CML 2025:
Updates in Management

Clark Alsfeld, MD

Leukemia, Stem Cell Transplantation, Cellular Therapy

Ochsner MD Anderson Cancer Center

The Gayle and Tom Benson Cancer Center

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Disclosures

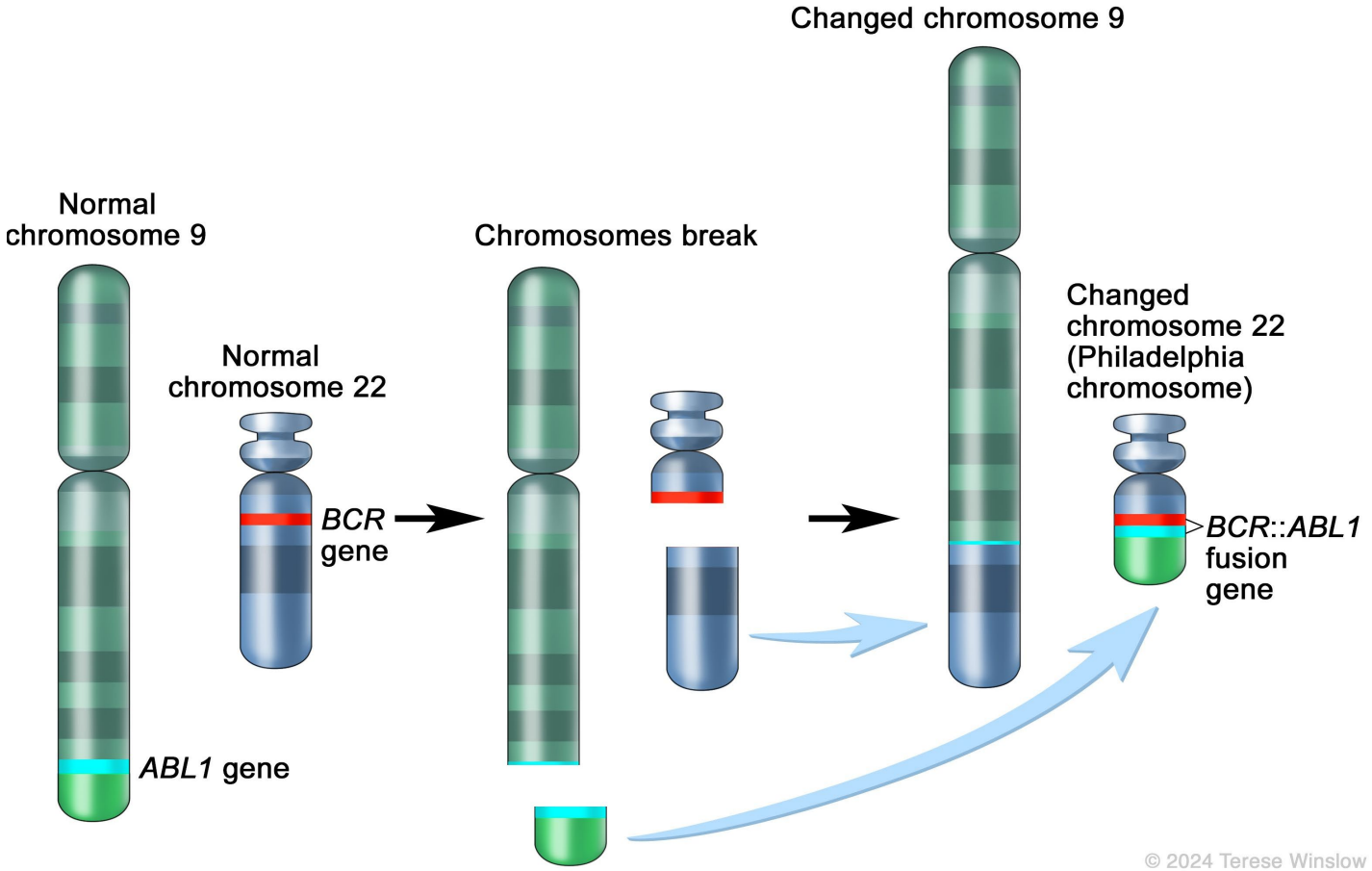
- Kite (Gilead) – Speaker
- Incyte – Speaker
- Bristol Myers Squibb – Consultant
- Amgen – Consultant

Outline

- Understand pathophysiology and risk stratification in chronic myeloid leukemia
- Discuss various treatment options in chronic myeloid leukemia
- Review an updated approach to chronic myeloid leukemia

Chronic myeloid leukemia

- Myeloproliferative neoplasm
- Results from fusion of Abelson murine leukemia (ABL1) gene on chromosome 9 and breakpoint cluster region (BCR) gene on chromosome 22.
  - Produces the oncoprotein BCR::ABL1 -> promotes expansion of CML cells through RAS, RAF, JUN kinase, MYC, and STAT signaling
- This usually produces an e13a2 or e14a2 = p210 oncoprotein



