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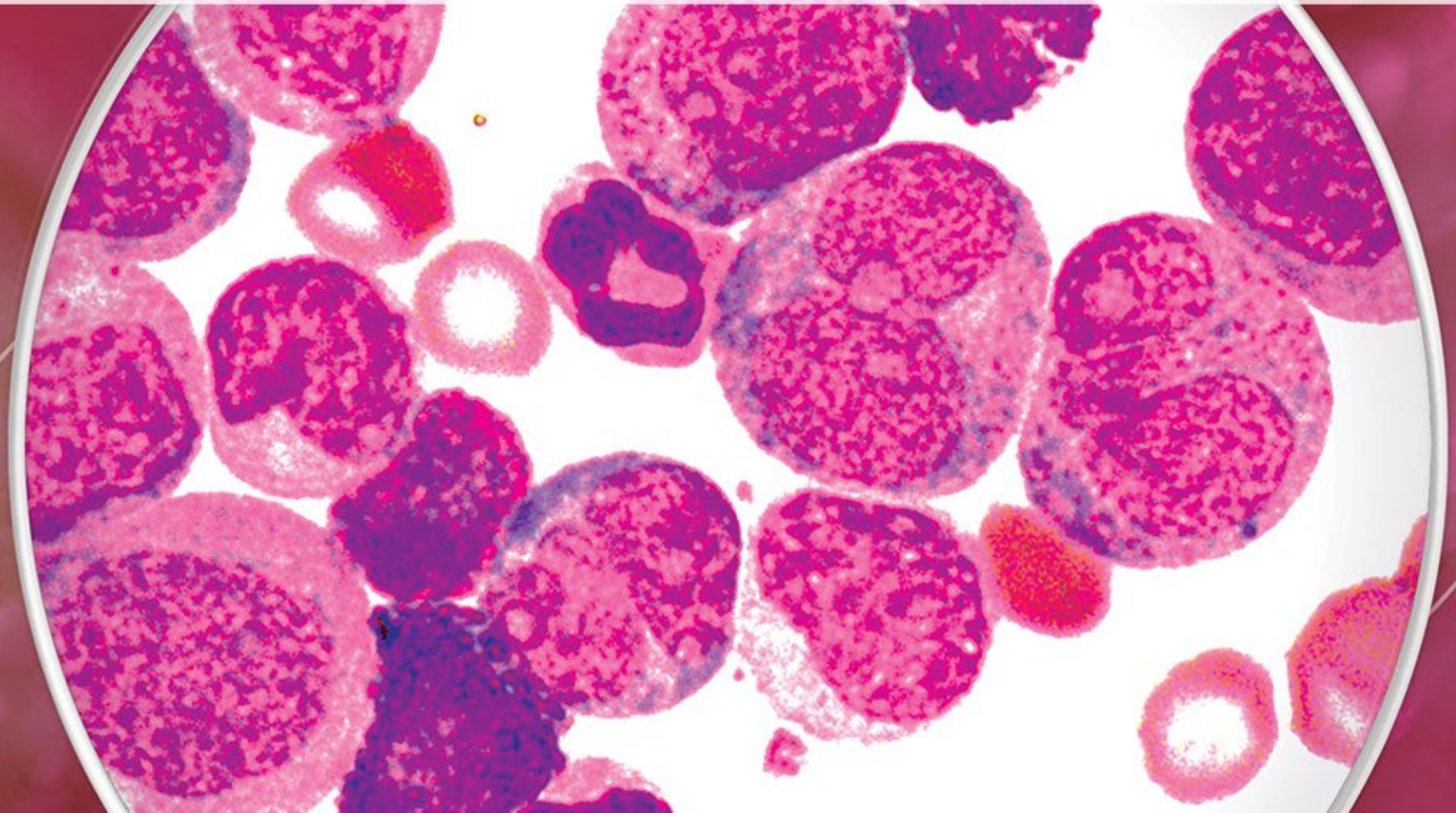
Novel Treatments for Newly Diagnosed Ph+ CML-CP:

Striking the Balance of Treatment with Patient Goals and QoL



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FDA, US Food and Drug Administration.

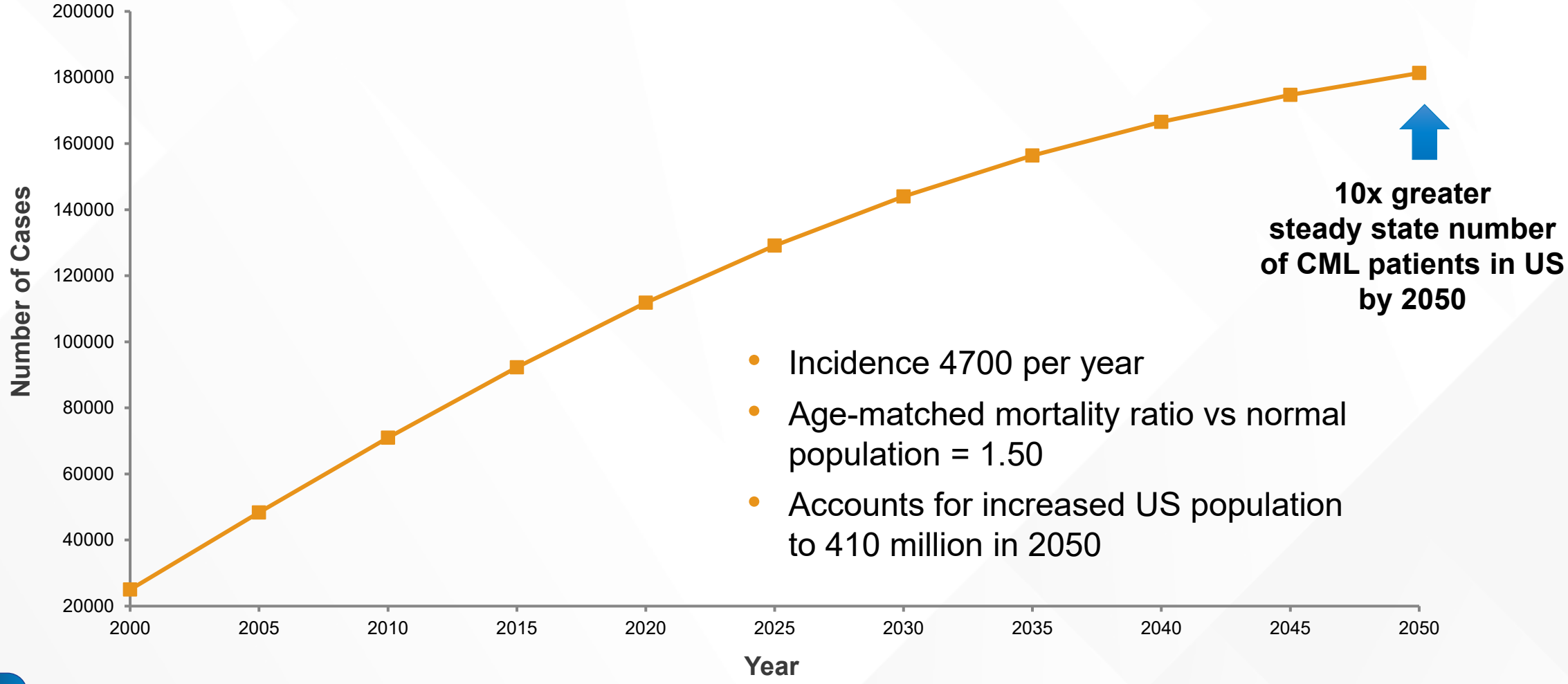
Learning Objectives

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

- Apply various TKI treatment options in the frontline setting based on updated guidelines, emerging trial data, and changes in real-world evidence when developing personalized treatment approaches for CML patients
- Integrate BCR-ABL transcript and mutational testing and other team-based strategies to inform TKI selection and achieve EMR, MMR, and DMR in patients with CML to potentially lead to treatment-free remission
- Plan effective team-based strategies for mitigation and management of potential AEs and drug resistance resulting from CML treatment, while optimizing adherence

Overview of Current Treatments: Intervention and Management of CML Patients

Increasing Prevalence of CML



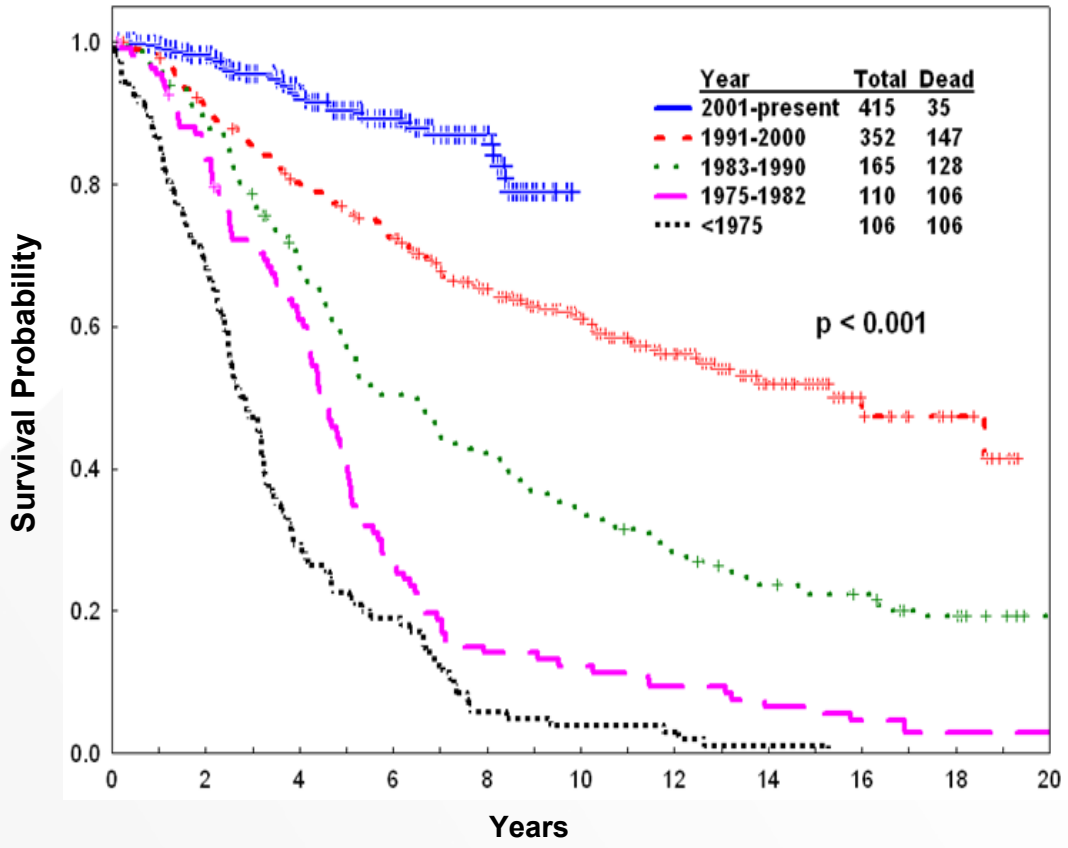
- Incidence 4700 per year
- Age-matched mortality ratio vs normal population = 1.50
- Accounts for increased US population to 410 million in 2050

CML, chronic myeloid leukemia.

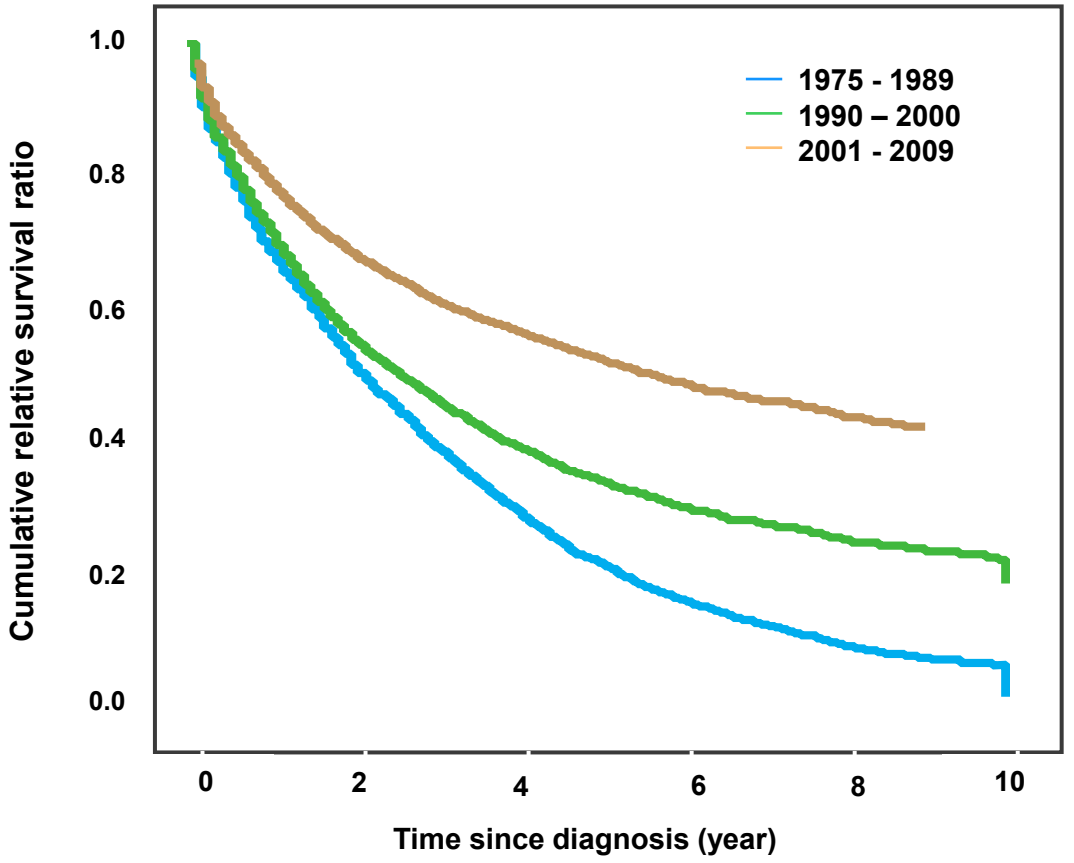
Huang X, et al. *Cancer.* 2012;118(12):3123-3127. Bower H, et al. *J Clin Oncol.* 2016;34:2851-2857.

Improving Long-Term Outcomes in CML

MDACC[1]



SEER[2]

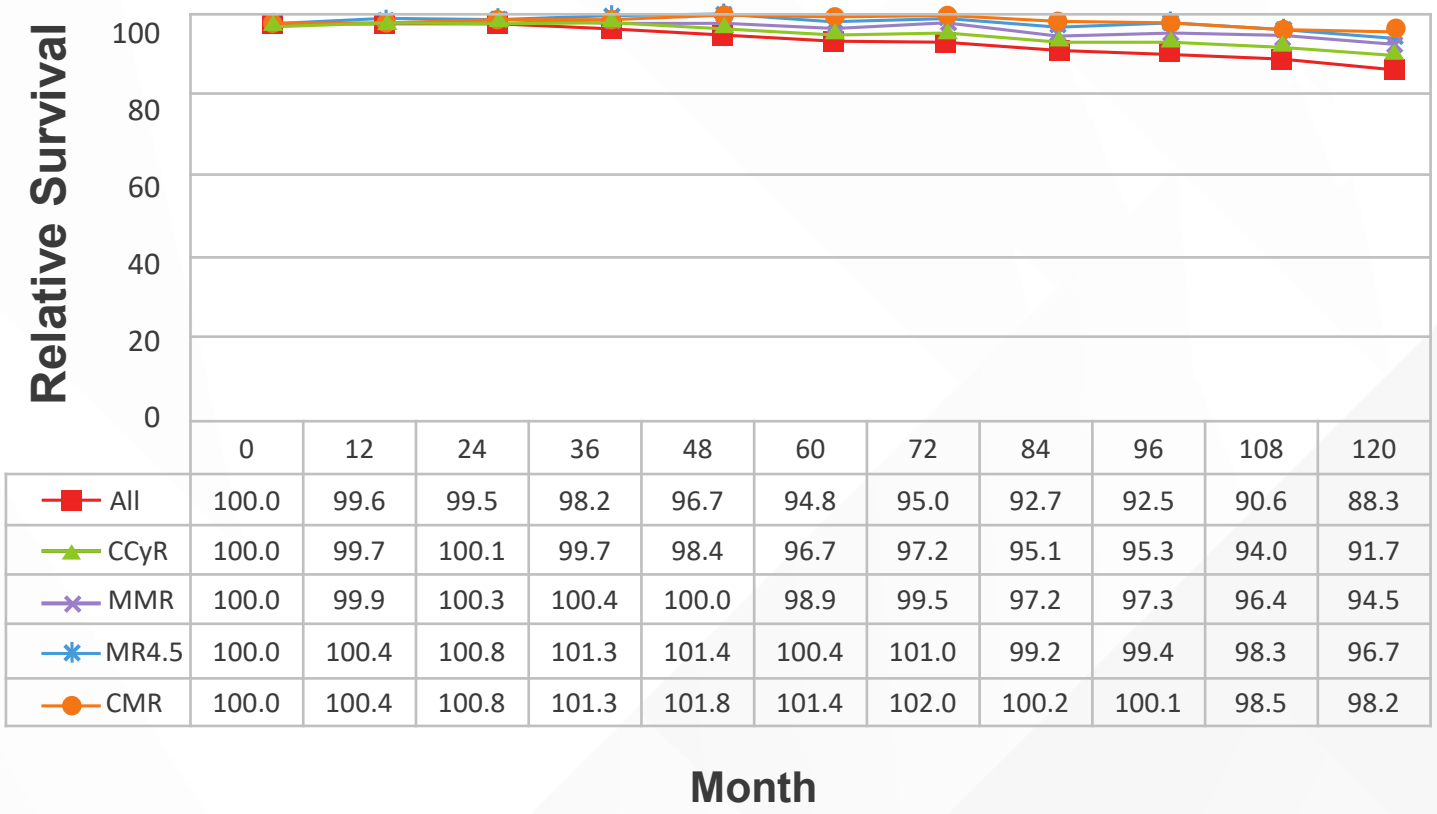


CML, chronic myeloid leukemia; MDACC, MD Anderson Cancer Center; SEER, Surveillance, Epidemiology, and End Results database.

1. Kantarjian H, et al. *Blood.* 2012;119(9):1981-1987. 2. Chen Y, et al. *Leuk Lymphoma.* 2013;54(7):1411-1417.

Relative Survival With TKI by Response to Therapy

- 483 pts with CML treated with imatinib 400mg (n=71), imatinib 800 mg (n=201), dasatinib (n=111) or nilotinib (n=101)
- 5-yr relative survival 94.8% [92.1 - 97.4]



	0	12	24	36	48	60	72	84	96	108	120
All	100.0	99.6	99.5	98.2	96.7	94.8	95.0	92.7	92.5	90.6	88.3
CCyR	100.0	99.7	100.1	99.7	98.4	96.7	97.2	95.1	95.3	94.0	91.7
MMR	100.0	99.9	100.3	100.4	100.0	98.9	99.5	97.2	97.3	96.4	94.5
MR4.5	100.0	100.4	100.8	101.3	101.4	100.4	101.0	99.2	99.4	98.3	96.7
CMR	100.0	100.4	100.8	101.3	101.8	101.4	102.0	100.2	100.1	98.5	98.2

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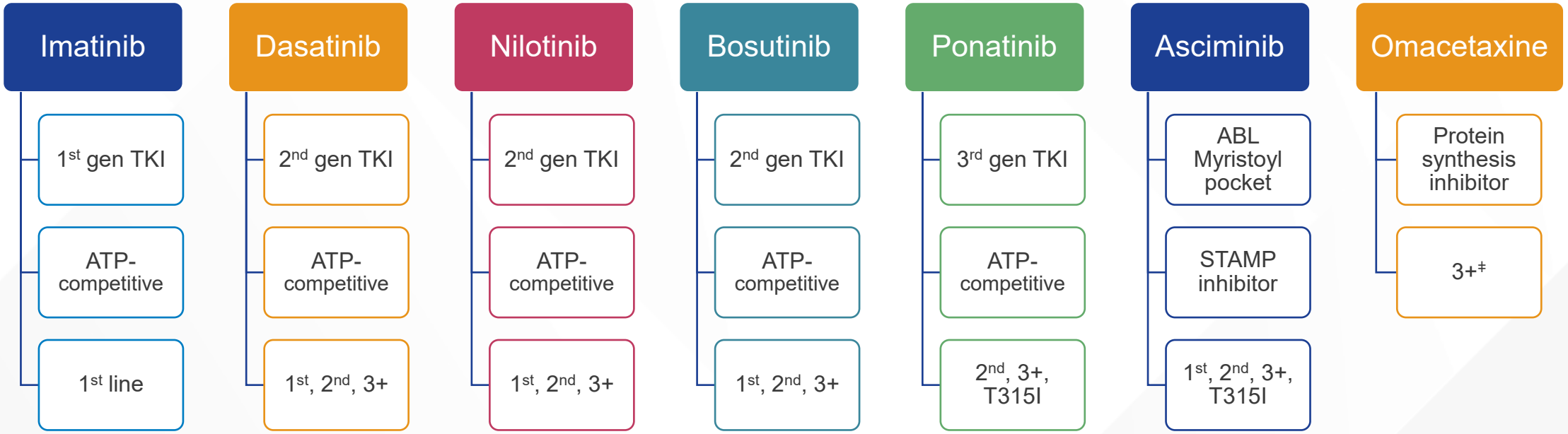
CCyR, complete cytogenetic response; CML, chronic myeloid leukemia; CMR, complete molecular response; MMR, major molecular response; MR4.5, molecular response by a 4.5 log reduction on the international scale; TKI, tyrosine kinase inhibitor.

Sasaki K, et al. *Lancet Haematol*. 2015;2(5):e186-e193.

