Chronic Myeloid Leukemia:

Diagnosis, Treatment, and Side Effect Management

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LEARNING OBJECTIVES

- Describe the various types and subtypes of chronic myeloid leukemia (CML)
- Identify tests used to diagnose disease and monitor treatment of CML
- Explain the overarching goals of treatment for the types of CML
- Explain approved and emerging treatment options for CML, including stem cell transplantation, and the role of clinical trials.
- Describe strategies to manage treatment side effects as well as potential long-term and late effects of treatments for CML
- Describe the healthcare professional's role in managing patients with CML

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FACULTY

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Disclosure Information
Jorge Cortes

- **I have the following financial relationships to disclose:**
  - **Grant or research support (to my institution) from: Ascentage, *Novartis*, *Sun Pharma***
  - **Paid Consultant for: *Novartis, Pfizer, Sun Pharma, Terns***
  - **Clinical Investigator for: Ascentage, Novartis, Sun Pharma**
- **AND**
  - **I will NOT include discussion of investigational or off-label use of a product in my presentation.**

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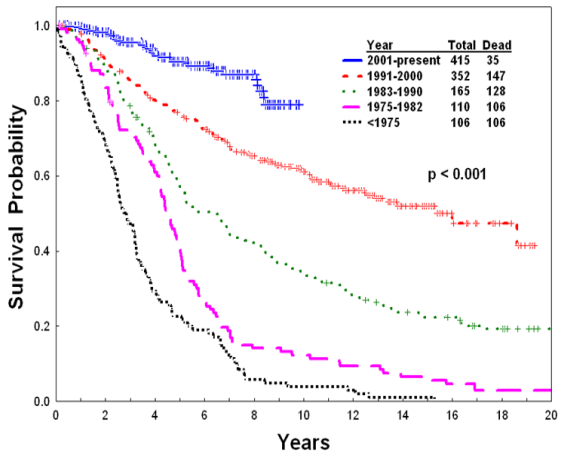
Improving Long-Term Outcome in CML

MDACC[1]



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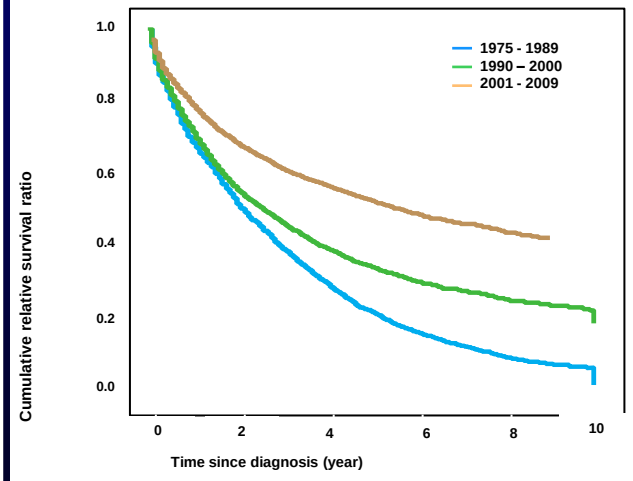

[1]Kantarjian et al. Blood 2012; 119: 1981-7; [2]Chen et al. Leuk Lymphoma. 2013; 54: 1411-7.

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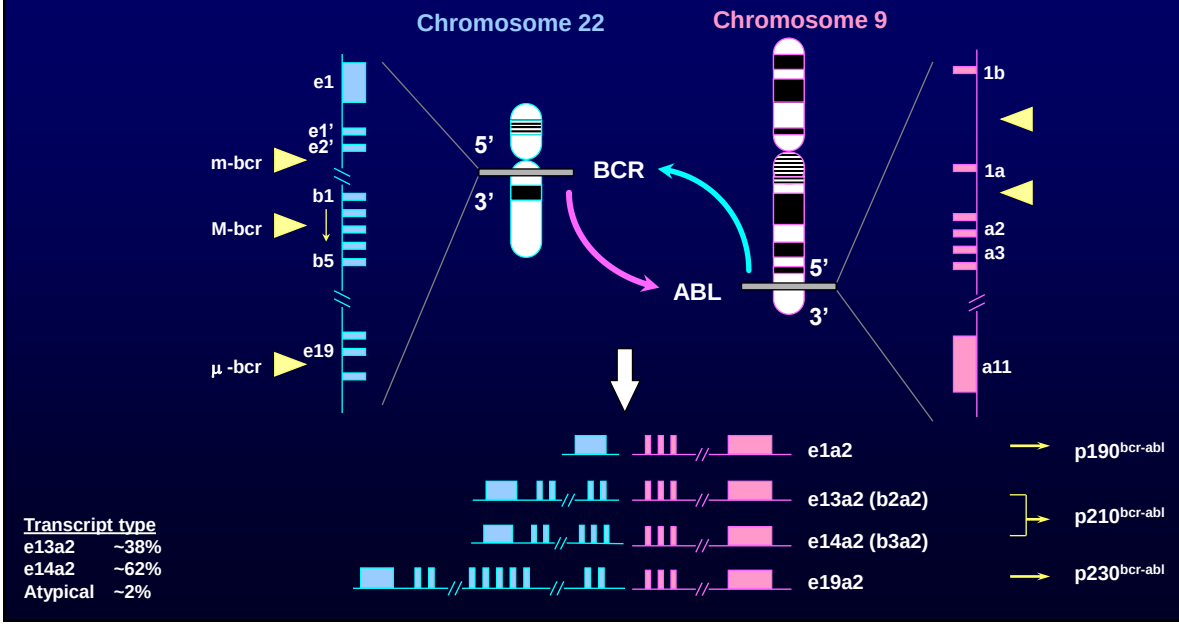
The Philadelphia Chromosome



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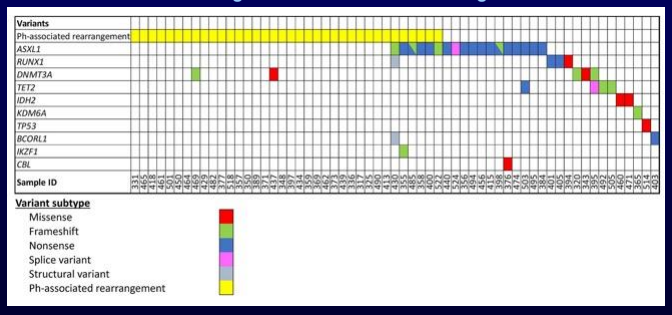
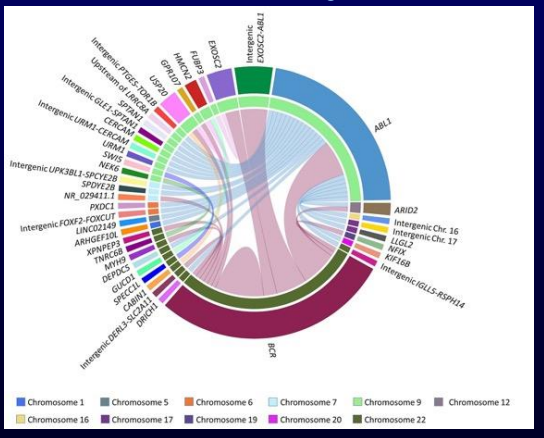
The Molecular Heterogeneity of CML

- 200 patients from TIDEL-II sequenced with RNA capture panel (126 genes)
- At diagnosis: 40 SNV and indels in cancer genes in 33 pts (16%) (across 10 genes); Ph-associated rearrangements in 36 patients (18%).

Additional genetic abnormalities at diagnosis



Ph-associated rearrangements



Shanmuganathan et al. Haematologica 2023; 108: 2380-95.

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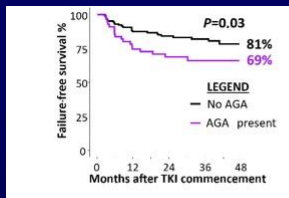
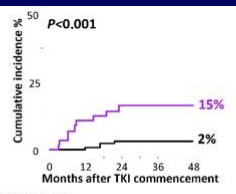
CML Molecular Heterogeneity: Outcome by Molecular Abnormalities

Failure-Free Survival



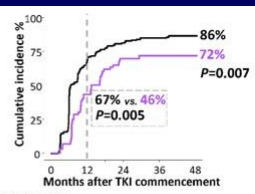
Number at risk						
No AGA	140	126	112	70	31
AGA	60	48	39	20	8

Acquisition of KD Mutations



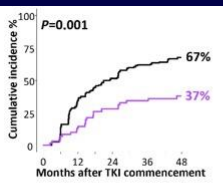
Number at risk						
No AGA	140	132	118	70	27
AGA	60	52	45	29	10

Achievement MMR



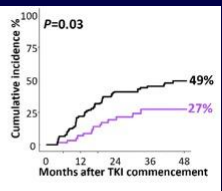
Number at risk						
No AGA	140	43	18	13	9
AGA	60	28	9	3	3

Achievement MR4



Number at risk						
No AGA	140	89	55	30	12
AGA	60	46	31	13	8

Achievement MR4.5



Number at risk						
No AGA	140	110	74	50	26
AGA	60	47	35	18	11

Shanmuganathan et al. Haematologica 2023; 108: 2380-95.

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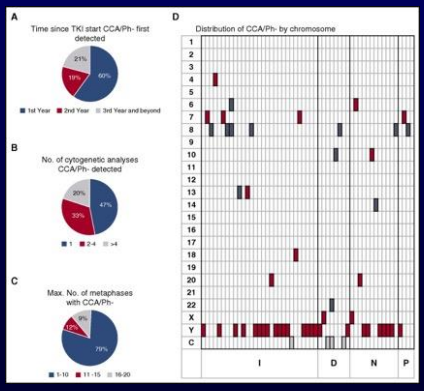
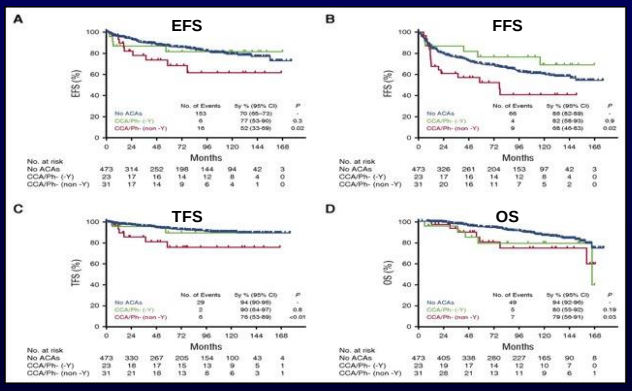
Additional Chromosomal Abnormalities (ACA) in CML

- 598 pts treated frontline with TKI
- Clonal chromosomal abnormalities in Ph- metaphases occurred in 58 (10%) pts
- Median time to appearance: 6 mo (3-78 mo) (1st occurrence after 12 mo in 39%)
- Transient (≤2 times) in 36 (62%)





Issa et al. Blood 2017; 130: 2084-91.

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CML Phases

	Chronic	Accelerated	Blast*
Past	3-5 years	12-18 months	3-9 months
Present	25+ years	4-5 years	6-12 months

- Asymptomatic (if treated)
- None of criteria for accelerated or blast phase

- Blasts ≥ 15%
- Bl + pros ≥ 30%
- Basophils ≥ 20%
- Plts < 100,000/mcl
- Clonal evolution

- Blasts ≥ 30%
- Extramedullary disease with localized immature blasts
- Increased lymphoblasts in PB or BM

* Blast phase is not AML or ALL

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2022 CML Classifications

- WHO
  - AP is omitted in favors of an emphasis on high-risk features associated with CP progression and resistance to TKI.
  - BP criteria: (1) ≥20% myeloid blasts in PB or BM; or (2) extramedullary proliferation of blasts; or (3) increased lymphoblasts in PB or BM. (The optimal cutoff for lymphoblasts and the significance of low-level B-lymphoblasts remain unclear and require additional studies.)
- ICC
  - AP criteria: (1) 10%-19% blasts in PB or BM; or (2) PB basophils ≥20%; or (3) additional clonal cytogenetic abnormality in Ph+ cells (ACA)[1].
  - BP criteria: (1) ≥20% blasts in PB or BM; or (2) myeloid sarcoma[2]; or (3) morphologically apparent lymphoblasts (>5%)[3] ("warrants consideration of lymphoblastic crisis")

[1]Second Ph, trisomy 8, isochromosome 17q, trisomy 19, complex karyotype, or 3q26.2 abnormalities. [2]Extramedullary blast proliferation. [3]Immunophenotypic analysis is required to confirm lymphoid lineage.

Khoury et al. Leukemia 2022; 36: 1703-19; Arber et al. Blood 2022; 140: 120-8.