Scoring Systems Overview

Scoring System	Variables Included	Classification	Notes
Sokal (1984)	• Age • Spleen size • Platelet count • % Blasts	• Low • Intermediate • High	• Developed in chemotherapy/interferon era • Still used historically
Hasford (Euro, 1998)	• Age • Spleen size • Platelet count • % Blasts • *% Eosinophils* • *% Basophils*	• Low • Intermediate • High	• Broader than Sokal • Developed in interferon era
EUTOS (2011)	• % Basophils • Spleen size	• Low • High	• Simpler • Predicts complete cytogenetic response at 18 months on imatinib
ELTS (2016)	• Age • Spleen size • Platelet count • % Blasts	• Low • Intermediate • High	• Uses Sokal-like variables but weighted differently • Predicts CML-related mortality in TKI era

My favorite stat

- In chronic myeloid leukemia in chronic phase, patients who achieve a complete cytogenetic response (CCyR) or major molecular response (MMR) within the first year can have a **life expectancy near that of the general age-matched population**.

Maas et al., BJH, 3.2022
Sasaki et al., Lancet Haematol, 5.2015

Defining the Responses

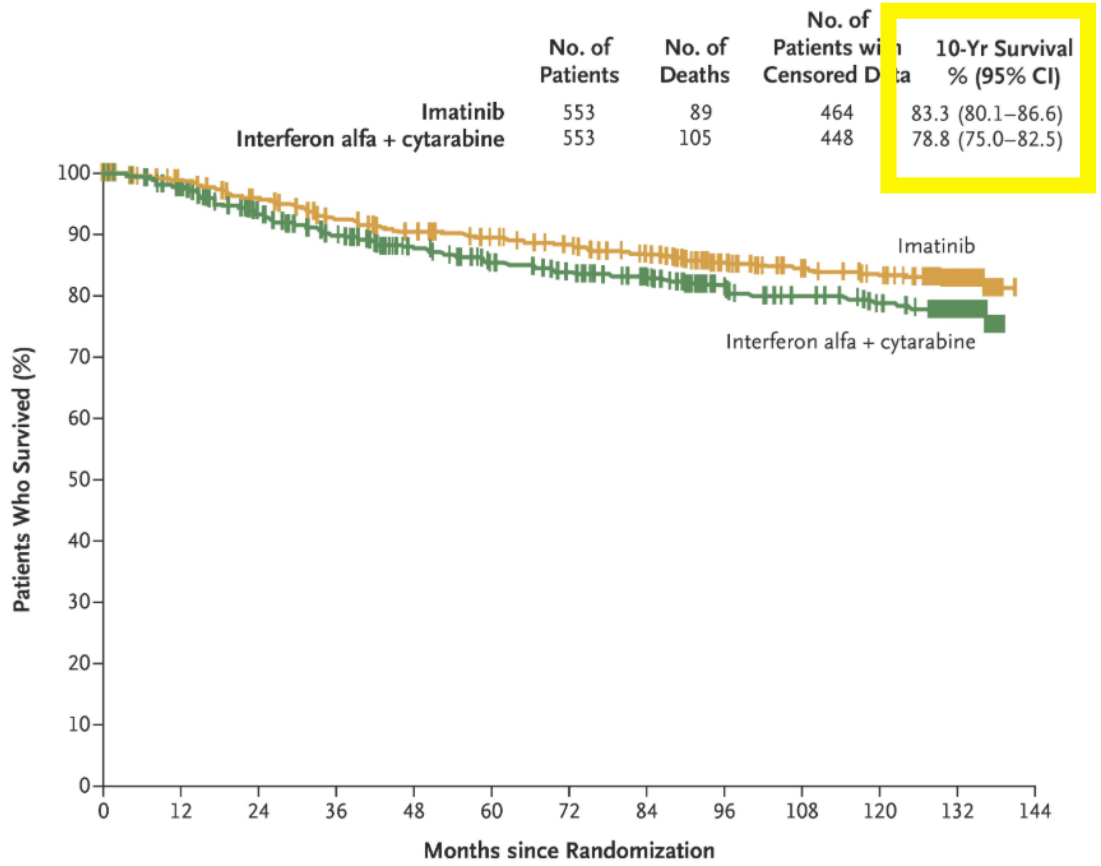
Milestone	Definition (IS or cytogenetics)	Clinical Significance
CHR (Complete Hematologic Response)	Normalization of WBC and platelets, no blasts in peripheral blood, disappearance of palpable splenomegaly	First treatment response, usually within 3 months
PCyR (Partial Cytogenetic Response)	1–35% Ph+ metaphases in bone marrow	Historical milestone, less emphasized in TKI era
CCyR (Complete Cytogenetic Response)	0% Ph+ metaphases in bone marrow	Equivalent to **BCR-ABL1 ≤1% IS**; strong predictor of long-term survival
MMR (Major Molecular Response)	BCR-ABL1 ≤0.1% IS	Standard deep molecular remission; ideal target milestone by 12 months
MR4 (Deep Molecular Response)	BCR-ABL1 ≤0.01% IS	Indicates very low disease burden; often a criterion for treatment discontinuation trials
MR4.5	BCR-ABL1 ≤0.0032% IS	Even deeper molecular response; supports sustained treatment-free remission (TFR) attempts
Relapse	Loss of hematologic response, loss of CCyR (BCR::ABL1 >1%), or 1-log increase in BCR::ABL1 transcript levels with loss of MMR (>0.1%) if in TFR	Requires reassessment of therapy