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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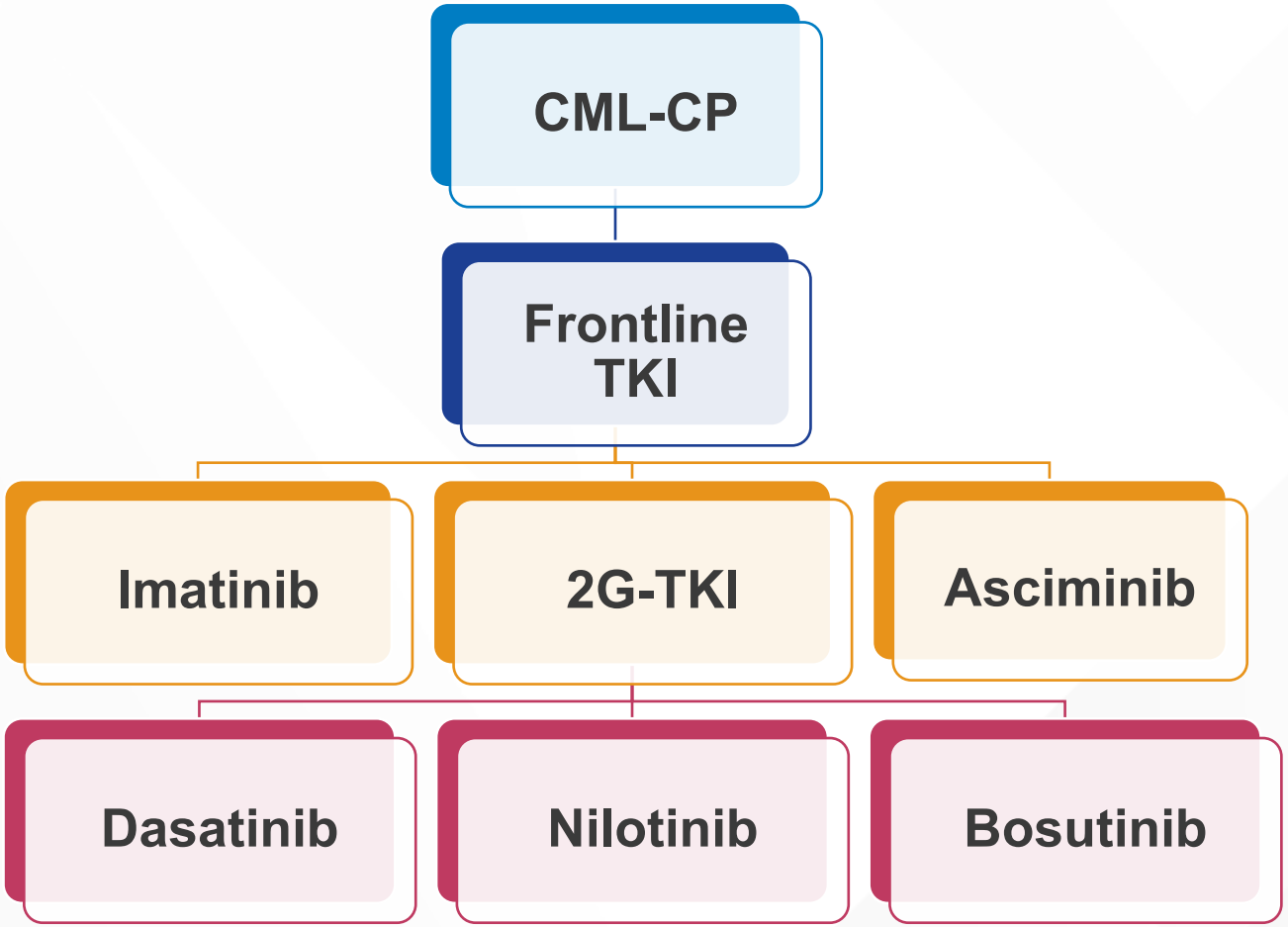
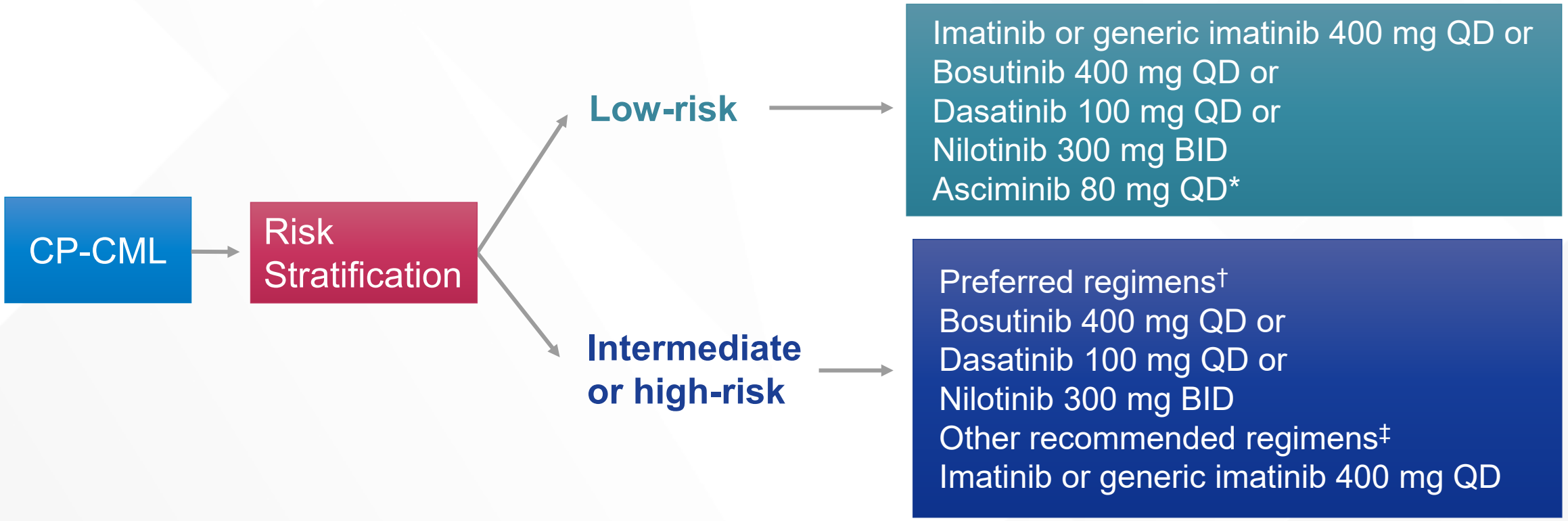
‡Only available in the US.
ATP, adenosine triphosphate; CML, chronic myeloid leukemia; CP, chronic phase; STAMP, specifically targeting the ABL myristoyl pocket; TKI, tyrosine kinase inhibitor.
Hochhaus A, et al. *Leukemia* 2020;34: 966-984. NCCN Guidelines. Chronic Myeloid Leukemia (V1.2024). NCCN.org. Garcia-Gutierrez V, et al. *J Hematol Oncol.* 2022;15:90.

Selecting Frontline TKI



2G, second generation; CML-CP, chronic myeloid leukemia; CP, chronic phase; TKI, tyrosine kinase inhibitor.

NCCN Guidelines: First-Line Treatment



*Either as 80 mg QD or 40 mg BID. For Ph+ CML-CP with the *T315I* mutation, 200 mg BID. †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.

BID, twice a day; CML, chronic myeloid leukemia; CP, chronic phase; NCCN, National Comprehensive Cancer Network; QD, once a day; TKI, tyrosine kinase inhibitor.

NCCN Guidelines. Chronic Myeloid Leukemia (V3.2025). NCCN.org.

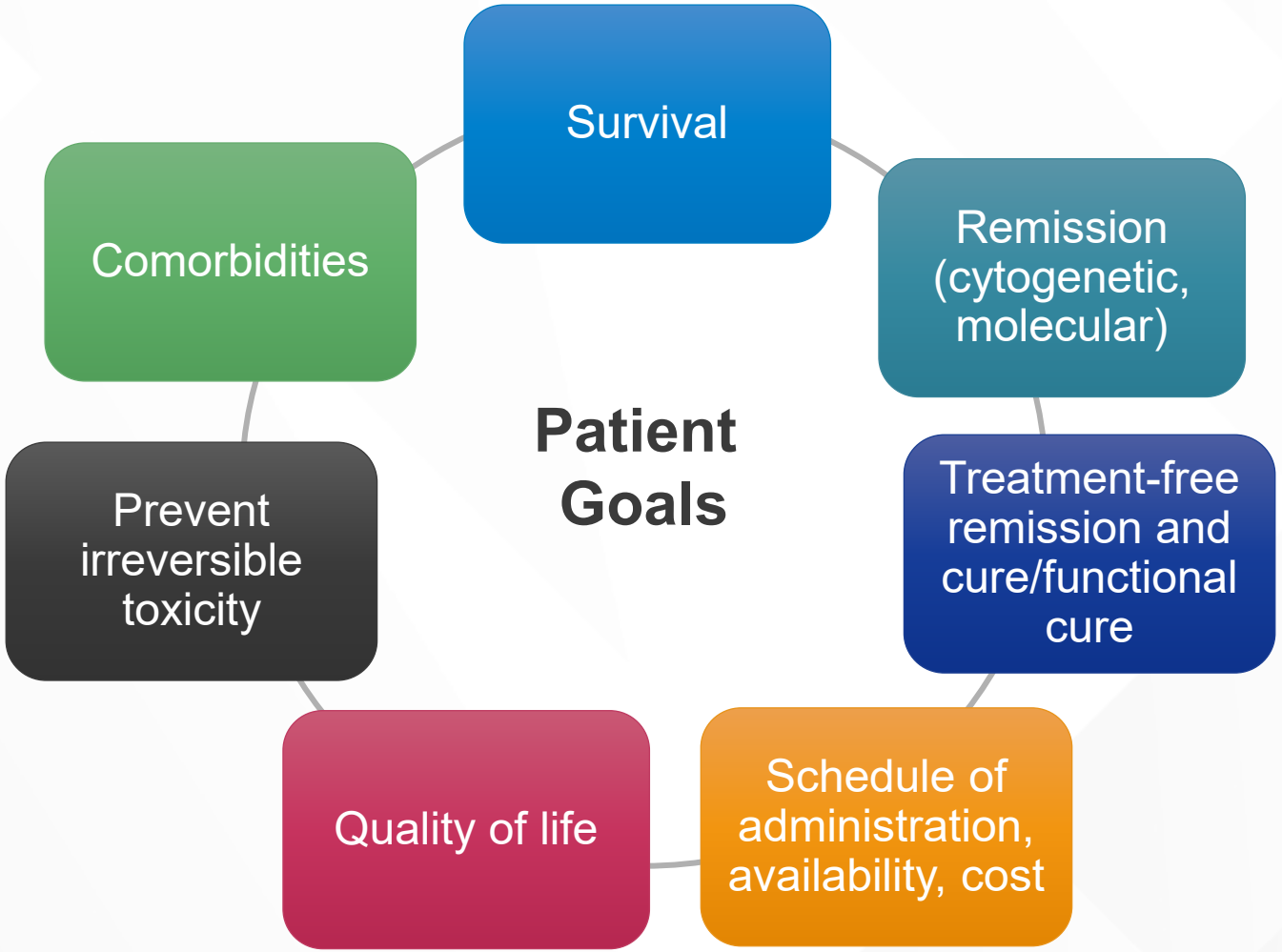
Prognostic Scores in CML

- Sokal: age, spleen, platelets, blasts
- Hasford (Euro): age, spleen, platelets, blasts, eosinophils, basophils
- EUTOS: spleen, basophils
- ELTS: age, spleen, platelets, blasts

CML, chronic myeloid leukemia; ELTS, EUTOS long-term survival score; EUTOS, European Treatment and Outcome Study.

European LeukemiaNet. https://www.leukemia-net.org/content/leukemias/cml/euro__and_sokal_score/index_eng.html
European LeukemiaNet. https://www.leukemia-net.org/content/leukemias/cml/eutos_score/index_eng.html

Other Considerations for Treatment Selection



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. Cortes J. Personal communication.

Outcome Across First-Line CML Studies

Parameter		DASISION		ENESTnd		BFORE	
		Dasatinib	Imatinib	Nilotinib	Imatinib	Bosutinib	Imatinib
Age	Median (range)	46 (18-84)	49 (18-78)	47 (18-85)	46 (18-80)	52 (18-84)	53 (19-84)
High risk[a]	%	19%	19%	28%	28%	20.7%	21.2%
EMR[b]	3 mo	84%	64%	91%	67%	80.6%	60.5%
MMR	12 mo	46%	28%	55%	27%	47.2%	36.9%
	24 mo	64%	46%	71%	44%	66%	57.4%
MR4	12 mo	NR	NR	20%	6%	20.7%	12.0%
	24 mo	NR	NR	39%	18%	26.6%	34.3%
MR4.5	12 mo	5%	3%	11%	1%	8.1%	3.3%
	18 mo	13%[c]	7%[c]	21%[c]	6%[c]		
	24 mo	17%	8%	25%	9%	20.4%	15.2%
Treatment change/ discontinued	1-3 yrs	23% (2 yrs)	25% (2 yrs)	25.5% (2 yrs)	32.5% (2 yrs)	18.3% (1 yr)	17.7% (1 yr)
	5 yrs	39%	37%	40.1%	50.2%	40.3%	41.9%

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[a]Sokal in JALSG, ENESTnd and BFORE, Hasford in DASISION, and ELTS in ASC4FIRST. [b]*BCR::ABL1* ≤10%. [c]Per trial design based on abstracts reporting median follow-up 18 mo.
CML, chronic myeloid leukemia; EMR, early molecular response; MMR, major molecular response; MR4/4.5, molecular response by a 4/4.5 log reduction on the international scale.
Veltmaat L, Cortes J. *Blood Adv*. 2024;8(20):5339-5341.

Persistent Challenges in CML

- ~40% change therapy by 5 yrs
- ~60% achieve MR4.5 by 10 yrs
- ~50% eligible for treatment discontinuation
- ~50% resume therapy after TFR
- Arterio-occlusive events with most TKIs
- Low-grade chronic AEs
- QoL

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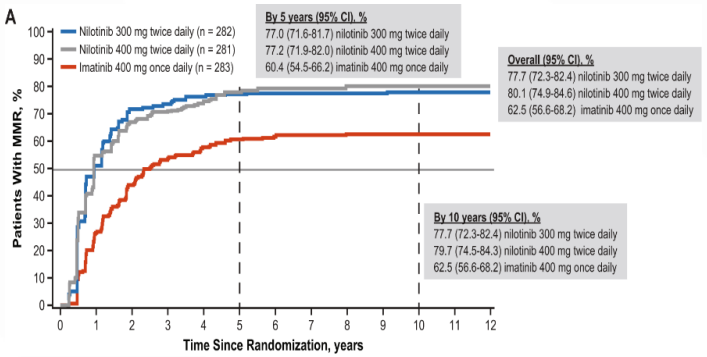
AE, adverse event; CML, chronic myeloid leukemia; MR4.5, molecular response by a 4.5 log reduction on the international scale; QoL, quality of life; TFR, treatment-free remission; TKI, tyrosine kinase inhibitor.

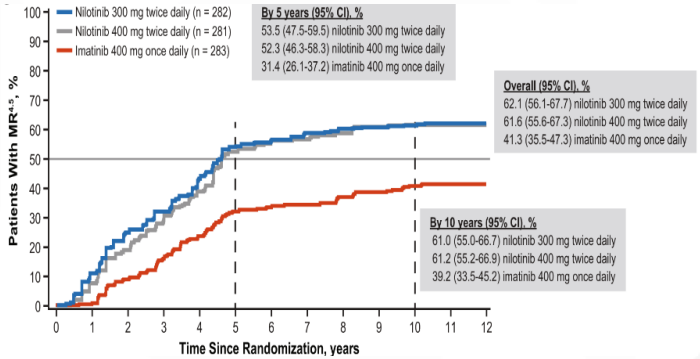
10-Year Results With Imatinib and Nilotinib

- Longest follow up for frontline TKI therapy
- Response plateau reached:
  - MMR ~80% with nilotinib, 65% with imatinib
  - MR4.5 ~60% with imatinib, 40% with imatinib

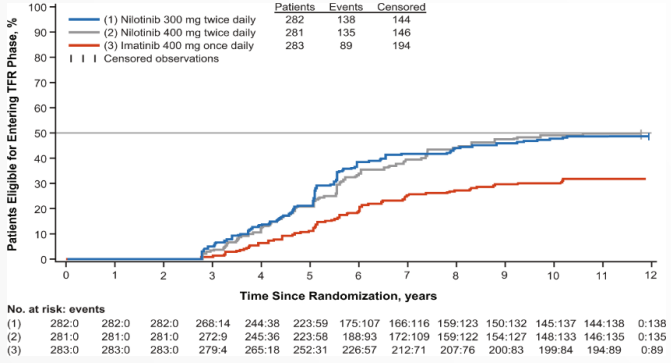
MMR



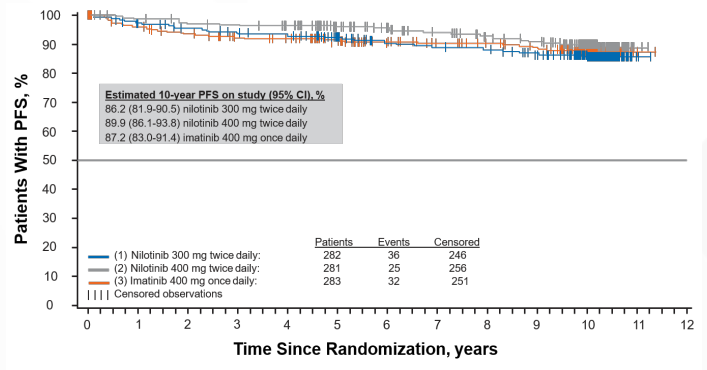
MR4.5



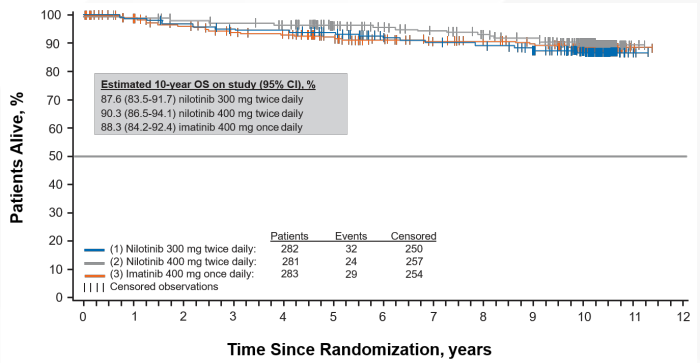
sMR4.5



PFS



OS

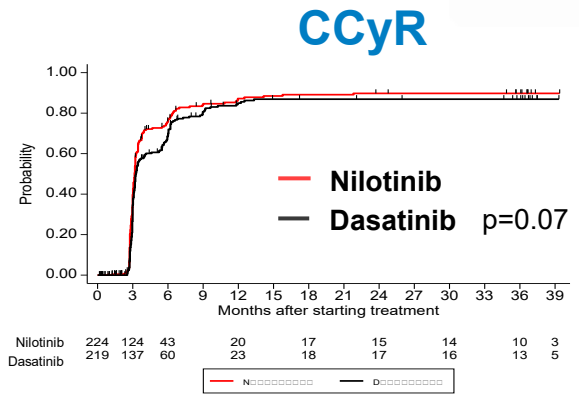


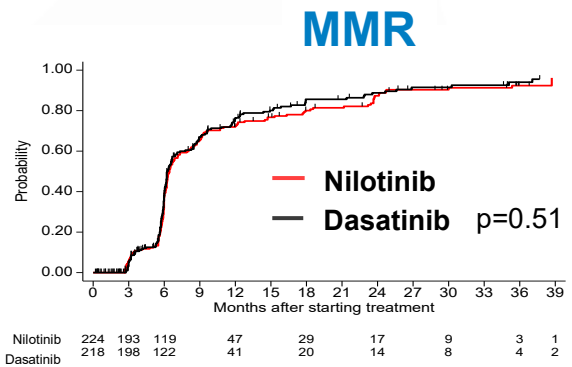
MMR, major molecular response; MR4.5, molecular response by a 4.5 log reduction on the international scale; OS, overall survival; PFS, progression-free survival; sMR4.5, sustained MR4.5; TKI, tyrosine kinase inhibitor.

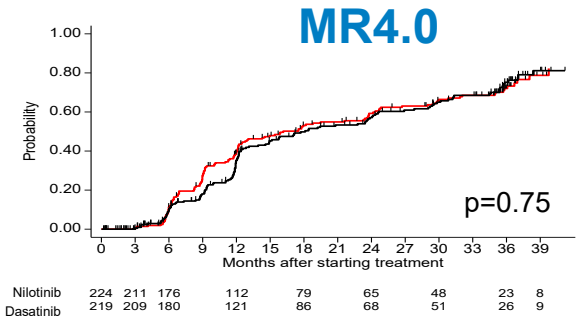
Kantarjian HM, et al. *Leukemia*. 2021;35(2):440-453.

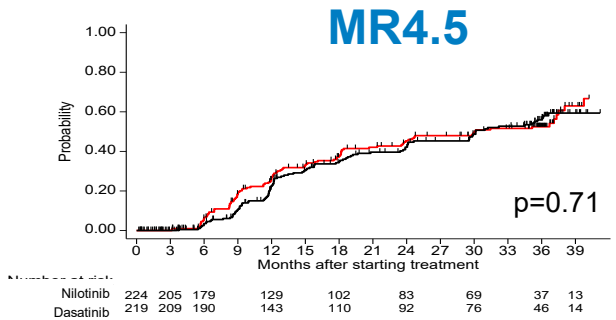
Similar Efficacy With 2nd Generation TKIs: Dasatinib vs Nilotinib for Frontline CML Therapy

- 454 patients randomized to 300 mg nilotinib BID or 100 mg dasatinib daily
- No significant difference in progression-free survival or overall survival
- Grade ≥3 neutropenia: nilotinib 4%, dasatinib 12.8%; thrombocytopenia nilotinib 4%, dasatinib 16.8%
- Other toxicity: pleural effusion with dasatinib 4.9%, angina with nilotinib 2.2%









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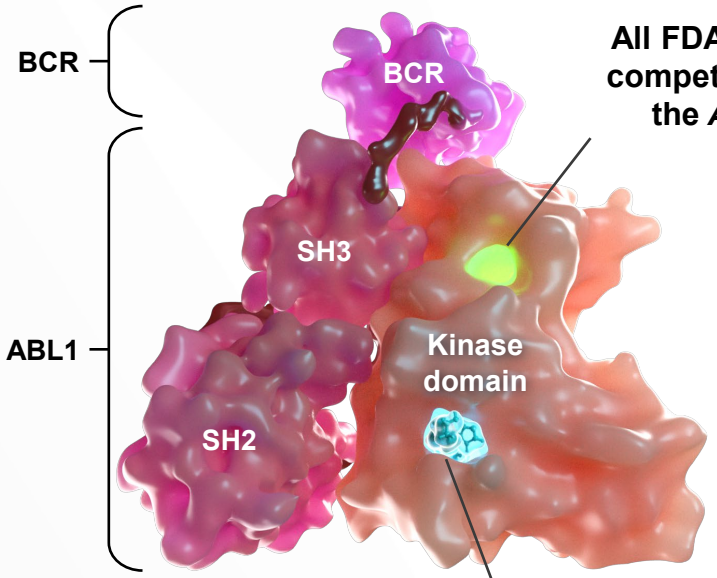
BID, twice a day; CCyR, complete cytogenetic response; CML, chronic myeloid leukemia; MMR, major molecular response; MR4/4.5, molecular response by a 4/4.5 log reduction on the international scale; TKI, tyrosine kinase inhibitor.

