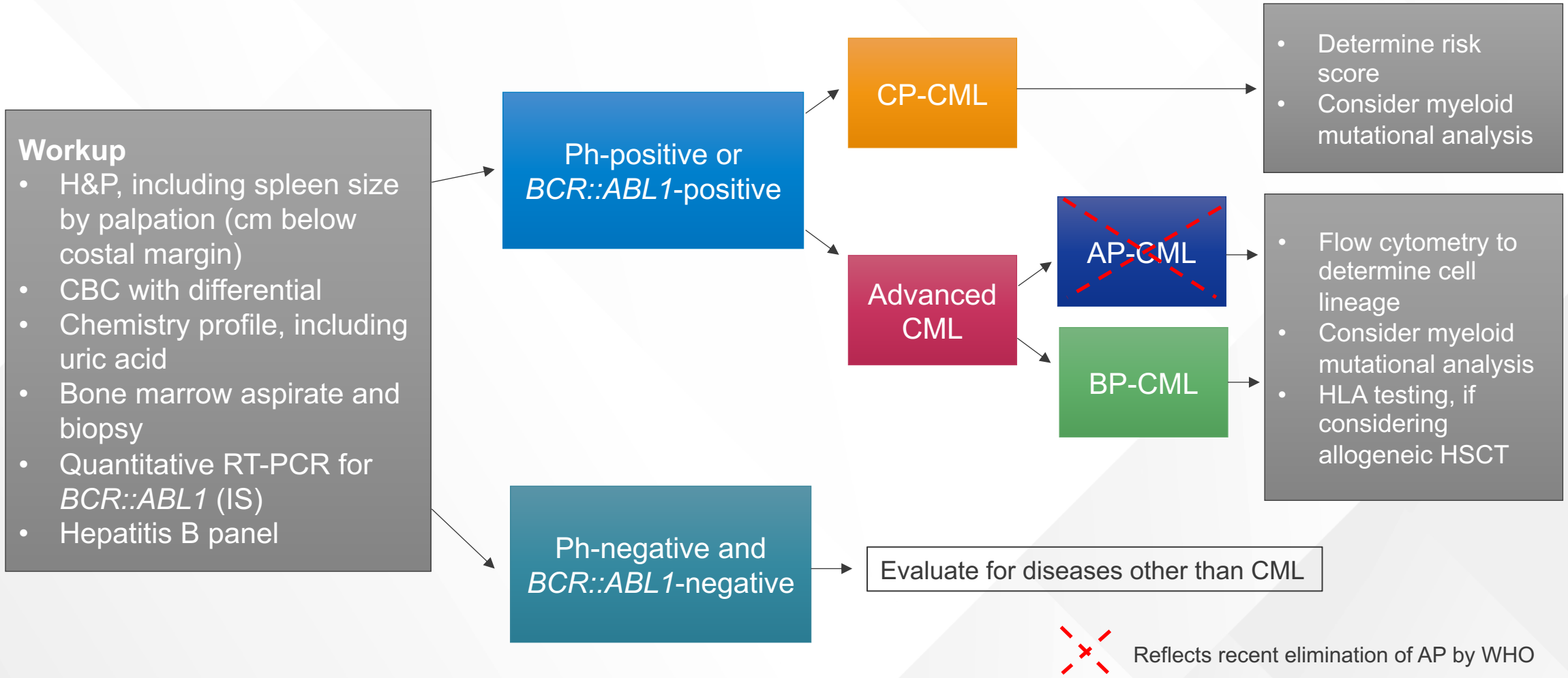
ATP, adenosine triphosphate; STAMP, specifically targeting the ABL myristoyl pocket; TKI, tyrosine kinase inhibitor.

Goal Considerations with Current Therapy



Senapati J, et al. *Blood Cancer J.* 2023;13(1):58. Mikhaeel S, et al. *Clin Lymphoma Myeloma Leuk.* 2023;23(5):333-339. Mahon FX. *Best Pract Res Clin Haematol*. 2016;29(3):308-313.

NCCN Guidelines for CML Workup



Shah NP, et al. NCCN Guidelines. Chronic Myeloid Leukemia. V1.2024. Khoury JD, et al. *Leukemia.* 2022;36:1703-1719.
AP, accelerated phase; BP, blastic phase; CBC, complete blood count; CML, chronic myeloid leukemia; CP, chronic phase; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplant; RT-PCR, reverse transcription polymerase chain reaction; WHO, World Health Organization.

Risk Stratification

	Sokal	Hasford	EUTOS
Year Introduced	1984	1998	2011
Factors	• Age • Spleen size • Platelet count • Percentage of blasts	• Age • Spleen size • Platelet count • Percentage of blasts • Percentage of basophils • Percentage of eosinophils	• Spleen size • Basophil count
Risk Groups	• High (score >1.2) • Intermediate (score 0.8–1.2) • Low (score <0.8)	• High (score >1,480) • Intermediate (score >780; ≤1480) • Low (score ≤780)	• High (score >87) • Low (score ≤87)

2016: EUTOS long-term survival score (ELTS) – superior to Sokal for prediction of survival in CML patients

Pinilla-Ibarz J, et al. *Onco Targets Ther.* 2016;9:4937-4957. Shah NP, et al. NCCN Guidelines. Chronic Myeloid Leukemia. V1.2024.
Pfirrmann M, et al. *Leukemia*. 2020;34:2138-2149.
CML, chronic myeloid leukemia.

Pearls for Front-Line Therapy Choice in CML

Specifics	Imatinib	Nilotinib	Dasatinib	Bosutinib
Generation	1st generation	2nd generation	2nd generation	2nd generation
Pearls	• Timing of dosing matters – with food, largest meal best • PM dosing to minimize waking hour side effects (like GI)	• Advise patients on food exclusion (fasting 2 hours before and 1 hour after taking) and strategies to minimize poor adherence • Always check for drug-drug interactions, given risk for QT prolongation • Avoid H2 blockers/PPIs if possible (not contraindicated)	• Advise patients to not start proton pump inhibitors as they can reduce drug exposure by 50% • PPIs are readily accessible but contraindicated	• While not on-label, many physicians start initially for a brief period at lower dose to minimize early onset diarrhea • Have patients prepared with anti-diarrhea medications
Possible contraindications/ Anticipatory concerns	None	Uncontrolled CV/vascular disease Severe diabetes QT prolonging conditions, required meds	Pre-existing PAH Severe pulmonary disease	Inflammatory bowel disease
Contraindications (FDA label)	None	Hypokalemia, hypomagnesemia, long QT syndrome	None	Bosutinib hypersensitivity
Dosing	400 mg once a day	300 mg twice a day (400 mg twice a day is the dose in ≥ 2nd line)	100 mg once a day	400 mg once a day (500 mg once a day is targeted dose in ≥ 2nd line)

Slide courtesy of Michael J. Mauro, MD

GI, gastrointestinal; PPI, proton pump inhibitor.

Response Definitions

CHR

Normalization of peripheral blood counts with leukocyte count <10 x 10^9/L

Platelet count <450 x 10^9/L

No immature cells in PB

No signs and symptoms of disease with resolution of palpable splenomegaly

Cytogenetic Response

CCyR: No Ph-positive metaphases

MCyR: 0%–35% Ph-positive metaphases

PCyR: 1%–35% Ph-positive metaphases

Minor cytogenetic response: >35%–65% Ph-positive metaphases

Molecular Response

EMR: *BCR::ABL1* (IS) ≤10% at 3 and 6 months

MMR: *BCR::ABL1* (IS) ≤0.1% or ≥3-log reduction in *BCR::ABL1* transcripts from the standardized baseline, if qPCR (IS) is not available

DMR: MR4.0: *BCR::ABL1* (IS) ≤0.01% or MR4.5: BCR::ABL1 (IS) ≤0.0032%

Relapse

- Any sign of loss of hematologic response
- Any sign of loss of CCyR or its molecular response correlate (MR2.0: *BCR::ABL1* [IS] ≤1%) – defined as an increase in *BCR::ABL1* transcript to >1% or its molecular response correlate (MR2.0: *BCR::ABL1* [IS] ≤1%) – defined as an increase in *BCR::ABL1* transcript to >1%
- 1-log increase in *BCR::ABL1* transcript levels with loss of MMR8

The loss of MMR in the presence of a CCyR does not necessarily indicate inadequate response to Tx.

Shah NP, et al. NCCN Guidelines. Chronic Myeloid Leukemia. V1.2024.

CCyR, complete cytogenetic response; CHR, complete hematologic response; DMR, deep molecular response; EMR, early molecular response; MCyR, major cytogenetic response; MMR, major molecular response; PB, peripheral blood; PCyR, partial cytogenetic response.

Monitoring Recommendations

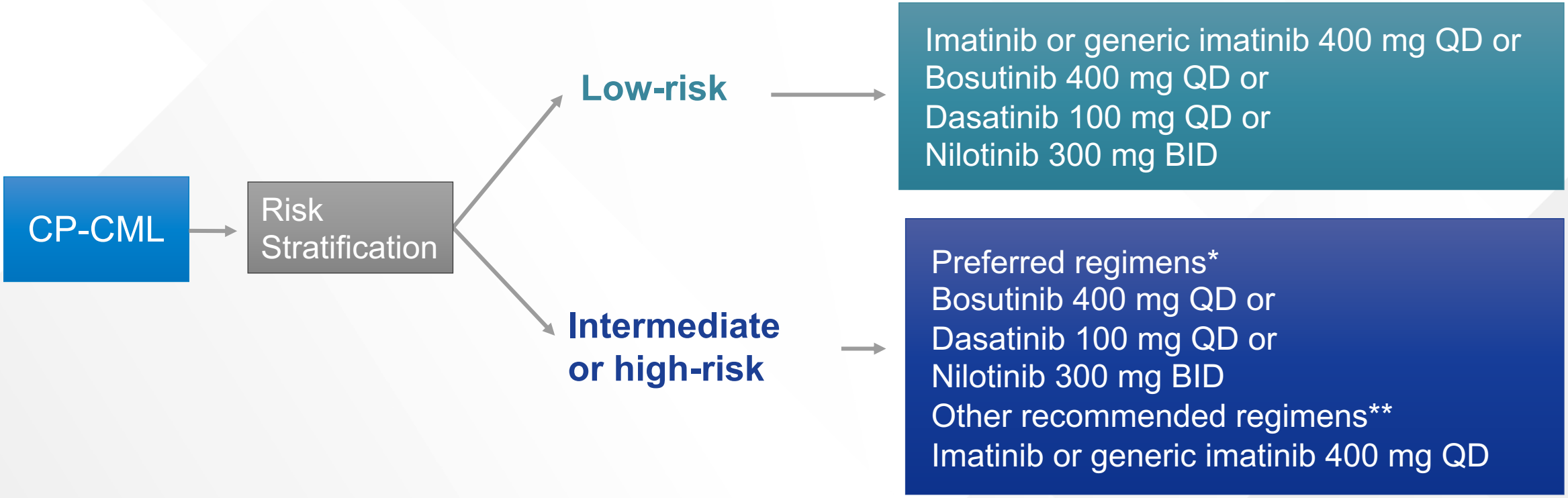
Test	Recommendation
Bone marrow cytogenetics	• At diagnosis • Response milestones not reached • Any sign of loss of hematologic response • Any sign of loss of CCyR or its molecular response correlate (MR2.0: *BCR::ABL1* [IS] ≤1%) – defined as an increase in *BCR::ABL1* transcript to >1%
qPCR using IS	• At diagnosis • Every 3 mos after initiating treatment • After *BCR::ABL1* (IS) ≤1% (MR2.0) has been achieved, every 3 mo for 2 y and every 3–6 mo thereafter • If there is a 1-log increase in *BCR::ABL1* transcript levels with MMR, qPCR should be repeated in 1–3 mo

BCR::ABL1 kinase domain mutation analysis	• CP-CML
	• Response milestones not reached
	  • Any sign of loss of hematologic response
	  • Any sign of loss of CCyR or its molecular response correlate (MR2.0: *BCR::ABL1* [IS] ≤1%) – defined as an increase in *BCR::ABL1* transcript to >1%
	  • 1-log increase in *BCR::ABL1* transcript levels and loss of MMR
	• Disease progression to AP-CML or BP-CML

Shah NP, et al. NCCN Guidelines. Chronic Myeloid Leukemia. V1.2024.

AP, accelerated phase; BP, blastic phase; CCyR, complete cytogenetic response; CML, chronic myeloid leukemia; CP, chronic phase; IS, International Scale; MMR, mismatch repair; qPCR, quantitative polymerase chain reaction.

NCCN Guidelines: First-Line Treatment



*Based on follow-up data from the BFORE, DASISION and ENESTnd trials, second-generation TKIs are preferred for patients with an intermediate- or high-risk score, especially for young women whose goal is to achieve a deep and rapid molecular response and eventual discontinuation of TKI therapy for family planning purposes. **Imatinib may be preferred for older patients with comorbidities such as cardiovascular disease

Shah NP, et al. NCCN Guidelines. Chronic Myeloid Leukemia. V1.2024.

BID, twice per day; CML, chronic myeloid leukemia; CP, chronic phase; QD, four times per day; TKI, tyrosine kinase inhibitor.

NCCN Response Milestones

BCR::ABL1 (IS)	3 mo	6 mo	12 mo
>10%	Possible TKI resistance	TKI-resistant disease	
>1% - 10%	TKI-sensitive disease		Possible TKI resistance
>0.1 - 1%	TKI-sensitive disease		TKI-sensitive disease
≤0.1%	TKI-sensitive disease		

Color	Concern	Clinical Considerations	Recommendations
	TKI-resistant disease	• Evaluate patient compliance and drug interactions • Consider mutational analysis	Switch to alternate TKI and evaluate for allogeneic HCT
	Possible TKI resistance	• Evaluate patient compliance and drug interactions • Consider mutational analysis • Consider bone marrow cytogenetic analysis to assess for MCyR at 3 mo or CCyR at 12 mo	Switch to alternate TKI or continue same TKI (other than imatinib) and consider evaluation for allogeneic HCT
	TKI-sensitive disease	• If treatment goal is long-term survival: ≤1% optimal • If treatment goal is TFR: ≤0.1% optimal	• If optimal: continue same TKI • If not optimal: shared decision-making with patient
	TKI-sensitive disease	• Monitor response and side effects	Continue same TKI

Shah NP, et al. NCCN Guidelines. Chronic Myeloid Leukemia. V1.2024.
CCyR, complete cytogenetic response; HCT, hematopoietic cell transplantation; IS, International Scale; TKI, tyrosine kinase. inhibitor.

European LeukemiaNet 2020 Recommendations

Time	ELN Optimal	ELN Warning	ELN Failure
Baseline	NA	High-risk ACA, high-risk ELTS score	NA
3 mo	≤ 10%	> 10%	> 10% if confirmed within 1-3 months
6 mo	≤ 1%	>1-10%	>10%
12 mo	≤ 0.1%	>0.1 - 1%	>1%
Any time	≤ 0.1%	>0.1 - 1%, loss of ≤ 0.1% (MMR)	>1%, resistance mutations, high-risk ACA

Hochhaus A, et al. *Leukemia*. 2020;34(4):966-984.
ACA, additional chromosomal abnormalities; ELTS, EUTOS long-term survival; MMR, mismatch repair.

Real-World Monitoring of CML

- TARGET-UK: ELN recommendations for monitoring CML not consistently performed, creating greater risk for relapse
  - 23% of patients with treatment failure did not switch treatment
  - 49% of patients switching due to treatment failure underwent kinase domain mutation analysis
- Other real-world studies have shown lower rates of switching than those observed in clinical trials
  - This may be due to protocol-mandated switching in clinical trials when inadequate treatment response is observed
- Patients who do not switch TKI are more likely to achieve clinical response
  - CCyR in 87.5% of patients switching TKI within 3 years of initiation vs 91.7% of non-switchers
- Intolerance is a key driver for switching
  - 3-yr OS: 95.3% switchers and 96.4% non-switchers

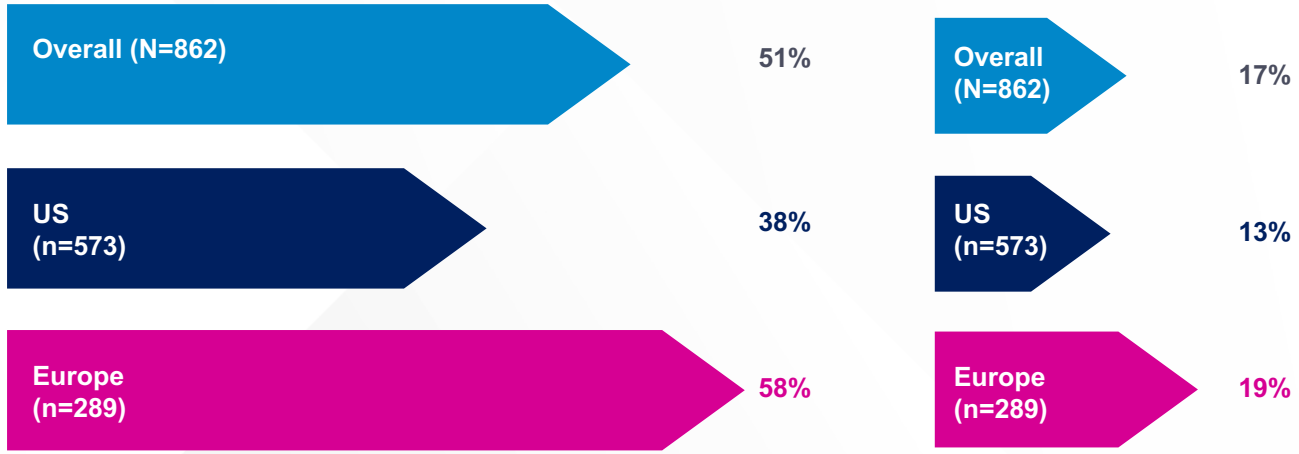
Milojkovic D, et al. *Br J Haematol*. 2021;192(1):62-74. Garcia-Gutierrez V, et al. *J Hematol Onc*ol. 2022;15(1):90. Gambacorti-Passerini C, et al. *Eur J Haematol*. 2021;106(1): 82-89.

CML, chronic myeloid leukemia; ELN, European LeukemiaNet; TKI, tyrosine kinase inhibitor.

