Meet The Professor
Optimizing the Management of Chronic Myeloid Leukemia

Jorge Cortes, MD
Director, Georgia Cancer Center
Cecil F Whitaker Jr, MD/GRA Eminent Scholar Chair in Cancer
Augusta University
Augusta, Georgia

Commercial Support

This activity is supported by an educational grant from Novartis.

Dr Love — Disclosures

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following companies: AbbVie Inc, Adaptive Biotechnologies Corporation, ADC Therapeutics, Agios Pharmaceuticals Inc, Alexion Pharmaceuticals, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, BeyondSpring Pharmaceuticals Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Coherus BioSciences, CTI BioPharma Corp, Daiichi Sankyo Inc, Eisai Inc, Elevation Oncology Inc, EMD Serono Inc, Epizyme Inc, Exact Sciences Corporation, the parent company of GHI, Exelixis Inc, Five Prime Therapeutics Inc, Foundation Medicine, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Genmab, Gilead Sciences Inc, GlaxoSmithKline, Grail Inc, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Mersana Therapeutics Inc, Natera Inc, Novartis, Novartis Pharmaceuticals Corporation on behalf of Advanced Accelerator Applications, Novocure Inc, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sanofi Genzyme, Seagen Inc, Servier Pharmaceuticals LLC, Sumitomo Dainippon Pharma Oncology Inc, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, Tesaro, A GSK Company, TG Therapeutics Inc, Turning Point Therapeutics Inc, Verastem Inc and Zymeworks Inc.

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Contracted Research	AbbVie Inc, Novartis, Pfizer Inc, Sun Pharmaceutical Industries Ltd
Stock Options/Ownership — Public Ineligible Company	Bio-Path Holdings

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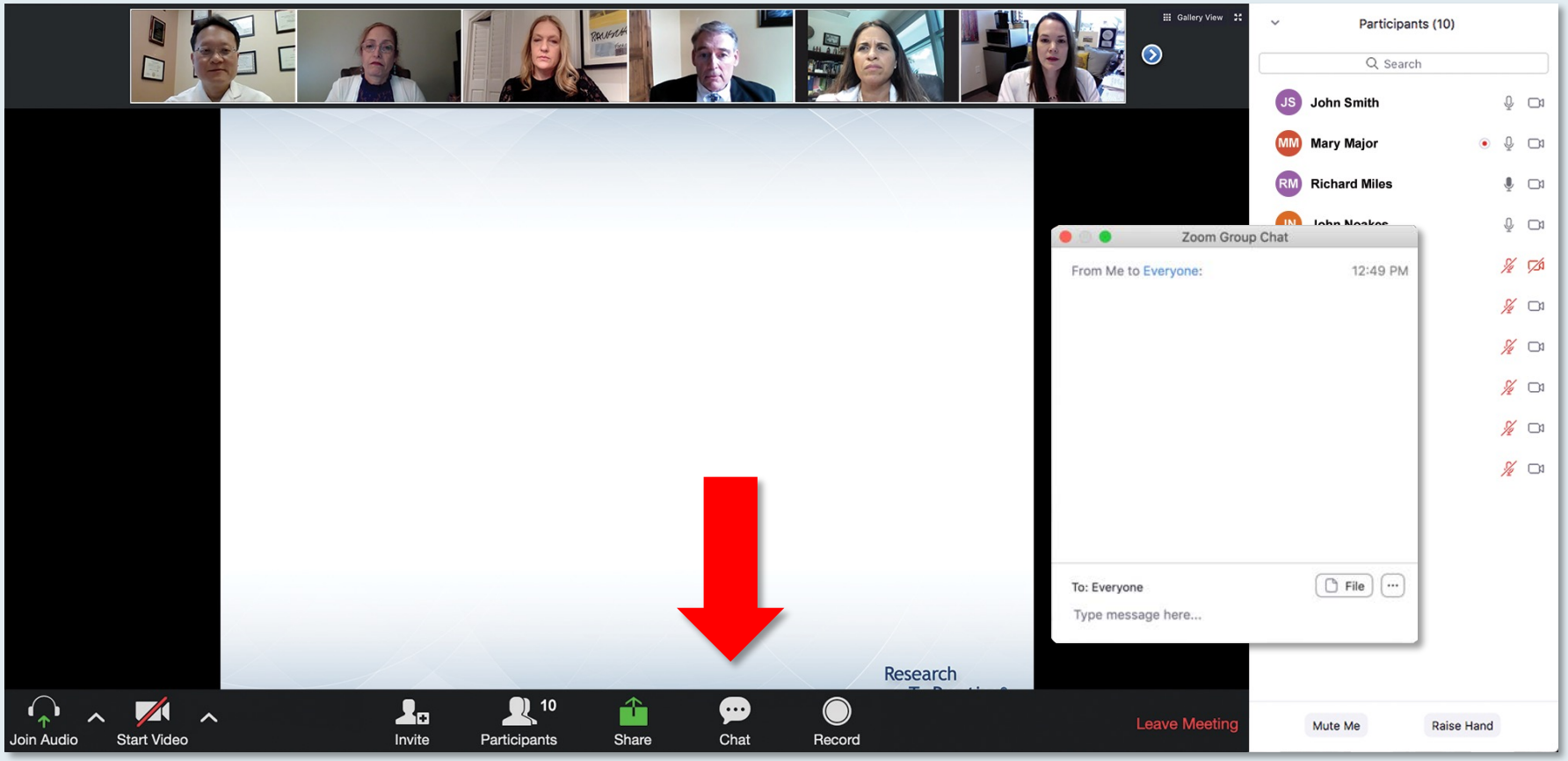
We Encourage Clinicians in Practice to Submit Questions



Feel free to submit questions now before the program begins and throughout the program.

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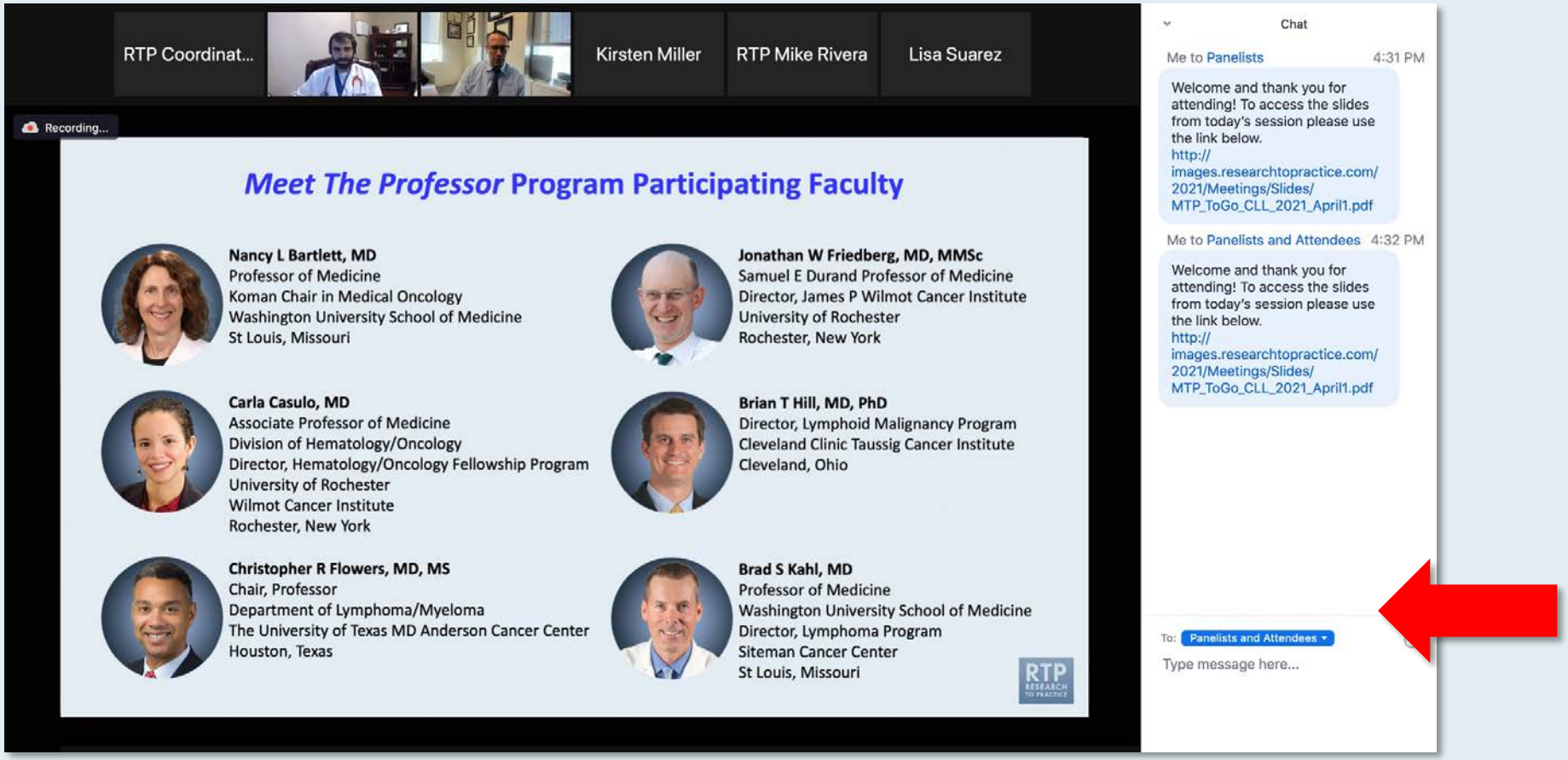
Expand chat submission box



Drag the white line above the submission box up to create more space for your message.

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Familiarizing Yourself with the Zoom Interface

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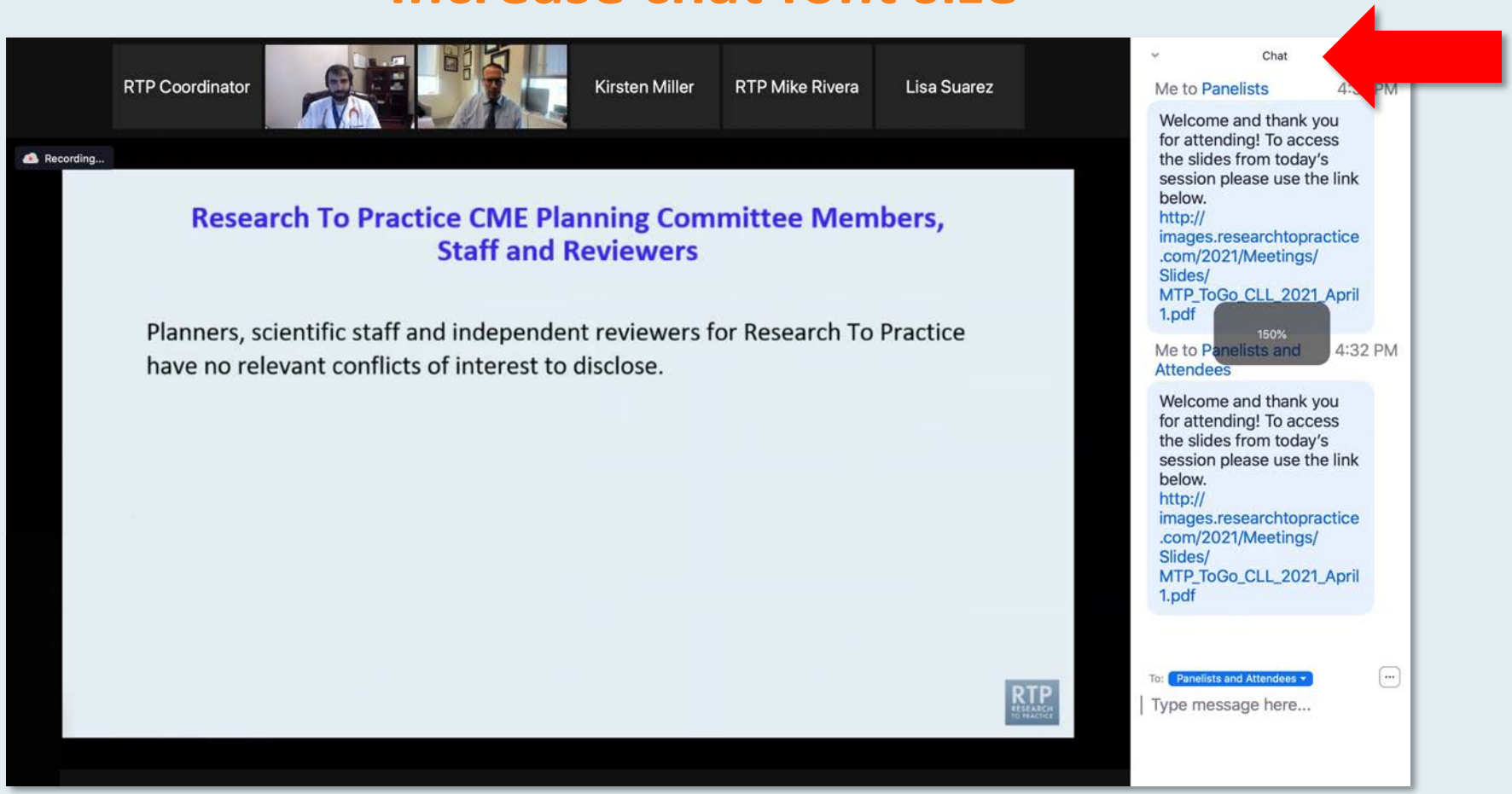

Press Command (for Mac) or Control (for PC) and the + symbol.
You may do this as many times as you need for readability.

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WITH DR NEIL LOVE

Key Presentations on Advances in Myeloproliferative Neoplasms from ASH 2021

DR PRITHVIRAJ BOSE

THE UNIVERSITY OF TEXAS
MD ANDERSON CANCER CENTER

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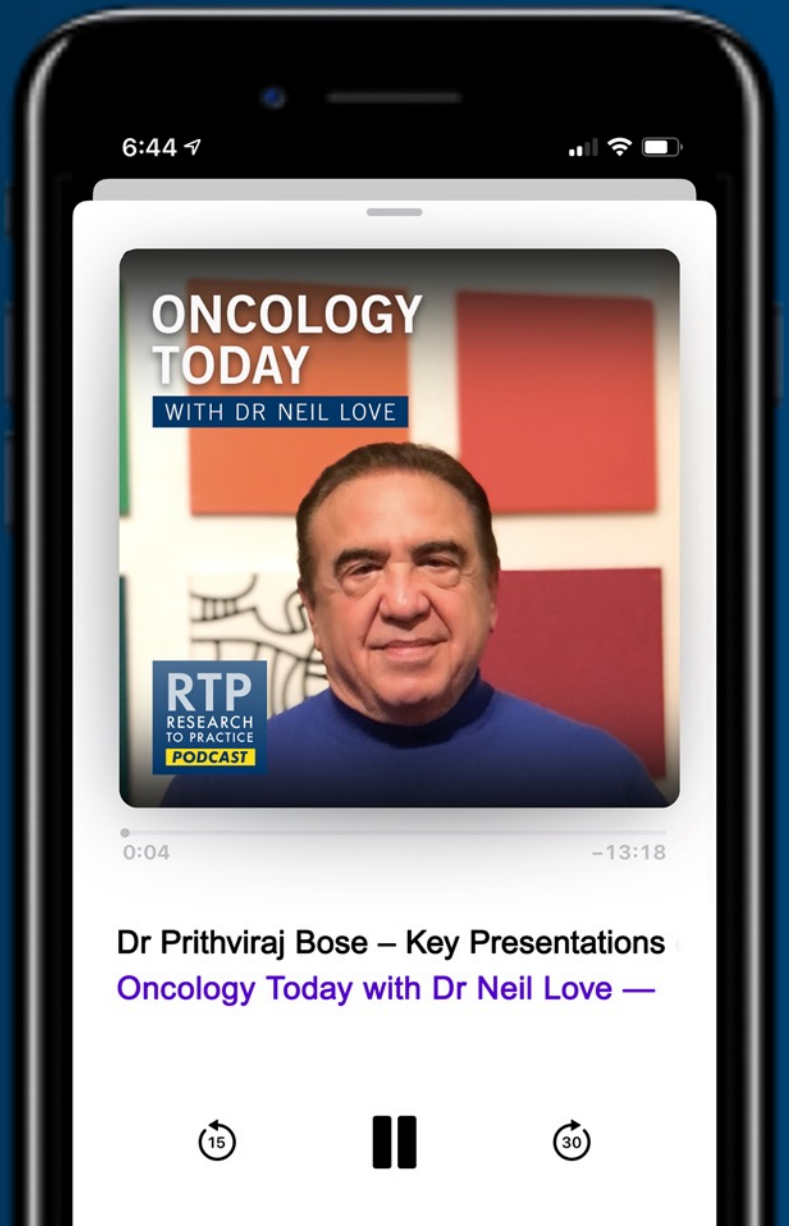

Meet The Professor

Current and Future Management of Non-Small Cell Lung Cancer with an EGFR Mutation

Thursday, June 30, 2022
5:00 PM – 6:00 PM ET

Faculty

Joel W Neal, MD, PhD

Moderator

Neil Love, MD

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Meet The Professor

Optimizing the Management of Ovarian Cancer

Wednesday, July 6, 2022
5:00 PM – 6:00 PM ET

Faculty

Ursula Matulonis, MD

Moderator

Neil Love, MD

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Meet The Professor

Optimizing the Management of Hepatobiliary Cancers

Thursday, July 7, 2022
5:00 PM – 6:00 PM ET

Faculty

Ghassan Abou-Alfa, MD, MBA

Moderator

Neil Love, MD

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Meet The Professor

Optimizing the Management of Gastroesophageal Cancers

Tuesday, July 12, 2022
5:00 PM – 6:00 PM ET

Faculty

Samuel J Klempner, MD

Moderator

Neil Love, MD

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Management of Acute Myeloid Leukemia and Myelodysplastic Syndromes – A Review of the 2022 ASCO Annual Meeting and EHA Congress

Wednesday, July 13, 2022
5:00 PM – 6:00 PM ET

Faculty

Richard M Stone, MD

Moderator

Neil Love, MD

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Meet The Professor

Optimizing the Management of Chronic Myeloid Leukemia

Tuesday, July 19, 2022
5:00 PM – 6:00 PM ET

Faculty

Daniel J DeAngelo, MD, PhD

Moderator

Neil Love, MD

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Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

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Optimizing the Management of Chronic Myeloid Leukemia

Jorge Cortes, MD
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Cecil F Whitaker Jr, MD/GRA Eminent Scholar Chair in Cancer
Augusta University
Augusta, Georgia

Meet The Professor Program Participating Faculty

Jorge Cortes, MD
Director, Georgia Cancer Center
Cecil F Whitaker Jr, MD/GRA Eminent Scholar
Chair in Cancer
Augusta University
Augusta, Georgia

Daniel J DeAngelo, MD, PhD
Chief, Division of Leukemia
Institute Physician
Dana-Farber Cancer Institute
Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Michael R Grunwald, MD
Chief, Leukemia Division
Director, Transplantation and Cellular Therapy Program
Associate Professor
Department of Hematologic Oncology and Blood Disorders
Levine Cancer Institute, Atrium Health
Charlotte, North Carolina

Neil P Shah, MD, PhD
Professor of Medicine
UCSF Helen Diller Comprehensive
Cancer Center
University of California, San Francisco
San Francisco, California

Kendra Sweet, MD
Associate Member
Malignant Hematology Department
Moffitt Cancer Center
Tampa, Florida

Moderator

Neil Love, MD
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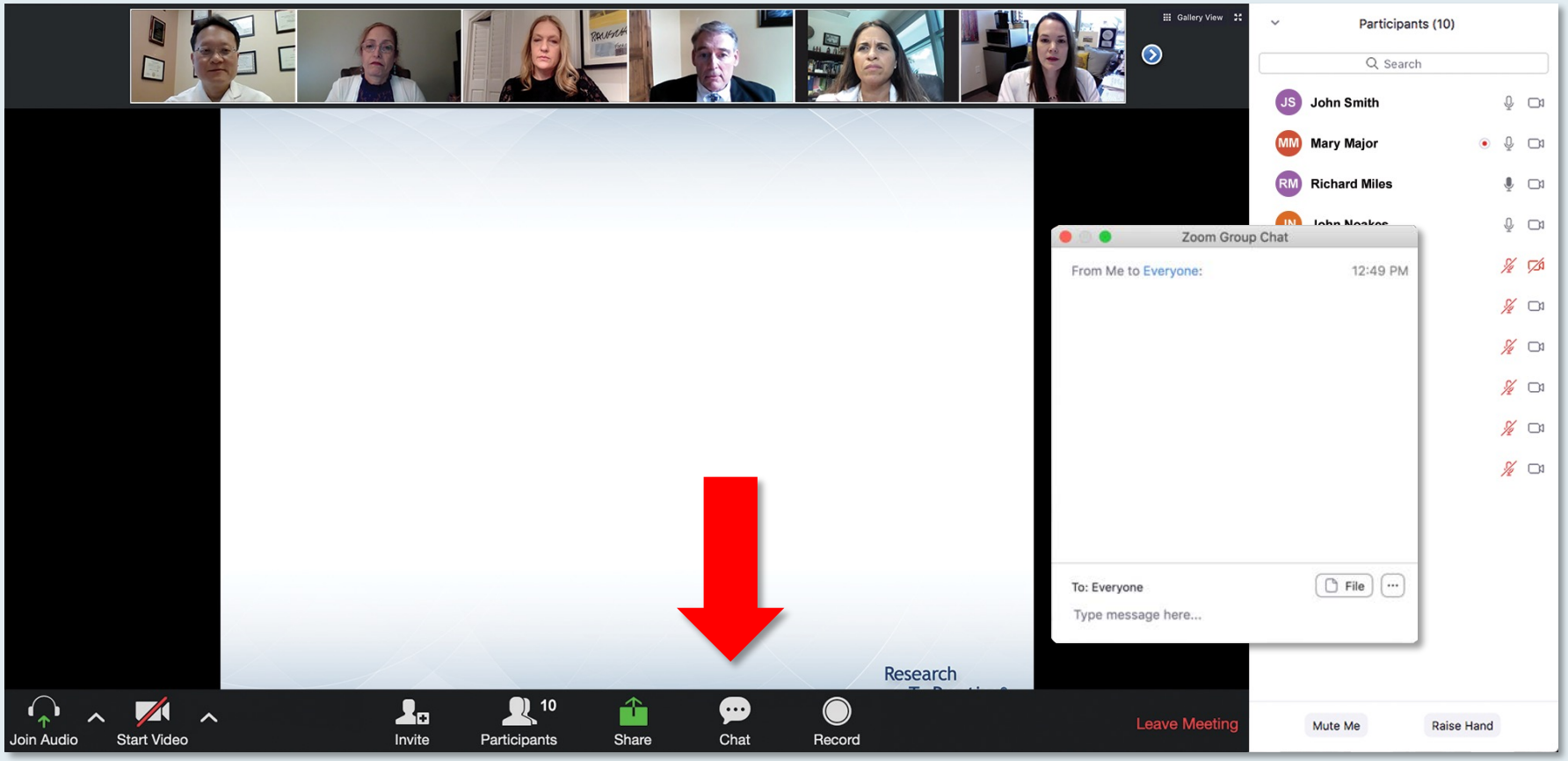

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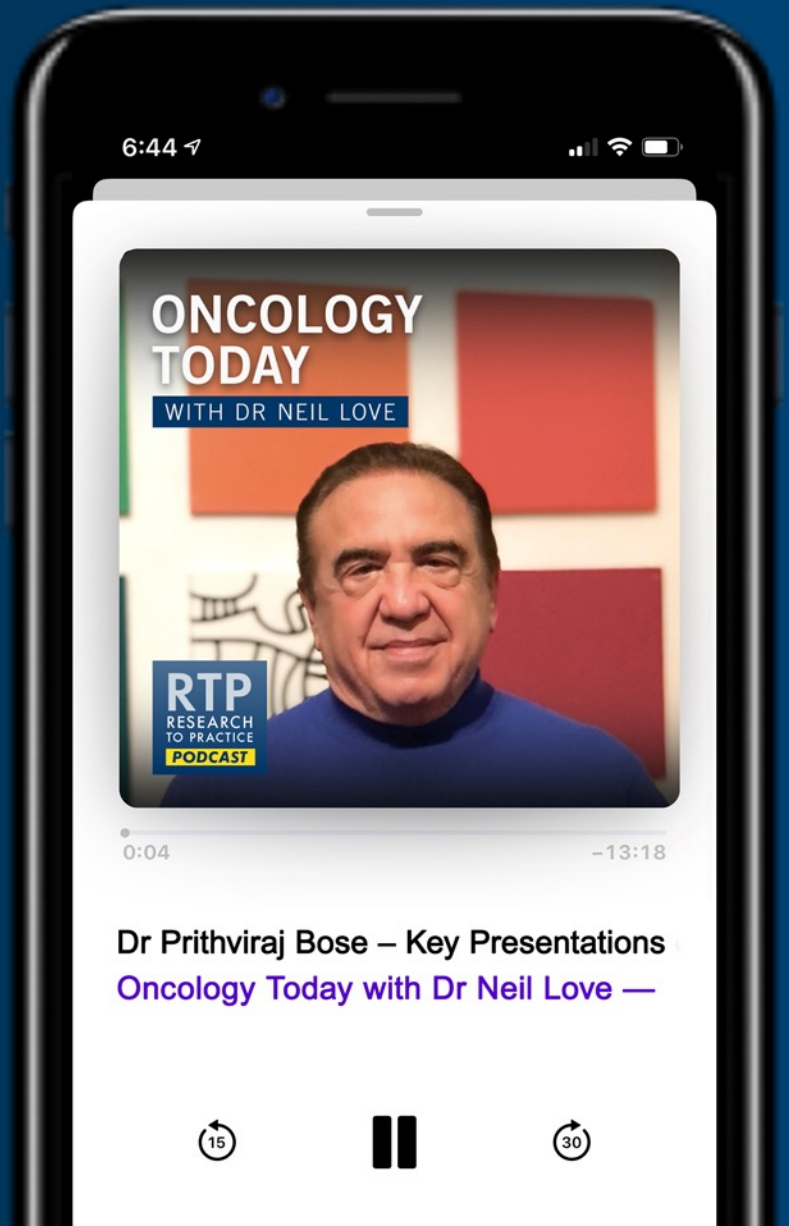

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Dr Cortes — Disclosures

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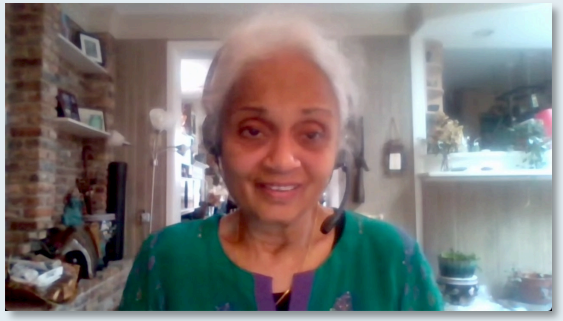
Bruce Bank, MD
Northwest Oncology and Hematology
Rolling Meadows, Illinois

Michael R Grunwald, MD
Atrium Health Levine
Cancer Institute
Charlotte, North Carolina

Shams Bufalino, MD
Advocate Aurora Health
Park Ridge, Illinois



Rajalaxmi McKenna, MD
Southwest Medical
Consultants SC
Willowbrook, Illinois

Gigi Chen, MD
John Muir Health
Pleasant Hill, California

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Meet The Professor with Dr Cortes

Introduction: Journal Club with Dr Cortes

MODULE 1: Case Presentations

- Dr McKenna: A 42-year-old man with CML and osteopenia after long-term imatinib therapy
- Dr Bank: A 60-year-old man with CP-CML and continued detectable BCR-ABL transcript on bosutinib
- Dr Chen: A 70-year-old man with chronic-phase CML (CP-CML) and notable toxicities from several BCR-ABL tyrosine kinase inhibitors (TKIs)
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MODULE 2: Appendix of Key Recent Data Sets

Meet The Professor with Dr Cortes

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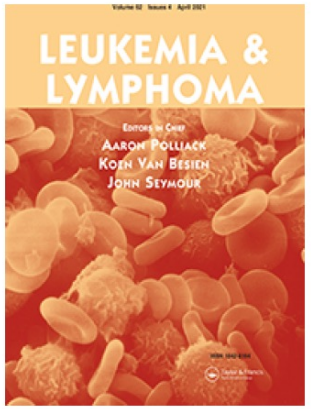
MODULE 2: Appendix of Key Recent Data Sets



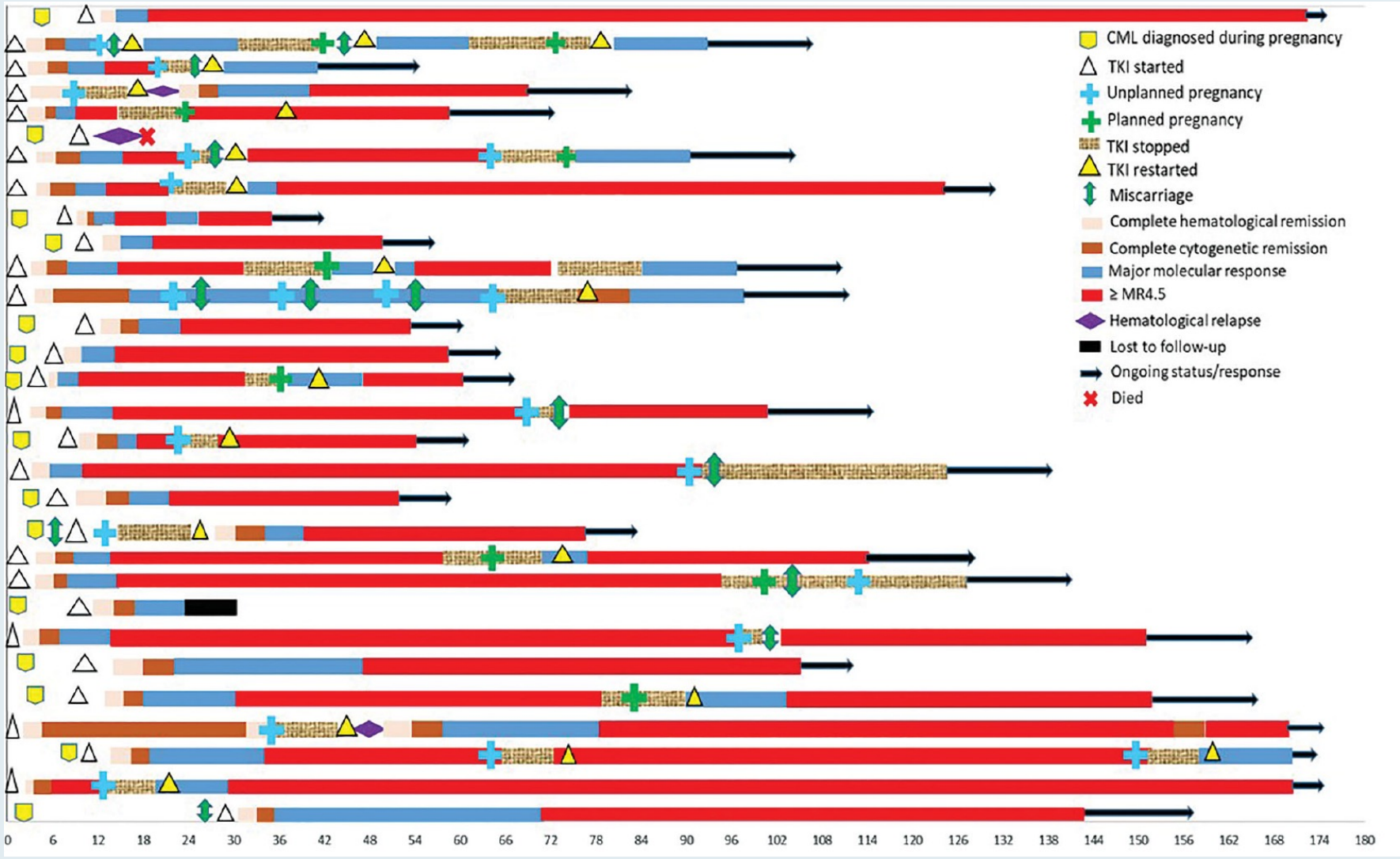
Leukemia & Lymphoma 2021;62(4):909-17.

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ilal20

Management of chronic myeloid leukemia during pregnancy among patients treated with a tyrosine kinase inhibitor: a single-Center experience

Rita Assi, Hagop Kantarjian, Michael Keating, Naveen Pemmaraju, Srdan Verstovsek, Guillermo Garcia-Manero, Farhad Ravandi, Gautam Borthakur, Jenny Dahl, Elias Jabbour & Jorge E. Cortes

Timeline of Pregnancies and Dynamics of Response in Women with CML Treated with TKIs



Assi R et al. *Leuk Lymphoma* 2021;62(4):909-17.