Matsumura I, et al. *Blood Adv.* 2024;8(20):5237-5247.

Asciminib and Classical TKIs Have Complementary Mutation Profiles

Asciminib: designed to improve efficacy and reduce off-target effects vs current ATP-competitive TKIs



All FDA-approved ATP-competitive TKIs target the *ATP-binding site*

Bosutinib
Ponatinib
Dasatinib
Nilotinib
Imatinib

Asciminib Specifically Targets the ABL *Myristoyl Pocket* (STAMP)

ATP, adenosine triphosphate; FDA, Food and Drug Administration; TKI, tyrosine kinase inhibitor.

Manley PW, et al. *Leuk Res*. 2020;98:106458.

Asciminib Indication

- Previously treated Ph+ CML in CP[1]
- Ph+ CML in CP with the T315I mutation[1]
- October 29, 2024: Granted accelerated approval from FDA for treatment of newly diagnosed Ph+ CML in CP[1,2]
  - Approval was based on findings from the ASC4FIRST trial (NCT04971226)[2]

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CML, chronic myeloid leukemia; CP, chronic phase; FDA, Food and Drug Administration; Ph+, Philadelphia chromosome-positive.

1. SCEMBLIX (asciminib). Prescribing information. Novartis; 2024. 2. FDA.gov. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-asciminib-newly-diagnosed-chronic-myeloid-leukemia

ASC4FIRST, A Head-to-Head Study Comparing Asciminib vs All Standard-of-Care TKIs in Newly Diagnosed CML Patients

NCT04971226

Key inclusion criteria

- Newly diagnosed Ph+ CML-CP with ***no*** prior TKIs[a]
- Age ≥18 years

Prerandomization TKI selection

- The TKI a patient will take if randomized to the investigator-selected (IS-TKI) arm
- Selected by the physician in consultation with the patient

Stratification by:

- Prerandomization TKI selection (IMA or 2G TKI)
- ELTS risk category

R 1:1

N=405

Asciminib (ASC) 80 mg QD

- **Imatinib stratum: ASC^{IMA}**
- **2G TKI stratum: ASC^{2G}**

All IS-TKIs at label doses

- **Imatinib stratum: IS-TKI^{IMA}**
- **2G TKI stratum: IS-TKI^{2G}**

Data cutoff: Nov. 28, 2023

Primary endpoints:

- MMR at week 48 for asciminib vs all investigator-selected TKIs
- MMR at week 48 for asciminib vs investigator-selected TKI within the imatinib stratum

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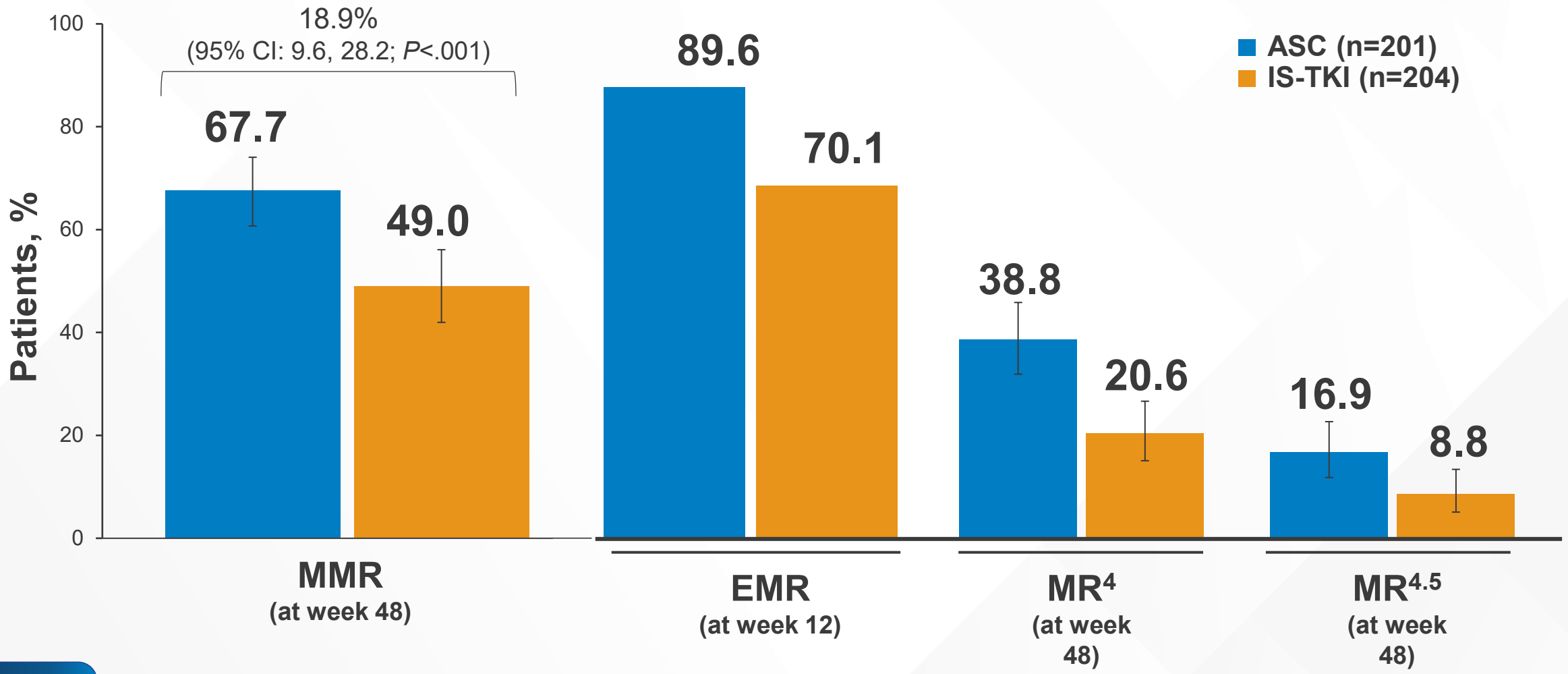
[a]Either imatinib, bosutinib, dasatinib, or nilotinib was allowed for up to 2 weeks prior to randomization. Treatment with other TKIs prior to randomization was not permitted.
[b]Patients will remain on study for 5 years after the last patient first dose, unless they have discontinued early due to treatment failure, disease progression, pregnancy, intolerance, or investigator or patient decision.
ASC, asciminib; CML, chronic myeloid leukemia; CP, chronic phase; ELTS, European Treatment and Outcome Study long-term survival score; IMA, imatinib; LPFT, last person first treatment; MMR, major molecular response; Ph, Philadelphia chromosome; QD, once a day; R, randomized; TKI, tyrosine kinase inhibitor.
Hochhaus A, et al. *N Engl J Med.* 2024;391(10):885-898.

Molecular Responses with Asciminib vs All IS-TKIs



Error bars represent 95% CIs.
ASC, asciminib; EMR, early molecular response; IS, investigator selected; MMR, major molecular response; MR4/4.5, molecular response by a 4/4.5 log reduction on the international scale; TKI, tyrosine kinase inhibitor.
Hochhaus A, et al. *N Engl J Med*. 2024;391(10):885-898.

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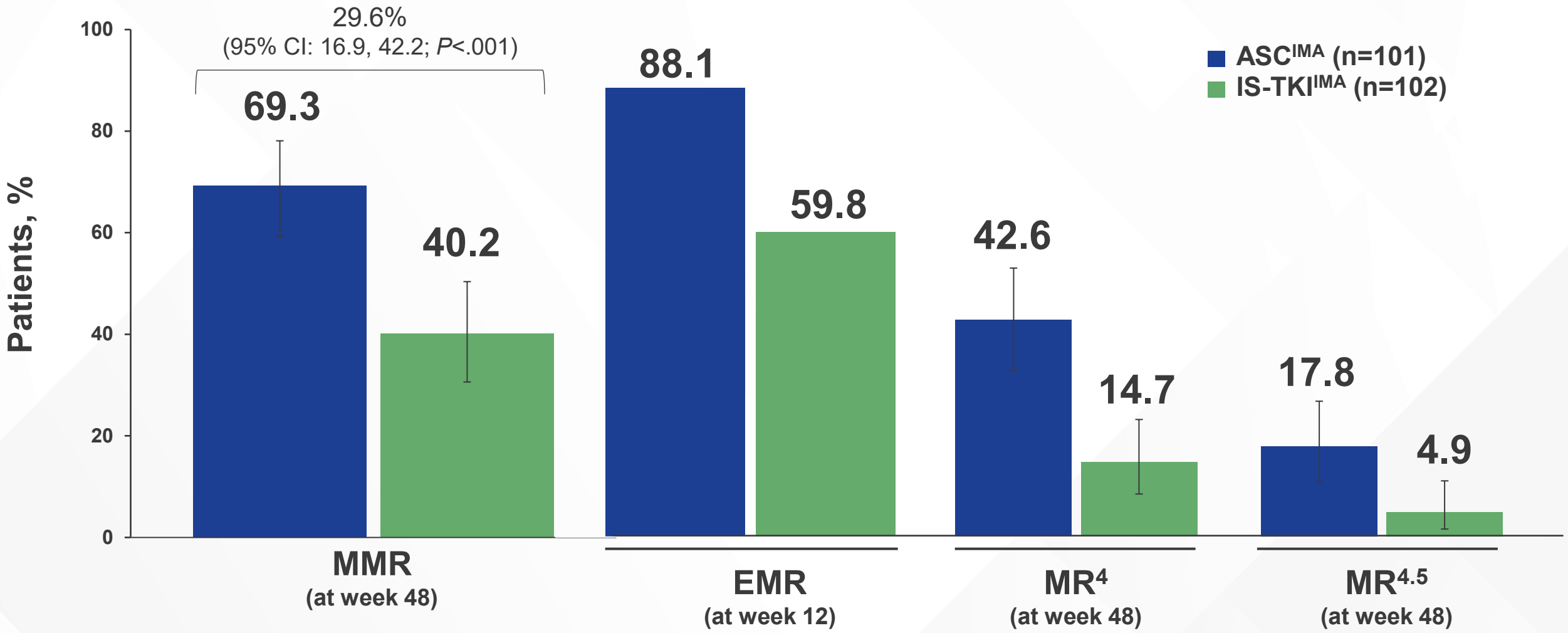
Molecular Responses ASC^{IMA} vs IS-TKI^{IMA}



Error bars represent 95% CIs.
ASC, asciminib; EMR, early molecular response; IMA, imatinib; IS, investigator selected; MMR, major molecular response; MR4/4.5, molecular response by a 4/4.5 log reduction on the international scale; TKI, tyrosine kinase inhibitor.
Hochhaus A, et al. *N Engl J Med*. 2024;391(10):885-898.

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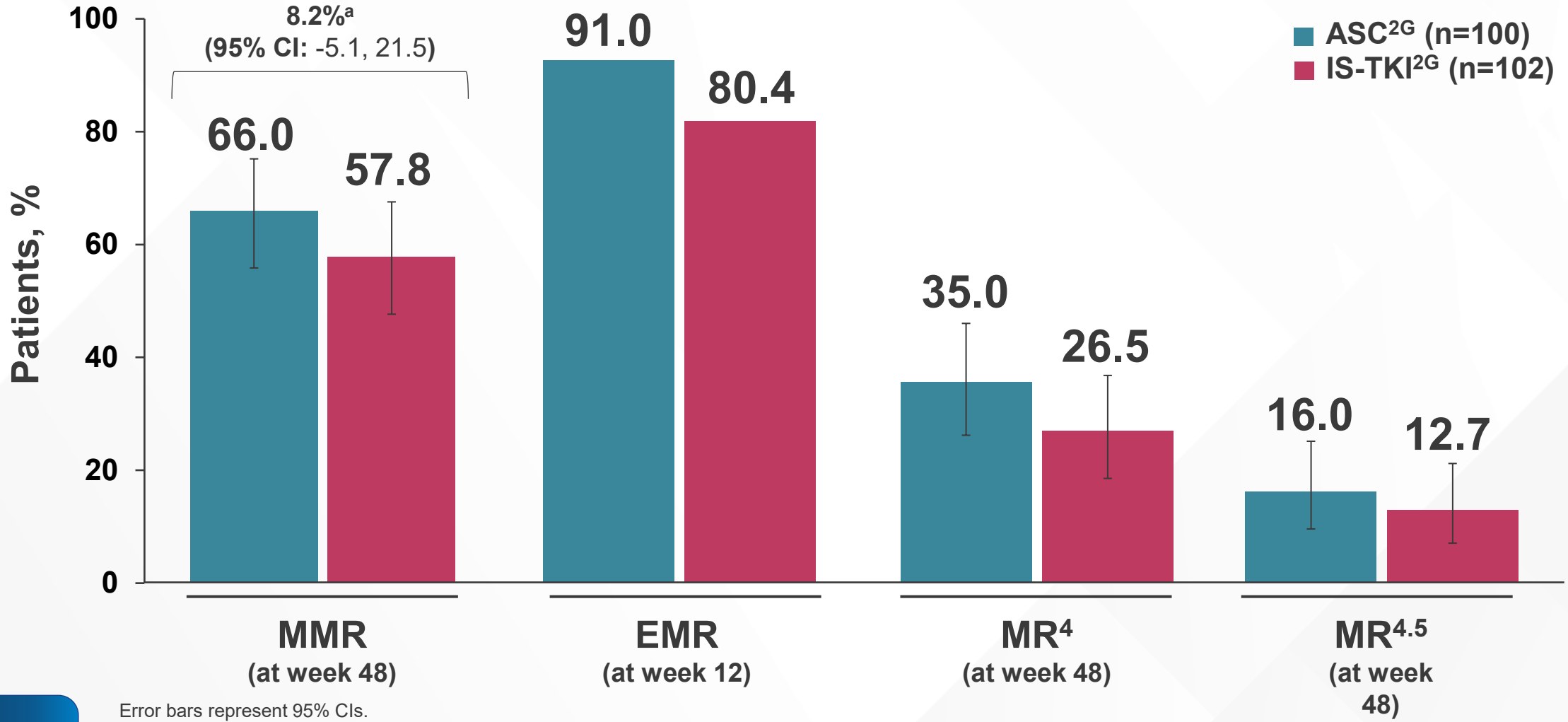
Molecular Responses Asciminib vs IS-TKI^{2G}



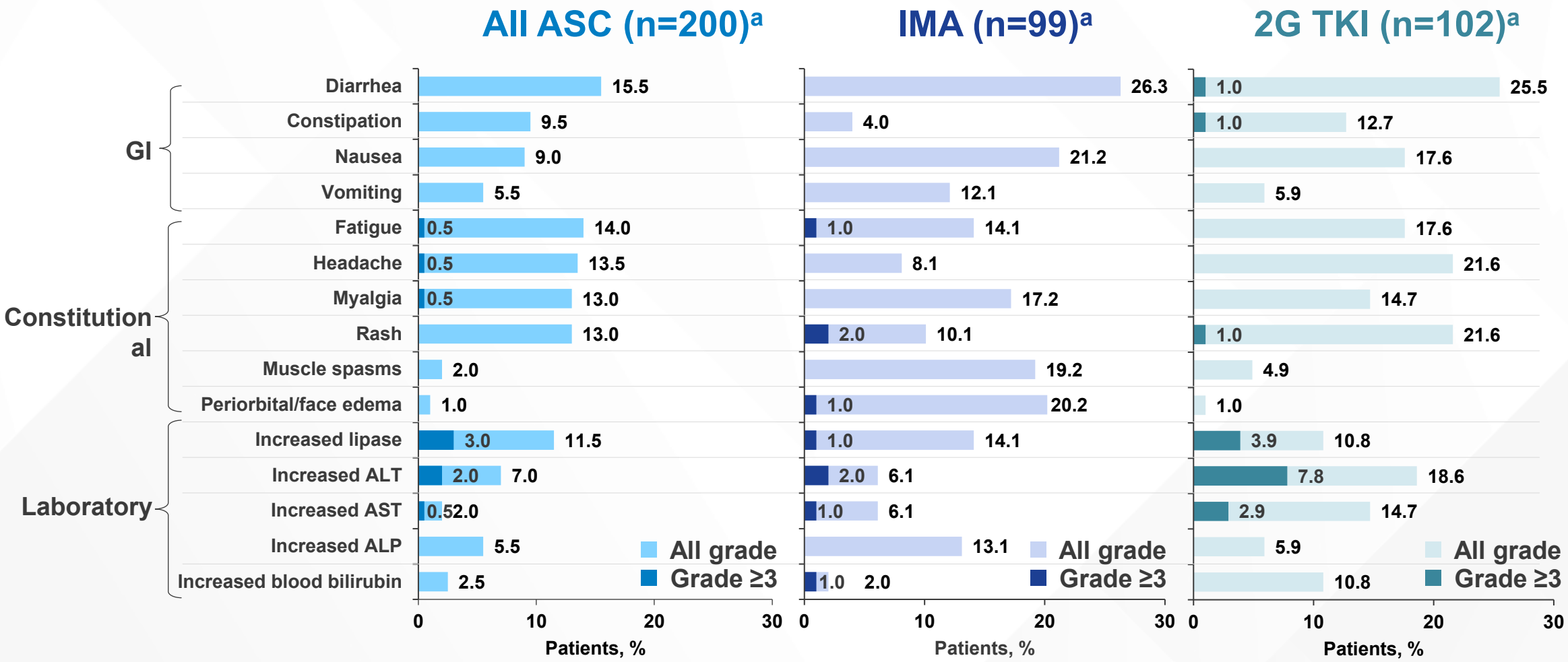
Error bars represent 95% CIs.

[a]The common treatment difference and 95% CI estimated by the Mantel-Haenszel method after stratifying for baseline ELTS (IRT data).

2G, second generation; ASC, asciminib; ELTS, EUTOS long-term survival; EMR, early molecular response; IMA, imatinib; IS, investigator selected; MMR, major molecular response; MR4/4.5, molecular response by a 4/4.5 log reduction on the international scale; TKI, tyrosine kinase inhibitor.

Hochhaus A, et al. *N Engl J Med*. 2024;391(10):885-898.

ASC4FIRST – Non-Hematologic Adverse Events



[a]Safety analyses consisted of patients who received ≥1 dose of study drug; numbers represent counts of patients. Shown are AEs that occurred during treatment or within 30 days after receiving the last dose of treatment. A patient with multiple severity grades for an AE is only counted under the maximum grade. AEs are ordered by system organ class. COVID-19 and upper respiratory tract infection are not shown.
2G, second generation; ALP, blood alkaline phosphatase; ALT; alanine aminotransferase; ASC, asciminib; AST; aspartate aminotransferase; GI, gastrointestinal; IMA, imatinib; TKI, tyrosine kinase inhibitor.
Hochhaus A, et al. *N Engl J Med.* 2024;391(10):885-898.

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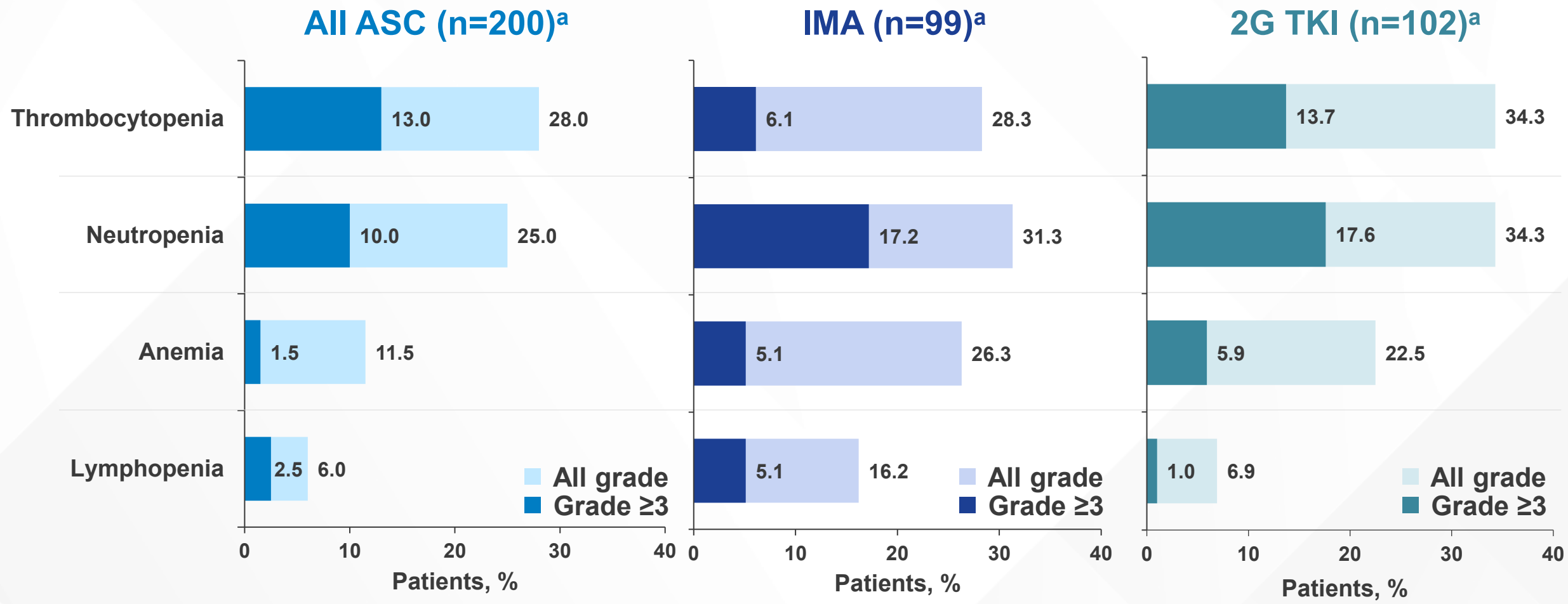
ASC4FIRST – Hematologic Adverse Events



[a]Safety analyses consisted of patients who received ≥1 dose of study drug; numbers represent counts of patients. Shown are AEs that occurred during treatment or within 30 days after receiving the last dose of study medication. A patient with multiple severity grades for an AE is only counted under the maximum grade. Leukopenia rates are not shown.
2G, second generation; ASC, asciminib; IMA, imatinib; TKI, tyrosine kinase inhibitor.
Hochhaus A, et al. *N Engl J Med.* 2024;391(10):885-898.

