# Understanding the Current Paradigm and New Approaches in the Care of Patients with Cancer

*A Complimentary NCPD Hybrid Symposium Series Held During the 50th Annual ONS Congress*

# Chronic Myeloid Leukemia

**Thursday, April 10, 2025**

**6:00 AM – 7:30 AM**

## Faculty

**Ilene Galinsky, RN, BSN, MSN, ANP-C**
**Michael J Mauro, MD**
**Neil P Shah, MD, PhD**
**Sara M Tinsley-Vance, PhD, APRN, AOCN**

## Moderator

**Neil Love, MD**

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# Faculty

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# Ms Galinsky — Disclosures

| | |
|---|---|
| **Advisory Committees** | Autolus Therapeutics, Blueprint Medicines, Bristol Myers Squibb, GSK, Novartis |
| **Consulting Agreements** | Novartis |

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# Dr Mauro — Disclosures

| | |
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| **Contracted Research** | Enliven Therapeutics, Novartis, Sun Pharma Advanced Research Company (SPARC), Sun Pharmaceutical Industries Ltd, Terns Pharmaceuticals |

# Dr Shah — Disclosures

| | |
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| **Contracted Research** | Kumquat Biosciences |
| **Honoraria** | Novartis (Delphi panel) |

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# Dr Tinsley-Vance — Disclosures

No relevant conflicts of interest to disclose

## Commercial Support

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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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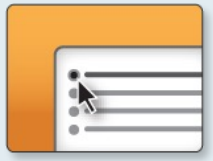
# Clinicians in the Meeting Room

**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. Survey questions will be discussed throughout the meeting.**

**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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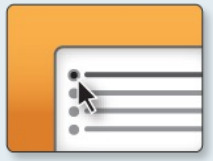
# Clinicians Attending via Zoom

**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. Survey questions will be discussed throughout the meeting.**

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

**Get NCPD Credit: An NCPD credit link will be provided in the chat room at the conclusion of the program.**

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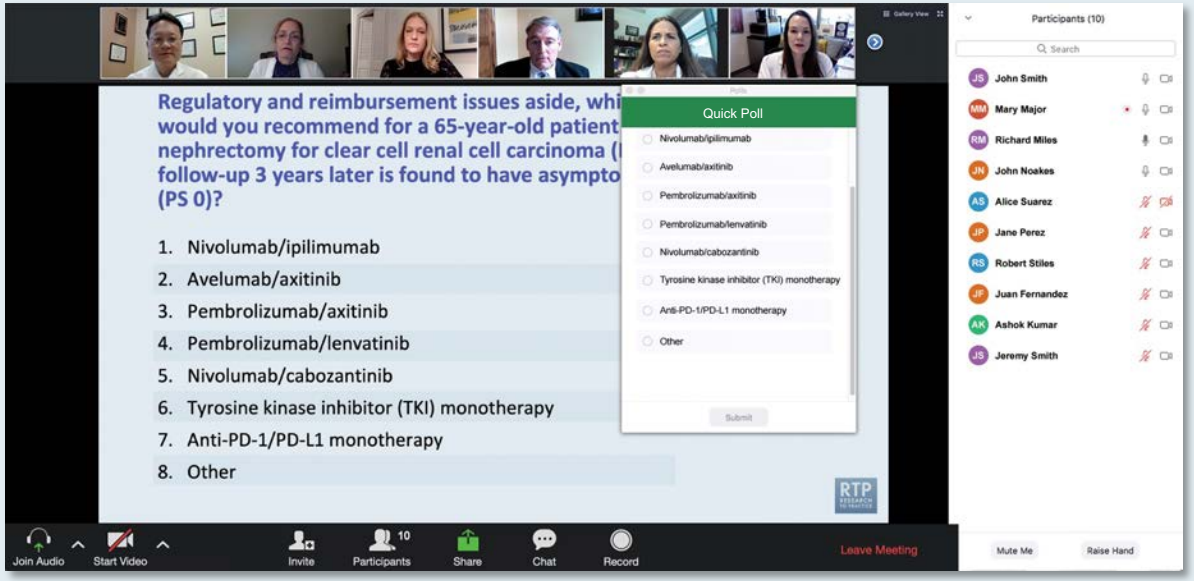
# Clinicians, Please Complete the Pre- and Postmeeting Surveys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# About the Enduring Program


- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based 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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# ONCOLOGY NURSING UPDATE WITH DR NEIL LOVE

## Bispecific Antibodies in Lymphoma Part 1 — An Interview with Ms Robin Klebig for Oncology Nurses

MS ROBIN KLEBIG
MAYO CLINIC

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Spotify

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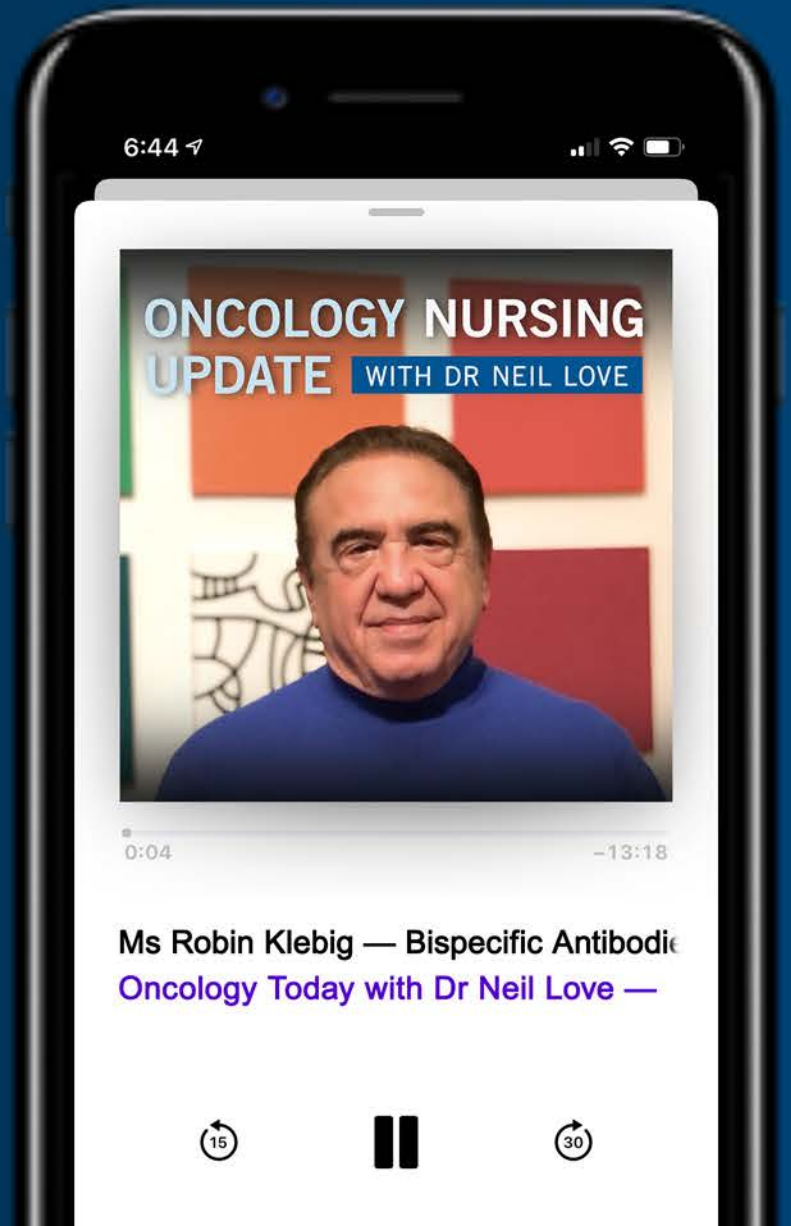
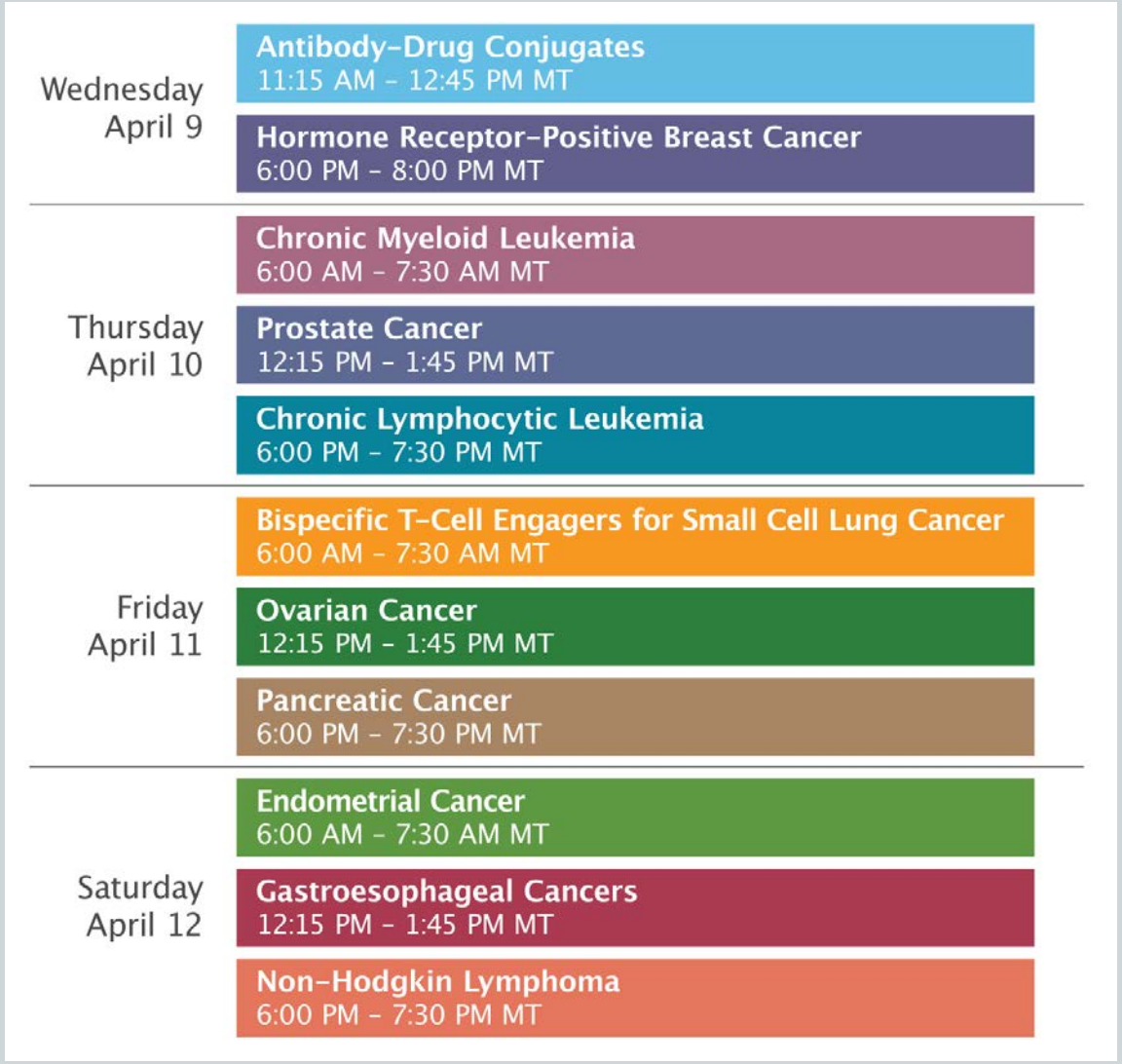


# “Understanding the Current Paradigm and New Approaches”
# Seventeenth Annual RTP-ONS NCPD Symposium Series

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# Understanding the Current Paradigm and New Approaches
# RTP Faculty at ONS 2025

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# The Core Oncology Triad
# Developing an Individualized Oncology Strategy


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# Understanding the Current Paradigm and New Approaches
# Denver, Colorado

## Symposia Themes

### Personalized oncology: Implementing an individualized oncologic strategy

- Tumor factors (eg, biomarkers, numeracy)
- Biopsychosocial factors (eg, adherence, available family support, comorbidities, mood)

### Novel agents and treatment strategies

- The new-agents revolution (beginning of the end?)

### The bond that heals (both ways)

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# Agenda

**Introduction:** Chronic Myeloid Leukemia (CML) as a Model for Targeted Treatment

**Module 1:** Biology of CML; Role of First- and Second-Generation Tyrosine Kinase Inhibitors (TKIs) as Initial Treatment for Chronic-Phase (CP)-CML

**Module 2:** Role of Asciminib for Newly Diagnosed CP-CML

**Module 3:** Feasibility of TKI Discontinuation for Patients with Sustained Response to Treatment

**Module 4:** Management of CP-CML After Failure of Initial Therapy

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**Introduction: Chronic Myeloid Leukemia (CML) as a Model for Targeted Treatment**

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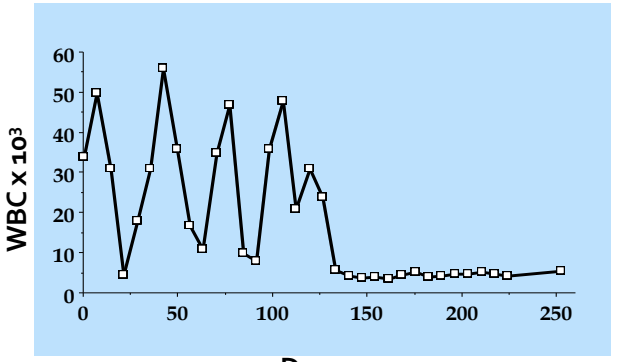
# The history of CML is long, the kinase inhibitor era short…

***2000:*** *Started my work in CML with Brian Druker (OHSU, Portland, Oregon)*


1845 1865 1879 1903 1953 1965 1968 1983 2001 2006 2012 2016 2021

First description of CML

Fowler's solution -1% arsenic trioxide

Staining methods for blood

Radiotherapy

Busulfan

Hydroxyurea

BMT

Interferon

Imatinib

Dasatinib

Nilotinib

Bosutinib

Ponatinib

Generic Imatinib

Asciminib

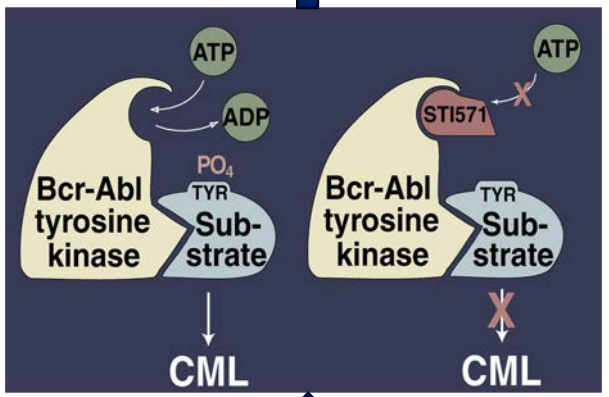
1845:
John Hughes Bennett reported a "Case of Hypertrophy of the Spleen and Liver in which Death Took Place from Suppuration of the Blood" in the Edinburgh Medical Journal; Virchow in Germany wrote up a similar observation

1960:
Nowell & Hungerford describe the Philadelphia Chromosome

1973:
Janet Rowley describes the 9:22 translocation

1983: Nora Heisterkamp and John Groffen, with others, describe the BCR-ABL fusion gene product

1998: After seminal preclinical work first clinical trials commence with STI571 (imatinib); 1999, target inhibition validated, resistance identified (T315I)




**A Minute Chromosome in Human Chronic Granulocytic Leukemia**

In seven cases thus far investigated (five males, two females), a minute chromosome has been observed replacing one of the four smallest autosomes in the chromosome complement of cells of chronic granulocytic leukemia cultured from peripheral blood. No abnormality was observed in the cells of four cases of *acute* granulocytic leukemia in adults or of six cases of acute leukemia in children. There have been several recent reports of chromosome abnormalities in a number of cases of human leukemia [including two of the seven cases reported here: Nowell and Hungerford, *J. Natl. Cancer Inst.* **25**, 85 (1960)], but no series has appeared in which there was a consistent change typical of a particular type of leukemia.

Cells of the five new cases were obtained from peripheral blood (and bone marrow in one instance), grown in culture for 24–72 hours, and processed for cytological examination by a recently developed air-drying technique (Moorhead, *et al., Exptl. Cell Research*, in press). The patients varied from asymptomatic untreated cases to extensively treated cases of several years duration in terminal myeloblastic crisis. All seven individuals showed a similar minute chromosome, and none showed any other frequent or regular chromosome change. In most of the cases, cells with normal chromosomes were also observed. Thus, the minute is not a part of the normal chromosome constitution of such individuals.

The findings suggest a causal relationship between the chromosome abnormality observed and chronic granulocytic leukemia.

PETER C. NOWELL
*School of Medicine, University of Pennsylvania*
DAVID A. HUNGERFORD
*Institute for Cancer Research*

Nowell & Hungerford, 1960 Science 132.1497

# Agenda

**Introduction:** Chronic Myeloid Leukemia (CML) as a Model for Targeted Treatment

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# Clinical Scenario

**A patient with newly diagnosed CP-CML who is about to start treatment with a first- or second-generation tyrosine kinase inhibitor**

# Biology of CML: Role of First- and Second-Generation TKIs as Initial Treatment for CP-CML

**Neil P. Shah, MD, PhD**
*Professor*
Division of Hematology/Oncology
University of California, San Francisco
San Francisco, California

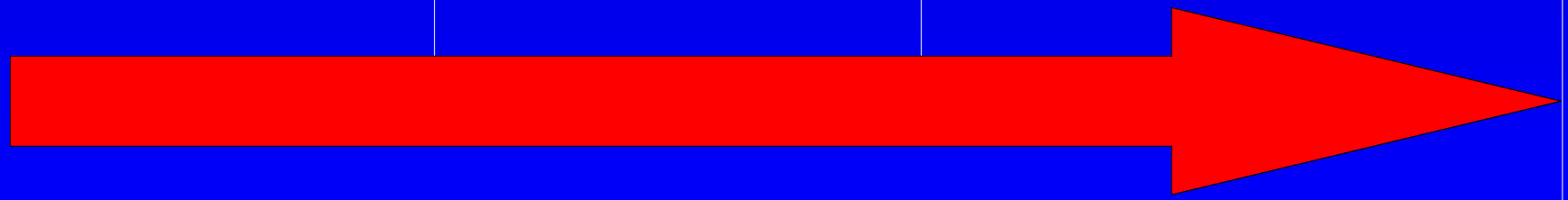
# Assigning Disease Phase

## Modified MDACC Criteria are Preferred (not WHO)

| Chronic Phase | Accelerated Phase | Blast Phase |
|---|---|---|
| <15% blasts in PB or BM | 15-29% blasts in PB/BM | ≥30% blasts |
| <30% blasts + promyelocytes | ≥30% blasts + promyelocytes in PB or BM (with <30% blasts) | |
| ≥100K platelets | <100K platelets (unrelated to tx) | |
| <20% basophils | ≥20% basophils | |
| No extramedullary disease (except liver/spleen) | Clonal evolution (additional karyotypic abnormalities not present at diagnosis) | |

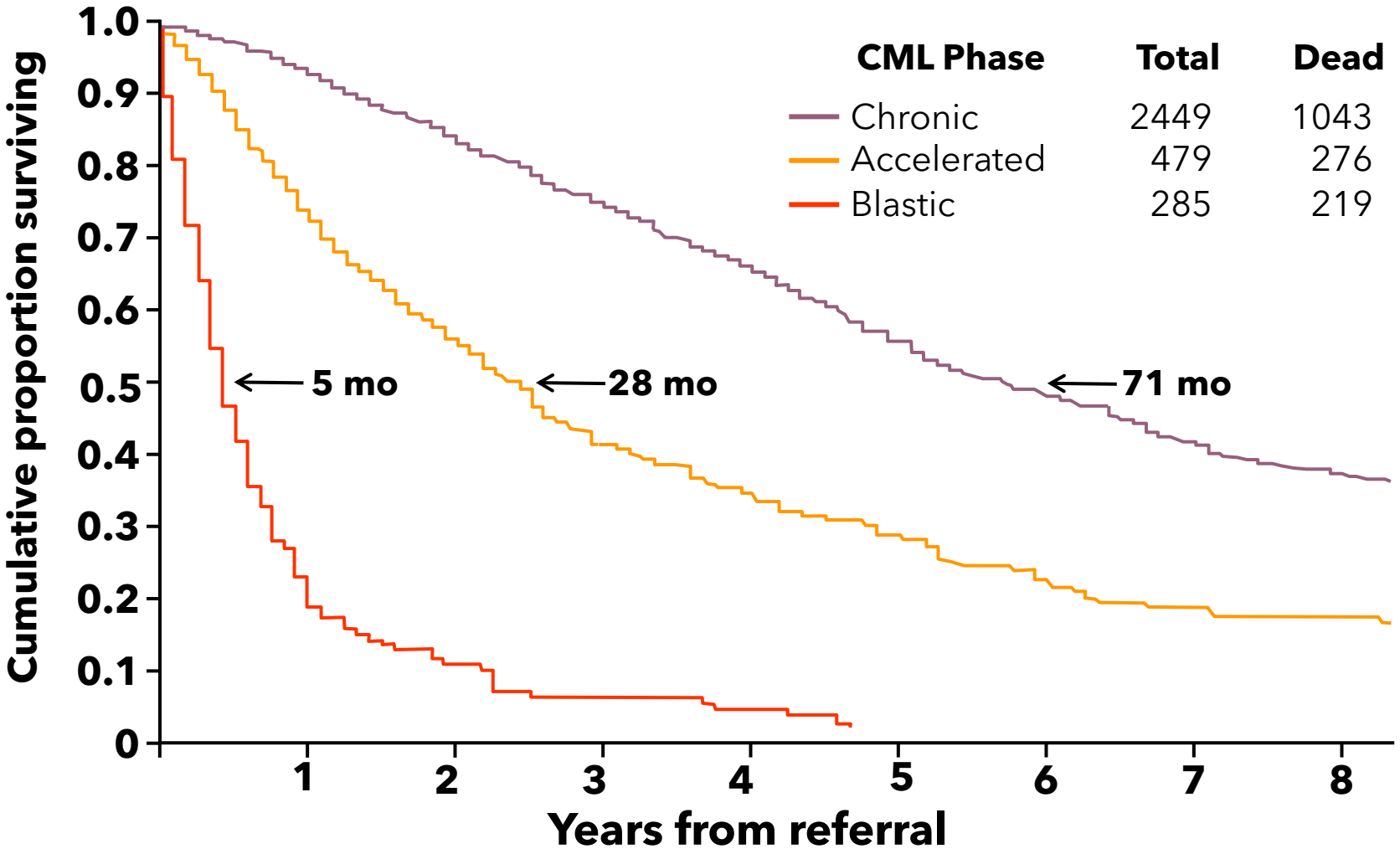
# Clinical Course: Phases of CML

| Chronic phase | Advanced phases | |
|---|---|---|
| | Accelerated phase | Blastic phase (blast crisis) |
| Median 4–6 years stabilization | Median duration up to 1 year | Median survival 3–6 months |

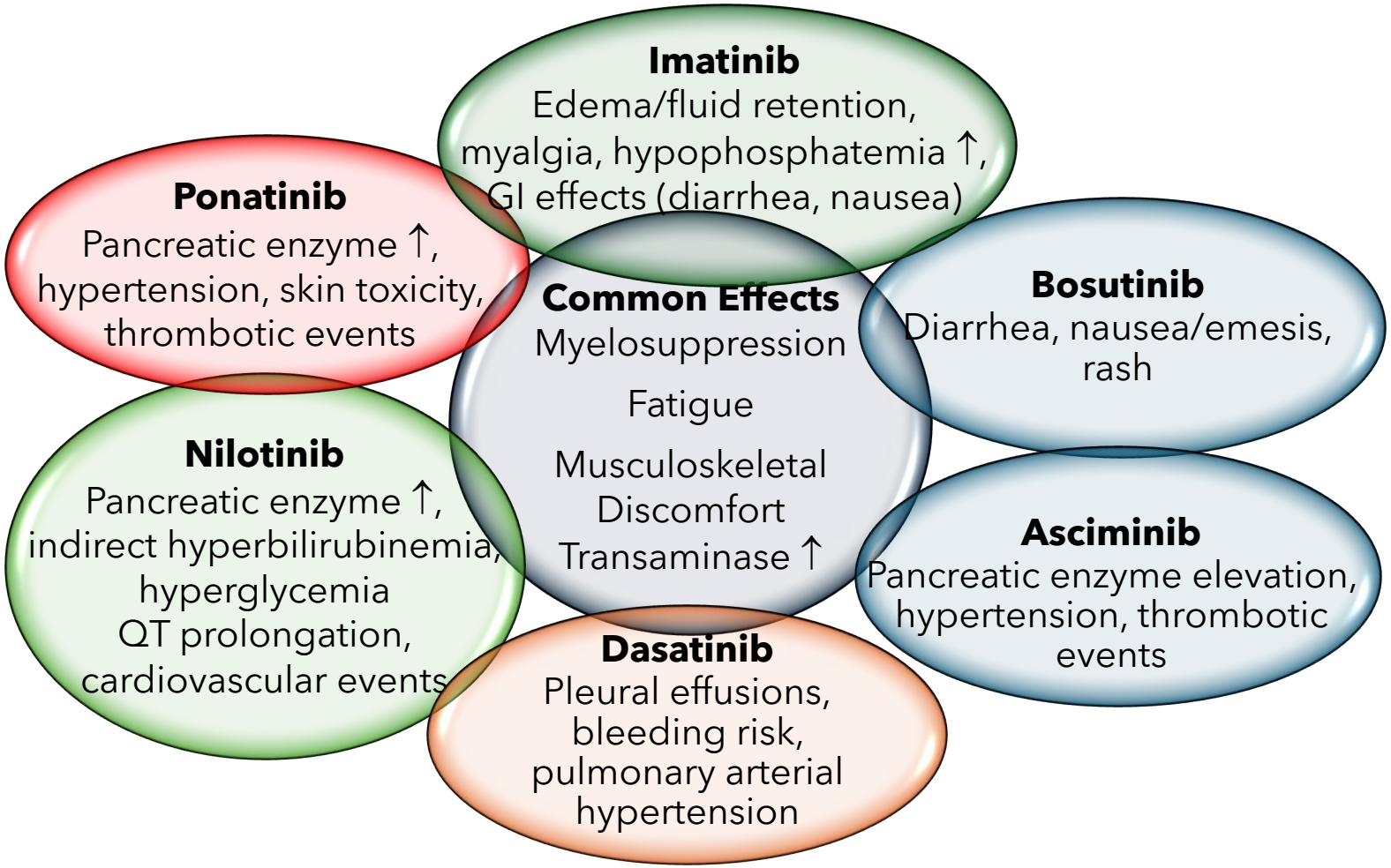


# Natural Course of CML: Historical Survival by Disease Phase

Circa 1980



# Common and Selective TKI-associated Toxicities



# Individualizing Targeted Therapy in Patients with CML and Specific History or Comorbidities

- When selecting frontline *BCR::ABL1* inhibitors, consider age, medical history, comorbidities, and AE profiles

| Comorbidity | Considerations for Drug Selection |
|---|---|
| Compromised pulmonary reserve | Avoid dasatinib |
| Pulmonary arterial hypertension | Avoid dasatinib |
| QTc prolongation | Avoid nilotinib |
| Risk of hemorrhagic complications | Avoid dasatinib (increased risk) |
| Challenges with treatment adherence | Avoid nilotinib |
| Hepatic impairment | Dose reduce bosutinib (200 mg QD) and ponatinib (30 mg QD) |
| Renal impairment | Dose reduce imatinib (50% decrease in recommended starting dose)<br>Caution with bosutinib |
| History of pancreatitis or at high risk for pancreatitis | Careful monitoring with nilotinib, asciminib, and ponatinib |
| Uncontrolled diabetes mellitus | Use nilotinib with caution |
| Coronary, cerebrovascular, or peripheral arterial disease | Use dasatinib, nilotinib, bosutinib, asciminib and ponatinib with caution |

Bosutinib PI. Dasatinib PI. Imatinib PI. Asciminib PI. Hochhaus. Ann Oncol. 2017;28:iv41.