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ELN 2020 - Diagnostic Work-up at Baseline

- Physical examination (spleen and liver size)
- Complete blood cell count with microscopic differential
- Bone marrow aspirate for cytologic examination and cytogenetics
  - Core biopsy on dry tap
- Chromosome banding analysis
- FISH (only in case of Ph-negativity)
- Qualitative PCR (for detection of BCR-ABL1 transcripts and identification of transcript type)
- ECG
- Standard biochemistry with hepatitis B-serology
- Consider mutation analysis for AP/BP (NCCN)

Hochhaus et al. Leukemia 2020; 34: 966-984.

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Prognostic Scores in CML

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

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

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Response Criteria for CML

Cytogenetic response	% Ph*	Molecular response	% BCR-ABL/ ABL (IS)
Minor (mCyR)	36-95		>10
Partial (PCyR)	1-35		1 to <10
			>0.01 to <1
Complete (CCyR)	0	Major (MMR; MR3)	≤0.1
		MR4	≤0.01
		MR4.5	≤0.0032
		Deep molecular response (DMR)	≤0.01 or ≤0.0032
		Undetectable	"0"

Good
Better
Best
Questionable

* At least 100,000 copies ABL needed

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7-Year Outcome by Molecular Response Among Patients with CCyR

Landmark		Percentage	
		MMR	No MMR
6 mo	EFS	85	93
	TFS	96	98
	OS	90	93
12 mo	EFS	91	92
	TFS	99	96
	OS	93	97
18 mo	EFS	95	86
	TFS	99	96
	OS	95	96

Hughes T, et al. Blood 2010; 116: 3758-65

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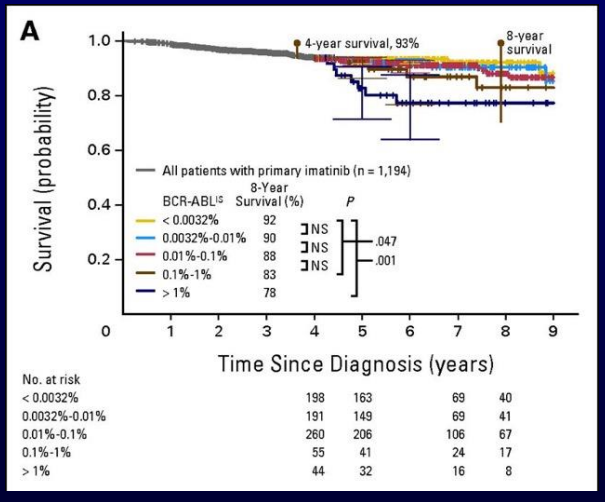
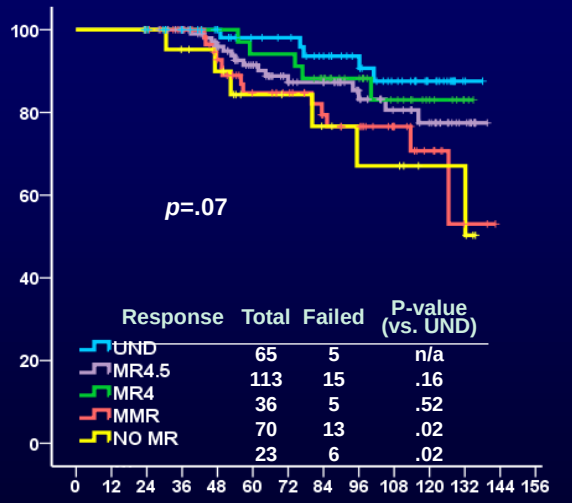
Outcome by Depth of Molecular Response

Overall Survival



Failure-Free Survival



Hehlmann et al. JCO 2014; 32: 415-23.
Falchi et al. Am J Hem 2013; 88: 1024-9.

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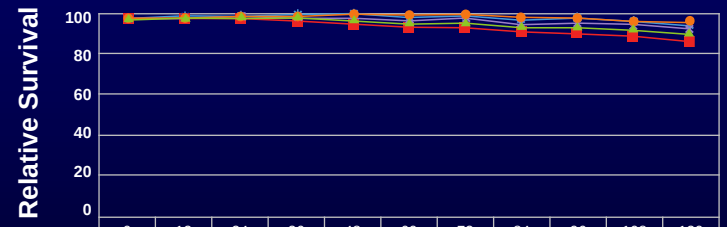
Relative Survival with TKI by Response to Therapy

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



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

Month

Sasaki et al. Lancet Hematology 2015

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Monitoring Recommendations for CML According to the ELN and NCCN* 2020

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

*For the latest information, access NCCN guidelines at www.NCCN.org.

Hochhaus et al. Leukemia 2020; 34: 966-984.

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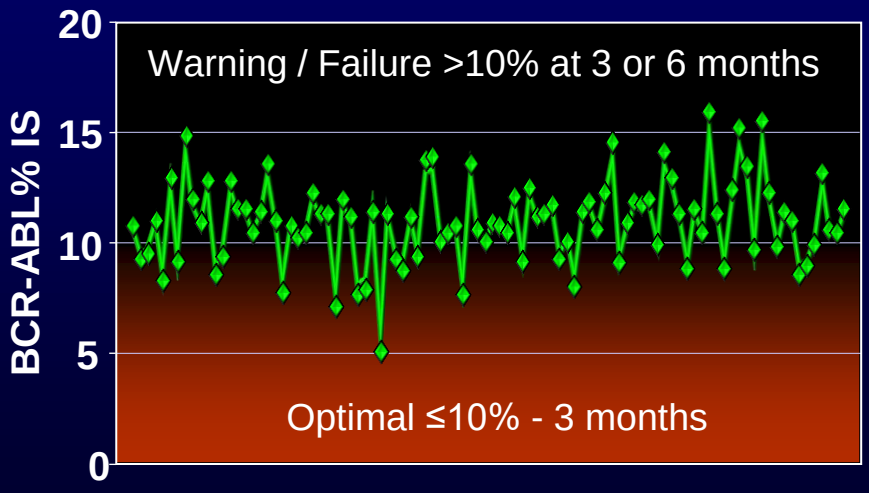
Variability of a BCR-ABL1 Positive Sample Measured 96 Times in a Single Centre Over Several Months

Mean BCR-ABL1 value = 11% (range 5-17%); CV 18%



Courtesy S. Branford, Adelaide, Australia.

Samples tested in Adelaide, Australia

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ELN 2020 Treatment Recommendations

First line
• Imatinib • Dasatinib • Nilotinib • Generic imatinib • Bosutinib
Second line and subsequent lines
• The criteria for the choice of 2nd-line TKI almost entirely patient related and depend on factors such as age, comorbidities and toxicity of 1st TKI
• Imatinib • Dasatinib • Nilotinib • Bosutinib: 2nd-line in patients with prior TKI failure/resistance or intolerance • Ponatinib: after failure of 2GTKI or T315I • Asciminib (NCCN): after failure of 2GTKI or T315I

Hochhaus et al. Leukemia 2020; 34: 966-984.

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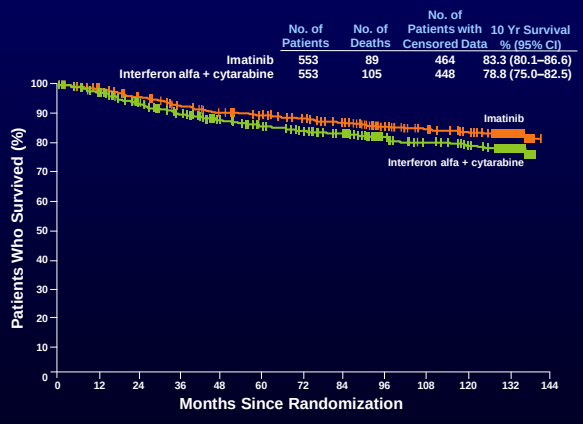
Results With Imatinib in Early CP CML the IRIS Trial at 10 Years

- 49% discontinued therapy
- 10 yr CCyR 92%, MMR 93%, MR4.5 63% (ITT 22%, 34%, 23%, respectively)
- 38 pts (7%) transformed to AP/BP (34 during 1st 4 yrs)
- 10-yr freedom from transformation 92%, EFS 80%



Hochhaus et al. NEJM 2017; 376(10): 917-927.

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Outcome Across 1st Line CML Studies

Response at, %	DASISION		ENESTnd		BFORE		TOPS	
	DAS	IMA	NIL[b]	IMA	BOS	IMA	IMA	IMA
CCyR 12m	77	66	80	65	77	66	70	66
MMR 3m	8	0.4	9	1	4.1	1.7	12	3
MMR 12m	46[a]	28[a]	44	22	47	37	47	40
MMR 5 yr	76	64	77	60	74	66	--	--
MR4.5 5 yr	42	33	54	31	46	36	--	--
AP/BP	2.3	5.0	1	6	2.2	2.6	1.9	3.2
PFS	94	92	96	94	NR	NR	97	94
OS	95.3	95.2	97	96	99	97	99	98

[a] MMR by 12 mo; [b] Nilotinib 300 mg BID

Cortes et al. JCO 2016; 34: 2333-40; Hochhaus et al. Leukemia 2016; 30: 1044-54;
Brümmendorf TH, et al. Leukemia 2022; 36: 1825-33; Cortes et al. JCO 2010; 28: 424-30.

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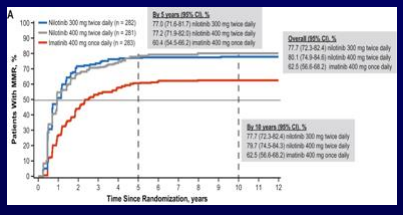
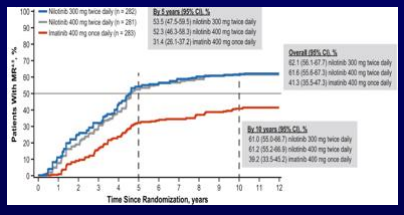
ENESTnd, 10-Year Results

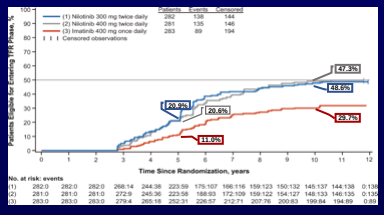
MMR



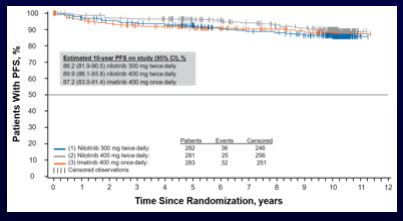
MR4.5



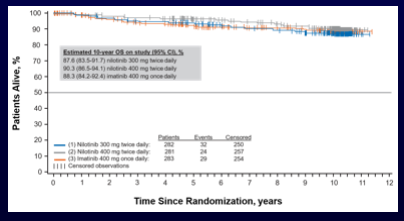
sMR4.5



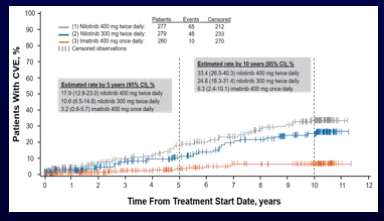
PFS



OS



CVE



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

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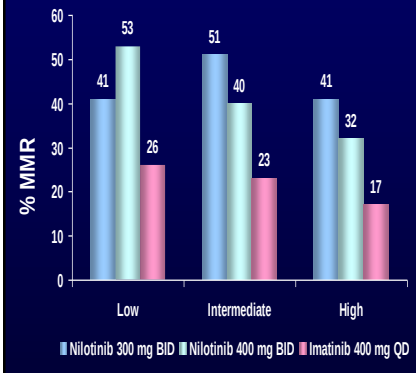
MMR by Sokal Score

ENESTnd



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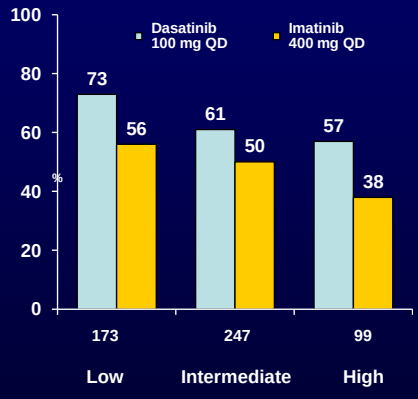

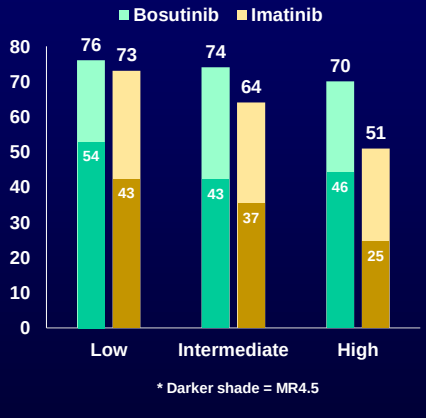

Saglio et al. Blood 2009; 114: abst# LBA-1; Kantarjian et al. ASCO 2011; abstract #6510; Brümendorf et al. ASH 2020; abstract #46