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ASCEND-CML Treatment Schema

Inclusion:

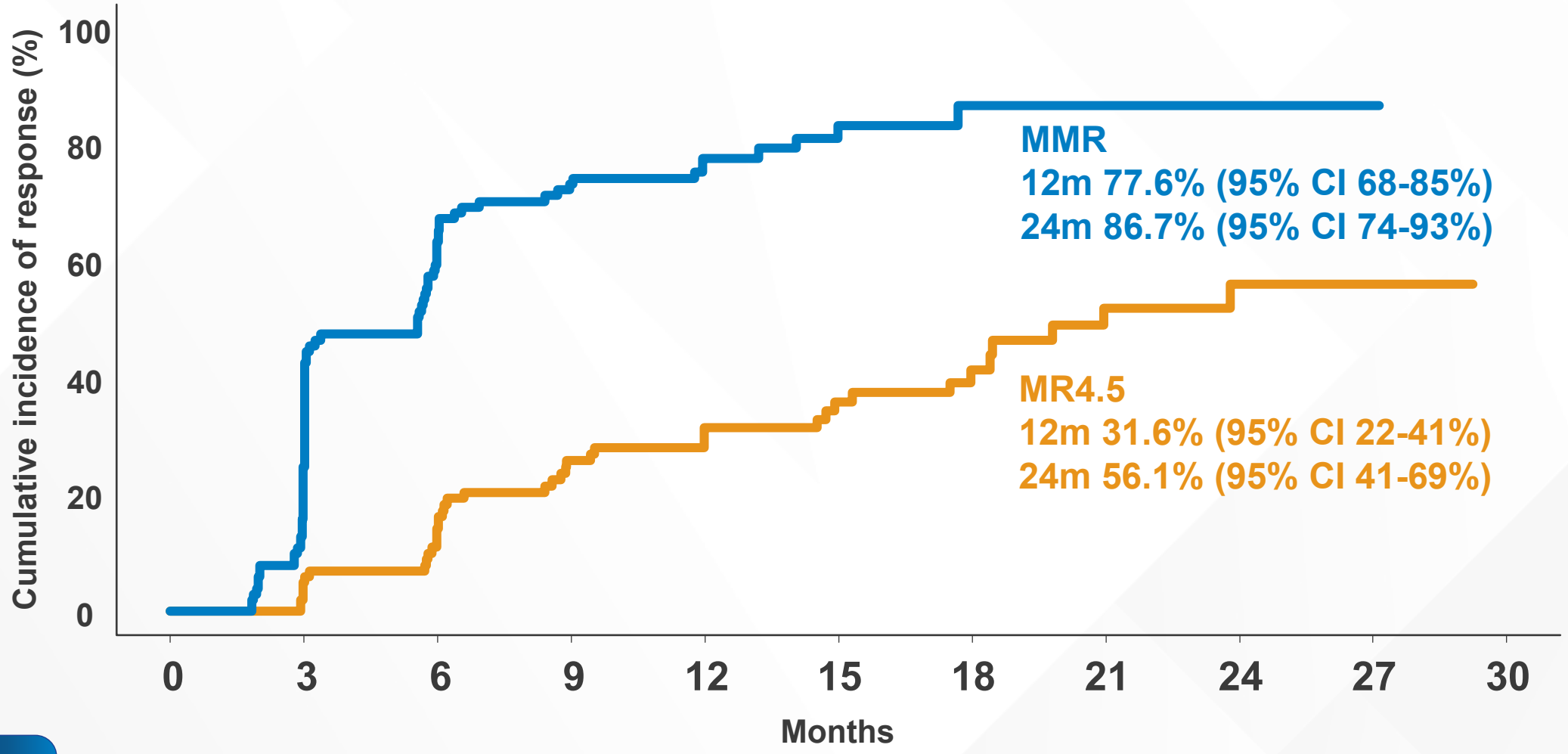
- CML-CP
- Aged 18+ yrs
- Good organ function
- ECOG 0-2
- e13/14a2 or e1a2

Asciminib 40mg BID

3 months	6 months	12 months	18 months
BCR::ABL1 > 10%	*BCR::ABL1* > 10%	*BCR::ABL1* > 1%	*BCR::ABL1* > 1%
Asciminib + addition of either nilotinib, dasatinib or imatinib (physician discretion)			
	BCR::ABL1 1.1 - 10%	*BCR::ABL1* 0.11 – 1%	*BCR::ABL1* 0.011 – 1%
Asciminib 80mg BID			
BCR::ABL1 ≤10%	*BCR::ABL1* ≤1%	*BCR::ABL1* ≤0.1%	*BCR::ABL1* ≤0.01%
Asciminib 40mg BID (80mg QD)			

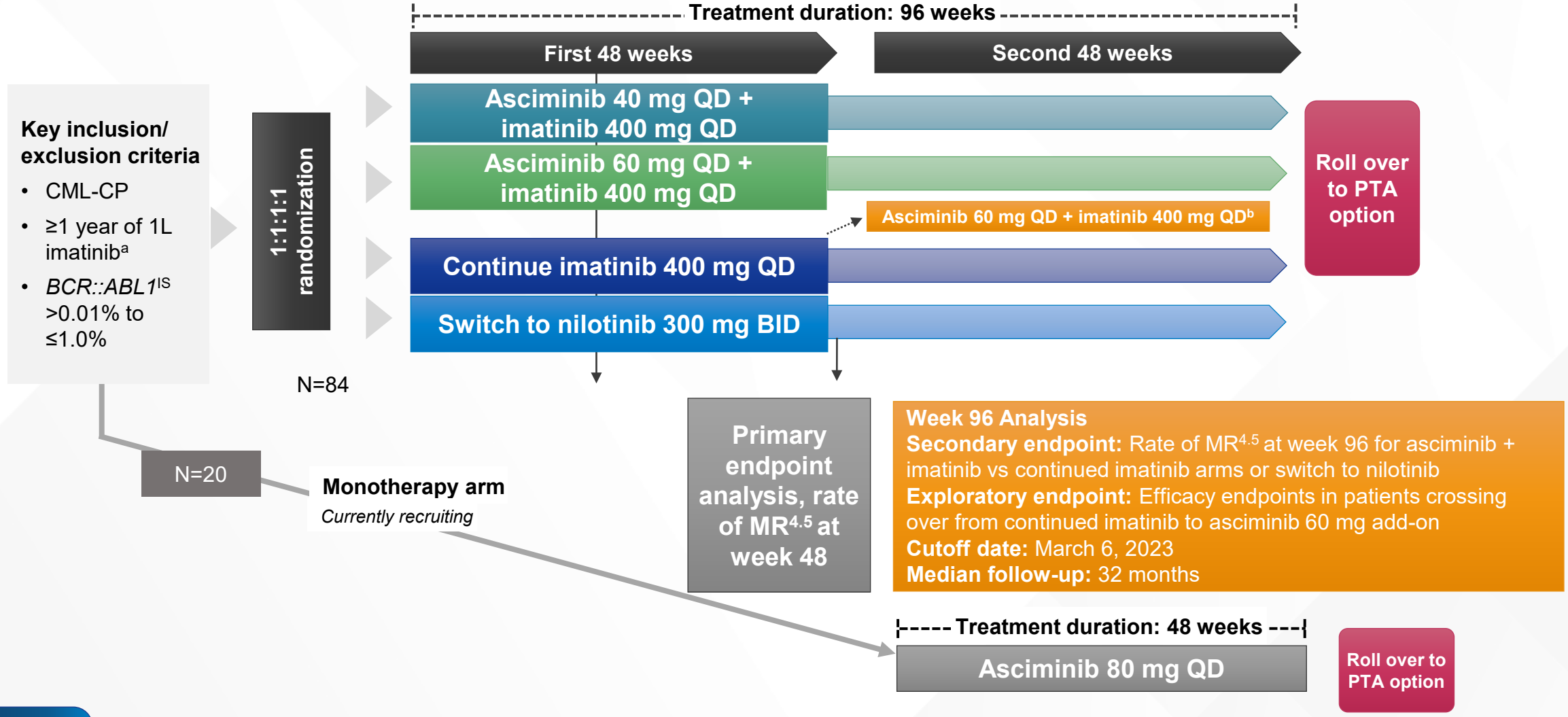
BID, twice a day; CML, chronic myeloid leukemia; CP, chronic phase; ECOG, Eastern Cooperative Oncology Group; QD, once a day.
Yeung DT, et al. ASH 2022. Abstract 79.

Cumulative Incidence of Response: ASCEND



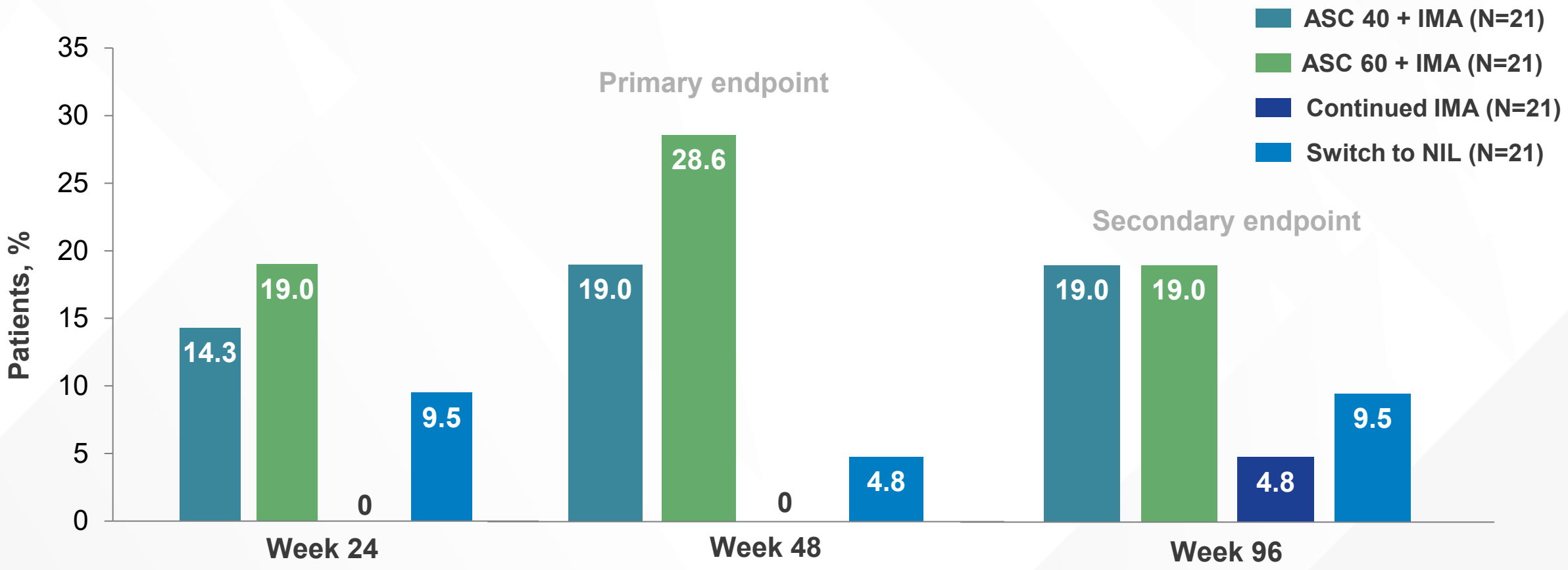
MMR, major molecular response; MR4/4.5, molecular response by a 4/4.5 log reduction on the international scale.
Yeung DT, et al. ASH 2023. Abstract 865.

ASC4MORE Study Design



[a]Protocol amendment to allow patients treated with imatinib ≥300 mg QD for ≥1 year and have not achieved DMR. [b]Crossover allowed for patients who have not achieved MR4.5.
BID, twice a day; CML, chronic myeloid leukemia; CP, chronic phase; MR4/4.5, molecular response by a 4/4.5 log reduction on the international scale; PTA, post-trial access; QD, once a day.
Cortes J, et al. ASH 2022. Abstract 80. Hughes TP, et al. ASH 2023. Abstract 866.

ASC4MORE: MR$^{4.5}$ at Weeks 24, 48, and 96

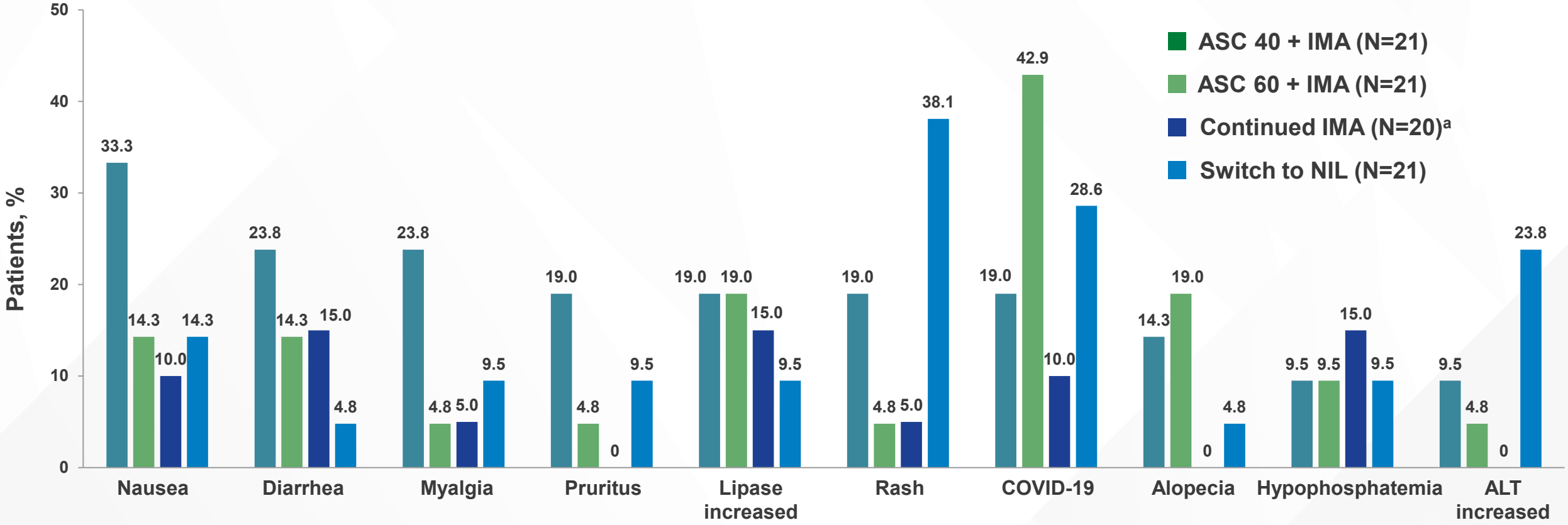


At weeks 24, 48, and 96, more patients who received **asciminib 40** and **60 mg add-on** were in MR$^{4.5}$ than those receiving **imatinib** or **nilotinib**

IMA, imatinib; MR4.5, molecular response by a 4.5 log reduction on the international scale; NIL, nilotinib.
Hughes TP, et al. ASH 2023. Abstract 866.

AXIS Medical Education

ASC4MORE: Any-Grade AEs (≥15% of Patients in Any Arm)



AEs experienced with **asciminib add-on** did not occur in a dose-dependent manner

AXIS Medical Education

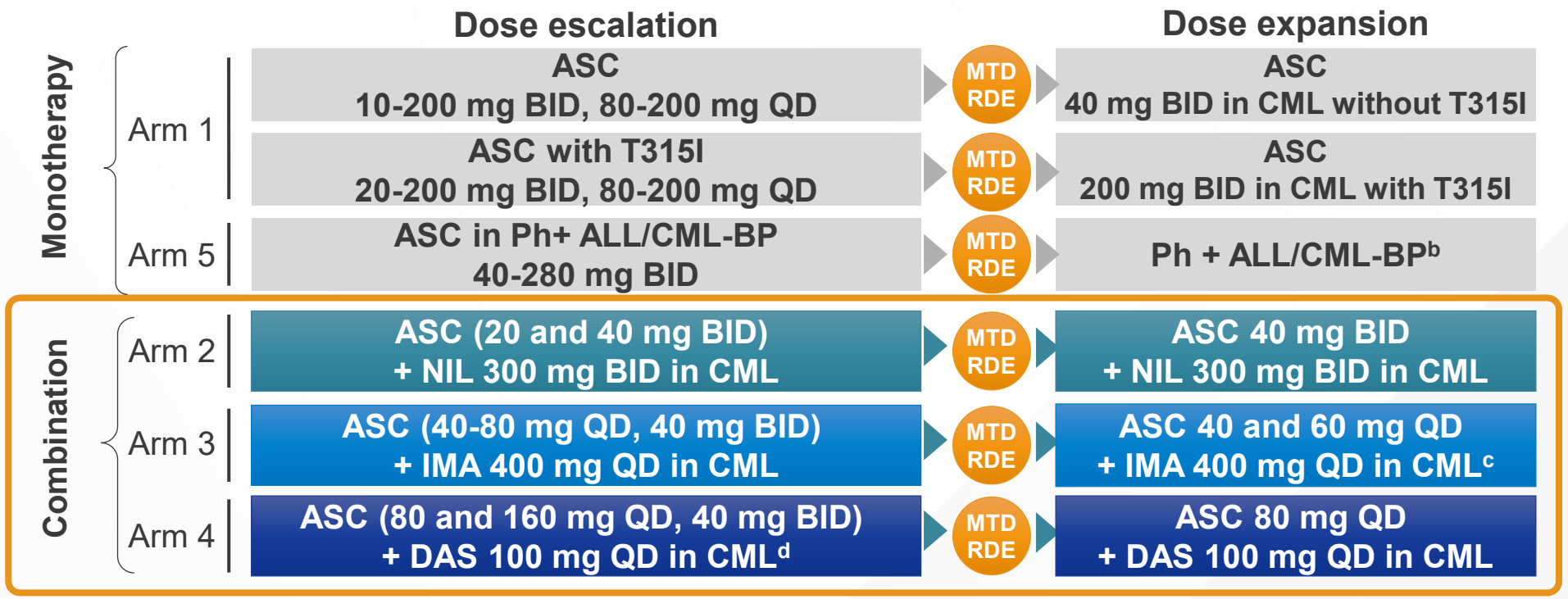
[a]One patient in the imatinib arm was not treated due to patient decision.
AE, adverse event; ALT, alanine transaminase; IMA, imatinib; NIL, nilotinib.
Hughes TP, et al. ASH 2023. Abstract 866.

Asciminib Phase 1 Study – Combinations: Study Design

Primary objective: MTD and/or recommended dose for expansion (RDE)
Secondary objectives: safety, PK, and efficacy

Key inclusion criteria

- Adults with **Ph+ CML-CP or -AP previously treated with ≥2 TKIs and with relapsed, refractory, or intolerant disease**[a]
- ECOG performance status 0-2

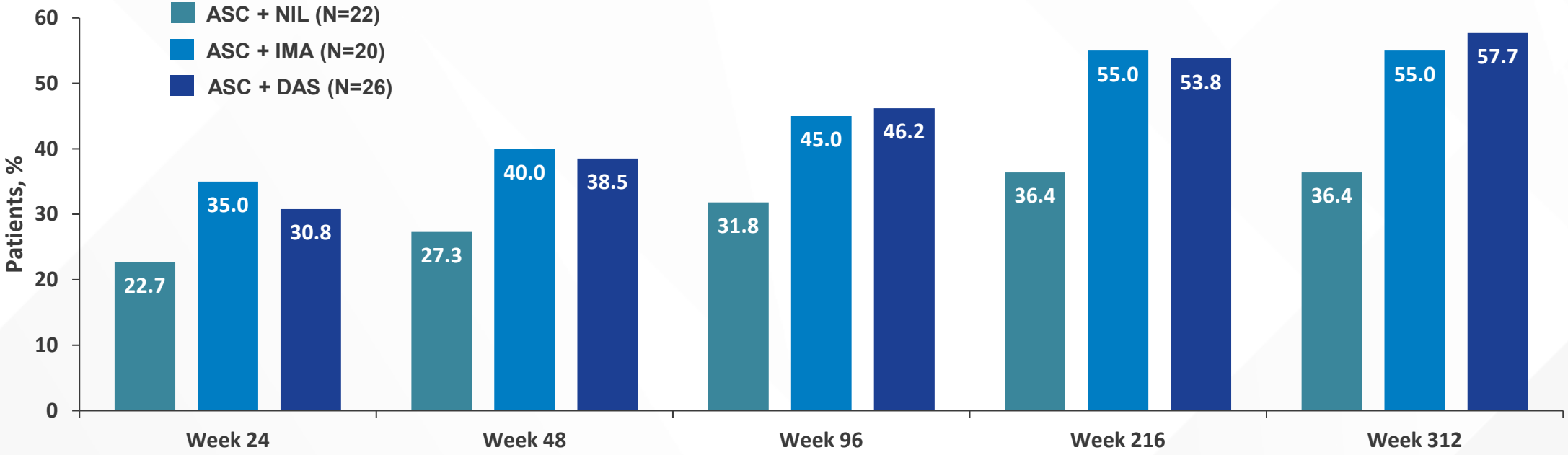


- **Duration of combination treatment: 2.1, 2.9, and 2.2 years in the ASC + NIL, ASC + IMA, and ASC + DAS arms, respectively**
- **End of study: All** patients enrolled had completed study treatment and all applicable study visits

AXIS Medical Education

aThose with a T315I mutation are eligible after ≥1 prior TKI if no other effective therapy was available. bRDE has not been determined and no dose-expansion cohort has been opened. cDose expansion of asciminib + imatinib is being assessed in a separate phase 2 study (NCT03578367). d9 additional patients in the dasatinib arm were enrolled between September 2020 and May 2021, after the primary analysis.
ALL, acute lymphoblastic leukemia; AP, accelerated phase; ASC, asciminib; BID, twice a day; BP, blast phase; CML, chronic myeloid leukemia; CP, chronic phase; ECOG, Eastern Cooperative Oncology Group; IMA, imatinib; MTD, maximum tolerated dose; NIL, nilotinib; Ph, Philadelphia chromosome; PK, pharmacokinetics; QD, once a day.
Cortes J, et al. ASH 2023. Abstract 868.