Seminar

Chronic myeloid leukaemia

Jorge Cortes, Carolina Pavlovsky, Susanne Saußele

Lancet 2021; 398: 1914–26
Published Online
August 20, 2021
https://doi.org/10.1016/
S0140-6736(21)01204-6

Tyrosine-kinase inhibitors have changed the natural history of chronic myeloid leukaemia in such a way that patients with adequate access to these agents, who are properly managed, and who respond well to this treatment can expect a near-normal life expectancy. Achieving this goal requires an adequate understanding of the patient's treatment goals, careful monitoring for the achievement of optimal response hallmarks, implementation of proper interventions according to the attainment of such endpoints, adequate recognition and management of adverse events, and acknowledgment of the relevance of comorbidities. Treatment with tyrosine-kinase inhibitors, once considered lifelong, has become terminable for at least some patients, and promising new agents are emerging for those whose disease does not respond to any of the multiple therapeutic options currently available. If these advances reach all patients with chronic myeloid leukaemia, cure might eventually become a reality in most instances.

***Lancet* 2021;398(10314):1914-26.**

JC JOURNAL CLUB RTP RESEARCH TO PRACTICE

Responses in Patients with CP-CML Treated with Second-Generation TKIs After Resistance or Intolerance to Imatinib at 24-Month Follow-Up

	Dasatinib*	Nilotinib†	Bosutinib
Complete haematological response	89%	77%	86%
Major cytogenetic response	59%	56%	57%
Complete cytogenetic response	44%	41%	44%
Progression-free survival‡	80%	64%	81%
Overall survival	91%	87%	91%

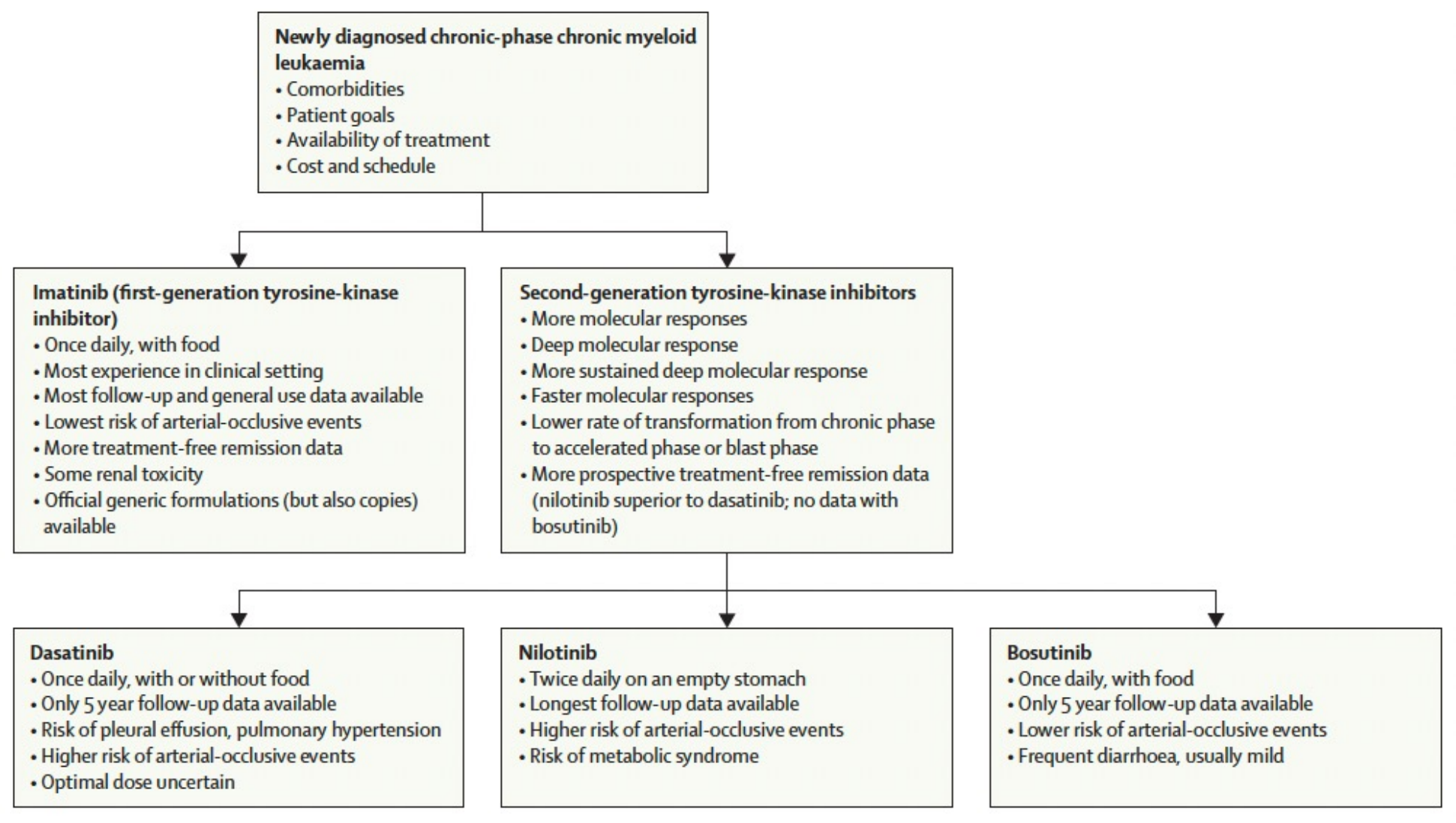
Cortes J et al. *Lancet* 2021;398(10314):1914-26.

Treatment Responses in Patients with CP-CML Treated with Second-Generation TKIs in the First-Line Setting (Compared to Imatinib)

	First-line dasatinib	Imatinib control	First-line nilotinib	Imatinib control	First-line bosutinib	Imatinib control
BCR-ABL1 ≤10% at 3 months	84·0%	64·0%	91·0%	67·0%	75·0%	57·0%
Complete cytogenetic response at 12 months	83·0%	72·0%	80·0%	65·0%	77·0%	66·0%
Major molecular response at 12 months	46·0%	28·0%	44·0%	22·0%	47·0%	37·0%
Treatment discontinuation by 24 months	23·0%	25·0%	26·0%	33·0%	29·0%	34·0%
Transformation to accelerated or blast phase at 24 months	3·5%	5·8%	0·7%	4·2%	2·2%	2·6%

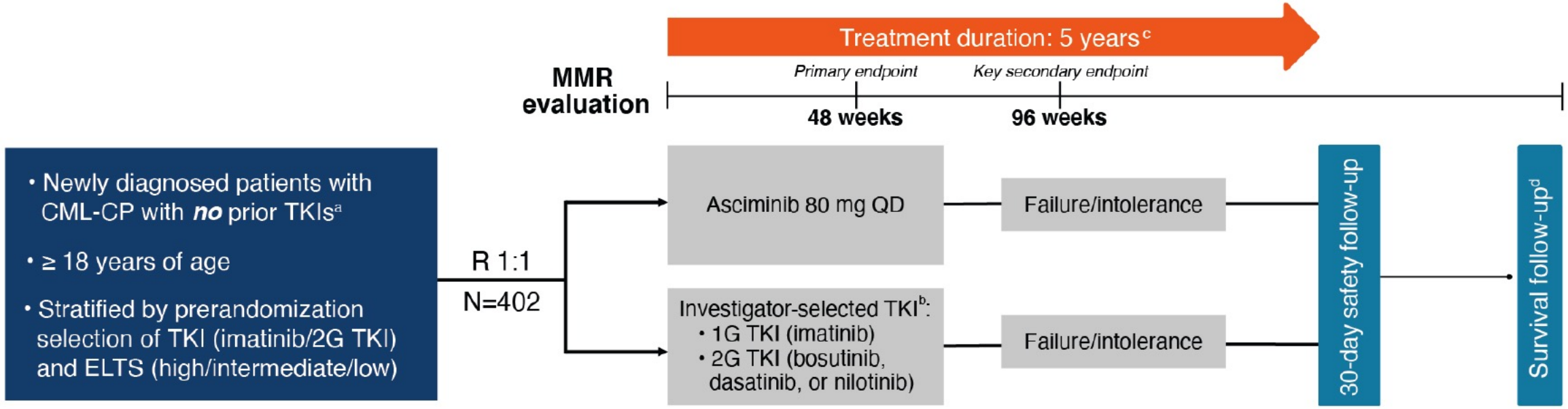
Cortes J et al. *Lancet* 2021;398(10314):1914-26.

Decision Algorithm for Newly Diagnosed CP-CML



Cortes J et al. *Lancet* 2021;398(10314):1914-26.

Schema of a Phase III Trial of Asciminib versus TKI for Newly Diagnosed CP-CML



1G, 1st generation; 2G, 2nd generation; CML-CP, chronic myeloid leukemia in chronic phase; ELTS, EUTOS long-term survival; EUTOS, European Treatment and Outcome Study; IS, International Scale; MMR, major molecular response (*BCR::ABL1*^{IS} ≤0.1%); QD, once daily; R, randomized; TKI, tyrosine kinase inhibitor.
[a] Only imatinib therapy ≤2 weeks is allowed. [b] The investigator-selected TKI treatment group will be distributed evenly between patients prerandomized to either 1G TKI or 2G TKI at their approved dose, with dose modifications for intolerance allowed at the investigator's discretion and in accordance with local labels.
[c] Patients will remain on study for 5 years after the last patient's 1st dose, unless they have discontinued early due to treatment failure, disease progression, intolerance, or investigator or patient decision. [d] Patients who discontinue early will continue to be followed up for survival and disease progression until the end of the study.

Hughes T et al. *EHA* 2022;Abstract PB1904.

Meet The Professor with Dr Cortes

Introduction: Journal Club with Dr Cortes

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MODULE 2: Appendix of Key Recent Data Sets

Case Presentation: A 42-year-old man with CML and osteopenia after long-term imatinib therapy

Dr Rajalaxmi McKenna (Willowbrook, Illinois)

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Contents lists available at ScienceDirect

Blood Reviews

journal homepage: www.elsevier.com/locate/issn/0268960X

Review

Long-term safety review of tyrosine kinase inhibitors in chronic myeloid leukemia - What to look for when treatment-free remission is not an option

Jeffrey H. Lipton [a,*], Tim H. Brümmendorf [b], Carlo Gambacorti-Passerini [c], Valentin Garcia-Gutiérrez [d], Michael W. Deininger [e], Jorge E. Cortes [f]

***Blood Rev* 2022;[Online ahead of print].**

Case Presentation: A 60-year-old man with CP-CML and continued detectable BCR-ABL transcript on bosutinib

Dr Bruce Bank (Rolling Meadows, Illinois)

Case Presentation: A 70-year-old man with CP-CML and notable toxicities from several BCR-ABL TKIs

Dr Gigi Chen (Pleasant Hill, California)

Blood 2020;136(22):2507-12.

blood®

Review Article

How to manage CML patients with comorbidities

Jorge Cortes

Georgia Cancer Center, Augusta, GA

Suggestions for TKI Selection for Front-Line Therapy Based on Comorbidities

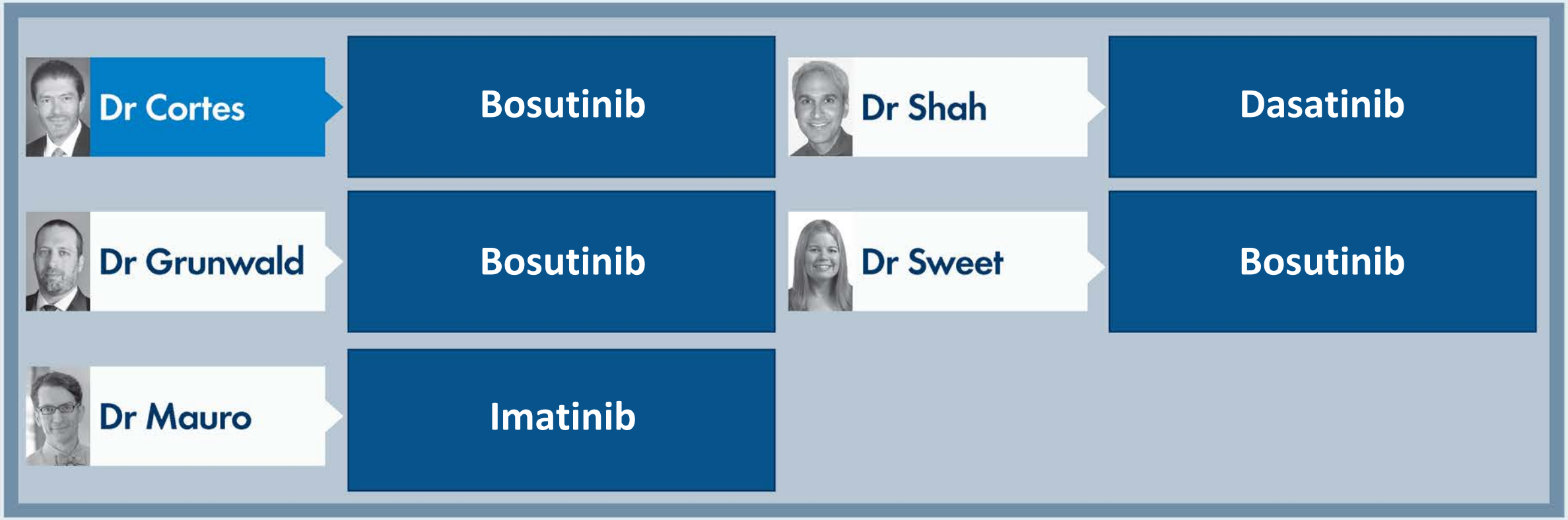
Comorbidity	Preferred	Less preferred
Diabetes	Imatinib, dasatinib, bosutinib	Nilotinib
Pulmonary disease/pulmonary arterial hypertension	Imatinib, bosutinib, nilotinib	Dasatinib
Gastrointestinal issues	Nilotinib, dasatinib	Imatinib, bosutinib
Cardiovascular	Imatinib, bosutinib	Nilotinib, dasatinib
Peripheral arterial	Imatinib, bosutinib (dasatinib?)	Nilotinib
Liver	Imatinib, dasatinib (nilotinib?)	Bosutinib
Renal	Nilotinib, dasatinib	Imatinib, bosutinib

Cortes J et al. *Blood* 2020;136(22):2507-12.

Which scoring system do you use to risk stratify patients with chronic-phase CML?

ELTS = EUTOS long-term survival

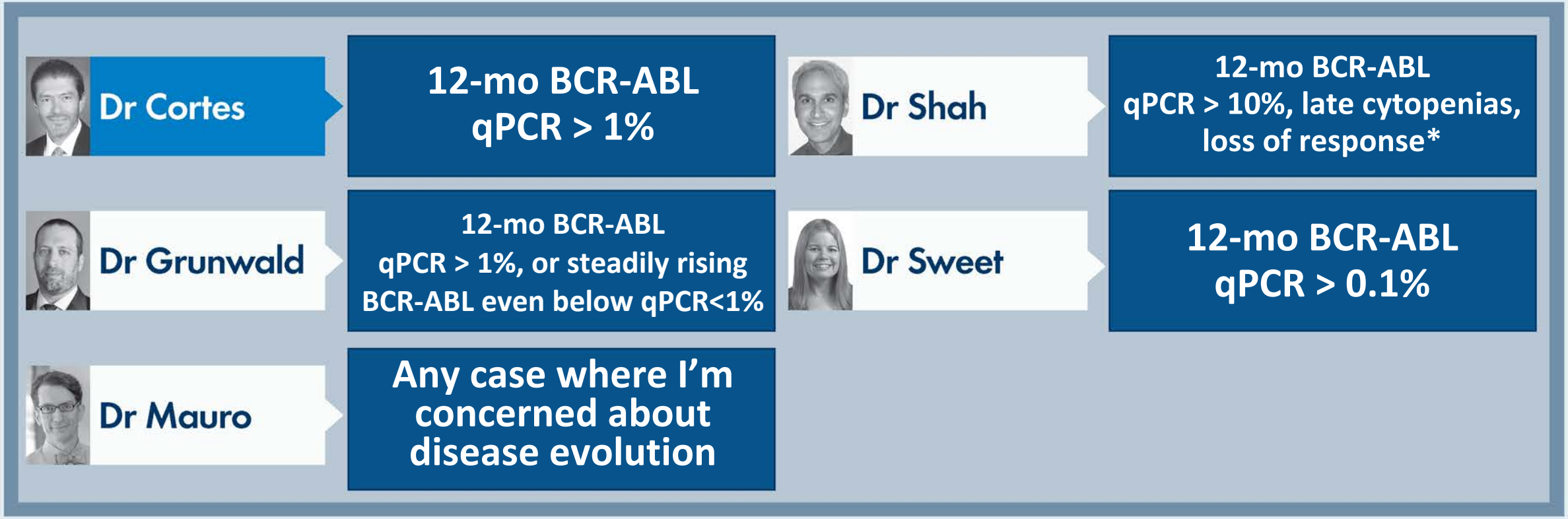
Regulatory and reimbursement issues aside, what initial therapy would you recommend for a 55-year-old woman with Sokal low-risk CML?



Regulatory and reimbursement issues aside, what initial therapy would you recommend for a 55-year-old woman with Sokal high-risk CML?

In general, how frequently do you monitor peripheral blood quantitative PCR in patients who have achieved a major molecular response?

In general, in what situations do you repeat a bone marrow biopsy for a patient who is receiving treatment for chronic-phase CML?



* Loss of hematologic or molecular response, without BCR-ABL1 kinase domain mutation

Case Presentation: A 48-year-old woman with CML in complete molecular response for more than 3 years with nilotinib

Dr Michael Grunwald (Charlotte, North Carolina)

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haematologica
Journal of The Ferrata Storti Foundation

Patient- and physician-reported pain after tyrosine kinase inhibitor discontinuation among patients with chronic myeloid leukemia

by Kathryn E. Flynn, Ehab Atallah, Li Lin, Neil P. Shah, Richard T. Silver, Richard A. Larson, Javier Pinilla-Ibarz, James E. Thompson, Vivian G. Oehler, Jerald P. Radich, Vamsi Kota, Michael J. Mauro, Charles A. Schiffer, Jorge Cortes, and Kevin P. Weinfurt

Haematologica **2022;[Online ahead of print].**

Research

JAMA Oncology | Original Investigation

Assessment of Outcomes After Stopping Tyrosine Kinase Inhibitors Among Patients With Chronic Myeloid Leukemia
A Nonrandomized Clinical Trial

Ehab Atallah, MD; Charles A. Schiffer, MD; Jerald P. Radich, MD; Kevin P. Weinfurt, PhD; Mei-Jie Zhang, PhD; Javier Pinilla-Ibarz, MD; Vamsi Kota, MD; Richard A. Larson, MD; Joseph O. Moore, MD; Michael J. Mauro, MD; Michael W. N. Deininger, MD; James E. Thompson, MD; Vivian G. Oehler, MD; Martha Wadleigh, MD; Neil P. Shah, MD, PhD; Ellen K. Ritchie, MD; Richard T. Silver, MD; Jorge Cortes, MD; Li Lin, MS; Alexis Visotcky, MS; Arielle Baim, BA; Jill Harrell, BS; Bret Helton, BS; Mary Horowitz, MD; Kathryn E. Flynn, PhD

JAMA Oncol 2021;7(1):42-50.

REGULAR ARTICLE

blood advances

Treatment-free remission in patients with chronic myeloid leukemia: recommendations of the LALNET expert panel

Carolina Pavlovsky,[1] Virginia Abello Polo,[2] Katia Pagnano,[3] Ana Ines Varela,[4] Claudia Agudelo,[5] Michele Bianchini,[6] Carla Boquimpani,[7] Renato Centrone,[8] Monica Conchon,[9] Nancy Delgado,[10] Vaneuza Funke,[11] Isabel Giere,[1] Ingrid Luise,[12] Luis Meillon,[10] Beatriz Moiraghi,[4] Juan Ramon Navarro,[13] Lilian Pilleux,[14] Ana Ines Prado,[15] Soledad Undurraga,[16] and Jorge Cortes[17]

Blood Adv 2021;5(23):4855-63.

JNCI J Natl Cancer Inst (2022) 114(1): djab184

doi: 10.1093/jnci/djab184
First published online September 7, 2021
Brief Communication

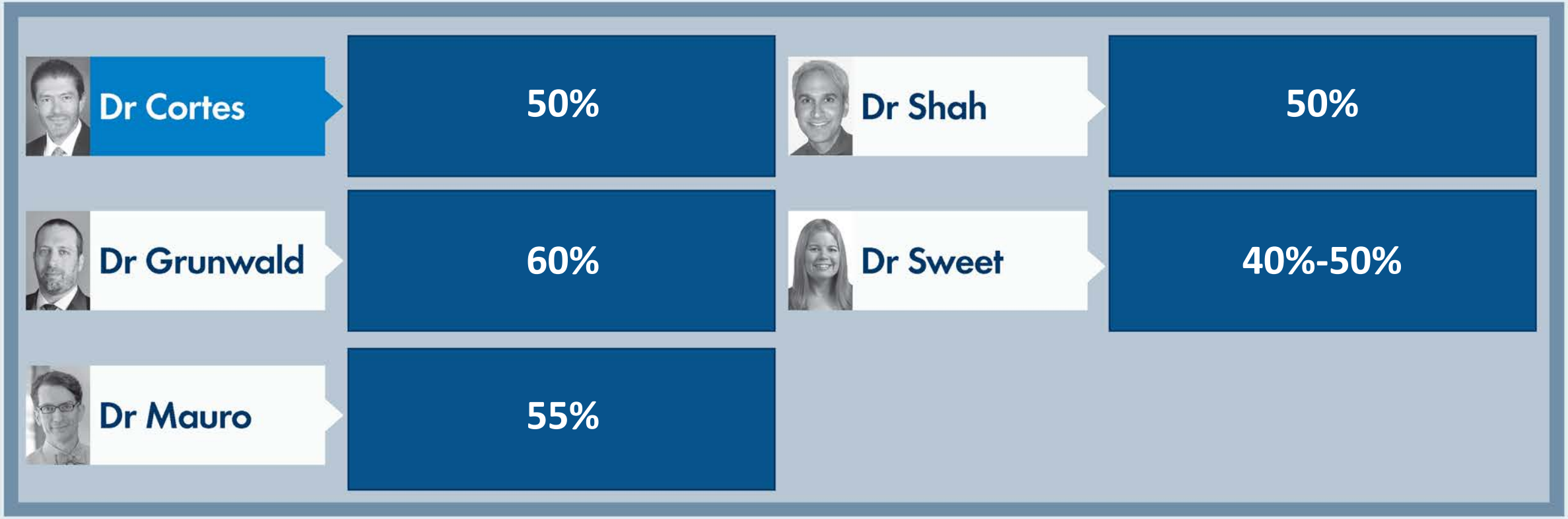
Patient-Reported Functional Outcomes in Patients With Chronic Myeloid Leukemia After Stopping Tyrosine Kinase Inhibitors

Kelly L. Schoenbeck, MD,[1] Ehab Atallah, MD,[2] Li Lin, MS,[3] Kevin P. Weinfurt, PhD,[3] Jorge Cortes, MD,[4] Michael W. N. Deininger, MD, PhD,[5] Vamsi Kota, MD,[4] Richard A. Larson, MD,[6] Michael J. Mauro, MD,[7] Vivian G. Oehler, MD,[8] Javier Pinilla-Ibarz, MD, PhD,[9] Jerald P. Radich, MD,[8] Charles A. Schiffer, MD,[10] Neil P. Shah, MD, PhD,[1] Richard T. Silver, MD,[11] James E. Thompson, MD,[12] Kathryn E. Flynn, PhD[2,*]

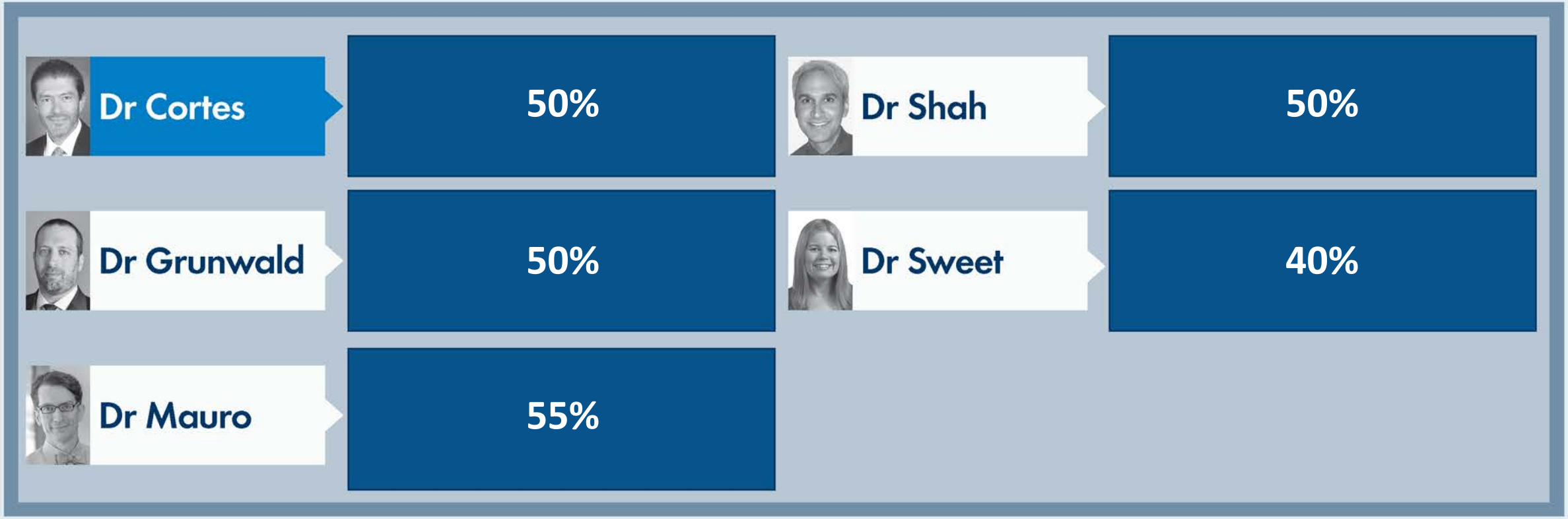
In what situation, if any, would you consider treatment discontinuation for a patient with chronic-phase CML in molecular remission?

 Dr Cortes	MR4.5 for at least 2 y, ideally 6 y
 Dr Grunwald	MR4.5 for at least 2 y
 Dr Mauro	Stable BCR-ABL transcript of <0.01% for 2 y
 Dr Shah	Stable BCR-ABL transcript of <0.01% for 2 y
 Dr Sweet	Stable BCR-ABL transcript of <0.01% for 2 y

What would you estimate to be the likelihood of 2-year disease recurrence for a patient with CML who has discontinued imatinib after achieving a sustained deep molecular response?



What would you estimate to be the likelihood of 2-year disease recurrence for a patient with CML who has discontinued a second-generation TKI after achieving a sustained deep molecular response?



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Case Presentation: A 65-year-old woman with CP-CML and negative BCR-ABL mutational analyses who experiences lack of disease response to several BCR-ABL TKIs

Dr Shams Bufalino (Park Ridge, Illinois)

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Case Presentation: A 41-year-old man with CP-CML who is found to have a T315I mutation

Dr Michael Grunwald (Charlotte, North Carolina)

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Case Presentation: A 41-year-old man with CP-CML who is found to have a T315I mutation (continued)

Dr Michael Grunwald (Charlotte, North Carolina)

Spectrum of BCR-ABL1 Mutations and Their Relationship with TKIs

TKI	Strong Resistance	Mild–Moderate Resistance
Imatinib	Y253–E255–T315	M244–L248–G250–Q252–F317–M351–M355–F359–H396
Dasatinib	T315	V299–F317
Nilotinib	T315	L248–Y253–E255–F359
Bosutinib	T315–V299	L248–G250–E255–F317
Ponatinib		T315–E255
Asciminib	A337–W464–P465–V468–I502	

P-loop mutations: M244, G250, Q252, Y253, and E255; gatekeeper residue (T315 and F317); SH2 contact and C-lobe (M351, F359); activation loop (H396).

De Novellis D et al. *Pharmaceutics* 2021;13(12):2201.

Blood 2018;132(4):393-404.

Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Ponatinib efficacy and safety in Philadelphia chromosome–positive leukemia: final 5-year results of the phase 2 PACE trial

Jorge E. Cortes,[1] Dong-Wook Kim,[2] Javier Pinilla-Ibarz,[3] Philipp D. le Coutre,[4] Ronald Paquette,[5] Charles Chuah,[6] Franck E. Nicolini,[7] Jane F. Apperley,[8] H. Jean Khoury,[9] Moshe Talpaz,[10] Daniel J. DeAngelo,[11] Elisabetta Abruzzese,[12] Delphine Rea,[13] Michele Baccarani,[14] Martin C. Müller,[15] Carlo Gambacorti-Passerini,[16] Stephanie Lustgarten,[17] Victor M. Rivera,[17] Frank G. Haluska,[17] François Guilhot,[18,19] Michael W. Deininger,[20] Andreas Hochhaus,[21] Timothy P. Hughes,[22] Neil P. Shah,[23] and Hagop M. Kantarjian[1]

PACE: Cumulative and Exposure-Adjusted Incidence of Treatment-Emergent AOEs and VTEs in CP-CML (N = 270)

	CP-CML, n = 270	
	AE	SAE
AOEs, n (%)	84 (31)*	69 (26)†
Cardiovascular	42 (16)	33 (12)
Cerebrovascular	35 (13)	28 (10)
Peripheral vascular	38 (14)	31 (11)
Exposure-adjusted AOEs, no. of patients with events per 100 patient-years	14.1	10.9
VTEs, n (%)	15 (6)	13 (5)
Exposure-adjusted VTEs, no. of patients with events per 100 patient-years	2.1	1.8

AOE = arterial occlusive event; VTE = venous thromboembolic event

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

Cortes and Lang *J Hematol Oncol* (2021) 14:44
https://doi.org/10.1186/s13045-021-01055-9

Journal of
Hematology & Oncology

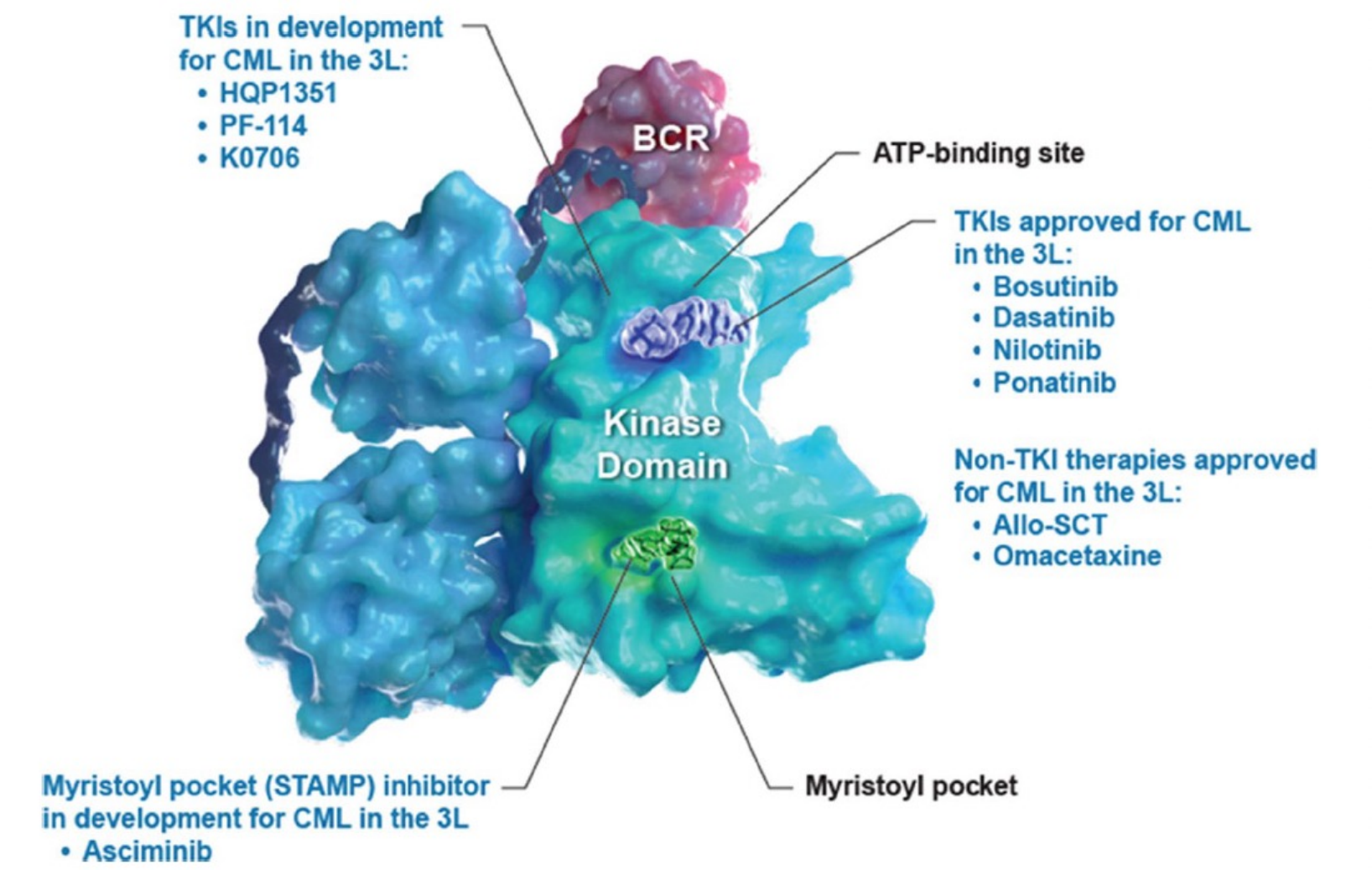
REVIEW

Open Access

Third-line therapy for chronic myeloid leukemia: current status and future directions

Jorge Cortes[1*] and Fabian Lang[2]

Therapies in Development versus Approved Therapies for CML in the Third-Line Setting or Later

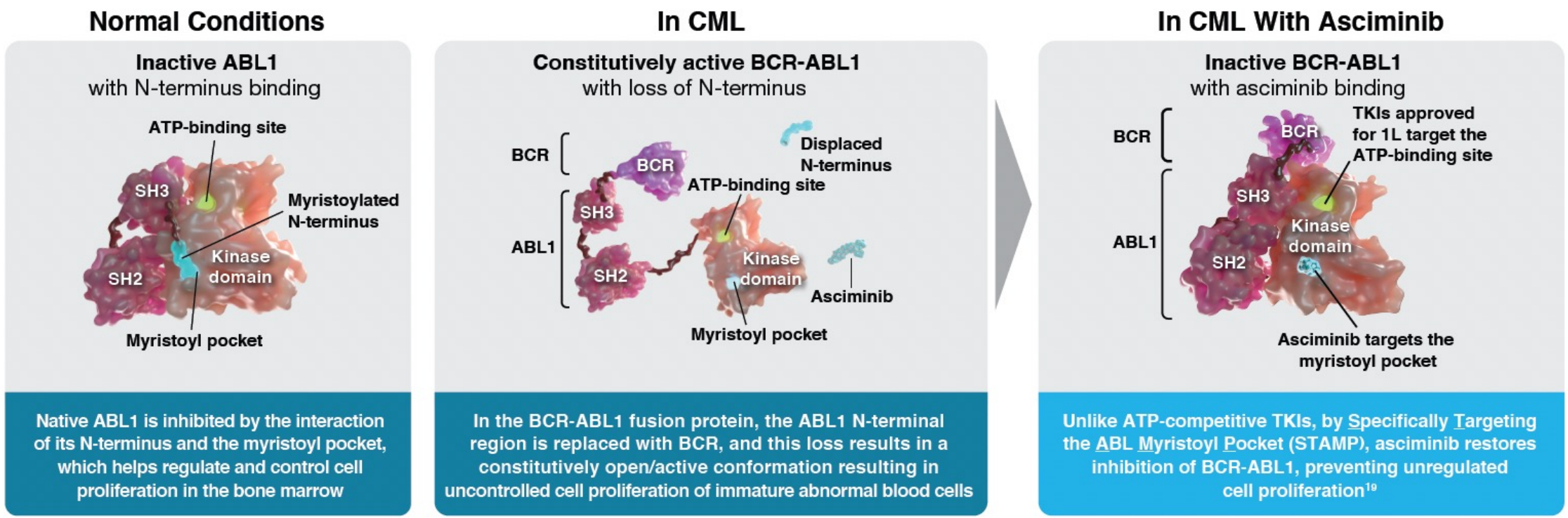


Cortes J, Lang F. *J Hematol Oncol* 2021;14:44.

