What Clinicians Want to Know: Addressing Current Questions and Controversies in the Management of Chronic Myeloid Leukemia

A CME Friday Satellite Symposium Preceding the 66th ASH Annual Meeting

Friday, December 6, 2024

7:30 AM – 9:00 AM PT (10:30 AM – 12:00 PM ET)

Faculty

Professor Andreas Hochhaus

B Douglas Smith, MD

Moderator

Michael J Mauro, MD

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Faculty

Professor Andreas Hochhaus
Hematology/Oncology
Jena University Hospital
Comprehensive Cancer Center Central Germany
Campus Jena
Jena, Germany

B Douglas Smith, MD
Professor, Oncology
Division of Hematologic Malignancies
Sidney Kimmel Comprehensive Cancer Center
at Johns Hopkins
Baltimore, Maryland

Moderator

Michael J Mauro, MD
Director, Chronic Myeloid Leukemia Program
Attending Physician, Leukemia Service
Memorial Sloan Kettering Cancer Center
New York, New York

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Prof Hochhaus — Disclosures
Faculty

Consulting Agreement	Novartis
Contracted Research	Enliven Therapeutics, Incyte Corporation, Novartis, Pfizer Inc, Terns Pharmaceuticals

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Dr Smith — Disclosures
Faculty

Consulting Agreements	Bristol Myers Squibb, Novartis, Pfizer Inc, Servier Pharmaceuticals LLC

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Dr Mauro — Disclosures
Moderator

Advisory Committees and Consulting Agreements	Bristol Myers Squibb, Enliven Therapeutics, Novartis, Takeda Pharmaceuticals USA Inc, Terns Pharmaceuticals
Contracted Research	Enliven Therapeutics, Novartis, Terns Pharmaceuticals, Sun Pharma Advanced Research Company (SPARC), Sun Pharmaceutical Industries Ltd

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Commercial Support

This activity is supported by an educational grant from Novartis.

Research To Practice CME Planning Committee Members, Staff and Reviewers

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This educational activity contains discussion of non-FDA-approved uses of agents and regimens. Please refer to official prescribing information for each product for approved indications.

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What Clinicians Want to Know: Addressing Current Questions and Controversies Regarding the Role of CAR T-Cell Therapy and Bispecific Antibodies in the Management of Lymphoma

A CME Friday Satellite Symposium and Webcast Preceding the 66th ASH Annual Meeting

Friday, December 6, 2024

11:30 AM – 1:30 PM PT (2:30 PM – 4:30 PM ET)

Faculty

Jennifer Crombie, MD

Martin Hutchings, MD, PhD

Matthew Lunning, DO

Tycel Phillips, MD

Moderator

Jeremy S Abramson, MD, MMSc

RTP RESEARCH TO PRACTICE

What Clinicians Want to Know: Addressing Current Questions and Controversies in the Management of Myelofibrosis

A CME Friday Satellite Symposium and Webcast Preceding the 66th ASH Annual Meeting

Friday, December 6, 2024

11:30 AM – 1:30 PM PT (2:30 PM – 4:30 PM ET)

Faculty

Prithviraj Bose, MD

Angela G Fleischman, MD, PhD

Abdulraheem Yacoub, MD

Moderator

Andrew T Kuykendall, MD

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What Clinicians Want to Know: Addressing Current Questions and Controversies in the Management of Acute Myeloid Leukemia

A CME Friday Satellite Symposium and Webcast Preceding the 66th ASH Annual Meeting

Friday, December 6, 2024

3:15 PM – 5:15 PM PT (6:15 PM – 8:15 PM ET)

Faculty

Alexander Perl, MD
Richard M Stone, MD
Eunice S Wang, MD
Andrew H Wei, MBBS, PhD

Moderator

Eytan M Stein, MD

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What Clinicians Want to Know: Addressing Current Questions and Controversies in the Management of Multiple Myeloma

A CME Friday Satellite Symposium and Webcast Preceding the 66th ASH Annual Meeting

Friday, December 6, 2024

3:15 PM – 5:15 PM PT (6:15 PM – 8:15 PM ET)

Faculty

Professor Philippe Moreau, MD
Robert Z Orlowski, MD, PhD
Noopur Raje, MD
Paul G Richardson, MD

Moderator

Sagar Lonial, MD

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Rounds with the Investigators: Compelling Teaching Cases Focused on the Management of Breast Cancer

A 3-Part CME Hybrid Satellite Symposium Series in Partnership with the 2024 San Antonio Breast Cancer Symposium®

HER2-Low and HER2-Ultralow Breast Cancer

Tuesday, December 10, 2024

7:15 PM – 8:45 PM CT

New Developments in Endocrine Treatment for Breast Cancer

Wednesday, December 11, 2024

7:15 PM – 9:15 PM CT

Management of Metastatic Breast Cancer

Thursday, December 12, 2024

7:00 PM – 9:00 PM CT

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Save The Date

Fourth Annual
National General Medical Oncology Summit

A Multitumor CME/MOC-, NCPD- and ACPE-Accredited Educational Conference Developed in Partnership with Florida Cancer Specialists & Research Institute

Friday to Sunday, February 28 to March 2, 2025

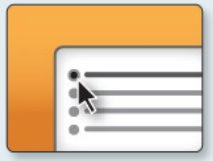
Fontainebleau Hotel, Miami Beach, Florida

Moderated by Neil Love, MD

Clinicians in the Meeting Room

Networked iPads are available.

Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.



Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.

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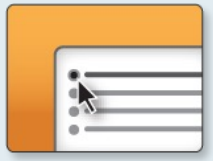
Clinicians Attending via Zoom

Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.



Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

Get CME Credit: A CME credit link will be provided in the chat room at the conclusion of the program.

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
  An email will be sent to all attendees when the activity is available.
- To learn more about our education programs, visit our website, **www.ResearchToPractice.com**

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What Clinicians Want to Know: Addressing Current Questions and Controversies in the Management of Chronic Myeloid Leukemia

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Michael J Mauro, MD

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Survey of General Medical Oncologists: November 22nd – December 5th

Results available on iPads and Zoom chat room

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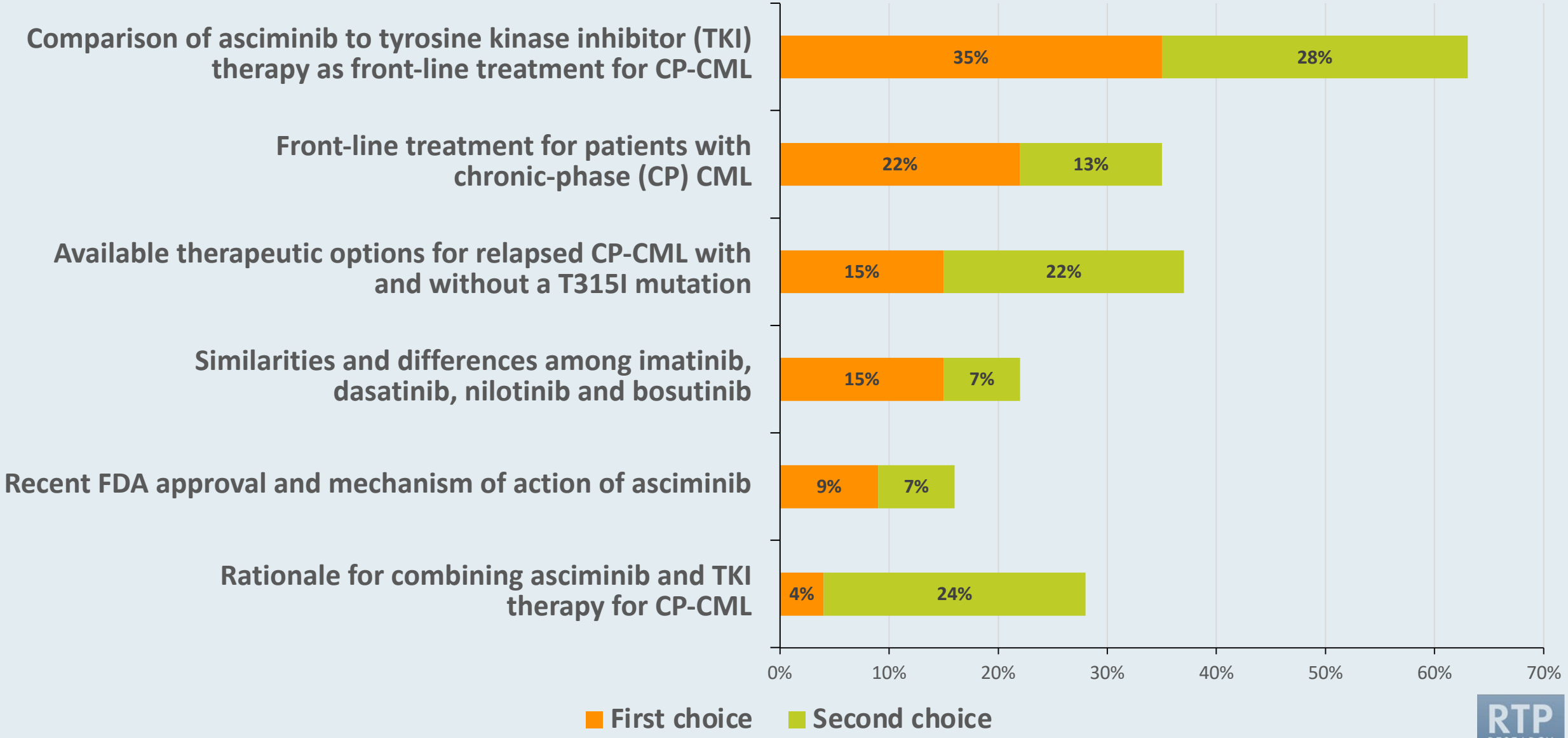
Agenda

Module 1: Up-Front Therapy for Chronic Myeloid Leukemia (CML) — Prof Hochhaus

Module 2: Management of Relapsed CML, Including in Patients with a T315I Mutation — Dr Mauro

Module 3: Tolerability and Other Practical Issues with Commonly Employed CML Therapies — Dr Smith

Topics of Interest for Future CME Programs



RTP RESEARCH TO PRACTICE

Agenda

Module 1: Up-Front Therapy for Chronic Myeloid Leukemia (CML) — Prof Hochhaus

Module 2: Management of Relapsed CML, Including in Patients with a T315I Mutation — Dr Mauro

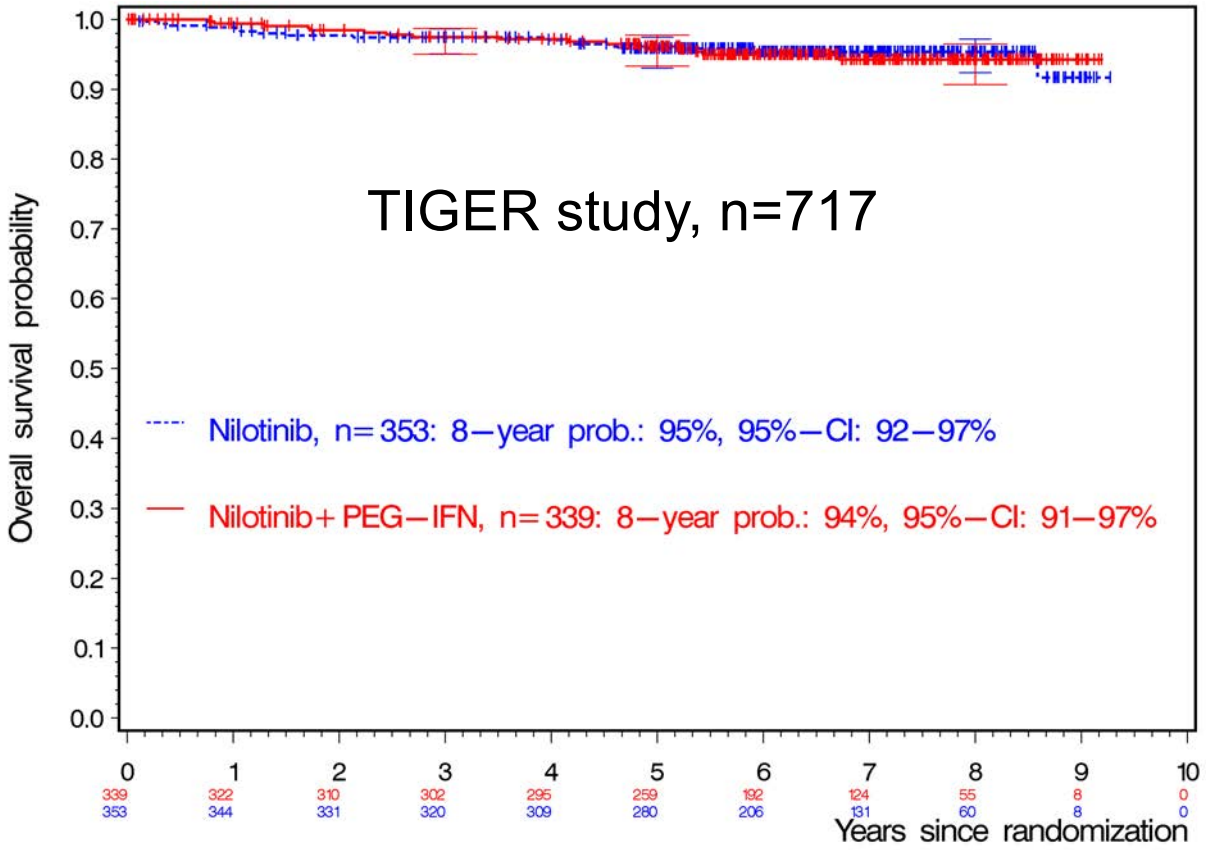
Module 3: Tolerability and Other Practical Issues with Commonly Employed CML Therapies — Dr Smith

Up-Front Therapy for Chronic Myeloid Leukemia

Andreas Hochhaus

Universitätsklinikum Jena
Comprehensive Cancer Center Central Germany
Jena, Germany

Survival of CML patients is close to survival of the normal population



8-year overall survival 95%

Treatment goals of CML patients in 2024

- ✓ Normal survival
- ✓ Lack of progression
- ✓ Optimal quality of life
- ✓ Optimal tolerability of the therapy
- ✓ Absence of long term side effects
- ✓ Chance to achieve treatment free remission (TFR)

Hochhaus et al. EHA 2023

Evolution of first line therapies 2001 – 2024

Registration	**2001** **Imatinib**	→	**2010** **Nilotinib / Dasatinib**			**2017** **Bosutinib**	→	**2024** **Asciminib**
Milestones	CCyR	→	2006 MMR		2012 EMR	2014 DMR		
			↓			↓		
Goals of therapy	Survival		Efficacy		Tolerability	TFR	→	Quality of life
Concerns	Global access Severe Adverse Events BCR::ABL1 mutations					BCR::ABL1 independent clonal evolution		

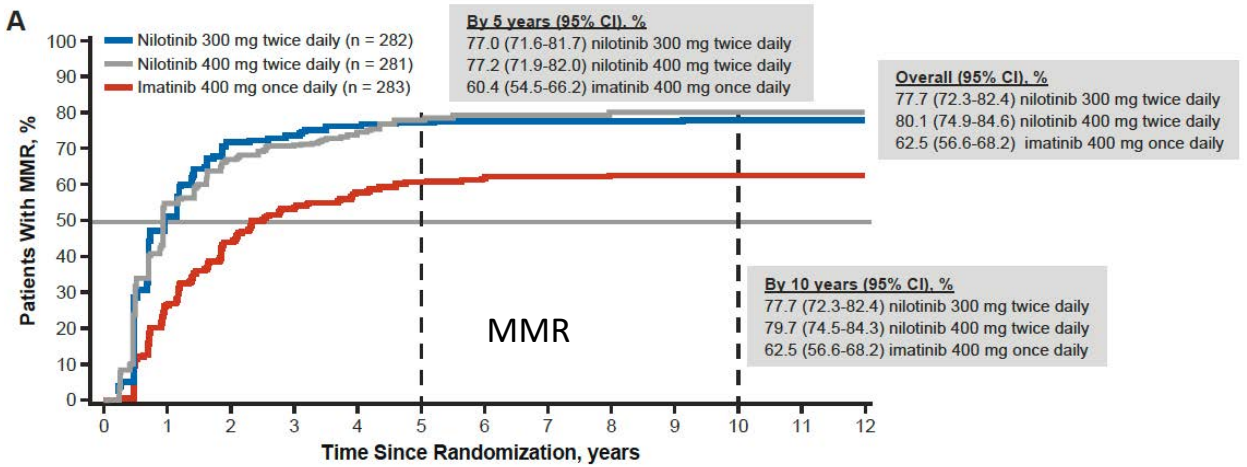
Treatment goals for patients with CML in chronic phase

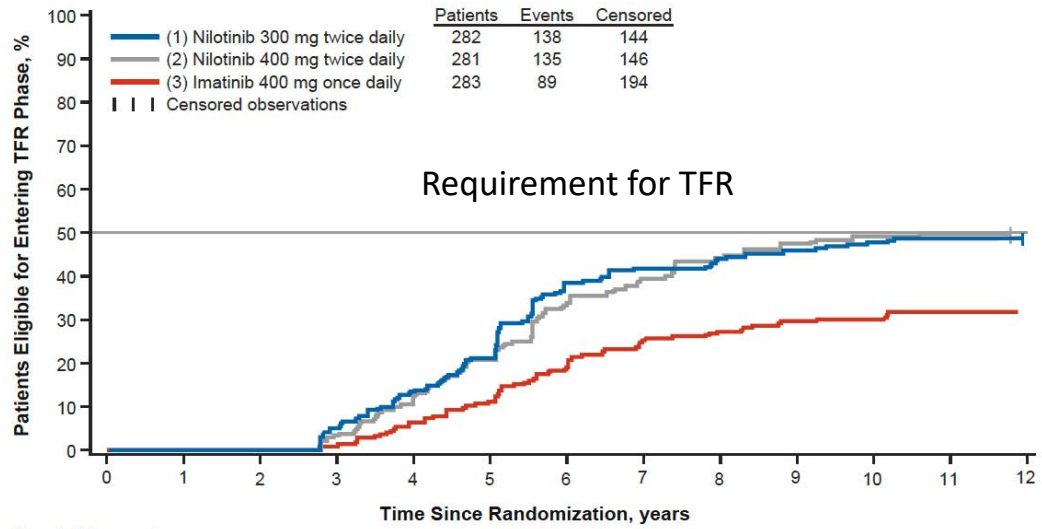
- As patients are living longer with the advent of TKI therapy, **QoL** has become an important treatment goal
- Patients with newly diagnosed CML-CP may wish to strive for **DMR** with the goal of **attempting TFR**
- ≥2nd line: **Prevention of disease progression** and achievement of CCyR or MMR within 12 mo. after 1st line therapy
- In resource-poor countries, the availability of effective drugs and essential monitoring may be limited, and the goal of treatment remains survival

More patients are eligible for a TFR attempt with 2G-TKI
ENESTnd: Nilotinib vs. Imatinib

Newly diagnosed Ph+ CML in CP

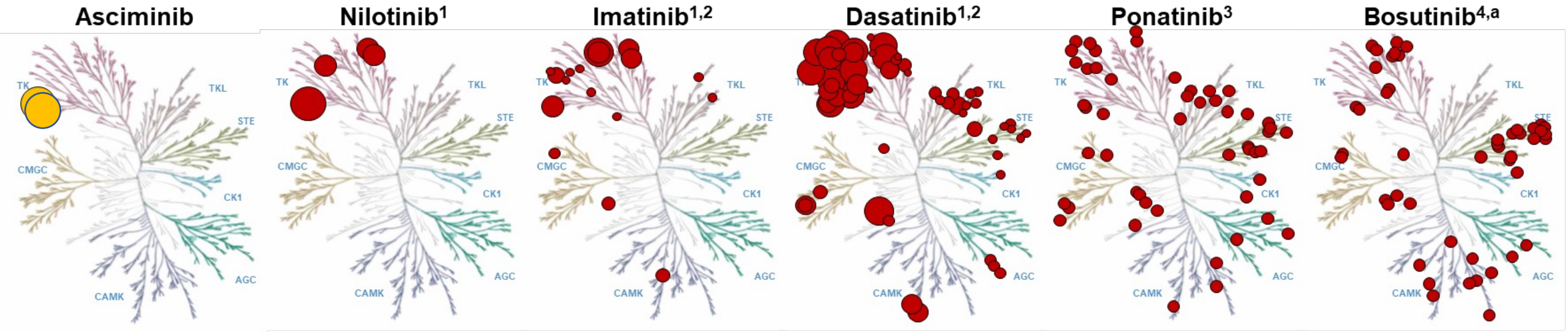
- Nilotinib 2*300 mg/d
- Nilotinib 2*400 mg/d
- Imatinib 400 mg/d





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

Selectivity of kinase inhibitors



Kinases bound by ATP-competitive TKIs are indicated by **red** circles.
Kinases bound by STAMP inhibitor are indicated by **yellow** circles.

[a] Bosutinib inhibits additional kinases that are not depicted in the dendrogram.
ATP, adenosine triphosphate; TKI, tyrosine kinase inhibitor;
STAMP, Specifically Targeting the ABL Myristoyl Pocket.

1. Steegmann JL, et al. Leuk Lymphoma. 2012;53:2351-2361.
2. Karaman MW, et al. Nat Biotechnol. 2008;26:127-132.
3. Lang JD, et al. Clin Cancer Res. 2018;24:1932-1943.
4. Remsing Rix LL, et al. Leukemia. 2009;23:447-485.

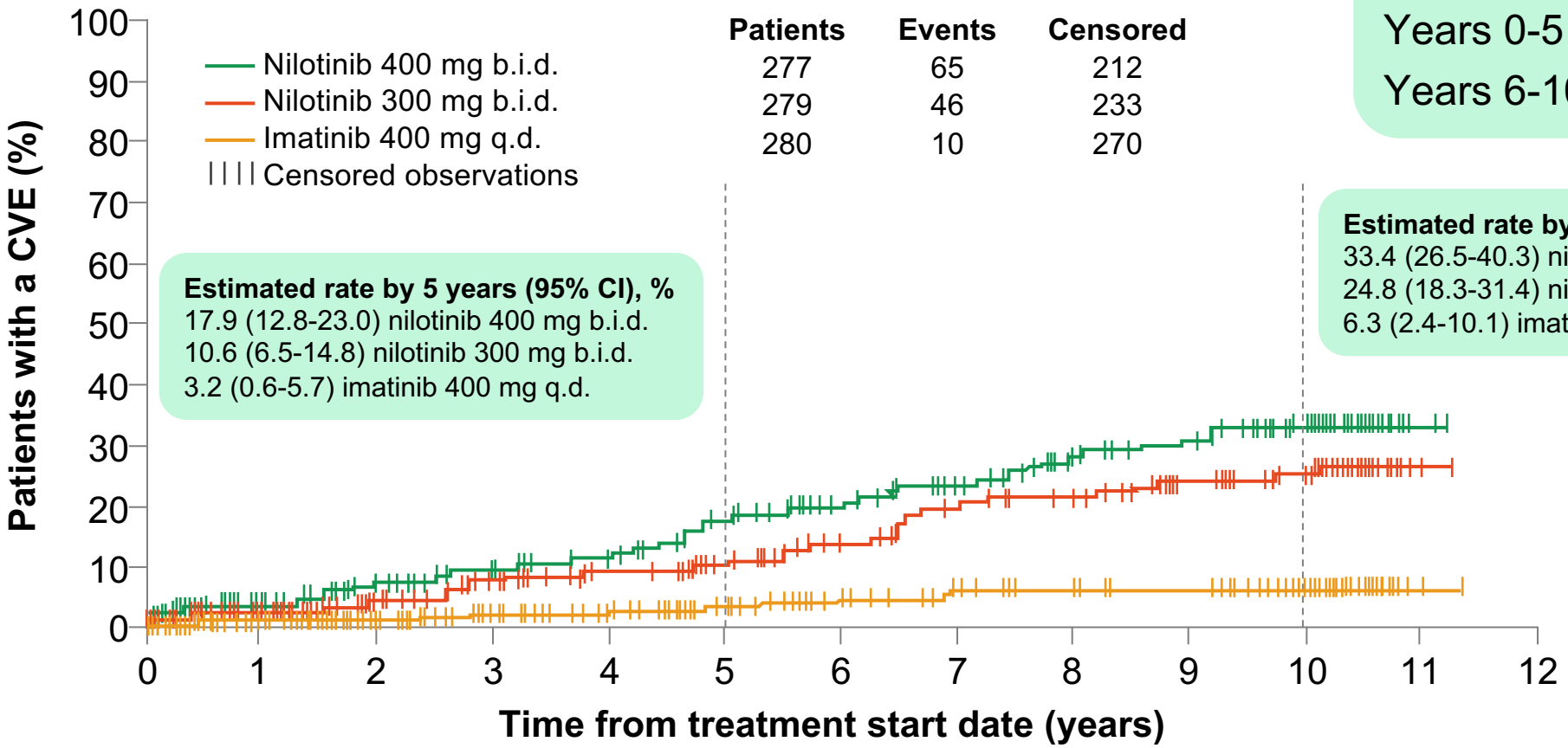
ENESTnd: Incidence of cardiovascular events increases for patients without chance of TFR

Incidence of cardiovascular events

Framingham low risk:

Years 0-5 Nilo 2.2% Ima 0.5%

Years 6-10 Nilo 8.7% Ima 1.1%



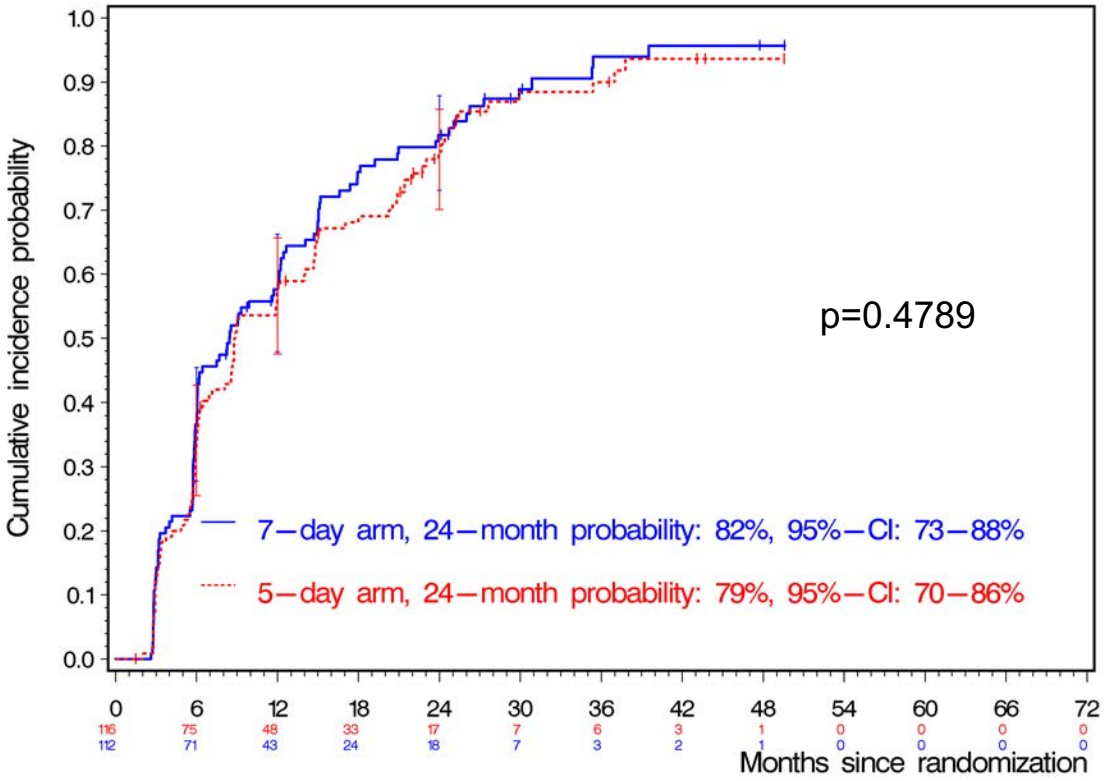
Hughes et al. ASH 2019. abstract 2924.