Available TKIs

- First generation
  - Imatinib (Gleevec)
- Second generation
  - Bosutinib (Bosulif)
  - Dasatinib (Sprycel)
  - Nilotinib (Tasigna)
- Third generation
  - Ponatinib (Iclusig)
- Allosteric inhibitor
  - Asciminib (Scemblix)

Imatinib: IRIS Trial

- IRIS: Imatinib vs IFN + Ara-C
- Superior cytogenetic and survival outcomes
  - CCyR at 18 months: 76% vs 14%
  - FFP at 18 months: 97% vs 92%
- Established imatinib as standard of care

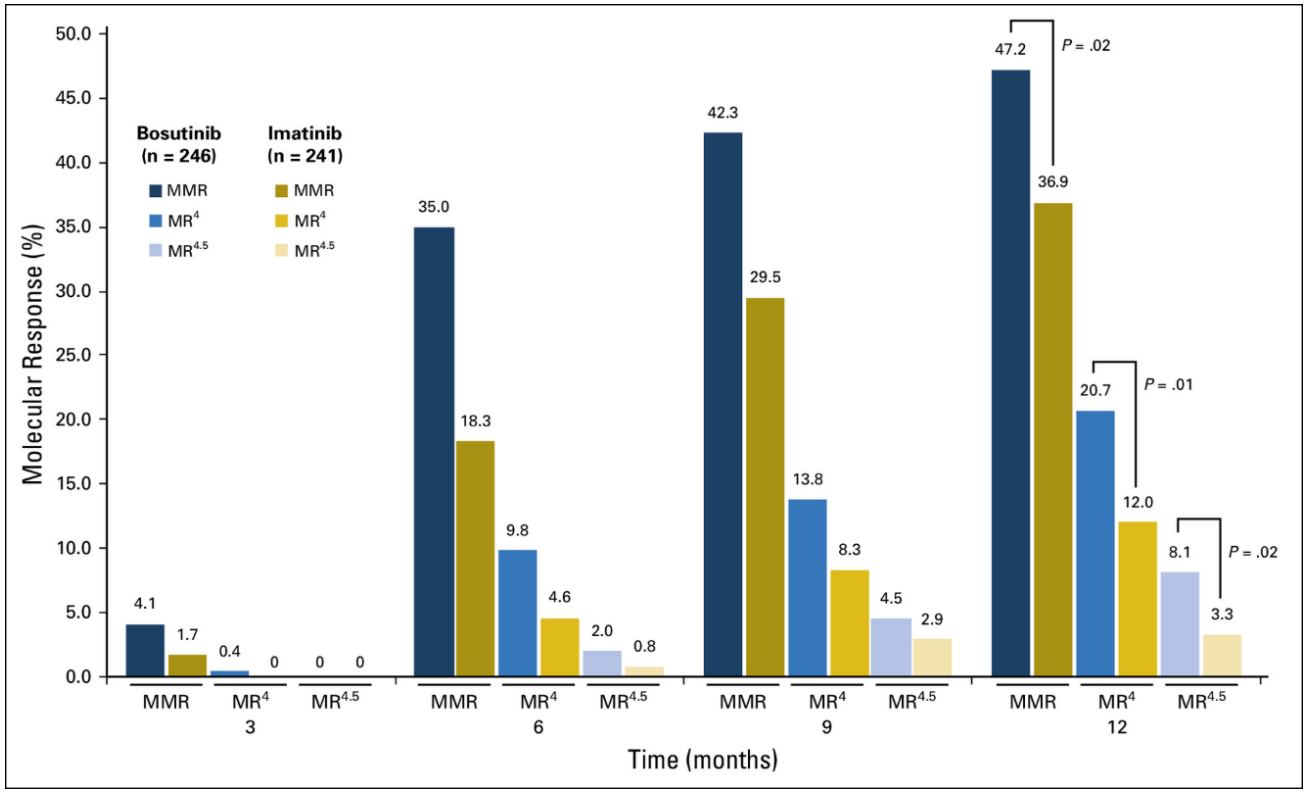


No. at Risk								
Imatinib	553	542	492	461	430	368	250	0
Interferon alfa + cytarabine	553	512	441	388	358	299	199	0
No. of Deaths								
Imatinib	0	6	41	57	71	82	88	89
Interferon alfa + cytarabine	0	12	52	73	83	96	104	105

O'Brien et al., NEJM, 3.2003.
Hochhaus et al., NEJM, 3.2017.