Asciminib Mechanism of Action

- Asciminib is a potent allosteric inhibitor of BCR-ABL1 that works by Specifically Targeting the ABL Myristoyl Pocket (STAMP)[17-19] (**Figure 1**)
  - The specificity of asciminib is intended to avoid off-target effects from inhibition of other kinases, potentially leading to reduced toxicity

Figure 1. Asciminib Specifically Targets the ABL Myristoyl Pocket (STAMP)



Cortes J et al. ASH 2021;Abstract 1478.

RTP RESEARCH TO PRACTICE

FDA Approves Asciminib for Philadelphia Chromosome-Positive Chronic Myeloid Leukemia

Press Release: October 29, 2021

"On October 29, 2021, the Food and Drug Administration granted accelerated approval to asciminib for patients with Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP), previously treated with two or more tyrosine kinase inhibitors (TKIs), and approved asciminib for adult patients with Ph+ CML in CP with the T315I mutation.

ASCEMBL (NCT03106779), a multi-center, randomized, active-controlled, open-label clinical trial, is evaluating asciminib in patients with Ph+ CML in CP, previously treated with two or more TKIs. A total of 233 patients were randomized (2:1) and stratified according to major cytogenetic response (MCyR) status to receive either asciminib 40 mg twice daily or bosutinib 500 mg once daily. Patients continued treatment until unacceptable toxicity or treatment failure occurred.

CABL001X2101 (NCT02081378), a multi-center, open-label clinical trial, is evaluating asciminib in patients with Ph+ CML in CP with the T315I mutation. Efficacy was based on 45 patients with the T315I mutation who received asciminib 200 mg twice daily. Patients continued treatment until unacceptable toxicity or treatment failure occurred."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-asciminib-philadelphia-chromosome-positive-chronic-myeloid-leukemia

Efficacy and Safety Results From ASCEMBL, a Phase 3 Study of Asciminib vs Bosutinib in Patients With Chronic Myeloid Leukemia in Chronic Phase After ≥2 Prior Tyrosine Kinase Inhibitors: Week 96 Update

Presenter: Jorge E. Cortes

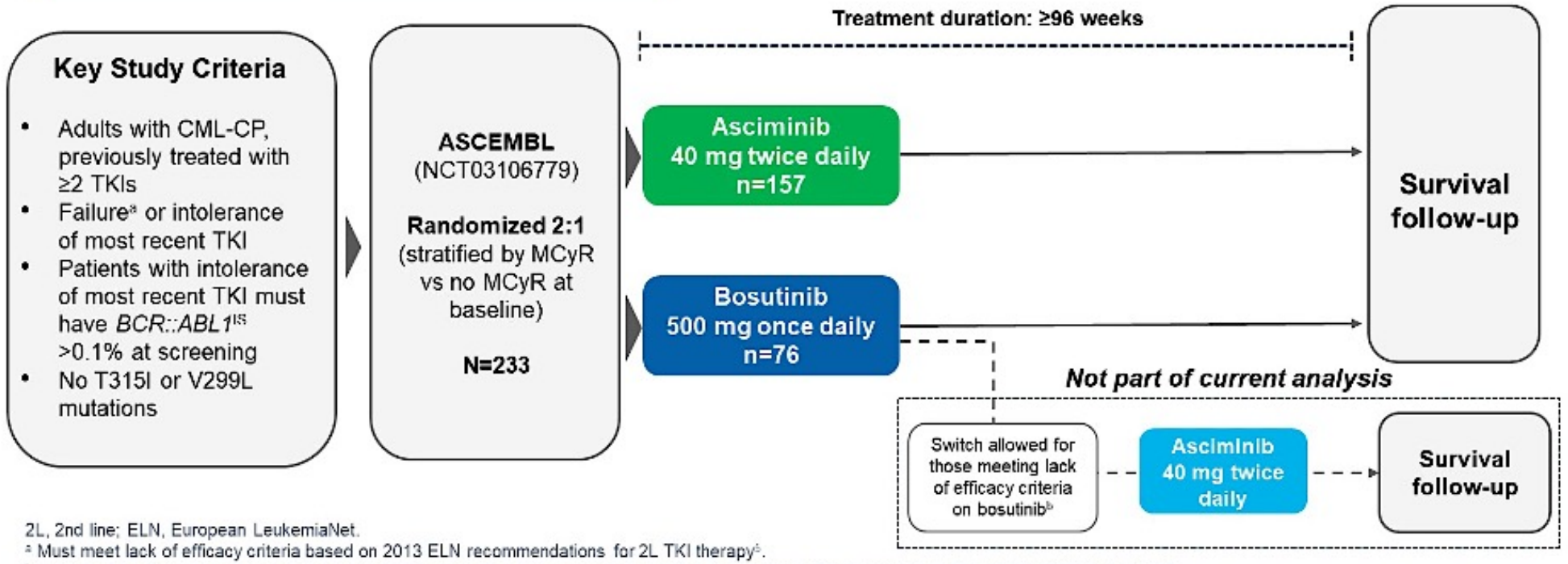
Delphine Réa,[1] Michael J. Mauro,[2] Andreas Hochhaus,[3] Carla Boquimpani,[4] Elza Lomaia,[5] Sergey Voloshin,[6] Anna Turkina,[7] Dong-Wook Kim,[8] Jane F. Apperley,[9] Jorge E. Cortes,[10] Koji Sasaki,[11] Shruti Kapoor,[12] Alex Allepuz,[13] Sara Quenet,[13] Véronique Bédoucha,[13] Yosuke Minami[14]

Oral presentation at: 2022 ASCO Annual Meeting; June 3-7, 2022; Chicago, IL, & online

ASCO 2022;Abstract 7004.

ASCEMBL Phase III Study Design

- **Data cutoff for current analysis:** October 6, 2021
- **Median duration of follow-up:** 2.3 years (120 weeks) from randomization to last contact date
- **Primary endpoint:** MMR rate at week 24
- **Key secondary endpoint:** MMR rate at week 96

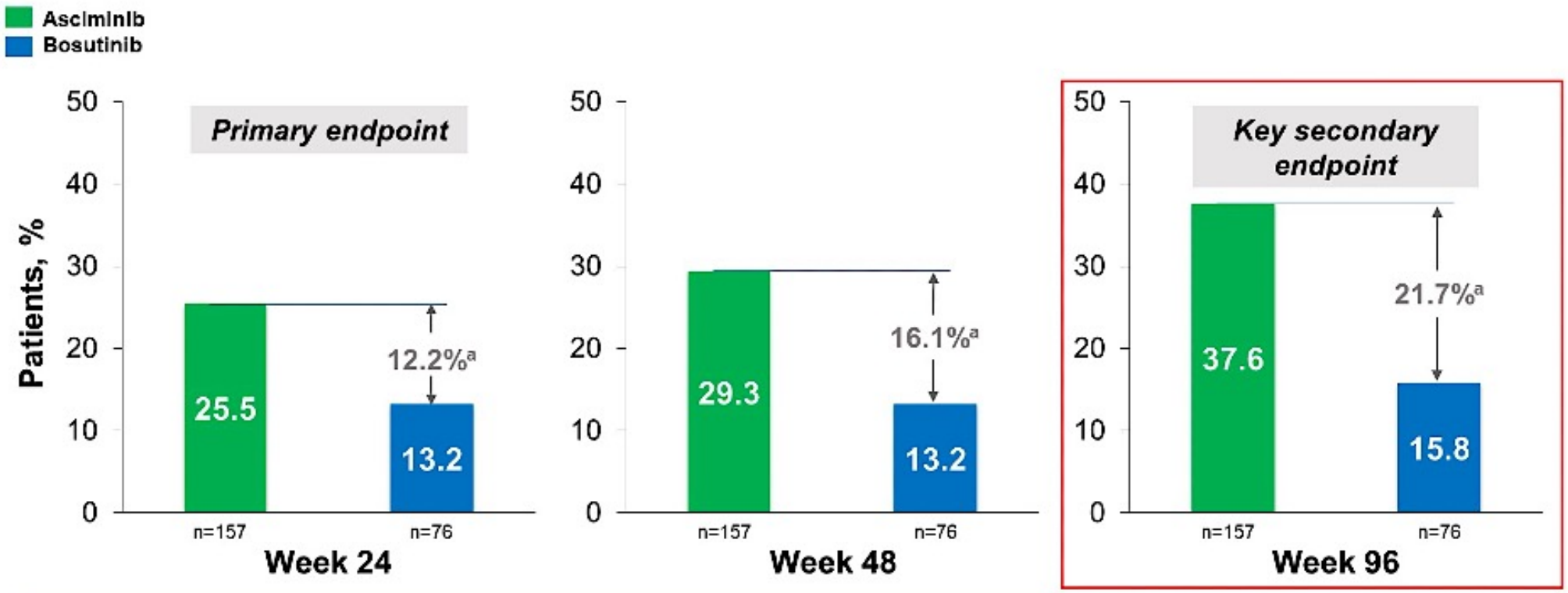


2L, 2nd line; ELN, European LeukemiaNet.
[a] Must meet lack of efficacy criteria based on 2013 ELN recommendations for 2L TKI therapy[5].
[b] Patients who discontinued bosutinib treatment due to intolerance or any reason other than lack of efficacy were *not* allowed to switch to asciminib.

Oral presentation at: 2022 ASCO Annual Meeting; June 3-7, 2022; Chicago, IL, & online

Réa D et al. ASCO 2022;Abstract 7004.

ASCEMBL Primary Endpoint: MMR Rate at Weeks 24, 48 and 96



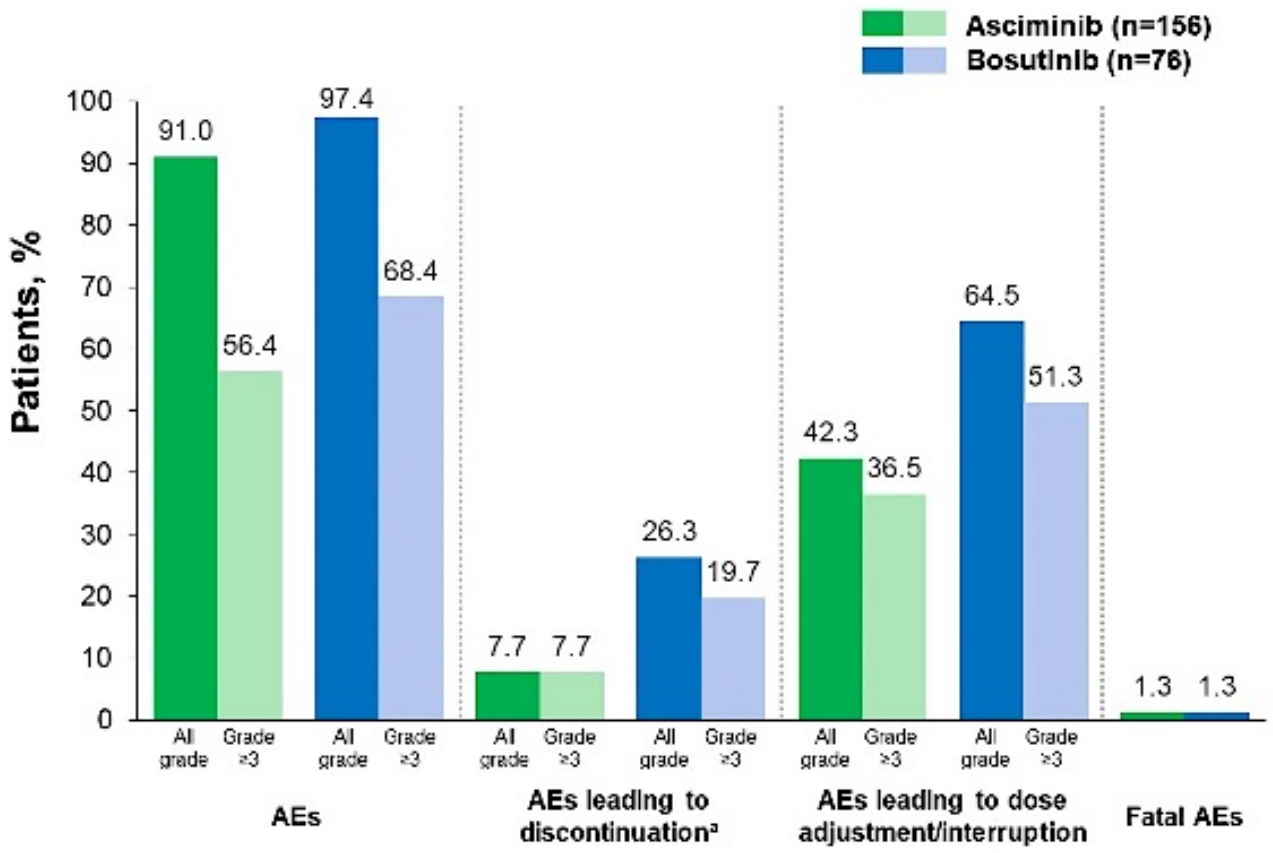
- The MMR rate with asciminib increased consistently over time suggesting the long-term benefit of continuing treatment with asciminib

[a] The treatment difference after adjusting for baseline MCyR status was 12.24% (95% CI, 2.19%-22.30%; 2-sided *P*=0.029) at week 24, 16.09% (95% CI, 5.69%-26.49%; 2-sided *P*=0.007) at week 48, and 21.74% (95% CI: 10.53%-32.95%; 2-sided *P*=0.001) at week 96.

Oral presentation at: 2022 ASCO Annual Meeting; June 3-7, 2022; Chicago, IL, & online

Réa D et al. ASCO 2022;Abstract 7004.

ASCEMBL: Overview of Adverse Events (AEs)



- Median duration of exposure:
  - **23.7 months** (range, 0.0-46.2 months) for **asciminib**
  - **7.0 months** (range, 0.2-43.3 months) for **bosutinib**
- Safety and tolerability of asciminib continued to be better than with bosutinib
  - No new or worsening safety findings
  - No on-treatment deaths in either arm since the primary analysis cutoff
- Most common AEs leading to treatment discontinuation did not change since the primary analysis:
  - Thrombocytopenia **(3.2%)** and neutropenia **(2.6%)** with **asciminib**
  - Increased ALT **(5.3%)** and neutropenia **(3.9%)** with **bosutinib**

ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a] Grade 1/2 AEs leading to discontinuation with bosutinib (n=5) included ALT/AST level increased, blood creatinine level increased, diarrhea, drug eruption, and pleural effusion.

Oral presentation at: 2022 ASCO Annual Meeting; June 3-7, 2022; Chicago, IL, & online

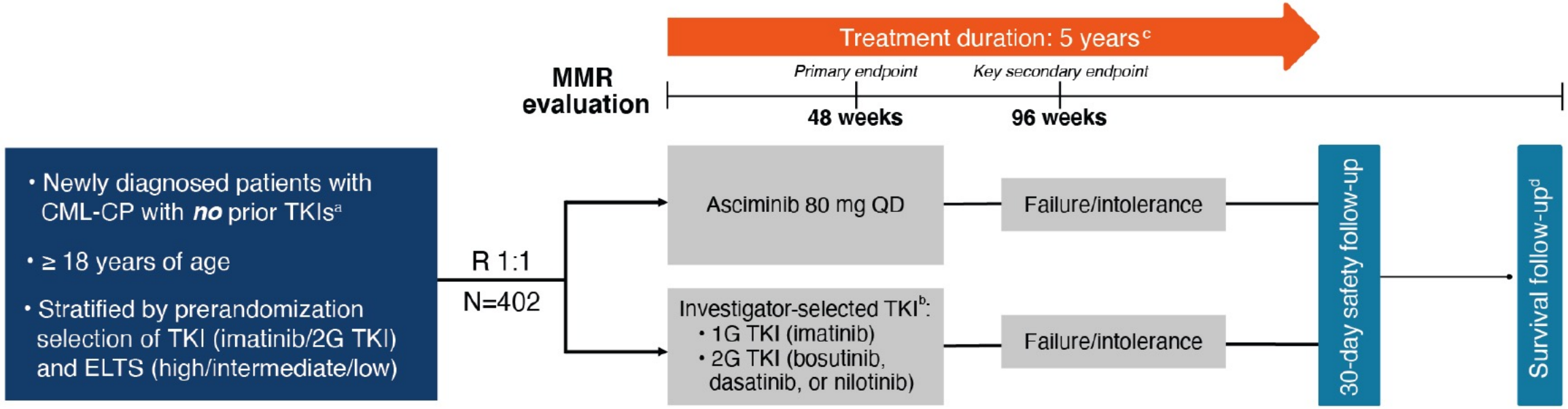
Réa D et al. ASCO 2022;Abstract 7004.

Trial in Progress: A Phase III Study of Asciminib vs an Investigator-Selected TKI in Patients with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP)

Hughes T et al.

EHA 2022;Abstract PB1904.

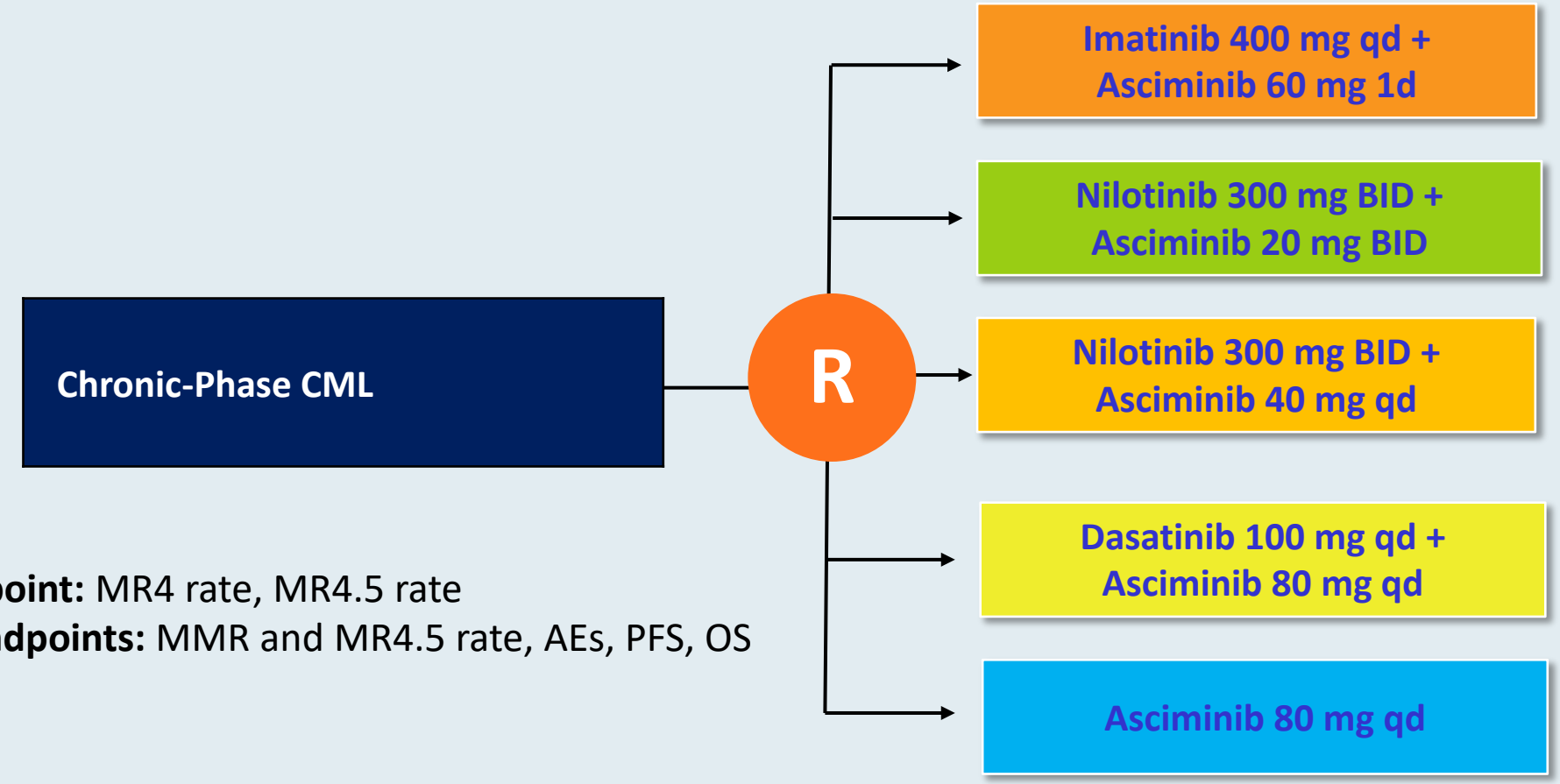
Schema of a Phase III Trial of Asciminib versus TKI for Newly Diagnosed CP-CML



1G, 1st generation; 2G, 2nd generation; CML-CP, chronic myeloid leukemia in chronic phase; ELTS, EUTOS long-term survival; EUTOS, European Treatment and Outcome Study; IS, International Scale; MMR, major molecular response (*BCR::ABL1*^{IS} ≤0.1%); QD, once daily; R, randomized; TKI, tyrosine kinase inhibitor.
[a] Only imatinib therapy ≤2 weeks is allowed. [b] The investigator-selected TKI treatment group will be distributed evenly between patients prerandomized to either 1G TKI or 2G TKI at their approved dose, with dose modifications for intolerance allowed at the investigator's discretion and in accordance with local labels.
[c] Patients will remain on study for 5 years after the last patient's 1st dose, unless they have discontinued early due to treatment failure, disease progression, intolerance, or investigator or patient decision. [d] Patients who discontinue early will continue to be followed up for survival and disease progression until the end of the study.

Hughes T et al. *EHA* 2022;Abstract PB1904.

FASCINATION (CMLXI) Phase II Study Design



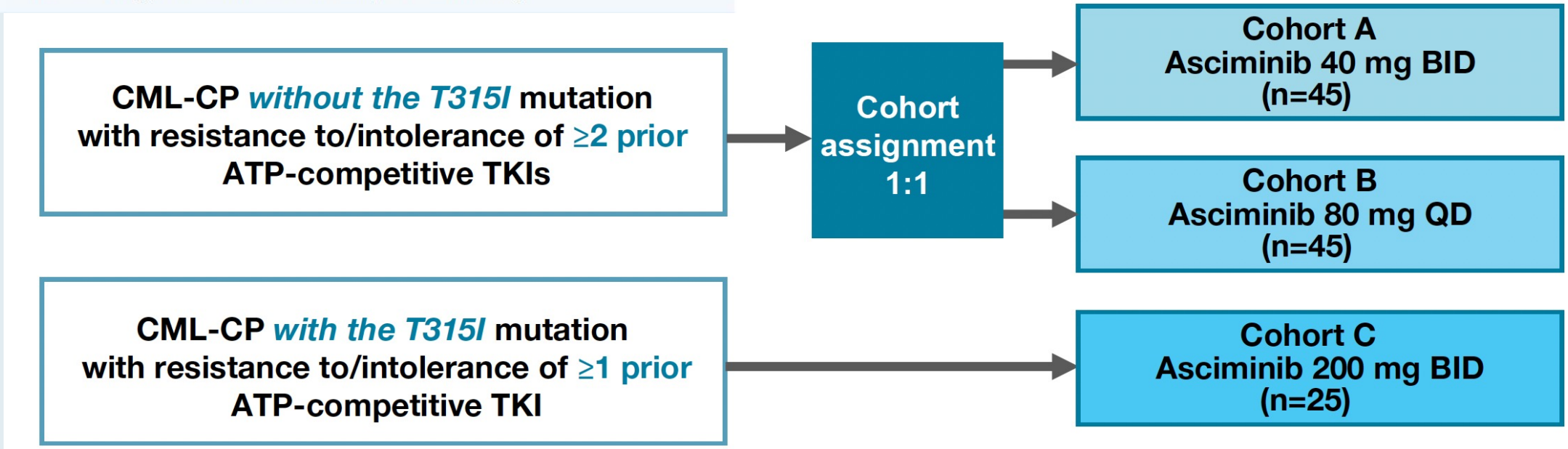
Primary endpoint: MR4 rate, MR4.5 rate
Secondary endpoints: MMR and MR4.5 rate, AEs, PFS, OS

www.clinicaltrials.gov. NCT03906292. Accessed May 2022.

AIM4CML Phase IIIb Study Design

Key inclusion criteria
Adults (≥18 years of age) with a diagnosis of CML-CP
Prior treatment with ≥2 ATP-competitive TKIs in patients without the T315I mutation ***or*** ≥1 ATP-competitive TKI in patients with the T315I mutation
Treatment failure (adapted from the 2020 ELN recommendations) with or intolerance of the most recent TKI at screening
Evidence of typical *BCR-ABL1* transcripts at screening

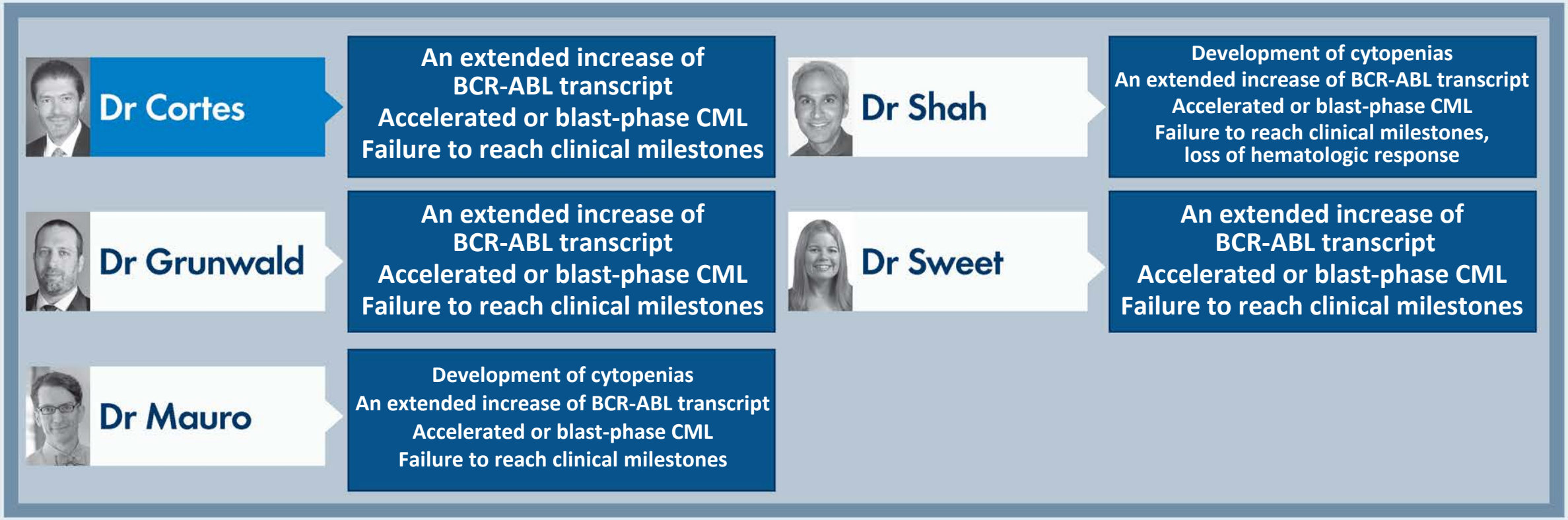
Primary Objective	• Evaluate the safety profile of asciminib monotherapy in patients in the 3L and beyond (3L+) in cohorts A and B for 24 weeks
Secondary Objectives	• Evaluate the safety profile of asciminib monotherapy in cohorts A, B, and C for 48 and 72 weeks • Estimate hematologic response and MR rates by specific time points • Estimate time to and duration of hematologic response and MR • Assess progression-free survival and overall survival during 72 weeks



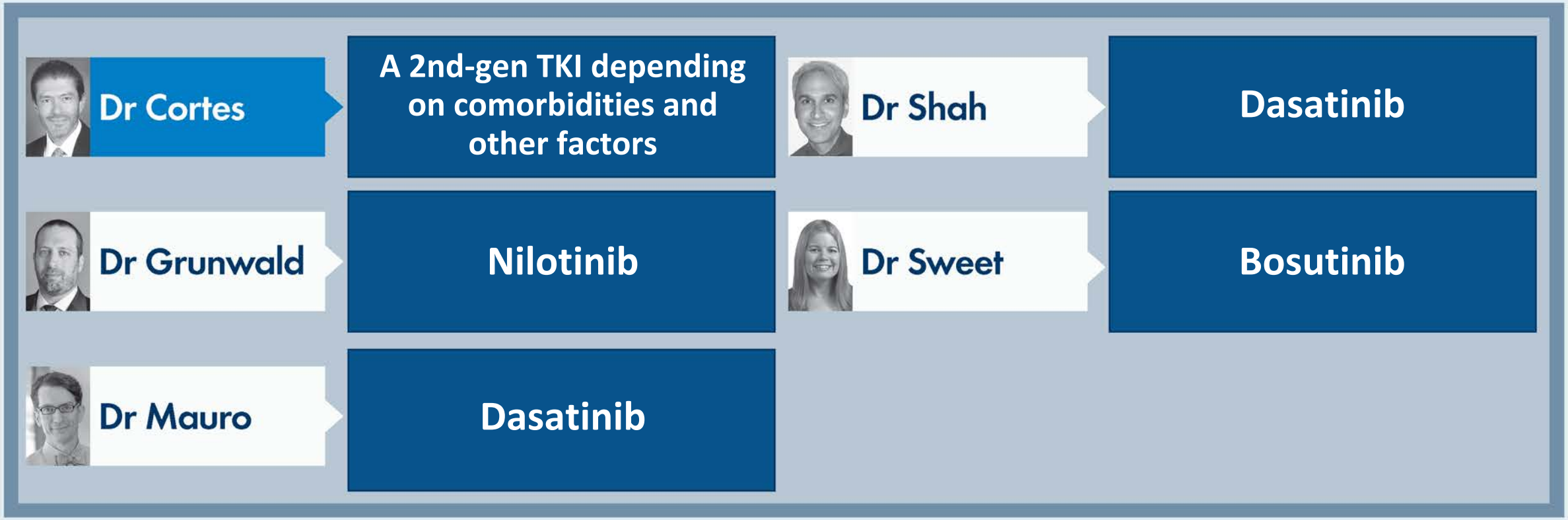
Andorsky D et al. ASH 2021;Abstract 3599.