Asciminib Phase 1 Study – Combinations: MMR by Time Point in Patients Not in MMR at Screening[a]



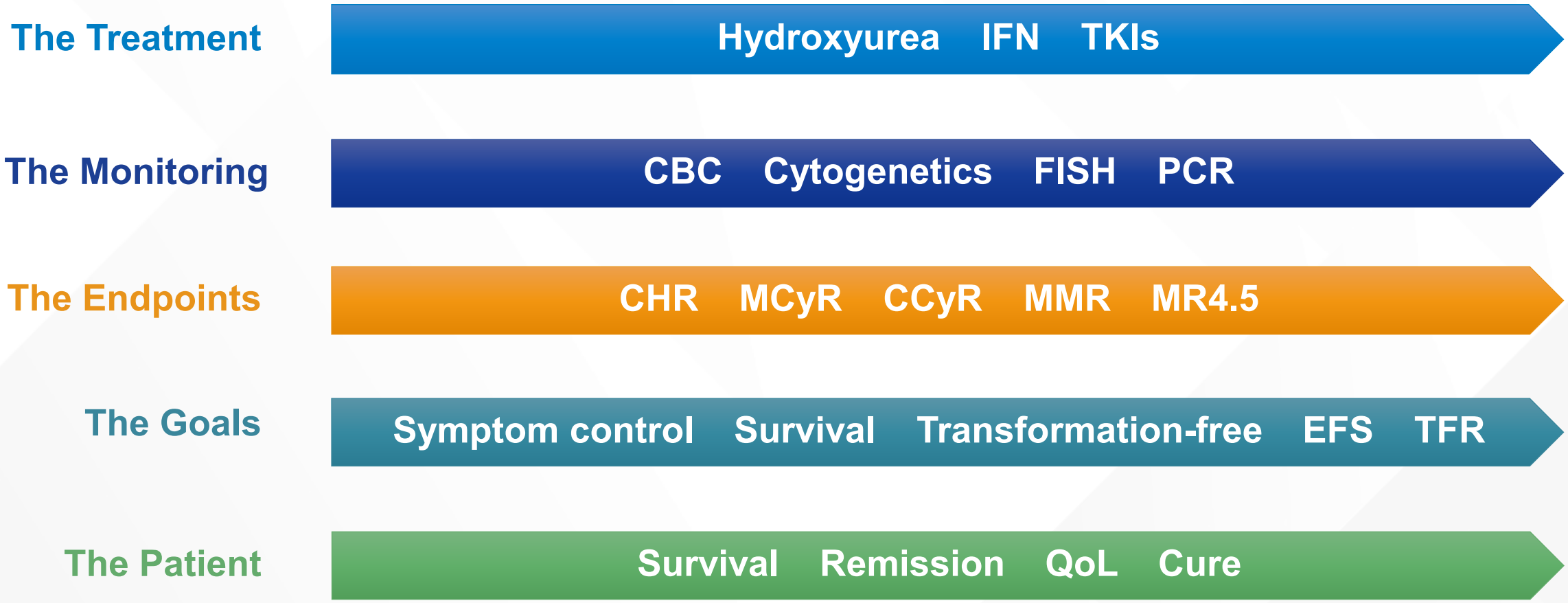
- Of **26**, 25, and **32** patients enrolled in the **ASC + NIL**, **ASC + IMA**, and **ASC + DAS** arms, respectively, **0**, **2**, and **2** patients were not evaluable for MMR due to atypical or unknown transcripts
- Responses were achieved rapidly, with MMR-evaluable patientsa achieving a median time to first MMR of **20.1**, **20.9**, and **22.1** weeks in the **ASC + NIL**, **ASC + IMA**, and **ASC + DAS** arms, respectively

AXIS Medical Education

aExcludes patients with atypical transcripts and those in MMR at baseline.
ASC, asciminib; DAS, dasatinib; IMA, imatinib; MMR, major molecular response; MTD, maximum tolerated dose; NIL, nilotinib.
Cortes J, et al. ASH 2023. Abstract 868.

What Are The Treatment Goals in CML?

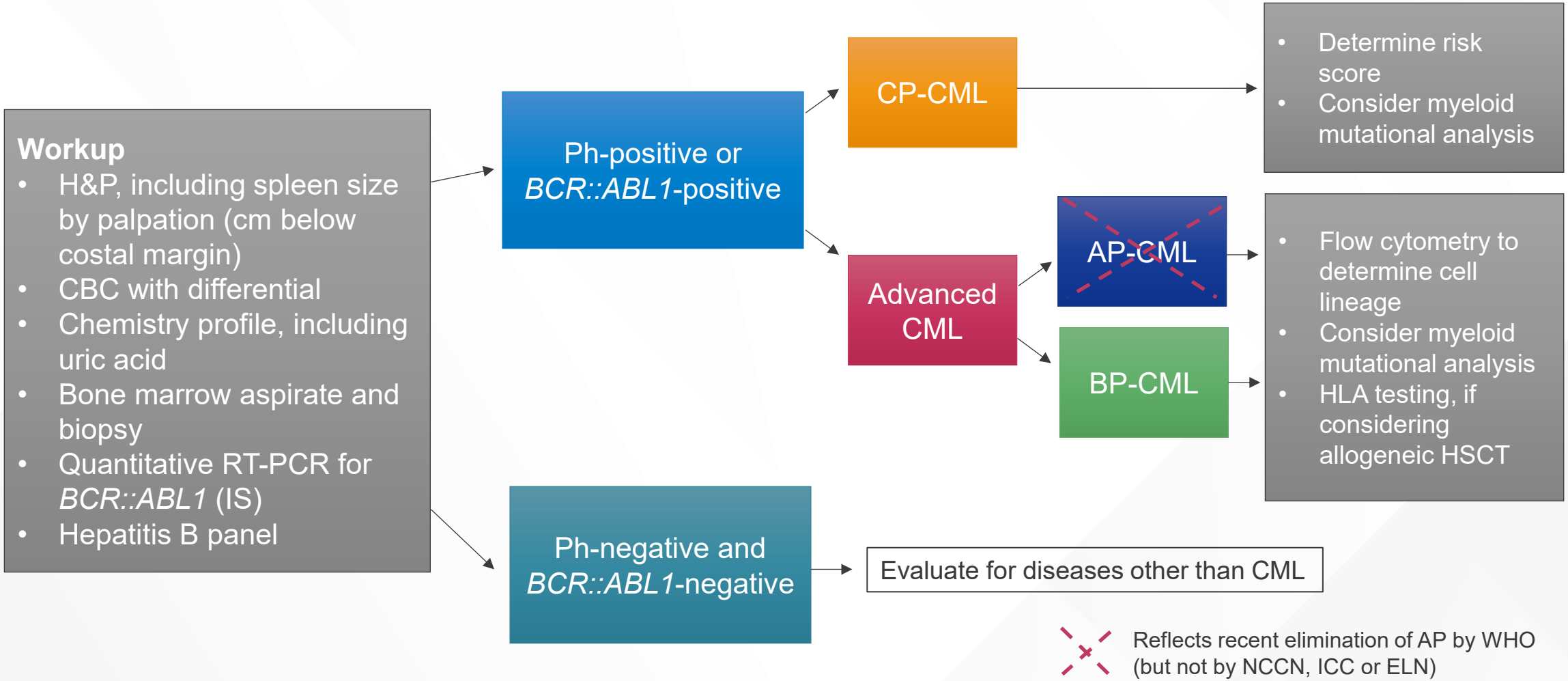
The Evolution of CML



Slide courtesy of Jorge Cortes, 2024.

CBC, complete blood count; CCyR, complete cytogenetic response; CHR, complete hematologic response; CML, chronic myeloid leukemia; EFS, event-free survival; FISH, fluorescence in situ hybridization; IFN, interferon; MCyR, major cytogenetic response; MMR, major molecular response; MR4.5, molecular response by a 4.5 log reduction on the international scale; PCR, polymerase chain reaction; QoL, quality of life; TFR, treatment-free remission; TKI, tyrosine kinase inhibitor.

NCCN Guidelines for CML Workup



AXIS Medical Education

AP, accelerated phase; BP, blast phase; CBC, complete blood count; CML, chronic myeloid leukemia; CP, chronic phase; ELN, European LeukemiaNet; H&P, history and physical examination; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplant; ICC, International Consensus Classification; IS, International Scale; NCCN, National Comprehensive Cancer Network; Ph, Philadelphia chromosome; RT-PCR, reverse transcription polymerase chain reaction; WHO, World Health Organization.

NCCN Guidelines. Chronic Myeloid Leukemia (Version 3.2025). NCCN.org.

Monitoring Recommendations for CML According to the ELN and NCCN 2020

When	ELN	NCCN
At diagnosis	• CG (BM aspiration) • FISH (in case of Ph-) • PCR	• CG (BM aspiration) • FISH (in case of Ph-) • PCR
During treatment	• PCR (IS) every 3 mo • In patients with atypical translocations, rare or atypical BCR-ABL1 transcripts that cannot be measured by qPCR, treatment failure/resistance to exclude ACA, and with progression to AP or BP • FISH may be needed in patients with atypical transcripts	• Every 3 months after start of therapy • After BCR-ABL1 ≤1% IS, continue every 3 months for 2 years • Then every 3-6 months • Repeat in 1-3 months if in MMR and 1-log increase
Failure, progression	• PCR (IS), mutation analysis, cytogenetics • Immunophenotype for BP	PCR (IS), mutation analysis, cytogenetics
Warning	Repeat PCR in 1-3 months	

AXIS Medical Education

ACA, additional chromosomal abnormalities; AP, accelerated phase; BM, bone marrow; BP, blast phase; CG, cytogenetics; CML, chronic myeloid leukemia; ELN, European LeukemiaNet; FISH, fluorescence in situ hybridization; IS, International Scale; MMR, major molecular response; NCCN, National Comprehensive Cancer Network; PCR, polymerase chain reaction; Ph, Philadelphia chromosome; qPCR, quantitative PCR.

Hochhaus A, et al. *Leukemia*. 2020;34(4):966-984.

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

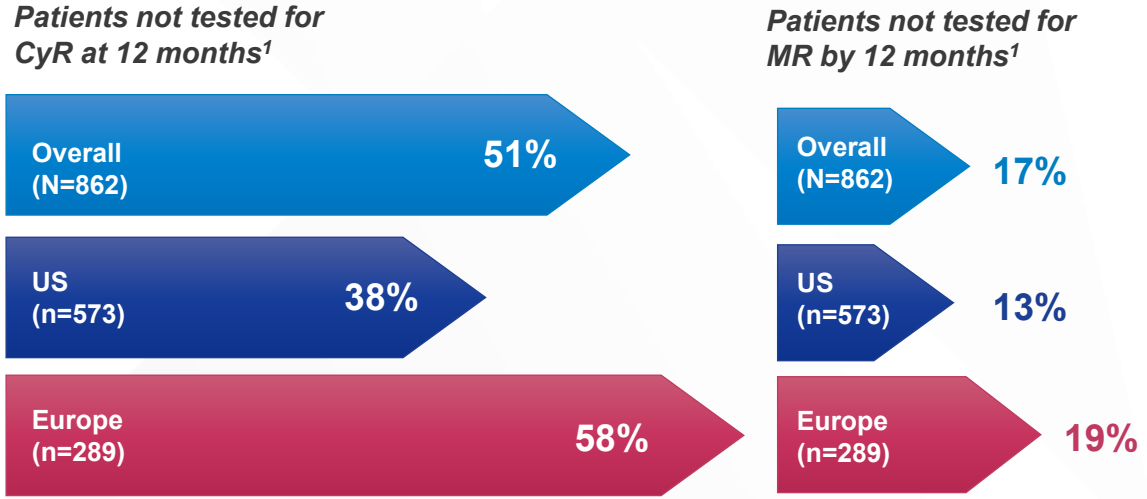
AXIS Medical Education

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

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.

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

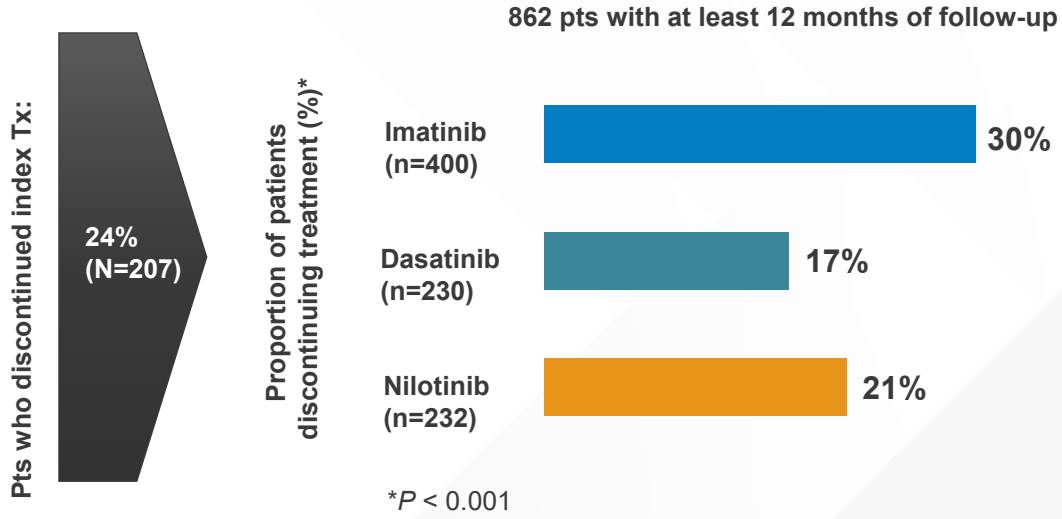
About 1 in every 5 patients are not tested for MR at 12 months and almost half are not tested for CyR



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 ($P < 0.05$)

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



*$P < 0.001$

CML, chronic myeloid leukemia; CyR, cytogenetic response; MR, molecular response; TKI, tyrosine kinase inhibitor.

Goldberg SL, et al. *J Clin Oncol.* 2014;32(suppl 15):7050. Goldberg SL, et al. *J Clin Oncol.* 2014;32(suppl 30):116.
1. Hehlmann R, et al. *Am J Hematol.* 2019;94(1):46-54.

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

MR4.0: *BCR::ABL1* (IS) ≤0.01%

MR4.5: BCR::ABL1 (IS) ≤0.0032%

DMR: MR4 + MR4.5

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.

CCyR, complete cytogenetic response; CHR, complete hematologic response; DMR, deep molecular response; EMR, early molecular response; IS, International Scale; MCyR, major cytogenetic response; MMR, major molecular response; MR, molecular response; PB, peripheral blood; Ph, Philadelphia chromosome; PCyR, partial cytogenetic response; qPCR, quantitative polymerase chain reaction.

NCCN Guidelines. Chronic Myeloid Leukemia (Version 1.2024). NCCN.org.

The Clinical Significance of Response to Therapy

Response	Translates into:
CCyR	Significantly improved **survival**
MMR	Improvement in **EFS**, possible longer duration CCyR
MR4.5	Possibility of considering **treatment discontinuation**

AXIS Medical Education

CCyR, complete cytogenetic response; MMR, major molecular response; MR4.5, molecular response by a 4.5 log reduction on the international scale.

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*	Second-line treatment
Red	TKI-resistant disease	• Consider mutational analysis • Consider bone marrow cytogenetic analysis to assess for ACA	• Switch to alternate TKI (other than imatinib), evaluate for alloHSCT
Yellow	Possible TKI resistance	• Consider mutational analysis	• Switch to alternate TKI, or • Continue same TKI (other than imatinib)
Orange	Possible TKI resistance	• Consider mutational analysis • Consider bone marrow cytogenetic analysis to assess for CCyR at 12 mo	• Consider switch to alternate TKI, or • Continue the same TKI if CCyR is achieved
Light Green	Possible TKI resistance	• If treatment goal is long-term survival: ≤1% optimal • If treatment goal is treatment-free remission: ≤0.1% optimal	• If optimal: continue same TKI • If not optimal: shared decision-making with the patient
Green	TKI-sensitive disease	• Monitor response	• Continue same TKI

AXIS Medical Education

*In all instances evaluate patient adherence and drug interactions

ACA, additional chromosomal abnormalities; allo, allogeneic; CCyR, complete cytogenetic response; HSCT, hematopoietic stem cell transplantation; IS, International Scale; NCCN, National Comprehensive Cancer Network; TKI, tyrosine kinase inhibitor.

NCCN Guidelines. Chronic Myeloid Leukemia (Version 3.2025). NCCN.org.

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

ACA, additional chromosomal abnormalities; ELN, European LeukemiaNet; ELTS, EUTOS long-term survival; MMR, mismatch repair.

Hochhaus A, et al. *Leukemia*. 2020;34(4):966-984.

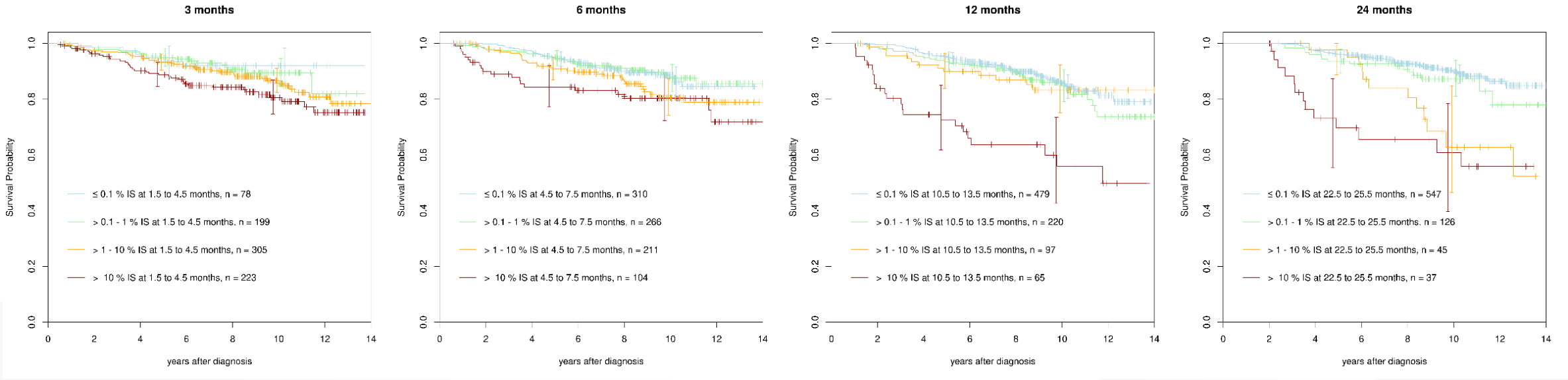
Recommendations for Management According to Response – ELN 2020

- Optimal: Continue
- Failure/resistance: Change
- Warning:
  - Carefully consider continuation or change, depending on patients' characteristics, comorbidities and tolerance
  - Additional qPCR testing may be indicated if the kinetics of the response are not clear, or if toxicity or intolerance cause dose interruptions or reductions

AXIS Medical Education

ELN, European LeukemiaNet; qPCR, quantitative polymerase chain reaction.
Hochhaus A, et al. *Leukemia*. 2020;34(4):966-984.

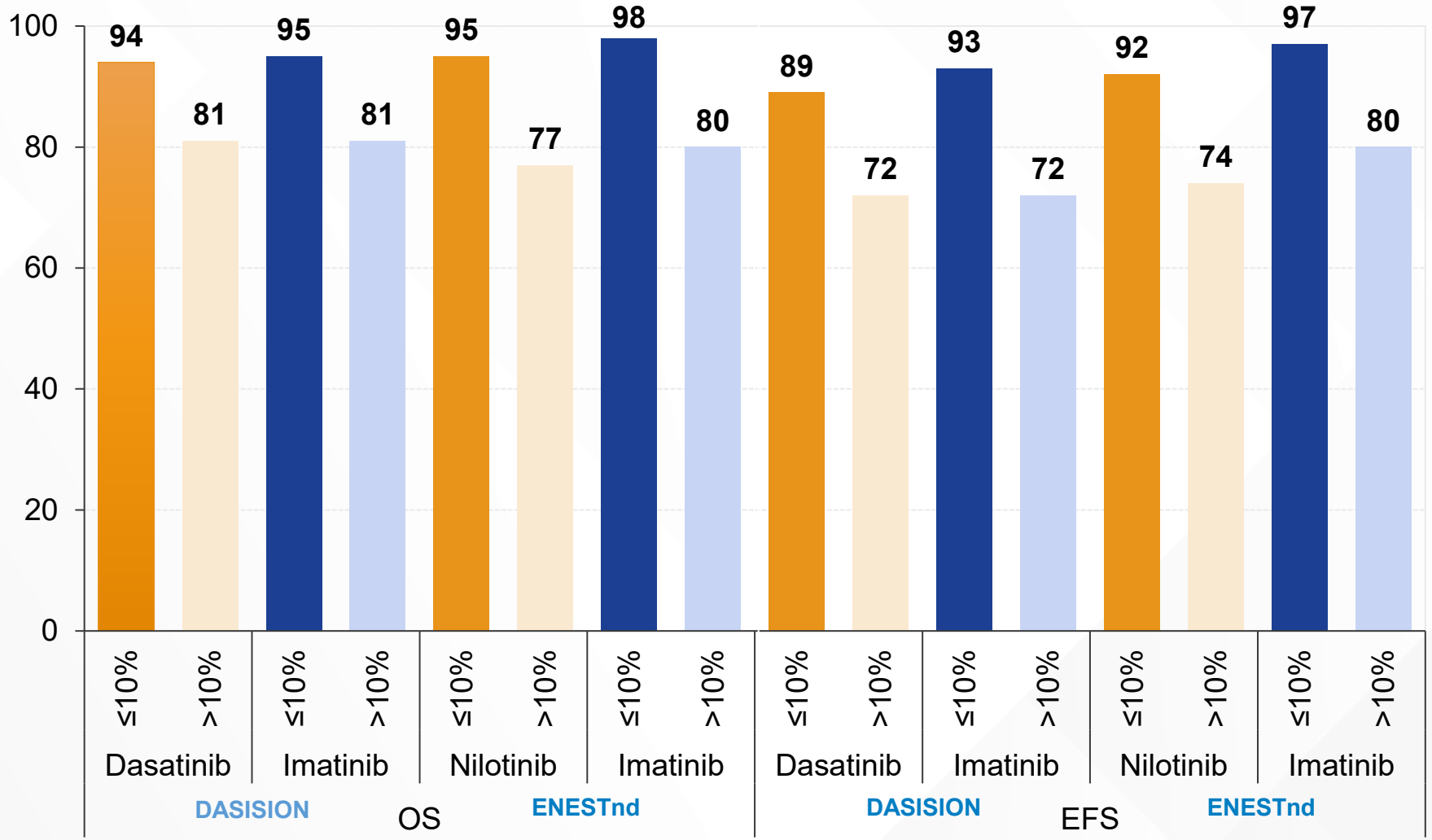
Benefit of TKI Treatment After Failing Milestones



TKI, tyrosine kinase inhibitor.