Real-World Monitoring and Switching TKIs in CML: SIMPLICITY Data

About 1 in every 5 patients are not tested for MR at 12 months and almost half are not tested for CyR

Patients not tested for CyR at 12 months[1]

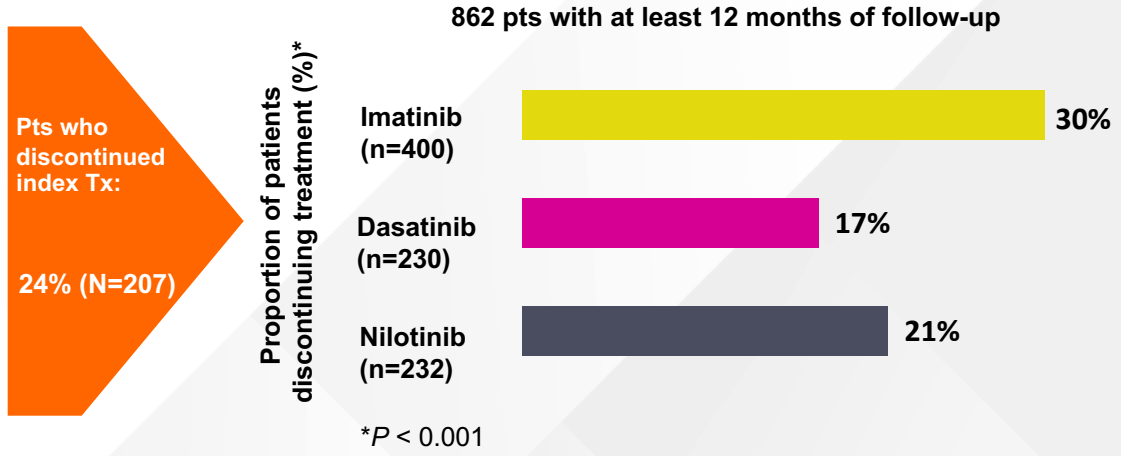


Patients not tested for MR by 12 months[1]

Age <65 years at initiation of first-line TKI, patients who had switched from first-line TKI and those seen in academic centers were more likely to be monitored by 12 months ($P < 0.05$)[2]

SIMPLICITY is a large observational study of front-line therapy for CML in both academic and community sites in the EU and US which has published several reports on monitoring, switching, and response outcomes

A quarter of SIMPLICITY patients discontinue TKI treatment in first 12 months



1. Goldberg SL, et al. *J Clin Oncol*. 2014;32(suppl 15):7050. 2. Goldberg SL, et al. *J Clin Oncol*. 2014;32(suppl 30):116.
CyR, cytogenetic response; MR, molecular response; TKI, tyrosine kinase inhibitor.

Treatment-Free Remission

Considerations

- Discussion of TFR is especially important for younger patients
- **Longer time in DMR (MR4 or MR4.5) yields better success**
  - Duration in DMR >2 years: 3-year TFR rates = 40%–50%
  - Duration ≥5 years: 5-year TFR rate of > 80%
- The ability to regularly and frequently monitor patients in TFR is critical

Factors influencing TFR Success

- Longer duration of imatinib treatment*
- Sokal risk score
- Fluctuations of *BCR::ABL1* levels
- Maintenance of MR4.5 in first 3-4 mo post TFR

*shorter exposure may be needed with 2G TKIs

García-Gutiérrez V, et al.. *J Hematol Oncol*. 2022;15(1):90.

DMR, deep molecular response; TFR, treatment-free remission.

Unmet Needs in CML Treatment

Recognizing Suboptimal Responses or Treatment Failures

Factors Influencing CML TKI Selection

First line

- Goals of therapy
- Patient comorbidities and risk of AEs
  - General health assessment; align with primary/subspecialty provider(s)
  - For many: assessment of CV risk
- Appraisal of patient concerns/questions regarding toxicity, dosing, etc
- Guidance on importance of adherence and chronicity of therapy
  - Minimum several years at present; potentially longer

Subsequent lines

- Disease specifics: phase, prior exposure, prior AEs, mutations
- If not initially assessed, formal CV risk assessment informative to guide AE avoidance and management

All lines

- Cost (payer, patient, healthcare system)
- Access

Osman AEG, et al. *Blood Rev.* 2021;49:100825.
AE, adverse event; CV, cardiovascular.

Key Discussions With Patients

- Life expectancy
- Impact of comorbidities
- QoL / how to minimize adverse events
- Medication adherence
- Treatment-free remission
- Costs
- Family planning

Shah NP, et al. NCCN Guidelines. Chronic Myeloid Leukemia. V1.2024.
QoL, quality of life.

Unmet Needs in CML in 2023

- Multi-TKI resistant disease
  - Exhausted all available TKIs
  - Resistance may be complex
  - Prior response may be limited/none, progression risk likely higher
- Multi-TKI resistance/intolerance
  - Limitations on TKI, dose, etc.
  - “Contraindications” to select TKIs
  - Prior response variable
- Optimal front-line therapy
  - Minimize resistance
  - Maximize efficiency and achievement of DMR
- Improve earlier salvage
  - Limited/poor response to aggressive front line (2G TKI)
  - Limit mutation-based resistance and ‘other’ resistance
- Improve management of select resistance (T315I)

Also: Blast phase disease (now redefined by WHO, encompassing prior accelerated phase), pediatrics, etc.

Slide courtesy of Michael J. Mauro, MD

CML, chronic myeloid leukemia; DMR, deep molecular response; TKI, tyrosine kinase inhibitor; WHO, World Health Organization

How Can Therapy Fail the CP-CML Patient?

- Primary hematologic resistance: exceedingly rare
- Minimal transcript reduction: slow/no "EMR," persistent *BCR::ABL* >1%-10% (no CCyR)
  - Ominous: may predict for inferior response to salvage
- CCyR but failure to achieve MMR: "kinetic failure" (18 to 24-mo window)
  - Protection from progression but EFS lower with higher resistance risk
- MMR but remains between 0.1% and 0.01%: "safe harbor," ? imperfect
- TFR based on current guidelines not feasible
- DMR (<0.01%) but PCR "positive": not failure

BCR::ABL1 (IS)	3 mo	6 mo	12 mo
>10%	Possible TKI resistance	TKI-resistant disease	
>1% - 10%	TKI-sensitive disease		Possible TKI resistance
>0.1 - 1%	TKI-sensitive disease		TKI-sensitive disease
≤0.1%	TKI-sensitive disease		

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Slide courtesy of Michael J. Mauro, MD. Table adapted from Shah NP, et al. NCCN Guidelines. Chronic Myeloid Leukemia. V1.2024.
CCyR, complete cytogenetic response; CML, chronic myeloid leukemia; CP, chronic phase; DMR, deep molecular response; EFS, event-free survival; EMR, early molecular response; MMR, major molecular response; PCR, polymerase chain reaction.TFR, treatment-free remission; TKI, tyrosine kinase inhibitor.

Know Your Tools: Comparing TKI Toxicities

Issue	Imatinib	Nilotinib	Dasatinib	Bosutinib	Ponatinib	Asciminib
Dosing	QD/BID, with food	BID, without food (2h)	QD, w/ or w/o food	QD, with food	QD, w/ or w/o food	QD or BID, w/o food; dosing varies (T315I or not)
Long term safety	Most extensive	Extensive; Emerging toxicity	Extensive; Emerging toxicity	Extensive, No emerging toxicity	More limited but increasing; Emerging toxicity	Emerging; long phase I data (8y)
Heme toxicity	Intermediate	Least	Most severe; ASA-like effect; Lymphocytosis	Comparable to dasatinb in 2nd, 3rd line; Comparable to nilotinib in 1st line	Thrombocytopenia ASA-like effect	Thrombocytopenia Neutropenia
Non-Heme toxicity	Edema, GI effects (diarrhea, nausea), Muscle cramps, ↓Phos	↑Lipase, ↑Bili, ↑Chol, ↑Glu, Fatigue, Musculo-skeletal symptoms, Black box: QT prolongation	Headache (early/transient) Pleural / pericardial effusions	Diarrhea; Transaminitis	↑Lipase, Pancreatitis, Rash, Hypertension, Black box: vascular occlusion, heart failure, and hepatotoxicity	↑Lipase, Pancreatitis, Hypertension, Hypersensitivity reaction, Possible cardiovascular adverse events
Potential special concerns	**Early question re: CHF, late renal effects**	**Vascular events (ICVE, IHD, PAD)**	**PAH (pulmonary arterial hypertension)**	**Mild renal effects**	**Vascular events (ICVE, IHD, PAD, VTE)**	**Longer follow-up needed re: cardiovascular AEs**

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Slide courtesy of Michael J. Mauro, MD. Content derived from Shah NP, et al. NCCN Guidelines. Chronic Myeloid Leukemia. V1.2024. Senapati J, et al. *Blood Cancer J.* 2023;13(1):58. BOSULIF (bosutinib). Package insert. Pfizer, Inc.; 2023. GLEEVEC (imatinib mesylate). Package insert. Novartis Pharmaceuticals Corp.; 2022. ICLUSIG (ponatinib). Package insert. Takeda Pharmaceuticals U.S.A., Inc.; 2022. SCEMBLIX (asciminib). Package insert. Novartis Pharmaceuticals Corp.; 2023. SPRYCEL (dasatinib). Package insert. Bristol Myers Squibb; 2023. TASIGNA (nilotinib). Package insert. Novartis Pharmaceuticals Corp.; 2021.
AE, adverse event; BID, twice per day; CHF, congestive heart failure; ICVE, ischemic cerebrovascular event; IHD, ischemic heart disease; PAD, peripheral artery disease; QD, four times per day; TKI, tyrosine kinase inhibitor; VTE, venous thromboembolism.

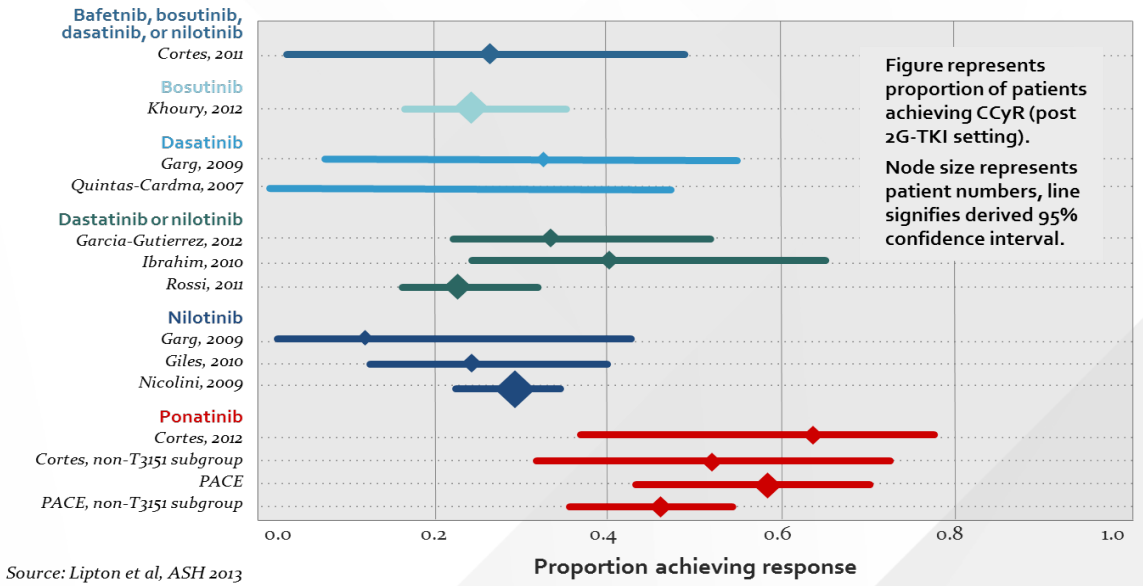
Key Steps When Milestones are Not Being Met

- Determine if milestones are not met due to toxicity or resistance
  - Discuss medication adherence
  - Ensure toxicities are being managed appropriately
    - Consider dose modifications
- *BCR::ABL1* resistance mutation analysis
  - Select next best agent based on mutation profile, prior TKI treatment, and patient comorbidities

Shah NP, et al. NCCN Guidelines. Chronic Myeloid Leukemia. V1.2024. Senapati J, et al. *Blood Cancer J.* 2023;13(1):58.
TKI, tyrosine kinase inhibitor.

Choosing Salvage

TKI	Dasatinib[1,2]		Nilotinib		Bosutinib
Follow-up	2 years[1,2] (minimum follow-up)	6 years[3] (data lock at 6y)	2 years[4] (minimum follow-up)	4 years[5] (minimum follow-up)	2 years[6] (minimum follow-up)
Number of pts	167*	167*	226	321*	200
Discontinued, n (%)	NR	114 (69)	197/321 (61)	224 (70)	108 (54)
MCyR	**63%***	NR	**56%**	59*	**58%**
CCyR	**50%***	NR	**41%**	45*	**46%**
PFS, %	**80***	49*	**64***	57*	**81***



Source: Lipton et al, ASH 2013

Point 1

2G TKI post imatinib: response is similar

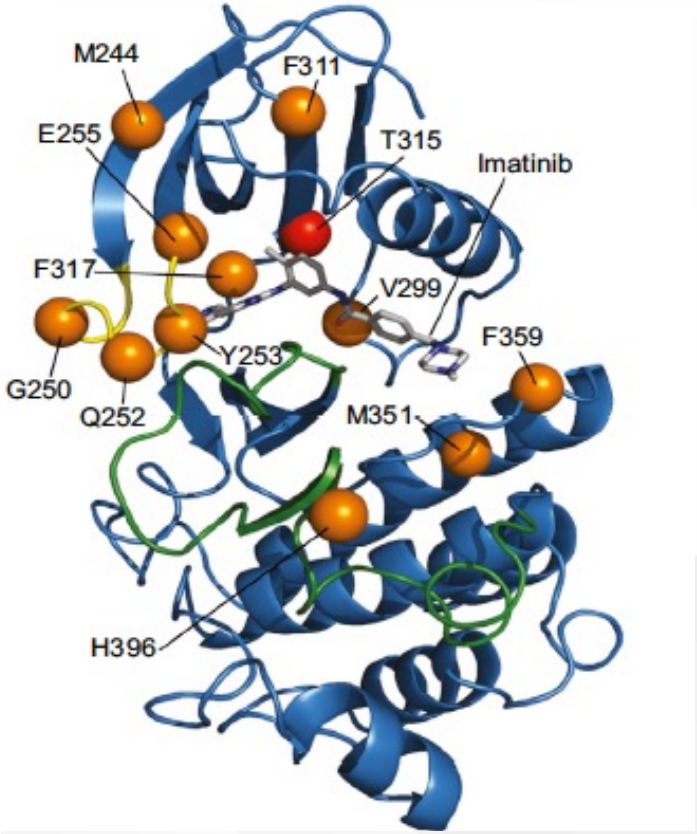
Point 2

"Recycling 2G TKIs" In this analysis, switching to ponatinib improved CCyR

1. SPRYCEL (dasatinib). Package insert. Bristol Myers Squibb; 2023. 2. Shah NP, et al. J Clin Oncol. 2010;28(suppl 15):6512. 3. Shah NP, et al. Blood. 2014;123(15):2317-244. 4. Kantarjian HM, et al. Blood. 2011;117(4):1141-1145. 5. Giles FJ, et al. Leukemia. 2013;27(1):107-112. 6. Gambacorti-Passerini C, et al. Am J Hematol. 2014;89(7):732-742. 7. Lipton J, et al. ASH 2013. Abstract 4010.
CCyR, complete cytogenetic response; MCyR, majorcytogenetic response; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

Resistance to TKIs: Point Mutations

- >100 mutations described in TKI-treated patients
- A handful (~10) of mutations account for the majority (~85%) of clinically observed mutations
- Single and compound mutations possible



Patel AB, et al. *Hematol Oncol Clin North Am*. 2017;31(4):589-612.
TKI, tyrosine kinase inhibitor.

Contraindicated *BCR::ABL1* Mutations By TKI[1]

Therapy	Contraindicated Mutations
Asciminib	A337T, P465S, or F359V/I/C
Bosutinib	T315I, V299L, G250E, or F317L
Dasatinib	T315I/A, F317L/V/I/C, or V299L
Nilotinib	T315I, Y253H, E255K/V, or F359V/C/I
Ponatinib, omacetaxine, allogeneic HCT, or clinical trial	None

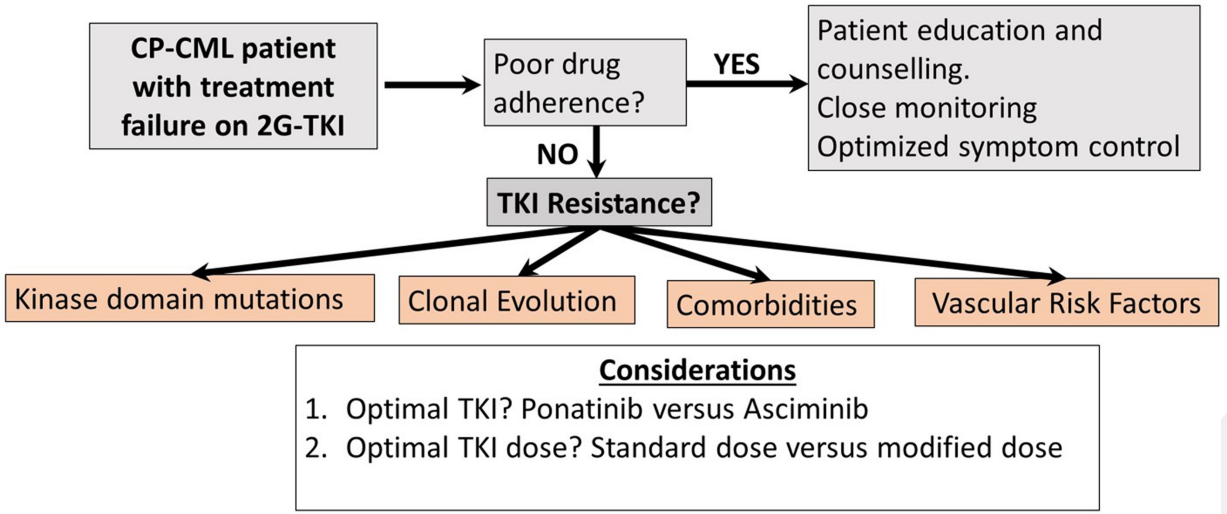
Caveat: myristoyl pocket mutations (A337T, P465S) are typically observed after asciminib exposure and are relatively uncommon[2]

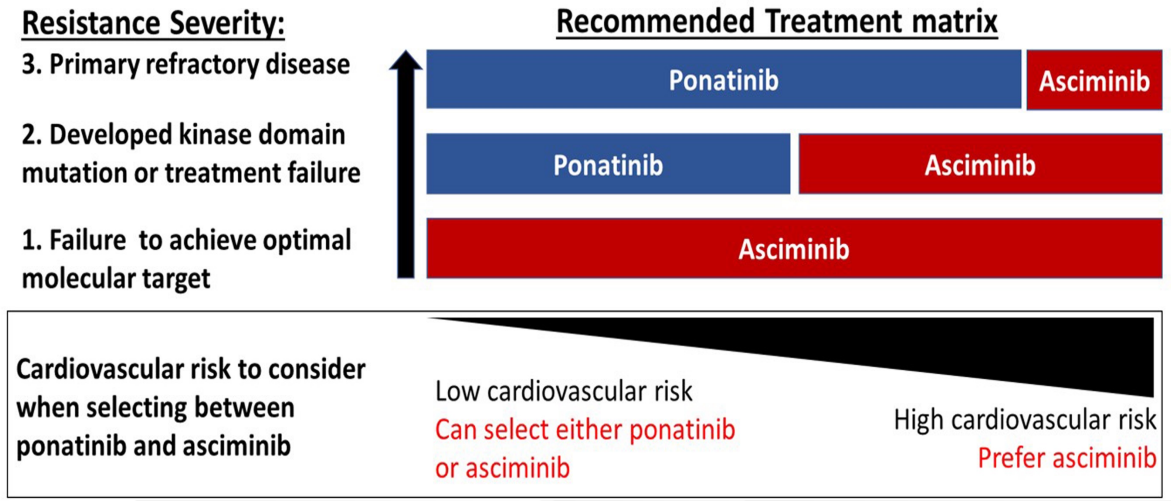
1. Shah NP, et al. NCCN Guidelines. Chronic Myeloid Leukemia. V1.2024.
2. Hochhaus A, et al. *Leukemia*. 2023;37(3):617-626.