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

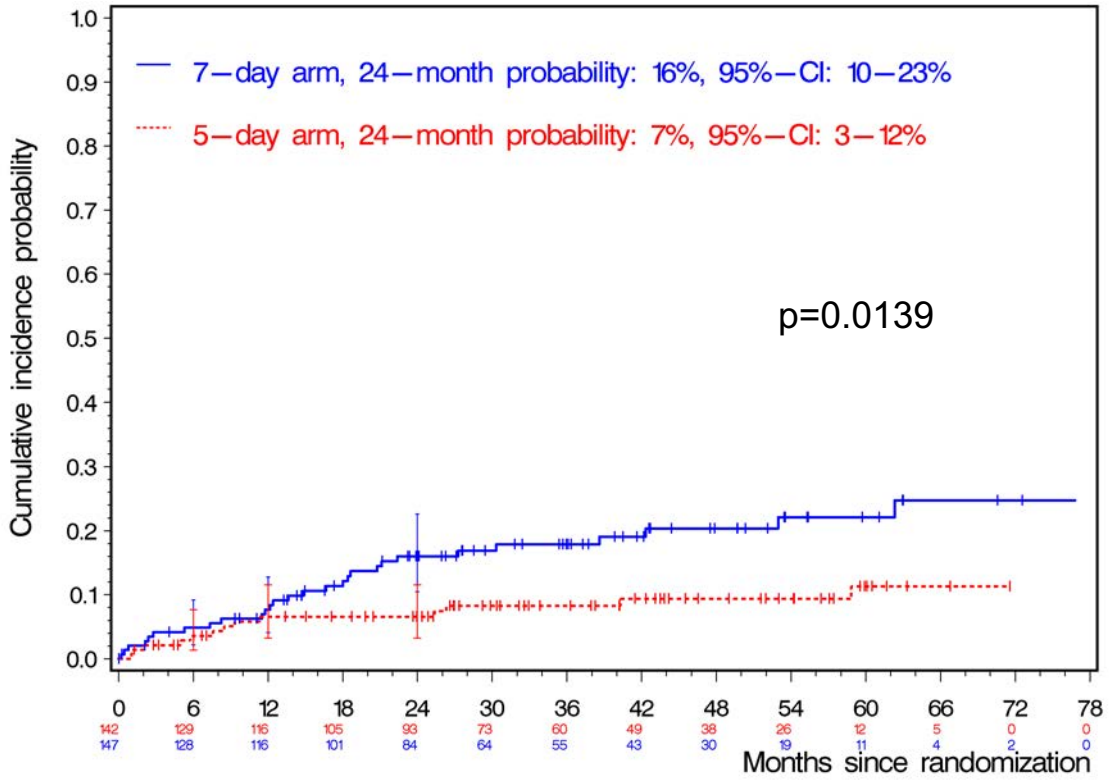
CVE, cardiovascular event.

DasaHIT: Better tolerability of dasatinib 5 days/week

Time to MMR / lack of inferiority



Time to pleural/pericardial effusion gr 2-4



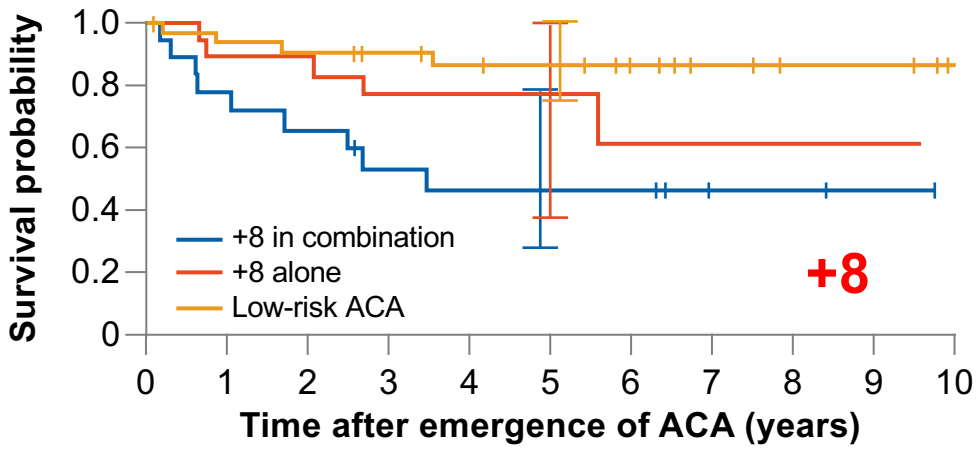
La Rosèe et al., EHA 2024, DGHO 2024

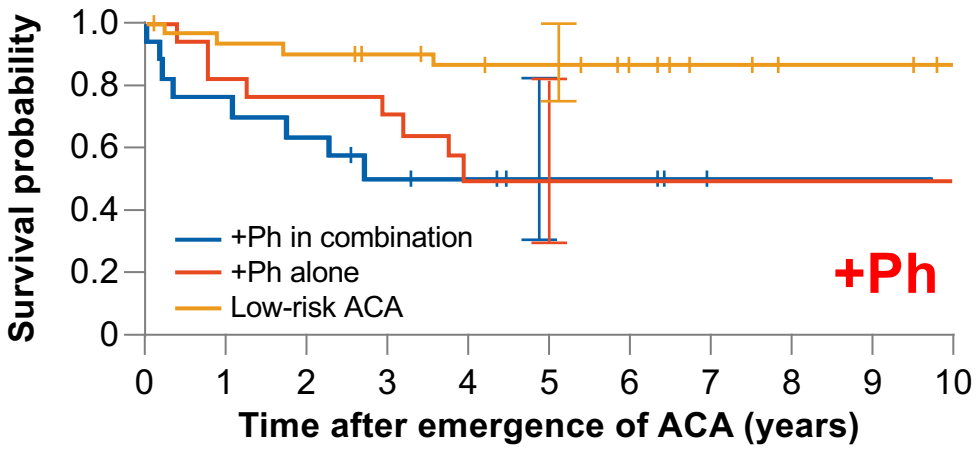
CML-CP: Prediction of prognosis

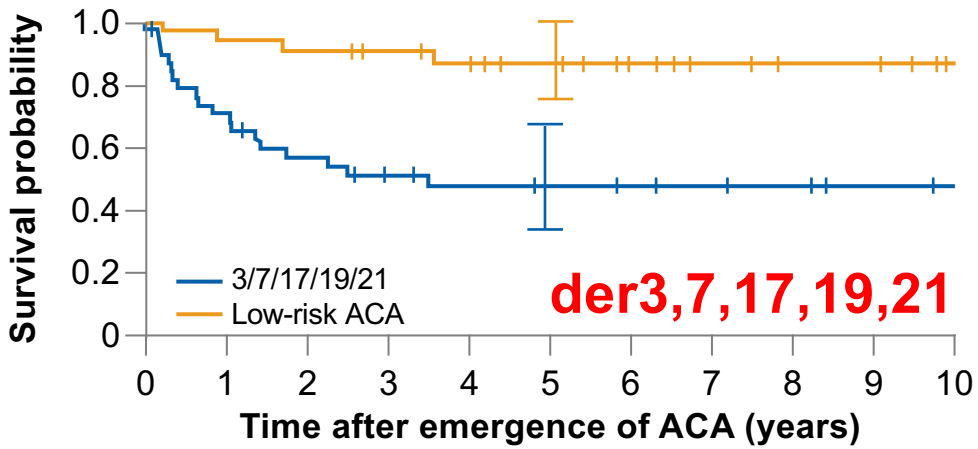
	Sokal 1984	EURO „Hasford“ 1998	EUTOS 2011	European Long Term Survival 2016*
Parameter	Age Spleen Blasts Platelets	Age Spleen Blasts Platelets Eosinophils Basophils	Spleen Basophils	Age Spleen Blasts Platelets
Therapy	Chemotherapy	IFN	Imatinib	Imatinib
Endpoint	Survival	Survival	CCyR	Survival (CML-rel. deaths)

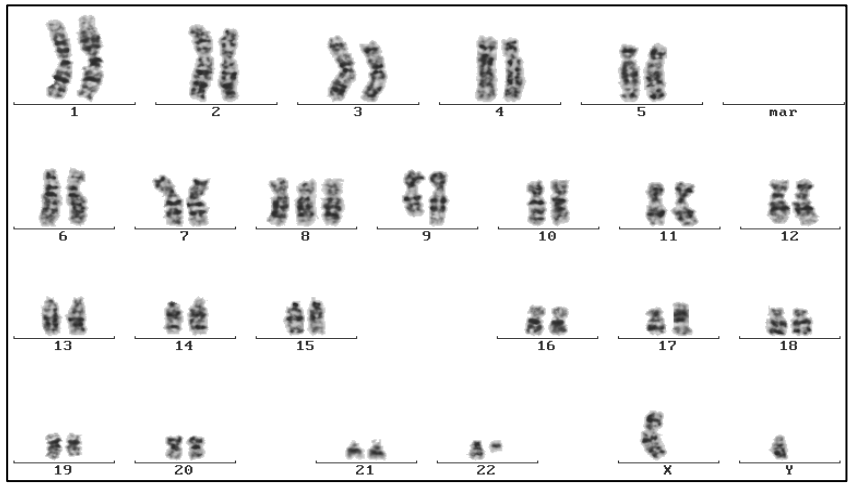
*Pfirrmann et al. Leukemia. 2016;30:48-56

High risk additional chromosomal aberrations predict survival probability: CML IV cohort





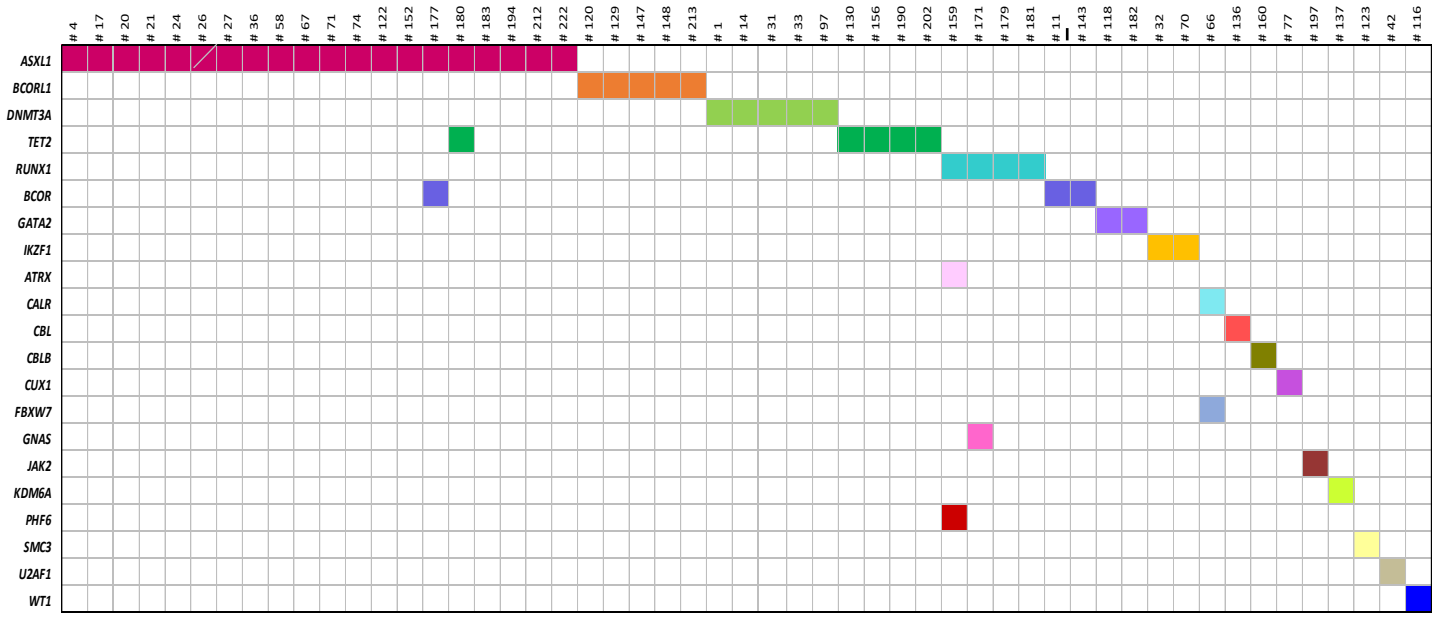


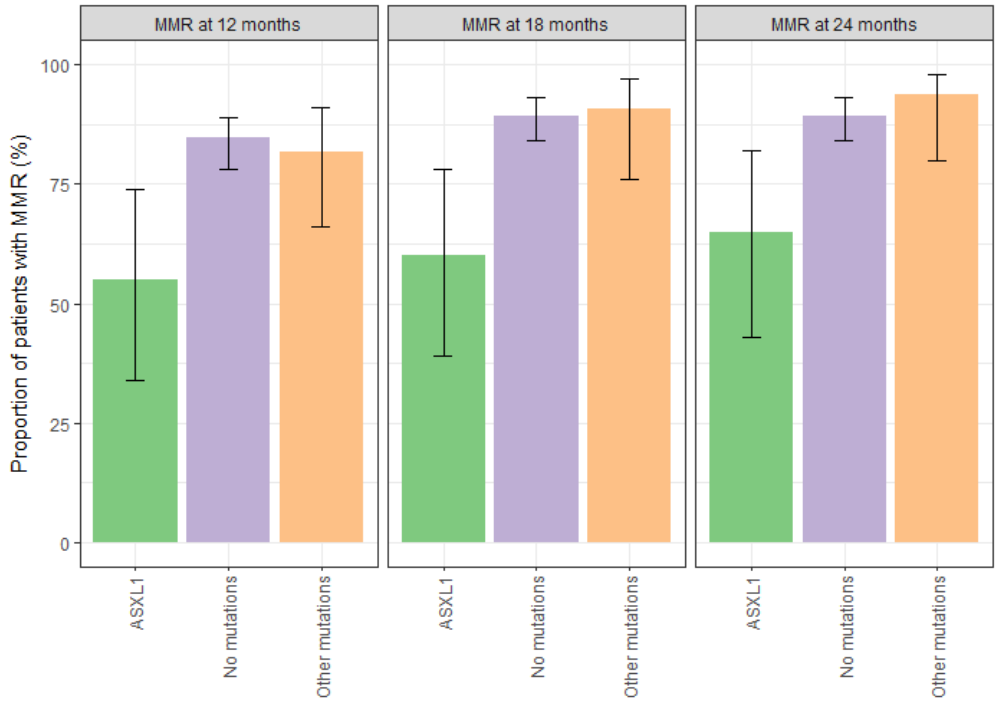


ACA, Additional cytogenetic abnormalities.

Hehlmann et al. Leukemia. 2020;34:2074-86

ASXL1 mutations predict inferior molecular response to nilotinib treatment in newly diagnosed CML patients in CP





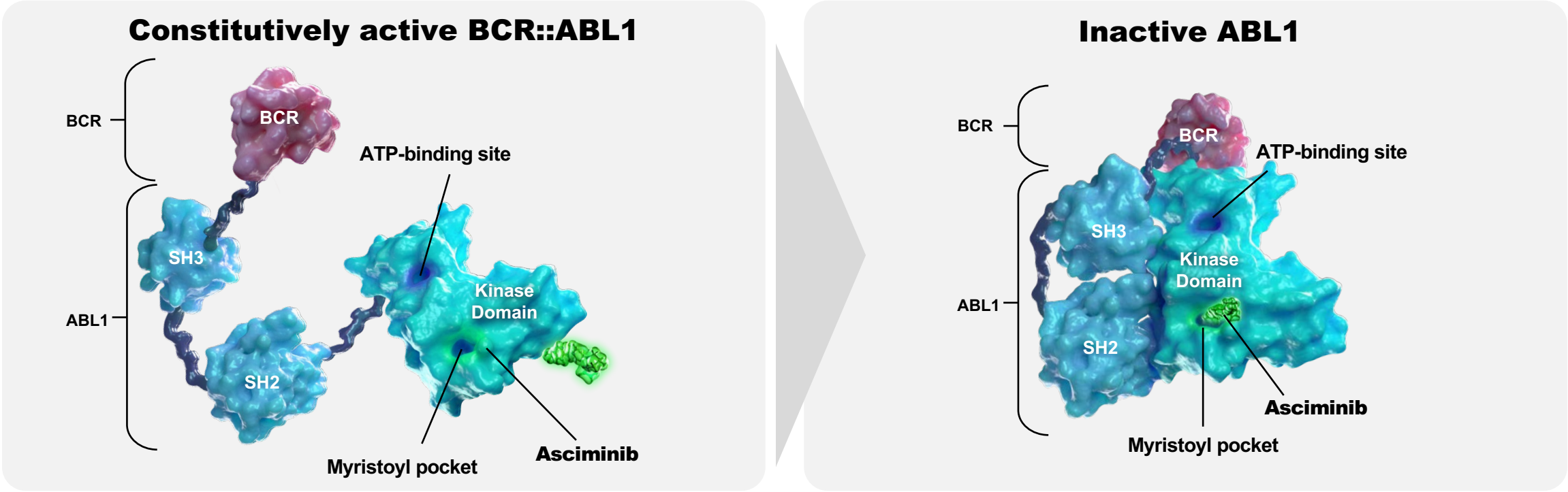
- Mutations in 24% (53/222) CML patients at diagnosis
- *ASXL1* being most commonly affected (n=20)
- Most patients only have one mutation in addition to *BCR::ABL1*
- Median age of affected patients: 54 years (range 19-78 years)

Schönfeld et al., Leukemia. 2022

First line options 2024

	Initial label	Concerns	Therapeutic window	New dose recommendations
Imatinib	400 mg QD	Muscle cramps, edema, renal failure	+	400 – 600 mg QD
Nilotinib	300 mg BID	Cardiovascular events, hyperglycemia	(+)	300 mg BID
Dasatinib	100 mg QD	Pleural effusions	+++	100 mg 5 days/week 50 mg QD
Bosutinib	500 mg QD	Gastrointestinal toxicity liver toxicity	+	200-300 mg QD, with gradual dose increase to 400 mg QD
Asciminib	40 mg BID or 80 mg QD	Lipase increase (?)	++	80 mg QD

Asciminib is a STAMP Inhibitor (Specifically Targeting the BCR::ABL1 Myristoyl Pocket)



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

ASC4FIRST, a pivotal phase 3 study of asciminib vs investigator-selected tyrosine kinase inhibitors (TKIs) for newly diagnosed CML

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 (high, intermediate, low)

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}**

End of study: LPFT + 5 years[b]

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

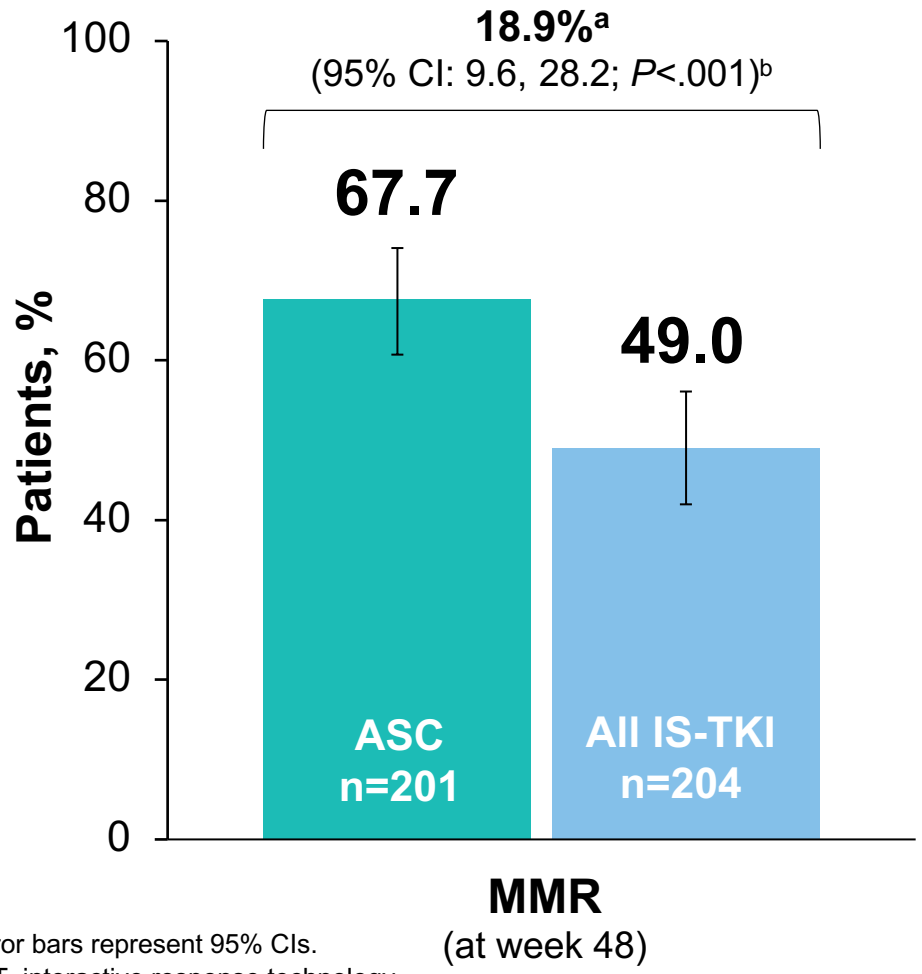
ASC, asciminib; ELTS, EUTOS long-term survival score; EUTOS, European Treatment and Outcome Study; IMA, imatinib; LPFT, last person first treatment; Ph, Philadelphia chromosome; QD, once daily; R, randomized.

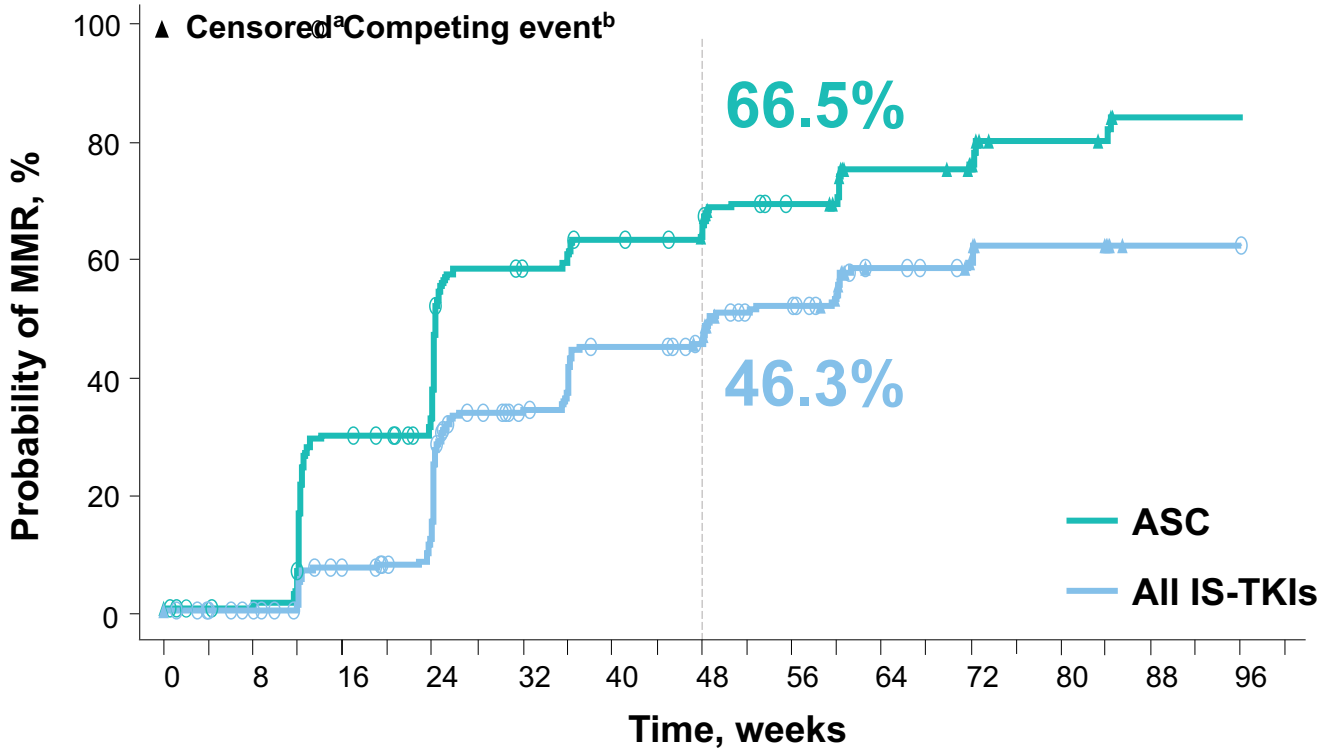
[a] Either imatinib, bosutinib, dasatinib, or nilotinib is allowed for up to 2 weeks prior to randomization. Treatment with other TKIs prior to randomization was not permitted.

[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.

Hughes TP et al. ASCO 2024;Abstract LBA6500. Hochhaus et al. NEJM. 2024;391:885-98

ASC4FIRST: MMR rate at week 48 was superior with asciminib vs all IS-TKIs, meeting the first primary endpoint





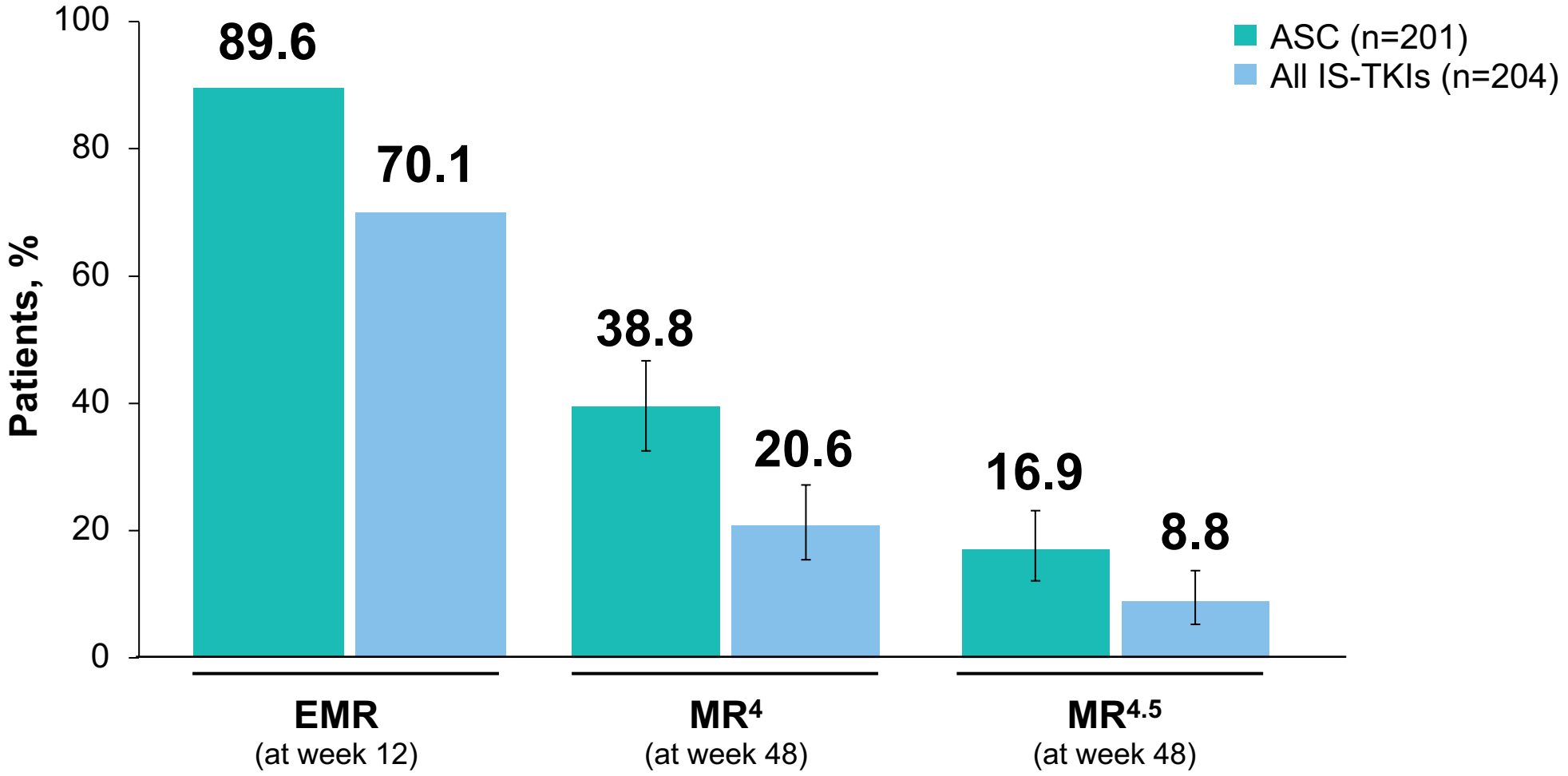
Error bars represent 95% CIs.
IRT, interactive response technology.

[a] The common treatment difference and its 95% CI were estimated using the Mantel-Haenszel method after stratifying for prerandomization-selected TKI and baseline ELTS risk groups (both IRT data).

[b] Adjusted 1-sided *P* value calculated based on the graphical gatekeeping procedure. The null hypothesis is rejected if the adjusted *P* value is ≤0.025.