# Considerations for Frontline TKI Selection

- Goals of Therapy (treatment discontinuation?)
- Dosing schedule
- Potential for adverse events
- Comorbidities
- Effective dose range
- Cost
- Availability
- Preferences, personal experience, and biases
- Insurance coverage

# Considerations for Frontline TKI Selection

- Goals of Therapy (treatment discontinuation?)
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- Effective dose range
- Cost
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- Preferences, personal experience, and biases
- Insurance coverage

# My Initial Frontline TKI Dosing Strategy in CP-CML Patients

- Imatinib - 400 mg daily with a meal and a large glass of water
- Dasatinib – 100 mg daily (with or without food) if younger than 60 or on PPI/H2 blocker. Otherwise, 50 mg daily
- Nilotinib – 300 mg  daily fasting
- Bosutinib – 200 mg daily initially with dose escalation after 2-3 weeks to 300 mg and 400 mg as tolerated and as necessary to achieve treatment milestone responses
- Asciminib – 80 mg daily fasting, 40 mg daily if frail

# Notable Characteristics of First Line TKIs for CML

| TKI | Efficacy | Daily Tolerability | Lack of Serious AND Irreversible Toxicity | Lack of vulnerability to resistance-conferring kinase domain mutations | Lowest Financial Burden to Society (of generic if available) | Ease of administration (based on frequency of dosing, fasting requirement) |
|---|---|---|---|---|---|---|
| imatinib | ++ | ++ | ++++ | + | ++++ | +++ |
| dasatinib | +++ | +++ | +++ | +++ | +++ | ++++ |
| nilotinib | +++ | +++ | ++ | +++ | + | + |
| bosutinib | +++ | +++ | +++ | +++ | + | +++ |
| asciminib | +++ | ++++ | +++ | ++ | + | ++ |

# Case

- A 46 year-old woman who works as a nurse was incidentally noted to have a WBC of 53.2K in January 2025. Prior CBC performed in 2023 was unremarkable. She was referred to a hematologist and diagnosed with chronic phase CML. Her PMH includes hypertension, bilateral hip osteoarthritis and anxiety. She was started on bosutinib at a dose of 500 mg by her hematologist.

- She developed problematic diarrhea after starting bosutinib for which she received IV hydration. Her LFTs were elevated at that time (AST 133, ALT 272) and her bosutinib was held. She presented to UCSF for a second opinion in mid-February 2025. She was prescribed dasatinib 100 mg, which she began in early March when her LFTs had normalized. In early April, 2025, her CBC/diff and LFTs were normal. She is tolerating treatment well to date.

# Roundtable Discussion

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# Newly Diagnosed Patient with Chronic Phase CML

What I tell my  patients about to start treatment
with 1st or 2nd generation TKIs.

Sara M Tinsley-Vance, PhD, APRN, AOCN

# A 20-year journey together with CML

# Flashback to the Journey's Start

- Diagnosed with CML-chronic phase in 1995
- **Pre-imatinib era**
- Started treatment with interferon
  - Tolerated very poorly and was discontinued
- Evaluated for allogeneic transplant
- No donor identified
- Underwent autologous stem cell transplant in 1998
- Relapsed late 1999- the timing was perfect for the start of STI-571 **(imatinib)** clinic trials

# Relapse post Autologous Stem Cell Transplant

- Enrolled in clinical trial STI-571
- Dose of STI-571 (imatinib) was 400mg PO bid
- Intermittently missed doses related to nausea and vomiting
- Experienced hematologic and cytogenetic response
- In 2004 WBC began to increase, Hb and platelets decrease
- Spleen enlarged to 14cm
- Kinase domain mutation analysis with mutation of H396P, sensitive to AMN as per in vitro studies.

| | |
|---|---|
| WBC | (H) 24.29 |
| RBC | (L) 3.53 |
| Hemoglobin | (L) 10.6 |
| Hematocrit | (L) 34.0 |
| Mean Cell Volume | (H) 96.3 |
| MCH | 30.0 |
| MCHC | (L) 31.2 |
| RDW | (H) 62.4 |
| Platelet Count | (L) 70 |
| **Differential (Misys)** | |
| Myelocytes | * (H) 1.21 |
| Metamyelocytes | * (H) 1.46 |
| Neutrophil,Bands | * (H) 0.97 |
| Neutrophil,Poly | * (H) 16.77 |
| Eosinophils | * 0.24 |
| Basophils | * (H) 0.24 |

# 2nd Clinical Trial

- Started clinical trial AMN 107 (nilotinib)
- 400mg PO BID
- Wife became pregnant 9 months into the study
- Concern for potential birth defects
- Dose reduced to 400mg daily for chest pain, hospitalization

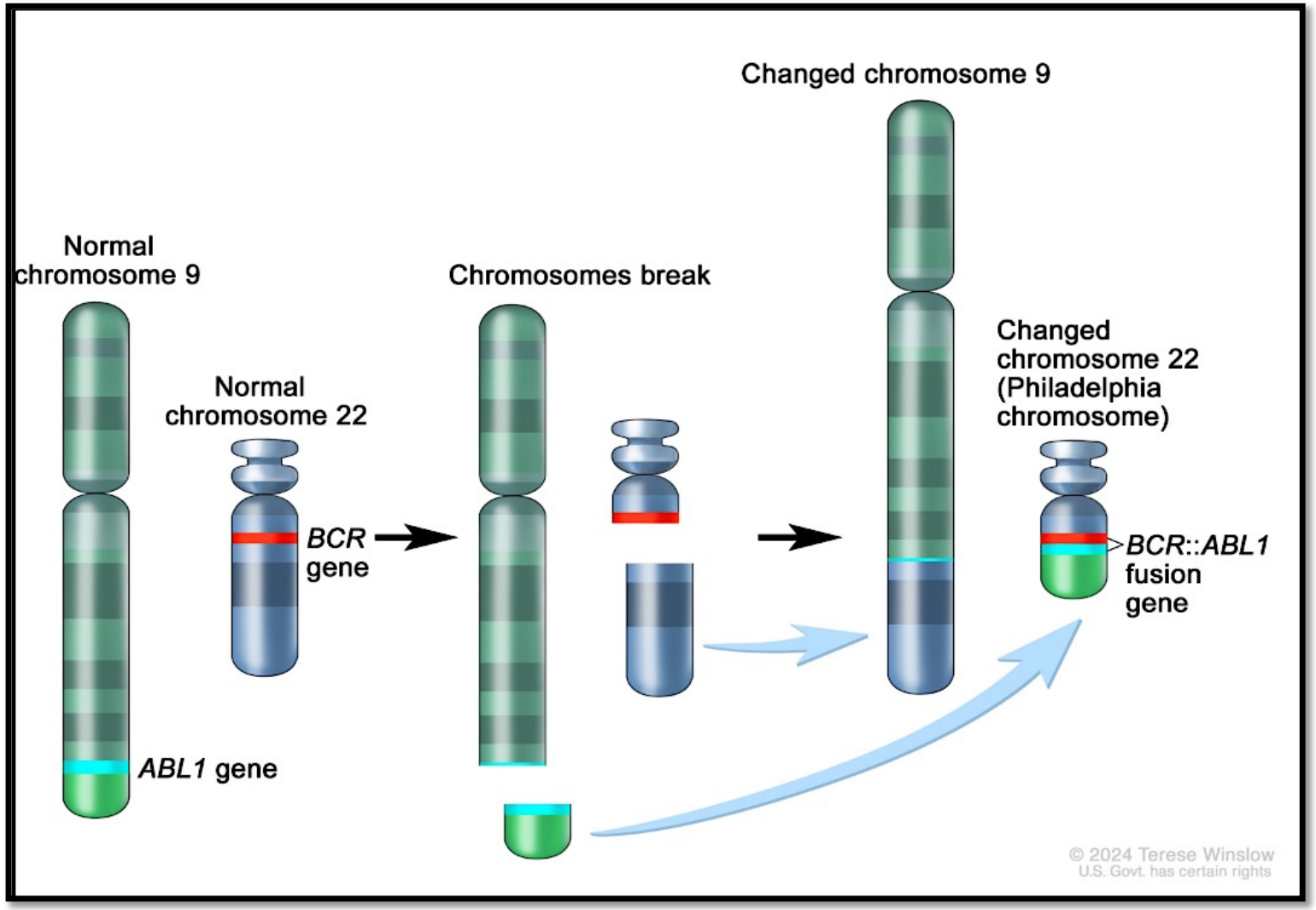
# Key Educational Points on Trial

- Regular EKGs
- Pharmacokinetics testing- frequent blood draws and study visits
- Fasting 2 hours before dose and 1-hour post-dose
- On trial, visits monthly
- Detailed medication list
- Symptoms and grading of toxicities
- Bone marrow biopsies every 3 months

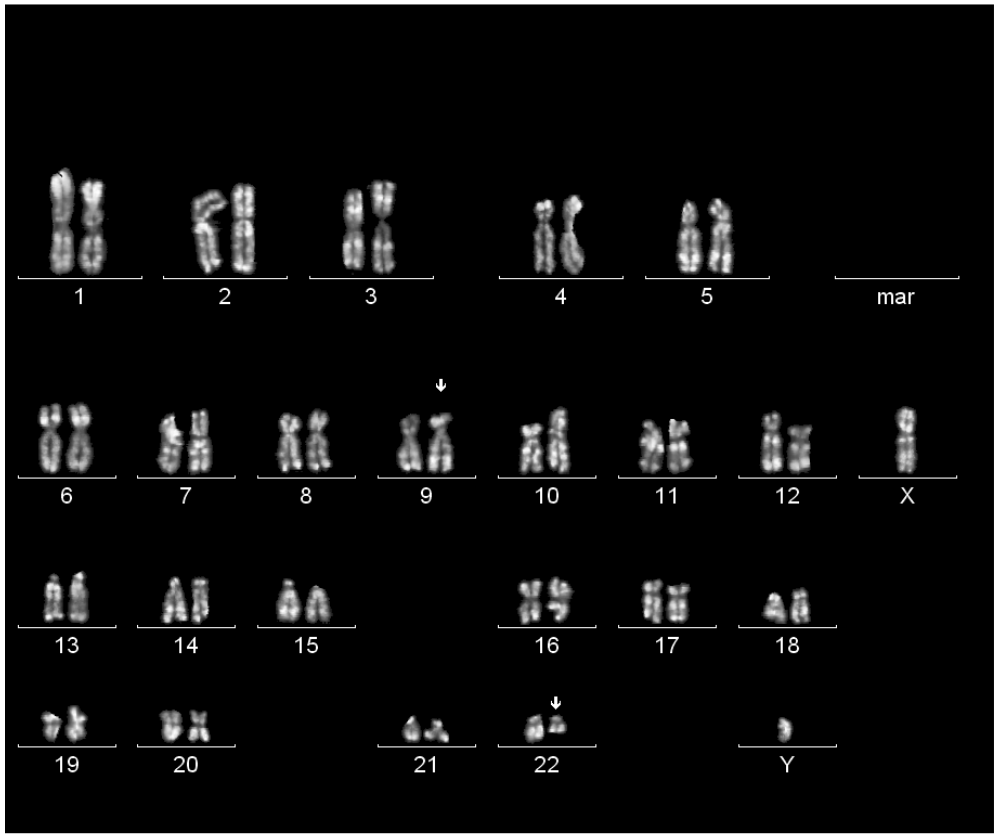
# At 18 months of AMN 107

- FISH for BCR/ABL was negative for BCR/ABL gene rearrangement
- PCR for BCR/ABL was below the reproducible, quantifiable limits of the assay
- Complete **hematologic, cytogenetic, and molecular response on** AMN 107

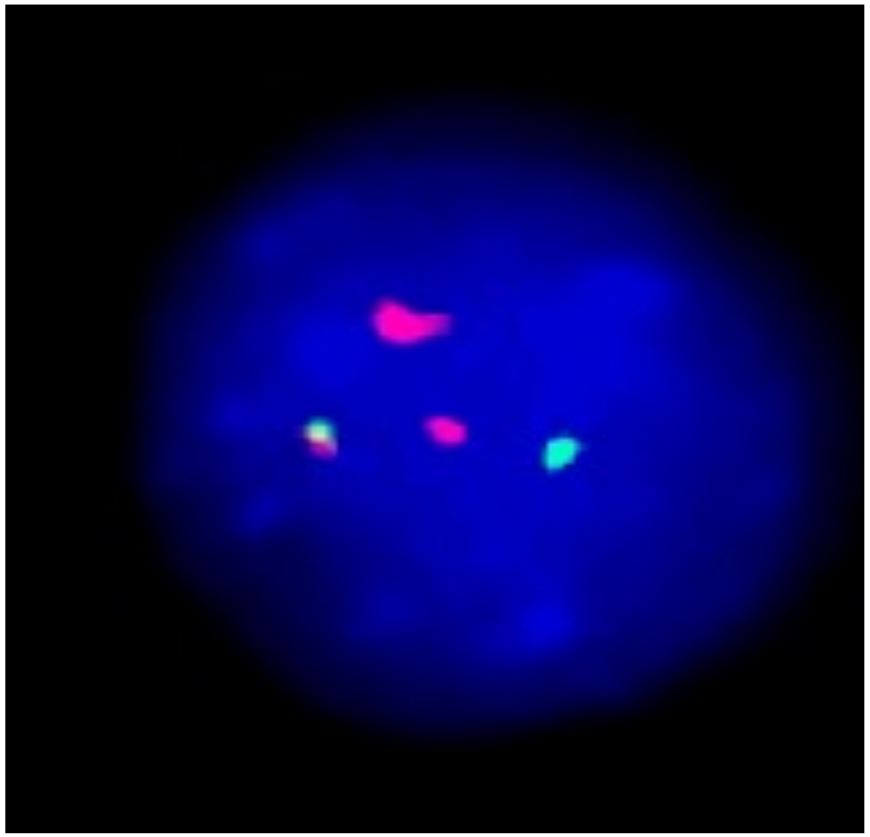
# Characterized by the Philadelphia Chromosome



# Tests Used to Identify the BCR/ABL gene




Karyotyping by G-banding technique from Bone marrow aspirate



Fluorescent in situ hybridization (FISH) for CML from bone marrow aspirate or peripheral blood

# Tests Used to Identify the BCR/ABL gene

- PCR (Polymerase Chain Reaction) for BCR-ABL is a molecular test used to detect and quantify the BCR-ABL fusion gene
- BCR-ABL1 Gene Rearrangement, Quantitative PCR (qPCR) test measures
  - Two P210 transcripts (e13a2 and e14a2)
  - P190 transcript (e1a2)
  - Rarely P230
- Results are standardized to the international scale (IS)
  - Allows direct comparison across different laboratories regardless of method variations
- Highly sensitive
- Can detect 1 tumor cell in 100,000 cells
- Measures the proportion of cells with the BCR/ABL gene

# Monitoring Response by qPCR for BCR/ABL

CBC with diff measures above the surface

qPCR measures depth of response-below the surface

# Tyrosine Kinase Inhibitors- How they work

- Oral medications that block the signals of the BCR/ABL gene that allow the cancer to grow
- “Unplugging the cancer from its energy source”
- If TKIs are not taken correctly or combined with medications that interfere with blocking the signal, then the CML or BCR/ABL gene can grow
- qPCR is used to measure the proportion of cells with the BCR/ABL gene

# How to know if the medication is working

- **Complete Hematologic Response**-1st level of response
  - Normal blood counts without immature cells such as myelocytes, promyelocytes, or blasts
  - Reduction of the spleen to normal size
  - Resolution of symptoms
- **Cytogenetic Response**-2nd level of response
  - No translocation or Philadelphia chromosome by FISH or karyotyping- **complete cytogenetic response**
  - Between 0 and 35% cells Ph+ **- Major cytogenetic response**
  - Between 36 and 65% cells Ph+ **- Minor cytogenetic response**

# How to know if the medication is working

- **Molecular Response**-3rd level of response
  - Measured with qPCR for BCR/ABL
  - Most patients (60-80%) achieve a complete cytogenetic response, and the depth of response can be monitored by qPCR
  - Major molecular response is
    - At least a 3-log reduction in BCR/ABL transcripts of **qPCR for BCR/ABL of 0.1%**
  - **Deep molecular response (bottom of the iceberg)**
    - 4-log reduction in BCR/ABL transcripts of **qPCR for BCR/ABL of 0.01%**
    - **MR4.5** is 4.5 log reduction in BCR/ABL transcripts or **≤ 0.0032%**

| TKI | Specificity of TKI | MMR | DMR | Changes to Another TKI | OS, PFS | Side Effect |
|---|---|---|---|---|---|---|
| Imatinib (IM) | 1G TKI the first choice for the treatment of CML | 20–59%/1 years<br>60–80%/5 years | MR4 or deeper:<br>35–68%/5 years | 37% [a] and 50% [b]/5 years<br>26.5% [c]/10 years | OS:<br>90–95%/5 years<br>82–85%/10 years<br>PFS:<br>80–90%/5 years<br>6%<br>leukemia-related death rate [c,d] | no life-threatening complications [c,d]<br>early fluid retention, gastrointestinal symptoms, muscle cramps, joint pain, skin rash, fatigue [e] |
| Nilotinib (NIL) | 2G TKI active against *BCR-ABL1* mutants: V299L, F317L/V/I/C, T315A | 77% [b]/5 years<br>82.6% [f]/10 years<br>98% [g]/10 years | MR4:<br>66%/5 years<br>73%/10 years<br>76% [g]/10 years<br>MR4.5:<br>54%/5 years<br>64%/10 years | 40%/10 years | OS:<br>94%/5 years<br>87.6%/10 years<br>94% [g]/10 years | cardiovascular events [h]<br>pancreatitis [b,f,g] |
| Dasatinib (DASA) | 2G TKI active against *BCR-ABL1* mutants: Y253H, E255V/K, F359V/I/C | 46% [a]/1 year<br>76% [a]/5 years | MR4.5:<br>42%/5 years | 39%/5 years | OS:<br>91%/5 years<br>PFS:<br>86%/5 years | pleuro-pulmonary toxicity<br>recurrent pleural effusions<br>rarely pulmonary arterial hypertension [a] |
| Bosutinib [i] (BOS) | 2G TKI active against *BCR-ABL1* mutants: Y253H, E255V/K, F359V/I/C, F317L/V/I/C, T315A | 47% [j]/1year | NR | NR | NR | transient diarrhea<br>transient elevations of transaminases [k] |

[a] [21] [b] [22] [c] [9] [d] [23] [e] [24,25] [f] [26] [g] [27] [h] in about 20% of patients over a 10-year period vs. 5% for IM [22,26,27] [i] data on clinical

Kwaśnik P, Giannopoulos K. Treatment-Free Remission-A New Aim in the Treatment of Chronic Myeloid Leukemia. J Pers Med. 2021 Jul 22;11(8):697. doi: 10.3390/jpm11080697. PMID: 34442340; PMCID: PMC8399881.

# Side Effect Management

- Cytopenias
  - Managed with close follow-up
    - CBC with diff weekly during the first month of treatment, monthly in months 2 and 3, and every 3 months once stabilized
    - Schedule adjusted based on level of cytopenias
  - Dose interruption according to prescribing guidelines
  - Dose reduction if recurrent after prolonged dose interruption
  - Growth factors (off-label use, although occurs in practice)
  - May need to change therapy
- Fatigue
  - Set expectations
  - Plan activities during periods of least fatigue
  - Rule out other contributing causes, such as poor sleep habits
- Fluid Retention
  - Decrease dietary salt intake

Jabbour, E., Deininger, M. & Hochhaus, A. Management of adverse events associated with tyrosine kinase inhibitors in the treatment of chronic myeloid leukemia. *Leukemia* **25**, 201–210 (2011). https://doi.org/10.1038/leu.2010.215

# Side Effect Management

- Fluid retention
  - Imatinib associated with periorbital edema, lower extremity edema
  - Manage with diuretics as needed
  - Dasatinib associated with pleural (28%) and pericardial effusions (1-2%)
    - Dose interruptions and dose reductions PRN
    - Thoracentesis for moderate to large pleural effusions with symptoms
    - Steroids
    - Diuretics
- Cardiotoxicity with nilotinib
  - Black box warning for potential QT prolongation and sudden death
  - Perform ECG
    - Baseline
    - 7 days after treatment initiation
    - Following dose adjustments
  - Correct hypokalemia and hypomagnesemia
  - Educate patients to not eat 2 hours before and 1 hour after taking nilotinib

Cortes JE, Jimenez CA, Mauro MJ, Geyer A, Pinilla-Ibarz J, Smith BD. Pleural Effusion in Dasatinib-Treated Patients With Chronic Myeloid Leukemia in Chronic Phase: Identification and Management. *Clinical Lymphoma Myeloma and Leukemia*. 2017/02/01/ 2017;17(2):78-82. doi:https://doi.org/10.1016/j.clml.2016.09.012

Jabbour, E., Deininger, M. & Hochhaus, A. Management of adverse events associated with tyrosine kinase inhibitors in the treatment of chronic myeloid leukemia. *Leukemia* **25**, 201–210 (2011). https://doi.org/10.1038/leu.2010.215

# Side Effect Management

- Metabolic
  - Grade 3-4 elevations in  aspartate aminotransferase (AST), alanine aminotransferases, and bilirubin (7% or less) with **nilotinib** and **imatinib**, <1% for dasatinib, bosutinib (up to 18%)
  - Manage by performing monthly CMP panels
  - Grade toxicity level and  interrupt and reduce dose as needed
  - Discuss potential contributors to hepatic toxicity (i.e. acetaminophen, alcohol) and limit their use

  - Nilotinib associated with increased lipase and pancreatitis (1-2%)
  - Nilotinib associated with hyperglycemia (12%)
  - Grade toxicity level and interrupt or reduce dose
  - Hospitalization may be necessary for pancreatitis
  - Avoid using nilotinib in individuals prone to increased lipase,  pancreatitis, or hyperglycemia

Cortes, J.E., Apperley, J.F., DeAngelo, D.J. et al. Management of adverse events associated with bosutinib treatment of chronic-phase chronic myeloid leukemia: expert panel review. J Hematol Oncol 11, 143 (2018). https://doi.org/10.1186/s13045-018-0685-2
Jabbour, E., Deininger, M. & Hochhaus, A. Management of adverse events associated with tyrosine kinase inhibitors in the treatment of chronic myeloid leukemia. *Leukemia* **25**, 201–210 (2011). https://doi.org/10.1038/leu.2010.215

# Side Effect Management

- Metabolic
  - Hypophosphatemia
    - Imatinib -50% incidence
    - Dasatinib or nilotinib -10%
    - Bosutinib-20%
  - Replace phosphorous and monitor periodically throughout treatment
- Musculoskeletal
  - Common with imatinib ~ 50% musculoskeletal pain and muscle cramps in the IRIS trial
  - Grade 3–4 musculoskeletal pain in 5% and myalgia 24%
  - Symptomatic relief with hydration, magnesium and calcium supplements

Cortes, J.E., Apperley, J.F., DeAngelo, D.J. et al. Management of adverse events associated with bosutinib treatment of chronic-phase chronic myeloid leukemia: expert panel review. J Hematol Oncol 11, 143 (2018). https://doi.org/10.1186/s13045-018-0685-2

Jabbour, E., Deininger, M. & Hochhaus, A. Management of adverse events associated with tyrosine kinase inhibitors in the treatment of chronic myeloid leukemia. *Leukemia* **25**, 201–210 (2011). https://doi.org/10.1038/leu.2010.215

Table 1.