HCT, hematopoietic cell transplantation; TKI, tyrosine kinase inhibitor.

Management Considerations: Multi-TKI Resistant CML

- Patients resistant to 2 or more TKIs have limited options; expert management is required to maximize available therapies
- Selection should be carefully considered based on patient-, disease-, and treatment-related factors
  - Switching from a 2nd generation TKI to a different 2nd generation TKI likely with more limited benefit
  - Ponatinib and asciminib are available for treatment of CP-CML after 2 or more prior TKIs or in the case of T315I mutations
  - Ponatinib is also indicated for AP and BP CML





Hughes TP, et al. *Hematology Am Soc Hematol Educ Program*. 2022;2022(1):129-137.

AP, accelerated phase; BP, blastic phase; CML, chronic myeloid leukemia; CP, chronic phase; TKI, tyrosine kinase inhibitor.

How Common Are Other Health Problems in CML Patients?

Table 3. All countries, chronic phase, baseline characteristics, recorded before any therapy ($n = 2388$)

Hematologic values		*Spleen*		*Comorbidities* (n = *2360*)	
Hb (g/dl), males, median ($n = 1\,286$)	12.5	**Spleen, cm@,** median ($n = 2331$)	0	Hypertension	25.7%
Hb, males, < 8.0	3.0%	Spleen, cm@, 0 (non palpable)	53.5%	Cardiovascular disorders	17.2%
Hb, males, 8.0–12.0	39.7%	Spleen, cm@, >0–4	19.6%	Diabetes mellitus, all types	9.5%
Hb, males, >12.0	57.3%	Spleen, cm@, >4 ⩽ 10	11.8%	Neurologic disorders	6.9%
Hb (g/dl), females, median ($n = 1\,095$)	11.7	Spleen, cm@, ⩾ 10	15.2%	Behavior disorders	2.3%
Hb, females, < 8.0	5.1%	**Cytogenetic data**		Chronic renal disease	2.6%
Hb, females, 8.0–11.0	32.9%	CCA/Ph+ ($n = 2018$)	9.4%	Chronic liver disease	2.2%
Hb, females, >11.0	62.0%	Variant translocations ($n = 2057$)	3.7%	Others, or unspecified	31.7%
Platelet count, $\times 10^9$/l, median ($n = 2\,381$)	395.0	**Molecular data—type of transcript ($n = 1533$)**			
Platelet count, $\times 10^9$/l, < 150	5.9%	b2a2	38.9%	Patients without comorbidities	44.5%
Platelet count, $\times 10^9$/l, 150 ⩽ 450	52.0%	b3a2+b2a2/b3a2	56.6%	Patients with one comorbidity	28.7%
Platelet count, $\times 10^9$/l, 450 ⩽ 1000	34.7%	Other	4.5%	Patients with two comorbidities	15.3%
Platelet count, $\times 10^9$/l, ⩾ 1000	7.4%			Patients with >2 comorbidities	11.5%
WBC count $\times 10^9$/l, median ($n = 2\,388$)	84.6				
WBC count $\times 10^9$/l, < 50	32.7%	***Sokal score (n = 2300)***		**ECOG/WHO score ($n = 2280$)**	
WBC count $\times 10^9$/l, 50 ⩽ 100	23.0%	Sokal low	34.5%	0–asymptomatic	57.1%
WBC count $\times 10^9$/l, 100 ⩽ 200	24.1%	Sokal intermediate	40.8%	1–symptomatic, compl. ambulatory	37.0%
WBC count $\times 10^9$/l, ⩾ 200	20.3%	Sokal high	24.7%	2–symptomatic, < 50% in bed/day	4.2%
Blast cells, %, median ($n = 2356$)	1.0	***EURO score (n = 2292)***		3–symptomatic, >50% in bed/day	1.2%
Basophils, %, median ($n = 2359$)	3.0	EURO low	37.4%	4–bedbound	0.5%
Eosinophils, %, median ($n = 2353$)	2.0	EURO intermediate	51.8%		
		EURO high	10.8%		
		EUTOS score (n = 2307)			
		EUTOS low	88.2%		
		EUTOS high	11.8%		

Abbreviations: CCA, clonal chromosome abnormalities; ECOG, Eastern Cooperative Oncology Group; EUTOS, European Treatment and Outcome Study for chronic myeloid leukemia; WBC, white blood cell; WHO, World Health Organization. @ cm below costal margin.

56% with comorbidities
42% cardiovascular

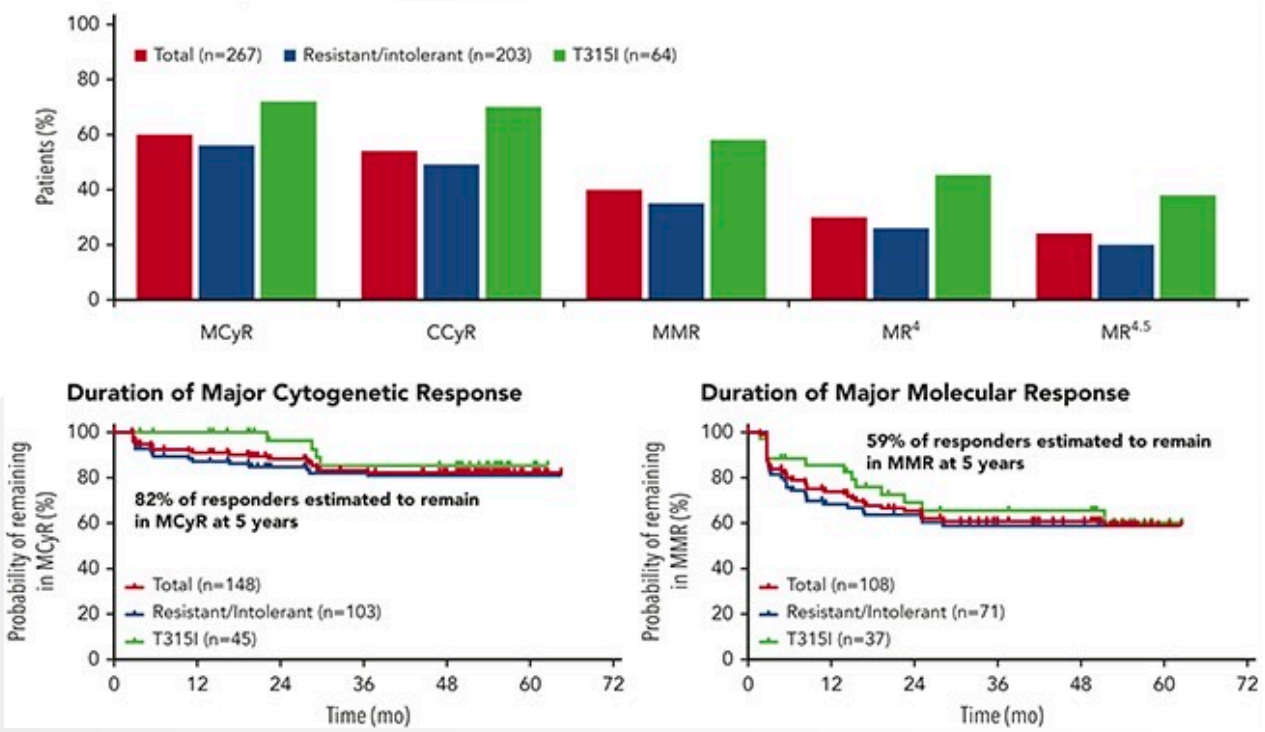
Hoffmann VS, et al. *Leukemia*. 2015;29:1336-1343.

Expanding Treatment Options for CML

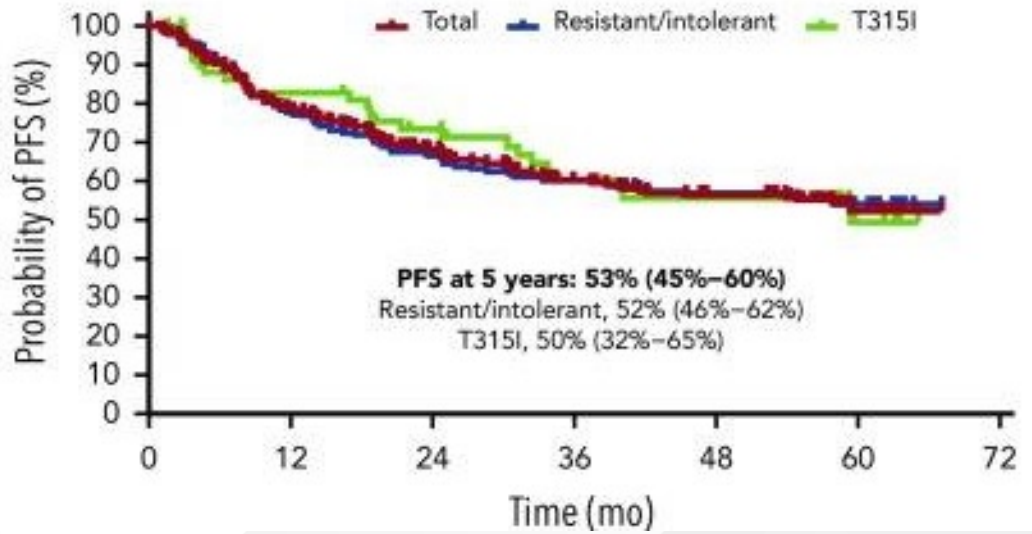
Phase 2 PACE Trial: 5-Year Follow-Up

- Ponatinib at 45 mg once daily in patients resistant or intolerant to dasatinib or nilotinib or with BCR::ABL1 T315I mutation; N = 270 CP-CML

Response



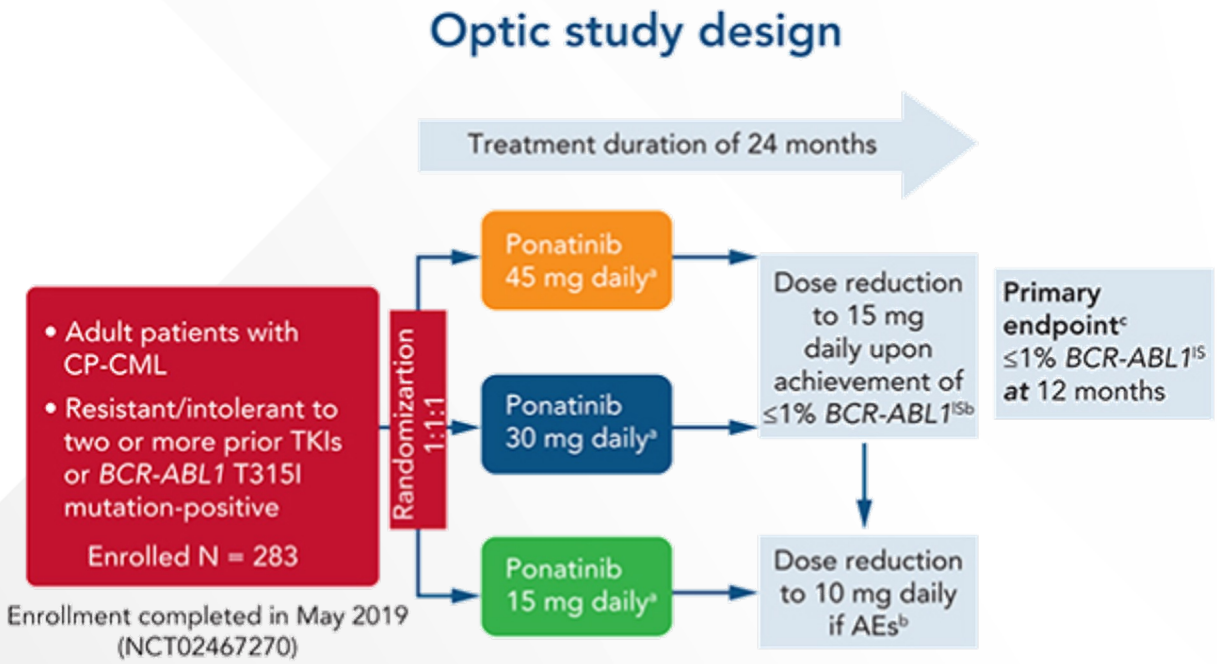
PFS at 5 yr

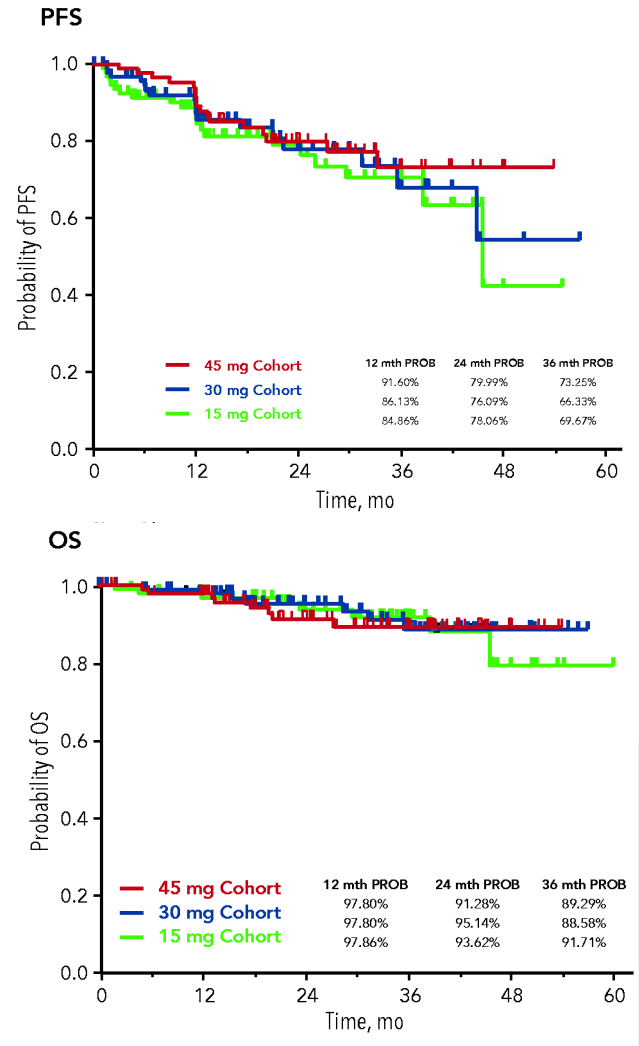


Cortes JE, et al. *Blood.* 2018;132(4):393-404.

CML, chronic myeloid leukemia; CP, chronic phase; PFS, progression-free survival.

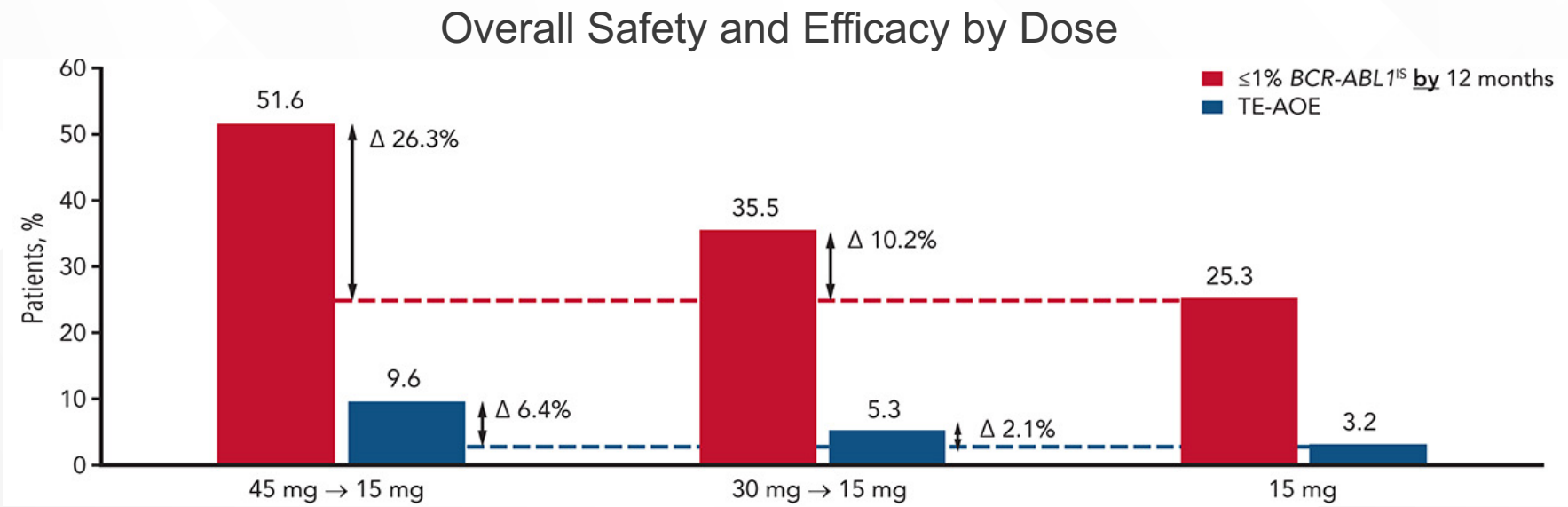
Phase 2 OPTIC Trial: Ponatinib Dose-Range Study





Cortes J, et al. *Blood.* 2021;138(21):2042-2050.
AE, adverse event; CML, chronic myeloid leukemia; CP, chronic phase; OS, overall survival; PFS, progression-free survival.

Phase 2 OPTIC Trial: Ponatinib Dose-Range Study



Response by Mutation Status	45 mg, %	30 mg, %	15 mg
T315I mutation	60.0	25.0	10.5
No T315I mutation	48.5	38.4	29.6
Mutation other than T315I	56.3	40.0	33.3
No mutation	46.0	37.9	28.3

Cortes J, et al. *Blood.* 2021;138(21):2042-2050.
TE-AOE, treatment-emergent arterial occlusive event.