Bosutinib: BFORE Trial

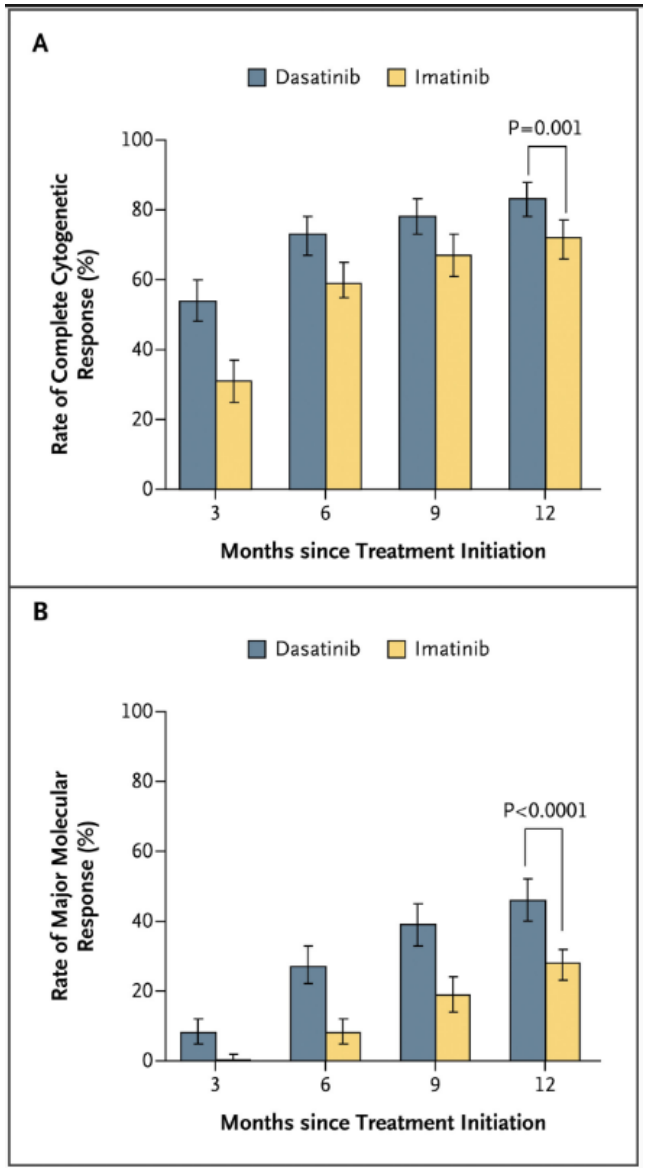
- Bosutinib vs imatinib (frontline)
- Higher MMR and deeper responses
  - MMR at 12 months: 47% vs 37%
  - CCyR at 12 months: 77% vs 66%
- Outcome maintained long-term
  - MMR at 5 years: 73.9% vs 64.4%
- Similar OS at 5 years
  - 94.5% vs 94.6%
- Tolerability profile distinct from other TKIs
  - Initially approved as 500mg daily for patients resistant or intolerant to other TKIs



Cortes et al., JCO, 1.2018.