Tabulated data for tyrosine kinase inhibitor (TKI) gastrointestinal adverse events (GI AEs) for the meta-analysis of 43 published studies and 10,789 chronic myeloid leukemia (CML) patients.

| Adverse Event | Bosutinib | Dasatinib | Imatinib | Nilotinib |
|---|---|---|---|---|
| Diarrhea (all) | 698/881 (79.2%) | 792/2815 (28.1%) | 282/1181 (23.9%) | 313/4398 (7.1%) |
| Diarrhea (severe) | 84/881 (9.5%) | 76/2696 (2.8%) | 20/1352 (1.5%) | 14/2775 (0.5%) |
| Vomiting (all) | 328/881 (37.2%) | 273/2249 (12.1%) | 167/1049 (15.9%) | 272/3860 (7.0%) |
| Vomiting (severe) | 27/881 (3.1%) | 16/2249 (0.7%) | 4/1220 (0.3%) | 15/1958 (0.8%) |
| Nausea (all) | 372/881 (42.2%) | 514/2680 (19.2%) | 346/1049 (33.0%) | 514/3881 (13.2%) |
| Nausea (severe) | 10/881 (1.1%) | 21/2680 (0.8%) | 3/1220 (0.2%) | 19/2327 (0.8%) |

Mohanavelu P, Mutnick M, Mehra N, White B, Kudrimoti S, Hernandez Kluesner K, Chen X, Nguyen T, Horlander E, Thenot H, Kota V, Mitchell CS. Meta-Analysis of Gastrointestinal Adverse Events from Tyrosine Kinase Inhibitors for Chronic Myeloid Leukemia. Cancers (Basel). 2021 Apr 1;13(7):1643. doi: 10.3390/cancers13071643. PMID: 33915952; PMCID: PMC8037766.

# GI Side Effect Management

- Bosutinib and imatinib should be taken with food and a full glass of water to **decrease GI side effects**
- Dasatinib may be taken with or without food
- Nilotinib should be taken on an empty stomach, at least 2 hours before or 1 hour after eating any food
- Provide dietary counseling for preventing diarrhea
  - Avoid spicy or fatty food, caffeine, alcohol, dairy products, and raw fruit and vegetables (except for bananas and apples)
  - Eat low-fiber starchy food and food that is high in sodium and potassium
  - Eat small meals, snack frequently, avoid very hot or cold food and drink
  - Re-introduce a balanced diet (high-fiber food, fruit, and vegetables) once diarrhea has resolved

# GI Side Effect Management

- Discontinue medications and supplements that exacerbate diarrhea
- Antidiarrheals as needed
- Emphasize the importance of adequate hydration
- Encourage them to continue and remind them that with time, this improves for most patients

# Roundtable Discussion

RTP
RESEARCH
TO PRACTICE

# Practical Nursing Considerations with the Use of TKIs for CML

Ilene Galinsky, RN, BSN, MSN, ANP-C

Dana-Farber Cancer Institute

Boston, Massachusetts

# Nursing considerations:

- The dosing of the TKI's vary based on phase- for purposes of this discussion the dosing is for those with chronic phase CML.
- Imatinib: 400 mg every day- can take with food and water any time of day- watery eyes, orbital edema-avoid grapefruit juice-myelosuppression- dose adjustment per guidelines
- Dasatinib:100 mg once per day- pleural effusions- muscle ache-rash-GI symptoms-can be taken with or without food-dose modifications as outlined
- Nilotinib: BLACK BOX WARNING- cardiovascular complications; QT syndrome; myelosuppression-avoid antacids; joint pain
- 400 mg BID (at least 12 hours apart)-Take on an empty stomach

# Nursing Consideration

- Bosutinib: starting dose is 400mg once per day 300mg for moderate renal dysfunction. Take once per day with food.

  Diarrhea; nausea; abdominal pain; headache- most patients are dose reduced

# General

- Work with all our patients, to notify us before they take any new medication or over the counter medications-teaching fact sheets-pharmacy support for oral medication
- St. Johns wort, antacids, PPI, Grapefruit Juice
- If you don’t take it, you are not going to have a response- showing them and discussing their PCR results; encouraging them to discuss symptoms so we can work together to come up with a solution so they do take their medication
- Discuss openly goals, stopping studies if milestones are met-they understand why they are on this medication

# 76-year-old female

- Dx with chronic phase CML- started imatinib at soc dose of 400mg per day
- Developed nausea and vomiting, diarrhea, elevated liver enzymes- treated with supportive care, including a drug holiday- liver enzymes resolved- dose decreased to 300mg per day- now developing severe headaches- several scans and neurology consult- unable to identify a cause- thought to be possibly related to imatinib- decreased dose to 200mg per day- still headaches “migraine like” continued- unable to remain on imatinib…

# What next?

- Patient with a history of cardiovascular disease; hyperlipidemia; hypertension--- what do we choose?

Options:

Dasatinib- concerned with fluid issues- pleural effusions

Nilotinib- cardiovascular issues- history of cardiovascular issues

Bosutinib- GI side effects (especially diarrhea)- history of GI issues

Asciminib: enrolled patient on clinical trial-started 80mg daily

# Results?

- She has now been on trial for two years
- Remains on starting dose
- Achieving PCR milestones- last PCR 0.0035%= 4.45 log reduction
- Nausea, vomiting, diarrhea, fatigue, arthralgias- improved
- Headaches improved now they come and go now receiving botulinum toxin injections PS = 0

# Roundtable Discussion

RTP
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TO PRACTICE

# Agenda

**Introduction:** Chronic Myeloid Leukemia (CML) as a Model for Targeted Treatment

**Module 1:** Biology of CML; Role of First- and Second-Generation Tyrosine Kinase Inhibitors (TKIs) as Initial Treatment for Chronic-Phase (CP)-CML

**Module 2: Role of Asciminib for Newly Diagnosed CP-CML**

**Module 3:** Feasibility of TKI Discontinuation for Patients with Sustained Response to Treatment

**Module 4:** Management of CP-CML After Failure of Initial Therapy

# Clinical Scenario

**A patient with newly diagnosed CP-CML who is about to start treatment with asciminib**

# Role of Asciminib in Newly Diagnosed Chronic Phase CML


**Michael J. Mauro, MD**

***Director*, Chronic Myeloid Leukemia Program**

**Memorial Sloan Kettering Cancer Center**

**New York, NY**



CYCLE FOR SURVIVAL

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FRED'S TEAM

IMAGINE A WORLD WITHOUT CANCER

CURE CML CONSORTIUM

THE NATIONAL CML SOCIETY

iCMLf International Chronic Myeloid Leukemia Foundation

LEUKEMIA & LYMPHOMA SOCIETY®

TEAM IN TRAINING®

The Max Foundation

TEAM922

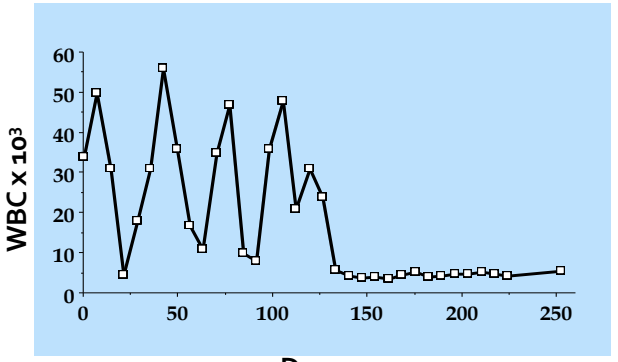
What is My PCR?

ASK ME

MyPCR.org

# The history of CML is long, the kinase inhibitor era short…

***2000:*** *Started my work in CML with Brian Druker (OHSU, Portland, Oregon)*


1845 1865 1879 1903 1953 1965 1968 1983 2001 2006 2012 2016 2021

First description of CML

Fowler's solution -1% arsenic trioxide

Staining methods for blood

Radiotherapy

Busulfan

Hydroxyurea

BMT

Interferon

Imatinib

Dasatinib

Nilotinib

Bosutinib

Ponatinib

Generic Imatinib

Asciminib

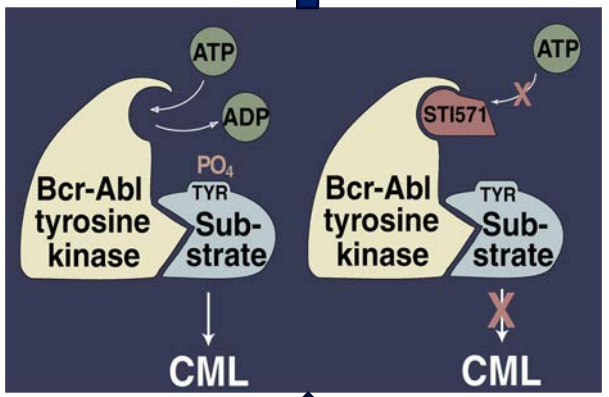
1845:
John Hughes Bennett reported a "Case of Hypertrophy of the Spleen and Liver in which Death Took Place from Suppuration of the Blood" in the Edinburgh Medical Journal; Virchow in Germany wrote up a similar observation

1960:
Nowell & Hungerford describe the Philadelphia Chromosome

1973:
Janet Rowley describes the 9:22 translocation

1983: Nora Heisterkamp and John Groffen, with others, describe the BCR-ABL fusion gene product

1998: After seminal preclinical work first clinical trials commence with STI571 (imatinib); 1999, target inhibition validated, resistance identified (T315I)




**A Minute Chromosome in Human Chronic Granulocytic Leukemia**

In seven cases thus far investigated (five males, two females), a minute chromosome has been observed replacing one of the four smallest autosomes in the chromosome complement of cells of chronic granulocytic leukemia cultured from peripheral blood. No abnormality was observed in the cells of four cases of *acute* granulocytic leukemia in adults or of six cases of acute leukemia in children. There have been several recent reports of chromosome abnormalities in a number of cases of human leukemia [including two of the seven cases reported here: Nowell and Hungerford, *J. Natl. Cancer Inst.* **25**, 85 (1960)], but no series has appeared in which there was a consistent change typical of a particular type of leukemia.

Cells of the five new cases were obtained from peripheral blood (and bone marrow in one instance), grown in culture for 24–72 hours, and processed for cytological examination by a recently developed air-drying technique (Moorhead, *et al., Exptl. Cell Research*, in press). The patients varied from asymptomatic untreated cases to extensively treated cases of several years duration in terminal myeloblastic crisis. All seven individuals showed a similar minute chromosome, and none showed any other frequent or regular chromosome change. In most of the cases, cells with normal chromosomes were also observed. Thus, the minute is not a part of the normal chromosome constitution of such individuals.

The findings suggest a causal relationship between the chromosome abnormality observed and chronic granulocytic leukemia.

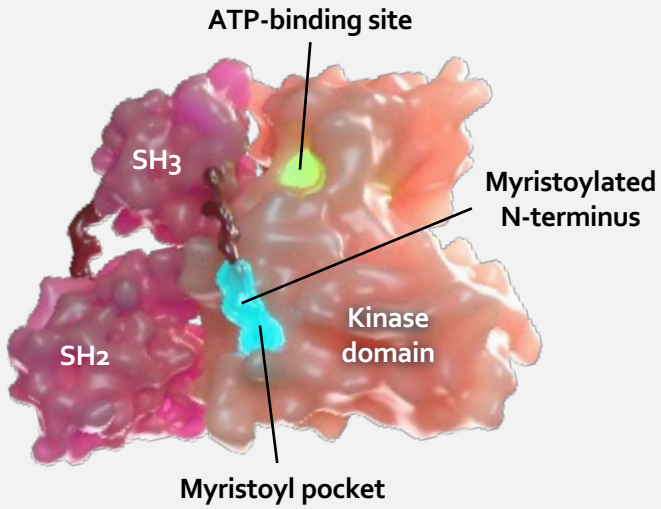
PETER C. NOWELL
*School of Medicine, University of Pennsylvania*
DAVID A. HUNGERFORD
*Institute for Cancer Research*

Nowell & Hungerford, 1960 Science 132.1497

# Asciminib is the 1st and only approved BCR::ABL1 inhibitor that works by STAMP (Specifically Targeting the ABL Myristoyl Pocket)

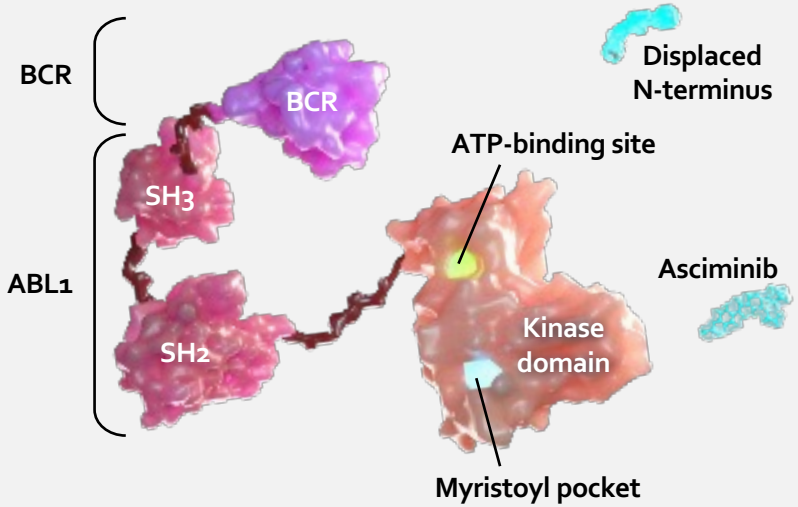
## Normal conditions

**Inactive ABL1**
with N-terminus binding



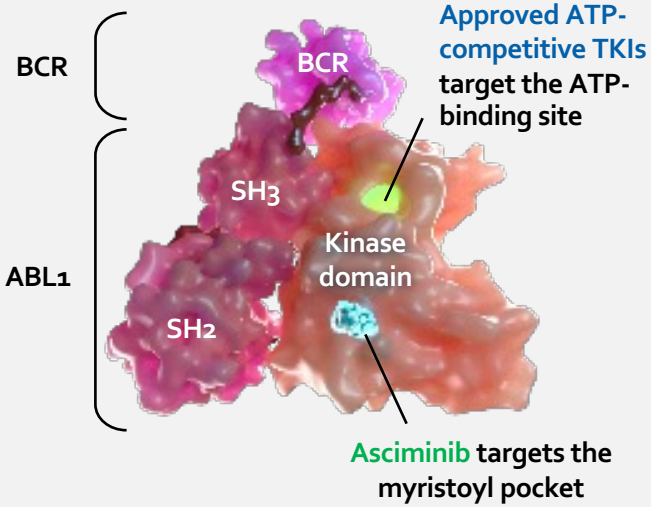

## In CML

**Constitutively active BCR::ABL1**
with loss of N-terminus




## In CML with asciminib

**Inactive BCR::ABL1**
with asciminib binding




Adapted from Manley PW, et al. *Leuk Res.* 2020;98:106458. Copyright © 2020 Elsevier Ltd.

1. Colicelli J. *Sci Signal*. 2010;3:re6. 2. Hughes TP, et al. *N Engl J Med.* 2019;381:2315-2326. 3. Hantschel O. *Genes Cancer*. 2012;3:436-446. 4. Manley PW, et al. *Leuk Res.* 2020;98:106458. 5. Mauro MJ, et al. Oral presentation at: 63rd ASH Annual Meeting & Exposition; December 11–14, 2021; San Diego, CA, and virtual. Presentation 310.

# Phase 3 ASC4FIRST study results in patients with newly diagnosed CML receiving asciminib or investigator-selected TKIs

Hochhaus A, et al. *N Engl J Med.* 2024;391(10):885-898.
Cortes JE, et al. Oral presentation at: 66th ASH Annual Meeting & Exposition; December 7-10, 2024; San Diego, CA. Oral presentation 475.

## Study design

**Key inclusion criteria**

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

**Prerandomization TKI selection**

- The TKI a patient will take if randomized to IS-TKI arm
- Selected by physician in consultation with patient

**Stratification by:**

- Prerandomization TKI selection (IMA or 2G TKI)
- ELTS risk category (low/intermediate/high)

R 1:1
N=405

**ASC 80 mg QD (n=201)**

- Imatinib stratum: $ASC^{IMA}$ (n=101)
- 2G TKI stratum: $ASC^{2G}$ (n=100)

**All IS-TKIs at label doses (n=204)**

- Imatinib stratum: $IS\text{-}TKI^{IMA}$ (n=102)
- 2G TKI stratum: $IS\text{-}TKI^{2G}$ (n=102)

End of study: LPFT + 5 years[b]

From Hochhaus A, et al. *N Engl J Med*. 2024;391(10):885-898. Copyright © 2024 Massachusetts Medical Society. Adapted with permission from Massachusetts Medical Society.

**Primary endpoints**

- MMR at week 48 with **ASC** vs all **IS-TKIs**
- MMR at week 48 with **$ASC^{IMA}$** vs **$IS\text{-}TKI^{IMA}$** (**imatinib stratum**)

**Data cutoff: Nov 28, 2023**

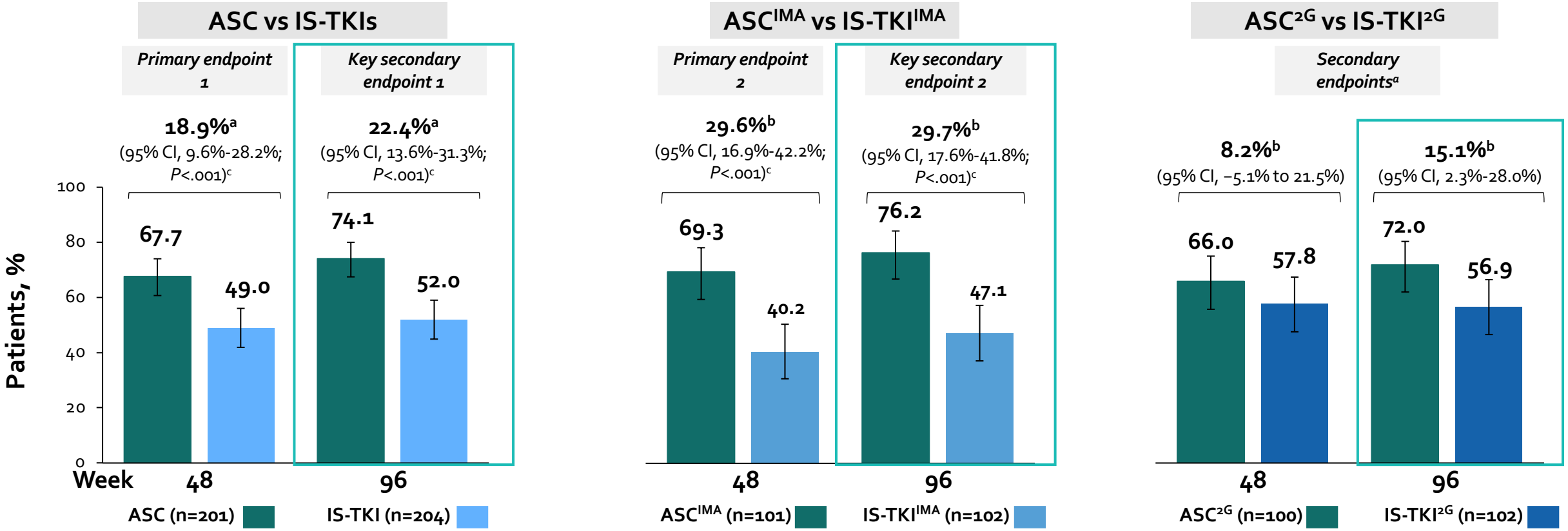
**Key secondary endpoints**

- MMR at week 96 with **ASC** vs all **IS-TKIs**
- MMR at week 96 with **$ASC^{IMA}$** vs **$IS\text{-}TKI^{IMA}$** (**imatinib stratum**)

**Data cutoff: Oct 22, 2024**

2G, 2nd generation; ASC, asciminib; CML-CP, chronic myeloid leukemia in chronic phase; ELTS, EUTOS long-term survival score; EUTOS, European Treatment and Outcome Study; IMA, imatinib; IS, investigator selected; LPFT, last person 1st treatment; MMR, major molecular response; Ph, Philadelphia chromosome; QD, once daily; R, randomized; TKI, tyrosine kinase inhibitor.
[a] Either imatinib, bosutinib, dasatinib, or nilotinib is allowed for ≤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 1st dose, unless they have discontinued early due to treatment failure, disease progression, intolerance, or investigator or patient decision.
Hochhaus A, et al. *N Engl J Med*. 2024;391(10):885-898.

# ASC4FIRST: MMR rates at time points (@2y)





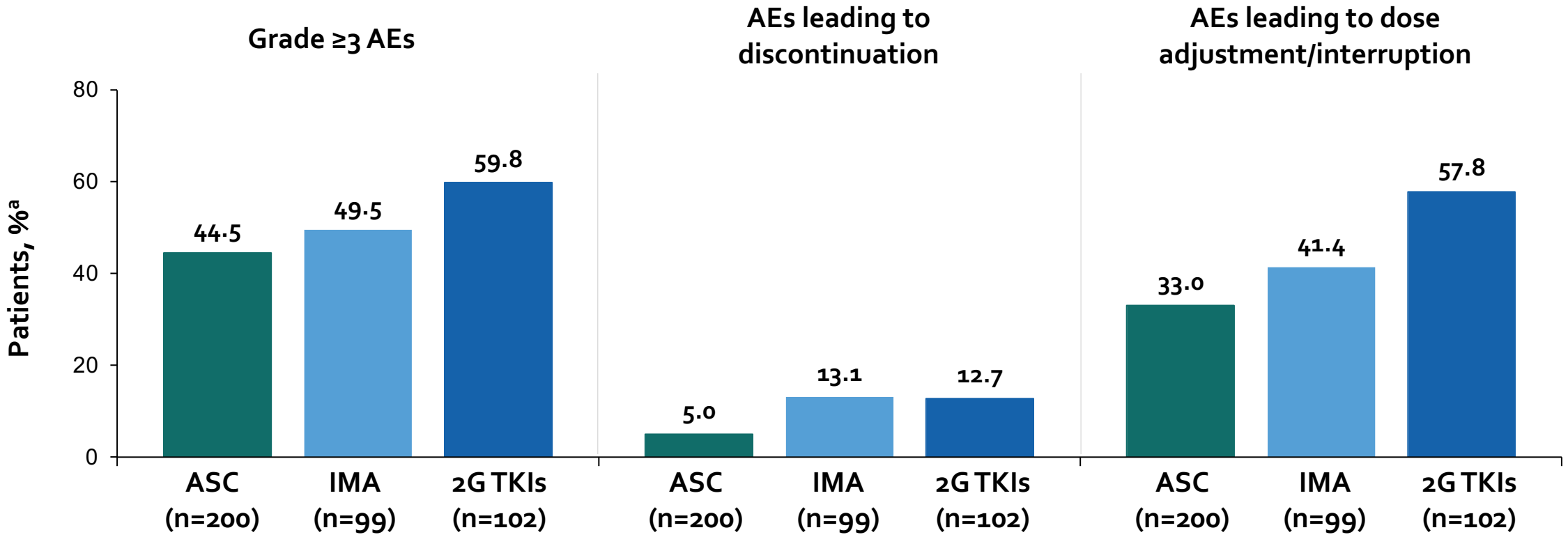

- MMR rate at week 96 continued to be superior with ASC vs all IS-TKIs, meeting the 1st key secondary endpoint
- MMR rate at week 96 continued to be superior with ASC$^{IMA}$ vs IS-TKI$^{IMA}$, meeting the 2nd key secondary endpoint
- Treatment difference for the MMR rate at week 96 between ASC$^{2G}$ and IS-TKI$^{2G}$ increased
- MMR rates at week 96 were consistently higher with ASC overall and across strata

2G, 2nd generation; ASC, asciminib; ELTS, EUTOS long-term survival score; EUTOS, European Treatment and Outcome Study; IMA, imatinib; IRT, interactive response technology; IS, International Scale; IS-TKI, investigator-selected tyrosine kinase inhibitor; MMR, major molecular response (*BCR::ABL1*$^{IS}$ ≤0.1%); TKI, tyrosine kinase inhibitor.