RTP RESEARCH TO PRACTICE

What is an indication for evaluating resistance in a patient with chronic-phase CML who initially responds well to imatinib therapy?



Regulatory and reimbursement issues aside, what second-line treatment would you recommend for a patient with chronic-phase CML who achieves a major molecular response with imatinib and experiences disease progression without evidence of BCR-ABL kinase domain mutation?



RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, what second-line treatment would you recommend for a patient with chronic-phase CML who achieves a major molecular response with a second-generation TKI and experiences disease progression without evidence of a BCR-ABL kinase domain mutation?

 Dr Cortes	Ponatinib	 Dr Shah	Ponatinib
 Dr Grunwald	Switch to a different 2nd-gen TKI	 Dr Sweet	Ponatinib
 Dr Mauro	Ponatinib or asciminib		

RTP RESEARCH TO PRACTICE

What third-line treatment would you recommend for a 65-year-old patient with chronic-phase CML who received imatinib for 3 years with disease progression followed by dasatinib with further disease progression after 18 months and no evidence of a BCR-ABL kinase domain mutation?

RTP RESEARCH TO PRACTICE

Based on current clinical trial data and your personal experience, how would you compare the efficacy of asciminib to the TKIs that are currently approved as first-line treatment for chronic-phase CML?

 Dr Cortes	Asciminib is more efficacious	 Dr Shah	About the same
 Dr Grunwald	I'm not sure	 Dr Sweet	I'm not sure
 Dr Mauro	I'm not sure		

Based on current clinical trial data and your personal experience, how would you compare the efficacy of asciminib to the TKIs that are currently approved as second-line treatment for chronic-phase CML?

 Dr Cortes	Asciminib is more efficacious	 Dr Shah	About the same
 Dr Grunwald	I'm not sure	 Dr Sweet	About the same
 Dr Mauro	Asciminib is more efficacious		

What second-line therapy would you recommend for a 75-year-old patient with chronic-phase CML who develops resistance to imatinib and is found to have a T315I mutation?

Based on available clinical data and your personal experience, in general, how would you compare the tolerability of asciminib to that of the second-generation TKIs?

RTP RESEARCH TO PRACTICE

Meet The Professor with Dr Cortes

Introduction: Journal Club with Dr Cortes

MODULE 1: Case Presentations

- Dr McKenna: A 42-year-old man with CML and osteopenia after long-term imatinib therapy
- Dr Bank: A 60-year-old man with CP-CML and continued detectable BCR-ABL transcript on bosutinib
- Dr Chen: A 70-year-old man with chronic-phase CML (CP-CML) and notable toxicities from several BCR-ABL tyrosine kinase inhibitors (TKIs)
- Dr Grunwald: A 48-year-old woman with CML in complete molecular response for more than 3 years with nilotinib
- Dr Bufalino: A 65-year-old woman with CP-CML and negative BCR-ABL mutational analyses who experiences lack of disease response to several BCR-ABL TKIs
- Dr Grunwald: A 41-year-old man with CP-CML who is found to have a T315I mutation

MODULE 2: Appendix of Key Recent Data Sets

Front-Line Management of CML

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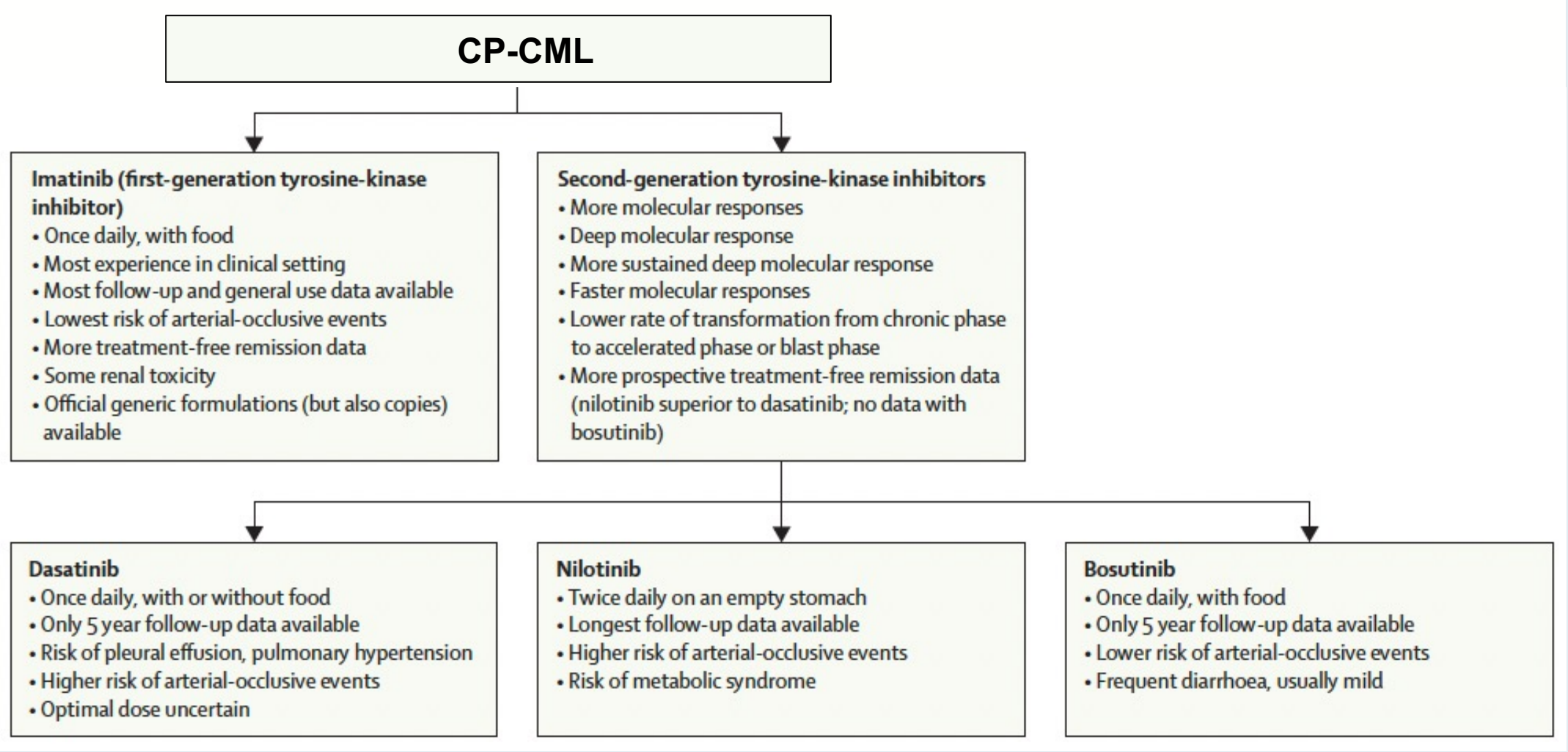
Considerations for Selection of Initial Therapy for Chronic-Phase (CP) CML



Adapted from Cortes J et al. *Lancet* 2021;398:1914-26.

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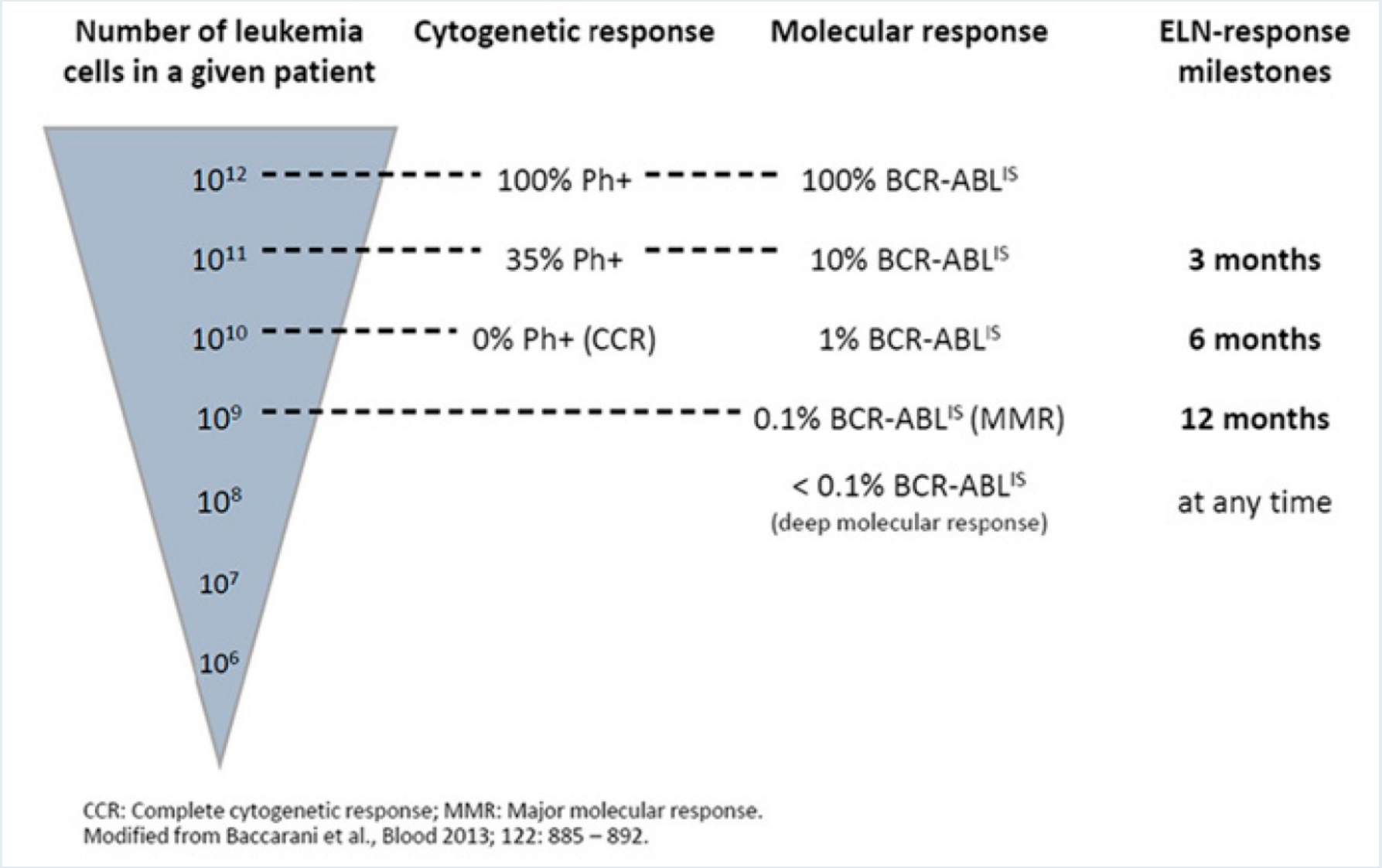
Risk Stratification Prognostic Scoring Systems

	Sokal[1]	Hasford (Euro)[2]	EUTOS[3]	EUTOS long-term (ELTS)[4]
Year introduced	1984	1998	2011	2016
Predominant treatment modality	Conventional chemotherapy	IFN-alpha-based regimens	Imatinib	Imatinib
Factors	• Age • Spleen size • Platelet count • % blasts	• Age • Spleen size • Platelet count • % blasts • % basophils • % eosinophils	• Spleen size • Basophil count	• Age • Spleen size • Platelet count • Blasts in peripheral blood
Risk group	• High: score >1.2 • Intermediate: score 0.8-1.2 • Low: score <0.8	• High: score >1,480 • Intermediate: score >780 and ≤1,480 • Low: score ≤780	• High: score >87 • Low: score ≤87	• High: score >2.2185 • Intermediate: score >1.5680 and ≤2.2185 • Low: score ≤1.5680

[1] Sokal J et al. *Blood* 1984;63:789-99; [2] Hasford J et al. *J Natl Cancer Inst* 1998;90;850-8; [3] Hasford J et al. *Blood* 2011;118:686-92.
[4] Pfirrman M et al. *Leukemia* 2016;30:48-56.

RTP RESEARCH TO PRACTICE

Correlation of Cytogenetic and Molecular Data with Leukemia Cell Mass and Response Milestones



Khoury HJ et al. ASCO 2017 Education Book.

Response Criteria and Equivalence by Log Reduction

	Approximate complete response equivalent	Molecular response	*BCR-ABL1* transcript levels in the International Scale	Undetectable transcripts (minimum number of copies of reference gene)
Baseline	..	..	100%	..
1·0 log	PCyR	..	≤10%	..
2·0 log	CCyR	..	≤1%	..
3·0 log	..	Major molecular response	≤0·1 %	..
4·0 log	..	Molecular response 4·0	≤0·01%	≥10 000 *ABL* (≥24 000 *GUSB*)
4·5 log	..	Molecular response 4·5	≤0·0032%	≥32 000 *ABL* (≥77 000 *GUSB*)
5·0 log	..	Molecular response 5·0	≤0·001%	≥100 000 *ABL* (≥240 000 *GUSB*)

CCyR=complete cytogenetic response. PCyR=partial cytogenetic response. *Log reduction is calculated in relation to a standardised baseline.

Cortes J et al. *Lancet* 2021;398:1914-26.

RTP RESEARCH TO PRACTICE

Early Treatment Response Milestones

BCR-ABL1 (IS)	3 months	6 months	12 months[l]
>10%[m]	YELLOW	RED	
>1%–10%	GREEN		YELLOW
>0.1%–1%	GREEN		LIGHT GREEN
≤0.1%	GREEN		

COLOR	CONCERN	CLINICAL CONSIDERATIONS	RECOMMENDATIONS
RED	TKI-resistant disease	• Evaluate patient compliance and drug interactions • Consider mutational analysis	Switch to alternate TKI (CML-5) and evaluate for allogeneic HCT
YELLOW	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 (CML-5) or Continue same TKI (other than imatinib) (CML-G)[n] or Increase imatinib dose to a max of 800 mg and Consider evaluation for allogeneic HCT
LIGHT GREEN	TKI-sensitive disease	• 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 patient[o,p]
GREEN	TKI-sensitive disease	• Monitor response (CML-E) and side effects	Continue same TKI (CML-G)[q]

NCCN® Guidelines, Chronic Myeloid Leukemia v3.2022

Monitoring Response to Tyrosine Kinase Inhibitor Therapy and Mutational Analysis

Test	Recommendation
Bone marrow cytogenetics[1]	• At diagnosis • Failure to reach response milestones • Any sign of loss of hematologic response • Any sign of loss of CCyR or its molecular response correlate defined as an increase in *BCR-ABL1* transcript to >1%
qPCR using IS	• At diagnosis • Every 3 months after initiating treatment. After *BCR-ABL1* (IS) ≤1%[2] has been achieved, every 3 months for 2 years and every 3–6 months thereafter • If there is a 1-log increase in *BCR-ABL1* transcript levels with MMR, qPCR should be repeated in 1–3 months
BCR-ABL1 kinase domain mutation analysis	• Chronic phase ▸ Failure to reach response milestones ▸ Any sign of loss of hematologic response ▸ Any sign of loss of CCyR or its molecular response correlate 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 accelerated or blast phase[3]

NCCN Guidelines, Chronic Myeloid Leukemia, v3.2022

Key Studies of Second-Generation TKIs as First-Line Therapy

Endpoint	DASISION (N = 519)		ENESTnd (N = 846)		BFORE (N = 536)	
	Dasatinib	Imatinib	Nilotinib	Imatinib	Bosutinib	Imatinib
BCR-ABL ≤10% at 3 mo	84%	64%	91%	67%	75%	57%
CCyR at 12 mo	83%	72%	80%	65%	77%	66%
MMR at 12 mo	46%	28%	44%	22%	47%	37%
Treatment discontinuation by 24 mo	23%	25%	26%	33%	29%	34%
Transformation to accelerated or blast phase at 24 mo	3.5%	5.8%	0.7%	4.2%	2.2%	2.6%

CCyR = complete cytogenetic response; MMR = major molecular response

Cortes J et al. *Lancet* 2021; 398:1914-26. Cortes JE et al. *J Clin Oncol* 2016;34:2333-40. Hochhaus A et al. *Leukemia* 2016;30:1044-54. Cortes JE et al. *J Clin Oncol* 2018;36:231-7.

Overview of Adverse Drug Reactions Associated with Tyrosine Kinase Inhibitors Approved for CML

	Imatinib[9]	Nilotinib[32]	Dasatinib[33]	Bosutinib[34]	Ponatinib[35]
Myelosuppression	++	+	+++	+	++
Fluid Retention	++	—	+++	—	—
Rash	+	++	—	—	++
Diarrhea	+	+	+	+++	+
Increased Glucose/Cholesterol	—	++	—	—	—
Vascular Occlusion	—	++	+	—	+++
Renal Insufficiency	+	—	(+)	?	?

Khoury HJ et al. ASCO 2017 Education Book.

Leukemia (2021) 35:440–453
https://doi.org/10.1038/s41375-020-01111-2

ARTICLE

Chronic myelogenous leukemia

Long-term outcomes with frontline nilotinib versus imatinib in newly diagnosed chronic myeloid leukemia in chronic phase: ENESTnd 10-year analysis

Hagop M. Kantarjian[1] · Timothy P. Hughes[2,3] · Richard A. Larson[4] · Dong-Wook Kim[5] · Surapol Issaragrisil[6] · Philipp le Coutre[7] · Gabriel Etienne[8] · Carla Boquimpani[9,10] · Ricardo Pasquini[11] · Richard E. Clark[12] · Viviane Dubruille[13] · Ian W. Flinn[14] · Slawomira Kyrcz-Krzemien[15] · Ewa Medras[16] · Maria Zanichelli[17] · Israel Bendit[18] · Silvia Cacciatore[19] · Ksenia Titorenko[20] · Paola Aimone[19] · Giuseppe Saglio[21] · Andreas Hochhaus[22]

ENESTnd: 10-Year Efficacy and Safety

Efficacy	Nilotinib 300 mg twice daily	Nilotinib 400 mg twice daily	Imatinib 400 mg once daily
MMR by 10 years	77.7%	79.7%	62.5%
MR4.5 by 10 years	69.5%	68.3%	49.5%
TFR eligibility rate	48.6%	47.3%	29.7%
Freedom from progression to AP/BP at 10 years	97.7%	98.5%	95.5%
Estimated 10-year OS (All)* <60 years old	87.6% 92.7%	90.3% 94.5%	88.3% 89.7%
Estimated 10-year PFS*	86.2%	89.9%	87.2%
Safety			
Cumulative cardiovascular event rate	16.5%	23.5%	3.6%

TFR = treatment-free eligibility
* Not significantly different from imatinib

Kantarjian HM et al. *Leukemia* 2021;35:440-53.

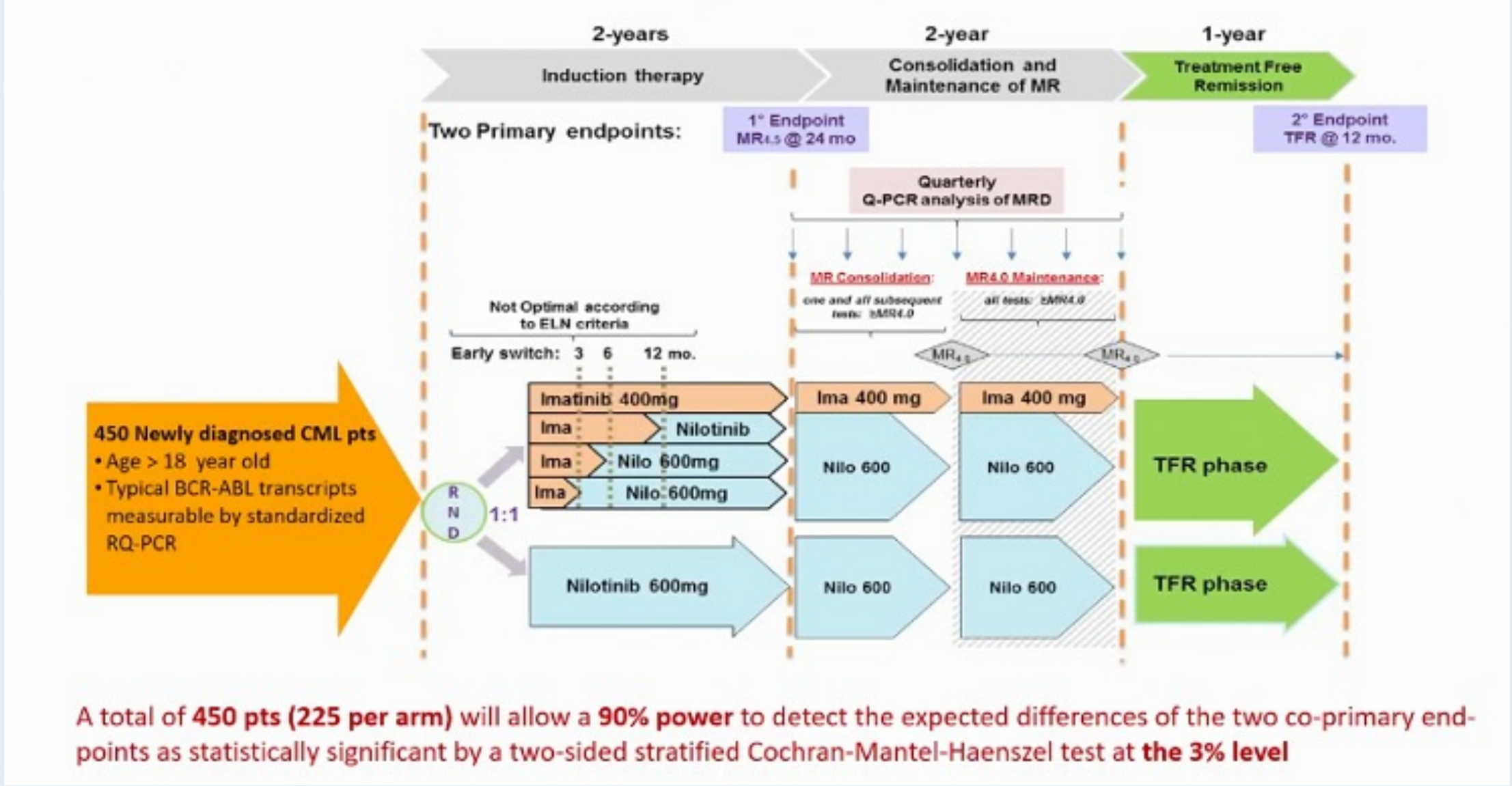
RTP RESEARCH TO PRACTICE

International, Prospective Study Comparing Nilotinib versus Imatinib with Early Switch to Nilotinib to Obtain Sustained Treatment-Free Remission in Patients with Chronic Myeloid Leukemia

Pane F et al.

EHA 2022;Abstract S156.

SUSTRENIM Study Design



A total of **450 pts (225 per arm)** will allow a **90% power** to detect the expected differences of the two co-primary end-points as statistically significant by a two-sided stratified Cochran-Mantel-Haenszel test at **the 3% level**

Pane F et al. EHA 2022;Abstract S156.

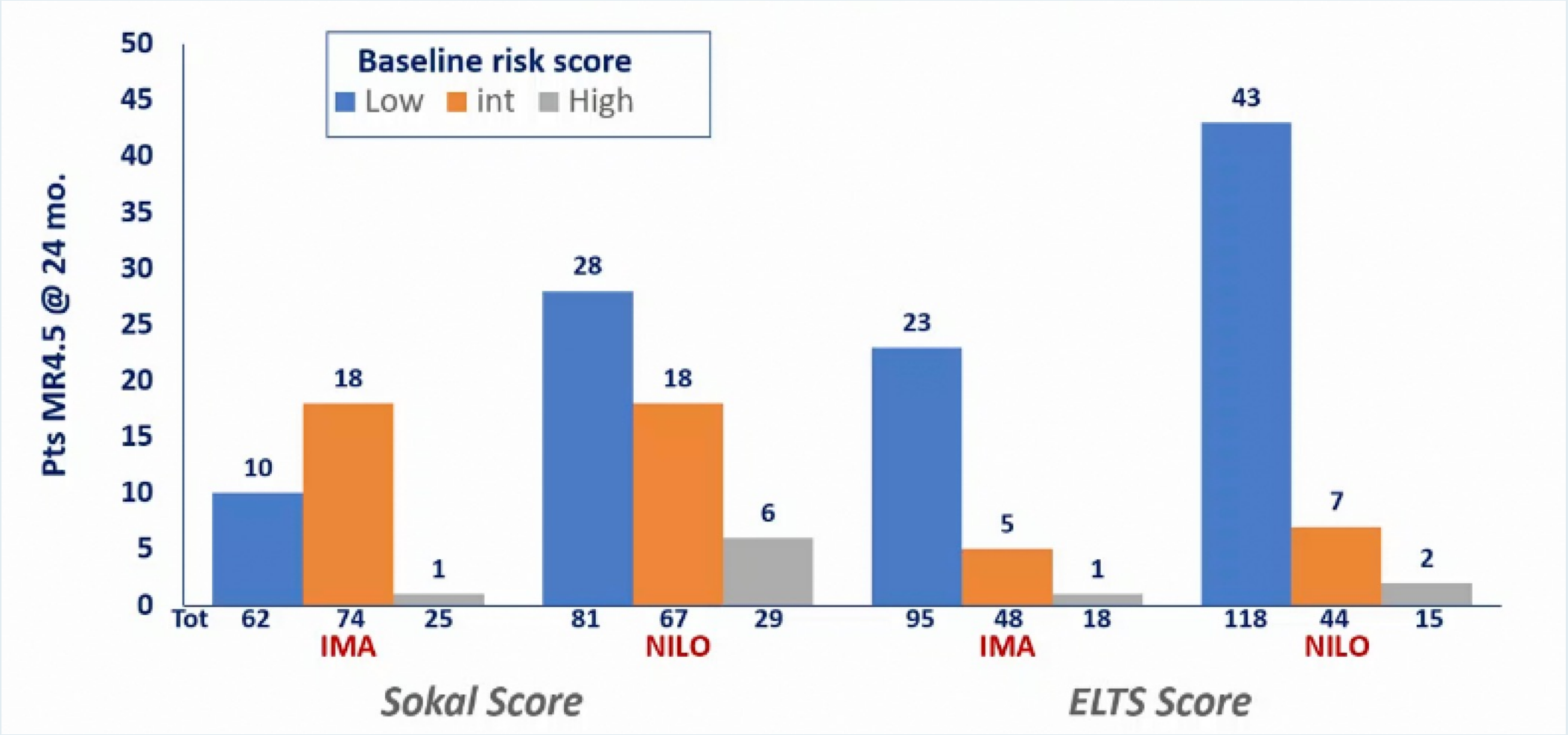
RTP RESEARCH TO PRACTICE

SUSTRENIM Primary Endpoint: MR4.5 Rate at 24 Months of Treatment

	n. of pts @24 mo. (n)	*MR4.5 (n, %)*		*Chi-square*
Imatinib arm	161	29	18.0%	P=0.0156
Nilotinib arm	177	52	29.4%	
Total cohort	339	81	23.9%	

Pane F et al. EHA 2022;Abstract S156.

SUSTRENIM: MR4.5 Rate at 24 Months of Treatment According to Treatment Arm and Risk Score



Pane F et al. EHA 2022;Abstract S156.

SUSTRENIM: Preliminary Conclusions

- The enrollment into the study has been completed in October 2020 (n=450 patients) and the median follow-up of the patients is around 32 mo.
- Nilo appears to be more effective than Ima to reach DMR at 24 mo. even when systematic early switching to Nilo has been applied in case of non optimal response to the Ima treated patients
- The efficacy of Nilo is prominent in the low baseline risk patients, particularly when ELTS score has been used
- We expect that further follow-up will contribute to answer the questions:
  - **Percentage of newly diagnosed** CML patients who have a successful **TFR**
  - **Appropriate treatment strategy** to achieve an higher rate of **TFR**

Pane F et al. EHA 2022;Abstract S156.

ARTICLE OPEN

CHRONIC MYELOGENOUS LEUKEMIA

Bosutinib versus imatinib for newly diagnosed chronic phase chronic myeloid leukemia: final results from the BFORE trial

Tim H. Brümmendorf[1,19]✉, Jorge E. Cortes[2,19], Dragana Milojkovic[3], Carlo Gambacorti-Passerini[4], Richard E. Clark[5], Philipp le Coutre[6], Valentin Garcia-Gutierrez[7], Charles Chuah[8], Vamsi Kota[2], Jeffrey H. Lipton[9], Philippe Rousselot[10], Michael J. Mauro[11], Andreas Hochhaus[12], Rafael Hurtado Monroy[13], Eric Leip[14], Simon Purcell[15], Anne Yver[16], Andrea Viqueira[17], Michael W. Deininger[18] and BFORE study investigators

***Leukemia* 2022;[Online ahead of print].**

Adherence to Treatment

VOLUME 28 · NUMBER 14 · MAY 10 2010

JOURNAL OF CLINICAL ONCOLOGY

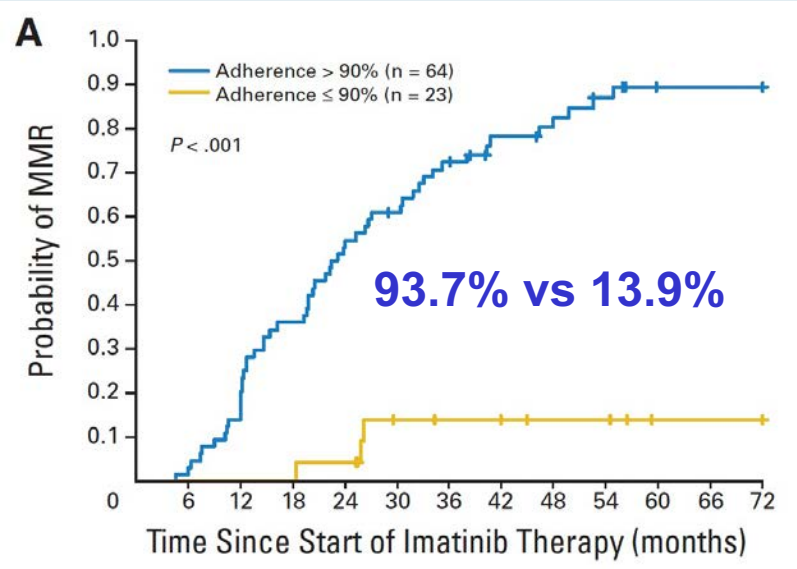
ORIGINAL REPORT

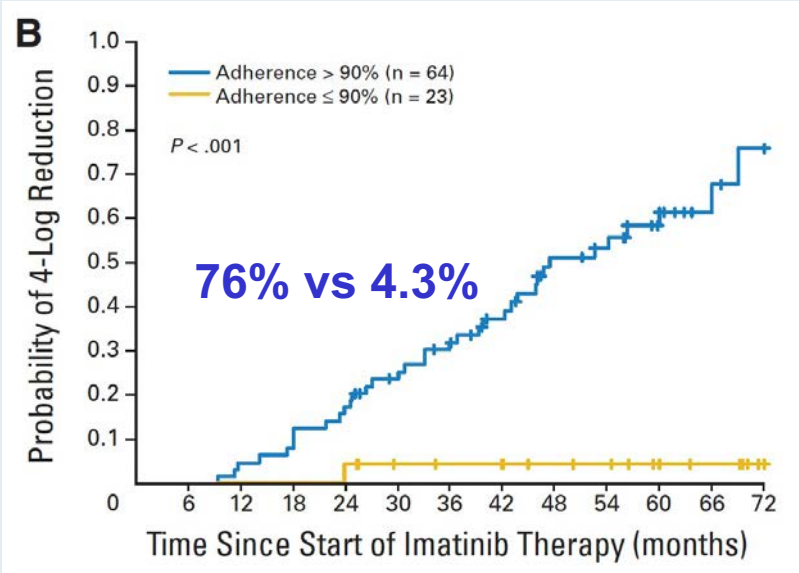
Adherence Is the Critical Factor for Achieving Molecular Responses in Patients With Chronic Myeloid Leukemia Who Achieve Complete Cytogenetic Responses on Imatinib

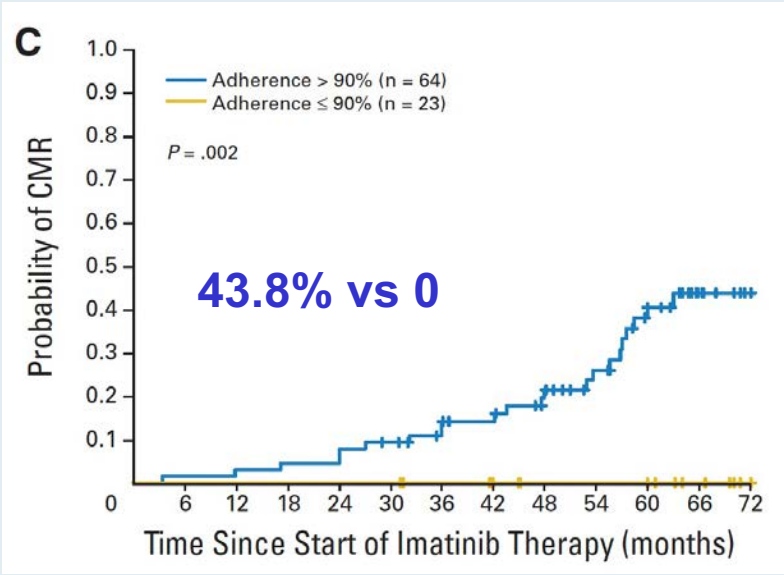
David Marin, Alexandra Bazeos, Francois-Xavier Mahon, Lina Eliasson, Dragana Milojkovic, Marco Bua, Jane F. Apperley, Richard Szydlo, Ritti Desai, Kasia Kozlowski, Christos Paliompeis, Victoria Latham, Letizia Foroni, Mathieu Molimard, Alistair Reid, Katy Rezvani, Hugues de Lavallade, Cristina Guallar, John Goldman, and Jamshid S. Khorashad

Six-Year Probability of MMR, 4-Log Reduction in Transcript Levels and CMR According to Adherence (>90% vs ≤90%)

Approximately 26% of 86 patients had adherence ≤90%; in 12 of these patients (14%), adherence was ≤80%







MMR = major molecular response

Marin D et al. *J Clin Oncol* 29(14):2381-8.