Hochhaus et al. NEJM. 2024;391:885-98

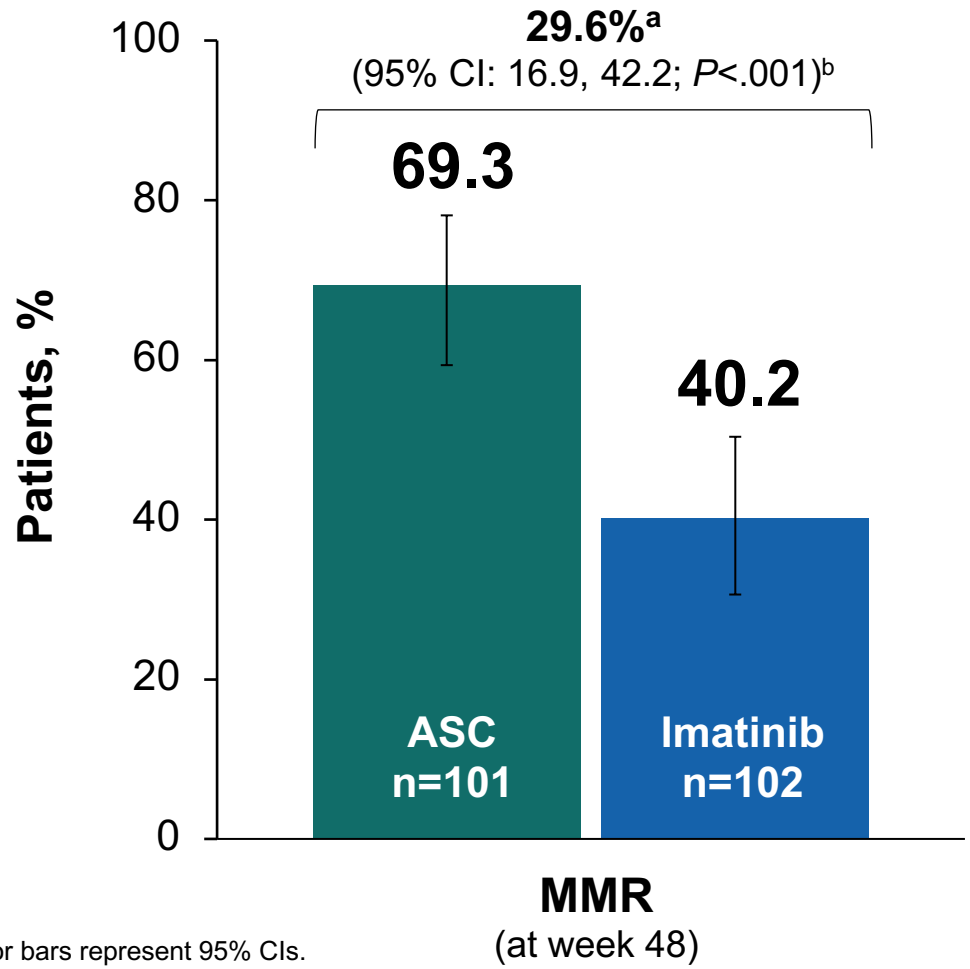
A higher proportion of patients achieved early and deep molecular responses with asciminib vs all IS-TKIs

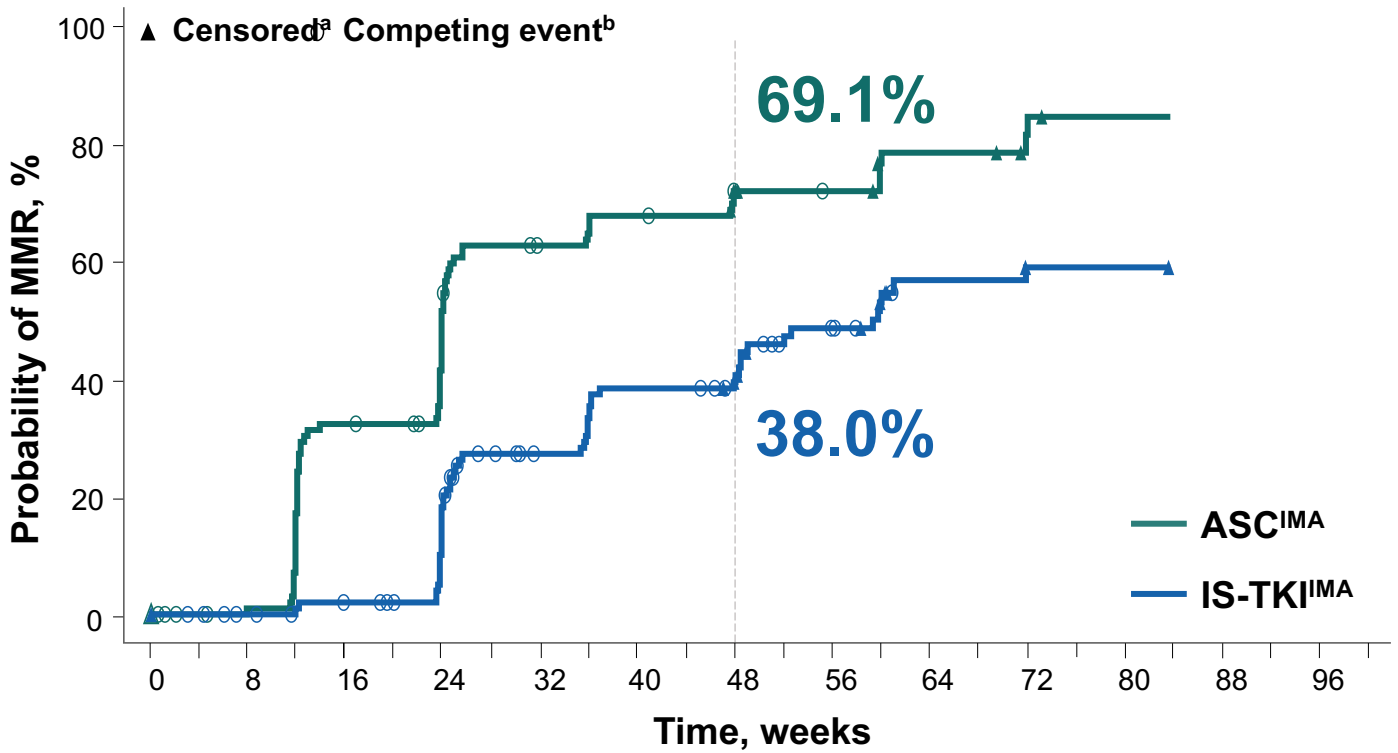


Error bars represent 95% CIs.

Hochhaus et al. NEJM. 2024;391:885-98

MMR rate at week 48 was superior with ASC^{IMA} vs IS-TKI^{IMA}, meeting the second primary endpoint





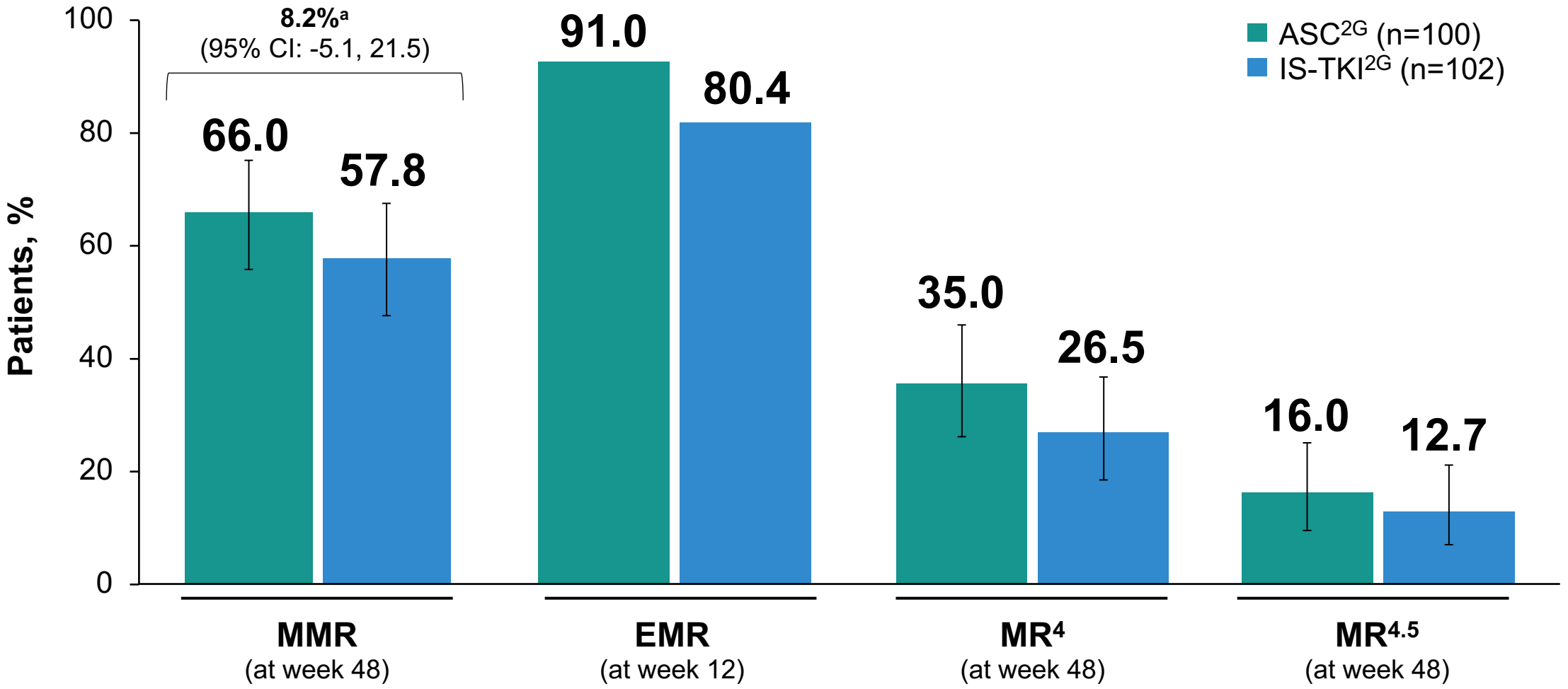
Error bars represent 95% CIs.

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

[b] Adjusted 1-sided p-value calculated based on the graphical gatekeeping procedure. The null hypothesis is rejected if the adjusted p-value is ≤0.025.

Hochhaus et al. NEJM. 2024;391:885-98

A numerically higher proportion of patients with ASC^{2G} achieved major, early, and deep molecular responses vs IS-TKI^{2G}

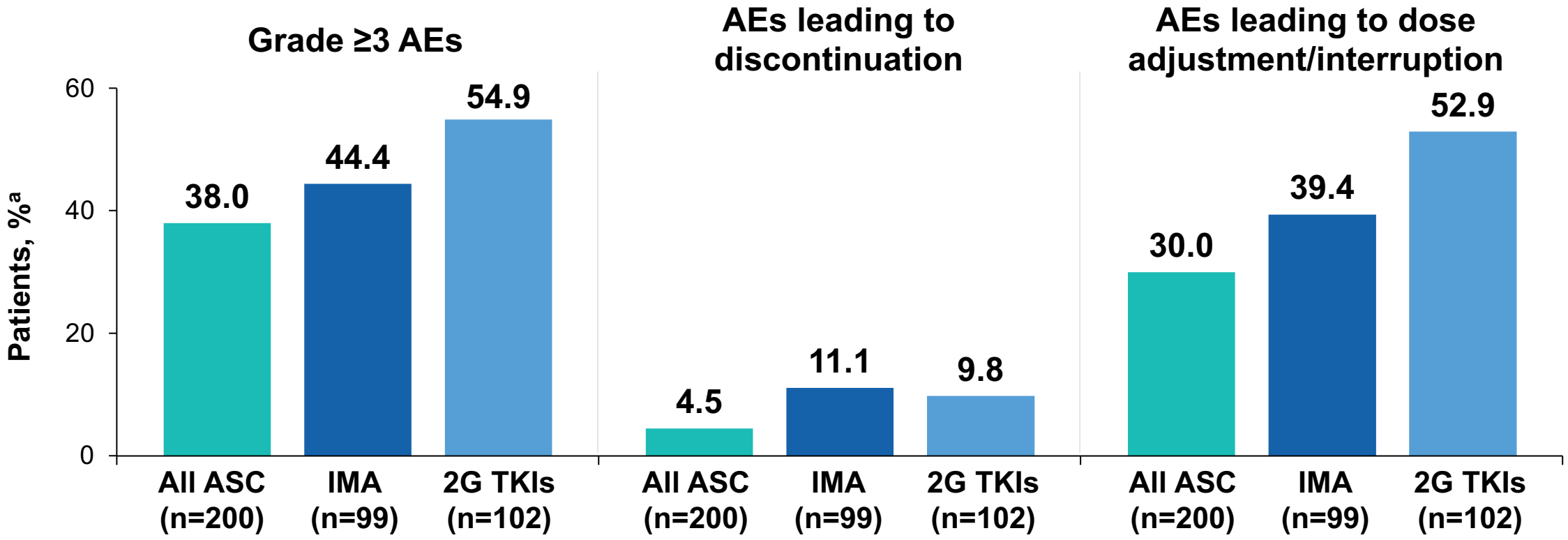


Error bars represent 95% CIs.

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

Hochhaus et al. NEJM. 2024;391:885-98

Asciminib demonstrated favorable safety and tolerability vs imatinib and 2G TKIs



- The median dose intensity was 80.0 mg/day with ASC, 400.0 mg/day with IMA, 595.1 mg/day with NIL, 98.9 mg/day with DAS, and 341.8 mg/day with BOS
- The most common AEs leading to treatment discontinuation were increased lipase with ASC (1.5%), diarrhea and lymphopenia with IMA (2.0% each), and pleural effusion with 2G TKIs (2.0%)

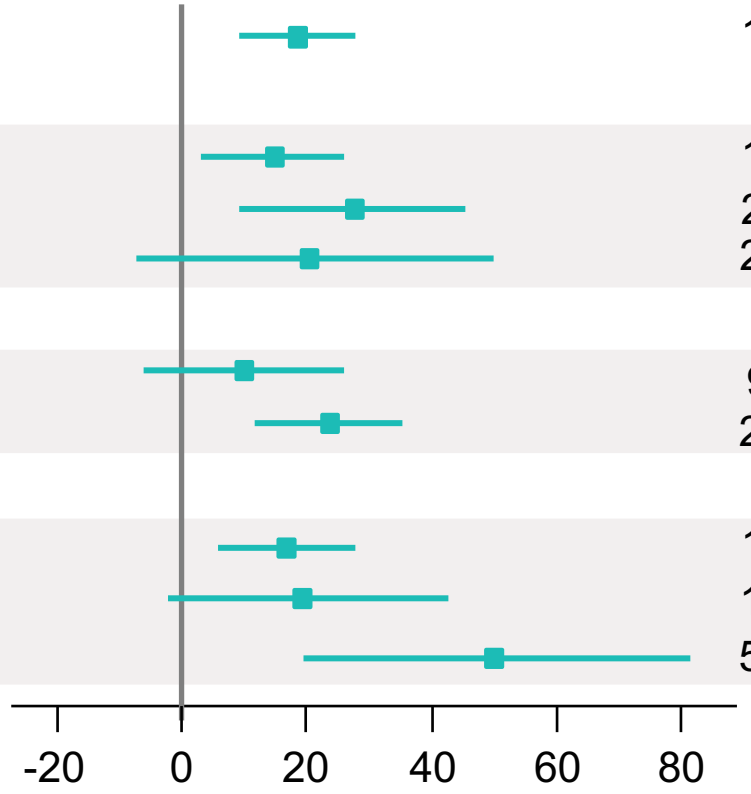
BOS, bosutinib; DAS, dasatinib; NIL, nilotinib.

[a] Safety analyses consisted of patients who received ≥1 dose of study drug. Patients were analyzed according to the study treatment received. A patient with multiple severity grades for an AE is only counted under the maximum grade.

Hochhaus et al. NEJM. 2024;391:885-98

Asciminib had higher MMR rates across all demographic and prognostic subgroups vs all IS-TKIs

Subgroup	MMR		Favors all IS-TKIs	Favors ASC	Treatment difference (95% CI)
	ASC, %	All IS-TKIs, %			
All patients	67.7	49.0			18.6 (9.2 to 28.1)
ELTS					
Low	72.1	57.6			14.5 (2.8 to 26.3)
Intermediate	64.3	36.8			27.4 (9.7 to 45.2)
High	52.2	31.8			20.4 (-7.9 to 48.6)
Sex					
Female	64.3	54.4			9.9 (-5.8 to 25.6)
Male	69.5	45.6			23.9 (12.1 to 35.6)
Age category					
18 to <65 years	64.5	48.4			16.1 (5.2 to 27.0)
65 to <75 years	75.0	55.9			19.1 (-2.8 to 41.0)
≥75 years	90.0	40.0			50.0 (19.0 to 81.0)



Hochhaus et al. NEJM. 2024;391:885-98

ASC4FIRST: All grade adverse events of special interest (%)

	Asciminib	Imatinib	2G-TKI
Diarrhea	15.5	**26.3**	**25.5**
Nausea	9.0	**21.2**	**17.6**
Periorbital edema	1.0	**20.2**	1.0
Lipase increase	**11.5**	**14.1**	**10.8**
ALAT increase	7.0	6.1	**18.6**
Bilirubin increase	2.5	2.0	**10.8**
Arterio-occlusive events	1.0	0	2.0
Thrombocytopenia	28.0	28.3	**34.3**
Neutropenia	25.0	**31.3**	**34.3**
Anemia	11.5	**26.3**	**22.5**

Sunday, December 8, 2024: 9:30 AM, abstract 475:
ASC4FIRST 96 week update

Hochhaus et al. NEJM. 2024;391:885-98

NCCN Guidelines Version 2.2025
Chronic Myeloid Leukemia

NCCN Guidelines Index
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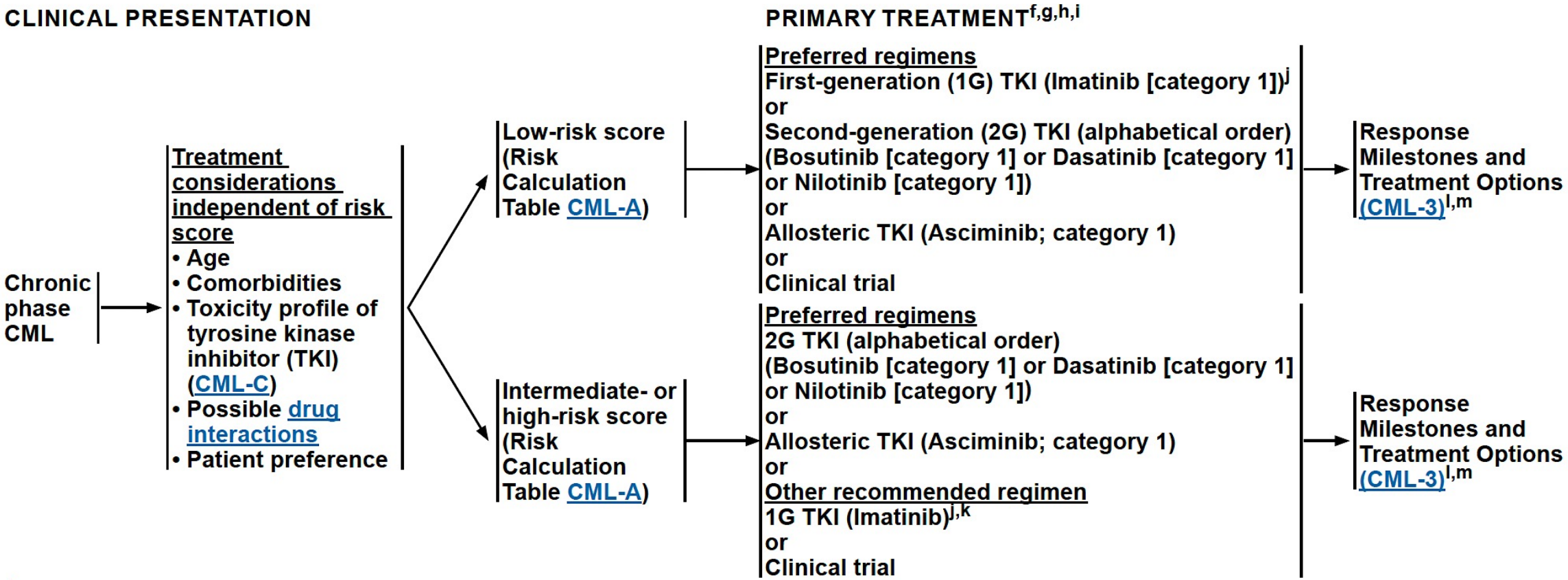
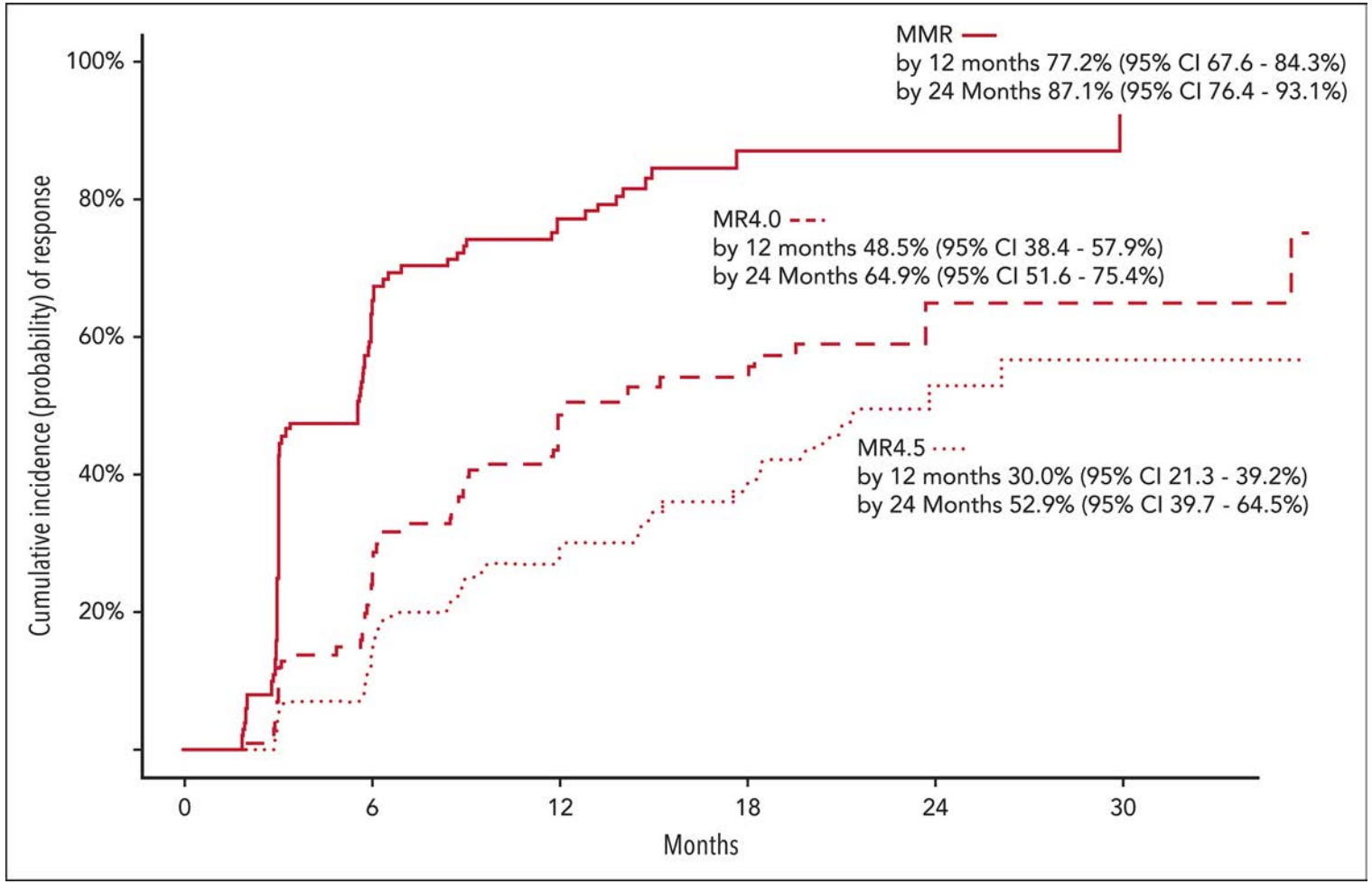
Discussion



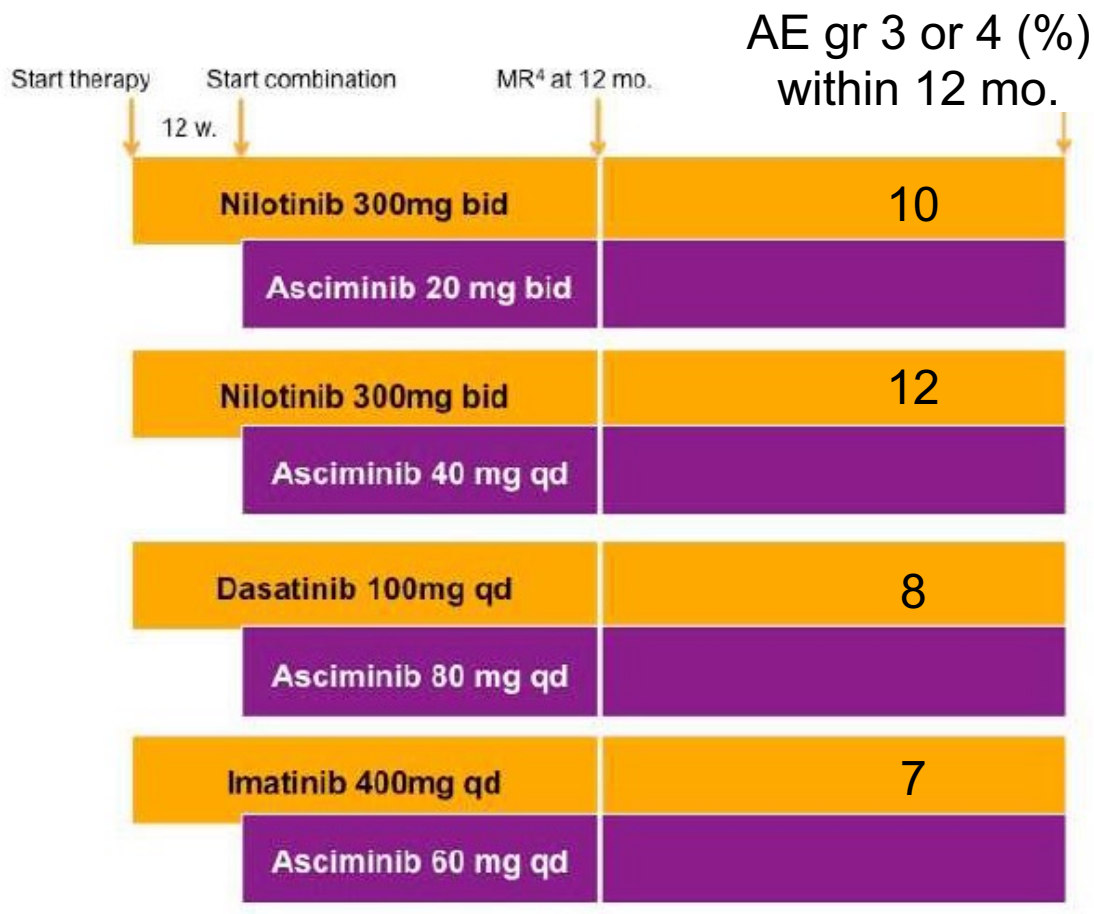
Asciminib monotherapy as frontline treatment of CML in CP: Results from the ASCEND study



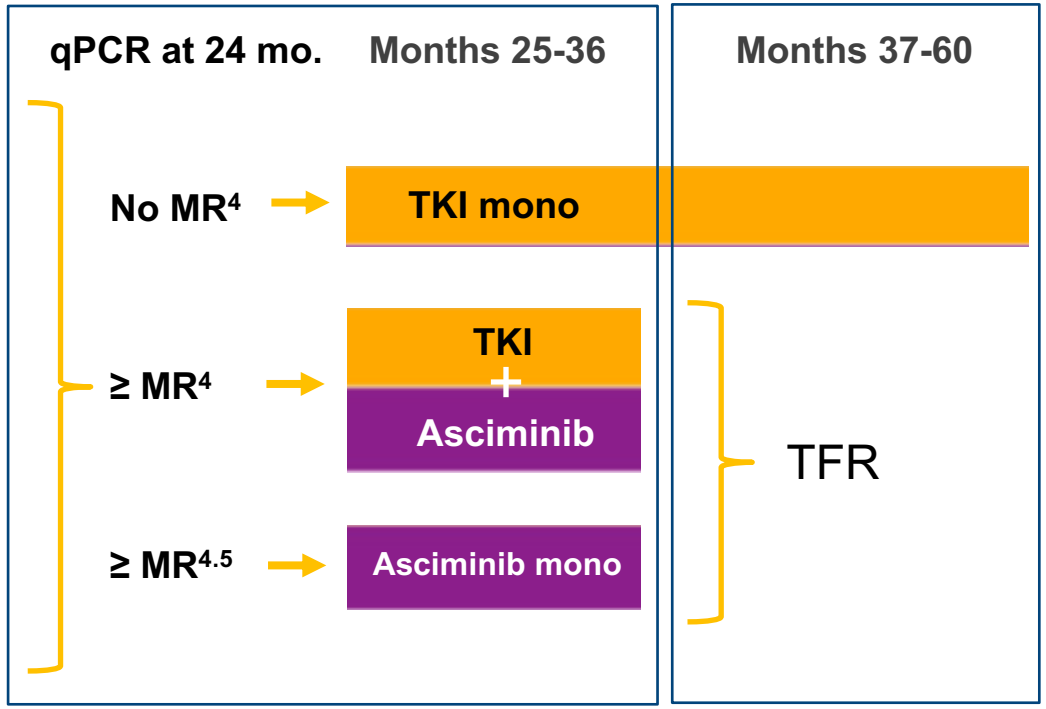
Total patients	n=101
Median age at diagnosis, y (range)	57 (19-88)
Gender, female, n (%)	39 (38.6%)
Race, n (%)	
White	79 (78.2%)
East or South-Central Asian	12 (11.9%)
Other	10 (9.9%)
ELTS risk, n (%)	
Low	73 (72.3%)
Intermediate	22 (21.8%)
High	5 (5.0%)
NA	1 (1.0%)
Therapies before asciminib, n (%)	
Prior hydroxyurea	50 (49.5%)
Prior leukapheresis	2 (2.0%)

Yeung et al. Blood. 2024;144):1993-2001

Frontline Asciminib in Combination: FASCINATION

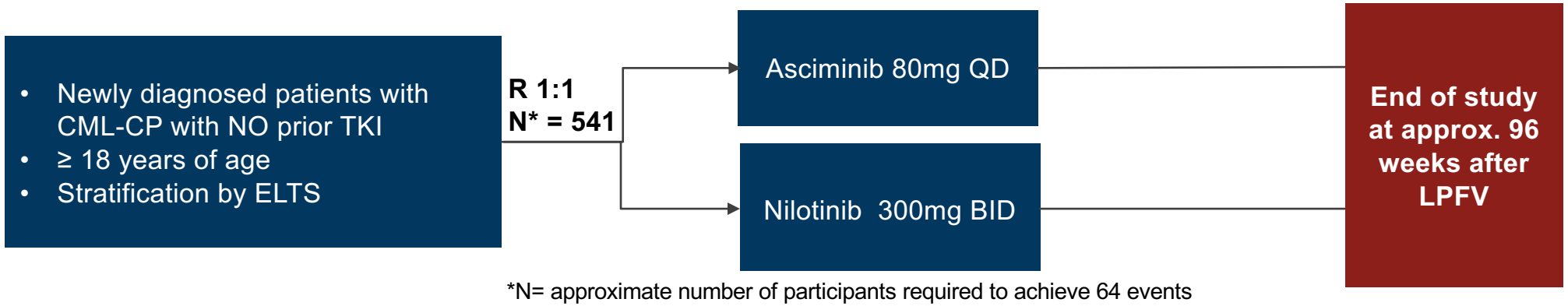


38%



Ernst et al., EHA 2023

ASC4START: Study Design



*N= approximate number of participants required to achieve 64 events

Objectives

- **Primary objective:**
  - **Time to Treatment Discontinuation due to AE** (TTDAE)
- **Secondary objectives:**
  - Efficacy: MMR, MR4, MR4.5, CHR, duration of response, PFS, OS
  - Safety: To characterize the safety and tolerability profile of asciminib versus nilotinib
  - Time to Treatment Discontinuation for any reason
  - QoL PROs: EORTC QLQ-C30, EORTC QLQ-CML24
- **Exploratory Objectives**
  - QoL PROs: PRO-CTCAE, FACT GP5
  - Mutational Analysis

Amendment: TFR

Impact of cancer gene variants on efficacy of asciminib in newly diagnosed CP CML patients

N. Shanmuganathan et al.: Strong Association between Cancer Gene Variants at Diagnosis, Especially *ASXL1*, and Emergence of Kinase Domain Mutation-Driven Resistance in CML Patients Despite Frontline Treatment with More Potent BCR::ABL1 Inhibitors

Monday, December 9, 2024: 4:30 PM, abstract 991

Among asciminib-treated patients with *ASXL1* variants,
the cumulative incidence of KD mutations at 24 months was 37%.
Non-*ASXL1* variants also predicted for inferior 12-month MMR.