Lauseker M, et al. *Leukemia.* 2023;37(11):2231-2236.

Decreased OS & EFS For Patients Without Early Molecular Response



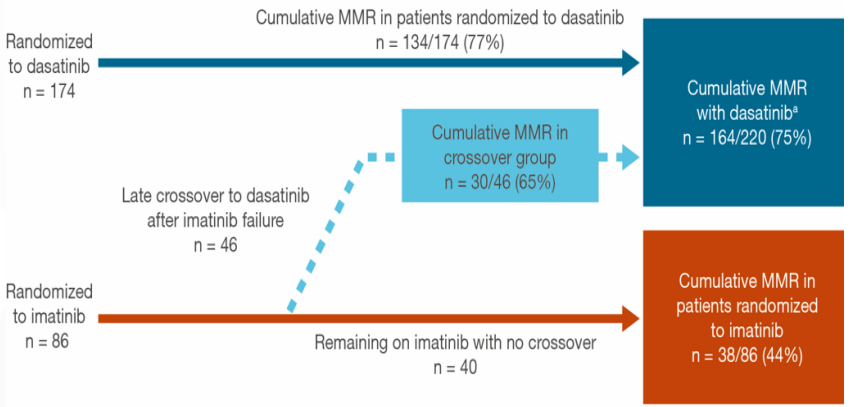
EFS, event-free survival; OS, overall survival.

Jabbour E, et al. *Blood.* 2014;123(4):494-500. Hughes TP, et al. *Blood.* 2014;123(9):1353-1360.

Changing Therapy After Failure to Achieve DMR – The DASISION Study

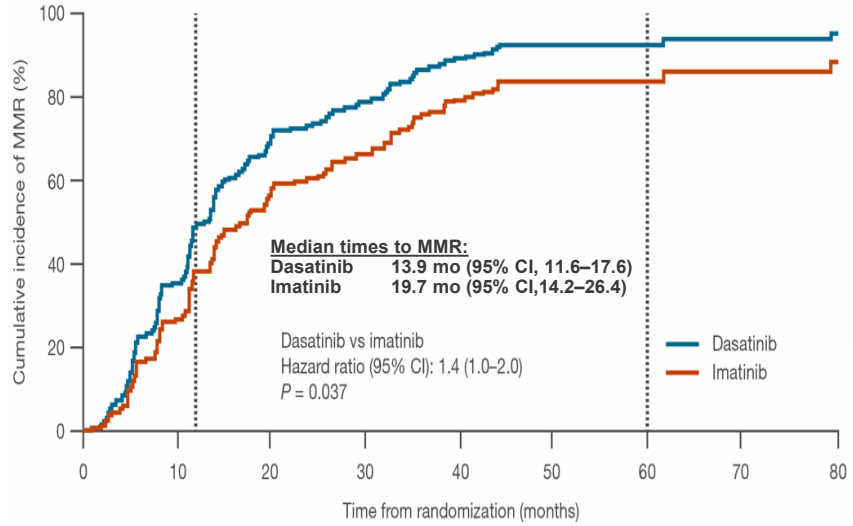
Adults with CML-CP on frontline imatinib with BCR::ABL 10% at 3 months

Cumulative incidence of MMR

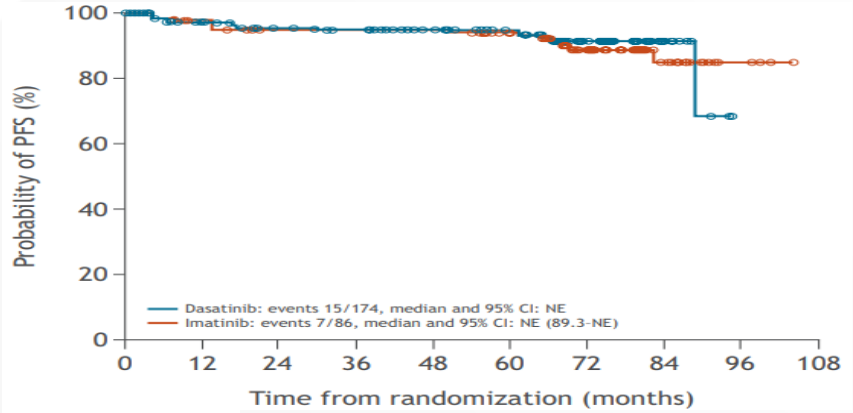


	Dasatinib	Imatinib
MR4	53	31
MR4.5	36	26

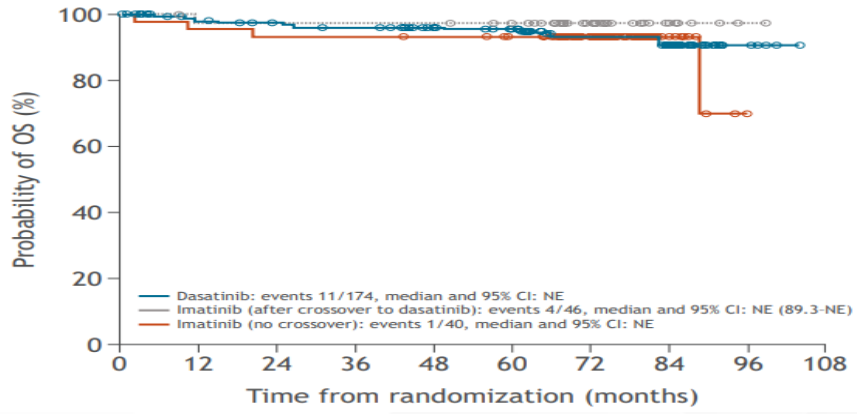
Cumulative incidence of MMR by ITT population[b]



PFS[c]



OS[c]



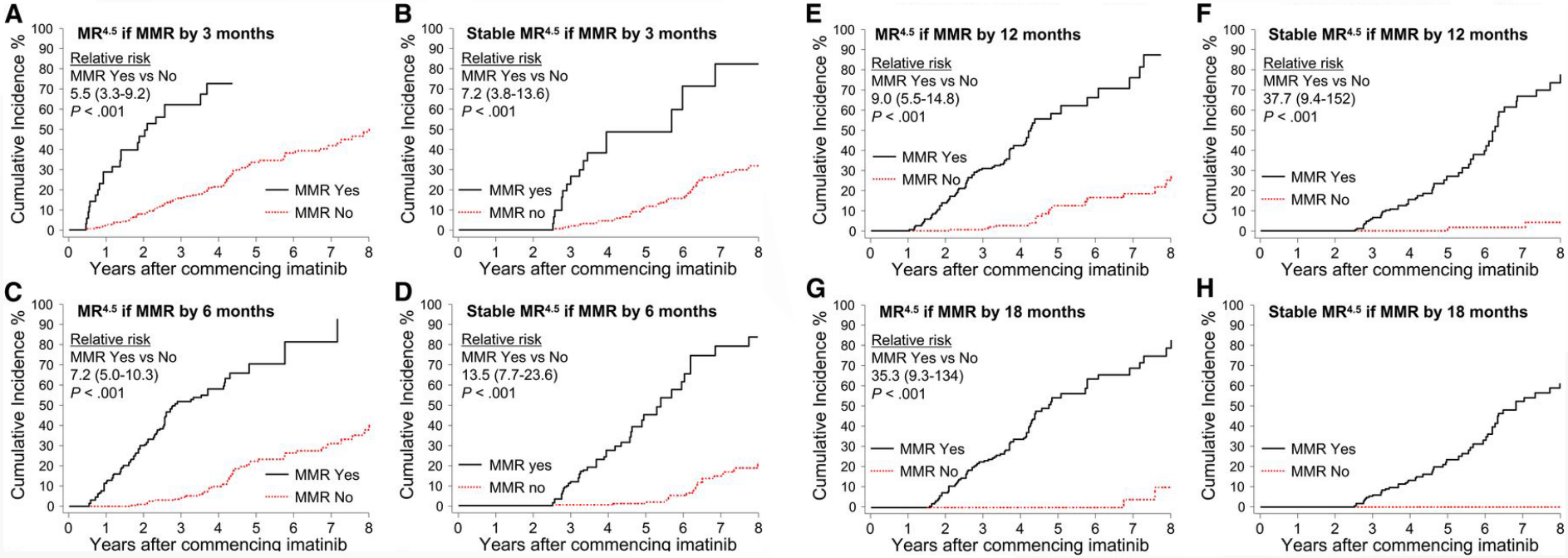
Modest improvement in MMR but no evidence of long-term benefit

[a]Four patients achieved then lost MMR and subsequently crossed over to dasatinib. [b]The Kaplan–Meier curve accounts for competing risk and censored patients. [c]Intention-to-treat analysis.
CML, chronic myeloid leukemia; CP, chronic phase; ITT, intent to treat; MMR, major molecular response; OS, overall survival; PFS, progression-free survival.
Cortes JE, et al. *Haematologica.* 2024;109(10):3251-3260.

AXIS Medical Education

Early Molecular Response Predicts Long-Term DMR

- 423 patients treated with imatinib frontline
- Long-term outcome analyzed according to early hallmarks



DMR, deep molecular response; MMR, major molecular response; MR4.5, molecular response by a 4.5 log reduction on the international scale.
Branford S, et al. *Blood.* 2013;121(19):3818-3824.

Requirements for TKI Discontinuation – ELN & NCCN 2020

ELN	NCCN
CML 1st **CP only** (Mand)	CP CML. **No history of AP or BP.**
TKI therapy >5 y (>4 y for 2GTKI) (Min)	On approved TKI ≥3 y
e13a2- or e14a2-BCR–ABL1 transcripts (Min)	Prior evidence of quantifiable BCR-ABL1 transcript.
Duration DMR **(MR^4 or better) >2 years** (Min)	**MR^4 for ≥2 years** (≥4 tests, performed ≥3 mo apart)
Access to high quality quantitative PCR using IS with **rapid turn-around for results** (Mand)	Access to a reliable qPCR test with sensitivity of at least MR4.5 IS and that provides **results within 2 wks.**
Patient's agreement to more frequent monitoring after stopping. **Monthly for the 1st 6 mo,** every 2 mo for mo 6-12, and every 3 mo thereafter. (Mand)	**Monthly molecular monitoring** for 6 m, then every 2 mo for the 6 m, and every 3 mo thereafter (indefinitely) is recommended.
Motivated patient with structured communication (Mand)	Age ≥18 years
1st-line therapy or 2nd-line if intolerance was the only reason for changing TKI (Min)	Prompt resumption of TKI within 4 wks of loss of MMR with monthly monitoring until MMR. If no MMR after 3 mo of resumption, order mutation testing and continue monthly molecular monitoring for another 6 mo.
No prior treatment failure (Min)	

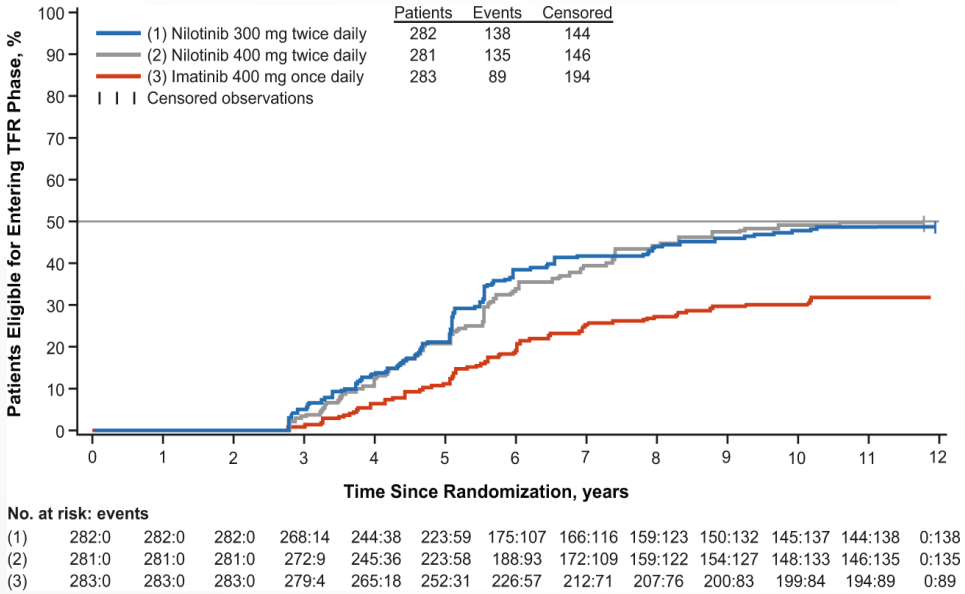
AXIS Medical Education

2G, second generation; AP, accelerated phase; BP, blast phase; CML, chronic myeloid leukemia; CP, chronic phase; DMR, deep molecular response; ELN, European LeukemiaNet; IS, International Scale; Mand; mandatory; Min, minimal; MMR, major molecular response; MR4/4.5, molecular response by a 4/4.5 log reduction on the international scale; NCCN, National Comprehensive Cancer Network; PCR, polymerase chain reaction; qPCR, quantitative PCR; TKI, tyrosine kinase inhibitor.

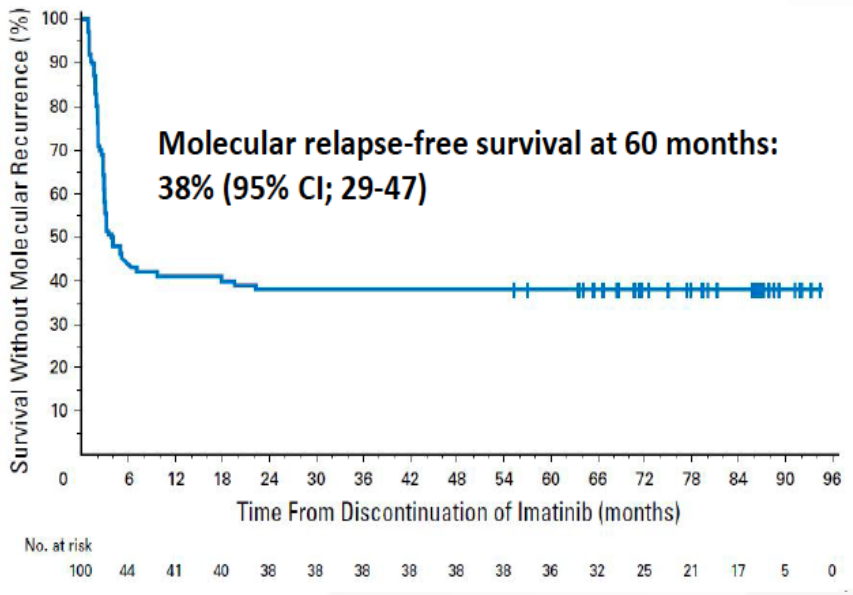
Hochhaus A, et al. *Leukemia.* 2020;34(4):966-984. NCCN Guidelines. Chronic Myeloid Leukemia (V3.2025). NCCN.org.

Challenges to Achieving Treatment-Free Remission

Eligibility
ENESTnd[1]



Recurrence
STIM[2]

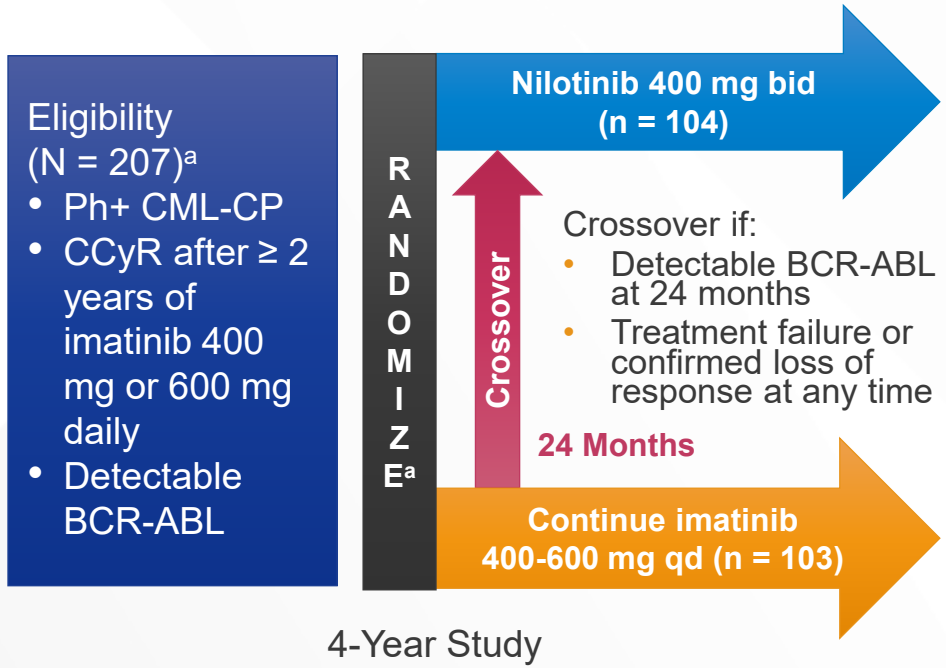


- Only a subset of patients is eligible for treatment discontinuation and many relapse
- TFR success with current strategies ~25-30%

AXIS Medical Education

TFR, treatment-free remission.
Kantarjian HM, et al. *Leukemia*. 2021;35(2):440-453. Etienne G, et al. *J Clin Oncol*. 2017;35(3):298-305.

Switching Therapy to Achieve DMR – The ENESTcmr Approach



- MR4.5 @48 mo:
  - Nilotinib: 54%; Imatinib: 32% (excluding crossover)
- AOEs:
  - Nilotinib: 13% (2 deaths, 1 from MI, 1 cardiopulmonary failure); Imatinib: 2%
- Conclusion: Improved rate of DMR but with high risk for AOEs

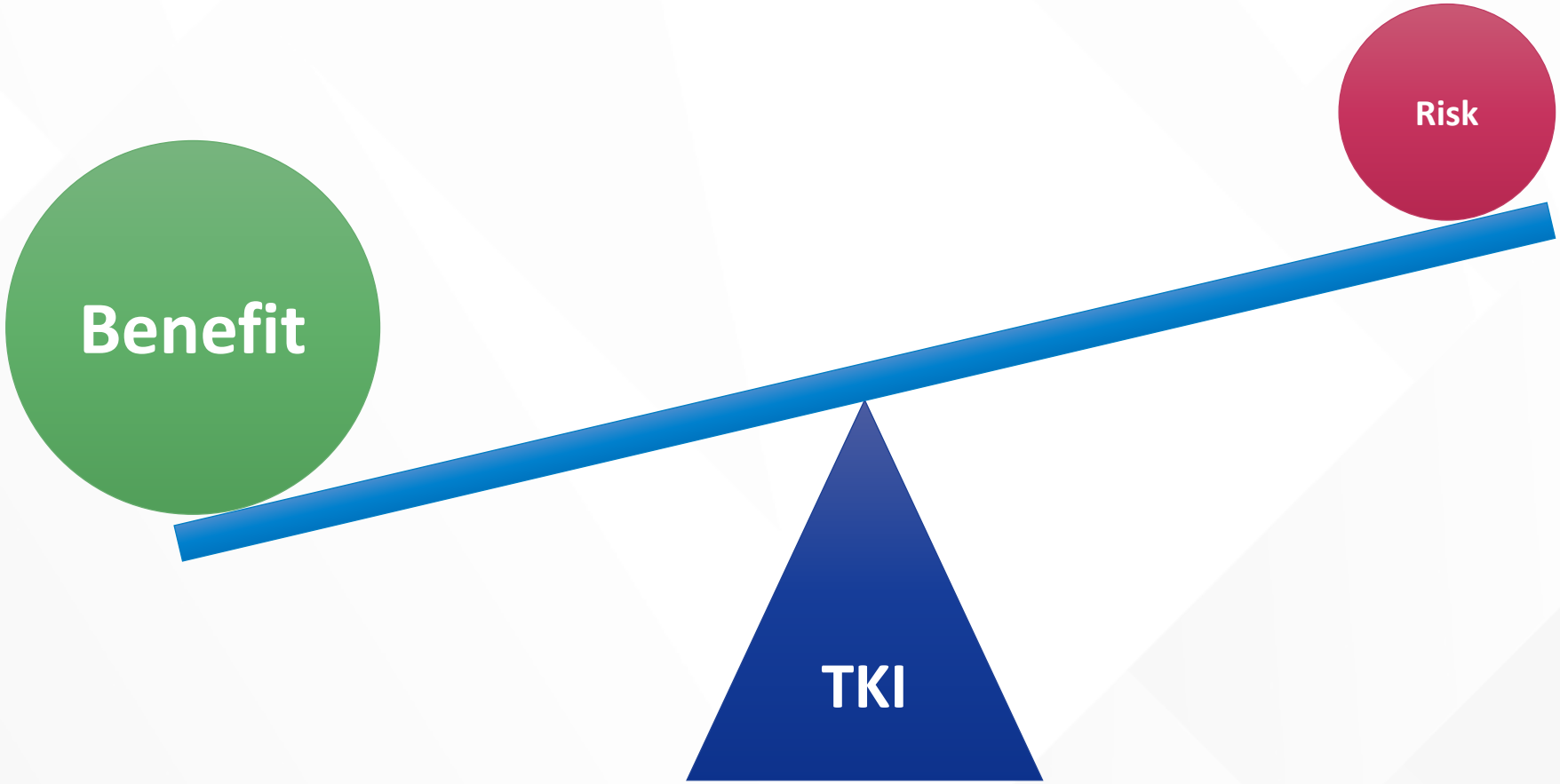
AXIS Medical Education

AOE, artery occlusive event; bid, twice a day; CCyR, complete cytogenetic response; CML, chronic myeloid leukemia; CP, chronic phase; DMR, deep molecular response; MI, myocardial infarction; MR4.5, molecular response by a 4.5 log reduction on the international scale; Ph, Philadelphia chromosome; qd, once a day.