NCCN: Managing Select Adverse Events With Ponatinib

Adverse Event	NCCN-Recommended Management Approach

Hematologic toxicity	• ANC <1.0 x 10^9/L and/or platelet count <50 x 10^9/L:
	  • 1st occurrence: Hold ponatinib until ANC ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L; resume at initial dose of 45 mg.
	  • 2nd occurrence: Hold ponatinib until ANC ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L and resume at 30 mg
	  • 3rd occurrence: Hold ponatinib until ANC ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L and resume at 15 mg
	  • Growth factors can be used for persistent neutropenia and thrombocytopenia
	• Grade 3/4 anemia: Check reticulocyte count, ferritin, iron saturation, B12, folate, and correct nutritional deficiencies if present. Transfuse if patient is symptomatic

Non-hematological Toxicity	• **Liver transaminase >3 x IULN** (grade ≥2): Monitor hepatic function. Hold drug until serum levels are <3 x IULN. Resume at lower dose after recovery (30 mg if patient is receiving 45 mg; 15 mg if patient is receiving 30 mg); discontinue ponatinib if patient is receiving 15 mg • **AST or ALT ≥3 x IULN** concurrent with bilirubin >2 x IULN and alkaline phosphatase <2 x IULN: Discontinue ponatinib. • **Serum lipase elevation**, grade 1 or 2 (asymptomatic): Consider dose interruption or reduction. Serum lipase elevation, grade 3 or 4 (>2 x IULN) (asymptomatic) or asymptomatic radiologic pancreatitis: Hold drug until serum levels are <1.5 x IULN. Resume at lower dose after recovery (30 mg if patient is receiving 45 mg; 15 mg if patient is receiving 30 mg); discontinue ponatinib if patient is receiving 15 mg • **Pancreatitis** (symptomatic), grade 3: Hold drug until serum lipase levels are ≤grade 1. Resume at lower dose after recovery (30 mg if patient is receiving 45 mg; 15 mg if patient is receiving 30 mg); discontinue ponatinib if patient is receiving 15 mg. Grade 4: Discontinue ponatinib.

AXIS Medical Education

Shah NP, et al. NCCN Guidelines. Chronic Myeloid Leukemia. V1.2024.
ANC, absolute neutrophil count; IULN, institutional upper limit of normal.

NCCN: Managing Select Adverse Events With Ponatinib (cont.)

Adverse Event	NCCN-Recommended Management Approach

Rare but serious	• **Hemorrhage:** Hemorrhagic events were reported in clinical trials. Cerebral and GI hemorrhage were the most commonly reported serious bleeding events. Serious hemorrhage should be managed with dose interruption
	• **Cardiac arrhythmias:** Advise patients to report signs and symptoms suggestive of alterations in heart rate (fainting, dizziness, chest pain, or palpitations)
	• **Tumor lysis syndrome**: Ensure adequate hydration and correct high uric acid levels prior to initiating therapy with ponatinib in patients with advanced phase CML
	• Specific Interventions
	  • **Fluid retention events** (ie, edema, ascites, pleural and pericardial effusion) are managed with dose interruption, dose reduction, or discontinuation of ponatinib as clinically indicated
	  • **Hypertension**: Monitor and manage blood pressure elevations
	  • **Rash**: Topical or systemic steroids, dose reduction, dose interruption, or dose discontinuation

Shah NP, et al. NCCN Guidelines. Chronic Myeloid Leukemia. V1.2024.
CML, chronic myeloid leukemia.

Adverse Event Management and Risk Mitigation

- AEs common to multiple TKIs:
  - Myelosuppression: mix of response and TKI effect
    - > Hold TKI for count thresholds: ANC <500 or 1000 (TKI dependent), platelets <50K
    - > Recurrent myelosuppression may be intrinsic to disease and very challenging
  - Transaminase elevation, hyperbilirubinemia
    - > ↑ AST/ALT intrinsic to TKI metabolism; ↑ bili potentially linked to Gilbert's phenotype
    - > Drug-induced liver injury (DILI) may be reversed with steroid therapy, rechallenge
  - Lipase elevation, pancreatitis
    - > Former more common than latter; required drug hold, investigation/assessment, dose reduction; MOA unknown, under-reported
  - Blood lipid increases (both HDL/LDL)
    - > Mechanism unclear; nilotinib, other TKIs as well
  - Hypertension
    - > Ponatinib (VEGF-like effect); Asciminib (less frequent)
  - Fatigue/musculoskeletal symptoms
    - > Increasingly studied, recognized (QOL/PRO data); potential direct TKI mechanisms

Slide courtesy of Michael J. Mauro, MD

AE, adverse event; ANC, absolute neutrophil count; AST, aspartate transferase; ALT, alanine transaminase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MOA, mechanism of action; PRO, patient-reported outcomes; QOL, quality of life; TKI, tyrosine kinase inhibitor.

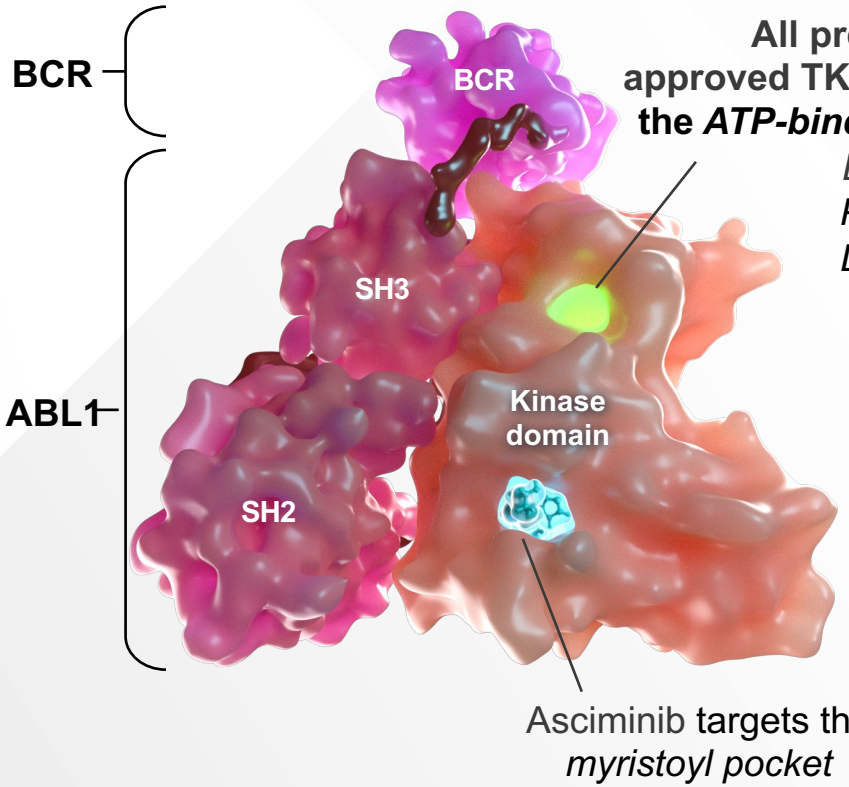
Adverse Event Management and Risk Mitigation (Cont.)

- AEs specific to select TKIs:
  - Headache: dasatinib
  - Hypophosphatemia: imatinib
  - Hyperglycemia, incremental need for diabetes intervention: nilotinib
  - Renal changes
  - Pleural/pericardial effusions
  - GI effects (osmotic diarrhea)
- AEs of special interest
  - AOEs: cardiovascular, cerebrovascular, and peripheral vascular
    - Arterial > venous; mechanism remains unclear
    - *Ponatinib > nilotinib > dasatinib, asciminib > bosutinib/imatinib*
    - *Pulmonary arterial hypertension: dasatinib*

Slide courtesy of Michael J. Mauro, MD
AE, adverse event; GI, gastrointestinal; AOE, arterial occlusive event.

Asciminib: Novel MOA

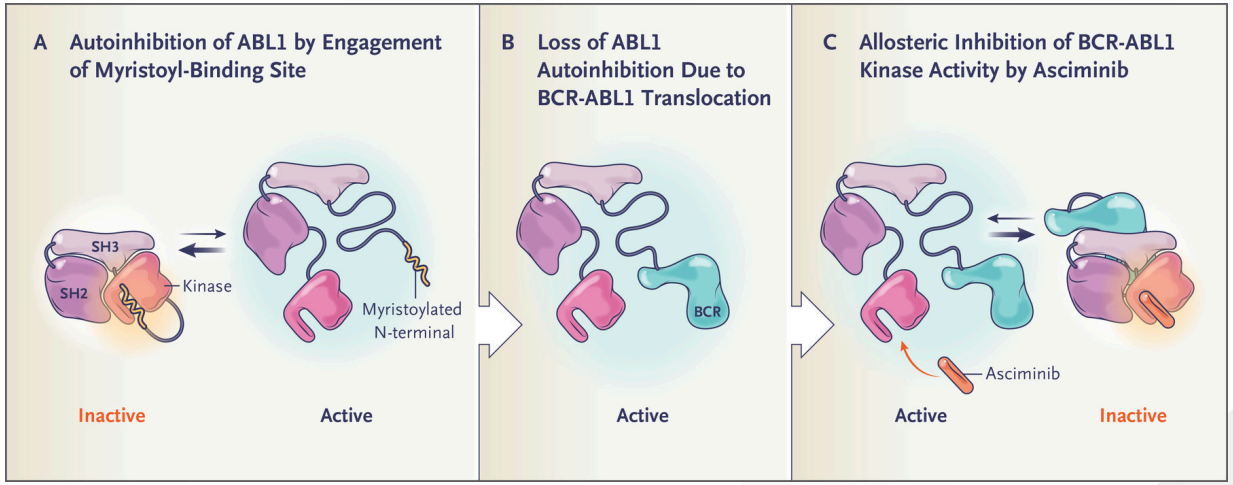
Targets the ABL Myristoyl Pocket (STAMP)



All previously approved TKIs target the *ATP-binding site*

Bosutinib
Ponatinib
Dasatinib
Nilotinib
Imatinib

Asciminib targets the *myristoyl pocket*



Previously Studied:

- Phase I: CP-CML, +/- T315I
- Phase III: *vs* BOS
- Combination (w/ATP-competitive TKIs (IM, NIL, DAS)

In Development

- Frontline
- Second-line
- Combination / optimization
- TFR (second>first)
- Advanced phase
- Pediatrics

AXIS Medical Education

Hughes TP, et al. *N Engl J Med.* 2019;381(24):2315-2326.
ATP, adenosine triphosphate; BOS, bosutinib; CML, chronic myeloid leukemia; CP, chronic phase; DAS, dasatinib; IM, imatinib; MOA, mechanism of action; NIL, nilotinib; TFR, treatment-free remission; TKI, tyrosine kinase inhibitor.

Asciminib Phase I Overall Response

Table 3. Hematologic, Cytogenetic, and Molecular Responses with Asciminib (Combined Once-Daily and Twice-Daily Schedules).*

Variable	Chronic-Phase CML						Accelerated-Phase CML					
	No T315I Mutation			T315I Mutation			No T315I Mutation			T315I Mutation		
	Overall (N=113)†	Response Achieved	Response Maintained	Overall (N=28)†	Response Achieved	Response Maintained	Overall (N=4)†	Response Achieved	Response Maintained	Overall (N=5)†	Response Achieved	Response Maintained
Median follow-up (range) — wk	72 (0.1–167)			37 (0.7–167)			46 (15–72)			16 (6–120)		
Patients remaining in the study — no. (%)	88 (78)			19 (68)			2 (50)			1 (20)		
Complete hematologic response — no./total no. (%)‡		34/37 (92)			14/16 (88)			3/3 (100)			4/5 (80)	
Major cytogenetic response — no./total no. (%)‡§	85/110 (77)	24/40 (60)	61/70 (87)	15/25 (60)	11/20 (55)	4/5 (80)	0/4	0/2	0/2	1/5 (20)	1/4 (25)	0/1
Complete cytogenetic response — no./total no. (%)‡§	77/110 (70)	31/57 (54)	46/53 (87)	11/25 (44)	9/22 (41)	2/3 (67)	0/4	0/2	0/2	1/5 (20)	1/4 (25)	0/1
Major molecular response — no./total no. (%)‡¶												
In all patients												
By 6 mo	37/99 (37)	19/80 (24)	18/19 (95)	5/20 (25)	4/19 (21)	1/1 (100)	0/4	0/3	0/1	1/5 (20)	1/5 (20)	0
By 12 mo	44/91 (48)	26/72 (36)	18/19 (95)	5/18 (28)	4/17 (24)	1/1 (100)	0/4	0/3	0/1	1/5 (20)	1/5 (20)	0
In patients with ≤2 previous TKIs‖												
By 6 mo	13/25 (52)	5/15 (33)	8/10 (80)	4/10 (40)	3/9 (33)	1/1 (100)	0/1	0/1	0			
By 12 mo	15/25 (60)	7/15 (47)	8/10 (80)	4/9 (44)	3/8 (38)	1/1 (100)	0/1	0/1	0			
In patients with >2 previous TKIs**												
By 6 mo	24/74 (32)	14/64 (22)	10/10 (100)	1/10 (10)	1/10 (10)	0	0/3	0/2	0/1	1/5 (20)	1/5 (20)	0
By 12 mo	29/66 (44)	19/56 (34)	10/10 (100)	1/9 (11)	1/9 (11)	0	0/3	0/2	0/1	1/5 (20)	1/5 (20)	0
In patients with resistance to or unacceptable side effects from ponatinib††												
By 6 mo	7/17 (41)	3/13 (23)	4/4 (100)	1/7 (14)	1/7 (14)	0/0				0/2	0/2	
By 12 mo	8/14 (57)	4/10 (40)	4/4 (100)	1/6 (17)	1/6 (17)	0/0				0/2	0/2	

HR

CyR

MolR

* For definitions of hematologic, cytogenetic, and molecular responses, see the Methods section in the Supplementary Appendix.
† Shown is the number of patients who received at least one dose of asciminib.
‡The total number is the number of patients who could be evaluated.
§Data on cytogenetic responses are based on patients who presented with Philadelphia chromosome-positive ML at baseline. Calculation of the number of patients in whom a major cytogenetic response or complete cytogenetic response was achieved is based on patients not in the respective response category at baseline.
¶ Molecular-response assessment is reported only for patients with the b2a2 or b3a2 transcripts; 7 patients had atypical BC.ABL 1 transcripts and were not included in the response assessment.
‖ The numbers of patients who received at least one dose of asciminib were as follows: 34 with chronic-phase CML without a T3151 mutation, 12 with chronic-phase CML with a T315t mutation, and 1 with accelerated-phase ML without a T3151 mutation.
** The numbers of patients who received at least one dose of asciminib were as follows: 79 with chronic-phase CML without a T315I mutation, 16 with chronic-phase CML with a T3151 mutation, 3 with accelerated-phase CML without a T3151 mutation, and 5 with accelerated-phase CML with a T315I mutation.
†† The numbers of patients who received at least one dose of asciminib were as follows: 18 with chronic-phase CML without a T315I mutation, 11 with chronic-phase CML with a T3151 mutation, and 2 with accelerated-phase ML with a T315I mutation.

Hughes TP, et al. *N Engl J Med.* 2019;381:2315-2326.
CyR, cytogenetic response; HR, hematologic response; MolR, molecular response.

Asciminib: Response by T315I Mutation Status, Phase I

Variable	Chronic-Phase CML						Accelerated-Phase CML					
	No T315I Mutation			T315I Mutation			No T315I Mutation			T315I Mutation		
	Overall (N=113)†	Response Achieved	Response Maintained	Overall (N=28)†	Response Achieved	Response Maintained	Overall (N=4)†	Response Achieved	Response Maintained	Overall (N=5)†	Response Achieved	Response Maintained
Median follow-up (range) — wk	72 (0.1–167)			37 (0.7–167)			46 (15–72)			16 (6–120)		
Patients remaining in the study — no. (%)	88 (78)			19 (68)			2 (50)			1 (20)		
Complete hematologic response — no./total no. (%)‡		34/37 (92)			14/16 (88)			3/3 (100)			4/5 (80)	
Major cytogenetic response — no./total no. (%)‡§	85/110 (77)	24/40 (60)	61/70 (87)	15/25 (60)	11/20 (55)	4/5 (80)	0/4	0/2	0/2	1/5 (20)	1/4 (25)	0/1
Complete cytogenetic response — no./total no. (%)‡§	77/110 (70)	31/57 (54)	46/53 (87)	11/25 (44)	9/22 (41)	2/3 (67)	0/4	0/2	0/2	1/5 (20)	1/4 (25)	0/1
Major molecular response — no./total no. (%)‡¶												
In all patients												
By 6 mo	37/99 (37)	19/80 (24)	18/19 (95)	5/20 (25)	4/19 (21)	1/1 (100)	0/4	0/3	0/1	1/5 (20)	1/5 (20)	0
By 12 mo	44/91 (48)	26/72 (36)	18/19 (95)	5/18 (28)	4/17 (24)	1/1 (100)	0/4	0/3	0/1	1/5 (20)	1/5 (20)	0

CHR

CCyR

MMR

Hughes TP, et al. *N Engl J Med*. 2019;381:2315-2326.
CCyR, complete cytogenic response; CHR, complete hematologic response; MMR, major molecular response

Asciminib: Categorical Response Shift, Phase 1

Variable	No T315I Mutation					T315I Mutation			
	Baseline *BCR-ABL1*^{IS}†					Baseline *BCR-ABL1*^{IS}†			
	≤0.01% (N=6)	>0.01 to 0.1% (N=13)	>0.1 to 1% (N=22)	>1 to 10% (N=21)	>10% (N=42)	>0.01 to 0.1% (N=1)	>0.1 to 1% (N=2)	>1 to 10% (N=5)	>10% (N=19)
Post-treatment *BCR-ABL1*^{IS} by 6 mo									
Patients who could be evaluated‡	6	13	23	18	39	1	1	5	13
Distribution — no. of patients (%)§									
≤0.01%	6 (100)	4 (31)	5 (22)	4 (22)	1 (3)	1 (100)	0	0	0
>0.01 to 0.1%	0	8 (62)	6 (26)	1 (6)	2 (5)	0	1 (100)	2 (40)	1 (8)
>0.1 to 1%	0	1 (8)	12 (52)	12 (67)	7 (18)	0	0	2 (40)	1 (8)
>1 to 10%	0	0	0	1 (6)	12 (31)	0	0	1 (20)	2 (15)
>10%	0	0	0	0	17 (44)	0	0	0	9 (69)
Post-treatment *BCR-ABL1*^{IS} by 12 mo									
Patients who could be evaluated‡	6	13	21	17	34	1	1	5	11
Distribution — no. of patients (%)§									
≤0.01%	6 (100)	5 (38)	6 (29)	5 (29)	1 (3)	1 (100)	0	2 (40)	0
>0.01 to 0.1%	0	7 (54)	6 (29)	3 (18)	5 (15)	0	1 (100)	0	1 (9)
>0.1 to 1%	0	1 (8)	9 (43)	8 (47)	6 (18)	0	0	2 (40)	1 (9)
>1 to 10%	0	0	0	1 (6)	12 (35)	0	0	1 (20)	1 (9)
>10%	0	0	0	0	10 (29)	0	0	0	8 (73)

*Percentages may not total 100 because of rounding. *BCR-ABL1*^{15} denotes the ratio of *BCR-ABL1* to *ABL1* measured on the International Scale.
†The number of patients is the number who received at least one dose of asciminib in each category of BCR-ABL1 transcript level at baseline. A total of 10 patients with chronic-phase CML (9 without a T3151 mutation and 1 with a T3151 mutation) had a missing *BCR-ABL1*^{15} value at baseline.
‡Shown is the number of patients who could be evaluated in each category of baseline BCR-ABL1 transcript level who had undergone assessment of molecular response at 6 (or 12) months after treatment or who had a major molecular response within 6 (or 12) months. For a detailed definition of molecular response, see the Methods section in the Supplementary Appendix. Response assessment is reported only for patients with the b2a2 or b3a2 transcripts.
§Percentages were calculated on the bases of the number of patients who could be evaluated.