Dasatinib: DASISION Trial

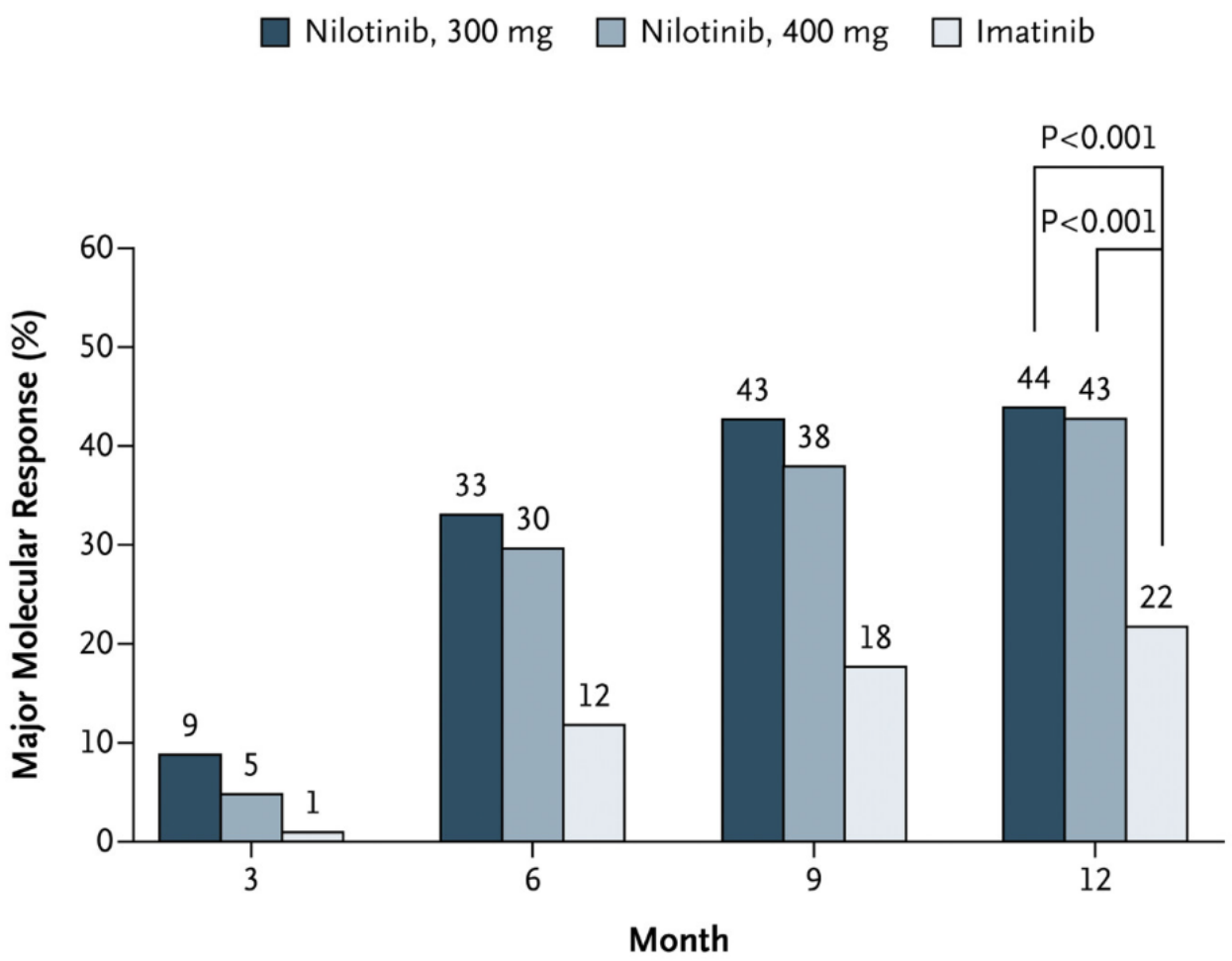
- Dasatinib vs imatinib in frontline CML
- Faster, deeper responses
  - CCyR at 12 months: 77% vs 66%
  - At 5 years, higher rates of CCyR, MMR, MR4.5
- Similar survival at 5 years
  - 91% vs 90%



Kantarjian et al., NEJM, 6.2010.
Cortes et al, JCO, 2016.

Nilotinib: ENESTnd Trial

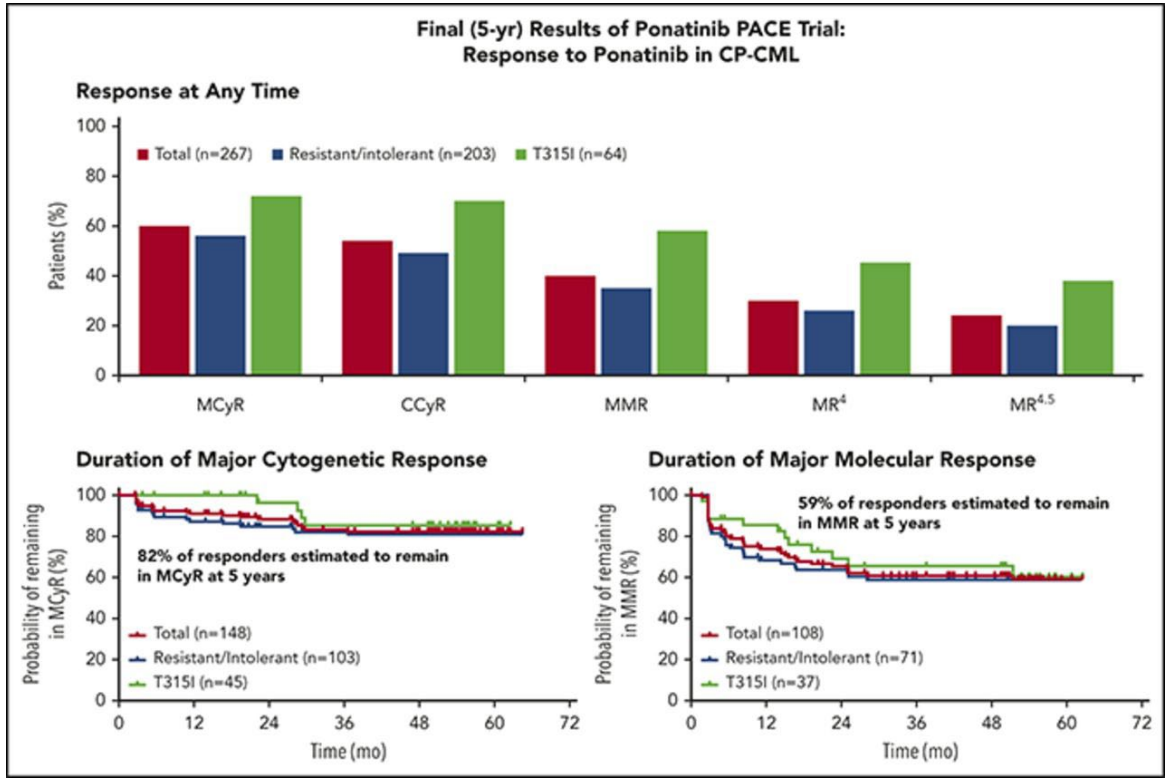
- Nilotinib vs imatinib (frontline)
  - Nilotinib 400mg BID, nilotinib 300mg BID, and imatinib 400mg daily
    - Nilotinib 400mg BID not approved
- Faster molecular responses, higher MMR
  - MMR at 12 months: 44%/43% vs 22%
  - CCyR at 24 months: 87%/85% vs 77%
- Great long-term data
  - MMR at 10 year: 77.7% vs 62.5%
- Similar OS data
  - 87.6% vs 88.3%