Error bars represent 95% CIs. The common treatment difference and its 95% CI were estimated using the Mantel-Haenszel method after stratifying for [a] prerandomization-selected TKI and baseline ELTS risk groups (both IRT data) or [b] baseline ELTS risk groups (IRT data). [c] Adjusted 1-sided *P* value was calculated based on the graphical gatekeeping procedure. The null hypothesis is rejected if the adjusted *P* value is ≤.025.

Cortes JE, et al. Oral presentation at: 66th ASH Annual Meeting & Exposition; December 7-10, 2024; San Diego, CA. Oral presentation 475.

# ASC4FIRST: Overview of Adverse Events (@2y)

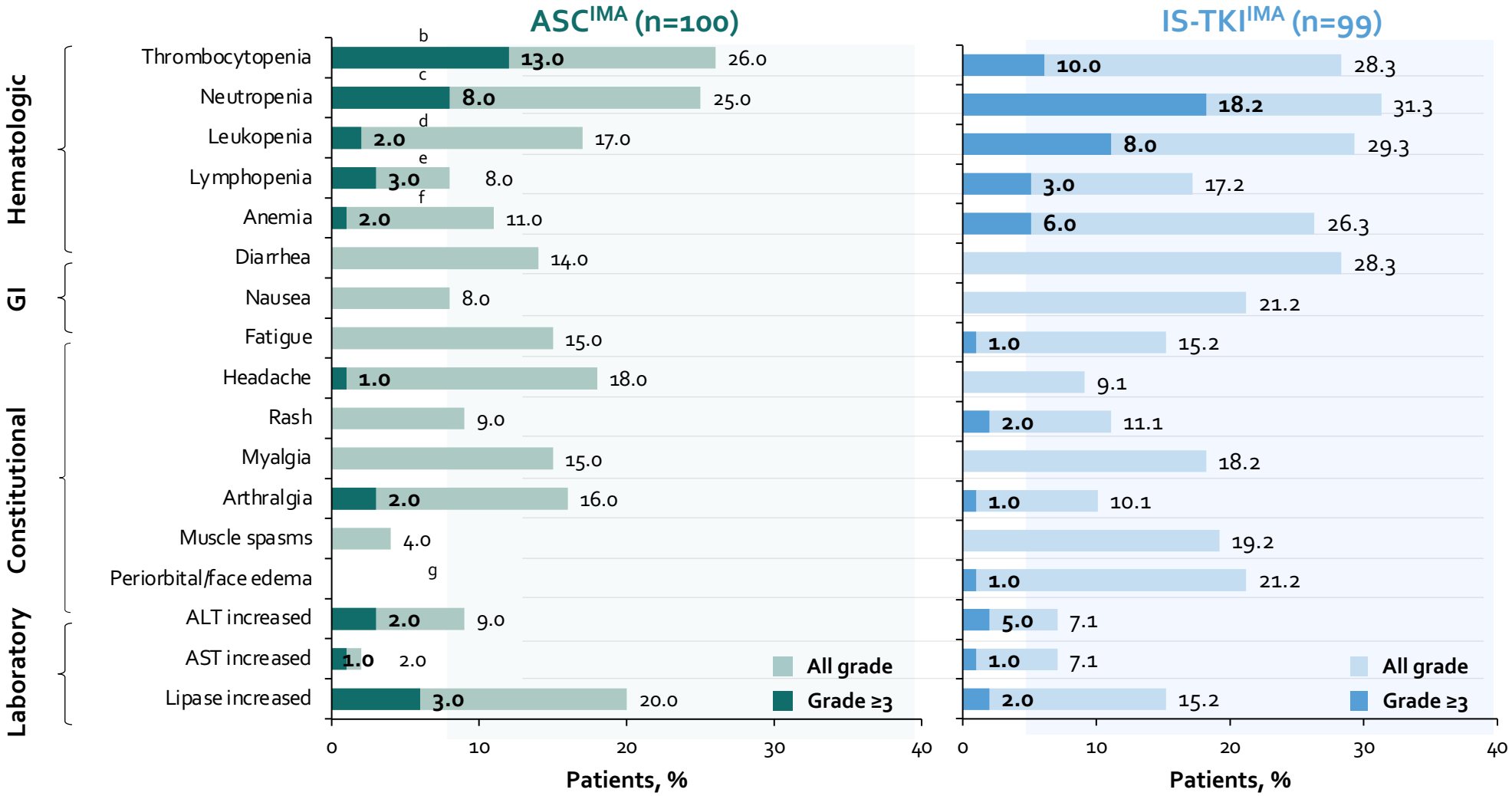





- The median average daily dose was 80 mg/day with ASC, 400 mg/day with IMA, 600 mg/day with NIL, 100 mg/day with DAS, and 316 mg/day with BOS
- The hazard ratio for time to treatment discontinuation due to AEs with ASC vs 2G TKIs was 0.46 (95% CI, 0.215-0.997)
  - Risk of discontinuation due to AEs[b] was 54% lower with asciminib than 2G TKIs

2G, 2nd generation; AE, adverse event; ASC, asciminib; BOS, bosutinib; DAS, dasatinib; IMA, imatinib; NIL, nilotinib; TKI, tyrosine kinase inhibitor.
[a] Safety analyses were done in 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. [b] Discontinuation for other reasons was a competing event.
Cortes JE, et al. Oral presentation at: 66th ASH Annual Meeting & Exposition; December 7-10, 2024; San Diego, CA. Oral presentation 475.

# ASC4FIRST: Most relevant AEs[a] with ASC$^{IMA}$ vs IS-TKI$^{IMA}$ (@2y)

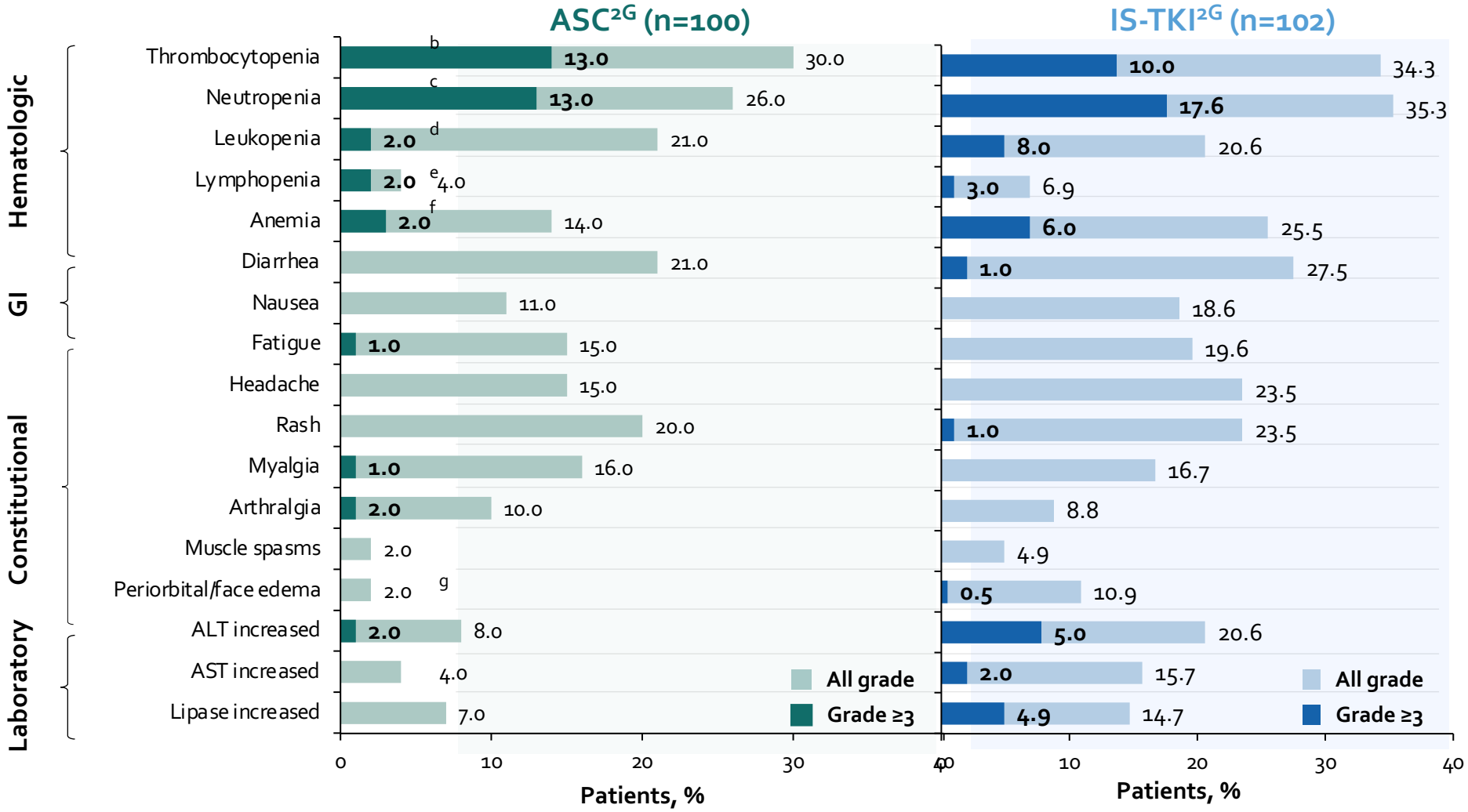



- Most relevant AEs were lower with ASC$^{IMA}$ than IS-TKI$^{IMA}$ by the week 96 cutoff



AE, adverse event; ALT, alanine aminotransferase; ASC, asciminib; AST, aspartate aminotransferase; GI, gastrointestinal; IMA, imatinib; IS-TKI, investigator-selected tyrosine kinase inhibitor.
[a] A patient with multiple severity grades for an AE is only counted under the maximum grade. COVID-19 is not listed. [b] Includes platelet count decreased and thrombocytopenia.
[c] Includes neutrophil count decreased and neutropenia. [d] Includes decreased white blood cell count and leukopenia. [e] Includes decreased lymphocyte count and lymphopenia.
[f] Includes anemia and red blood cell count decreased and hematocrit decreased. [g] Includes periorbital edema and face edema.
Cortes JE, et al. Oral presentation at: 66th ASH Annual Meeting & Exposition; December 7-10, 2024; San Diego, CA. Oral presentation 475.

# ASC4FIRST: Most relevant AEs[a] with ASC[2G] vs IS-TKI[2G] (@2y)




- Most relevant AEs were lower with ASC[2G] than IS-TKI[2G] by the week 96 cutoff



2G, 2nd generation; AE, adverse event; ALT, alanine aminotransferase; ASC, asciminib; AST, aspartate aminotransferase; GI, gastrointestinal; IS-TKI, investigator-selected tyrosine kinase inhibitor.
[a] A patient with multiple severity grades for an AE is only counted under the maximum grade. COVID-19 is not listed. [b] Includes platelet count decreased and thrombocytopenia.
[c] Includes neutrophil count decreased and neutropenia. [d] Includes decreased white blood cell count and leukopenia. [e] Includes decreased lymphocyte count and lymphopenia.
[f] Includes anemia and red blood cell count decreased and hematocrit decreased. [g] Includes periorbital edema and face edema.
Cortes JE, et al. Oral presentation at: 66th ASH Annual Meeting & Exposition; December 7-10, 2024; San Diego, CA. Oral presentation 475.

# ASC4FIRST: Arterial Occlusive Events (@2y)

| Patients, n (%) | All ASC (n=200)[a] | | IMA (n=99)[a] | | 2G TKIs (n=102)[a] | |
|---|---|---|---|---|---|---|
| | All grade | Grade ≥3 | All grade | Grade ≥3 | All grade | Grade ≥3 |
| **Patients with ≥1 AOE** | **4 (2.0)** | **1 (0.5)** | **0** | **0** | **3 (2.9)** | **1 (1.0)** |
| Angina pectoris | 1 (0.5) | 0 | 0 | 0 | 0 | 0 |
| Peripheral arterial occlusive disease | 1 (0.5)[b] | 0 | 0 | 0 | 0 | 0 |
| Arteriosclerosis coronary artery | 2 (1.0)[b] | 0 | 0 | 0 | 0 | 0 |
| Cerebrovascular accident | 1 (0.5) | 1 (0.5) | 0 | 0 | 0 | 0 |
| Cerebral infarction | 0 | 0 | 0 | 0 | 1 (1.0) | 0 |
| Myocardial infarction | 0 | 0 | 0 | 0 | 1 (1.0)[c] | 1 (1.0)[c] |
| Myocardial ischemia | 0 | 0 | 0 | 0 | 1 (1.0)[c] | 0 |
| Vertebral artery arteriosclerosis | 0 | 0 | 0 | 0 | 1 (1.0) | 0 |



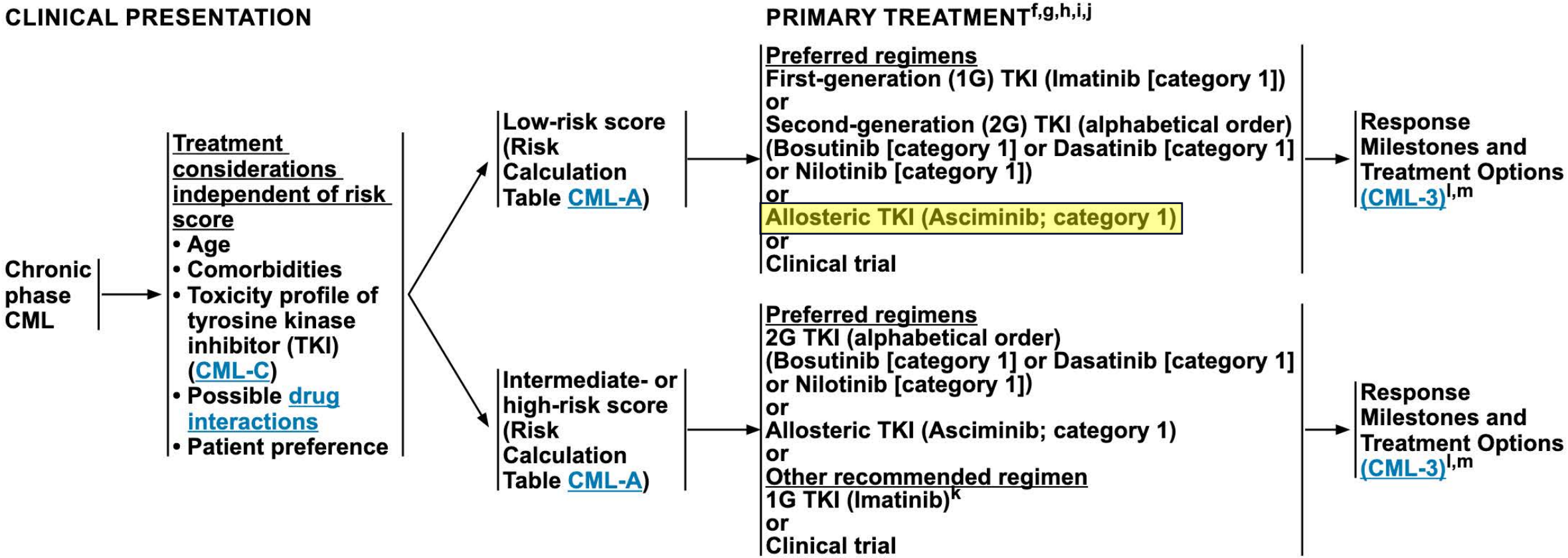
- Since the week 48 cutoff, 2 additional patients had AOEs with ASC (angina pectoris and peripheral arterial occlusive disease [in the patient who had arteriosclerosis coronary artery in the week 48 analysis] and arteriosclerosis coronary artery), and 1 additional patient had an AOE with bosutinib (cerebral infarction)
- AOEs occurred in 2 patients with $ASC^{IMA}$ stratum and 2 with $ASC^{2G}$

2G, 2nd generation; AOE, arterial occlusive event; ASC, asciminib; IMA, imatinib; TKI, tyrosine kinase inhibitor.
[a] Safety analyses were done in patients who received ≥1 dose of study drug. Patients were analyzed according to the study treatment received. [b] 1 patient who had arteriosclerosis coronary artery at the week 48 analysis presented with new peripheral arterial occlusive disease. [c] Myocardial infarction and myocardial ischemia occurred in the same patient with 2G TKIs.
Cortes JE, et al. Oral presentation at: 66th ASH Annual Meeting & Exposition; December 7-10, 2024; San Diego, CA. Oral presentation 475.

National Comprehensive Cancer Network®

# NCCN Guidelines Version 3.2025
# Chronic Myeloid Leukemia

# US Front Line TKI Recommendations




Step 1: precise diagnosis, baseline measurements

Step 2: informed and careful discussion and choice of therapy

# Case: New Diagnosis CML

- 39yo interior designer splitting time between New York and London noted on routine health check to have fatigue, change in menses pattern, abd cramps/pain preceding cycle
- no significant 'b' sx such as night sweats, weight loss; no bruising, bleeding, other changes; bloodwork one year prior WNL
- initial bloodwork 5/2023 with mild leukocytosis (12-13k), plts 600k; reactive lymphs noted in diff, no immature forms but unclear if manual differential (London)
- f/u bloodwork in NYC 6/2023: wbc 19 hgb 13.7 hct 42.8 plt 705 differential 4% myelocytes 2% eos 9% basophils 1% blasts

# Case: New Diagnosis CML

- Despite travel requirement, enrolled in Khoury Cure CML Consortium front line study (phase II frontline Asciminib)
- NO adverse effects
- 3mo response near MR4
- 6mo response deep MR
- Ongoing deep MR; TFR planned

**BCR/ABL1 P210 Analysis Report**

| Draw Date | BCR/ABL to ABL Ratio(%) | Specimen Type | Ordering Doctor |
|---|---|---|---|
| 06/26/2023 | 26.96<br>*The result corresponds to MR 0.57.* | Peripheral Blood | MICHAEL JOHN MAURO MD |
| 09/21/2023 | 0.014<br>*The result corresponds to MR 3.85.* | Peripheral Blood | MICHAEL JOHN MAURO MD |
| 12/14/2023 | 0.0063<br>*The result corresponds to MR 4.20.* | Peripheral Blood | MICHAEL JOHN MAURO MD |
| 02/29/2024 | UNDETECTED | Peripheral Blood | MICHAEL JOHN MAURO MD |
| 05/30/2024 | < 0.0030<br>*The result corresponds to >MR 4.52.* | Peripheral Blood | MICHAEL JOHN MAURO MD |
| 08/22/2024 | <0.0030<br>*The result corresponds to >MR 4.52.* | Peripheral Blood | MICHAEL JOHN MAURO MD |

# Principles in the Treatment of Chronic Myeloid Leukemia

## *First line*

### Early and comprehensive diagnosis

Clinical/pathological stage, features

- WHO shift on biphasic versus triphasic disease

Appraisal of BCR-ABL, and likely non-BCR ABL, mechanisms

Comorbidities

### Goals of therapy

Is it treatment free remission, or remission with preserved QOL?

### Capacity and limitations: provider, patient

Monitoring, adherence, follow-up, collaboration

Access to diagnostics including comprehensive resistance testing; ***Access to TKIs (approved versus reimbursed)***

Breadth of options: allografting, alternative TKIs

### Running the marathon that CML is

Paradigm of chronic disease on chronic therapy warrants specific approaches

- Continual reassessment of adverse events, comorbidities- *with special attention to emerging events*

Treatment is several years minimum and lifelong for many

## *Subsequent line*

### Disease specifics: phase, prior exposure / adverse events, mutation status, other resistance mechanisms

### If not initially assessed, formal cardiovascular risk assessment informative to guide AE avoidance, management in later line therapy

Attribution of CV AEs challenging if no baseline data

### Optimization as early as possible to minimize risk and maximize stability and QOL

## *Beyond*

### 'Survivorship'

Treatment free remission + chronic maintenance cohorts

TKI specific long term adverse events

- Cardiac, Pulmonary, Neurocognitive, Renal, Gastrointestinal / Pancreatic, Musculoskeletal, Dermatologic
- Nonheme second cancers, CH/other hematologic disorders

# The (Tougher) Reality: The Spectrum of Adverse Events with BCR::ABL TKIs

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

# Putting it all together in 2025?

## Front-line IMA

- Lowest cost in many systems
- Global access best
  - Remains primary tx for many
- OS despite 'suboptimal / warning' status remains good
  - Competing comorbidity risk?
  - Risk dying from CML low
- Broader resistance possible
- Higher AE rate-> discontinuation?
- Slower/lower deep MR
- More time on therapy needed / lifelong for more?