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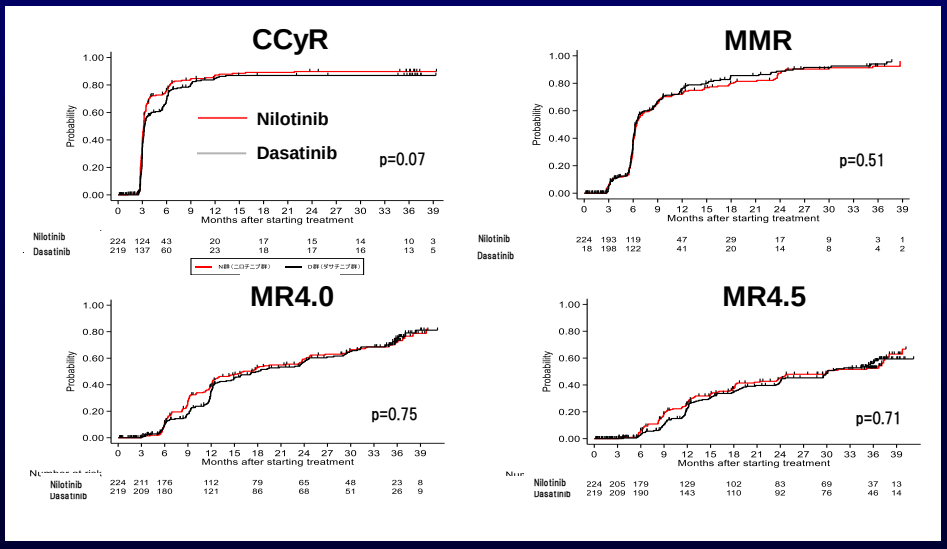
CML212: Randomized Trial of Dasatinib vs Nilotinib for Frontline CML Therapy



Matsumura I, et al Blood Advances [In press].

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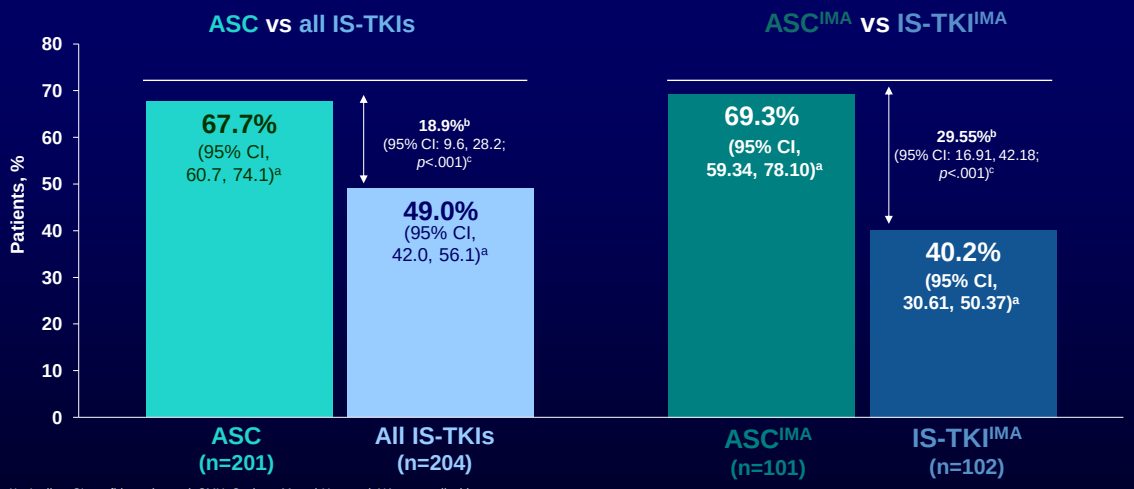
MMR Rate at Week 48 (Primary endpoint)



1L, 1st line; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; NA, not applicable.
[a] Clopper-Pearson 95% CI.
[b] The common risk difference and its 95% CI estimated using the Mantel-Haenszel method after stratifying for (a) pre-randomization selected TKI, and (b) baseline ELTS risk groups (both IRT data).
[c] Adjusted 1-sided p-value calculated based on the graphical gatekeeping procedure. The null hypothesis is rejected if the adjusted p-value is less than or equal to 0.025.

Hochhaus et al. NEJM 2024; Online ahead of print.

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Recommendations for Management According to Response – ELN 2020

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

Hochhaus et al. Leukemia 2020; 34: 966-984.

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CML Recommendations ELN & NCCN*

ELN 2020

	Optimal	Warnings	Failure
Baseline	NA	High-risk ACA, high-risk ELTS score	NA
3 months	BCR-ABL1 ≤10%	BCR-ABL1 >10%	BCR-ABL1 >10%, if confirmed within 1-3 months
6 months	BCR-ABL1 ≤1%	BCR-ABL1 >1%-10%	BCR-ABL1 >10%
12 months	BCR-ABL1 ≤0.1%	BCR-ABL1 >0.1%-1%	BCR-ABL1 >1%
Then, at any time	BCR-ABL1 ≤0.1%	BCR-ABL1 >0.1%-1% Loss of ≤0.1% (MMR)[a]	BCR-ABL1 >1%, resistance mutations, high-risk ACA

NCCN

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

COLOR	CONCERN	CLINICAL CONSIDERATIONS[p]	RECOMMENDATIONS[p]
RED	TKI-resistant disease[o]	• Evaluate patient adherence and drug interactions • Consider *BCR::ABL1* kinase domain mutational analysis[q] • 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[o]	• Evaluate patient adherence and drug interactions • Consider *BCR::ABL1* kinase domain mutational analysis[q] • Consider bone marrow cytogenetic analysis to assess for MCyR at 3 mo or CCyR at 12 mo	Switch to alternate TKI (CML-5) or Continue same TKI (CML-G)[r] and Consider evaluation for allogeneic HCT
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 (CML-G) • If not optimal: shared decision-making with patient[q,s]
GREEN	TKI-sensitive disease	• Monitor response (CML-E) • Evaluate patient adherence and drug interactions	Continue same TKI (CML-G)[t]

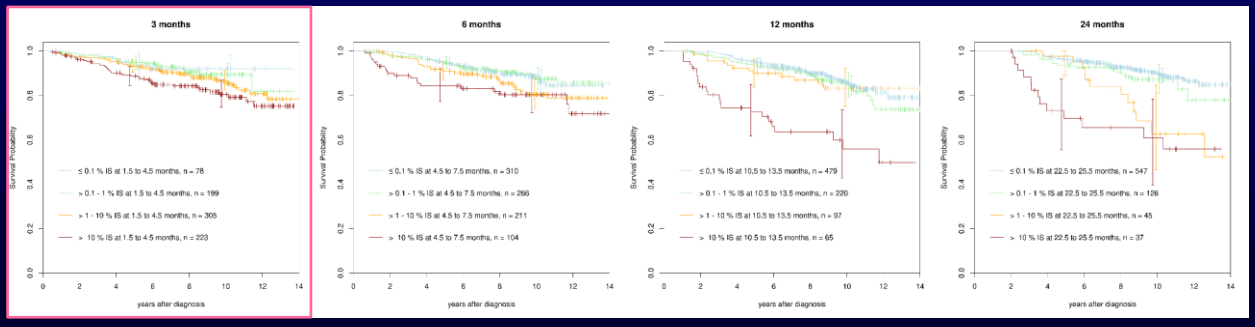
Major differences:
- No baseline features in NCCN (warning only in ELN)
- 6-month >1-10% optimal by NCCN, warning by ELN
- 12-month >1-10% "yellow" by NCCN, failure by ELN
- Losses not included in NCCN ("Early treatment milestones")

*For the latest information, access NCCN guidelines at www.NCCN.org.

Hochhaus et al. Leukemia 2020; 34: 966-984;
NCCN Version 2.2024 – December 5, 2023 (https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf)

28

Benefit of TKI Treatment After Failing Milestones

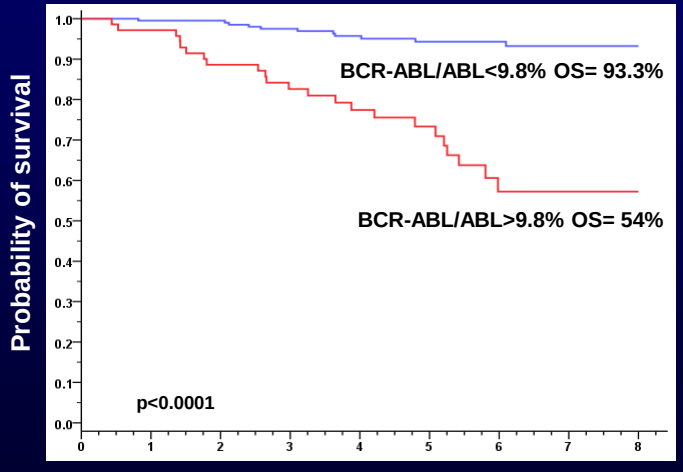


Lauseker et al. Leukemia 2023; 37: 2231–36

29

Survival After Imatinib Therapy by Molecular Response Achieved at 3 Months

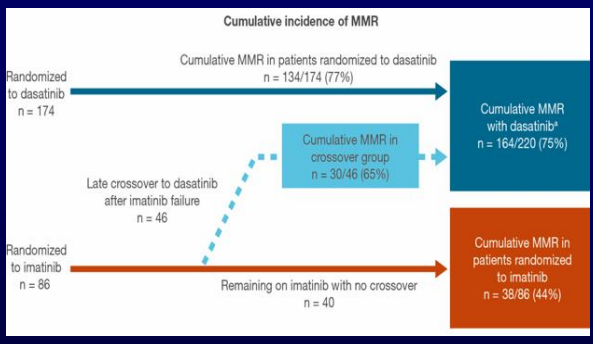
- Optimal PCR value determined by receiver operating characteristic (ROC) curve

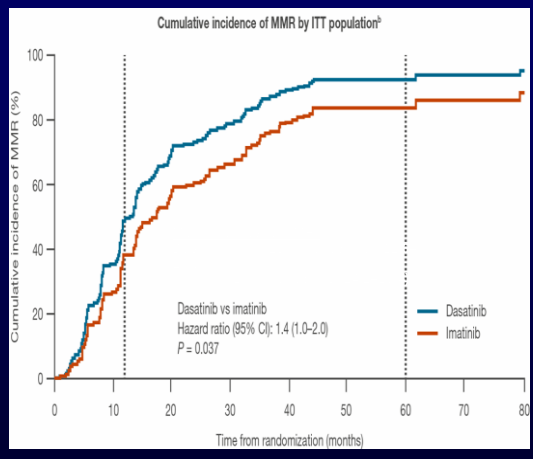


Marin et al, JCO 2012; 30: 232-8

30

DASCERN - Cumulative Incidence of Response





	Dasatinib	Imatinib
MR4	53	31
MR4.5	36	26

[a]Four patients achieved then lost MMR and subsequently crossed over to dasatinib; [b]The Kaplan–Meier curve accounts for competing risk and censored patients.

Cortes JE, et al. Haematologica 2024. Online ahead of print.

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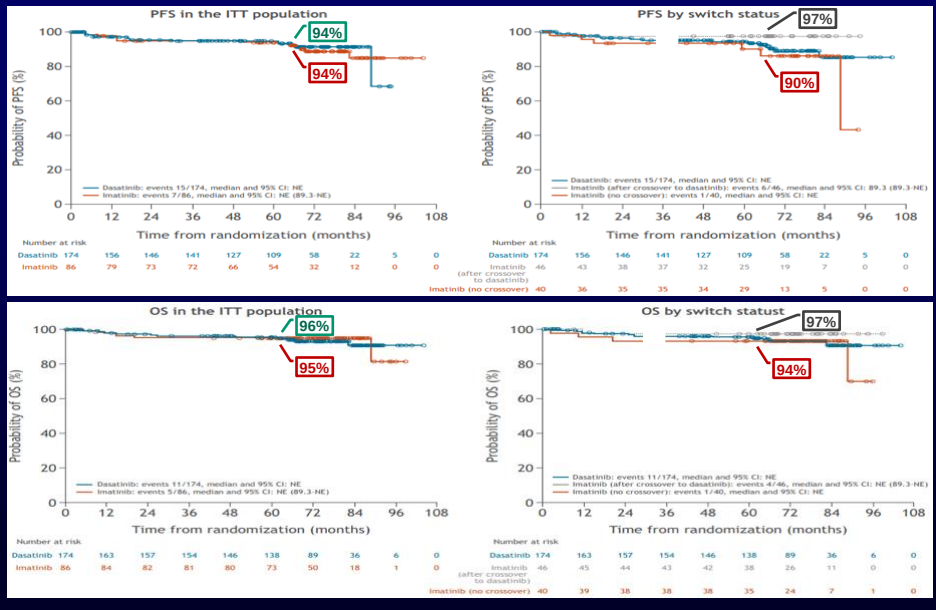
DASCERN - PFS & OS (ITT and By Switch Status)



Cortes JE, et al. Haematologica 2024. Online ahead of print.