Hughes TP, et al. *N Engl J Med*. 2019;381:2315-2326.

Phase 3 ASCEMBL Study: Asciminib vs Bosutinib in Patients With CML-CP Previously Treated With ≥2 TKIs

Key Study Criteria

- Adults with CML-CP, previously treated with ≥2 TKIs
- Failure as defined in the 2013 European LeukemiaNet (ELN) recommendations for patients receiving a 2L TKI or intolerance of most recent TKI
- Patients with intolerance to most recent TKI must have *BCR::ABL1*^{IS} >0.1% at screening
- No T315I or V299L mutations

ASCEMBL
(NCT03106779)

Randomized 2:1
(stratified by MCyR vs no MCyR at baseline)

N = 233

Treatment duration: ≥96 weeks

Asciminib
40 mg twice daily
n = 157

Bosutinib
500 mg once daily
n = 76

Survival follow-up

Not part of current analysis

Switch allowed for those meeting lack of efficacy criteria on bosutinib

Asciminib
40 mg twice daily

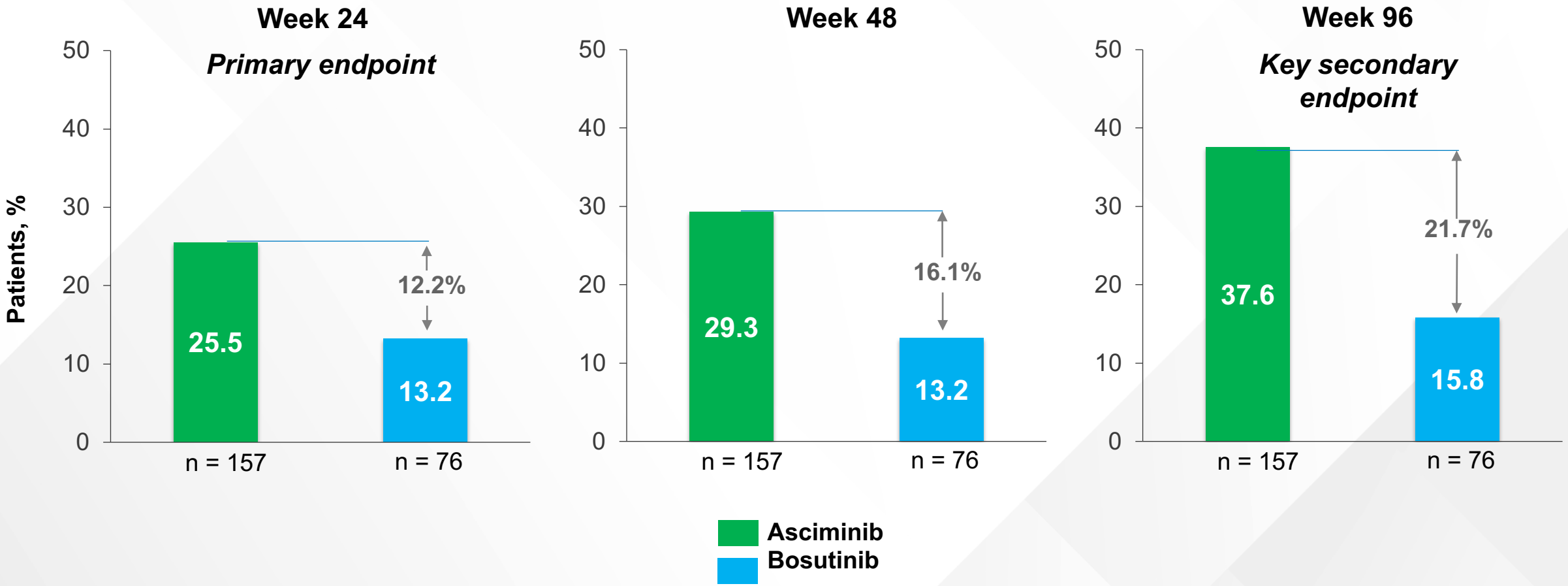
Survival follow-up

Primary endpoint: MMR rate at week 24

Key secondary endpoint: MMR rate at week 96

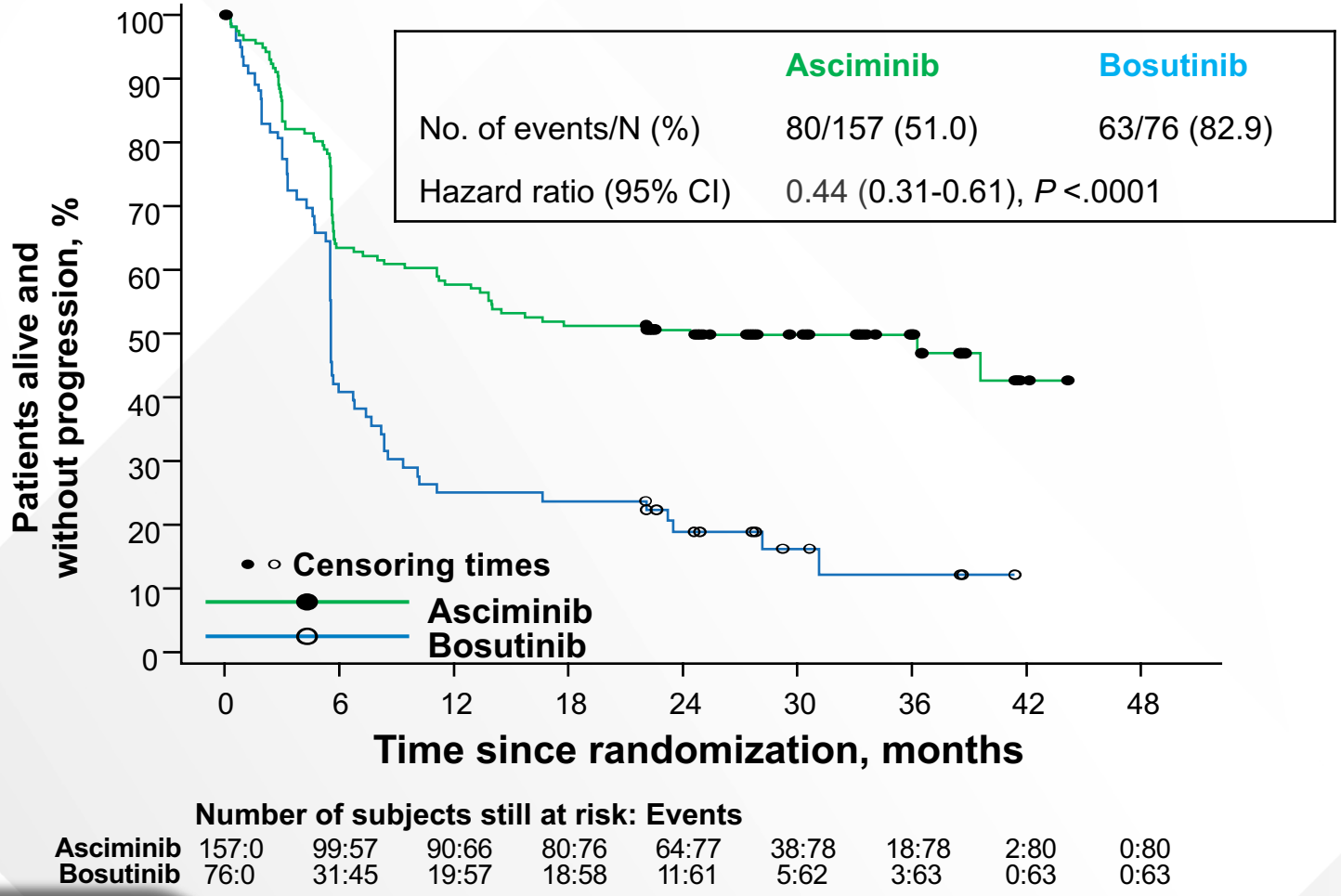
1. Réa D, et al. *Blood.* 2021;138(21):2031-2041. 2. Mauro MJ, et al. 2021 ASH Annual Meeting. Abstract 310. Hochhaus A, et al. *Leukemia.* 2023;37(3):617-626.
CML, chronic myeloid leukemia; CP, chronic phase; MCyR, major cytogenetic response; MMR, major molecular response; TKI, tyrosine kinase inhibitor.

ASCEMBL Study: Initial MMR Rates



Réa D, et al. 2022 ASCO Annual Meeting. Abstract 7004. Réa D, et al. 2022 EHA Congress. Abstract S155.
MMR, major molecular response (BCR::ABL1IS ≤0.1%).

Time to Treatment Failure in the Phase 3 ASCEMBL Study



- By data cutoff, fewer patients experienced treatment failure* with **asciminib (51.0%)** than **bosutinib (82.9%)**
- The K-M–estimated proportion of patients without treatment failure by **2 years** was **50.6%** (95% CI, 42.5%-58.2%) with **asciminib** vs **18.9%** (95% CI, 10.8%-28.6%) with **bosutinib**
- Median time to treatment failure was substantially longer with **asciminib (24 months)** vs **bosutinib (6 months)**

AXIS Medical Education

* Treatment failure was defined as lack of efficacy (per 2013 ELN recommendations for 2L patients) or discontinuation for any reason

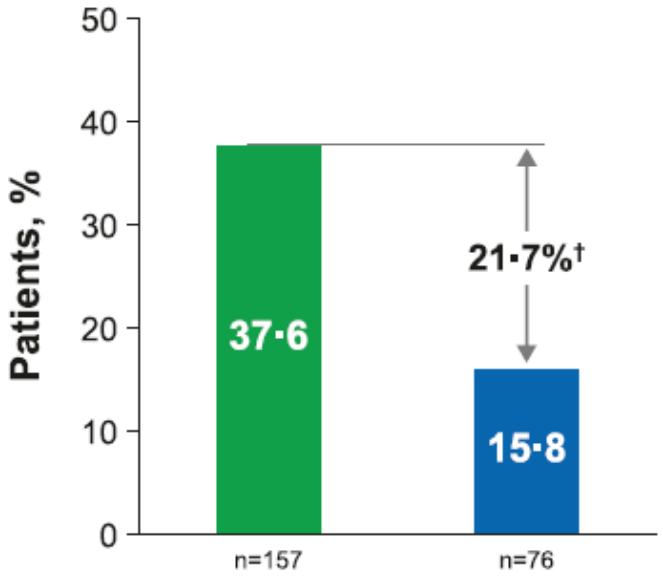
Réa D, et al. 2022 ASCO Annual Meeting. Abstract 7004.

2L, 2nd line; ELN, European LeukemiaNet; KM, Kaplan-Meier.

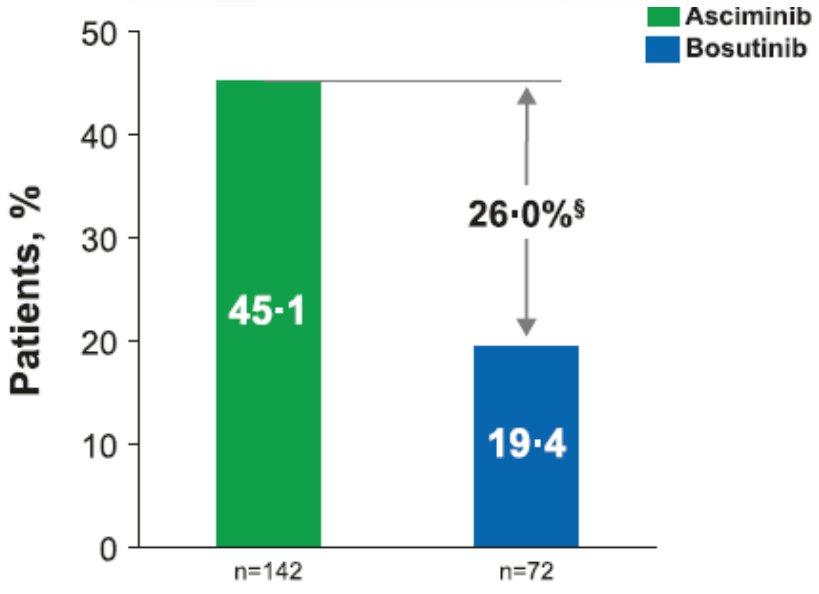
ASCEMBL Study: Longer Follow-Up

- Median follow-up: 2 years
- 54% of patients on asciminib remained on therapy vs 20% of patients on bosutinib

MMR at 96 wks

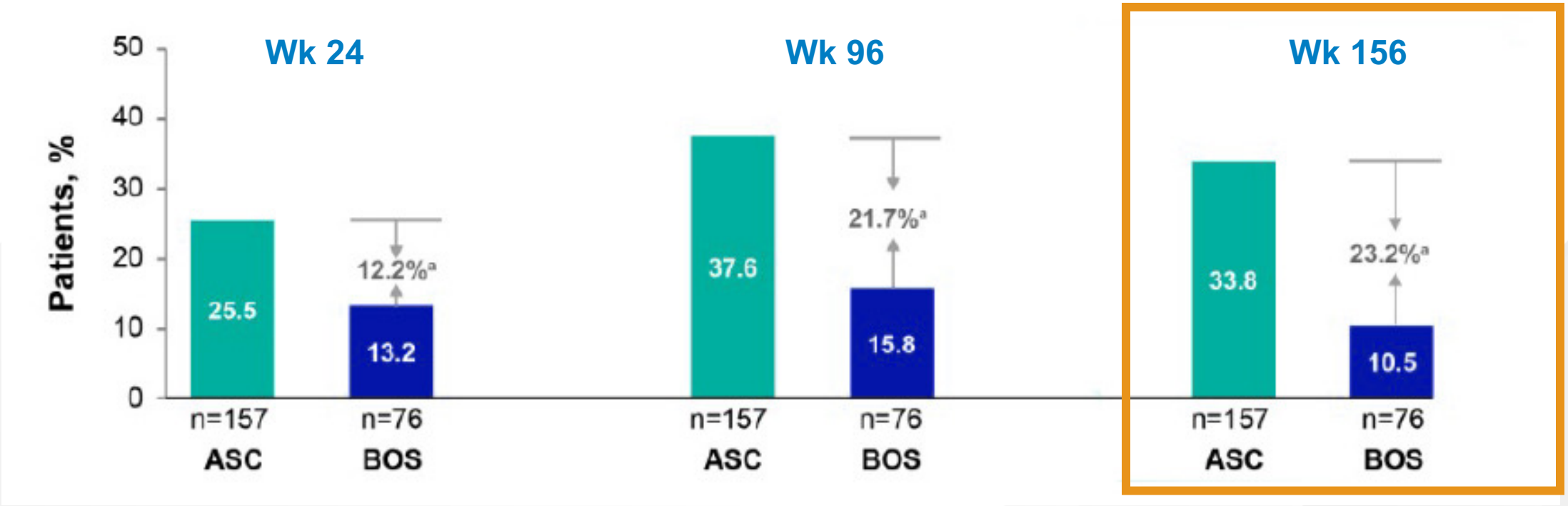


***BCR::ABL1*^{IS} ≤1% at 96 wks**



Hochhaus A, et al. *Leukemia.* 2023;37(3):617-626.
MMR, major molecular response.

ASCEMBL Study: MMR Rate at Weeks 24, 96, and 156



[a]MMR rate difference between arms after adjusting for baseline MCyR: 12.24% (95% CI, 2.19%-22.30%; 2-sided *P*=0.29) at week 24; 21.74% (95% CI, 10.53%-32.95%; 2-sided *P*=.001) at week 96; and 23.16% (95% CI, 13.14%-33.18%; 2-sided *P*<.001) at week 156.

Mauro M, et al. ASH 2023. Abstract 4536.

ASC, asciminib; BOS, bosutinib; MCyR, major cytogenetic response; MMR, major molecular response.

AXIS Medical Education

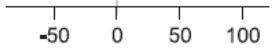
ASCEMBL: Switch Population

- Of 28 pts who discontinued bosutinib for lack of efficacy, 25 switched to asciminib
  - Almost all switch patients (96%) had *baseline BCR::ABL1*^{IS} >10% prior to switch
- No-switch patients achieved MMR at or by week 48 post switch
  - However, at week 48, 24% achieved *BCR::ABL1*^{IS} ≤10% and 8% achieved *BCR::ABL1*^{IS} ≤1%
- The safety profile of asciminib in switch patients was consistent with that in patients receiving asciminib in the randomized period
  - Most frequent (≥10%) grade ≥3 AEs: neutropenia (32.0%), thrombocytopenia (24.0%)
  - AEs leading to treatment discontinuation: 8.0%

Mauro M, et al. ASH 2023. Abstract 4536.
AE, adverse event; MMR, major molecular response.