T. Ernst et al.: The Combination of Asciminib with ATP Competing Tyrosine Kinase Inhibitors Might Overcome the Negative Impact of ASXL1 Mutations on Molecular Response in Newly Diagnosed CML Patients

Saturday, December 7, 2024, Poster, abstract 1774

No negative impact of *ASXL1* mutations on combination therapy: At month 12, 8/9 (89%) and 7/9 (78%) patients harboring *ASXL1* mutations at diagnosis showed MMR and MR^4, respectively.

Questions from General Medical Oncologists

- **When administering first-line treatment to patients with high-risk CP-CML, how often would you initially monitor response to therapy after baseline assessment?**
- **A patient with CP-CML has received 12 months of first-line imatinib with no clinical evidence of disease progression and BCR::ABL1 transcript levels decreasing from 21% at 3 months to 4% now. What would you recommend?**

Questions from General Medical Oncologists

- In general, what factors do you consider (i.e., age, comorbidities, blood counts, etc.) to determine which TKI to use upfront? Do you have a preferred TKI, and if so, which one?
- How does asciminib differ from the other available TKIs? When would you use it upfront?
- Is it reasonable to combine asciminib with TKI therapy as upfront treatment? If so, in what situations would you offer this combination?

Questions from General Medical Oncologists

- I have an 88-year-old gentleman with CP-CML, intermediate-risk by Sokal, good PS, normal renal and hepatic function, no significant comorbidities. Is there any specific TKI that is better? What expectations can I set regarding the rate and depth of responses with a TKI in elderly patients?
- Which TKI would you recommend as initial treatment for a patient with thrombocytopenia? What about heart failure?
- From your point of view, are all second-generation TKIs equally efficacious, and is your choice between them driven more based on tolerability?

Agenda

Module 1: Up-Front Therapy for Chronic Myeloid Leukemia (CML) — Prof Hochhaus

Module 2: Management of Relapsed CML, Including in Patients with a T315I Mutation — Dr Mauro

Module 3: Tolerability and Other Practical Issues with Commonly Employed CML Therapies — Dr Smith

Management of Relapsed Chronic Myeloid Leukemia, Including in Patients with a T315I Mutation

Michael J Mauro, MD
Director, Chronic Myeloid Leukemia Program
Attending Physician, Leukemia Service
Memorial Sloan Kettering Cancer Center
New York, New York

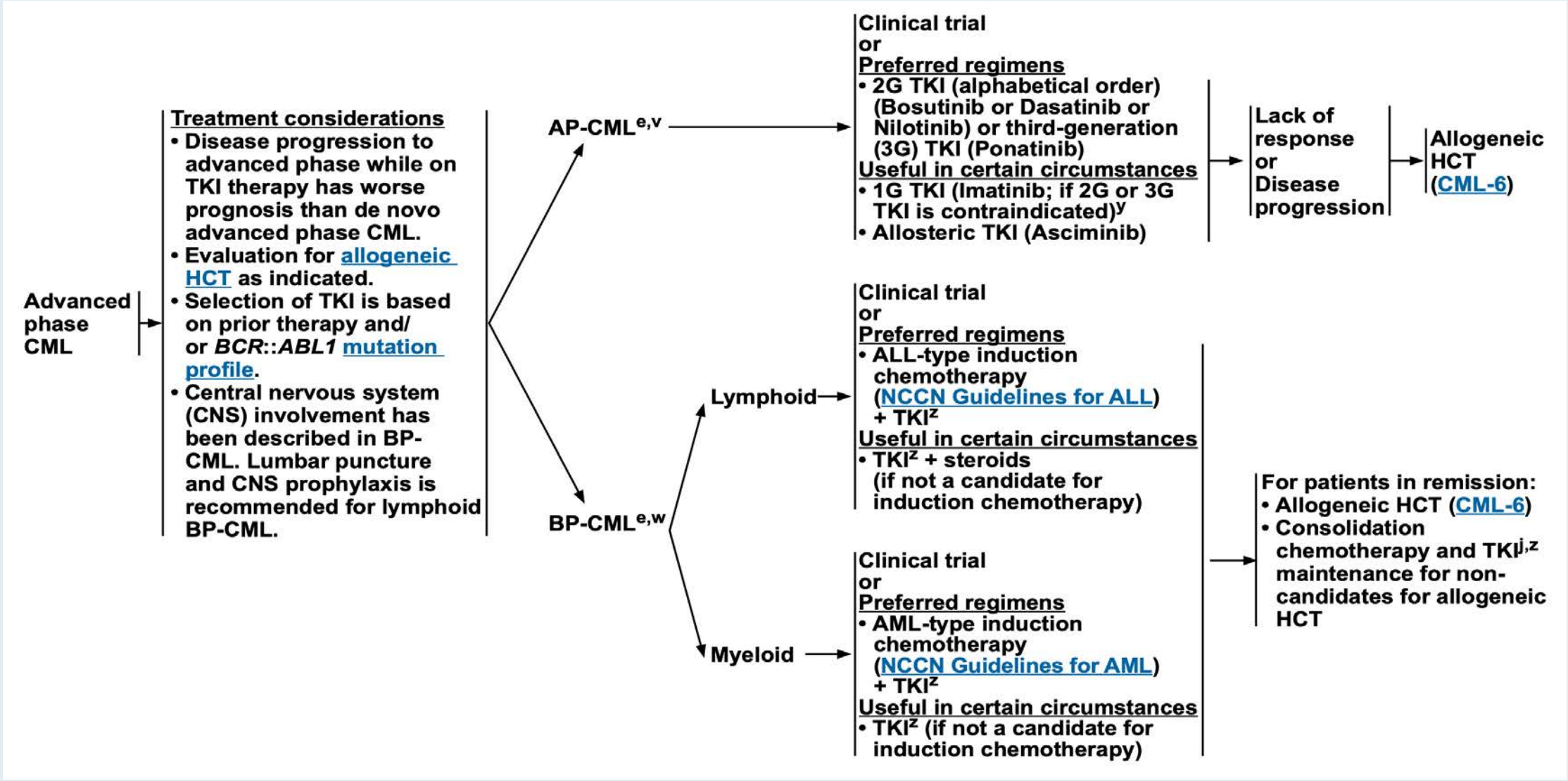
NCCN Treatment Milestones

BCR::ABL1 (IS)	3 months	6 months	12 months[n]
>10%[o]	YELLOW	RED	
>1%–10%[p]	GREEN		ORANGE
>0.1%–1%	GREEN		LIGHT GREEN
≤0.1%	GREEN		

COLOR	CONCERN	CLINICAL CONSIDERATIONS[r]	RECOMMENDATIONS[r,i]
RED	TKI-resistant disease[q]	• Evaluate patient adherence and drug interactions • Consider *BCR::ABL1* kinase domain mutational analysis[s] • Consider bone marrow cytogenetic analysis to assess additional chromosomal abnormalities (ACAs)	Switch to alternate TKI (CML-5) (other than imatinib) and evaluate for allogeneic HCT
YELLOW	Possible TKI resistance[q]	• Evaluate patient adherence and drug interactions • Consider *BCR::ABL1* kinase domain mutational analysis[s]	Switch to alternate TKI (CML-5) or Continue same TKI[o]
ORANGE **NEW**	Possible TKI resistance[q]	• Evaluate patient adherence and drug interactions • Consider *BCR::ABL1* kinase domain mutational analysis[s] • Consider bone marrow cytogenetic analysis to assess for CCyR at 12 mo	Consider switch to alternate TKI[p] (CML-5) or Continue the same TKI if CCyR is achieved
LIGHT GREEN	TKI-sensitive disease	• Evaluate patient adherence and drug interactions • 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[q,t]
GREEN	TKI-sensitive disease	• Evaluate patient adherence and drug interactions • Monitor response (CML-G)	Continue same TKI[u]

TKI = tyrosine kinase inhibitor; CML = chronic myeloid leukemia; HCT = hemotopoietic cell transplant; CCyR = complete cytogenic response

NCCN Recommendations for Disease Progression on First-Line TKI



BP-CML = blastic-phase CML; ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia

NCCN Guidelines®. Chronic Myeloid Leukemia — V.3.2025.

RTP RESEARCH TO PRACTICE

NCCN Recommendations for Treatment with TKI Based on Mutation Profile

- **Patients with disease resistant to primary treatment with imatinib should be treated with an alternate TKI, taking into account *BCR::ABL1* kinase domain mutation status.**
- **Patients with disease resistant to primary treatment with asciminib, bosutinib, dasatinib, or nilotinib can be treated with an alternate TKI (other than imatinib), taking into account *BCR::ABL1* kinase domain mutation status. Subsequent therapy with an alternate TKI would be effective only in patients with identifiable *BCR::ABL1* mutations that confer resistance to TKI therapy. Ponatinib is preferred for patients with no identifiable *BCR::ABL1* mutations.**
  - **Asciminib is a treatment option for patients with CP-CML having the T315I mutation and/or previously treated CP-CML.**
  - **Ponatinib is a treatment option for patients with a T315I mutation in any phase (preferred for AP-CML or BP-CML). It is also a treatment option for CP-CML with resistance or intolerance to at least two prior TKIs or for patients with AP-CML or BP-CML for whom no other TKI is indicated.**
- ***BCR::ABL1* kinase domain mutations that should NOT be treated with asciminib, bosutinib, dasatinib, or nilotinib are listed in the table below.**

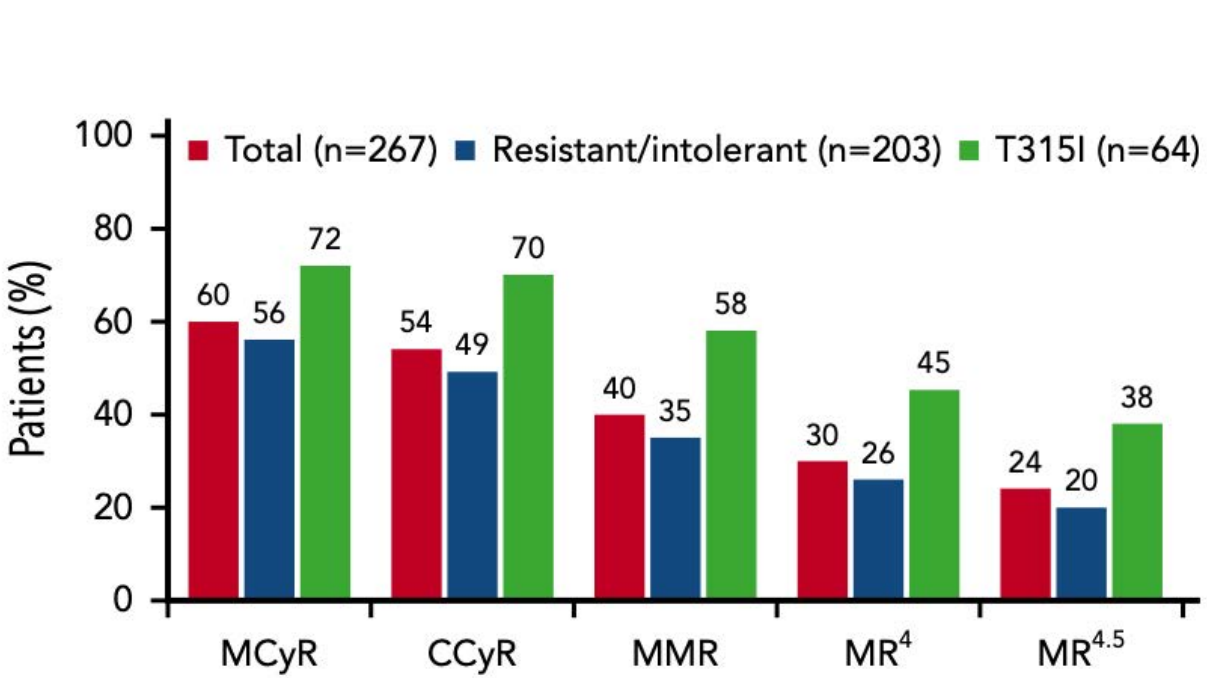
THERAPY	CONTRAINDICATED MUTATIONS[aa]
Asciminib	A337T, P465S, M244V, or F359V/I/C
Bosutinib	T315I, V299L, G250E, or F317L[bb]
Dasatinib	T315I/A, F317L/V/I/C, or V299L
Nilotinib	T315I, Y253H, E255K/V, or F359V/C/I
Ponatinib or allogeneic HCT (CML-6)	None[cc]

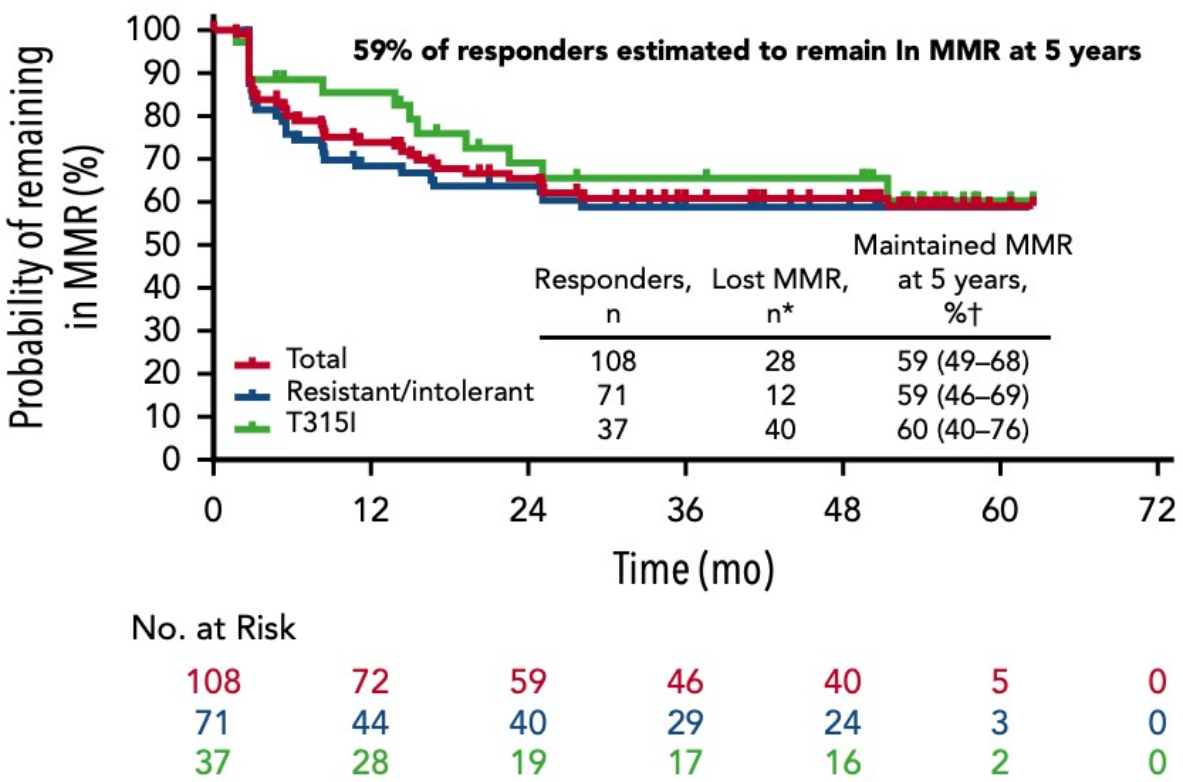
CP-CML = chronic-phase CML; AP-CML = acute-phase CML

NCCN Guidelines®. Chronic Myeloid Leukemia — V.3.2025.

Ponatinib Efficacy and Safety in CML: Final 5-Year Results of the Phase II PACE Trial – Response

The PACE trial evaluated the efficacy and safety of ponatinib at a starting dose of 45 mg once daily in 270 patients with CP-CML **resistant/intolerant to dasatinib or nilotinib, or with BCR::ABL1^{T315I}**



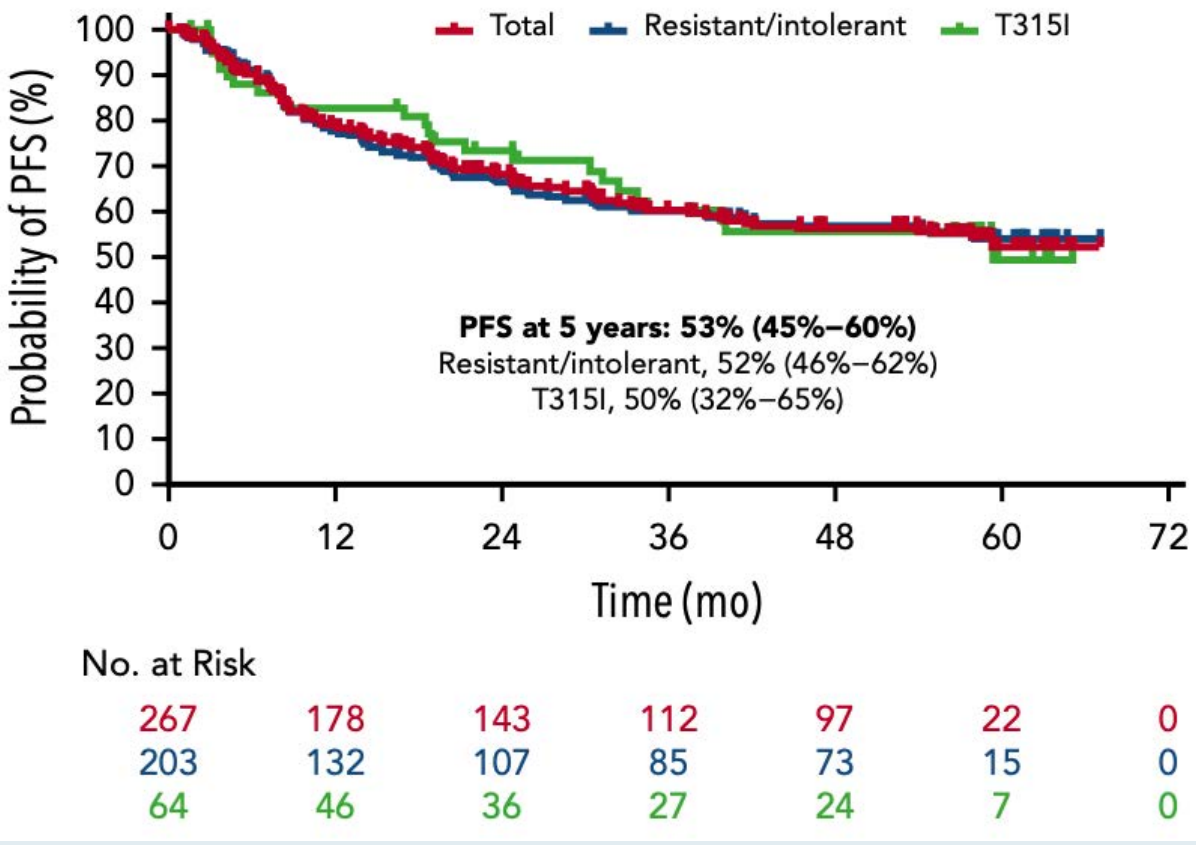


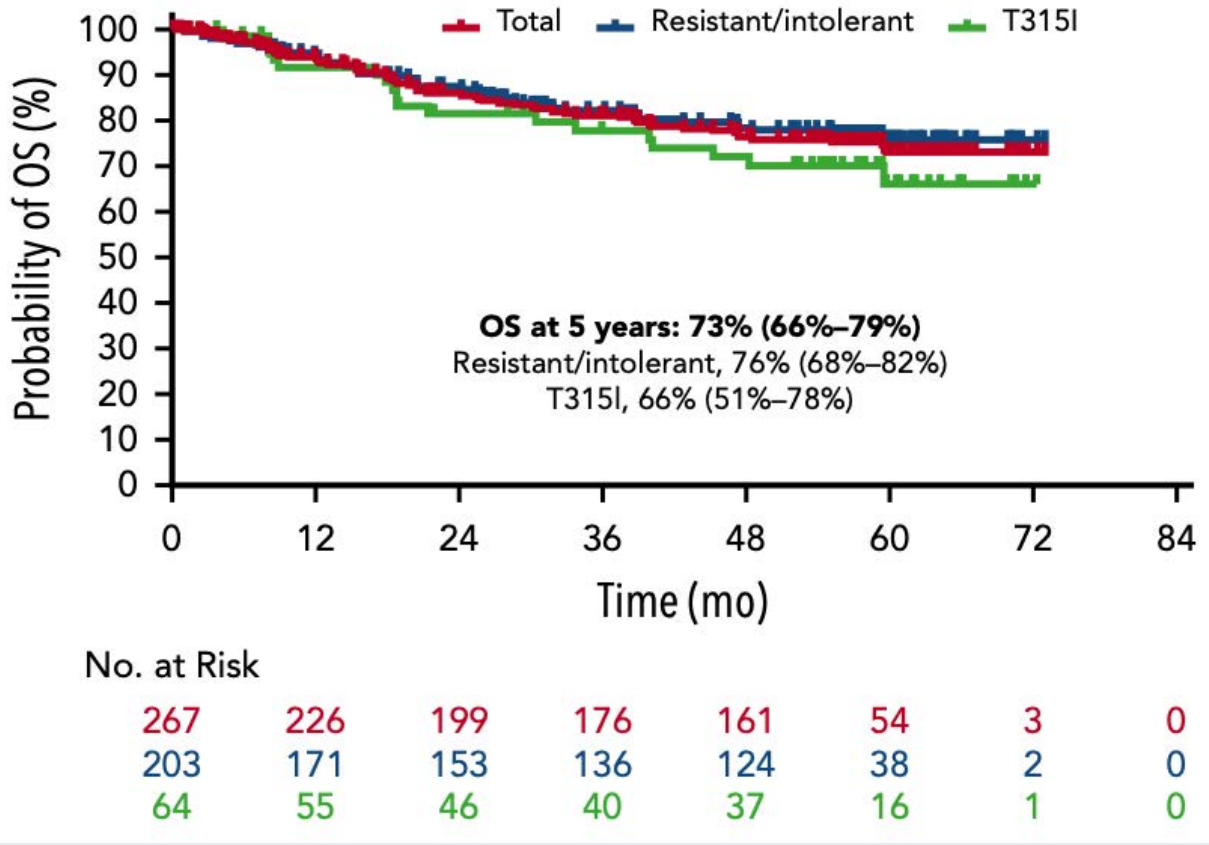
MR = molecular response; MMR = major molecular response; MCyR = major cytogenic response

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

RTP RESEARCH TO PRACTICE

Ponatinib Efficacy and Safety in CML: Final 5-Year Results of the Phase II PACE Trial – Survival





PFS = progression-free survival; OS = overall survival

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

Ponatinib: Final 5-Year Results of the Phase II PACE Trial – Safety

	CP-CML, n = 270	
	Any grade	Grade 3/4
Nonhematologic AEs, n (%)		
Abdominal pain	125 (46)	28 (10)
Rash*	127 (47)	10 (4)
Constipation	112 (41)	7 (3)
Headache	116 (43)	9 (3)
Dry skin	114 (42)	9 (3)
Fatigue	81 (30)	6 (2)
Hypertension†	99 (37)	37 (14)
Pyrexia	70 (26)	3 (1)
Arthralgia	90 (33)	8 (3)
Nausea	79 (29)	2 (<1)
Diarrhea	54 (20)	2 (<1)
Increased lipase	73 (27)	34 (13)
Vomiting	50 (19)	4 (1)
Myalgia	65 (24)	3 (1)
Pain in extremity	65 (24)	8 (3)
Hematologic AEs, n (%)		
Thrombocytopenia	123 (46)	95 (35)
Neutropenia	53 (20)	45 (17)
Anemia	53 (20)	28 (10)

	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

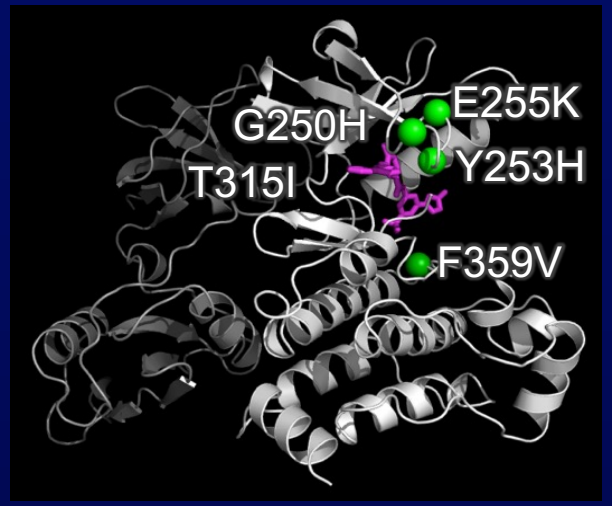
AE = adverse event; SAE = serious adverse event; AOE = arterial occlusive event; VTE = venous thromboembolic event