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Treatment Discontinuation by TKI

	DASISION		ENESTnd		BFORE	
	Dasatinib	Imatinib	Nilotinib	Imatinib	Bosutinib	Imatinib
2 yrs	23	25	26	33	29	31
Efficacy	9	11	9	17	5	15
Safety	9	5	9	10	19	11
5 yrs	39	37	39	50	40	42
Efficacy	11	14	13	25	6	18
Safety	21	9	12	14	25	13
10 yrs	-	-	53[a]	48[b]	-	-
Efficacy	-	-	5[a]	6[b]	-	-
Safety	-	-	22	35	-	-

[a] 62% including those who switched to imatinib or increased to nilotinib 400 mg BID (14% for efficacy)
[b] 65% including those who switched to nilotinib or increased imatinib dose (24% for efficacy)

Cortes et al. JCO 2016; 34: 2333-40; Hochhaus et al. Leukemia 2016; 30: 1044-54; Kantarjian et al. Blood 2012; 119: 1123-9;
Kantarjian et al. Lancet Oncology 2011; 12: 841-51; Cortes et al. J Clin Oncol 36, 2018 (suppl; abstr 7002); Brümmendorf et al. ASH 2020; abstract #46.

33

Mechanisms of Resistance to Imatinib

- BCR-ABL-Dependent
  - Mutations in ABL
  - Amplification/overexpression
  - Remigration of BCR-ABL to cytoplasm
- BCR-ABL-Independent
  - Decreased hOCT1 expression
  - Increased MDR expression
  - Increased alpha-1 acid glycoprotein
  - Overexpression of Src-related kinases
- Quiescent stem cells (Persistence)

LeCoutre Blood 95: 1758, 2000.Weisberg Blood 95: 3498, 2000.
Mahon Blood 96: 1070, 2000. JNCI 92:1641, 2000. Vigneri Nature Medicine 7: 228, 2001.

34

Recommended TKIs in Case of BCR-ABL1 Resistance Mutations – ELN 2020

Mutation	Recommended TKI
T315I	Ponatinib
F317L/V/I/C, T315A	Nilotinib, bosutinib* or ponatinib
V299L	Nilotinib or ponatinib
Y253H, E255V/K, F359V/I/C	Dasatinib, bosutinib* or ponatinib

*** There are limited data available regarding mutations associated with clinical resistance to bosutinib in vivo. Some in vitro data suggest that the E255K and, to a lesser extent, the E255V mutation, might be poorly sensitive to bosutinib.**

- **Asciminib not in 2020 ELN because it was not available at the time, but it can be recommended in all instances**

Hochhaus et al. Leukemia 2020; 34: 966-984.

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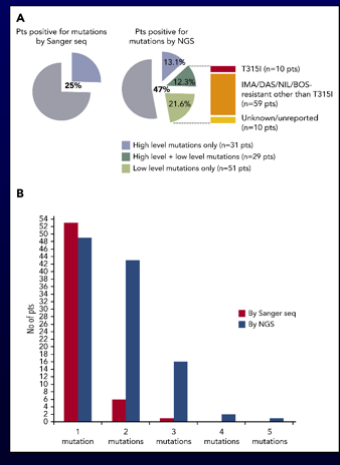
BCR-ABL1 KD Mutations After TKI Failure/Warning

- **236 consecutive CML patients with a non-optimal response to TKI therapy, 124 (53%) failure, 112 (47%) warning**

	Mutations by SS	Mutations by NGS
1st-line failure	13/57 (23)	27/57 (47)
1st-line warning	7/68 (10)	23/68 (34)
2nd-line failure	15/39 (38)	20/39 (51)
2nd-line warning	6/37 (18)	17/37 (49)
3rd-line failure	14/21 (67)	17/21 (80)
3rd-line warning	1/7	3/7
4th or 5th-line failure	4/7	4/7
Total	60/236 (25)	111/236 (47)



Soverini et al. Blood 2020; 135: 534-41.

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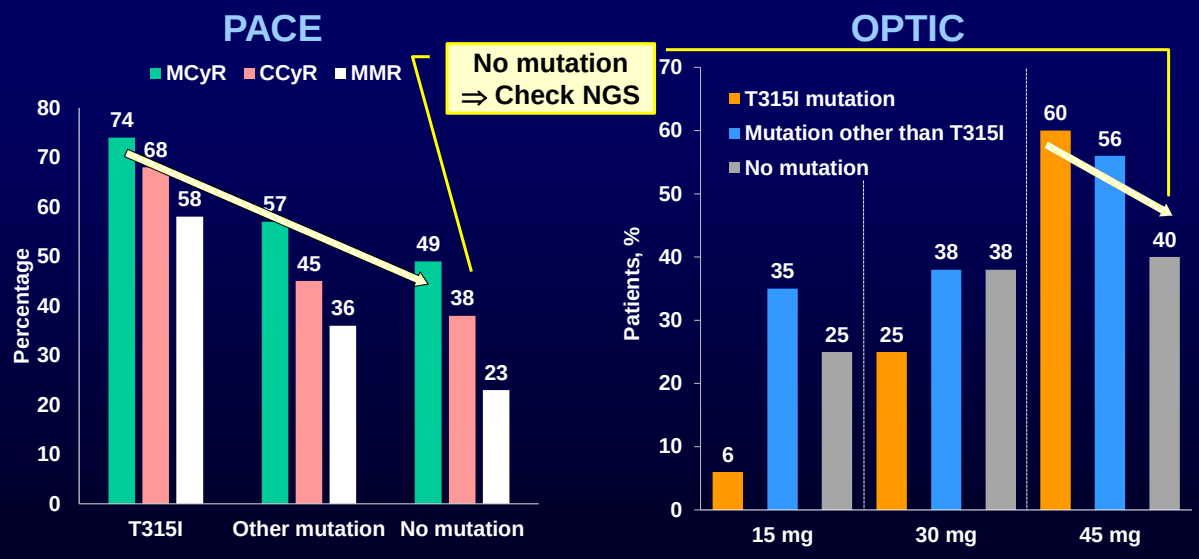
Response to Ponatinib by Mutation



Cortes et al. NEJM 2013; 369: 1783-96; Cortes et al. Blood 2021; 138: 2042-50.

37

2nd Generation TKI in CML CP Post-Imatinib Resistance

Response	Percentage		
	Dasatinib†	Nilotinib‡	Bosutinib
FU (mo)	>24	>24	>24
CHR	89	77	85
MCyR	59	56	57
CCyR	44	41	41
24 mo PFS*	80%	64%	79%
24 mo OS*	91%	87%	92%

† 7-yr MMR 43%, PFS 42%, OS 65%; discontinued 78%
‡ 4-yr PFS 57%, OS 78%; discontinued 70%
* All patients (resistant + intolerant)

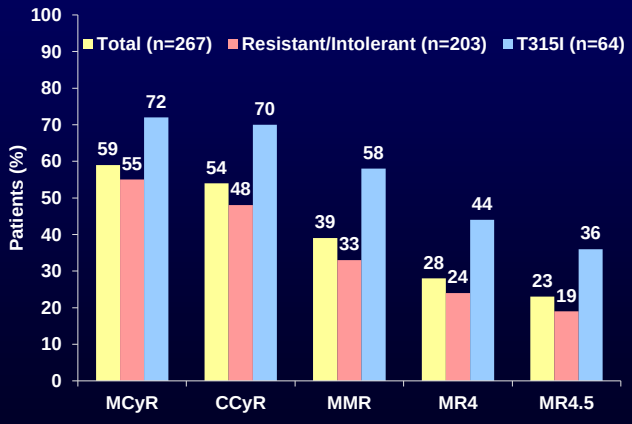
Shah et al. Haematologica 2010; 95: 232-40; Shah et al. Am J Hematol 2016; 91: 869-74.
Kantarjian et al. Blood 2011; 117: 1141-45; Giles et al. Leukemia 2013; 27: 107-112.
Cortes et al. Blood 2011; 118; 4567-76; Gambacorti-Passerini et al. Am J Hematol 2014; 89: 732-42.

38

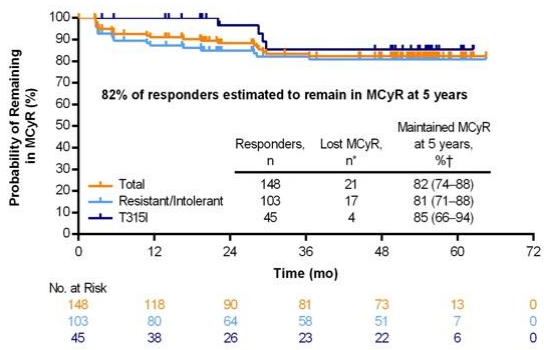
Efficacy of Ponatinib in CP-CML

- Median times to MCyR 2.8 (1.6–24.5) mo, CCyR 2.8 (1.6–35.7) mo, and MMR 5.5 (1.8–32.9) mo

Responses at Any Time



Duration of MCyR



Cortes et al. Blood 2018; 132: 393-404.

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Ponatinib Dosing: Response-Adjusted Dosing (OPTIC)

- CML CP ≥2 prior TKIs or T315I

45 mg QD
30 mg QD
15 mg QD

→ BCR-ABL ≤1% →

15 mg QD

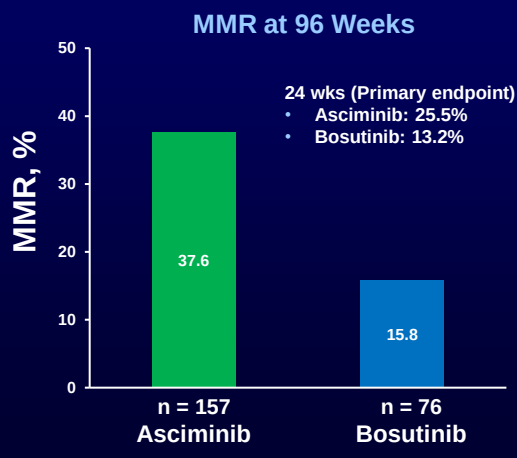
- 12-month BCR-ABL1 ≤1%: 44% vs 27% vs 27%
  - 48-month: 60% vs 41% vs 40%
- 48-month MMR: 45% vs 29% vs 24%
- Lost response after dose reduction: 27% & 24%
  - Re-gained response after increase: 69% & 80%
- Adjudicated AOEs (per 100 pt-years): 3.87 vs 3.66 vs 1.73
- Other grade ≥3 AEs (>5%):
  - Heme: thrombocytopenia 27%, neutropenia 18%, anemia 8%
  - Non-heme: hypertension 9%, lipase elevation 7%

Cortes et al. Blood 2021; 138: 2042-50; Cortes et al. ASH 2023; abstract #3164.

40

ASCEMBL – Asciminib vs Bosutinib in R/R CML CP

- 233 pts previously treated with ≥2 TKIs randomized 2:1 to asciminib 40 mg BID or bosutinib 500 mg QD
- T315I and V299L excluded



- Median wks to MMR: asciminib 12.7 vs bosutinib 14.3
- Median wks exposure: asciminib 43.4 (0.1-129.9), bosutinib 29.2 (1.0-117.0)
- Other efficacy endpoints:
  - CCyR: 40.8% v 24.2% (96 w: 45.1% v 19.4%)
  - MR4: 10.8% v 5.3%
  - MR4.5: 8.9% v 1.3%
- TEAEs ≥G3 >2%: thrombocytopenia 22%, neutropenia 19%, hypertension 6.4%, ↑ lipase 3.8%
- AOEs (per 100 pts-years): asciminib 3.0, bosutinib 1.4

41

Hochhaus et al. Leukemia 2023; 37: 617-26; Rea et al. Blood 2021; 138: 2031-2041

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Asciminib for T315I CML - Response

- Asciminib 200 mg twice daily

Patients, n (%)	MMR	MR4	MR4.5
All patients (n = 49)	23 (46.9)	13 (26.5)	10 (20.4)
Ponatinib naive (n = 21)	12 (57.8)	8 (38.1)	7 (33.3)
Ponatinib pretreated (n = 28)	8 (28.6)	5 (17.9)	3 (10.7)

- Median time to MMR: 12.1 weeks (range, 4 to 48 weeks)
  - Kaplan-Meier-estimated MMR duration at 144 weeks (2.8 years): 87% (95% CI: 68.4%, 100%)
- Median time to MR4: 20 weeks (range, 8 to 33 weeks)
- Median time to MR4.5: 20 weeks (range, 8 to 49 weeks)

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Cortes JE, et al. Leukemia 2024; Online ahead of print.