Saglio et al., NEJM, 6.2010.

Ponatinib: PACE/OPTIC Trials

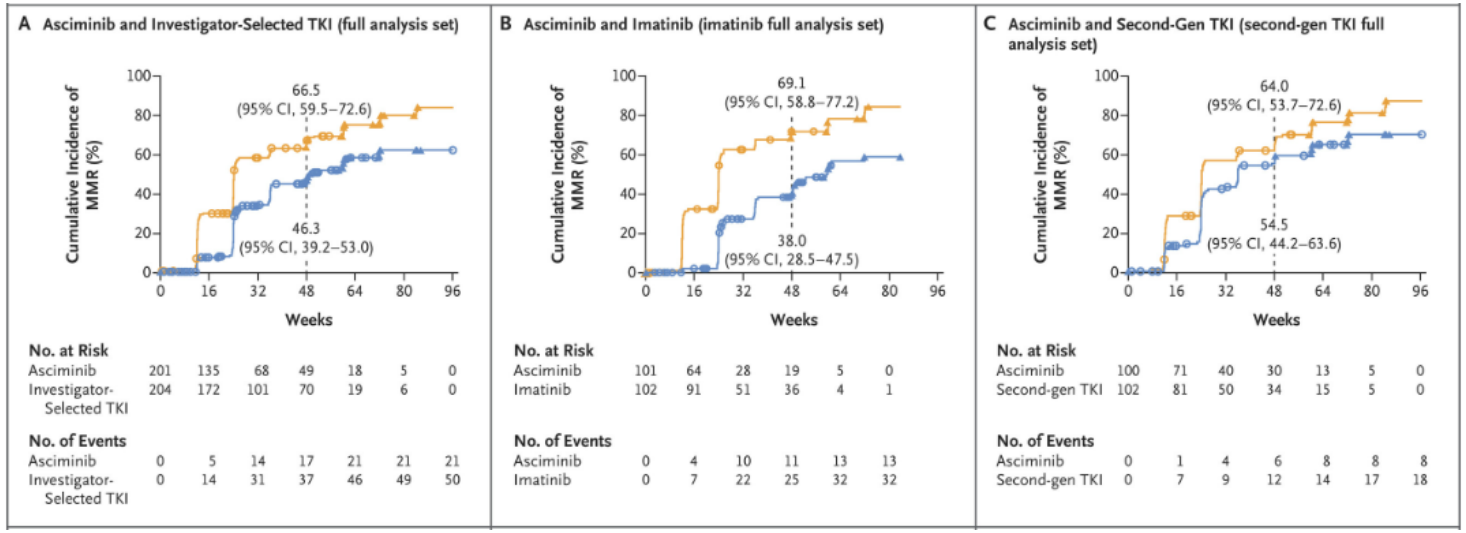
- Effective in resistant disease, incl. T315I mutation
- PACE: strong activity in heavily pretreated patients
  - MCyR at 12 months: 56%
    - With T315I mutation: 70%
  - MCyR at 5 years: 60%
    - 40% MMR or better
  - 31% of patients developed AOEs
- OPTIC: dose optimization reduces vascular risk
  - Higher response rates in T315I mutated (60% vs 25% vs 10%)
    - Similar responses in non-T315I mutated
  - Fewer dose reductions and AOEs



Cortes et al., Blood, 7.2018.
Cortes et al., Blood, 11.2021.

Asciminib: ASCEMBL/ASC4FIRST Trials

- Novel allosteric mechanism (STAMP inhibitor)
- Asciminib vs bosutinib after ≥2 TKIs
- Higher MMR rates, better tolerability
  - MMR at 6 months: 25.5% vs 13.2%
  - MMR at 2 years: 37.6% vs 15.8%
    - This resulted in initial FDA approval
- Ascimnib vs investigator choice in 1L
  - MMR at 12 months: 67.7% vs 49%
- Improved safety profile:
  - Treatment discontinuation: 4.5% vs 11.1% (1st Gen) vs 9.8% (2nd Gen)



Rea et al., Blood, 11.2021.
Hochhaus et al., NEJM, 5.2024.