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

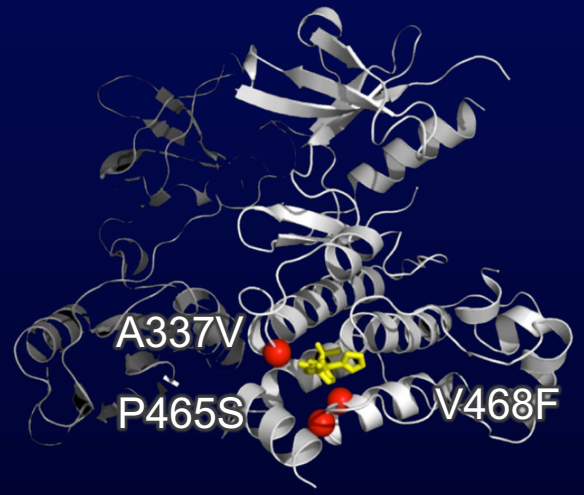
RTP RESEARCH TO PRACTICE

Asciminib and Classical TKIs Have Complementary Mutation Profiles

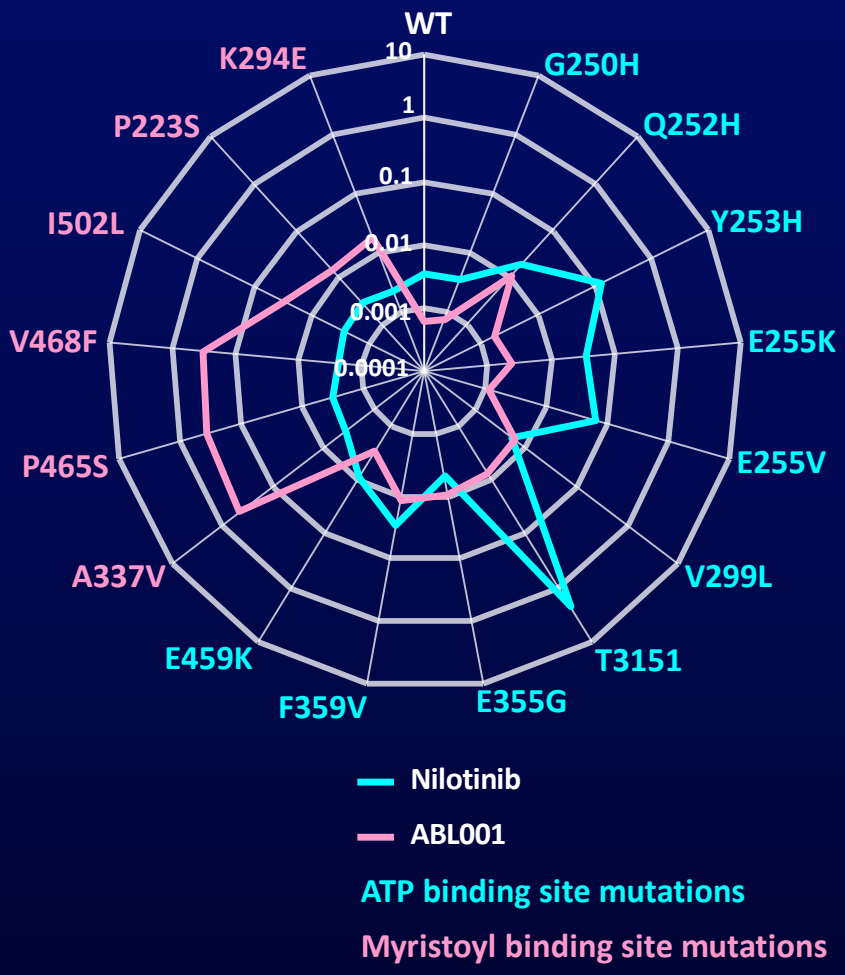
ATP Binding Site Mutations



Myristoyl Binding Site Mutations

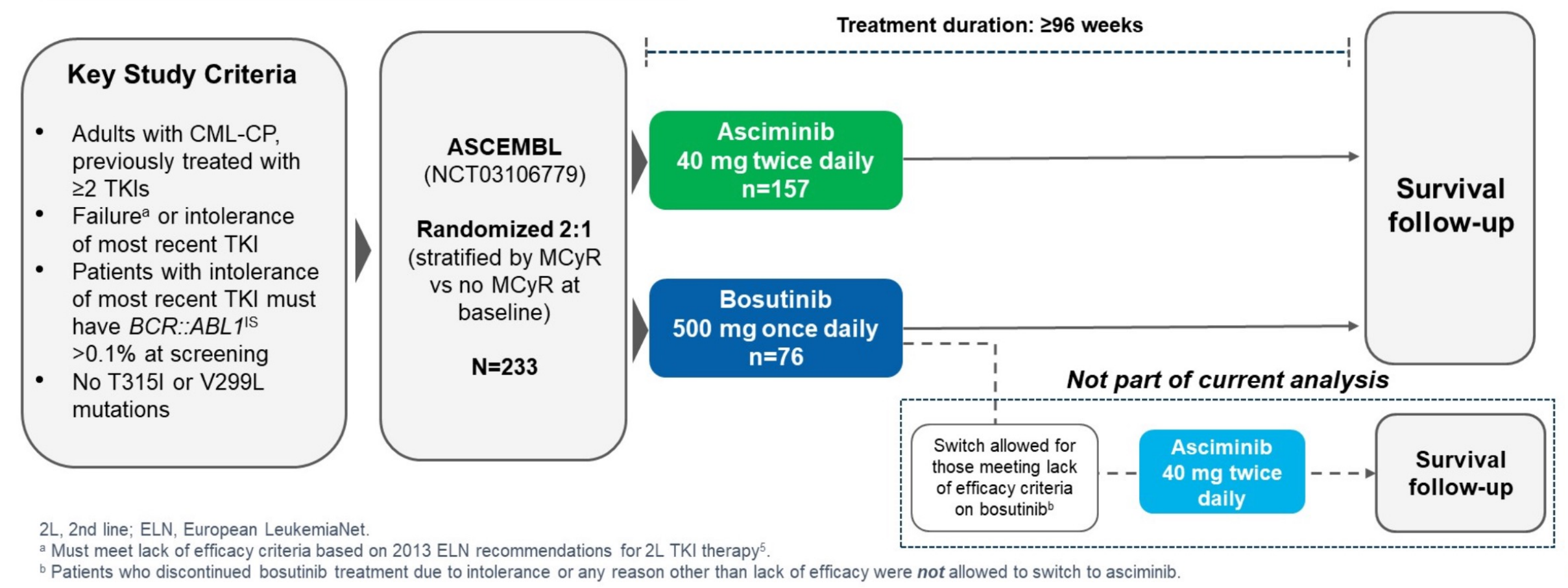


Proliferation IC_{50} Profiles in Ba/F3 *BCR-ABL1*–Mutant Lines



Courtesy of Jorge Cortes, MD

ASCEMBL: A Phase III Study of Asciminib versus Bosutinib for CML-CP (Chronic-Phase CML) After ≥2 Prior TKIs

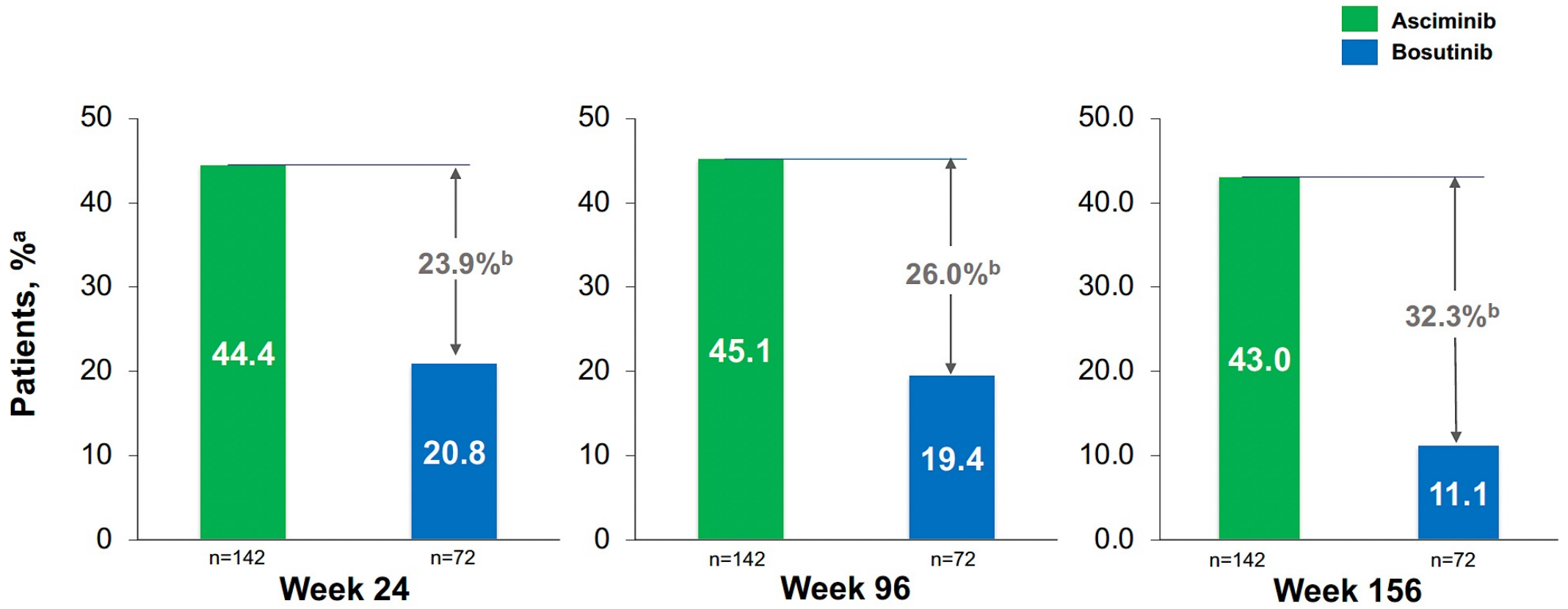


2L, 2nd line; ELN, European LeukemiaNet.
[a] Must meet lack of efficacy criteria based on 2013 ELN recommendations for 2L TKI therapy[5].
[b] Patients who discontinued bosutinib treatment due to intolerance or any reason other than lack of efficacy were ***not*** allowed to switch to asciminib.

MCyR = major cytogenic response

Rea D et al. ASCO 2022;Abstract 7004. Hochhaus A et al. *Leukemia* 2023;37(3):617-26.

ASCEMBL: BCR::ABL1^{IS} ≤1% Rates at Weeks 24, 96 and 156

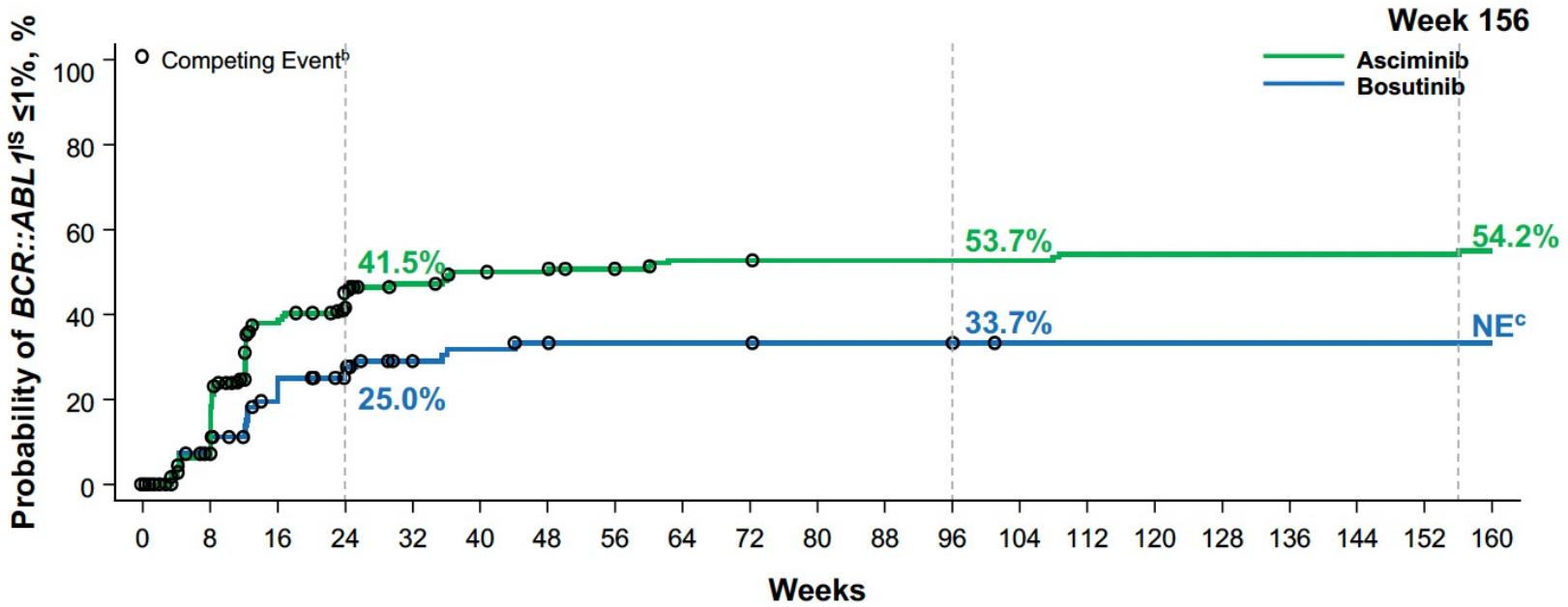


- With longer follow-up, the rate of *BCR::ABL1*^{IS} ≤1% at week 156 in patients with *BCR::ABL1*^{IS} >1% at baseline remained higher with **asciminib** compared with **bosutinib**

Mauro M et al. ASH 2023;Abstract 4536.

RTP RESEARCH TO PRACTICE

ASCEMBL: Cumulative Incidence of BCR::ABL1^{IS} ≤1%



No. at risk

Asciminib	142	120	62	48	19	13	12	8	4	4	3	3	3	3	1	1	1	1	1	1	0
Bosutinib	72	58	37	25	8	6	4	3	3	3	2	2	2	0	0	0	0	0	0	0	0

Cumulative no. of competing events

Asciminib	0	8	26	35	56	58	59	62	63	63	64	64	64	64	64	64	64	64	64	64	64
Bosutinib	0	8	19	29	43	43	44	45	45	45	46	46	46	48	48	48	48	48	48	48	48

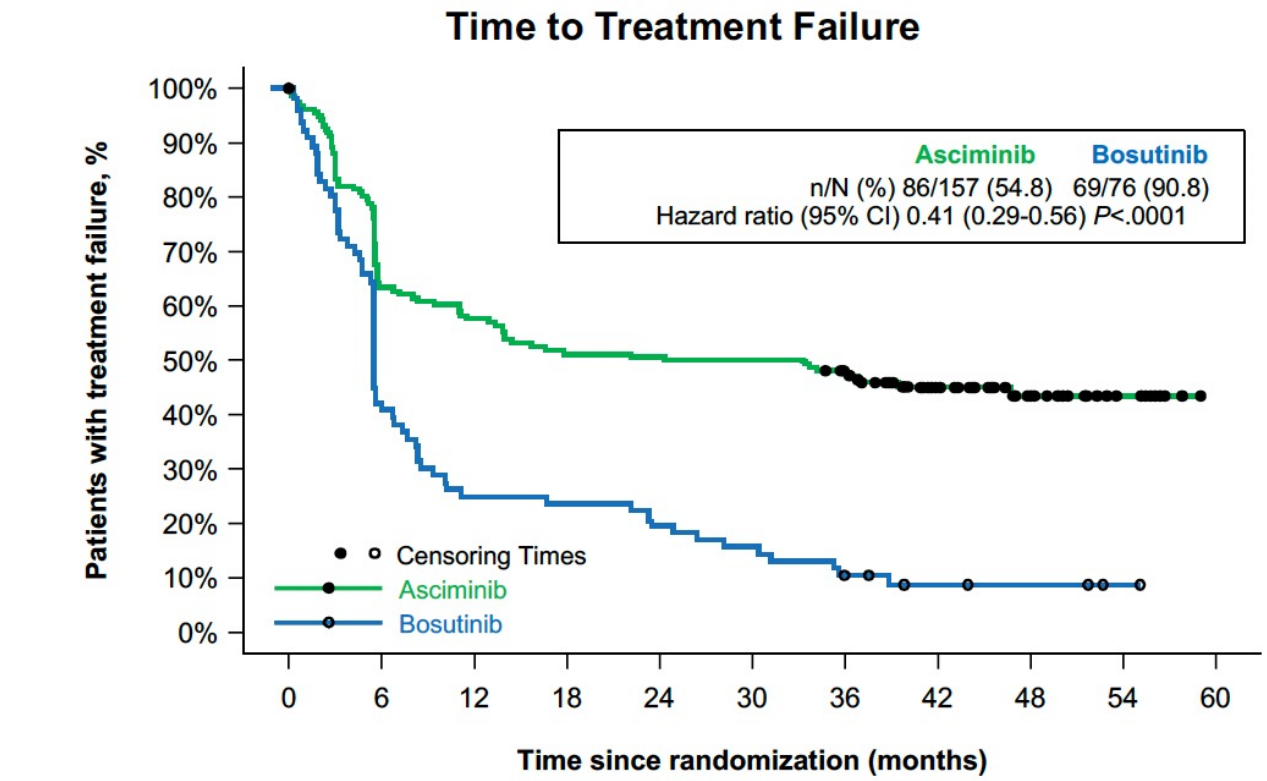
- The cumulative incidence of *BCR::ABL1*^{IS} ≤1% continued to increase over time with **asciminib** and by week 156, was **not evaluable** with **bosutinib**

Durability of *BCR::ABL1*^{IS} ≤1%

- The probability of maintaining *BCR::ABL1*^{IS} ≤1% for ≥120 weeks was **94.7%** with **asciminib** and **95.0%** with **bosutinib**
- Rates of *BCR::ABL1*^{IS} ≤1% were durable in both treatments arms, with most patients who achieved *BCR::ABL1*^{IS} ≤1% with **asciminib (74 of 78 patients)** and **bosutinib (23 of 24 patients)**, maintaining *BCR::ABL1*^{IS} ≤1% at the time of their last molecular assessment

Mauro M et al. ASH 2023;Abstract 4536.

ASCEMBL: Time to Treatment Failure



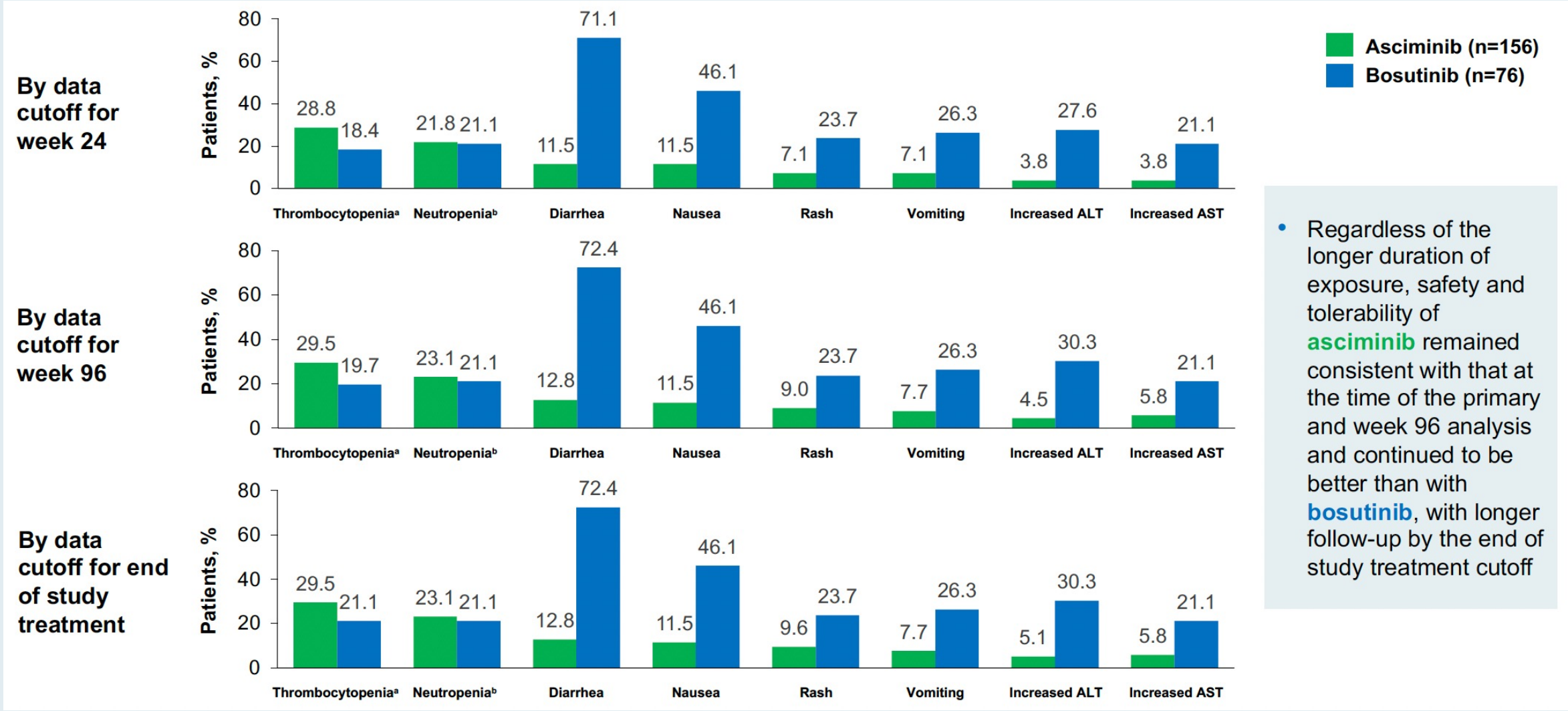
No. at risk:events

Asciminib	157:0	99:57	90:66	80:76	79:77	78:78	69:82	40:85	22:86	11:86	0:86
Bosutinib	76:0	31:45	19:57	18:58	15:61	12:64	7:68	4:69	3:69	1:69	0:69

- By 3 years, the probability of experiencing treatment failure continued to be lower with **asciminib (52.6%)** than with **bosutinib (89.5%)**, and the median time to treatment failure was shorter for **bosutinib (0.5 years)** compared with **asciminib (2.4 years)**

Mauro M et al. ASH 2023;Abstract 4536.

ASCEMBL: Most Frequent All-Grade Adverse Events



- Regardless of the longer duration of exposure, safety and tolerability of **asciminib** remained consistent with that at the time of the primary and week 96 analysis and continued to be better than with **bosutinib**, with longer follow-up by the end of study treatment cutoff

Mauro M et al. ASH 2023;Abstract 4536.

ASCEMBL: Adverse Events (AEs) Leading to Treatment Discontinuation

	Asciminib 40 mg twice daily (n=156)		Bosutinib 500 mg once daily (n=76)	
Event, n (%)[a]	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**
Number of patients with ≥1 adverse event	13 (8.3)	12 (7.7)	21 (27.6)	15 (19.7)
Thrombocytopenia[c]	5 (3.2)	5 (3.2)	1 (1.3)	1 (1.3)
Neutropenia[d]	4 (2.6)	4 (2.6)	3 (3.9)	3 (3.9)
Lipase increased	3 (1.9)	3 (1.9)	0	0
Amylase increased	1 (0.6)	1 (0.6)	0	0
Cerebral disorder	1 (0.6)	1 (0.6)	0	0
Ejection fraction decreased	1 (0.6)	1 (0.6)	0	0
Ischemic stroke	1 (0.6)	1 (0.6)	0	0
Pregnancy	1 (0.6)	0	0	0
ALT increased	0	0	4 (5.3)	3 (3.9)
AST increased	0	0	2 (2.6)	1 (1.3)
Blood creatinine increased	0	0	1 (1.3)	0
Diarrhea	0	0	3 (3.9)	1 (1.3)
Diffuse large B-cell lymphoma	0	0	1 (1.3)	1 (1.3)
Drug eruption	0	0	1 (1.3)	0
Pleural effusion[e]	0	0	4 (5.3)	3 (3.9)
Pyrexia	0	0	1 (1.3)	1 (1.3)
Rash	0	0	1 (1.3)	1 (1.3)
Squamous cell carcinoma	0	0	1 (1.3)	1 (1.3)

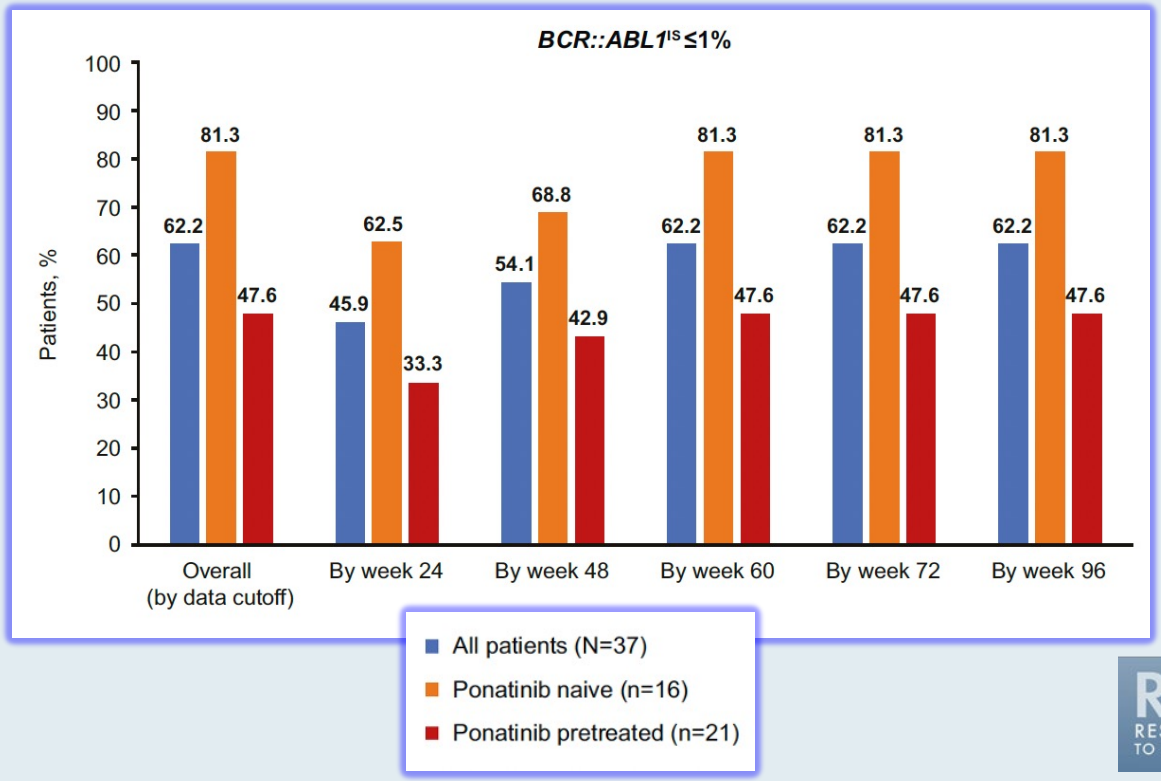
- The proportion of patients with AEs leading to treatment discontinuation was lower with **asciminib** compared with **bosutinib** and no new discontinuations due to grade ≥3 AEs occurred with **asciminib** since the week 96 cutoff

Mauro M et al. ASH 2023;Abstract 4536.