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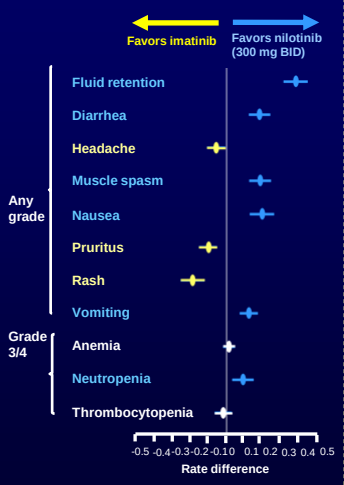
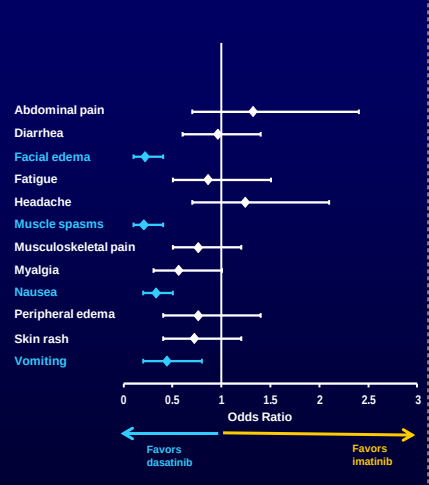
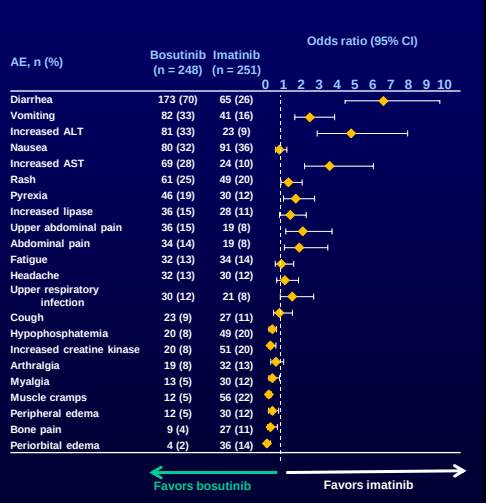
Adverse Events of 2nd Generation TKI in Randomized Trials





- Pleural effusion: dasatinib 28%, imatinib 1%
  - Pulmonary hypertension: dasatinib 12 pts, imatinib 1



AE, n (%)	Bosutinib (n = 248)	Imatinib (n = 251)
Diarrhea	173 (70)	65 (26)
Vomiting	82 (33)	41 (16)
Increased ALT	81 (33)	23 (9)
Nausea	80 (32)	91 (36)
Increased AST	69 (28)	24 (10)
Rash	61 (25)	49 (20)
Pyrexia	46 (19)	30 (12)
Increased lipase	36 (15)	28 (11)
Upper abdominal pain	36 (15)	19 (8)
Abdominal pain	34 (14)	19 (8)
Fatigue	32 (13)	34 (14)
Headache	32 (13)	30 (12)
Upper respiratory infection	30 (12)	21 (8)
Cough	23 (9)	27 (11)
Hypophosphatemia	20 (8)	49 (20)
Increased creatine kinase	20 (8)	51 (20)
Arthralgia	19 (8)	32 (13)
Myalgia	13 (5)	30 (12)
Muscle cramps	12 (5)	56 (22)
Peripheral edema	12 (5)	30 (12)
Bone pain	9 (4)	27 (11)
Periorbital edema	4 (2)	36 (14)

Hochhaus et al. Leukemia 2016; 30: 1044-54; Cortes et al. JCO 2016; 34: 2333-40; Cortes JE, et al. Am J Hematol. 2016;91(6):606-616.

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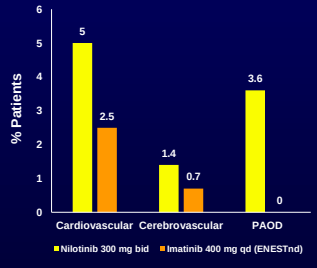
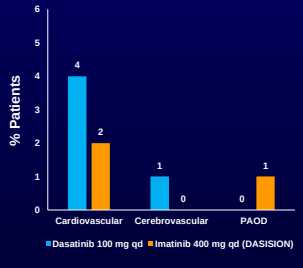
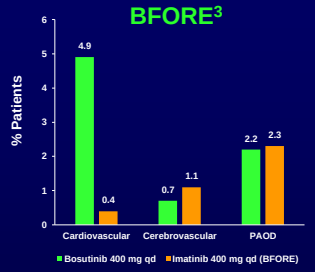
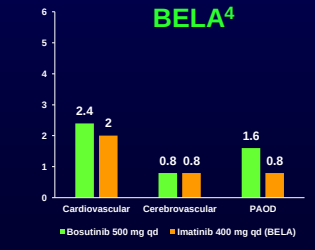
Ischemic Events by TKI From Randomized Trials at 5 years









[1]Hochhaus et al. Leukemia 2016; 30: 1044-54; [2]Cortes et al. JCO 2016; 34: 2333-40; [3]Brümmendorf et al. ASH 2020; abstract #46; [4]Cortes JE, et al. Am J Hematol. 2016; 91(6):606-616

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Requirements for TKI Discontinuation – ELN & NCCN* 2020

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

* For the latest information, access NCCN guidelines at www.NCCN.org.

Hochhaus et al. Leukemia 2020; 34: 966-984; NCCN Version 3.2021 – January 13, 2021 (https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf).

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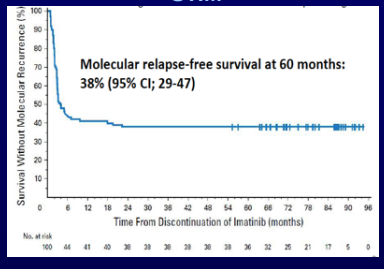
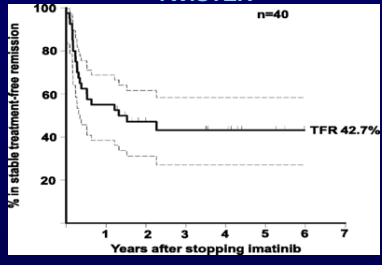
Treatment-Free Remission

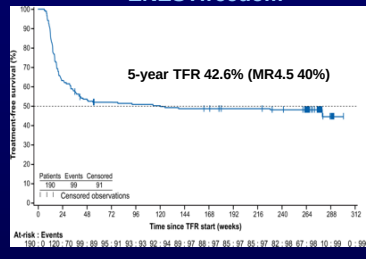
STIM[1]



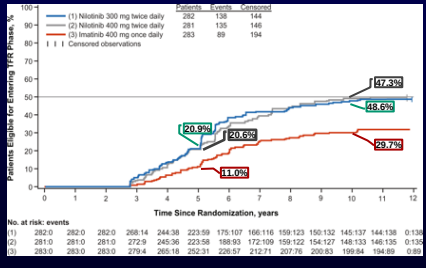
TWISTER[2]



ENESTfreedom[3]



ENESTnd[4]



BFORE[5]

- 2-year sustained MR4: bosutinib 32.5% vs imatinib 26.5% (OR 1.33 [95% CI, 0.92, 1.93])

~47% eligible
X
~60% TFR
~28% Success

[1]Etienne et al. JCO 2017; 35: 298-305; [2]Ross et al. Blood 2013; 122: 515-22; [3]Radich et al. Leukemia 2021; 35: 1344-55;
[4]Kantarjian et al. Leukemia 2021; 35: 440-53; [5]Brümmendorf TH, et al. *Blood.* 2020;136(Suppl 1): Abstract 46.

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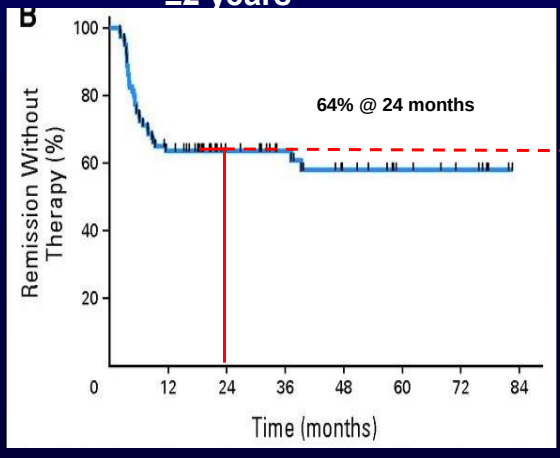
Treatment-Free Remission in CML

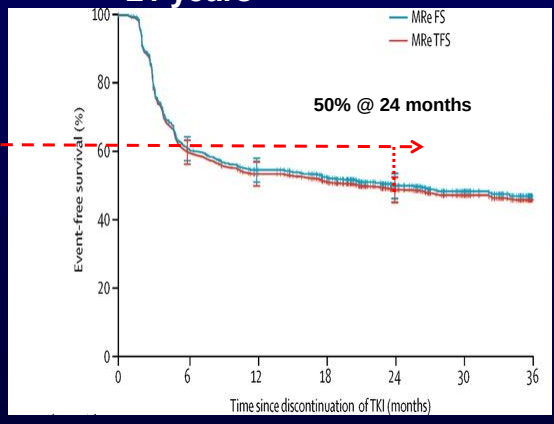
A-STIM

- MR4.5
- ≥2 years



EURO-Ski

- MR4
- ≥1 years



- Occasional relapse in BP (probably <1%) (Alfayez et al. *Br J Hematol* 2019;187:543-545; Rea D, et al. ASH 2019; abstract #30)

Rousselot et al. JCO 2014; 32: 424-30; Saussele et al. Lancet Oncol 2018; 19: 747-757

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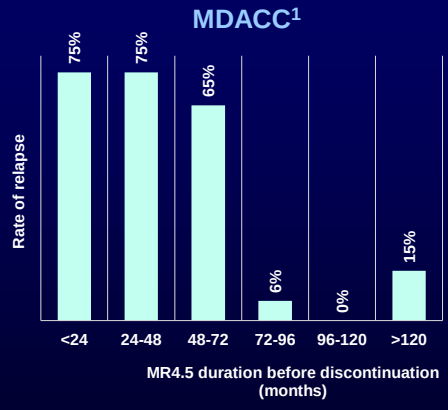
How to Improve TFR Success? – Wait Longer

MDACC[1]



- MVA: MR$^{4.5}$ duration >72 mo before discontinuation only predictor for durable response (p < 0.001, HR 0.08 [CI 95%, 0.02- 0.27])

EURO-SKI[2]

Years DMR	n/N	% (95% CI) without relapse
1–2	13/28	46% (28–66)
>2 to ≤3	17/31	55% (36–73)
>3 to ≤4	22/37	59% (42–75)
>4 to ≤5	11/17	65% (38–86)
>5 to ≤6	14/20	70% (46–88)
>6 to ≤7	9/15	60% (32–84)
>7	15/23	65% (43–84)

Yearly increase of ~3% in the probability of staying in MMR at 6 months over the observed range of DMR durations.

Chamoun et al. J Hematol Oncol 2019; 12: 1-10; Saussele et al. Lancet Oncology 2018; 19: 747-57.