RTP RESEARCH TO PRACTICE

Leukemia Research 111 (2021) 106734

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

No margin for non-adherence: Probabilistic kaplan-meier modeling of imatinib non-adherence and treatment response in CML (ADAGIO study)

Mavis Obeng-Kusi [a], Karen MacDonald [b], Marie-Anne van Lierde [c], Christopher S. Lee [d,e], Sabina De Geest [f,g], Ivo Abraham [a,b,*]

ADAGIO (N = 169): Treatment Response as a Function of 90-Day Pill Count Adherence

Pill count ratio	CHR	CCyR	MMR	Optimal response
100%	0.84	0.83	0.77	0.82
90%	0.37	0.37	0.39	0.35
Fold change	2.25	2.24	1.95	2.35

CHR = complete hematologic response
CCyR = complete cytogenetic response
MMR = major molecular response

Obeng-Kusi M et al. *Leuk Res* 2021;111:106734.

Am J Hematol 2011;86:471-4.

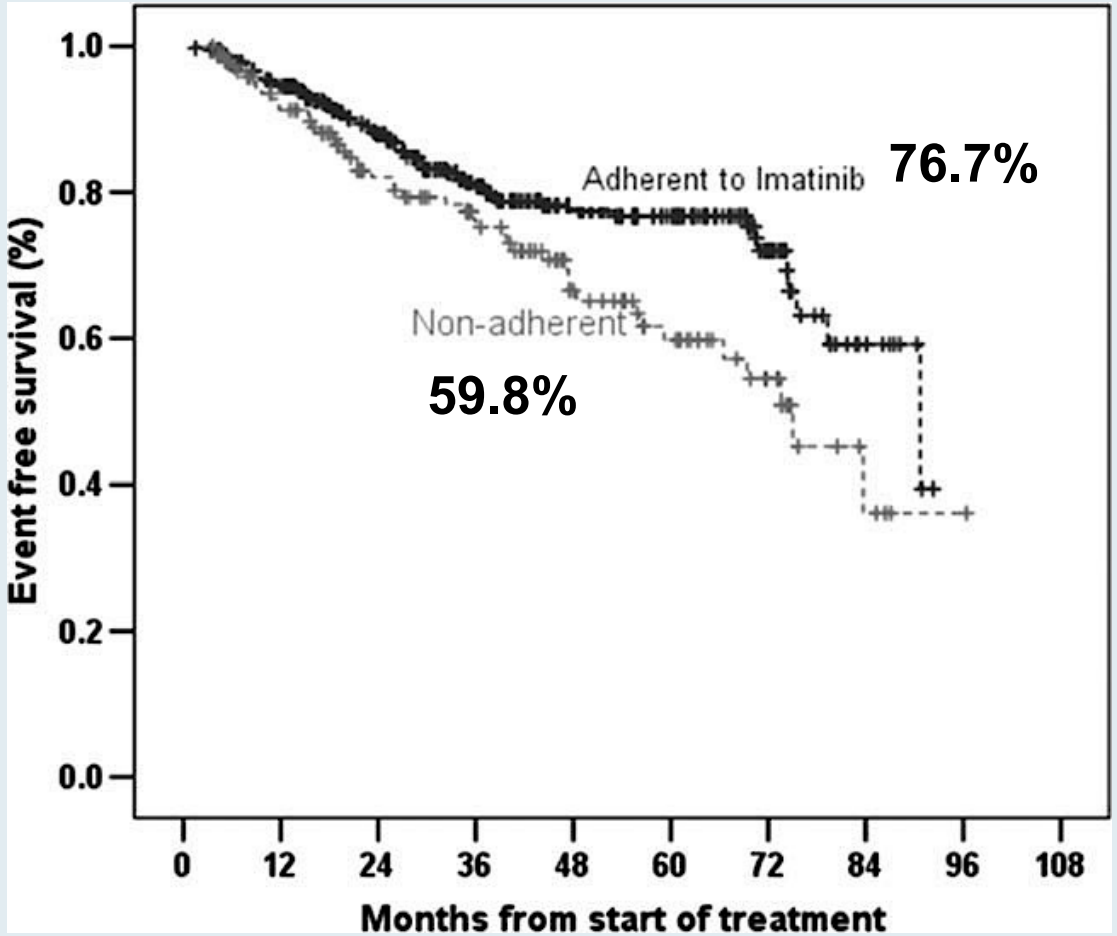
Research Article

Nonadherence to Imatinib adversely affects event free survival in chronic phase chronic myeloid leukemia

Prasanth Ganesan,* Tenali Gnana Sagar, Biswajit Dubashi, Rejiv Rajendranath, Krishnarathinam Kannan, Sanju Cyriac and Manjunath Nandennavar

Five-Year Event-Free Survival According to Adherence

- **Nearly 1/3 of 516 patients were treatment nonadherent, defined as unwarranted interruption of treatment >1 week**



Ganesan P et al. *Am J Hematol* 2011;86:471-4.

Discontinuation of Treatment

General Considerations for Discontinuation of TKI Therapy

- **Discontinuation of TKI therapy appears to be safe in select patients with CML**
- **Consult with a CML specialist to review the appropriateness for TKI discontinuation and potential risks and benefits of treatment discontinuation, including TKI withdrawal syndrome**
- **Clinical studies that have evaluated the safety and efficacy of TKI discontinuation have employed strict eligibility criteria and have mandated more frequent molecular monitoring than typically recommended for patients on TKI therapy**
- **Some patients have experienced significant adverse events that are believed to be due to TKI discontinuation**
- **Discontinuation of TKI therapy should only be performed in consenting patients after a thorough discussion of the potential risks and benefits**
- **Consultation with an NCCN Panel Member or center of expertise is recommended for:**
  - **Any significant adverse event believed to be related to treatment discontinuation**
  - **Progression to accelerated or blast phase CML at any time**
  - **Failure to regain MMR after 3 months following treatment reinitiation**

NCCN Criteria for Discontinuation of TKI Therapy

- Age ≥ 18 years
- Chronic phase CM, with no prior history of accelerated or blast phase CML
- On approved TKI therapy for at least 3 years
- Prior evidence of quantifiable BCR-ABL1 transcript
- Stable molecular response (MR4; BCR-ABL1 ≤ 0.01% IS) for ≥ 2 years
  - Documented on at least 4 tests, performed at least 3 months apart
- Access to a reliable qPCR test with a sensitivity of detection of at least MR4.5 (BCR-ABL1 ≤ 0.0032% IS) and that provides results within 2 weeks
- Monthly molecular monitoring for the first 6 months following discontinuation, bimonthly during months 7-12 and quarterly thereafter (indefinitely) for patients who remain in MMR (MR3; BCR-ABL1 ≤ 0.1% IS)
- Prompt resumption of TKI within 4 weeks of a loss of MMR with monthly molecular monitoring until MMR is re-established

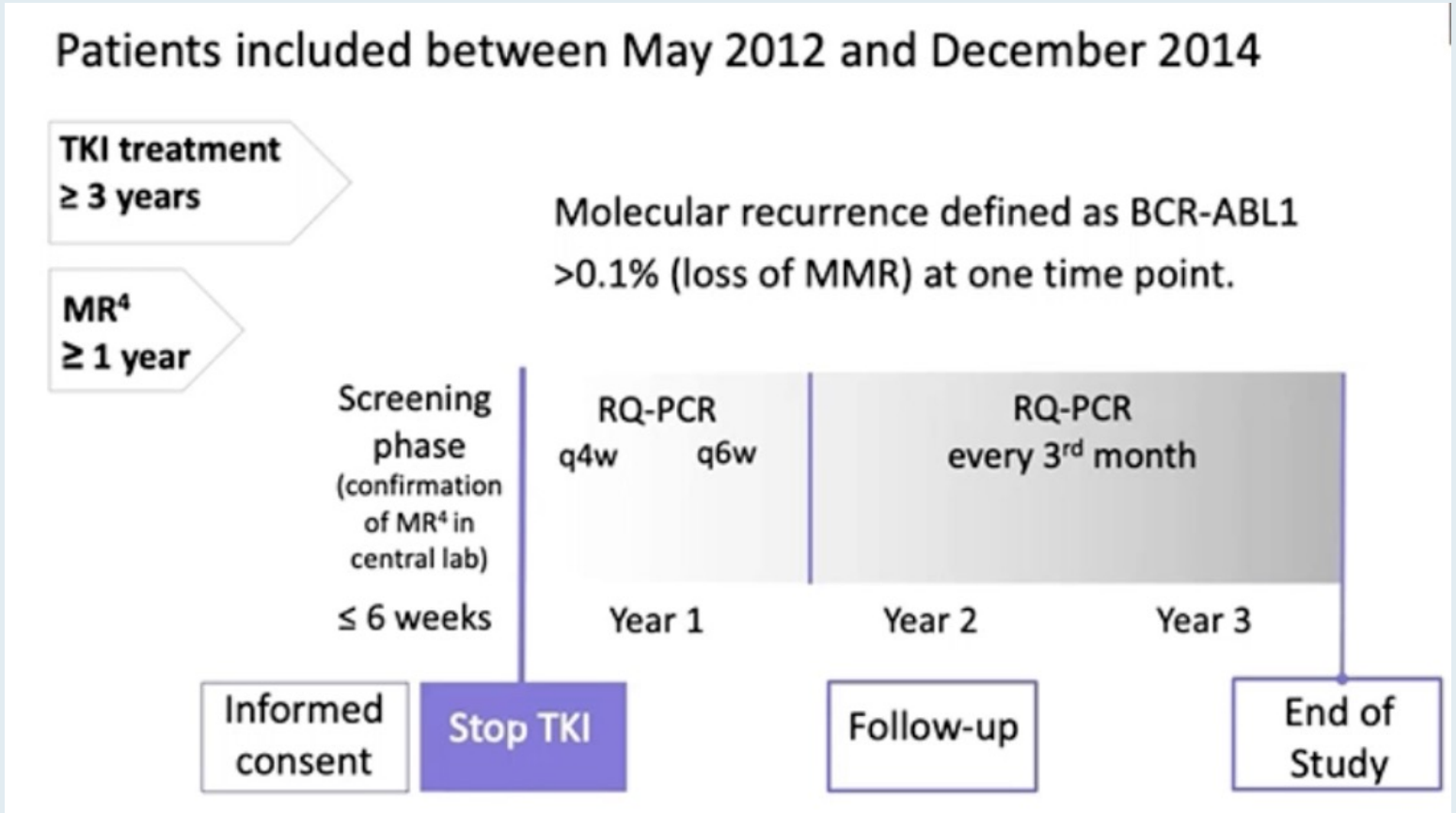
Chronic Myeloid Leukemia NCCN Guidelines v3.2022

FINAL ANALYSIS OF A PAN EUROPEAN STOPE TYROSINE KINASE INHIBITOR TRIAL IN CHRONIC MYELOID LEUKEMIA: THE EURO-SKI STUDY

Francois-Xavier Mahon, Johan Richter, Andreas Hochhaus, Panayiotis Panayiotidis, Antonio Almeida, Jiri Mayer, Henrik Hjorth-Hansen, Jeroen J. W. M. Janssen, Satu Mustjoki, Joaquin Martinez-Lopez, Hanne Vestergaard, Hans Ehrencrona, Veli Kairisto, Stéphanie Dulucq, Katerina Machová Poláková, Franck E. Nicolini, Wolf-Karsten Hofmann, Joelle Guilhot, Susanne Saussele, Markus Pfirrmann

ASH 2021;Abstract 633

EURO-SKI Study Schema



First and second primary endpoints: Molecular recurrence-free survival at 6 and 36 months, hypothesized to be >40% and >35%, respectively

Mahon F-X et al. ASH 2021;Abstract 633.

EURO-SKI: Molecular Recurrence-Free Survival and Cumulative Incidence of MMR Loss (N = 728)

Probabilities	6 months	12 months	36 months
MRecFS	62%	55%	46%
MRecTFS	61%	54%	45%
Loss of MMR	38%	44%	50%
Death/restart	1	2	3

MRecFS = molecular recurrence-free survival
MRecTFS = molecular treatment-free survival

Mahon F-X et al. ASH 2021;Abstract 633.

VOLUME 35 · NUMBER 3 · JANUARY 20, 2017

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Long-Term Follow-Up of the French Stop Imatinib (STIM1) Study in Patients With Chronic Myeloid Leukemia

Gabriel Etienne, Joëlle Guilhot, Delphine Rea, Françoise Rigal-Huguet, Franck Nicolini, Aude Charbonnier, Agnès Guerci-Bresler, Laurence Legros, Bruno Varet, Martine Gardembas, Viviane Dubruille, Michel Tulliez, Marie-Pierre Noel, Jean-Christophe Ianotto, Bruno Villemagne, Martin Carré, François Guilhot, Philippe Rousselot, and François-Xavier Mahon

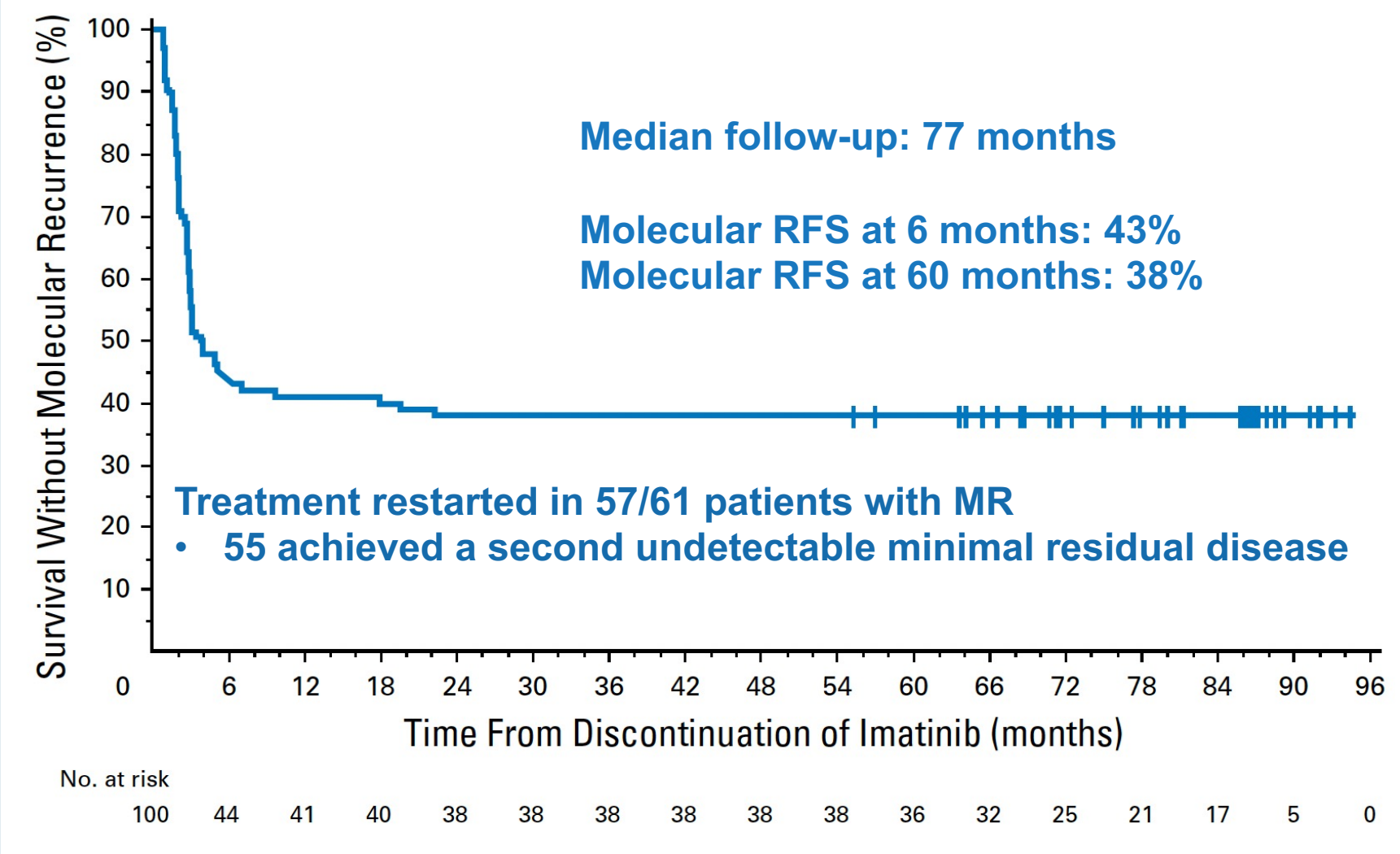
STIM1: Baseline Patient Characteristics

Characteristic	All Patients (N = 100)
Sex, %	
Male	48
Female	52
Median age at inclusion, years (range)	59.4 (29-81)
Sokal risk score, %	
Low	49
Intermediate	39
High	11
Missing	1
Median time from diagnosis to imatinib onset, months (range)	2.5 (0-195.1)
Median time from diagnosis to imatinib discontinuation, months (range)	72.1 (36-243)
Median time receiving imatinib, months	58.8 (35-112)
Median time from imatinib onset to sustained UMRD, months (range)	18.1 (3-68)
Median sustained UMRD duration before imatinib discontinuation, months (range)	36.4 (24-107)

Abbreviation: UMRD, undetectable molecular residual disease.

Etienne G et al. *J Clin Oncol* 2017;35(3):298-305.

STIM1: Molecular Recurrence-Free Survival After Imatinib Discontinuation



Etienne G et al. *J Clin Oncol* 2017;35(3):298-305.

Cancer 2017;123:4403-10.

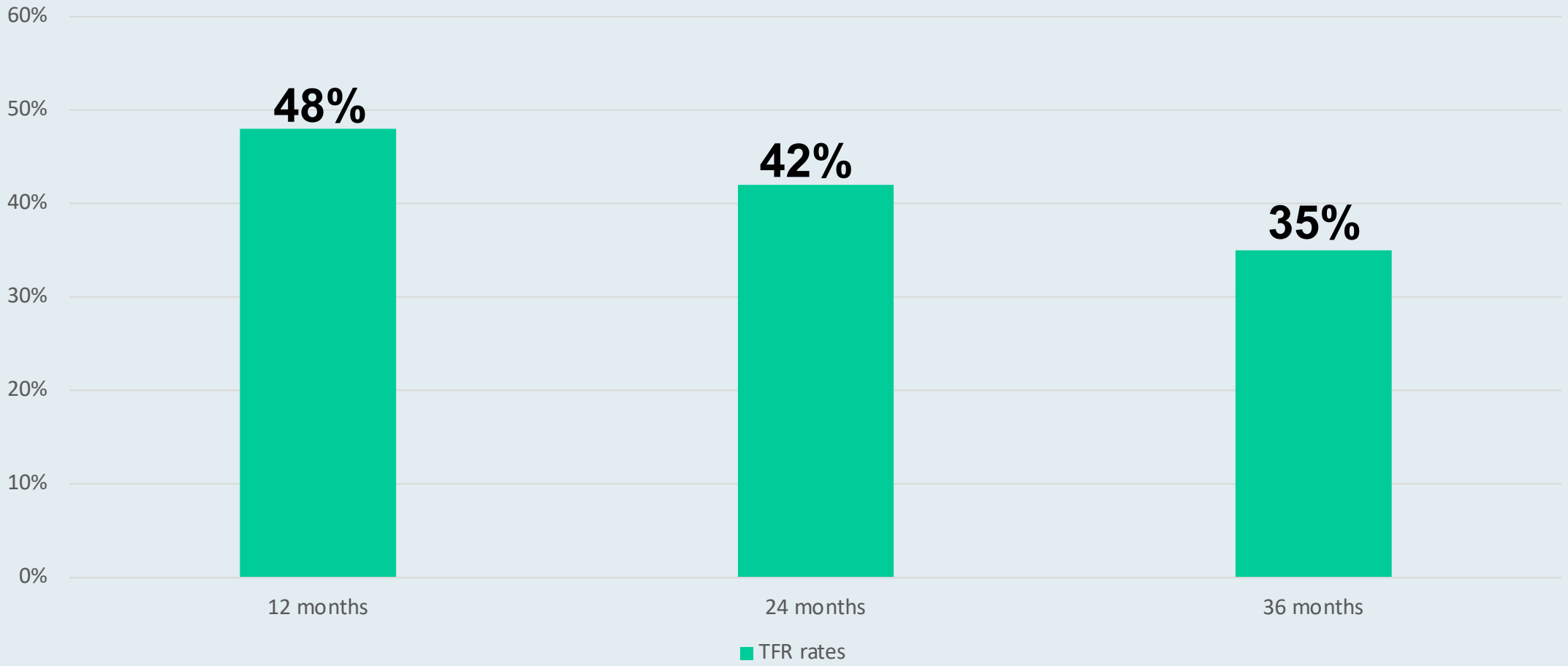
Original Article

Second Tyrosine Kinase Inhibitor Discontinuation Attempt in Patients With Chronic Myeloid Leukemia

Laurence Legros, MD, PhD [1,2]; Franck E. Nicolini, MD, PhD[3,4]; Gabriel Etienne, MD, PhD [5]; Philippe Rousselot, MD, PhD[6]; Delphine Rea, MD, PhD[7]; Stéphane Giraudier, MD, PhD[8]; Agnès Guerci-Bresler, MD, PhD[9]; Françoise Huguet, MD[10]; Martine Gardembas, MD[11]; Martine Escoffre, MD[12]; Jean-Christophe Ianotto, MD, PhD[13]; Marie-Pierre Noël, MD[14]; Bruno R. Varet, MD, PhD[15]; Thomas Pagliardini[1]; Irit Touitou, PhD[1]; Stéphane Morisset, MS[16]; and Francois-Xavier Mahon, MD, PhD[17]; on behalf of the French Intergroup for Chronic Myeloid Leukemias

- Evaluated treatment-free remission (TFR) in 70 patients who re-attempted TKI discontinuation after a first unsuccessful attempt
- After the second TKI discontinuation attempt, the trigger for treatment re-introduction was the loss of a major molecular response in all patients

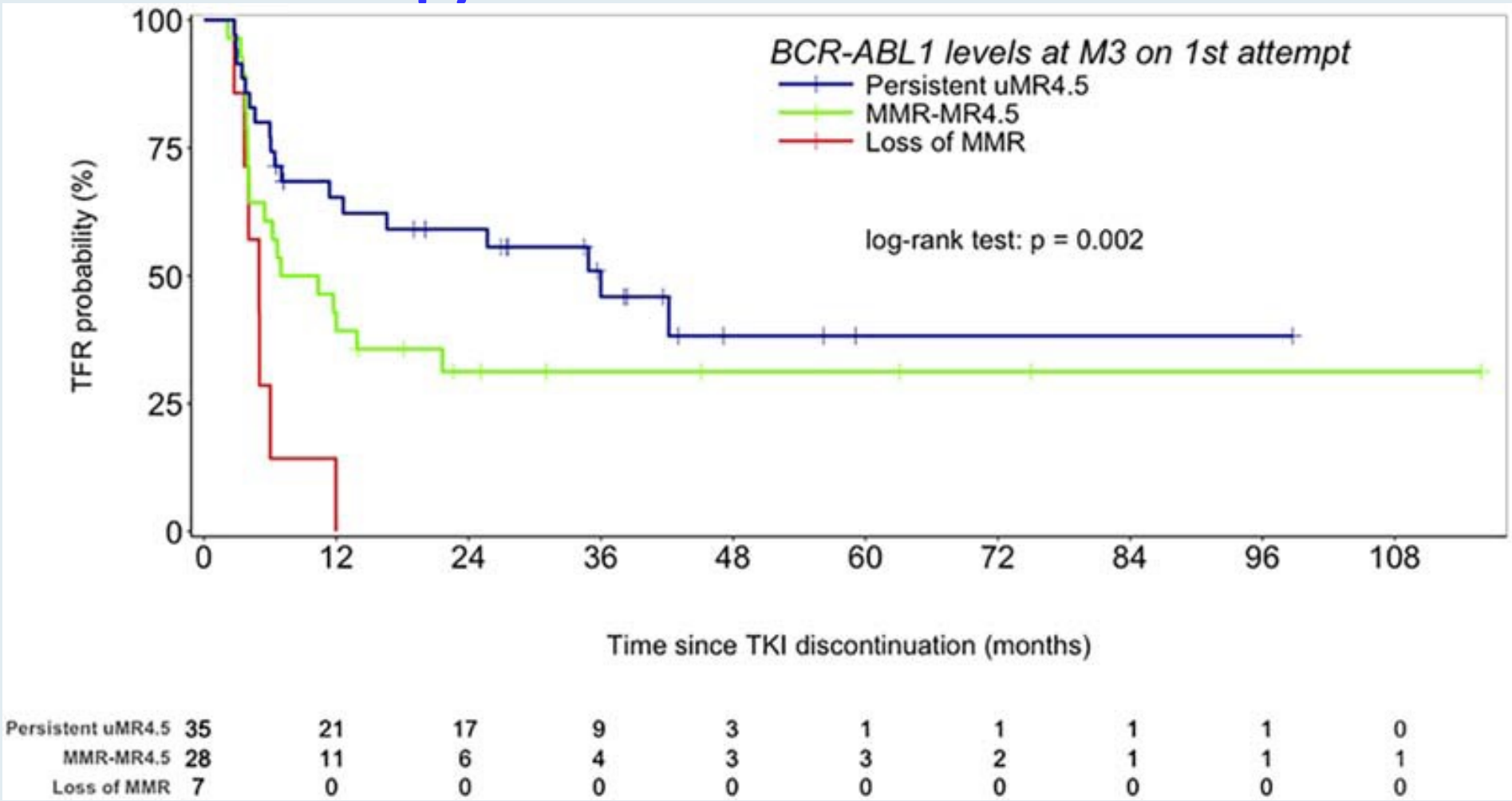
RE-STIM: Treatment-Free Remission After Second TKI Discontinuation Attempt



Legros L et al. *Cancer* 2017;123:4403-10.

RTP RESEARCH TO PRACTICE

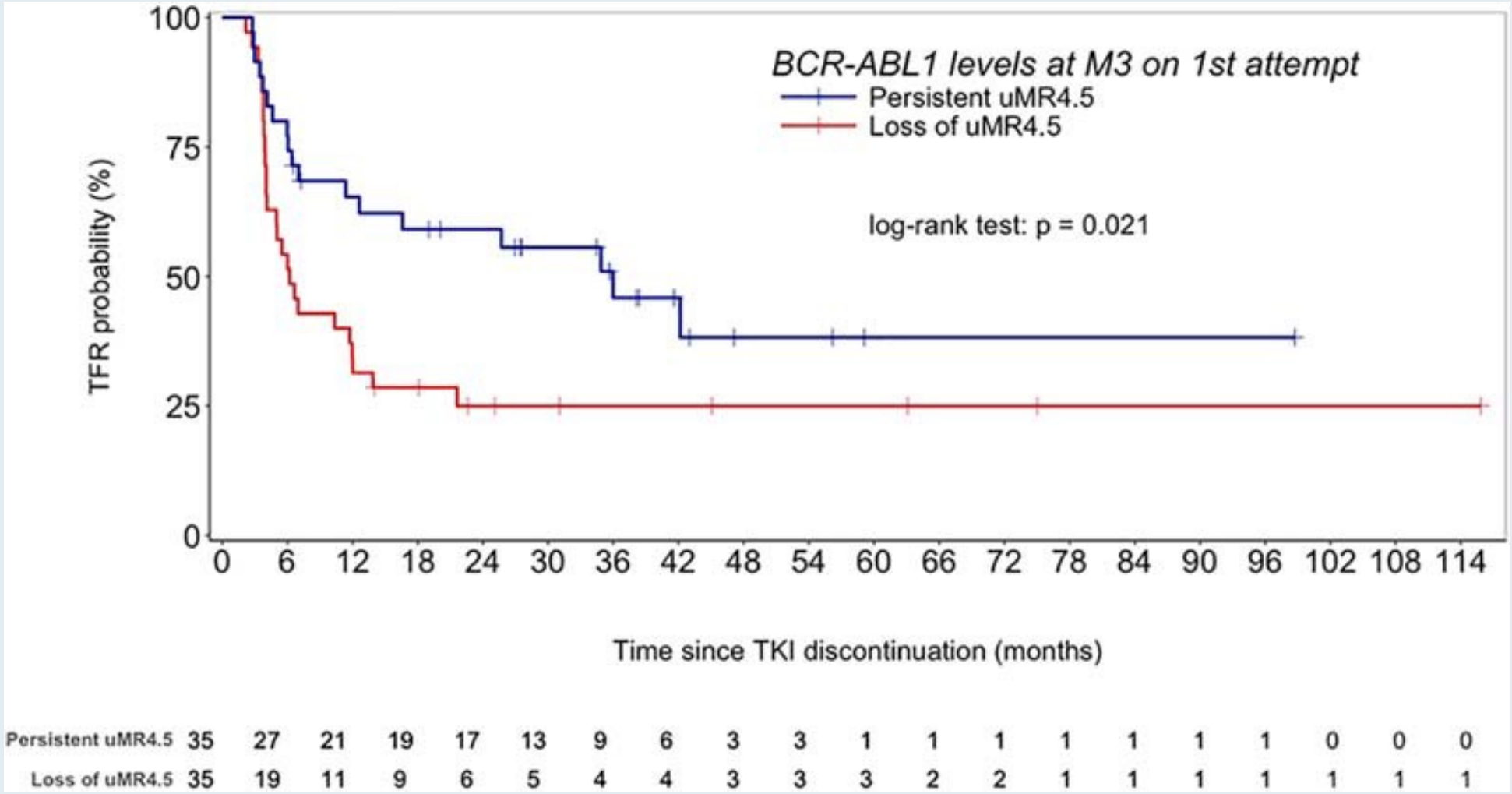
RE-STIM: Probability of Achieving TFR According to Molecular-Response Status at 3 Months After the First Attempt to Discontinue TKI Therapy



Legros L et al. *Cancer* 2017;123:4403-10.

RTP RESEARCH TO PRACTICE

RE-STIM: Probability of Achieving TFR According to Undetectable/Detectable MR Status at 3 Months After the First Attempt to Discontinue TKI Therapy



Legros L et al. *Cancer* 2017;123:4403-10.

Selection and Sequencing of Treatment After Failure of Initial TKI Therapy

Spectrum of BCR-ABL1 Mutations and Their Relationship with TKIs

TKI	Strong Resistance	Mild–Moderate Resistance
Imatinib	Y253–E255–T315	M244–L248–G250–Q252–F317–M351–M355–F359–H396
Dasatinib	T315	V299–F317
Nilotinib	T315	L248–Y253–E255–F359
Bosutinib	T315–V299	L248–G250–E255–F317
Ponatinib		T315–E255
Asciminib	A337–W464–P465–V468–I502	

P-loop mutations: M244, G250, Q252, Y253, and E255; gatekeeper residue (T315 and F317); SH2 contact and C-lobe (M351, F359); activation loop (H396).