Asciminib Monotherapy for CP-CML with the T315I Mutation After ≥1 Prior TKI: Demographics and Response

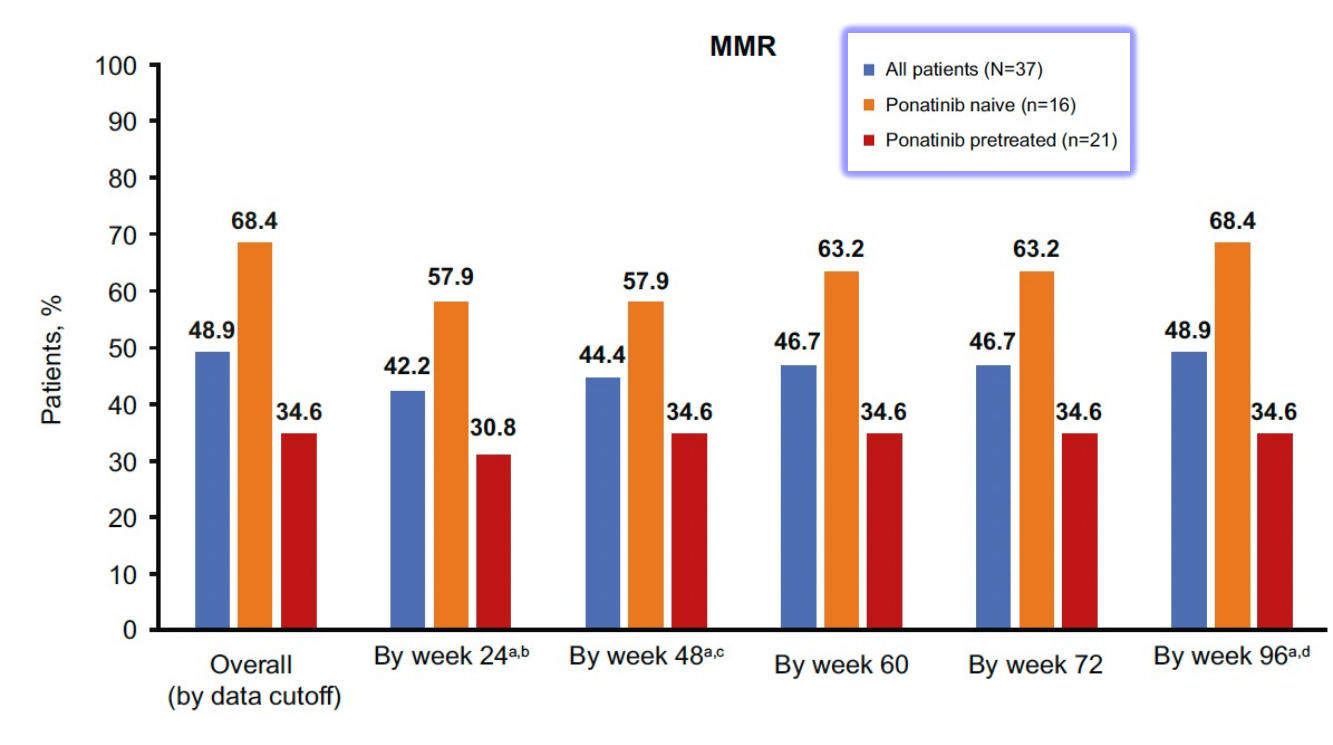
Demographic variable	All patients N = 48	Evaluable patients N = 45
No. of prior TKIs		
1[a]	8 (16.7)	8 (17.8)
2	15 (31.3)	14 (31.1)
3	17 (35.4)	16 (35.6)
≥4	8 (16.7)	7 (15.6)
Individual prior TKIs		
Bosutinib	3 (6.3)	2 (4.4)
Dasatinib	33 (68.8)	33 (73.3)
Imatinib	27 (56.3)	25 (55.6)
Nilotinib	26 (54.2)	23 (51.1)
Ponatinib	29 (60.4)	26 (57.8)
Radotinib	4 (8.3)	4 (8.9)
Reason for discontinuation of last dose of ponatinib		
Intolerance	9 (31.0)	7 (26.9)
Resistance	14 (48.3)	13 (50.0)
Other	6 (20.7)	6 (23.1)
Mutations at screening, n (%)		
T315I alone	46 (95.8)	43 (95.6)
T315I and E255K	1 (2.1)	1 (2.2)
T315I and E355G	1 (2.1)	1 (2.2)

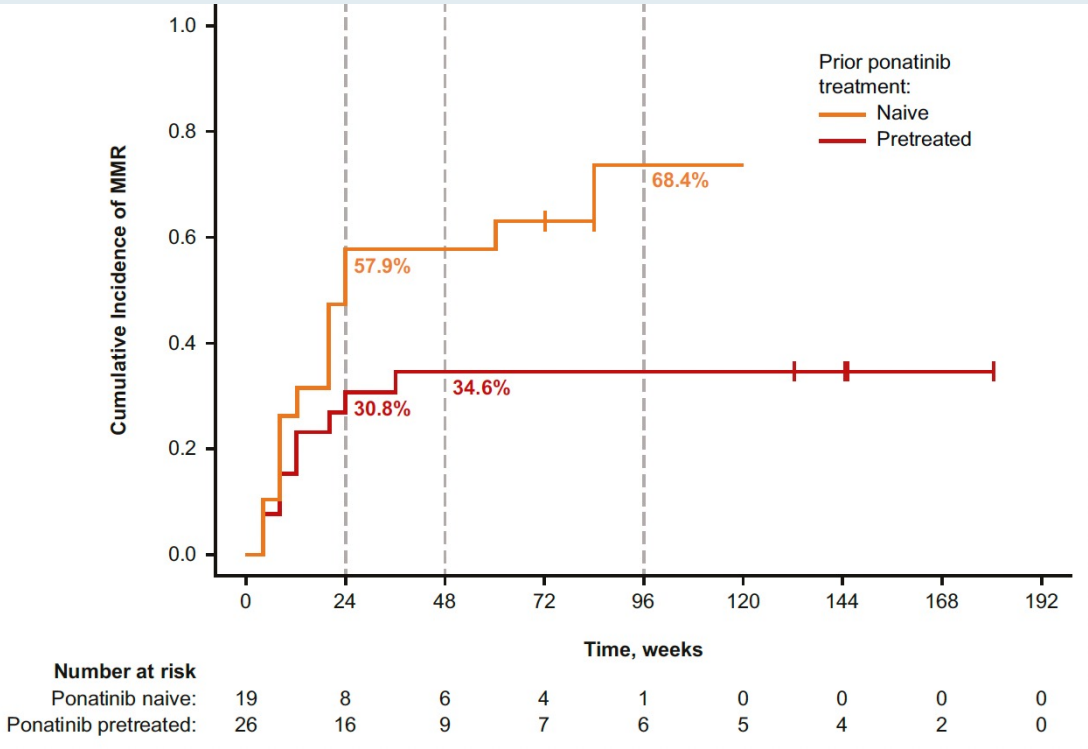
Demographic variable	All patients N = 48	Evaluable patients N = 45
BCR::ABL1^{IS} at screening, n (%)		
>0.01% to 0.1%	0	0
>0.1% to 1%	8 (16.7)	8 (17.8)
>1% to 10%	11 (22.9)	11 (24.4)
>10%	26 (54.2)	26 (57.8)
Atypical /e1a2/unknown transcripts[b]	3 (6.3)	0



Cortes JE et al. *Leukemia* 2024;38(7):1522-33.

Asciminib Monotherapy for CP-CML with the T315I Mutation After ≥1 Prior TKI: Major Molecular Response (MMR) Outcomes





Cortes JE et al. *Leukemia* 2024;38(7):1522-33.

A Phase Ib Study of Olverembatinib After Failure of TKI, Including Ponatinib or Asciminib

Olverembatinib (HQP1351) is a novel third-generation BCR::ABL1 TKI approved in China for adults with chronic-phase CML, accelerated-phase CML with the T315I variant or chronic-phase CML resistant to and/or intolerant of first-generation and second-generation TKIs.

Previous Chinese trials demonstrated that olverembatinib was efficacious, safe and well tolerated in patients with CML heavily pretreated with TKIs, irrespective of the ABL1 genotype.

The data presented in this open-label, Phase Ib dose-randomized clinical trial are from non-Chinese patients.

Characteristic	No. (%) Chronic-phase CML (n = 62)
Race[a]	
Asian	2 (3.2)
Black	7 (11.3)
White	50 (80.6)
Other race or ethnicity[b]	3 (4.8)

Characteristic	No. (%) Chronic-phase CML (n = 62)
ABL1 T315I variant	18 (29.0)
BCR::ABL1 levels at baseline, %	
<1	5 (8.1)
1-10	13 (21.0)
>10	43 (69.4)
Prior TKI treatment	
1	0
2	12 (19.4)
3	18 (29.0)
≥4	32 (51.6)
Prior ponatinib treatment	31 (50.0)
Resistant[c]	21 (33.9)
Intolerant[d]	7 (11.3)
Other[e]	3 (4.8)
Prior asciminib treatment	17 (27.4)
Resistant[c]	12 (19.4)
Intolerant[d]	3 (4.8)
Other[e]	2 (3.2)

Jabbour E et al. *JAMA Oncol* November 21, 2024;[Online ahead of print].

RTP RESEARCH TO PRACTICE

Phase Ib Study of Olverembatinib After Failure of TKI, Including Ponatinib or Asciminib: Response Data

Table 2. Cytogenetic and Molecular Responses in Patients With Chronic-Phase Chronic Myeloid Leukemia

Outcome	No.							
	Olverembatinib dose every other day			With T315I variant	With non-T315I variant	Without T315I variant	No variants	Total
	30 mg	40 mg	50 mg					
Efficacy population	28	24	8	18	9	42	33	60
Cytogenetic response								
Evaluable patients	23	20	8	18	8	33	25	51
Complete cytogenetic response, No. (%)	11 (47.8)	15 (75.0)	5 (62.5)	10 (55.6)	4 (50.0)	21 (63.6)	17 (68.0)	31 (60.8)
Molecular response								
Evaluable patients	28	23	8	18	9	41	32	59
Major molecular response, No. (%)	10 (35.7)	12 (52.2)	3 (37.5)	8 (44.4)	3 (33.3)	17 (41.5)	14 (43.8)	25 (42.4)

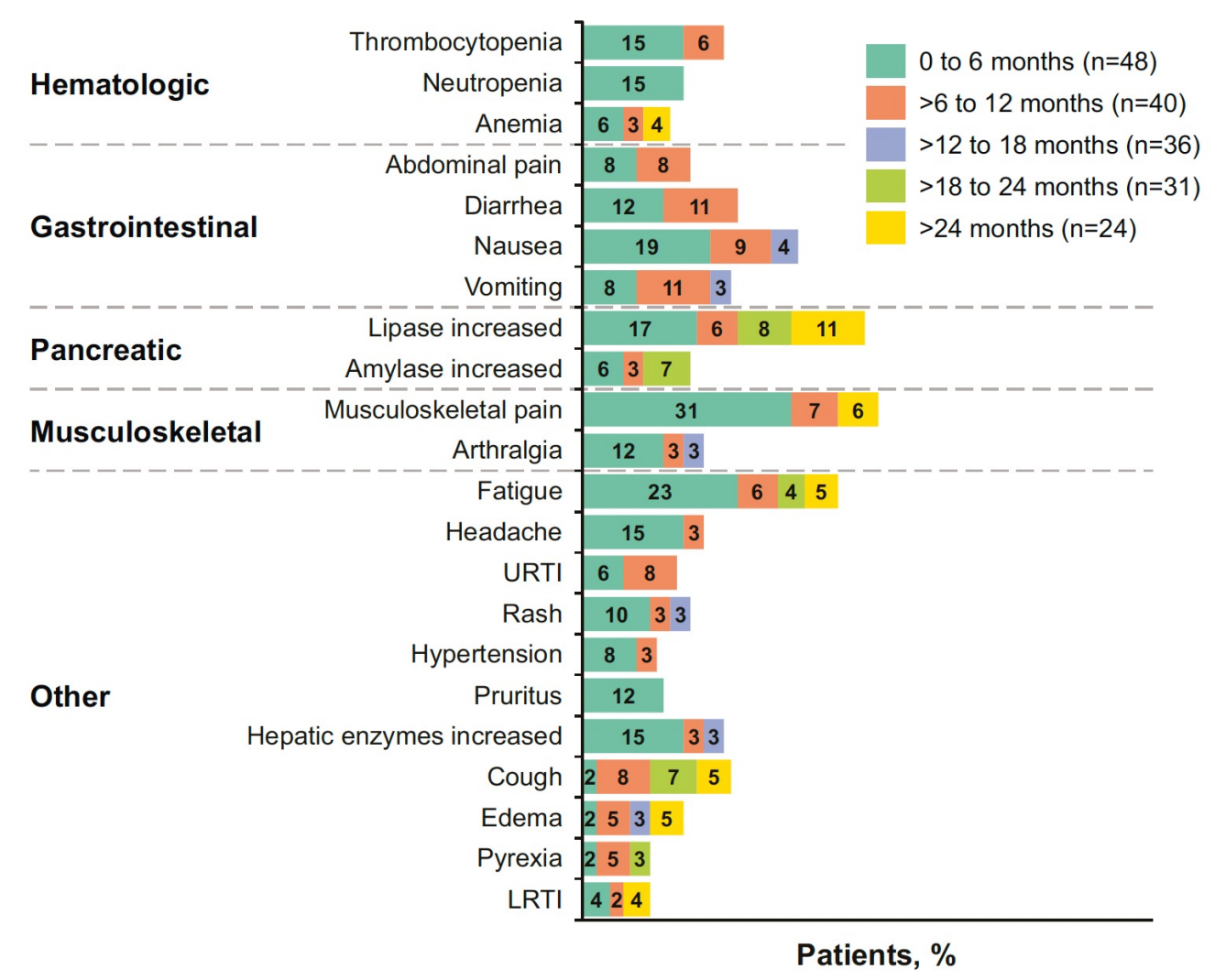
Jabbour E et al. *JAMA Oncol* November 21, 2024;[Online ahead of print].

Phase Ib Study of Olverembatinib After Failure of TKI, Including Ponatinib or Asciminib: Response Data by Prior Exposure

Outcome	No. With T315I variant	No T315I variant	Resistant	Intolerant
Ponatinib				
Ponatinib pretreated				
Efficacy population	13	17	21	6
Cytogenetic response				
Evaluable patients	13	13	19	4
Complete cytogenetic response, No. (%)	8 (61.5)	7 (53.8)	10 (52.6)	3 (75.0)
Molecular response				
Evaluable patients	13	17	21	6
Major molecular response, No. (%)	6 (46.2)	5 (29.4)	9 (42.9)	1 (16.7)
Asciminib				
Asciminib pretreated				
Efficacy population	3	14	12	3
Cytogenetic response				
Evaluable patients	3	7	8	0
Complete cytogenetic response	1 (33.3)	5 (71.4)	4 (50.0)	0
Molecular response				
Evaluable patients	3	14	12	3
Major molecular response, No. (%)	1 (33.3)	4 (28.6)	4 (33.3)	0

Jabbour E et al. *JAMA Oncol* November 21, 2024;[Online ahead of print].

Asciminib Monotherapy for CP-CML with the T315I Mutation After ≥1 Prior TKI: Safety



Preferred term, n (%)	All patients N = 48	
	All grades	Grade ≥ 3
No. of patients with ≥1 event	48 (100)	29 (60.4)
Lipase increased	14 (29.2)	9 (18.8)
Fatigue	14 (29.2)	1 (2.1)
Nausea	13 (27.1)	0
Diarrhea	10 (20.8)	1 (2.1)
Vomiting	9 (18.8)	3 (6.3)
Musculoskeletal pain[a]	9 (18.8)	0
Thrombocytopenia	8 (16.7)	7 (14.6)
Headache	8 (16.7)	1 (2.1)
Arthralgia	8 (16.7)	0
Alanine aminotransferase increased	7 (14.6)	3 (6.3)
Abdominal pain	7 (14.6)	3 (6.3)
Cough	7 (14.6)	0
Amylase increased	6 (12.5)	2 (4.2)
Back pain	6 (12.5)	1 (2.1)
Pruritus	6 (12.5)	0
Aspartate aminotransferase increased	6 (12.5)	1 (2.1)
Hypertension	5 (10.4)	3 (6.3)
Anemia	5 (10.4)	3 (6.3)
Edema peripheral	5 (10.4)	2 (4.2)

URTI = upper respiratory tract infection; LRTI = lower respiratory tract infection

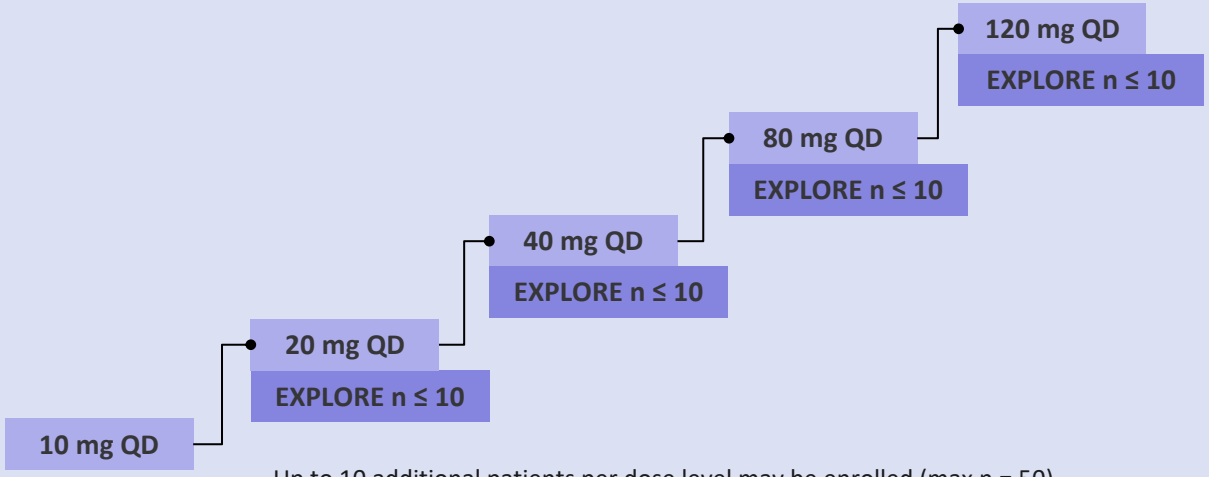
Cortes JE et al. *Leukemia* 2024;38(7):1522-33.

ENABLE (ELVN-001-101): Trial Design

Key eligibility criteria:

- Chronic Phase CML (CP-CML)
- Failed, intolerant to, or not a candidate for, available therapies known to be active for treatment of their CML[a]

Phase 1a: Dose Escalation[b]



Up to 10 additional patients per dose level may be enrolled (max n = 50)

Phase 1b: Dose Expansion

Dose level 1	Dose level 2	T315I
Phase 1b expansion in CP-CML no T315I mutations; n=20	Phase 1b expansion in CP-CML no T315I mutations; n=20	Phase 1b expansion in CP-CML with T315I mutations; n=20

Additional expansion cohorts may be opened for patients based on emerging data

Primary endpoints:

- Incidence of dose limiting toxicities, adverse events, clinically significant laboratory abnormalities and ECG abnormalities

Secondary endpoints (Phase 1a[d]):

- Pharmacokinetics parameters[c]
- Molecular response (MR) by central qPCR using the International System (measured every 4 weeks x 6, then every 12 weeks)

Clinicaltrials.gov Identifier: NCT05304377.

CML = Chronic myeloid leukemia. CP = Chronic phase. QD = Once daily. qPCR = Quantitative reverse transcriptase polymerase chain reaction. [a] In the United States, S. Korea, Australia, EU; at least 2 prior therapies known to be active for treatment of their CML are required in Canada. [b] Re-enrollment and intra-subject dose escalation allowed if meeting specific criteria; BID (twice daily) dosing may be explored [c] area under the curve (AUC), maximum concentration (C_{max}), time at which C_{max} is observed (T_{max}), minimum concentration (C_{min}), terminal half-life ($t_{1/2}$) [d] Phase 1b additional secondary endpoints: duration of MR, BCR::ABL1 qPCR ≤ 1%, complete hematological response.

Positive Data Update from the Phase I Clinical Trial of ELVN-001 for CML

Press Release: September 28, 2024

"[The manufacturer] announced updated, positive data from the Phase 1 clinical trial evaluating ELVN-001 in patients with chronic myeloid leukemia (CML) that has failed, or the patient is intolerant to or not a candidate for, available therapies known to be active for treatment of their CML.

The updated data presented ... includes 39 patients across various dose levels. ...Of the enrolled patients, 18 with typical transcripts and without T315I mutations were evaluable for molecular response by 24 weeks.

- ELVN-001 achieved a cumulative MMR rate of 44.4% (8/18) by 24 weeks.
- Among the 16 patients previously evaluated for efficacy, all 16 had stable or deepening responses between weeks 12 and 24.
- Among TKI-resistant patients, ELVN-001 achieved a cumulative MMR rate of 41.7% (5/12) by 24 weeks.
- **Among post-asciminib patients, ELVN-001 achieved a cumulative MMR rate of 40.0% (4/10) by 24 weeks.**
- Among patients that were not in MMR at baseline, 23.1% (3/13) achieved MMR by 24 weeks."

https://ir.enliventherapeutics.com/news-releases/news-release-details/enliven-therapeutics-announces-positive-data-update-phase-1

TERN701-1012: CARDINAL Study Design

Multicenter, open-label Phase 1 clinical trial to evaluate the safety, PK, and efficacy of TERN-701 in participants with previously treated CP-CML

Part 1 Dose Escalation (non-T315I and T315Im)

BOIN Design with optional backfill cohorts

TERN-701 Once-Daily Monotherapy (N=~24-36)

- 500 mg, N ≥ 3
- 400 mg, N ≥ 3
- 320 mg, N ≥ 3
- *Starting dose* → 160 mg, N ≥3
- 80 mg, N ≥ 3

RDE Selection‡

R

Part 2 Dose Expansion (non-T315Im)

- **TERN-701 Dose 2* N = 20**
- **TERN-701 Dose 1* N = 20**

Stratify randomization according to:

- BCR::ABL1 transcript levels (<1% or ≥1%)
- Presence or absence of BCR::ABL1 mutations other than T315I

‡RDE: recommended dose for expansion will be selected following a Part 1 interim analysis

**Dose 1 expected to be ≥ 160mg. Dose 2 targeted be a dose level > 160mg Qday with sufficiently non-overlapping exposures and comparable safety to Dose 1

BOIN = Bayesian optimal interval; CP-CML = chronic phase-chronic myeloid leukemia; RDE = recommended dose for expansion

Positive Data Update from the Phase I Clinical Trial of TERN-701 for CML

Press Release: December 3, 2024

The data presented includes 15 patients across various dose levels. Of the enrolled patients, 60% had BCR::ABL levels >1% (40% greater than 10%), 13% T315I, and 80% 3 or more lines of therapy, including 5 patients with prior asciminib exposure

- Early, promising safety and efficacy profile in a small number of difficult to treat patients (n=15)
  - 88% of patients with BCR::ABL>1% responding, including rapid deep remission in 5th line
- No DLTs, AE-related treatment discontinuations or dose reductions, SAEs, >Grade 3 treatment related AEs
- Robust and continuous coverage over target efficacious exposures at all dose levels

https://ir.ternspharma.com/news-releases/news-release-details/terns-pharmaceuticals-announces-positive-early-data-phase-1

RTP RESEARCH TO PRACTICE

Questions from General Medical Oncologists

- What biomarkers, if any, might predict resistance to TKIs? Should gene expression profiling be done for all patients who are progressing on first-line TKI?
- What is the significance of the BCR::ABL1 T315I mutation? Why is asciminib more effective in this setting?
- Is asciminib effective in patient who failed to respond to first-line treatment of CP-CML?
- How do you choose a second-line and third-line TKI after progression on initial therapy if there are no identified mutations?

Questions from General Medical Oncologists

- **64-year-old patient first diagnosed with CP-CML in 2016, on imatinib who has now progressed to blast phase (70% blasts in the marrow, 2% in the peripheral blood), acquired T315I mutation. What are your thoughts? Are ponatinib and asciminib equally good options here?**

Questions from General Medical Oncologists

- A patient with CP-CML has remained asymptomatic with normal blood counts on nilotinib for the past 2 years. The last 4 BCR::ABL1 transcript levels per qPCR are 0.009% 9 months ago, 0.006% 6 months ago, 0.04% 3 months ago and 0.6% now. Regulatory and reimbursement issues aside, what would you most likely recommend if mutational analysis revealed a T315I mutation?
- Which TKI would you most likely recommend for a patient with CP-CML whose disease has progressed on first-line imatinib followed by second-line dasatinib who is found to have a BCR::ABL1 F317L mutation?

Questions from General Medical Oncologists

- A 40-year-old woman with Sokal high-risk CP-CML on front-line imatinib at 400 mg/day for 3 months; CHR, but BCR-ABL1^{IS} 12%. Should I do a bone marrow analysis to confirm? Should I adjust therapy for this patient now or wait until 6 or 12 months to declare treatment resistance? If adjusting now, what would the panel recommend — increase the dose of imatinib or switch to a second-generation TKI? Which one? Any data to guide us in this decision?

Agenda

Module 1: Up-Front Therapy for Chronic Myeloid Leukemia (CML) — Prof Hochhaus

Module 2: Management of Relapsed CML, Including in Patients with a T315I Mutation — Dr Mauro

Module 3: Tolerability and Other Practical Issues with Commonly Employed CML Therapies — Dr Smith

Tolerability and Other Practical Issues with Commonly Used CML Therapies

B. Douglas Smith, MD

Professor, Oncology

Kimmel Cancer Center at Johns Hopkins

Early Growth of Oral Anticancer Medicines: 1953-2013

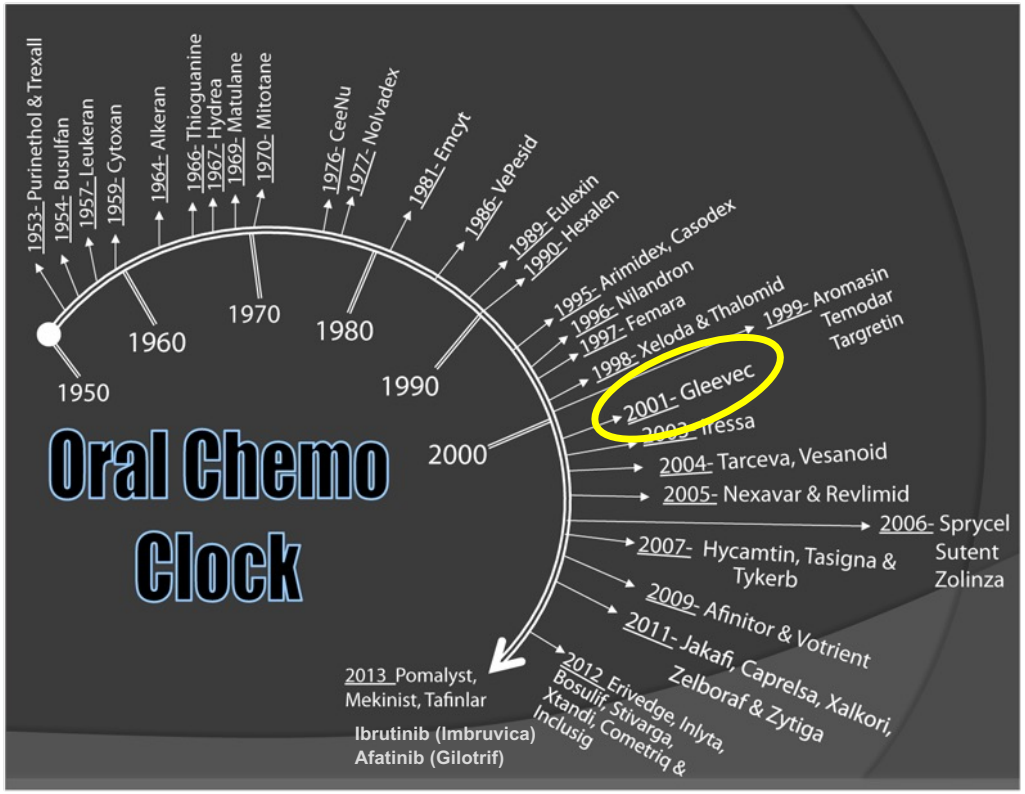


Figure: Timeline of the Introduction of Oral Oncolytics—Between 1953 and 2003, 27 oral chemotherapy agents were introduced, yet the same number of new oral chemotherapy agents (27) have been introduced between 2004 and the present.