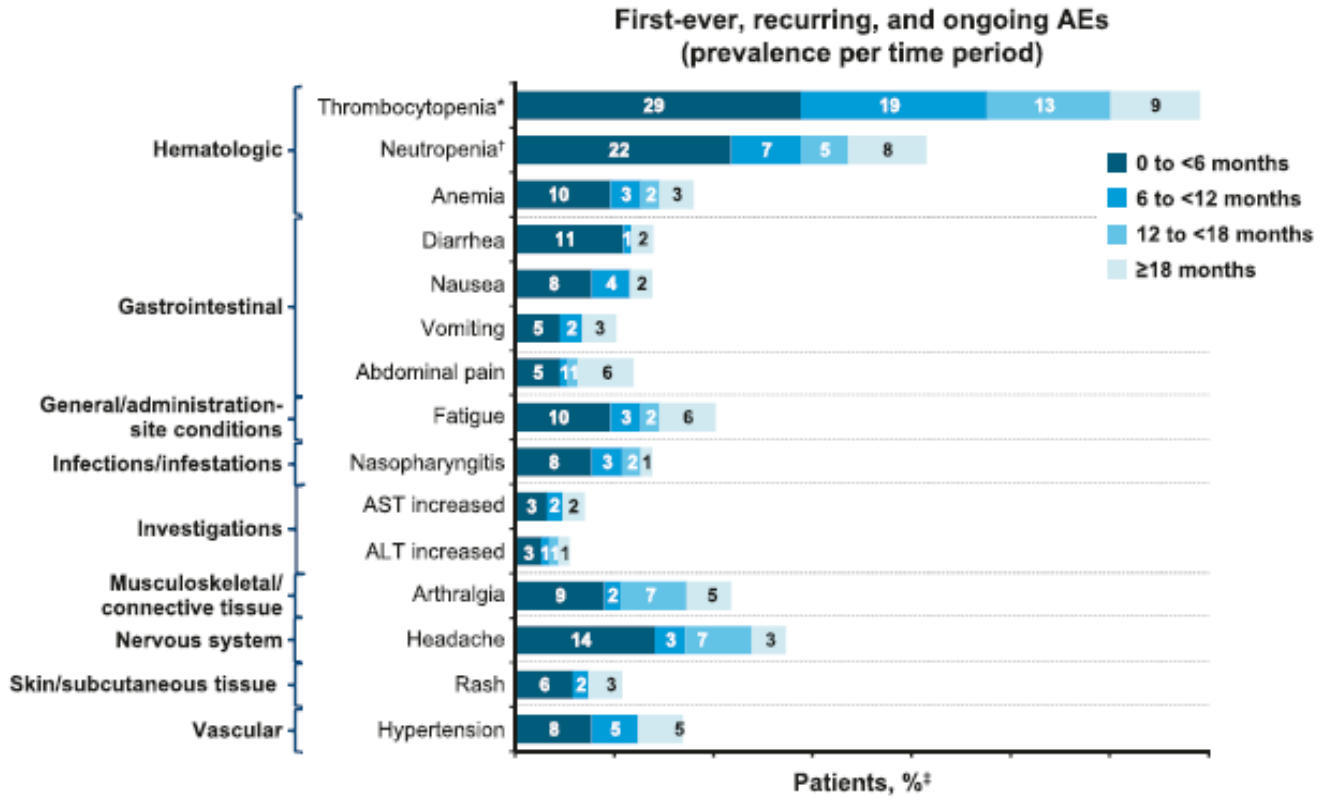
ASCEMBL Study: MMR Subgroup Analysis at 96 Weeks

Subgroup	Asciminib, n/N (%)	Bosutinib, n/N (%)	Risk difference, % (95% CI)
All patients	59/157 (37·6)	12/76 (15·8)	21·8 (10·6 to 33·0)
Strata based on randomization data			
Major cytogenetic response	25/46 (54·4)	3/22 (13·6)	40·7 (20·4 to 61·0)
No major cytogenetic response	34/111 (30·6)	9/54 (16·7)	14·0 (0·8 to 27·1)
Sex			
Female	30/75 (40·0)	3/45 (6·7)	33·3 (20·1 to 46·6)
Male	29/82 (35·4)	9/31 (29·0)	6·3 (−12·7 to 25·4)
Race			
Asian	8/22 (36·4)	2/11 (18·2)	18·2 (−12·2 to 48·6)
White	44/118 (37·3)	9/56 (16·1)	21·2 (8·2 to 34·2)
Others	7/17 (41·2)	1/9 (11·1)	30·1 (−1·1 to 61·2)
Age category			
18 to <65 years	48/128 (37·5)	7/61 (11·5)	26·0 (14·4 to 37·6)
≥65 years	11/29 (37·9)	5/15 (33·3)	4·6 (−25·1 to 34·3)
≥75 years	4/4 (100)	1/2 (50·0)	50·0 (−19·3 to 100·0)
Reason for discontinuation of the last prior TKI			
Lack of efficacy	29/95 (30·5)	4/54 (7·4)	23·1 (11·5 to 34·7)
Intolerance	30/59 (50·9)	8/22 (36·4)	14·5 (−9·3 to 38·3)
Number of prior TKI therapies			
2	38/89 (42·7)	9/33 (27·3)	15·4 (−2·9 to 33·8)
3	19/53 (35·9)	3/33 (9·1)	26·8 (10·5 to 43·0)
≥4	2/15 (13·3)	0/10 (0·0)	13·3 (−3·9 to 30·5)
Line of therapy of randomized treatment			
3	34/82 (41·5)	9/30 (30·0)	11·5 (−8·1 to 31·0)
4	16/44 (36·4)	3/29 (10·3)	26·0 (8·0 to 44·0)
≥5	9/31 (29·0)	0/17 (0·0)	29·0 (13·1 to 45·0)
BCR::ABL1* mutations at baseline			
Not detected	47/125 (37·6)	10/63 (15·9)	21·7 (9·3 to 34·1)
Detected	7/17 (41·2)	2/8 (25·0)	16·2 (−21·9 to 54·2)
***BCR::ABL1*^{IS} transcript level at baseline**			
≥1%	49/142 (34·5)	10/72 (13·9)	20·6 (9·4 to 31·8)
<1%	10/15 (66·7)	2/4 (50·0)	16·7 (−37·8 to 71·2)



Hochhaus A, et al. *Leukemia.* 2023;37(3):617-626.

ASCEMBL Study: Adverse Events



EAIR, *n* (per 100 patient-treatment years)[a,b]	Asciminib 40 mg twice daily (*n* = 156)	Bosutinib 500 mg once daily (*n* = 76)
Cardiac failure (clinical events)	3 (1.1)	1 (1.3)
Edema and fluid retention	16 (6.4)	7 (10.1)
Gastrointestinal toxicity	52 (26.6)	60 (319.2)
Hemorrhage	19 (7.4)	8 (11.1)
Hepatotoxicity (including AEs related to laboratory value abnormalities)	17 (6.8)	25 (40.8)
Hypersensitivity[c]	32 (14.0)	26 (48.2)
Pancreatic toxicity	13 (5.1)	7 (10.2)
QTc prolongation	6 (2.3)	1 (1.3)
Reproductive toxicity[d]	3 (1.1)	1 (1.3)

Hochhaus A, et al. *Leukemia.* 2023;37(3):617-626.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; AE, adverse event; EAIR, exposure-adjusted incidence rate.

ASCEMBL Study: Arterial Occlusive Events

	Asciminib 40 mg BID (n = 156)	Bosutinib 500 mg QD (n = 76)
Patients with AOEs, n (%)	**8 (5.1)**	**1 (1.3)**
Patients with events observed by the cutoff for week 24 analysis, n (%)		
Myocardial ischemia[a]	2 (1.3)[b,c]	0
Acute coronary syndrome	0	1 (1.3)
Coronary artery disease[a]	1 (0.6)	0
Ischemic stroke	1 (0.6)[b]	0
Mesenteric artery embolism/thrombosis[d]	1 (0.6)[b,c]	0
Additional patients with events observed by cutoff for week 96 analysis, n (%)		
Cerebral infarction	1 (0.6)[b,c]	0
Myocardial infarction	1 (0.6)[b]	0
Troponin increased	1 (0.6)[b]	0
Exposure-adjusted AOE rate (per 100 patient-years)		
Primary analysis	3.3	2.0
Current analysis	3.0	1.4

Risk over time

- Exposure-adjusted AOE rate (per 100 patient-years) in the week 96 analysis (**3.0**) was comparable to that in the primary analysis (3.3)
- Of the 8 patients with AOEs receiving asciminib, **7 had prior exposure to nilotinib, 6 to dasatinib, and 3 to ponatinib**
- The patient with an AOE in **the bosutinib** arm had prior exposure to nilotinib and ponatinib

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a Myocardial ischemia (n=2) and coronary artery disease (n=1) in patients receiving asciminib occurred without clinical manifestations and was identified based on ECG performed per protocol after dosing and coronary arteriography performed due to medical history, respectively. b Patients had prior exposure to dasatinib. c Patients had prior exposure to ponatinib. d Mesenteric artery embolism/thrombosis occurred 15 days after asciminib discontinuation and following ponatinib treatment for 7 days.

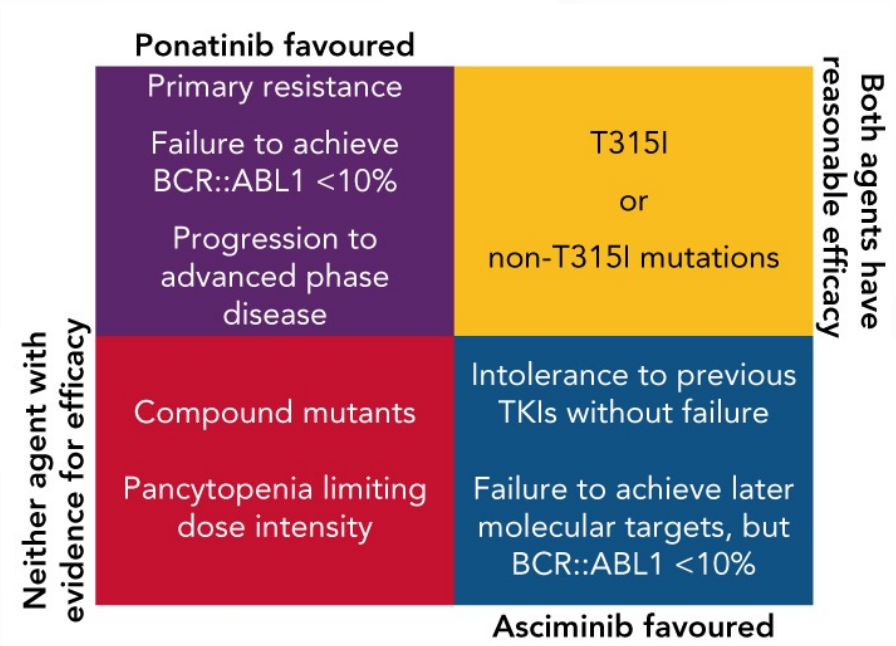
Réa D, et al. 2022 ASCO Annual Meeting. Abstract 7004. Réa D, et al. 2022 EHA Congress. Abstract S155.

AOE, arterial occlusive event; BID, twice daily; ECG, electrocardiogram; QD, once daily.

What Have We Learned from Ponatinib and Asciminib Trials?

PONATINIB

- PACE:
  - Efficacy in MDR CML
  - Efficacy in T315I
  - AOEs significant, dose dependent, stable over time, lag time (persistent)
- OPTIC:
  - 45mg start optimal, esp T315I (sl less difference in nonT315I cohorts)
  - Adjudicated AOEs sl less
- EPIC
  - Frontline incremental response increase over 2GTKI possible
  - Risk too great



≤0.1% BCR::ABL1^{IS} (MMR rate)	PACE (all pts)	OPTIC (all pts)	ASCEMBL (all pts)
12mo	28	20	29.3
24mo	34	34	37.6
60mo	37	n/a	n/a

ASCIMINIB

- Phase I (x2101)
  - Confident single agent efficacy
  - Toxicity similar across dose range (up to 200mg BID)
  - Mutational based resistance less, myristoyl mutations possible
- ASCEMBL
  - Optimal third-line agent: superior tolerance and efficacy versus BOS
  - AOEs minimal and small difference vs BOS; further study to confirm
- ASCEND
  - Frontline efficacy may be highest yet

AXIS Medical Education

1. Réa D, et al. *Blood*. 2021;138(21):2031-2041. 2. Réa D, et al. EHA 2022 Congress. Abstract S155. 3. Kantarjian HM, et al. *Am J Hematology*. In press.
4. Deininger MW, et al. *Blood*. 2021;138(suppl 1):307. 5. Cortes J, et al. *Blood*. 2021;138(21):2042-2050. 6. Yeung DT, et al. *Blood*. 2022;139 (24):3474-3479.
AOE, arterial occlusive event; BID, twice daily; BOS, bosutinib; CML, chronic myeloid leukemia; esp, especially; MDR, multidrug resistance; MMR, major molecular response pts, patients; sl, slightly; TKI, tyrosine kinase inhibitor.

Considerations for Therapy Sequencing

Problem	Next Step
Intolerance to initial TKI	Imatinib or alternative 2nd generation TKI
Resistance to first-line imatinib	Nilotinib, dasatinib, bosutinib
Resistance to nilotinib, dasatinib, or bosutinib	Alternate 2nd generation TKI Ponatinib, asciminib (if more than 2 prior TKIs)
Any line T315I mutation	Ponatinib, asciminib, or clinical trial

Shah NP, et al. NCCN Guidelines. Chronic Myeloid Leukemia. V1.2024.
TKI, tyrosine kinase inhibitor.

NCCN: Managing Select Adverse Events With Asciminib

Adverse Event	NCCN-Recommended Management Approach
Thrombocytopenia/ Neutropenia	• ANC <1.0 x 10^9/L and/or platelet count <50 x 10^9/L: Hold asciminib until ANC ≥1.0 x 10^9/L and/or platelet count ≥50 x 10^9/L • Resume at starting dose (if resolved within 2 weeks) or at reduced dose (if resolved after 2 weeks)
Elevated amylase/lipase (>2x ULN)	• Hold asciminib and resume at reduced dose after serum levels return to <1.5 x ULN • If AE recurs at reduced dose, or if serum levels do not return to <1.5 x ULN, permanently discontinue • Conduct diagnostic testing to rule out pancreatitis
Hypertension	• Monitor BP and manage as clinically indicated. Interrupt, dose reduce, or permanently discontinue if HTN not medically controlled
Hypersensitivity	• Monitor for signs and symptoms of hypersensitivity and treat as clinically indicated • Grade ≥3: Hold until grade ≤1 and resume at reduced dose. If not resolved, permanently discontinue
CV toxicity	• Monitor patients with history of CV risk factors for CV signs and symptoms, and treat as clinically indicated • Grade ≥3: Hold until grade ≤1 and resume at reduced dose. If not resolved, permanently discontinue

Shah NP, et al. NCCN Guidelines. Chronic Myeloid Leukemia. V1.2024.
AE, adverse event; ANC, absolute neutrophil count; CV, cardiovascular; ULN, upper limit of normal.

Future Directions

The Future of CML

- Improve rates of TFR
- More options for relapse and mutation-guided treatment
- Strategies
  - Combinations with currently available TKIs
    - > Another TKI (asciminib + ATP-competitive TKIs)
    - > Non BCR-ABL targeting agents (proapoptotic drugs, epigenetic modulators…)
    - > Immune targeting agents (check point inhibitors)
  - Bringing new treatments into earlier line
  - Novel agents
- Improve care for patients with AP/BP

AP, accelerated phase; ATP, adenosine triphosphate; BP, blastic phase; TFR, treatment-free remission; TKI, tyrosine kinase inhibitor.

Increasing the Cure Fraction: More Aggressive Front-Line Therapy

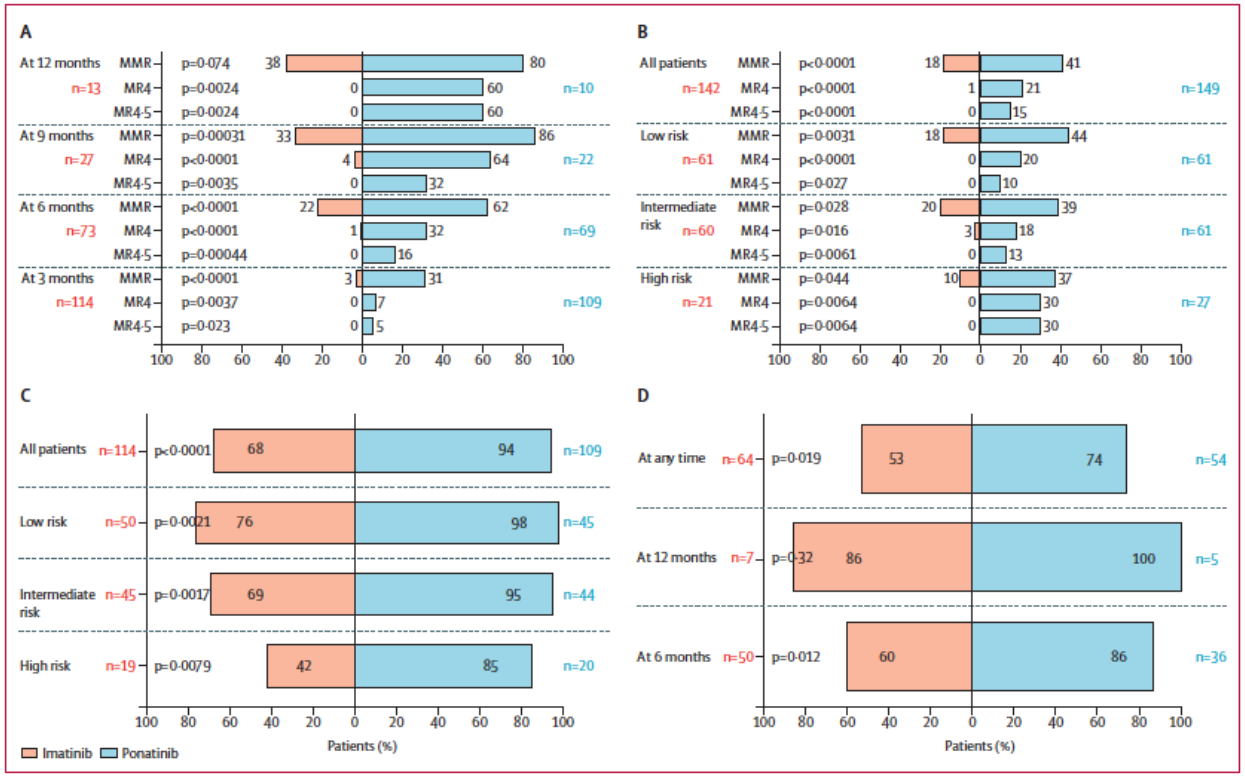


Figure 2: **Efficacy in the EPIC trial**
(A) Molecular response for assessable patients at 3, 6, 9, and 12 months. Patients who met the criteria for major molecular response, MR4, and MR4·5 at 3, 6, 9, and 12 months are shown; patients must have been recorded as having a molecular response at the specified timepoint. Symmetrical time periods around each timepoint were used. (B) Best overall molecular response for all assessable patients with post-treatment molecular response data at any time, and by Sokal risk score. (C) Achievement of *BCR-ABL1* transcript levels of less than 10% (international scale) for all assessable patients at 3 months, and by Sokal risk score. (D) CCyR for all assessable patients with post-treatment cytogenetic response data at any time, at 6 months, and at 12 months. Patients must have been recorded as having CCyR at the specified timepoint. MMR=major molecular response. MR=molecular response. CCyR=complete cytogenetic response. n=total numbers of patients assessable at the indicated timepoint. Patients classified as achieving MR4 or MR4·5 will necessarily also achieve MMR.

Evaluation of Ponatinib versus Imatinib in Chronic Myeloid Leukemia (EPIC) Study

Lipton JH, et al. *Lancet Oncol.* 2016;17(5):612-621.

New Strategies with Asciminib

- Asciminib versus investigator's choice (ASC4FIRST)
- Asciminib versus nilotinib (ASC4START)
- Asciminib single arm, with option to add nilotinib to improve DMR (CML Consortium)

Cortes JE, et al. *Future Oncol.* 2022;18(38):4161-4170. Hochhaus A, et al. *Hemasphere.* 2023;7(Suppl):e5851092.
CML, chronic myeloid leukemia; DMR, deep molecular response.