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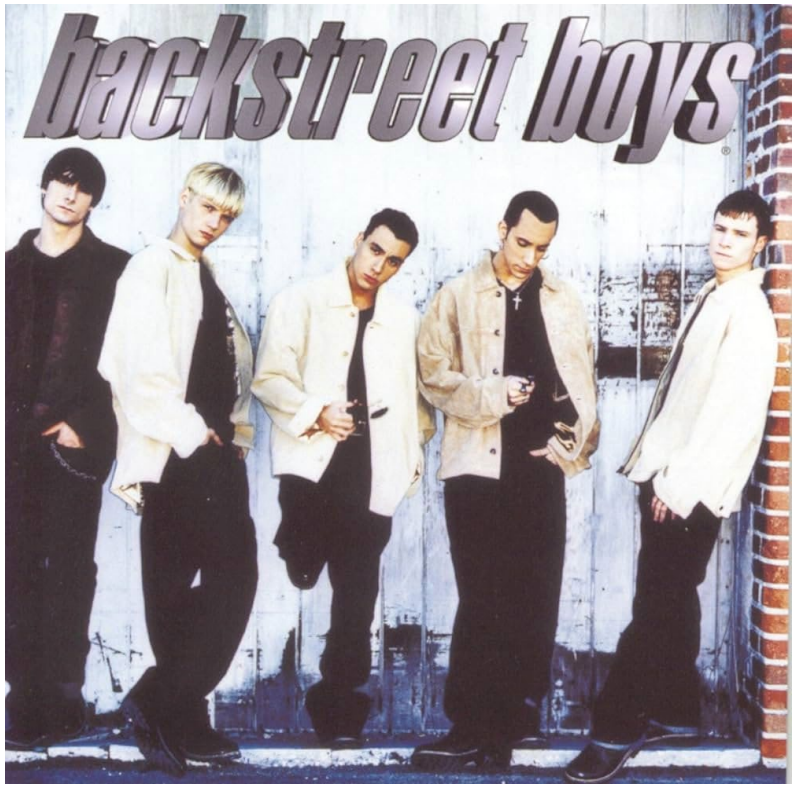
Imatinib

Second Generation TKIs



Bosutinib

Dasatinib

Nilotinib

Ponatinib

Asciminib

Appropriate Dose Reductions

Tyrosine kinase inhibitor	Maximum tolerated dose (FDA approved), mg/day		Optimal biologic dose, mg/day	Lowest effective dose, mg/day
	Frontline	Later line		
Imatinib	400	400	400	100–300
Dasatinib	100	100	50	20
Nilotinib	300 bid	400 bid	300 bid	150–200
Bosutinib	100–400	500	400	100–300
Ponatinib	NA	45	30 if non-T315I 45 if T315I	7.5–15 (once *BCR::ABL1* transcript <1%)

Kantarjian et al., Cancer, 7.2025

Quick Review of Drug-Specific Risks

TKI	Drug-Specific Risks
Imatinib	Fluid retention (pleural effusion, ascites), GI upset, muscle spasms
Dasatinib	Pleural effusion, pulmonary hypertension, bleeding risk
Nilotinib	QT prolongation, arterial/vascular events, hyperglycemia, pancreatitis, rash
Bosutinib	Hepatotoxicity, pleural effusion (less than dasatinib), GI toxicity (diarrhea)
Ponatinib	Arterial occlusive events (dose-dependent), pancreatitis, severe hypertension
Asciminib	Pancreatitis, hypertension

Prohibitive Toxicities

TABLE 2 Prohibitive tyrosine kinase inhibitors (TKI) toxicities that require TKI change rather than lowering the dose.

Toxicities	TKI
Pulmonary hypertension	Dasatinib
Recurrent (more than once) pleural effusions	Dasatinib, (rare with others)
Pancreatitis	Ponatinib, nilotinib
AOEs (CVA, MI, and TIA) or VOEs or PAOEs	Ponatinib, nilotinib
Dementia-like, Lewy-body, ALS, Parkinsonism	Any TKI (rare)
Enterocolitis	Bosutinib
Immune-mediated myocarditis, hepatitis, nephritis	Any TKI

Abbreviations: ALS, amyotrophic lateral sclerosis; AOEs, arterial occlusive events; CVA, cerebral vascular accident; MI, myocardial infarction; PAOEs, peripheral arterial occlusive events; TIA, transient ischemic attack; VOEs, venous occlusive events.