De Novellis D et al. *Pharmaceutics* 2021;13(12):2201.

Cancer 2009;115(18):4136-47.

Dasatinib or High-Dose Imatinib for Chronic-Phase Chronic Myeloid Leukemia Resistant to Imatinib at a Dose of 400 to 600 Milligrams Daily

Two-Year Follow-Up of a Randomized Phase 2 Study (START-R)

Hagop Kantarjian, MD[1]; Ricardo Pasquini, MD[2]; Vincent Lévy, MD, PhD[3]; Saengsuree Jootar, MD[4]; Jerzy Holowiecki, MD, PhD[5]; Nelson Hamerschlak, MD, PhD[6]; Timothy Hughes, MD[7]; Eric Bleickardt, MD[8]; David Dejardin, MSc[8]; Jorge Cortes, MD[1]; and Neil P. Shah, MD, PhD[9]

START-R: Response and PFS with Dasatinib versus High-Dose Imatinib for CP-CML Resistant to Standard-Dose Imatinib

	Dasatinib (n = 101)	High-dose imatinib 800 mg (400 mg BID) (n = 49)
CHR rate	93%	82%
MCyR rate	53%	33%
CCyR rate	44%	18%
MMR rate	29%	12%
Estimated 24-month PFS	86%	65%

Kantarjian H et al. *Cancer* 2009;115(18):4136-47.

CLINICAL TRIALS AND OBSERVATIONS

Imatinib mesylate dose escalation is associated with durable responses in patients with chronic myeloid leukemia after cytogenetic failure on standard-dose imatinib therapy

Elias Jabbour,[1] Hagop M. Kantarjian,[1] Dan Jones,[2] Jenny Shan,[1] Susan O'Brien,[1] Neeli Reddy,[2] William G. Wierda,[1] Stefan Faderl,[1] Guillermo Garcia-Manero,[1] Srdan Verstovsek,[1] Mary Beth Rios,[1] and Jorge Cortes[1]

Departments of [1]Leukemia and [2]Hematopathology, University of Texas M. D. Anderson Cancer Center, Houston

***Blood* 2009;113:2154-60.**

Twenty-one patients with hematologic failure and 63 with cytogenetic failure had their imatinib dose escalated from 400 to 800 mg daily (n = 72) or from 300 to 600 mg daily (n = 12)

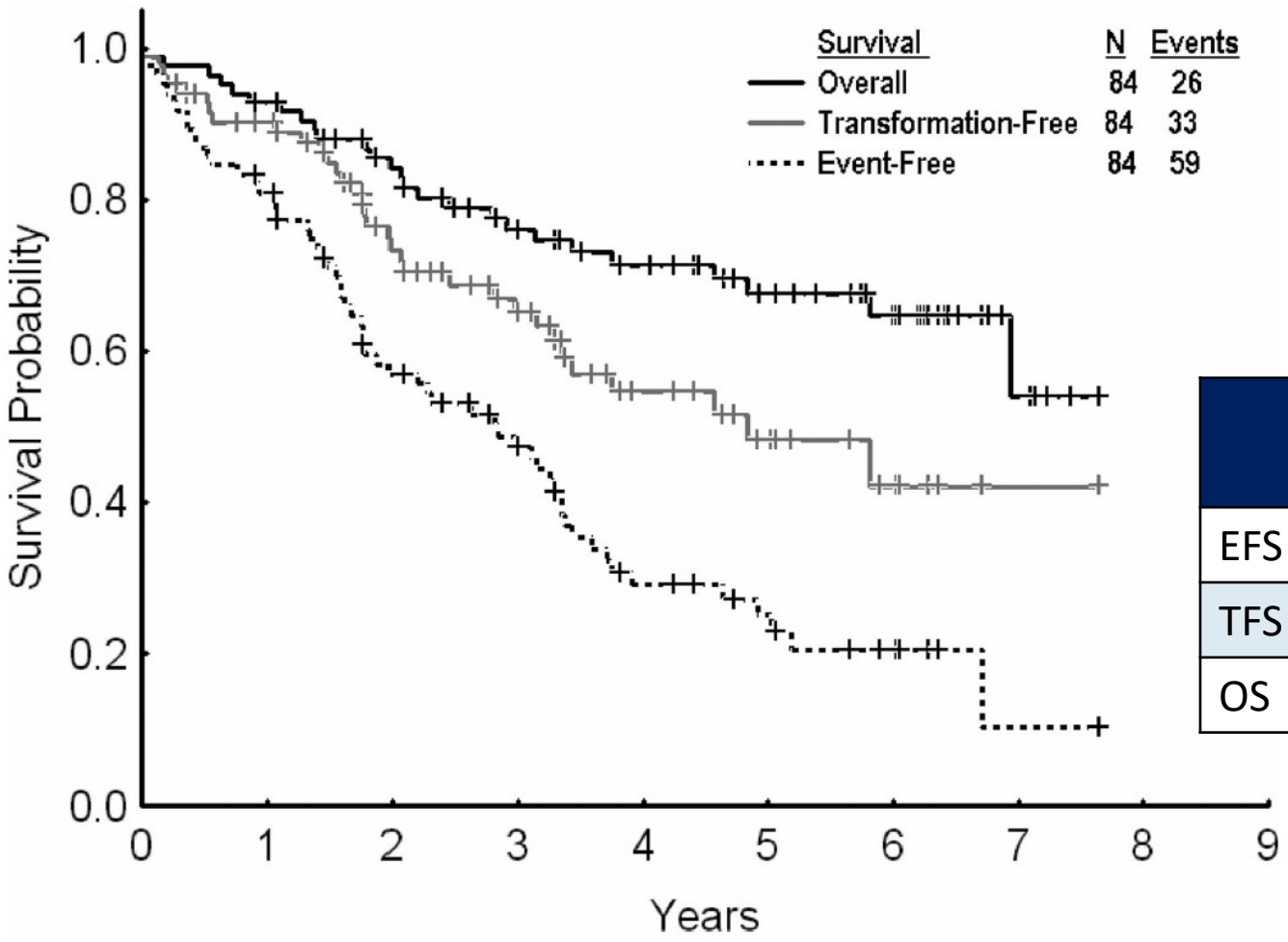
Response After Dose Increase for Patients After Imatinib Failure

Outcome	Total, n = 84	Cytogenetic failure, n = 63	Hematologic failure, n = 21	*P*
Cytogenetic response, n (%)				
Any	50 (60)	47 (75)	3 (14)	< .001
Partial*	10 (14)	8 (16)	2 (10)	.77
Complete	34 (40)	33 (52)	1 (5)	< .001
% 2-year				
EFS	57	65	36	< .001
FFS	29	38	5	< .001
TFS	73	80	51	.004
OS	84	90	67	< .001

EFS = event-free survival; FFS = failure-free survival; TFS = transformation-free survival

Jabbour E et al. *Blood* 2009;113:2154-60.

Overall, Event-Free and Transformation-Free Survival for All Patients Receiving Imatinib Dose Escalation After Imatinib Failure



	Estimated 2-year rate	Estimated 3-year rate
EFS	57%	47%
TFS	73%	65%
OS	84%	76%

Jabbour E et al. *Blood* 2009;113:2154-60.

Responses in Patients with CML Treated with Second-Generation TKIs After Resistance or Intolerance to Imatinib at 24-Month Follow-Up

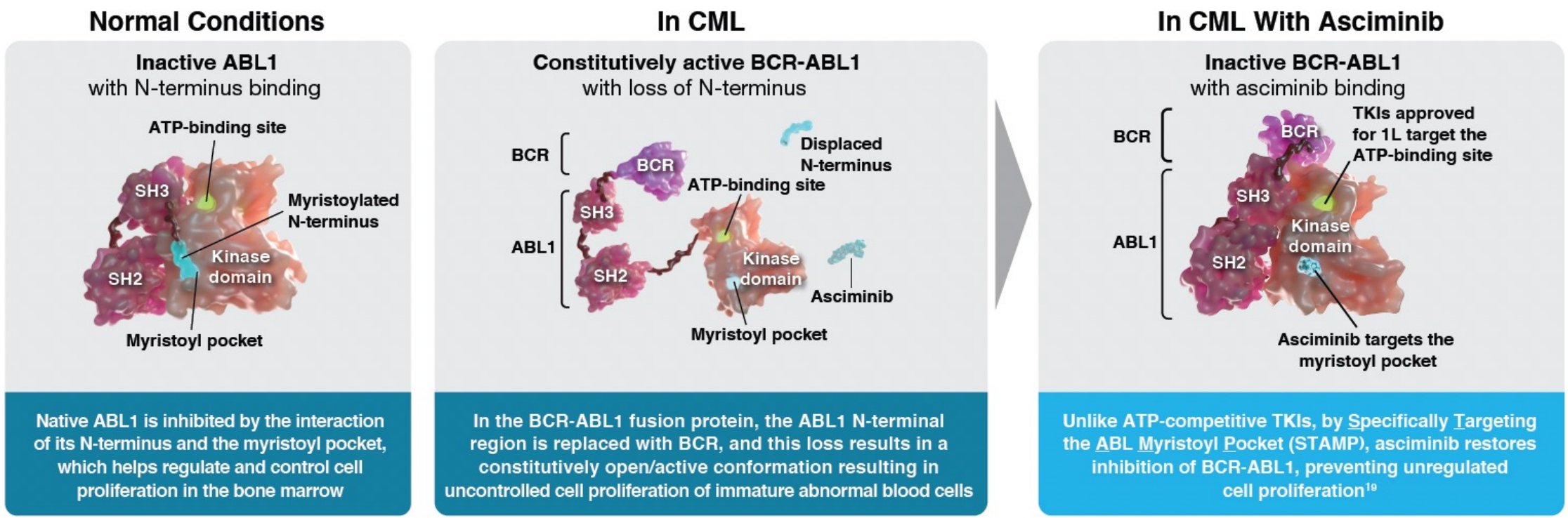
	Dasatinib*	Nilotinib†	Bosutinib
Complete haematological response	89%	77%	86%
Major cytogenetic response	59%	56%	57%
Complete cytogenetic response	44%	41%	44%
Progression-free survival‡	80%	64%	81%
Overall survival	91%	87%	91%

Cortes J et al. *Lancet* 2021; 398:1914-26.

Asciminib Mechanism of Action

- Asciminib is a potent allosteric inhibitor of BCR-ABL1 that works by Specifically Targeting the ABL Myristoyl Pocket (STAMP)[17-19] (**Figure 1**)
  - The specificity of asciminib is intended to avoid off-target effects from inhibition of other kinases, potentially leading to reduced toxicity

Figure 1. Asciminib Specifically Targets the ABL Myristoyl Pocket (STAMP)



Cortes J et al. ASH 2021;Abstract 1478.

RTP RESEARCH TO PRACTICE

FDA Approves Asciminib for Philadelphia Chromosome-Positive Chronic Myeloid Leukemia

Press Release: October 29, 2021

"On October 29, 2021, the Food and Drug Administration granted accelerated approval to asciminib for patients with Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP), previously treated with two or more tyrosine kinase inhibitors (TKIs), and approved asciminib for adult patients with Ph+ CML in CP with the T315I mutation.

ASCEMBL (NCT03106779), a multi-center, randomized, active-controlled, open-label clinical trial, is evaluating asciminib in patients with Ph+ CML in CP, previously treated with two or more TKIs. A total of 233 patients were randomized (2:1) and stratified according to major cytogenetic response (MCyR) status to receive either asciminib 40 mg twice daily or bosutinib 500 mg once daily. Patients continued treatment until unacceptable toxicity or treatment failure occurred.

CABL001X2101 (NCT02081378), a multi-center, open-label clinical trial, is evaluating asciminib in patients with Ph+ CML in CP with the T315I mutation. Efficacy was based on 45 patients with the T315I mutation who received asciminib 200 mg twice daily. Patients continued treatment until unacceptable toxicity or treatment failure occurred."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-asciminib-philadelphia-chromosome-positive-chronic-myeloid-leukemia

Jorge E. Cortes
Jorge.cortes@augusta.edu

Efficacy and Safety Results From ASCEMBL, a Phase 3 Study of Asciminib vs Bosutinib in Patients With Chronic Myeloid Leukemia in Chronic Phase After ≥2 Prior Tyrosine Kinase Inhibitors: Week 96 Update

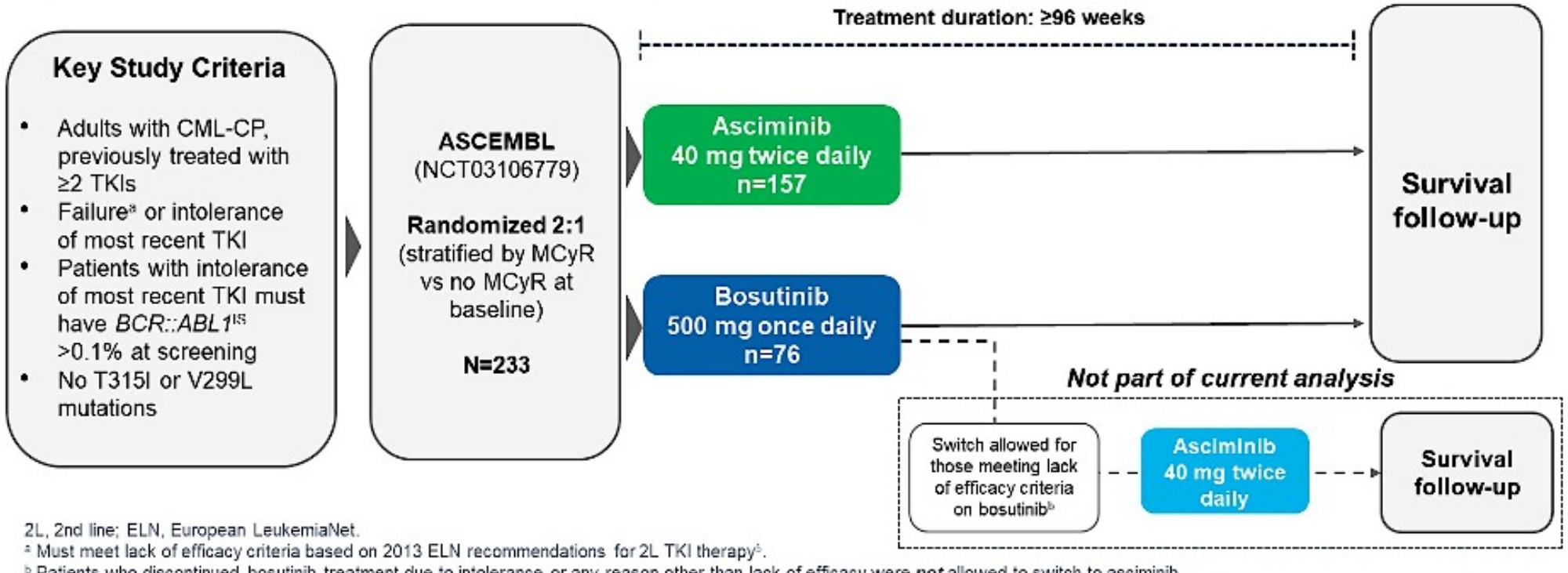
Presenter: Jorge E. Cortes

Delphine Réa,[1] Michael J. Mauro,[2] Andreas Hochhaus,[3] Carla Boquimpani,[4] Elza Lomaia,[5] Sergey Voloshin,[6] Anna Turkina,[7] Dong-Wook Kim,[8] Jane F. Apperley,[9] Jorge E. Cortes,[10] Koji Sasaki,[11] Shruti Kapoor,[12] Alex Allepuz,[13] Sara Quenet,[13] Véronique Bédoucha,[13] Yosuke Minami[14]

Oral presentation at: 2022 ASCO Annual Meeting; June 3-7, 2022; Chicago, IL, & online

ASCEMBL Phase III Study Design

- **Data cutoff for current analysis:** October 6, 2021
- **Median duration of follow-up:** 2.3 years (120 weeks) from randomization to last contact date
- **Primary endpoint:** MMR rate at week 24
- **Key secondary endpoint:** MMR rate at week 96



2L, 2nd line; ELN, European LeukemiaNet.
[a] Must meet lack of efficacy criteria based on 2013 ELN recommendations for 2L TKI therapy[5].
[b] Patients who discontinued bosutinib treatment due to intolerance or any reason other than lack of efficacy were *not* allowed to switch to asciminib.

Oral presentation at: 2022 ASCO Annual Meeting; June 3-7, 2022; Chicago, IL, & online

Réa D et al. ASCO 2022;Abstract 7004.

ASCEMBL: Patient Disposition

Variable, n (%)	Asciminib 40 mg twice daily (n=157)	Bosutinib 500 mg once daily (n=76)
Patients randomized		
Treated	156 (99.4)[a]	76 (100.0)
Treatment ongoing[b]	**84 (53.5)**	**15 (19.7)**
Discontinued treatment	**72 (45.9)**	**61 (80.3)**
Before week 24	26 (16.6)	25 (32.9)
Week 24 to before week 48	25 (15.9)	29 (38.2)
Week 48 to before week 96	17 (10.8)	3 (3.9)
After week 96	4 (2.5)	4 (5.3)
Reason for discontinuation		
Lack of efficacy	**38 (24.2)**	**27 (35.5)**
Adverse event	**11 (7.0)**	**19 (25.0)**
Physician decision	14 (8.9)	6 (7.9)
Patient decision	5 (3.2)	4 (5.3)
Death	1 (0.6)	0
Lost to follow-up	1 (0.6)	2 (2.6)
Progressive disease	1 (0.6)	3 (3.9)
Protocol deviation	1 (0.6)	0
Switched to receive asciminib	NA	24 (31.6)

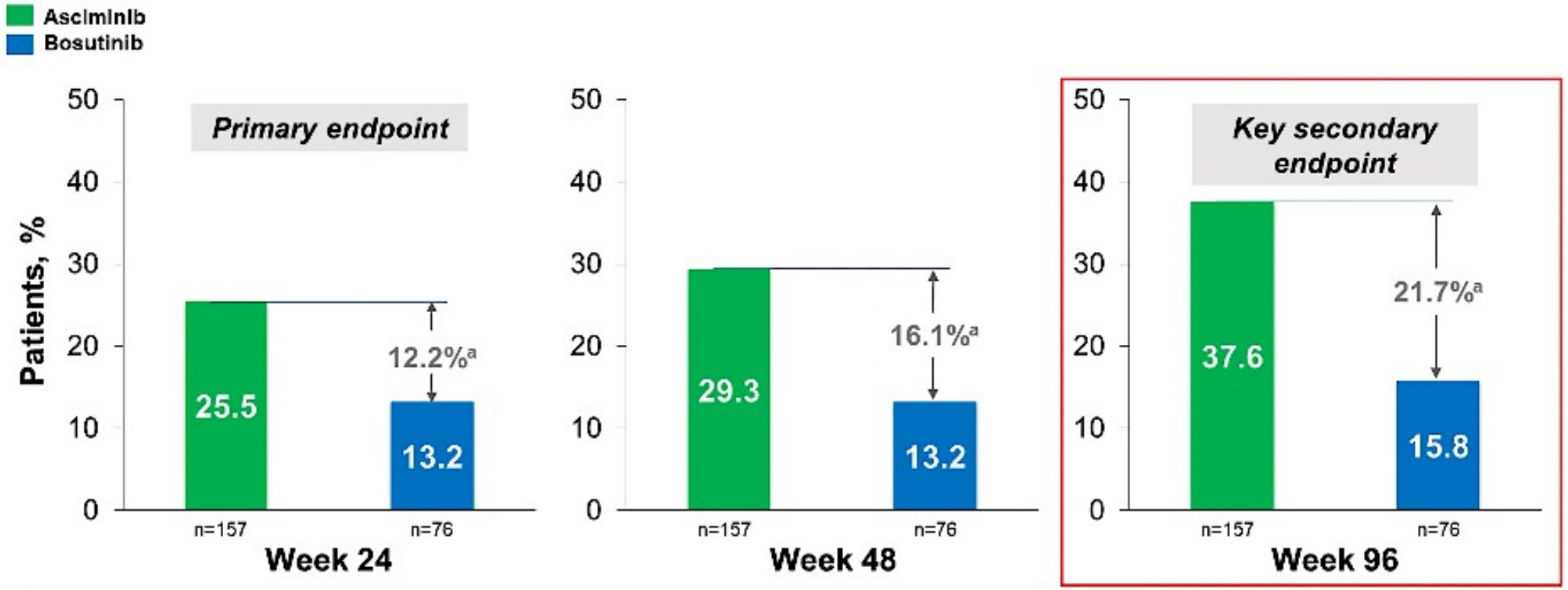
NA, not applicable.
[a] 1 patient developed cytopenia after randomization and was not treated per investigator's decision.
[b] Ongoing at the time of data cutoff: October 6, 2021.

Oral presentation at: 2022 ASCO Annual Meeting; June 3-7, 2022; Chicago, IL, & online

- The median duration of exposure was **23.7 months** for **asciminib** vs **7.0 months** for **bosutinib**
- The rate of discontinuations due to AEs continued to be low on asciminib, with minimal increase since the primary analysis

Réa D et al. ASCO 2022;Abstract 7004.

ASCEMBL Primary Endpoint: MMR Rate at Weeks 24, 48 and 96



- The MMR rate with asciminib increased consistently over time suggesting the long-term benefit of continuing treatment with asciminib

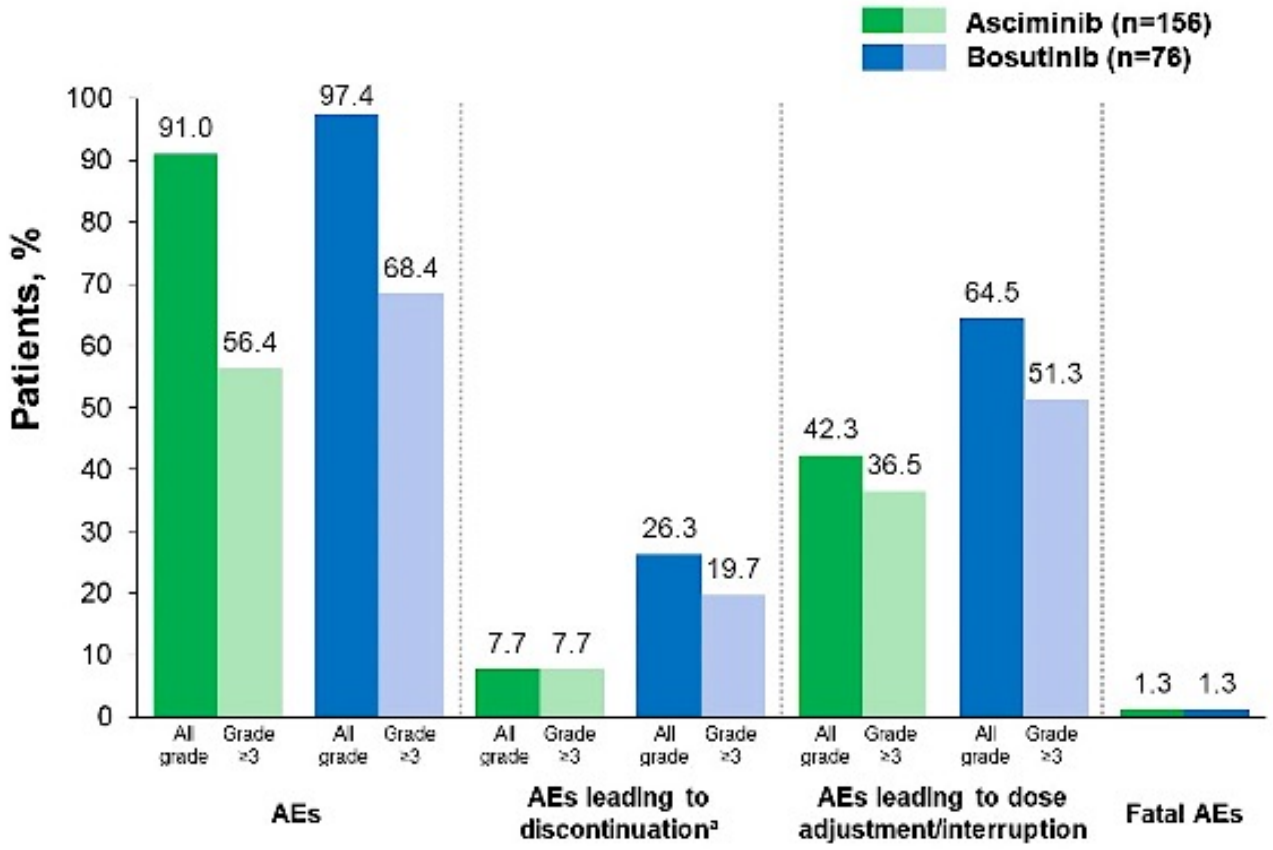
[a] The treatment difference after adjusting for baseline MCyR status was 12.24% (95% CI, 2.19%-22.30%; 2-sided *P*=0.029) at week 24, 16.09% (95% CI, 5.69%-26.49%; 2-sided *P*=0.007) at week 48, and 21.74% (95% CI: 10.53%-32.95%; 2-sided *P*=0.001) at week 96.

Oral presentation at: 2022 ASCO Annual Meeting; June 3-7, 2022; Chicago, IL, & online

Réa D et al. ASCO 2022;Abstract 7004.

RTP RESEARCH TO PRACTICE

ASCEMBL: Overview of Adverse Events (AEs)



- Median duration of exposure:
  - **23.7 months** (range, 0.0-46.2 months) for **asciminib**
  - **7.0 months** (range, 0.2-43.3 months) for **bosutinib**
- Safety and tolerability of asciminib continued to be better than with bosutinib
  - No new or worsening safety findings
  - No on-treatment deaths in either arm since the primary analysis cutoff
- Most common AEs leading to treatment discontinuation did not change since the primary analysis:
  - Thrombocytopenia **(3.2%)** and neutropenia **(2.6%)** with **asciminib**
  - Increased ALT **(5.3%)** and neutropenia **(3.9%)** with **bosutinib**

ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a] Grade 1/2 AEs leading to discontinuation with bosutinib (n=5) included ALT/AST level increased, blood creatinine level increased, diarrhea, drug eruption, and pleural effusion.

Oral presentation at: 2022 ASCO Annual Meeting; June 3-7, 2022; Chicago, IL, & online

Réa D et al. ASCO 2022;Abstract 7004.

ASC4FIRST Phase III Study Design

Key Inclusion Criteria

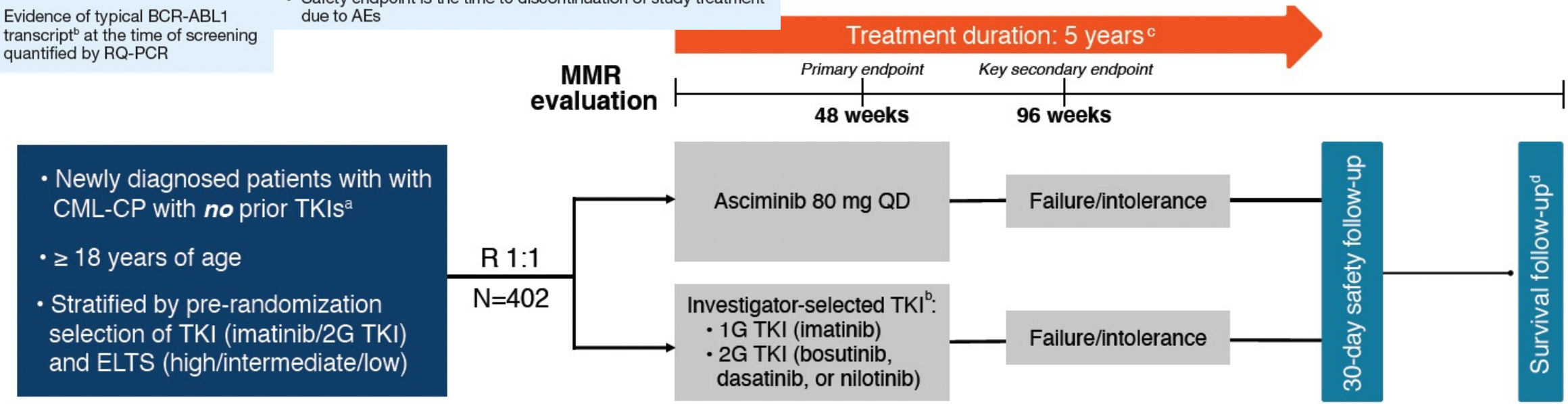
- Adults (≥ 18 years of age) with CML-CP[a]
- CML-CP within 3 months of diagnosis that meets ELN criteria[5]
- ECOG performance status of 0 or 1
- Evidence of typical BCR-ABL1 transcript[b] at the time of screening quantified by RQ-PCR

Primary endpoints[a]

- Multiple primary endpoints are:
  - MMR at week 48 for asciminib vs investigator-selected TKI
  - MMR at week 48 for asciminib vs imatinib subgroup alone

Secondary endpoints

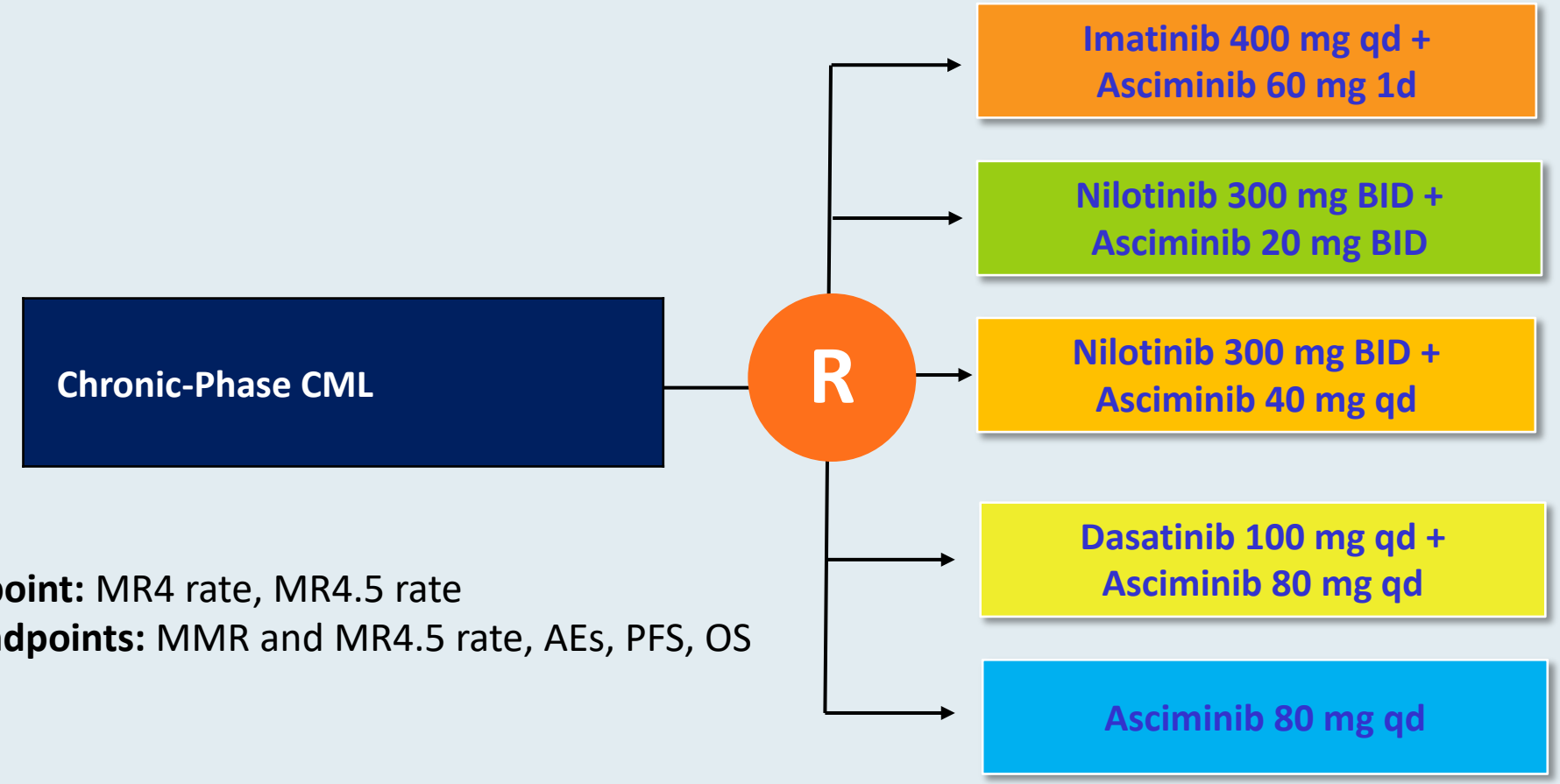
- Key secondary endpoint is MMR at week 96
- Safety endpoint is the time to discontinuation of study treatment due to AEs



[a] Only imatinib ≤2 weeks is allowed. [b] 50% 1G TKI and 50% 2G TKI at their approved dose. [c] Patients will remain on study for 5 years after the last patient's 1st dose, unless they have discontinued early due to treatment failure, disease progression, intolerance, or investigator or patient decision. [d] Patients who discontinue early will continue to be followed up for survival and disease progression until the end of the study.