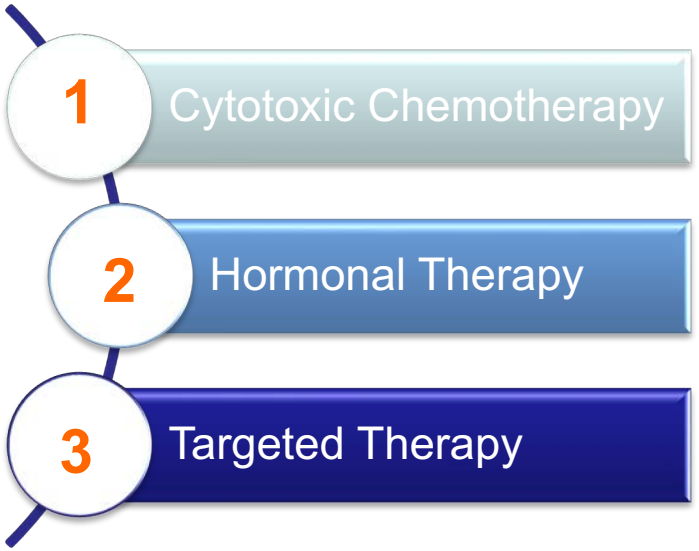
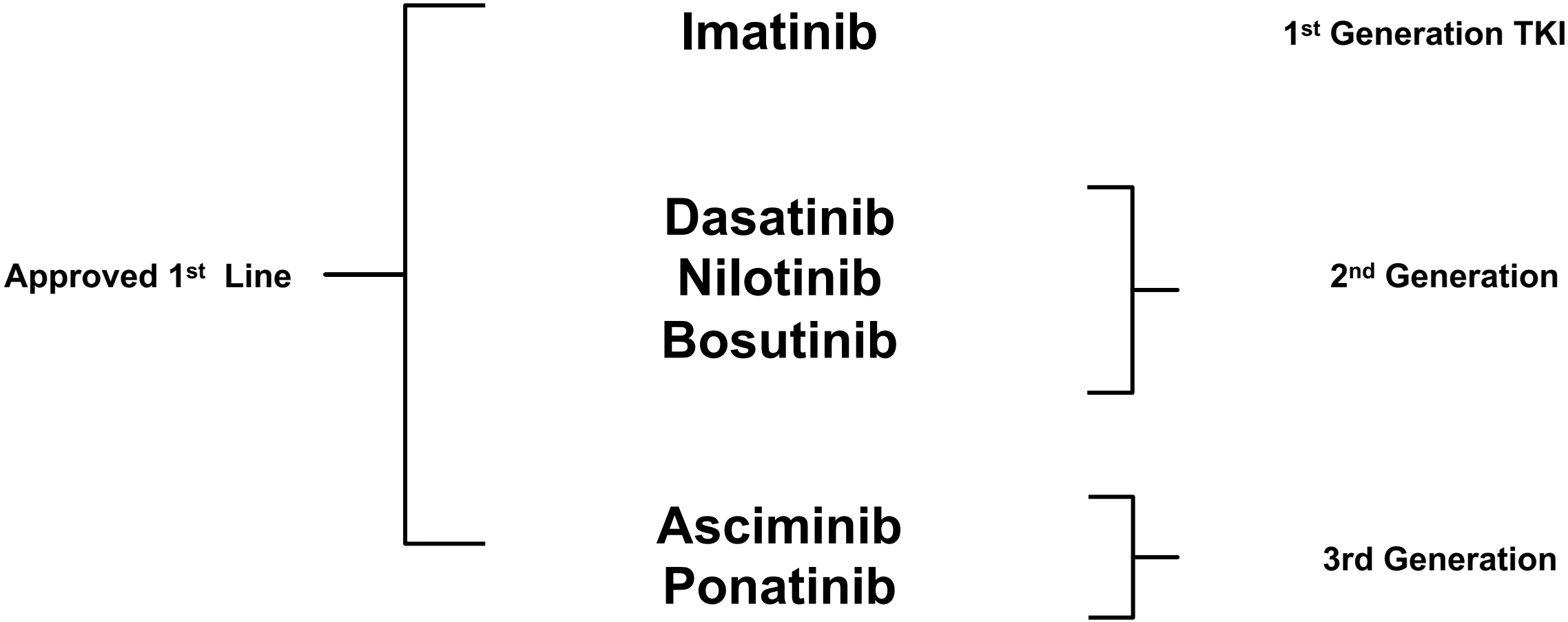


Image from: http://www.cancernetwork.com/practice-policy/oral-oncolytics-part-1-financial-adherence-and-management-challenges

Treatment Options for CML 2024-25



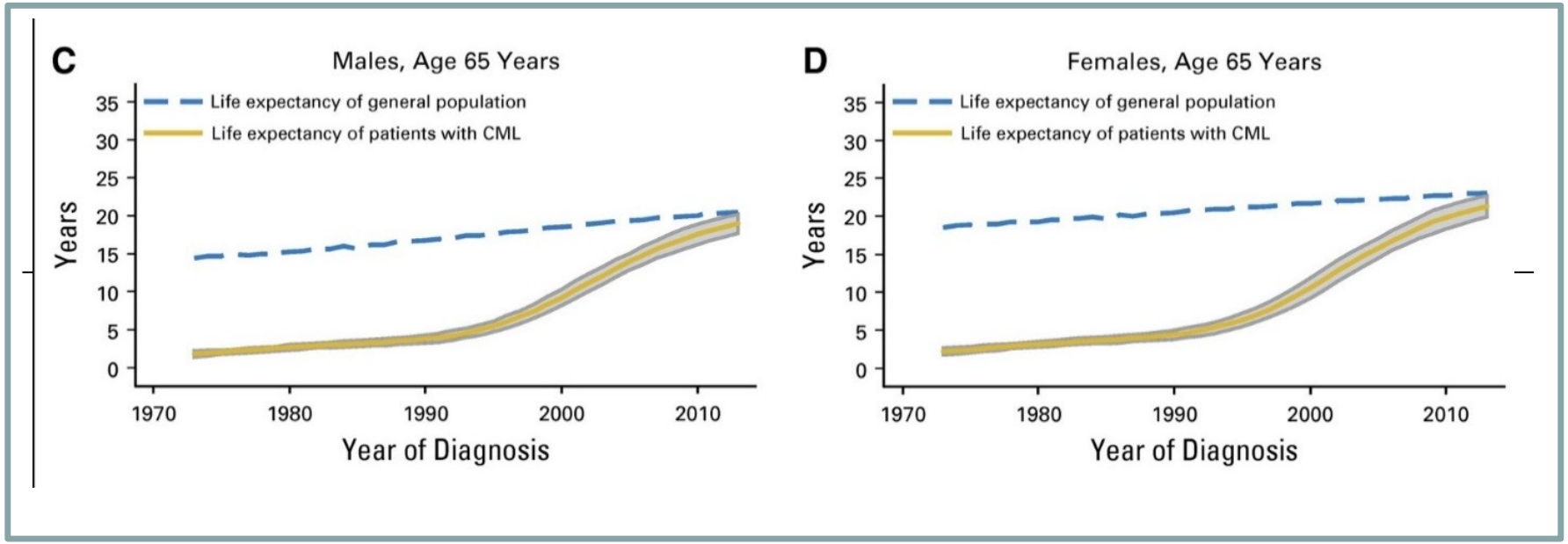
Oral Anticancer Medicines – Promises

- **Promises:**
  - **Precision and Personalized Medicine – started with CML**
  - **Perceived benefits**
    - **Safety (?) Less burdensome administration (?)**
      Compliance (?)
  - **Efficacy**

Life Expectancy of Pts with CML in TKI ERA

Swedish Cancer Registry Study – "Loss in Expected Life Analysis"

- **Pts diagnosed with CML btwn 1973 and 2013**
- **Age 50 yrs or greater**
- **Total 2662 pts: males = 1446 (54.3%); females = 1216 (45.7%)**



Patients diagnosed with CML are within 3 life-years of matched controls

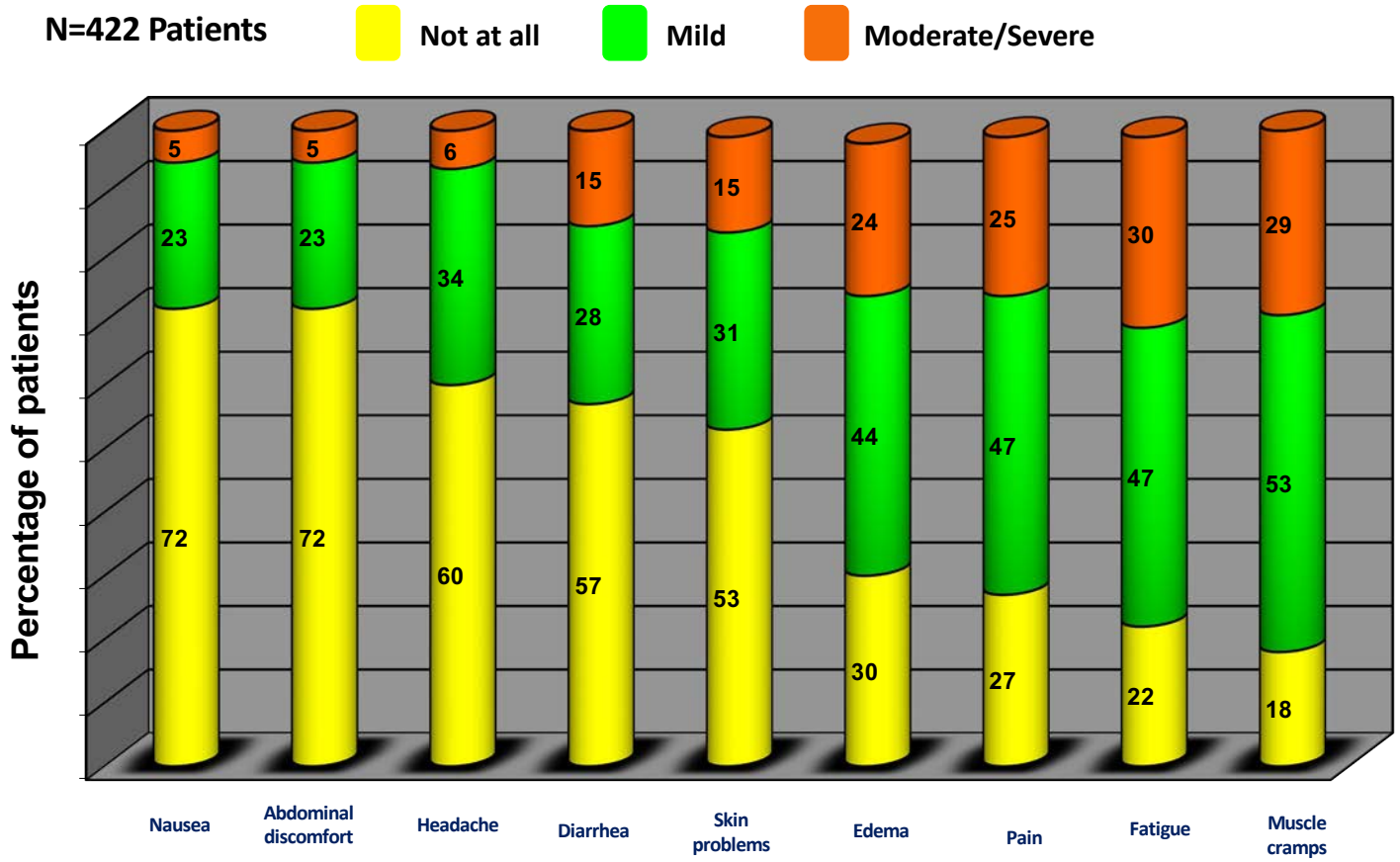
Bower et al. J Clin Oncol.2016 Aug 20;34(24):2851-7

Oral Anticancer Medicines – Pitfalls

- Promises:
  - Precision and Personalized Medicine – started with CML
  - Perceived benefits
    - Safety (?) Less burdensome administration (?) Compliance (?)
  - Efficacy
- **Pitfalls:**
  - **Fewer side effects – "simpler" and "safer"…"like taking a multivitamin"**
  - **Drug-drug interactions**
  - **Less burdensome administration vs adherence**
    - **Pt may equate it to taking an antibiotic or their BP meds – maybe ok to miss doses periodically?**

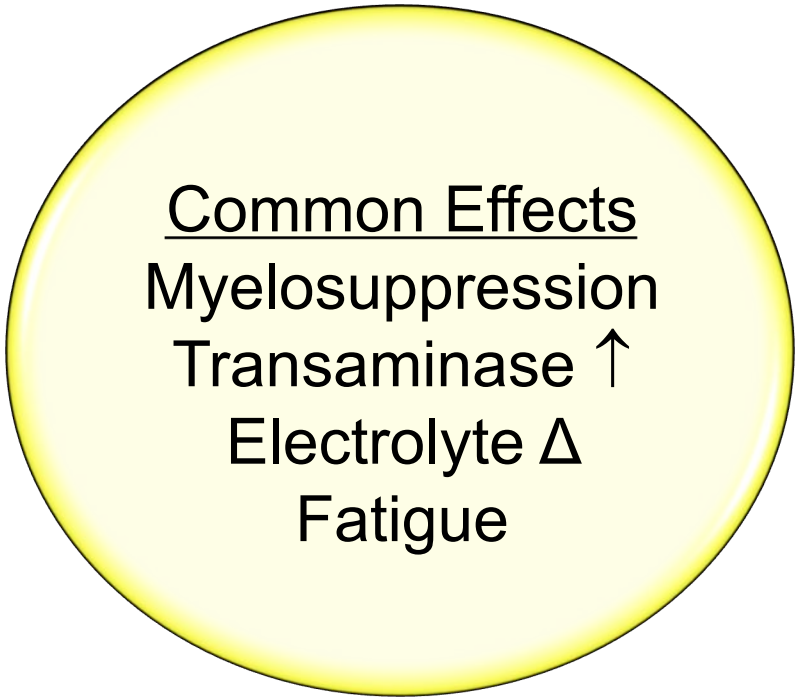
Pt Reported Symptoms in CML Pts on Long-Term Imatinib

Median 5 years on imatinib



Efficace et al, Leukemia 2013

Treatment Options Based on Adverse Event Spectrum of TKIs in CML



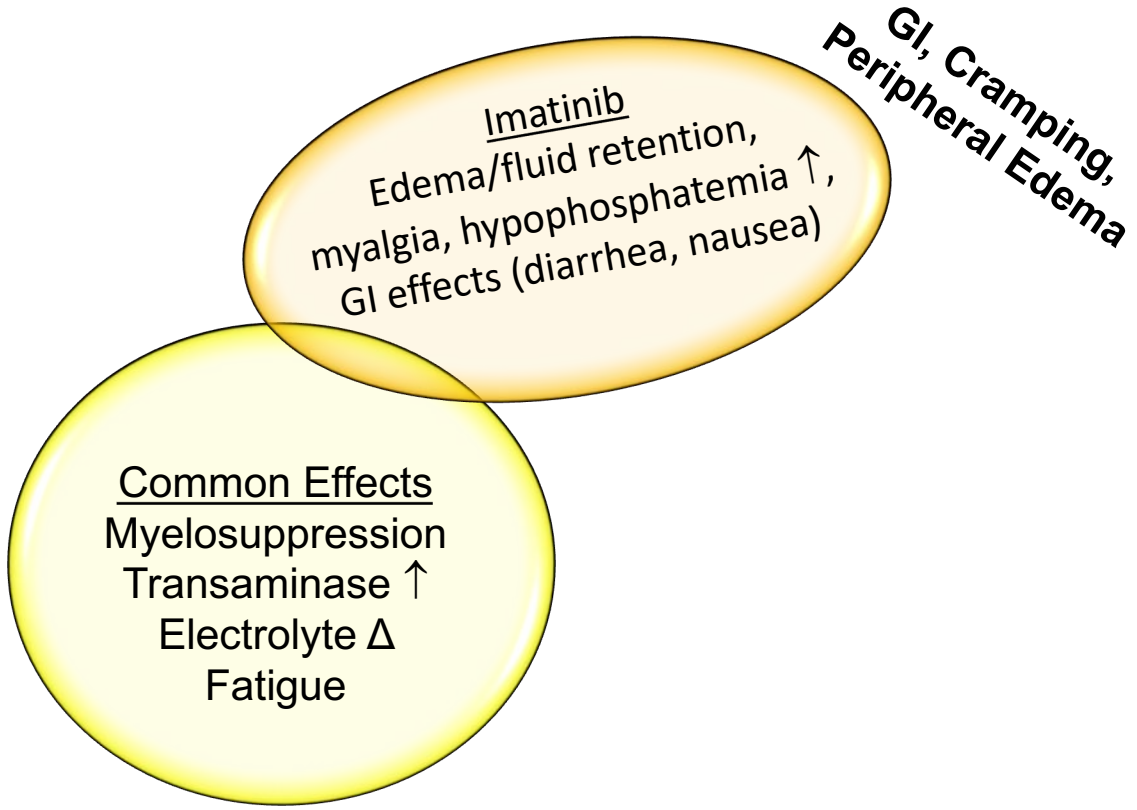
Early Monitoring of Patients on Oral Anticancer Medicines

- **Bone marrow and peripheral counts:** ***weekly thru nadir***
  - **Early cytopenias – can be significant**
  - **Late cytopenias – must determine etiology**

- **Liver and renal function vital:** ***every 7-14 days, first month***
  - **Metabolism and clearance** ***(ongoing – watch new medications)***
  - **Electrolyte changes important**

- **TKIs and Cardiovascular impact:** ***ECG early, CV = ongoing***
  - **Early impact on ECG, fluid retention**
  - **Late impact on cardiac risk factors** ***(HTN, peripheral vasculature)***

Treatment Options Based on Adverse Event Spectrum of TKIs in CML

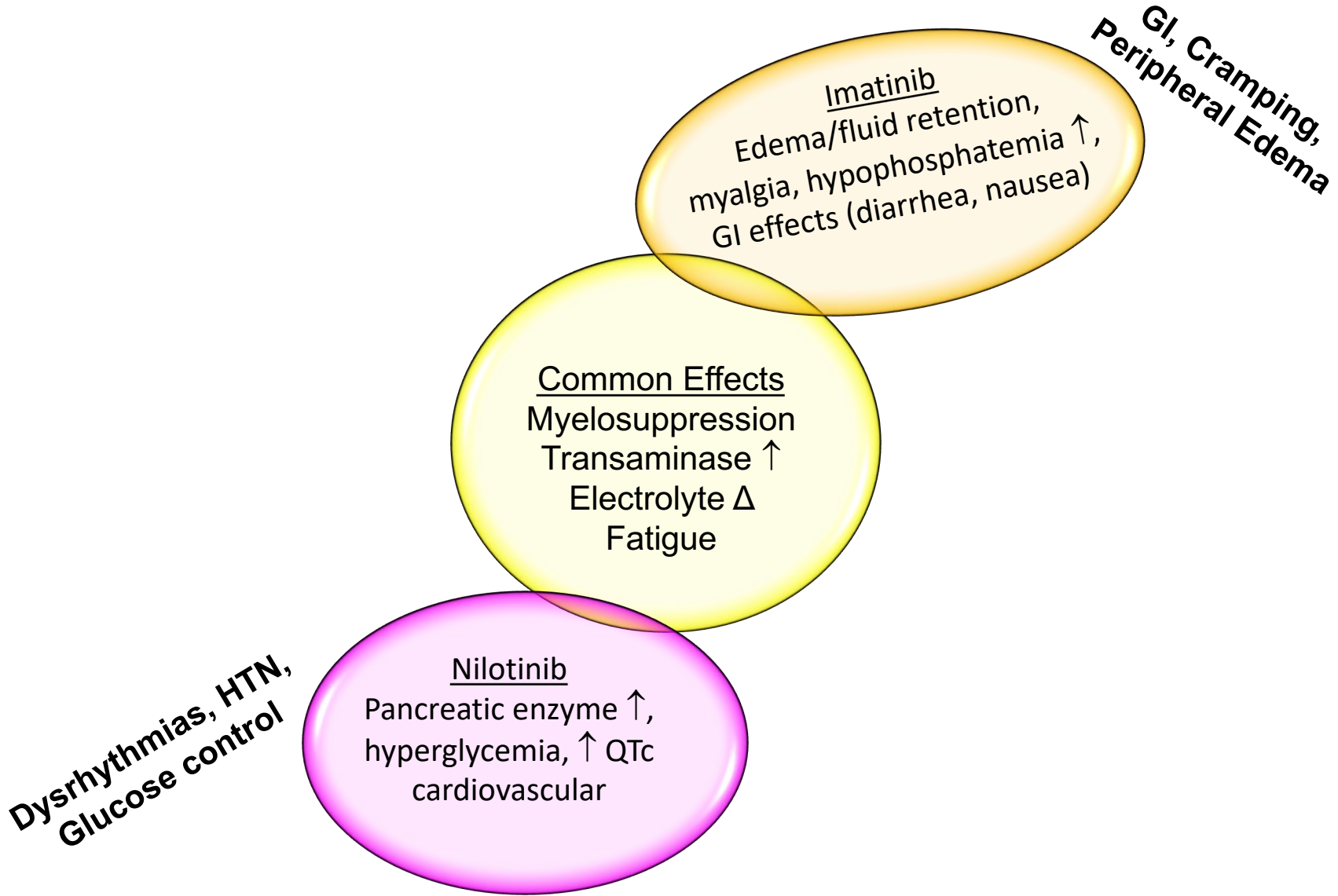


IRIS 5-yr: Grade 3-4 Toxicity to First-line Imatinib

	Overall Cumulative incidence (n=551)	Onset after 2 years (n=456)	Onset after 4 years (n=409)
Hematologic / Liver		**% of patients**	
Neutropenia	**16.7**	**3.7**	**1.0**
Thrombocytopenia	**8.9**	**1.5**	**0.2**
Anemia	**4.4**	**1.8**	**0.5**
Elevated liver enzymes	**5.3**	**0.4**	**0.0**
Other drug-related AEs	**17**	**5.0**	**2.0**

Drucker, et al. NEJM 2006

Treatment Options Based on Adverse Event Spectrum of TKIs in CML



ENESTnd: Laboratory Abnormalities Reported During Study

Laboratory Abnormality, %	Nilotinib 300 mg BID (n = 279)		Nilotinib 400 mg BID (n = 277)		Imatinib 400 mg QD (n = 280)	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Lipase ↑	24	7	30	7	11	3
Amylase ↑	16	< 1	20	1	13	1
ALT ↑	67	4	74	9	23	3
AST ↑	41	1	49	3	25	1
Total bilirubin ↑	54	4	63	8	11	< 1
Glucose ↑	38	6	42	4	22	0
Albumin ↓	4	0	5	0	4	0
Cholesterol ↑	22	0	22	< 1	3	0
Phosphorous ↓	33	5	37	6	49	8
ALP ↑	21	0	27	0	33	< 1
Creatinine ↑	5	0	6	0	13	< 1
Calcium ↓	3	< 1	5	< 1	11	0

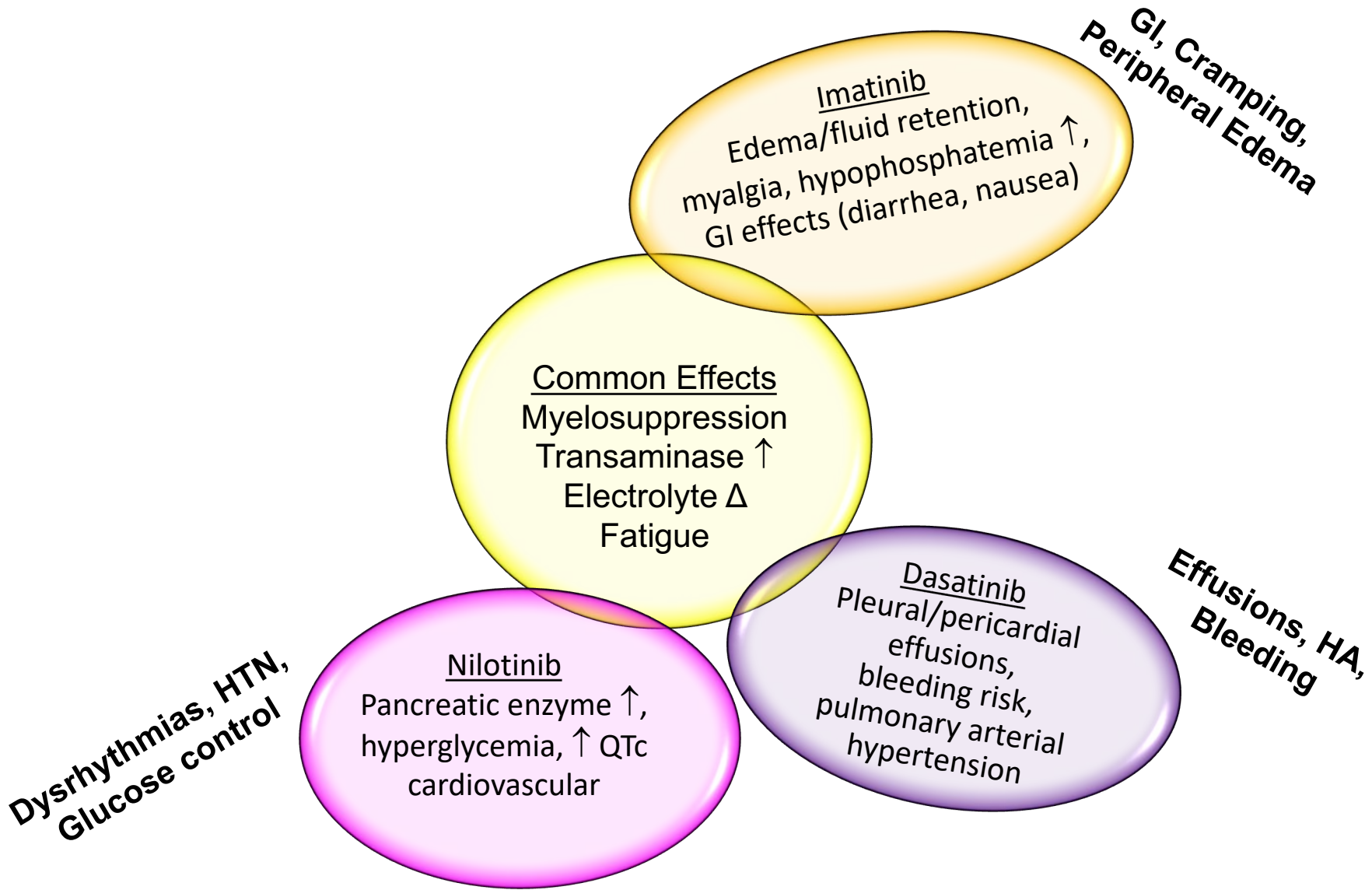
Larson RA, et al. Leukemia 2012

ENESTnd: Drug-Related Non-Laboratory Adverse Events

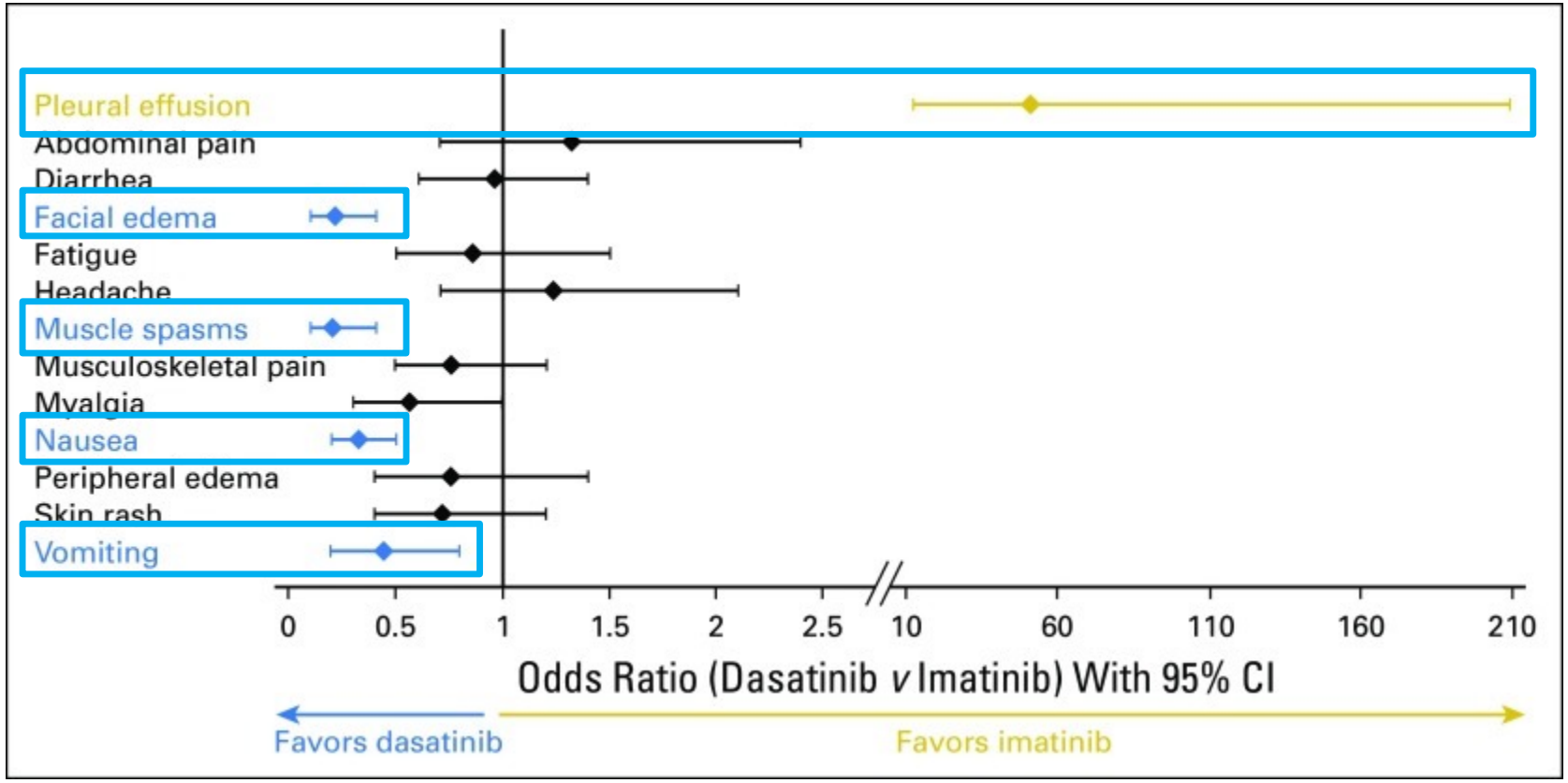
Adverse Event (Incidence ≥ 10% in Any Group), %	Nilotinib 300 mg BID (n = 279)		Nilotinib 400 mg BID (n = 277)		Imatinib 400 mg QD (n = 280)	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Nausea	12	< 1	20	1	33	0
Muscle spasms	7	0	6	< 1	26	< 1
Diarrhea	8	< 1	6	0	24	1
Vomiting	5	0	9	1	16	0
Rash	32	< 1	37	3	12	1
Headache	14	1	22	1	8	0
Pruritus	15	< 1	13	< 1	5	0
Alopecia	8	0	13	0	4	0
Myalgia	10	< 1	10	0	10	0
Fatigue	11	0	9	< 1	9	< 1