Hughes TP, et al. *Leukemia.* 2017;31(11):2529-2531.

Practice Strategies for Adverse Events (AEs) Related to TKIs

Balancing Risk and Benefit



Slide courtesy of Jorge Cortes, 2024.
TKI, tyrosine kinase inhibitor.

Factors Affecting Adherence to TKIs – A Patient's Perspective

Characteristics associated with probability of high adherence (vs low adherence)

- 2546 questionnaires completed by CML patients from 63 countries
- Median age 51 years (range, 18–96); 52% male
- 61% imatinib, 22% nilotinib, 13% dasatinib, 4% other

Response: "high adherence"	Reference category or increment	OR	95% CI	p
Age	Per year	1.022	1.018–1.032	<0.0001
Sex	Female	1.302	1.093–1.558	0.0032
Living with someone	No	–	–	–
Chronic phase	No	–	–	–
Years since diagnosis	<2	0.592	0.475–0.739	<0.0001
Management of side effects	**Not well managed (vs none or well managed)**	**1.679**	**1.366–2.064**	**<0.0001**
Doses	>one	1.800	1.468–2.206	<0.0001
Other medications	No	–	–	–
Time on current medication	<6 months (vs 6 months to 3 years)	–	–	–
	<6 months (vs more than 3 years)	–	–	–
Personal payment obligations	<50 EUR	–	–	–
Use of reminding tools	No	0.740	0.604–0.907	0.036
Informed about risks	No	–	–	–
Satisfied with information on CML	4 stages from 'not at all' to 'very'	1.388	1.186–1.625	<0.0001

AXIS Medical Education

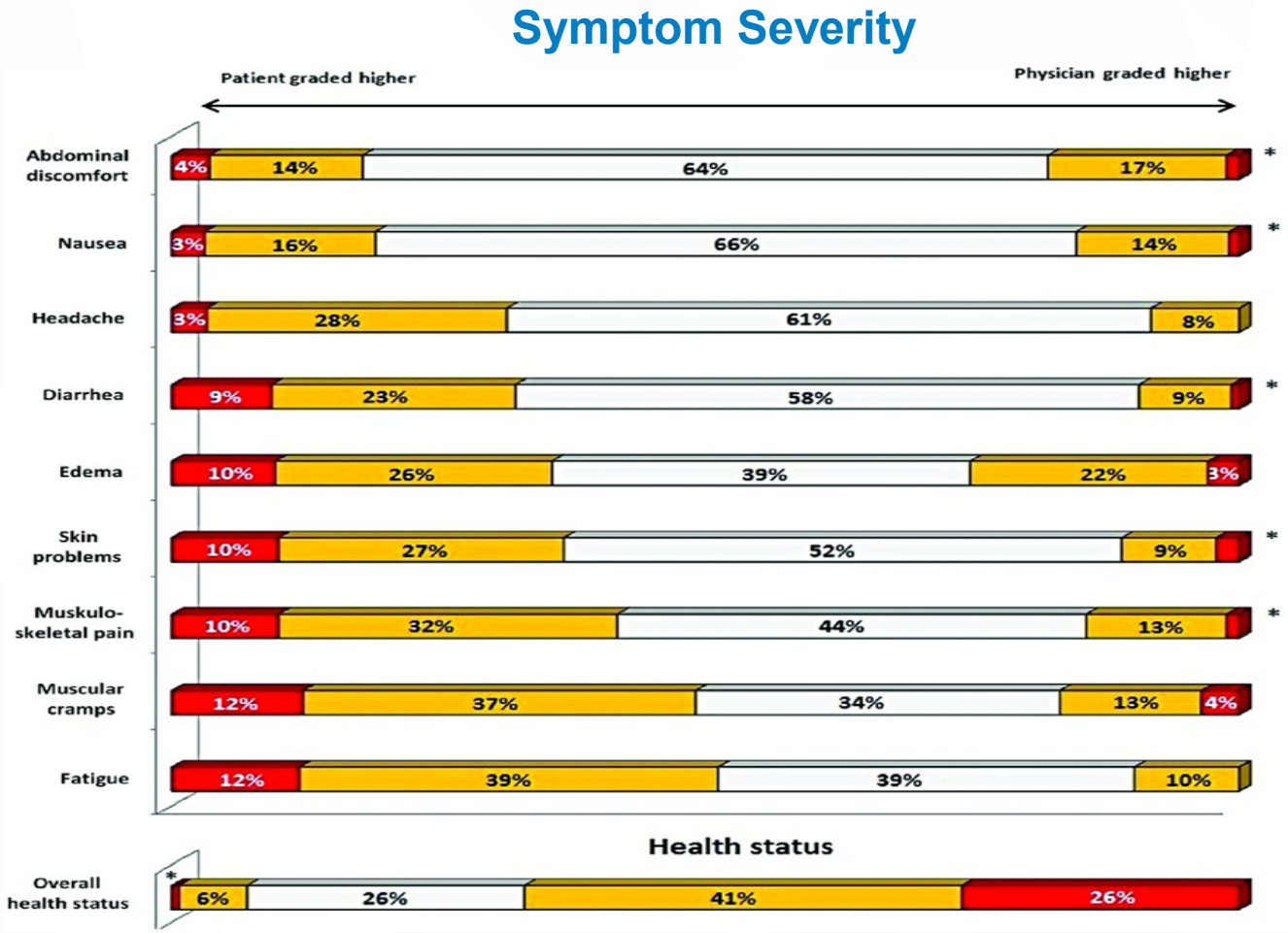
CML, chronic myeloid leukemia; EUR, Euros; TKI, tyrosine kinase inhibitor.
Geissler J, et al. *J Cancer Res Clin Oncol.* 2017;143(7):1167-1176.

Patient vs Physician Reporting of Symptoms in CML

- Symptoms scored as “not at all”, “a little”, “quite a bit” & “very much”.

Minor disagreement (difference = 1)

Major disagreement (difference ≥2)



CML, chronic myeloid leukemia.

Efficace F, et al. *Haematologica.* 2014;99(4):788-793.

Warnings and Precautions for TKIs – US Prescribing Information

Imatinib	Dasatinib	Nilotinib	Bosutinib	Ponatinib	Asciminib
No black-box warnings	No black-box warnings	Black-box warning: QT prolongation, sudden death. Avoid food 2-h prior and 1-h after	No black-box warnings	Black-box warning for arterio-occlusive events, heart failure, venous thromboembolism, hepatoxicity	No black-box warnings
• Fetal harm • Edema, severe fluid retention • Myelosuppression* • Severe congestive heart failure, LV dysfunction • Severe hepatotoxicity • Grade ¾ hemorrhage and GI perforations • Cardiogenic shock/LV dysfunction (conditions with eosinophilia) • Bullous dermatologic reactions • Hypothyroidism • Growth retardation • TLS • Renal toxicity • Motor-vehicle accidents	• Embryo-fetal toxicity • Myelosuppression* • Bleeding events • Fluid retention: pleural effusions • Cardiovascular toxicity • Pulmonary arterial hypertension • QT prolongation • Severe dermatologic reactions • TLS • Effects on growth and development (pediatric)	• Embryo-fetal toxicity • Myelosuppression* • Cardiac and arterial vascular occlusive events • Pancreatitis, elevated lipase • Hepatotoxicity • Electrolyte abnormalities • TLS • Hemorrhage • Fluid retention: pleural effusion, pericardial effusion, ascites, or pulmonary edema • Effects on growth and development (pediatric) • Treatment discontinuation	• Embryo-fetal toxicity • GI • Myelosuppression* • Hepatic • Cardiovascular: cardiac failure, left ventricular dysfunction, and cardiac ischemic events • Fluid retention: pericardial effusion, pleural effusion, pulmonary edema, and/or peripheral edema • Renal: decline in GFR	• Embryo-fetal toxicity • Hypertension • Pancreatitis • Neuropathy: peripheral, cranial • Hemorrhage: cerebral, GI • Ocular toxicity • Fluid retention: peripheral edema, pleural effusion, pericardial effusion, & peripheral swelling • Cardiac arrhythmias • Myelosuppression* • TLS • Reversible posterior leukoencephalopathy syndrome • Compromised wound healing, GI perforation	• Embryo-fetal toxicity • Pancreatic toxicity • Myelosupression • Hypertension • Cardiovascular toxicity: ischemic cardiac and CNS conditions, arterial thrombotic and embolic conditions, cardiac failure • Hypersensitivity

*Myelosuppression: anemia, thrombocytopenia, neutropenia.

CNS, central nervous system; GFR, glomerular filtration rate; GI, gastrointestinal; LV, left ventricular; TKI, tyrosine kinase inhibitor; TLS, tumor lysis syndrome.

GLEEVEC (imatinib mesylate). Prescribing information. Novartis; 2024. SPRYCEL (dasatinib). Prescribing information. Bristol Myers Squibb; 2024. TASIGNA (nilotinib). Prescribing information. Novartis; 2024. BOSULIF (bosutinib). Prescribing information. Pfizer; 2024. ICLUSIG (ponatinib). Prescribing information. Takeda; 2024. SCEMBLIX (asciminib). Prescribing information. Novartis; 2024.

TKI Selection Based on Co-Morbidities and Risk of Adverse Events

History with prior TKI or co-morbidity	Preferred	Less preferred
Diabetes	Dasatinib, Bosutinib	Nilotinib
Pulmonary disease/PAH	Bosutinib, Nilotinib	Dasatinib
GI Issues	Nilotinib, Dasatinib	Bosutinib
Cardio-vascular	Bosutinib	Nilotinib, Dasatinib
Peripheral arterial	Bosutinib (Dasatinib?)	Nilotinib
Liver	Dasatinib (Nilotinib?)	Bosutinib
Renal	Nilotinib, Dasatinib	Bosutinib

Suggestions should be considered in the whole clinical context of the patient and considering all available options

GI, gastrointestinal; PAH, pulmonary arterial hypertension; TKI, tyrosine kinase inhibitor.
Cortes J. *Blood*. 2020;136(22):2507-2512.

Management of TKI-Associated Myelosuppression

- Monitor CBC weekly 2-3 mo, then every 6-8 wk
- Hold therapy if:
  - ANC <1x109/L
  - Platelets <50x109/L
- Holding for anemia as clinically indicated
- Monitor CBC at least weekly after holding
- Restart when ANC ≥1x109/L, platelets ≥50x109/L
  - If recover in <2 wk, start same dose
  - If recovery ≥2 wk, ⇓ dose (no <300mg/d)
- Use of growth factors, eltrombopag have been reported, not standard

AXIS Medical Education

ANC, absolute neutrophil count; CBC, complete blood count; TKI, tyrosine kinase inhibitor.

Quintas-Cardama A, et al. *Cancer*. 2004;100(12):2592-2597. Cortes J, et al. *Cancer*. 2004;100(11):2396-2402. Ault P, et al. *Leuk Res*. 2004;28(6):613-618.

Management of Common Adverse Events With TKI

Toxicity	Management
Nausea, vomiting	Take with food (imatinib), antiemetics
Rash	Topical/systemic steroids
Diarrhea	Imodium, lomotil
Cramps	Tonic water, quinine, calcium gluconate
Fluid retention	Diuretics
Periorbital edema	Preparation H
Bone pain	NSAID
Weight gain	Diuretics, diet

NSAID, nonsteroidal anti-inflammatory drug; TKI, tyrosine kinase inhibitor.

Adverse Event Management and Risk Mitigation

AEs common to multiple TKIs

- 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 (lower dose)
- 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
  - Reported with all TKIs; most frequently with ponatinib (VEGF-like effect)
- Fatigue/musculoskeletal symptoms
  - Increasingly studied, recognized (QOL/PRO data); potential direct TKI mechanisms

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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; VEGF, vascular endothelial growth factor.

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; AOE, arterial occlusive event; GI, gastrointestinal.

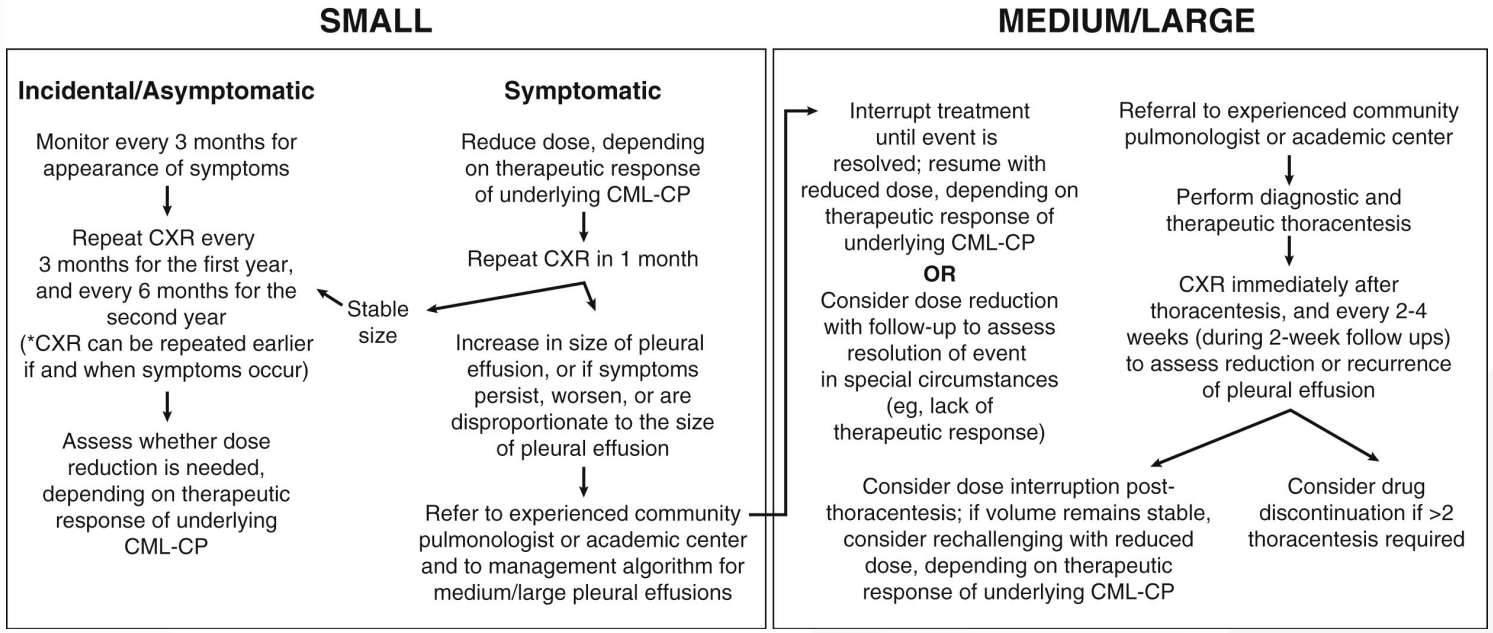
Management of Dasatinib-Associated Pleural Effusions

Symptoms

- Pulmonary and respiratory symptoms including dyspnea, persistent/dry cough of unknown cause, chest pressure
- Decreased exercise tolerance
- Cardiac symptoms (eg, palpitations, tachycardia)
- Constitutional symptoms (eg, fatigue)

Workup/Diagnostic tests

- Medical history and physical exam to determine temporal relationship with use of dasatinib, and evaluate degree of symptoms
- Consider other workups and potential causes before ruling in pleural effusion: PFT, ECHO
- Establish diagnosis of dasatinib-associated pleural effusion with CXR

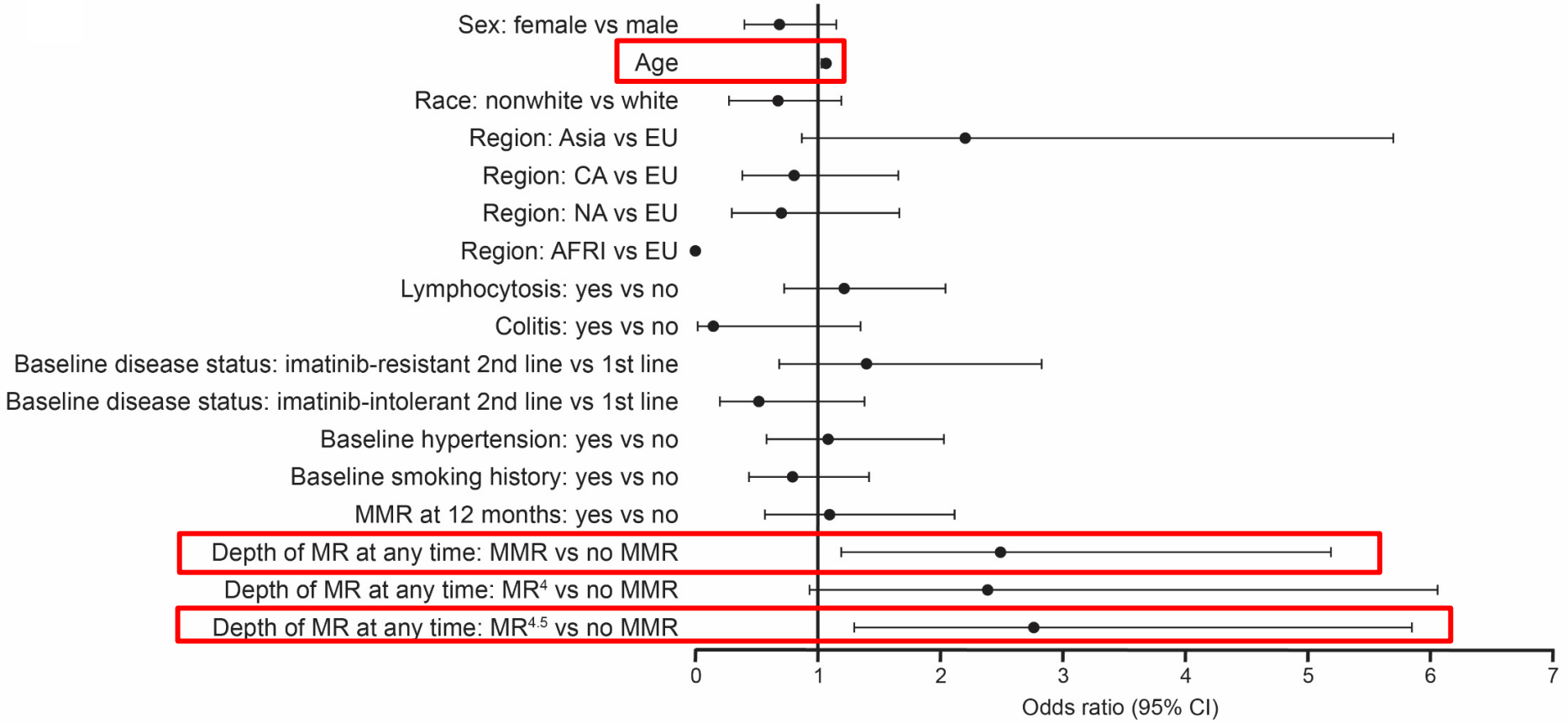


CML, chronic myeloid leukemia; CP, chronic phase; CXR, chest X-ray; ECHO, echocardiography; PFT, pulmonary function test.

Cortes JE, et al. *Clin Lymphoma Myeloma Leuk.* 2017;17(2):78-82.

Risk Factors for Dasatinib-Associated Pleural Effusion

Multivariate Analysis of DASISION and 034 Combined

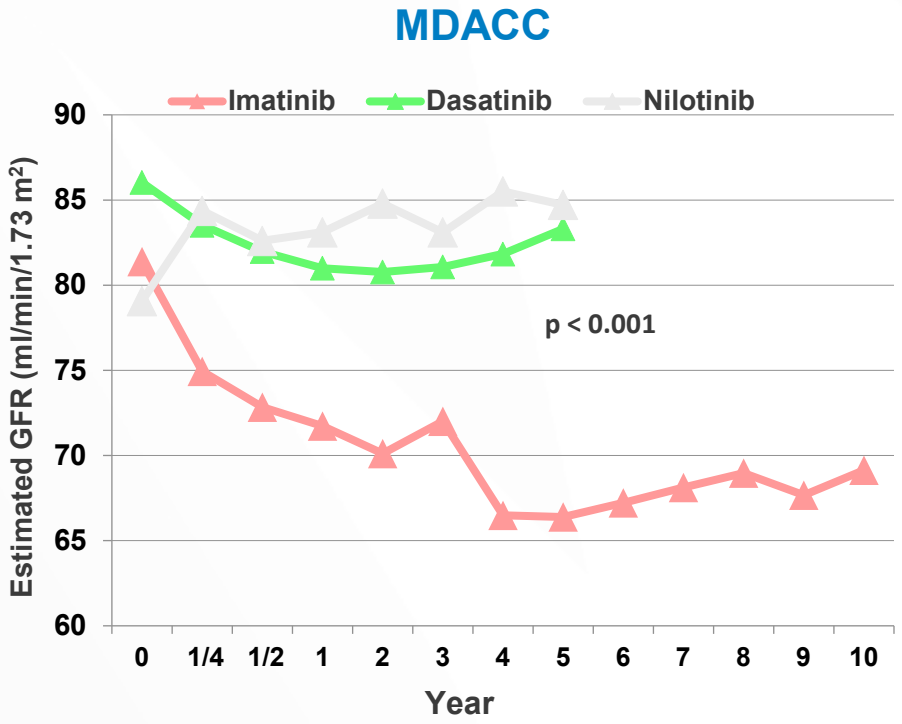


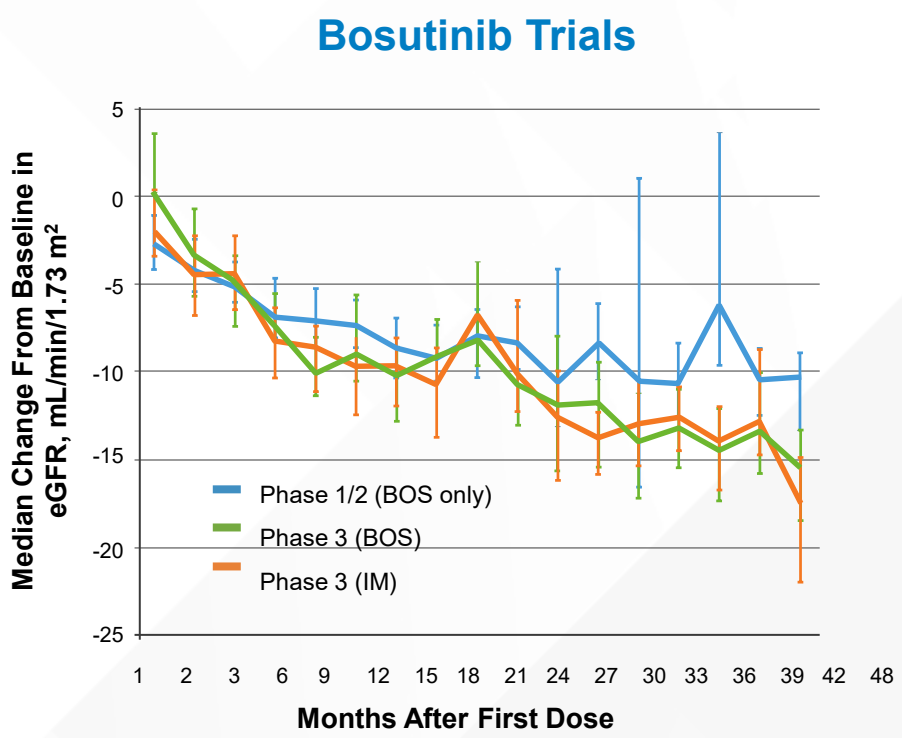
AFRI, Africa; CA, Canada; EU, European Union; MMR, major molecular response; MR, molecular response; MR4/4.5, molecular response by a 4/4.5 log reduction on the international scale; NA, North America.