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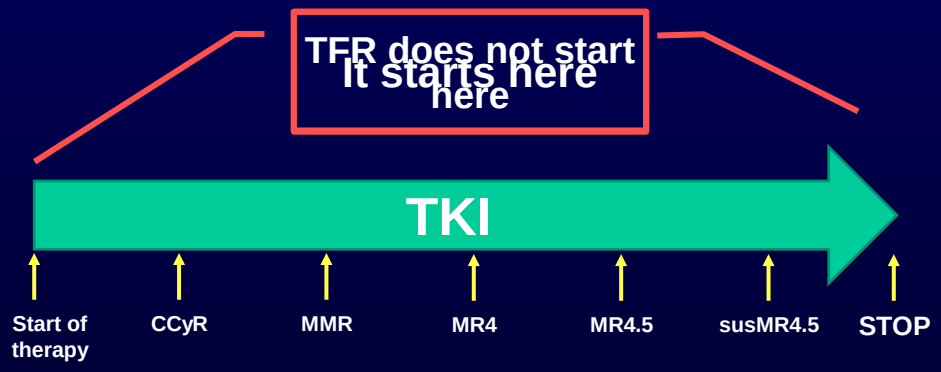
TKI TFR



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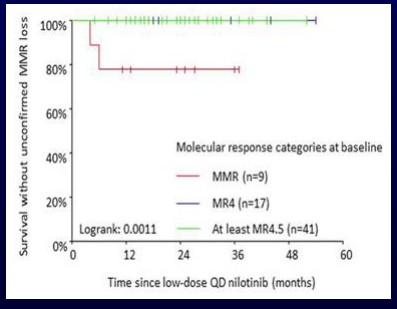
Dose Reduction after MMR/DMR achievement

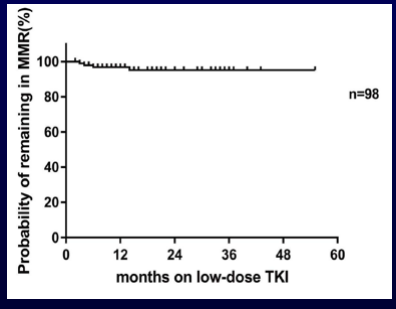
Molecular recurrence-free survival after dose reduction

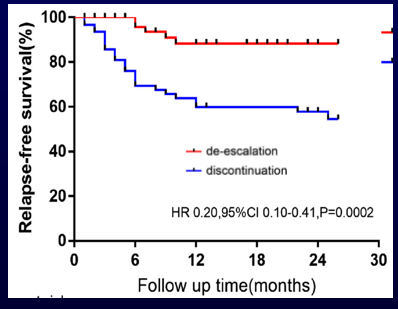
Reference	Study title
Rea, 2017 (Abs)	NILO-RED, RWE

Reference	Study title
Chen, 2022	Retrospective

Reference	Study title
Luo, 2022*	Randomised







*Patients were randomized to dose reduction (n=42) or discontinuation (n=42)

Rea D, et al. Blood. 2017;130(Suppl.1):318; Chen Y, et al. Haematologica. 2022;107(8):1966-1970; Luo J, et al. eJHaem. 2022;3:1220-1230.

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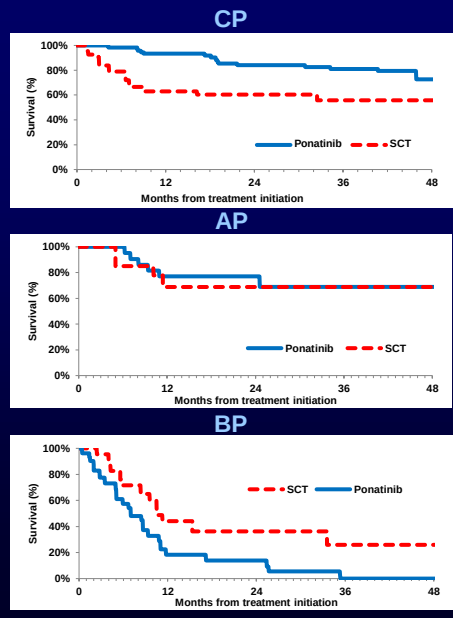
Ponatinib or SCT for T315I CML

- Pts ≥18 yrs with CML T315I in any stage enrolled in PACE (n=449) or EBMT (1999-2010; n=222)
- Median age (yr): CP 53 vs 48; AP 55 vs 46; BP 47 vs 44; Ph+ ALL 55 vs 36

Disease group	Median survival (mo)	
	PACE	EBMT
CP	NR	103
AP	NR	56
BP	7	11
Ph+ ALL	7	32



Nicolini et al et al. Cancer 2017; 123: 2875-80.

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Summary - CML 2024

- Excellent therapy available
- CCyR: gold standard for response (improves OS)
  - Deeper molecular responses: improve EFS (MMR) and option of treatment discontinuation (MR4.5)
- Early response (3-6 mos) predictive
  - Benefit of early switch uncertain
- Adequate management and monitoring mandatory for optimal outcome
- Change of therapy indicated for failure (not warning)
- Advanced phase:
  - AP: TKI as good as SCT
  - BP: TKI (± chemo, depending on goals) + SCT in CHR

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Questions?

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Pharmacist Role in Managing Patients with Chronic Myeloid Leukemia

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Pharmacist's Role

Benefits of oral cancer therapies

- Patient convenience
- Reduced healthcare visits

Challenges of oral cancer therapies

- Maintaining adherence
- Limited monitoring opportunities

Main areas for pharmacist involvement

- Screen for drug interactions & discuss with provider
- Medication access
- Patient and caregiver education
- Patient and provider information resource

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Patient Case

- MM is a 71-year-old female with a diagnosis of CML since 2013. CML therapy has consisted of imatinib followed more recently by nilotinib. She has been in CMR for greater than 5 years. Six months ago, the nilotinib was discontinued due to her cardiac comorbidities. She was managed with frequent hematologic and molecular monitoring.

- Recent molecular monitoring results demonstrated a progressive increase in BCR-ABL PCR levels. Therefore, MM was started on dasatinib. Her prescription was processed and filled by her mail order pharmacy.

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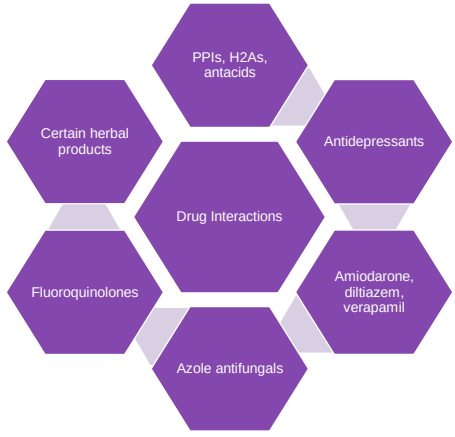
Screening for Drug-Drug Interactions

- Primarily metabolized by cytochrome P450 enzymes, especially CYP3A4
- QTc prolongation risk with nilotinib
- Concomitant acid-reducing medications affect absorption of bosutinib, dasatinib, nilotinib, and ponatinib
- Drug-food interactions
  - Nilotinib and asciminib require administration on an empty stomach
  - Others may be taken with food to avoid GI upset and nausea
  - Avoid foods that can inhibit CYP3A4 (grapefruit, star fruit, Seville oranges)



Chronic Myeloid Leukemia. NCCN v2.2024.
Lexi-Drugs. Lexicomp [online]. Wolters Kluwer Clinical Drug Information, Inc. 2020.

Screening for Drug-Disease Interactions

QT prolongation (nilotinib, dasatinib, bosutinib)
- EKG monitoring recommended for nilotinib

Cardiac and vascular toxicities
- All TKIs and asciminib may lead to an increased risk of one or more CV toxicities such as CHF, thrombosis, hypertension
- PAOD most reported with nilotinib and ponatinib
- Manage CV risk factors, monitor closely

Pancreatitis (nilotinib, ponatinib, asciminib)
- Additional monitoring if history of alcoholism or pancreatitis

Hyperglycemia (nilotinib)
- Relative consideration as diabetic patients on ENESTnd did not show clinically relevant changes

Lung disease (dasatinib)

Fertility and Pregnancy
- Avoid TKI during first trimester at a minimum as well as during breastfeeding
- Consideration for achieving milestones to permit TFR to conceive

CHF, congestive heart failure; PAOD, Peripheral arteria occlusive l disease;
CV, cardiovascular; EKG, electrocardiogram; TKI, tyrosine kinase inhibitor; TFR, treatment free remission.
Niltonib (Tasigna). Package insert. Novartis; 2010. Chronic Myeloid Leukemia. NCCN v2.2024.

Medication Access

- Out-of-pocket costs can impact oral cancer therapy
- Retrospective review of the impact of cost sharing on TKI discontinuation and nonadherence in CML patients (N = 1,541)
  - Patients with higher out-of-pocket costs are more likely than those with lower costs to:
    - Discontinue medications (aRR = 1.7; 95% CI 1.3-2.22)
    - Be nonadherent (aRR = 1.42; 95% CI 1.19-1.69)
  - Mean monthly total expenditure nearly doubled from 2002 to 2011

TKI, tyrosine kinase inhibitor; aRR, adjusted risk ratio; CI, confidence interval; CML, chronic myeloid leukemia
Dusetzina SB, et al. J Clin Oncol 2014; 32(4): 306-11.

Pharmacist's Role with Access

- Initial therapy
  - Assist with prior authorization process
  - Identify resources to assist with high out-of-pocket patient costs (e.g. co-pay assistance)
  - Inform team and patient on when to expect medication to be received by the patient
- Subsequent prescriptions
  - Educate patient on how to manage refills to avoid missed doses
  - Assist with managing impact of changes in patient insurance coverage

Patient Case Continued

- MM's PMH includes CAD, Afib, CKD, and DM.
- MM's home medications include baby aspirin, atorvastatin, carvedilol, furosemide, insulin glargine, losartan, and warfarin.
- MM was counseled on the increased risk of bleeding with the concomitant use of dasatinib and anticoagulants. MM agreed to report any new or unusual bleeding to her healthcare team.
- One month after starting dasatinib, MM contacts the clinic and reports seeing bright red blood on the toilet paper after wiping. The MD was contacted, the dasatinib was held, and a GI work-up was begun.

CAD, coronary artery disease; Afib, atrial fibrillation; CKD, chronic kidney disease; DM, diabetes mellitus; GI, gastrointestinal; MD, physician; PMH, previous medical history

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Pharmacist's Role in Education
Initial Teaching

- ✓Reinforce goals of therapy
- ✓Review directions for use
  - How to take
  - Medications/foods to avoid
  - What to do with missed doses or overdoses
- ✓Explain AEs and how to self-manage if appropriate
  - Common AE
  - Rare but serious AE
- ✓Review monitoring of therapy
  - Laboratory/diagnostic tests
  - Clinic follow-up visits
- ✓Describe appropriate storage and handling
- ✓Explain who the patient should contact to report issues

AE, adverse effect

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Pharmacist's Role in Education
Follow-up

- Best practice - phone follow-up shortly after the patient receives the first prescription, regularly for a time after initiating therapy, then periodically thereafter depending on need
- Reinforce
  - Goals of therapy
  - Directions for use
- Ask open-ended questions regarding missed doses and barriers to taking the oral therapy
- Review the AE profile and patient reported AEs
- Ask about any changes to other medications and medical conditions

AE, adverse effect

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Pharmacist's Role in Education
General Recommendations

- Identify and manage factors that influence adherence

Patient:	Emotional, mental or physical conditions, socioeconomic status, awareness of outcomes
Treatment:	Goals of therapy, regimen complexity, evidence of benefit, AE, cost
Healthcare system:	Provider relationship, patient education, patient satisfaction, convenience of access

- Provide written materials appropriate for the patient
- Encourage the patient to maintain and carry a current list of all medications (including OTC and supplements)
  - Share this list with all healthcare providers
- Encourage patient to maintain a journal of adverse effects
  - Share this information at each visit
  - Report new, severe, or worsening AE immediately

AE, adverse effect; OTC, over the counter

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Medication Adherence

- Adherence: extent to which patients comply with prescribed therapy
  - Barriers: access, toxicity / tolerability, health literacy, etc.
- Adherence impacts outcomes
  - Chronic phase CML patients in CCR on imatinib for at least 2 years had adherence electronically monitored during a 3-month period (N = 87)
    - Adherence rate (≤90% vs >90%) was the *only* independent predictor of CMR on the multivariate analysis (RR = 19.35; p = 0.004)
- Pharmacist-managed oral anticancer therapy program can improve outcomes
  - Pharmacist-managed oral anticancer therapies in CML patients (N = 56)
    - Higher adherence rate than usual care (88.6% vs. 65.8%, p =0.0046)

CCR, complete cytogenetic response; RR, relative risk; PFS, progression-free survival; NR, not reached; CMR, complete molecular response; CML, chronic myeloid leukemia

Marin D, et al. J Clin Oncol 2010; 28(14): 2381-8.
Lam MSH, Cheung N. J Oncol Pharm Practice 2016; 22(6): 741-8.
Chronic Myeloid Leukemia. NCCN v2.2024.

Patient Case Continued

- MM's work-up revealed a lower GI bleed. Her INR was therapeutic at the time of the bleeding event.
- Given the concern of increased bleeding risk with resuming dasatinib and previous concerns of nilotinib affecting MM's cardiac comorbidities, it was decided to switch MM's CML therapy to bosutinib.
- MM was educated on bosutinib therapy, received her medication from her mail order pharmacy and continues on bosutinib with no issues to date.