Jabbour et al., AJH, 7.2024

Treatment Milestones

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2026
Chronic Myeloid Leukemia

NCCN Guidelines Index
Table of Contents
Discussion

EARLY TREATMENT RESPONSE MILESTONES
CRITERIA FOR RESPONSE AND RELAPSE

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

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

Treatment Milestones

- Initially agreed upon as it was thought that these would correlate with long-term survival.
- Some milestones do not correlate with survival.
  - BCR::ABL1 >10% at 3-6 months
  - MMR after 2+ years
- These may result in unnecessary changes in TKIs.
  - Additional cost
  - New/added toxicity

Kantarjian et al., Cancer, 7.2025

Proposed Treatment Milestone

Time since TKI start, months	Response	
	Consider TKI change	Continue same TKI
3	No CHR; Philadelphia chromosome, 100%	CHR
6	*BCR::ABL1* (IS) >10%	*BCR::ABL1* (IS) ≤10%
12 and beyond	• *BCR::ABL1* (IS) >1% • Wait longer if *BCR::ABL1* (IS) 1%–10% in older patients • Resistance mutations • High-risk ACAs	*BCR::ABL1* (IS) ≤1%; CCyR or MR2

Kantarjian et al., Cancer, 7.2025

Discontinuing TKIs

- Per NCCN guidelines (1.2026)

Criteria for TKI Discontinuation

- CP-CML. No prior history of AP-CML or BP-CML.
- On approved TKI therapy for at least 3 years.[a,b]
- 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.[b]
- 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.

Allogeneic Stem Cell Transplant

- Don’t forget about transplant!
- When to consider stem cell transplantation:
  - Advanced phases (AP and BP)
  - Resistance to second generation TKIs
  - T315I mutation present
  - MECOM rearrangement present
  - Recurrent cytopenias resulting in inconsistent administration

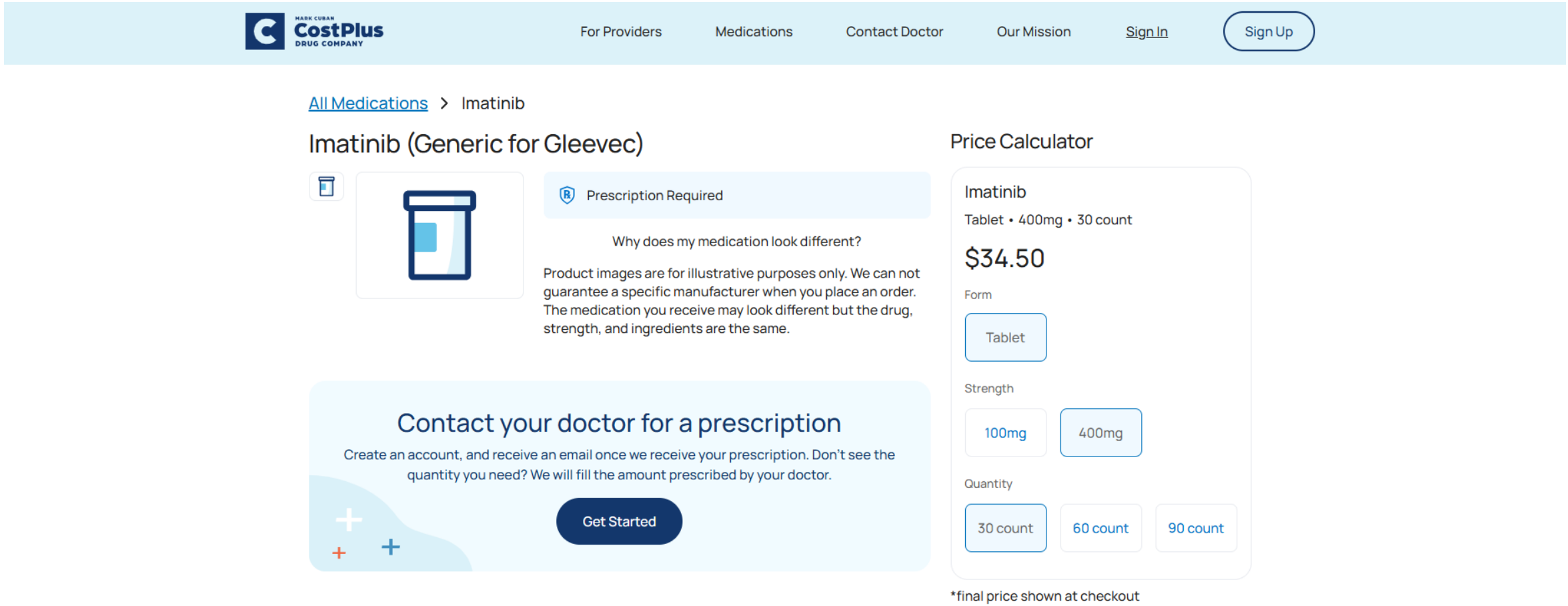
- 5-year OS of 60-96% with non-relapse mortality of 12-21%

Kantarjian et al., Cancer, 7.2025
Chalandon et al., Am J Hematol, 10.2022
Lubking et al., BMT, 11.2019
Niederweiser et al., ASH Edu, 2022

My Approach

1. **Patient preference/opinion**
   - What are their goals of treatment?
2. Is cost a factor?
3. Young or older?
4. What are the comorbidities?
5. Does once daily or twice daily dosing matter?
6. What will insurance cover?
7. Second half adjustments
   1. Tolerability
   2. Response

CostPlus Drug Company



Questions

- Thank you!