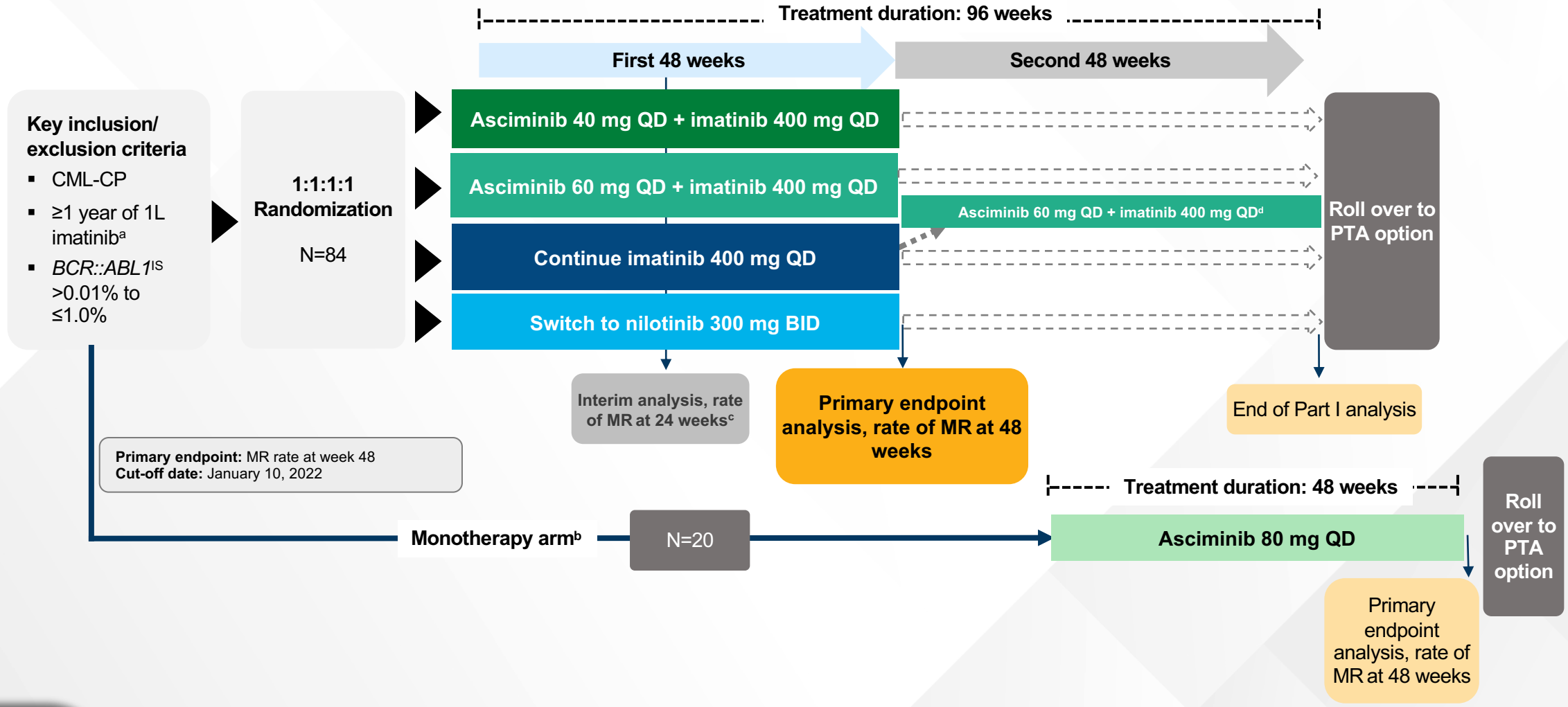
The Hanna Jean Khoury Cure CML Consortium (HJKC3) Trials: TFR/Second TFR Agenda

- HJKC3-001: LAST Study (TFR after primary TKI (IM, NIL, DAS, BOS) per NCCN, QOL assessment; published
- HJKC3-002: TKI (IM, NIL, DAS, BOS) + ruxolitinib **second TFR**
- HJKC3-003: Imatinib + asciminib (ABL001) **second TFR**

https://curecml.org/. Accessed September 2, 2023.

BOS, bosutinib; CML, chronic myeloid leukemia; DAS, dasatinib; IM, imatinib; NIL, nilotinib; TFR, treatment-free remission; TKI, tyrosine kinase inhibitor.

ASC4MORE Study Design



a With no change of dose in the past 3 months. b The monotherapy arm was added in a protocol amendment on July 12, 2022 to estimate the safety and efficacy of single agent asciminib and is now enrolling. c Patients may discontinue treatment at the time of interim analysis if there is excessive toxicity without added benefit is observed in 1 of the observational arms. Patients who choose to discontinue in the asciminib 60 mg add-on arm will have the opportunity to continue the study in the asciminib 40 mg add-on arm if the investigator believes it is in the best interest of the patient. d Crossover allowed for patients who have not achieved MR4.5 (not included in this analysis).

Cortes JE, et al. ASH 2022. Abstract 80.

AXIS Medical Education

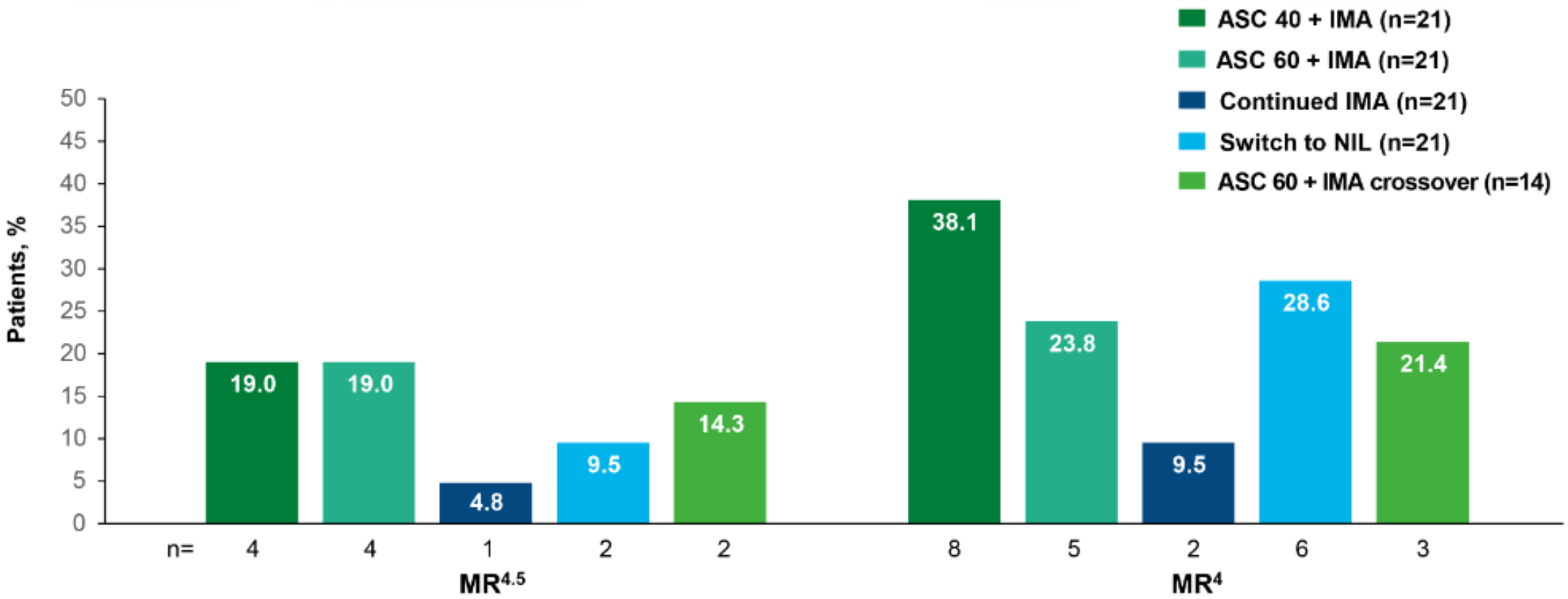
Overview of Adverse Events

Category, n (%)	ASC 40 + IMA n=21		ASC 60 + IMA n=21		IMA n=20		NIL n=21	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
AEs	21 (100)	8 (38.1)	19 (90.5)	8 (38.1)	15 (75.0)	2 (10.0)	21 (100)	9 (42.9)
Serious AEs	3 (14.3)	2 (9.5)	4 (19.0)	3 (14.3)	1 (5.0)	1 (5.0)	5 (23.8)	4 (19.0)
Fatal serious AEs	1 (4.8)[a]	1 (4.8)[a]	0	0	0	0	0	0
AEs leading to discontinuation	1 (4.8)	1 (4.8)	3 (14.3)	3 (14.3)	0	0	7 (33.3)	6 (28.6)
AEs leading to dose adjustment/interruption	7 (33.3)	4 (19.0)	8 (38.1)	6 (28.6)	2 (10.0)	1 (5.0)	5 (23.8)	5 (23.8)
AEs requiring additional therapy	15 (71.4)	3 (14.3)	17 (81.0)	5 (23.8)	9 (45.0)	2 (10.0)	17 (81.0)	9 (42.9)

[a]On-treatment death was due to cardiac arrest and was reported previously in the primary analysis. This patients was a 70-year-old man treated with imatinib from 2008-2020 with a previous history of hypertension, type 2 diabetes hypercholesterolemia, and past cardiac stent(s) placed, and in February 2021 surgery from gastric cancer and cholecystolithiasis. Approximately 6 months after the first dose of study medications and 3 months after gastric surgery, the patient was hospitalized due to abdominal pain and shortness of breath and died of cardiac arrest 5 days later. The patients was on this study for 186 days.

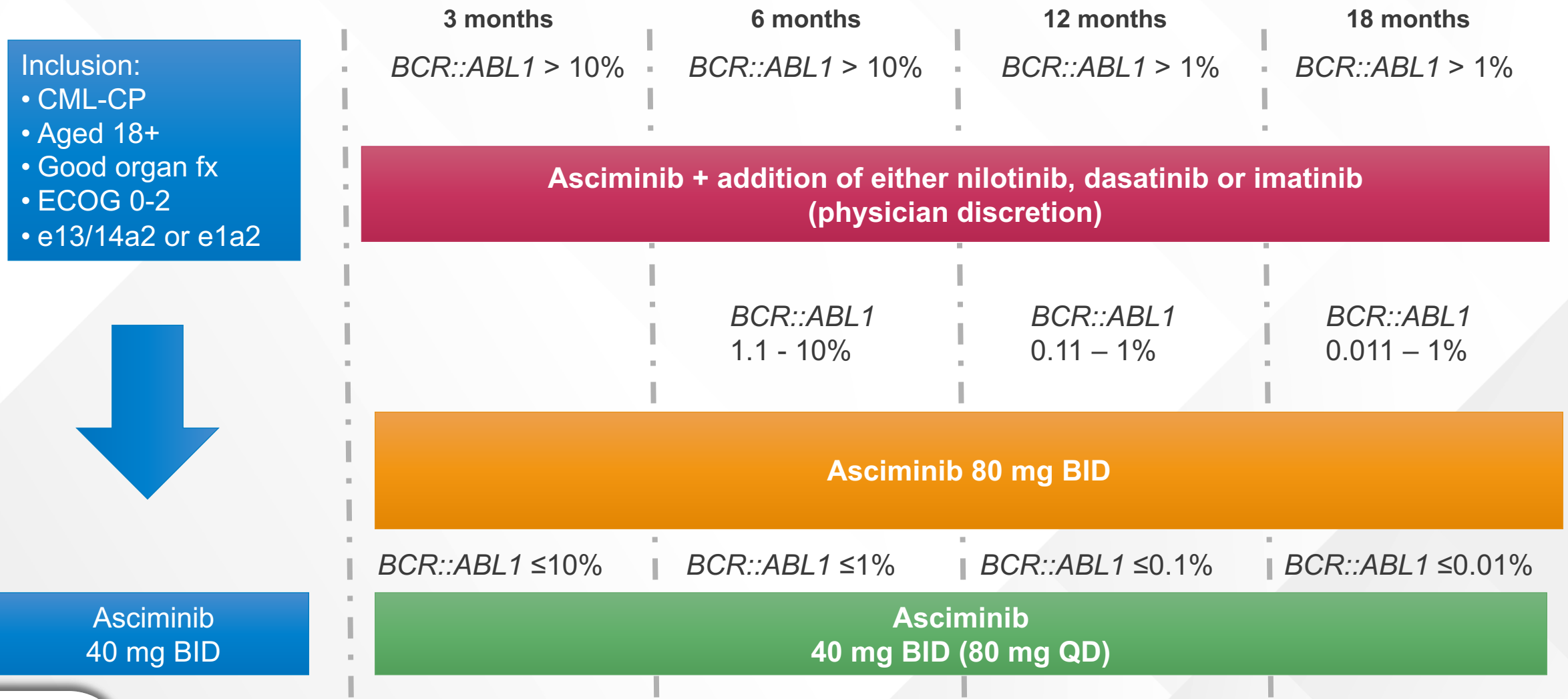
Hughes TP, et al. ASH 2023. Abstract 866.
AE, adverse event; ASC, asciminib; IMA, imatinib; NIL, nilotinib.

Deep Molecular Responses at Week 96



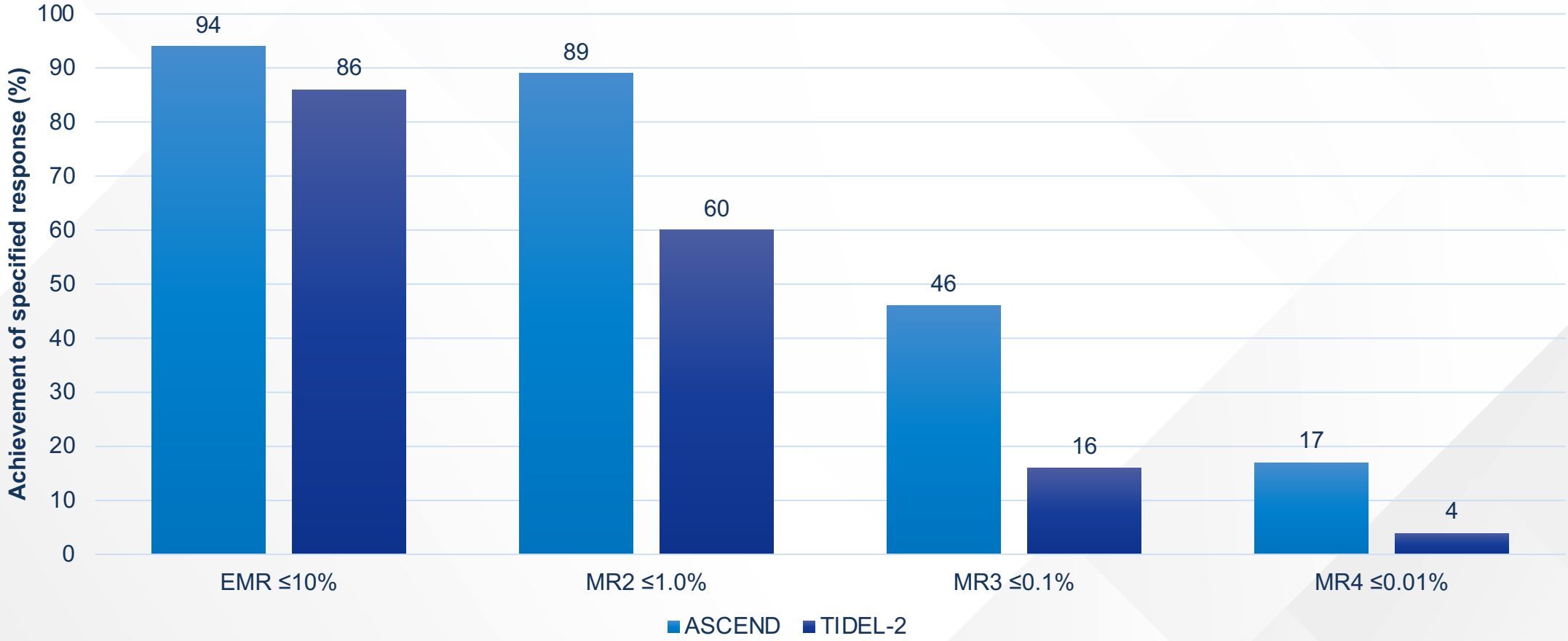
Hughes TP, et al. ASH 2023. Abstract 866.
ASC, asciminib; IMA, imatinib; MR, molecular response; NIL, nilotinib.

ASCEND-CML Treatment Schema



Yeung DT, et al. *Blood.* 2022;140(Suppl 1):192-194.
BID, twice daily; CML, chronic myeloid leukemia; CP, chronic phase; QD, once daily.

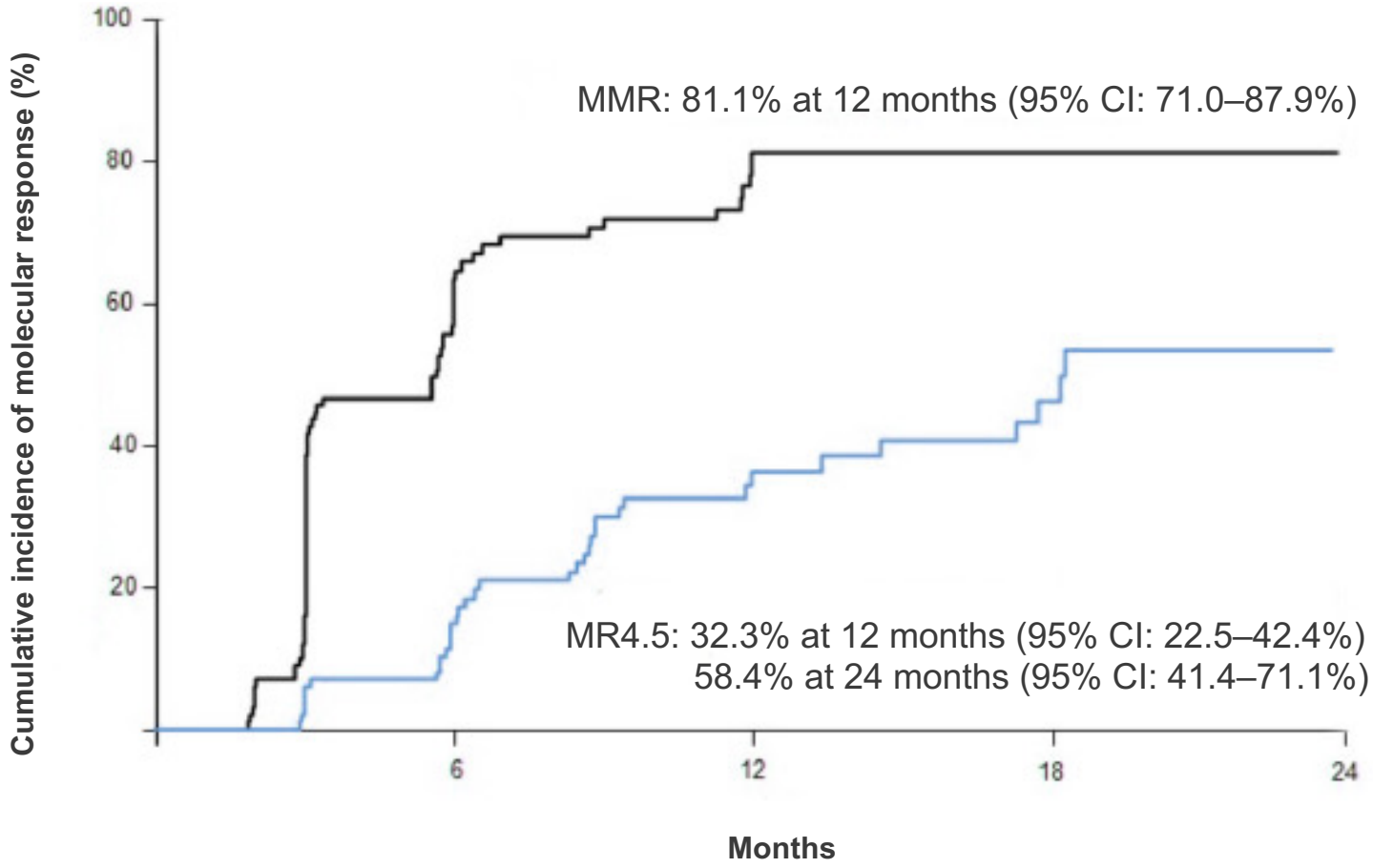
Molecular Response at 3 Months (N=79)



Yeung DT, et al. *Blood.* 2022;140(Suppl 1):192-194. Yeung DT, et al. *Blood.* 2015;125(6):915-923.
EMR, early molecular response.