## Front-line 2GTKI

- Lower cost emerging
- Lower dose proposed
- Many choices
- Faster / deeper remissions
- No improvement in TFR success -> cure
- AEs with greater morbidity
- Select resistance (T315I , others)

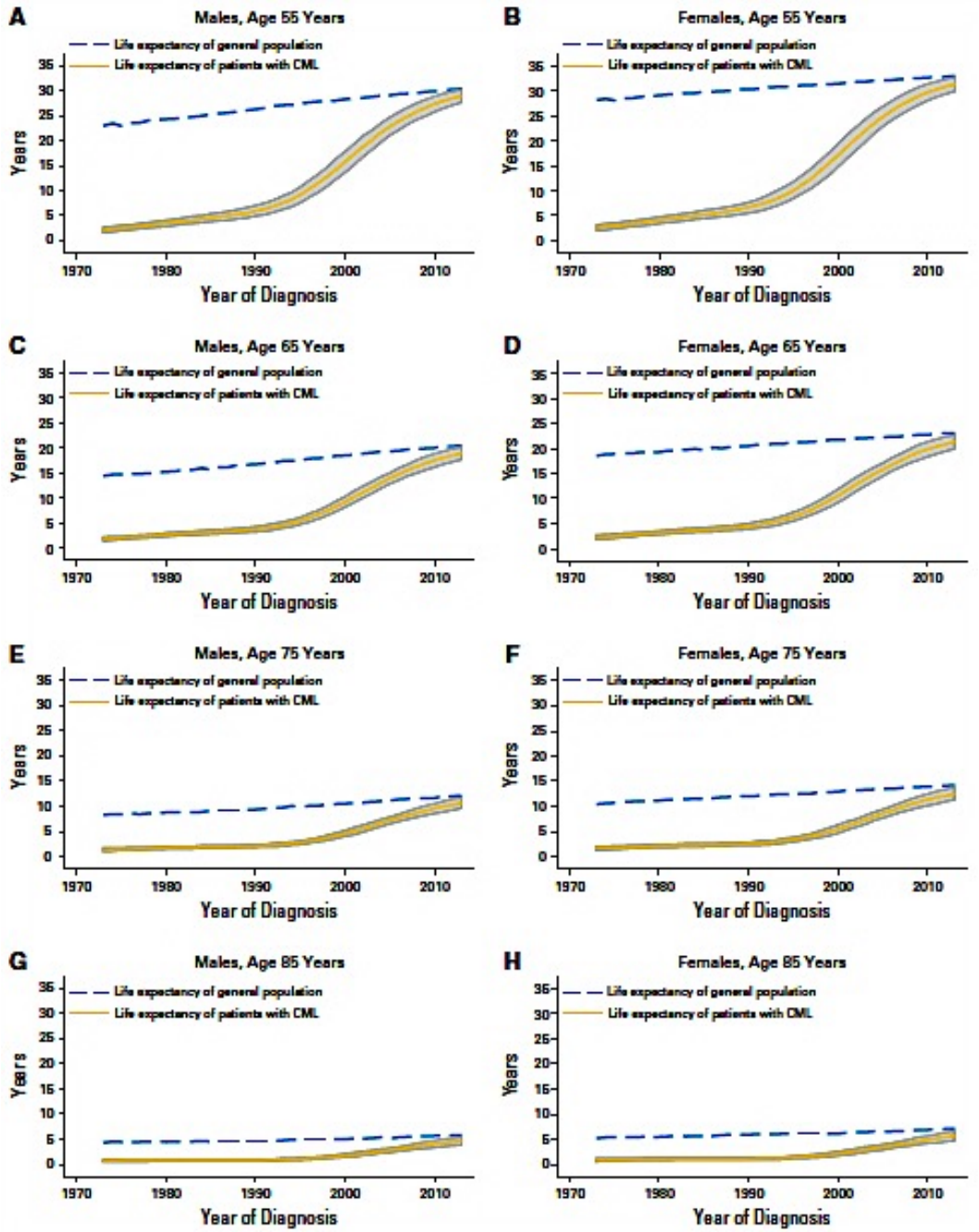
## Front-line ASC

- **Comparative superiority in efficacy in frontline**
- **Comparative improvement in tolerability**
- **Safety data extremely reassuring**
- Higher cost, not accessible / fully accessible yet in many HC systems
- Select resistance (myristoyl site dominant, select ATP site mutations)
- Specificity->vulnerability regarding non-BCR-ABL mutations (ASXL1); amenable to ATP competitive TKIs

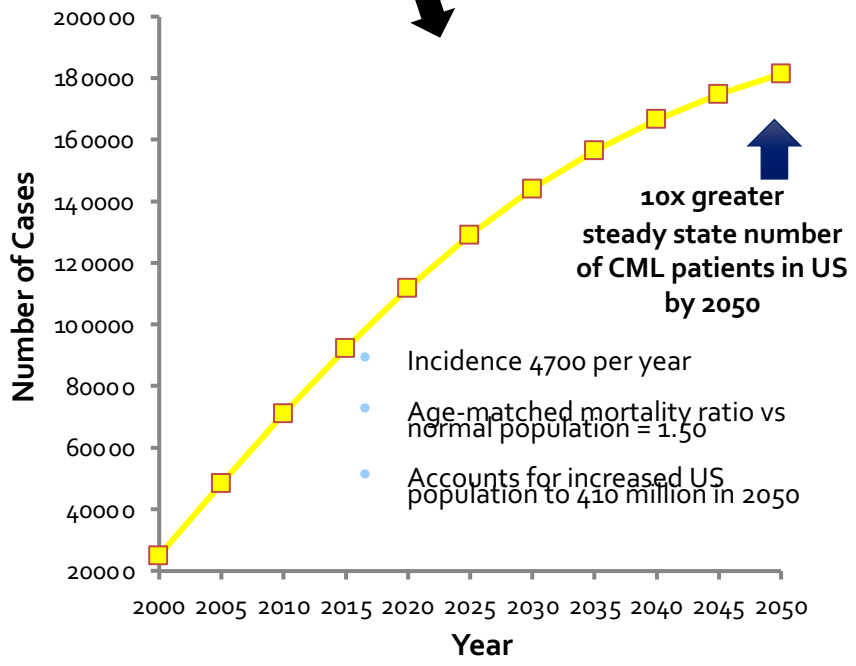
**Asciminib should offer increased eligibility for TFR; will it offer increase in success?**

# CML is an increasingly prevalent and survivable cancer

*lifespan* ➡




*prevalence* ➡




Huang et al, *Cancer* 118:3123-3127, 2012.
Bower H et al, *J Clin Oncol 34:2851-57, 2016.*

# Roundtable Discussion

RTP
RESEARCH
TO PRACTICE

# Asciminib in newly diagnosed patient with CP-CML

Ilene Galinsky, RN, BSN, MSN, ANP-C

Dana-Farber Cancer Institute

Boston, Massachusetts

# Pre starting Asciminib-I have mostly used it as second line or intolerance to other- aware of the new data however- like to have in our back pocket

- Discuss with the patient why we are switching therapies- patient did not tolerate their dasatinib due to recurrent pleural effusions.
- Always check for mutational analysis
- More potent and more specific
- Less side effects than other TKI's-better tolerated
- Mild muscle ache
- Mild GI symptoms
- Mild increase in BP

# Side effect management

- I encourage patients to note their symptoms and to communicate them to me.
- Most side effects are easily managed- by adjusting time of drug administration, supportive medications
- Suggest taking in am when you get up (can’t take for at least two hours after eating)

# Patient

- 24-year-old female, failed imatinib and dasatinib both to intolerance- enrolled on first Asciminib phase one trial- enrolled on the highest cohort dosing, hx of depression
- First drug she was on that she had manageable side effects. She had no GI symptoms, nor rash, or fluid retention, she did develop thrombocytopenia early on (due to her disease- that required romiplostim) - responded both by CBC and PCR
- Tried to become pregnant so it was stopped and she was switched to interferon- major worsening of depression and unable to conceive- returned to Asciminib- 2018

# Patient continued

- 2025- continues on 160 mg BID of Asciminib; PCR 0.014%, mother of an adopted baby boy!
- In her words- “this drug has saved my life and kept me from needing a transplant”

# Roundtable Discussion

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# Practical Nursing Considerations with the Use of Asciminib for CML

Sara M Tinsley-Vance, PhD, APRN, AOCN

# New Treatment on the Block - Asciminib

- On October 29, 2024, the Food and Drug Administration granted accelerated approval to asciminib for adult patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP).
- On October 29, 2021, the Food and Drug Administration granted accelerated approval to asciminib for adult patients with Ph+ CML in CP with the T315I mutation.

# CML Chronic Phase with T315I Mutation

# Rocky Journey with the Same Cancer

- 56-year-old with CML diagnosed in 2000
- Started on imatinib
  - In remission- no details beyond “remission”
    - ? Normal blood counts
    - ? Cytogenetic remission
    - ? Molecular remission
  - Local oncologist discontinued medication
  - “Relapse” in 2013
  - Started on nilotinib
    - Lost insurance coverage
    - Lost to follow up until 2022

# Life Threatening Complications

- Hospitalized, requiring multiple blood transfusions with pRBC and platelets
- Diagnosed with deep venous thrombosis
- Started on bosutinib and remained on treatment for 1 year
- Bone marrow biopsy completed showing CML

**Addendum:**

**CONVENTIONAL CYTOGENETICS NEOGENOMICS CASE (CY24-32422)**

**Karyotype: 46,XX,t(9;22)(q34.1;q11.2)[20]**

# Kinase Domain Mutation Analysis

- Diagnosed with T315I mutation
- Treatment options limited to:
  - Ponatinib
  - Asciminib
- Started on ponatinib
- Tolerated ponatinib poorly with hospitalization and increased need for transfusions with blood and platelets
- Started Asciminib- suboptimal dose due to recurrent cytopenias
- Awaiting vital organ testing to proceed with allogeneic stem cell transplant if passes vital organ testing

# Challenges with CML

- Chronic leukemia with a major breakthrough in treatment and survival
- Not treated as potentially deadly if not treated appropriately
- Patients feel well -sometimes until it is too late
- Guidelines and expert recommendations not followed
- Disparities exist when patients don’t have access to TKIs and experts in the treatment and management of CML

# Asciminib in Newly Diagnosed  Chronic Phase CML

- 80 mg PO daily OR 40 mg PO BID
- **Take without food**
- Avoid eating for at least 2 hours before and 1 hour after taking a dose
- Once-daily dosing: Administer orally at about the same time each day
- Swallow tablets whole; do NOT break, crush, or chew

- **Missed dose**
  - Once-daily dosing regimen: If a dose is missed by >12 hr, skip the dose and take the next dose as scheduled
  - Twice-daily dosing regimen: If a dose is missed by >6 hr, skip the dose and take the next dose as scheduled

Asciminib. Prescribing information.

# Asciminib dosing for chronic phase CML with T315I mutation

- 200 mg orally twice daily
- **Take without food**
- Avoid food for at least 2 hours before and 1 hour after taking
- Swallow tablets whole
- Do not break, crush, or chew the tablets

Asciminib. Prescribing information.

# Dosing Considerations with Asciminib

- Fasting condition is challenging for many patients
- Difficult to manage daily meals and schedules
- Impacts adherence and long-term compliance
  - Potentially impacting response
- 35.8% of patients taking their medication once daily were highly adherent
- 24.9% of patients taking their medication twice daily were highly adherent
- Consider once-daily dosing for non-T315I patients with CML

Combes, F.P., Sy, S.K.B., Li, Y.F. et al. Dose Justification for Asciminib in Patients with Philadelphia Chromosome-Positive Chronic Myeloid Leukemia with and without the T315I Mutation. Clin Pharmacokinet 63, 1301–1312 (2024). https://doi.org/10.1007/s40262-024-01411-1.

Geissler J, Sharf G, Bombaci F, Daban M, De Jong J, Gavin T, et al. Factors influencing adherence in CML and ways to improvement: results of a patient-driven survey of 2546 patients in 63 countries. J Cancer Res Clin Oncol. 2017;143(7):1167–76.

# Other Dosing Considerations

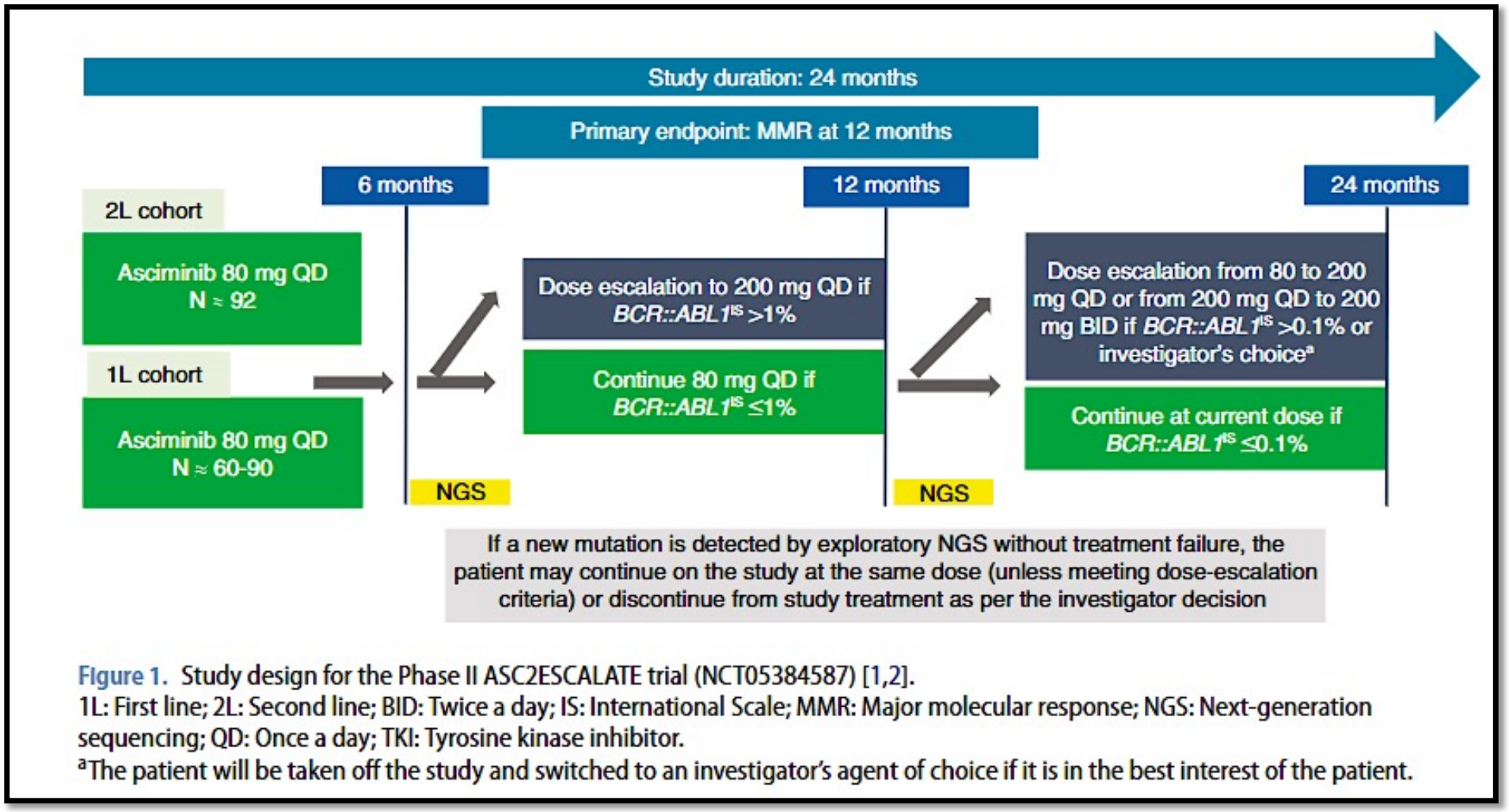


Figure 1. Study design for the Phase II ASC2ESCALATE trial (NCT05384587) [1,2].
1L: First line; 2L: Second line; BID: Twice a day; IS: International Scale; MMR: Major molecular response; NGS: Next-generation sequencing; QD: Once a day; TKI: Tyrosine kinase inhibitor.
[a]The patient will be taken off the study and switched to an investigator's agent of choice if it is in the best interest of the patient.

Atallah, E. L., Mauro, M. J., Sasaki, K., Levy, M. Y., Koller, P., Yang, D., … Cortes, J. E. (2024). Dose-escalation of second-line and first-line asciminib in chronic myeloid leukemia in chronic phase: the ASC2ESCALATE Phase II trial. Future Oncology, 20(38), 3065–3075. https://doi.org/10.1080/14796694.2024.2402680

# Drug Interactions with Asciminib

- 716 drugs known to interact with Asciminib
  - 67 major
  - 602 moderate
  - 47 minor
- Educate the patient to inform your team of any new medications or over-the-counter medications including supplements
- Review of medications is critical for every patient visit to ensure patient safety
- Encourage patient/family to keep a current list of medications
- If possible, have access to other outside medications prescribed
  - Cerner (Oracle Health) capability

https://www.drugs.com/drug-interactions/asciminib.html

# Common Major Interactions

- Itraconazole Oral Solution and other azoles
- Clarithromycin
- Cannabis
- Grapefruit and grapefruit juice
- Warfarin
- Statins
- Midazolam
- Repaglinide
- Rosiglitazone

Asciminib. Prescribing information.

# Encouraging Clinical Trial Participation

- Develop rapport with the patient and their family and friends
- Explain the study in understandable terms
- Allow time for questions
- Discuss the advantages and risks associated with the trial and include
  - Time commitment
  - Visits
  - Procedures
  - Billing concerns
- Provide a written explanation of the study for review
- Do not pressure the patient into participation
- Arrange follow-up if needed to discuss further

# Barriers to Clinical Trial Participation

- Distance from treatment center
- Fear of increased expenses not covered by insurance
- Bias from previous research in race and ethnicities
- The best approach is exploring each person’s values, goals, and preferences.
- *Tailor the visit and discussion to the individual patient*

# Roundtable Discussion

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# Agenda

**Introduction:** Chronic Myeloid Leukemia (CML) as a Model for Targeted Treatment

**Module 1:** Biology of CML; Role of First- and Second-Generation Tyrosine Kinase Inhibitors (TKIs) as Initial Treatment for Chronic-Phase (CP)-CML

**Module 2:** Role of Asciminib for Newly Diagnosed CP-CML

**Module 3: Feasibility of TKI Discontinuation for Patients with Sustained Response to Treatment**

**Module 4:** Management of CP-CML After Failure of Initial Therapy

# Clinical Scenario

**A patient with CP-CML who has been receiving a first-line TKI for 3 years and would like to discontinue therapy**

# Feasibility of TKI Discontinuation in Patients with Sustained Response to Treatment

**Neil P. Shah, MD, PhD**
*Professor*
Division of Hematology/Oncology
University of California, San Francisco
San Francisco, California

# Following CML Patients on TKI Therapy

CBC/diff every 1-2 weeks for 6-8 weeks following TKI initiation to assess for significant cytopenias

Office visit after 4 weeks of treatment to assess tolerability

Office visit, CBC/diff, CMP, BCR::ABL1 quantitative PCR after three months of treatment and every three months thereafter

## EARLY TREATMENT RESPONSE MILESTONES
## CRITERIA FOR RESPONSE AND RELAPSE

| *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 | | |

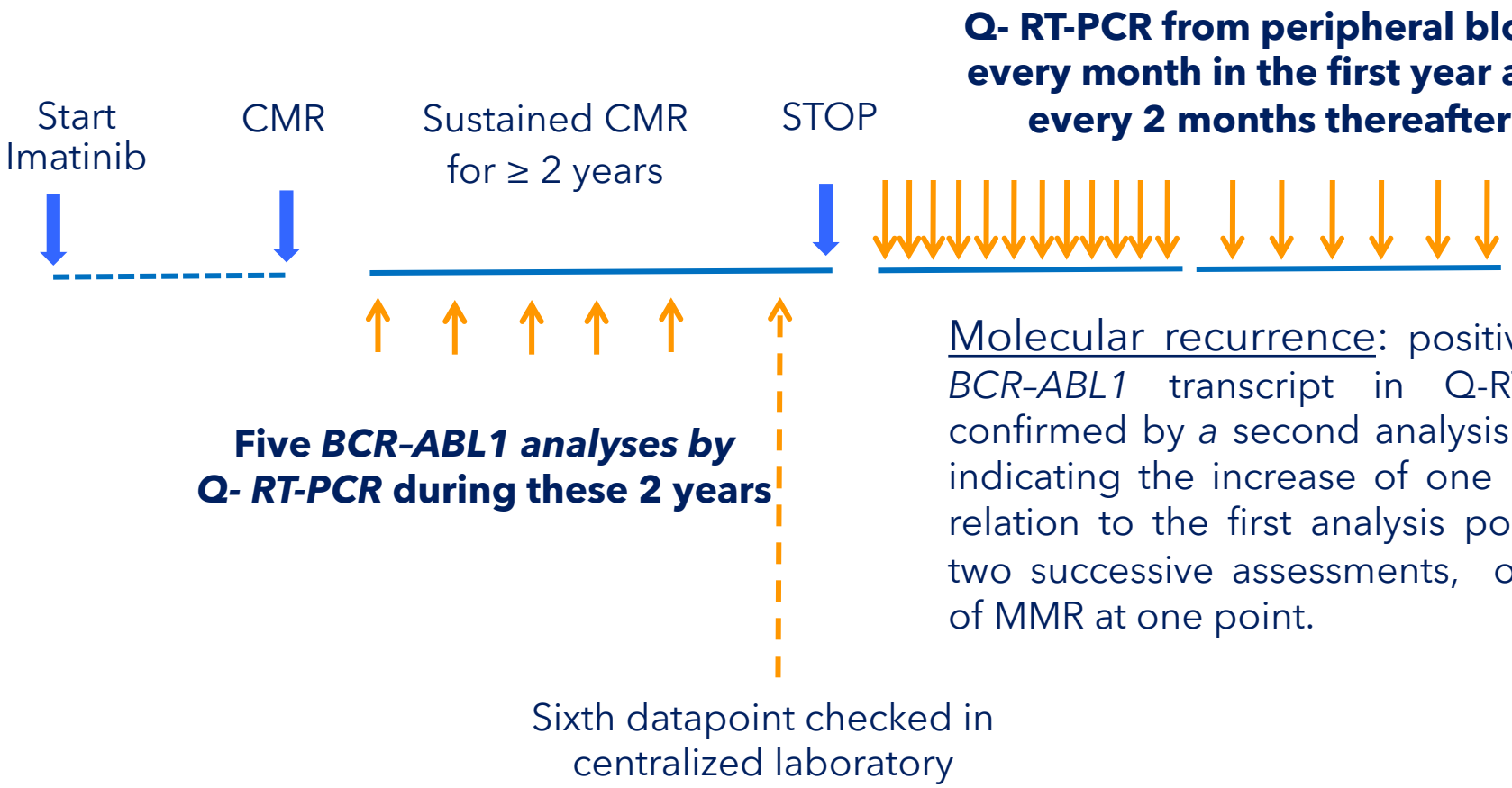
| COLOR | CONCERN | CLINICAL CONSIDERATIONS[r] | RECOMMENDATIONS[r,i] |
|---|---|---|---|
| RED | TKI-resistant disease[q] | • Evaluate patient adherence and drug interactions<br>• Consider *BCR::ABL1* kinase domain mutational analysis[s]<br>• Consider bone marrow cytogenetic analysis to assess additional 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<br>• Consider *BCR::ABL1* kinase domain mutational analysis[s] | Switch to alternate TKI (CML-5) or<br>Continue same TKI[o] |
| ORANGE **NEW** | Possible TKI resistance[q] | • Evaluate patient adherence and drug interactions<br>• Consider *BCR::ABL1* kinase domain mutational analysis[s]<br>• Consider bone marrow cytogenetic analysis to assess for CCyR at 12 mo | Consider switch to alternate TKI[p] (CML-5) or<br>Continue the same TKI if CCyR is achieved |
| LIGHT GREEN | TKI-sensitive disease | • Evaluate patient adherence and drug interactions<br>• If treatment goal is long-term survival: ≤1% optimal<br>• If treatment goal is treatment-free remission: ≤0.1% optimal | • If optimal: continue same TKI<br>• If not optimal: shared decision-making with patient[q,t] |
| GREEN | TKI-sensitive disease | • Evaluate patient adherence and drug interactions<br>• Monitor response (CML-G) | Continue same TKI[u] |

Footnotes on CML-3A

**Note: All recommendations are category 2A unless otherwise indicated.**

# Stop Imatinib (STIM) study design

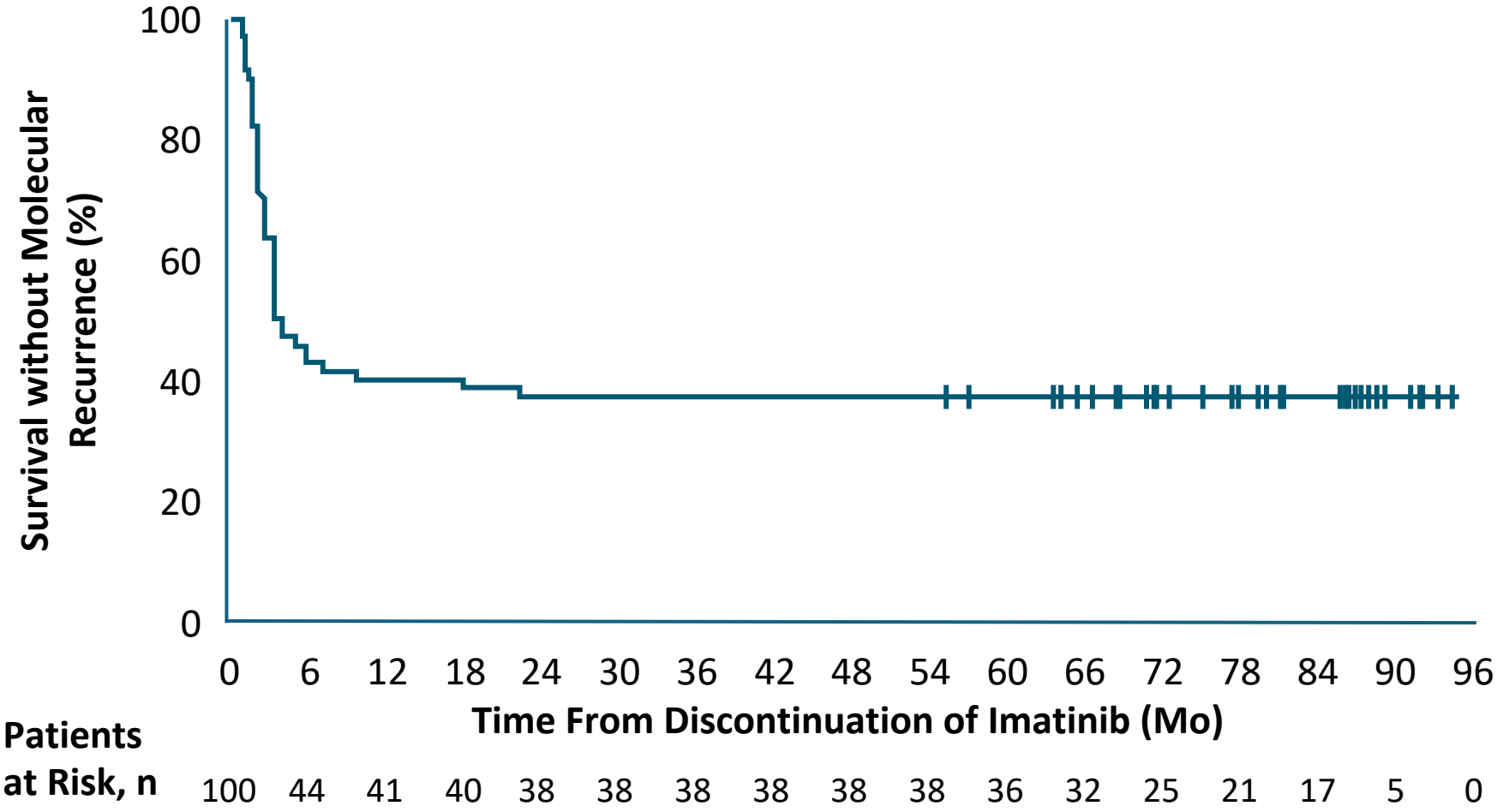
N=100




Molecular recurrence: positivity of *BCR–ABL1* transcript in Q-RT-PCR confirmed by *a* second analysis point indicating the increase of one log in relation to the first analysis point, at two successive assessments, or loss of MMR at one point.