Hughes TP, et al. *Haematologica*. 2019;104(1):93-101.

Renal Dysfunction with TKI

- 475 pts treated with imatinib (n=253), dasatinib (n=99), or nilotinib (n=116)
- ARF (↑ creatinine ≥0.3 mg/dl): IM 6%, dasatinib 1%, nilotinib 2%
- CRF (GFR ≤60 ml/min/1.73 m2 x ≥90 d): IM 22%, dasatinib 5%, nilotinib 4%
- No effect of ARF or CRF on outcome

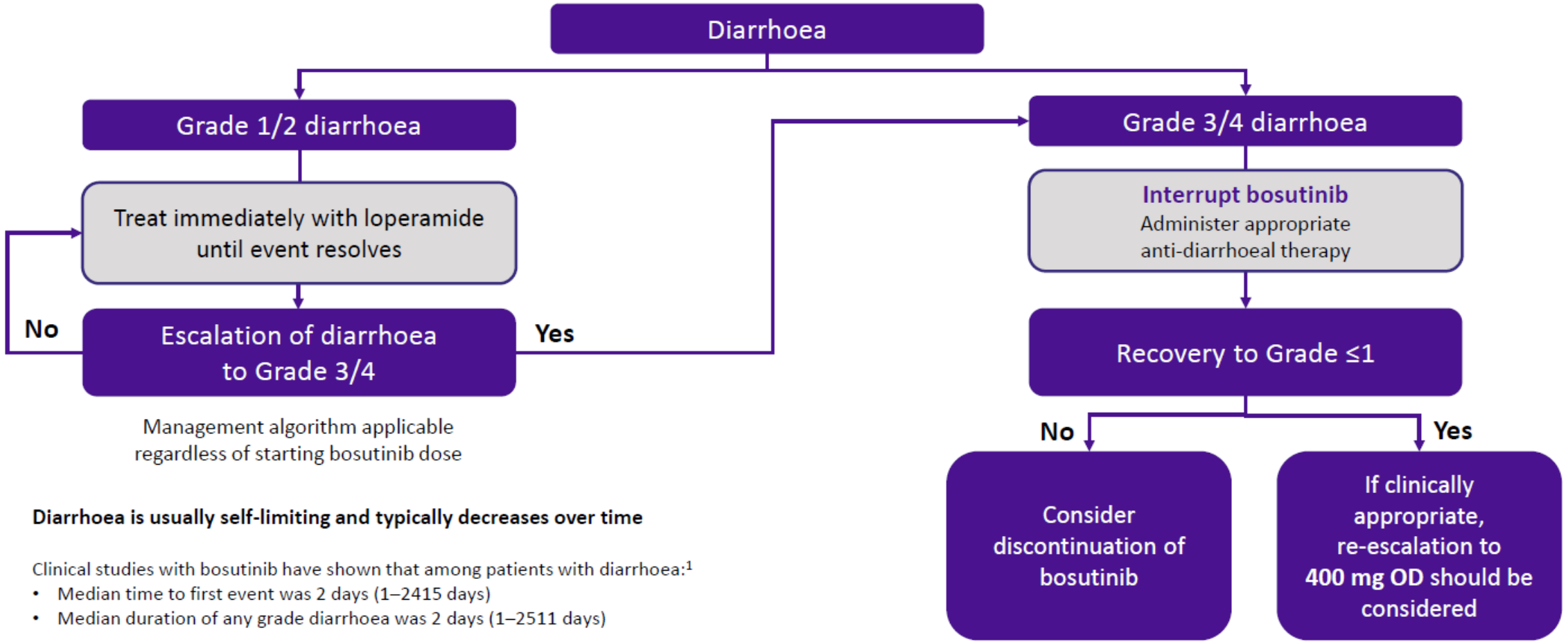




ARF, acute renal failure; IM, imatinib; CRF, chronic renal failure; GFR, glomerular filtration rate; MDACC, MD Anderson Cancer Center; TKI, tyrosine kinase inhibitor.

Yilmaz M, et al. *Cancer.* 2015;121(21):3894-3904. Cortes JE, et al. *Clin Lymphoma Myeloma Leuk.* 2017;17(10):684-695.e6.

Proposed Management of Bosutinib-Associated Diarrhea



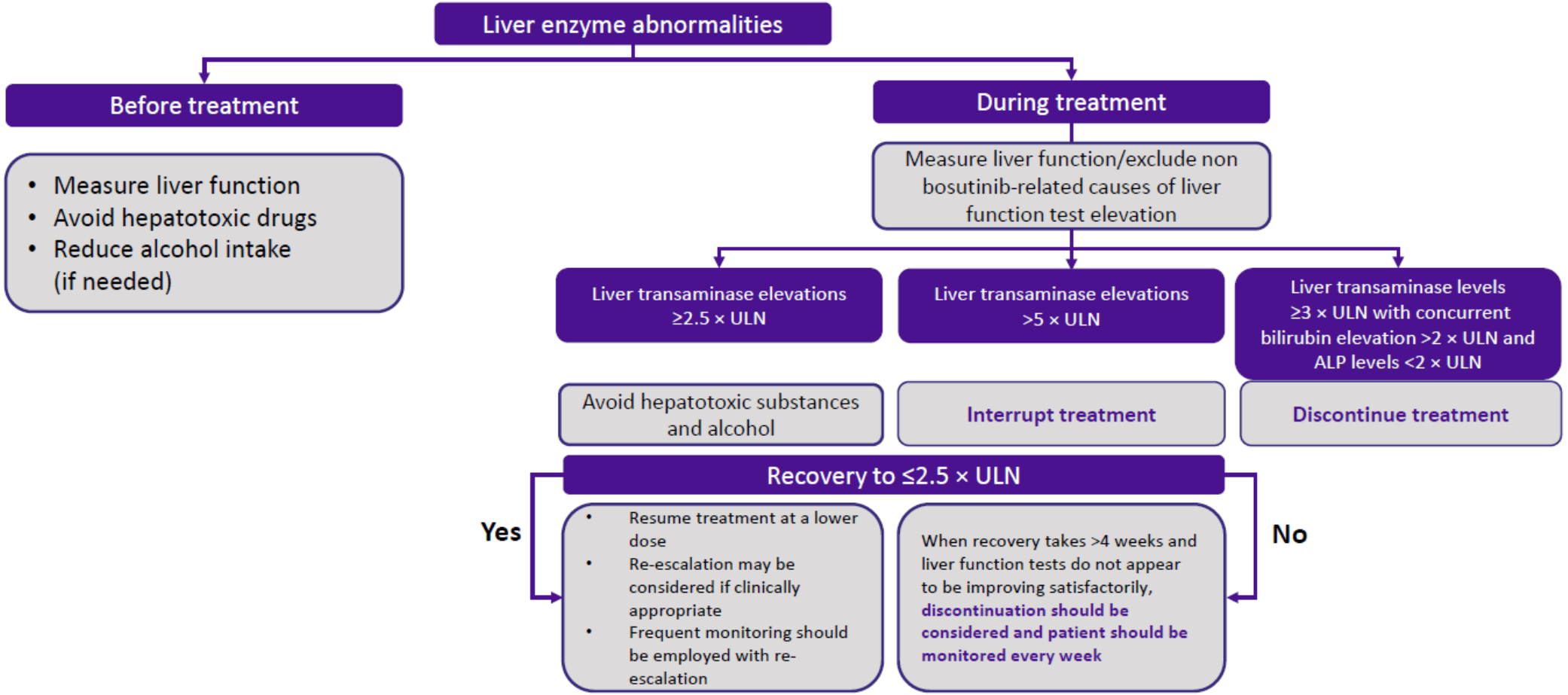
Diarrhoea is usually self-limiting and typically decreases over time

Clinical studies with bosutinib have shown that among patients with diarrhoea:[1]

- Median time to first event was 2 days (1–2415 days)
- Median duration of any grade diarrhoea was 2 days (1–2511 days)

Benson AB 3rd, et al. *J Clin Oncol.* 2004;22(14):2918-2926.
Cortes JE, et al. *J Hematol Oncol.* 2018;11(1):143.

Proposed Management of Bosutinib-Associated Elevated Liver Function Tests



ULN, upper limit of normal.

Cortes JE, et al. *J Hematol Oncol.* 2018;11(1):143.

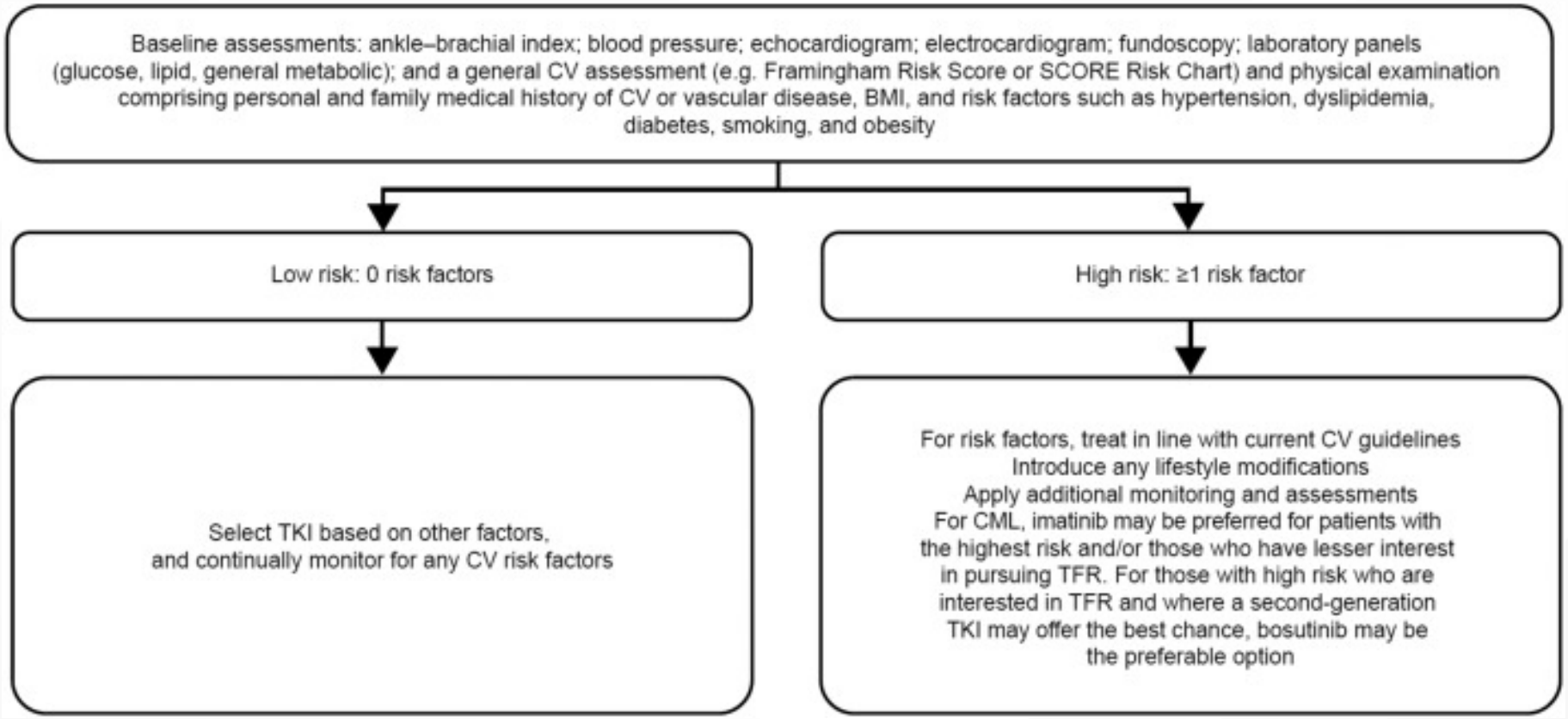
Meta-Analysis of Cardiovascular Events With TKI

Source	Peto Odds Ratio (95% CI)	P value
Bosutinib		
NCT00574873-BELA	2.77 (0.39-19.77)	.31
Subtotal	2.77 (0.39-19.77)	.31
Dasatinib		
NCT00070499	7.39 (0.15-372.38)	.32
NCT00103844-START-R	4.46 (0.23-86.51)	.32
NCT00320190	0.09 (0.00-4.61)	.23
NCT00481247-DASISION	4.86 (1.30-18.12)	0.02
NCT00852566-NordCML006	8.09 (0.16-409.34)	.30
Subtotal	3.86 (1.33-11.18)	.01
Nilotinib		
NCT00471497-ENESTnd	3.31 (1.95-5.61)	<.001
NCT00760877-ENESTcmr	4.45 (0.99-20.02)	.052
Subtotal	3.42 (2.07-5.63)	<.001
Ponatinib		
NCT01650805-EPIC	3.47 (1.23-9.78)	.02
Subtotal	3.47 (1.23-9.78)	.02
Overall	**3.45 (2.30-5.18)**	**<.001**

TKI, tyrosine kinase inhibitor.

Douxfils J, et al. *JAMA Oncol.* 2016;2(5):625-632.

Suggested Guidelines and Monitoring for CV Risk Factors in Patients With CML



CML, chronic myeloid leukemia; CV, cardiovascular; SCORE, Systematic Coronary Risk Evaluation; TFR, treatment-free remission; TKI, tyrosine kinase inhibitor.
Lipton JH, et al. *Blood Rev.* 2022;56:100968.

Cross-Intolerance Between TKI

- Many AEs occur with various TKI
- No significant cross-intolerance
- Re-occurrence of AEs relatively frequent; treatment discontinuation less frequent
- Cross-intolerance uncommon even for AEs common to 2nd TKI (eg, imatinib discontinuation for diarrhea → 20% bosutinib discontinuation for diarrhea)
- Some AEs occur more frequently with subsequent TKI if they occurred with previous (eg, pleural effusion)
- More cross-intolerance for hematologic AEs
- Some “AEs” likely to persist (eg, fatigue, memory issues)
- Arterio-thrombotic event cross-intolerance not explored

AXIS Medical Education

AE, adverse event; TKI, tyrosine kinase inhibitor.

Khoury HJ, et al. *Clin Lymphoma Myeloma Leuk.* 2016;16(6):341-349.e1.
Cortes JE, et al. *Blood.* 2011;117(21):5600-5606.

Switching TKI for Low-Grade AEs: A Delicate Balance

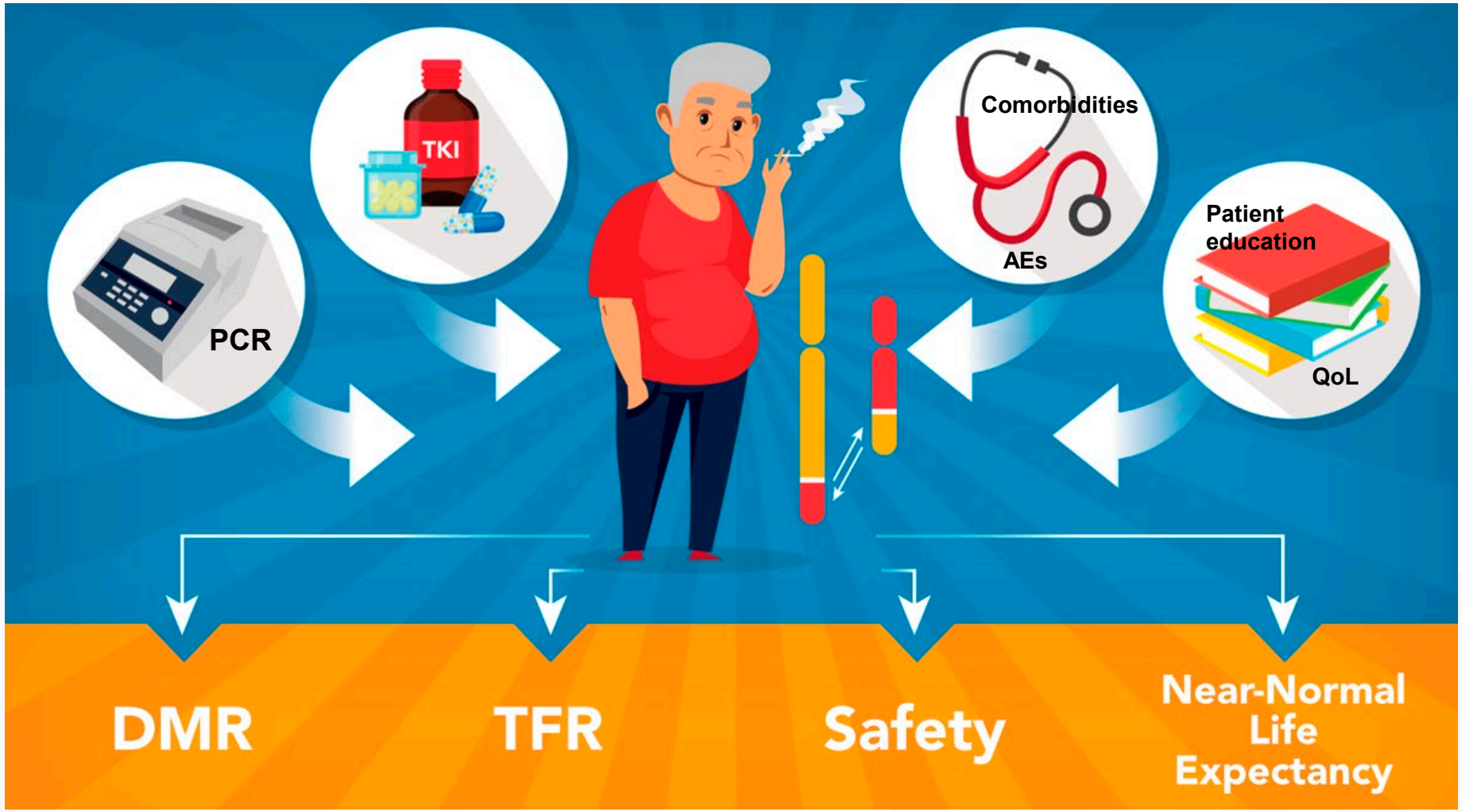
- The ENRICH Trial: 52 pts on imatinib with G1/2 non-hematologic AE persisting >2 mo or recurred >3x despite best supportive care
- Switch to nilotinib 300 mg BID
- 132/210 (63%) AEs resolved, 6% improved, 3% worsened
- 85% of patients improved by 12 cycles
- 30 pts (58%) improved all symptoms (6% none)
- 50% improved QoL (14% worsened)
- However:
  - 85% had nilotinib-related AEs; 31% grade 3
  - 44% dose reduction/interruption; 15% discontinued

AXIS Medical Education

AE, adverse event; BID, twice a day; G1/2, grade 1/2; QoL, quality of life.

Cortes JE, et al. *Clin Lymphoma Myeloma Leuk.* 2016;16(5):286-296.

Holistic Management of Patients with CML



AE, adverse event; DMR, deep molecular response; PCR, polymerase chain reaction; QoL, quality of life; TFR, treatment-free remission.
Cortes J. *Blood*. 2020;136(22):2507-2512.

Practical Application
Case-Based Learning Lab

Case 1

- 72-year-old man with diagnosis of CML
- He is diabetic with a mildly elevated HbA1c, and hypertensive with moderate control under lisinopril
- He receives statins for hypercholesterolemia
- Initially treated with imatinib but achieved only a minor cytogenetic response after 12 months of therapy
- The treatment was changed to dasatinib 100 mg
- He achieved a complete cytogenetic response but never MMR
- After 2 years on this therapy you now find a BCR-ABL/ABL of 2.3% and a cytogenetic analysis shows 1/20 metaphases with Ph
- Sequencing demonstrates a *T315I* mutation

Your recommendation now is:

a) Increase dasatinib to 140 mg
b) Change to imatinib 600 mg daily
c) Change to nilotinib 400 mg twice daily
d) Change to bosutinib 500 mg daily
e) Change to ponatinib 30 mg daily
f) Change to asciminib 200 mg twice daily
g) SCT

Rationale

- Imatinib, dasatinib, nilotinib or bosutinib have no clinical benefit in patients with T315I
- Ponatinib is an adequate option, but the dose is important
- These patients in particular require a full dose of 45 mg daily to experience optimal benefit
- Because of the patient's co-morbidities, asciminib is a better option for this patient
- Although SCT can be considered, the age and co-morbidities may make this a higher risk proposition

Case 2

- A 35-year-old female patient is diagnosed with CML
- A bone marrow confirms she is in chronic phase, has no additional chromosomal abnormalities, and her Sokal risk is low
- She is interested in eventually starting a family and being able to stop therapy at some point

Your recommendation for initial therapy is:

a) Imatinib
b) Dasatinib
c) Nilotinib
d) Bosutinib
e) Asciminib

Rationale

- All options are adequate and approved as initial therapy
- Asciminib may give the better probability of reaching a deep molecular response that is required for an attempt at treatment discontinuation

AXIS Medical Education

Novel Treatments for Newly Diagnosed Ph+ CML-CP:

Striking the Balance of Treatment with Patient Goals and QoL