Updated Molecular Response

Median follow-up: 20 months (range, 0-29 months)



Data cut off: May 2023
Yeung DT, et al. ASH 2023. Abstract 865.
MR, molecular response; MMR, major molecular response.

Safety Findings

Grade ¾ AEs, %	Patients (N = 101)
Neutropenia	6
Thrombocytopenia	5
Increased lipase/amylase	8
Clinical pancreatitis	2
Anemia	2
Infection	1
Increased AST/ALT	1
Back pain	1
Abdominal pain	1
Chest pain from PE	1

- Treatment-emergent stroke in a male patient aged 73 with pre-existing diabetes and hypertension
  - Occurred after 20 months of asciminib
- Study discontinuations: 15 patients
  - AEs: 6
  - Lost to follow-up: 3
  - Resistant disease: 6

Yeung DT, et al. ASH 2023. Abstract 865.
AE, adverse event; ALT, alanine transaminase; AST, aspartate aminotransferase; PE, pulmonary embolism.

AIM4CML Study

Patient Population

CML-CP without T315I mutation with ≥2 prior ATP-site TKIs

CML-CP without T315I mutation with ≥1 prior ATP-site TKIs

Cohort A (n=45)
Asciminib 40 mg BID

Cohort B (n=45)
Asciminib 80 mg QD

Cohort C (n=25)
Asciminib 200 mg BID
(for T3151 mutation only)

Primary endpoint:
Safety at week 24 – AEs, Including AEs of special interest, serious AEs

Secondary endpoints:
12/24-week efficacy end points (CHR, MR^2, MMR); 48/72-week efficacy end points (CHR, MR^2, MMR, MR^1, and $MR^{4.5}$)

Exploratory endpoints

30-day safety follow-up

Andorsky D, et al. *Blood.* 2021;138(suppl 1):3599.
AE, adverse event; ATP, adenosine triphosphate; BID, twice daily; CHR, complete hematologic response; CML, chronic myeloid leukemia; CP, chronic phase; MR, molecular response; MMR, major molecular response; TKI, tyrosine kinase inhibitor; QD, four times daily.

AIM4CML: Baseline Characteristics

	Asciminib 40 mg BID (N=22)	Asciminib 80 mg QD (N=20)
Age, median (range), years	58.5 (30.0-81.0)	52.5 (22.0-84.0)
Female, n (%)	14 (63.6)	12 (60.0)
ECOG PS, n (%)		
0	10 (45.5)	8 (40.0)
1	10 (45.5)	11 (55.0)
2	1 (4.5)	1 (5.0)
Missing	1 (4.5)	0
Patients with resistance to prior therapy		
No	13 (59.1)	10 (50.0)
Yes	8 (36.4)	10 (50.0)
Missing	1 (4.5)	0
Number of prior TKI therapies		
1	1 (4.5)	0
2	7 (31.8)	8 (40.0)
3	9 (40.9)	8 (40.0)
≥4	4 (18.2)	4 (20.0)
Missing	1 (4.5)	0
Prior TKIs		
Bosutinib	7 (31.8)	9 (40.9)
Dasatinib	19 (86.4)	18 (81.9)
Imatinib	17 (77.3)	13 (59.1)
Nilotinib	12 (54.5)	14 (63.6)
Ponatinib	1 (4.5)	2 (9.1)
Time since initial diagnosis,[a] median (range), years	2.98 (0.71-17.57)	5.43 (1.22-17.53)
Baseline *BCR::ABL1*^{IS} median, range, %	1.1 (0-88.38)	6.9 (0.01-94.03)

Andorsky D, et al. *Blood.* 2021;138(suppl 1):3599. Andorsky D, et al. ASH 2023. Abstract 3172.
BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; QD, four times daily; TKI, tyrosine kinase inhibitor.

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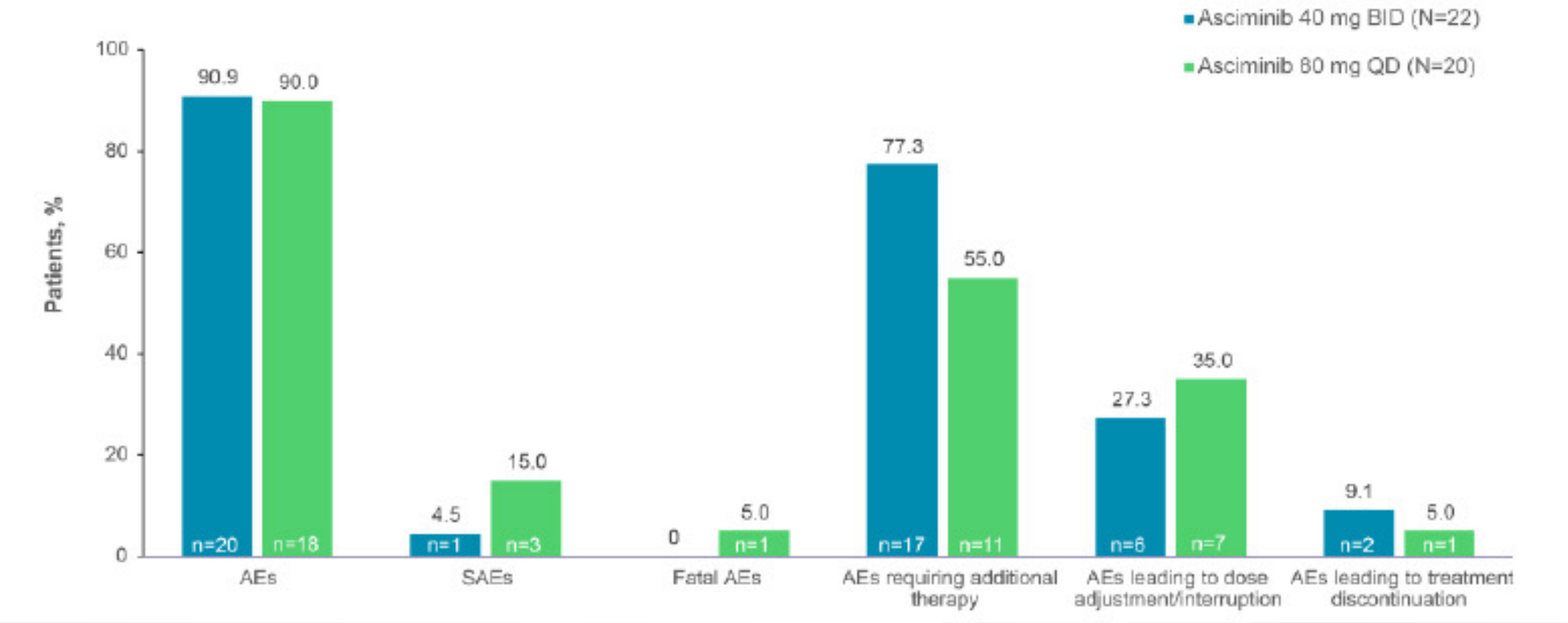
AIM4CML Study: Overview of AEs by Week 24



Andorsky D, et al. *Blood.* 2021;138(suppl 1):3599. Andorsky D, et al. ASH 2023. Abstract 3172.
AE, adverse event; BID, twice daily; QD, four times daily; SAE, serious adverse event.

Secondary Endpoints

Measure	Cohort A (n = 22)	Cohort B (n = 20)
Patients with ≥1 molecular response assessment, n		
Week 4	18	17
Week 12	19	17
Week 24	20	18
Proportion of pts who maintained or achieved *BCR::ABL1*^{IS} ≤1%, %		
Week 4	50.0	52.9
Week 12	63.2	76.5
Week 24	65.0	88.9
MMR rate, *		
Week 4	33.3	23.5
Week 12	42.1	47.1
Week 24	45.0	61.1
Deep molecular response rates,* %		
Week 4	27.8	5.9
Week 12	31.6	11.8
Week 24	30.0	27.8

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*Defined as (MR^4; *BCR::ABL1*^{IS} ≤0.01%)

Andorsky D, et al. *Blood.* 2021;138(suppl 1):3599. Andorsky D, et al. ASH 2023. Abstract 3172.

MMR, major molecular response.

The Spectrum of BCR::ABL Inhibitors

	1st Generation TKI	2nd Generation TKI	3rd Generation TKI	Allosteric TKI
Approved (FDA/EMA)	Imatinib	Bosutinib Dasatinib Nilotinib	Ponatinib	Asciminib
Ex-US Licensed/Approved	Flumatinib	Radotinib	Olverembatinib	
In development			Vodobatinib Vamotinib (PF-114) ENLV-001	TERN-701 TGRX-678

FDA, U.S. Food and Drug Administration; EMA; European Medicines Agency; TKI, tyrosine kinase inhibitor.

Novel Agents in Development

- ATP-competitive inhibitors
  - Olverembatinib (formerly GZD824 and HQP1351) (China)
  - PF-114
  - Vodobatinib (formerly K0706)

ATP, adenosine triphosphate.

Olverembatinib: TKI in CML with T315I

- 64 patients enrolled in two open-label single-arm multicenter trials of patients with CML-CP or CML-AP

Parameter	CML-CP, %	CML-AP, %
CHR	100	74
MCyR	83	52
CCyR	71	52
MMR	58	48
3-y PFS	86	57
3-y OS	95	70

- Thrombocytopenia and skin pigmentation observed in 70% and 56.1% of CML-CP patients, respectively
- Proteinuria and hypocalcemia reported in 56.5% and 52.2% of CML-AP patients, respectively

Jiang Q, et al. ASH 2022; Abstract 83.
AP, accelerated phase; CCyR, complete cytogenetic response; CHR, complete hematologic response; CML, chronic myeloid leukemia; CP, chronic phase; MCyR, major cytogenetic response; MMR, major molecular response; TKI, tyrosine kinase inhibitor.

Olverembatinib in Heavily Pretreated/Refractory CML-CP and Ph+ ALL

- 76 patients enrolled including
  - CML-CP: n = 57
  - Ph+ALL, n =19
- Patients were randomized to olverembatinib QOD 30, 40, or 50 mg in continuous 28-day cycles
- Number of prior TKIs:
  - 2: 11 (14.5%) patients
  - 3: 23 (30.3%) patients
  - ≥4: 39 (51.3%) patients
- Prior ponatinib: 52.6% of all patients
  - Resistant: 67.5%
  - Intolerant: 25.0%
  - Treatment failure for other reasons: 7.5%
- Prior asciminib: 27.6% of all patients
  - Resistant: 71.4%
  - Intolerant: 19.1%
  - Treatment failure due to other reasons: 9.5%

Jabbour E, et al. ASH 2023. Abstract 1798.
CML, chronic myeloid leukemia; CP, chronic phase; Ph+ ALL; Philadelphia chromosome-positive acute lymphoblastic leukemia; QOD, once every other day; TKI, tyrosine kinase inhibitor.

Olverembatinib Monotherapy Responses in CML

CML-CP	Total	*T315I* mutation		Ponatinib pretreated		Asciminib pretreated	
		Positive	Negative	Resistant	Intolerant	Resistant	Intolerant
Efficacy population	50	16	34	16	6	8	2
Cytogenetic response							
No. of evaluable subjects-n	44	15	29	15	4	7	0
CCyR, n (%)	25 (56.8)	9 (60.0)	16 (55.2)	8 (53.3)	3 (75.0)	3 (42.9)	0
Molecular response							
No. of evaluable subjects-n	49	16	33	16	6	8	2
MMR, n (%)	21 (42.9)	7 (43.8)	14 (42.4)	6 (37.5)	1 (16.7)	3 (37.5)	0

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Jabbour E, et al. ASH 2023. Abstract 1798.

CCyR, complete cytogenetic response; CML, chronic myeloid leukemia; CP, chronic phase; MMR, major molecular response.

Vodobatinib

- Third generation TKI (no activity with T315I mutation)
- Phase 1/2 trial of patients with failure of ≥3 TKIs, including ponatinib-treated and ponatinib-naïve
  - Complete hematologic response: 65.1%
  - Complete cytogenetic response: 55.8%
  - Major molecular response in overall: 46.5%
- Thrombocytopenia most common grade ≥3 AEs
- Two cardiovascular adverse events ≥ grade 3 reported (transient worsening of hypertension in ponatinib-treated patient and intracranial hemorrhage associated with blast phase progression)

Cortes JE, et al. *Blood.* 2022;140:205-207.
AE, adverse event; TKI, tyrosine kinase inhibitor.

PF-114

- ATP-competitive 4th generation TKI (based on ponatinib scaffold)
- Phase I dose-finding study of patients with CML-CP/AP resistant or intolerant to multiple TKIs or with T315I with ≥6 months therapy
  - Complete hematologic response: 8/19 patients
  - Major cytogenetic response: 6/21 patients
  - Major molecular response: 2/18 patients
- Reversible grade 3 skin toxicity observed

Turkina AG, et al. *Blood.* 2021;138(Supplement 1):1482.

AP, accelerated phase; ATP, adenosine triphosphate; CML, chronic myeloid leukemia; CP, chronic phase; TKI, tyrosine kinase inhibitor.

Thoughts on Allografting in the Era of Increasingly Potent TKIs

Status	TKIs	Transplant	Future
Accelerated or blast transformation	Interim treatment (TKI, TKI+chemo, novel tx) to best response/minimal residual disease	ASAP	Nontransplant remedies? CAR-T?
IM/2GTKI failure in chronic phase, T315I (+)	Ponatinib or asciminib	If no response to ponatinib/asciminib	Olverembatinib; ELVN-001; TERN-701
IM/2GTKI failure in chronic phase without clonal evolution, mutations, good response	Long-term 2nd or 3rd line TKIs *with consideration of risk vs benefit*	Late line of therapy failure; young patient with limited response, high risk TKI	Consolidation/optimization with novel TKIs (asciminib?)
IM/2GTKI failure in chronic phase with clonal evolution, mutations, poor response	Interim treatment to best response; consider NGS; favor 3rd gen TKI; "mutator phenotype" may benefit from asciminib	Taken case by case	Need more data on role of non-ABL mutations and combinations (asciminib+ponatinib?)
Older age (≥65-70) post IM/2GTKI failure	Long-term 2nd or 3rd line TKIs with consideration of risk vs benefit	May forgo allo SCT for many years of QOL; lesser degrees of response may be relevant (CCyR, MMR)	Consolidation/optimization with novel TKIs (asciminib?)
Failure after ponatinib/asciminib	Complex issue; mutation driven ? Role for switch to alternate (ATP↔Myristoyl site inhibitors)	Planning ASAP	Alternate STAMP inhibitors; combinations?

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Slide courtesy of Michael J. Mauro, MD.

CAR-T, chimeric antigen receptor T-cell; CCyR, complete cytogenetic response; NGS, next generation sequencing; SCT, stem cell transplantation; QOL, quality of life; STAMP, specifically targeting the ABL myristoyl pocket; TKI, tyrosine kinase inhibitor.

Conclusions

- Patients with CML can have life spans approaching the general population
- “Functional Cure” fraction needs boosting as a primary goal
  - ~75% DMR over time, IM/2GTKI
  - ~35-40% successful TFR
  - Majority of patients thus remain on TKI
- Adherence and toxicity management is important
- New therapies are providing options for patients with multi-TKI-resistant disease
- Future strategies focus on combinations and novel treatments which may prevent resistance and improve TFR rates

CML, chronic myeloid leukemia; DMR, deep molecular response; TFR, treatment-free remission; TKI, tyrosine kinase inhibitor.

Case Studies

Case Study #1: Patient Presentation and History

- A 62-year-old electrical engineer presents with weight loss and fatigue
- Physical exam positive for splenomegaly (approximately 9 cm below the costal margin)
- WBC: 109,000 cells/mm^3
- Hemoglobin: 11.2 g/dL
- Platelets: 209,000 cells/mm^3
- Hypercellular marrow with 2% blasts
- 46,XX, t(9;22)(q34;q11.2)

- Female
- BMI: 34
- No smoking history
- Hypertension for 6 years moderately controlled with hydrochlorothiazide

Case #1 (Cont.)

- Diagnosis: CP-CML
- Sokal score: intermediate risk
- Initial treatment: imatinib
  - *BCR::ABL1* (IS) 0.1% at 12 months maintained for 2 yrs
  - At 49 months *BCR::ABL1* begins to rise and CCyR is lost
  - Mutation analysis reveals an F317L mutation
- Patient started on nilotinib with initial response, but *BCR::ABL1* begins to rise at 6 months and again at 9 months
- Since initial diagnosis, develops peripheral vascular disease, worsening hypertension and CAD requiring stent placement
- Mutation analysis reveals a T315I mutation

CAD, coronary artery disease; CCyR, complete cytogenetic response; CML, chronic myeloid leukemia; CP, chronic phase.

Case #1 Question

What is your next step with this patient?

a) Continue nilotinib
b) Begin treatment with asciminib
c) Begin treatment with bosutinib
d) Begin treatment with ponatinib
e) Unsure

Case Study #2: Patient Presentation and History

- A 73-year-old retired physical education teacher presents with weight loss and fatigue
- Physical exam positive for splenomegaly (approximately 7 cm below the costal margin)
- WBC: 82,000 cells/mm^3
- Hemoglobin: 10.1 g/dL
- Platelets: 275,000 cells/mm^3
- Hypercellular marrow with 5% blasts
- 46,XX, t(9;22)(q34;q11.2)

- Male
- BMI: 25
- No smoking history
- BPH well controlled with tamsulosin

BPH, benign prostatic hyperplasia; WBC, white blood cell.

Case #2 (Cont.)

- Diagnosis: CP-CML
- Sokal score: high risk

- Initial treatment: dasatinib
  - BCR::ABL1 (IS) 9% at 3 months, 8% at 6 months with pCyR
  - At 9 months BCR::ABL1 begins to rise and CyR is lost
  - Mutation analysis reveals a T3151I mutation

CyR, cytogenetic response; CML, chronic myeloid leukemia; CP, chronic phase; pCyR, cytogenetic response.

Case #2 Question

What is your next step with this patient?

a) Continue dasatinib
b) Begin treatment with asciminib
c) Begin treatment with bosutinib
d) Begin treatment with ponatinib
e) Unsure

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Response Matters:

Transforming the Standard of Care in CML by Mastering Response-Guided Treatment