*Mahon FX et al. The Lancet Oncology, 2010;11(11): 1029-1035.*

# Long-term Follow-up From Stop Imatinib (STIM) Trial in CP-CML: Survival Without Recurrence




Etienne. JCO. 2017;35:298.

Similar data have been obtained from numerous studies with other TKIs, using higher disease thresholds for stopping (e.g. MR4) and restarting (loss of MR3) treatment

# Data from Numerous TKI Discontinuation Trials: ~50 Percent Likelihood of Success

| Study | Treatment prior to discontinuation | No. of patients | Depth and duration of molecular response (MR) required for discontinuation | Trigger to resume TKI therapy | Median duration of follow-up | Treatment-free remission (TFR) rate |
|---|---|---|---|---|---|---|
| **STIM1**[167,168] | Imatinib ± interferon | 100 | MR5.0 for at least 2 years | Loss of MR5.0 | 77 months | 43% at 6 months; 38% at 60 months |
| **STIM2**[169] | Imatinib | 124 | MR5.0 for at least 2 years | Loss of MR5.0 | 12 months | 61% at 12 months |
| **TWISTER**[170] | Imatinib ± interferon | 40 | MR4.5 for at least 2 years | Loss of MR5.0 | 42 months | 47% at 24 months |
| **HOVON**[171] | Imatinib + cytarabine | 15 | MR4.5 for at least 2 years | Loss of MR4.5 | 36 months | 33% at 24 months |
| **A-STIM**[172] | Imatinib ± interferon | 80 | MR5.0 for at least 2 years | Loss of MMR | 31 months | 64% at 24 months; 61% at 36 months |
| **ISAV**[173] | Imatinib | 112 | CMR for at least 18 months | Loss of MMR | 22 months | 52% |
| **KIDS**[175] | Imatinib ± interferon | 90 | MR4.5 for at least 2 years | Loss of MMR | 27 months | 62% at 12 months; 58.5% at 24 months |
| **Stop 2G-TKI**[179] | Dasatinib/Nilotinib (first-line or second-line) | 60 | MR4.5 for at least 2 years | Loss of MMR | 47 months | 63% at 12 months; 53.6% at 48 months |
| **DADI**[174] | Dasatinib (second-line) | 63 | MR4.0 for at least 1 year | Loss of MR4.0 | 20 months | 49% at 6 months |
| **ENESTFreedom**[178] | Nilotinib (first-line) | 190 | MR4.5 for at least 1 year | Loss of MMR | 48 weeks | 52% |
| **ENESTop**[177] | Nilotinib (second-line) | 126 | MR4.5 for at least 1 year | Loss of MR4.0 or Loss of MMR | 48 weeks | 58% |
| **EuroSKI**[176] | Imatinib/Dasatinib/Nilotinib (first-line or second-line) | 755 | MR4.0 for at least 1 year | Loss of MMR | 27 months | 50% at 12 months |
| **DASFREE** | Dasatinib (first-line or second-line) | 84 | MR4.5 for at least 1 year | Loss of MMR | 18 months | 48% at 18 months |
| **LAST** | Imatinib/Dasatinib/Nilotinib /Bosutinib | 173 | MR4.0 for at least 2 years | Loss of MMR | 12 months | 66% at 12 months |

## DISCONTINUATION OF TKI THERAPY

### General Considerations

- 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 patients who give consent after a thorough discussion of the potential risks and benefits.
- Consultation with an NCCN Panel Member or center of expertise is recommended in the following circumstances:
  - Any significant adverse event is believed to be related to treatment discontinuation.
  - There is progression to AP-CML or BP-CML at any time.
  - MMR is not regained after 3 months following treatment reinitiation.
- Outside of a clinical trial, discontinuation of TKI therapy should be considered only if ***all*** of the criteria included in the list below are met.

### Criteria for TKI Discontinuation

- Age ≥18 years.
- CP-CML. No prior history of AP-CML or BP-CML.
- On approved TKI therapy for at least 3 years.[1,2]
- Prior evidence of quantifiable *BCR::ABL1* transcript.
- Stable molecular response (MR4; *BCR::ABL1* ≤0.01% IS) for ≥2 years, as documented on at least 4 tests, performed at least 3 months apart.[2]
- 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.
- Molecular monitoring every 1–2 months 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, then every 3 months thereafter is recommended indefinitely for patients who have reinitiated TKI therapy after a loss of MMR. If MMR is not achieved after 3 months of TKI resumption, *BCR::ABL1* kinase domain mutation testing should be performed, and monthly molecular monitoring should be continued for another 6 months.

[1] The feasibility of TFR following discontinuation of TKIs other than dasatinib, imatinib, or nilotinib has not yet been evaluated in clinical studies. It is reasonable to assume that the likelihood of TFR following discontinuation would be similar irrespective of TKI in patients who have achieved and maintained DMR (MR4.0; ≤0.01% *BCR::ABL1* IS) for ≥2 years, based on the extrapolation of findings from the studies that have evaluated TFR following discontinuation of imatinib, dasatinib, or nilotinib.
[2] Data from the EURO-SKI study suggest that MR4.0 (*BCR::ABL1* ≤0.01% IS) for ≥3 years was the most significant predictor for successful discontinuation of imatinib. Total duration of imatinib therapy for at least 6 years was also predictive of successful discontinuation (Saussele S, et al. Lancet Oncol 2018;19:747-757).

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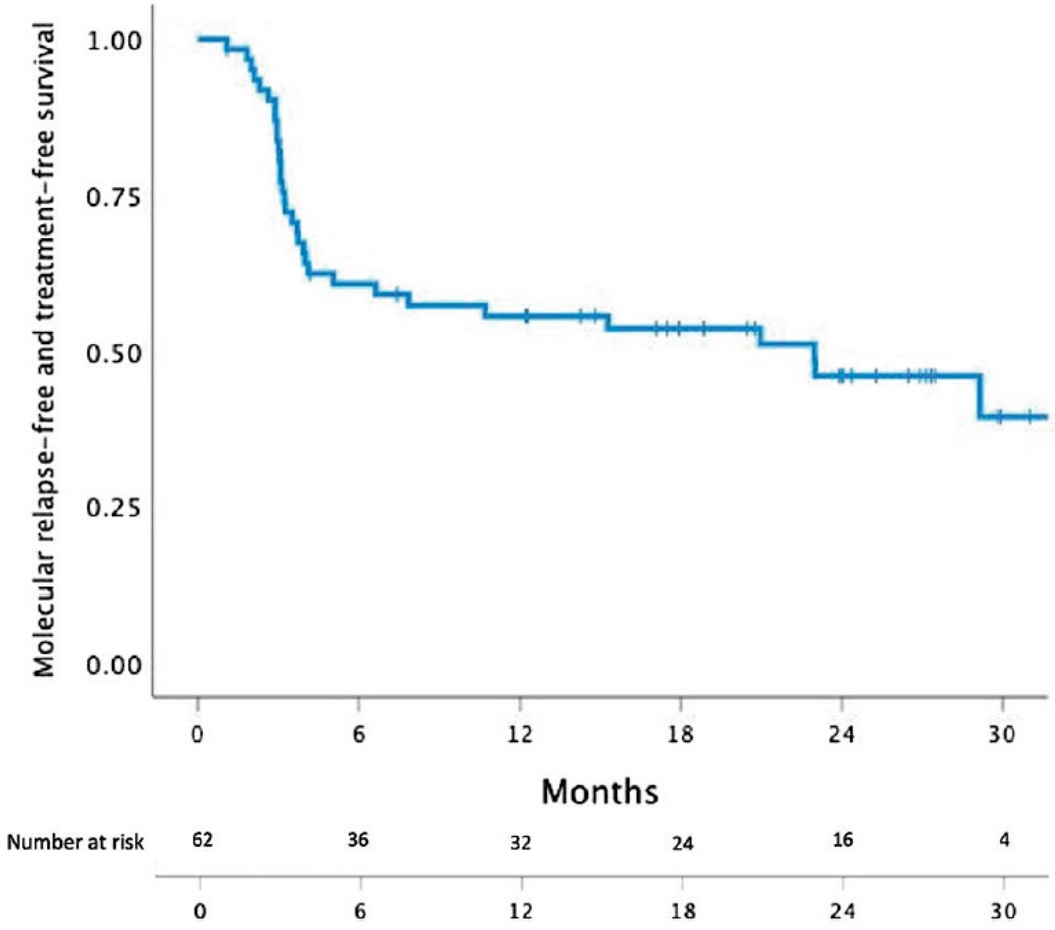
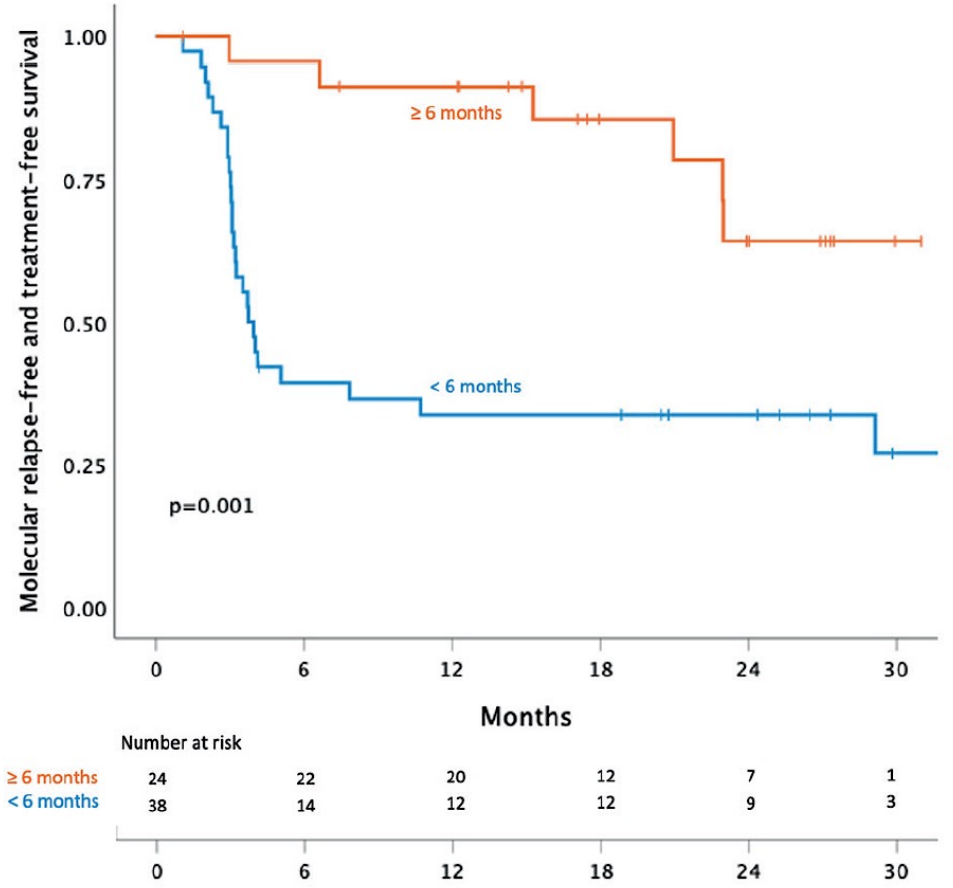
**Note: All recommendations are category 2A unless otherwise indicated.**

# Can TFR Be Successful the Second Time Around?




**Treatment-free remission (TFR) after second tyrosine kinase inhibitor (TKI) discontinuation.** TFR probability at 6, 12 and 24 months was 61, 56 and 46% respectively.




**Treatment-free remission (TFR) after second tyrosine kinase inhibitor (TKI) discontinuation by first TFR duration.** Patients with a second discontinuation divided by whether the time to molecular relapse after the first discontinuation attempt was more or less than 6 months. The log rank test was used when comparing groups.

Flygt et al, Leukemia 2024

# Common Reasons for Attempting Treatment-free Remission (TFR)

Bothersome side effects

Financial toxicity (individual, societal)

Concern about known and currently unknown late toxicities

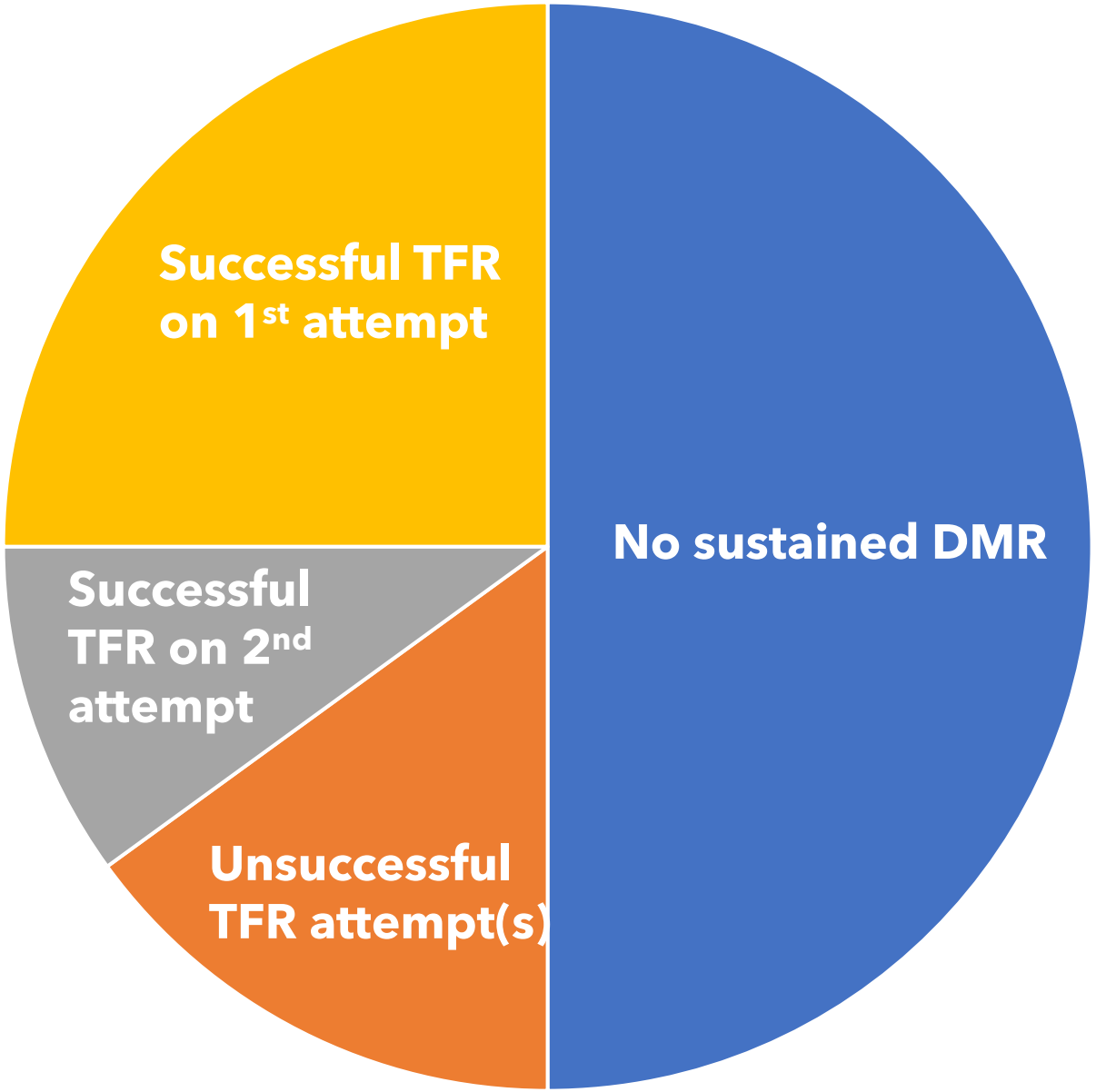
Preference to avoid medications if possible

# Known Risks of Attempting TFR

- TKI withdrawal syndrome (~25%)
  - New musculoskeletal pain
- Follow-up to date is less than 10 years
- More frequent testing, which can provoke anxiety
- Risk of progressive disease (anecdotal, appears <1%)
  - Has been observed during TFR period as well as months or years after resuming TKI

*Attempting TFR should be driven by the patient after a thorough discussion of the risks/benefits*

# At least 65-70% of CML Patients Will Require Lifelong Treatment: Maximizing QoL Assumes Great Importance in Responding Patients




Maximizing QoL Assumes Greater Importance with Need for Prolonged Treatment.

Reduced TKI Doses can be Better Tolerated in Some Instances

# Case 1

- A 41 year-old woman who works as a PICC line nurse was incidentally noted to have thrombocytosis of 509K in February 2012 that had persisted for over six months. Prior CBC performed in 2023 was unremarkable. She was referred to a hematologist who ordered a BCR::ABL1 quantitative PCR that was grossly positive and bone marrow biopsy/aspiration confirmed a diagnosis of chronic phase CML. Her PMH includes hypertension. She initiated dasatinib 100 mg which was associated with generalized skin hypopigmentation but otherwise well-tolerated and transferred her care to UCSF. After 3 months, her BCR::ABL1 transcript was undetectable and remained undetectable on subsequent tests. As her BP had declined, she discontinued her anti-hypertensive.

- In December 2014, she elected to enroll in a TKI discontinuation study that required a minimum of 2 years of TKI therapy and one year of persistent MR4.5. She Stopped dasatinib, and her skin tone returned to normal. Her BP rose above the normal range requiring resumption of antihypertensive medication. She remains in a deep molecular remission off TKI as of April 2025.

# Case 2

- A 34 year-old woman who works as a Labor & Delivery nurse was noted to have mild leukocytosis in April 2011 while pregnant and in the first trimester. Leukocytosis persisted following an uneventful delivery in November 2011. PMH includes hypercholesterolemia and pyelonephritis s/p ureteral stent placement. She was referred to a hematologist in February 2012. At that time her WBC was 19.2K and a BCR::ABL1 test was grossly positive. Bone marrow biopsy and aspiration confirmed chronic phase CML. She initiated dasatinib 100 mg daily, on which she had substantial musculoskeletal discomfort and she transferred care to UCSF. Her dose was reduced to 50 mg in September 2012 but her pain persisted and her dasatinib dose was further reduced to 20 mg daily in December 2012.

- She first achieved MMR in August 2012 and persistent MR4.5 in November 2012. She enrolled in a TKI discontinuation study in December 2015 but lost MMR in August 2016 and resumed dasatinib 20 mg, on which she recaptured MR4.5. She elected to attempt TFR again in August 2021 and has continued to have no detectable CML off treatment as of March 2025.

# Roundtable Discussion

RTP
RESEARCH
TO PRACTICE

# Agenda

**Introduction:** Chronic Myeloid Leukemia (CML) as a Model for Targeted Treatment

**Module 1:** Biology of CML; Role of First- and Second-Generation Tyrosine Kinase Inhibitors (TKIs) as Initial Treatment for Chronic-Phase (CP)-CML

**Module 2:** Role of Asciminib for Newly Diagnosed CP-CML

**Module 3:** Feasibility of TKI Discontinuation for Patients with Sustained Response to Treatment

**Module 4: Management of CP-CML After Failure of Initial Therapy**

# Clinical Scenario

**A patient with CP-CML who has been receiving imatinib for several years but is now experiencing progression with T315I-mutant disease and is about to start treatment with asciminib**

# Management of CP-CML after Failure of Initial Therapy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**New York, NY**




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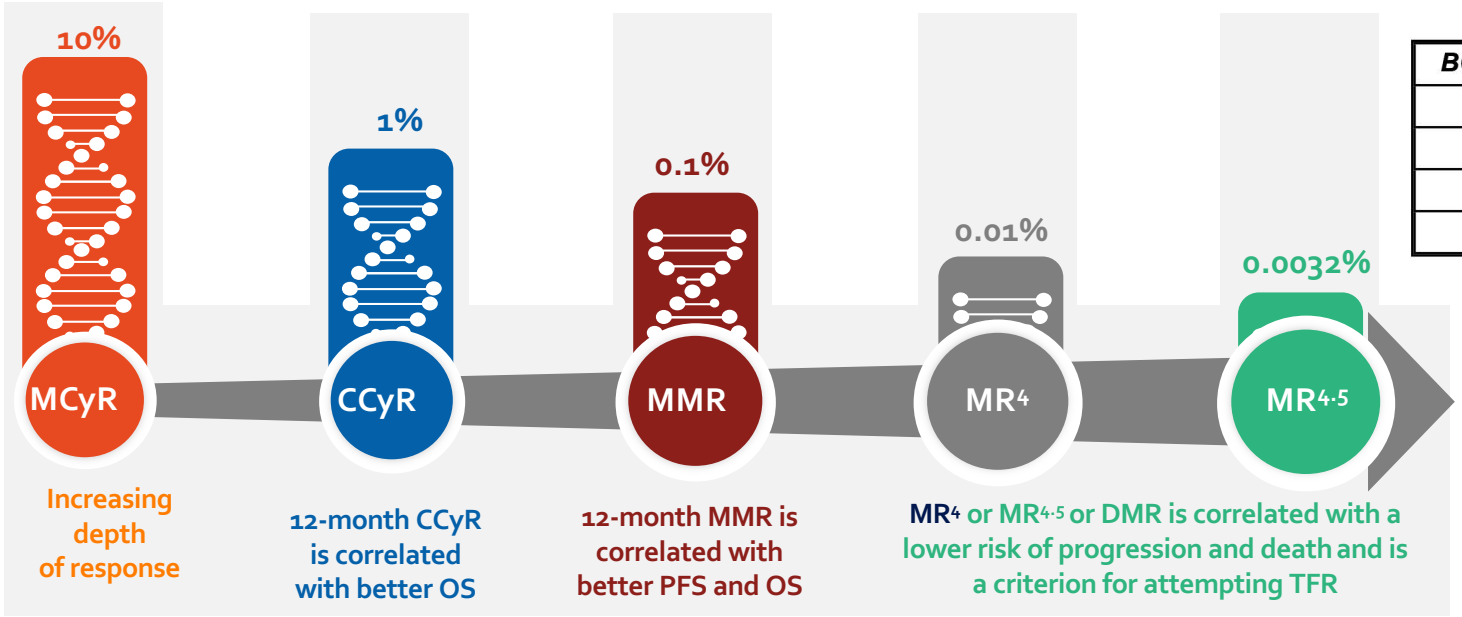
# How Can Therapy Fail the CP-CML Patient?

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




| *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 | | |

NCCN

**'traffic light' guide**

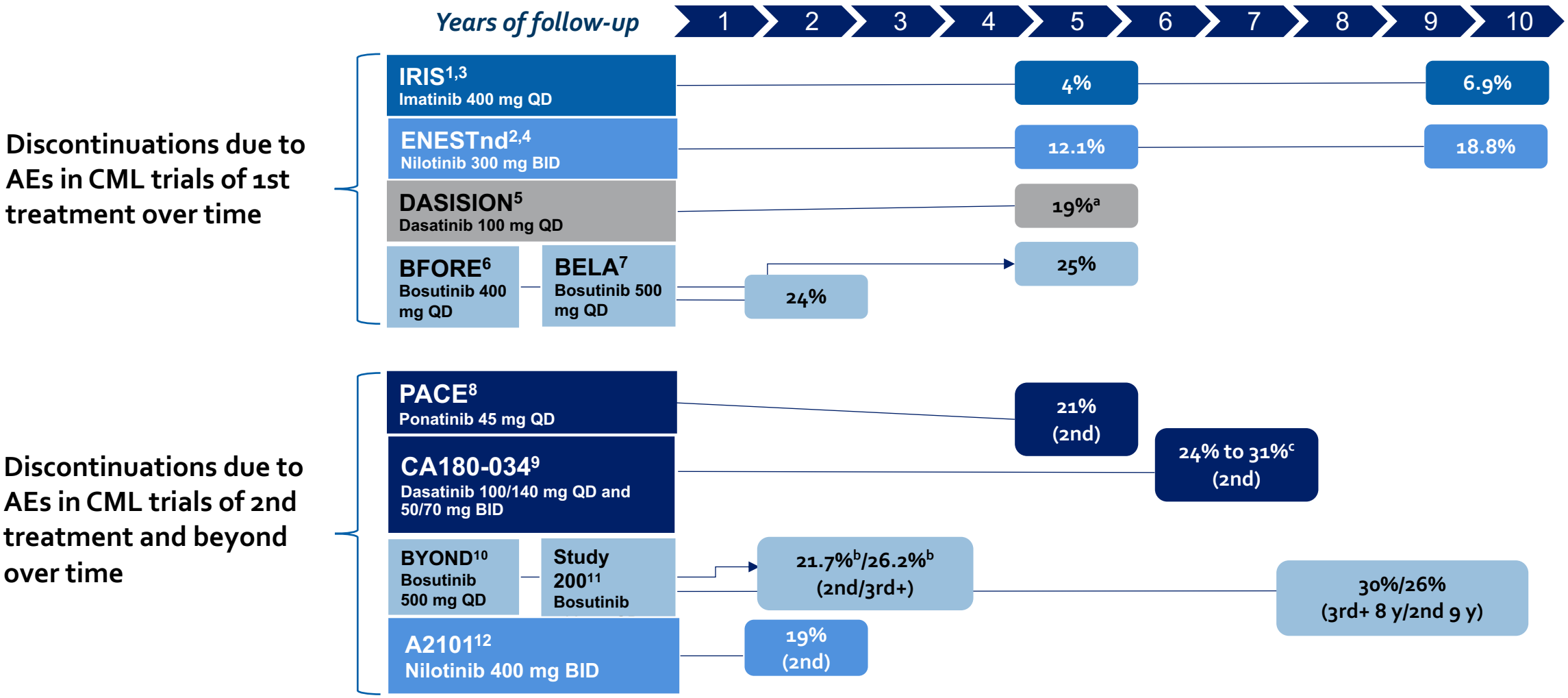
NCCN Guidelines®. Chronic Myeloid Leukemia — V.3.2025.