Pharmacist's Role as an Information Resource

Patients and Caregivers

- Follow-up phone calls
- Adherence aids
  - Diaries, pillboxes, electronic reminders
- Financial assistance resources
- Local and national support groups

Healthcare Providers

- Assess and manage adherence barriers
- Medication access
- Drug-drug and drug-disease interaction screening
- AE management recommendations

Selected Resources

- Medication Access
  - Manufacturer's patient assistance programs
  - Leukemia & Lymphoma Society co-pay
    - co-pay assistance (www.lls.org/copay)
  - NeedyMeds (www.needymeds.org)
- Disease Information for Patients
  - The Leukemia & Lymphoma Society (www.lls.org)
  - American Cancer Society (www.cancer.org)
  - ASCO (www.cancer.net)
- Disease Information for Healthcare Providers
  - NCCN (www.nccn.org)
- Standards for Safe Administration & Management of Oral Cancer Therapies
  - ASCO/ONS (http://ascopubs.org/doi/pdf/10.1200/JOP.2016.017905)
- Patient Education Tools for Oral Cancer Therapies
  - MASCC (https://mascc.org/resources/assessment-tools/mascc-oral-agent-teaching-tool-moatt/)
  - ONS Oral Anticancer Medication Toolkit (https://www.ons.org/clinical-practice-resources/oral-adherence-toolkit)

Summary

- Oral cancer therapies, the backbone of the CML management, present opportunities and challenges.
- Adherence can significantly impact achieving therapeutic goals and should be addressed at each healthcare encounter.
- Pharmacists are one of many healthcare providers that may be involved in the care of patients on oral cancer therapies.
- Pharmacists can assist with:
  - Discussion on medication selection given interactions and comorbidities
  - Medication access
  - Patient and caregiver education, or
  - Guiding patients and providers to appropriate resources

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Thank You

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CML: TKI Side Effects and Management

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The What, Where, and When of TKI's

Drug Name	Place In Therapy	Dosing Schedule
Imatinib mesylate (Gleevec®)	First line	Daily or twice daily dosing
Dasatinib (Sprycel®)	First line or subsequent	Daily dosing
Bosutinib (Bosulif®)	First line or subsequent	Daily dosing
Nilotinib (Tasigna®)	First line or subsequent	Twice daily dosing
Ponatinib (Iclusig®)	Subsequent and/or T315i mutation	Daily dosing
Asciminib (Scemblix®)	Subsequent and/or T315i mutation	Daily or twice daily dosing

Imatinib package insert, 3/2022; Dasatinib package insert, 2023; Bosutinib package insert, 2023; Nilotinib package insert, 2021; Ponatinib package insert, 2024; Asciminib package insert, 2023

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Common Class Side Effects

- Hematologic toxicities
- Gastrointestinal toxicities
- Rash (may be severe)
- Fluid retention
- Hypophosphatemia
- Musculoskeletal complaints
- Headache
- Fatigue
- Transaminitis

All cause fetal harm=> counsel on contraception and fertility preservation

Shyam Sunder S, Sharma UC, Pokharel S. *Signal Transduct Target Ther*. 2023 Jul 7;8(1):262.

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Agent Specific Side Effect

- **Imatinib:** fluid retention/edema, *hepatotoxicity, congestive heart failure, renal impairment, hypothyroidism*
- **Dasatinib:** pleural effusion, *QT prolongation, pulmonary arterial hypertension, cardiac dysfunction, bleeding*
- **Nilotinib:** hyperglycemia, elevated amylase/lipase, dyslipidemia, ***QT prolongation/sudden death***, *pancreatitis, hepatotoxicity, pleural effusion, arterial thrombotic events*
- **Bosutinib:** diarrhea, *hepatotoxicity, pleural effusion, pancreatitis, hypersensitivity*
- **Ponatinib:** hypertension, elevated amylase/lipase, *pancreatitis,* ***arterial thrombotic events***, ***venous thrombotic events***, ***hepatotoxicity***, *cardiac arrhythmias,* ***congestive heart failure***, *bleeding*
- **Asciminib:** *pancreatitis, hypertension, hypersensitivity, cardiovascular toxicity (ischemic cardiac, CNS, arterial thrombotic, and embolic), heart failure, prolonged QT*

Imatinib package insert, 3/2022; Dasatinib package insert, 2023; Bosutinib package insert, 2023; Nilotinib package insert, 2021; Ponatinib package insert, 2024; Asciminib package insert, 2023

Italicized = rare/serious adverse effect
Bold = Prescribing Information Boxed Warning

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Edema/Fluid Retention

Drug	Manifestation	Diagnostic Testing	Supportive Care
Imatinib Dasatinib Bosutinib Nilotinib Ponatinib	• Periorbital edema • Pleural effusions • Pericardial effusions • Pulmonary edema • Peripheral edema	Monitor weight Chest X-ray ECHO	Use of diuretics as needed Low Sodium diet Hold/dose adjustment/discontinuation Thoracentesis Oxygen if needed Cold compress to eyes Topical Hydrocortisone cream Use of corticosteroids
Imatinib Nilotinib	• Ascites	Abd ultrasound Monitor weight	Use of diuretics as needed Low Sodium diet Hold/dose adjustment/discontinue Paracentesis

Imatinib package insert, 3/2022; Dasatinib package insert, 2023; Bosutinib package insert, 2023; Nilotinib package insert, 2021; Ponatinib package insert, 2024; NCCN, 2024

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Myelosuppression

Drug	Manifestation	Diagnostic Testing	Supportive Care
ALL TKIs	• Anemia • Neutropenia • Thrombocytopenia • Hemorrhage • Bleeding events	Monitor CBC regularly Check iron and nutritional labs	Hold/dose adjustment Growth factor support Blood product transfusion support Correct any nutritional deficiencies Review medications - Concomitant use of antiplatelet or anticoagulants

Imatinib package insert, 3/2022; Dasatinib package insert, 2023; Bosutinib package insert, 2023; Nilotinib package insert, 2021; Ponatinib package insert, 2024; Asciminib package insert, 2023 NCCN, 2024

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Cardiovascular Toxicities

Drug	Manifestation	Diagnostic Testing	Supportive Care
Imatinib Bosutinib Ponatinib Asciminib	• Congestive Heart Failure • Left Ventricular Dysfunction	ECHO ECG Monitor Electrolytes Monitor heart rate Check Pro-BNP	Treat CV event per standard of care Correct electrolytes abnormalities Referral to Cardiology or Cardio-Oncology Review medications Hold/adjust dose/Discontinue
Imatinib Dasatinib Bosutinib Ponatinib Asciminib	• Prolonged QT • Arrhythmias		

Imatinib package insert, 3/2022; Dasatinib package insert, 2023; Bosutinib package insert, 2023; Ponatinib package insert, 2024; Asciminib package insert, 2023 NCCN, 2024

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Cardiovascular Toxicities

Drug	Manifestation	Diagnostic Testing	Supportive Care
Nilotinib **Assess Cardiac risk prior to start	Prolonged QT/Sudden death	Monitor Electrolytes (K+ and Mg) -prior to start then periodically -correct deficiencies before starting Monitor ECG -Baseline, 7 days after start, then periodically and 7 days after dose adjustments	• DO NOT ADMINISTER TO PATIENTS WITH HYPOKALEMIA, HYPOMAGNESIA, OR LONG QT SYNDROME. • Correct electrolytes • Medication review-> avoid concomitant drugs known to prolong QT • Consult Cardiology/Cardio-Oncology • Hold/dose adjustment/discontinuation

RED= Black Box Warning

Nilotinib package insert, 2021; NCCN, 2024

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Cardiovascular Toxicities

Drug	Manifestation	Diagnostic Testing	Supportive Care
Nilotinib	• Arterial vascular occlusive events • Ischemia heart disease related events • Peripheral arterial occlusive disease	ECHO ECG Cardiac enzymes Duplex u/s	If confirmed = Discontinue treatment Treat any cardiac events per standard of care
Nilotinib Asciminib	Hyperlipidemia	Monitor lipid profile prior to start and periodically during first year then annually	May need to start lipid lowering agent - Review for drug-drug interactions

Nilotinib package insert, 2021; Asciminib package insert, 2023 NCCN, 2024

Cardiovascular Toxicities

Drug	Manifestation	Diagnostic Testing	Supportive Care
Ponatinib **Assess Cardiac risk prior to start	Arterial Occlusive Events - MI, stroke, etc	ECHO ECG Cardiac enzymes Duplex u/s CT head Revascularization/heart cath	Per standard of care Hold/discontinue based on severity
Ponatinib	Venous thromboembolic events (VTE's)	Monitor for evidence of VTE's	Per standards of care Hold/discontinue based on severity

RED= Black Box Warning

Ponatinib package insert, 2024; NCCN, 2024

Cardiovascular Toxicities

Drug	Manifestation	Diagnostic Testing	Supportive Care
Ponatinib	Heart failure	Monitor for s/sx of heart failure ECHO Pro-BNP	Per standards of care Hold/discontinue for new or worsening heart failure
Ponatinib Asciminib	Hypertension Hypertensive Crisis	Monitor blood pressure	Manage blood pressure with antihypertensives Hold/adjust dose/discontinue

RED= Black Box Warning

Ponatinib package insert, 2024; Asciminib package insert, 2023 NCCN, 2024

Cardiovascular Toxicities

Drug	Manifestation	Diagnostic Testing	Supportive Care
Dasatinib	Pulmonary Arterial Hypertension (PAH) *Evaluate for s/sx of underlying cardiopulmonary disease prior to starting	ECHO CT Chest PFT's	If PAH is confirmed = discontinuation

Dasatinib package insert, 2023; NCCN, 2024

Gastrointestinal Toxicities

Drug	Manifestation	Diagnostic Testing	Supportive Care
ALL TKI's	• Nausea • Vomiting • Diarrhea • Abd pain	Evaluate CBC and CMP Stool studies Abd imaging (i.e. ultrasound or CT) Check Amylase & Lipase	Antiemetics prior to dose and as needed Ginger hard candy Imodium® (loperamide)/Lomotil® (diphenoxylate and atropine) as needed for diarrhea Adequate Hydration Diet modification (BRAT diet) Avoid spicy, fatty foods, caffeine
Bosutinib Nilotinib Ponatinib Asciminib	Pancreatitis Elevated serum lipase	Evaluate CBC and CMP Check Amylase & Lipase Abd imaging (i.e. ultrasound or CT)	Per standard of care Hold medication until resolution/ decrease dose May require discontinuation

Imatinib package insert, 3/2022; Dasatinib package insert, 2023; Bosutinib package insert, 2023; Nilotinib package insert, 2021; Ponatinib package insert, 2024; Asciminib package insert, 2023 NCCN, 2024

Gastrointestinal Toxicities

Drug	Manifestation	Diagnostic Testing	Supportive Care
Bosutinib Nilotinib Ponatinib	Constipation		Stool softeners/laxatives for constipation
Ponatinib	GI perforation	Evaluate CBC and CMP Abd imaging (i.e. ultrasound or CT)	**GI Perforation= Discontinue**

Bosutinib package insert, 2023; Nilotinib package insert, 2021; Ponatinib package insert, 2024; NCCN, 2024

Dietary Considerations/Restrictions

Drug	Food?	Restrictions	Antacids?
Imatinib	Take with food and water	No Grapefruit juice	No restrictions
Dasatinib	Take with food and water	Avoid in lactose intolerant patients No Grapefruit juice	No Antacids 2 hours before or after administration. Avoid H2 Antagonists & PPI
Bosutinib	Take with food and water	No Grapefruit juice	No Antacids 2 hours before or after administration. Avoid H2 Antagonists & PPI
Nilotinib	Take on empty stomach - Avoid food 2 hours before and 1 hour after dose	Avoid in lactose intolerant patients No Grapefruit juice	No Antacids 2 hours before or after administration. Avoid H2 Blockers for 10 hours before and 2 hours after
Ponatinib	Take with or without food	Avoid in lactose intolerant patients No Grapefruit juice	No restrictions
Asciminib	Take on empty stomach - Avoid food 2 hours before and 1 hour after dose	No restrictions	No restrictions

Imatinib package insert, 3/2022; Dasatinib package insert, 2023; Bosutinib package insert, 2023; Nilotinib package insert, 2021; Ponatinib package insert, 2024; Asciminib package insert, 2023 NCCN, 2024

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Hepatotoxicity

Drug	Manifestation	Diagnostic Testing	Supportive Care
Imatinib Dasatinib Bosutinib Nilotinib	Elevated liver functions Abd pain Jaundice	Check liver function test • Prior to start of therapy • As clinically indicated (q2-3 months)	Hold/dose adjustment May require discontinuation Medication review
Ponatinib	Liver Failure	Check liver function test • Baseline, then monthly or as clinically indicated	Hold/discontinue based on severity