Cortes J et al. ASH 2021;Abstract 1478.

FASCINATION (CMLXI) Phase II Study Design



Primary endpoint: MR4 rate, MR4.5 rate
Secondary endpoints: MMR and MR4.5 rate, AEs, PFS, OS

www.clinicaltrials.gov. NCT03906292. Accessed May 2022.

Strategies Targeting the T315I Mutation

N Engl J Med 2019;381:2315-26.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Asciminib in Chronic Myeloid Leukemia after ABL Kinase Inhibitor Failure

T.P. Hughes, M.J. Mauro, J.E. Cortes, H. Minami, D. Rea, D.J. DeAngelo, M. Breccia, Y.-T. Goh, M. Talpaz, A. Hochhaus, P. le Coutre, O. Ottmann, M.C. Heinrich, J.L. Steegmann, M.W.N. Deininger, J.J.W.M. Janssen, F.-X. Mahon, Y. Minami, D. Yeung, D.M. Ross, M.S. Tallman, J.H. Park, B.J. Druker, D. Hynds, Y. Duan, C. Meille, F. Hourcade-Potelleret, K.G. Vanasse, F. Lang, and D.-W. Kim

Hematologic, Cytogenetic and Molecular Response with Asciminib (Combined Once-Daily and Twice-Daily Schedules)

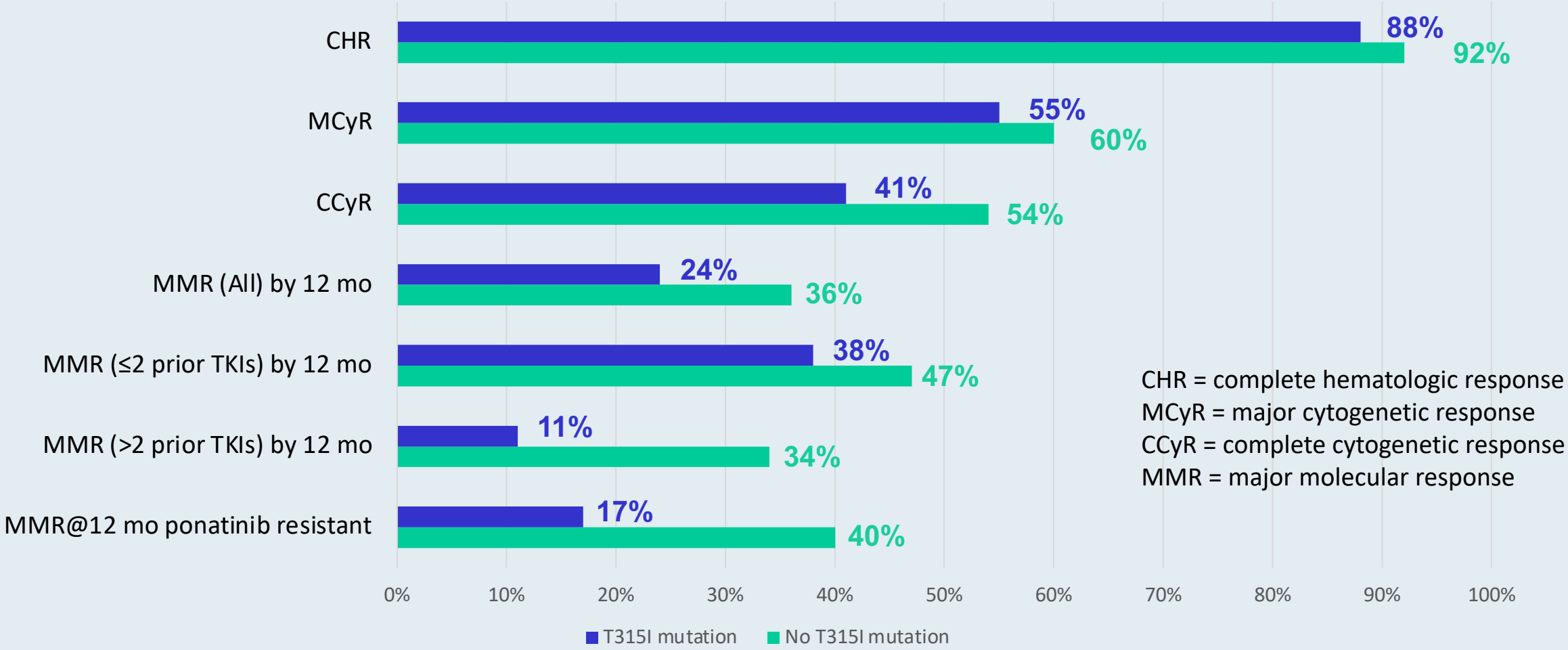
	No T315I mutation			T315I mutation		
	Overall (N = 113)	Response achieved	Response maintained	Overall (N = 28)	Response achieved	Response maintained
CHR		92%			88%	
MCyR	77%	60%	87%	60%	55%	80%
CCyR	70%	54%	87%	44%	41%	67%
MMR (all) by 12 mo	48%	36%	95%	28%	24%	100%
MMR (≤2 prior TKIs) by 12 mo	60%	47%	80%	44%	38%	100%
MMR (>2 prior TKIs) by 12 mo	44%	34%	100%	11%	11%	0
MMR (resistant or intolerant to ponatinib) by 12 mo	57%	40%	100%	17%	17%	0

CHR = complete hematologic response; MCyR = major cytogenetic response; CCyR = complete cytogenetic response; MMR = major molecular response

Hughes TP et al. *N Engl J Med* 2019;381:2315-26.

Hematologic, Cytogenetic and Molecular Response Achieved with Asciminib in Patients with CP-CML

For patients who did not meet the response criteria at baseline

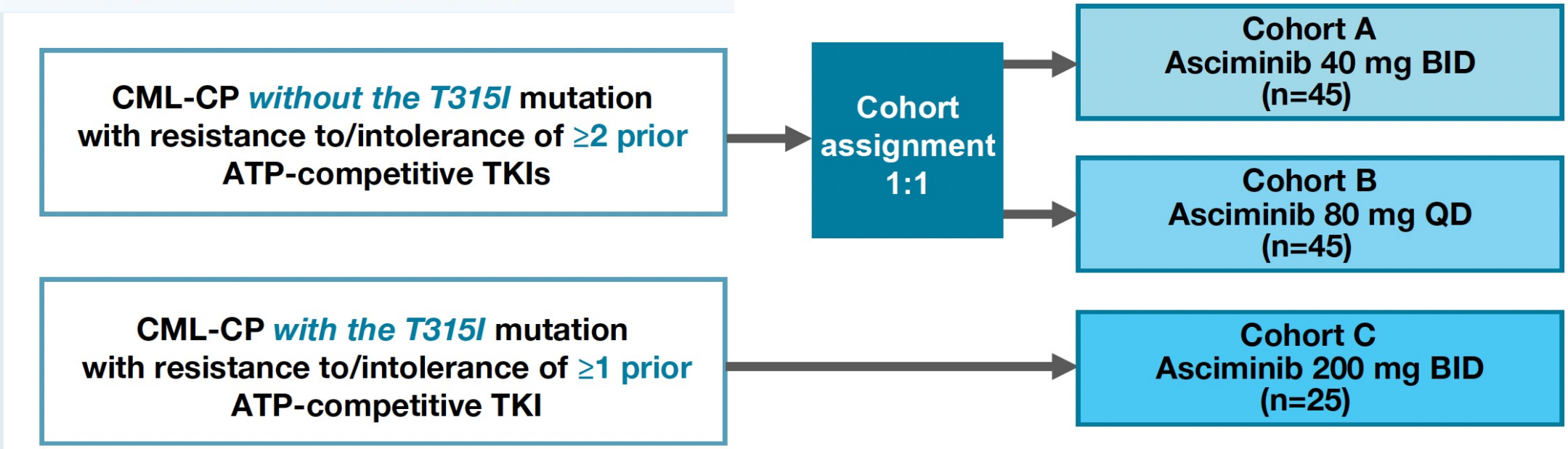


Hughes TP et al. *N Engl J Med* 2019;381:2315-26.

AIM4CML Phase IIIb Study Design

Key inclusion criteria
Adults (≥18 years of age) with a diagnosis of CML-CP
Prior treatment with ≥2 ATP-competitive TKIs in patients without the T315I mutation ***or*** ≥1 ATP-competitive TKI in patients with the T315I mutation
Treatment failure (adapted from the 2020 ELN recommendations) with or intolerance of the most recent TKI at screening
Evidence of typical *BCR-ABL1* transcripts at screening

Primary Objective	• Evaluate the safety profile of asciminib monotherapy in patients in the 3L and beyond (3L+) in cohorts A and B for 24 weeks
Secondary Objectives	• Evaluate the safety profile of asciminib monotherapy in cohorts A, B, and C for 48 and 72 weeks • Estimate hematologic response and MR rates by specific time points • Estimate time to and duration of hematologic response and MR • Assess progression-free survival and overall survival during 72 weeks



Andorsky D et al. ASH 2021;Abstract 3599.

RTP RESEARCH TO PRACTICE

Blood 2018;132(4):393-404.

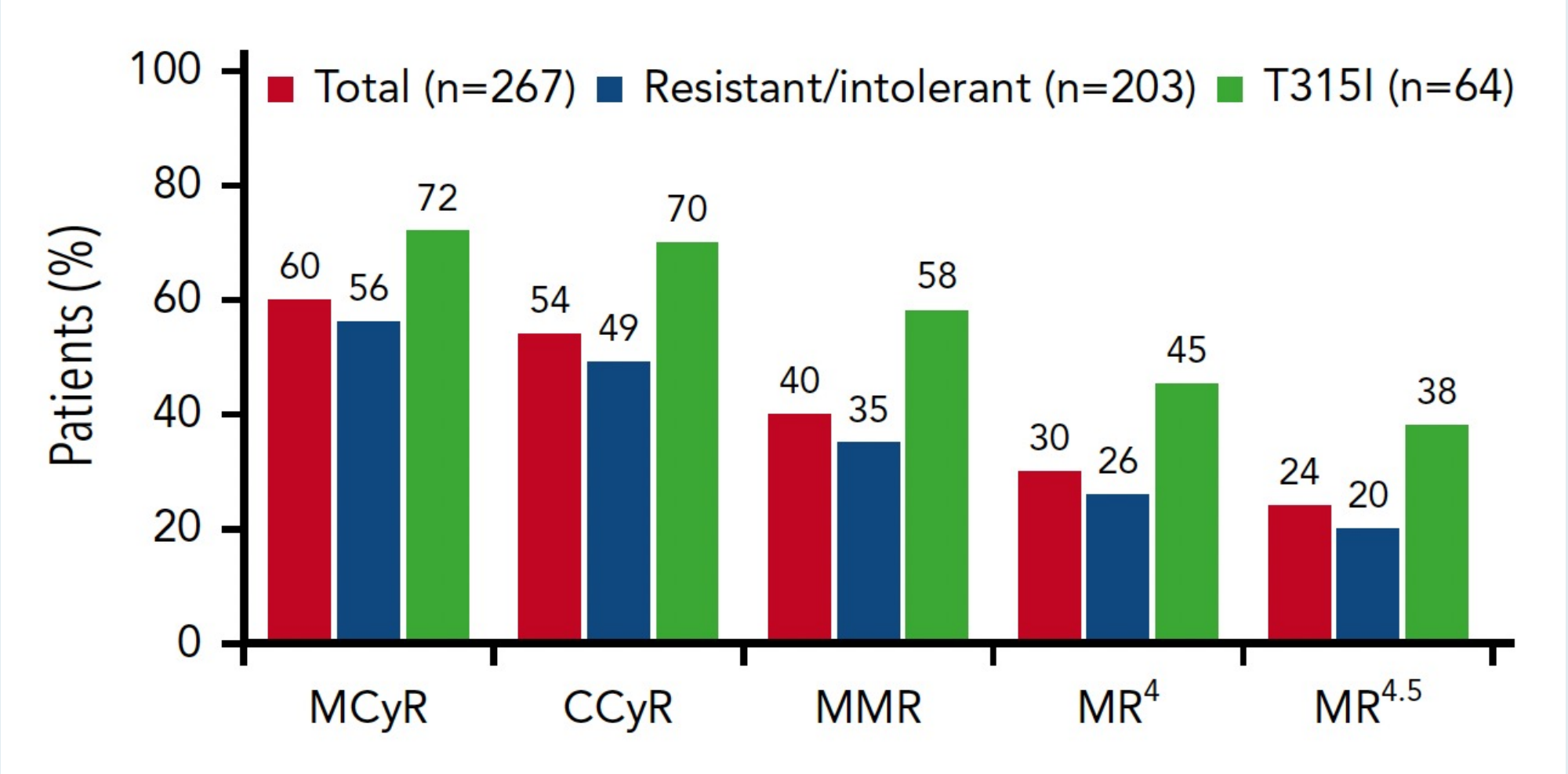
Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Ponatinib efficacy and safety in Philadelphia chromosome–positive leukemia: final 5-year results of the phase 2 PACE trial

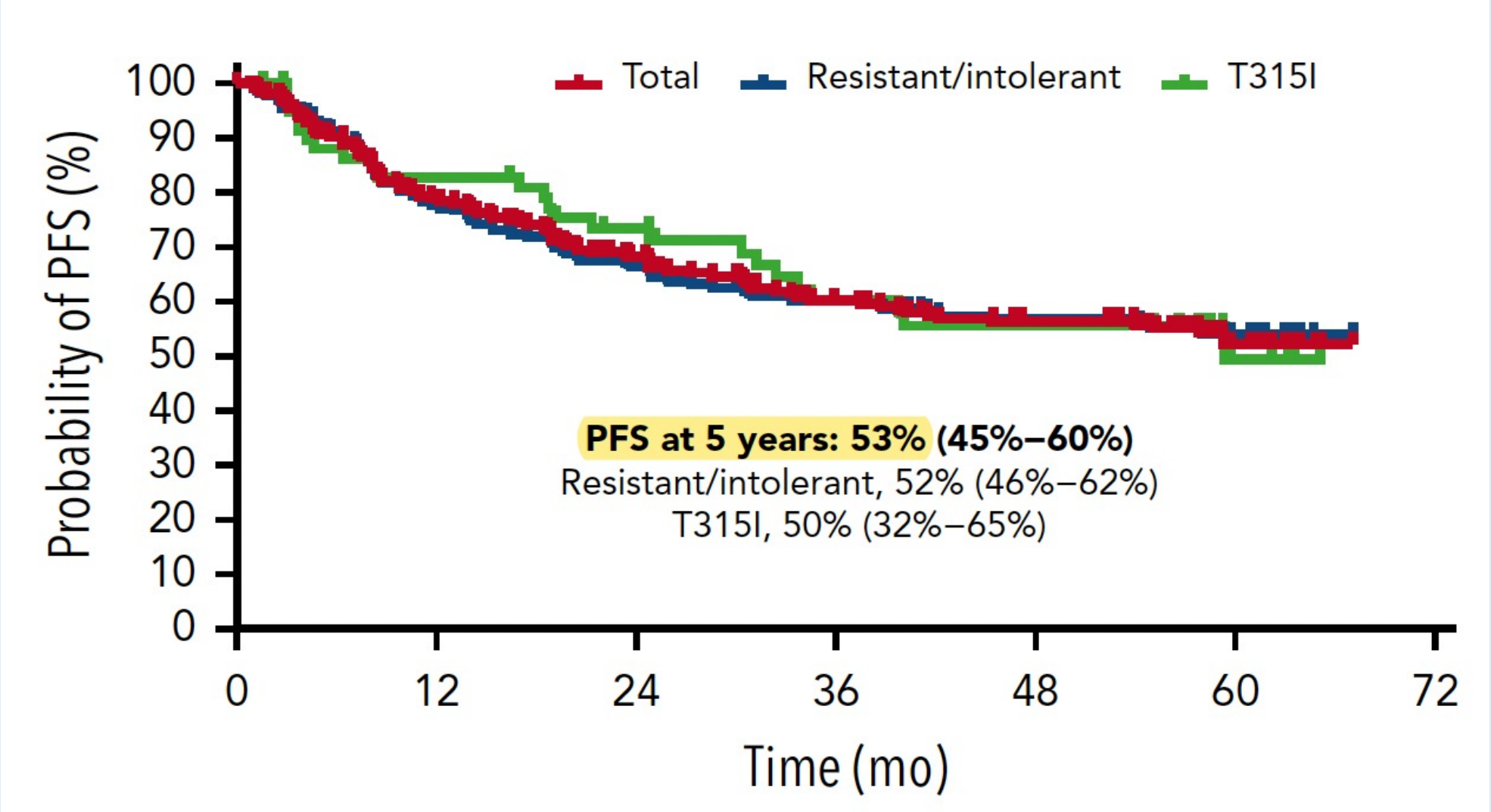
Jorge E. Cortes,[1] Dong-Wook Kim,[2] Javier Pinilla-Ibarz,[3] Philipp D. le Coutre,[4] Ronald Paquette,[5] Charles Chuah,[6] Franck E. Nicolini,[7] Jane F. Apperley,[8] H. Jean Khoury,[9] Moshe Talpaz,[10] Daniel J. DeAngelo,[11] Elisabetta Abruzzese,[12] Delphine Rea,[13] Michele Baccarani,[14] Martin C. Müller,[15] Carlo Gambacorti-Passerini,[16] Stephanie Lustgarten,[17] Victor M. Rivera,[17] Frank G. Haluska,[17] François Guilhot,[18,19] Michael W. Deininger,[20] Andreas Hochhaus,[21] Timothy P. Hughes,[22] Neil P. Shah,[23] and Hagop M. Kantarjian[1]

PACE: Response to Ponatinib



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

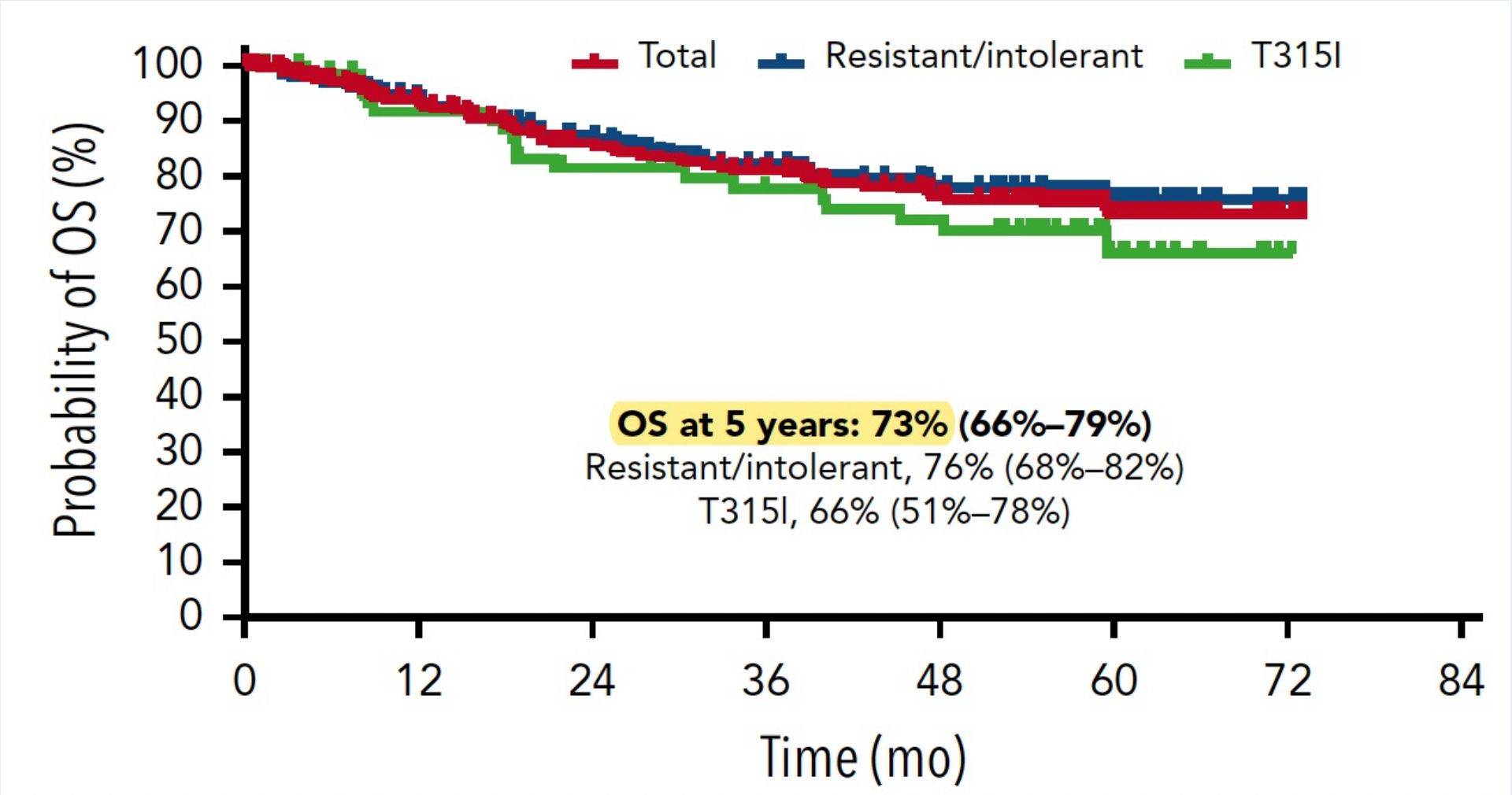
PACE: Progression-Free Survival at 5 Years



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

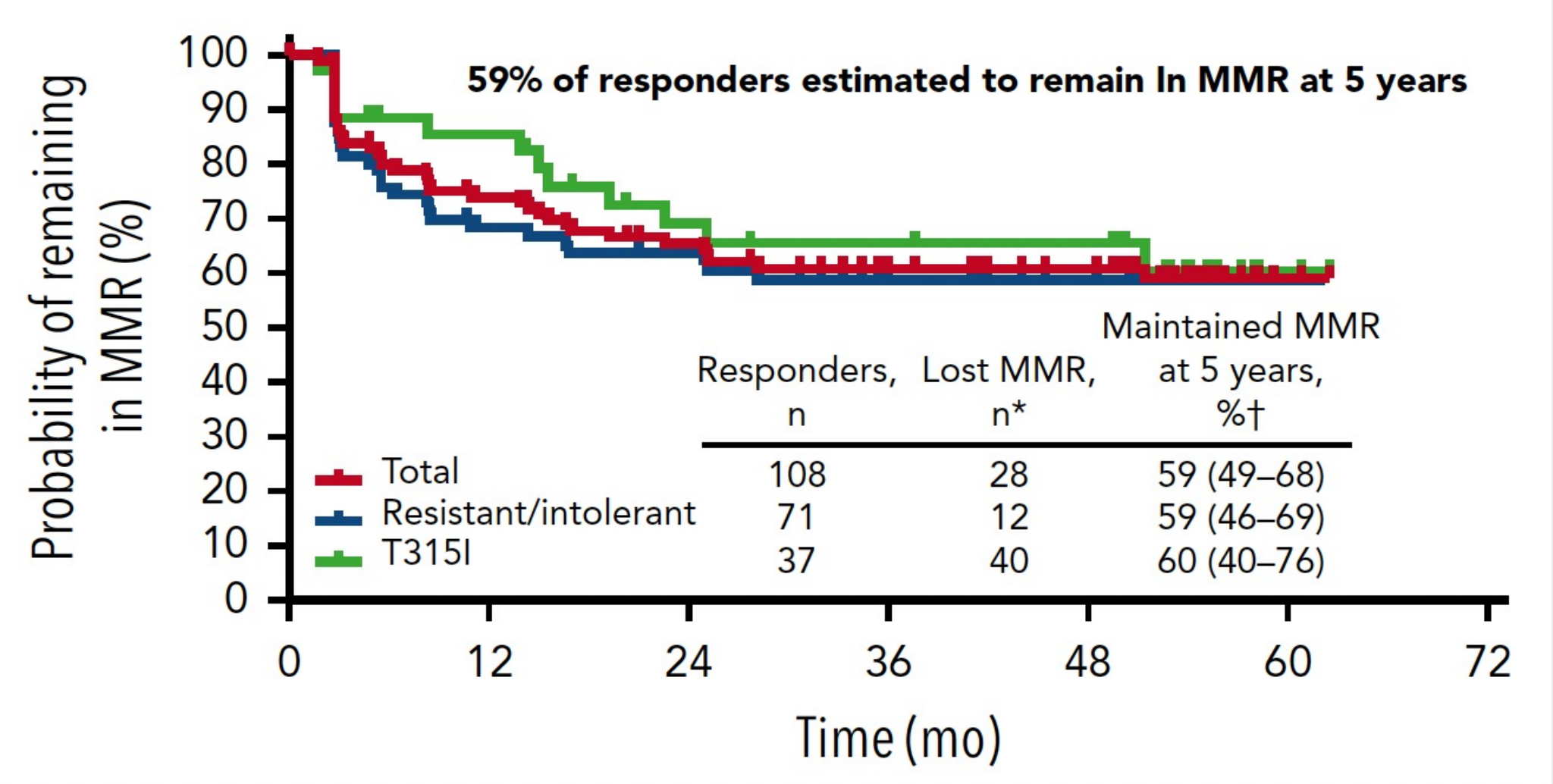
RTP RESEARCH TO PRACTICE

PACE: Overall Survival at 5 Years



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

PACE: Responders Remaining in MMR at 5 Years



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

PACE: Select Adverse Events in Patients with CP-CML (N = 270)

Adverse event	Any grade	Grade 3/4
Hematologic AEs		
Thrombocytopenia	46%	35%
Neutropenia	20%	17%
Anemia	20%	10%
Nonhematologic AEs		
Abdominal pain	46%	10%
Rash	47%	4%
Hypertension	37%	14%
Increased lipase	27%	13%

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

PACE: Cumulative and Exposure-Adjusted Incidence of Treatment-Emergent AOEs and VTEs in CP-CML (N = 270)

	CP-CML, n = 270	
	AE	SAE
AOEs, n (%)	84 (31)*	69 (26)†
Cardiovascular	42 (16)	33 (12)
Cerebrovascular	35 (13)	28 (10)
Peripheral vascular	38 (14)	31 (11)
Exposure-adjusted AOEs, no. of patients with events per 100 patient-years	14.1	10.9
VTEs, n (%)	15 (6)	13 (5)
Exposure-adjusted VTEs, no. of patients with events per 100 patient-years	2.1	1.8

AOE = arterial occlusive event; VTE = venous thromboembolic event

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

Blood 2021;138(21):2042-50.

Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Ponatinib dose-ranging study in chronic-phase chronic myeloid leukemia: a randomized, open-label phase 2 clinical trial

Jorge Cortes,[1] Jane Apperley,[2] Elza Lomaia,[3] Beatriz Moiraghi,[4] Maria Undurraga Sutton,[5] Carolina Pavlovsky,[6] Charles Chuah,[7] Tomasz Sacha,[8] Jeffrey H. Lipton,[9] Charles A. Schiffer,[10] James McCloskey,[11] Andreas Hochhaus,[12] Philippe Rousselot,[13] Gianantonio Rosti,[14] Hugues de Lavallade,[15] Anna Turkina,[16] Christine Rojas,[17] Christopher Kevin Arthur,[18] Lori Maness,[19] Moshe Talpaz,[20] Michael Mauro,[21] Tracey Hall,[22] Vickie Lu,[23] Shouryadeep Srivastava,[24] and Michael Deininger[25]

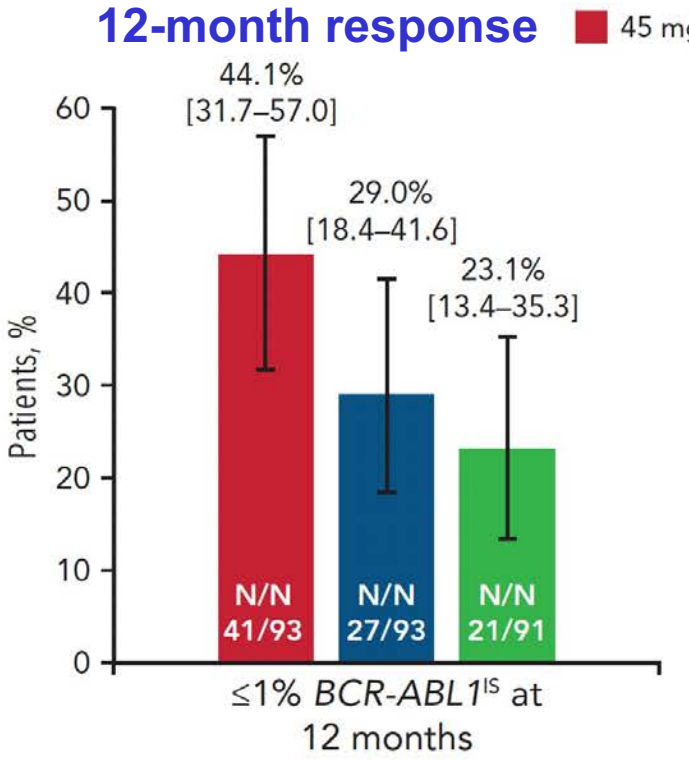
OPTIC: Patient Demographics and Baseline Disease Characteristics

Characteristic	Cohort		
	45 mg (n = 94)	30 mg (n = 94)	15 mg (n = 94)
Patients with CV risk factors			
Hypertension	26 (28)	25 (27)	22 (23)
Diabetes mellitus	5 (5)	3 (3)	7 (7)
Hyperlipidemia	19 (20)	14 (15)	16 (17)
Patients with ≥1 CV risk factor	32 (34)	30 (32)	32 (34)
Patients with >1 CV risk factor	5 (5)	4 (4)	4 (4)
***BCR-ABL1* mutations**			
No mutation	51 (54)	58 (62)	54 (57)
Any mutation	41 (44)	35 (37)	39 (42)
T315I	25 (27)	21 (22)	21 (22)
Reason prior therapy stopped			
Resistant	92 (98)	94 (100)	94 (100)
Best response to last prior therapy			
CHR or worse	61 (65)	55 (59)	57 (61)
≤1% *BCR-ABL1*^{IS} or better	2 (2)	7 (7)	7 (7)

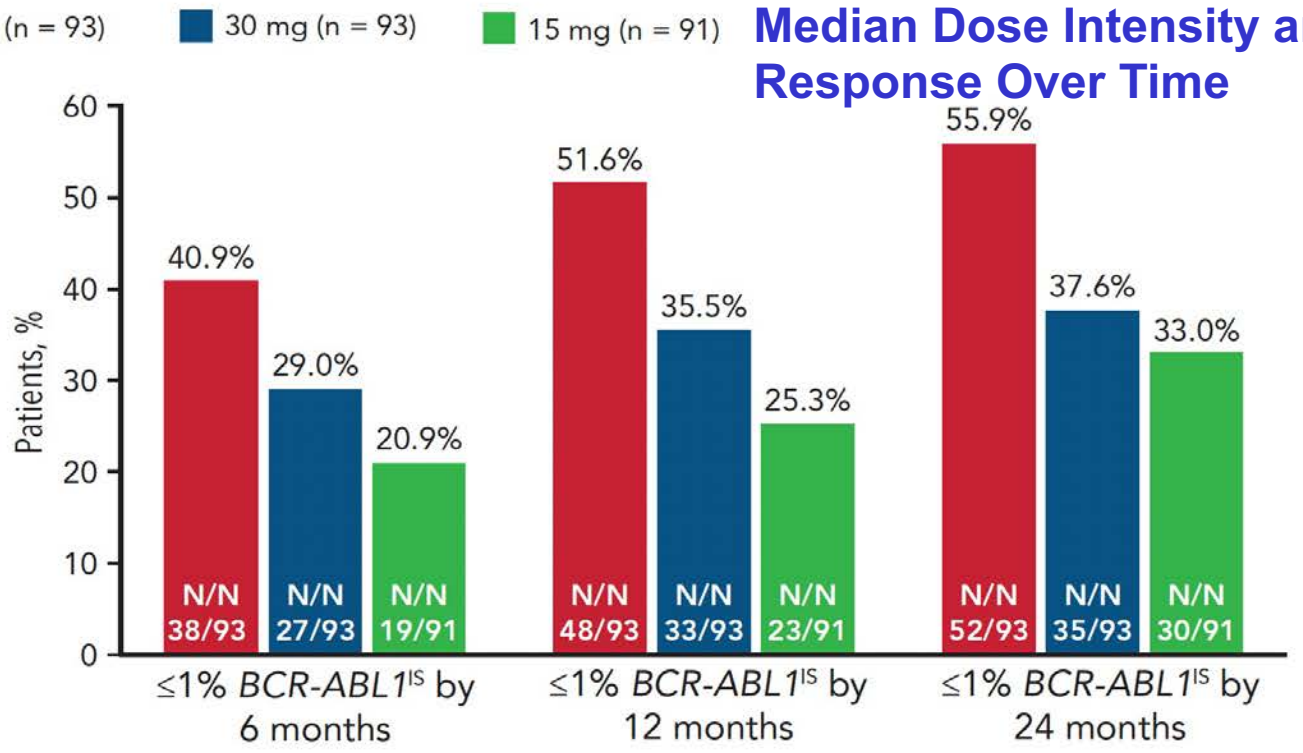
Cortes J et al. *Blood* 2021;138(21):2042-50.