# NCCN Treatment Milestones; Mutation Guidance

| COLOR | CONCERN | CLINICAL CONSIDERATIONS[r] | RECOMMENDATIONS[r,i] |
|---|---|---|---|
| RED | TKI-resistant disease[q] | • Evaluate patient adherence and drug interactions<br>• Consider *BCR::ABL1* kinase domain mutational analysis[s]<br>• 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<br>• Consider *BCR::ABL1* kinase domain mutational analysis[s] | Switch to alternate TKI (CML-5) or<br>Continue same TKI[o] |
| ORANGE **NEW** | Possible TKI resistance[q] | • Evaluate patient adherence and drug interactions<br>• Consider *BCR::ABL1* kinase domain mutational analysis[s]<br>• Consider bone marrow cytogenetic analysis to assess for CCyR at 12 mo | Consider switch to alternate TKI[p] (CML-5) or<br>Continue the same TKI if CCyR is achieved |
| LIGHT GREEN | TKI-sensitive disease | • Evaluate patient adherence and drug interactions<br>• If treatment goal is long-term survival: ≤1% optimal<br>• If treatment goal is treatment-free remission: ≤0.1% optimal | • If optimal: continue same TKI<br>• If not optimal: shared decision-making with patient[q,t] |
| GREEN | TKI-sensitive disease | • Evaluate patient adherence and drug interactions<br>• Monitor response (CML-G) | Continue same TKI[u] |

| 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] |

# TKI intolerance remains a primary reason for treatment discontinuation



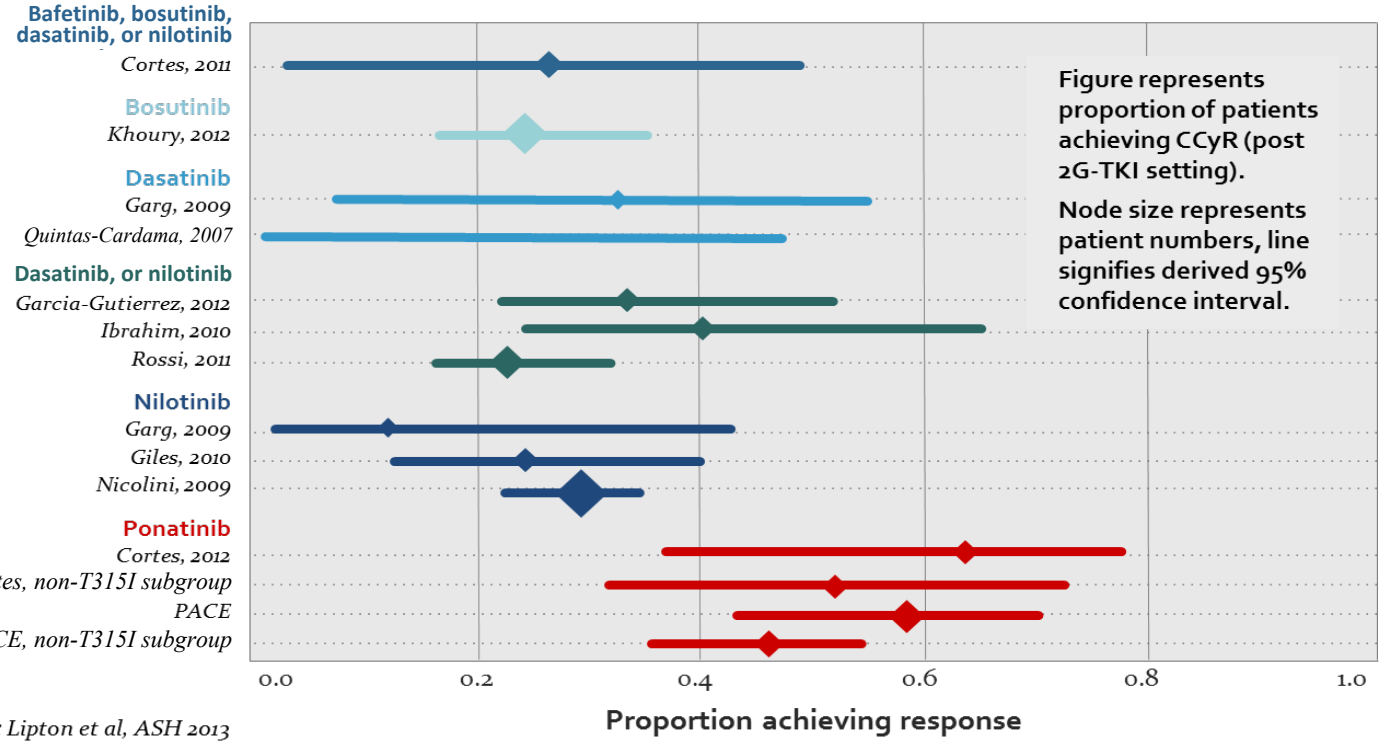

1. Hochhaus A, et al. *N Engl J Med*. 2017;376: 917-927. 2. Kantarjian HM, et al. *Leukemia*. 2021;35:440-453. 3. Druker BJ, et al. *N Engl J Med*. 2006;355:2408-2417. 4. Hochhaus A, et al. *Leukemia.* 2016;30:1044-1054. 5. Cortes JE, et al. *J Clin Oncol.* 2016;34:2333-2340. 6. Brümmendorf TH, et al. *Blood.* 202m 0;136(suppl 1). Abstract 46. 7. Brümmendorf TH, et al. *Br J Haematol.* 2015;168:69-81. 8. Cortes JE, et al. *Blood.* 2018;132:393-404. 9. Shah NP, et al. *Am J Hematol*. 2016;91:861-874. 10. Hochhaus A, et al. *Leukemia.* 2020;34:2125-2137. 11. Cortes JE, et al. Presented at: EHA25 Virtual; June 11-21, 2020. Abstract EP766. 12. Kantarjian HM, et al. *Blood.* 2011;117(4):1141-1145.

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

***Point 1: 2G TKI post imatinib: Response is similar***

# Choosing Salvage

***Point 2: 'Recycling 2G TKIs'- Switch to 3rd gen (here Ponatinib) improved CCyR***




*Source: Lipton et al, ASH 2013*

*Includes imatinib-intolerant patients. NR, not reported.

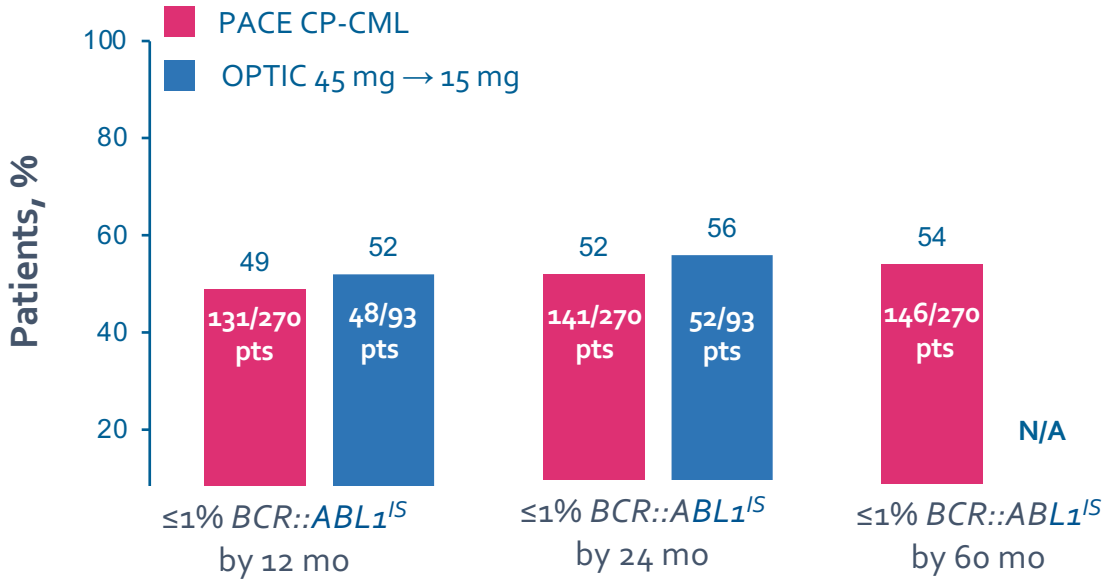

1. Dasatinib. Official prescribing information
2. Shah NP, et al. J Clin Oncol. 2010;28:15s (abstract 6512)
3. Shah NP, et al. Blood. 2014;123:2317-24
4. Kantarjian HM et al. Blood. 2011;117:1141-1145
5. Giles FJ, et al. Leukemia. 2013;27:107-12
6. Gambacorti-Passerini C, et al. Am J Hematol. 2014

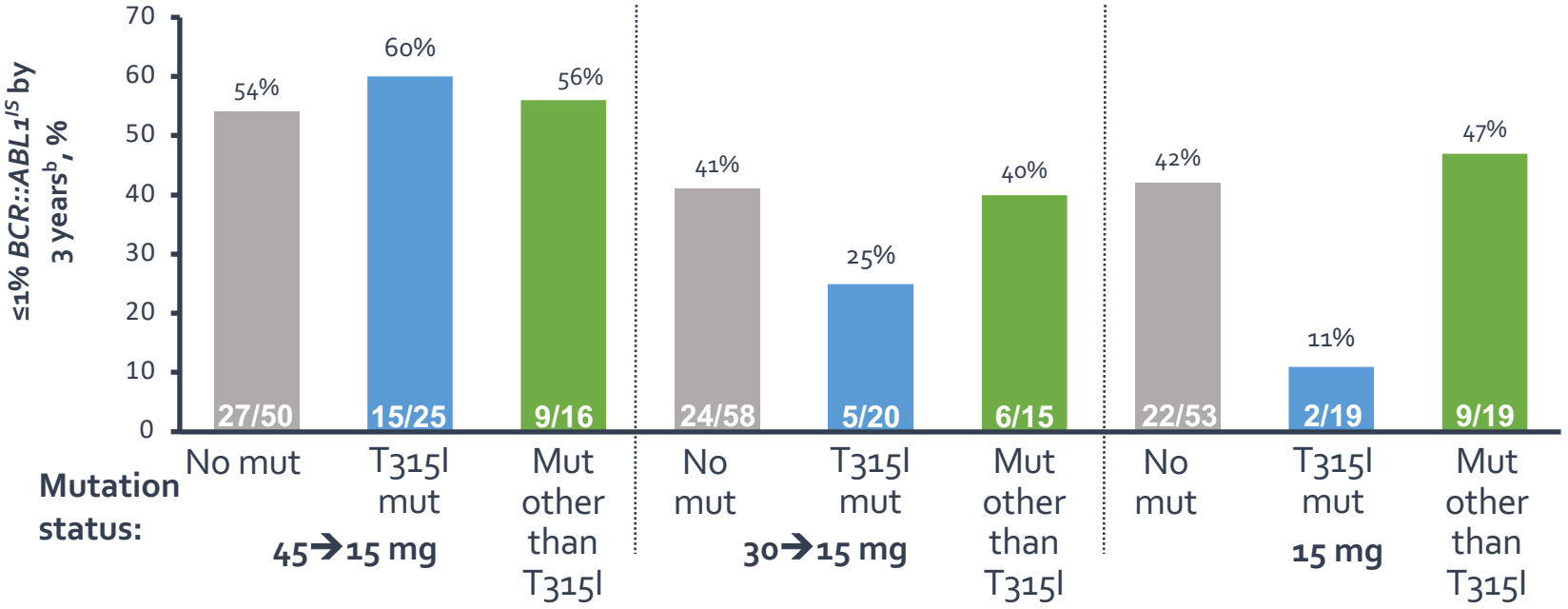
Lipton J, et al. ASH 2013. Abstract 4010.

# Ponatinib data: PACE, OPTIC

| MMR rate ≤0.1% *BCR::ABL1*$^{IS}$ | PACE (all patients) | OPTIC (all patients) |
|---|---|---|
| 12mo | 28 | 20 |
| 24mo | 34 | 34 |
| 6omo | 37 | n/a |

## Overall Efficacy Outcomes in OPTIC and PACE



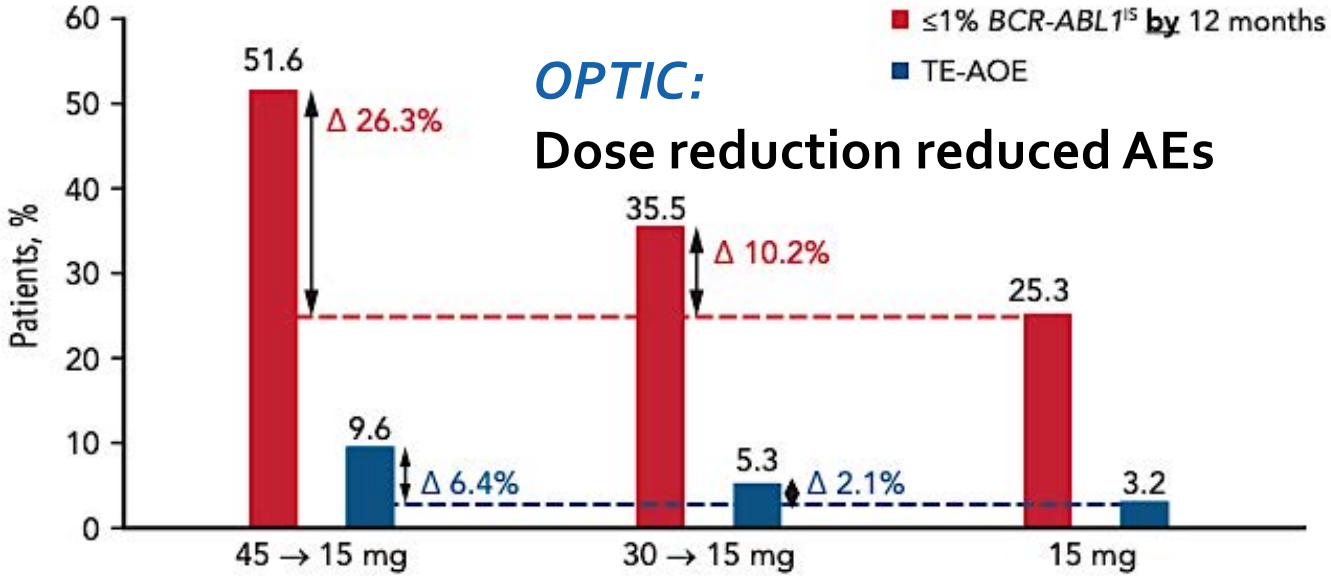

## OPTIC: ≤1% *BCR::ABL1*$^{IS}$ Response Rate by Mutation Status

☞ 45mg remains appropriate start dose, esp for T315I; same for other cases?

# Ponatinib: PACE, OPTIC

| PACE | 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) |

| PACE study AOEs | 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 |




***OPTIC:***

**Dose reduction reduced AEs**

***Unmet need:***

**novel, T315I active BCR::ABL inhibitors with greater safety margin…**

Kantarjian HM et al, *Am J Hematology*, in press; Deininger MN et al, ASH 2021; Cortes J, et al. Blood (2021) 138 (21): 2042–50.

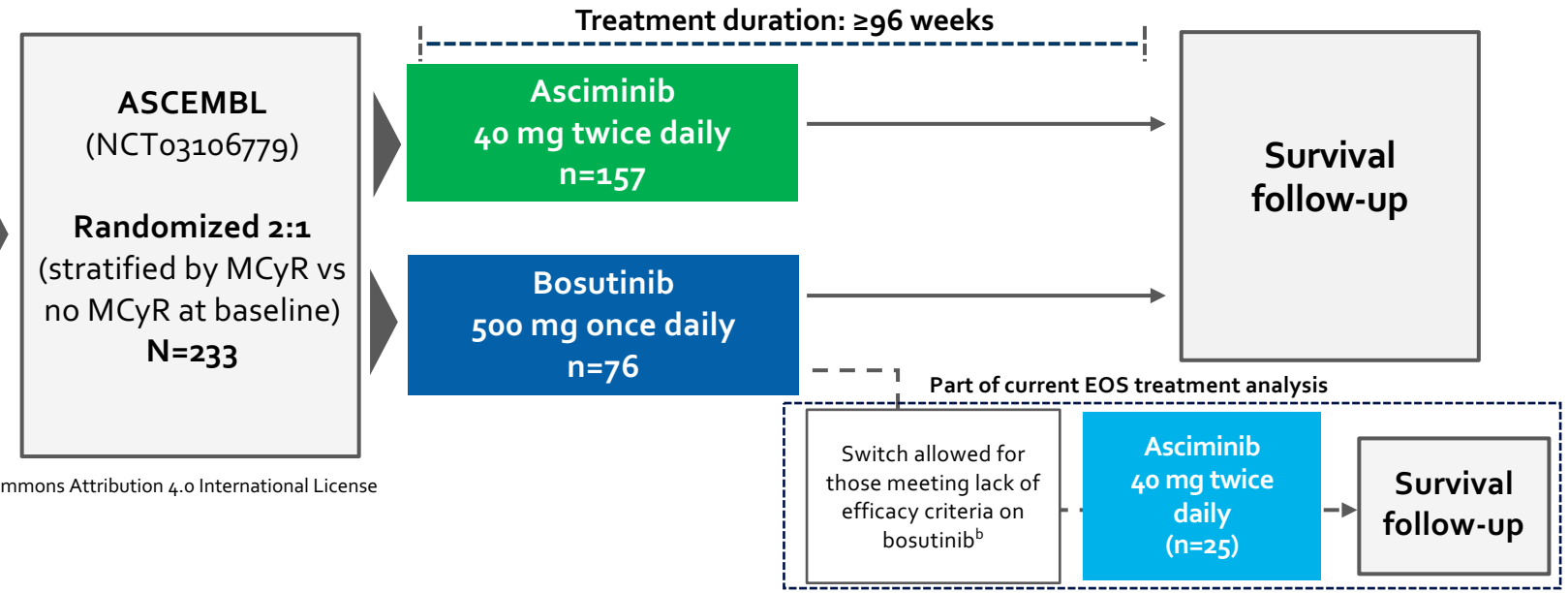
# Phase III ASCEMBL, End of Study (EOS): a phase III trial of asciminib vs bosutinib in patients with CML-CP previously treated with ≥2 TKIs[1-5]

Réa D, et al. Oral presentation at: 2022 ASCO Annual Meeting: June 3-7, 2022; Chicago, IL & online. Abstract 7004.
Réa D, et al. Oral presentation at: EHA2022 Hybrid Congress; June 9-12, 2022; Vienna, Austria, & online. Abstract S155.
Hochhaus A, et al. *Leukemia*. 2023;37(3):617-626.

- Data cutoff for EOS treatment analysis: March 22, 2023
- Median duration of follow-up: 3.7 years (16.8 months of additional follow-up since the week 96 analysis)
- EOS treatment: ≤96 weeks after the last patient received their first dose or ≤48 weeks after the last patient switched to asciminib, whichever was longer, unless patients had discontinued treatment earlier

**Key inclusion criteria**

- Adults with CML-CP, previously treated with ≥2 TKIs
- Failure[a] with or intolerance of most recent TKI
- Patients with intolerance of most recent TKI must have *BCR::ABL1*$^{IS}$ >0.1% at screening
- No T315I or V299L mutations

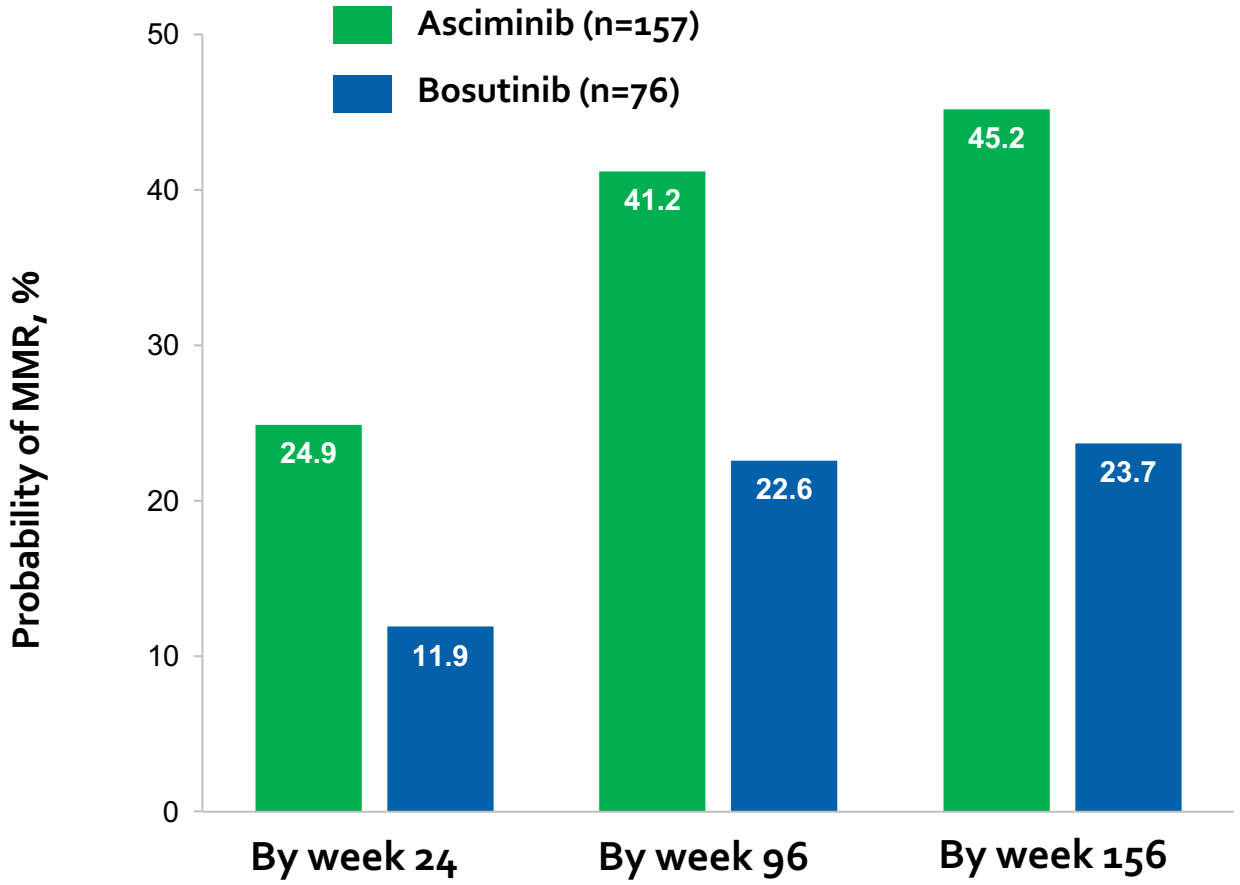





CML-CP, chronic myeloid leukemia in chronic phase; ELN, European LeukemiaNet; EOS, end of study; IS, International Scale; MCyR, major cytogenetic response; MMR, major molecular response (*BCR::ABL1*$^{IS}$ ≤0.1%); TKI, tyrosine kinase inhibitor.
[a] This trial was recently completed, and secondary analyses presented here are based on data collected after all randomized patients had completed their EOS treatment visit or discontinued earlier. [b] Must meet lack of efficacy criteria based on 2013 ELN recommendations for patients treated with 1 prior TKI.
[c] Patients who discontinue bosutinib treatment due to intolerance or any reason other than lack of efficacy are not allowed to switch to asciminib.