RED= Black Box Warning

Imatinib package insert, 3/2022; Dasatinib package insert, 2023; Bosutinib package insert, 2023; Nilotinib package insert, 2021; Ponatinib package insert, 2024; NCCN, 2024

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Renal Toxicity

Drug	Manifestation	Diagnostic Testing	Supportive Care
Imatinib Bosutinib	Renal dysfunction	Evaluate renal function prior to start of therapy then as clinically indicated	Adequate hydration Dose adjustment
Imatinib Dasatinib Nilotinib Ponatinib	Electrolyte Abnormalities - Tumor Lysis Syndrome	Monitor electrolytes Monitor uric acid	Correct uric acid prior to start Adequate hydration Allopurinol prophylaxis Correct electrolyte abnormalities Dialysis

Imatinib package insert, 3/2022; Dasatinib package insert, 2023; Bosutinib package insert, 2023; Nilotinib package insert, 2021; Ponatinib package insert, 2024; NCCN, 2024

Dermatological Toxicity

Drug	Manifestation	Diagnostic Testing	Supportive Care
ALL TKIs	Rash - bullous dermatologic reactions (erythema multiforme and Stevens-Johnson Syndrome) Itching	Skin assessment Skin biopsy	Moisturizing skin cream Avoid sun exposure Hold/adjust dose/discontinue Antihistamines Corticosteroids Dermatology referral
Ponatinib	Impaired wound healing		Hold for 1 week prior to surgery and 2 weeks after surgery or until adequate wound healing

Imatinib package insert, 3/2022; Dasatinib package insert, 2023; Bosutinib package insert, 2023; Nilotinib package insert, 2021; Ponatinib package insert, 2024; Asciminib package insert, 2023 NCCN, 2024

Ocular Toxicity

Drug	Manifestation	Diagnostic Testing	Supportive Care
Ponatinib	Blurred vision Dry eyes	Comprehensive Eye Exam - Baseline then periodically	Lubricating eye drops for dry eyes

Ponatinib package insert, 2024; NCCN, 2024

Endocrine Complications

Drug	Manifestation	Diagnostic Testing	Supportive Care
Nilotinib	Elevated Blood Glucose - Avoid in patient with diabetes	Monitor Blood Glucose - Prior to start of therapy then as clinically indicated	May need to start medications for glucose management (per standards of care
Imatinib	Hypothyroidism • Patients with history of thyroidectomy and on levothyroxine	Monitor TSH	Adjust levothyroxine

Imatinib package insert, 3/2022; Nilotinib package insert, 2021; NCCN, 2024

Fatigue

Drug	Manifestation	Diagnostic Testing	Supportive Care
ALL TKI's	Fatigue No energy	Fatigue Assessment Score	Adequate Hydration Exercise Adjust time of administration

Imatinib package insert, 3/2022; Dasatinib package insert, 2023; Bosutinib package insert, 2023; Nilotinib package insert, 2021; Ponatinib package insert, 2024; Asciminib package insert, 2023 NCCN, 2024

Musculoskeletal Complications

Drug	Manifestation	Diagnostic Testing	Supportive Care
Imatinib Dasatinib Ponatinib Asciminib	• Joint pain • Musculoskeletal pain • Myalgia • Muscle cramps • Arthralgias	Monitor electrolytes (BMP, Mg, Phos)	Adequate Hydration Tonic water, tomato juice Potassium supplements Magnesium supplements Calcium supplements Muscle relaxers

Imatinib package insert, 3/2022; Dasatinib package insert, 2023; Ponatinib package insert, 2024; Asciminib package insert, 2023 NCCN, 2024

Infections and Fevers

Drug	Manifestation	Diagnostic Testing	Supportive Care
Bosutinib Asciminib	Respiratory Tract Infections	Respiratory Viral Panel Chest imaging (Chest XR, CT)	Cough suppressants/expectorants Albuterol inhalers Antibiotics/antivirals if needed
Bosutinib	Fevers	Evaluate for infections - Blood cultures - CBC - UA and urine culture	Acetaminophen or NSAIDS in moderation Antibiotics

Bosutinib package insert, 2023; Asciminib package insert, 2023 NCCN, 2024

Neurological Complications

Drug	Manifestation	Diagnostic Testing	Supportive Care
ALL TKI's	Headaches	Consider CT Head	Acetaminophen or NSAIDs in moderation
Ponatinib	Neuropathy	Monitor for symptoms of peripheral or cranial neuropathy	Hold/dose reduce/discontinue
Ponatinib	Reversible Posterior Leukoencephalopathy syndrome (RPLS)	MRI brain	Hold dose until resolution/discontinue

Gleevec (Imatinib) package insert, 3/2022; Dasatinib package insert, 2023; Bosutinib package insert, 2023; Nilotinib package insert, 2021; Ponatinib package insert, 2024; Asciminib package insert, 2023 NCCN, 2024

Medication Adherence is the Key

- Medication only works if you take it
- Non-adherence is common (30%-70% of patients)
- Adherence = response:
  - Patients who took > 90% of their doses had a 94.5% probability of achieving MMR
  - Patients who took < 90% of doses, who had a 28% incidence of MMR
  - Treatment adherence is the only independent predictor of achieving CMR.
  - Patients with suboptimal responses missed 24% of doses, as opposed to those with optimal responses, who missed 7% of doses.

Communication and prompt management of side effects is essential!

Marin D et al. J Clin Oncol 28(14):2381-8, 2010.
Noens L et al. Blood 113(22):5401-11, 2009.

Discontinuation of Therapy??

Reason to Discontinue
- Decrease medication burden
- Financial toxicity
- Side effects
- Physician advice
- Fertility/Pregnancy

Reasons To Continue
- If it isn't broke…
- Fear of relapse

Discontinuation of TKI therapy should only be performed in consenting patients after a thorough discussion of the potential risks and benefits

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Chronic Myeloid Leukemia
Version 1.2025 — August 8, 2024. https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf.

Review the NCCN Guidelines at www.NCCN.org

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Discontinuation Withdrawal Syndrome

- Occurs in about 30% of patients
- Characterized by musculoskeletal pain that begins 1-3 months after discontinuation
- Females > Males
- Treat with anti-inflammatory drugs, analgesics, steroids, or muscle relaxants
- Rarely may require resuming TKI

Murbach et al., *Blood* 2023; 142 (Supplement 1): 6368. doi: https://doi.org/10.1182/blood-2023-189925

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Thank You!!

- Questions???
  - Contact Me:
    - sajimenez@augusta.edu
    - Sarah Jimenez DNP, AGACNP-BC, AOCNP | LinkedIn

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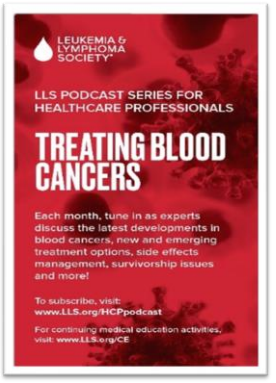
FREE LLS RESOURCES FOR HEALTHCARE PROFESSIONALS

- ❑ CME & CE courses: www.LLS.org/CE
- ❑ Fact Sheets for HCPs: www.LLS.org/HCPbooklets
- ❑ Videos for HCPs: www.LLS.org/HCPvideos
- ❑ Podcast series for HCPs: www.LLS.org/HCPpodcast

CLICK HERE TO PARTICIPATE



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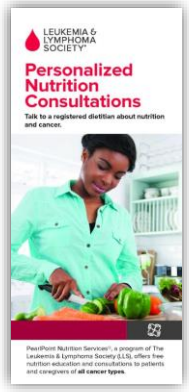
FREE LLS RESOURCES FOR PATIENTS

- **Information Specialists** – Personalized assistance for managing treatment decisions, side effects, and dealing with financial and psychosocial challenges (IRC).
  - www.LLS.org/IRC
- **Nutrition Education Services Center** – one-on-one consultation with a registered dietician for patients/caregivers of all cancer types (NESC).
  - www.LLS.org/Nutrition
- **Clinical Trial Nurse Navigators** – RNs and NPs provide a personalized service for patients seeking treatment in a clinical trial, sift through the information and provide information to bring back to their HC team (CTSC).
  - www.LLS.org/CTSC
- **Reach out** **Monday–Friday, 9 am to 9 pm ET**
  - Phone: (800) 955-4572
  - Live chat: www.LLS.org/IRC
  - Email: infocenter@LLS.org
  - HCP Patient Referral Form: www.LLS.org/HCPreferral



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HERE TO HELP: LLS COMMITMENT

to providing education & resources to help patients access clinical trials

CLINICAL TRIAL SUPPORT CENTER

- A team of highly trained nurses and nurse practitioners experienced with hematological malignancies and clinical research.
- Provide education to patients about clinical trials, treatment options, and other disease specific information.
- Provide patients, families, and their caregivers with a professional, detailed, individualized search to discuss with their HCP.
- Provide guidance and serve as advocates throughout the clinical trial process. Help make connections between the patient and the trial site to facilitate enrollment as appropriate.
- Provide a personal connection and develop long term relationships to help better serve our patients.

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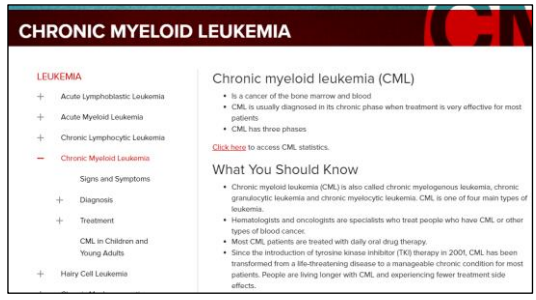
FREE LLS RESOURCES FOR PATIENTS AND CAREGIVERS

- **Webcasts, Videos, Podcasts, booklets**:
  - www.LLS.org/Webcasts
  - www.LLS.org/EducationVideos
  - www.LLS.org/Podcast
  - www.LLS.org/Booklets
  - **www.LLS.org/Leukemia**

- **Support Resources**
  - Financial Assistance: www.LLS.org/Finances
    - Urgent Need
    - Patient Aid
    - Travel Assistance
  - Other Support: www.LLS.org/Support
    - LLS Regions
    - Online Weekly Chats Facilitated by Oncology SW
    - LLS Community Social Media Platform
    - First Connection Peer to Peer Program



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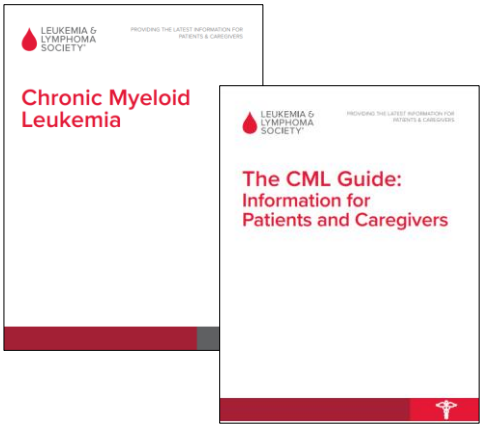
FREE LLS RESOURCES FOR YOUR PATIENTS



BOOKLETS AND FACT SHEETS

English – www.LLS.org/Booklets
Spanish – www.LLS.org/Materiales

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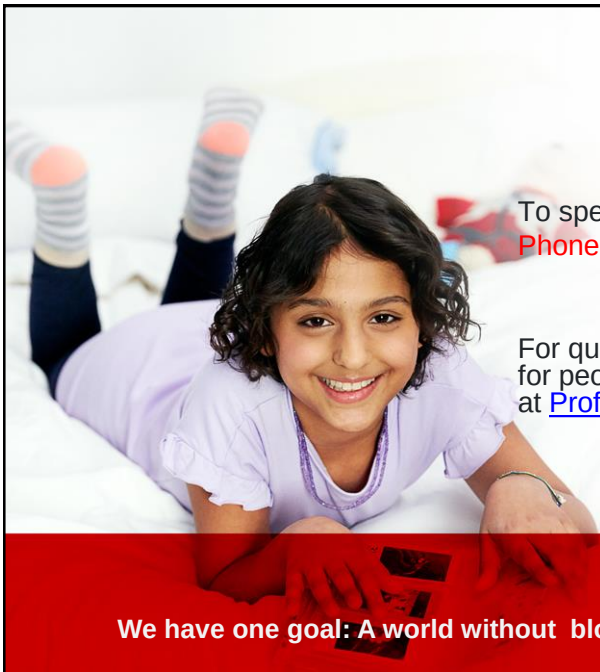
THANK YOU



To speak with an Information Specialist or to refer a patient:
Phone (800) 955-4572 Email: Infocenter@LLS.org

For questions about this program, concerns, or assistance for people with disabilities or grievances, please contact us at Profeducation@LLS.org

We have one goal: A world without blood cancers

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