Larson RA, et al. Leukemia 2012

Treatment Options Based on Adverse Event Spectrum of TKIs in CML

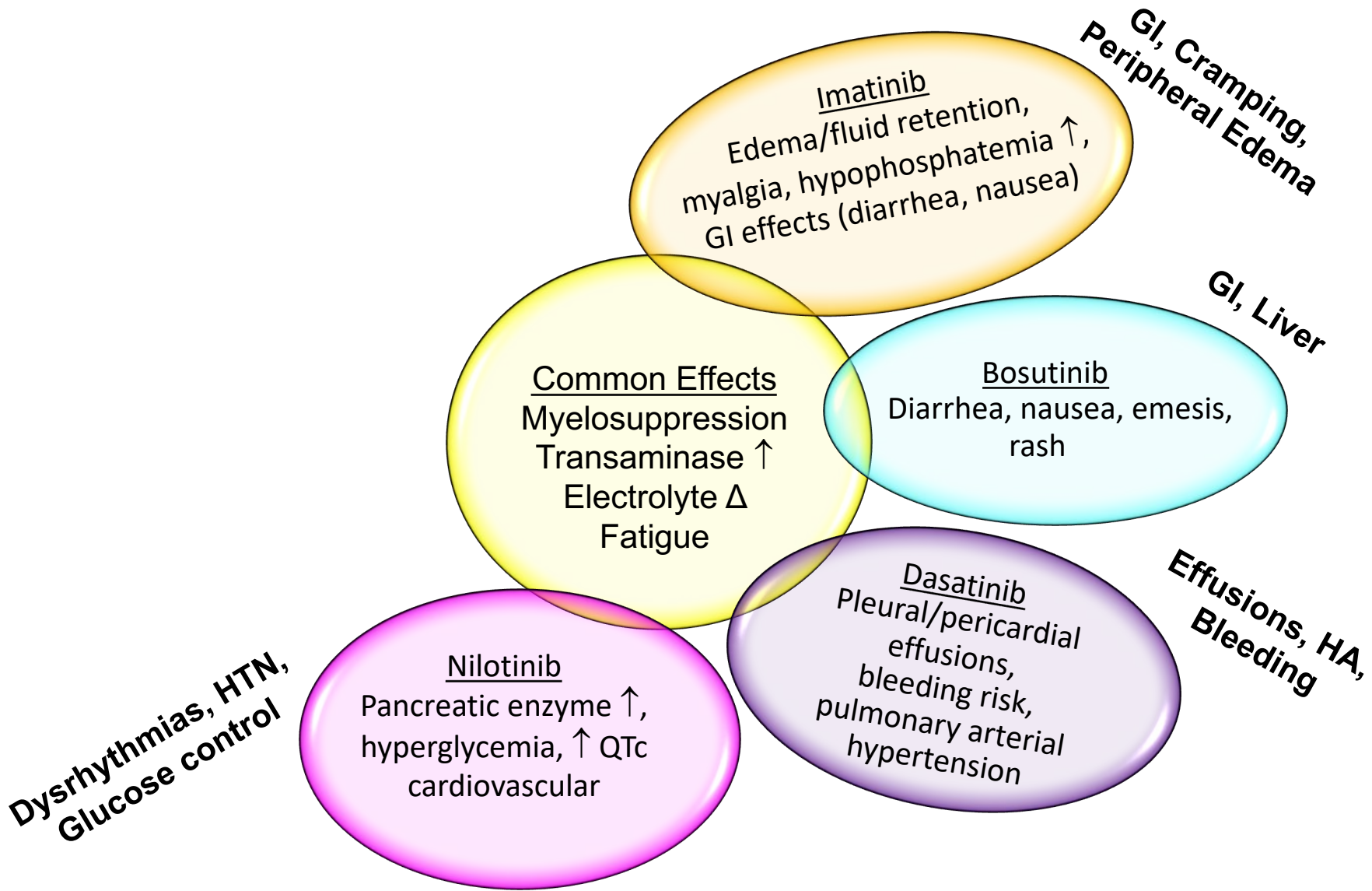


DASISION – 5 Year Follow-up



Cortes, et al, JCO. 2016

Treatment Options Based on Adverse Event Spectrum of TKIs in CML



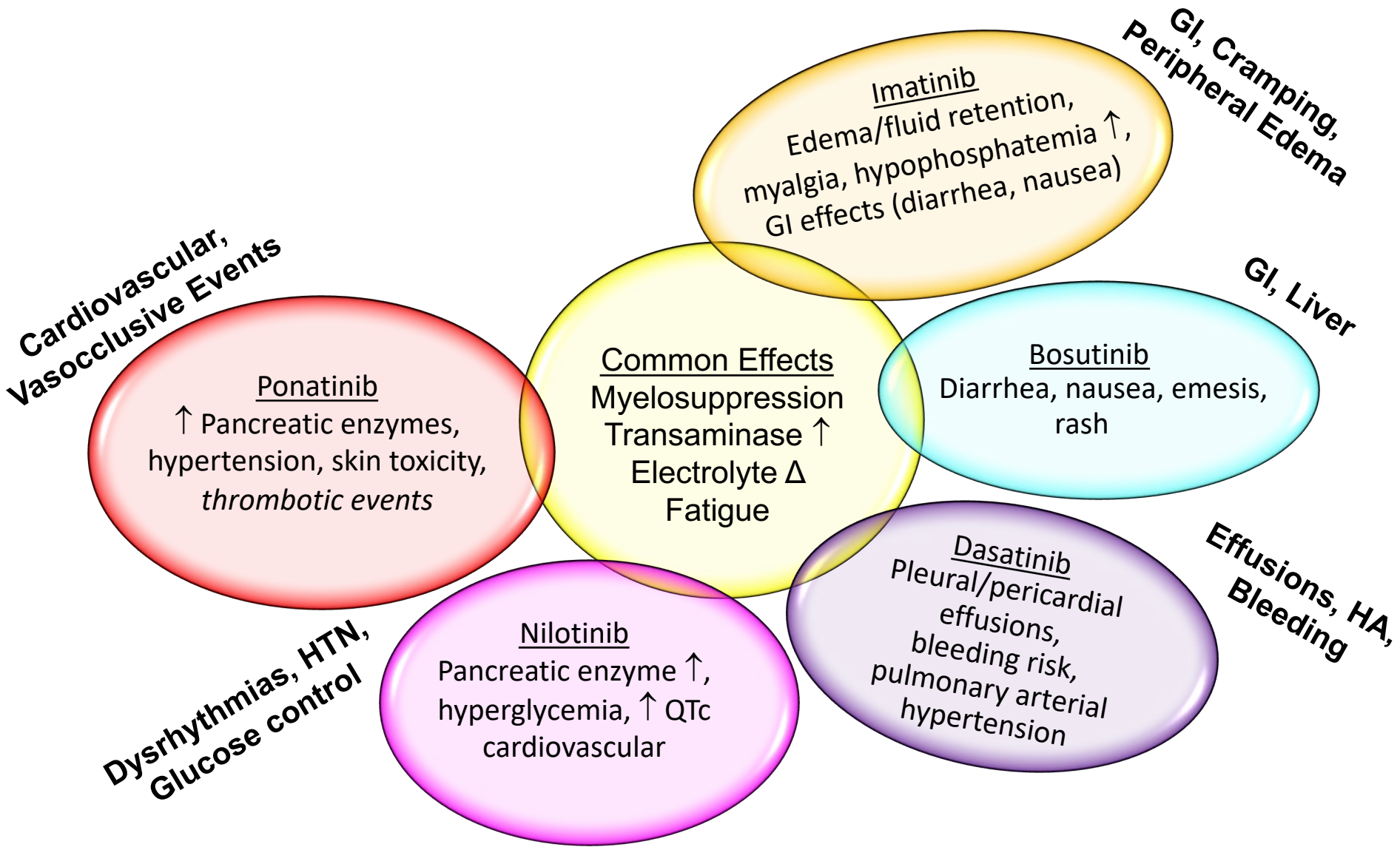
BEFORE: 5 Year Safety Data

Most common (≥20%) all-grade ARs in any arm*

Adverse reaction	Bosutinib n=268 (%)	Imatinib n=265 (%)
Diarrhea	75	40
Hepatic dysfunction	45	15
Rash	40	30
Abdominal pain	39	27
Nausea	37	42
Fatigue	33	30
Respiratory tract infection	27	25
Headache	22	15
Vomiting	21	20
Edema	15	46

Bosutinib Prescribing Information. 2021.

Treatment Options Based on Adverse Event Spectrum of TKIs in CML



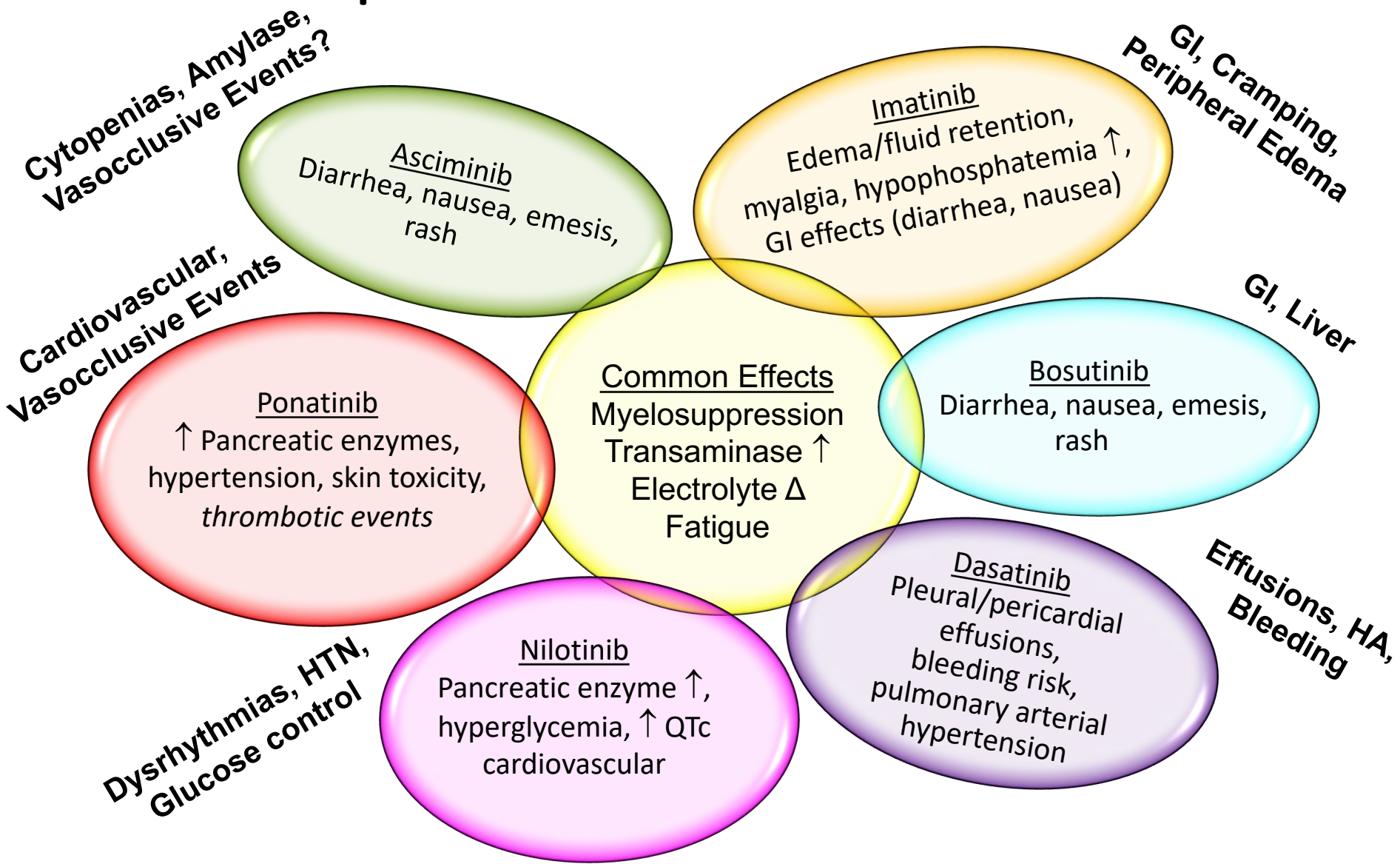
Ponatinib: 5 year follow-up of PACE

Cumulative and exposure-adjusted incidences of treatment-emergent AOEs and VTEs

	CP-CML, n = 270		Total, N = 449	
	AE	SAE	AE	SAE
AOEs, n (%)	84 (31)	69 (26)	111 (25)	90 (20)
Cardiovascular	42 (16)	33 (12)	59 (13)	44 (10)
Cerebrovascular	35 (13)	28 (10)	41 (9)	33 (7)
Peripheral vascular	38 (14)	31 (11)	48 (11)	38 (8)
Exposure-adjusted AOEs, no. of patients with events per 100 patient-years	14.1	10.9	13.8	10.6
VTEs, n (%)	15 (6)	13 (5)	27 (6)	23 (5)
Exposure-adjusted VTEs, no. of patients with events per 100 patient-years	2.1	1.8	2.8	2.4

Cortes, et al, Blood: July 2018

Treatment Options Based on Adverse Event Spectrum of TKIs in CML



Asciminib in Newly Diagnosed CML

Table 2. Most Frequent Adverse Events That Occurred in at Least 10% of Patients (Safety Set).*

Adverse Event	Asciminib		Investigator-Selected TKI					
	All Asciminib (N=200)		Imatinib (N=99)		Second-Generation TKI (N=102)		All Comparators (N=201)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)							
At least one adverse event	187 (93.5)	76 (38.0)	93 (93.9)	44 (44.4)	102 (100)	56 (54.9)	195 (97.0)	100 (49.8)
Thrombocytopenia†	56 (28.0)	26 (13.0)	28 (28.3)	6 (6.1)	35 (34.3)	14 (13.7)	63 (31.3)	20 (10.0)
Neutropenia‡	50 (25.0)	20 (10.0)	31 (31.3)	17 (17.2)	35 (34.3)	18 (17.6)	66 (32.8)	35 (17.4)
Leukopenia§	38 (19.0)	4 (2.0)	29 (29.3)	10 (10.1)	20 (19.6)	5 (4.9)	49 (24.4)	15 (7.5)
Coronavirus disease 2019	35 (17.5)	0	18 (18.2)	0	21 (20.6)	1 (1.0)	39 (19.4)	1 (0.5)
Diarrhea	31 (15.5)	0	26 (26.3)	0	26 (25.5)	1 (1.0)	52 (25.9)	1 (0.5)
Fatigue	28 (14.0)	1 (0.5)	14 (14.1)	1 (1.0)	18 (17.6)	0	32 (15.9)	1 (0.5)
Headache	27 (13.5)	1 (0.5)	8 (8.1)	0	22 (21.6)	0	30 (14.9)	0
Myalgia	26 (13.0)	1 (0.5)	17 (17.2)	0	15 (14.7)	0	32 (15.9)	0
Rash	26 (13.0)	0	10 (10.1)	2 (2.0)	22 (21.6)	1 (1.0)	32 (15.9)	3 (1.5)
Anemia	23 (11.5)	3 (1.5)	26 (26.3)	5 (5.1)	23 (22.5)	6 (5.9)	49 (24.4)	11 (5.5)
Increased lipase	23 (11.5)	6 (3.0)	14 (14.1)	1 (1.0)	11 (10.8)	4 (3.9)	25 (12.4)	5 (2.5)
Constipation	19 (9.5)	0	4 (4.0)	0	13 (12.7)	1 (1.0)	17 (8.5)	1 (0.5)
Nausea	18 (9.0)	0	21 (21.2)	0	18 (17.6)	0	39 (19.4)	0
Increased alanine aminotransferase	14 (7.0)	4 (2.0)	6 (6.1)	2 (2.0)	19 (18.6)	8 (7.8)	25 (12.4)	10 (5.0)
Upper respiratory tract infection	14 (7.0)	0	10 (10.1)	1 (1.0)	8 (7.8)	0	18 (9.0)	1 (0.5)
Lymphopenia¶	12 (6.0)	5 (2.5)	16 (16.2)	5 (5.1)	7 (6.9)	1 (1.0)	23 (11.4)	6 (3.0)
Increased blood alkaline phosphatase	11 (5.5)	0	13 (13.1)	0	6 (5.9)	0	19 (9.5)	0
Vomiting	11 (5.5)	0	12 (12.1)	0	6 (5.9)	0	18 (9.0)	0
Increased blood bilirubin	5 (2.5)	0	2 (2.0)	1 (1.0)	11 (10.8)	0	13 (6.5)	1 (0.5)
Increased aspartate aminotransferase	4 (2.0)	1 (0.5)	6 (6.1)	1 (1.0)	15 (14.7)	3 (2.9)	21 (10.4)	4 (2.0)
Muscle spasms	4 (2.0)	0	19 (19.2)	0	5 (4.9)	0	24 (11.9)	0
Periorbital edema	2 (1.0)	0	10 (10.1)	0	1 (1.0)	0	11 (5.5)	0
Facial edema	0	0	10 (10.1)	1 (1.0)	0	0	10 (5.0)	1 (0.5)

* The safety set comprised all patients who received at least one dose of a trial drug. Adverse events listed occurred during treatment or within 30 days after receiving the last dose of trial medication. A patient with adverse events of multiple severity grades is counted only under the maximum grade.
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Hochhaus, et. al, N Engl J Med, Volume 391(10):885-898, September 12, 2024

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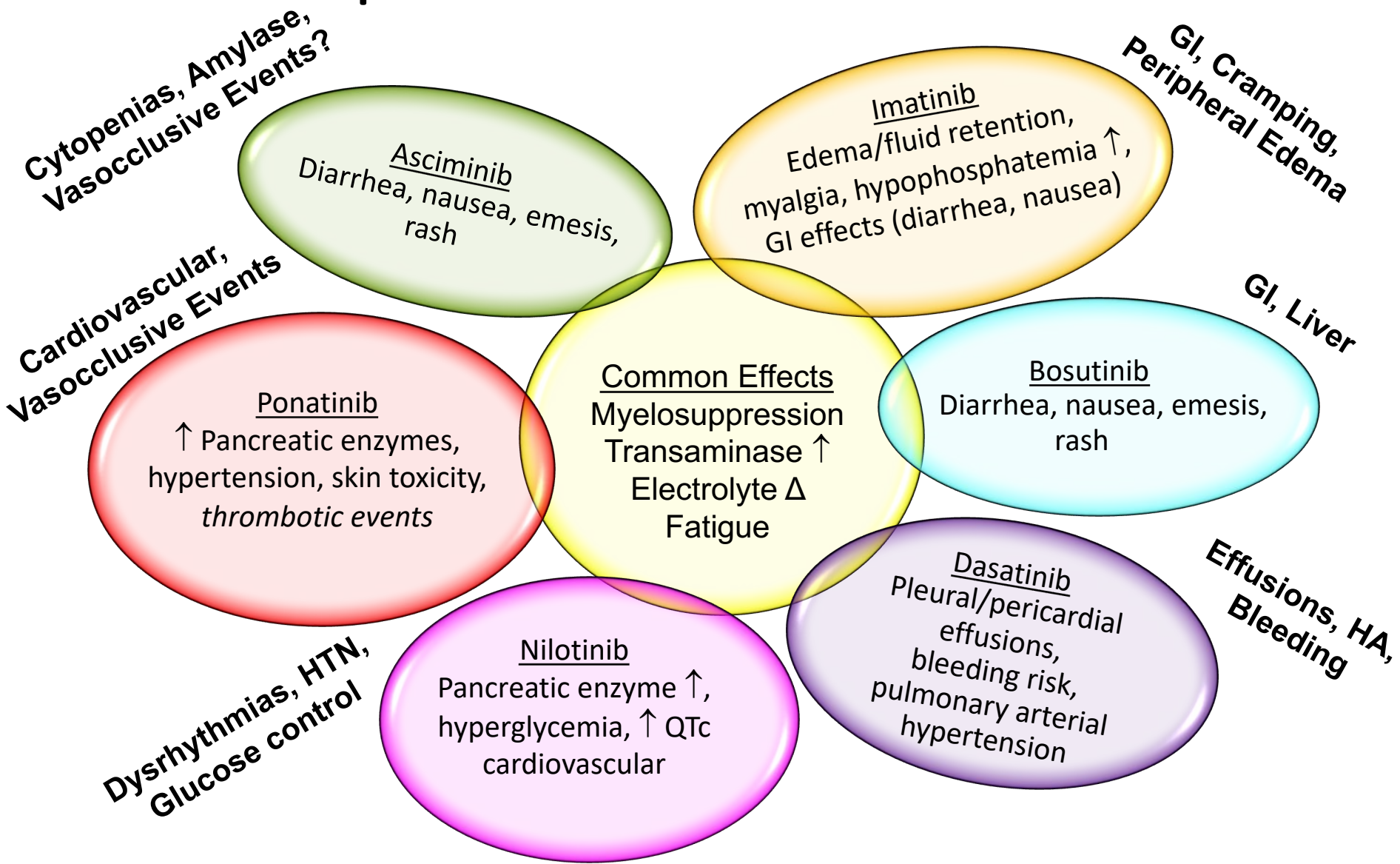
Treatment Options Based on Adverse Event Spectrum of TKIs in CML



Oral Anticancer Medicines – CML Tips and Tricks

- **Promises:**
  - **Precision and Personalized Medicine is possible for many CML pts**
    - **6 FDA-approved TKIs with 5 available upfront**
    - **Important to become comfortable with each, develop a monitoring plan**

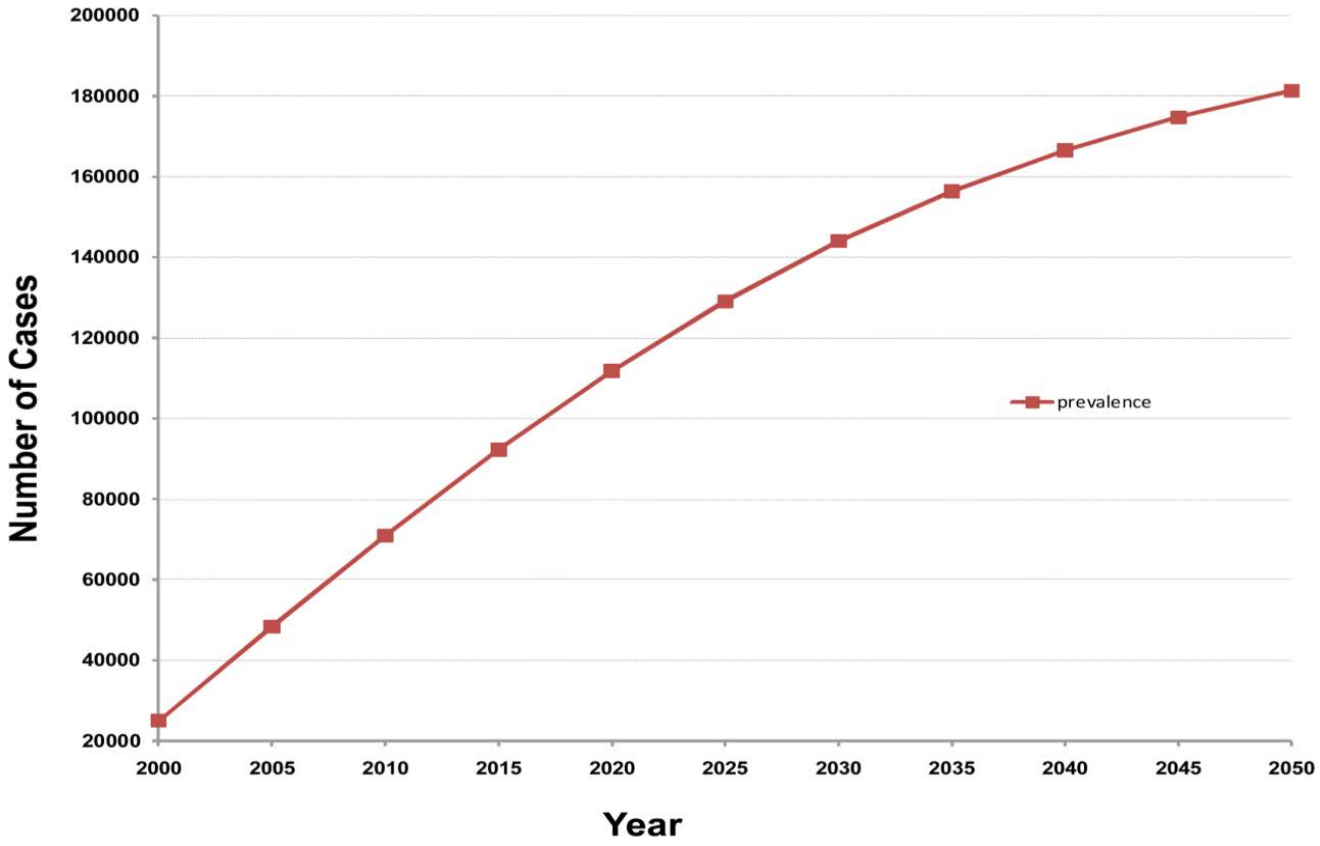
  - **Side Effect Profiles becoming well established**
    - **Imatinib – facial edema, cramping**
    - **Nilotinib – EGC, HTN, glucose, pancreas, rash**
    - **Dasatinib – effusions, PAH, bleeding, headache**
    - **Bosutinib – diarrhea, nausea, liver**
    - **Ponatinib – cardiovascular, thromboembolic**
    - **Asciminib – liver, pancreas, rash**

Annual Price of TKIs

TKI	Dose	AWP (12 mos)
Imatinib generic	400 mg daily	~ $35,300
Imatinib	400 mg daily	$95,000
Dasatinib	100 mg daily	$228,000
Nilotinib	300 mg BID	$240,000
Bosutinib	400 mg daily	$250,000
Ponatinib	45 mg daily	$271,000
Asciminib	40 mg BID	$258,000

Adapted from Kantarjian, Lancet Haematology, 2022

CML Prevalence in the US



- **Current prevalence ≅ 40,000 patients**
- **Current annual cost of TKIs ≅ $100,000**
- **Annual cost of TKIs in the US ≅ $4,000,000,000**

- **By 2050 the prevalence of CML will plateau at 180,000**

Factors Associated with Non-Adherence

- Complex regimens
- Substantial behavior change required
- *Inconvenient/insufficient clinics and supervision*
- *Poor communication with healthcare providers*
- Patient dissatisfaction with care
- Patient health beliefs
- *Inadequate social support*
- History of non-adherence
- History of mental illness

Partridge, et al. *J Natl Cancer Inst*. 2002;94:652-661.

Questions from General Medical Oncologists

- **Which approved TKI has the most favorable tolerability profile when administered as first-line therapy for CP-CML?**
- **A 64-year-old man with CP-CML on front-line dasatinib, met all response milestones, deep molecular response (DMR) by 12 months. On dasatinib with sustained MR4 for over 2 years. He wants to take a treatment break. What is the faculty's opinion?**
- **68-year-old morbidly obese woman on imatinib is unable to tolerate due to GI toxicity. Would asciminib be an option?**

Questions from General Medical Oncologists

- 42 yo woman on bosutinib developed severe myalgias with elevated CPK and LDH within a month. She had to discontinue bosutinib. Since asciminib was associated with more musculoskeletal symptoms, what would be your preferred TKI for this patient frontline?
- 37 yo woman on dasatinib, diagnosed with COVID with fever and respiratory symptoms without drop in O2. Should dasatinib be held or continued? Would you restart dasatinib or switch to another TKI?

What Clinicians Want to Know: Addressing Current Questions and Controversies Regarding the Role of CAR T-Cell Therapy and Bispecific Antibodies in the Management of Lymphoma

A CME Friday Satellite Symposium and Webcast Preceding the 66th ASH Annual Meeting

Friday, December 6, 2024

11:30 AM – 1:30 PM PT (2:30 PM – 4:30 PM ET)

Faculty

Jennifer Crombie, MD

Martin Hutchings, MD, PhD

Matthew Lunning, DO

Tycel Phillips, MD

Moderator

Jeremy S Abramson, MD, MMSc

RTP RESEARCH TO PRACTICE

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Andrew T Kuykendall, MD

RTP RESEARCH TO PRACTICE

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