1. Réa D, et al. *Blood.* 2021;138(21):2031-2041. 2. Réa D, et al. Oral presentation at: 2022 ASCO Annual Meeting; June 3-7, 2022; Chicago, IL, and virtual. Abstract 7004. 3. Réa D, et al. Oral presentation at: EHA 2022; June 9-17, 2022; Vienna, Austria. Abstract S155. 4. Hochhaus A, et al. *Leukemia*. 2023;37:617-626. 5. Mauro MJ, et al. Presented at 65th ASH Annual Meeting & Exposition; December 9-12, 2023; San Diego, California & virtual. Abstract 4536.

# ASCEMBL (EOS):
# Cumulative incidence of MMR by weeks 24, 96, and 156[1-4,a,b]




- MMR was achieved rapidly and remained consistently higher with **asciminib** than with **bosutinib** by week 156; the difference in cumulative incidence of MMR between the treatment arms became evident by week 12[1-4]

**Durability of MMR**

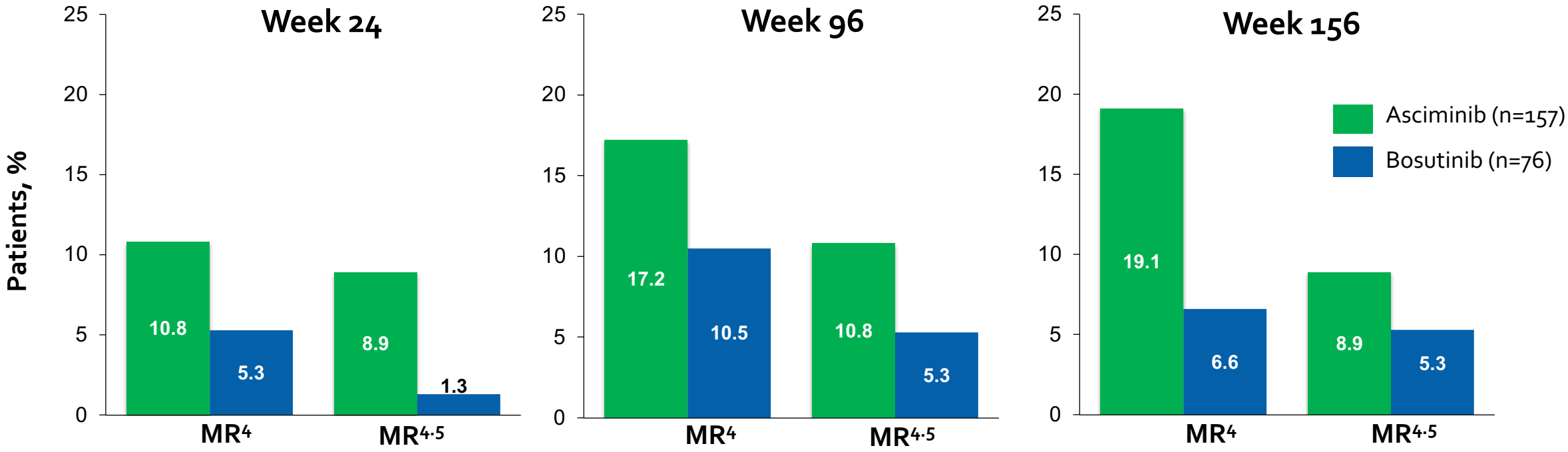
- The probability (95% CI) of maintaining MMR for ≥120 weeks was **97.0%** (88.6%-99.2%) with **asciminib** and **92.9%** (59.1%-99.0%) with **bosutinib,** and response rates were highly durable[4]

CI, confidence interval; EOS, end of study; MMR, major molecular response (*BCR::ABL1*[IS] ≤0.1%).

[a] Non-responders were censored at their last molecular assessment date. [b] Discontinuation from treatment for any reason without prior achievement of MMR is considered a competing event.

1. Rea D, et al. Oral presentation at: 2022 ASCO Annual Meeting; June 3-7, 2022; Chicago, IL, and virtual. Abstract 7004. 2. Rea D, et al. Oral presentation at: EHA 2022; June 9-17, 2022; Vienna, Austria. Abstract S155. 3. Hochhaus A, et al. *Leukemia*. 2023;37:617-626.4. Mauro MJ, et al. Presented at 65th ASH Annual Meeting & Exposition; December 9-12, 2023; San Diego, California & virtual. Abstract 4536.

# ASCEMBL (EOS):
## MR$^4$ and MR$^{4.5}$ rates at weeks 24, 96, and 156[1-4]



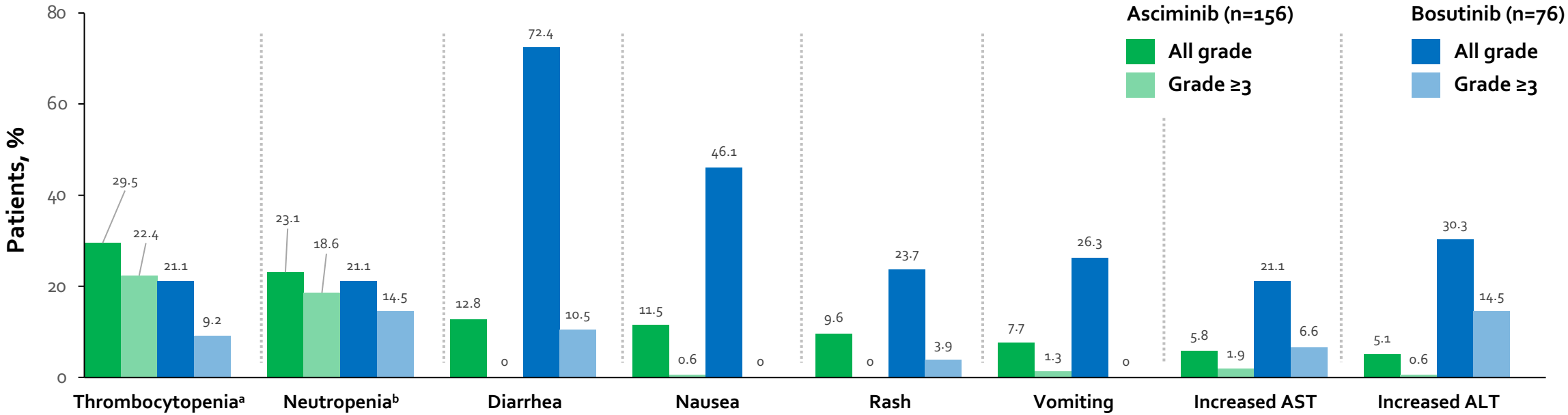

- At week 156, deep molecular response rates continued to be higher with **asciminib** than **bosutinib**[4]

Rea D, et al. Presented at European Hematology Association 2022 Congress. Abstract S155. Reprinted with permission by the author.

IS, International Scale; MR$^4$, *BCR::ABL1*$^{IS}$ ≤0.01%; MR$^{4.5}$, *BCR::ABL1*$^{IS}$ ≤0.0032%.

1. Rea D, et al. Oral presentation at: ASCO 2022; June 3-7, 2022. Chicago, IL and virtual. Abstract 7004. 2. Rea D, et al. Oral presentation at: EHA 2022; June 9-17, 2022. Vienna, Austria and virtual. Abstract S155. 3. Hochhaus A, et al. *Leukemia*. 2023;37:617-626. 4. Mauro MJ, et al. Presented at 65th ASH Annual Meeting & Exposition; December 9-12, 2023; San Diego, California & virtual. Abstract 4536.

# ASCEMBL (EOS):
# Most frequent AEs by the end of study treatment cutoff (in ≥20% of patients in any treatment arm)




Mauro MJ, et al. Presented at the 65th American Society of Hematology Annual Meeting & Exposition 2023. Abstract 4536. Reprinted with permission by the author.

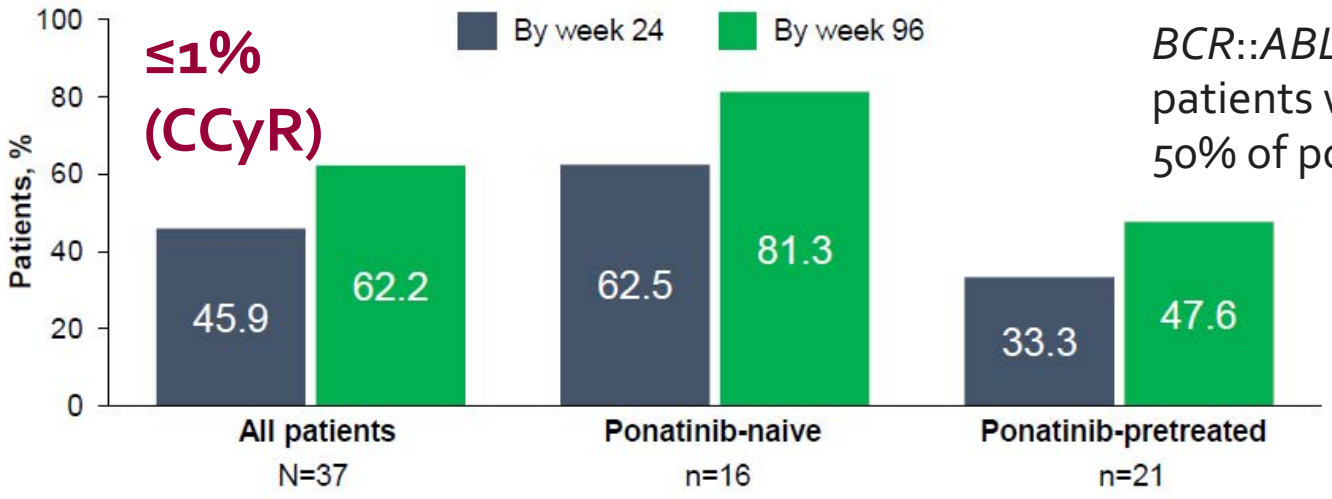
- The safety and tolerability of **asciminib** continued to be favorable and better than that of **bosutinib** with longer follow-up and duration of exposure[1-3]
- The most frequently reported grade ≥3 AEs with **asciminib** were the same by EOS as by week 96 and included thrombocytopenia and neutropenia[1-3]

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

[a] Includes thrombocytopenia and platelet count decreased. [b] Includes neutropenia and neutrophil count decreased.

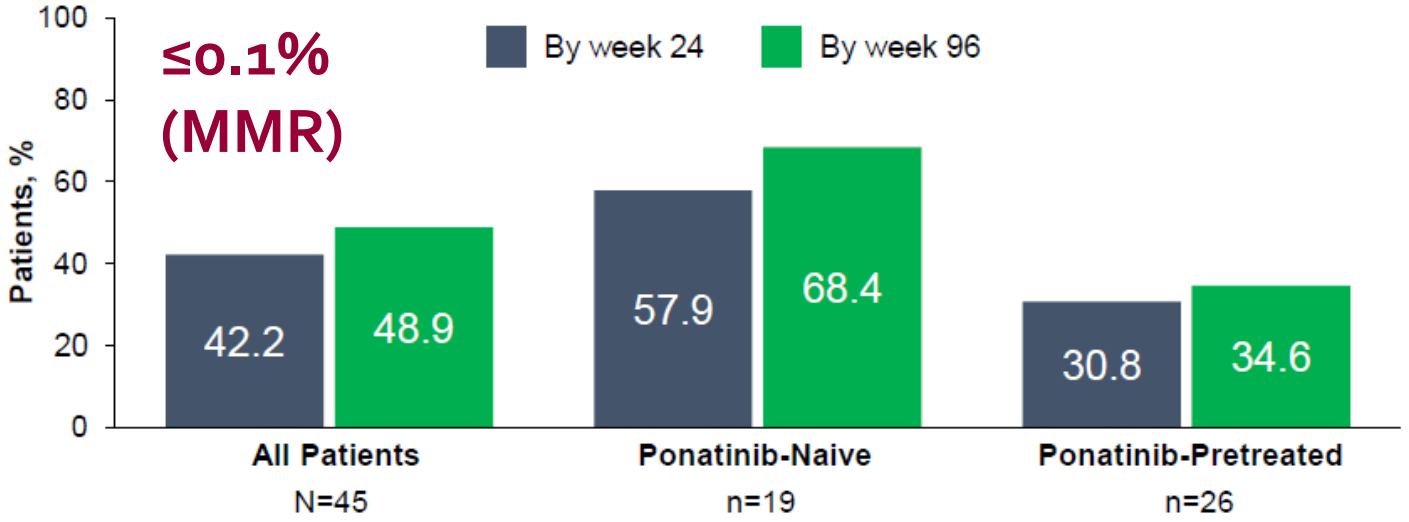
1. Mauro MJ, et al. Presented at 65th ASH Annual Meeting & Exposition; December 9-12, 2023; San Diego, California & virtual. Abstract 4535. 2. Rea D, et al. *Blood*. 2021;138:2031-3041. 3. Hochhaus A, et al. *Leukemia*. 2023;37:617-626.

# Asciminib X2101 T315I Cohort: Cumulative *BCR*::*ABL1*$^{IS}$ ≤1%, ≤0.1%




*BCR*::*ABL1*$^{IS}$ ≤1% was achieved by a high proportion (62.2%) of patients without this response at baseline (n=37), including almost 50% of ponatinib-pretreated patients

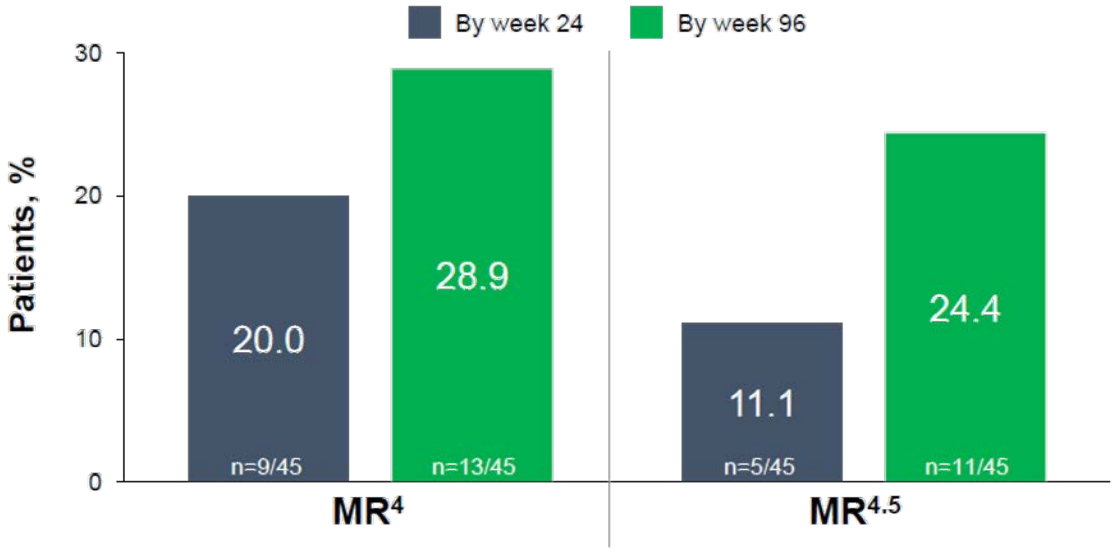
- 45 of 48 patients were evaluable for MMR / DMR; 3 were excluded for *BCR*::*ABL1* atypical/unknown transcripts
- Almost half of patients (22/45 [48.9%]) achieved MMR by week 96;responses were durable regardless of prior ponatinib treatment
- 19/22 patients maintained MMR or improved to a deeper level of response up to the cutoff date




The KM–estimated **probability of maintaining MMR for ≥96 weeks** was:

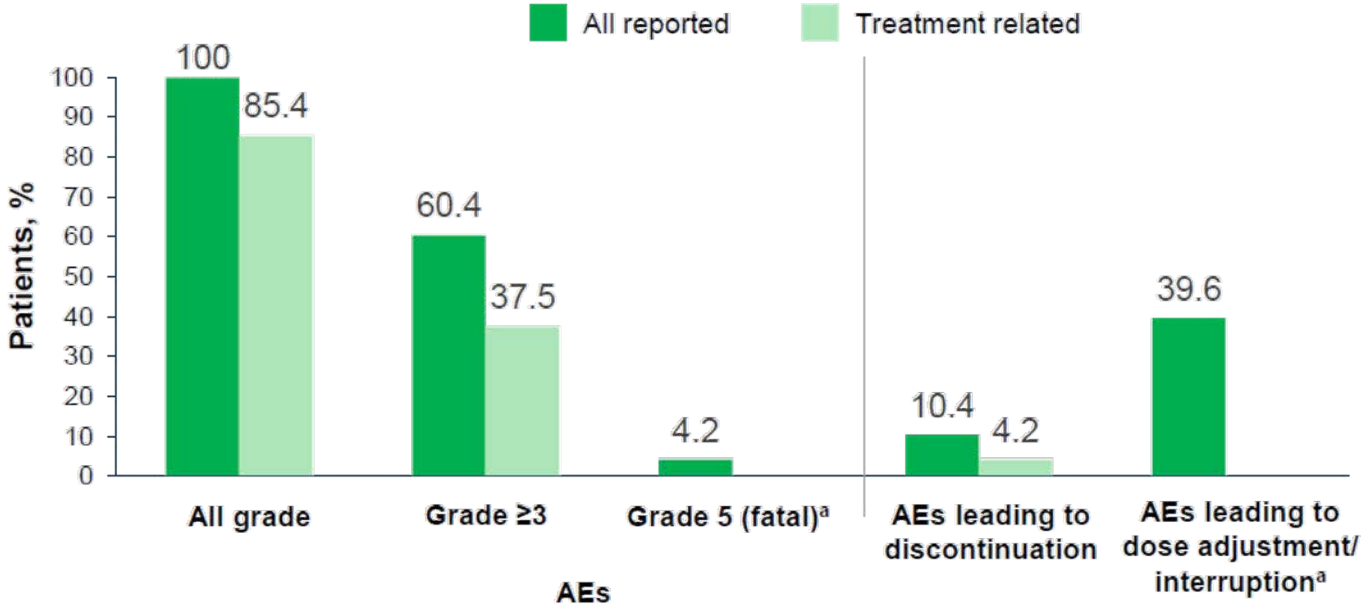
- **84%** (95% CI, 68.1%-100.0%) in **all patients**
- **91%**(95% CI, 73.9%-100.0%) in **ponatinib-naive patients**
- **78%** (95% CI, 50.6%-100.0%) in **ponatinib-pretreated patients**

# Asciminib X2101 T315I Cohort: Deep Molecular Response, Overall AEs




>50% of patients who achieved MMR improved to a deeper molecular response level ($MR^4$ or $MR^{4.5}$), with most achieving deeper responses by week 60

- Even after >2 years of median exposure, asciminib maintained a favorable safety/tolerability profile
  - After ≈9 months of added exposure, there was <5% difference in incidences of AEs compared to the previous cutoff
- AEs leading to discontinuation included COVID-19 pneumonia (grade 5 with fatal outcome) in 2 patients and pancytopenia (grade 4), thrombocytosis (grade 2), and lipase increased (grade 3) in 1 patient each



# Case: Resistant/Intolerant CML

- 43yo pediatric RN diagnosed with CML in chronic phase, 2014 (Sokal high, 1.28, and Hasford intermediate, 945.9, at diagnosis)
- Initial therapy with **Dasatinib 100 mg** with good early molecular (EMR) then major molecular response (MMR)
- Loss of MMR 2-2.5y into therapy; found to have T315I mutation
- Seen at MSKCC, saw cardio-oncology for evaluation prior to therapy change; familial hypercholesterolemia only noted)
- Fit, bodybuilder, no  history of hypertension or other CV disease

# Case: Resistant/Intolerant CML

- Moved to **30 mg ponatinib**; improvement and stable for a prolonged period of time with ongoing molecular response (>MMR; best response 10/17 0.0264% IS)
- Unprovoked increase in LFTs prompting hepatology evaluation, drug hold, steroid therapy for drug induced liver injury
- Rechallenged with lower dose ponatinib (15 mg) with continued low dose steroid; persistent LFT rise and CML proliferation (loss of CCyR)
- Stopped ponatinib on 2/16/19; significant relapse with PCR 2/19 20.4% IS

# Case: Resistant/Intolerant CML

- Enrolled on phase I study with **ABL001 200mg BID**, initiated therapy 2/22/2019
- PCR trajectory:

| start | 1mo | 2mo | 3mo | 4mo | 5mo | 6mo | 7mo |
|---|---|---|---|---|---|---|---|
| 20.4% | 0.96% | 0.14% | 0.073% | 0.041% | 0.023% | 0.010% | 0.006% |

- Deep MR with fluctuation until Jan 2022; since then, all values <0.01%
- No adverse events; worked in nursing field through pandemic
- Transitioned to commercial drug supply at end of study
- Deep MR (<0.01%) since Jan 2020

# What have we learned from PON and ASC trials? How are these agents positioned?

## PONATINIB

### PACE:

Efficacy in MDR CML

Efficacy in T315I

AOEs significant, dose dependent, stable over time, lag time (persistent)

### OPTIC:

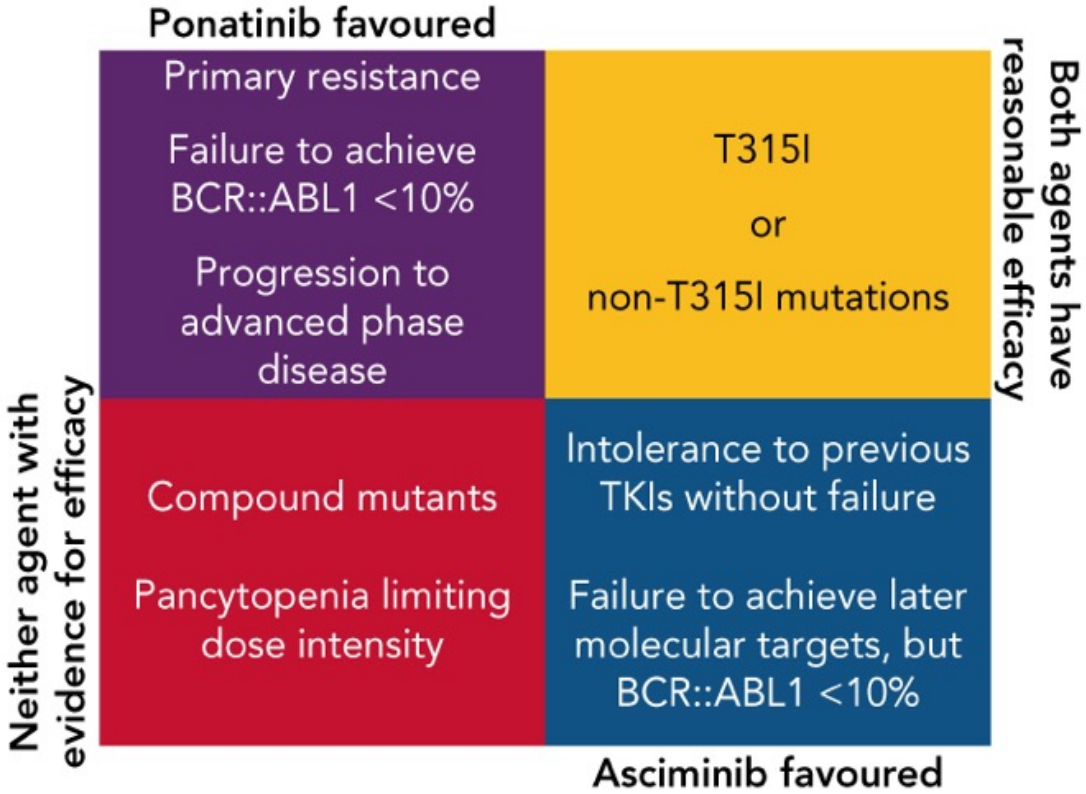
45mg start optimal, esp T315I (sl less difference nonT315I)

Adjudicated AOEs sl less

### EPIC

Frontline incremental response increase over 2GTKI possible

Risk too great




Yeung DT, Shanmuganathan N, Timothy P. Hughes TP; *Blood* 2022; 139 (24): 3474–3479

## ASCIMINIB

### Phase I (x2101)

Confident single agent efficacy

Toxicity similar across dose range (up to 200mg BID)

Mutational based resistance less, myristoyl mutations possible

### ASCEMBL

Optimal third line agent: superior tolerance and efficacy versus BOS

AOEs minimal and small difference vs BOS; further study to confirm

### ASC4FIRST / ASCEND

Frontline efficacy may be highest yet

Tolerability superior

Resistance predictable

Next question: TFR fraction / success

# Roundtable Discussion

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# Understanding the Current Paradigm and New Approaches in the Care of Patients with Cancer

*A Complimentary NCPD Hybrid Symposium Series Held During the 50th Annual ONS Congress*

## Prostate Cancer

**Thursday, April 10, 2025**

**12:15 PM – 1:45 PM**

### Faculty

**Rahul Aggarwal, MD**
**Monica Averia, MSN, AOCNP, NP-C**
**Kathleen D Burns, RN, MSN, AGACNP-BC, OCN**
**William K Oh, MD**

### Moderator

**Neil Love, MD**

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