OPTIC: Response to Once-Daily Ponatinib

12-month response



Median Dose Intensity and Response Over Time



Median dose intensity, mg/d			
Cohort	6 months	12 months	24 months
45 mg	35.2	15.0	15.0
30 mg	30.0	28.0	15.0
15 mg	15.0	15.0	15.0

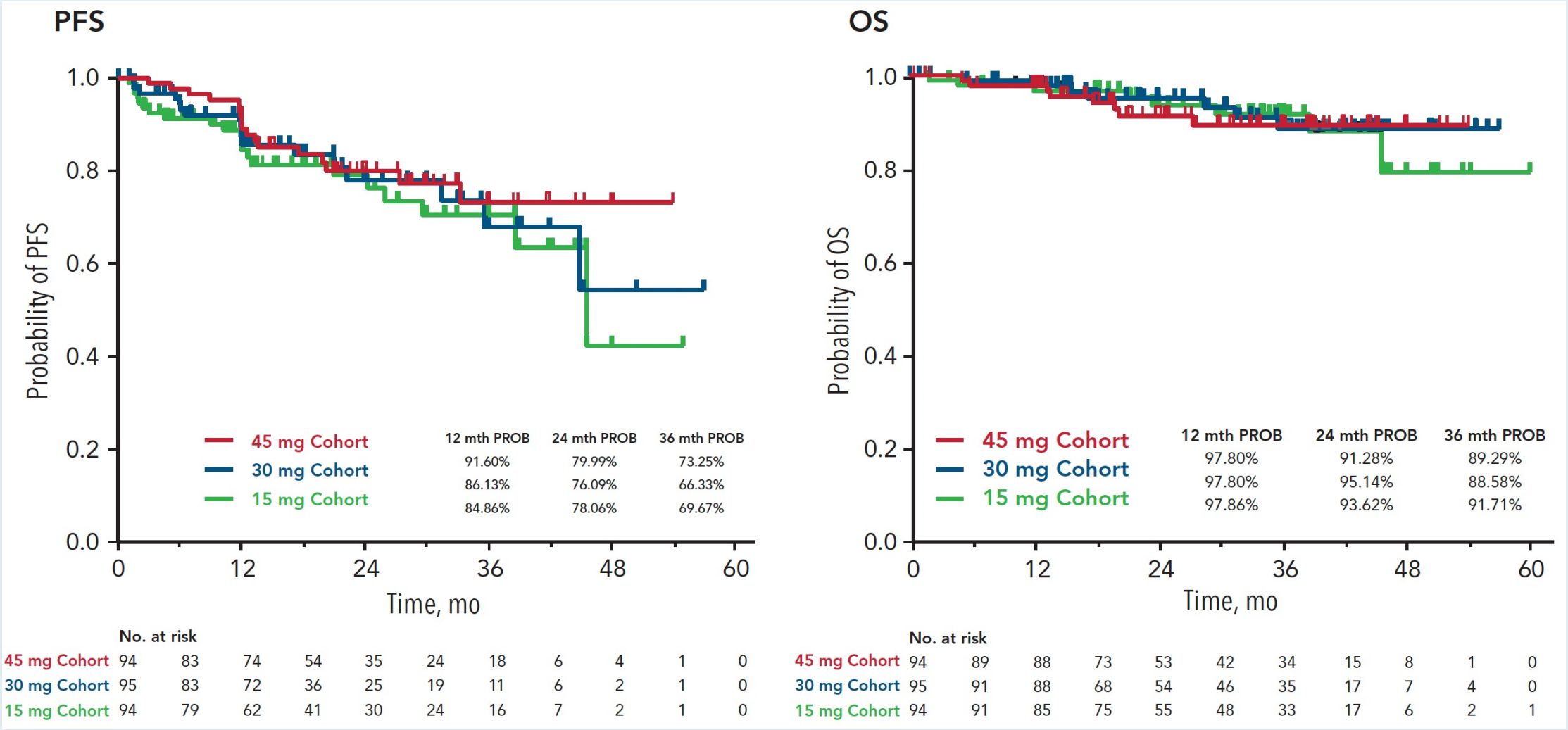
Cortes J et al. *Blood* 2021;138(21):2042-50.

OPTIC: Summary of Response Rates

Response	Cohort, n/n (%)		
	45 mg	30 mg	15 mg
≤1% *BCR-ABL1*^{IS} by 12 mo	48/93 (51.6)	33/93 (35.5)	23/91 (25.3)
Mutation status at baseline*			
T315I mutation	15/25 (60.0)	5/20 (25.0)	2/19 (10.5)
No T315I mutation	32/66 (48.5)	28/73 (38.4)	21/71 (29.6)
Mutation other than T315I	9/16 (56.3)	6/15 (40.0)	6/18 (33.3)
No mutation	23/50 (46.0)	22/58 (37.9)	15/53 (28.3)
Best response to last prior therapy			
CHR or worse	27/54 (50)	11/53 (20.8)	8/52 (15.4)
Better than CHR	14/28 (50)	17/29 (58.6)	9/23 (39.1)

Cortes J et al. *Blood* 2021;138(21):2042-50.

OPTIC: Survival Analyses



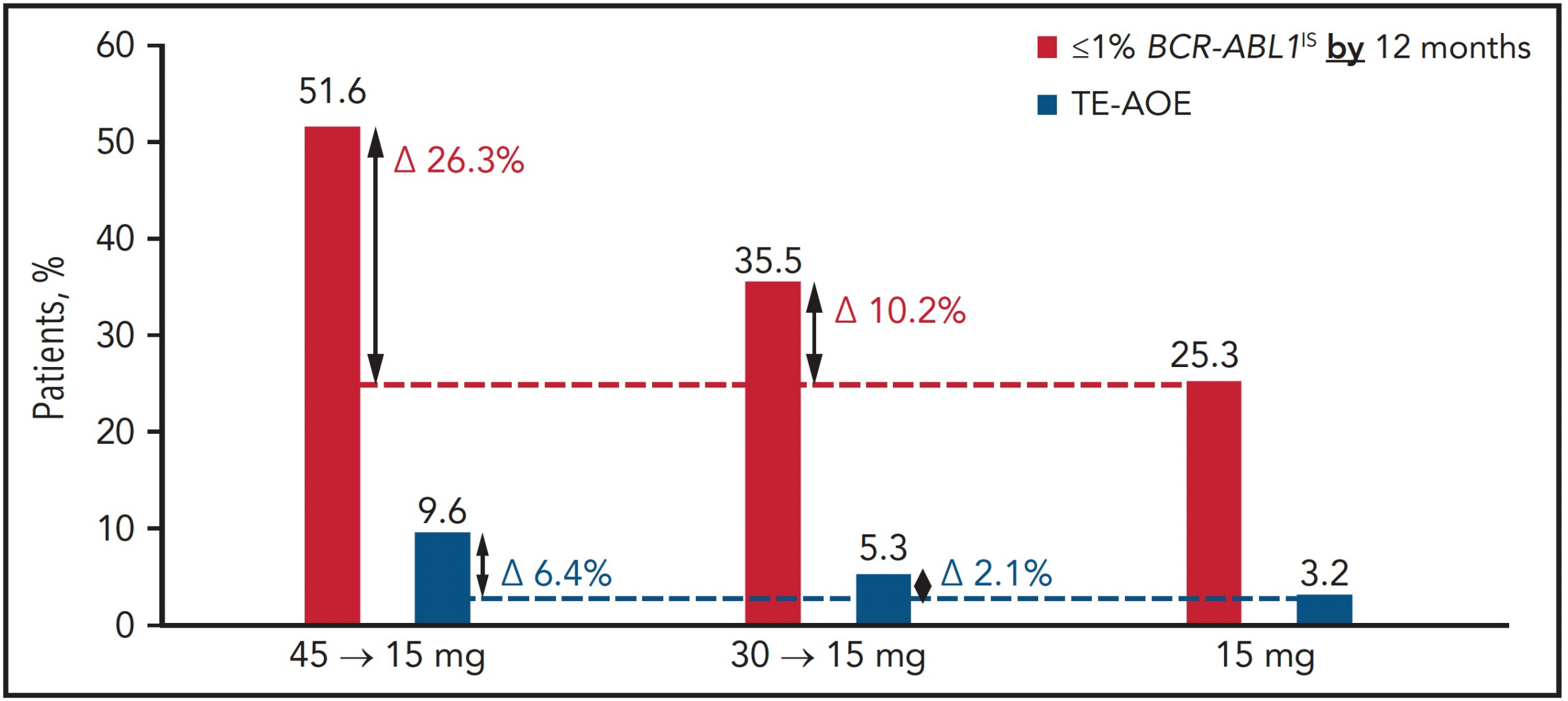
Cortes J et al. *Blood* 2021;138(21):2042-50.

OPTIC: Summary of Adverse Events

	Cohort, n (%)		
	45 mg (n = 94)	30 mg (n = 94)	15 mg (n = 94)
TEAEs			
Any TEAE	94 (100)	88 (93.6)	89 (94.7)
Grade ≥3 TEAEs	64 (68.1)	58 (61.7)	60 (63.8)
Serious TEAEs	32 (34)	24 (25.5)	31 (33.0)
Grade 5 TEAEs	2 (2.1)	0	2 (2.1)
Dose modifications for TEAEs			
Discontinuation	18 (19.1)	15 (16.0)	13 (13.8)
Reduction	43 (45.7)	33 (35.1)	30 (31.9)
Interruption	67 (71.3)	58 (61.7)	55 (58.5)
TE-AOEs			
Any AOE	9 (9.6)	5 (5.3)	3 (3.2)
Serious TE-AOEs	4 (4.3)	4 (4.3)	3 (3.2)
Grade ≥3 TE-AOEs	5 (5.3)	5 (5.3)	3 (3.2)
Dose modifications for AOE			
Discontinuation	4 (4.3)	3 (3.2)	1 (1.1)
Reduction	0	1 (1.1)	0
Interruption	2 (2.1)	3 (3.2)	1 (1.1)

Cortes J et al. *Blood* 2021;138(21):2042-50.

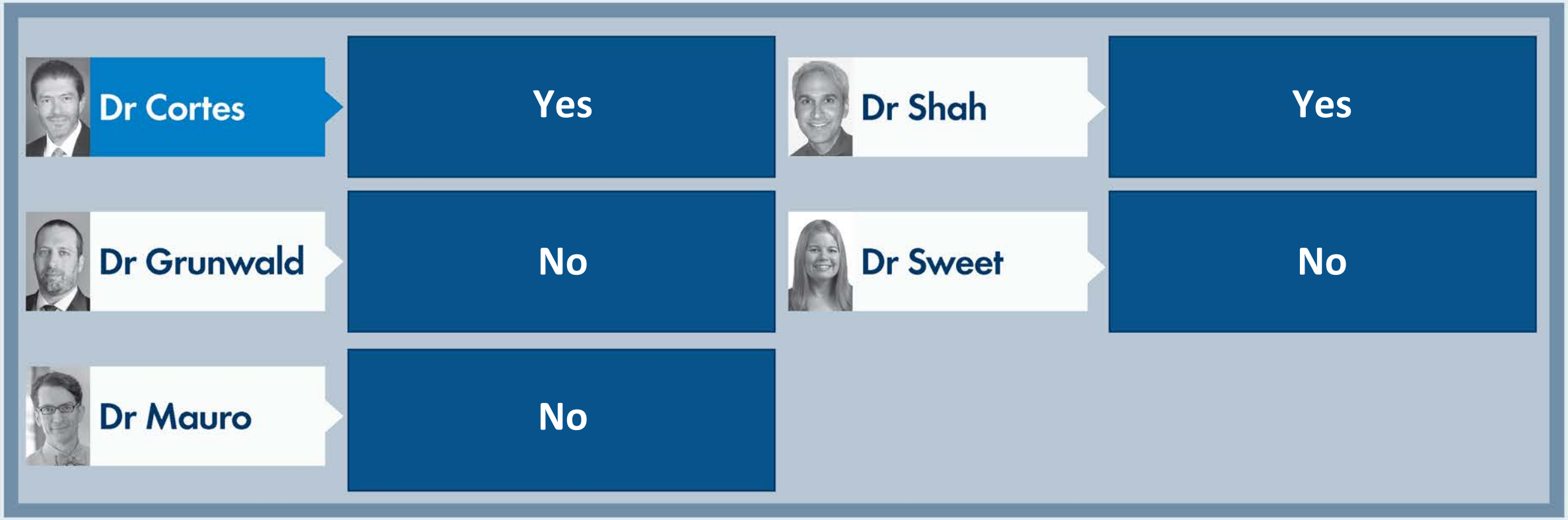
OPTIC: Overall Safety and Efficacy by Starting Dose



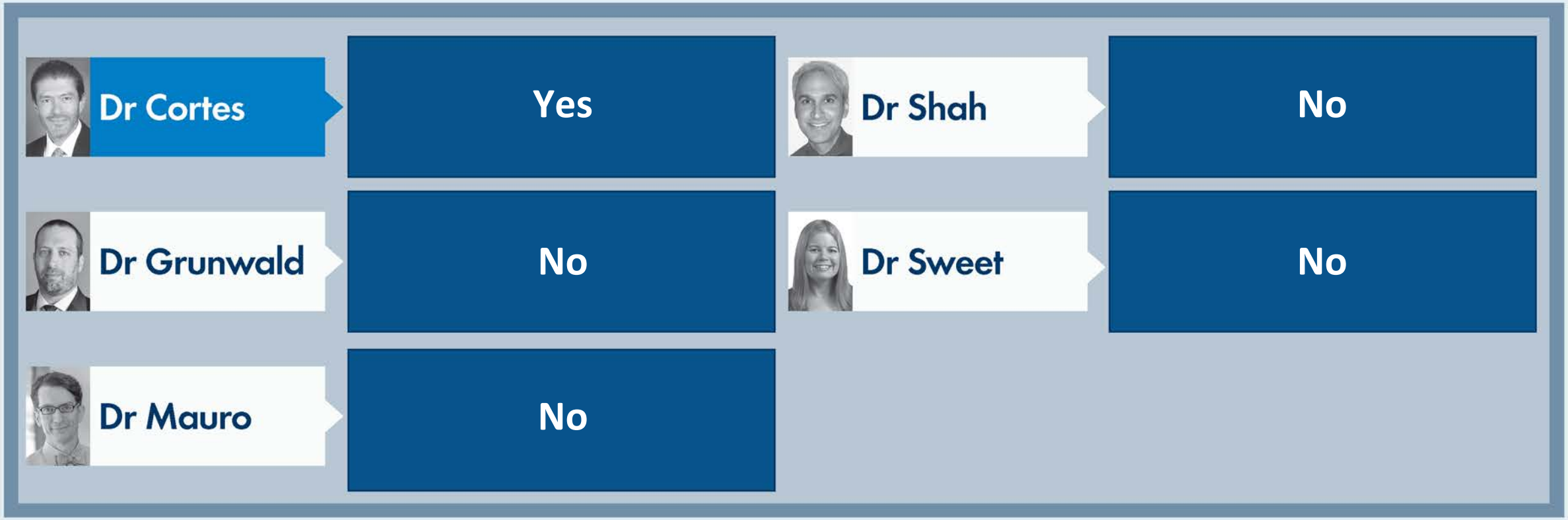
Cortes J et al. *Blood* 2021;138(21):2042-50.

Faculty Survey

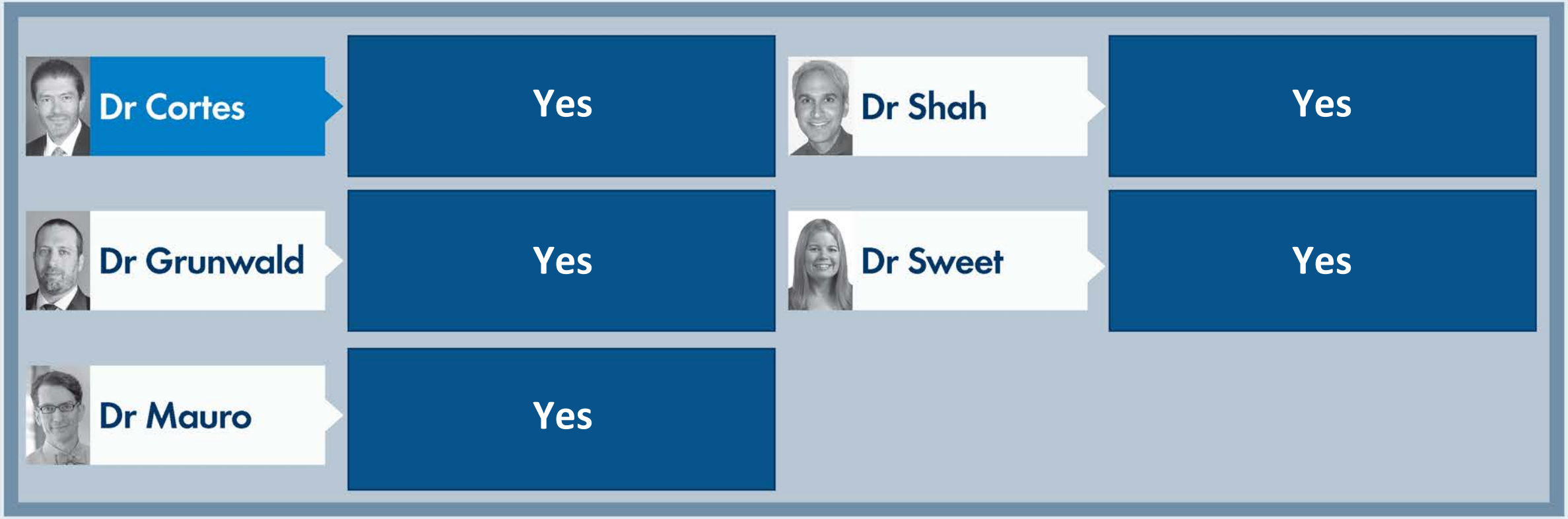
Have you observed any patients who experienced cardiovascular events that you believe to be related to treatment with ponatinib?



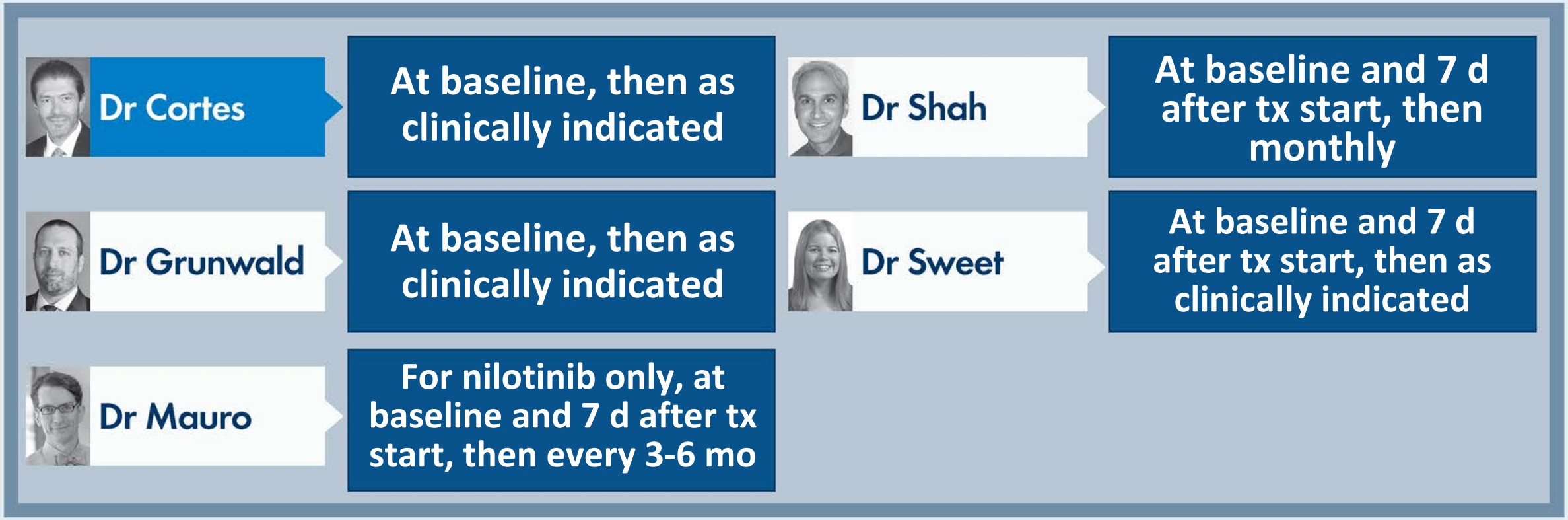
Have you observed any patients who experienced cardiovascular events that you believe to be related to treatment with imatinib?



Have you observed any patients who experienced cardiovascular events that you believe to be related to treatment with a second-generation TKI?



How often do you order an EKG for patients with chronic-phase CML who have started treatment with nilotinib, bosutinib or dasatinib?



How often do you order an EKG for patients with chronic-phase CML who have started treatment with asciminib?

 Dr Cortes	At baseline, then as clinically indicated
 Dr Grunwald	At baseline, then as clinically indicated
 Dr Mauro	As clinically indicated
 Dr Shah	As clinically indicated
 Dr Sweet	As clinically indicated

What is your preferred management strategy for a patient with chronic-phase CML who develops a cardiac arrhythmia on a TKI?

Dr Cortes

Hold therapy for full assessment of contributing factors, including referral to cardiologist

Dr Grunwald

Switch to an alternate TKI

Dr Mauro

Continue TKI tx and manage cardiovascular issues separately

Dr Shah

Hold drug and restart with dose reduction after tx of arrhythmia

Dr Sweet

Approach varies depending on the TKI

RTP RESEARCH TO PRACTICE

Based on available clinical data and your personal experience, how do the severity and frequency of gastrointestinal side effects associated with asciminib compare to those with other TKIs in the treatment of CML?

Dr Cortes

Less frequent and severe with asciminib

Dr Shah

Less frequent and severe with asciminib

Dr Grunwald

Less frequent and severe with asciminib

Dr Sweet

Less frequent and severe with asciminib

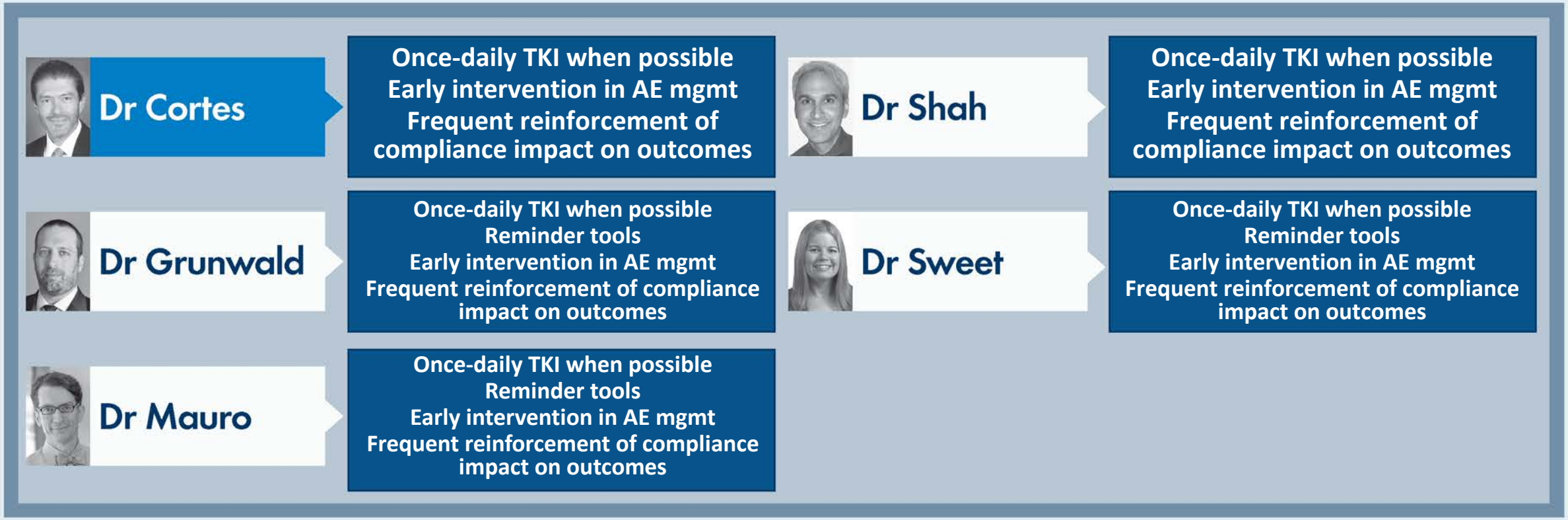
Dr Mauro

Less frequent and severe with asciminib

RTP RESEARCH TO PRACTICE

Based on available clinical data and your personal experience, how do the severity and frequency of dermatologic side effects associated with asciminib compare to those with other TKIs in the treatment of CML?

Which tools do you use to encourage compliance with TKI therapy?



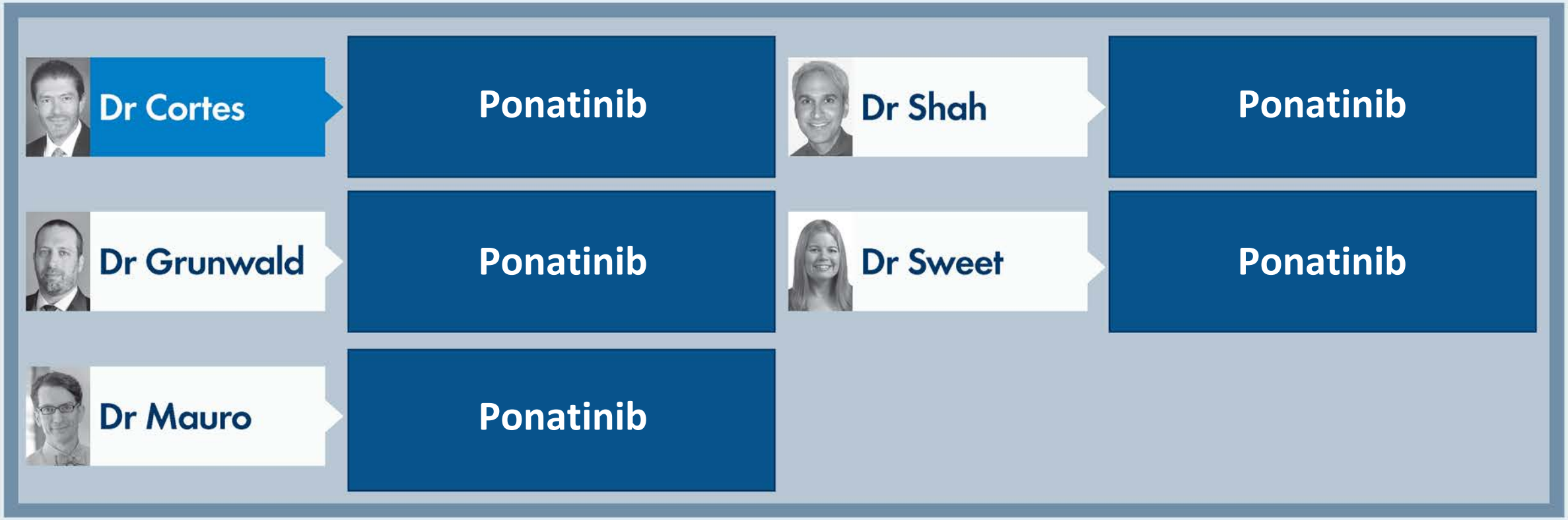
RTP
RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, what second-line treatment would you recommend for a patient with chronic-phase CML who develops disease progression after imatinib and is found to have a V299L BCR-ABL kinase domain mutation?

 Dr Cortes	Nilotinib	 Dr Shah	Nilotinib
 Dr Grunwald	Nilotinib	 Dr Sweet	Nilotinib
 Dr Mauro	Ponatinib or asciminib		

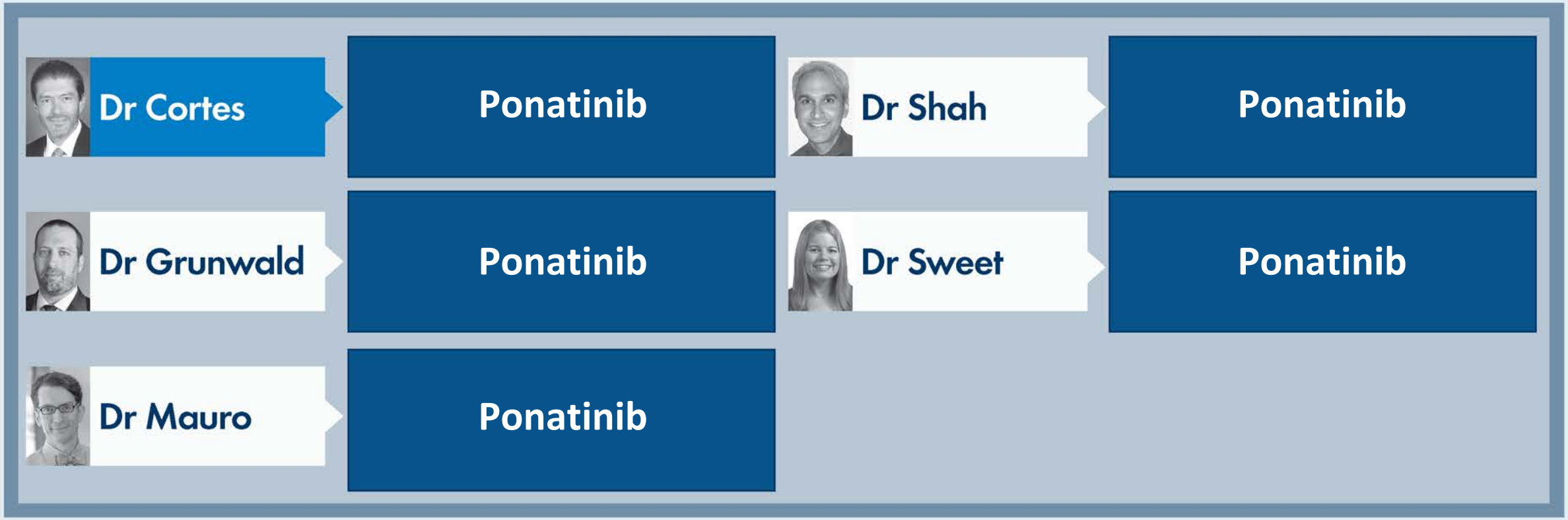
Regulatory and reimbursement issues aside, what second-line treatment would you recommend for a patient with chronic-phase CML who develops disease progression after imatinib and is found to have an E255V BCR-ABL kinase domain mutation?

What second-line therapy would you recommend for a 50-year-old patient with chronic-phase CML who develops disease resistance to dasatinib and is found to have a T315I mutation?



Based on available clinical data and your personal experience, how would you compare the efficacy of ponatinib to that of asciminib for the treatment of chronic-phase CML with a T315I mutation?

What would be your preferred TKI for a patient with well controlled hypertension and chronic-phase CML with a T315I mutation?



What would be your preferred TKI for a patient with a history of coronary artery disease and chronic-phase CML with a T315I mutation?

What is your preferred dose and schedule of asciminib for patients with chronic-phase CML with a T315I mutation?

What is your preferred starting dose and schedule of ponatinib for patients with chronic-phase CML with a T315I mutation?

Based on available clinical data and your personal experience, how would you compare the tolerability of asciminib to that of ponatinib?

Dr Cortes

About the same

Dr Shah

Asciminib is better tolerated

Dr Grunwald

Asciminib is better tolerated

Dr Sweet

Ponatinib is better tolerated

Dr Mauro

Asciminib is better tolerated

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In general, what would be your preferred agent for the treatment of chronic-phase CML with compound T315I and Y253H mutations?

Regulatory and reimbursement issues aside, what would be your preferred initial treatment for a patient with a history of COPD with chronic-phase CML?

Based on available clinical data and your personal experience, in general, which TKI has the best overall toxicity/tolerability profile?

Based on available clinical data and your personal experience, in general, which TKI has the lowest incidence of requiring dose reductions, dose delays or discontinuation for toxicity?

Meet The Professor

Non-Small Cell Lung Cancer with an Actionable Target Beyond EGFR

Thursday, June 30, 2022
5:00 PM – 6:00 PM ET

Faculty

Joel W Neal, MD, PhD

Moderator

Neil Love, MD

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Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

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